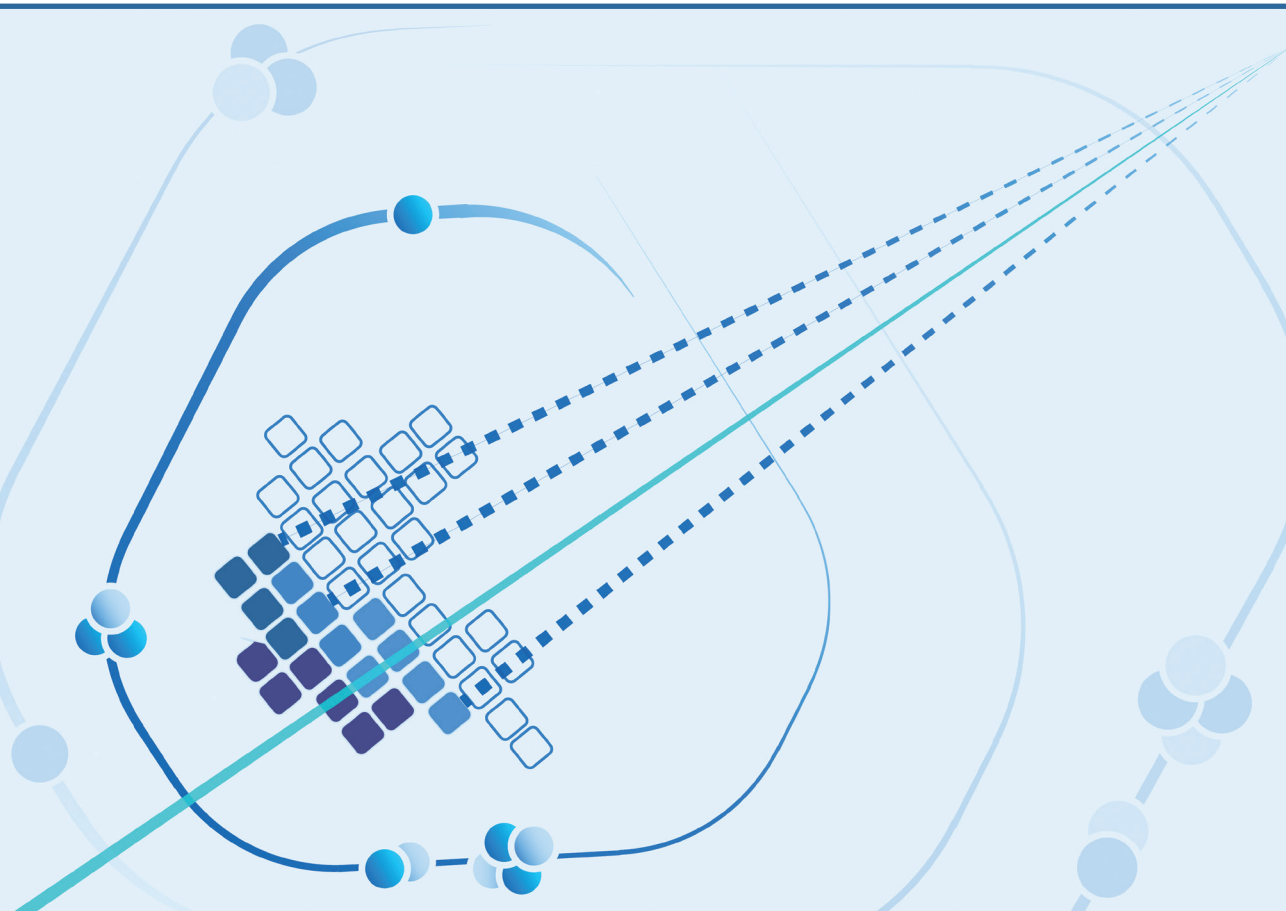


Kristaps Paļskis

**APPLICATION OF FLASH EFFECT FOR LIGHT
ION THERAPY AND DEVELOPMENT OF RANGE
VERIFICATION METHODS**

Doctoral Thesis



RIGA TECHNICAL UNIVERSITY

Faculty of Natural Sciences and Technology
Institute of Particle Physics and Accelerator Technologies

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Doctoral Student of the Study Programme
“Particle Physics and Accelerator Technologies”

**APPLICATION OF FLASH EFFECT FOR
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OF RANGE VERIFICATION METHODS**

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FLASHlab@PITZ



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**DOCTORAL THESIS PROPOSED TO RIGA
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SCIENTIFIC DEGREE OF DOCTOR OF SCIENCE**

To be granted the scientific degree of Doctor of Science (PhD) in Physics and Astronomy, the present Doctoral Thesis has been submitted for defence at the open meeting of the RTU Promotion Council on 14 September 2026 at 10:00 at the Faculty of Natural Sciences and Technology of Riga Technical University, Paula Valdena iela 3, Room 272.

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DECLARATION OF ACADEMIC INTEGRITY

I hereby declare that the Doctoral Thesis submitted for review to Riga Technical University for promotion to the scientific degree of Doctor of Science (PhD) is my own. I confirm that this Doctoral Thesis has not been submitted to any other university for promotion to a scientific degree.

Kristaps Paļskis

Date:

The Doctoral Thesis has been written in English. It consists of 12 Chapters, including Introduction; Conclusions and Recommendations; 86 figures; 25 tables; 129 appendices; the total number of pages is 333, not including appendices. The Bibliography contains 1022 references.

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The reward of a thing well done, is to have done it.

- Ralph Waldo Emerson

Abstract

Keywords: particle therapy, helium ion therapy, *FLASH* effect, UHDR delivery, range verification, particle radiography, PET-based verification, prompt gamma verification

With cancer remaining as one of the most prevalent diseases and causes of death globally, radiotherapy is one of the primary treatment methods, delivering a high, localized dose of ionizing radiation to the tumour while sparing normal tissue. Typically, high-energy X-rays are used, though use of positively charged ions (protons or carbon-12) can improve dose conformality due to localized energy deposition maximum - the Bragg peak. With limitations for both proton and carbon ion therapy, renewed interest is growing for the use of helium-4 ions. Dedicated accelerator systems for this approach do not yet exist – a challenge tackled at CERN by NIMMS group via development of HeLICS system.

Beyond dose conformality improvement by the use of helium-4 ions, biological effects can also be used to increase treatment effectiveness. The *FLASH* effect is one such perspective approach, providing increased normal tissue sparing with preserved tumour control at ultra-high dose rate and high dose levels. Key questions remain on necessary delivery parameters and underlying mechanisms of *FLASH* effect, while achieving it with heavier ions remains under-studied. Furthermore, as the Bragg peak advantage is limited by range uncertainty and precise delivery is critical for *FLASH* effect, advanced range verification is essential for development of light ion *FLASH* therapy.

Integration of approaches as use of helium-4 ions, advanced range verification and ultra-high dose rate delivery, holds promise to improve treatment outcomes and quality of life post-treatment. Through medical physics and particle accelerator applications, this Thesis contributes to the developments necessary to enable light ion *FLASH* therapy with dedicated range verification to achieve the required precision.

Addressing this, the Doctoral Thesis is structured into two main parts – “*Investigations on FLASH effect and applications in light ion beam therapy*” (Chapters 3 to 7) and “*Investigations on novel range verification methods for helium ion therapy*” (Chapters 8 to 12). Each part consists of one scientific literature review chapter and four chapters presenting methodology and results of performed research.

Part I “*Investigations on FLASH effect and applications in light ion beam therapy*” starts with Chapter 4, presenting a study radiochemistry based modelling approach to evaluate the scaling of *FLASH* effect dose threshold with ion type, assessing also the influence on achievable dose conformality. Developed model suggests increasing *FLASH* effect dosimetric thresholds for heavier ions, with optimum performance achievable by helium and lithium ions, if dose conformality is also considered.

Chapter 5 presents experimental campaign on radiochemical changes under ultra-high dose rate irradiation with X-ray photon and electron beams. Experiments focused on the role of solvated electrons, validating the theoretical assumptions presented in Chapter 4. Experiments with X-ray photons found decreased hydrogen peroxide yield with increasing average dose rate, though the dependency was diminished in presence of solvated electron scavengers. Additionally, experiments with electron beam of varying temporal structure found pulse and bunch dose rates as better predictors of radiochemical changes compared to average dose rate, indicating the role of radical-radical recombination under ultra-high dose rate conditions.

Chapters 6 and 7 focus on technological aspects of ultra-high dose rate delivery with ion beams. Chapter 6 presents and validates a novel pencil beam algorithm for calculation of dose, dose rate and other parameters as relevant for model in Chapter 4. Novel “Gaussian + Double Logistic” function was proposed for lateral dose kernel parametrization, employing 3 component calculation for linear energy transfer and associated parameters. Developed model achieved high accuracy with respect to Monte Carlo reference data outperforming existing pencil beam algorithm approaches.

Finally, Chapter 7 explores different technological approaches for ultra-high dose rate delivery with ion beams via a literature review-based comparative analysis. Comparison focuses on the achievable treatment plan quality and dose rate level, as well as technological and workflow complexity necessary for implementation. In context of HeLICS accelerator design, proton transmission beams and use of 3-dimensional range modulators with protons or helium-4 ions were found as most promising approaches.

Part II “*Investigations on novel range verification methods for helium ion therapy*” opens with Chapters 9 and 10, developing particle radiography specifically for helium ion beam therapy. Chapter 9 proposes anatomy verification before treatment with high energy protons and helium-3 ions, evaluating achievable image quality. 330 to 500 MeV was found as optimum energy range in proton radiography for full-body imaging. Novel helium-3 ion radiography achieves comparable image quality with helium-4 ion approach, while indicating favourable characteristics for technological implementation. Additionally, use of focus stacking in image reconstruction was assessed for 3-dimensional feature localization. Novel, standard deviation-based approach was developed, having significantly improved performance over conventional edge detection based approach.

Chapter 10 proposes the use of mixed helium-deuteron beams as a method for patient position monitoring during treatment delivery. For range measurement, a mixing ratio of 1:100 was found suitable for clinically significant shift detection with negligible contribution to treatment dose distribution. For 2-dimensional imaging, novel data filtering routine prior to reconstruction was developed specific to mixed beams and a higher mixing ratio of 1:10 was found necessary to maintain adequate image quality.

To evaluate the delivered dose distribution itself, Chapters 11 and 12 investigate secondary particle detection based *in vivo* range verification for helium-4 ion beam therapy. Chapter 11 focuses on positron emission tomography-based range verification

by evaluating induced β^+ activity distribution. Due to helium-4 ion interactions with oxygen nuclei, unique β^+ activity patterns were found from induced fluorine-17 and fluorine-18 nuclei. Resulting β^+ activity spatial distribution was found to have improved correlation with respect Bragg peak position compared to proton therapy.

Chapter 12 proposes and evaluates a method to increase prompt gamma emissions for real-time range verification by using oxygen-18 as a contrast agent. Spectral, spatial and temporal characteristics of prompt gamma emissions were evaluated and compared to a reference scenario. Oxygen-18 as contrast agent was found to significantly increase number of detectable prompt gamma photons in low energy range, thus decreasing dose level necessary to reach statistically significant range measurement. Alternatively, measurement of unique spectral line intensity could enable monitoring of delivered integral dose to a region of interest.

Research presented in the Thesis provides a significant step towards implementation of light ion *FLASH* therapy and dedicated range verification methods, outlining strong foundational basis and general feasibility assessment necessary for technological development of novel cancer treatment approaches.

The Doctoral Thesis has been written in English. The total number of pages is 333, containing 86 Figures and 25 Tables. Additionally, the Doctoral Thesis is supplemented by Book of Appendices of 510 pages in total, containing 129 appendices. Combined Bibliography for the Doctoral Thesis and supplementary Book of Appendices contains 1022 references.

Anotācija

FLASH efekta pielietojums vieglo jonu terapijā un jonu noskrējiena verifikācijas metožu izstrāde

Atslēgvārdi: daļiņu terapija, hēlija jonu terapija, *FLASH* efekts, ļoti augstas dozas jaudas piegāde, noskrējiena verifikācija, daļiņu radiogrāfija, uz PET balstīta verifikācija, verifikācija ar tūlītējiem gamma fotoniem

Vēzis joprojām ir viena no visizplatītākajām slimībām un galvenajiem nāves cēloņiem pasaulē, kura viena no primārajām ārstēšanas metodēm ir staru terapija, piegādājot augstu, lokalizētu jonizējošu starojuma dozu audzējā, vienlaikus saudzējot veselos audus. Tipiski tiek izmantoti augstas enerģijas rentgenstarojuma fotoni, taču pozitīvi lādētu jonu (protoni vai oglekļa-12 joni) izmantošana ļauj uzlabot dozas konformalitāti, pateicoties lokalizētam atdotās enerģijas maksimumam – Brega pīķim. Ņemot vērā gan protonu, gan oglekļa jonu terapijas ierobežojumus, atjaunota interese tiek pievērsta hēlija-4 jonu izmantošanai. Šai pieejai paredzētas specializētas paātrinātāju sistēmas vēl nepastāv – izaicinājums, ko risina CERN NIMMS grupa, izstrādājot HeLICS sistēmu.

Papildus dozas konformalitātes uzlabošanai ar hēlija-4 joniem, terapijas efektivitāti iespējams uzlabot arī izmantojot bioloģiskos efektus. Viena no perspektīvākajām pieejām ir *FLASH* efekts – pievadot starojumu ar ļoti augstu dozas jaudu un augstu dozu, tiek uzlabota veselo audu aizsardzība, saglabājot audzēja kontroli. Joprojām pastāv būtiski jautājumi par nepieciešamajiem starojuma piegādes parametriem un *FLASH* efekta mehānismiem, vēl jo vairāk – efekta realizācija ar smagākiem joniem ir maz pētīta. Tā kā Brega pīķa priekšrocības ierobežo noskrējiena nenoteiktības, bet *FLASH* efekta realizācijai nepieciešama īpaši precīza starojuma piegāde, jaunu noskrējiena verifikācijas metožu izstrāde ir būtiska vieglo jonu *FLASH* terapijas attīstībai.

Hēlija-4 jonu terapija, inovatīvu noskrējiena verifikācijas metožu un ļoti augstas dozas jaudas starojuma piegādes integrācija ir ar potenciālu uzlabot ārstēšanas rezultātus un pacientu dzīves kvalitāti pēc terapijas. Balstoties uz medicīnas fiziku un daļiņu paātrinātāju tehnoloģiju pielietojumiem, šis promocijas darbs sniedz ieguldījumu pētniecībā, kas nepieciešama vieglo jonu *FLASH* terapijas realizācijai ar pielāgotām noskrējiena verifikācijas metodēm, lai sasniegtu nepieciešamo precizitāti.

Lai to sasniegtu, promocijas darbs ir strukturēts divās galvenajās daļās – “*FLASH efekta pētījumi un pielietojums vieglo jonu terapijā*” (3. līdz 7. nodaļa) un “*Jaunu noskrējiena verifikācijas metožu pētījumi hēlija jonu terapijā*” (8. līdz 12. nodaļa). Katrā daļā ietverta viena zinātniskās literatūras apskata nodaļa un četras nodaļas, kas apraksta pētījumos izmantoto metodoloģiju un sasniegtos rezultātus.

I daļa “*FLASH efekta pētījumi un pielietojums vieglo jonu terapijā*” sākas ar 4. nodaļu, kurā prezentēts pētījums par uz radioķīmiju balstīta modeli *FLASH* efekta dozas sliekšņvērtības izvērtēšanai atkarībā no jonu tipa, analizējot arī ietekmi uz sasniedzamo dozas konformalitāti. Izstrādātais modelis norāda uz *FLASH* efekta dozimetrisko sliekšņvērtību pieaugumu smagākiem joniem, norādot uz optimālu veikspēju, izmantojot hēlija un litija jonus, ja tiek ņemta vērā arī dozas konformalitāte.

5. nodaļā apskatīti eksperimentālie mērījumi radioķīmisko izmaiņu izpētei ļoti augstas dozas jaudas apstākļos ar rentgenstaru fotonu un elektronu kūļiem. Eksperimenti fokusējās uz hidratēto elektronu lomu, validējot 4. nodaļā izvirzītos teorētiskos pieņēmumus. Eksperimentos ar rentgenstaru fotoniem tika novērota ūdeņraža peroksīda radioķīmiskā iznākuma samazināšanās, palielinoties vidējai dozas jaudai, taču šī atkarība izzuda hidratēto elektronu uztvērēju klātbūtnē. Eksperimenti ar mainīgas pulsu struktūras elektronu kūli atklāja, ka pulsa un kūlīša dozas jauda ir galvenie parametri radioķīmisko izmaiņu prognozēšanai, salīdzinot ar vidējo dozas jaudu, kas norāda uz radikāļu-radikāļu rekombinācijas nozīmi ļoti augstas dozas jaudas apstākļos.

6. un 7. nodaļa veltīta tehnoloģiskajiem aspektiem ļoti augstas dozas jaudas piegādes nodrošināšanai ar jonu kūļiem. 6. nodaļā prezentēts un validēts jauns zīmulkūļa algoritms dozas, dozas jaudas un citu parametru aprēķinam, kas nepieciešami 4. nodaļā aprakstītajam modelim. Laterālā dozas profila parametrizācijai izstrādāta jauna “Gausa + Divkārsā Logistiskā” funkcija, izmantojot trīs komponentu pieeju lineārās enerģijas pārnese un saistīto parametru aprēķinam. Izstrādātais modelis sasniedza augstu precizitāti, salīdzinot ar Montekarlo references datiem un pārspējot esošās zīmulkūļa algoritmu pieejas.

7. nodaļā analizētas dažādas tehnoloģiskās pieejas ļoti augstas dozas jaudas nodrošināšanai ar jonu kūļiem, veicot uz literatūras apskatu balstītu salīdzinājumu. Salīdzinājums fokusējās uz sasniedzamo terapijas plānu kvalitāti un dozas jaudas līmeni, kā arī tehnoloģisko un darba plūsmas sarežģītību, kas nepieciešama ieviešanai. HeLICS paātrinātāja kontekstā kā perspektīvākās pieejas tika identificētas protonu transmisijas kūļi un 3-dimensionālo noskrējiena modulatoru izmantošana ar protoniem vai hēlija-4 joniem.

II daļa “*Jaunu noskrējiena verifikācijas metožu pētījumi hēlija jonu terapijā*” sākas ar 9. un 10. nodaļu, izskatot hēlija jonu terapijai pielāgotu daļiņu radiogrāfiju. 9. nodaļā izskatīta anatomijas verifikācija pirms ārstēšanas, izmantojot augstas enerģijas protonus un hēlija-3 jonus, izvērtējot sasniedzamo attēla kvalitāti. 330 - 500 MeV tika noteikts kā optimālais enerģijas diapazons protonu radiogrāfijā pilna ķermeņa attēlveidošanai. Jaunā hēlija-3 jonu radiogrāfijas pieeja nodrošina salīdzināmu attēla kvalitāti ar pieeju, izmantojot hēlija-4 jonus, vienlaikus demonstrējot perspektīvas īpašības tehnoloģiskai ieviešanai. Papildus tika izvērtēta fokusgrupēšanas metode attēlu rekonstrukcijā 3-dimensionālai objektu lokalizācijai. Tika izstrādāta jauna, uz standartnovirzi balstīta pieeja ar būtiski uzlabotu veikspēju salīdzinot ar konvencionālo pieeju, kas balstīta uz malu detektēšanu.

10. nodaļā izskatīta jauktu hēlija-deitronu kūļu izmantošana pacientu pozīcijas monitorēšanai terapijas laikā. Noskrējiena mērījumiem fluenču attiecība 1:100 tika noteikta kā piemērota, lai nodrošinātu klīniski nozīmīgu nobīžu detektēšanu ar minimālu ietekmi uz terapijas dozas sadalījumu. 2-dimensionālai attēlveidošanai izstrādāta jauna, jauktiem kūļiem pielāgota datu filtrēšanas pieeja pirms rekonstrukcijas, un tika noteikts, ka augstāka fluenču attiecība 1:10 ir nepieciešama adekvātas attēla kvalitātes nodrošināšanai.

Piegādātā dozas sadalījuma tiešai izvērtēšanai, 11. un 12. nodaļā analizētas uz sekundāro daļiņu detektēšanu balstītas *in vivo* noskrējiena verifikācijas metodes hēlija-4 jonu terapijai. 11. nodaļā aplūkota uz pozitronu emisijas tomogrāfiju balstīta verifikācija, analizējot inducētās β^+ aktivitātes sadalījumu. Hēlija-4 jonu mijiedarbības ar skābekļa kodoliem rezultātā konstatēti unikāli β^+ aktivitātes profili, ko rada fluora-17 un fluora-18 kodoli. Inducētajam β^+ aktivitātes sadalījumam tika novērota uzlabota korelācija ar Brega pīķa pozīciju, salīdzinot ar protonu terapiju.

12. nodaļā izstrādāta un izvērtēta metode tūlītējo gamma fotonu emisiju pastiprināšanai reāllaika noskrējiena verifikācijai, izmantojot skābekli-18 kā kontrastvielu. Tika izvērtētas tūlītējo gamma fotonu spektrālās, telpiskās un temporālās īpašības, salīdzinot tās ar references scenāriju. Skābeklis-18 kā kontrastviela būtiski palielināja detektējamo tūlītējo gamma fotonu skaitu zemas enerģijas diapazonā, tādējādi samazinot nepieciešamo primāro daļiņu skaitu statistiski nozīmīga noskrējiena mērījuma iegūšanai. Alternatīvi, unikālo spektrālo līniju intensitātes mērījumi varētu nodrošināt piegādātās integrālās dozas monitorēšanu interesējošajā reģionā.

Promocijas darbā prezentētie pētījumi sniedz ievērojamu soli pretim vieglo jonu *FLASH* terapijas un pielāgotu noskrējiena verifikācijas metožu ieviešanai, nodrošinot nozīmīgu fundamentālu pamatu un vispārēju realizējamības izvērtējumu, kas nepieciešams jauno vēža ārstēšanas pieeju tehnoloģiskai attīstībai.

Promocijas darbs ir uzrakstīts angļu valodā. Kopējais darba apjoms ir 333 lappuses, ietverot 86 attēlus un 25 tabulas. Promocijas darbu papildina pielikumu sējums ar kopējo apjomu 510 lappuses, iekļaujot 129 pielikumus. Kopējā promocijas darba un pielikumu sējuma bibliogrāfija ietver 1022 atsauces.

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List of Abbreviations

1D	1-dimensional
2D	2-dimensional
2G	sum of two Gaussian functions
2G+L	sum of two Gaussian and a logistic function
3D	3-dimensional
3D-RM	3-dimensional range modulator
3G	sum of three Gaussian functions
APB	along-path binning
aPSF	annihilation point spread function
APTCB	Advanced Particle Therapy Centre for the Baltic States
CDF	cumulative probability density function
CERN	European Organization for Nuclear Research
CNR	contrast-to-noise ratio
CPE	charged particle equilibrium
CSDA	continuous slowing down approximation
CT	computed tomography
DESY FLASHlab@PITZ	FLASHlab at Photo Injector Test Facility at the German Electron Synchrotron
DKFZ	The German Cancer Research Centre
DMF	dose-modifying factor
DNA	deoxyribonucleic acid
DR	dose rate
d-Rad	deuteron radiography
DSB	double strand breaks
EBRT	external beam radiation therapy
ED-FS	edge detection based focus stacking
EM	electromagnetic
FS	focus stacking
FTB	front tracker binning
FWHM	full width at half-maximum
G+2L	sum of a Gaussian and two logistic functions
G+V	sum of a Gaussian function and Voigt profile
G-value	radiolytic yield
He3-Rad	helium-3 ion radiography
He4-Rad	helium-4 ion radiography
He-D	helium-deuteron (in context of mixed-beam)
He-D-Rad	helium-deuteron mixed beam radiography

HeLICS	Helium Light Ion Compact Synchrotron
He-Rad	helium ion radiography
HIT	Heidelberg Ion Beam Therapy Centre
HSG	human salivary gland (cell line)
IBT	ion beam therapy
IDD	laterally integrated depth dose
IMPT	intensity modulated proton therapy
i-Rad	particle/ion radiography
ISL	inverse square law
KC	Kiefer-Chatterjee track structure model
LBNL	Lawrence Berkeley National Laboratory
LEM	local effect model
LET	linear energy transfer
LET_d	dose-weighted linear energy transfer
LINAC	linear accelerator
lp/mm	line pairs per millimetre
LQM	linear quadratic model
LSE	lateral scattering equilibrium
LV-FS	local water equivalent path length variation based focus stacking
MC	Monte Carlo
MCS	multiple Coulomb scattering
MEE	multi energy extraction
MKM	microdosimetric kinetic model
MLP	most likely path algorithm
mMKM	modified microdosimetric kinetic model
MTF	modulation transfer function
NIMMS	Next Ion Medical Machine Study
NTCP	normal tissue complication probability
OD	optical density
OER	oxygen enhancement ratio
PB	pencil beam
PBS	pencil beam scanning
PDD	percentage depth dose
PDF	probability density function
PET	positron emission tomography
PG	prompt gamma
PGS	prompt gamma photon spectroscopy
PIB	plane-of-interest binning
pO₂	partial pressure of oxygen
p-Rad	proton radiography
PT	proton therapy

PTV	planning target volume
RBE	relative biological effectiveness
RCF	radiochromic films
RF	radiofrequency
RGB	red-green-blue
Ri-Fi	ridge filter
RM	range modulator
ROI	region of interest
ROS	reactive oxygen species
RSP	relative stopping power
RT	radiation therapy (radiotherapy)
RTB	rear tracker binning
SAD	source-to-axis distance
SBRT	stereotactic body radiation therapy
SE	slow extraction
SNR	signal-to-noise ratio
SOBP	spread-out Bragg peak
SOD	superoxide dismutase
SPECT	single photon emission computed tomography
SRS	stereotactic radiosurgery
SSB	single strand breaks
TCP	tumour control probability
ToF	time-of-flight
UHDR	ultra-high dose rate
VHEE	very high energy electrons
WEPL	water equivalent path length
WET	water equivalent thickness

Introduction

1.1. Motivation for the Thesis

Cancer remains one of the most prevalent diseases and significant causes of death globally. As per World Health Organization GLOBOCAN data, 19.98 million new cancer cases were registered in 2022 alone, and about 1 in 5 people are estimated to develop cancer during their lifetime [1-2]. As for mortality, cancer is also one of the leading causes with 9.3 million deaths registered in 2022 - approximately 1 in 9 men and 1 in 12 women diagnosed die from the disease [2]. Throughout the years, cancer incidence rates have increased in several geographical regions, with the global burden of the disease expected to grow in the future. Current estimates of International Agency for Research on Cancer predict an increase of almost 3 times by year 2050 - 35.3 million new cases registered globally [3]. With cancer burden on the rise globally, effective management strategies in healthcare systems are of crucial importance, along with development of novel treatment methods.

Cancer treatment is based on three primary methods - surgery, chemotherapy, and radiotherapy, while approaches as immunotherapy, gene therapy and targeted therapies are also evolving [4]. Radiotherapy uses ionizing radiation to fully eradicate or control the growth of the malignant cancer cells, by targeting cellular DNA and depositing sufficiently high and localized energy. As a treatment modality, radiotherapy is beneficial and required in more than 50% of patients during their course of care [5]. Radiotherapy is frequently used in the treatment of the most common cancers, such as breast, lung, colorectal, cervical and others [6].

The main clinical goal of radiotherapy is to deliver localised, high dose of ionizing radiation to cancer cells, while minimizing the exposure of normal tissue and critical organs. Normal tissue exposure can result in various adverse side effects and needs to be limited to avoid functional organ impairment and debilitating complications after the treatment. To limit adverse side effects, adequate differentiation between cancerous and normal tissue exposure must be ensured. One of the approaches is to physically increase the localisation and conformality of delivered dose distribution via specific delivery technologies or use of different ionizing radiation types. While high energy X-ray photons are predominantly used - conventional radiotherapy [5], improved conformality of delivered dose can be achieved by particle therapy.

Particle therapy is a specific radiotherapy modality, using positively charged ions such as protons and carbon-12 ions [7]. Use of charged ions for cancer treatment is favourable due to physical interaction mechanisms with matter. Energy deposition of

charged ions exhibits a localized maximum - so-called Bragg peak - at an energy-specific depth, with limited energy deposition proximal and distal to the peak [7]. These characteristics motivate the use of protons and carbon-12 ions for highly precise and localized energy deposition in the cancerous cells, limiting normal tissue exposure. Proton therapy has shown benefits in the reduction of normal tissue complications in selected types of cancer [8-9], while carbon ion therapy - in treatment of radioresistant and hypoxic tumours [10-11]. Despite the improved physical characteristics, access to particle therapy treatment globally is challenged due to increased costs of machine used for delivery - particle accelerator (specifically, cyclotron or synchrotron). Currently, only 140 particle therapy systems exist worldwide with the majority (123 facilities) operating only with proton beams [12]. Nevertheless, the number of facilities has increased exponentially over the years, with the same trend observed for the number of treated patients [12-13]. Globally, by year 2022, around 310 000 patients had been treated with proton therapy and around 50 000 - with carbon-12 ion therapy [13]. Due to limited access of particle therapy, the clinical evidence base is still increasing [14].

Despite mentioned advantages, the two particle therapy modalities also have certain limitations. Proton therapy exhibits significant lateral scattering, limiting its applicability for deep-seated tumours, while carbon-12 ions have increased energy deposition distally to the peak and require significantly larger and more expensive infrastructure [7]. As an alternative, growing interest in helium-4 ion use for cancer therapy has recently emerged [15]. Compared to protons, helium-4 ions could increase the conformality of delivered dose and increase the biological effectiveness, while compared to carbon-12 ions - reduced distal energy deposition and smaller and less demanding accelerator system is required [15]. Clinical use of helium-4 ions was already explored during the early research in particle therapy at Lawrence Berkeley National Laboratory [16]. Current renaissance has emerged in Heidelberg Ion Beam Therapy centre (HIT), with first patient treated in 2022 [17], and initial clinical trials started by 2025 [18]. Other European particle therapy centres also investigate the technical feasibility of helium-4 ion therapy implementation [19]. Dedicated accelerator systems do not exist yet for helium-4 ion therapy, with current experimental studies done with adaptations of carbon-12 ion synchrotrons, limiting achievable capabilities. A study hosted by European Organization for Nuclear Research (CERN) - NIMMS (Next Ion Medical Machine Study) - is one of the initiatives working towards the development of compact particle accelerator for helium-4 ion therapy - HeLICS [20].

For all particle therapy modalities, despite the attractive properties of Bragg peak phenomenon, an intrinsic drawback exists - uncertainty of its position. As the maximum energy deposition is highly localized, just a small variation of its position could cause significant overexposure of normal tissue or underexposure of cancerous cells, affecting the therapeutic outcome. Bragg peak position variations can be caused by various uncertainty sources: the patient (positioning, physiological movements), treatment planning process (calibration and artefacts of images used) and the particle

beam itself (energy of the beam, variations of physical interactions) [21]. Overall, these sources result in a Bragg peak position uncertainty of about 3 to 5% [21]. This significantly limits the potential of all particle therapy modalities as safety margins of several millimetres need to be added during treatment planning process [21]. This results in higher normal tissue exposure, limiting the full potential of particle therapy. Several approaches - range verification methods - are actively researched for the application of verifying patient position before and during the treatment, or direct verification of delivered dose distribution during the treatment [21-23]. Although range verification methods hold a great promise to improve accuracy of particle therapy treatment delivery, several limitations exist for their clinical implementation [21-23]. Additionally, range verification method adaptation for novel modalities as helium ion therapy has not yet been studied. The importance of treatment accuracy and necessity of range verification becomes even more pronounced at high dose levels delivered per single treatment fraction - statistical averaging of the errors as in fractionated therapy does not hold and adaptive approaches are necessary.

While physical dose conformality is one of the approaches to decrease normal tissue exposure, biological approaches mitigating adverse effects can also be considered. Biological effectiveness of radiotherapy can be improved by either increasing the sensitivity of cancer cells or resistance of normal tissue to ionizing radiation. To note, the inherent difference in radiosensitivity between normal and cancer cells is one of the key factors that allow the clinical use of radiotherapy [24]. Nowadays, one of the most promising and actively researched approaches to increase the radioresistance of normal tissues is the so-called *FLASH* effect. Terms of “*FLASH* effect” and “*FLASH* therapy” have been introduced into scientific and clinical community by the pivotal work of Favaudon et al. in 2014 [25]. *FLASH* effect is an observed differential effect between normal and cancerous cells - greatly reduced adverse effects in normal tissue with unaffected tumour response when the irradiation is performed at ultra-high dose rate [25-26]. For comparison, conventional radiotherapy dose rates are on the scale of few Grays per minute, with the radiation delivery timescale of minutes. Typically reported ultra-high dose rates to achieve *FLASH* effect are higher than 40 Grays per second, with the radiation delivery timescale of milliseconds [26]. Clinical introduction of *FLASH* effect into radiotherapy could significantly reduce the adverse side effects and allow possibilities for dose escalation in cancers with poor tumour control. Additionally, length of the treatment course could be significantly reduced and the impact of intra-fractional physiological motion (breathing, heartbeat, peristalsis etc.) on the delivered dose distribution would be mitigated. Despite the enormous clinical potential, several open questions on *FLASH* effect remain - tissue type dependency, dosimetric thresholds (dose level and dose rate) necessary to induce the effect, impact of fractionation and many others [26]. Furthermore, the underlying mechanisms of the differential *FLASH* effect are still under debate with no unified theory currently to explain the sparing and corresponding to the experimental *in vitro* and *in vivo* evidence [26-27]. Lastly, magnitude

of *FLASH* effect normal tissue sparing and necessary dosimetric conditions could be different between various ionizing radiation types - X-ray photons, electrons, protons, and heavier charged ions [26]. *FLASH* effect with heavier charged ions remains understudied, compared to other ionizing radiation modalities - electrons and protons [26]. Additionally, with reportedly high dose levels necessary to induce *FLASH* effect sparing, accurate treatment delivery becomes crucial. In light ion-based *FLASH* therapy, this translates to necessity of advanced range verification methods to ensure the required level of precision.

With all the arguments above, integration and combined use of:

- novel particle therapy modalities as helium-4 ions;
- ultra-high dose rate delivery for *FLASH* effect induced normal tissue radioresistance;
- and range verification methods to enable the level of precision and accuracy needed for the high dose *FLASH* delivery with light ion beams;

holds promise to significantly increase cancer treatment effectiveness - improving treatment outcomes and patient quality of life after the treatment. Development of such a combination requires multi-disciplinary contributions from physics, biology, radiochemistry, and accelerator technology science, with future pre-clinical and clinical sciences. Thus, **the motivation of this Thesis is to contribute from the perspectives of medical physics and medical applications of particle accelerator technologies in the development of approaches and computational tools to be used for *FLASH* effect application in light ion therapy and necessary range verification methods to ensure required precision level.**

To address the motivation of the Thesis, the Thesis focused on the following objectives and areas of work (see Figure 1.1.):

- investigating the influence of ultra-high dose rate on radiochemical interactions;
- developing theoretical framework and computational tools to assess *FLASH* effect application with light ion beams;
- analysing technological delivery approaches for ultra-high dose rate light ion beams;
- to ensure the accuracy and precision necessary for high dose levels in light ion *FLASH* therapy, developing and quantitatively analysing range verification methods:
 - imaging of patient anatomical position;
 - direct Bragg peak localisation.

The studies performed in the Thesis are done in collaboration with CERN NIMMS and the context of establishing a novel helium-4 ion therapy particle accelerator - HeLICS. Radiochemical studies were done in collaboration with German Cancer Research Centre (DKFZ) - E041 “Biomedical Physics in Radiation Oncology” division.

1.2. Aim of the Thesis. Scope of the Thesis

The Thesis aims to investigate the influence of ultra-high dose rate on water radiolysis chemical interactions relevant to the FLASH effect and to develop computational models and delivery approaches necessary for implementation of light ion FLASH therapy – methods for realizing ultra-high dose rate delivery and methods for range verification to ensure required precision and accuracy by anatomical imaging or Bragg peak localization.

The scope of the Thesis includes the development of methodology and providing a set of quantitative results as the physical basis necessary for light ion FLASH therapy and dedicated range verification method technological implementation. The scope of the Thesis does not include radiobiological studies of the FLASH effect and dedicated technological implementation of proposed physical principles.

Throughout the Thesis, special focus is given towards helium-4 ion therapy as an emerging future modality of light ion therapy. To achieve the Aim of the Thesis, structure as indicated in Figure 1.1. was adopted with Main tasks identified in Section 1.3.

1.3. Main tasks of the Thesis

1. To perform scientific literature review-based “state-of-the-art” analysis on:
 - current hypotheses on *FLASH* effect mechanisms, dosimetric thresholds and necessary delivery parameters, and experimental evidence with ion beams;
 - beam delivery approaches enabling UHDR, limitations in light ion therapy;
 - current methods and technologies for ion beam range verification, focusing on limitations and clinical application challenges.
2. To experimentally evaluate the influence of the dose rate and beam temporal structure on water radiolysis chemistry, focusing on the role of solvated electrons.
3. Based on the results of Task 2, to develop a theoretical framework and associated computational tools necessary for assessment of FLASH effect application in light ion therapy:
 - to develop a theoretical model for prediction of *FLASH* effect dose threshold for ion beam irradiation; based on the model, to perform a comparison study between different ion types;
 - to develop a pencil-beam algorithm for calculation of dose, dose rate and other relevant dosimetric parameters; to perform validation of the algorithm.
 - to conduct a comparative literature-based analysis on technological solutions for ultra-high dose rate delivery with light ion beams;
4. To quantitatively evaluate particle radiography modalities for patient anatomical position verification with a compact synchrotron-based light ion therapy system:
 - to develop a simulation and image reconstruction framework for particle radiography modalities.

- to quantitatively evaluate the achievable image quality of high energy proton, helium-3 and helium-4 ion radiography for pre-treatment position verification.
 - to develop an image reconstruction framework for different focus stacking approaches with high energy proton, helium-3 and helium-4 ion radiographs and to quantitatively evaluate and compare reconstructed image quality improvement and 3-dimensional feature localization.
 - to assess the feasibility of mixed helium-deuteron beam use for position monitoring
 - quantitative evaluation of range sensitivity and 2-dimensional image quality.
5. To perform simulation-based quantitative evaluation for range verification approaches using direct Bragg peak position localisation, in context of helium-4 ion therapy:
- to quantitatively evaluate spatial and temporal correlation of absorbed dose and electron-positron annihilation event signal induced for application in positron emission tomography-based range verification.
 - to assess the feasibility of using oxygen-18 as a contrast enhancement method for range verification with prompt gamma photons by quantitative evaluation of achievable Bragg peak localisation sensitivity and accuracy.
6. Summarise the results achieved in the research, developing scientifically based conclusions and recommendations for practical application of achieved results.

**Topic of
the Thesis**

Subtopics

**Main areas
of work**

**Chapters of
the Thesis**

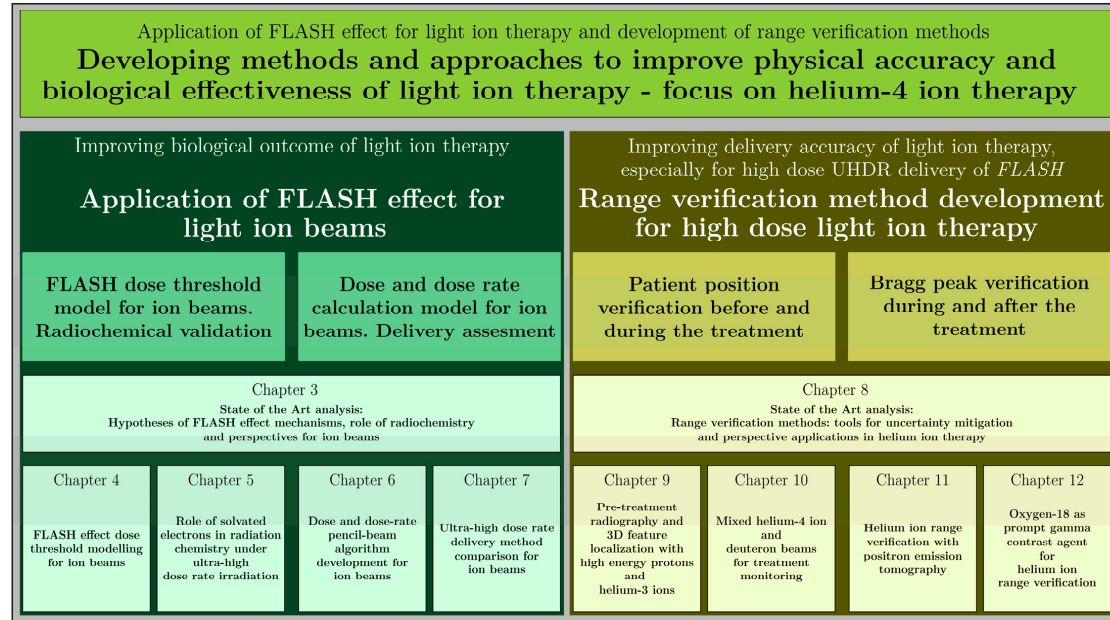


Figure 1.1. Structure of the Thesis, identifying Subtopics, Main areas of Work and corresponding individual Chapters

1.4. Thesis statements to be defended

1. Developed theoretical model of *FLASH* effect dose threshold is applicable to evaluate scaling between different ion types, predicting 1.2 - 1.3 times and 2 - 2.5 times higher threshold dose levels for helium-4 and carbon-12 ions, respectively.
2. With average dose rate increasing up to 100 Gy/s, hydrogen peroxide yield in aerated water decreases (p-value < 0.05) by up to 38%; this dependency is diminished (p-value > 0.05) in presence of solvated electron scavengers (> 250 μM NaNO_3).
3. Linear regression analysis between hydrogen peroxide yield and pulse or bunch dose rate indicates coefficient of determination R^2 of 0.93 and 0.92, respectively, for average dose rate - 0.55, indicating the significance of temporal beam microstructure on radiochemical changes.
4. The developed pencil-beam algorithm, employing “Gaussian + Double Logistic” function for lateral dose kernel, accurately (deviations < 1 % in region of interest) reproduces reference Monte Carlo data for dose, linear energy transfer, solvated electron yield and microdosimetric parameters for protons, helium, lithium and carbon ions in energy range relevant for clinical use.
5. For synchrotrons with limited energy reach, several radiography modalities enable full-body imaging (32 cm phantom) and can be used for anatomic verification:
 - helium-3 ion radiography achieves higher energy reach, comparable image quality (spatial resolution within 0.2 lp/mm, CNR within 3 %, same WEPL accuracy) and dose reduction of 10-15% (at same CNR) with respect to helium-4 ions.
 - 330 - 500 MeV proton radiography achieves optimum in image quality (compromise between spatial resolution of 0.5 - 0.8 lp/mm and CNR of 9 - 15) for full-body imaging.
 - local water-equivalent path length variation based focus stacking can enable high, object depth independent water equivalent path length accuracy (mean deviation ± 1.5 mm) in reconstructed radiographical images and possibility to estimate imaged object depth within ± 5 mm.
 - mixed helium-deuteron beams (fluence ratio of 100:1) can be used for position monitoring during treatment, detecting range shifts of ± 1 mm (with lateral extent >20% of the beam size), with <0.1% contribution to treatment dose.
 - using double Gaussian relative angle filtering and fluence ratio 10:1, mixed helium-deuteron beams achieve adequate 2-dimensional radiographic image quality - spatial resolution of 0.4 - 0.6 lp/mm, CNR of 20 and WEPL accuracy < 1.5 mm.
6. Uniquely to helium-4 ion beams, induced fluorine-18 (^{18}F) and fluorine-17 (^{17}F) β^+ decay signals can improve Bragg peak localisation with positron emission tomography in oxygen-rich tissue. ^{18}F peak in electron-positron annihilation event spatial distribution is closely correlated with Bragg peak with deviations < 1.5 mm for timescales above 30 minutes, while ^{17}F : < 5 mm for timescales below 10 minutes.
7. By introduction of ^{18}O -based contrast agent (100% concentration), detectable number of prompt gamma photons in the energy range 0.5 - 3 MeV is increased by > 20 % compared ^{16}O reference scenario (depending on tumour geometry); number of primary particles

necessary to reach range uncertainty <1 mm is decreased by about 2-4 times for idealized spatial and temporal characteristic detection approaches.

8. By monitoring the intensity of spectral lines specific to ^{18}O -based contrast agent - 0.87, 1.94 and 1.98 MeV -, delivered integral tumour dose could be monitored with a sensitivity of $8 \cdot 10^6$ to $9 \cdot 10^7$ counts per Gray (idealized scenario with 2 Gy delivery).

1.5. Scientific novelty

Results achieved in the Thesis have a significant contribution to the fields of medical physics and medical applications of accelerator technologies, especially in ion therapy and development of helium ion therapy:

1. Development of radiochemistry-based theoretical model for *FLASH* effect dose threshold (or dose rate threshold) prediction for different ion types. Comparison of different clinically relevant ion types, indicating *FLASH* effect threshold increase with increasing mass of the ion.
2. Experimental demonstration of (1) ultra-high dose rate (< 100 Gy/s) induced reduction of hydrogen peroxide yield in aerated water with X-ray and electron beams and (2) diminishing of this dependency in presence of solvated electron scavengers. This highlights the role of solvated electrons in ultra-high dose rate induced radiochemical changes and serves as validation for theoretical framework in Point 1.
3. Experimental demonstration of the impact of varying beam temporal structure on hydrogen peroxide yield dose rate dependency, indicating stronger correlation for pulse and bunch dose rates with respect to average dose rate. This highlights the importance of beam temporal microstructure on radiochemical changes.
4. Development of a pencil-beam algorithm with introduction of novel lateral dose kernel parametrization approach, that accurately reproduces dose, linear energy transfer, solvated electron yield and microdosimetric parameter spatial distributions with respect to Monte Carlo simulations.
5. Monte Carlo simulation-based demonstration of a novel particle radiography approach with helium-3 ion beams and in-depth analysis of achievable image quality for this approach with respect to helium-4 ion radiography. Monte Carlo simulation-based demonstration of proton radiography image quality dependency on energy (250 - 700 MeV) and suitability of 330 - 500 MeV range for full-body imaging. Development and Monte Carlo simulation-based demonstration of novel focus stacking approaches in ion radiography imaging to improve reconstructed image quality and precision of 3-dimensional feature localization compared to existing approaches.
6. Monte Carlo simulation-based demonstration of novel mixed helium-deuteron beam approach use for patient position monitoring during helium-4 ion therapy delivery via range shift detection or 2-dimensional imaging. Development of data filtering framework for 2-dimensional imaging, applicable also for mixed carbon-helium beams.

7. Monte Carlo simulation-based demonstration of unique electron-positron annihilation event spatial distribution patterns after irradiation with helium-4 ion beams. Demonstration of helium-4 ion induced fluorine-18 (^{18}F) and fluorine-17 (^{17}F) β^+ decay signal applicability in positron emission tomography-based range verification.
8. Monte Carlo simulation-based demonstration of a novel approach for prompt gamma emission signal enhancement for range verification in helium-4 ion therapy using ^{18}O -based contrast agent. Comparative analysis of proposed contrast agent and ^{16}O as a reference scenario, focusing on achievable sensitivity with different detection approaches.

1.6. Practical significance

The practical significance of the achieved results mirrors the motivation of the Thesis: developing approaches and methods to improve biological treatment outcomes of light ion therapy via delivery using *FLASH* effect and to improve delivery accuracy via range verification methods. Special focus within light ion therapy is given towards helium-4 ion therapy and respective future developments. The practical significance of both aspects for improving light ion therapy is discussed below.

Results presented in Part I “*Investigations on FLASH effect and applications in light ion beam therapy*” have significance in practical future developments of *FLASH* therapy using ultra-high dose rate beams, especially for light ion therapy. Comparative analysis done with the developed *FLASH* dose threshold model in Chapter 4 provides estimates of dosimetric parameters necessary to reach *FLASH* effect with different types of ions, indicating necessary requirements of particle accelerators for ultra-high dose rate delivery. Chapter 5 provides experimentally based results on radiochemical changes under ultra-high dose rate irradiation, as well as the possible impact of temporal structure of beam delivery. These findings have a significant role in developing the understanding of *FLASH* effect mechanism - crucial for future clinical translation of *FLASH* therapy. Results on the impact of beam temporal structure parameters can assist in optimizing ultra-high dose rate delivery technical parameters for not just light ion beams, but also electrons and photons. Lastly, the pencil-beam calculation algorithm developed in Chapter 6 can be efficiently used to explore and optimize ultra-high dose rate delivery approaches with light ions. Comparative analysis of such delivery approaches is presented in Chapter 7 - providing critical evaluation to facilitate adoption of light ion *FLASH* therapy and aid in the design of dedicated particle accelerators and beam delivery systems.

The range verification approaches proposed in Part II “*Investigations on novel range verification methods for high dose light ion therapy*” have significant potential to improve dose delivery accuracy in light ion therapy and enable the level of precision necessary for high dose delivery of *FLASH* therapy. Additionally, improved accuracy

could allow to reduce treatment margins of the tumour volume, further reducing normal tissue exposure to ionizing radiation. Range verification methods are developed and investigated in the context of the innovative helium-4 ion therapy. As helium-4 ion therapy developments are still in the early stage, proposed approaches can be considered for implementation already at the stage before clinical translation - optimizing delivery system and clinical workflow accordingly. Pre-treatment particle radiography studies presented in Chapter 9 provide results on possible anatomical imaging methods with compact particle accelerators - synchrotrons - dedicated for helium-4 ion therapy, achieving full-body radiography capabilities. As technical limitations of such a dedicated synchrotron - CERN NIMMS HeLICS - were considered throughout the Thesis. Thus, achieved results can aid in further design development of CERN NIMMS HeLICS, enabling implementation of full-body radiography with high energy protons or helium-3 ions. The developed local water-equivalent pathlength variation based focus stacking method in Chapter 9 offers improved pre-treatment verification of patient position via ion radiography by enabling highest achievable spatial resolution and water-equivalent pathlength value precision, as well as 3-dimensional feature localization with improved precision over currently proposed approaches. The innovative mixed helium-deuteron beam approach proposed and analysed in Chapter 10 could allow patient position monitoring during the treatment with helium-4 ions - important for accounting physiological motions such as breathing and others. Although detailed future studies are necessary on the technical feasibility of this approach, presented physics results serve as the basis to further develop this method, improving accuracy of helium-4 ion treatments in anatomies with moving tumours. Furthermore, data filtering methods developed in this Chapter can be applied for the analogous approach in carbon ion therapy - carbon-helium mixing. Finally, helium-4 ion Bragg peak position localisation approaches proposed and analysed with positron emission tomography in Chapter 11 and with prompt gamma photon contrast agent in Chapter 12, provide pathways to verify delivered dose distribution itself. Results presented in Chapter 11 could aid in positron emission tomography verification method adoption for helium-4 ion beam therapy - for in-beam, in-room, and off-line approaches. As for results of Chapter 12, improved prompt gamma photon signal counts and unique characteristics with ^{18}O contrast agent address some of the limitations of currently proposed verification approaches. Presented method could also offer pathways to monitor Bragg peak position and deviations integral tumour dose via spectroscopy of unique ^{18}O emission energies. Furthermore, proposed ^{18}O contrast agent could also be used for delivery accuracy improvement of other ion therapy modalities. Altogether, the set of methods proposed and analysed in Part II would allow to verify both patient position and delivered dose distribution at different treatment stages - before, during and after -significantly improving the accuracy of dose delivery. Such methods are crucial to ensure precision required for high dose delivery in the *FLASH* therapy of Part I.

Altogether, the results of the Thesis provide innovative approaches and methods for advancing ion therapy by improving biological effectiveness and delivery accuracy. *FLASH* therapy with light ions, while ensuring accurate delivery of the high dose levels via range verification, holds a great potential as a highly effective approach for cancer treatment. Results of the Thesis and proposed approaches serve as basis for future research necessary for translation into clinical setting. Presented findings can also aid the technical design process of next generation particle accelerators for ion therapy. Additional focus throughout the Thesis was given towards helium-4 ion therapy, thus contributing to further development of this novel therapy modality.

As the Thesis was performed in the framework of CERN NIMMS, presented results can be used for implementation and technical design adaptation of the innovative helium-4 ion synchrotron - HeLICS. Active implementation of proposed approaches could further improve capabilities of the machine for highly accurate treatments. Lastly, the investigations and results of the Thesis could also aid in the future developments of “*Advanced Particle Therapy Centre for the Baltic States*” initiative [28] - envisioned establishment of joint scientific research centre and clinical treatment facility based on HeLICS design in the three Baltic States - Lithuania, Latvia and Estonia.

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Theoretical background

Therapeutic effect of ionizing radiation used in radiotherapy is based on multiple interrelated concepts in the domains of physics, chemistry, and biology. This Chapter lays the theoretical foundation of these concepts as relevant to Thesis objectives.

Firstly, Section 2.1. outlines the main concepts of radiotherapy and general clinical rationale of its use for cancer treatment. As ionizing radiation effects in biological systems can be described as cascade of physical, chemical, and biological phenomena - a sequence, which is also followed in Sections 2.2 to 2.4. Principles of physical interaction mechanisms of ionizing radiation with matter are given in Section 2.2. This Section covers all ionizing radiation types used in the modelling and experimental studies in this Thesis - primarily protons and heavier ions, while also considering photons and electrons for experimental part. Section 2.3. follows the chain, outlining radiation chemistry concepts with focus on water radiolysis process. Finally, biological concepts of ionizing radiation interactions with living organisms are given in Section 2.4. This Section also introduces the modern radiobiological concept of *FLASH* effect - key investigation topic in Part I of Thesis - which is reviewed and discussed in greater detail within Chapter 3.

As Part II of the Thesis focuses on range verification methods in ion beam therapy, Section 2.5. introduces the concepts of ion imaging and approaches for *in vivo* range verification methods, which are reviewed and discussed in greater detail within Chapter 8. In this context, the Section also focuses on nuclear interactions as relevant for therapeutic beams.

Finally, Section 2.6. provides key concepts on machines used to produce ionizing radiation beams for radiotherapy - particle accelerators. Operational principles of linear accelerators, cyclotrons and synchrotrons are given, with focus on capabilities of high output dose rate generation by each particle accelerator type.

Bibliography of this Chapter also includes references used in **Appendices 1.1 to 1.16**.

2.1. Main concepts of radiotherapy

Management of cancer is based on three main treatments methods: surgery, systemic therapy (as chemotherapy), and radiotherapy (RT), while approaches as immunotherapy, gene therapy and targeted therapies are also evolving in clinical practice [1]. Historically, development of RT is linked to the discovery of X-rays in 1895 by Wilhelm Röntgen, with the newly discovered type of radiation used for medical treatments already the next year [2]. In its essence, RT aims to fully eradicate or control the growth of the malignant cancer cells, by delivering sufficiently high and localized energy to cellular DNA via ionizing¹ radiation. Chain of the mechanisms resulting in the therapeutic effect of ionizing radiation are further discussed in Sections 2.2, 2.3 and 2.4. By approach of delivery, RT can be divided into external beam (EBRT) and brachytherapy [3-4]. Further in this Thesis, EBRT is referred to as RT.

The main goal of RT has always been to deliver sufficiently high dose (see Subsection 2.2.4) of ionizing radiation to cancer, while minimizing the exposure of normal tissue and critical organs. Normal tissue exposure to ionizing radiation can result in various adverse side effects such as skin irritation, urinary and gastrointestinal complications, joint stiffness, and others [6-8]. Thus, exposure needs to be accurately limited according to normal tissue tolerance as overexposure can lead to serious functional organ impairment and debilitating complications as loss of vision or hearing, inflammation, or tissue necrosis [6-8].

Although curative effect in cancer cells could be reached at sufficiently high dose, it is typically limited by the tolerance of surrounding normal tissue. The curative effect of ionizing radiation on cancer cells is characterized by tumour control probability (TCP), while the adverse effects are quantitatively described by normal tissue complication probability (NTCP) [4,10]. Both TCP and NTCP values vary between different tissue types. Dose dependency of these parameters defines the so-called treatment window - treatment-suitable dose levels having sufficient TCP without significant NTCP [4,10]. Example of TCP and NTCP variation with dose level and resulting treatment window is depicted in Figure 2.1.

Additional information on main concepts of radiotherapy is given in **Appendix 1.1**.

¹ Via ionization one or more electrons are removed from atoms, creating electrically charged particles, which can produce significant chemical and biological effects in irradiated material

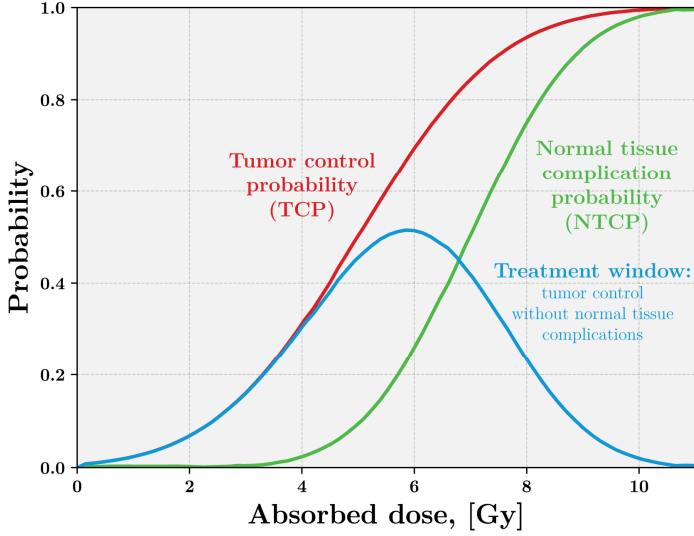


Figure 2.1. Absorbed dose dependency of TCP and NTCP and resulting treatment window in conventional radiotherapy

For definition of “absorbed dose”, see Subsection 2.2.4. Schematic created by Author, based on [11].

2.2. Interactions of ionizing radiation with matter

This Section provides main concepts on physical interaction mechanisms for different types of ionizing radiation with matter, also outlining key physical quantities as relevant for RT. In the scope of this Thesis, photon and electron interactions are covered as these beams have been used in the experimental work outlined in Chapter 5, though the focus is given for positively charged particles - proton and heavy ions. With information relevant for ion beams presented in sub-section 2.2.1., overview of photon physical interactions with matter is given in **Appendix 1.2.**, while phenomena relevant to electron beams are described in **Appendix 1.3.**

2.2.1. Ion beams: protons and heavier ions

Due to the unique physical characteristics, positively charged particles as protons and heavier ions can also be used for RT. RT with these particles has been referred under various names as particle therapy, ion therapy, hadron² therapy (physically most proper description) or distinctively for proton beams simply as proton or light ion therapy and heavy ion therapy for ions heavier than protons. With discussion on proper nomenclature provided elsewhere [47], throughout this Thesis, the two

² Any sub-atomic particle that is a composite of two or more quarks

modalities will be referred to as proton therapy (PT) and ion beam therapy (IBT). To penetrate the tissue and reach deep-seated tumours, PT uses protons with energies from around 50 to 250 MeV [48]. In case of IBT, beams of carbon-12 ions are primarily used, accelerated to energies of 50 to 430 MeV/u [49]. Although carbon-12 is the main type of ion with a more wide-spread clinical use, helium-4 and oxygen-16 ions are also actively researched for future translation [50]. Throughout the history of IBT, various other ions have been studied for applications in RT - silicon, neon, and argon ions [51].

As electrons, protons and heavier ions are electrically charged, therefore primarily interacting via Coulomb force with orbital electrons or atomic nuclei, losing kinetic energy, or being scattered and deflected from initial path. Contrary to electrons though, as hadronic particles, protons and ions can also undergo inelastic nuclear interactions. Following subsections briefly describe energy loss and scattering processes for protons and heavier ions, outlining also other key aspects unique for these particles. Nuclear interactions will be discussed in greater detail in Section 2.5.1. **References [34-35, 38, 48-49, 52-53] have been used throughout following subsections for summary of the main physical processes of ion beam interactions with matter.**

Energy loss

Protons and ions lose their energy primarily through collisional losses. Compared to electrons, bremsstrahlung production via radiative losses is extremely low for heavy particles at RT relevant energies, becoming significant only at high energies. In contrast to electrons, protons and ions could undergo collisional energy losses both with atomic orbital electrons and the atomic nucleus:

- energy losses due to inelastic collisions with orbital electrons are defined by electronic stopping power S_{el} ;
- transfer of kinetic energy is also possible to whole nucleus via elastic collisions - defined by nuclear stopping power S_{nuc} .

As depicted in Figure 2.2., nuclear stopping power is significant only at low energies (keV range), therefore, for PT and IBT in MeV energy range, electronic stopping power. Electronic stopping power S_{el} (in units of MeV/cm) can be described by the Bethe-Bloch formula:

$$S_{el} = \rho \, 4\pi r_e^2 m_e c^2 \, z_p^2 \, \frac{N_A Z}{A} \, \frac{1}{\beta_p^2} \left(\frac{1}{2} \ln \frac{2m_e c^2 \beta^2 \gamma^2 W_{max}}{I^2} - \beta_p^2 - \frac{\delta}{2} - \frac{C}{Z} \right) + L \quad (2.1)$$

In Equation 2.1, properties of the target material are reflected by the physical density ρ , ratio between the atomic number and weight Z/A and mean excitation energy I (in units of eV). Projectile particle is characterized by the electrical charge z_p and the relativistic parameters: velocity β_p and Lorentz factor γ . Parameter W_{max} (in units of MeV) describes the maximum energy transfer possible in a single collision between a particle of mass M_p and an orbital electron and can be calculated as:

$$W_{max} = \frac{2m_e c^2 \beta_p^2 \gamma^2}{1 + 2\gamma \frac{m_e}{M_p} + \left(\frac{m_e}{M_p}\right)^2} \quad (2.2)$$

δ corresponds to density correction relevant for high particle energies as mentioned in Section 2.2.2. C/Z corresponds to shell correction, which accounts for non-stationary electrons and is relevant at low particle energies. L accounts for higher order corrections as Barkas-Andersen-effect (accounting for the sign of particle charge, relevant for low energies) and Felix Bloch-correction (accounting for the wave-like nature of particles, relevant for high energies).

For ions heavier than protons, the concept of effective charge is also important. While interacting with matter atoms, positively charged ions at low energies can capture orbital electrons effectively reducing the charge of the projectile. To account for this, the effective charge z_{eff} should be used in formula 2.15 instead of z_p and can be calculated by the Thomas-Fermi estimate:

$$z_{eff} = z_p \left(1 - e^{-125\beta_p z_p^{-2/3}}\right) \quad (2.3)$$

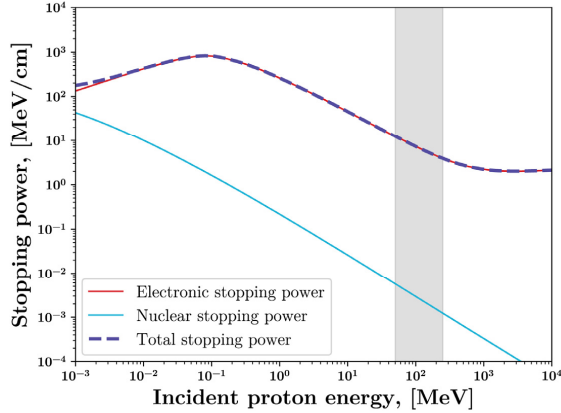


Figure 2.2. Electronic, nuclear, and total stopping power in water depending on the incident proton energy

Shaded regions correspond to PT relevant proton energy range. Data reproduced from ASTAR program in NIST database [54]

In clinical context of PT and IBT, different patient tissues such as muscle, bone and lung are encountered. Dosimetric calculations for treatment planning use reference data in water, introducing parameter of relative stopping power (RSP) for tissue differentiation. RSP corresponds to the ratio between electronic stopping power $S_{el_{mat}}$ in certain material and to that in water $S_{e_{water}}$:

$$RSP = \frac{S_{el_{mat}}}{S_{el_{water}}} \quad (2.4)$$

RSP is nearly constant over the energy range relevant for PT and IBT with a variation below 1%. Nevertheless, to mitigate additional uncertainties nominal RSP value is taken at 100 MeV/u for all particle species [55-56].

Range. Energy and range straggling

Due to energy loss process, protons and ions have a finite, maximum penetration depth in matter - referred to as depth. From Equation 2.1, electronic stopping power is inversely proportional to particle velocity squared β^2 , thus the maximum energy deposition for protons and ions occurs when the residual velocity of the particle is very small - near the end of the range. This causes the Bragg peak phenomenon, which is highly attractive for clinical application - as depicted in Figure 2.3, maximum energy is deposited deep within the material. Bragg peak occurs at the end of particle track, and this depth is dependent on the initial particle energy $E_{initial}$. Under continuous slowing down approximation (CSDA) the range R_{CSDA} can be calculated by integration of inverse electronic stopping power:

$$R_{CSDA}(E_{initial}) = \int_0^{E_{initial}} \frac{1}{S_{el}(E)} dE \quad (2.5)$$

From the Equation 2.5, it can be calculated that with increasing mass of the ion acceleration to higher initial energies is necessary for the same range as illustrated in Figure 2.4. For example, for range of 30 cm in water, initial energies of around 217 MeV, 217 MeV/u, 420 MeV/u and 500 MeV/u are necessary for protons, helium-4, carbon-12 and oxygen-16 ions, respectively.

Equations 2.1 and 2.5 describe the mean values for energy loss and range. While traversing matter, charged particles undergo a large, but finite number of interactions. As the process of energy loss is statistical by nature, two identical charged particles will undergo different number of collisions and different amount of kinetic energy will be transferred in each of the collisions. After passing a fixed thickness of material there will exist a distribution rather than a single value for residual particle energy - energy straggling. Energy straggling is the cause of range straggling - fluctuations of particle range for the same amount of energy loss (and initial energy). Range straggling causes broadening of the Bragg peak as can be observed in Figure 2.3. Analytical description of energy straggling functions is a complex mathematical problem and is covered in greater detail in **Appendix 1.4**.

Relative range straggling is nearly independent of target material over energy range relevant to PT and IBT. For the same mean range heavier particles have reduced range straggling. This highlights one of the rationales for IBT over PT - due to reduced range straggling, heavy ions provide “sharper” energy deposition profiles near the Bragg

peak as illustrated in Figure 2.3., ensuring increased conformality longitudinally (in the direction of the beam).

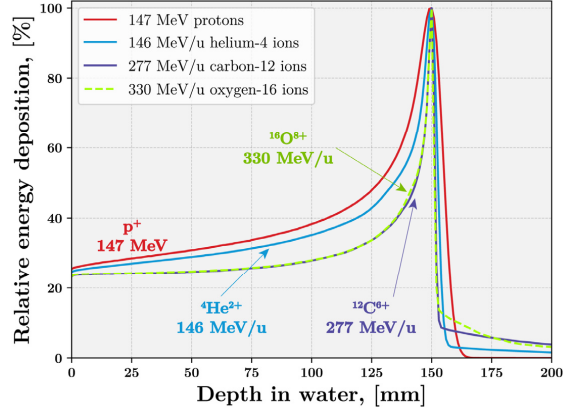


Figure 2.3. Relative energy deposition depth profiles for protons, helium-4, carbon-12, and oxygen-16 ions for a range of 15 cm in water

Data normalized to maximum energy deposition and given along central axis. Data given for point-like beams simulated with an empirically scaled initial energy spread. Data simulated in Geant4 environment by Author.

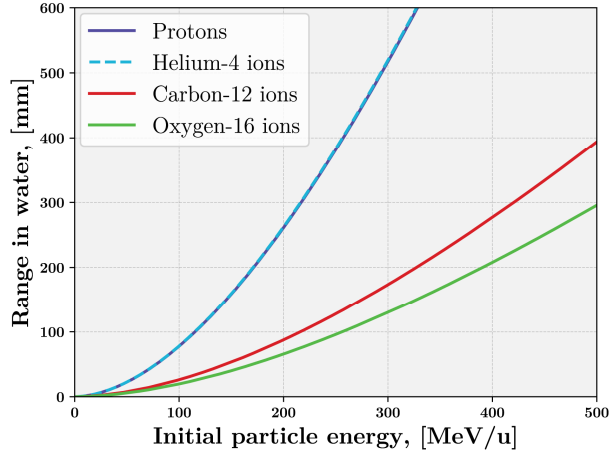


Figure 2.4. Particle range in water depending on the initial energy for protons, helium-4, carbon-12, and oxygen-16 ions

Data calculated by Author solving Bethe-Bloch equation under CSDA

MCS for protons and heavier ions

As mentioned in **Appendix 1.3.**, protons and heavier ions experience MCS. In contrast to electrons, scattering is primarily caused by deflection in elastic collisions with atomic nuclei. As MCS is the result of many small angular deflections, the resulting angular distribution is nearly Gaussian. Small number of single large-angle scattering events cause tails in the distribution, which in full can be described by Molière theory. The Gaussian core of the distribution encompasses $\sim 99\%$ of all particles, thus a Gaussian approximation is reasonable for MCS modelling in dosimetric calculations of PT and IBT. The root-mean squared (RMS) width of the Gaussian distribution can be calculated by Highland's model, with refinements by Lynch and Dahl [58]:

$$\theta_{RMS} = \frac{13.6 \text{ MeV}}{\beta_p c p} z \sqrt{\frac{x}{X_0}} \left(1 + 0.038 \ln \left(\frac{x z^2}{X_0 \beta_p^2} \right) \right) \quad (2.6)$$

where $\beta_p c$, p and z corresponds to velocity, momentum, and electrical charge of the particle, x - material thickness and the material itself is characterized by radiation length X_0 . The refined Highland's model in this form is valid only for thin slabs - change of particle velocity and momentum due to energy loss is negligible. For thick material slabs, as relevant for PT and IBT, particle transport under Gaussian approximation of MCS is calculated using Fermi-Eyges theory [43]. Under Fermi-Eyges theory, the probability to localize a particle at depth u_{fin} with lateral displacement y and angular deflection θ can be calculated as:

$$P(u_{fin}, y, \theta) = \frac{1}{2\pi\sqrt{B(u_{fin})}} \exp \left[\frac{1}{2} \frac{A_0(u_{fin})u_{fin}^2 - 2A_1(u_{fin})u_{fin}\theta + A_2(u_{fin})\theta^2}{B} \right] \quad (2.7)$$

A_0 , A_1 and A_2 are the moments of scattering power T corresponding to variance of angular deflection, co-variance between the two parameters and variance of lateral displacement. Moments of the scattering power T in general form and parameter B are given as:

$$A_n(u_{fin}) = \int_0^{u_{fin}} (u_{fin} - u)^n T(u) du \quad (2.8)$$

$$B = A_0 A_2 - A_1^2 \quad (2.9)$$

In Equation 2.8, scattering power T is a depth-dependent quantity, reflecting the change of mean squared angular deviation along the path of the particle:

$$T(u) = \frac{d(\theta_{RMS})^2}{du} \quad (2.10)$$

Historically, different mathematical approaches have been suggested for the calculation of scattering power, though the integral form of Highland's formula is most widely used [42]. General form from Equation 2.10 was expanded as integral for thick slabs by

Highland with further additions by Gottschalk [59]. Full descriptions for the moments of scattering power T in a homogeneous slab are of the form:

$$A_n(u_{fin}) = (13.6 \text{ MeV})^2 \left(1 + 0.038 \ln \left(\frac{x}{X_0} \right) \right) z^2 \int_0^{u_{fin}} \frac{(u_{fin} - u)^n}{p(u)^2 v(u)^2} \frac{1}{X_0(u)} du \quad (2.11)$$

Quantity $p(u)v(u)$ is the so-called momentum-velocity function, which for a known kinetic energy depth profile $E_{kin}(u)$ and a particle of mass M_p can be calculated as:

$$\frac{1}{p(u)^2 v(u)^2} = \frac{(E_{kin}(u) + M_p c^2)^2}{(E_{kin}(u) + 2M_p c^2)^2 E_{kin}^2(u)} \quad (2.12)$$

Comparing the magnitude of MCS for different ions, using Equation 2.11, root mean squared values of lateral displacement and angular deflection decrease with increasing mass of the ion. This dependency is visually illustrated in Figure 2.5. Due to reduced MCS for heavier ions, IBT can ensure more conformal energy deposition laterally compared to PT. Increased conformality both laterally and longitudinally (reduced range straggling) are the main attractive physical characteristics of ion beams over protons for clinical use.

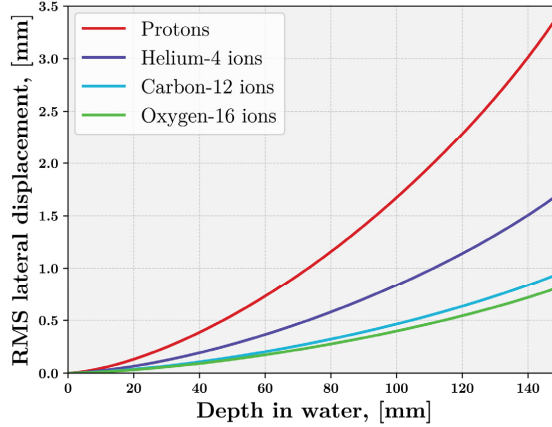


Figure 2.5. RMS lateral displacement of particle path due to MCS in water as a function of depth for protons, helium-4, carbon-12, and oxygen-16 ions
 RMS lateral displacement corresponds to square root of second moment of scattering power $\sqrt{A_2}$. Data given for particle energies corresponding to CSDA range of 15 cm. Data calculated by Author using integral Highland formula for scattering power and Fermi-Eyges definition of scattering power moments, kinetic energy distribution calculated using Bethe-Bloch equation under CSDA

2.2.3. Physical quantities

To assess chemical, biological, and clinical effects of ionizing radiation in RT, quantitative characterization of the energy deposition is necessary for different ionizing

radiation types. Following subsections describe main physical quantities of energy deposition as relevant for RT: absorbed dose and dose rate, characteristics of energy deposition spatial distribution and linear energy transfer. **References [36-38,48] have been used throughout following subsections for summary of the main physical quantities characterizing interaction processes.**

Absorbed dose. Dose rate

Fundamental parameter in RT to quantify the energy imparted by ionizing radiation in biological matter is absorbed dose. It is the key parameter to quantify the treatment and assess the effects in cancerous and normal tissue. Absorbed dose D is a non-stochastic quantity measuring energy deposited per unit mass, calculated simply as the ratio:

$$D = \frac{d\bar{\varepsilon}}{dm} \quad (2.13)$$

where $\bar{\varepsilon}$ is the mean energy imparted by radiation in a finite volume of matter with mass m . $\bar{\varepsilon}$ is a stochastic quantity referring to the sum of energy entering the volume subtracted by energy leaving the volume. Absorbed dose can be characterize both directly and indirectly ionizing radiation, referring to secondary particle energy deposition in the latter case. Absorbed dose is measured in Grays [Gy], with 1 Gray corresponding to energy of 1 Joule deposited in 1 kg of mass.

It is also important to quantify the rate of energy deposition in matter, especially in context of *FLASH* effect explored in the Thesis. Corresponding physical parameter is dose rate (DR) $\dot{D}$, quantifying the change of absorbed dose over time:

$$\dot{D} = \frac{dD}{dt} \quad (2.14)$$

Typical measure is the average DR, which compared to the instantaneous value calculated by Equation 2.14 is simply the ratio between the total absorbed dose delivered ΔD in a certain time Δt .

The simplistic expressions of DR given above are valid only for constant fluence delivery over whole irradiation area. As discussed in greater detail in Chapters 3, 6 and 7, this assumption is not valid for modern radiation delivery technologies, especially in PT and IBT, with complex absorbed dose pattern both spatially and temporally [60]. As DR has a key role in *FLASH* effect, other DR calculation methods have been developed for complex patterns of dose delivery [60] and are discussed in greater detail in Chapter 3, 6 and 7.

Spatial distribution: Percentage depth dose and lateral penumbra

As discussed in previous Sections, each of ionizing radiation types has a different characteristic energy deposition depth profile due to physical interaction mechanisms. In RT, the energy deposition depth profile is referred to as percentage depth dose (PDD). PDD is normalized to 100% at the depth of maximum energy deposition. PDD is one of the key parameters in choice of ionizing radiation type used RT.

PDD characterizes the absorbed dose distribution longitudinally, while dose profiles are used for lateral description. Dose profiles are typically normalized to 100% at the central axis of the beam. Due to scattering, the absorbed dose at the edge of irradiation field decreases gradually rather than drops abruptly. To characterize this, the term of lateral penumbra is used. Lateral penumbra refers to the width of dose fall-off at the field edge between 80% and 20% isodose levels. Small lateral penumbra is essential to ensure the conformality of dose distribution to the tumour and limiting the exposure of normal tissue. For the ionizing radiation types discussed in previous Sections, lateral penumbra is largest for megavoltage electrons and smallest for heavy ions.

Linear Energy Transfer

As will be discussed in more detail within Section 2.4, macroscopically identical absorbed dose distributions for different ionizing radiation types can result in significantly different effects on a biological system. This difference is caused by the microstructure of energy deposition events - how the energy is deposited along the particle track. One of the quantitative parameters for characterization of this microstructure is linear energy transfer (LET). LET is closely related to electronic stopping power and is sometimes referred to as restricted energy loss. To distinguish the two, electronic stopping power refers to energy losses by charged particle traversing the medium, while LET refers to the average energy deposited per path length via electronic interactions in a restricted volume around the primary particle track. Detailed mathematical description of LET definition and calculation for electron and heavy ion beams is given in **Appendix 1.5**.

LET indicates the density of ionization events around the particle track, which consecutively determines the effect of radiation on biological system. X-rays³ and electrons are considered as sparsely ionizing radiation types due to generated secondary electrons forming long tracks and depositing energy away from primary interaction. In contrast, ions heavier than protons are densely ionizing radiation with high concentration of ionization events around the primary track. As for protons, interactions at the end of the range are densely ionizing, while in the entrance region - sparsely ionizing.

In context of PT and especially IBT, characterization of LET spatial distribution is crucial for dosimetric calculations. Contrary to megavoltage photons and electrons with approximately constant LET value in energy range relevant to RT, considerable energy dependence can be observed for protons and heavier ions. In a limited volume, these particles have an energy spectrum due to straggling, translating to a spectrum of LET values. Furthermore, as will be discussed in Section 2.5, ions undergo nuclear interactions creating a “mixed beam” - lighter ion fragments having large LET differences compared to primary particles. To calculate the average LET value in a volume, weighing of the spectrum is performed based on either fluence⁴ $\overline{LET}_f$ or dose $\overline{LET}_d$ [65-66]:

³ In context of X-rays, LET is defined for the secondary electrons generated by photoelectric effect, Compton scattering and pair production

⁴ Referred to also as track-averaged LET

$$\overline{LET}_f = \frac{\sum_i \Phi_i * LET_i}{\sum_i \Phi_i} \quad (2.15)$$

$$\overline{LET}_d = \frac{\sum_i D_i * LET_i}{\sum_i D_i} \quad (2.16)$$

where Φ_i and D_i refer to number of particles or absorbed dose by particles with LET value of LET_i . For dosimetric calculations and biological effect assessment $\overline{LET}_d$ values are typically used [65-66]. In contrast to fluence weighing, dose weighed $\overline{LET}_d$ is highly sensitive to secondary particles included in calculation, especially heavy target fragments in PT [67-68].

LET values are spatially varying for proton and heavier ion beams. LET is most significantly affected longitudinally with increasing depth. The average kinetic energy of particles decreases with depth, thus LET is increasing and reaches maximum value in the Bragg peak region⁵, as illustrated in Figure 2.6. Laterally, LET depends on the secondary particle and kinetic energy spectrum - LET variation with respect to off-axis distance is dependent on ion type considered.

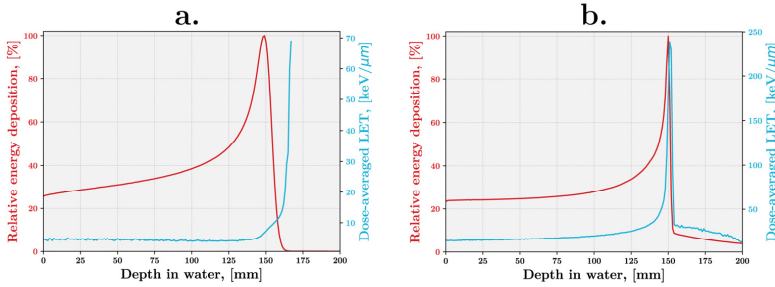


Figure 2.6. Dose-averaged LET as a function of depth for protons (a) and carbon-12 ions (b) with a range of 15 cm in water

Note the different scale of LET value secondary axis for protons (a) and carbon-12 ions (b). Data of relative energy deposition depth profile provided for correlation, normalized to maximum value. Data given for point-like beams simulated with an empirically scaled initial energy spread. Data simulated in Geant4 environment by Author, LET dose-averaging performed for both projectile and target fragments.

2.3. Radiation chemistry and water radiolysis

Physical interaction mechanisms described in Section 2.2. are the first step in chain of events leading to biologically relevant changes of RT. Ionization and excitation events of primary physical interactions occur in timescale from 10^{-18} to 10^{-15} seconds [69], subsequently followed by chemical and finally biological effect stages. This Section focuses

⁵ LET maximum is slightly downstream of the Bragg peak for protons and light ion species, at the Bragg peak for carbon ions and slightly upstream for even heavier ions

on the main concepts relevant for chemical reactions induced by ionizing radiation. **References [36-38,70] have been used throughout this Section for summary of the main chemical processes relevant to ionizing radiation interactions.**

Chemically, ionizing radiation interactions lead to atomic and molecular alterations and bond breakage for functionally relevant molecules in the cell. Damage on cellular proteins and lipids has a role in the overall effect of RT, though the critical component of radiation induced damage is located within the cellular nucleus (see Section 2.4) - deoxyribonucleic acid (DNA). DNA contains the genetic information of the cell and is essential for the replication process. Structurally, DNA molecules are characterized by a double helix, where each of the strands consists of a sequence of monomers - nucleotides. Each nucleotide is composed of a sugar and phosphate group with one of the four bases: purines - adenine (A) and guanine (G) - and pyrimidines - thymidine (T) and cytosine (C).

Interaction of ionizing radiation with biological molecules can be classified into two distinctive pathways: direct and indirect action. Schematic representation of the two pathways is given in Figure 2.7. Direct action is characteristic to densely ionizing radiation (high-LET), while sparsely ionizing radiation (low-LET) will primarily act via indirect action. Direct action refers to process when ionizations and excitations are induced in the critical biomolecules. The process leads to breakage of chemical bonds, creating atoms and molecules with unpaired electrons at outermost shells - free radicals. Short-lived free radicals are highly reactive, interacting with cellular oxygen, proteins, lipids, and DNA, disrupting crucial biomolecules, and inhibiting correct cell functionality.

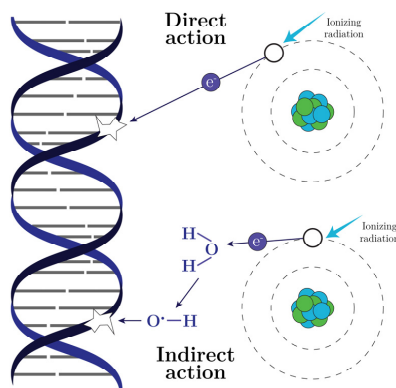


Figure 2.7. Direct and indirect ionizing radiation interaction with cellular DNA

Schematic created by Author.

Ionizations and excitations in functionally non-relevant atoms or molecules within the cell also lead to production of free radical species. Through diffusion, these species can interact with biomolecules, damaging the cell. This two-stage mechanism is

referred as indirect action. For low-LET such as X-rays, indirect action accounts for about two thirds of all interactions. Indirect action is primarily caused via water molecules, constituting ~70 to 80% of the cell. After water molecule exposure to ionizing radiation, series of complex chemical interactions take place, forming free radicals - a process called water radiolysis. Detailed description of water radiolysis process and main relevant chemical interactions is given in **Appendix 1.6**.

Figure 2.8. presents a schematic overview of the main water radiolysis interactions. Three primary radiolysis species - solvated electrons e_{aq}^- , hydroxyl $OH^\bullet$ and hydrogen $H^\bullet$ radicals - are short lived (1 to 100 microseconds in water, 0.1 to 1 microsecond in biological medium) and are extremely reactive with the functional biomolecules of the cell. Hydroxyl radicals are strongly oxidizing, therefore can efficiently interact with hydrogen atoms of DNA, disrupting the molecule and its functionality. During the chemical stage (up to 1 microsecond from primary energy deposition event), other chemical species contributing to cellular damage can be created such as superoxide anion (O_2^-), hydrogen peroxide (H_2O_2) and hydroperoxyl radical ($HO_2^\bullet$) (see **Appendix 1.6**). Chemical interactions producing hydrogen peroxide are discussed within Chapters 3 and 5.

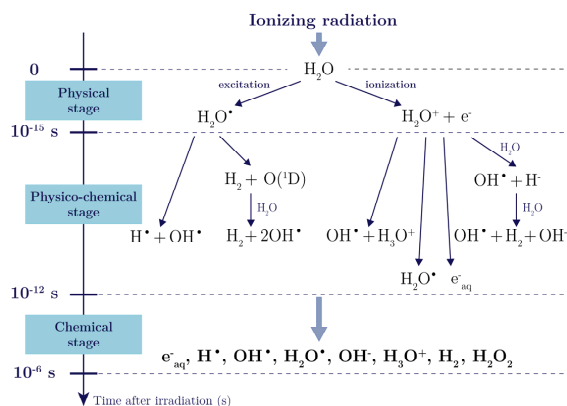


Figure 2.8. Overview of the main stages and interaction mechanisms of water radiolysis process

Schematic created by Author, based on [69].

Majority of chemical species created in water radiolysis process are from reactive oxygen species (ROS) group. Another contribution to indirect action comes from reactive nitrogen species, created in reactions between cellular oxygen and nitrous oxide, initiated by ionizing radiation. Together, ROS and reactive nitrogen species act as the mediators of cellular damage via indirect action.

To quantify the production of chemical species via interactions with ionizing radiation, radiolytic yield is used, which is also referred to as the G-value. G-value

characterizes the number of specific molecules produced per unit of ionizing radiation energy deposited in the medium. G-value typically has the units of “molecules per 100 eV”, though sometimes $[\mu\text{mol}/J]$ is also used. G-values of water radiolysis process is usually defined at two moments during the process:

- **primary yield:** at the end of physico-chemical stage - at 1 picosecond;
- **escape yield:** at the end of chemical stage at 1 microsecond.

Differences in ionization event spatial distribution at different LET correspond to changes in G-values of the water radiolysis process. Increased ionization density at high-LET leads to increased spatial proximity of primary radiolysis species, increasing radical recombination reactions in competition with diffusion [72]. LET dependency of G-values for water radiolysis products is further discussed in Chapter 4 of the Thesis.

2.4. Concepts of radiobiology

Free radicals formed via direct and indirect action are key in reactions of biomolecules - disrupting structure and leading to cellular damage and biological effects of RT. This Section introduces the main radiobiological concepts of cellular damage by ionizing radiation, discussing also the main numerical quantities in radiobiology as relevant from a “perspective of a physicist”. At the end of the Section, *FLASH* effect - one of the main phenomena investigated in the Thesis - is introduced as a modern concept in radiobiology, further discussed in Chapter 3. **References [36-38,48,73-76] have been used throughout this Section for summary of the main biological processes relevant to ionizing radiation interactions.**

Target of RT is the smallest organizational unit of a living organism - the cell. Human cells are eukaryotic and encased in a double layer lipid membrane. Cell interior consists of cytoplasm medium and various structural units encased by a separate membrane - organelles. Lipid membrane and organelles as mitochondria, endoplasmic reticulum, Golgi apparatus, and lysosomes are affected by ionizing radiation and contribute to overall cellular damage. Nevertheless, from radiobiological perspective, cellular nucleus is considered as the main target in RT due to the genetic information contained in DNA - essential in the process of cell replication.

Structural damage in DNA can lead to cellular death - the goal of RT in cancerous cells. Numerous biological factors influence the response of tumour and normal tissue cells after exposure to ionizing radiation, with most important ones referred to as “the five Rs of Radiobiology”. Types of structural DNA damage and biological factors influencing cell response to radiation are discussed with greater detail in **Appendix 1.7**.

Description of the radiobiological mechanisms caused by ionizing radiation and various factors impacting these processes is rather complex. For the clinical effect modelling, several quantitative parameters have been developed in radiobiology to aid treatment evaluation via numerical calculations. Sections 2.4.1 to 2.4.3. discuss the key

radiobiological quantities as relevant for the Thesis. Special focus is given on the differences between high-LET and low-LET ionizing radiation types.

2.4.1. Cell survival and Linear Quadratic Model

The standard quantity used to measure cell response to ionizing radiation - radiosensitivity - is “retention of reproductive integrity”. This refers to the ability of a cell to consecutively undergo at least 5 to 6 replications and produce a colony with at least 50 cells - cell survival. Several mathematical models have been developed to characterize the cell survival post-irradiation, with Linear Quadratic Model (LQM) being most used in practice due to extensive validation experimentally and clinically [73-76, 79]. According to LQM, the cell survival can be expressed as:

$$S = e^{-\alpha D - \beta D^2} \quad (2.17)$$

where S corresponds to the survival probability for cells exposed to a certain absorbed dose level D . Parameters α and β characterize the unique response of a specific cell type, with higher values corresponding to increased radiosensitivity. An example of typical LQM cell survival curves is given in Figure 2.9.a. Cell survival curves have a linear part in low dose region, with quadratic dependence for higher dose levels. The linear part is associated with DNA damage caused by lethal single-track events (DBS, complex damage), while the quadratic part - joint effect of independent sub-lethal damage events.

Cell types can be characterized by the ratio of the two LQM parameters - α/β ratio. Mathematically, α/β ratio corresponds to the dose level, where contribution to overall survival is the same for the linear and quadratic component. Tissue with low α/β ratio (below 2-3 Gy) has a late response to ionizing radiation, while early responding tissue are characterized by a high α/β ratio (around 10 Gy and higher). α/β ratio also characterizes the response to dose fractionation.

If the total dose D is fractionated in n number of sessions each delivering a dose d , the LQM can be adapted as:

$$S = \left(e^{-\alpha d - \beta d^2} \right)^n \quad (2.18)$$

In fractionated treatment, as illustrated in Figure 2.9.b, the shape of overall survival curve dramatically changes due to DNA repair in-between individual dose deliveries.

The concept of biologically equivalent dose (BED), allows the comparison of different fractionation schemes, by characterizing fractionated delivery as equivalent single high dose level:

$$BED = D \left(1 + \frac{d}{\alpha/\beta} \right) \quad (2.19)$$

RT is typically given in multiple fractions of 2 Gy, thus “equivalent dose at 2 Gy fraction” EQD_2 is also used as comparison metric.

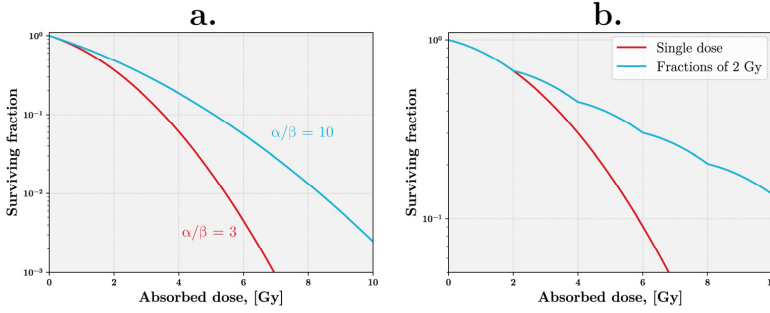


Figure 2.9. Comparison of cell survival after irradiation depending on α/β ratio (a) and for single and fractionated delivery (b)

Data calculated by Author using LQM for single and fractionated dose delivery.

Despite the widespread use of LQM, open questions exist on the absorbed dose range, where the model is valid. Considering low dose levels, hypersensitivity below 500 mGy has been reported in *in vitro* studies for a range of cell types and ionizing radiation types. On the other hand, dose hypofractionation - delivering high doses over a small number of fractions - is growing in modern RT with the advent of stereotactic radiosurgery (SRS) and stereotactic body RT (SBRT) techniques. High dose levels are also of interest in context of *FLASH* therapy, as will be discussed in Chapter 3. Several experimental studies and mechanistic models have suggested that the shape of cell survival curve at high dose levels due to DNA mis-repair phenomenon cannot be reproduced by standard LQM, underestimating survival [80-81]. Because of this, there have been considerable efforts in development of alternative radiobiological models. Alternatives include modifications of LQM, for example, introducing a new parameter proportional to the cube of dose (“linear-quadratic-cubic” model) [82-83] or introducing a threshold dose and linearization at high dose range - “linear-quadratic-linear” model [84]. More mechanistic approach for modelling of hypofractionation has been proposed by Guerrero and Li in “modified LQM” [82]. Use of “lethal potentially lethal” model has also been suggested as a potential solution for high dose irradiation.

Despite the identified limitations, standard LQM remains as the dominant approach in pre-clinical modelling, as well as radiobiological estimations in clinical environment. Standard LQM is agreed to be valid in the dose range up to about 5-10 Gy [73-76]. Studies have shown that the standard approach can be extended to high dose range (up to ~20 Gy) if the values of α and β used in conventional range are adapted [85-88].

2.4.2. Relative Biological Effectiveness

As illustrated in Figure 2.10., a significant difference in cell survival dose dependence can be observed between low and high-LET ionizing radiation types. This is

attributable to increased ionization event density on nanoscale, leading to a higher probability of irreparable DNA damage. Relative biological effectiveness (RBE) is a quantitative metric to account for these differences of biological response between different ionizing radiation types. RBE is an essential concept in PT and IBT, defined as the ratio between doses needed to achieve the same biological effect S with a reference ionizing radiation type D_{ref} and type with a different LET D_{LET} :

$$RBE(S) = \frac{D_{ref}}{D_{LET}} \quad (2.20)$$

Historically, 250 keV X-rays were considered as reference radiation type, though nowadays RBE is calculated relative to 1 MeV gamma photons of Cobalt-60 source.

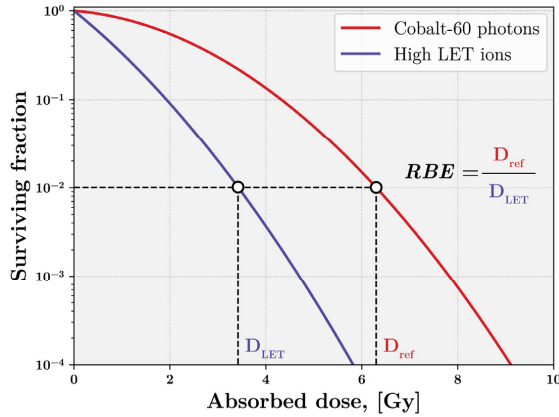


Figure 2.10. Comparison of cell survival curves for low and high LET ionizing radiation

Data calculated by Author using LQM for single dose delivery.

Parametrization of RBE is complex as it is influenced by numerous factors as absorbed dose level and fractionation scheme, biological endpoint considered, cell type, and DR of the irradiation, though the primary change corresponds to LET of radiation used [89]. Figure 2.11. illustrates RBE as a function of positively charged particle beam LET. Although LET is the primary factor, biological responses for different particles with the same LET can differ due to different ionization nanoscale patterns. RBE peaks around LET of $100 \text{ keV}/\mu\text{m}$, with maximum values reported in the range of about 3 - 5 in IBT and up to 20 for neutron and low-energy alpha particle beams. With LET increasing above $100 \text{ keV}/\mu\text{m}$, RBE is reduced due to the so-called “overkill” effect, due to two possible mechanisms. Firstly, the energy deposition by a single-track is higher than the level for cellular inactivation - excess dose is essentially wasted. Secondly, “overkill” effect could also be attributed to track structure on a molecular level. At high

LET, spatial distribution of ionization events is extremely narrow, limiting the number of DNA molecules in interaction - insufficient to cause cell death.

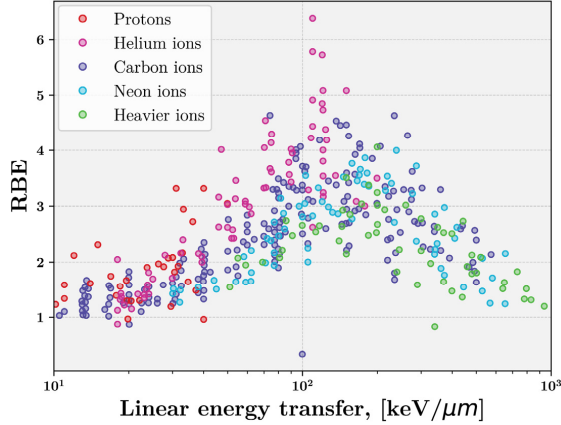


Figure 2.11. Relative biological effectiveness as a function of particle LET for protons, helium, carbon, neon, and heavier ions

Figure recreated by Author, using the data of GSI PIDE as reported in [90]

Increased RBE is one of the motivations from radiobiological perspective for clinical PT and IBT, improving TCP for certain cancer types. Furthermore, differential RBE is important concept in IBT. Carbon ions have significantly higher LET in the Bragg peak region (within the tumour) compared to lower LET in the entrance plateau region (normal tissue). This translates to RBE differential in tumour and normal tissue, leading to increased TCP while maintaining low NTCP. RBE differential established carbon IBT clinically, as heavier ions, such as neon, silicon, and argon, in early clinical trials indicated high NTCP due to high RBE in entrance plateau.

As LET is spatially varying within irradiation field and increasing with depth in matter for proton and ion beams. This translates into variable RBE and needs to be considered in dosimetric calculations. In PT, it is accepted to use a constant, spatially independent RBE value of 1.1 [91-92]. This approach is under discussion as *in vitro* experimental evidence has clearly indicated RBE variability with proton beams [91-92]. Nevertheless, possibly increased RBE in the dose fall-off region is considered in treatment planning as a possible source of range uncertainty - as discussed further in Chapter 8.

For ions heavier than protons, spatial RBE variation is significant, requiring explicit modelling for IBT planning. Clinically, RBE in IBT is calculated via one of the two approaches: Local Effect Model (LEM) or Microdosimetric Kinetic Model (MKM). The main differences in the physical description of the two models are summarized in **Appendix 1.8**. LEM is widely used in Europe for carbon IBT calculations, while use of MKM is more prominent in Japan [93]. Both models can be tuned for clinical use, though

extra care should be taken for direct inter-comparison between the two [93-95]. Broader overview of MKM and its modified approach - mMKM - as it has been used for the studies within this Thesis is given in **Appendix 1.8**.

For a given dose of $D_{ref}(S)$ with reference radiation type for a particular cell survival level, the RBE value with mMKM can be calculated as:

$$RBE = \frac{D_{ref}(S) * 2\beta}{-(\alpha_0 + \beta z_{1D}^*) + \sqrt{(\alpha_0 + \beta z_{1D}^*)^2 - 4 \ln(S) \beta}} \quad (2.21)$$

Using the α_X and β_X parameters of LQM for reference cobalt-60 photon beam, Equation 2.21 for RBE calculation at a certain dose level D can also be rewritten as:

$$RBE = \frac{\alpha_X/\beta_X}{2D} \left(-1 + \sqrt{1 + \frac{4}{\alpha_X/\beta_X} \left(\frac{\alpha_0 + \beta z_{1D}^*}{\alpha_X} D + \frac{(\sqrt{\beta/\beta_X} D)^2}{\alpha_X/\beta_X} \right)} \right) \quad (2.22)$$

Oxygen has an important role in cell response to ionizing radiation. Throughout the history cellular oxygen has been repeatedly demonstrated to act as a strong radiosensitizer - response to ionizing radiation is increased with better tissue oxygenation compared hypoxia. For quantification of this phenomenon the concept of oxygen enhancement ratio (OER) is used. Additional details on OER parametrization are given in **Appendix 1.9**.

2.4.3. Introduction to *FLASH* effect

This Subsection briefly introduces the concept of the *FLASH* effect, with more in-depth review and analysis given in Chapter 3.

Apart from spatial distribution of the dose, also the time domain - DR - has historically been shown to have a significant impact on RT outcomes. In the DR range relevant to brachytherapy and EBRT - from ~ 0.1 Gy per hour to several Gy per minute - the fraction of cell kill for a given dose decreases with decreasing DR [74]. Increased radioresistance at lower DR is associated with repair of sub-lethal DNA damage lesions [74]. Nevertheless, specific cell lines have also shown the inverse of this effect - decreased survival due to radiosensitivity variation during cell cycle [74].

DR higher than ones used in conventional RT - on the order of tens to thousands of Grays per second - are referred to as ultra-high dose rates (UHDR). The effects of UHDR on biological systems were first investigated in 1959 by Dewey and Boag - in bacteria *Serratia marcescens* [104]. Results showed that oxygenated ($pO_2 = 1\%$) bacteria irradiated at a DR of 10^8 Gy/s exhibited increased radioresistance compared to conventional DR of 10 Gy/min. Furthermore, exhibited dose response at UHDR was found to be similar as in hypoxic case at conventional DR. Similar results in bacteria were also found in studies done in 1968 [105]. It was theorized, that the underlying effect of these findings was associated with transient oxygen depletion. At UHDR, rapid energy deposition chemically consumes oxygen too quickly for diffusion processes to maintain

sufficient level of oxygenation, inducing a transient state of hypoxia. Tissue sparing with UHDR was also observed in mammalian cells in 1967 [106].

Research into UHDR effects on biological systems in present day was re-emerged by the pivotal work of Favaudon et al. in 2014 [107]. Using mice tumour model, the study showed significant differences in the biological responses between short pulse (< 500 ms) UHDR (> 40 Gy/s) and conventional DR irradiation. Greatly increased normal tissue sparing was observed under UHDR irradiation, with reduced lung fibrosis and radiation-induced apoptosis in smooth muscle and epithelial cells. On the other hand, the tumour cell response was similar between both DR. The observed differential effect - greatly reduced adverse effects in normal tissue with unaffected tumour response - under UHDR irradiation has been termed the *FLASH*⁶ effect. Possible clinical application of the *FLASH* effect - *FLASH* RT - is highly attractive as it could expand the therapeutic window as illustrated in Figure 2.12. *FLASH* effect could significantly reduce the adverse side effects of RT, while also allowing possibilities for dose escalation in scenarios with poor tumour control.

Clinical potential of the *FLASH* effect has led to numerous *in vitro* and *in vivo* studies, investigating how the sparing effect varies in different tissues and organs and what are the necessary irradiation parameters. Current studies have indicated that the *FLASH* effect in biological tissue is induced under two dosimetric thresholds:

- if the **average DR** is **higher** than about **40 Gy/s**;
- if the **absorbed dose level** is **higher** than about **8-10 Gy**.

The two thresholds are general values, with more complex influence of delivery parameter space discussed in Chapter 3. Apart from average DR, the *FLASH* effect can be influenced by temporal beam-structure parameters such as pulse DR, dose per pulse, and irradiation time. The level of *FLASH* effect varies between different tissue types, with sparing magnitude increasing with absorbed dose level. *FLASH* effect has been mainly observed with electron and proton beam irradiation [108], with fewer studies using photon or heavier ion (helium, carbon) beams. Impact of ionizing radiation type is expected as main mechanisms theorized underlying *FLASH* effect exhibit LET dependence. All these aspects are discussed in greater detail within Chapter 3.

From the discovery of *FLASH* effect, numerous theories have been proposed to explain the underlying mechanisms of the differential effect. With more details given in Chapter 3, mechanisms of transient oxygen depletion, radical-radical recombination, peroxidized compound metabolism, protection of circulating immune system cells and others have been suggested as possible contributors to the *FLASH* effect. Nevertheless, no unified theory currently exists to fully explain and quantify the effect.

Apart from increased therapeutic window, *FLASH* RT could offer other clinical advantages:

⁶ *FLASH* is not an acronym

- **reduced treatment course length:** as *FLASH* effect necessitates high dose levels, the length of the treatment course could be significantly reduced - hypofractionation.
- **motion uncertainty mitigation:** as the whole treatment is delivered in sub-seconds, *FLASH* RT would reduce the impact of physiological motion (breathing, heartbeat, peristalsis etc.) on the delivered dose distribution.

Along with active investigations of the biological basis of *FLASH* effect, development of UHDR delivery technologies is necessary for future clinical translation. UHDR delivery capabilities depend on particle accelerator type used and physical interaction mechanisms of the specific ionizing radiation type. Technological challenges of UHDR beam production and clinically relevant delivery methods are discussed and analysed in Chapter 7.

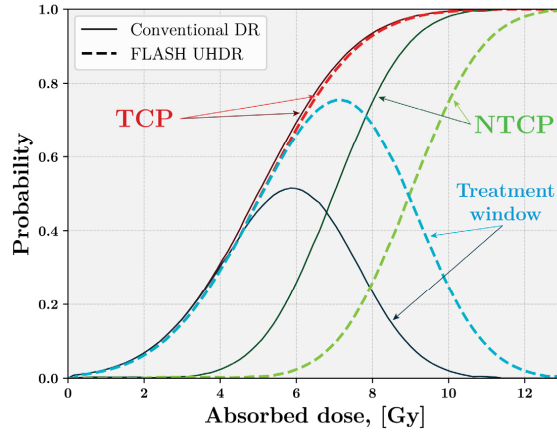


Figure 2.12. Comparison of TCP, NTCP and resulting treatment window for conventional irradiation and *FLASH* effect under UHDR

Solid lines in the Figure correspond to dose dependency curves under conventional irradiation, while dashed lines - for UHDR irradiation. Figure recreated by Author, using the data as reported in [109]

2.5. Nuclear interactions in ion beam therapy and corresponding role in range verification

With Section 2.2.3 having focused on electromagnetic (EM) interactions of protons and heavier ions, heavy positively charged particles can also undergo nuclear interactions mediated by the strong force. This Section describes the main concepts of these interactions in context of PT and IBT. Large fraction of secondary particles produced in nuclear interactions are energetic, possibly exiting the primary target and providing opportunities for detection. Second part of this section briefly introduces physical concepts of range verification - use of secondary particles or other signals for localisation of the Bragg peak position. In addition to secondary particle detection-based

range verification, main concepts of anatomical imaging via particle radiography are also introduced. In-depth review and analysis of the different range verification methods is provided in Chapter 8. **References [48-49, 52, 110-113] have been used throughout this Section for summary of the physical processes relevant to nuclear interactions.**

2.5.1. Nuclear interactions in ion beam therapy

Although EM interactions are dominant, nuclear interactions between projectile particles and target nuclei are not a rare process. Modelling of nuclear interactions in PT and IBT is essential for correct dosimetric calculations and RBE estimations. Additionally, as discussed in Section 2.5.2 - nuclear interaction products provide opportunities to improve precision of treatment delivery.

In accordance with ICRU report 63, nuclear interactions can be classified into three groups [114]:

- **elastic** - incident projectile scatters off target nucleus, conserving total kinetic energy - state of target nucleus and projectile unchanged;
- **nonelastic** - total kinetic energy is not conserved - breakup of target nucleus, particle transfer reactions etc.;
- **inelastic** - specific type of nonelastic interactions, when the nucleus remains structurally unchanged, though is excited into higher energetic state.

Initial beam particles undergoing EM interactions are referred to as primaries, while primaries undergoing elastic interactions and particles created in inelastic and nonelastic nuclear interactions are defined as secondaries, even if the particle is of the same type as primary particle. In PT and IBT, nuclear interactions cause the loss of primary particles with increasing depth as illustrated in Figure 2.13. Additional information on mathematical description of nuclear interactions is given in **Appendix 1.10**.

Generated heavy secondaries can be separated in two groups - target and projectile fragments, with additional information on two fragment types outlined in **Appendix 1.10**. In context of PT, no projectile fragmentation can occur and most of secondaries are neutrons, protons or γ photons. Secondary protons can be generated both elastically and inelastically, with latter occurring at large emission angles. Secondary protons mainly contribute to the so-called “nuclear halo”. In smaller fraction, low energy target fragments (primarily alphas) and recoil nuclei are also generated. Due to the high mass and low energy, these target fragments have high LET and can have a significant effect on RBE. This is however offset by the low dose contribution of these fragments, though various studies have suggested that target fragment influence on RBE in PT might not be negligible.

For ions heavier than protons, projectile fragmentation is prevalent. As generated projectile fragments have lower mass and almost the same kinetic energy as primaries, their range is larger. Due to this, projectile fragments deposit energy beyond

the Bragg peak, generating the so-called fragmentation tail as illustrated in Figures 2.3 and 2.14. Dose level in fragmentation tail is proportional to the energy and mass of the primary. Furthermore, projectile fragmentation generates “mixed beam”, increasing the complexity of LET and RBE calculation in IBT. For example, primary carbon ion beam can generate various isotopic fragments of boron, beryllium, lithium, helium, and hydrogen, creating complex kinetic energy and LET spectrum, which needs to be accounted for in calculations. Visual representation of the projectile fragment depth profiles for fluence and dose contribution are given in Figure 2.14.

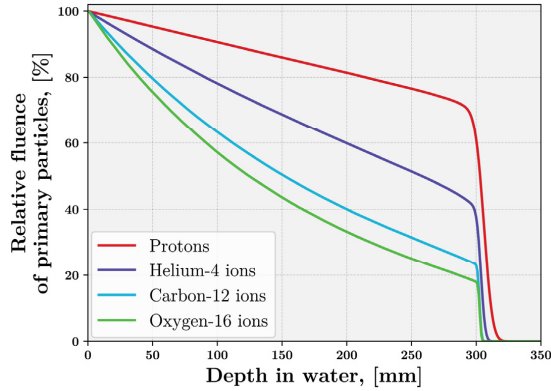


Figure 2.13. Primary particle fluence loss as a function of depth for protons, helium-4, carbon-12, and oxygen-16 ions with a range of 30 cm in water

Data normalized to maximum particle fluence at surface for each ion type. Data given for point-like beams simulated with an empirically scaled initial energy spread. Data simulated in Geant4 environment by Author.

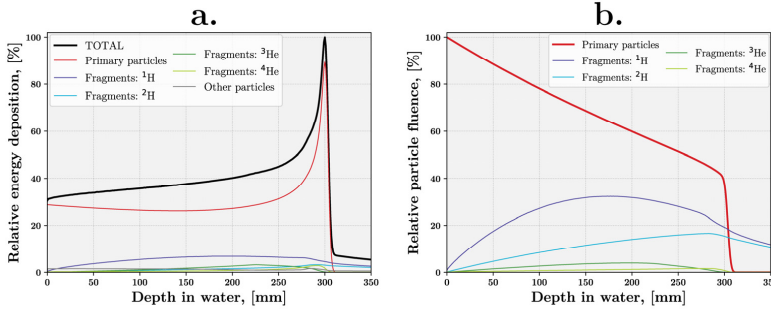


Figure 2.14. (a) Energy deposition depth profile for helium-4 ions and contributions to total energy deposition by different nuclear fragments
(b) Relative fluences for primary helium-4 ions and secondary nuclear fragments as a function of depth

Data are given in water for a range of 30 cm, corresponding to initial energy of 220 MeV/u. In Subfigure (a), all the data are normalized to maximum total energy deposition. In Subfigure (b), all the data are normalized to primary helium-4 ion fluence at the surface. Data given for point-like beams simulated with an empirically scaled initial energy spread. Data simulated in Geant4 environment by Author.

2.5.2. Approaches to range verification: Bragg peak localisation and anatomical imaging

One of the main drawbacks of PT and IBT are range uncertainties. Due to the high dose gradients of Bragg peak, severe discrepancies in delivered dose can occur by even small shifts of Bragg peak position. Shifts can be introduced by anatomical changes of the patient, physiological organ movement, deviations of accelerator energy, uncertainties in treatment planning process and other factors. To mitigate these uncertainties, apart from conventional approaches, various range verification methods could be. Range verification methods can be divided in two larger groups:

- **Bragg peak localisation** - detection of secondary particle (or signals from other processes) physical characteristics (spatial, temporal, or spectral). Estimation of Bragg peak shifts done by observing deviations in registered signal;
- **anatomical imaging** - although no direct monitoring of Bragg peak position, specific imaging approaches can provide sufficient information for range estimation and/or monitoring.

This subsection briefly introduces main physical concepts of range verification methods considered in the scope of this Thesis, while in-depth analysis and discussion is given in Chapter 8 and other chapters of Part II. References [48,118-120] have been used throughout this Section for summary of the physical processes relevant to range verification methods.

Positron emission tomography [121-122]

Both stable and radioactive nuclei can be formed as fragments in nuclear interactions. Neutron deficient radioactive nuclei decay via β^+ channel:



emitting electron neutrino ν_e and a positron e^+ . Emitted positrons e^+ will travel a certain range in the tissue, before annihilating with an electron e^- (largest fraction). In annihilation process two antiparallel⁷ photons with energy of 511 keV each are created, which are coincidentally registered with a positron emission tomography (PET) system, allowing to reconstruct the position of annihilation event. The reconstructed PET image of radioactivity induced by the treatment beam is compared to a reference image to assess possible Bragg peak shifts and verify the dose distribution delivered to the patient.

The idea to use positron-emitting nuclei for verification in PT and IBT dates to the days of early research of these modalities and was first proposed in 1960s. Positron emitting nuclei generated by interactions of proton and ion beams have various half-lives in the range of few milliseconds to tens of minutes. Therefore, the induced β^+ activity could be measured with a PET system both during and after beam delivery - in-beam, in-room and off-line verification approaches covered in Chapter 8. Each approach has certain gains and limitations related to the characteristics of radioactive nuclei, detector interfacing with beam delivery system and impact of physiological processes in patient's body.

Multiple challenges exist for PET verification approach both from physical and biological perspectives. Main limiting factors include low annihilation photon counts, no direct correlation with dose distribution, positron range effects, time dependency of the signal and physiological washout. Further analysis is provided in Chapter 8.

Prompt gamma emissions [123]

Fragments generated in nucleus-nucleus collisions can also be in higher energetic state. De-excitation of these fragments emits gamma photons. Timescale of de-excitation is typically on the order of few femtoseconds to picoseconds, thus the term “prompt gamma (PG) photons” is used. Detection of PG photons as a method for range verification was first proposed in 2003, with proof-of-concept validated in 2006. PG photon spatial, temporal, and spectral characteristics are correlated with dose distribution, allowing verification or Bragg peak shift estimation by detection of these photons. This approach enables instant on-line monitoring as signal outside of the patient could be registered in few nanoseconds after irradiation event.

Emitted PG photons are typically in the range of 2 - 15 MeV and the number of emissions gradually decreases for higher photon energies. The main contributions in emission spectrum are discrete lines corresponding to de-excitation of different nuclei

⁷ With a small uncertainty due to non-negligible motion of electrons in the medium and probability of annihilation-in-flight

present in the irradiated material and their respective nuclear energy level structure. High energy PG photons have emission maximum spatially closer to the Bragg peak, and they are less scattered in patient before signal registration. Nevertheless, the detection of high energy PG photons complicates the detector design.

PG photon emission yields are reasonable for detection (on the order of 10^{-5} to 10^{-4} per incident particle), though the main challenge for clinical use is detection system. Typical gamma photon detectors, such as the ones used in diagnostic imaging with single photon emission computed tomography (SPECT), are optimized for use at low energies. Active developments towards a suitable PG photon detection system are ongoing with main approaches summarized in Chapter 8. Data filtering is also important as PG photon signal needs to be distinguished from background induced by neutrons.

Main PG photon detection approaches use spatial or temporal characteristics. As emission energies uniquely depend on the nuclei present, spectroscopic approaches have also been suggested. PG photon spectroscopy could allow to identify chemical composition of irradiated tissue and monitor changes over the course of the treatment.

Particle radiography [124]

While PET and PG registration methods aim to determine the Bragg peak position or delivered dose distribution in the patient, pre-treatment imaging can be used to limit uncertainties due to patient anatomical changes and positioning. As further discussed in Chapter 8., conventional pre-treatment imaging with X-rays is sub-optimal for PT and IBT due to different physical interaction mechanisms. With X-ray imaging limited in capabilities to assess parameters as RSP and range, particle radiography (i-Rad) approach has been suggested as alternative. Protons or heavier ions as used for treatment beam are accelerated to higher energies - transmission energies - and used to pass through the object for image registration. Due to relatively high energy necessary, proton radiography (p-Rad) approach is mainly considered, though use of heavier particles is also explored. Brief introduction to main physical concepts of i-Rad, while more in-depth analysis on imaging methods, detector technologies and reconstruction approaches is given in Chapter 8, as well in Chapters 9 and 10.

For a given initial energy of heavy charged particle, measurement of residual energy exiting an object is proportional to thickness and density traversed. Thus, image contrast is achieved by 2-dimensional (2D) measurements of residual energy, using the concept of water equivalent path length (WEPL)⁸. WEPL refers to the thickness of water that would correspond to the same energy loss experienced by the particle as it traverses a certain material (or composition) of a given thickness and density. If a particle of initial energy E_{init} has a residual energy E_{res} after traversing a given object, WEPL of this object can be described as:

⁸ Referred to as water equivalent thickness (WET), as well

$$WEPL = \int_{E_{init}}^{E_{res}} \frac{dE}{S_{water}} \quad (2.24)$$

where S_{water} corresponds to stopping power in water. WEPL can also be defined as line integral of the spatial distribution of RSP. Possibility of directly measuring RSP integral and WEPL values underlines the main advantage of i-Rad over conventional X-ray radiography. As X-ray image contrast corresponds to electron density of the material, conversion procedures are necessary and introduce additional uncertainties. i-Rad could provide improved low contrast resolution, reduce metallic implant artefacts and reduce imaging dose compared to X-ray radiography. Additional introductory information on i-Rad is given in **Appendix 1.11**.

Other approaches

Apart from approaches mentioned, ionoacoustics and interaction vertex imaging have also been considered for range verification and are briefly discussed in Chapter 8.

Energy deposition from ionizing radiation causes a local temperature increase. Due to associated thermal expansion, a pressure wave is generated, which could be registered with an ultrasound transducer in frequency range from 1-10 MHz. Ionoacoustics [126] approach aims to use these thermoacoustic emissions to assess dose distribution. Some of the key challenges are related to the modelling of pressure wave propagation in patient tissue, signal analysis, and the impact of beam temporal structure.

As discussed, ions heavier than protons produce projectile fragments with sufficiently high energies to exit the patient. Interaction vertex imaging [127] aims to measure these fragments emitted from the patient to reconstruct the point of production. Method is considered for carbon IBT, by primarily measuring secondary protons.

2.6. Particle accelerators in radiotherapy

Having considered the different physical interaction mechanisms and biological effects of different ionizing radiation types, it is important to discuss technological systems used for production of such beams for medical use. This Section introduces main physical and technical concepts of particle accelerators used for production of X-ray photon, electron, proton, and heavy ion beams for medical applications. While this Section focuses on production of ionizing radiation, RT delivery techniques, and technical challenges for UHDR beams are discussed and analysed in Chapter 7. **References [36-38,48-49,128-136] have been used throughout this Section for summary of the particle accelerators used for medical applications.** Sub-sections below summarize main aspects relevant to linear accelerators and synchrotrons, while summary on X-ray tubes and cyclotrons is provided in **Appendix 1.12.** and **Appendix 1.14.**, respectively.

2.6.1. Linear accelerator

As it becomes technically challenging and inefficient to accelerate particles above few tens of MeV with direct current accelerators, approaches employing radiofrequency EM are used. Thus, to achieve megavoltage X-ray photons, electrons impinging on a tungsten target are accelerated with the use linear accelerators (LINAC). LINAC is a single pass machine accelerating charged particles in a linear trajectory by time-varying radiofrequency (RF) electric field. Concept of an RF LINAC was originally proposed in 1924 and first built in 1928 by Rolf Widerøe, operating at 1 MHz to accelerate potassium ions from 25 to 50 keV. This earliest concept was expanded by Luis Alvarez in 1947, introducing what is known as the drift-tube LINAC. In this approach, positive and negative terminals of an RF oscillator were connected to metal drift-tubes - hollow structures, such that electric fields cannot penetrate inside, allowing particles to drift in an electric field-free region. In this arrangement, gaps between drift-tubes have opposite polarity on each side, accelerating charged particles. Lengths of the drift-tubes must be synchronized with the velocity of particles, ensuring the same electric field phase at each gap. To increase electric field potential differences, accelerating gaps are placed inside a cylindrical or rectangular structure - waveguide - made from a highly conductive metal with a geometry corresponding to the operational resonant RF frequency. This ensures storing RF energy for long time and greatly increased accelerating potential for a given input power. To control the beam size, focusing magnets as quadrupoles or solenoids are used. It should be noted that LINACs can accelerate only bunched beams - achieved by controlled grid after the gun for electron beams, while for protons and heavier ions - dedicated pre-acceleration devices as radiofrequency quadrupoles and bunchers.

RF cavity LINACs can be divided into two main classes: standing and travelling wave structures. For a standing wave structure, both ends of accelerating waveguide are terminated by a conducting disc, reflecting the RF power. RF waves continue travelling back and forth in the structure, building up the field in each cavity and forming a standing wave pattern. On the contrary, in a travelling wave structure the RF power enters waveguide at one end and propagates towards the other, where the waves are either fully absorbed or exit the structure.

Instead of using the accelerated electron beam for X-ray production, it can be directly used for clinical treatment. Scattering foils are used to angularly spread the accelerated pencil-like beam and achieve irradiation field size relevant for RT. As noted in Section 2.2.2., high electron energies are necessary to treat deep-seated tumours - VHEE. Historically circular accelerators as betatrons and racetrack microtrons were considered for developing VHEE, though efforts never flourished due to the complexity of these machines, induced activation, and limited beam output. It was only after advances in LINAC technology (higher accelerating gradients), that VHEE was again considered for clinical use. Currently, main VHEE research accelerators are CLEAR (50-220 MeV), SPARC (170 MeV) and NLCTA (50-120 MeV), with at least 5 other

facilities under construction, majority operating at S-band or X-band frequencies [44,139]. Advances in X-band accelerating structures, increased accelerating gradient and possibilities of laser wake-field acceleration could contribute to clinical adoption of VHEE.

LINAC operation usually uses pulsed RF power, forming macro-pulses with a repetition frequency up to a few hundred Hz and variable duty cycle. Within the macro-pulse, multiple micro-pulses are present corresponding to individual particle bunches at the operational frequency of the accelerating structure. Typical temporal structure of a beam at LINAC output is given in Figure 2.15.

LINACs are also used for proton and heavy ion acceleration, though just as pre-accelerators for synchrotrons. In a typical IBT complex, employing a synchrotron, before a LINAC, particles are generated in an ion source and pre-accelerated and bunched in low-energy transfer line, radiofrequency quadrupole, and medium-energy transfer line. Before injection into synchrotron, LINAC accelerates the beam up to few MeV/u. Proton and heavy ion LINACs operate at RF frequencies in hundred MHz range, with 216.8 and 352.2 MHz being the most common. Typically, Alvarez drift-tube or interdigital H-mode accelerating structures are used, with the latter used in 3 of European IBT centres - HIT, CNAO and MedAustron [140]. Unlike electrons, protons and heavy ions are not relativistic at acceleration energies, thus the length of accelerating cavities must gradually increase with the velocity of particles along the LINAC. Direct delivery of PT and IBT via a LINAC system has also been considered by initiatives such as AVO-ADAM (see **Appendix 1.13.**).

Additional information on main concepts relevant for LINAC operation is given in **Appendix 1.13.**

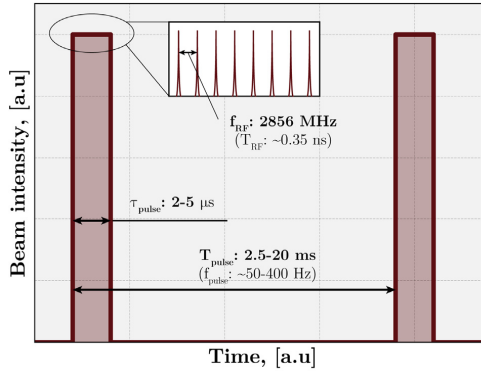


Figure 2.15. Typical temporal structure of output beam of electron LINACs used in conventional radiotherapy

Typical RT LINAC operation frequency of 2.856 GHz assumed. Schematic recreated by Author, data on beam temporal characteristics adapted from [141]

2.6.2. Circular accelerators: cyclotrons and synchrotrons

To limit the size of the particle accelerator and use lower accelerating voltage, a single accelerating cavity could be used for multiple passes of the same particle - circular accelerators. Circular accelerators are differentiated as cyclotrons (see **Appendix 1.14.**) and synchrotrons, though the same physical principle - Lorentz force - is used in both. Lorentz force $\overrightarrow{F_{Lorentz}}$ exerted on a particle with a velocity $\vec{v}$ in circular accelerator can be described as:

$$\overrightarrow{F_{Lorentz}} = q(\vec{E} + \vec{v} \times \vec{B}) \quad (2.25)$$

where $\vec{E}$ corresponds to electric field intensity and $\vec{B}$ - magnetic flux density. The simple expression of Lorentz force underlines the main operational principle of circular machines - electric fields generated with RF cavities accelerate particles, while magnetic fields by dipoles and higher order multipole magnets are used to control particle trajectories. Summary relevant to synchrotrons is provided below, with additional data on cyclotrons presented in **Appendix 1.14.**

Synchrotrons

Ions heavier than protons demand higher energies for clinical application - impractically large cyclotron radius with used magnetic field flux densities. This prompted to rethink the “single block”-type technology and to develop another circular accelerator concept - the synchrotron. In a synchrotron, particle accelerator functions are assigned to individual technological components arranged in a closed, periodic structure - lattice - with a circular trajectory. Main components of a synchrotron lattice include:

- **RF cavity** for acceleration;
- **dipole magnets** for trajectory deflection;
- **quadrupole magnets** for beam focusing in horizontal and vertical planes;

Lattice design ensures oscillating movement of particles around a constant, closed trajectory - design orbit. These small oscillations - betatron oscillations - ensure stability of synchrotron operation. Schematic representation of a synchrotron is given in Figure 2.16.

Particle acceleration is ensured by synchronization of increasing particle energy in every turn around the machine with operational frequency of RF cavity and magnetic field flux density in dipole magnets. Mathematical description for synchronization of these parameters is given in **Appendix 1.15.**

An important synchrotron design parameter is the beam rigidity $B\rho$ - product of dipole magnet bending radius and flux intensity, given in units $T * m$. Synchrotron with a given beam rigidity can accelerate a certain particle only up to a maximum momentum p of:

$$p = qB\rho \quad (2.26)$$

Equation 2.26 indicates that for increasing particle energy either larger synchrotron must be constructed (increased ρ) or stronger dipole magnets should be used (increased B).

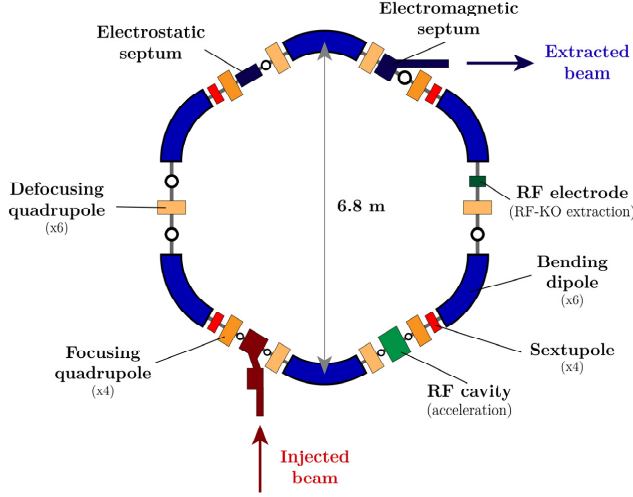


Figure 2.16. Structure and main components of a medical synchrotron

White circles in the schematic correspond to beam instrumentation and other components. HITACHI 250 MeV proton synchrotron structure is used in the schematic as reported in [145]

Apart from the main elements, synchrotron ring also contains multiple beam instrumentation devices for monitoring the beam, corrector magnets for adjusting beam trajectory and higher order multipole magnets. Sextupole magnets are essential in medical synchrotrons, correcting for chromatic aberrations and used for inducing controlled resonances for beam extraction.

Synchrotrons cannot accelerate particles from zero energy, therefore injection by pre-accelerator is necessary - a LINAC for medical machines. The accelerated particle beam also cannot be directly extracted from synchrotron due to closed particle trajectories. Either fast-ramped kicker or septum magnets can be used to perturb particle trajectories and extract the beam. Quality of the particle beam delivered to patient for IBT treatment depends on the extraction process. For beam extraction, two approaches exist:

- **fast extraction** - whole beam extracted in one turn;
 - **slow extraction (SE)** - continuous extraction of the beam over many turns.
- SE is used for medical synchrotrons due to stability necessary for modern delivery techniques. Extracted beam pulse is referred to as spill. For SE in medical machines, synchrotrons are operated near the 3rd order resonance. When beam needs to be extracted, particles are brought to unstable phase space region defined by resonant sextupole magnet. Under this condition, the amplitude of particle oscillations continues to grow until reaching septum magnets, where they are extracted from the synchrotron towards patient. Mainly, three methods are considered for SE in medical machines, with summary

provided in **Appendix 1.16**. In context of UHDR irradiation, other SE approaches have also been proposed and briefly introduced in Chapter 3.

Currently, all operational IBT centres use synchrotrons with normal conducting magnets⁹. Ongoing research projects investigate also superconducting magnets as possibility for compact solutions in IBT. Synchrotrons can accelerate the beam to any necessary final energy, contrary to cyclotrons, thus high-quality output beam characteristics can be maintained irrespective of the treatment energy. Compared to cyclotrons, synchrotrons have lower beam intensity due to limitations of maximum number of particles per single injection, while also having longer response time for intensity variation. For clinical delivery, synchrotrons are also limited in energy layer switching time due to separate acceleration cycles necessary for different energy spills, as further discussed in Chapter 7. As for the temporal structure of the output beam, it can be considered as quasi-continuous (microstructure from operational RF frequency), though the macrostructure depends on the SE method chosen.

2.6.3. Helium ion therapy and HeLICS synchrotron

Among the various heavy charged particle species considered for IBT, special focus in this Thesis is on helium-4 ions and their clinical potential. This subsection briefly introduces the physical and radiobiological potential of helium-4 ions, while the historical and current perspectives on possible clinical use are reviewed in Chapter 8. Subsection also gives an overview of a compact synchrotron technology developed for helium-4 ions, considered throughout several Chapters of the Thesis.

From perspective of physical interactions with matter, helium-4 ions offer certain advantages over protons and carbon-12 ions [146]. As outlined in Section 2.2.3., compared to protons, helium-4 ions exhibit reduced range straggling and MCS caused lateral deflection. Clinically, this translates to significantly improved dose conformality both longitudinally and laterally - important for treatment of tumours located near critical organs. Nucleons in helium-4 are tightly bound, thus are less likely to fragment, limiting the dose level in fragmentation tail. Compared to carbon-12 ions, helium-4 ions undergo less nuclear interactions, thus reducing dose distally to the Bragg peak due to fragmentation. This also corresponds to reduced secondary neutron fluence, favouring helium-4 ions in clinical cases, where integral dose and “low-dose bath” reduction is important - such as paediatrics. As for the same range lower energies are necessary for helium-4 ions compared to carbon-12 ions, less demanding and more compact synchrotron systems can be designed [146].

Apart from benefits of physical interactions, helium-4 ions offer certain radiobiological advantages [146]. As the LET is higher compared to protons, RBE is increased in the tumour, while also increasing RBE differential, offering advantages for

⁹ Though superconducting solutions are implemented in some of the PT cyclotrons and currently designed C400 cyclotron for IBT (see Appendix 1.14.)

certain treatment scenarios. Increased LET also slightly reduces OER - applications for tumours of low-level hypoxia could be envisioned, though *in vitro* and *in vivo* studies are necessary. From treatment planning perspective, spatial dependence of RBE for helium-4 ions needs to be explicitly modelled like for carbon-12 ions. While increase in RBE and OER reduction are not as significant as for carbon-12 ions, helium-4 ions offer certain advantages from the biological effect modelling perspective. With reduced nuclear fragmentation compared to carbon-12 ions, complexity of the “mixed beam” in the treatment volume is reduced using helium-4 ions. This could improve the accuracy and reduce uncertainties in clinical modelling. With LET in range from 4 to 40 $\text{keV}/\mu\text{m}$, clinical helium-4 ion energies do not result in “overkill” effect of RBE, present in the distal Bragg peak edge of carbon-12 ions [146].

Historically, helium-4 ions have already been considered for clinical use in early IBT developments at Lawrence LBNL - first used in 1957 [147]. Pioneering clinical trials showed benefits of helium-4 ions in treating small tumours in proximity to critical organs [147]. Despite the initial success, research in helium-4 ion use was discontinued, focusing on development in PT and carbon-12 IBT. Use of helium-4 for IBT has seen its revival in recent decade at Heidelberg Ion Beam Therapy Centre (HIT). In this new era, first patient was clinically treated in 2021 [148]. With mentioned physical and radiobiological benefits of helium-4 ion, a significant interest is growing both in research and clinical communities for possible future translation of this modality [149]. More in-depth review of historical and future perspective of helium-4 IBT is provided in Chapter 8.

Such a dedicated synchrotron system optimized for helium-4 IBT is also developed within CERN by *Next Ion Medical Machine Study* (NIMMS) collaboration [150-152]. Within the Thesis, the design of this machine has been considered and used as a reference in multiple Chapters, with brief technical overview given in the following paragraph. HeLICS (*Helium Light Ion Compact Synchrotron*) is a compact synchrotron system optimized for accelerating helium-4 ions up to treatment energies of 220 MeV/u , while enabling possible operation with proton beams. In current design iteration, lattice of HeLICS consists of 6 dipole magnets in a triangular configuration operating with magnetic flux density of 1.65 T with design beam rigidity of 4.52 $T * m$. Injection energies of 10 MeV and 5 MeV/u are considered for proton and helium-4 ion beams, respectively. Injection is ensured by using radiofrequency quadrupole and a novel LINAC design. Maximum beam intensities at injection correspond to the number of particles necessary to deliver a dose of 2 Gy to a volume of 1 litre. SE methods optimized for UHDR delivery are also considered in the design of HeLICS, along with possibility of multi-energy extraction (MEE) to further increase temporal performance of the machine. Proton beams could be accelerated to energies sufficient for full-body radiography - further explored in Chapter 9. A schematic representation of HeLICS lattice is given in Figure 2.17., while Table 2.1. provides an overview of main technical parameters.

HeLICS technology development is to be finalized in upcoming years. A possible integration of the technology into a clinical treatment and scientific research facility is

under consideration within the Baltic States - *Advanced Particle Therapy Centre for the Baltic States* (APTCB) initiative [153]. Translation of HeLICS technology into a facility is also considered in Switzerland [154].

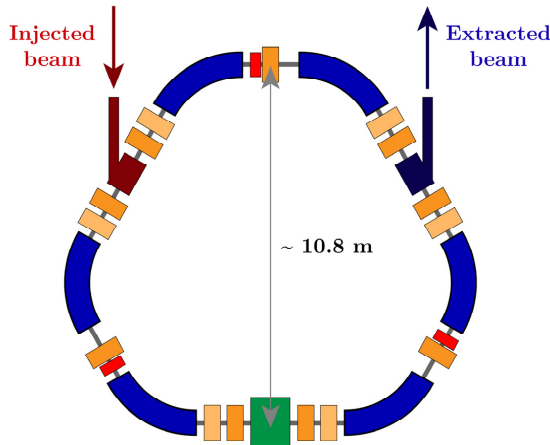


Figure 2.17. Structure and main components of the NIMMS HeLICS synchrotron

Component visual representation corresponds to the one used in Figure 2.16.

Schematic created by Author, based on technical data reported in [150-152].

Table 2.1.

Main technical parameters of HeLICS synchrotron [150-152]

Parameter	Value
Particle species	Design: ^4He ^1H acceleration possible
Circumference	35 m
Maximum beam rigidity	4.52 T*m
Maximum acceleration energies	^4He : 220 MeV/u ^1H : ~ 700 MeV (theoretically)
Beam intensity (particles per spill)	^4He : $8.2 \cdot 10^{10}$ ions ^1H : $2.6 \cdot 10^{11}$ protons
Ramp up time to maximum energy	650 ms
Energy switching time	200 ms
Possible operational modes	Multi-energy extraction, UHDR delivery

Bibliography

List of bibliography used within this Chapter of the Thesis is provided in **Appendix 1.17**.

Part I

**Investigations on FLASH effect
and
applications in light ion beam
therapy**

Main research object in Part I of the Thesis is the *FLASH* effect - a novel approach to improve biological and clinical outcomes of RT. Part I focuses on radiochemical interaction changes under UHDR irradiation and their possible role in *FLASH* effect, modelling and evaluation for application of *FLASH* effect with light ion beams and necessary dosimetric and technical requirements for corresponding UHDR delivery.

Chapter 3 presents literature review on hypotheses of *FLASH* effect mechanism, dosimetric parameter space of UHDR delivery and experimental results with light ion beams. Current state of research is analysed, identifying relevant existing research gaps as basis for Chapters 4 to 7.

Sufficient dose and DR threshold values are necessary to achieve *FLASH* effect. Chapter 4 presents a study on dose threshold modelling for light ion beams. A novel radiochemical approach is proposed to evaluate the scaling of *FLASH* effect dose threshold for different ion types. Comparison of different ion types for possible therapeutic application of *FLASH* effect is studied, by evaluating the influence of ion type on dose conformality and *FLASH* dose threshold.

Theoretical assumptions in the model presented in Chapter 4 are experimentally validated in Chapter 5. The Chapter presents experimental findings of radiochemical changes under UHDR irradiation with X-ray photon and electron beams, focusing on the role solvated electrons. Implications of experimental finding on possible UHDR effects with ion beams are assessed.

Chapters 6 and 7 focus on aspects of UHDR delivery with ion beams. Chapter 6 presents a novel pencil beam algorithm for calculation of dose and DR, as well as radiobiological and radiochemical parameters relevant for *FLASH* therapy, as proposed in model of Chapter 4. Accuracy of the algorithm is validated with respect MC simulations.

Chapter 7 explores different technical approaches for UHDR delivery with ion beams via a literature review-based comparative analysis. UHDR delivery challenges specific to ion beams are presented. Various possible approaches are compared based on the achievable treatment plan quality and technological complexity necessary for implementation.

Each Chapter finishes with conclusions and discussion on light ion beam application potential for *FLASH* therapy based on research findings. Throughout Part I, limitations of the presented studies are also discussed, suggesting necessary future research.

State of the Art analysis:

Hypotheses of *FLASH* effect mechanisms, role of radiochemistry and perspectives for ion beams

To build upon the knowledge on the various aspects of *FLASH* effect as relevant for the Thesis objectives and to identify existing research gaps, scientific literature review was performed. This Chapter outlines the methodology used for the literature review and presents a “state-of-the-art” analysis overview on relevant and recent research work on *FLASH* effect topic.

Firstly, Section 3.1 presents methodology used to perform the literature review, outlining the used data sources and search keywords.

Literature review findings are presented in Section 3.2. Section 3.2 is divided in multiple subsections covering the reviewed aspects of the *FLASH* effect and possibilities for future clinical implementation: mechanisms underlying the *FLASH* effect, role of radiochemical effects under UHDR irradiation with a focus on hydrogen peroxide as experimental measurement probe, dosimetric thresholds necessary to achieve *FLASH* effects, while also discussing possible role of beam temporal structure. Lastly, focus was given to review *in vitro* and *in vivo* biological studies of *FLASH* effect performed with ion beams - helium, carbon, and oxygen.

The Chapter concludes with Section 3.3, outlining main conclusions from literature review and identified research areas for the Thesis to address current gaps.

3.1. “State of the Art” analysis methodology

“State of the Art” analysis was based on scientific literature review. Search of scientific articles relevant to the analysis was performed using the following databases and browsing tools: *Google Scholar* and *PubMed* by the National Center for Biotechnology Information were used as primary sources, while *Scopus* and *ScienceDirect* - as secondary, where applicable. To include most research results, the time frame of article publication focused on the last 10 years - 2015 to 2025. Nevertheless, for historical perspective, additional articles were included in the analysis as necessary - search directly done by Author or citations included in primary articles.

Keywords used during the analysis as queries are summarized in **Appendix 2.1**. Analysis started with broad review articles, followed by focused searches on specific *FLASH* effect hypotheses, radiochemical studies performed under UHDR irradiation, *FLASH* effect dosimetric thresholds, impact of beam temporal structure and results achieved with UHDR ion beams - helium, carbon, and oxygen ions. Analysis included both modelling and experimental studies. After initial query, abstracts of scientific articles were analysed by Author, assessing the relevance for analysis.

After initial review, **112** scientific articles were used in the analysis.

Bibliography of this Chapter also includes references used in parts of literature review presented in respective **Appendix 2.2**.

3.2. Results of the “State of the Art” analysis

As introduced in Chapter 2., DR influence on effects for biological systems after exposure to ionizing radiation was first observed in 1959 [1], followed by similar findings in 1967 [2] and 1968 [3]. Initial findings in bacteria [1,3] and mammalian cells [2] were followed by few *in vivo* studies in mice model using pulsed low energy electron beams [4-8] in the period from 1970s to 1980s. *In vivo* experiments evaluated only normal tissue response, indicating reduced acute skin reactions for DRs higher than about 10 Gy/s and induction of hypoxic environment at high dose levels [4-6], though effects in tumour tissue were not studied. At the time, findings of decreased biological effect at high DRs were not explainable by existing radiobiological mechanisms, prompting development of relevant theories [9]. Already then, two main biophysical phenomena possibly contributing to the reduced biological effect were proposed [6,8] - directly quoting study of [6]:

“ ... results have been explained by local oxygen depletion or recombination of
ionizations and/or radicals ... ”

Despite these intriguing observations, no further studies followed for several decades on possible implementation of this radiobiological effect in clinical RT practice.

UHDR research was revitalized by the pivotal work of Favaudon et al. in 2014 [10], also first introducing the term “*FLASH* effect”. This pivotal study was the first to investigate and compare the effects of high doses (15 - 30 Gy) delivered at conventional DR (about 0.03 Gy/s) and UHDR (> 40 Gy/s delivered in less than 500 ms) on both healthy and tumour tissue. Term “*FLASH* effect” was used for the observed differential response [10] - the tumour control was maintained at same level for both DRs, though UHDR resulted in significantly reduced normal tissue complications - acute apoptosis of blood vessels, bronchi, smooth muscle and epithelial cells, as well long-term lung fibrosis. Discovery of *FLASH* effect has led to a surge of studies in several scientific domains over recent years - biological *in vitro* and *in vivo*, biophysical modelling, technological developments of UHDR delivery, dedicated dosimetry methods, and many others. Prospect of *FLASH* therapy is one of the most researched topics in modern RT due to the possibility of extended therapeutic window - decreasing NTCP and/or enabling strategies for dose escalation for improved TCP. Through continued research efforts, first clinical UHDR use for patient treatment has been reported in 2019, using a 5.6 MeV electron beam for treatment of T-cell cutaneous lymphoma [11]. From November 2020 to October 2021, first clinical trial - *FAST-01* - was conducted by the University of Cincinnati. High energy proton beams were used for treatment of bone metastasis in extremities for a cohort of 10 patients [12]. A continuation - *FAST-02* - was started in February 2023, focusing on bone metastasis in thorax, with an estimated completion in 2025 [13]. *FLASH* effect application for treatment in skin lesions is also assessed in clinical trials *IMPulse* and *Lance* held at University Hospital of Lausanne, using conventional megavoltage electron beams [14].

Despite the significant progress made and increasing number of on-going investigations, several open questions remain as crucial topics for future clinical translation of UHDR into *FLASH* therapy - some of which are discussed in this analysis. Mechanism of *FLASH* effect - induction of differential normal tissue sparing at UHDR - is one of the most crucial questions and critical for quantitative modelling. **Brief summary of literature review is provided in following sub-sections, while detailed literature review is provided in Appendix 2.2.** Current hypotheses of *FLASH* effect and their respective limitations are summarized in subsection 3.2.1 (in **Appendix 2.2.** – A.2.2.1). Additional focus is given for radical-radical recombination theory, outlining possible role of radiochemistry and supporting experimental studies in subsection 3.2.2 (in **Appendix 2.2.** – A.2.2.2). Parameter space - dose, dose level and beam temporal structure - of UHDR delivery necessary to induce *FLASH* effect is discussed in subsection 3.2.3 (in **Appendix 2.2.** – A.2.2.3). Finally, within the scope of the Thesis, focus is given on *FLASH* effect studies with ions heavier than protons in subsection 3.2.4 (in **Appendix 2.2.** – A.2.2.4), discussing the possible LET role in *FLASH* effect mechanisms.

3.2.1. Current hypotheses of *FLASH* effect: biophysical, radiochemical, and biological perspectives

First *in-vivo* experiments in 1970-1980s [1-7] prompted research into radiobiological mechanisms of UHDR. For the biological differential of *FLASH* effect, several hypotheses have been proposed - transient oxygen depletion, radical-radical recombination and others.

Molecular oxygen is crucial in biological effects via indirect action - influencing ROS production and fixating DNA damage [29]. Transient oxygen depletion hypothesis proposes rapid radiochemical consumption of oxygen during short delivery of high dose levels. In normal tissue, this would induce transient hypoxia (radioresistance) as oxygen diffusion from vasculature is slower [9,15]. Differential aspect of *FLASH* effect is theorized to be due to oxygen concentration differences within normal and tumour cells [9,15], though validity of this hypothesis has been under debate [9,15]. While oxygen is expected to play a crucial role, recent experimental work and modelling indicate that oxygen consumption alone is insufficient for *FLASH* effect at doses of 10 - 20 Gy, as observed via *in-vitro* and *in-vivo* studies [43,45].

Radical-radical recombination hypothesis also focuses on indirect action - water radiolysis and production of ROS and free radicals. Compared to conventional DR, UHDR produces high instantaneous concentrations of ROS and free radicals in localized volumes [9,15]. In such scenario, self-recombination is in competition with reactions of DNA damage - reducing concentration of ROS and free radicals, and possibly - cellular damage. Modelling study of [50] indicated role of peroxy radical ($\text{ROO}^\bullet$) concentration as metric for *FLASH* effect prediction. Biological differential between cancerous and normal cells is associated with varying oxygen levels or metabolism [9,15]. Despite attractive theoretical results [50], significant developments in basic *in-vivo* studies are necessary.

3.2.2. Radiochemistry under UHDR: hydrogen peroxide as probe for radical-radical recombination theory

While radical-radical recombination hypothesis is perspective explanation of *FLASH* effect mechanism, experimental validation is infeasible due to short lifetime of free radicals [9,15]. Hydrogen peroxide as long-lived water radiolysis product has been suggested as surrogate for measurements. Several studies have reported decreased production of hydrogen peroxide with increasing DR at pO_2 levels of 4 or ~21% [41,61-67]. In addition, decreased oxygen consumption at UHDR has been observed [62,65]. These trends indicate DR-dependent radiochemistry, possibly attributable to radical-radical recombination in water radiolysis.

Almost all MC simulation studies [68-75] are in contrast with experimental findings, indicating increased hydrogen peroxide production, possibly attributable to

other reactions apart from recombination. This underscores the need to improve MC simulation models and/or methodology of the experimental measurements.

Results of experimental studies performed in water cannot be extrapolated to *in-vivo* systems due to differences in chemical environment and interactions mechanisms. Future *in-vivo* studies are necessary to evaluate biological relevance of radical-radical recombination.

3.2.3. Dosimetric thresholds of *FLASH* effect. Impact of beam temporal structure

Table 3.1. (reproduced from [17]) summarises typical temporal beam parameters for two most used modalities [9] in research of *FLASH* effect: electrons and protons.

Table 3.1.

Summary of main temporal characteristics* of electron and proton beams used for
UHDR delivery in *FLASH* effect research

Beam parameter	Conventional delivery		UHDR	
	<i>electrons</i>	<i>protons</i>	<i>electrons</i>	<i>protons</i>
Average dose rate	0.01 Gy/s	0.1-0.9 Gy/s	$\geq 30\text{-}40$ Gy/s	90-100 Gy/s
Pulse dose rate	1000 Gy/s	-	$\geq 10^6$ Gy/s	-
Dose per pulse	0.001 Gy	9 - 20 Gy	≥ 1 Gy	10-20 Gy
Length of the pulse	$\sim 1 \mu\text{s}$	-	$\sim 1.8 \mu\text{s}$	-
Number of beam pulses	~ 1000	1	≤ 20	1
Total irradiation time	~ 360 s	100 s	100 - 200 ms	$\sim 1 - 100$ ms

*absolute values might differ between studies, though the order of magnitude remains

Results comparing the influence of average DR and instantaneous pulse DR on UHDR radiochemistry and biological *FLASH* effect so far are conflicting [76-79], with average DR typically indicated as main determinant with a threshold of ~ 40 Gy/s. *FLASH* effect also exhibits absorbed dose level threshold. Typically, threshold of about 8-10 Gy has been reported [9], with sparing magnitude increasing with absorbed dose level and saturating at around 40-50 Gy [88]. Clinically, high dose levels and hypofractionation is expected as necessity to benefit from *FLASH* effect. Maintaining *FLASH* effect with fractionated and multi-field delivery with relatively long pauses remains under debate [90].

3.2.4. Perspectives of *FLASH* effect application in light ion beam therapy

Majority of research into *FLASH* effect has been performed with electrons and protons due to infrastructure availability [9]. With limited infrastructure for ions heavier than protons (high LET), only 10 *in-vitro* and *in-vivo* studies have been reported:

- **3 with helium ions:** 2 *in-vitro* [95-96] and 1 *in-vivo* [97];
- **6 with carbon ions:** 4 *in-vitro* [98-101] and 2 *in-vivo* [102-103];
- **1 with oxygen ions:** study of [104]: both *in-vitro* and *in-vivo* experiments.

LET directly affects proposed hypothetical *FLASH* effect mechanisms, with modelling suggesting reduced sparing with heavier ions, though current *in-vitro* and *in-vivo* evidence is not conclusive. Required dosimetric parameter space for equivalent *FLASH* effect sparing magnitude could differ for heavier ions, compared to protons or electrons. Possible clinical use of ion *FLASH* can be evaluated only after systematic *in-vivo* studies on LET dependency.

3.3. Conclusions and identified research areas

Chapter 3 presented literature review based “state-of-the-art” analysis on *FLASH* effect topicality as relevant for the Thesis scope and objectives: mechanisms underlying the *FLASH* effect, role of radiochemical effects under UHDR irradiation, a hydrogen peroxide as experimental measurement probe for radical-radical recombination theory, dosimetric thresholds and beam temporal structure necessary to achieve *FLASH* effect and review of *in vitro* and *in vivo* biological studies of *FLASH* effect performed with ion beams - helium, carbon and oxygen.

Main conclusions from the presented literature review based “state-of-the-art” analysis can be summarized as:

1. Several biophysical and biological hypotheses have been proposed to explain the underlying mechanisms of differential *FLASH* effect sparing. From biophysical perspective, theories of transient oxygen depletion and radical-radical recombination are main proposed mechanisms.
2. Both hypotheses on biophysical mechanisms underlying *FLASH* effect have faced inherent limitations in experimental validation:
 - 2.1. recent *in-silico*, *in vitro* and *in vivo* studies indicate that change in cellular oxygen concentration induced by transient oxygen depletion is insufficient to account for *FLASH* effect sparing at investigated dose levels of 10 - 50 Gy;
 - 2.2. while mathematical modelling studies of radical-radical recombination has indicated excellent agreement with *in vitro* and *in vivo* data, hypothesis needs to be further developed to account for differential nature of the effect and is inhibited by infeasible experimental validation.

No unified mechanism for *FLASH* effect exists currently.

3. Measurements of hydrogen peroxide production changes with respect to DR have been proposed as probe for radical-radical recombination hypothesis. While hydrogen peroxide cannot reliably characterise UHDR response for whole ROS production chain, it provides valuable insights on underlying radiochemistry phenomena.
4. Several experimental studies [41,61-67] have observed significant reduction of hydrogen peroxide production with increasing DR in water and biologically relevant media. Majority of MC simulation studies [68-74] have observed the opposite effect, indicating the role of radiolysis interactions competing with radical-radical recombination, necessity of mathematical modelling improvements and harmonization of experimental set-up. Nevertheless, findings via hydrogen peroxide production yield measurements cannot be directly translated to biological systems, necessitating future *in vivo* studies.
5. DR parameter space necessary to induce *FLASH* effect varies between beam temporal structures:
 - 5.1. for continuous and quasi-continuous beams, average DR of ~40 Gy/s has been reported as threshold value;
 - 5.2. for pulsed beam: in addition to average DR definition, parameters as dose per pulse, pulse length, pulse repetition rate, and overall irradiation time need to be considered.

Evidence on comparison between average and instantaneous DR as main determinant for *FLASH* effect sparing is inconclusive.

6. Threshold dose value of 8-10 Gy has been reported as necessary to induce *FLASH* effect for electron and proton beams, though sparing magnitude (DMF) increases with increasing dose levels up to 50 Gy.
7. Due to millisecond delivery timescale of UHDR and possibly underlying mechanisms of *FLASH* effect, dose fractionation and multi-beam delivery need to be further evaluated in future *in vivo* studies as current findings indicate possible reduction of sparing magnitude.
8. With limited particle accelerator infrastructure for ions heavier than protons, *FLASH* effect research with ions heavier than protons is currently limited to 10 *in vitro* and *in vivo* studies: 3 with helium, 6 with carbon and 1 with oxygen ions. While findings of these studies have indicated clear impact of pO₂ and absorbed dose level, LET influence on *FLASH* sparing magnitude is inconclusive.
9. Despite the growing evidence for *FLASH* effect induced by ions heavier than protons, possible clinical use of ion can be evaluated only after systematic *in vivo* studies on LET dependency.
10. Proposed biophysical mechanisms of *FLASH* effect are directly affected by LET, with modelling studies suggesting reduced sparing for heavier ions. Thus, dosimetric

parameter space to achieve same *FLASH* effect sparing could be different for heavier ions compared to protons or electrons.

Based on the presented literature review based “state-of-the-art” analysis and existing research gaps, following research areas have been identified to be addressed within Chapters 4 to 7:

- *expected LET dependency; lack of FLASH effect dosimetric parameter space investigations for ions heavier than protons* - evaluation of dosimetric parameter scaling for ions heavier than protons based on biophysical hypotheses of *FLASH* effect (Chapter 4);
- *disagreement between hydrogen peroxide production DR dependency experimental measurements and MC simulations, inconclusive evidence on role of average and instantaneous DR as main determinant for FLASH effect sparing, inconclusive role of competing radiochemical interaction within radical-radical recombination theory*: evaluation of experimental hydrogen peroxide production DR dependency in presence of chemical scavengers to identify competing radiochemical interactions and comparison between different beam temporal structures (Chapter 5);
- *technical limitations of particle accelerators for ions heavier than protons to deliver UHDR, inconclusive evidence on fractionated and multi-field delivery for preserving FLASH effect sparing*: evaluation of clinical beam delivery methods for light ion beams, while ensuring UHDR and sufficient *FLASH* effect conditions (dose level, DR and multi-field delivery aspects) (Chapter 7) and development of necessary tools for future quantitative evaluation of such deliver methods, while incorporating biophysical phenomena in estimations (Chapter 6).

Bibliography

List of bibliography used within this Chapter of the Thesis is provided in **Appendix 2.3**.

***FLASH* effect dose threshold modelling for ion beams**

Chapter 4 presents modelling study on dosimetric thresholds, particularly the dose threshold, necessary to achieve the *FLASH* effect. Novel radiochemistry-based modelling approach for dose threshold estimation and scaling is presented, along with dose distribution optimization approach to account for it. Dose thresholds for *FLASH* effect are assessed for 12 different ion types, in various simplified treatment geometries and *FLASH* effect prescription strategies. Considering necessary *FLASH* conditions, dose conformality and RBE, ion types suited for *FLASH* effect application are suggested.

Modelling studies presented in this Chapter and throughout the Thesis have used MC simulations. In Section 4.1., overview of MC approach principles is given, presenting the simulation environment and physics model used throughout the Thesis.

Section 4.2. describes the specific modelling approaches used for the study in this Chapter: definition of simulation geometry, parameter scoring, calculation of RBE, dose distribution optimization process and the implementation of the proposed *FLASH* effect dose threshold estimation. Analysis methods for evaluation of resulting dose distributions and *FLASH* effect conditions are also presented. Uncertainty sources of MC simulations are identified, with additional sources discussed at the end of the Chapter.

Findings of the modelling study are presented in Section 4.3. Conclusions of this Chapter are presented in Section 4.4, discussing the possible application of different ion types for *FLASH* therapy and identifying possible limitations of the current work.

Contributions of the Author: All work presented in this Chapter has been performed solely by the Author, indicating used literature sources where applicable.

Approbation of the results presented in this Chapter:

- Poster presentation at 2nd *FLASH* Radiotherapy and Particle Therapy conference (FRPT'22) in Barcelona, Spain, 2022
K.Pałskis, M.Vretenar, T.Torims, M.Sapinski, J.Seco “Assessing particle *FLASH*-RT effectiveness by modelling solvate electron production dependency on particle LET”
- Poster presentation at 61st Annual Conference of the Particle Therapy Cooperative Group (PTCOG'23) in Madrid, Spain, 2023
K.Pałskis, T.Torims, M.Vretenar, M.Sapinski, J.Seco “*FLASH*-RT dose threshold effect estimation for particle beams by modelling solvate electron production dependency on particle LET 3D distribution”
- Poster presentation at 3rd *FLASH* Radiotherapy and Particle Therapy conference (FRPT'23) in Toronto, Canada, 2023
K.Pałskis, T.Torims, M.Sapinski, M.Vretenar, J.Seco “The best particle for ion-beam based *FLASH*: investigating the compromise between threshold dose and dose conformality”

4.1. Monte Carlo simulation environment used

Within Chapter 4. and multiple following ones, MC simulations are used for modelling of radiation transport and scoring of physical quantities. MC approach is widely used for various applications in RT, including treatment machine modelling, dose distribution calculation of patient treatment plans, radiation detector characterization, and others [1-2]. This Section briefly introduces the specific simulation environment and physics model settings used throughout the Thesis. MC environment settings presented here are repeatedly used in subsequent Chapters of the Thesis, unless stated otherwise, when specific adjustments have been made for the particular study. Additional information on principles of MC approach and simulation environment is given in **Appendix 3.1.**

Geant4 (v. 11.0.1.) has been used for Monte Carlo (MC) simulations of radiation transport and scoring of physical quantities [7]. In *Geant4*, physical processes are mathematically described by various models, each tailored for a specific energy range and application, and are unified in, so called, physics lists. Physics lists best suited for applications in PT and IBT were chosen based on *G4-Med* group report [8] and are summarized in Table 4.1. Simulation runs used 10^6 to 10^8 primaries (uncertainty $< 1\%$), step limit of 1 mm and range cut of 0.5 mm - specific adaptations given in respective Chapter.

Table 4.1.

Geant4 physics lists used for the MC environment in the scope of the Thesis

Physics lists used	
Electromagnetic physics	G4EmStandardPhysics_option4, G4EmExtraPhysics
Hadronic physics	G4HadronPhysicsQGSP_BIC_HP, G4HadronElasticPhysicsHP, G4IonBinaryCascadePhysics, G4StoppingPhysics
Additional	G4DecayPhysics, G4RadioactiveDecayPhysics, G4NeutronTrackingCut

All MC simulations performed in the Thesis have been done using the computational resources of High-Performance Computing Centre of Riga Technical university.

4.2. Modelling and analysis methodology

This Section provides brief summary of the modelling and analysis methodology used within the study, while additional methodological details are given in **Appendix 3.2.**

Relevant dosimetric parameters were scored in a $\emptyset 40$ cm $\times$ 45 cm water cylinder for 12 different ions - ^1H , ^2H , ^3He , ^4He , ^6Li , ^7Li , ^9Be , ^{10}B , ^{12}C , ^{14}N , ^{16}O and ^{20}Ne . Set of initial kinetic energies was chosen for clinically relevant ranges in water - from 25 to

350 mm in steps of 1 mm. Scored dosimetric parameters included energy deposition (dose), dose-weighted LET, dose averaged saturation-corrected specific energy z_{1D}^* and solvated electron production yield (G-value) derived from LET.

In the Thesis, radiochemical hypothesis was developed for *FLASH* effect dose threshold, using solvated electron concentration as surrogate metric. At UHDR, high instantaneous concentrations of solvated electrons and hydroxyl radicals shift competing reaction kinetics. This potentially leads to saturation or decrease of hydroxyl radical and hydrogen peroxide concentration under UHDR - two chemical species with significant cellular DNA damaging capacity. Detailed analysis on relevant chemical interactions is given in Chapters 4 and 5 of the Thesis.

Critical concentration of solvated electrons is taken as a surrogate metric of cellular DNA damage saturation and calculated as:

$$[e^-_{aq}] = C \times G_{e^-_{aq}} \times D_{phys} \left[\frac{mol}{l} \right] \quad (4.1)$$

where C corresponds to unit conversion constant - 1.04×10^{-7} , $G_{e^-_{aq}}$ is the G-value of solvated electrons (in molecules/100 eV) and D_{phys} is the physical dose level. Mathematical threshold value was calculated from experimental *in-vitro* studies for computations only - $0.375 \mu\text{mol/l}$ subject to several biological factors.

For mathematical implementation of the model and assessment of *FLASH* effect dose threshold, spread-out Bragg peaks (SOBP) were optimized for simplified tumour geometries (varying size and depth) to uniform biologically effective dose. mMKM was used for RBE modelling, with input parameters calculated by Author and validated with relevant literature [30]. To implement *FLASH* effect dose threshold, solvated electron concentration was constrained at a specific *FLASH* effect prescription point (varied between surface, mid-plateau and near SOBP) to the threshold value. Schematic overview is given in Figure 4.1.

For quantitative assessment, physical dose level at *FLASH* prescription point and average biologically effective dose in simulated tumour region were extracted from optimized SOBP distributions, as well as dose conformity metrics - peak-to-plateau ratios, conformity index and gradient index for several isodose levels.

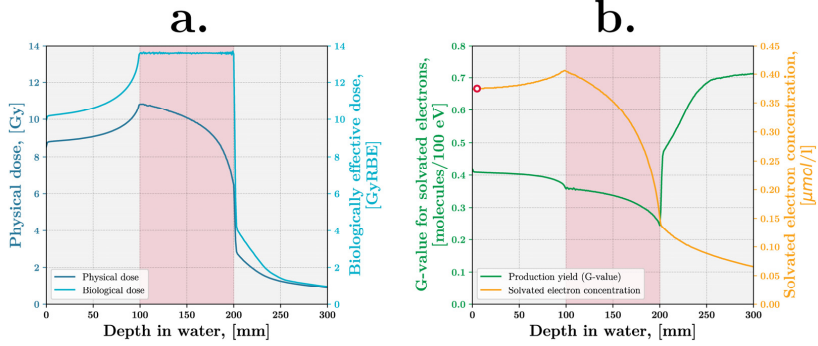


Figure 4.1. Schematic overview of biologically effective dose driven SOBP optimization process, incorporating *FLASH* effect dose threshold

4.3. Results of the modelling

Calculate input parameters of mMKM used for calculations in this Chapter are presented in **Appendix 3.3**.

Influence of ion type on spatial distribution of solvated electron concentration

Surrogate metric - solvated electron concentration - is used for *FLASH* effect dose threshold estimation within the model proposed. As solvated electron concentration depends on the physical dose level and solvated electron G-value (dependent on particle LET), the interplay between these parameters is crucial. Changes in spatial distributions of both parameters would impact the distribution of solvated electron concentration and thus - conditions for *FLASH* effect. Figure A.3.7. of **Appendix 3.4**. presents calculated solvated electron concentration distributions for all 12 ion types studied for idealized SOBP of a shallow tumour. Idealized SOBP optimization was performed with *FLASH* effect dose threshold estimation implemented as discussed in Methodology section. Data presented in Figure A.3.7. of **Appendix 3.4** correspond to *FLASH* prescription central axis at 5 mm depth. Shallow scenario, with distal edge at 150 mm depth is illustrated for tumour of size 100x100x100 mm. For clarity, presented solvated electron concentration distributions (1 μs after irradiation) are achieved by optimization of the physical dose level at *FLASH* prescription point such that the estimated threshold concentration of 0.375 μmol/l is reached.

Analysing data presented in Figure A.3.7. of **Appendix 3.4**, it can be observed that the region with solvated electron concentration above the estimated threshold value decreases with increasing mass of the ion. In the plateau region (corresponding to normal tissue region in the simulated scenario), comparable coverage of threshold solvated electron concentration be observed for protons, both helium and lithium isotope ions and beryllium-9 ions. For heavier ions as boron-10 and carbon-12, solvated electron concentration gradually decreases at irradiation field edges. Considering heaviest ions,

nitrogen-14, oxygen-16 and neon-20 ions, significantly higher solvated electron concentration loss can be observed, also on central axis. In the theoretical model considered, loss of solvated electron concentration would correspond to loss of radiochemical conditions necessary to achieve *FLASH* effect sparing, possibly reducing it. Observed solvated electron concentration loss is attributable to increased LET of heavier ions, reducing solvated electron G-value. In-depth analysis on observed phenomena due to interplay of RBE, physical dose, LET and solvated electron production yield is provided as last subsection of Results section.

Even more pronounced differences between ion types can be observed by analysing solvated electron concentration distribution within the tumour region. Solvated electron concentration above threshold value in most of the tumour volume can be observed only for proton beams. With increasing mass of the ion, volume covered by solvated electron threshold concentration (or above) gradually decreases in the tumour region, reaching negligible level for boron-10 ions and heavier. Gradual decrease of solvated electron concentration can be observed in the distal part of the simulated tumour volume. This attributable to interplay between physical dose and solvated electron production yield depth variations. To achieve uniform biologically effective dose with ion beams, spatial variation of RBE must be accounted for - as RBE increases with increasing depth, correspondingly - physical dose level must decrease with depth (as illustrated in Figure 4.1) with magnitude increasing for heavier ions. Heavy ions are characterized by high-LET in the tumour region, increasing with depth - solvated electron G-value is decreased. As both quantities of Equation 4.1. decrease, resulting solvated electron concentration decreases as observed in Figure A.3.7. of **Appendix 3.4**.

As LET, solvated electron yield and physical dose distribution would be affected by tumour geometry, Figure 4.2 illustrates calculated solvated electron concentration distributions for all 12 ion types in deep-seated tumour scenario. Data presented in Figure 4.2. correspond to simulated tumour with distal edge at 300 mm depth, with all the other SOBP optimization parameters, including *FLASH* prescription point position, being the same as for data illustrated in Figure A.3.7. of **Appendix 3.4**.

Significant influence of simulated tumour depth on solvated electron concentration distribution can be observed by comparative analysis between data presented in Figures 4.2 and A.3.7. of **Appendix 3.4**. Comparable volumetric coverage of threshold solvated electron concentration can be observed for lightest particles studied - protons, deuterons, helium-3 and helium-4 ions. Differences in solvated electron concentration volumetric coverage can be observed already for lithium-6 and lithium-7 ions between shallow and deep-seated tumour scenarios. Threshold solvated electron concentration coverage is lost near the field edges, attributable to slight off-axis LET increase, reducing solvated electron G-value. Significant decrease of solvated electron concentration can be observed at central depths of plateau region. This is attributable to the shape of physical dose profile due to primary lithium ion (same for heavier ions) fluence loss with increasing depth. For deep-seated tumours, slight decrease in physical

dose depth profile at shallow depths can be observed. Such reduction along with gradually increasing LET (reduced solvated electron G-value) results in decreased solvated electron concentration as per Equation 4.1.

Most significant differences can be observed for ions as beryllium-9 and heavier. In deep-seated tumour scenario, volumetric coverage of threshold solvated electron concentration is completely lost, localized just at *FLASH* prescription point. As heavy ions experience nuclear fragmentation and primary particle fluence loss, the resulting physical dose gradually decreases with increasing depth. Together with LET increase and associated solvated electron G-value decrease, this results in solvated electron concentration decrease with depth as observed in Figure 4.2. Observed phenomena for heavy ions could be offset by choice of different *FLASH* prescription point location as will be discussed further.

In addition to depth, impact of another simulated tumour geometrical parameter - tumour size - was evaluated. Change of tumour size affects physical depth dose distribution, as well as LET distribution, thus solvated electron G-value, within the irradiated volume. Impact of deep-seated tumour size on the resulting solvated electron concentration distribution is illustrated **Appendix 3.5** for protons and helium-4 ions, respectively. With more detailed discussion provided in **Appendix 3.5.**, the impact of tumour size considered is less pronounced as change in depth localisation. Nevertheless, significant differences in volumetric coverage of threshold solvated electron concentration can be observed for small tumour volumes considered, due to loss of LSE and changes in particle energy spectrum and LET.

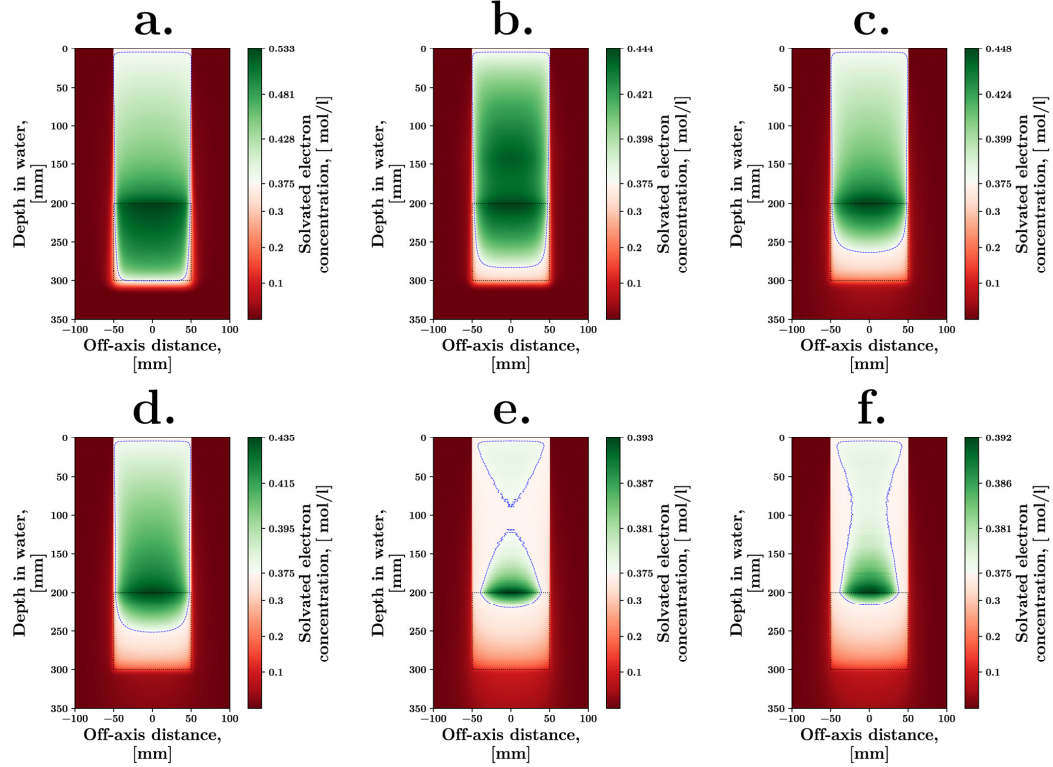


Figure 4.2. Spatial distribution of solvated electron concentration generated by different ion types (deep-seated tumour) Data illustrated for the central plane, SOBPs optimized for 100×100×100 mm tumour with distal edge at 300 mm depth. *FLASH* prescription point - at 5 mm depth. Blue dashed line indicates the isoline of threshold solvated electron concentration - 0.375 $\mu\text{mol/l}$, black dashed line - the location of simulated tumour. Data given for protons (Subfigure (a)), deuterons (Subfigure (b)), ^3He (Subfigure (c)), ^4He (Subfigure (d)), ^6Li (Subfigure (e)) and ^7Li (Subfigure (f)) ions.

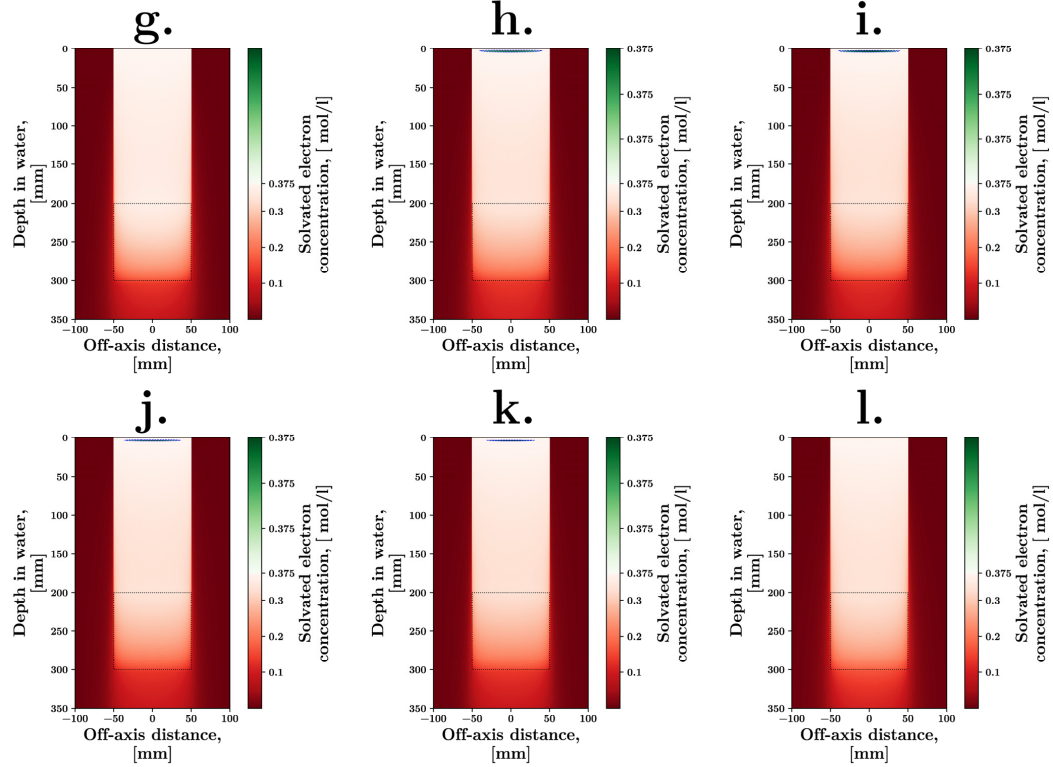


Figure 4.2. cont. Spatial distribution of solvated electron concentration generated by different ion types (deep-seated tumour) Data illustrated for the central plane, SOBPs optimized for $100 \times 100 \times 100$ mm tumour with distal edge at 300 mm depth. *FLASH* prescription point - at 5 mm depth. Blue dashed line indicates the isoline of threshold solvated electron concentration - $0.375 \mu\text{mol/l}$, black dashed line - the location of simulated tumour.

Data given for ^9Be (Subfigure (g)), ^{10}B (Subfigure (h)), ^{12}C (Subfigure (i)), ^{14}N (Subfigure (j)), ^{16}O (Subfigure (k)) and ^{20}Ne (Subfigure (l)) ions.

Influence of *FLASH* “prescription point” on spatial distribution of solvated electron concentration

Solvated electron concentration has significant variation with respect to depth in the irradiated object due to interplay between physical dose and solvated electron G-value (arising from LET) distributions. With gradient of solvated electron concentration observed, it could be theorized that volumetric coverage of threshold concentration would be affected by depth of *FLASH* effect prescription point in the proposed model. For different *FLASH* prescription point location, varying solvated electron G-value can be expected, which needs to be accounted for by a change in physical dose level delivered according to Equation 4.1. Three *FLASH* effect prescription point locations were considered in the simulated “normal tissue” region - near the surface, mid-plateau and near to the proximal edge of SOBP. The impact of *FLASH* effect prescription point on threshold solvated electron concentration distribution for helium-4 and carbon-12 ions is given in **Appendix 3.6**.

Comparatively analysing the data for light (helium-4, Figure A.3.10. of **Appendix 3.6.**) and heavier ions (carbon-12, Figure A.3.11. of **Appendix 3.6.**), different influence of *FLASH* prescription point location can be observed. In case of helium-4 ions, threshold solvated electron concentration volumetric coverage is reduced for increasing depth of *FLASH* prescription point. This is attributable to solvated electron concentration as a function of depth for light ions - physical dose for light ions slightly increases with increasing depth, while LET increase is low compared to heavier ions - less reduction of solvated electron G-value. Overall - solvated electron concentration is increasing with depth for light ions. This holds true for ions lighter than beryllium-9. With the increasing gradient of solvated electron concentration, deeper *FLASH* effect prescription point corresponds to higher concentration level for threshold normalization during optimization - as deeper *FLASH* effect prescription point corresponds to higher solvated electron concentration level relative to other positions, the respective volumetric coverage is reduced.

Observed effect is reversed for beryllium-9 and heavier ions. For heavier ions, physical dose slightly decreases with increasing depth due to primary particle fluence loss via nuclear interactions. The significant LET increase with depth for heavier ions reduces solvated electron production yield, together resulting in decreased solvated electron concentration profile with respect to depth in irradiated object. Deeper *FLASH* effect prescription point corresponds to lower (with respect to other positions) solvated electron concentration level used for threshold normalization - volumetric coverage of threshold concentration is increased upstream of the prescription point.

Described phenomena and interplay with *FLASH* prescription point depth are also illustrated for central axis solvated electron concentration in Figures 4.3. and A.3.12. of **Appendix 3.6**. Figure A.3.12. of **Appendix 3.6**. illustrates the impact of *FLASH* prescription point depth in shallow tumour scenario, while Figure 4.3 - previously discussed deep-seated tumour scenario. Data are given for all 12 ion types considered.

Data in Figure 4.3. re-iterate the previously described interplay between *FLASH* prescription point depth and solvated electron concentration gradient with respect to depth. In a shallow tumour scenario, as indicated in Figure A.3.12. of **Appendix 3.6.**, almost all ion types considered exhibit increasing solvated electron concentration gradient, thus following similar trend as light ions in deep-seated tumour scenario. Only significant difference can be observed for heaviest ions considered - neon-20. As the increase of gradient is relatively low, the resulting dependency on *FLASH* prescription point depth is similar to lithium ions in deep-seated tumour scenario.

Influence of ion type on *FLASH* effect dose threshold and resulting treatment dose level

This subsection focuses on the physical dose level necessary to achieve volumetric coverage of threshold solvated electron concentration indicated previously. As indicated in Equation 4.1. and Figure 4.1., the developed model optimizes the physical dose level at *FLASH* effect prescription point such that threshold solvated electron concentration is reached. For heavier ions, higher LET values are expected, reducing solvated electron G-value. Thus, higher physical dose levels could be necessary for heavy ions to maintain thresholds condition at *FLASH* prescription point via Equation 4.1. Figure 4.4. summarizes calculated physical dose levels to reach *FLASH* effect threshold at prescription point for different ion types. Presented data also illustrate the influence of tumour geometry - depth and size - and *FLASH* effect prescription point depth. Physical dose level values are given relative to protons, as absolute value of threshold solvated electron concentration in this work is computational value in current iteration of the model and would depend on various biological factors in the realistic scenario. Data provided in Figure 4.4. serve to provide estimates of *FLASH* effect dosimetric condition scaling between the different ion types.

As expected by solvated electron concentration definition in Equation 4.1 and solvated electron production yield reduction, Figure 4.4. illustrates an increase of physical dose necessary to deliver for heavier ions to achieve *FLASH* effect. Discussion on how the scaling could be considered for both absolute dose level and the DR necessary for *FLASH* effect is presented at the end of this Chapter. As an example, for deep-seated 100×100×100 mm tumour (Subfigure (d)) with *FLASH* effect prescription point at 5 mm depth, about 1.19 and 1.78 times higher physical doses would be necessary to achieve *FLASH* effect according to the developed model with helium-4 and carbon-12 ions, respectively, compared to protons. For heaviest studied ion type - neon-20, the necessary increase is even higher - 2.88 times.

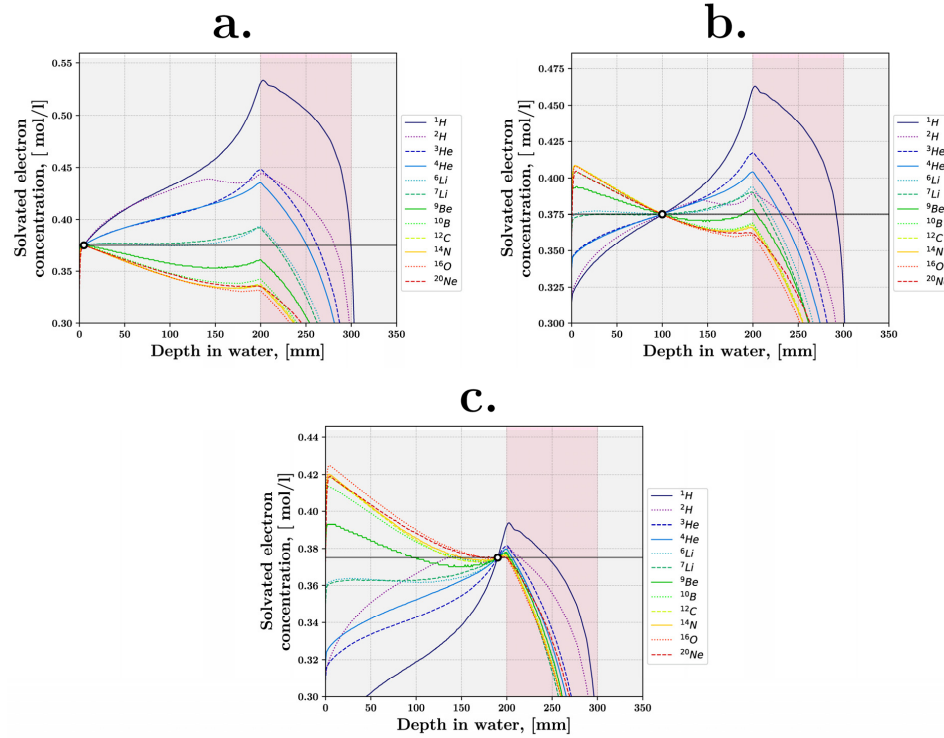


Figure 4.3. Central axis distribution of solvated electron concentration generated by different ion types with varying *FLASH* prescription point depth (deep-seated tumour)

SOBP optimized for 100×100×100 mm tumour with distal edge at 300 mm depth. Black line indicates the threshold solvated electron concentration - 0.375 $\mu\text{mol/l}$, red shaded region - the location of simulated tumour. *FLASH* prescription point location indicated by the black marker.

Data given for *FLASH* prescription point depths of 5 mm (Subfigure (a)), mid-plateau at 100 mm (Subfigure (b)) and 5 mm proximal to tumour at 195 mm (Subfigure (c))

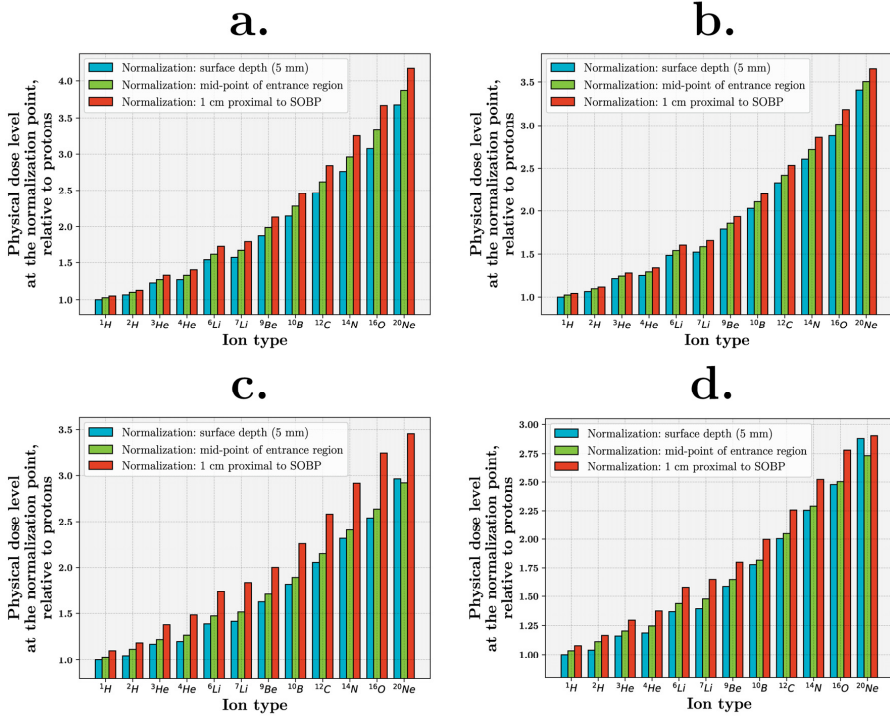


Figure 4.4. Physical dose level - *FLASH* effect dose threshold - at the prescription for different ion types, with varying *FLASH* prescription point depth and simulated tumour geometries

Physical dose levels given as relative values in comparison to protons in each simulated tumour geometry scenario with a *FLASH* prescription point at 5 mm depth.

Data for shallow tumours (distal edge at 150 mm) given in Subfigure (a) for size of 50×50×50mm and in Subfigure (b) - for 100×100×100 mm. Data for deep-seated tumours (distal edge at 300 mm) given in Subfigure (c) for size of 50×50×50mm and in Subfigure (d) - for 100×100×100 mm.

Impact of *FLASH* prescription point depth is also observed and attributable to higher LET at larger depths, reducing solvated electron G-value, necessitating higher physical dose delivered. LET variation with depth is higher for heavier ions, deep-seated and smaller tumours, reflected in the *FLASH* effect threshold dose variation in Figure 4.4. As example, for protons, comparing surface and near SOBP positions of *FLASH* prescription point, 5.1% and 4.1% increase of physical dose is necessary to maintain threshold solvated electron concentration in the latter scenario for 50×50×50 and 100×100×100 mm tumours with distal edge at depth of 150 mm. If the same tumour size has a distal edge at depth of 350 mm, 10.2% and 7.7% increase is necessary, respectively. Considering helium-4 ions, the necessary additional physical dose increase at prescription point near SOBP with respect to surface location for the 4 geometries is respectively

10.4%, 6.9%, 23.7% and 15.8%. For carbon-12 ions, the additional increases are 14.5%, 8.4%, 24.3% and 12.3%. Additional details on geometry impact are given in **Appendix 3.7**.

If an absolute value of 10 Gy is considered as *FLASH* effect threshold, according to the proposed scaling model, around 12 - 15 Gy would be necessary for helium-4 ions to reach the same sparing magnitude, while for carbon-12 ions - 20 - 28 Gy, depending on the considered tumour geometry and prescription point depth. These values are delivered at the *FLASH* effect prescription point in normal tissue, with biologically effective dose possibly even slightly higher, though the interplay between RBE and *FLASH* sparing is yet understudied. Considering the dose level at *FLASH* prescription point, an even higher biologically effective dose level would be delivered in the tumour - around 15 - 20 GyRBE for helium-4 ions and 25 - 40 GyRBE for carbon-12 ions, as simulated in this work for the different tumour geometries and *FLASH* prescription point locations. **Appendix 3.8**. summarizes the calculated average biologically effective dose levels within the simulated SOBP to reach *FLASH* effect at prescription point for different ion types. Biologically effective dose levels were evaluated based on RBE calculated by LQM, validity of which is discussed at the end of this Chapter.

Similarly to physical dose threshold level at *FLASH* effect prescription point, an increase of resulting biologically effective dose in the tumour can be observed for increasing ion mass. Though, the impact of tumour geometry and *FLASH* prescription point location is different compared to *FLASH* dose threshold level. This is attributable due to additional influence factors - peak-to-plateau ratios of different ion types, resulting SOBP dose distribution, spatial variation of RBE and RBE dependency on dose level. The main aspect to be noted - there is a different impact of prescription point depth between ions lighter or heavier than beryllium, attributable to previously discussed differences in solvated electron gradient with respect to depth, with additional details given in **Appendix 3.8**.

Summarizing, proposed model suggests that for increasingly heavier ions, higher physical dose levels are necessary in the normal tissue to achieve the same level of *FLASH* effect sparing, with the resulting biologically effective dose levels in the tumour also increased. The increase would be considerably low for helium and lithium ions with respect to protons - on average 1.49 and 1.54 times higher, respectively, for physical dose threshold and 1.59 and 1.65 times higher for biologically effective dose in the tumour. For heavier ions as carbon-12, the increase would be significant - 2.57 times for *FLASH* threshold and 3.04 times for tumour dose level. Observed *FLASH* effect condition scaling by the proposed model would suggest the use of dose levels higher than clinical practice for heavy ion *FLASH* application.

Influence of ion type on dose conformality

Another important aspect to consider for *FLASH* effect application with light ions is the achievable dose conformality with the different ion types. For clinical

application, combination of biological sparing via *FLASH* effect with low dosimetric thresholds and improved dose conformality would ensure improved normal tissue sparing. For comparison of ion types, biologically effective dose distributions, when *FLASH* effect dose threshold is considered during the optimization process, are illustrated in Figure 4.5. Data are provided for deep-seated tumour of 100×100×100 mm size.

The general trends of ion dependency of dose conformality observed in Figure 4.5. are in line with the theoretical reasoning provided in Chapter 2. With increasing ion mass:

- lateral scattering via MCS is reduced, thus improved penumbra characteristics for lateral conformality;
- range straggling is reduced, thus improving the high dose conformality at the proximal and distal edge of the tumour;
- nuclear fragmentation increases, thus increasing the intermediate and low dose levels distally to the tumour.

Additional aspect needs to be considered, especially for deep-seated tumour scenario, associated with higher physical dose levels necessary for *FLASH* effect application. Comparing physical dose distributions of protons and carbon-12 ions, the peak-to-plateau ratio of SOBP dose distribution is better for protons. Nevertheless, carbon-12 ions have significant RBE differential between the tumour and normal tissue region compared to protons. For biologically effective dose distribution and considering RBE differential, significantly improved peak-to-plateau ratio for carbon-12 ions is observed with respect to protons. This holds true for relatively low dose levels considered for routine clinical use - about 2 - 5 GyRBE. For *FLASH* effect use, as indicated previously, significantly higher dose levels need to be delivered. At higher dose levels, RBE is reduced as discussed in Chapter 2, possibly affecting RBE differential. This is clearly illustrated by Figure 4.5. as higher relative biologically effective dose levels at the entrance and mid-plateau are observed for ions heavier than beryllium, compared to protons and helium ions.

Described phenomena can also be affected by tumour geometry irradiated, as illustrated by biologically effective dose distributions for protons, helium-4 ions and carbon-12 ions for varying simulated tumour sizes provided in **Appendix 3.9**.

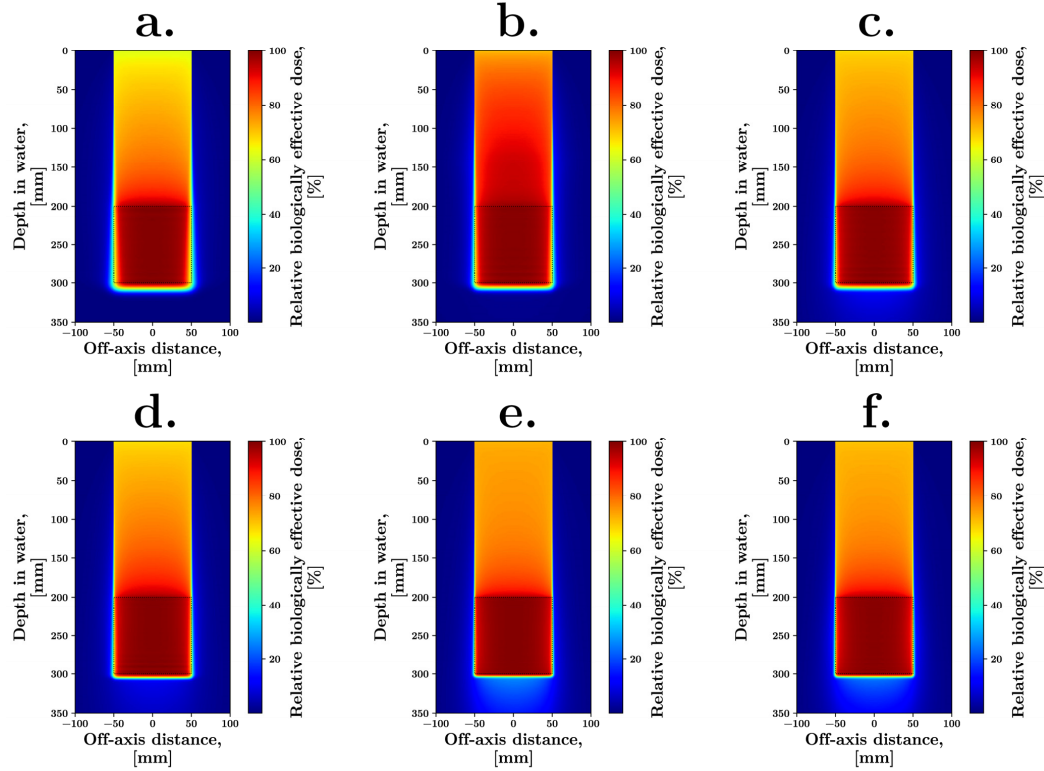


Figure 4.5. Relative biologically effective dose spatial distributions of different ion types (deep-seated tumour)

Data illustrated for the central plane, SOBPs optimized for $100 \times 100 \times 100$ mm tumour with distal edge at 300 mm depth. *FLASH* prescription point - at 5 mm depth. Biologically effective dose values normalized to maximum value. Black dashed line indicates the location of simulated tumour.

Data given for protons (Subfigure (a)), deuterons (Subfigure (b)), ^3He (Subfigure (c)), ^4He (Subfigure (d)), ^6Li (Subfigure (e)) and ^7Li (Subfigure (f)) ions.

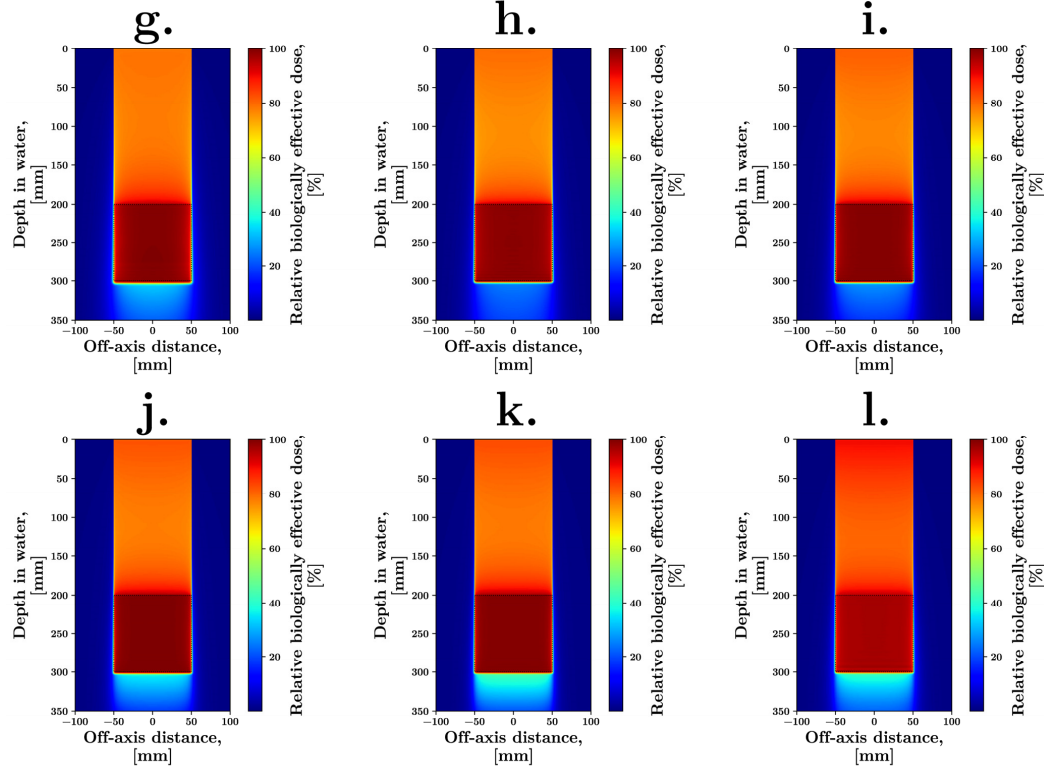


Figure 4.5. cont. Relative biologically effective dose spatial distributions of different ion types (deep-seated tumour)

Data illustrated for the central plane, SOBp optimized for $100 \times 100 \times 100$ mm tumour with distal edge at 300 mm depth. *FLASH* prescription point - at 5 mm depth. Biologically effective dose values normalized to maximum value. Black dashed line indicates the location of simulated tumour.

Data given for ^9Be (Subfigure (g)), ^{10}B (Subfigure (h)), ^{12}C (Subfigure (i)), ^{14}N (Subfigure (j)), ^{16}O (Subfigure (k)) and ^{20}Ne (Subfigure (l)) ions.

Analysing results presented in **Appendix 3.9.**, attention is given to entrance biologically effective dose values for 25, 50, 75 and 100 mm cubic tumour sizes, respectively:

- **protons:** 48.3%, 52.5%, 57.7% and 62.2%;
- **helium-4 ions:** 50.2%, 59.3%, 63.9% and 67.8%;
- **carbon-12 ions:** 55.6%, 73.0%, 75.1% and 80.4%.

Numerical values of entrance biologically effective dose value scaling indicate the role of RBE differential at high dose levels necessary for *FLASH* effect: differential RBE is decreased, with highest entrance dose values observed for heavier ions, resulting in unfavourable dose distributions with respect to lighter particles as protons and helium ions.

For further quantitative evaluation of dose conformality, 95% isodose conformity index was calculated for the idealized SOBP dose distributions (see **Appendix 3.2.**). Data on biologically effective dose distribution conformity indices for the tumour geometries evaluated in the study are illustrated in Figure 4.6. for all ion types studied.

In both shallow and deep-seated tumour scenarios, protons and deuterons exhibited worst performance - highest conformity indices in the range 1.15 - 1.36 and 1.12 - 1.20, respectively. Best high dose - 95% isodose - conformity was observed for boron-10 ions in the range 1.03 - 1.04. For light ions up to boron-10, the dose conformity index decreased, due to lower MCS magnitude. Nevertheless, for ion heavier than boron-10, a slight increase was observed. While results of carbon-12 were comparable with boron-10, increased values were observed for nitrogen-14, oxygen-16 and neon-20, attributable to slightly increased nuclear fragmentation at the distal edge, but more importantly - the high dose level near proximal edge of the tumour due to lack of RBE differential as discussed before. For comparison, helium-4 ions indicated dose conformity indices in the range 1.06 - 1.10. With increasing depth of the tumour, conformity indices increased due to higher magnitude of MCS.

Additionally, for assessment of low and intermediate dose conformality, gradient indices for 80%, 50% and 10% isodose levels were calculated and are illustrated in **Appendix 3.10.** For 80% isodose conformality, best performance was observed for boron-10 ions with gradient index in the range 1.13 - 1.48, with similar ion type dependency as for conformity index. Comparatively, 80% isodose gradient index for helium-4 ions was in the range 1.29 - 1.98.

Different dependency on ion type was observed for 50% gradient index - decrease for light ions up to lithium isotopes and beryllium-9, with no further reduction observed. Lowest observed 50% gradient index values were around 1.57 and 2.06 for 50- and 100-mm tumour in shallow scenario, 3.42 and 5.75, respectively, in deep-seated scenario. The significant variation with respect to tumour geometry is attributable to single field studied. For the 4 geometry scenarios, 50% isodose gradient indices of 1.67, 2.23, 4.07 and 7.11 were observed for helium-4 ions. For low-dose level - 10%, lowest gradient

indices were observed ions in the range from lithium to boron, with helium-4 ions indicating comparable performance.

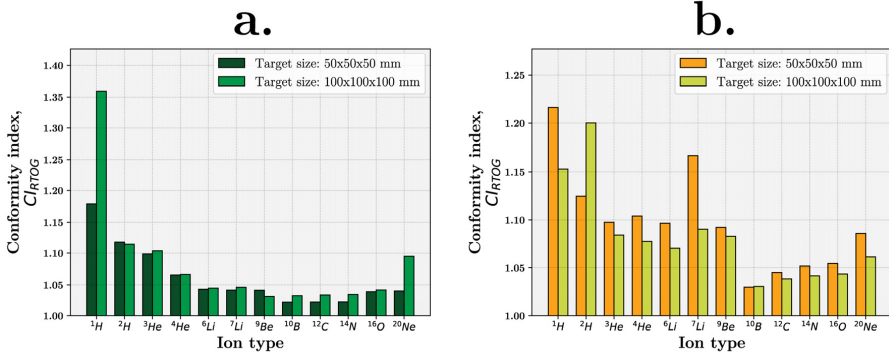


Figure 4.6. Dependence of the biologically effective dose conformity index on the ion type for different simulated tumour geometries

Conformity indices calculations based on recalculated biologically effective dose distributions with fluence extension to account for 95% isodose coverage of simulated tumour volume.

Data given for shallow tumours with distal edge at 150 mm (Subfigure (a)) and deep-seated tumours with distal edge at 300 mm (Subfigure (b)).

Summarizing, for idealized SOBP distributions, incorporating dose threshold levels necessary for *FLASH* effect, the best dose conformity in terms of entrance dose, conformity index and intermediate and low isodose gradient indices was observed for ions in the range from helium to boron.

Analysis of interplay between dosimetric parameters as basis of the study findings

Throughout the results presented before, observed dependencies are attributable to the interplay between dosimetric parameters relevant in IBT and developed *FLASH* effect dose threshold model:

- **physical dose distribution** - changes due to nuclear fragmentation for heavy ions in the entrance plateau, increased RBE variation in the tumour region and impact of tumour geometry;
- **dose-weighted LET and resulting solvated electron production yield** - changes due to the LET increase for heavier ions and impact of tumour geometry (impact of secondary particle scattering);
- **RBE value and differential variation:** changes due to increase for heavier ions and the impact of increased physical dose level for *FLASH* effect, decreasing RBE values and differential between the entrance plateau and tumour region;

Interplay of these parameters leads to the observed differences in *FLASH* effect physical dose threshold, resulting biologically effective dose level in the tumour and dose conformity metrics.

Detailed data analysis on ion type influence on evaluated dosimetric parameters is given in **Appendix 3.11**. Presented results in **Appendix 3.11.**, clearly indicated all the effects as discussed before for increasing mass of the ion, attributing to the presented results on threshold solvated electron concentration distribution and *FLASH* effect dose threshold scaling:

- increasingly higher RBE for heavier ions, necessitating a decrease in physical dose distribution within the tumour as function of depth;
- solvated electron concentration depth gradient varies due to interplay between physical dose distribution (RBE and nuclear fragmentation impact) and reduced solvated electron G-value at higher LET.

4.4. Conclusions and discussion

Chapter 4 presented development of a radiochemistry-based model for *FLASH* effect threshold modelling using produced solvated electron concentration as a surrogate metric. Choice of solvated electron concentration as a metric for *FLASH* effect dose threshold is based on the role of respective chemical specie in hydroxyl radical generation - one of the main contributors to cellular DNA damage. In water medium, as also further presented in Chapter 5, hydroxyl radicals can be scavenged by solvated electrons. In biologically relevant media, by interaction with molecular oxygen, solvated electrons produce superoxide anions. With superoxide dismutase as catalyst, superoxide anions produce hydrogen peroxide, which via Fenton reactions attributes to production of hydroxyl radicals. If a sufficiently high, spatially localized concentration of solvated electrons is attained in a short time frame, as under UHDR irradiation, a shift in radiochemical interaction kinetics can be expected. Scavenging of hydroxyl radicals by solvated electrons would be increased, while also lowering the fraction of solvated electrons able to interact with molecular oxygen for superoxide anion production. Overall, this would result in decreased residual concentration of hydroxyl radicals, lowering cellular DNA damage as observed for *FLASH* effect. Additional contribution is to be expected due to increased hydrogen peroxide scavenging via solvated electrons (outlined in Results) - reducing concentration of another radiolytic specie relevant to cellular DNA damage.

Using the proposed model, a mathematical framework was developed to incorporate *FLASH* effect dose threshold in optimization of dose distribution. In this case, idealized SOBP optimization approach accounted for spatial variation of RBE, generating uniform biologically effective dose distributions in the simulated tumour region, while maintaining the necessary solvated electron concentration at *FLASH* effect prescription point. In context of heavy ions, increased local physical dose level was

necessary to mitigate decreased solvated electron production yield with increasing LET. Comparative analysis was performed for 12 different ion types. Evaluation focused on comparison in terms of dose levels necessary to reach *FLASH* effect and achievable conformality of biologically effective dose distribution.

Main conclusions from the presented results can be summarized as:

1. Radiochemistry-based model has been developed for evaluation of *FLASH* effect dose threshold scaling for different ion types. Mathematical framework of model implementation into biologically effective dose distribution optimization process has also been developed.
2. According to the proposed model, higher physical dose levels need to be delivered for ions with increasing mass, due to solvated electron production yield decrease for increasing LET. For example, with respect to protons, helium-4 ions require about 1.2 - 1.3 times higher dose, depending on the geometry of tumour, while for carbon-12 ions an increase of about 2 - 2.5 times is necessary.
3. With increased physical dose necessary at *FLASH* prescription point in normal tissue region, corresponding average biologically effective dose level delivered to the tumour also increases with increasing mass of the ion. For example, with respect to protons, helium-4 ions would deliver about 1.1 - 1.5 times higher dose, depending on the geometry of tumour, while for carbon-12 ions an increase of about 2 - 3 times is necessary.
4. Due to solvated electron production yield decrease with increasing LET, lighter ions as protons and helium ions provide improved volumetric coverage of threshold solvated electron concentration. This is important if normal tissue in the planning treatment volume need to be spared, while also providing sparing in plateau region.
5. Due to increased dose levels necessary to achieve *FLASH* effect, the RBE differential between plateau and tumour region is reduced, especially for heavier ions. This results in unfavourable biologically effective dose distributions for heavy ions with significantly increased entrance dose level.
6. Improved conformality of biologically effective dose distributions (high, intermediate, and low isodose levels) is achieved for ions between lithium and boron if dose level necessary for *FLASH* effect and reduced RBE differential is considered.
7. Considering both *FLASH* effect dose threshold requirements and achievable biologically effective dose conformality, optimum performance could be obtained via the use of lithium or helium ions.

Limitations of the performed research. Additional notes and implications of the work

Considering the methodology and results presented in this Chapter, following limitations and additional implications of the performed study were identified:

- currently, solvated electron concentration threshold in the proposed model was considered as a mathematical value within the developed framework. As discussed

within the Methodology and corresponding Appendix of this Chapter, for biology driven implementation of this model solvated electron concentration threshold would depend on several biological factors such as tissue type, tissue oxygen level, biological endpoint considered for *FLASH* effect threshold. Thus, further work should focus on adapting and validating the model with more *in-vitro* and *in-vivo* data.

- as high dose levels are used in the model for *FLASH* effect threshold, accuracy of LQM for RBE calculation in the optimization process could be limited. As outlined in Chapter 2 and corresponding Appendix, several possible extensions of LQM model exist for high dose levels, thus further work could focus on comparing RBE calculation accuracy with general LQM and model extensions.
- as study focused on *FLASH* effect threshold model development and general assessment of the model, no specific beam delivery method and associated limitations were considered, using simple, uniform distributions. Use of different delivery methods would result in varying conformality of dose distribution, while also having impact on calculated dose weighed LET distributions. As further discussed in Chapter 7, delivery method also has significant effect on achievable dose rate level.
- as study focused on *FLASH* effect threshold model development and general assessment of the model, simple irradiation field geometries were considered. As observed dose threshold level scaling and dose conformality differences between different ions could be significantly affected by irradiated tumour geometry and biological parameters of surrounding tissue, further work should focus on performing evaluations within clinically relevant geometries.
- presented dose threshold model was based on the assumption that the certain dose level is delivered at UHDR necessary to achieve *FLASH* effect. As possible impact of ion type on UHDR level threshold is of even higher significance from perspective of particle accelerator technological limitations, further work should address this aspect. Presented results could also be considered from the perspective that a higher dose level needs to be delivered within a fixed time window for heavier ions to achieve *FLASH* effect, suggesting scaling of UHDR level threshold. Nevertheless, this assumption needs to be validated via radiochemical simulations or radiobiological measurements.
- considering existing radiochemical studies on LET dependency described in Chapter 3 and corresponding Appendix, slightly decreased oxygen consumption was observed for higher LET [26]. General trends observed in the presented modelling study suggest similar effects, though necessitate further validation.

Future research outlooks

Considering the methodology, results and study limitations presented in this Chapter, following pathways for future additional research were identified:

- with current work having focused on single field delivery, future study on multi-field delivery and resulting differences between different ion types could be considered. Multi-field delivery study should be evaluated in clinically relevant geometry, to also

assess the impact of complex tumour shape and biological differences of surrounding tissue.

- to validate the observed *FLASH* effect dose threshold scaling with increasing mass of the ion, comparison with *in vitro* and *in vivo* data would be of highest importance as part of future research work. As presented in Chapter 3, results on *FLASH* effect *in-vitro* and *in-vivo* data with heavier ion beams are rather limited, thus systematic LET dependency *FLASH* effect studies should be designed and performed.
- with solvated electron concentration threshold defined as the main parameter in the proposed *FLASH* effect dose threshold model, the impact of biological parameters as tissue type, tissue oxygen level, biological endpoint considered for *FLASH* effect should be evaluated and validated.
- a study on possible application or extension of the model to assess DR threshold scaling with respect to ion type should be designed. Evaluating possible DR threshold scaling for heavier ions has significant role for establishing future particle accelerator design requirements.

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Role of solvated electrons in radiation chemistry under ultra-high dose rate irradiation

FLASH effect dose threshold estimation approach and modelling study presented in Chapter 4 is based on the theoretical assumption of solvated electron role in radiochemical processes under UHDR irradiation. Chapter 5 presents validation of this assumption via experimental measurements. Presented experimental work investigates changes in radiochemistry by measurement of hydrogen peroxide - one of the long-lived water radiolysis products. Changes between conventional and UHDR irradiation are evaluated, while investigating the importance of solvated electrons in these changes by use of chemical scavengers. Experimental work has been performed with two different low-LET ionizing radiation types: X-ray photons and megavoltage electrons.

Section 5.1 outlines the measurement methods used in the experimental study including the choice of solvated electrons scavengers, sample preparation procedures and approaches for dosimetry and hydrogen peroxide measurement. Measurement uncertainty sources are identified, presenting uncertainty calculation methods and additional measurements performed for specific uncertainties. Statistical analysis methods to evaluate the significance of experimental findings are also presented.

Results on hydrogen peroxide production DR dependency are demonstrated in Section 5.2., along with the influence of solvated electron scavenger presence. Conclusions and implications of the experimental findings are discussed in Section 5.3. Significance of the presented findings with X-ray and electron beams is also analysed in the context of IBT.

Contributions of the Author: Original idea of solvated electron impact assessment in UHDR radiochemistry and nitrous oxide as a scavenging species has been proposed by Tengda Zhang (at the time DKFZ), along with hydrogen peroxide measurement method. Solvated electron scavenging by nitrous oxide has also been proposed in [1]. Phantom used in X-ray photon measurements has been developed by Christina Stengl (DKFZ), with additional parts of setup developed by Elpida Theodoridou (DKFZ).

Author has expanded the measurement method: use of sodium nitrate as scavenger, improved sample-by-sample dosimetry and development of analysis software, detailed uncertainty assessment. For electron beam measurements, the phantom design was developed by the Author. Experimental planning of reported measurements has been done by the Author. Measurement process was supported by Konstantinos Koristeidis (at the time DKFZ), Konstantinos Kostakis (at the time DKFZ), Tengda Zhang (at the time DKFZ) and Patrick Kudis (DKFZ). Analysis of all measurements and graphical representation has been performed by the Author. Used literature sources are indicated, where applicable. Electron beam used in the study was provided by DESY PITZ operator team and DESY FLASHlab@PITZ team contributing

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-

5.1. Measurement methods. Data analysis

This Section provides brief summary of the measurement and data analysis methodology used within the study, while additional methodological details are given in Appendix 4.1.

Hydrogen peroxide production DR dependency and the role of solvated electrons was evaluated, validating theoretical model of Chapter 4. Role of solvated electrons was assessed by comparison between pure water and solvated electron scavenger solutions: nitrous oxide as reference following studies [88-89], and sodium nitrate, as method developed by the Author. Sodium nitrate can scavenge not only solvated electrons, but also water cation and pre-thermalization electrons depending on concentration level used [90].

Pure water and e_{aq}^- scavenger solution aerated (pO_2 of ~21%) samples were prepared using deionized *MilliQ* water. ACS reagent grade crystalline sodium nitrate (*Sigma-Aldrich*, Germany) was used for several concentrations between $0.1 \mu M^{10}$ and 1 M. Samples were prepared in plastic 200 μL eppendorf tubes.

Absorbed dose for each sample was measured using *Gafchromic EBT-XD* radiochromic films. Obtained optical density values (*Epson 10000XL* flatbed scanner, red colour channel) were calibrated to dose using a custom script in *ImageJ* developed by the Author.

After irradiation (< 5 minutes), hydrogen peroxide concentration was measured with *Amplex UltraRed* assay. Validation measurements of the method were performed initially, indicating no interference between the assay and sodium nitrate. Due to light sensitivity, all irradiated samples were placed in an opaque container. 50 μL of the sample was mixed with 50 μL of *Amplex UltraRed* working solution and incubated for 30 minutes before fluorescence intensity reading. After incubation, fluorescence intensity was measured using well-plate readers: *BMG Labtech Clariostar* and *Tecan infinite 200Pro* for X-ray and electron beam measurements, respectively, with an individual calibration curve for each session (hydrogen peroxide solutions of 1, 3, 5 and 7 μM). Unirradiated sample (background) fluorescence intensity was subtracted from sample readings.

G-values were calculated as final metric for analysis:

$$G_{H_2O_2} = \frac{C_{H_2O_2}}{D_{avg}} \quad (5.1)$$

where $C_{H_2O_2}$ corresponds to the average H_2O_2 concentration in the sample and D_{avg} - average dose absorbed by the sample. Average over three measurements of hydrogen peroxide concentration was taken for each sample, with three samples for each condition. Uncertainties for each measured parameter were evaluated and propagated to G-value.

¹⁰ M refers to molar concentration, corresponding to moles per 1 litre

Following [52], linear regression was performed between hydrogen peroxide G-value and logarithm of the DR, evaluating resulting coefficient of determination and statistical significance of the fit by hypothesis testing via t-test (significance level of 95%).

Two measurement campaigns were performed with low LET ionizing radiation types:

- **X-ray beam:** 200 kV, 17.9 mA with no filtration, continuous beam by X-ray tube; performed at DKFZ - DR varied by changing distance to sample;
- **electron beam:** 18 MeV, pulsed beam as produced by a linear accelerator; performed at DESY FLASHlab@PITZ - temporal structure varied for average, pulse and bunch DR.

Main technical parameters of irradiation are summarized in Table 5.1 and Table 5.2

Table 5.1.

Average dose rates used in the X-ray study and corresponding technical set-up parameters

Average dose rate	SAD	Irradiation time
0.1 Gy/s	498 mm	110 s
2 Gy/s	123 mm	5 s
5 Gy/s	79 mm	3 s
10 Gy/s	59 mm	2 s

Table 5.2.

Parameters of the LINAC-produced electron beam used in the study and corresponding dose rate values

Parameter	Setting 1	Setting 2	Setting 3	Setting 4
Technical beam parameters				
Bunch length	~15 ps	~10 ps	~10 ps	~6 ps
Bunch charge*	~500 pC	~100 pC	~100 pC	~10 pC
Bunch spacing	0.22 μ s			
Bunches per RF pulse	42	42	210	42
RF pulse spacing	100 ms			
Number of RF pulses	2	10	2	100
Dose rate values**				
Average DR	~100 Gy/s	~100 Gy/s	~11 Gy/s	~1 Gy/s
RF pulse DR	~5.5*10 ⁵ Gy/s	~1.1*10 ⁵ Gy/s	~1.1*10 ⁵ Gy/s	~1.1*10 ⁴ Gy/s
Bunch DR	~7.9*10 ⁹ Gy/s	~2.4*10 ⁹ Gy/s	~2.4*10 ⁹ Gy/s	~4.0*10 ⁸ Gy/s

* Bunch charge is defined at electron gun in photoinjector system

** DR values assuming delivered dose of 10 Gy, recalculated on sample basis during experiments

5.2. Measurement results

Influence of average dose rate on hydrogen peroxide production under X-ray irradiation in presence of nitrous oxide

For the experimental campaign conducted with X-rays, first measurements were performed with nitrous oxide as solvated electron scavenger. Figure 5.1. illustrates hydrogen peroxide G-value DR dependency for pure water and N₂O saturated water for pO₂ of 21% under X-ray irradiation.

As illustrated in Figure 5.1., for pure, aerated water samples an average¹¹ H₂O₂ G-value of 2.19 ± 0.16 *molecules/100 eV* was observed at the lowest X-ray beam average DR studied - 0.10 ± 0.002 Gy/s. Even though experiments were done in a rather narrow average DR range of 0.1 to ~10 Gy/s, decrease in H₂O₂ G-value was observed for pure, aerated water. At average DR of 10.32 ± 0.74 Gy/s, H₂O₂ G-value decreased to 1.93 ± 0.13 *molecules/100 eV*. Figure 5.1. also illustrates that addition of N₂O - solvated electron scavenger - resulted in increased H₂O₂ G-value in the samples for both low and high DRs. At average DR of 0.10 ± 0.002 Gy/s H₂O₂ G-value was 2.32 ± 0.09 *molecules/100 eV*, while at average DR of 9.02 ± 0.82 Gy/s - 2.29 ± 0.13

¹¹ Average values in the text are reported as mean over the 3 samples for the same irradiation conditions

molecules/100 eV. Qualitatively, it can be observed that addition of N_2O diminished H_2O_2 G-value decrease of pure water with increasing DR.

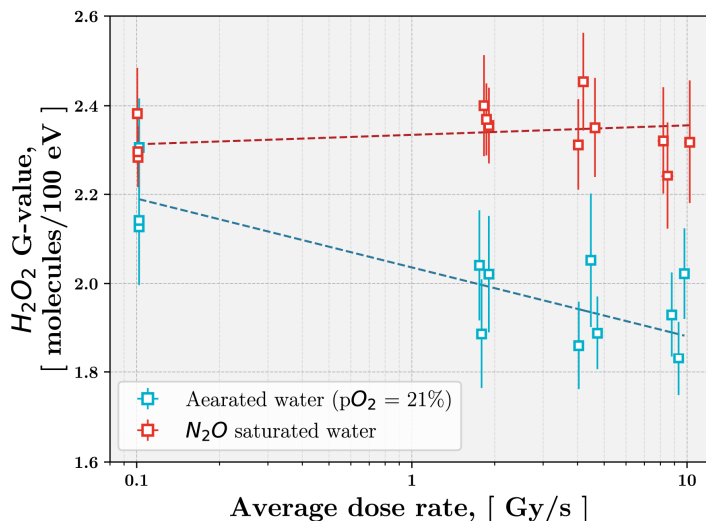


Figure 5.1. Hydrogen peroxide production yield (G-value) dependency on average dose rate in aerated (21% pO_2) samples of pure water and nitrous oxide (N_2O) saturated water irradiated with X-rays

Average DR given in logarithmic scale. 1σ uncertainty bars given at each data point for both hydrogen peroxide G-value and average DR. Dashed lines indicate the linear fit between hydrogen peroxide G-value and decimal logarithm of average DR as calculated via orthogonal distance regression.

For evaluation of the statistical significance of experimental findings, linear fit was performed using orthogonal distance regression between the H_2O_2 G-value and decimal logarithm of average DR, following the approach proposed in [24]. Summary of the statistical analysis on experimental finding significance is summarized in Table 5.3.

Analysis of experiments (Table 5.3.) for pure, aerated water indicates a statistically significant ($p < 0.05$) decrease of H_2O_2 G-value with respect to decimal logarithm of average DR - slope of -0.154 ± 0.035 ($\frac{\text{molecules}}{100 \text{ eV}} / \lg(\frac{Gy}{s})$). Experimental findings of reduced H_2O_2 production with increasing DR align with the results of similar studies [1-2,24,26-29]. Addition of N_2O as solvated electron scavenger, diminished the DR dependency with no statistically significant changes ($p > 0.05$) observed [1-2].

While detailed modelling of water radiolysis product generation and further chemical interaction kinetics is necessary to provide quantitative explanation for the observed phenomena, Author provides general idea of possible mechanisms underlying the observed results. Main reactions for water radiolysis process and solvated electron scavenging are briefly summarized in **Appendix 4.2.**, providing the radiochemical basis for observed phenomena throughout the Results section.

Table 5.3.

Statistical analysis of hydrogen peroxide production yield dependency on average dose rate in aerated (21% pO₂) samples of pure water and nitrous oxide (N₂O) saturated water irradiated with X-rays

Slope of linear fit*	p-value**	Coefficient of determination for linear fit, R ^{2***}
$k \pm \sigma_k$		
Pure aerated (21% pO ₂) water samples		
-0.154 ± 0.035	0.0012	0.669
Nitrous oxide (N ₂ O) saturated water samples		
0.021 ± 0.019	0.2928	0.118

* Fit parameters and respective standard deviations of fit parameters calculated using orthogonal distance regression between hydrogen peroxide G-value and decimal logarithm of average DR, accounting for measurement uncertainties of both parameters

** t-test for slope of the fit, degrees of freedom - 10 (12 measurement points), H₀: k = 0. 95% confidence level chosen. Statistically insignificant p values (p > 0.05) indicated in red, while statistically significant (p < 0.05) indicated in green for positive k and blue for negative k.

*** Weighed coefficient of determination $R^2_{weighted}$ was calculated based on Appendix 4.1.

Characterization of sodium nitrate as solvated electron scavenger

In this work, Author proposed another scavenger - sodium nitrate (NaNO₃) - as alternative to nitrous oxide, improving measurement methodology. Before DR dependency measurements, initial validation measurements were performed to characterize the system, outlined in detail within **Appendix 4.3**. No pH variation for NaNO₃ solutions with respect to pure water and no interaction between NaNO₃ and *Amplex UltraRed* assay was observed. Thus, the proposed scavenger can be reliably used in hydrogen peroxide measurements performed in this work.

Influence of average dose rate on hydrogen peroxide production under X-ray irradiation in presence of sodium nitrate

After the initial characterization of sodium nitrate as solvated electron scavenging system, DR dependency of hydrogen peroxide G-value. Measurements were performed with varying concentration of sodium nitrate to assess the impact of different scavenging pathways and their role on DR dependency of hydrogen peroxide G-value. Figure 5.2 illustrates the DR dependency of hydrogen peroxide G-value, as evaluated for NaNO₃ solutions of both low (Subfigure (a)) and high (Subfigure (b)) concentrations. As experiments were done separately from nitrous oxide study reported previously, repeated measurements for aerated, pure water samples were done. For pure water samples, H₂O₂ G-value of 2.37 ± 0.08 molecules/100 eV was observed at average DR of 0.10 ± 0.002 Gy/s, decreasing to 1.96 ± 0.14 molecules/100 eV at 10.32 ± 0.74 Gy/s.

Evaluation of observed results reveals significant differences between low and high NaNO_3 concentrations. For a 100 μM sodium nitrate solution, H_2O_2 G-value of 2.79 ± 0.16 molecules/100 eV was observed at average DR of 0.10 ± 0.001 Gy/s, with a decrease to 2.35 ± 0.15 molecules/100 eV at 9.96 ± 0.87 Gy/s. On the contrary, no DR dependency was observed for 1 M sodium nitrate solution with hydrogen peroxide G-value of 0.76 ± 0.07 and 0.80 ± 0.06 molecules/100 eV for average DRs of 0.10 ± 0.002 and 10.62 ± 0.61 Gy/s, respectively.

Same as for nitrous oxide experiments, statistical significance of findings was assessed, as summarized in Table 5.4. Analysing the slope values for linear fit of the DR dependency in Table 5.4 as function of sodium nitrate concentration, a trend can be observed, illustrated in Figure 5.3.

As for experiments reported with N_2O , pure, aerated water indicates a statistically significant ($p < 0.05$) decrease of H_2O_2 G-value with respect to decimal logarithm of average DR - slope of -0.226 ± 0.022 ($\frac{\text{molecules}}{100 \text{ eV}})/\lg(\frac{\text{Gy}}{\text{s}})$. Impact of NaNO_3 as solvated electron scavenger on the DR dependency varies with the concentration in solution. For concentrations in range from 1 to 100 μM - increased G-value with respect to pure water -, statistically significant ($p < 0.05$) DR dependency of H_2O_2 G-value can be observed. Though, the slope of H_2O_2 G-value dependency decreases with respect to pure water. DR dependency of G-value is diminished ($p > 0.05$) for concentrations of 250 μM and 1 mM, with G-value reduced with respect to pure water. Interestingly, a statistically significant ($p < 0.05$) increase of H_2O_2 G-value with increasing DR can be observed for NaNO_3 concentrations of 10 mM to 1 M, with slope of 0.065 ± 0.015 and 0.019 ± 0.008 ($\frac{\text{molecules}}{100 \text{ eV}})/\lg(\frac{\text{Gy}}{\text{s}})$, respectively.

Figure 5.3 illustrates an increase of linear fit slope between H_2O_2 G-value and decimal logarithm of average DR with increasing NaNO_3 concentration. For NaNO_3 concentrations in the range from 1 to 100 μM , an increase of hydrogen peroxide G-value with respect to pure water was observed, maintaining similar magnitude of DR dependency. For low concentrations, scavenging of solvated electrons or precursor electrons via Reactions of A.4.3. and A.4.5. is primary. For low-DRs, at short timescales hydrogen peroxide production is increased via decreasing Reaction A.4.29 with respect to A.4.19., also inhibiting reduction of hydrogen peroxide via Reaction A.4.30. On longer measurement timescale, hydroperoxyl recombination for hydrogen peroxide production would also be reduced, though offset by increase in hydroxyl radical recombination - an overall increase of hydrogen peroxide G-value.

In contrast to nitrous oxide, DR dependency can still be observed for low sodium nitrate solutions. As measurements are performed on long time scales, both short timescale hydroxyl radical and longer timescale hydroperoxyl radical pathways should be considered. In pure water, hydroxyl radical recombination pathways have significant DR dependency due to increased hydrogen peroxide reduction pathways from Reactions A.4.29 and A.4.30 via interactions with solvated electrons. Low concentrations of sodium nitrate scavenge solvated electrons, thus decreasing DR dependency of hydroxyl radical

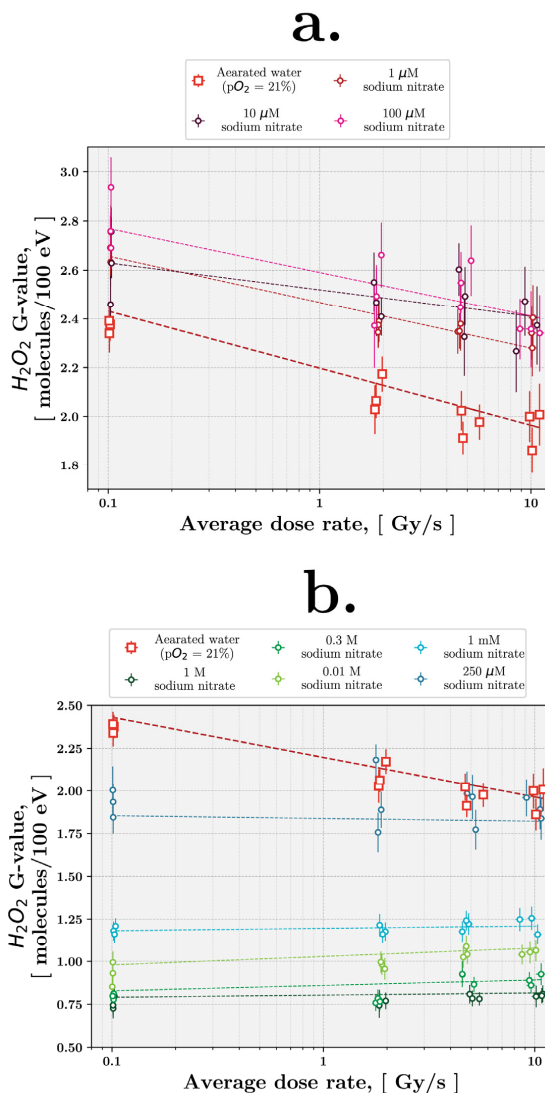


Figure 5.2. Hydrogen peroxide production yield (G-value) dependency on average dose rate in aerated (21% pO_2) samples of pure water and sodium nitrate ($NaNO_3$) solutions of varying concentration irradiated with X-rays

1σ uncertainty bars given at each data point for both hydrogen peroxide G-value and average DR. Dashed lines indicate the linear fit between hydrogen peroxide G-value and decimal logarithm of average DR as calculated via orthogonal distance regression.

Data for sodium nitrate concentrations of 1, 10 and 100 μM given in Subfigure (a), while data for concentrations of 1 M, 0.3 M, 0.01 M, 1 mM and 250 μM are given in Subfigure (b). Data of pure water given for comparison in both Subfigures.

Table 5.4.

Statistical analysis of hydrogen peroxide production yield dependency on average dose rate in aerated (21% pO₂) samples of pure water and nitrate (NaNO₃) solutions of varying concentration sodium irradiated with X-rays

Sodium nitrate concentration in the solution	Slope of linear fit* $k \pm \sigma_k$	p-value**	Coefficient of determination for linear fit, R^{2***}
Pure aerated (21% pO ₂) water samples			
-	-0.226 ± 0.022	0.0000	0.913
Aerated (21% pO ₂) sodium nitrate (NaNO ₃) solution samples			
1 M	0.019 ± 0.008	0.0342	0.378
300 mM	0.046 ± 0.019	0.0353	0.373
10 mM	0.065 ± 0.015	0.0018	0.640
1 mM	0.014 ± 0.012	0.2831	0.116
250 μ M	-0.004 ± 0.051	0.9363	0.002
100 μ M	-0.179 ± 0.034	0.0004	0.738
10 μ M	-0.110 ± 0.037	0.0139	0.487
1 μ M	-0.189 ± 0.026	0.0000	0.841

* Fit parameters and respective standard deviations of fit parameters calculated using orthogonal distance regression between hydrogen peroxide G-value and decimal logarithm of average DR, accounting for measurement uncertainties of both parameters

** t-test for slope of the fit, degrees of freedom - 10 (12 measurement points), H₀: $k = 0$. 95% confidence level chosen. Statistically insignificant p values ($p > 0.05$) indicated in red, while statistically significant ($p < 0.05$) indicated in green for positive k and blue for negative k.

*** Weighed coefficient of determination $R^2_{weighted}$ was calculated based on Appendix 4.1.

recombination and increasing hydrogen peroxide G-value. On the contrary, it can be theorized that the longer timescale hydroperoxyl radical recombination interaction exhibits DR dependency - as solvated electrons are scavenged by sodium nitrate, superoxide anion production is inhibited (Reaction A.4.24), decreasing production of hydroperoxyl radicals. The combination of both pathways would explain observed increase of hydrogen peroxide G-value and maintained DR dependency for measurements performed at minute timescale. The contrasting behaviour with respect to nitrous oxide can also be attributed to Reaction A.4.33 - no additional hydroxyl radicals are generated by sodium nitrate acting as scavenger, as is the case for nitrous oxide. For higher concentrations of sodium nitrate, hydrogen peroxide G-value is reduced with respect to pure water, as additionally to solvated electron scavenging, molecular water cations are directly scavenged via Reaction A.4.4. For short timescales, this inhibits hydroxyl radical production via Reaction A.4.22 and subsequent hydrogen peroxide production via

recombination in Reaction A.4.19. On longer timescales, the hydroperoxyl recombination is also decreased due increased solvated electron scavenging at high sodium nitrate concentrations (inhibiting chain of A.4.24, A.4.25 and A.4.23). Decreased production in both pathways results in the observed reduction in hydrogen peroxide G-value.

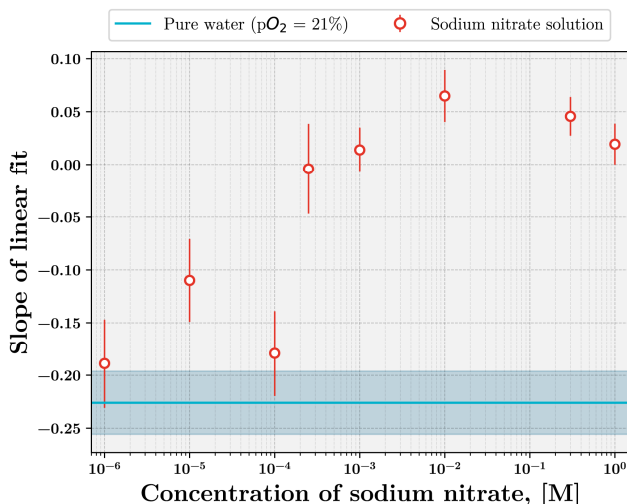


Figure 5.3. Slope of linear fit between hydrogen peroxide production yield (G-value) and average dose rate as function of sodium nitrate (NaNO_3) concentration in the aerated (21% pO_2) solution

1σ uncertainty bars given at each data point for linear fit slope, as calculated via orthogonal distance regression. For comparison, data in pure water are given by the blue line with shaded region corresponding to 1σ uncertainty.

For high sodium nitrate concentration, DR dependency is completely diminished or slightly reversed (slight increase of G-value with increasing DR). One possible contribution to this effect could be the reduced competition between Reactions A.4.19, A.4.29. and A.4.30 on immediate timescale, as less hydroxyl radicals are produced due to molecular water cation scavenging, while Reactions A.4.29 and A.4.30 are also inhibited by scavenging of solvated electrons. Secondly, on longer time scale, the hydroperoxyl production pathway is also effectively quenched due solvated electron scavenging, diminishing any possible DR effects. It could also be theorized, that hydrogen peroxide production for high concentration of sodium nitrate is dependent also on nitrate ion radiolysis itself, with hydroxyl and hydroperoxyl radical recombination inhibited, and production of hydroxyl radicals via reactions A.4.34 and A.4.35. Theorized pathway would be DR independent with no significantly competing radiochemical interactions.

Influence of oxygen level on hydrogen peroxide production average dose rate dependency under X-ray irradiation

As discussed before, hydrogen peroxide production, especially for longer timescales, could be significantly affected by hydroperoxyl radical recombination. As hydroperoxyl radicals are formed in reaction involving molecular oxygen, it was of interest to also investigate hydrogen peroxide G-value for pure water and sodium nitrate solutions at lower oxygen concentration. **Appendix 4.4** summarizes the results on the DR dependency of hydrogen peroxide G-value for pure water and solutions of selected NaNO_3 concentrations with reduced pO_2 of 4%.

Assessment of additional dose distribution and dose rate uncertainties under X-ray irradiation

Measurement uncertainties were directly considered for statistical analysis of the results discussed before. Summary of measured quantity - dose, DR and H_2O_2 concentration - and calculated H_2O_2 G-value uncertainties is provided in **Appendix 4.5**. No significant differences can be observed in measurement quality between the two experimental campaigns -nitrous oxide and sodium nitrate - with average relative uncertainties in ranges of 1.6-4.5%, 2.5-4.9% and 4.4-5.9% for dose (and DR), H_2O_2 concentration and H_2O_2 G-value, respectively.

Numerical evaluation of other identified uncertainty sources for X-ray beam setup - dose inhomogeneity within the sample and finite rise and fall-off time of X-ray tube - is given in **Appendix 4.1**. Overall, the magnitude of these uncertainty sources is relatively low and would not affect the observed trends.

Influence of dose rate with varying beam pulse structure on hydrogen peroxide production in pure aerated water under electron irradiation

All measurements reported with X-rays were done with continuous beam. As discussed in Chapter 3., several studies [24,32-35] have shown the importance of temporal structure and different DR distribution definitions if pulsed beams are considered. Second experimental campaign with pulsed electron beam focused on analysing possible dependency of hydrogen peroxide G-value on different beam temporal structure and DR definitions in pure water and solvated electron scavenger solutions. Higher average DRs were available with the electron beam - up ~ 120 Gy/s, providing broader DR range for analysis.

Firstly, Figure 5.4. illustrates hydrogen peroxide G-value DR dependency for pure water (pO_2 of 21%) under pulsed electron beam irradiation for different DR definitions - average (Subfigure (a)), pulse (Subfigure (b)) and bunch (Subfigure (c)) DR. For aerated pure water samples, H_2O_2 G-value of 2.44 ± 0.20 molecules/100 eV was observed at the lowest investigated DRs (Beam setting 4): average DR 1.02 Gy/s, pulse dose rate $1.12 \cdot 10^4$ Gy/s and bunch DR $4.02 \cdot 10^8$ Gy/s (relative 1σ uncertainty of 5.82%). Decrease of H_2O_2 G-value was observed for highest DRs studied (Beam setting 2) - average DR 118.9 Gy/s, pulse DR $6.59 \cdot 10^5$ Gy/s and bunch DR $9.43 \cdot 10^9$ Gy/s (relative

1σ uncertainty of 5.82%) - to a value of 1.47 ± 0.11 molecules/100 eV. Similarly to X-ray studies, hydrogen peroxide G-value DR dependency was observed, with analysis on statistical significance indicated in Table 5.5 and discussed in depth in next subsection.

Impact of beam temporal structure and DR definition on hydrogen peroxide G-value was also evaluated. As indicated in Table 5.2., beam settings 1 and 2 had the same average DR, with different pulse and bunch DRs, while settings 2 and 3 had the same pulse and bunch DRs with different average DRs. Data in Figure 5.4. illustrate, that the observed hydrogen peroxide G-value dependency in aerated, pure water samples is best described by pulse or bunch DR, rather than average DR. Data points corresponding to beam settings 2 and 3 (same pulse and bunch, different average DR) had comparable hydrogen peroxide G-value. On the contrary, in Figure 5.4 (a) for data points of settings 1 and 2 (same average, different pulse and bunch DR) a significant difference in hydrogen peroxide production was observed. With in-depth statistical analysis in the next subsection, determination coefficient R^2 of linear fit between H_2O_2 G-value with respect to decimal logarithm of DR was evaluated. While pulse and bunch DRs as descriptors exhibited R^2 of 0.932 and 0.918, respectively, a significant decrease was observed for average DR as descriptor - R^2 of 0.548.

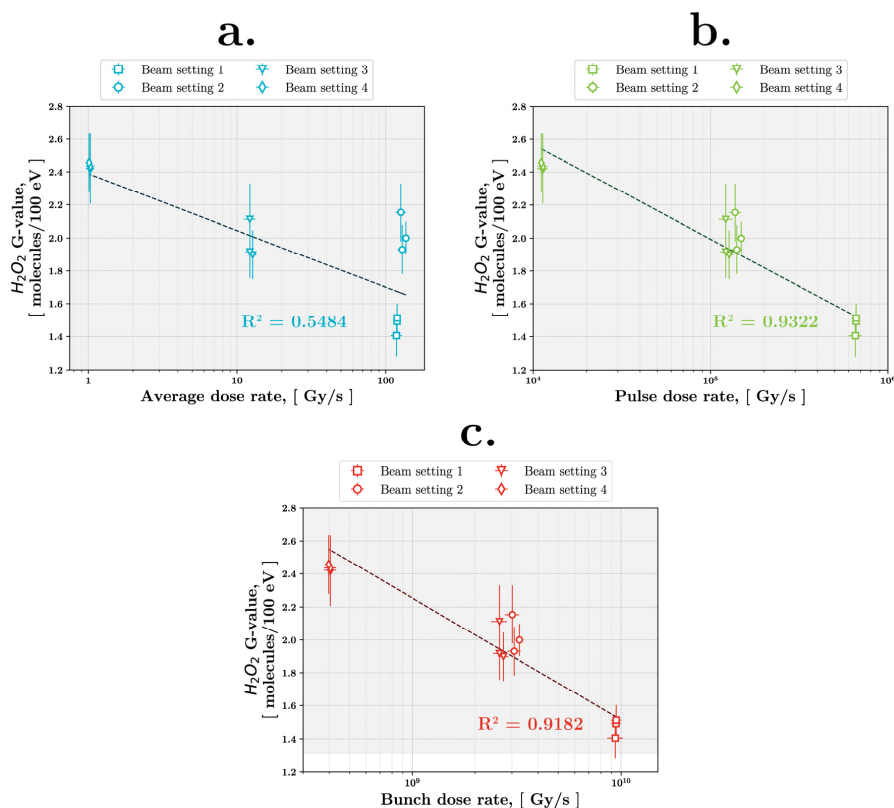


Figure 5.4. Hydrogen peroxide production yield (G-value) dependency on average (a), pulse (b) and bunch (c) dose rates in aerated (21% pO_2) samples of pure water irradiated with pulsed electron beam

Beam settings indicated correspond to definitions in Table 5.2. 1σ uncertainty bars given at each data point for both hydrogen peroxide G-value and average DR. Dashed lines indicate the linear fit between hydrogen peroxide G-value and decimal logarithm of average DR as calculated via orthogonal distance regression. Coefficient of determination R^2 for linear fit indicated in each Subfigure for clarification.

Influence of sodium nitrate and oxygen level on hydrogen peroxide production dose rate dependency under electron irradiation with varying beam pulse structure. Statistical analysis of the results.

Besides samples of aerated pure water, hydrogen peroxide G-value DR dependency was evaluated also for sodium nitrate solutions at pO_2 of 21% with concentrations of 1 μM , 250 μM and 10 mM, with 250 μM solution evaluated also at pO_2 of 4%. Corresponding data are illustrated in Figure 5.5.

Observed sodium nitrate concentration impact on hydrogen peroxide G-value absolute values followed similar trends as in experimental campaign with X-rays - sodium

nitrate concentration of 1 μM slightly increased the production with respect to pure water, while concentrations of 250 μM and 10 mM - reduced it. Reduction of pO_2 from 21% to 4% in 250 μM solutions resulted in additional decrease of absolute hydrogen peroxide G-value. The observed hydrogen peroxide G-value at lowest DRs - beam setting 4 - were 2.24 ± 0.48 , 2.37 ± 0.50 , 1.22 ± 0.32 and 0.72 ± 0.26 *molecules/100 eV* for 1 μM , 250 μM and 10 mM at pO_2 of 21%, and 250 μM at pO_2 of 4%, respectively. At highest DR - beam setting 2 - the values were respectively 1.44 ± 0.29 , 1.55 ± 0.34 , 1.20 ± 0.28 and 0.62 ± 0.19 *molecules/100 eV*. Measured hydrogen peroxide G-values for beam setting 4 of pulsed electron beam - average DR of ~ 1 Gy/s - were similar and within measurement uncertainty compared to values under continuous X-ray irradiation. Comparing observed values between highest and lowest DR values, DR dependency of hydrogen peroxide production is present for 1 μM and 250 μM sodium nitrate solutions at pO_2 of 21%, while dependency is reduced or diminished for 10 mM at pO_2 of 21% and 250 μM at pO_2 of 4%.

Analysis of result statistical significance is summarized in Table 5.5. Linear fit between hydrogen peroxide production and decimal logarithm of DR was evaluated separately for each DR definition considered - average, pulse, and bunch DR.

In pure water samples, hydrogen peroxide production DR dependency was best described by pulse and bunch DR definitions. For definitions of average, pulse and bunch DRs, slopes of linear fit between hydrogen peroxide production and decimal logarithm of DR were -0.344 ± 0.104 , -0.574 ± 0.051 and -0.741 ± 0.072 ($\frac{\text{molecules}}{100 \text{ eV}} / \lg(\frac{\text{Gy}}{\text{s}})$), respectively, with determination coefficients R^2 of 0.548, 0.932 and 0.918. Hydrogen peroxide G-value DR dependency was statistically significant ($p < 0.05$) for all DR definitions.

While the possible mechanisms behind decrease of hydrogen peroxide production have been already addressed with experimental results with X-rays, application of pulsed electron beam introduces the additional aspect - how temporal structure of the beam influences the DR dependency. Presented results illustrated bunch and pulse DR definitions as better descriptors of hydrogen peroxide production changes at UHDR. Approximately the same hydrogen peroxide G-values were achieved with two beam settings having the same pulse and bunch DRs, but different average DRs. The impact of short time scale dose delivery over temporal average in pure, aerated water could be attributed to immediate radiochemistry in short timescales. As discussed, reduced hydrogen peroxide production with increasing DR is mainly attributable to increased reduction of hydroxyl radicals (Reaction A.4.29), inhibiting hydroxyl radical recombination to form hydrogen peroxide (Reaction A.4.19), while also directly reducing hydrogen peroxide (Reaction A.4.30). Reactions A.4.29 and A.4.30 would prevail in competition with Reaction A.4.19 at higher DRs. Both reactions have high reaction rate constants, thus they contribute to immediate radiochemistry at short timescales - dose delivered in short time could be main factor of influence. For the same dose level produced over longer time, competition between Reactions A.4.29 and A.4.30 with respect to

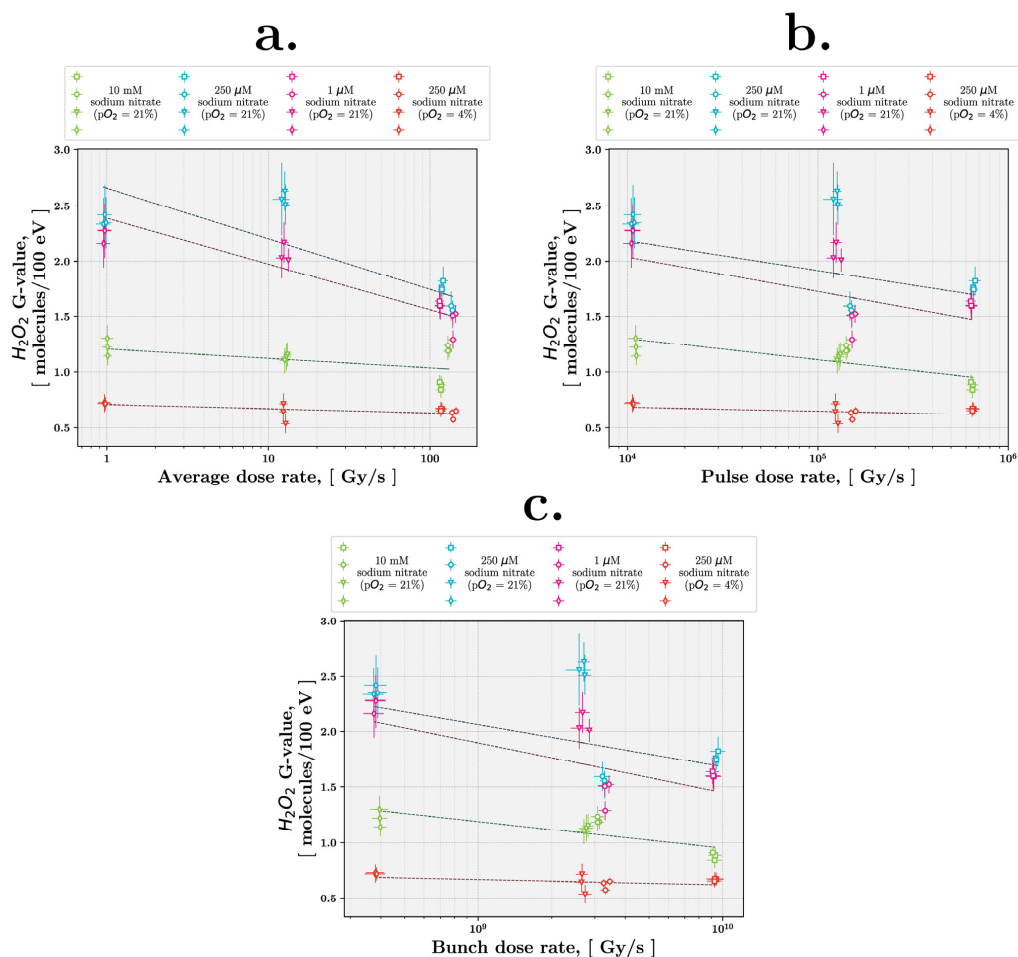


Figure 5.5. Hydrogen peroxide production yield (G-value) dependency on average (a), pulse (b) and bunch (c) dose rates in aerated (21% pO₂) and physioxenic (4% pO₂) samples of sodium nitrate (NaNO₃) solutions of varying concentration irradiated with pulsed electron beam

1 σ uncertainty bars given at each data point for both hydrogen peroxide G-value and average DR. Dashed lines indicate the linear fit between hydrogen peroxide G-value and decimal logarithm of average DR as calculated via orthogonal distance regression. Marker shape used in all Subfigures corresponds to beam setting definition used in Figure 5.4.

Reaction A.4.19 would be favourable for the latter, with lower instantaneous solvated electron concentration. Competition of these reactions could explain the role of pulse and bunch DRs. In contrast to X-ray measurements, DR dependency was observed also at 250 μ M sodium nitrate concentration. This can be attributed to lower DR range studied

in X-ray measurements - 0.1 to 10 Gy/s, with respect to 1-100 Gy/s (average). With a low slope, hydrogen peroxide production decrease might not be detected in smaller DR range. Analysing Figure 5.5 (a) similar level of hydrogen peroxide G-value can be observed between 1 and 10 Gy/s average DR, explaining the discrepancy between X-ray and pulsed electron beam measurements.

In presence of solvated electron scavengers, contrasting hydrogen peroxide production dependency can be observed with respect to pure, aerated water. For aerated ($pO_2 = 21\%$) sodium nitrate solutions of concentrations 1 and 250 μM , the hydrogen peroxide G-value DR dependency is best described by average DR definition, not pulse or bunch DR. For average DR definition, slopes of linear fit between hydrogen peroxide production and decimal logarithm of DR were -0.414 ± 0.061 and -0.458 ± 0.095 ($\frac{\text{molecules}}{100 \text{ eV}}$)/ $\lg(\frac{Gy}{s})$ for 1 and 250 μM , respectively, with determination coefficients R^2 of 0.836 and 0.726. Hydrogen peroxide G-value average DR dependency in both solutions was statistically significant ($p < 0.05$). As for pulse and bunch DR influence, the slope of linear fits was not statistically significant ($p > 0.05$) with poor description of data points indicated also by R^2 values - 0.282 and 0.245 for pulse DR definition and 0.317 and 0.267 - bunch DR, respectively.

In presence of solvated electron scavengers, the role of immediate radiochemical interactions competition as described for pure aerated water could be diminished. With solvated electrons scavenged by nitrate ions - Reactions A.4.29 and A.4.30 are inhibited. Thus, hydrogen peroxide production increases via hydroxyl radical recombination (Reaction A.4.19) as competition with Reaction A.4.29 is decreased. The impact of fast reactions is lowered with respect to pure water scenario, with higher role in resulting DR dependency possibly associated with long-term measurement setup of the experiments (as discussed for X-rays) - hydroperoxyl radical recombination. With DR dependency already theorized for X-ray measurements, the average DR is better descriptor as hydroperoxyl recombination is relatively slow reaction (Reaction A.4.23). Thus, time-average concentrations of radiolytic species participating in Reactions in A.4.24, A.4.25 and A.4.23 are relevant for rate of hydroperoxyl recombination, possibly attributable to hydrogen peroxide G-value dependency on average DR.

For 250 μM sodium nitrate solutions at pO_2 of 4%, no statistically significant ($p > 0.05$) hydrogen peroxide G-value dependency can be observed for any DR definition. As already theorized for X-rays beam measurements, this could be attributed to quenching of hydroperoxyl radical recombination with lack of molecular oxygen and solvated electron scavenging, inhibiting reactions A.4.29 and A.4.30, possibly allowing DR independent hydroxyl radical recombination.

For 10 mM sodium nitrate solution at pO_2 of 21%, comparatively lower, but statistically significant ($p < 0.05$) hydrogen peroxide production dependency was observed with respect to pulse and bunch DR, while no statistically significant ($p > 0.05$) dependency was observed for average DR. Although the role of molecular water ion scavenging and subsequent reduction of hydroxyl radical production could be theorized

Table 5.5.

Statistical analysis of hydrogen peroxide production yield dependency on average, pulse, and bunch dose rates in samples of pure water and sodium nitrate (NaNO_3) solutions of varying concentration irradiated with pulsed electron beam

Sodium nitrate concentration and pO_2 in the solution	Slope of linear fit* $k \pm \sigma_k$	p-value**	Coefficient of determination for linear fit, R^{2***}
Dose rate definition: average dose rate			
Pure water, 21%	-0.344 ± 0.104	0.0079	0.548
10 mM, 21%	-0.084 ± 0.053	0.1422	0.213
250 μM , 21%	-0.458 ± 0.095	0.0007	0.726
1 μM , 21%	-0.414 ± 0.061	0.0001	0.836
250 μM , 4%	-0.038 ± 0.017	0.0448	0.363
Dose rate definition: pulse dose rate			
Pure water, 21%	-0.574 ± 0.051	0.0000	0.932
10 mM, 21%	-0.191 ± 0.049	0.0028	0.611
250 μM , 21%	-0.269 ± 0.192	0.1915	0.245
1 μM , 21%	-0.312 ± 0.183	0.1265	0.282
250 μM , 4%	-0.036 ± 0.028	0.2285	0.165
Dose rate definition: bunch dose rate			
Pure water, 21%	-0.741 ± 0.072	0.0000	0.918
10 mM, 21%	-0.241 ± 0.065	0.0042	0.581
250 μM , 21%	-0.381 ± 0.248	0.1551	0.267
1 μM , 21%	-0.448 ± 0.233	0.0905	0.317
250 μM , 4%	-0.049 ± 0.035	0.1913	0.187

* Fit parameters and respective standard deviations of fit parameters calculated using orthogonal distance regression between hydrogen peroxide G-value and decimal logarithm of respective DR, accounting for measurement uncertainties of both parameters

** t-test for slope of the fit, degrees of freedom - 10 (12 measurement points), H_0 : $k = 0$. 95% confidence level chosen. Statistically insignificant p values ($p > 0.05$) indicated in red, while statistically significant ($p < 0.05$) indicated in green for positive k and blue for negative k .

*** Weighed coefficient of determination R^2_{weighted} was calculated based on Appendix 4.1.

to be influenced by short term DR, it should be noted that the observed dependency is lower compared to other scenarios, with slightly worse description of data by the linear

fit, with R^2 of 0.611 and 0.581 for pulse and bunch DRs. This scenario can be considered as limited by measurement uncertainty level.

Summary of measured quantity - dose, DR and H_2O_2 concentration - and calculated H_2O_2 G-value uncertainties during experimental campaign with pulsed electron beams is provided in **Appendix 4.6**. In contrast to X-ray beam measurements and setup condition dependent uncertainties, no significant trends can be observed between the different beam settings. Average relative uncertainties in ranges of 6.5-9.9%, 3.2-6.7% and 5.4-8.9% for dose (and DR), H_2O_2 concentration and H_2O_2 G-value, respectively.

While H_2O_2 concentration uncertainties were of similar level to X-ray experiment campaign, the observed dose (and DR) uncertainties were significantly higher and main contributors to G-value uncertainty. With the limited field size, samples were irradiated axially with respect to the beam. The limited field size cannot ensure LSE, thus depth dose distribution of used 18 MeV electron beam has. This contributes to relatively high dose gradient across the sample. Additionally, large dose deviations were observed transversally - dipole magnet just before irradiation station introduces high dispersion for the output beam (significant intensity variation transversally).

No additional uncertainty measurements were done for the pulsed electron beam experimental campaign due to beam time limitations.

5.3. Conclusions and discussion

Chapter 5 presented experimental validation measurements of solvated electron role in radiochemical changes under UHDR irradiation. Performed experimental campaign aimed to validate theoretical assumptions of the model developed in Chapter 4. As measurable quantity of interest, G-value of hydrogen peroxide was evaluated due to its relatively long lifetime compared to other radiochemical species. Impact of DR on measured hydrogen peroxide production yield was evaluated with low-LET particle beams - X-rays and electrons. Measurements with a continuous X-ray beam were done in the average DR range of 0.1 to 10 Gy/s. For pulsed electron beam, measurements were performed in the average DR range from 1 to 100 Gy/s, with varying beam temporal structure.

Reference measurements were performed in pure, distilled water for two pO_2 levels of 21% and 4% to investigate the impact of oxygen level. To investigate the impact of solvated electrons on radiochemical changes during UHDR irradiation, 2 different scavenger species were used - nitrous oxide for reference [2] and sodium nitrate as a method developed by the Author. Using different concentrations of sodium nitrate, different chemical pathways can be probed with the goal to assess the role of solvated electrons in radical-radical recombination interactions under UHDR.

Main conclusions from the presented results can be summarized as:

1. For X-ray irradiation, in pure, aerated ($\text{pO}_2 = 21\%$) water hydrogen peroxide G-value has a statistically significant ($p < 0.05$) reduction with respect to increasing average

DR in range 0.1 to 10 Gy/s. With average DR increasing up to 10 Gy/s, hydrogen peroxide yield in aerated water decreased by up to 17 %;

2. Hydrogen peroxide G-value DR dependency in pure, aerated ($pO_2 = 21\%$) is diminished ($p > 0.05$) by addition of nitrous oxide as solvated electron scavenger.
3. Method, using sodium nitrate as solvated electron scavenger, has been developed, improving the reliability of measurements with respect to nitrous oxide and allowing flexibility to explore solvated electron scavenging capacity related effects.
4. Hydrogen peroxide G-value DR dependency was observed ($p < 0.05$) in aerated ($pO_2 = 21\%$) sodium nitrate solutions with concentration below 100 - 250 μM , though is completely diminished ($p > 0.05$) for higher sodium nitrate concentration ($> 250 \mu M$).
5. Reducing pO_2 level from 21% to 4%, hydrogen peroxide G-value DR dependency in pure water was diminished ($p > 0.05$).
6. For pulsed electron beam irradiation, in pure, aerated ($pO_2 = 21\%$) water hydrogen peroxide production yield has a statistically significant ($p < 0.05$) reduction with respect to increasing DR (average, pulse and bunch). With average DR increasing up to 100 Gy/s, hydrogen peroxide yield in aerated water decreased by up to 38%;
7. For pulsed electron beam irradiation of pure, aerated ($pO_2 = 21\%$) water, hydrogen peroxide G-value reduction is best described by pulse or bunch DR increase (R^2 of 0.932) in comparison to average DR (R^2 of 0.548). Findings indicate possible role of beam microstructure on UHDR radiochemical effects relevant for *FLASH*.
8. For pulsed electron beam irradiation, DR dependency of hydrogen peroxide yield is diminished ($p > 0.05$) by high concentration of solvated electron scavenger - sodium nitrate ($> 250 \mu M$) - or decreased pO_2 level - from 21% to 4%.
9. For pulsed electron beam irradiation, DR dependency of hydrogen peroxide G-value is better described by average DR for low concentration (100 - 250 μM) sodium nitrate solutions.
10. All finding indicated that solvated electrons have a significant role in UHDR radiochemical changes in water medium, disrupting radical-radical recombination due to scavenging of hydroxyl radical and molecular hydrogen peroxide.

Limitations of the performed research. Additional notes and implications of the work

Considering the methodology and results presented in this Chapter, following limitations and additional implications of the performed study were identified:

- focusing first on average DR, presented results on hydrogen peroxide G-value decrease with increasing DR is in agreement with similar studies as [24, 26-29] and others summarized in Appendix of Chapter 3. The magnitude of hydrogen peroxide G-value does slightly differ between among similar studies as well as presented results, though it should be noted that several differences between the medium used and oxygen level in the sample can be observed as summarized in Appendix of Chapter 3. Considering the impact of beam temporal structure and findings on pulse and bunch DR as

primary determinants, differences with other studies can be observed. Only study of [24] can be considered for direct comparison – while [24] also observed impact of pulse and bunch DR, mean dose rate was found as the main determinant contrasting findings of this work. It should be noted that a different medium and oxygen level was used in [24], possibly attributable to observed differences and prompting further research. Nevertheless, debate on whether average DR or pulse DR is the primary determinant of *FLASH* effect remains open with differing results also observed within *in-vitro* and *in-vivo* studies [32-35]. Presented results also contribute to the observed difference with MC study results [36-43], further prompting the necessity to re-evaluate and improve existing MC models for radiochemical simulations.

- while presented results were acquired with low-LET irradiation (photons, electrons), observed phenomena can be discussed in context of high-LET ion beams. Presented findings, hypotheses on the underlying interplay of water radiolysis interactions under UHDR conditions and clear role of solvated electrons as one of main determinants of UHDR induced radiochemical changes validate the assumptions made during development of the model presented in Chapter 4. Hypothesised interplay of water radiolysis interactions would suggest decreased hydrogen peroxide G-value DR dependency with high-LET ions due to limited diffusion of radiolytic species and inter-track effects. This hypothesis would suggest higher DR and dose level threshold with ion beams as presented in Chapter 4. Nevertheless, these hypotheses need to be validated in a dedicated future experimental campaign, which would be of crucial importance to assess radiochemical changes under UHDR and by extension – necessary *FLASH* effect conditions – with ion beams.
- while the majority of the presented results focused on normoxic conditions, additional results briefly presented in Appendix of this Chapter suggest different hydrogen peroxide G-value dependency for varying oxygen level. Considering the oxygen level differences between normal and tumour tissue, additional future studies systematically evaluating the impact of oxygen on UHDR induced radiochemical changes would be of great importance to explore the differential response of *FLASH* effect. Adaptations of the setup to enable accurate measurement of initial oxygen level within the sample would be crucial for these studies.
- due to measurement setup and beam condition limitations, relatively high uncertainties were observed in calculation of absorbed dose and dose rate. While statistical significance was maintained for the observed phenomena, possible adaptations could be considered for the setup to further reduce the uncertainty. To reduce the dose and hydrogen peroxide concentration non-uniformity within the sample, smaller sample size should be considered for limited beam size conditions. With sufficient technical capabilities of X-ray tube or electron linear accelerator, higher X-ray energy and increased field size, respectively, would reduce dose non-uniformity within the sample. In case of electrons beams, if sufficiently high energy and field size would be feasible, LSE conditions and plateau within the PDD

could be achieved. For possible future studies with high-LET radiation, excellent dose uniformity could be achieved in the plateau region, though additional setup adaptations would need to be considered for measurements at highest LET near the Bragg peak.

- as interplay between radiochemical interactions on different timescales was hypothesised as key determinant of observed radiochemical changes, presented has slight limitations due to hydrogen peroxide measurement approach. To clearly distinguish the role of immediate and long timescale radiochemical interactions, adaptations of the setup to enable online measurements of hydrogen peroxide concentration would be of great benefit for future research.

Future research outlooks

Considering the methodology, results and study limitations presented in this Chapter, following pathways for future additional research were identified:

- dedicated, systematic experimental campaign on hydrogen peroxide G-value dependency with high-LET radiation would be the first important step to experimentally assess the possible differences of dosimetric conditions necessary to achieve *FLASH* effect with ion beams.
- dedicated, systematic experimental campaign on the impact of oxygen should be performed as oxygen level clearly plays a role within observed radiochemical changes. As differences in oxygen levels can be observed between normal and tumour tissue, experimental findings in radiochemistry could play a significant role in better understanding the differential response of *FLASH* effect.
- future studies should also expand the dose rate range studied, considering technological limitations. Such results would be of high relevance for ion beam delivery due to locally high instantaneous DR for PBS delivery.
- as presented findings were observed in water, future studies with both low-LET and high-LET should also evaluate radiochemical changes in biologically relevant media
- to facilitate further improvement of MC simulation models, experimental measurements should be used as validation for radiochemical modelling algorithms.

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Dose and dose rate pencil-beam algorithm development for ion beams

Chapter 6 focuses on the development of a versatile algorithm for dose, DR and other relevant dosimetric parameter calculation to be used for comparisons of UHDR ion beam delivery approaches discussed in Chapter 7, while implementing the model developed in Chapter 4. To achieve computationally inexpensive calculation and higher versatility in beam parameter adaptation, PB type algorithm was developed in favour of full MC approaches. Following the results presented in Chapter 4, the algorithm was developed for use with light ion beams - protons, helium, and lithium ions.

Section 6.1 presents the methods used for the development of PB algorithm: reference data MC simulations, depth dose and lateral profile parametrization, parametrization of other relevant dosimetric parameters and DR calculation approach. Methods for validation of developed algorithm accuracy are also discussed.

Results on the developed algorithm and its accuracy are reported in Section 6.2. Conclusions on the developed algorithm are given in Section 6.3. Accuracy and versatility of the proposed algorithm is compared to similar approaches developed in previous studies. Limitations of the current algorithm are identified, discussing necessities for full-scale treatment planning system development.

As the results in Chapter 4. indicated favourable *FLASH* effect dosimetric conditions with low-LET ionizing radiation, VHEE could be considered as another promising modality to be used comparatively. Thus, the developed PB algorithm was also adapted for VHEE beams, to expand the delivery method evaluation in future research work with respect to Chapter 7. VHEE parametrization results are summarized in **Appendix 5.3.** of the Thesis.

Contributions of the Author: All work presented in this Chapter has been performed solely by the Author, indicating used literature sources where applicable.

Approbation of the results presented in this Chapter:

- Oral presentation at 3rd CERN Baltic conference (CBC'23) in Riga, Latvia, 2023
K.Pajskis, M.Sapinski, J.Seco, T.Torims, M.Vretenar “Analytical pencil beam dose and dose-rate engine development for FLASH therapy studies of heavy ion and very high energy electron beams”
-

6.1. Modelling and analysis methodology

This Section provides brief summary of the modelling and analysis methodology used within the study, while additional methodological details are given in Appendix 5.1.

Versatile algorithm for dose, other relevant dosimetric parameter and DR calculation was developed for comparison of UHDR ion beam delivery methods and to implement the model of Chapter 4. For higher versatility and computational efficiency, pencil-beam (PB) type algorithm was developed with dose distribution parametrized as:

$$D(x, x', y, y', z) = IDD(z) * DP(r, x', y', z) \quad (6.1)$$

where $IDD(z)$ is laterally integrated depth dose (IDD) at depth z and $DP(r, x', y', z)$ corresponds to relative value of lateral dose profile for a beam centred at coordinates (x', y') .

MC base data for protons, helium-3, helium-4, lithium-6, lithium-7 and carbon-12 were simulated for energies corresponding to ranges in water between 20 and 360 mm with step of 20 mm - scoring dose, LET_d, mMKM parameters and solvated electron G-values.

IDD data were spatially renormalized to the mean range R_{mean} and used as a lookup table for interpolation [91]. 5 different approaches for lateral dose profile parametrization were evaluated: sum of double Gaussian function, sum of a double Gaussian and single logistic function, sum of single Gaussian and double logistic function, triple Gaussian function and sum of a Gaussian function and a Voigt profile distribution. First Gaussian term was analytically described by MCS according to Highland formula. As other terms correspond to “halo” by secondary nuclear fragments - complexly dependent on both initial particle kinetic energy and depth in material - relevant parameters were acquired by fitting procedure.

To model the off-axis behaviour of LET (and other associated parameters), lateral dose profile model was used as the basis, following [92], assigning constant LET at each depth for terms of dose profile function. Thus, LET at depth z and radial position r can be described as:

$$LET_d(z, r) = \frac{w_1(z)f_1(z, r) * LET_1(z) + w_2(z)f_2(z, r) * LET_2(z) + w_3(z)f_3(z, r) * LET_3(z)}{w_1(z)f_1(z, r) + w_2(z)f_2(z, r) + w_3(z)f_3(z, r)} \quad (6.2)$$

where f_1, f_2 and f_3 are terms of lateral dose profile model, w_1, w_2 and w_3 - weights of each term, and LET_1, LET_2 and LET_3 are LET values assigned for each term at depth z . $LET_1(z)$, $LET_2(z)$ and $LET_3(z)$ are acquired via fitting Equation 6.2 output to MC results.

Accuracy of parametrization approaches was assessed with MC results as reference.

Methodology as relevant for parametrization of VHEE beams is additionally given in Appendix 5.2.

6.2. Results on the developed algorithm

Validation of integrated depth dose interpolation accuracy

For protons and light ions, accuracy of IDD was evaluated based on a dataset of discrete energy levels as indicated in Table A.5.2 (see **Appendix 5.1.**). Good agreement for interpolated IDD was observed for all particle types studied with respect to MC reference data for energy levels as indicated in Table A.5.2 (see **Appendix 5.1.**). Relative deviations of less than $\pm 0.5\%$ were observed in the plateau region, while less than $\pm 1\%$ - in the Bragg peak.

Results as relevant for future ion beam comparison with VHEE beams are given in **Appendix 5.3.**

Comparison of functions for lateral dose profile parametrization

The main investigated aspect in the PB algorithm development was comparative study of different functions for lateral dose profile parametrization. Lateral dose profile parametrization function comparison is illustrated in Figures 6.1. and 6.2 for protons and helium-4, respectively. **Appendix 5.4.** provides data for lithium-6 and carbon-12 ions, with data on helium-3 and lithium-7 having same observed trends as helium-4 and lithium-6. Subfigures (a) indicate qualitative comparison of dose profile shape for the different parametrization functions, while Subfigures (b) - quantitative comparison based on average deviations observed for normalized lateral dose profile distributions.

Data Figures 6.1., 6.2. and **Appendix 5.4.** illustrate that the central part of lateral dose profile is sufficiently well described as it corresponds to the small angle MCS - Gaussian with standard deviation of σ_{MCS} . Accuracy of lateral dose profile description between the different parametrization functions mainly differs in the low dose “halo” region, which physically corresponds to contributions of large angle MCS, scattered secondary nuclear fragments and high-energy scattered secondary electrons. While clinically sufficient accuracy can be achieved with all the considered lateral parametrization functions, quantitative comparison was of interest as lateral dose profile modelling accuracy corresponds also to LET and other parameter modelling accuracy in the developed PB algorithm.

Subfigures (b) indicate worst accuracy for Double Gaussian, attributable to smaller number of free parameters compared to other functions, thus is excluded from qualitative analysis of Subfigures (a).

Example results for proton beams in Figure 6.1 (b), indicated best performance for “2G+L”, “G+2L” and “G+V” parametrization functions. Compared to lateral parametrization functions that are a sum of multiple Gaussians, these functions significantly better can describe the low-dose part of the distribution. Gaussian parametrization functions - “2G” and “3G” - are unable to accurately model lateral dose profile beyond 0.1% of central axis value, significantly underestimating the low dose “halo”. PDFs of logistic and Voigt profile functions have significantly higher “tails” compared to Gaussian function, thus are better suited for low dose “halo” description.

Introduction of logistic or Voigt profile function terms in the lateral dose profile parametrization function resulted in slightly decreased average deviation, as illustrated in Figure 6.1 (a). “Halo” dose levels are quite low - $< 0.1\%$ - thus contributing less to average deviation evaluated quantitatively, thus the quality of lateral dose profile shape parametrization was also evaluated qualitatively in Figure 6.1 (a). Qualitative evaluation indicates that lateral dose profile shape of proton beams is best described by “2G+L” and “G+2L”, with slightly better performance of the latter. “G+V” parametrization function can achieve sufficient accuracy for dose levels $> 0.05\%$ of central axis dose level, though it overestimates lower doses by up to a magnitude with respect to MC reference.

Similar trends can be observed for helium-4 ions, illustrated in Figure 6.2. Quantitative evaluation of deviations (subfigure (b)) for modelled lateral dose profile with respect to MC reference data indicated best performance for “G+2L” parametrization function, with comparable accuracy for “2G+L” and “G+V” parametrization. Qualitative evaluation in Subfigure (a) indicates that for dose levels $> 0.01\%$ of central axis value, dose profile shape is most accurately described by “G+2L” function. “2G+L” and “G+V” parametrization slightly underestimates and overestimates, respectively, the relative dose values in range $0.01\% - 0.1\%$ of central axis value. For dose levels $< 0.01\%$, the performance of “G+2L” and “G+V” parametrizations are comparable underestimating and overestimating, respectively the low dose levels by up to a magnitude, respectively.

For lithium-6 ions in **Appendix 5.4**, similar trends as for helium-4 ions were observed - best performance for “G+2L” parametrization function for dose levels $> 0.01\%$ of central axis value was observed. For dose levels $< 0.01\%$ of central axis value, “G+V” parametrization better reproduces the shape of MC reference dose profile compared to “G+2L”. Relatively lower deviations with respect to MC reference data in this low dose region were also observed for “G+V” parametrization, compared to “G+2L”. Nevertheless, “G+V” parametrization tends to overestimate dose values in range 0.01 to 0.1% of central axis value.

Compared to lithium-6 ions, identical performance trends of each lateral dose profile parametrization function were observed for carbon-12 ions as illustrated in **Appendix 5.4**. Low-dose levels $< 0.01\%$ (with respect to central axis value) are modelled significantly worse by “G+2L” function, underestimating the dose levels by several orders of magnitude. Nevertheless, “G+2L” parametrization maintains best accuracy for more clinically relevant dose levels of $> 0.01\%$ with respect to central axis value.

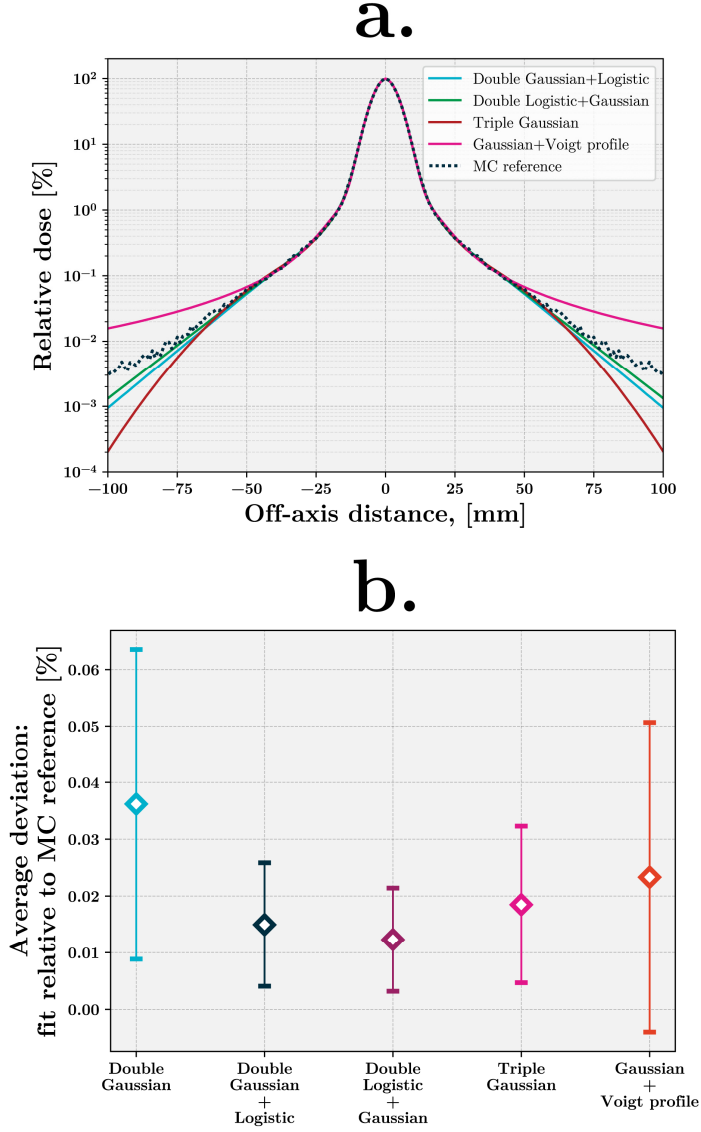


Figure 6.1. Comparison of studied fitting functions for lateral dose profile parametrization of protons

Subfigure (a): Example lateral dose profile given for proton PB of 219.3 MeV (range 300 mm) at 250 mm depth, values are normalized to central axis value.

Subfigure (b): Comparison of average deviation between MC reference data and different fitting functions for proton PB of 219.3 MeV. Calculations based on difference between whole lateral profile data (normalized to central axis) at all depths up to dose maximum depth. Average deviation with 1σ uncertainty indicated.

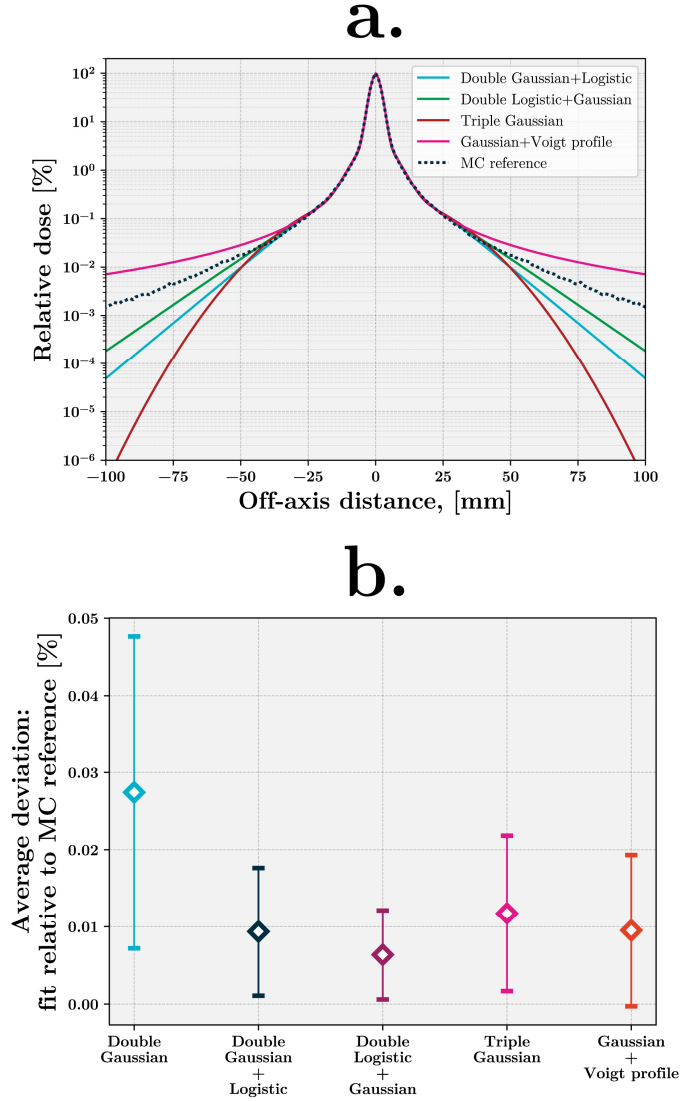


Figure 6.2. Comparison of studied fitting functions for lateral dose profile parametrization of helium-4 ions

Subfigure (a): Example lateral dose profile given for helium-4 ion PB of 217.4 MeV/u (range 300 mm) at 250 mm depth, values are normalized to central axis value.

Subfigure (b): Comparison of average deviation between MC reference data and different fitting functions for helium-4 ion PB of 217.4 MeV/u. Calculations based on difference between whole lateral profile data (normalized to central axis) at all depths up to dose maximum depth. Average deviation with 1σ uncertainty indicated.

Summarizing the performance of the different parametrization functions for ion types studied, the “G+2L” function proposed within the Thesis indicates the best description of lateral dose profile with respect to MC reference data for clinically relevant dose levels of $>0.01\%$ with respect to central axis value. While “G+V” parametrization provides improved description of the very low level - $<0.01\%$ with respect to central axis values - dose “halo”, especially for heavier ion types as lithium-6, lithium-7 and carbon-12, it slightly overestimates dose levels in 0.01 - 0.1% range. While the focus of other dosimetric parameter modelling will be considered with “G+2L” parametrization, the other proposed approaches will still be considered.

Results as relevant for future ion beam comparison with VHEE beams are given in **Appendix 5.3**.

Lateral dose profile parametrization functions: analysis of free parameters

Values of functional term scale parameters (as σ_1 , s_2 and s_3) and weights of each term (w_1 , w_2 and w_3) as function of depth were evaluated for lateral profile parametrization. For considered “G+2L” lateral dose profile function, visual examples of scale parameter and functional term weight dependency of depth in irradiated object are illustrated in Figures 6.3 and 6.4. for protons and helium-4, respectively. **Appendix 5.5**. provides data for lithium-6 and carbon-12 ions, with data on helium-3 and lithium-7 having same observed trends as helium-4 and lithium-6.

From illustrated data, the fixed term σ_1 corresponding to analytically calculated MCS contribution decreases in magnitude for increasing mass of the ion. This reflects the reduced MCS magnitude for heavier particles, as discussed in Chapter 2. Weight of MCS contribution w_1 is highest for ion all ion types considered, indicating the role of MCS as primary process contributing to the shape of lateral dose profile. Weight w_1 decreases with increasing depth, indicating higher contribution of secondary particle “low-dose halo” to lateral dose profile at larger depths in the irradiated object. Analysing w_1 values for beam energies corresponding to range of 260 mm in water, primary particle MCS Gaussian contribution is higher than approximately 65%, 85%, 95% and 90% of lateral dose profile for protons, helium-4, lithium-6 and carbon-12 ions, respectively. Increasing contribution of MCS Gaussian for heavier ions is attributable to lower contribution of low dose “halo”. This is also visually illustrated by lateral dose profiles in Figure 6.1., 6.2. and **Appendix 5.4**. Lower contribution of secondary particles for heavier ions is attributed to significantly higher energy loss of heavy primary particles undergoing MCS, compared to scattered light fragments. Additionally, the kinematics of secondary particle production also contribute to decreased contribution of low-dose halo. In case of lightest ions considered - protons - secondary nuclear fragments are of the same mass (protons or neutrons) and are scattered at large angles, thus contributing more to the low dose “halo”. In contrast for heavier ions, secondary fragments mainly are produced via nuclear fragmentation of primary particles, thus maintaining large fraction of initial momentum. Thus, majority of the secondary fragments of heavy ion beams are “forward peaked”,

with their contribution to lateral dose profile sufficiently described by the MCS Gaussian function.

Reasoning of reduced low dose “halo” from secondary nuclear fragments for heavier ion beams is further illustrated by logistic function term scale parameter - s_2 and s_3 - dependency on depth in irradiated object (Subfigures (a) in Figure 6.3., 6.4. and **Appendix 5.5.**). Maximum value of scale parameter s_2 of first logistic function term in lateral dose profile function decreases with increasing ion mass, reaching values of about 3.8 mm, 3.1 mm, 2.8 and 1.8 mm for protons, helium-4, lithium-6 and carbon-12 ions, respectively. Similar, though less pronounced, trend can be observed for maximum value of scale parameter s_3 of second logistic function with maximum values of about 11.5 mm, 12.2 mm, 9.5 mm, and 5.7 mm, respectively. Observed dependency of scale parameters s_2 and s_3 indicates narrower low dose “halo” of the lateral dose profile distribution for heavier ions.

As discussed in Methodology section, the depth dependency of secondary, non-MCS functional term scale parameters cannot be accurately described analytically. As scale parameters of second and third functional terms correspond to secondary particles generated via nuclear interactions, more complex depth dependency is expected for these parameters with respect to EM interactions of MCS, as clearly observed in Figures 6.3., 6.4. and **Appendix 5.5.** Scale parameter and functional term weight depth dependencies are stored as lookup tables for the implementation of PB algorithm for all discrete energy levels used in the development process. For lateral dose profile parametrization in the fragmentation tail region, no analytical description was used for any of the functional terms, thus all the stored parameter values were acquired via fitting process.

Results as relevant for future ion beam comparison with VHEE beams are given in **Appendix 5.3.**

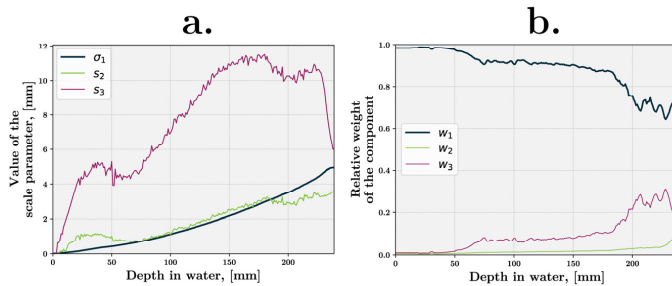


Figure 6.3. Example of scale parameters (a) and weights (b) of each fitting function term as a function of depth for proton pencil beam

Data are given for proton PB of 201.5 MeV (range 260 mm) up to dose maximum depth.

σ_1 and w_1 correspond to the Gaussian part of the fit, with s_2, w_2 and s_3, w_3 corresponding to each logistic function, respectively

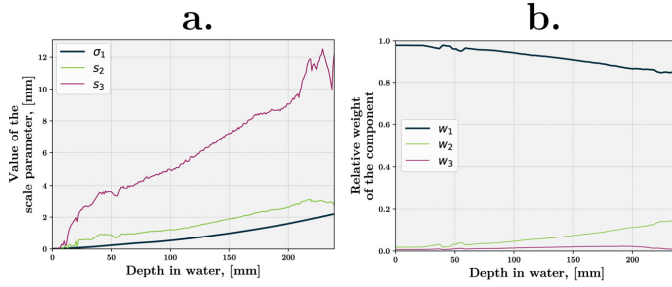


Figure 6.4. Example of scale parameters (a) and weights (b) of each fitting function term as a function of depth for helium-4 ion pencil beam

Data are given for helium-4 ion PB of 200.0 MeV/u (range 260 mm) up to dose maximum depth. σ_1 and w_1 correspond to the Gaussian part of the fit, with s_2, w_2 and s_3, w_3 corresponding to each logistic function, respectively

Accuracy of spatial dose distribution calculated with the developed model

With both IDD distribution interpolation and lateral dose profile parametrization validated, resulting spatial dose distributions were evaluated. Figures 6.5. and 6.6 present central plane 2D dose distributions calculated by the developed PB algorithm (for beam energies corresponding to 300 mm range in water) and comparison with MC reference data for protons and helium-4, respectively. For comparison, dose distributions are normalized to value at Bragg peak on central axis. **Appendix 5.6.** provides data for lithium-6 and carbon-12 ions, with data on helium-3 and lithium-7 having same observed trends as helium-4 and lithium-6.

Good agreement was observed between the data calculated by developed PB algorithm with respect to MC reference data. Observed maximum point-to-point deviations of relative dose distribution with respect to MC reference data were in the range $\pm 1\%$, with majority of deviations of $\pm 0.5\%$ for all ion types studied. Comparing ion types, largest deviations were observed for proton beams. Analysing the spatial variations, largest deviations were observed at very low depth near the entrance surface of the irradiated object.

Results as relevant for future ion beam comparison with VHEE beams are given in **Appendix 5.3.**

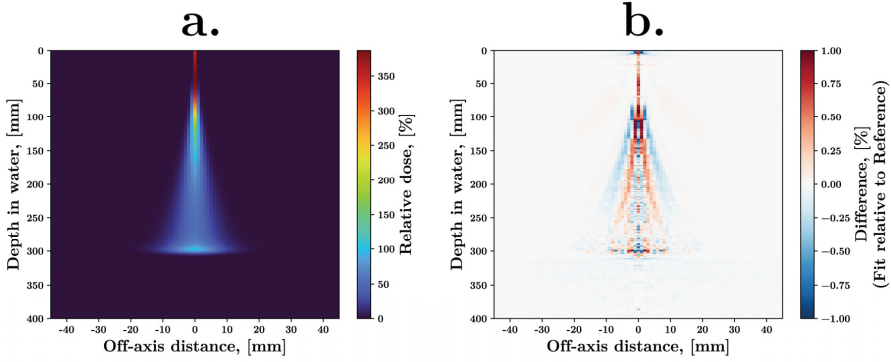


Figure 6.5. Accuracy of central plane dose distribution calculation with developed PB algorithm for protons in water

Data are given for proton PB of 219.3 MeV (range 300 mm). Dose distributions of MC reference and PB algorithm are both normalized to central axis dose value at Bragg peak position.

Subfigure(a): Dose distribution as modelled by developed PB algorithm

Subfigure(b): Difference of PB algorithm calculated dose distribution with respect to MC reference.
Difference calculated between the normalized dose distributions.

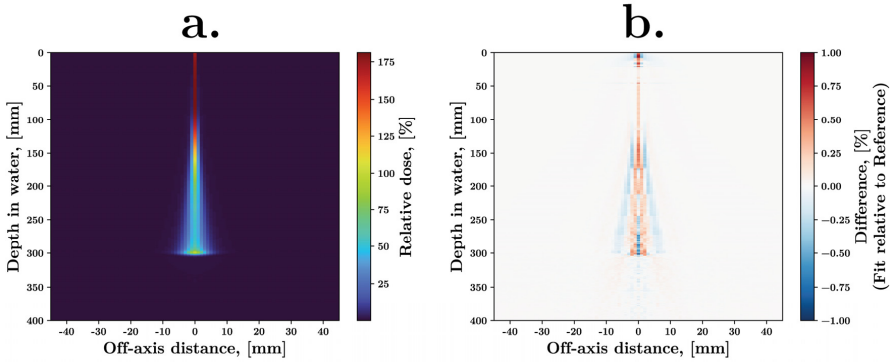


Figure 6.6. Accuracy of central plane dose distribution calculation with developed PB algorithm for helium-4 ions in water

Data are given for helium-4 ion PB of 217.4 MeV/u (range 300 mm). Dose distributions of MC reference and PB algorithm are both normalized to central axis dose value at Bragg peak position.

Subfigure(a): Dose distribution as modelled by developed PB algorithm

Subfigure(b): Difference of PB algorithm calculated dose distribution with respect to MC reference.
Difference calculated between the normalized dose distributions.

Comparison of approaches for LET spatial distribution modelling

In context of PT and IBT, it is important to also model LET for RBE estimation. For *FLASH* dose threshold model implementation developed in Chapter 4., spatial distributions of microdosimetric parameters and solvated electron G-value are necessary. Parametrization of depth distribution and off-axis dependency of these

parameters was done in the development of the PB algorithm. As these parameters are inter-related, results only for LET modelling are presented here. The same parametrization was used for the other two parameters, with trends and accuracy similar to those shown for LET. Results on LET modelling - depth distribution and off-axis dependency - with the developed PB algorithm are summarized in Figures 6.7 and 6.8 for protons and helium-4, respectively. Subfigures (a) provide the comparison between 2 and 3 component modelling for off-axis dependency, Subfigures (b) - off-axis dependency modelling accuracy for different parametrization functions, while Subfigures (c) - depth dependency accuracy. Comparison is evaluated with respect to MC data as reference. **Appendix 5.7.** provides data for lithium-6 and carbon-12 ions, with data on helium-3 and lithium-7 having same observed trends as helium-4 and lithium-6.

All dose-weighted LET data illustrated in Figures 6.7., 6.8. and **Appendix 5.7**, correspond to particle scoring with only primary particles and secondary fragments with the same or lower atomic number considered. As discussed in Methodology section, three scoring approaches for dose-weighted LET (and other parameters) were considered: the one mentioned - primary particles and secondary fragments with the same or lower atomic number -, secondly - addition of secondary fragments with atomic number one unit higher than primary particle and thirdly - scoring of all particles. The second and third approach, to varying extent, includes nuclear fragments from target fragmentation reactions, while first approach includes only secondary particles from projectile fragmentation. Such dose-weighted LET scoring approach comparison has been also investigated in other studies [2-3]. For light ion beams, as protons and helium-4 ions, the dose-weighted LET is increased with inclusion of target fragments (in other parameter context - increased microdosimetric parameters and reduced solvated electron G-value). Heavy target fragments are produced at low kinetic energies, having significantly higher LET values compared to primary light ions or projectile fragments. Fluence of heavy target fragments is very low and with very little contribution to overall dose distribution. Nevertheless, as LET values of these fragments are one or even two orders of magnitude higher than for primary particles and projectile fragments, they do have non-negligible impact on dose weighed LET values due to mathematical formalism used weighing, as discussed in Chapter 2. The inclusion of target fragments in dose-weighted LET is still under research [2-3], attributable also to the reduced precision for modelling of respective nuclear production pathways.

In this work, it was observed that for proton, helium-3 and helium-4 ions, inclusion of target fragments in dose weighing did increase calculated LET values. Though, in context of both depth variation and off-axis dependency characterization, inclusion of target fragments resulted in significant noise in LET values of MC reference dataset. This resulted in decreased parametrization accuracy for whole LET distribution, especially in regions corresponding to clinically relevant dose levels. Therefore, LET and other considered parameter modelling was performed based on datasets including only primary particles and secondary fragments with the same or lower atomic number. The

differences observed between different LET scoring approaches were lower for lithium-6, lithium-7 and carbon-12 ions, as due to high LET of heavy primary particles and projectile fragments, the impact of target fragment LET was mathematically comparable and with overall negligible contribution to calculation.

Before comparing the depth distribution and off-axis dependency parametrization accuracy, it is also of importance to briefly analyse the processes resulting in the observed LET distributions. For all ion types considered, LET values increased with increasing depth reaching the maximum near the Bragg peak, attributable to mechanisms discussed in Chapter 2. For ions heavier than protons, LET values in fragmentation tail region are lower than near the Bragg peak due to contributions of high energy lighter projectile fragments with lower LET values. For off-axis dependency evaluation, clear differences can be observed between lighter (protons and both helium isotopes) and heavier (both lithium isotopes and carbon) ions. For lighter ions dose-weighted LET tends to increase with increasing off-axis distance. In case of protons, secondary protons scattered laterally are with lower kinetic energy compared to central axis, thus higher LET value. Similarly for helium-3 and helium-4 ions, the off-axis dependency mainly is attributable to low energy secondary helium ions or protons with higher LET compared to central region dominated by higher energy primary particles (lower LET). For heavy ions, the mechanisms are different. In case of both lithium and carbon ions, mainly light projectile fragments are scattered laterally - relatively high kinetic energies with low-LET. The central part of the distribution is dominated by heavy primary particles with high-LET, thus in contrast to light ions - LET decreases with increasing off-axis distance for heavy ions. This dependency is influenced by depth in irradiated object due to varying kinetic energy spectrum of secondary and primary particles and is significantly different between entrance plateau, Bragg peak, and fragmentation tail.

Analysing the parametrization accuracy of central axis LET depth dependency, data provided in Subfigures (c) illustrate no significant variation between the different parametrization functions considered. No significant deviations (all below $<0.5\%$) were observed between modelled values and MC reference data for central axis LET for depths up to the Bragg peak. Larger variations ($\sim 10\%$) were observed for modelled values with respect to MC reference data in fragmentation tail region, though statistical noise in the reference data for this region should be considered.

One of key aspects for accuracy of LET modelling by the PB algorithm is off-axis description. As mentioned in Methodology section, along with novel approach for lateral dose profile parametrization, an adapted approach for off-axis description of LET is considered. While studies as [22] have presented the approach to use two-term function for LET off-axis dependency modelling, approach to benefit from all three functional terms separately is explored. This comes at the expense of computational efficiency as slightly larger input dataset must be stored, though it could provide improved accuracy with respect to two-term modelling of LET off-axis dependency. Subfigures (a) in Figures

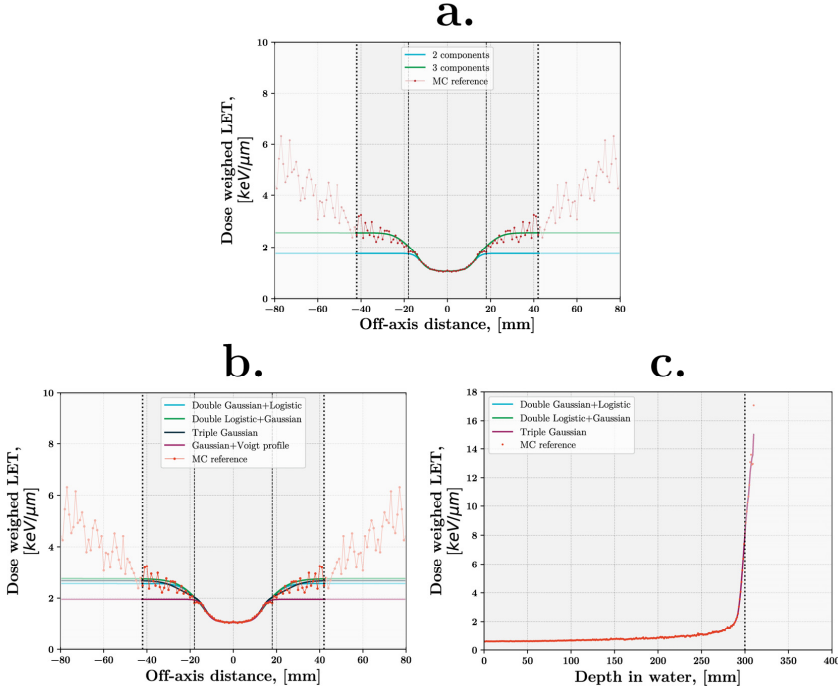


Figure 6.7. Comparison of studied approaches for dose-weighted LET parametrization for proton pencil beams

Data given for proton PB of 219.3 MeV (range 300 mm). Example LET_d off-axis dependency is given at 250 mm depth (Subfigures (a) and (b)). Dose-averaging of LET values in MC simulations is performed only for fragments of the same or smaller atomic number as incident particle ($Z \leq 1$)

Subfigure(a): Comparison of LET_d off-axis dependency fit with “Double Logistic+Gaussian” function using both logistic functions as free parameters (3 components) or the sum of the two as free parameter (2 components). Inner dashed lines indicate 1% dose level (normalized to central axis), outer - 0.1 % dose.

Subfigure(b): Comparison of LET_d off-axis dependency fit using 3 component approach with different combination of fitting functions. Inner dashed lines indicate 1% dose level (normalized to central axis), outer - 0.1 % dose.

Subfigure(c): Comparison of LET_d depth dependency fit using 3 component approach with different combination of fitting functions. Bragg peak position indicated with dashed line.

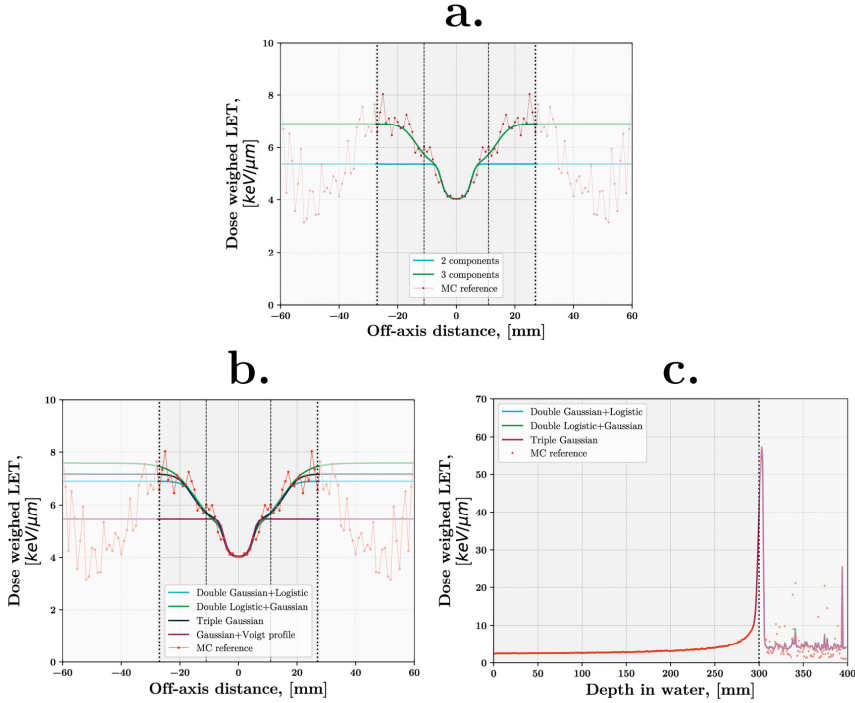


Figure 6.8. Comparison of studied approaches for dose-weighted LET parametrization for helium-4 ion pencil beams

Data given for helium-4 ion PB of 217.4 MeV/u (range 300 mm). Example LET_d off-axis dependency is given at 250 mm depth (Subfigures (a) and (b)). Dose-averaging of LET values in MC simulations is performed only for fragments of the same or smaller atomic number as incident particle ($Z \leq 2$)

Subfigure(a): Comparison of LET_d off-axis dependency fit with “Double Logistic+Gaussian” function using both logistic functions as free parameters (3 components) or the sum of the two as free parameter (2 components). Inner dashed lines indicate 1% dose level (normalized to central axis), outer - 0.1 % dose.

Subfigure(b): Comparison of LET_d off-axis dependency fit using 3 component approach with different combination of fitting functions. Inner dashed lines indicate 1% dose level (normalized to central axis), outer - 0.1 % dose.

Subfigure(c): Comparison of LET_d depth dependency fit using 3 component approach with different combination of fitting functions. Bragg peak position indicated with dashed line.

6.7, 6.8. and **Appendix 5.7.** present the comparison of two and three-term parametrization with “G+2L” function as the basis. For proton and helium-4 ion beams, both parametrization approaches provide comparable LET value description with respect to MC reference data in regions, where absorbed dose is higher than 1% of central axis value. For larger off-axis distance, the two-term approach is unable to account for further LET increase, which is appropriately modelled only by three-term approach. Three-term approach can adequately model off-axis LET increase for regions, where absorbed dose is higher than 0.1% of central axis value. For heavier ions - lithium-6 and carbon-12, similar

results were observed. Both two-term and three-term approaches reached comparable accuracy for off-axis distances in the region with absorbed dose level $>1\%$ of central axis value, though for carbon-12 ions better fit can be observed by three-term approach. For off-axis distances in the region, where absorbed dose level is $0.1 - 1\%$ of central axis value, LET off-axis dependency is better modelled by three-term approach, though comparable quality can be observed for lithium-6 ions. Better off-axis dependency description was achieved for proton and helium-4 ion beams, with a slight decrease in fit quality for lithium-6 and carbon-12 ions.

For three-term LET off-axis dependency modelling considered, different parametrization functions, as presented previously for lateral dose profile, were considered, with results presented in subfigures (b) in Figures 6.7, 6.8. and **Appendix 5.7**. “G+V” parametrization function data correspond to two-term approach, as a sum of only two functions. Overall, no significant differences were observed between “2G+L”, “G+2L” and “3G” parametrization function for three-term description of LET off-axis dependency, with slightly better performance of “G+2L” function for proton and helium-4 ion beams. “G+V” parametrization function performed comparatively worse as it corresponds to a two-term approach for LET off-axis dependency description. Similar performance was observed for all depths and different energies considered in the PB algorithm dataset, with results shown only for a single energy level and depth.

Summarizing the results on parametrization function comparison for both lateral dose profile and LET off-axis dependency description of proton and ion beams, “G+2L” parametrization function indicated best performance. For lateral dose profile, it provided most accurate modelling for off-axis dose levels $>0.01\%$ with respect to central axis value. For LET off-axis dependency description, used together with three-term approach, this function provided dose weighed LET (and other relevant dosimetric parameter) value accuracy of $< 1\%$ with respect to MC reference data at off-axis distances, where absorbed dose corresponds to $>1\%$ of central axis value, and $1-5\%$ - at off-axis distance, where absorbed dose corresponds to $0.1-1\%$ of central axis value.

Results as relevant for future ion beam comparison with VHEE beams are given in **Appendix 5.3**.

PB modelling for a realistic beam. Dose rate modelling approach

Although, no illustrative results are indicated on DR modelling, **Appendix 5.8**. introduces the approach for DR calculation considered for developed PB algorithm.

6.3. Conclusions and discussion

Chapter 6 presented the development of a pencil beam-based dose and DR calculation algorithm, which is suitable for calculations relevant for the model presented in Chapter 4. and able to account for parameters relevant for actual ion beam delivery. Developed pencil beam algorithm is aimed to be used as a tool in future research work

necessary for evaluation of specific ion beam delivery technologies relevant for UHDR irradiation.

Throughout the pencil beam algorithm development process, different analytical approaches were evaluated and compared for parametrization of lateral dose profile and off-axis dependency of LET, microdosimetric parameters and solvated electron production yield. Most of the analytical parametrization functions used for comparison were based on literature review, with a new approach - sum of a Gaussian and two logistic functions - proposed by the Author. Additionally, for parametrization of off-axis dependency of LET and other mentioned parameters, the Author proposed three-term function, comparing the achievable accuracy with two-term approach presented in literature. Accuracy of the developed PB algorithm was validated with respect to MC simulation data as reference. Additionally, implementation of the proposed pencil beam dose calculation was used also for DR spatial distribution calculation with different definitions relevant for UHDR delivery with ion beams.

Additionally, though not the focus, as results in Chapter 4. and 5. indicate favourable performance of low-LET particles, developed pencil beam algorithm approach was also used in context of VHEE, similarly exploring lateral dose profile and LET off-axis dependency parametrization, while also evaluating approaches for integrated depth dose parametrization for varying energy levels.

Main conclusions from the presented results can be summarized as:

1. A PB algorithm capable of accurate dose, LET, microdosimetric parameter and solvated electron production yield spatial distribution calculation has been developed for protons, helium-3, helium-4, lithium-6, lithium-7, and carbon-12 ions. Algorithm is valid for clinically relevant energies with range in water up to 36 cm, as well as for transmission energies - range in water up to 60 cm.
2. Lateral dose profile of studied ions can be best parametrized by a sum of Gaussian and two Logistic functions. Proposed parametrization approach has best agreement with MC reference data, in comparison to approaches in literature [11-19], for dose levels above 0.01% level with respect to central axis value.
3. Using the IDD interpolation and proposed lateral dose profile parametrization, developed PB algorithm achieves calculated central plane dose distribution accuracy of $\pm 1\%$ with respect to MC reference data in water.
4. Three-term parametrization approach for LET, microdosimetric parameter and solvated electron production yield off-axis dependency modelling has been proposed. Compared to other analytical approaches in literature [22-23], it improves agreement with MC reference data. While analytical approaches in literature can accurately predict LET (and other parameter) off-axis dependency only for regions with dose above 1% of central axis value, three-term approach also accurately predicts LET in lower dose regions - 0.1 to 1% of central axis value.
5. Using sum of Gaussian and two Logistic functions for lateral dose profile description and three-term parametrization approach, LET (and other parameters) are modelled

with deviation of <1% with respect to MC data for regions with absorbed dose above 1% of central axis value and 1-5% - for regions with dose of 0.1-1%.

6. Developed PB algorithm is compatible with DR calculation in active pencil beam scanning delivery, implementing various DR definitions as outlined in [24].
7. Developed PB algorithm can be adapted for VHEE beams, providing similar level of accuracy with respect to ion beams (see **Appendix 5.2** and **5.3**).

Limitations of the performed research. Additional notes and implications of the work

Considering the methodology and results presented in this Chapter, following limitations and additional implications of the performed study were identified:

- result validation of the proposed PB algorithm currently focused on simple geometry and uniform material density. While maintaining the core base of PB algorithm developed in this Chapter, additional algorithm developments should focus on handling irregular entrance surface geometries and varying tissue densities. As developed PB algorithm also enables LET, RBE and other related parameter calculation, developments on analytically modelling changes in nuclear fragmentation due to varying tissue elemental composition should also be considered.
- while PB algorithm was chosen for development in this Chapter due to high flexibility and computational efficiency, considering comparison of different beam delivery patterns in future studies, accuracy limitations in complex, highly heterogeneous anatomies as encountered in clinical treatment planning need to be considered. In treatment planning, PB algorithm accuracy is mainly limited in highly heterogeneous anatomical localizations such as head and thorax due to presence of air, resulting in significant under- or overestimation of the dose. If the flexibility and computation efficiency of PB algorithm is to be maintained, while approaching the accuracy of full MC simulations, significant future developments are necessary for treatment planning compliant implementation.

Future research outlooks

Considering the methodology, results and study limitations presented in this Chapter, following pathways for future additional research were identified:

- further adaptations of the proposed PB algorithm to include heterogeneity correction effects as relevant and necessary for clinical patient anatomies.
- quantitative comparison study, using the developed PB algorithm, for the different UHDR delivery approaches with light ion beams as presented in Chapter 7, focusing on the differences between achievable dose distribution conformality, DR level and LET distribution.
- quantitative comparison study, using the developed PB algorithm, between VHEE and light ion beams, focusing on differences for achieving *FLASH* effect threshold conditions (as defined by the model presented in Chapter 4), achievable dose distribution conformality and DR level.

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Review and comparison of ultra-high dose rate delivery methods for light ion beams

As briefly indicated in Chapter 3, UHDR delivery with light ion beams poses a significant challenge from technological perspective - achieving sufficient beam current and DR, while maintaining adequate dose conformality. Via “state-of-the-art” analysis, this Chapter evaluates challenges and possible solutions for UHDR technological delivery with light ion beams. Analysis was based on literature review as methodology, providing a summary on recent scientific research work on the topicality.

Similarly to Chapter 3., this Chapter starts with overview of the methodology used to perform the literature review in Section 7.1. Methodology outlines the used data sources and search keywords. Overview of literature analysis findings is presented in the subsections of Section 7.2. Section starts with brief introduction to UHDR delivery challenges of megavoltage X-ray photon and electron beams, identifying the necessity of light ion UHDR development due to limitations for these modalities. Introduction to treatment beam delivery method concepts at conventional DR - passive scattering and active pencil beam scanning - and identification of general UHDR challenges with light ion beams is presented next. Majority of this Section focuses on reviewing specific UHDR delivery approaches with light ion beams - use of transmission beams, use of beam modifying devices for 3D conformal *FLASH*, possibilities for full 3D active pencil beam scanning at UHDR and other approaches.

An in-depth comparative analysis of all presented technological UHDR delivery approaches with light ion beams is given in Subsection 7.2.1. - comparison for proton beams and identification for possible implementation challenges with helium-4 ion beams.

At the end of this Chapter, Section 7.3 summarizes main conclusions of the literature review and comparative analysis on light ion beam UHDR delivery methods. Implications for proton and helium-4 ion beam delivery with HeLICS is discussed. Chapter is concluded with outline of future research work necessary for quantitative evaluation and comparison of delivery methods using PB algorithm developed in Chapter 6.

Contributions of the Author: All work presented in this Chapter has been performed solely by the Author, indicating used literature sources where applicable.

Approbation of the results presented in this Chapter: Presented literature review results have not yet been presented or published.

7.1. Methodology of literature review used in the analysis

Comparative analysis of UHDR delivery approaches for light ion beams was based on scientific literature review. Search of scientific articles relevant to the analysis was performed using following databases and browsing tools: *Google Scholar* and *PubMed* by National Center for Biotechnology Information were used as primary sources, while *Scopus* and *ScienceDirect* - as secondary, where applicable. Additionally, official information provided by main commercial vendors of PT and IBT - IBA, Varian Medical Systems¹², Mevion, Hitachi, Sumitomo, and others - was also considered during the analysis. For certain technological solutions, patent search engine *Google Patents* was also used.

To include most research results, the time frame of article publication focused on last 10 years - 2015 to 2025. Nevertheless, for historical perspective, additional articles were included in the analysis as necessary - search directly done by Author or citations included in primary articles.

Keywords used for the literature review as queries are summarized in **Appendix 6.1**. To provide brief introduction into other modalities, compared to light ion beams, brief focus was given on broader review type articles on electron and high-energy photon UHDR delivery. For comparative perspective, literature search then focused on general aspects and most recent developments in clinical light ion beam delivery at conventional DRs, evaluating both passive scattering and active pencil beam scanning approaches. Finally, main focus of the literature review was on approaches specific to UHDR delivery with light ion beams.

After initial query, abstracts of scientific articles were analysed by Author, assessing the relevance for the comparative analysis. After the initial review, 164 scientific articles were used for analysis and comparison.

For comparative analysis, following criteria were considered - achievable DR, achievable conformality of dose distribution, requirements and complexity of technological aspects of delivery, requirements and complexity in overall treatment workflow. Considered delivery approaches are also evaluated in context of ion type influence.

Bibliography of this Chapter also includes references used in parts of literature review presented in respective **Appendix 6.2**.

Brief summary of literature review is provided in following subsections, while detailed literature review is provided in Appendix 6.2.

¹² Independent operation under Siemens Healthineers as of August 2020

7.2. Literature-based analysis of ultra-high dose rate delivery methods

Based on the literature review, possible approaches for UHDR delivery methods with light ion beams are presented along with brief comparative analysis.

Therapeutic UHDR delivery is technologically challenging with any ionizing radiation modality, thus Subsection A.6.2.1. of **Appendix 6.2.** presents summary on respective challenges for electron and high-energy photon beams. With the focus on light ion beams, Subsection A.6.2.2. of **Appendix 6.2.** summarizes respective delivery methods at conventional DRs, with challenges and general overview of possible solutions for UHDR delivery given in Sub-section 7.2.1. below and Subsection A.6.2.3. of **Appendix 6.2.** More in-depth analyses on specific UHDR delivery methods are given in Subsections 6.2.4 - 6.2.7 of **Appendix 6.2.** Comparative analysis on possible light ion UHDR delivery approaches is given below in Subsection 7.2.2.

7.2.1. Overview of challenges and possible solutions for ultra-high dose rate delivery with light ion beams. Aspects for delivery with a synchrotron.

Delivery aspects discussed in the previous subsection are considered for conventional DR of about 2 Gy/min. With growing interest in therapeutic use of *FLASH* effect, light ion beam delivery approaches need to be rethought and readapted to deliver UHDR. Additionally, due to different beam temporal structures, UHDR capabilities are influenced by particle accelerator type used. This subsection introduces main technical parameters and associated challenges for UHDR delivery with light ion beams. As within the scope of the Thesis, the focus is on HeLICS system, technical challenges and on-going research will be focused on synchrotrons. Previously discussed clinical beam delivery approaches might be unfit to enable UHDR - challenges and general possibilities are discussed in this subsection, followed by dedicated analysis of specific delivery solutions in next subsections.

As introduced in Chapter 3., magnitude of *FLASH* sparing effect can be influenced by several biological parameters, as well as technical parameters of delivered UHDR beam. With ongoing research into *FLASH* effect, no deterministic relationship between all UHDR delivery parameters and magnitude of tissue sparing has been developed. Main technical UHDR delivery parameters that could affect *FLASH* effect magnitude include [4]:

- ionizing radiation type used, and in case of protons and heavy ions - LET and its spatial variation;
- average DR;
- pulse DR and dose delivered per pulse;
- variation in beam temporal microstructure and macrostructure;
- total irradiation time;

- delivered dose level, fractionation used and number of beams per treatment plan;
- spatial variation of delivered DR and dose level;
- in context of active PBS - spatially overlapping dose distributions from separate spots and temporal delivery of these spots.

For PT and IBT delivery with synchrotrons, beam is quasi-continuous over a single spill, similarly to a cyclotron, with temporal microstructure reflecting the revolution frequency of the machine - several MHz. As with cyclotrons, main characteristics for UHDR delivery with synchrotrons are average DR and total irradiation time [4]. While DR definition is rather straightforward for passive scattering, active PBS is complicated due to sequential delivery of individual spots and spatial overlap of neighbouring spots. With average DR calculated as ratio between total dose and irradiation time, local DRs of a single spot can be several times higher. Spatial overlap of neighbouring spot dose distributions results in inhomogeneous local DR within a voxel. As discussed in Chapter 6., there are several approaches for alternative DR definition in active PBS [71], though no consensus exists yet. Based on *in vitro* and *in vivo* studies with protons, study of [4] summarized main critical parameters of UHDR delivery - given in Table 7.1. With lower experimental evidence, such a parameter summary has not been evaluated for carbon and helium ion beams, though technical parameters in respective studies are summarised in Chapter 3.

Focusing on specifics of synchrotron, at conventional DRs PT and IBT machines use SE for delivery. After injection and acceleration, stored beam in the synchrotron ring is gradually extracted over multiple turns - commonly via betatron core or radiofrequency knock-out methods - and delivered to the patient. Multi-turn SE typically delivers the beam in 0.5 - 5 second spills (up to a minute), with beam currents in the range of 0.1 to few nA [4]. Conventional SE schemes deliver a single energy per spill, followed by a few second “dead time” until next energy layer can be delivered - an important limitation for UHDR. As alternative to SE, whole stored beam can be extracted in a single turn, with resulting beam current of about 100 to 1000 μA [4]. Maximum number of particles (for specification of HeLICS see **Appendix 6.2**) that can be injected into the synchrotron ring for a single spill is limited by space charge - in the range of $6 \cdot 10^9$ to $6 \cdot 10^{11}$ particles for PT. While beam intensities achievable with synchrotrons appear feasible for UHDR in limited geometry, high beam transmission with reduced beam losses must be ensured. Subsection A.6.2.3. of **Appendix 6.2.** provides further review on SE technical challenges for UHDR timescales.

Table 7.1.

Critical technical parameters of UHDR delivery with proton beams

Parameter	Expected value
Minimum average dose rate	> 40 Gy/s (> 60 - 80 Gy/s reported experimentally)
Minimum absorbed dose	> 8 Gy*
Pulse (spill) duration	< 100 ms**
Maximum total irradiation time	< 300 ms
Preclinical: Beam energy	> 35 MeV for SOBP; > 70 MeV for transmission
Preclinical: Irradiation field size	> 2 cm (no recommendations yet for spot size)

* Value corresponds to estimated dose threshold based on electron beam measurements

** Pulse duration - synchrocyclotrons, in case of synchrotrons - spill duration

After beam extraction, the next challenge is the delivery to patient - ensuring sufficiently conformal dose distribution within UHDR timescale. Considering active PBS delivery at UHDR timescale, several technical challenges arise [4, 78, 87-90]:

- **interplay between achievable beam intensity (DR) and field size** - as discussed previously (and in **Appendix 6.2**), number of particles than can be accelerated per single spill in a synchrotron limits achievable field size for irradiation, as higher DRs can be achieved for smaller field sizes. In case of typical cyclotrons, the field size achieving sufficient UHDR is limited to $\sim 50 \times 50$ mm - estimations for HeLICS synchrotron are provided at the end of this Chapter.
- **energy switching time** - to use energy stacking for active PBS delivery fast energy switching is necessary - on the order of 3 ms [78]. Such performance is well beyond capabilities of clinical synchrotrons - conventional energy switching time is 1-2 seconds [91]. Energy switching time can be reduced with recent advances in multi-energy extraction [91] - decelerating the beam and varying energy within the same spill. Nevertheless, the reduction to about 100-200 ms [91] is insufficient for energy stacking. Similar performance is expected with HeLICS synchrotron - 200 ms energy switching time with multi-energy extraction.
- **scanning magnet speed** - to ensure sufficient UHDR throughout the treated volume, high scanning speed is necessary. As estimated in [78] (for $50 \times 50 \times 50$ mm tumour), the fast-scanning axis should operate with:
 - 750 mm/ms for discrete spot scanning and 430 mm/ms for raster scanning, if energy switching is considered (idealized ~ 3 ms)
 - around 25 mm/ms, using single energy layer (approaches discussed in following subsections)

Scanning speeds estimated for layer switching are not compatible with current technologies. For single energy layer delivery, challenges do exist, but delivery is feasible - scanning speeds of more than 100 mm/ms have been reported with systems

at NIRS [92] and more than 150 mm/ms at HIMAK with commercial Hitachi synchrotron system [93-94].

- **multiple angle delivery:** as introduced in Chapter 3., no consensus yet exists on the fractionation with *FLASH* effect [95]. For UHDR timescales, multi-field delivery essentially equates to fractionation - it has been theorized and shown experimentally that pauses (moving the gantry) in multi-field delivery could diminish *FLASH* sparing effect [95]. Additionally, *FLASH* effect sparing is observed at high dose levels - hypofractionation is necessary. This further complicates multi-field delivery - high doses are necessary for each field if *FLASH* effect is to be achieved, resulting in superposition - dose levels in the tumour clinically not acceptable. Most of pre-clinical studies have considered single high-dose delivery, with clinical *FLASH* therapy trials also adopting this approach. In some preclinical studies, multi-field irradiation is explored by delivering each field as high dose fraction separately. From technological perspective, solutions like high-energy photon PHASER system (see **Appendix 6.2**), for angular delivery from fixed beam ports have been proposed also for PT and IBT - GaToroid, for example [96].
- **spot size and spot spacing:** while not a challenge, the impact of spot size on DR should be noted. Higher DRs can be achieved by increasing spot size and spot spacing, though slight reduction is necessary to increase the DR in entrance plateau (where *FLASH* effect would be prescribed). Treatment planning strategies as spot reduction have been considered to increase the DR [97].

Considering the limitations for conventional active PBS at UHDR, alternative treatment delivery approaches need to be considered with primary focus on reducing the number of energy layers. With faster delivery enabled by passive scattering, transition back to the historically used method could be of interest for *FLASH* therapy with protons and ions, despite the increased neutron dose and workflow complexity [4, 98]. Summarizing current research results on UHDR delivery, as well as on-going initiatives, three main approaches could be used clinically:

- **transmission beams:** use of single layer at sufficiently high energy fully traversing patient, delivered via active PBS;
- **conformal *FLASH* with beam modifying devices:** use of single energy layer tailored for the tumour geometry, with dose conformality ensured via beam modulation methods - as in passive scattering or adapted;
- **conformal *FLASH* with direct energy switching:** full 3D active PBS as in conventional therapy.

First two approaches are the most prominent ones, having been used in several treatment planning, *in vitro* and *in vivo* studies, with transmission beams also used in clinical trials. Final approach mentioned provides summary by the Author for on-going research efforts and novel technological designs towards enabling UHDR 3D active PBS. Each of the approaches is summarized in subsections A.6.2.4, A.6.2.5 and A.6.2.6. of **Appendix 6.2**.

respectively, providing current perspectives and technological challenges, while discussing application as relevant to HeLICS synchrotron - with proton and helium ion beams.

7.2.2. Ultra-high dose rate light ion beams: comparative analysis of delivery methods

Based on presented review of various treatment delivery approaches for UHDR timescales, comparative analysis is provided in Table 7.2. Comparison is considered in perspective of delivery with HeLICS system - accounting for operational aspects of a synchrotron and considering application with both proton and helium ion beams. Main factors considered for the comparison included:

- achievable dose conformality and DR level;
- modulation capabilities for individual treatment plans;
- overall workflow complexity;
- robustness to treatment uncertainties;
- single vs multi-field delivery;
- compatibility with *FLASH* effect thresholds;
- flexibility for adaptive therapy scenarios;
- complexity and necessary accuracy of beam control;
- technological complexity and necessary adaptation for implementation.

With literature review based on PT delivery, additional considerations need to be made for use with helium ion beams enabled with HeLICS. While main aspects on helium ion UHDR delivery with considered approaches are already introduced in subsection 7.2., summary and additional aspects are provided in Table 7.2.

Table 7.2.

Comparison of possible UHDR delivery approaches* with HeLICS

Delivery approach	Advantages and disadvantages (proton beams)	Specifics for ⁴ He ions compared to protons
Transmission beams	<i>Advantages:</i> ▪ Highest achievable DR and shortest delivery time ▪ Whole treatment volume can be covered by a single beam ▪ No beam- and patient-specific range modulation devices necessary; suitable for adaptative therapy ▪ Reduced sensitivity to setup and range uncertainties, possibilities for margin reduction ▪ No RBE-related end of range effects ▪ In case of HeLICS - proton energies suitable for traversing even large anatomies ▪ Could enable radiographic imaging during the treatment for verification ▪ Smaller lateral penumbra ▪ <i>Biological verification needed</i> - high dose levels in normal tissue, thus improved <i>FLASH</i> sparing <i>Disadvantages and Limitations:</i> ▪ Loss of Bragg peak and distal conformality ▪ High entrance dose (uniform in whole volume) ▪ Slight reduction of RBE ▪ In most scenarios, multiple beams necessary to increase dose conformality, thus gantry or rotating patient required ▪ Multiple beam irradiation - lower dose in normal tissue, possibly reducing <i>FLASH</i> sparing; ▪ Multiple beam irradiation - time between irradiation fields with conventional gantry possibly diminishing <i>FLASH</i> sparing	▪ For HeLICS, protons suitable for all anatomies, while helium energy of 220 MeV/u - intracranial, head and neck, extremities and possibly some thoracic localisations (for example, breast) ▪ Using entrance region, significantly reduced RBE in the tumour compared to conventional delivery ▪ Helium ions have improved lateral penumbra, though comparable with highest possible proton energy ▪ Due to loss of primary particle fluence, absorbed dose is slightly decreasing with depth, compared to uniform protons ▪ More demanding on scanning magnets due increased beam rigidity ▪ Although dosimetric studies needed, no significant improvements are expected compared to protons
Dynamic ridge filters	<i>Advantages:</i> ▪ High dose conformality ▪ Resulting dose distribution suitable for single field delivery ▪ Instantaneous SOBP delivery per single spot ▪ No beam- and patient-specific range modulation devices necessary; suitable for adaptative therapy ▪ In HeLICS system - no range shifter is needed for highest energy variation, increasing DR and beam quality <i>Disadvantages and Limitations:</i> ▪ Range uncertainties and RBE end-of-range effects as in conventional delivery ▪ Increased secondary neutron and other fragment production with respect to conventional delivery and transmission beams ▪ Lower DR compared to transmission beams	▪ Possibly increased secondary neutron and other fragment production ▪ Decreased penumbra broadening and range straggling after traversing Ri-Fi ▪ Ri-Fi shape must account for distal RBE increase ▪ Possibly more sensitive to position errors of individual Ri-Fi attenuators ▪ More demanding on scanning magnets due increased beam rigidity

* In grey - earlier research stage, technological developments, and/or treatment planning studies necessary

Table 7.2. continued

Comparison of possible UHDR delivery approaches* with HeLICS

Delivery approach	Advantages and disadvantages (proton beams)	Specifics for ^4He ions compared to protons
Dynamic ridge filters (continued)	<i>Disadvantages and Limitations:</i> - Increased spot penumbra and range straggling after traversing Ri-Fi, compared to pristine beam - Dynamic Ri-Fi requires mechanical drive system, operating at speeds of about 10 m/s and 0.1 mm positional accuracy of individual attenuators - currently not feasible	-
Bragg peak tracking with compensators	<i>Advantages:</i> - High dose conformality - Compared to 3D range modulators - easier manufacturing of compensators - In HeLICS - no range shifter needed for energy variation, increasing DR and beam quality <i>Disadvantages and Limitations:</i> - Beam- and patient- specific compensators need to be manufactured - Not suitable for adaptative therapy - Only possible with multi-field delivery - Multiple beam irradiation - lower dose in normal tissue, possibly reducing <i>FLASH</i> sparing; - Multiple beam irradiation - time between irradiation fields with conventional gantry possibly diminishing <i>FLASH</i> sparing - Inhomogeneous dose distributions are more sensitive to anatomical motion on multi-field timescales - Range uncertainties and RBE end-of-range effects as in conventional delivery - Increased secondary neutron and other fragment production with respect to conventional delivery and transmission beams - Increased spot penumbra and range straggling after traversing compensator, compared to pristine beam - Lower DR compared to transmission beams	- Method overall needs to be evaluated for helium ions - can spot intensity optimization account for spatial RBE variation and ensure uniform biologically effective dose within the tumour - With higher peak-to-plateau ratio, entrance doses (and DRs) are decreased in multi-field delivery - further reduction of <i>FLASH</i> sparing - Possibly increased secondary neutron and other fragment production - Decreased penumbra broadening and range straggling after traversing compensator - More demanding on scanning magnets due increased beam rigidity - Possibly more sensitive to compensator positioning errors
3D range modulators	<i>Advantages:</i> - High dose conformality - Resulting dose distribution suitable for single field delivery - Instantaneous SOBP delivery per single spot - In HeLICS - no range shifter needed for energy variation, increasing DR and beam quality	- Possibly increased secondary neutron and other fragment production - Decreased penumbra broadening and range straggling after traversing range modulator - Individual pin shape must account for distal RBE increase

* In grey - earlier research stage, technological developments and/or treatment planning studies necessary

Table 7.2. continued

Comparison of possible UHDR delivery approaches* with HeLICS

Delivery approach	Advantages and disadvantages (proton beams)	Specifics for ^4He ions compared to protons
3D range modulators (continued)	<i>Disadvantages and Limitations:</i> ▪ Beam- and patient- specific compensators need to be manufactured ▪ Not suitable for adaptative therapy ▪ Stringent manufacturing requirements and quality assurance procedures for verification ▪ Dose distributions sensitive to positioning accuracy of the range modulator ▪ Range uncertainties and RBE end-of-range effects as in conventional delivery ▪ Increased secondary neutron and other fragment production with respect to conventional delivery and transmission beams ▪ Increased spot penumbra and range straggling after traversing range modulator, compared to pristine beam ▪ Lower DR compared to transmission beams ▪ Distance to patient needs to be increased to avoid fluence ripple in entrance region, possibly increasing lateral penumbra quality. Though, it has been theorized fluence ripple introduces benefits from effects as in mini-beam therapy	▪ More sensitive to manufacturing inaccuracies and range modulator positioning accuracies due to reduced scattering ▪ Increased fluence ripple at entrance channel due to reduced scattering ▪ More demanding on scanning magnets due increased beam rigidity
Active 3-D PBS with energy switching	<i>Advantages:</i> ▪ Pristine beam characteristics preserved at all energies ▪ High dose conformality ▪ No beam- and patient-specific range modulation devices necessary; suitable for adaptative therapy ▪ Relatively high DR could be achieved, as no range modulation device is introduced in the beam <i>Disadvantages and Limitations:</i> ▪ More demanding control and monitoring system compared to transmission beams or passive range modulation - synchronization for spot positions, beam intensity, and energy on UHDR timescale ▪ Range uncertainties and RBE end-of-range effects as in conventional delivery ▪ For same magnet scanning speeds, longer delivery times compared to transmission beams or passive range modulation (single field) ▪ Technically not feasible with current synchrotron capabilities - limited energy switching time; though certain treatment geometries could be considered with multi-energy extraction ▪ Higher magnet scanning speeds are required compared to transmission or passive range modulation (multi-layer delivery)	▪ More demanding on scanning magnets due increased beam rigidity

* In grey - earlier research stage, technological developments, and/or treatment planning studies necessary

Table 7.2. continued

Comparison of possible UHDR delivery approaches* with HeLICS

Delivery approach	Advantages and disadvantages (proton beams)	Specifics for ^4He ions compared to protons
Active 3-D PBS with RF range modulator and deflector	<i>Advantages:</i> ▪ Millisecond energy switching, compatible with UHDR timescales ▪ Improved transversal scanning speed with RF deflector compared to magnets ▪ High dose conformality ▪ No beam- and patient-specific range modulation devices necessary; suitable for adaptative therapy ▪ Relatively high DR could be achieved, as no range modulation device is introduced in the beam <i>Disadvantages and Limitations:</i> ▪ More demanding control and monitoring system compared to transmission beams or passive range modulation - synchronization for spot positions, beam intensity, and energy on UHDR timescale ▪ Range uncertainties and RBE end-of-range effects as in conventional delivery ▪ Possibly - different dosimetric characteristics of the beam compared to magnetic scanning ▪ Current design limited to about ± 5 cm range modulation and ± 10 cm field size (at 150 MeV energy) ▪ Technologically more complex compared to conventional scanning magnet systems ▪ Larger spatial footprint compared to scanning magnet systems ▪ Possibly additional requirement for gantry design, though more easily implementable with static beam lines or rotating chair systems	▪ More demanding on RF design - higher accelerating voltage for modulator and higher angular kick necessary by deflector ▪ Different overall modulator and deflector design possibly necessary due to different charge-to-mass ratio (1/2 compared to 1)
Column scanning	<i>Advantages:</i> ▪ High dose conformality ▪ No beam- and patient-specific range modulation devices necessary; suitable for adaptative therapy ▪ Resulting dose distribution suitable for single field delivery ▪ Magnet scanning speed requirements are reduced compared to other UHDR delivery approaches <i>Disadvantages and Limitations:</i> ▪ Biological validation necessary to assess the local DR role in <i>FLASH</i> effect ▪ More demanding control and monitoring system compared to transmission beams or passive range modulation - synchronization for spot positions, beam intensity, and energy on UHDR timescale ▪ Range uncertainties and RBE end-of-range effects as in conventional delivery	▪ More demanding on scanning magnets due increased beam rigidity ▪ Decreased penumbra broadening and range straggling after traversing range shifter ▪ With reduced lateral penumbra, spatial overlap of different columns might be reduced, reducing DR variation

* In grey - earlier research stage, technological developments, and/or treatment planning studies necessary

Table 7.2. continued

Comparison of possible UHDR delivery approaches* with HeLICS

Delivery approach	Advantages and disadvantages (proton beams)	Specifics for ^4He ions compared to protons
Column scanning (continued)	<i>Disadvantages and Limitations:</i> - Increased secondary neutron and other fragment production with respect to conventional delivery, transmission beams, and possible passive range modulation - Increased spot penumbra and range straggling after traversing range shifter, compared to pristine beams and passive range modulation - Lower DR compared to transmission beams - Fast and accurate system is needed for dynamic range shifter modulation - currently ~10 ms switching times reported	-
Arc delivery	<i>Advantages:</i> - No beam- and patient-specific range modulation devices necessary; suitable for adaptative therapy - Feasible within gantry rotation speed limits - Highly conformal dose distributions - As arc delivery - LET optimization in target <i>Disadvantages and Limitations:</i> - Biological validation necessary to assess the local DR role in <i>FLASH</i> effect - Gantry or rotating patient chair necessary - Temporal requirements of control system could be less demanding compared to other approaches - Low dose levels in normal tissue, possibly decreasing (or diminishing) <i>FLASH</i> effect sparing - Complex beam control system - Sensitive to uncertainties - long delivery time	- More conformal dose distributions achievable - With increased LET and RBE - LET painting possibilities within the tumour - With increased conformality, entrance dose levels even lower, possibly further decreasing <i>FLASH</i> effect sparing
Quadrupole focused beams	<i>Advantages:</i> - Relatively high DR could be achieved, as no range modulation device is introduced in the beam - Conformal dose distributions for small volumes - broader “pseudo-Bragg” peak compared to pristine - No RBE-related end of range effects - If multi-field scenario considered - less fields necessary compared to transmission <i>Disadvantages and Limitations:</i> - Necessitates high energy - transmission level - Installation of additional quadrupole magnets; large quadrupole magnet aperture necessary - Short dose maximum in depth direction - possible extension to “pseudo-SOBP” by fast quadrupole strength variation - Small transversal size of dose distribution - PBS strategies need to be developed, though possibly infeasible due to limited quadrupole aperture and challenging beam optics	- For HeLICS, protons suitable for all anatomies, while helium energy of 220 MeV/u - intracranial, head and neck, extremities and possibly some thoracic localisations (for example, breast) - Significantly reduced RBE in the tumour compared to conventional delivery - Higher quadrupole magnetic strengths necessary - Similarly to transmission beams, no significantly improved performance to be expected over protons

* In grey - earlier research stage, technological developments, and/or treatment planning studies necessary

7.3. Conclusions and discussion

Chapter 7 presented literature review-based “state-of-the-art” analysis on identifying challenges and solutions for possible UHDR technological delivery for light ion beams. Chapter also provides a comparative analysis of UHDR technological delivery solutions in perspective of HeLICS synchrotron - evaluating necessities for conventional DR delivery, summarizing options for UHDR proton beams, and analysing necessary adaptations for respective methods for helium-4 ion use.

Main conclusions from the presented literature review and comparative analysis of UHDR delivery methods can be summarized as:

1. Currently, UHDR delivery suited for deep-seated tumour treatment can only be envisioned with protons and heavier ions, as high-energy photons necessitate significant developments in both LINAC and bremsstrahlung target designs, while megavoltage electrons can enable UHDR treatment of only superficial tumours, with active research in developing VHEE.
2. Two conventional delivery methods are used in treatment with PT and IBT at conventional DR - passive scattering and active PBS -, with the latter predominantly used nowadays due to superior performance. Nevertheless, hybrid approaches of the two are considered for UHDR delivery, benefitting from high transmission lateral beam spreading of active PBS and instant longitudinal Bragg peak broadening with passive scattering.
3. Main aspects to address UHDR delivery with synchrotron-produced light ion beams include development of SE methods with low beam intensity variation and time structure suitable for active monitoring, limitations of maximum beam intensity and scanning magnet speeds. While approaches as MEE could enable faster energy switching in synchrotrons, it is insufficient for clinical 3D active PBS delivery at *FLASH* timescales.
4. UHDR delivery with light ion beams can be realized via three main technological approaches:
 - 4.1. transmission beams, using energy levels passing through the patient;
 - 4.2. conformal *FLASH* delivery with RM devices - broadening Bragg peak via static or dynamic Ri-Fi or 3D-RM or using multi-field Bragg peak tracing with field-specific compensators;
 - 4.3. conformal *FLASH* delivery with active energy switching - use of RF-based energy modulator and deflector or column scanning approach with fast switching range shifter.

Other approaches include optimized arc delivery or quadrupole focused beams, though further research from biophysical or technological aspects is necessary for these methods.

5. While transmission beams lose the benefits of the Bragg peak and necessitate multi-field delivery to maintain adequate dose conformality, they enable highest DR,

sharper lateral penumbra compared to conventional treatment and reduced sensitivity to patient setup and anatomy variations and distal RBE increase effects.

6. While additional research into mechanical design is necessary to enable dynamic Ri-Fi operation, 3D-RM and multi-field compensator (Bragg peak tracking) methods can enable UHDR dose distributions, while maintaining sufficient dose conformality. This comes at the expense of more complex treatment and quality assurance workflow for individualized RM devices, sensitivity to device setup errors, increased secondary neutron contribution and other effects.
7. Evaluating applicability of discussed UHDR delivery methods for helium-4 ion beams:
 - 7.1. transmission beams - helium-4 ion beam performance is expected to be slightly worse compared to protons due to IDD characteristics;
 - 7.2. multi-field compensator (Bragg peak tracking) method - possibility to maintain uniform biologically effective dose within the tumour must be assessed;
 - 7.3. 3D-RM method - feasible with helium-4 ions, though optimization of 3D-RM design is necessary, accounting for increased setup error sensitivity.Quantitative modelling studies are necessary to further assess the limitations of discussed UHDR delivery methods for helium-4 ion beams.
8. In context of HeLICS system, considering compromise between achievable DR, dose conformality, technological complexity and workflow efficiency, UHDR delivery could be realized via high energy (up to 700 MeV) proton transmission beams or proton/helium-4 conformal *FLASH* using 3D-RM. multi-field compensator (Bragg peak tracking) method needs to be assessed for helium-4 ion beams, while considering multi-field delivery limitations.

Limitations of the performed research. Additional notes and implications of the work.

Considering the methodology and results presented in this Chapter, following limitations and additional implications of the performed study were identified:

- number of studies on clinical UHDR delivery methods or necessary adaptations for ions heavier than protons is relatively limited, thus qualitative estimates were done for helium ion beams, which necessitate further quantitative validation.
- with the review focusing on identifying possible UHDR delivery methods and qualitatively comparing their respective advantages and disadvantages, no quantitative comparison was performed. Further work on quantitatively evaluating and comparing the different discussed UHDR delivery methods would enable to estimate achievable technical parameters, clearly define technical requirements for particle accelerators and optimize the delivery parameters of the specific UHDR delivery methods.

Future research outlooks

Considering the methodology, results and study limitations presented in this Chapter, following pathways for future additional research were identified:

- quantitative comparison study, using the developed PB algorithm of Chapter 6, for the different UHDR delivery approaches with light ion beams, focusing on the differences between achievable dose distribution conformality, DR level and LET distribution.
- special focus should be given in quantitatively evaluating transmission beams, multi-field compensator (Bragg peak tracking) method and 3D-RM method with helium ion beams and comparing achievable dose conformality and DR level with respect to protons.
- optimization study on delivery parameters for different UHDR delivery approaches with light ion beams, focusing spot size, spot spacing and spot scanning sequence to increase achievable DR.
- optimization study on 3D-RM design for helium ion beams.
- quantitative comparison study, using the developed PB algorithm of Chapter 6, between VHEE and light ion beams, focusing on achievable dose distribution conformality and DR level.

7.3.1. Considerations for technological implementation

While the results presented in this Chapter mainly focused on the comparison of overall physical feasibility of novel UHDR delivery approaches with light ion beams, following key considerations were identified for technological implementation of these approaches, especially in context of HeLICS system:

- with improved *FLASH* effect possibly achievable with higher DR, number of particles injected into the synchrotron should be maximised, while minimising the extraction time. Achievable maximum beam current defines the interplay between maximum DR and maximum field size, maintaining the DR. In case of current HeLICS design, a 5x5 cm field size could be possibly achievable, maintaining the 40 Gy/s DR threshold, though is dependent on the delivery method chosen.
- from control system perspective to achieve adequate beam monitoring and dose delivery control on UHDR timescale, pulsed beams would be favourable and could be achieved via radiofrequency knock-out [79-80] or phase displacement slow extraction [80-81]. Stringent monitoring and beam control with large intensity variations of continuous beam at UHDR becomes impractical and possibly not feasible (see **Appendix A.6.2.3**).
- even with MEE, achieving energy layer switching in timescales compliant with *FLASH* effect thresholds is challenging for conventional synchrotrons, such as HeLICS. Thus, alternative delivery approaches as discussed should be considered for beam delivery implementation.
- if transmission beams are considered as the UHDR delivery approach, additional care should be taken regarding the radiation safety requirements. As the beam would fully

traverse the patient solutions as absorber after the patient, additional room shielding or specific delivery angles should be considered.

- multi-field compensator (Bragg peak tracking) method or 3D-RM method is considered as the delivery method, additional care needs to be taken in the design of the treatment nozzle to allow the insertion and exchange of patient specific beam modifying devices. In case of 3D-RM method, pin design adaptations specific to helium ions must be made.
- sufficiently fast scanning magnets with both proton and helium ions beams should be designed and implemented, following the technical requirements outlined in this Chapter.

Bibliography

List of bibliography used within this Chapter of the Thesis is provided in **Appendix 6.3**.

Part II

Investigations on novel range verification methods for helium ion therapy

As high treatment doses are necessary to achieve *FLASH* effect, accurate delivery of the beam is crucial to avoid erroneous normal tissue exposure. To achieve this precision, multiple range verification approaches in IBT, specifically helium-4 IBT, are proposed and explored via MC simulations in Part II.

Literature review on range uncertainties, existing range verification approaches and corresponding technological solutions is presented in Chapter 8. Special focus is given to studies relevant for possible applications to helium-4 IBT, while also identifying relevant research gaps to be addressed in further Chapters.

In Chapters 9 and 10, particle radiography methods specifically for helium IBT are developed. Chapter 9 proposes and presents two particle radiography methods for patient anatomy verification before treatment - with high energy protons and helium-3 ions, while also developing focus stacking approach for reconstruction. Achievable image quality was assessed in different clinically relevant scenarios, while also identifying particle accelerator technical parameters necessary for implementation.

To account for physiological and other intrafractional patient motions, real-time monitoring approaches are necessary. Radiography with mixed helium-deuteron beam is proposed and presented in Chapter 10 as a method for patient monitoring during treatment delivery. Proposed method is evaluated for range measurement and 2D imaging scenarios, identifying achievable positional accuracy and image quality. Limitations and considerations for technical implementation of the method are also discussed.

Radiography can assess the accuracy only from perspective of patient anatomy, while *in vivo* range verification methods can be used to evaluate delivered dose distribution itself. “Secondary particle detection”-based *in vivo* range verification methods for helium-4 IBT are investigated in Chapters 11 and 12. Chapter 11 focuses on PET-based range verification by evaluating induced β^+ activity distribution. β^+ activity patterns in unique to helium-4 IBT are presented. Corresponding accuracy and considerations for technological implementation are explored for both in-beam and off-line registration approaches.

A method to increase prompt gamma signal for real-time range verification in helium-IBT is proposed and investigated in Chapter 12. Proposed method would use oxygen-18 as a contrast agent to increase the number gamma emissions, especially at low energies. Spatial and temporal characteristics of prompt gamma signal achievable with the proposed method are evaluated. Corresponding accuracy and challenges of technological implementation are also investigated.

Overall conclusions on the proposed range verification methods are given at the end of each Chapter, while also discussing the applicability of these methods for other IBT modalities and corresponding technical implementation challenges. Limitations of the studies are also identified, suggesting experimental validation approaches and further research necessities.

State of the Art analysis:

Range verification methods: tools for uncertainty mitigation and perspective applications in helium ion beam therapy

This Chapter presents the “state-of-the-art” analysis on uncertainties associated with PT and IBT and corresponding mitigation approaches to increase treatment delivery precision via the use of range verification methods. Analysis was based on literature review as methodology, providing a summary on recent scientific research work on the topicality. The review focuses on possible application of range verification methods to helium IBT.

Similarly to Chapter 3., this Chapter starts with overview of the methodology used to perform the literature review in Section 8.1. Methodology outlines the used data sources and search keywords.

Overview of literature analysis findings is presented in the multiple subsections of Section 8.2. Findings start with an overview of treatment uncertainty sources and mitigation approaches used in PT and IBT. Recent advancements, possible technological solutions, and existing clinical implementation challenges of range verification methods are presented next. Focus is given to patient anatomy verification approaches as particle radiography and direct Bragg peak localisation methods - PET imaging and prompt gamma photon registration. Section concludes with possible range verification approaches in helium IBT, also outlining the current stage of development of this novel IBT modality in general.

At the end of this Chapter, Section 8.3 summarizes main conclusions of the literature review and identified research gaps.

8.1. “State of the Art” analysis methodology

“State of the Art” analysis was based on scientific literature review. Search of scientific articles relevant to the analysis was performed using following databases and browsing tools: *Google Scholar* and *PubMed* by National Centre for Biotechnology Information were used as primary sources, while *Scopus* and *ScienceDirect* - as secondary, where applicable.

To include most research results, the time frame of article publication focused on last 10 years - 2015 to 2025 . Nevertheless, for historical perspective, additional articles were included in the analysis as necessary - search directly done by Author or citations included in primary articles.

Keywords used during the analysis as queries are summarized in **Appendix 7.1**. Initially, broad review articles were analysed on the topic of uncertainty sources in PT and IBT and mitigation strategies clinically, followed by focused searches on specific uncertainty management methods. Main part of the analysis focused on range verification methods, focusing the database search on approaches considered in the scope of the Thesis - imaging of patient anatomy via particle radiography and direct Bragg peak localisation via PET or PG photon detection. Broad review articles were evaluated first, followed by focused searches on specific aspects of each method. Database search on other range verification methods, not considered in the scope of the Thesis such as ionoacoustics and vertex imaging, was limited to brief introduction. Finally, articles on helium IBT were evaluated, focusing both on physical and clinical aspects. For all the aspects mentioned, analysis included both modelling and experimental studies. Focus on the analysis is given towards currently achievable range precision with each method and technical challenges for clinical implementation.

After initial query, abstracts of scientific articles were analysed by Author, assessing the relevance for analysis.

After initial review, **377** scientific articles were used in the analysis.

Bibliography of this Chapter also includes references used in parts of literature review presented in respective **Appendices 7.2., 7.3, 7.4. and 7.5.**

Brief summary of literature review is provided in following sub-sections, while detailed literature review is provided in Appendices 7.2., 7.3, 7.4. and 7.5.

8.2. Results of the “State of the Art” analysis

8.2.1. Treatment uncertainties: main sources and general mitigation strategies in proton and ion beam therapy

As with any other RT modality, delivered absorbed dose distributions in PT and IBT are prone to possible deviations from planned and uncertainties. With respect

to conventional RT, sensitivity to uncertainties is significantly increased for PT and IBT due to localized dose deposition and high gradient of the Bragg peak. With unavoidable nature of uncertainties, it is necessary to identify them, minimize their impact (if possible) and develop strategies to account or mitigate the detrimental effects [1].

For PT and IBT, main sources of uncertainty can be divided into two main groups [1]:

- **patient related:** positioning of the patient, physiological motion, and anatomical changes (intra-fractional and inter-fractional);
- **delivery and physical interaction related:** accuracy and reproducibility of particle accelerator output, accuracy of the delivery system, inherent range uncertainties due to physical interactions and uncertainties in treatment planning and dose calculation process.

Detailed analysis on the uncertainty sources is given in **Appendix 7.2**.

8.2.2. Overview of range verification methods: achievable accuracy, technological solutions, and challenges for clinical implementation

Due to range uncertainties, treatment planning strategies in PT and IBT use more robust rather than conformal beam arrangements and require safety margins for irradiated PTV. In modern RT practice, reduction of safety margins and tightly conformal dose distributions is one of the main goals, allowing to increase TCP, while limiting NTCP. Uncertainty mitigation strategies outlined in **Appendix 7.2** can contribute to a certain extent, though are limited by the inability to directly monitor the key parameter - ion interactions with patient anatomy -, limiting capabilities of *in vivo* verification.

This challenge can be addressed by so-called range verification methods¹³. Range verification methods are non-invasive and based on correlation of delivered dose with various secondary particle (photon, charged particle or neutron) emissions or physical effects due to energy deposition (thermoacoustic effect) [1]. In context of the Thesis, the Author also refers to i-Rad as another range verification method - verification and/or monitoring of anatomy using charged particle beams with high energies, ensuring transmission through the patient.

Application of range verification methods in clinical practice could [1]:

- enable proper beam range assessment before and during the treatment;
- enable verification of delivered dose *in vivo* - during and after the treatment;
- provide means of independent validation of whole treatment chain;
- enable real-time identification of unexpected changes in patient anatomy and/or delivered dose deviations with respect to planned;

¹³ Also referred to as *in vivo* range monitoring methods

- provide means to promptly inhibit incorrect treatment delivery.

The latter two aspects are crucial in enabling adaptive treatment approaches via dose guided RT - crucial in hypofractionation. As hypofractionated RT uses only a single or a few (3 - 5) treatment fractions, statistical averaging out and/or compensation strategies as in conventional fractionated delivery cannot be considered. As discussed in Part I of the Thesis - hypofractionation and high dose levels are also necessary for enabling *FLASH* therapy. Thus, the development and clinical implementation of range verification is crucial to enable safe and accurate delivery of hypofractionation and *FLASH* therapy with light ion beams.

Following Subsections outline summary of key developments and “state-of-the-art” for range verification methods considered within the Scope of the Thesis: i-Rad, PET-based verification and PG photon detection. More detailed information on each approach is provided in **Appendix 7.2**.

Patient anatomy verification and monitoring: Approaches in particle radiography

i-Rad, specifically - proton radiography (p-Rad) - has been investigated since late 1960s [48-47]. High energy protons pass through the patient - by registering exit kinetic energy WEPL can be estimated. Tracking of particle position and relative angles of motion at entrance and exit of the patient, provides 2-dimensional images of patient anatomy (single particle tracking approach) [48-47]. Most attractive characteristic of i-Rad - direct imaging of WEPL/RSP.

To provide improvements over conventional X-ray imaging, p-Rad system should achieve spatial resolution ≤ 1 mm and WEPL value uncertainty ≤ 1 mm [48-47]. Depending on anatomy, energies in range from 200 to >330 MeV are necessary - trade-off between spatial resolution and WEPL accuracy [48-47]. Studies on high energy p-Rad are limited [48-47].

Single particle tracking i-Rad, compared to integrating i-Rad, offers lowest imaging dose and highest image quality at the expense of increased detector complexity [48-47]. Most likely path (MLP) algorithm is typically used for image reconstruction to account for curved particle trajectories due to MCS, improving spatial resolution [48-47].

Ions heavier than protons have reduced MCS and could improve spatial resolution in i-Rad, though have increased imaging dose and nuclear interaction rate [75]. Helium ions (He-Rad) are very attractive modality - spatial resolution increased by a factor of two with respect to p-Rad, maintaining high WEPL value accuracy, at the expense of slightly increased imaging dose (though lower compared to X-rays) [75,88]. Increased nuclear fragmentation in He-Rad contributes to noise and artefacts in reconstructed images [88-90], which can be mitigated by approaches as $\Delta E - E$ based particle identification filtering [90].

i-Rad is primarily considered for verification before the treatment, though two approaches can be considered for monitoring during delivery - fast energy switching [103]

and mixed beam [104-107]. The latter has been proposed for carbon IBT - mixed carbon-helium beams, having the same charge-to-mass ratio can be accelerated simultaneously to same energy per nucleon and helium ions, having 3 times higher range at the same energy, will exit patient for imaging. Fluence ratio of 1:10 has been proposed [104-107] for mixed carbon-helium beams to maintain distinguishable signal with ~1% contribution to treatment dose. Main challenges arise with synchrotron technical implementation - beam injection, acceleration and extraction.

Bragg peak localisation with positron emission tomography

PET-based range verification dates to early research of PT and IBT - first proposed in 1960s. Dominant β^+ emitters in soft tissue are ^{15}O ($T_{1/2} \approx 2$ min), ^{11}C ($T_{1/2} \approx 20$ min) and ^{13}N ($T_{1/2} \approx 10$ min), with ^{12}N also relevant for fast imaging ($T_{1/2} \approx 11$ ms) [1,44,124].

For lighter ions ($Z < 5$), only target fragmentation reactions are possible, with β^+ activity induced along the track, having fall-off few millimetres upstream of the Bragg peak [1,44,124]. For heavier ions ($Z \geq 5$) projectile fragmentation also contributes, having a prominent β^+ activity maximum slightly up-stream of the Bragg peak [1,44,124].

PET-based range verification has three data acquisition modes [1,44,124]: off-line (conventional PET outside treatment room, scanning 10 - 20 minutes after irradiation), in-room (conventional PET installed in treatment room, scanning immediately after or within 1 to 2 minutes after irradiation) and in-beam (data acquisition during beam delivery, technologically most demanding with specific detector designs). The three approaches differ in overall workflow, technical requirements of detection system and particle accelerator, registrable event counts, as well as achievable accuracy and impact of biological washout from physiological processes. Achievable range accuracy with PET-based verification is about 1 - 5 mm [1,44,124]. PET imaging is inherently delayed with respect to irradiation.

PET-based verification studies have been mainly limited to proton and carbon ion beams. Spatial patterns and temporal evolution of induced β^+ activity strongly depend on the projectile particle and associated nuclear interaction cross-sections. While last Subsection of this analysis discusses the few studies on helium ion use for PET-based verification, lack of research into the topic is evident, motivating the studies performed in Chapter 11.

Bragg peak localisation with prompt gamma photons and perspectives of contrast agents

PG photon detection for range verification was first proposed in 2003, with proof-of-concept validated in 2006 [1,44,206-212]. It could enable real-time monitoring, though necessitates efficient detection system for photon energies in range of 2 - 10 MeV. Several detection approaches have been proposed based on different physical parameters [1,44,206-212]:

- **spatial distribution:** mechanical collimation via pinhole, knife-edge or multi-slit collimators or electronic collimation via Compton imaging system;
- **timing information:** registration of PG photon time-of-flight (ToF);
- **energy spectrum:** registration of PG photon energy for absolute range verification and/or assessment of tissue elemental composition.

For spot-by-spot verification, range accuracy within < 3 mm could be achieved in clinically relevant scenarios, though main challenge arises from limited event counts [1,44,206-212]. Strategies to address this have been proposed, including use of “contrast agents” to enhance PG photon signal or provide unique spectral characteristics for fast detection of critical delivery inaccuracies.

PG photon detection becomes more challenging for heavier ion irradiation. With the comparisons given between proton and carbon ions, the last Subsection of this analysis presents the studies on focal point of the Thesis - helium ions. With decreased PG photon counts for heavier ions, increased detection efficiency, or approaches for signal enhancement to statistically significant levels are necessary. The latter option, using “contrast agents” could prove more viable in certain scenarios, motivating the studies presented in Chapter 12.

Other range verification methods

Apart from approaches discussed above, several others have been proposed for Bragg peak localisation and dose distribution verification. While not in the scope of this Thesis, main concepts of ionoacoustic signal registration and secondary particle vertex imaging are introduced in **Appendix 7.2.** to provide complete summary of main range verification methods.

8.2.3. Development of helium ion therapy as novel ion beam therapy modality. Perspectives of range verification in helium ion therapy

Previous Subsections of the analysis focused on range verification approaches for clinically available modalities - PT and carbon IBT. As conceptually introduced in Chapter 2., another approach in IBT is currently actively researched for cancer treatment - helium IBT. With intermediate technical requirements and physical and biological characteristics, helium IBT has great perspective in future developments of IBT. As the scope of the Thesis, especially II part, focuses on helium IBT, this Subsection builds on general concepts introduced in Chapter 2. by providing a summary of current research on development of this modality. Main biophysical considerations and technological developments are presented, while also outlining clinical perspective - historical evidence, current dosimetric studies and future outlooks and clinical trials. Finally, perspectives of range verification in helium IBT are presented at the end of this Subsection - summarizing current studies and future outlooks for unique approaches. Complementary

data for following sub-sections from literature review relevant to helium IBT are provided in **Appendices 7.3., 7.4. and 7.5.**

Biophysical rationale. Development of dedicated accelerator technologies

As introduced in Chapter 1 and 2, helium IBT as another perspective modality of IBT has seen a significantly increased interest in recent years - from both clinical and scientific research communities [302-303]. Current developments in helium IBT are mainly associated with the pivotal work in Heidelberg Ion-Beam Therapy Centre (HIT) [304]. As outlined in Chapter 2, the potential of helium ions as one of the future therapeutic modalities is facilitated by intermediate physical and radiobiological properties in comparison to established proton and carbon ion beams. Summarizing the detailed biophysical phenomena, with respect to protons, helium ions have [302-303]:

- reduced lateral penumbra due to reduction of MCS magnitude (especially important for deep-seated geometries);
- reduced proximal and distal fall-off due to decreased range straggling;
- increased RBE and possibilities to overcome low-level hypoxia due to increased LET and higher ionization event density;
- increased RBE differential between entrance and Bragg peak regions could further improve normal tissue sparing.

With these characteristics, helium ions could provide clinically significant improvement of dose conformality with respect to protons, thus decreasing normal tissue exposure. On the other hand, with respect to carbon ions as the other clinical modality [302-303]:

- helium ion “fragmentation tail” is lower, decreasing distal dose after the Bragg peak - possibly outperforming dose conformality of carbon ions in certain scenarios;
- with decreased nuclear fragmentation, RBE modelling uncertainties are slightly reduced;
- decreased number of secondary neutrons and associated dose (neutron dose could be even lower than with protons [302])
- helium ions require lower energy per nucleon to reach the same depth in tissue - reduced magnetic rigidity requirements - reduced synchrotron dimensions and/or dipole magnetic flux density.

Considering all aspects, helium ions provide attractive performance as intermediate option with respect to existing clinical modalities - acting as an evolution of PT and reducing technical requirements with respect to carbon IBT.

Globally, only HIT facility currently has necessary technological capabilities and commissioned beam for clinical delivery of helium IBT [304]. Future use is also envisioned in other facilities as MedAustron (Austria), having started necessary commissioning work [310-311], multi-IBT initiative *Quantum Scalpel* at NIRS [312-313], and long-term research programme at CNAO (Italy) [314]. Implementation of helium IBT at HIT, as well as mentioned future initiatives, is done via the use of carbon ion synchrotrons.

Subsidiary of *Ion Beam Applications - Normandy Hadrontherapy* - is also working towards a commercial multi-ion cyclotron system, enabling use of helium ion beam [315].

In context of synchrotrons, while beamlines and delivery systems allow operation, optimized design for carbon beams reduces performance of helium ions with respect to theoretically achievable. As noted, necessary beam rigidity for treatment energy range of helium ions is lower compared to carbon ions - reduction of accelerator dimensions. These two aspects have motivated research into compact synchrotron designs dedicated for helium IBT. NIMMS HeLICS system is one of such initiatives reaching design maturity. HeLICS is also considered within the scope of the Thesis, with presented research directly translatable to future design adaptations of the system. Earliest concepts relevant for HeLICS design were presented in [316], with technical details of latest, detailed design iterations [317-319] discussed in Chapter 2. System is designed for helium-4 ion acceleration up to 220 MeV/u energy, corresponding to ~30 cm range in water, while also enabling proton beams to treatment energies and beyond - transmission delivery and radiography applications. Another compact synchrotron design dedicated for helium IBT has also been recently proposed by researchers in Shanghai, China [320]. Alternatively, a non-scaling fixed field alternating gradient accelerator design dedicated for helium ion delivery has also been proposed - HEATHER [321]. With the design consisting of 2 superconducting rings, the system could accelerate helium ions to energies of 225 MeV/u for treatment, while use of hydrogen ions (H_2^+) was envisioned for imaging purposes.

Additional information on biophysical rationale and development of dedicated accelerator technologies for helium IBT are presented in **Appendix 7.3**.

Clinical application: past evidence, present studies, and future outlooks

Modern day helium IBT is still in active research and early clinical translation phase. While large-scale investigations are necessary, the current efforts do not start from nothing and are more of renaissance - historical clinical evidence as basis does exist from initial research phase of PT and IBT in LBNL. More detailed overview of helium IBT clinical application is presented in **Appendix 7.4**.

Perspectives of range verification in helium ion therapy

Existing research and future perspectives of range verification methods in helium IBT are summarized in **Appendix 7.5**. as the basis of subsequent research Chapters 9 to 12. Due to lack of technological capabilities and infrastructure for helium ion delivery, research is more limited in comparison to proton and carbon ion beams, as presented previously. Nevertheless, a couple of simulation and experimental studies have focused on range verification possibilities for helium ions, summarized in **Appendix 7.5**.

Overall, along the developments in physical and radiobiological modelling and investigations on clinical applications of helium ions, initial studies have explored range verification possibilities. Helium ions could offer a couple of new strategies for range

verification with respect to protons. Nevertheless, approaches to mitigate challenges of limited secondary particle counts for some of the methods also need to be explored. As mentioned before, significant improvements are necessary for differential cross section data to accurately model nuclear interactions - crucial for reference image or signal estimation for several verification approaches.

8.3. Conclusions and identified research areas

Chapter 8 presented literature review based “state-of-the-art” analysis on range verification topicality in PT and IBT as relevant for the Thesis scope and objectives: overview of PT and IBT treatment uncertainty sources and role in hypofractionation (as relevant for *FLASH* RT); recent advancements, possible technological solutions and clinical implementation challenges for patient anatomy verification approaches as i-Rad and direct Bragg peak localisation methods as PET imaging and PG photon detection; role of helium IBT as clinical modality and respective challenges for possible range verification approaches.

Main conclusions from the presented literature review based “state-of-the-art” analysis can be summarized as:

5. PT and IBT is more sensitive to treatment uncertainties, both machine- and patient-related, with respect to conventional RT, requiring specific strategies to ensure accurate treatment delivery. Ensuring robustness of treatment plan leads to reduction in dose conformality. This clinical compromise hinders full potential of PT and IBT due to necessity of additional safety margins.
6. Considering patient related uncertainties, real-time monitoring of internal anatomy and/or dose delivery is desirable, to achieve minimum safety margins and maximum dose conformality. Such monitoring approaches become crucial for treatment adaptation at hypofractionated schemes - high dose levels in few fractions, as also relevant for *FLASH* RT delivery.
7. X-ray based patient anatomy verification in PT and IBT has limitations due to inherent differences in photon and ion interactions. These limitations could be overcome with the use of i-Rad, providing clinically relevant information for PT and IBT - spatial distribution of WEPL and/or RSP.
8. i-Rad could be used for pre-treatment patient position and WEPL distribution verification, adaptation of planning CT data and position monitoring during the treatment. Best imaging quality can be achieved with single particle tracking approach, necessitating more complex, larger detection system and dedicated reconstruction algorithms compared to approach of integrating i-Rad.
9. Apart from detector related challenges, clinical implementation of i-Rad is also limited by accelerator capabilities - maximum energy reach and operation at low beam intensities. This aspect becomes even more crucial for heavier ion i-Rad - as highly

- attractive He-Rad, which has indicated favourable performance over p-Rad and other i-Rad approaches.
10. While i-Rad is primarily used for patient position and WEPL distribution verification pre-treatment, approaches as fast beam switching [103] and mixed beam i-Rad for carbon IBT [104-111] have been proposed.
 11. With several strategies of PET verification - off-line, in-room and in-beam - it has several challenges limiting implementation and clinically relevant accuracy. Main factors include inherent delay with respect to irradiation limiting capabilities of real-time treatment monitoring, technological integration challenges, low signal counts and large integration times necessary, positron range effects, biological washout, and accuracy of nuclear cross-section data for reference image calculation. These aspects limit achievable range accuracy with this method to about 1 - 5 mm [206].
 12. Apart from low signal counts, induced β^+ activity strongly depends on the projectile particle and associated nuclear interaction cross-sections. For light ion beams as protons, this limits correlation with absorbed dose distribution and impacts overall accuracy of the method.
 13. By detection of different PG photon physical characteristics - spatial information, ToF and energy - range information with accuracy < 3 mm in clinically relevant scenarios could be achieved on spot-by-spot level. PGS approach could also enable quantitative evaluation of elemental composition of irradiated tissue.
 14. PG photon detection could enable real-time monitoring - unique with respect to other range verification approaches, though several challenges must be addressed, including detector design for operation with high PG photon energies (> 2 MeV) and low signal counts. "Contrast agent" strategies have been proposed to address the latter challenge by increasing PG photon signal or provide unique spectral lines for fast detection.
 15. Helium IBT is highly perspective modality for future clinical use due to intermediate biophysical characteristics and technical requirements with respect to PT and carbon IBT. With historical evidence from clinical trials in LBNL, retrospective dosimetric studies (see **Appendix 7.4**) indicating clinical potential and first ever modern helium IBT clinical trial at HIT reported in 2025 [361], helium IBT could possibly become a future evolution of PT. Though, further dosimetric studies and prospective clinical trials are necessary to assess the role of this modality.
 16. With lack of technological infrastructure suitable for helium IBT delivery, the research in dedicated range verification methods for delivery of this modality is sparse.

Based on the presented literature review based "state-of-the-art" analysis and existing research gaps, following research areas have been identified to be addressed within Chapters 9 to 12:

- *lack of quantitative evaluation of p-Rad at higher energies for large anatomies, perspectives of He-Rad and limitations of HeLICS energy range full-body He4-Rad - quantitative evaluation of high energy p-Rad image quality and comparison of new He3-Rad approach for HeLICS design with He4-Rad (Chapter 9);*
- *necessity of patient position monitoring during the treatment, lack of mixed-beam approaches for helium IBT in comparison to carbon IBT: quantitative evaluation of mixed He-D beam use for range verification and 2-dimensional He-D-Rad;*
- *low counts of PET signal limiting statistical accuracy, spatial distribution of e^+e^- annihilation events corresponds to target fragmentation only for projectiles lighter than boron (decreased correlation): quantitative evaluation of e^+e^- annihilation events spatial distribution induced by helium-4 ion beams, focusing on possible contributions by fluorine-17 and fluorine-18;*
- *low PG photon emission counts limiting statistical accuracy, majority of PG photon emissions are high energy (> 2 MeV): quantitative evaluation for contrast agent use to increase low energy PG photon counts; contrast agent considered - ^{18}O -enriched water.*

Bibliography

List of bibliography used within this Chapter of the Thesis is provided in Appendix 7.6.

Pre-treatment radiography and 3D feature localization with high energy protons and helium-3 ions

Particle radiography (i-Rad) could be used as one of the approaches to mitigate uncertainties related to changes in patient anatomy or position by acquiring 2D images of WEPL distribution before treatment. Furthermore, i-Rad beam pulses could also be used in-between treatment beam pulses for position monitoring. With the potential to improve the accuracy of IBT delivery, this Chapter proposes two i-Rad approaches tailored for compact circular accelerators designed for helium IBT - using high energy protons (p-Rad) and helium-3 ions (He3-Rad) - and investigates the achievable image quality of each modality. High energy p-Rad is investigated from perspective of an optimum imaging energy, while He3-Rad is investigated as a novel approach and compared to He4-Rad.

Additionally, i-Rad image quality has inherent dependency on depth of image reconstruction. Thus, recently focus stacking (FS) based approaches have been proposed to extract 3D information from planar i-Rad data – depth of imaged object. For further development of FS approach, this Chapter also develops alternative methods for 3D feature localization and investigates ion type and kinetic energy influence on imaged object depth estimation.

i-Rad images in this Study were acquired based on MC simulated data. Section 9.1 outlines the methods used for MC simulations and i-Rad image reconstruction: choice of geometry and phantom setups for simulations, physical parameter scoring, data filtering routines, and MLP formalism used for image reconstruction. Methods used to assess image quality metrics of reconstructed images are outlined in Section 9.1: spatial resolution, contrast-to-noise ratios, imaging dose, low contrast resolution, and others. Section 9.1 also presents methods used to assess the uncertainties related to simulated i-Rad image reconstruction. Finally, Section 9.2 outlines the methods used for investigations of FS in i-Rad: adaptations to MLP reconstruction algorithm and approaches to quantitatively assess depth dependent metrics in reconstructed planar i-Rad images. Section 9.2. also outlines image analysis methods used to evaluate and compare different FS approaches in terms of imaged object depth estimation accuracy and i-Rad image quality improvement.

Results on the proposed pre-treatment i-Rad methods are presented in Section 9.3. Image quality metric dependency on proton energy is evaluated, while for He3-Rad

approach - comparisons are made with He4-Rad. Results in Section 9.4. also provide quantitative comparison of different FS approaches for imaged object depth estimation and reconstructed image quality improvement. Section 9.5 provides conclusions and discussion on the achieved results, while a special focus is given for necessities and challenges for a possible technological implementation of the proposed i-Rad methods in Subsection 9.5.1.

Contributions of the Author: Methodology of the MC simulations, image reconstruction and image analysis has been developed by the Author, indicating used literature sources, where applicable. Under the supervision of the Author, developed methodology was implemented into MC simulation codes and *python* scripts by both Ilze Baumgarte (RTU) and Aurēlija Viņķe (RTU). Under the supervision of the Author, MC simulations and i-Rad image reconstruction was performed by Ilze Baumgarte (RTU) and Aurēlija Viņķe (RTU). Reconstructed image analysis and data visualization presented in the Thesis has been done by the Author, based on previously generated data by supervised students. Image uncertainty analysis was designed and performed by the Author, based on previously generated data by supervised students.

Student research work supervised related to the results presented in this Chapter:

- CERN Summer Student project:
Vinke, A. (2024). *Simulation-Based Assessment of Proton Radiography Across Energy Levels: Investigations on optimum imaging energy*. CERN, Supervisors: **K.Paļskis**, M.Vretenar
- CERN Summer Student project:
Baumgarte, I. (2024). Investigation of helium-3 ion usage in radiography for patient position verification in particle therapy. CERN, Supervisors: **K.Paļskis**, M.Vretenar
- Bachelor thesis:
Ilze Baumgarte “*Dependence of ion radiographic image quality characteristics on the utilized helium isotope*”, Riga Technical University, Submission: May 2025, Supervisor: **K.Paļskis**

Approbation of the results presented in this Chapter:

- Oral presentation at 5th CERN Baltic Conference (CBC’25) in Kaunas, Lithuania, 2025
K.Paļskis, I.Baumgarte, A.Viņķe, T.Torims, M.Vretenar, J.Seco, M.Sapinski “*Towards the last millimeters in helium ion therapy: developing dedicated range verification methods*”
 - Poster presentation at 4th CERN Baltic conference (CBC’24) in Tallinn, Estonia, 2024
A.Viņķe (presenting), **K.Paļskis**, M.Vretenar “*Simulation-Based Assessment of Proton Radiography Across Energy Levels: Investigations on optimum imaging energy*”
 - Poster presentation at 4th CERN Baltic conference (CBC’24) in Tallinn, Estonia, 2024
I.Baumgarte (presenting), **K.Paļskis**, M.Vretenar “*Investigation of Helium-3 Usage in Radiography for Patient Position Verification in Particle Therapy*”
 - Poster presentation at 5th CERN Baltic conference (CBC’25) in Kaunas, Lithuania, 2025
I.Baumgarte (presenting), **K.Paļskis** “*Enabling the Third Dimension in Planar Radiographic Imaging - Feasibility of Focus Stacking with Helium Ion Radiography*”
 - Oral presentation at 17th International Conference and Workshop “*Medical Physics in the Baltic States 2025*” in Kaunas, Lithuania, 2025
I.Baumgarte (presenting), **K.Paļskis**, “*³He ion usage in particle radiography for patient position verification in particle therapy*”
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9.1. Modelling, radiographic image reconstruction and radiographic image analysis methodology

This Section provides brief summary of the modelling, image reconstruction and image analysis methodology used within the study, while additional methodological details are given in Appendix 8.1.

General MC setup. Characteristics of the simulated beam. Choice of initial particle energies.

For patient position verification, within CERN NIMMS HeLICS design limitations [15], three different radiography approaches were considered:

- **high energy proton radiography:** evaluating image quality dependency on proton energy: 250, 330, 400, 500, 600 and 700 MeV;
- **helium-3 radiography:** comparing helium-3 ions (He3-Rad) at 261 and 364 MeV/u (16 and 32 cm test object) with respect to helium-4 ions (He4-Rad) at 220 and 305 MeV/u.

10×10 cm irradiation fields with realistic beam energy spread and divergence were simulated, impinging on 16 and 32 cm thick water test objects.

2 mm thick volumes of air at the front and rear surfaces of test object were “ideal detectors”, scoring positions (x and y) and momentum direction angles relative to Z axis (θ_x and θ_y) of all hadronic particles, with kinetic energy E_{exit} also registered at the rear surface. For He-Rad studies, following [77], 2 mm thick polystyrene layer at the exit surface acted as $\Delta E - E$ filter, scoring kinetic energy and energy deposited per step length to reject secondaries. Geometry used in simulations is indicated in Figure 9.1. Two phantom setups were considered: high contrast ($2 \times 2 \times 2$ cm aluminium cube) and low contrast (different material cylinders with varying length for contrast levels of $\pm 0.5\%$, $\pm 1.0\%$ and $\pm 2.5\%$ relative to water, 6 different diameters of 0.5, 2, 4, 7, 10 and 15 mm).

Image reconstruction in i-Rad necessitates data corresponding only to primary particle electromagnetic interactions, thus different data filtering stages were applied: 3σ particle energy filter, removal of ambiguous events and 3σ relative scattering angle filter, following [93-94], while for He-Rad - also 3σ $\Delta E - E$ filter [77]. MLP formalism as in Schulte et al. [94] was used for image reconstruction, with detailed mathematical formalism provided in **Appendix 8.1.** of the Thesis. From exiting particle kinetic energy, WEPL was estimated by pre-calculated lookup tables based on Bethe-Bloch equation. Plane-of-interest binning was used, with reconstruction at test object mid-plane - 8 and 16 cm depth, respectively. WEPL data were binned with 0.2 mm resolution.

Several reconstructed image quality metrics were quantitatively evaluated: spatial resolution via modulation transfer function (MTF) analysis, contrast-to-noise ratio (CNR), imaging dose, low contrast resolution and accuracy of reconstructed WEPL values. Reconstructed WEPL value uncertainties were also evaluated.

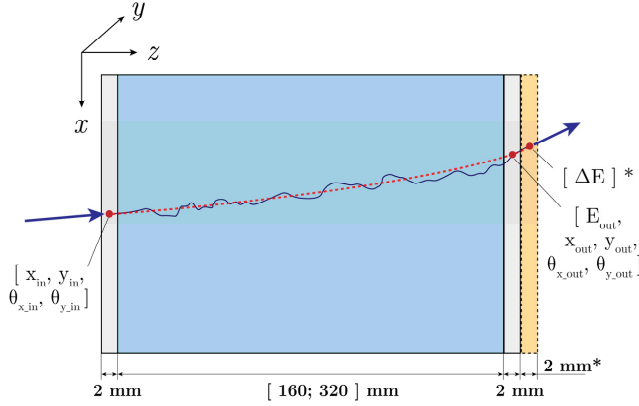


Figure 9.1. Geometry used for high energy proton and helium-3 ion radiography simulations

Grey regions correspond to idealized air detectors and the blue region - water test object. The additional polystyrene layer for $\Delta E - E$ implementation in helium ion simulations is indicated with the light-yellow region. Set of physical parameters registered within each volume is indicated with the points. True particle trajectory is indicated in blue, MLP estimate used for image reconstruction - in red.

9.2. Modelling, image reconstruction and image analysis methodology for evaluation of focus stacking approach in ion radiography

This Section provides brief summary of the modelling, image reconstruction and image analysis methodology used to evaluate different approaches for imaged object depth estimation and radiographical image quality improvement via focus stacking. Additional methodological details are given in Appendix 8.1.

To further improve reconstructed radiographical image quality in complex anatomies and enable possibility of 3D localization for imaged features, several focus stacking (FS) implementation methods were developed and quantitatively compared in this work, following the approach originally proposed in [17,27]. FS for radiographical imaging was evaluated for all proton, helium-3 and helium-4 ion energies outlined in Section 9.1. using the same beam, test object and idealized detector setup as discussed previously. Two phantom setups were considered in the study:

- high contrast – with three $2 \times 2 \times 2$ cm aluminium cubes spread laterally and centred at depths 20, 80 and 140 mm for 16 cm thick test object, while for 32 cm thick test object – 20, 160 and 300 mm.
- low contrast – following the same setup as for single plane radiography studies.

Following the same data filtering routine and MLP formalism as outlined in Section 9.1., a stack of radiographical images was reconstructed by varying reconstruction plane depth in 1 mm increments.

With additional considerations on physical rationale and mathematical formalism given in Appendix 8.1., per-pixel WEPL value and estimated object depth were calculated from a stack of radiographical images with different reconstruction plane depths using two different FS approaches:

- **edge detection based (ED-FS):** maximum spatial resolution of a specific object is achieved, when reconstruction plane is coincident with the object depth, thus maximum image signal amplitude after applying convolution with de-noising and edge detection kernels was used as FS metric, following [17,27]. Mathematically, this FS formalism can be described as:

$$(d^F)_{i,j} = \arg \max (|WEPL_n^{raw} \otimes DN \otimes ED|)_{i,j} \quad n \in [1; N] \quad (9.1)$$

$$WEPL_{i,j}^F = (WEPL_{d^F}^{raw})_{i,j} \quad (9.2)$$

where $(d^F)_{i,j}$ is calculated focus depth for a pixel with coordinates i and j , DN and ED corresponds to de-noising and edge detection kernel, respectively, used in convolution, $WEPL_n^{raw}$ is planar WEPL distribution calculated via PIB at reconstruction plane depth n , with n varying between depths of 1 mm to N (160 or 320 mm in respective test object geometry). After focus depth d^F estimation, WEPL value at each pixel in final reconstructed image $WEPL_{i,j}^F$ is taken as WEPL value from stack of PIB reconstructed radiographs at focus depth d^F for respective pixel $(WEPL_{d^F}^{raw})_{i,j}$. Both Gaussian kernels (σ of 1, 1.5, 2, 2.5 and 5 pixels) and median filters (2, 3, 4, 5 and 7 pixels) were evaluated and compared for de-noising, with several kernels evaluated for edge detection – Laplacian, Sobel, Scharr and Prewitt. For additional details on mathematical implementation of each edge detection kernel see Appendix 8.1.;

- **local WEPL variation based (LV-FS):** minimum WEPL value standard deviation after binning within a pixel at a specific object boundary is achieved, when reconstruction plane is coincident with the object depth, thus minimum per-pixel WEPL value standard deviation was used as FS metric, a novel approach proposed by Author. Using the notation introduced for Equations 9.1. and 9.3., mathematically this FS formalism can be described as:

$$(d^F)_{i,j} = \arg \min (|\sigma(WEPL_n^{raw} \otimes DN)|)_{i,j} \quad n \in [1; N] \quad (9.3)$$

$$WEPL_{i,j}^F = (WEPL_{d^F}^{raw})_{i,j} \quad (9.4)$$

where $\sigma(WEPL_n^{raw})$ is planar distribution of per-pixel WEPL standard deviation calculated via PIB at reconstruction plane depth n . Prior to FS, de-noising using both Gaussian kernels and median filters with sizes discussed previously was evaluated and compared.

Based on FS metric for each approach, per-pixel estimated object depth was calculated from the stack of PIB reconstructed radiographs (Equations 9.1. and 9.3.), while assigning WEPL value from respective reconstruction plane to final reconstructed image (Equations 9.2. and 9.4.). While proposed in [17,27] as method to decrease the impact of noise, no data smoothening with Savitzky-Golay filter along the depth axis was applied.

WEPL value accuracy in final radiographical images reconstructed with ED-FS and LV-FS were evaluated with respect to theoretical reference images. From distributions of per-pixel estimated object depths, 3-D localization precision was evaluated by comparing the results with actual positions in the phantom setup. Impact of particle type, energy and respective FS approach parameters on reconstructed WEPL value accuracy and 3-D localization precision was evaluated.

9.3. Results of the modelling: Image quality metric comparison between the proposed radiography methods

Reconstructed high contrast object radiographs with high energy protons and helium ions. Comparison with theoretical calculations

Firstly, reconstructed images are evaluated for high energy p-Rad, focusing on the energy-dependent characteristics. Reconstructed images for varying proton energies of high contrast phantom embedded in the 32 cm test object are illustrated in Figure 9.2 (data for the 16 cm test object in Figure A.8.10 of **Appendix 8.2.**). Accuracy of reconstructed WEPL distributions is quantitatively evaluated by comparison to theoretical WEPL distributions of reference images. Observed WEPL deviations are presented in **Appendix 8.2.** (Figure A.8.9 for 32 cm and Figure A.8.11 for 16 cm).

Results in Figure 9.2. and **Appendix 8.2** qualitatively illustrate impact of proton energy on achievable spatial resolution. With higher magnitude of lateral deviations of MCS at low energies, high contrast object edges are not clearly distinguishable and appear blurred for 250 MeV protons. Reduction of image quality is mitigated with increasing proton energy, displaying clearly distinguishable high contrast object edges for proton energies in the range from 500 to 700 MeV.

Relative WEPL value deviations presented in **Appendix 8.2.** additionally highlight shortcomings of lower energy p-Rad imaging. Highest WEPL value deviations are present in reconstructed images with 250 MeV protons - up to $\pm 4\%$ near the boundaries of high contrast object due to MCS. Size of the region with prominent WEPL value deviations decreases with increasing proton energy, with significant deviations only in a narrow region at imaged object boundary for 700 MeV scenario.

Observed impact of proton energy is more pronounced for 32 cm test object thickness. Results presented in **Appendix 8.2.**, display that blurring of imaged object boundary is lower for 16 cm test object thickness (with decreased region of prominent WEPL value deviations). This is attributable to MCS magnitude dependency on object thickness. Qualitatively, no significant blurring can be observed for 16 cm test object

already at energies of 330 to 400 MeV. Nevertheless, WEPL deviations relative to reference images are of higher magnitude in 16 cm test object case with respect to 32 cm case - up to $\pm 10\%$. This is attributable to higher particle exit energies for 16 cm test object case - WEPL calculation is more sensitive to energy straggling, causing higher deviations.

Data in Figure 9.2 and **Appendix 8.2** also illustrate one of drawbacks with higher energies for p-Rad imaging - increased imaging noise. Increased noise present in images acquired with higher energy protons is attributable to two main factors. Firstly, number of particles retained for image reconstruction slightly decreases with increasing proton energy due to increased nuclear interactions, as quantitatively discussed later in this Section. Secondly, higher initial proton energies have increased particle exit energies, thus WEPL value reconstruction is more sensitive to energy straggling. Data in Figure A.8.9 of **Appendix 8.2** illustrate that at 250 MeV WEPL relative deviations in homogeneous regions are in the range $\pm 0.5\%$, increasing to around $\pm 1.5\%$ at 700 MeV proton energy.

As the second modality for pre-treatment i-Rad, the novel approach of He3-Rad was evaluated with comparison to He4-Rad. Reconstructed images for high contrast phantom with both He3-Rad and He4-Rad are illustrated in Figure 9.3, with accuracy of reconstructed WEPL distributions presented in **Appendix 8.3**.

By qualitative evaluation, no significant differences could be observed in the reconstructed images of He3-Rad and He4-Rad presented in Figure 9.3. Similarly, relative WEPL value deviations with respect to references were comparable between the two helium isotopes (see **Appendix 8.3**). Compared to protons, both He3-Rad and He4-Rad showcase improved image quality and WEPL value accuracy at lower particle energies¹⁴ necessary for imaging. No significant high contrast object boundary blurring is observed with only localized WEPL value deviations of around $\pm 4\%$ and $\pm 10\%$ for 32 and 16 cm test objects, respectively. This is attributable to decreased MCS magnitude with increased mass and charge of particle. Figure 9.3 and **Appendix 8.3** also illustrate reduced imaging noise in homogeneous regions in comparison to protons.

¹⁴ By comparison with range in water, studied helium-4 ion energies approximately correspond to proton imaging scenarios of 250 and 330 MeV

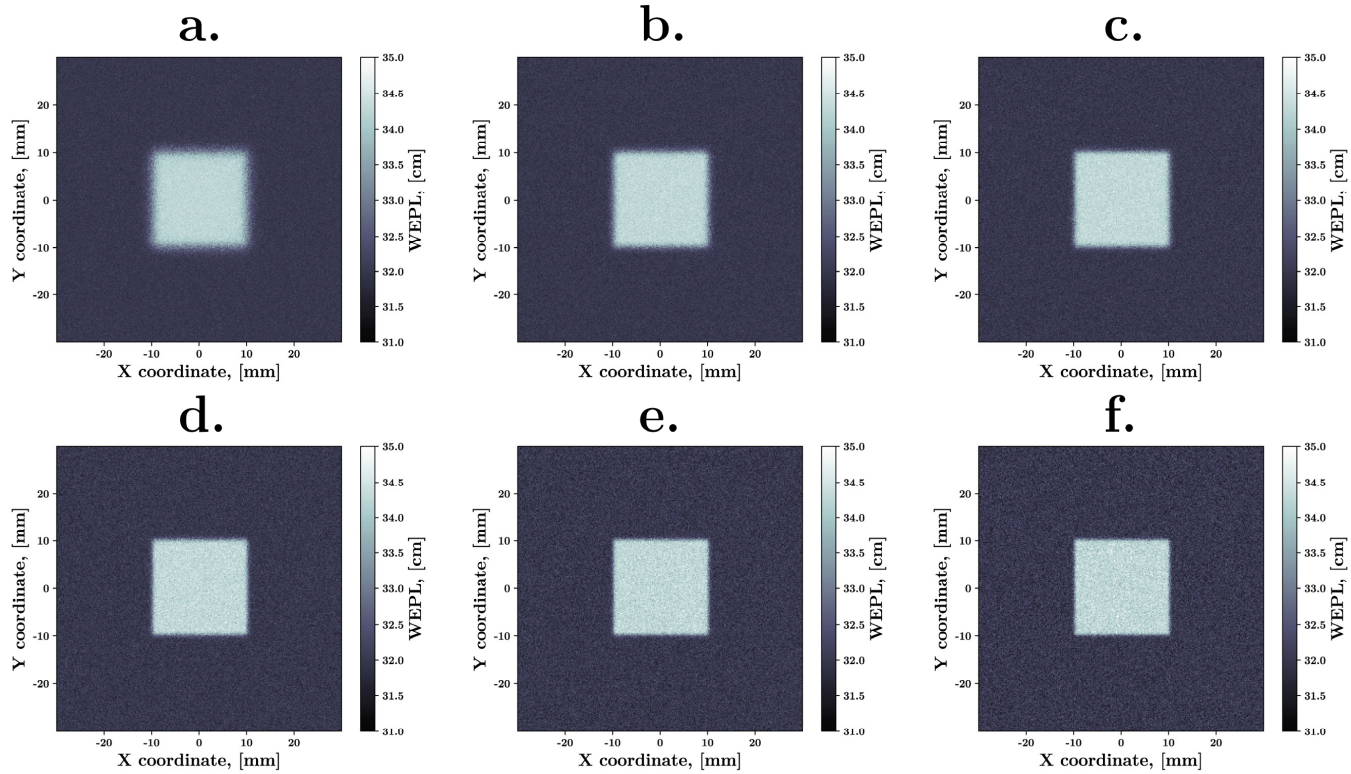


Figure 9.2. Reconstructed radiographic images of high contrast phantom in 32 cm test object for different initial proton energies
Radiographic images reconstructed with pixel size of 0.2 mm, PIB at test object mid-plane, central 60×60 mm ROI illustrated. Data given for protons with initial energies of 250 (Subfigure (a)), 330 (Subfigure (b)), 400 (Subfigure (c)), 500 (Subfigure (d)), 600 (Subfigure (e)) and 700 (Subfigure (f)) MeV

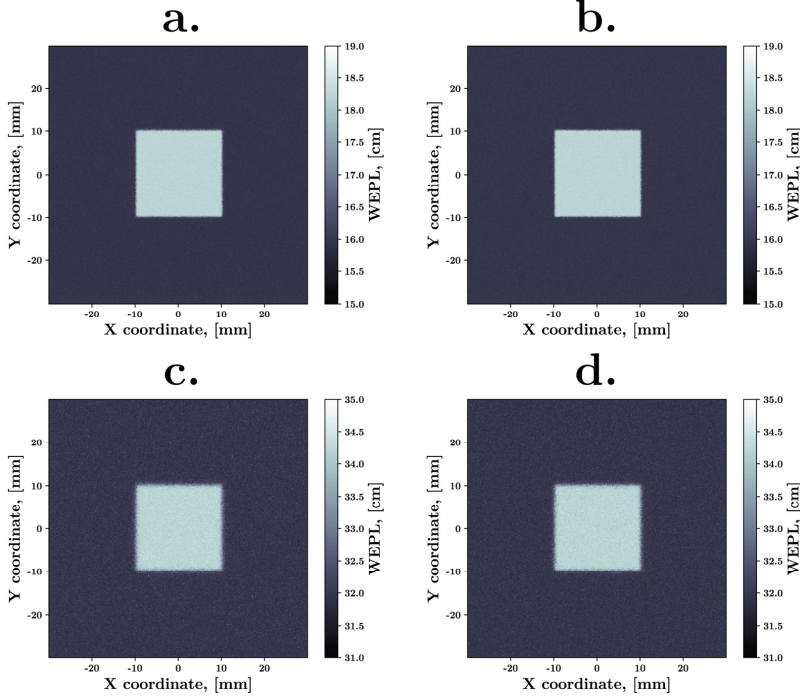


Figure 9.3. Reconstructed radiographic images of high contrast phantom in 16 and 32 cm test objects for different initial helium-3 and helium-4 ion energies

Radiographic images reconstructed with pixel size of 0.2 mm, PIB at test object mid-plane, central 60×60 mm ROI illustrated.

Data given for 261 MeV/u helium-3 ions in 16 cm test object (Subfigure (a)), 220 MeV/u helium-4 ions in 16 cm test object (Subfigure (b)), 364 MeV/u helium-3 ions in 32 cm test object (Subfigure (c)) and 305 MeV/u helium-4 ions in 32 cm test object (Subfigure (d))

Spatial resolution of radiographic images with high energy protons and helium ions

For quantitative evaluation of spatial resolution dependency on energy used for p-Rad and comparison between He3-Rad and He4-Rad, spatial frequencies corresponding to 10% and 50% of MTF were extracted as metrics for analysis. Figure 9.4(a) presents spatial resolution dependency on energy used for p-Rad in both 16 and 32 cm test object, while Figure 9.4(b). illustrates comparison of He3-Rad and He4-Rad.

Results in Figure 9.4(a) illustrate a non-linear increase of spatial frequency corresponding to 10% MTF with increasing proton energy used for imaging (data for 50% MTF given in **Appendix 8.4**). In 16 cm test object, 1.15 lp/mm are distinguishable at 10% MTF for 250 MeV protons. Distinguishable spatial frequency increases 1.6 times (1.79 lp/mm) at 400 MeV, reaching a maximum of 2.3 times higher value (2.63 lp/mm)

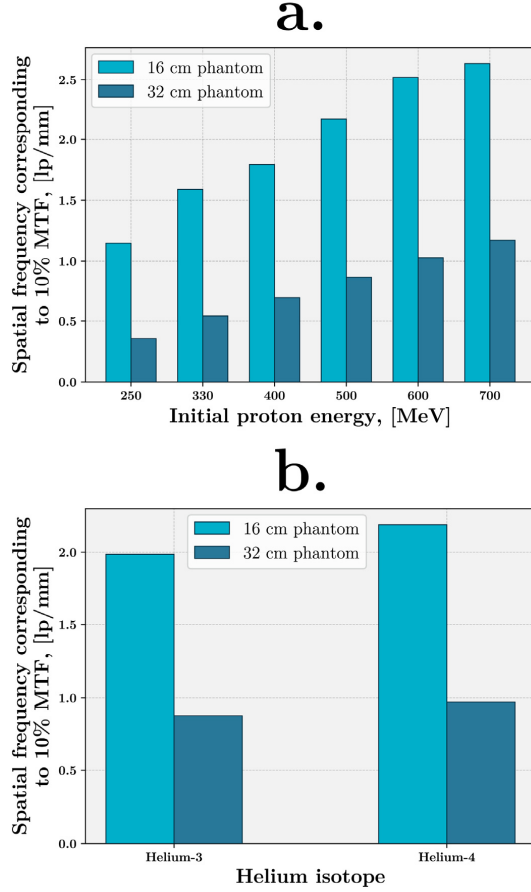


Figure 9.4. Spatial resolution dependency on initial proton energy (a) and used helium isotope (b) in high contrast phantom radiographic images

Spatial resolution defined as spatial frequency corresponding to 10% MTF in reconstructed high contrast object radiographic images (pixel size of 0.2 mm, PIB at test object mid-plane). Data given in both 16 and 32 cm test objects.

In Subfigure (b) helium-3 ion energies of 261 and 364 MeV/u correspond to 16 and 32 cm test objects, respectively, while for helium-4 ions - energies of 220 and 350 MeV/u.

at 700 MeV. Similar trend can be observed for 32 cm test object, though distinguishable spatial frequencies are significantly lower compared to 16 cm test object (2.2 times lower at 700 MeV, 3.2 - at 250 MeV). At 250 MeV, distinguishable spatial frequency for 32 cm test object is 0.34 lp/mm at 250 MeV increasing 3.3 times to 1.17 lp/mm at 700 MeV. Quantitatively increased image quality - spatial resolution - can be observed for higher

energy p-Rad, due reduced MCS magnitude. Due to MCS, higher spatial resolution is achieved for smaller imaged objects.

Comparison of He3-Rad and He4-Rad in Figure 9.4(b). indicates subtle changes in spatial resolution. For 16 cm test object, 1.99 lp/mm are distinguishable for He3-Rad, while 2.19 lp/mm are distinguishable for He4-Rad. Similarly, for 32 cm test object, spatial frequencies at 10% MTF were 0.88 and 0.98 lp/mm, respectively. For both test object thicknesses, ~10% increase of distinguishable spatial frequencies for He4-Rad in comparison to He3-Rad is observed - minor spatial resolution improvement. This is attributable to slightly higher mass of helium-4 ions, reducing the magnitude of MCS. Nevertheless, the differences between the two He-Rad methods are not significant and performance of He3-Rad and He4-Rad can be considered comparable.

Comparing the results between p-Rad and both He-Rad methods, higher spatial resolution can be achieved with He3-Rad and He4-Rad with lower energies necessary for imaging compared to p-Rad. Spatial resolution of He4-Rad at 220 MeV/u energy (16 cm test object) is comparable to 500 MeV p-Rad, while at 350 MeV/u (32 cm test object) - to 600 MeV p-Rad. Furthermore, spatial resolution reduction between 32 cm and 16 cm test objects for He3-Rad and He4-Rad is around 2.3 times, similarly to 700 MeV protons, indicating He-Rad spatial resolution performance as comparable to high energy p-Rad.

CNR of radiographic images with high energy protons and helium ions. Assessment of imaging dose and impact on CNR. WEPL uncertainty.

CNR was used as a metric to quantitatively evaluate imaging noise and achievable contrast of p-Rad, He3-Rad and He4-Rad. Figure 9.5(a) illustrates CNR dependency on the energy used for p-Rad in 16 and 32 cm test objects, while Figure 9.5(b). illustrates the comparison between He3-Rad and He4-Rad.

Contrary to spatial resolution, results in Figure 9.5(a) illustrate a decrease of CNR with increasing energy used for p-Rad - approximate inverse proportionality of CNR with respect to energy used. In 16 cm test object, CNR of 24.9 at 250 MeV energy decreases by 1.6 times at 400 MeV (CNR of 16.0), reaching minimum CNR of 9.3 at 700 MeV - 2.7 times lower. Similar trend can be observed for 32 cm test object, though CNR values are approximately 1.4 times lower compared to 16 cm object for all energies. At 250 MeV, CNR of 17.1 is achieved, decreasing 2.5 times to value of 6.8 at 700 MeV. Energy dependency of CNR for p-Rad provides quantitative measure of increased imaging noise and decreased contrast performance for higher energies. CNR performance is contrary to increased spatial resolution, suggesting necessity of an optimum energy for p-Rad imaging. Decrease of CNR with increasing proton energy can be attributable to increased probability of nuclear interactions and higher WEPL sensitivity to straggling at high exit energies - both explored further in the Results section.

Subtle changes in performance of CNR performance can be observed for He3-Rad and He4-Rad comparison in Figure 9.5(b). For 16 cm test object, CNR of 39.2 is reached for He3-Rad, while 38.2 for He4-Rad. For 32 cm test object, the difference in CNR is almost negligible with values of 16.2 and 16.5 for He3-Rad and He4-Rad,

respectively. Results correspond to only about 2.7% higher CNR for He3-Rad in 16 cm test object and 1.6% higher for He4-Rad in 32 cm test object. Results indicate minor changes of CNR for the two He-Rad methods - comparable imaging noise and contrast.

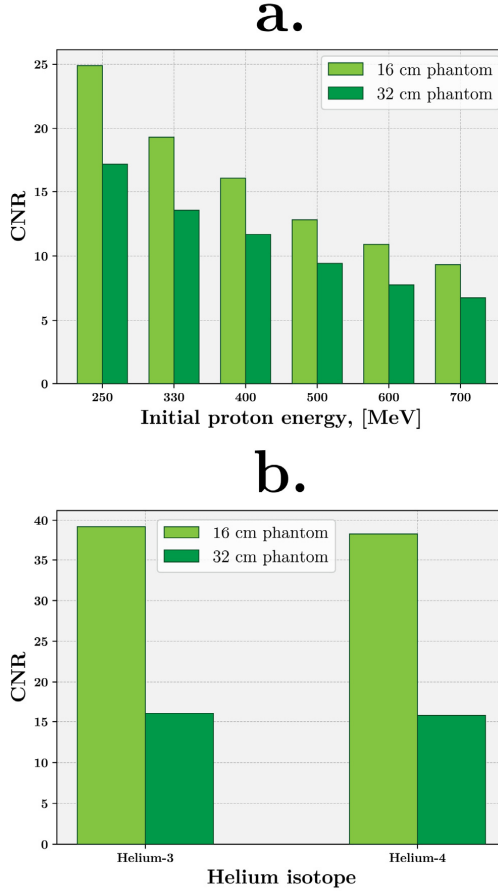


Figure 9.5. CNR dependency on initial proton energy (a) and used helium isotope (b) in high contrast phantom radiographic images

CNR calculated based Appendix 8.1., in reconstructed high contrast phantom radiographic images (pixel size of 0.2 mm, PIB at test object mid-plane). Only standard deviation of WEPL values within the ROI were used in the calculation, not accounting for intrinsic pixel-level standard deviation.

Data given in both 16 and 32 cm test objects.

In Subfigure (b) helium-3 ion energies of 261 and 364 MeV/u correspond to 16 and 32 cm test objects, respectively, while for helium-4 ions - energies of 220 and 350 MeV/u.

Comparing results between p-Rad and both He-Rad methods, higher CNR can be achieved with He3-Rad and He4-Rad with respect to best performance of p-Rad at

250 MeV energy in 16 cm test object. On the contrary, in 32 cm test object 250 MeV p-Rad provides slightly higher CNR value with respect to both He-Rad methods - about 3.6% increase. Improved He-Rad performance - reduced imaging noise - can be expected for smaller object imaging, while in case of larger objects, He-Rad performance is similar, possibly attributable to higher loss of primaries for helium ions with respect to protons.

CNR is dependent on imaging dose used - number of primaries used for image acquisition. Higher imaging dose could provide higher CNR, though it should be kept minimum to reduce patient exposure. Imaging dose data as calculated for nominal 10^7 primaries is given for p-Rad, He3-Rad and He4-Rad in Table 9.1. For p-Rad, imaging dose slightly decreases for the same number of primaries with increasing proton energy - about 0.02 and 0.04 mGy between 250 and 700 MeV for 16 and 32 cm test objects, respectively. Decrease is attributable to slight decrease of energy loss (energy deposition per length) with increasing proton energy. With same reasoning, increased energy loss of helium ions corresponds to about 4 to 5 times higher imaging dose compared to p-Rad. Analysing differences between the He3-Rad and He4-Rad, He3-Rad has 13 and 11% lower imaging dose in simulated scenarios compared to He4-Rad for same number of primaries, attributable to slightly decreased energy loss of helium-3 ions.

To evaluate the “imaging dose-CNR” relationship for p-Rad, He3-Rad and He4-Rad, both metrics were re-calculated for varying number of primaries. Figure 9.6(a) illustrates CNR dependency for different energies of p-Rad, while Figure 9.6(b) demonstrates comparison between He3-Rad and He4-Rad.

Data in Figure 9.6(a) re-iterate improved CNR performance of lower energy p-Rad as increased imaging dose is necessary to achieve the same level of CNR with higher energy protons. For example, to achieve CNR of 10 in 16 cm test object, around 6 times higher imaging dose is necessary for 700 MeV p-Rad compared to 250 MeV.

Comparing CNR and imaging dose relationship for He3-Rad and He4-Rad, lower imaging dose is necessary with He3-Rad in both 16 and 32 cm test objects to achieve the same level of CNR - around 10 - 15 % lower. Findings indicate slightly favourable performance of He3-Rad with respect to He4-Rad in terms of imaging dose and CNR.

Imaging noise in this work was also characterized via assessment of WEPL value uncertainties - intrinsically per pixel and for a homogeneous ROI (extrinsically). Data on intrinsic and extrinsic WEPL value uncertainties are given in **Appendix 8.5.** - for different energy p-Rad in Table A.8.5. and for He-Rad methods in Table A.8.6. Similarly, the image noise characterization with CNR, data in Table A.8.5. of **Appendix 8.5** illustrate WEPL value uncertainty increase with increasing energy for p-Rad. For 10^7 primary particles, with energy increasing from 250 to 700 MeV, intrinsic pixel-level uncertainty increased from 2.0% to 4.8%, while extrinsic uncertainty in homogeneous ROI - from 0.4% to 0.9%. Increased uncertainty is mainly attributable to increased WEPL sensitivity to energy straggling at higher energies and higher loss of primaries reducing the number of particles retained for image reconstruction. Around 10 times

more particles are necessary to achieve the same level of extrinsic WEPL uncertainty with 700 MeV protons compared to 250 MeV.

Data presented in Table A.8.6. of **Appendix 8.5** illustrate that almost no difference can be observed for extrinsic WEPL uncertainty between the He3-Rad and He4-Rad, with negligible $\sim 0.06\%$ decrease of intrinsic uncertainty for He4-Rad. Compared to p-Rad, both He-Rad methods indicate greatly improved imaging noise performance - intrinsic and extrinsic WEPL uncertainties were lower for He-Rad compared to best performance of 250 MeV p-Rad.

Table 9.1.

Calculated imaging dose of high energy proton and helium ion radiography scenarios for 16 and 32 cm test object with embedded high contrast phantom

Ion type, initial energy	Calculated imaging dose*	
	for 16 cm test object	for 32 cm test object
High energy proton radiography scenarios		
protons, 250 MeV	0.076 mGy $\pm$ 0.03%	0.099 mGy $\pm$ 0.06%
protons, 330 MeV	0.065 mGy $\pm$ 0.04%	0.076 mGy $\pm$ 0.06%
protons, 400 MeV	0.060 mGy $\pm$ 0.04%	0.067 mGy $\pm$ 0.05%
protons, 500 MeV	0.055 mGy $\pm$ 0.04%	0.061 mGy $\pm$ 0.05%
protons, 600 MeV	0.053 mGy $\pm$ 0.04%	0.058 mGy $\pm$ 0.05%
protons, 700 MeV	0.052 mGy $\pm$ 0.04%	0.057 mGy $\pm$ 0.05%
Helium ion radiography scenarios		
helium-3 ions, 261 MeV/u	0.274 mGy $\pm$ 0.03%	-
helium-3 ions, 364 MeV/u	-	0.230 mGy $\pm$ 0.03%
helium-4 ions, 220 MeV/u	0.309 mGy $\pm$ 0.03%	-
helium-4 ions, 350 MeV/u	-	0.257 mGy $\pm$ 0.03%

* Imaging dose calculated as total energy deposition within irradiated volume - $10 \times 10 \times 16$ or $10 \times 10 \times 32$ cm for 16 and 32 cm test objects. 1σ uncertainty of imaging dose given as relative value. Data given for 10^7 initial particles.

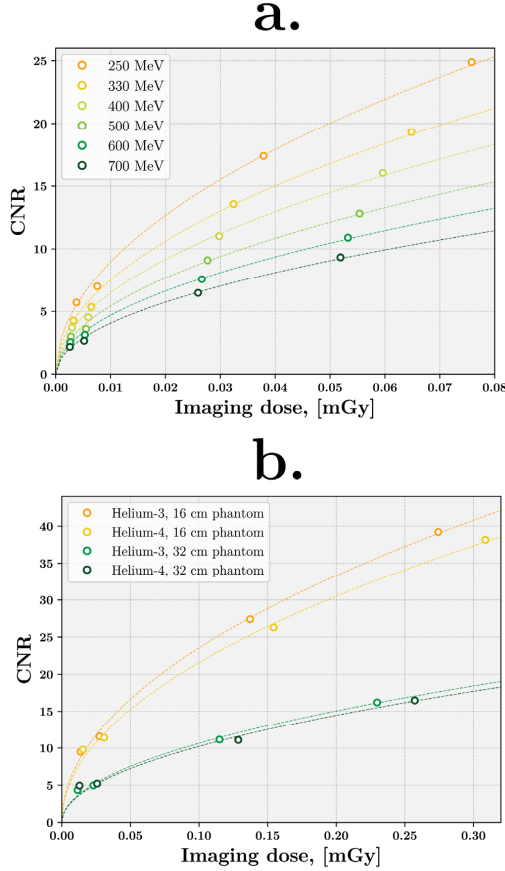


Figure 9.6. CNR as a function of imaging dose, depending on initial proton energy (a) and used helium isotope (b) in high contrast phantom radiographic images

Data in Subfigure (a) given for 16 cm test object, data in Subfigure (b) - for both 16 and 32 cm test objects. CNR calculated as described for Figure 9.5. Imaging dose calculated as total energy deposition within irradiated volume - $10 \times 10 \times 16$ or $10 \times 10 \times 32$ cm for 16 and 32 cm test objects, respectively.

Markers correspond to simulated and analysed data points for $5 \cdot 10^5$, 10^6 , $5 \cdot 10^6$ and 10^7 initial particles, while dashed lines correspond to a fitting function of form $a \cdot \sqrt{D}$ (D - imaging dose) to reflect the Poissonian nature of CNR dependency on imaging dose. Imaging dose 1σ uncertainties not illustrated - in range of 0.03 to 0.18%.

In Subfigure (b) helium-3 ion energies of 261 and 364 MeV/u correspond to 16 and 32 cm test objects, respectively, while for helium-4 ions - energies of 220 and 350 MeV/u.

Low contrast resolution of radiographic images with high energy protons and helium ions. Impact of detector energy resolution

Ability to distinguish small changes of WEPL values of the different studied i-Rad approaches were evaluated next, using low contrast phantom. P-Rad images of low contrast phantom embedded in 16 and 32 cm test object for varying energy levels are illustrated in Figure A.8.14. and A.8.15. of **Appendix 8.6**. An idealized setup was considered initially, assuming no limit on energy resolution of the detector - main factor for WEPL resolution.

Results presented in **Appendix 8.6**. illustrate the impact of energy used for p-Rad on the achievable low contrast resolution. Firstly, none of the considered proton energies can provide image quality sufficient to distinguish inserts with 0.5 mm diameter, due to the spatial resolution limitations of p-Rad. In 32 cm test object scenario, 250 MeV and 330 MeV also have inadequate reconstruction of 1 mm diameter inserts, with perturbed WEPL values due to blurring from MCS. In the idealized setup, all investigated energies indicate difficulties to reconstruct low contrast level of +0.5%. None of energy levels could adequately reconstruct 2 mm diameter of +0.5% insert, while energies higher than 500 MeV struggle to reconstruct also 4- and 7-mm diameter inserts.

Idealized setup of low contrast phantom was also evaluated for He3-Rad and He4-Rad, with reconstructed images illustrated in A.8.16. of **Appendix 8.6**. Contrary to p-Rad, both He-Rad methods could reconstruct 0.5 mm diameter inserts with contrast levels of -2.5% and +2.5% in 16 cm test object. In 16 cm test object, inserts with diameters of 4 mm and larger could be clearly distinguished for all contrast levels. In 32 cm test object, same inserts could be distinguished except for 4 mm diameter with +0.5% contrast. No significant changes were observed between He3-Rad and He3-Rad low contrast resolution.

One of the main limitations of realistic i-Rad detector system is energy resolution. Ability to clearly distinguish two kinetic energy levels of particles exiting imaged object impacts the ability to distinguish two WEPL levels. Thus, energy resolution of the detector is main limiting factor for low contrast resolution. With no specific detector considered in this work, energy resolution impact on WEPL resolution was assessed by perturbation of registered kinetic energy data before image reconstruction - a limited energy resolution of $\pm 1\%$ (1σ) was considered. Impact of energy resolution on low contrast resolution was first evaluated for p-Rad. Low contrast phantom images for energy levels of p-Rad with applied exit energy perturbation are illustrated in A.8.17. of **Appendix 8.7** for 16 cm test object and Figure 9.7 - 32 cm test object.

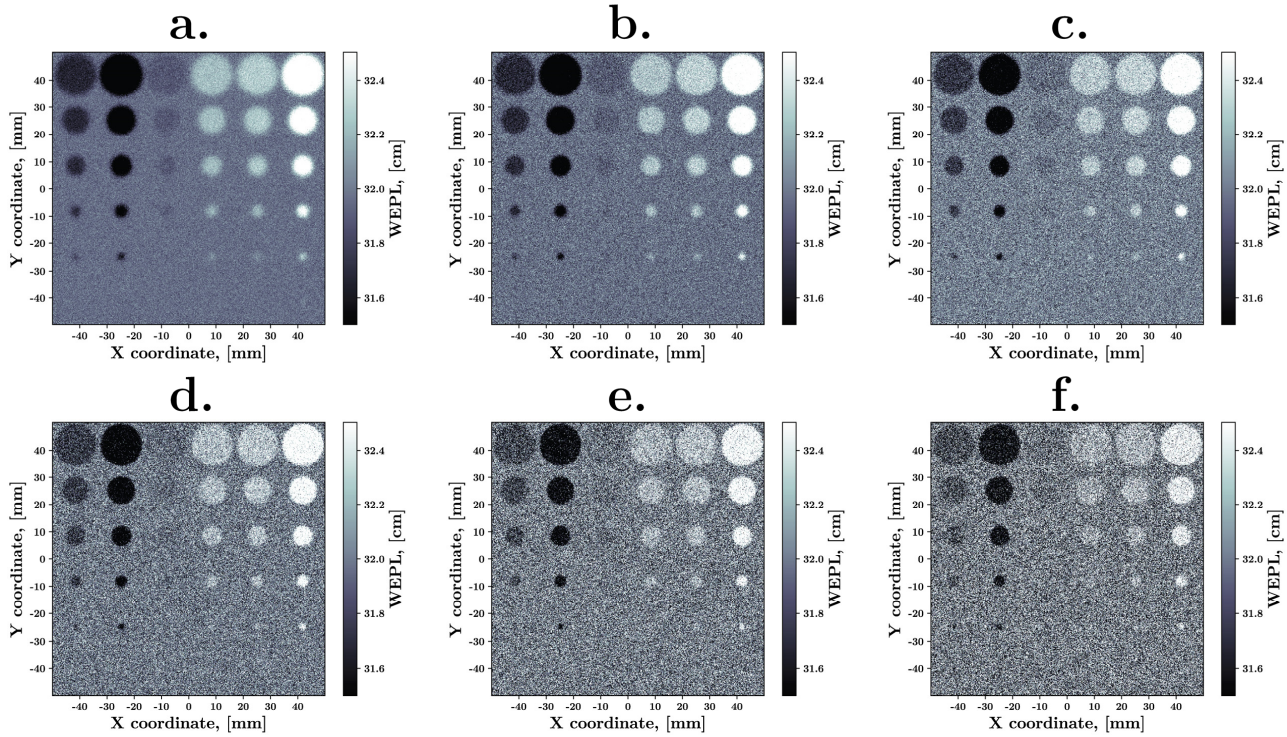


Figure 9.7. Reconstructed radiographic images of low contrast phantom in 32 cm test object for different initial proton energies with $\pm 1\%$ (1σ) energy resolution perturbation

Radiographic images reconstructed with pixel size of 0.2 mm, PIB at test object mid-plane, full ROI of 100×100 mm illustrated.

Data given for protons with initial energies of 250 (Subfigure (a)), 330 (Subfigure (b)), 400 (Subfigure (c)), 500 (Subfigure (d)), 600 (Subfigure (e)) and 700 (Subfigure (f)) MeV

Qualitative analysis of data presented in Figure A.8.17. of **Appendix 8.7** and Figure 9.7. clearly indicate higher imaging noise and reduced low contrast resolution for higher energy p-Rad. With introduced energy resolution limit, 1% change in energy for 700 MeV p-Rad scenario corresponds to higher change in WEPL than for 250 MeV p-Rad. Evaluating low contrast resolution, none of p-Rad energy levels can reconstruct 0.5 mm diameter. In 16 cm test object illustrated in A.8.17. of **Appendix 8.7**, while only +0.5% contrast 2 mm cylinder cannot be identified for 250 MeV scenario, number of distinguishable inserts gradually decreases with energy increasing to 700 MeV. For p-Rad with 700 MeV, none of 2 mm cylinders can be distinguished, for 4 mm cylinders - only +2.5 and -2.5% contrast levels could be identified, while for +0.5% contrast level - none of inserts could be identified. In 32 cm test object, low contrast performance does decrease with increasing proton energy, though more inserts can be distinguished compared to 16 cm case. This indicates low contrast resolution dependency on the size of imaged object - for same initial kinetic energy, smaller imaged object will have higher exit energy, which is more sensitive to energy resolution and straggling, increasing WEPL uncertainties.

Impact of limited energy resolution on low contrast resolution was also evaluated for He3-Rad and He4-Rad. Reconstructed images are illustrated in Figure 9.8. No significant changes in low contrast resolution were observed for He3-Rad and He4-Rad with energy resolution limit considered. In 16 cm test object, 0.5 mm inserts with contrast levels of +2.5% and -2.5% appear to be more clearly distinguishable for helium-3 ions.

Contrary to p-Rad, introduction of exit kinetic energy perturbation due to limited detector resolution did not have as pronounced effect on low contrast resolution with both He-Rad methods. In both 16 and 32 cm test objects, it was possible to distinguish the same inserts as for unperturbed scenario. This is attributable to reduced WEPL value relative variation for same relative variation in energy for helium-3 and helium-4 ions compared to protons.

Accuracy of reconstructed WEPL values. Impact of RSP energy dependency

Based on acquired low contrast phantom images, quantitative accuracy of reconstructed WEPL values was evaluated, also considering the impact theoretical energy resolution of detector system as discussed before. Data on reconstructed WEPL values with varying energy p-Rad and comparison with theoretically calculated values is summarized in Table A.8.7 of **Appendix 8.8**. Presented data correspond to largest cylindrical inserts - 15 mm diameter.

Analysing data in Table A.8.7 of **Appendix 8.8**., WEPL values using p-Rad can be reconstructed with high accuracy in both 16 cm and 32 cm test objects, with deviations from theoretical values below 1 mm - maximum errors of 0.4 and 0.9 mm in 16 cm and 32 cm test objects, respectively. No significant dependency of deviations was observed with respect to energy used, though for smaller inserts deviations were lower for higher energies due to reduced blurring from MCS. Although observed deviations are independent of p-Rad energy used, the uncertainty of reconstructed WEPL values

increases with increasing energy, if detector resolution is considered. Due to physical phenomena described before, WEPL value uncertainty of around 1 mm at 250 MeV increased to 5-6 mm at 700 MeV.

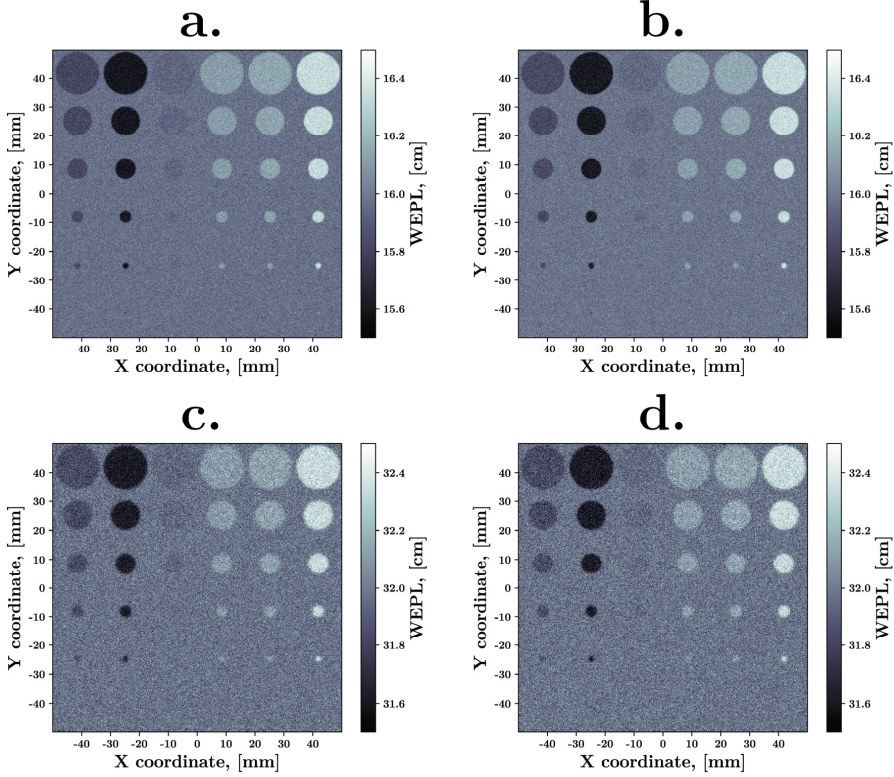


Figure 9.8. Reconstructed radiographic images of low contrast phantom in 16 and 32 cm test objects for different initial helium-3 and helium-4 ion energies with $\pm 1\%$ (1σ) energy resolution perturbation

Radiographic images reconstructed with pixel size of 0.2 mm, PIB at test object mid-plane, full ROI of 100×100 mm illustrated.

Data given for 261 MeV/u helium-3 ions in 16 cm test object (Subfigure (a)), 220 MeV/u helium-4 ions in 16 cm test object (Subfigure (b)), 364 MeV/u helium-3 ions in 32 cm test object (Subfigure (c)) and 305 MeV/u helium-4 ions in 32 cm test object (Subfigure (d))

WEPL accuracy was also evaluated for He3-Rad and He4-Rad with data presented in Table A.8.8 of **Appendix 8.8**. No significant differences both in accuracy and uncertainties of reconstructed WEPL values were observed between the two. Both He3-Rad and He4-Rad had WEPL deviation lower than 0.5 mm in 16 cm test object and

0.8 mm in 32 cm test object. Uncertainties were lower than for p-Rad, with average uncertainty of 0.7 mm in 16 cm test object and 1.3 mm in 32 cm test object.

Additional systematic WEPL value uncertainty in i-Rad could arise from energy dependency of RSP. Due to RSP energy dependency WEPL values reconstructed with higher energies of i-Rad could have an offset relative to RSP values relevant for treatment delivery energy levels. Evaluation of RSP energy dependency in biologically relevant materials is given in **Appendix 8.9**. RSP value normalization was done with reference to helium-4 ions at 100 MeV/u.

For p-Rad, magnitude of relative RSP value deviation increases with increasing proton energy. Highest deviations are observed for cortical bone (+0.4% at 250 MeV increasing to +0.8% at 700 MeV) and adipose tissue (-0.2% at 250 MeV increasing to -0.4% at 700 MeV), with deviation below -0.2% observed for the other biological materials considered. Findings suggest the use of lower energy p-Rad to acquire WEPL values relevant for treatment delivery with helium-4 ions, mitigating RSP energy dependency.

For the investigated He3-Rad and He4-Rad energies, deviations in the range from -0.4% to 0.5% are observed, with most of the materials having RSP deviations in the range from 0 to -0.1%. As higher energies per nucleon are necessary to accelerate helium-3 ions to the same range as helium-4 ions, RSP deviations for helium-3 ions are slightly higher, though still below 0.1 % and essentially negligible.

Detected particle data filtering and rejection rates in radiographic imaging with high energy protons and helium ions

Image quality metrics, such as CNR, are influenced by the particle count retained for image reconstruction. This depends both on the number of nuclear interactions contributing to loss of primaries and the particle rejection rates during data filtering stages. Detailed summary of data on particle rejection rates during image reconstruction process, as well as retained number of primary particles, are given in **Appendix 8.10**.

In the simple phantom geometries considered in this work, no difficulties in data filtering were observed as the variation of WEPL values was not large within the imaged object. For clinical scenarios, more severe WEPL variations could be expected due to complex patient anatomy. In context of He-Rad this could be an issue for separation of primaries for image reconstruction from lighter fragments [13]. In this context, another important finding in comparison of He3-Rad and He4-Rad is the data filtering necessities from technical implementation perspective and discrimination capabilities. In case of He4-Rad, fragmentation into protons, deuterons, tritons, and helium-3 ions is possible. As proposed by Volz et. al. [13], the $\Delta E - E$ filter can be used to separate helium-4 ions from lighter fragments. Nevertheless, as can be observed in Figure 9.9.(b)., $\Delta E - E$ distribution of helium-4 ions has a slight overlap with helium-3 fragments - potentially introducing imaging noise and artefact in reconstructed image. In case of He3-Rad, fragmentation is possible only to protons, deuterons, and tritons. As illustrated in Figure 9.9.(a), helium-3 ions can be more clearly distinguished from secondary fragments.

Considering this, less complex data filtering and possibly - less complex detector setup could be achieved with He3-Rad.

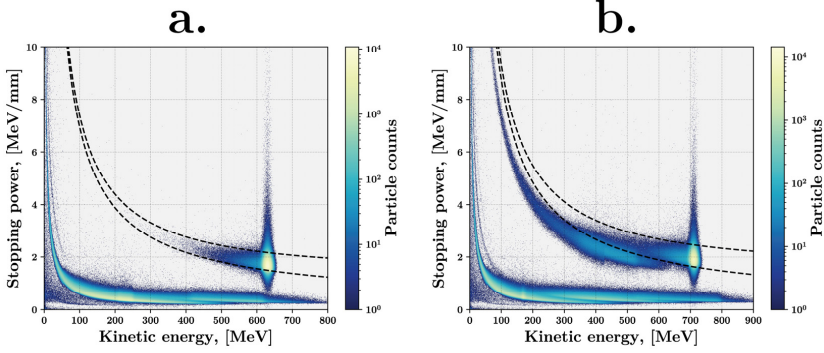


Figure 9.9. Identification $\Delta E - E$ filter - stopping power as function of kinetic energy - for particles registered at the exit surface of the test object for helium-3 (a) and helium-4 (b) ions.

Data given for low contrast phantom in 32 cm test object using nominal value of 10^7 initial particles.

Registered particle counts given in logarithmic scale. Kinetic energy data grouped in bins of 1 MeV, stopping power - 0.01 MeV/mm. Black lines correspond to nominal stopping power curve in polystyrene as function of kinetic energy with $\pm 3\sigma$ energy straggling uncertainty band for helium-3 ions (Subfigure (a)) and helium-4 ions (Subfigure (b))

Impact of MLP and WEPL perturbations on radiographic image quality with high energy protons and helium ions

As final part of the work, impact of imaging and reconstruction process uncertainties was evaluated for p-Rad, He3-Rad and He4-Rad. Perturbations of energy resolution, as discussed in low contrast resolution part, and MLP reconstruction process were evaluated. Calculated absolute difference distributions of MLP and energy resolution perturbations for varying energy p-Rad, He3-Rad and He4-Rad are given in **Appendix 8.11**.

With quantitative evaluation given in the next Subsection, qualitative observations can be made based on data in **Appendix 8.11**. The intrinsic uncertainty of MLP reconstruction process is more prominent near boundaries of imaged objects. Uncertainty exhibits higher magnitude and is prominent in larger region near object boundaries for lower proton energies, attributable to MCS energy dependency. In homogeneous regions, higher noise can be observed for higher proton energies. MLP-associated uncertainty distributions are comparable between He3-Rad and He4-Rad, with decreased magnitude compared to protons.

WEPL perturbations from limited energy introduce significant uncertainty and noise in whole reconstructed image. Magnitude of this uncertainty increases from ± 0.5 cm at 250 MeV to ± 3 cm at 700 MeV (slightly increased for 32 cm test object

compared to 16 cm). Energy resolution induced uncertainty distributions are comparable between He3-Rad and He4-Rad, with decreased magnitude compared to p-Rad - ± 0.4 cm for 16 cm test object and ± 1 cm for 32 cm test object.

Uncertainty assessment in radiographic imaging with high energy protons and helium ions

Identified uncertainty sources were quantitatively evaluated for p-Rad, He3-Rad and He4-Rad. WEPL uncertainties for varying energy p-Rad (a) and as a comparison between He3-Rad and He4-Rad (b) are given in Figure A.8.27 of **Appendix 8.12.** and 9.10. for 16 and 32 cm test objects, respectively. Data are given as stacked histograms to visually represent the different contributions, with 1σ uncertainty reported in further analysis calculated via variance summation (see **Appendix 8.1**).

In p-Rad, main contributions arise from WEPL binning uncertainties at pixel level and detector energy resolution perturbation, both increasing with increasing proton energy. On the contrary, the uncertainty of MLP reconstruction process and deviation from theoretical image decreases with increasing proton energy due changes in MCS magnitude. The latter uncertainty contributions significantly depend on the complexity of the imaged object - higher contribution of these uncertainty sources could be expected for complex geometries such as a realistic patient anatomy.

In case of 16 cm test object, the overall WEPL uncertainty of p-Rad increases with increasing proton energy - from 0.54 cm at 250 MeV to 1.08 cm at 700 MeV. For 32 cm test object, uncertainties associated with MCS process have more significant contribution, thus minimum uncertainty is reached for 400 MeV energy - 1.00 cm. Higher uncertainties were observed for both 250 and 700 MeV energies - 1.15 and 1.37 cm, respectively. This indicates the necessity to choose an optimum energy for radiographic imaging for larger anatomies in full-body radiography, such as pelvis. Proton energies in the range of 330 to 500 MeV would be considerable as optimum in this case, offering balance between WEPL uncertainty, spatial resolution, and CNR, though the optimum would depend on the size and complexity of the imaged object.

For He-Rad modalities, main uncertainty contribution is WEPL binning at pixel level, though, contrary to p-Rad, detector energy resolution perturbation is significantly decreased. In both 16 and 32 cm test object scenarios, He4-Rad exhibited slightly decreased overall uncertainty compared to He3-Rad. For 16 cm test object, 0.31 cm uncertainty for He4-Rad and 0.33 cm for He3-Rad was observed, while in 32 cm test object - 0.64 and 0.70 cm, respectively. Observed uncertainties of both He-Rad approaches were significantly lower compared p-Rad.

Evaluation of uncertainties significantly depends on complexity of the imaged object and in context of this work - ROI selected for evaluation. Further work should focus on evaluations in complex geometries.

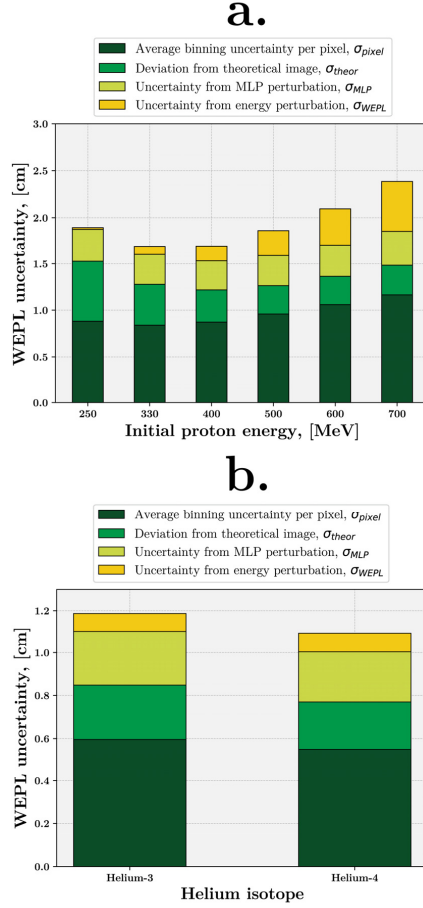


Figure 9.10. Dependency of different WEPL uncertainty sources on initial proton energy (a) and used helium isotope (b) for radiographic images of high contrast phantom in 32 cm test object

Data given as stacked histogram for reconstructed high contrast phantom radiographic images (pixel size of 0.2 mm, PIB at test object mid-plane). All uncertainty given as 1σ value calculated based on methodology described previously for each individual source. Illustrative data of uncertainty contributions presented, overall uncertainty calculated via variance summation.

Uncertainties were analysed in “ring-like” ROI of ± 2 mm around the edge of high contrast object. In Subfigure (b) helium-3 ion energy of 364 MeV/u and helium-4 ion energy of 350 MeV/u was used.

9.4. Results of the modelling: Comparison of imaged object depth estimation and radiographical image quality improvement with different focus stacking approaches

Image reconstruction depth dependent quantities in ion radiography

While the Results presented in Section 9.3. focused on rather simple phantom geometries to evaluate main i-Rad image quality metrics, in realistic patient anatomies the imaged geometry is far more complex. Apart from significant variation of WEPL for different tissues, the imaged features are located at various depths within the anatomy. Due to the physical nature of MLP formalism and inherent 3D information on single particle trajectory, studies as [7] have shown that image quality, especially the achievable spatial resolution, depends on the interplay between the depth of the imaged feature and reconstruction plane position used for the MLP estimations and. Results of [7] have indicated that, while sub-optimal spatial resolution is achieved by FPB or RPB approaches, the maximum spatial resolution of a particular object can be achieved by PIB, setting the position of reconstruction plane near the actual depth of the imaged feature. Illustratively, an example for the dependency of spatial resolution in i-Rad image on reconstruction plane position is given in upper line of Figure 9.11. for 16 cm test object, while example in 32 cm test object is given in the upper line of Figure A.8.28 of **Appendix 8.13**. Example of i-Rad images given in Figure 9.11. and **Appendix 8.13**. clearly indicates the maximum spatial resolution for a particular object, when the reconstruction plane of PIB is coincident with the location of the object. Furthermore, if reconstruction plane of PIB is positioned further away from the depth of a particular object, it results in blurring of the object boundary due to additional lateral displacement by MCS, with more prominent change observed in larger anatomies.

While alternative binning approaches as APB in the reconstruction process could improve the overall image quality for complex anatomies with imaged objects located at various depths, the spatial resolution for a particular object is nevertheless inferior to PIB at reconstruction plane coincident with object depth [7]. As MLP formalism enables 3D trajectory calculation in case of single particle tracking i-Rad, a stack of i-Rad images could be calculated via PIB with different reconstruction planes. Stack of i-Rad images could then be postprocessed by recently developed FS, specifically ED-FS, approach [17,26], that could enable the best overall image spatial resolution and more uniquely – enable possible estimation of imaged feature depth. While quantitative description of spatial resolution itself via MTF could be used as metric for focal depth estimation in FS, this approach would be relatively computationally expensive. Thus, as proposed in [17,26], spatial resolution depth dependency for FS can be evaluated by convolution of i-Rad image with image processing kernel used for edge detection. In the resulting convolved image, maximum image signal amplitude at the border of a particular object would be achieved if spatial resolution is maximum and can be thus used as metric for FS as mathematically described by Equations 9.1. and 9.2. In following sub-sections, this

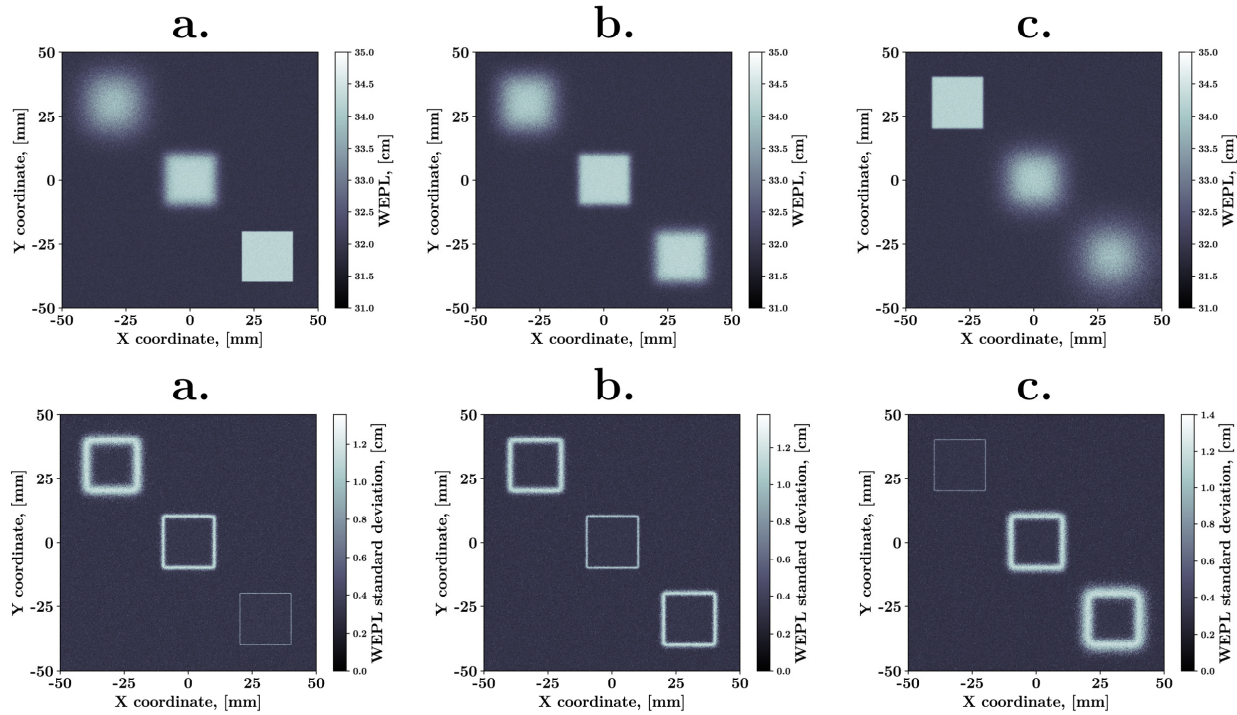


Figure 9.11. Influence of image reconstruction plane depth on reconstructed WEPL spatial distribution (*upper line*) and local WEPL variation (*lower line*) for “multi-depth” phantom in 16 cm test object for 250 MeV initial proton energy
Radiographic images reconstructed with pixel size of 0.2 mm, full ROI of 100×100 mm illustrated. *Upper line*: reconstructed average per pixel WEPL value, *lower line*: respective per pixel WEPL standard deviation
Data given for PIB method with image reconstruction plane at 20 mm (Subfigures (a)), 80 mm (Subfigures (b)) and 140 mm (Subfigures (c))) depth.

FS approach is denoted as edge detection based FS (ED-FS). Results presented in following sub-sections build on the work presented [17,26] by evaluating the impact of parameters used for de-noising and edge detection image processing kernels on performance of FS, while also quantitatively assessing the dependency of performance of FS on particle type and kinetic energy used for i-Rad.

When binning the WEPL values via PIB during image reconstruction process, per-pixel WEPL value standard deviation could also be estimated apart from mean WEPL value used for final image. Local, per-pixel WEPL value standard deviation is higher near the imaged object boundaries due to slight overlap of curved single particle trajectories that have or have not traversed a particular object. As particles with these slightly different trajectories will have traversed slightly different WEPL, binning in the same pixel will increase the respective local standard deviation. For PIB with varying position of reconstruction plane, the additional lateral displacement due to MCS must be considered, if reconstruction plane is not coincident with depth of the particular object, as discussed previously. Focusing on the region near an object boundary, if reconstruction plane of PIB is not coincident with the object depth, curved single particle trajectories will have increased lateral displacement, thus overlap between more single particle trajectories that have or have not traversed a particular object (carrying different WEPL information) can be expected to increase. Thus, for reconstruction plane of PIB being further away from imaged object depth the local, per-pixel WEPL value standard deviation is expected to increase, while maintaining minimum value if the reconstruction plane is coincident with object depth. Illustratively, an example for the dependency of local, per-pixel WEPL standard deviation on reconstruction plane position is given in lower line of Figure 9.11. for 16 cm test object, while example in 32 cm test object is given in the lower line of Figure A.8.28 of **Appendix 8.13**. Results illustrated in these Figures clearly indicate lower per-pixel WEPL standard deviation near a particular object boundary if PIB reconstruction plane is coincident with the depth of the respective object, while also exhibiting smaller region around the object boundary with increased WEPL standard deviation. Similarly as for spatial resolution, this dependency is even more pronounced for larger imaged objects.

Discussed physical rationale of local, per-pixel WEPL standard deviation dependency on PIB reconstruction plane depth prompted the Author to develop an alternative approach to ED-FS – local WEPL variation based focus stacking (LV-FS). Contrary to using maximum image signal amplitude after convolution with edge detection image processing kernel in ED-FS, LV-FS directly uses the information on local, per-pixel WEPL standard deviation with minimum value serving as focal depth metric (see Equations 9.3 and 9.4.). Results in further sub-sections indicate the performance of LV-FS approach and quantitatively compare it to the already proposed ED-FS approach. Intuitively, LV-FS could possibly overcome one of the shortcomings identified for ED-FS approach in [17]. Use of edge detection kernels in homogenous WEPL regions results in large variation of estimated focal depth. This in turn results in increased image noise for

homogenous WEPL regions, when comparing ED-FS reconstructed i-Rad image to a conventionally PIB reconstructed image. As LV-FS approach assigns per-pixel WEPL values from a plane within PIB reconstructed image stack that has the lowest local per-pixel WEPL standard deviation, accurate WEPL information can be expected even in homogenous regions. Furthermore, following this physical rationale, LV-FS approach could possibly enable highest CNR from all i-Rad reconstruction approaches.

Comparison of focus stacking approaches in terms of imaged object depth estimation accuracy and planar radiographical image quality improvement

For the proposed ED-FS and LV-FS approaches, several implementation variations were studied and compared. For ED-FS, prior de-noising with either Gaussian kernel or median filter was evaluated with different kernel sizes and combined with different edge detection kernels (Laplace, Sobel, Scharr and Prewitt) – 40 different implementation variations altogether. On the other hand, for LV-FS only prior de-noising with either Gaussian kernel or median filter was evaluated, yielding 10 different variations. Summary of ED-FS and LV-FS approach implementation variation is given within Table A.8.10. of **Appendix 8.14.**

As outlined before, the possible advantages of FS are improved image quality over other reconstruction approaches and the possibility to estimate the depth of an imaged object. Thus, both of these aspects were compared quantitatively between the different ED-FS and LV-FS approach implementation variations by evaluation of WEPL value deviation with respect to theoretical reference images and precision of estimated object depth. Full comparison between all ED-FS and LV-FS approach implementation variations is given in Figures A.8.29 and A.8.30 of **Appendix 8.14.**, respectively, with analysis presented in the following paragraphs. Illustratively, Figure 9.12. presents reconstructed i-Rad images via a few different implementations of ED-FS and LV-FS approaches, while Figure 9.13. gives the corresponding spatial distributions of estimated object depths. This sub-section mainly gives the focus on comparison between the different FS approaches, with additional, in-depth quantitative evaluation of both ED-FS and LV-FS given in further sub-sections.

As de-noising kernels are applied prior to final image reconstruction in both ED-FS and LV-FS approaches, the focus is first given on the impact of de-noising filter used and the size of the respective kernel. Evaluating the WEPL value deviation in reconstructed images, results presented in Figure A.8.29 of **Appendix 8.14.** clearly indicate that use of a Gaussian kernel for de-noising has favourable performance over median filter. For example, with Laplace kernel used for edge detection in a scenario of 16 cm thick test object and 250 MeV proton energy, mean WEPL value deviations in a ROI near object boundary varied between 0.9 to 2.0 mm, if Gaussian kernel was used for de-noising, while in the case of median filter – 1.8 to 2.3 mm. The difference between the two de-noising approaches was slightly more pronounced in case of 32 cm thick test object with deviations between 1.9 to 6.0 mm and 4.7 to 5.7 mm, respectively. Magnitude of WEPL value deviation uncertainty was comparable between the two de-noising

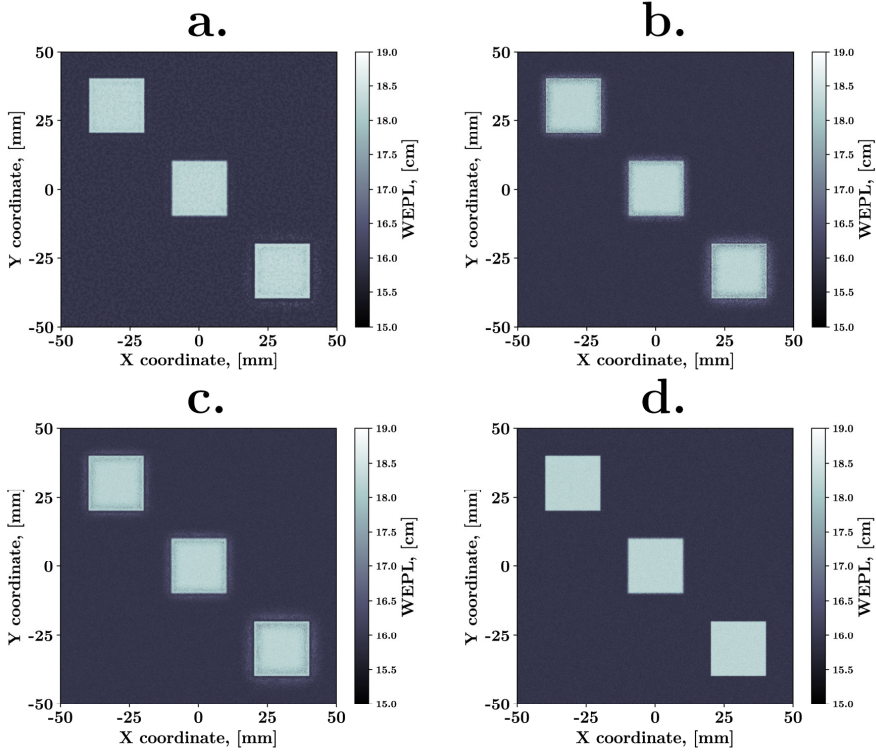


Figure 9.12. Radiographic images for “multi-depth” phantom in 16 cm test object for 250 MeV initial proton energy reconstructed with different focus stacking methods. Radiographic images reconstructed with pixel size of 0.2 mm, full ROI of 100×100 mm illustrated, no data smoothing applied along depth axis. Data given for following focus stacking methods:
 Subfigure (a): de-noising with Gaussian filter ($\sigma=2$ pixels) and Laplace filter for depth estimation
 Subfigure (b): de-noising with median filter (5 pixels) and Laplace filter for depth estimation
 Subfigure (c): de-noising with Gaussian filter ($\sigma=2$ pixels) and Sobel operator for depth estimation
 Subfigure (d): de-noising with Gaussian filter ($\sigma=5$ pixels) and local standard deviation for depth estimation

approaches for ED-FS with slightly lower uncertainty for Gaussian kernel. Evaluating the impact of kernel size for de-noising, for both Gaussian kernel and median filter it was observed that mean WEPL deviation in i-Rad images reconstructed with ED-FS decreased with increasing kernel size. In the case of LV-FS approach, the impact of de-noising kernel type and kernel size on the mean WEPL deviations was less pronounced and overall better performance was observed. For a scenario with 250 MeV protons in 16 cm test object mean WEPL deviations varied between 0.88 to 0.93 mm with Gaussian

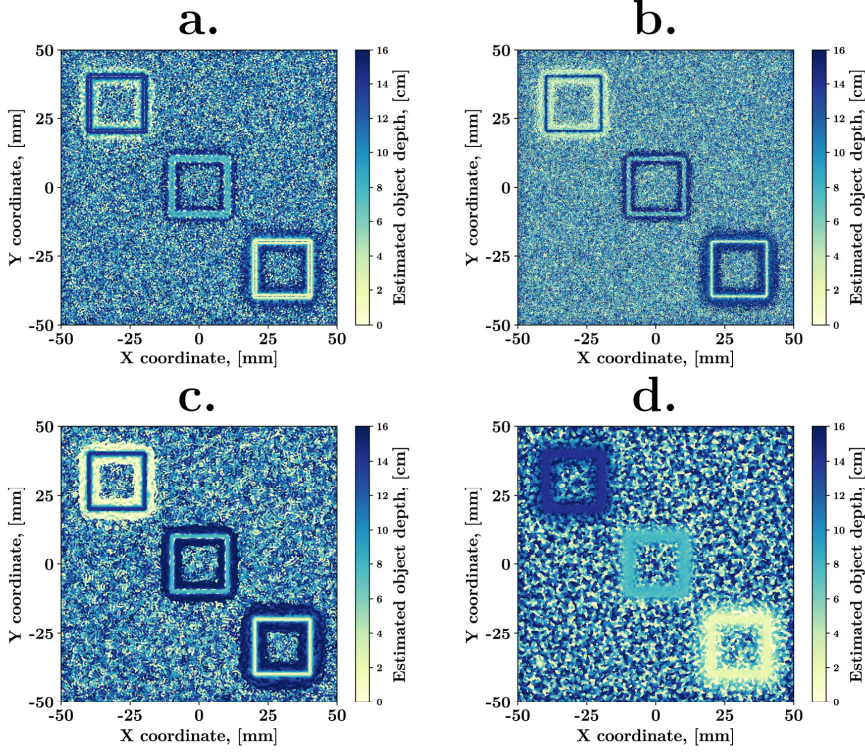


Figure 9.13. Spatial distribution of estimated object depth for “multi-depth” phantom in 16 cm test object for 250 MeV initial proton energy reconstructed with different focus stacking methods

Pixel size of 0.2 mm, full ROI of 100×100 mm illustrated, no data smoothing applied along depth axis.

Data given for following focus stacking methods:

Subfigure (a): de-noising with Gaussian filter ($\sigma=2$ pixels) and Laplace filter for depth estimation

Subfigure (b): de-noising with median filter (5 pixels) and Laplace filter for depth estimation

Subfigure (c): de-noising with Gaussian filter ($\sigma=2$ pixels) and Sobel operator for depth estimation

Subfigure (d): de-noising with Gaussian filter ($\sigma=5$ pixels) and local standard deviation for depth estimation

kernel, while with median filter – 0.87 to 0.89 mm. In case of 32 cm test object, WEPL deviations varied between 1.4 to 1.5 mm for both de-noising approaches.

Comparing mean WEPL deviations between different edge detection kernels for ED-FS approach, results presented in Figure A.8.29 of **Appendix 8.14**. indicate slightly improved or comparable performance for kernels based on first order derivatives (Sobel, Scharr and Prewitt) in comparison to kernels using second order derivatives (Laplace). For a scenario with 250 MeV protons in 32 cm test object and using a Gaussian kernel with σ of 1 pixel, mean WEPL deviation of 6.0 mm was observed using Laplace kernel,

while with Sobel (and almost identical results for Scharr and Prewitt) kernel – 4.4 mm. Upon increasing the size of the Gaussian kernel to of 5 pixels, mean WEPL deviations for the two kernels were 1.9 and 3.1 mm, respectively. Thus, use of Laplace kernel for edge detection could possibly decrease mean WEPL deviations of reconstructed images compared to Sobel kernels, if sufficiently large size of de-noising kernel is used – aspect, which needs to be evaluated also from perspective of estimated object depth precision. It should be noted that in current work no significant differences were observed between Sobel, Scharr and Prewitt kernels, which could be partially attributable to rather simple geometries studied. As the three kernels have slightly different response in terms of rotation symmetry, varying performance could be expected and should be studied in more complex, patient-like anatomies. Thus, for following result analysis only Sobel operator is considered as first order derivative edge detection kernel.

Figure 9.12. provides additional qualitative insights on previously discussed quantitative comparison of the different ED-FS and LV-FS implementation variations. In the illustrated 16 cm test object thickness case, clearly increased image noise in homogenous WEPL regions can be observed in ED-FS approaches (sub-figures (a), (b) and (c)) compared to LV-FS approach (sub-figure (d)). Additionally, while increased spatial resolution can be observed at object boundary, ED-FS can introduce additional artefacts in homogenous regions near the boundary compared to PIB reconstructed image for the specific object. As indicated in Figure A.8.31. of **Appendix 8.15.**, these effects become even more pronounced in larger anatomies (test object thickness of 32 cm). Nevertheless, LV-FS approach (sub-figures (d)) maintains excellent image quality in test object thickness, indicating only spatial resolution limitations at the middle of imaged object (same as using PIB with reconstruction plane at object midplane) due to MLP approach. Quantitatively evaluating discussed aspects on image noise via CNR for aluminium cube in the middle, following values were observed for 16 and 32 cm test objects, respectively, in the example case with 250 MeV protons:

- **ED-FS with sub-figure (a) implementation:** 17.4 and 4.7;
- **ED-FS with sub-figure (b) implementation:** 10.5 and 4.6;
- **ED-FS with sub-figure (c) implementation:** 12.0 and 6.3;
- **LV-FS with sub-figure (d) implementation:** 23.4 and 9.2.

For comparison, for i-Rad image with reconstruction plane at the middle of the test object, calculated CNR was 25.1 and 9.3 for the different thicknesses, respectively. As already noted in [17], this clearly indicated that ED-FS does increase image noise in homogenous regions compared to PIB reconstruction. Nevertheless, if FS is performed using LV-FS approach, CNR of an object is maintained at the same level that is acquired by PIB with reconstruction plane set at depth of respective object.

Apart from reconstructed image quality improvement with FS in i-Rad image reconstruction, it needs to be balanced with precision of estimated object depth precision for 3D feature localization. Evaluating the results presented in Figure A.8.30 of **Appendix 8.14.** in terms of de-noising filter choice for ED-FS, significant differences

can be observed between Gaussian kernel and median filter. For example, with Laplace kernel used for edge detection in a scenario of 16 cm thick test object and 250 MeV proton energy, for a cube centred at 80 mm mean estimated depth deviation varied between -3.7 to +3.2 mm, if Gaussian kernel was used for de-noising, while in the case of median filter -4.9 to +4.2 mm. Apart from estimated depth deviation, the uncertainty of estimated depth was also evaluated. For the previously described example scenario, the standard deviation of estimated depth varied between 7.1 to 28.8 mm with Gaussian kernel, while with median filter - 23.3 to 35.1 mm. In case of LV-FS, with the use of Gaussian kernel in the described example scenario, estimated depth deviation varied between -3.6 to -3.1 mm with standard deviation of 1.8 to 6.1 mm. Using median filter, deviations varied between -4.3 to -3.1 mm with standard deviation of 4.7 to 13.3 mm. Overall, while no significant differences in terms of estimated depth deviations from actual positions could be observed between Gaussian kernel and median filter for de-noising, ED-FS and LV-FS with Gaussian kernel indicated significant reduction for estimated depth uncertainty. It should also be noted that the impact of kernel size on object depth estimation capabilities with FS is different compared to image quality improvement. Depending on the test object thickness and edge detection kernel used for ED-FS, Gaussian kernel with σ between 1.5 to 2.5 pixels and median filter with size of 5 to 7 pixels yielded lowest uncertainty of estimated object depth. In case of LV-FS, lowest uncertainty of estimated object depth was observed with largest kernel sizes - σ of 5 pixels for Gaussian kernel and median filter with size of 7 pixels.

Comparing object depth estimation precision between different edge detection kernels for ED-FS approach, results presented in Figure A.8.30 of **Appendix 8.14**, indicate significantly improved performance for kernels based on first order derivatives (Sobel) in comparison to kernels using second order derivatives (Laplace). For a scenario with 250 MeV protons in 16 cm test object and using a Gaussian kernel with σ of 1 pixel, estimated object depth deviation was +3.2 mm with uncertainty of 28.9 mm using Laplace kernel, while with Sobel kernel -3.2 mm with uncertainty of 5.9 mm. Upon increasing the size of the Gaussian kernel to σ of 2.5 pixels, estimated object depth deviations for the two kernels were -3.7 and -3.0 mm, respectively, with uncertainties of 7.1 and 3.0 mm. While both edge detection kernels have comparable performance in terms of mean estimated object depth, ED-FS with Sobel kernel indicated significant reduction of uncertainty for the estimated depth.

As illustrated in Figure 9.13., it should also be noted that the different ED-FS and LV-FS approaches for imaged object depth estimation differ significantly in terms of ROI near object boundary that can be used to extract depth information. These differences were taken into account during the analysis and apparent increase of ROI with useful quantitative information was observed for ED-FS with Sobel kernel and LV-FS.

Considering both image quality improvement and object depth estimation accuracy as discussed previously, best performance for both parameters could be observed with following FS implementation approaches:

- **for ED-FS:** using a Gaussian kernel with σ between 1.5 to 2.5 pixels (2 pixels used in sub-sequent sub-sections) for de-noising and Sobel kernel for edge detection;
- **for LV-FS:** using a Gaussian kernel with σ of 5 pixels prior to using local standard deviation information.

These two approaches were further quantitatively evaluated in terms of ion type and ion kinetic energy dependency as presented in next sub-sections. Nevertheless, alternative settings (de-noising kernel type and size, edge detection kernel type) for both ED-FS and LV-FS could be reconsidered in future research. As already discussed in [26], use of median filter for de-noising compared to Gaussian kernel better maintains complex image information. Thus, optimization of ED-FS and LV-FS approaches should be revisited with simulation studies in more complex, patient-like anatomies.

Edge detection and local WEPL variation based focus stacking: planar radiographical image quality improvement and dependency on ion type and ion kinetic energy

Having discussed general aspects and parameter optimization for both ED-FS and LV-FS, this sub-section and the following presents more in-depth analysis on how choice of ion type and ion kinetic energy impacts the improvement of image quality and precision of object depth estimation, respectively, via FS reconstruction.

Focusing first on quantitative image quality improvement, Figures 9.14. and 9.15. present the influence of proton energy on absolute WEPL value deviation in i-Rad images reconstructed with ED-FS and LV-FS, respectively. Data in Figures 9.14. and 9.15. correspond to 16 cm test object thickness, with additional data in 32 cm test object given in Figures A.8.32. and A.8.33 of **Appendix 8.16.** for ED-FS and LV-FS, respectively. Data for helium ions in both test object thickness are given in Figures A.8.34. and A.8.35. of **Appendix 8.16.** for ED-FS and LV-FS, respectively.

Illustratively, influence of proton energy used for imaging on absolute WEPL value deviation in i-Rad images reconstructed with ED-FS and LV-FS is also given in sub-figures (a) of Figures 9.16. and 9.17., respectively, for 16 cm test object. Corresponding data for 32 cm test object thickness is given in sub-figures (a) of Figures A.8.38. and A.8.39. within **Appendix 8.18.**, while data for helium ions are presented in Figure A.8.40. of **Appendix 8.19.**

Analysing the spatial distributions of absolute WEPL value deviation, it can be observed that lower deviations can be observed near object boundaries with increasing proton energy for ED-FS. Increase of proton energy also reduces deviations in the homogenous WEPL regions near object boundary for ED-FS, especially in case of larger anatomies (32 cm test object thickness). This is attributable to higher spatial resolution due to reduced MCS at higher proton energies, as already discussed in Section 9.3. Also, increased noise can be observed with increasing proton energy in homogenous regions.

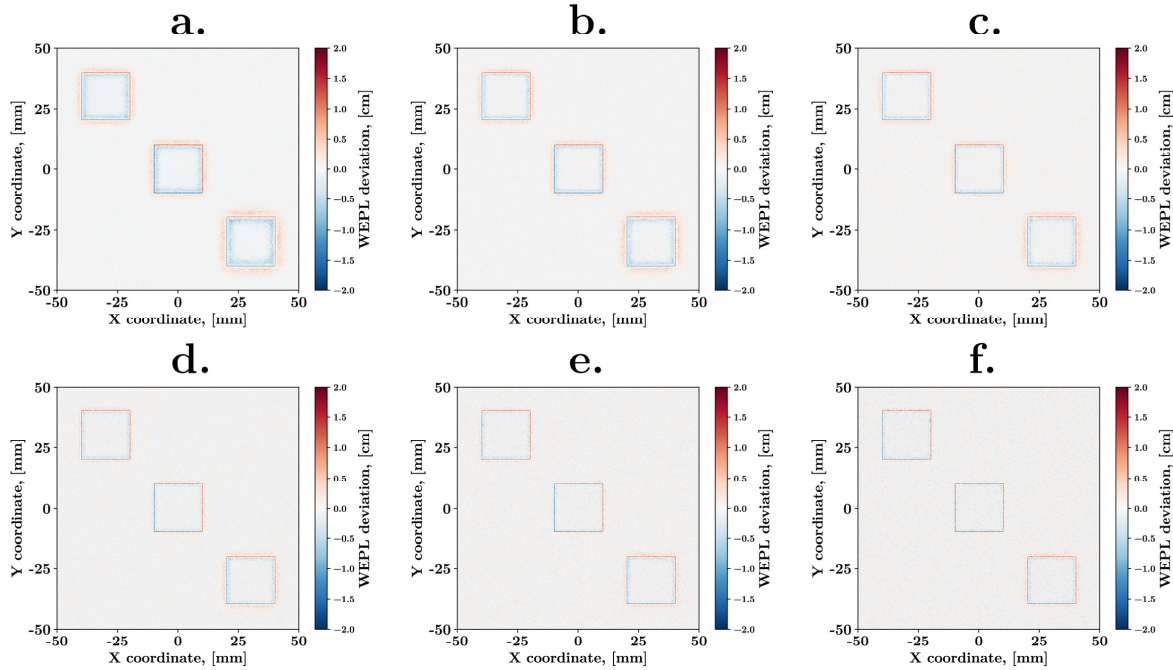


Figure 9.14. Absolute WEPL value deviation with respect to theoretically calculated reference in focus stacked radiographical images of “multi-depth” phantom in 16 cm test object for different initial proton energies, using Sobel operator for depth estimation. Reference images calculated and radiographical images reconstructed with pixel size of 0.2 mm, full ROI of 100x100 mm illustrated. Material properties as defined in Table A.8.2. used for reference image calculation, with energy independent average RSP for aluminium of 2.14. For de-noising, Gaussian filter ($\sigma=2$ pixels) used, no data smoothing applied along depth axis. Data given for protons with initial energies of 250 (Subfigure (a)), 330 (Subfigure (b)), 400 (Subfigure (c)), 500 (Subfigure (d)), 600 (Subfigure (e)) and 700 (Subfigure (f)) MeV.

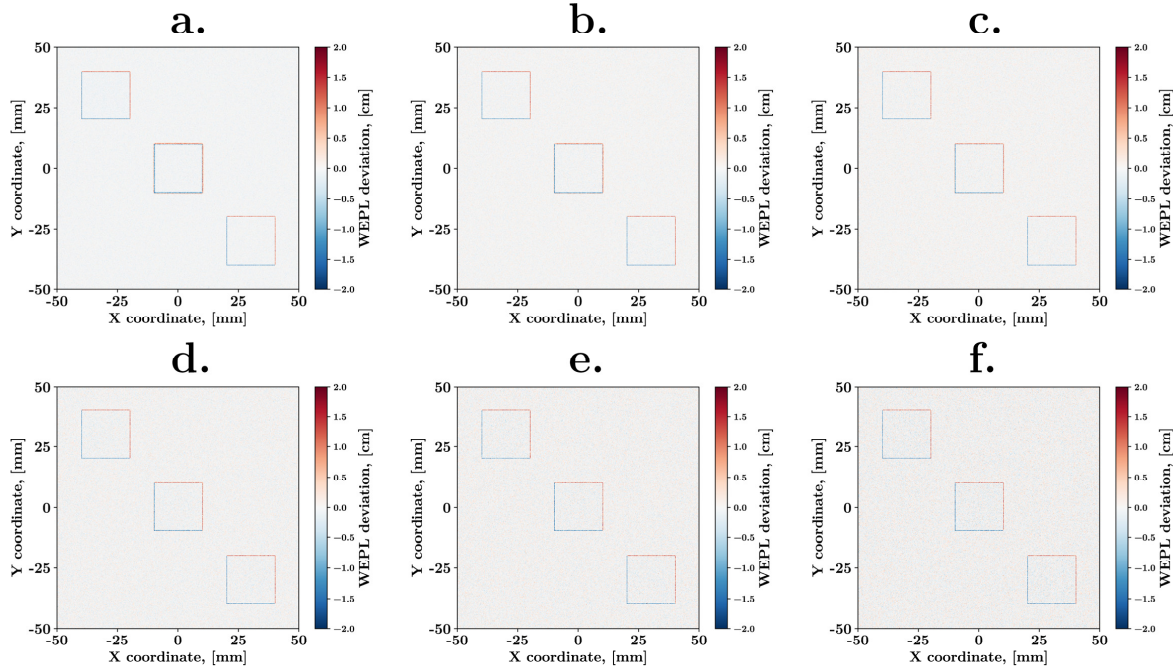


Figure 9.15. Absolute WEPL value deviation with respect to theoretically calculated reference in focus stacked radiographical images of “multi-depth” phantom in 16 cm test object for different initial proton energies, using local standard deviation for depth estimation. Reference images calculated and radiographical images reconstructed with pixel size of 0.2 mm, full ROI of 100x100 mm illustrated. Material properties as defined in Table A.8.2. used for reference image calculation, with energy independent average RSP for aluminium of 2.14. For de-noising, Gaussian filter ($\sigma=5$ pixels) used, no data smoothing applied along depth axis. Data given for protons with initial energies of 250 (Subfigure (a)), 330 (Subfigure (b)), 400 (Subfigure (c)), 500 (Subfigure (d)), 600 (Subfigure (e)) and 700 (Subfigure (f)) MeV.

In case of LV-FS, significantly lower WEPL deviations can be observed compared to ED-FS. Minor deviations are observed only near the object boundary, though no artefacts are introduced in homogenous regions as with ED-FS. In case of 32 cm thick test object, Figure A.8.33 of **Appendix 8.16.** illustrates that higher WEPL deviations can be observed for the aluminium cube located at the middle of test object due to limitations MLP reconstruction and spatial resolution as discussed previously in Section 9.3. Due to improved spatial resolution of He-Rad with respect to p-Rad as discussed in Section 9.3., Figures A.8.34. and A.8.35. illustrate slightly decreased WEPL deviations using ED-FS and LV-FS, respectively, with He-Rad approaches.

To quantitatively assess the impact of ion type and ion kinetic energy on WEPL value precision reconstructed with ED-FS and LV-FS, WEPL value deviations were first evaluated in ring-like ROI near the boundaries of imaged cubes. Information in such ROI would indicate the influence of ion type and kinetic energy on spatial resolution, as well as additional artefacts introduced by ED-FS approach. In 16 cm test object, WEPL value deviations (with 1σ indicated) were 1.63 ± 2.01 , 1.38 ± 1.78 and 1.67 ± 1.80 mm for 250, 400 and 700 MeV protons, if ED-FS is used. For 32 cm test object case, WEPL value deviations were 3.80 ± 2.99 , 2.86 ± 2.52 and 2.71 ± 2.46 mm, respectively. WEPL value deviations were slightly reduced for LV-FS: 0.88 ± 1.60 , 1.06 ± 1.56 and 1.65 ± 1.75 mm, respectively, in 16 cm test object case and 1.47 ± 2.20 , 1.52 ± 1.88 and 2.30 ± 2.13 mm – in 32 cm test object. Comparing He3-Rad and He4-Rad, no significant differences were observed. With ED-FS in 16 cm test object, WEPL value deviations were 1.11 ± 1.81 and 1.01 ± 1.79 mm for He3-Rad and He4-Rad, respectively, while in 32 cm test object – 2.36 ± 2.53 and 2.21 ± 2.45 mm. As in the case with p-Rad, deviations were reduced with LV-FS – 0.07 ± 1.52 and 0.06 ± 1.53 mm for 16 cm test object and 1.08 ± 1.76 and 1.04 ± 1.72 mm for 32 cm test object.

As discussed previously, choice between ED-FS and LV-FS can also impact image noise in homogenous WEPL regions. Thus, to additionally evaluate image noise performance and possibly introduced artefacts by ED-FS approach, mean WEPL value deviation was evaluated for whole image, considering only 32 cm test object thickness. For 250, 400 and 700 MeV protons, if ED-FS is used, observed WEPL value deviations were 1.79 ± 2.63 , 1.64 ± 2.24 and 2.14 ± 2.15 mm. Lower deviations were observed with LV-FS: 1.01 ± 1.32 , 1.31 ± 1.29 and 2.15 ± 1.79 mm, respectively. For He3-Rad and He4-Rad, deviations using ED-FS were 1.23 ± 4.38 and 1.20 ± 5.01 mm, respectively, while using LV-FS: 0.85 ± 1.54 and 0.83 ± 2.18 mm.

Overall, significantly better performance in terms of decreased WEPL value deviation was observed for LV-FS compared to ED-FS, mainly attributable to artefacts introduced by the latter in homogenous WEPL regions. With interplay between increased spatial noise and increased image noise for increasing energy used for p-Rad, different energy dependency was observed between the two FS approaches. In case of ED-FS, improved performance could be observed in energy range between 330 to 500 MeV. On the other hand, 250 to 330 MeV indicated favourable performance with LV-FS approach.

Due to physical characteristics described previously in Section 9.3., both He-Rad approaches were comparable with slightly improved performance over p-Rad.

Edge detection and local WEPL variation based focus stacking: image object depth estimation accuracy and dependency on ion type, ion kinetic energy and contrast level

While previous sub-section focused on image quality improvement via FS, this sub-section focuses on the other unique characteristics – possibility to estimate imaged object depth and influence of ion type and kinetic energy on the precision of this approach.

Focusing first on reconstructed estimated object depth distributions, Figures A.8.36. and A.8.37. of **Appendix 8.17.** visually illustrate the dependency of these distributions on proton kinetic energy used. Figure A.8.36. of **Appendix 8.17.** indicates that ROI near an object boundary spatially decreases with increasing proton energy, if ED-FS is considered. This is attributable to increased spatial resolution, thus after convolution with edge detection kernel, a smaller region with high image signal amplitude is used for analysis via Equations 9.1. and 9.2., increasing the uncertainty of estimated object depth. This rationale also applies for heavier ions and smaller imaged object thickness. Similarly, increased spatial resolution also reduces the region with high standard deviation for LV-FS approach, as indicated in Figure A.8.37. of **Appendix 8.17.**, nevertheless ROI with information relevant for Equations 9.3. and 9.4. is larger, thus possibly decreasing uncertainty associated with depth estimation.

Initially considering object depth estimation from per-pixel information as proposed in [17], sub-figures (b), (c) and (d) within Figures 9.16 and 9.17 present estimated depths of imaged aluminium cubes and associated uncertainty as function of proton energy used, as reconstructed with ED-FS and LV-FS approach, respectively. Figures 9.16. and 9.17. provide data for 16 cm test object scenario, while data for 32 cm test object are provided in respective sub-figures of Figures A.8.38. and A.8.39. of **Appendix 8.18.** Numerical data for both He-Rad approaches are given in Tables A.8.11. and A.8.12. of **Appendix 8.19.**

As discussed previously, when comparing ED-FS and LV-FS approach – while the deviation of estimated object with respect to actual position is not significantly impacted by the choice of FS method, associated uncertainty is significantly reduced for LV-FS. Considering studied energy range for p-Rad in 16 cm thick test object case, for example, deviations of estimated depths of aluminium cubes varied between +0.8 to 3.7, -3.3 to -2.7 and 0.8 to 1.2 mm for central cube depths of 20, 80 and 140 mm, respectively, using ED-FS approach. The associated 1σ uncertainties ranged from 5.3 to 12.2, 3.5 to 7.0 and 1.4 to 4.9 mm, respectively. Comparatively, using LV-FS approach deviations of estimated depths ranged between 1.5 to 2.5, -3.2 to -2.5 and 0.5 to 1.3 mm, respectively, with associated uncertainties between 1.8 to 7.3, 1.8 to 3.4 mm and 0.7 to 2.3. Thus, estimated depth uncertainty decrease of about 2 times was observed using LV-FS approach instead of ED-FS.

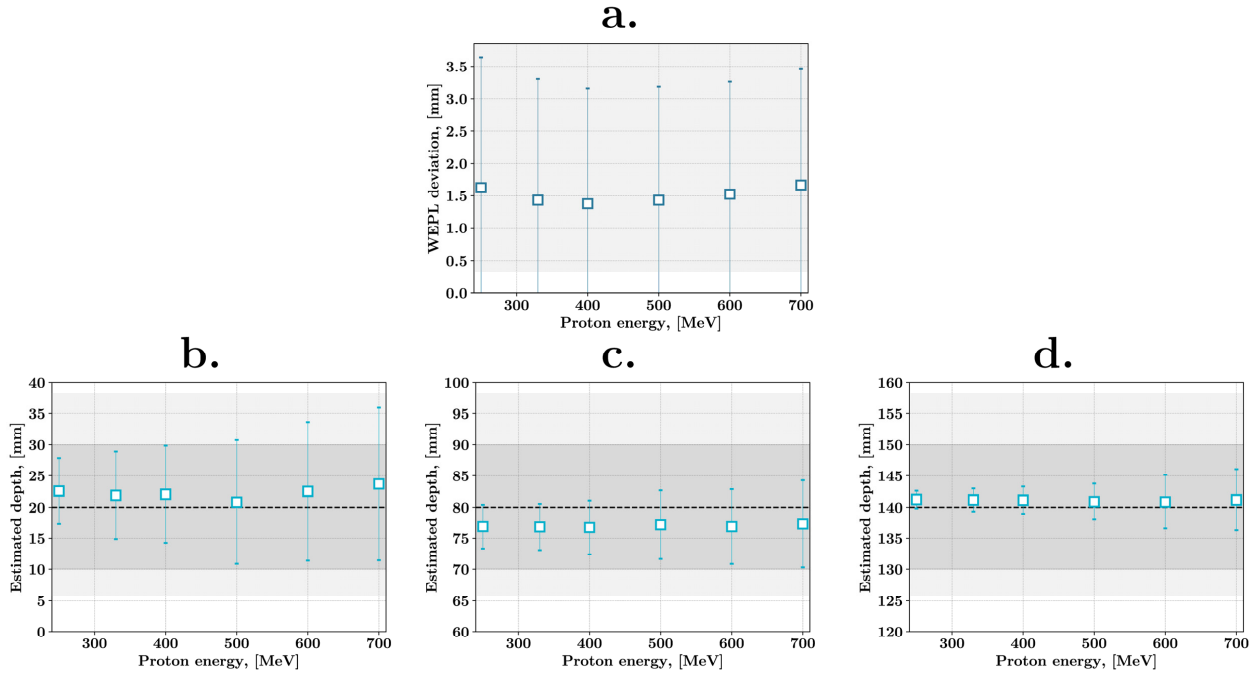


Figure 9.16. Influence of initial proton energy on WEPL value accuracy (*upper line*) and estimated imaged object depth (*lower line*) in focus stacked radiographical images of “multi-depth” phantom in 16 cm test object, using Sobel operator for depth estimation

Upper line: WEPL deviations calculated following formalism given for Figures 9.14. and 9.15, with absolute values used for calculations. Data points correspond to average absolute WEPL deviation value in ring-like ROI around aluminium cubes with 1σ uncertainty given.

Lower line: Data points correspond to average estimated object depth value in ring-like ROI around each aluminium cube with 1σ uncertainty given. Shaded region corresponds to physical extend of aluminium cube, with dashed line indicating middle of each cube. Data given for aluminium cubes located at 20 mm (Subfigure (b)), 80 mm (Subfigure (c)) and 140 mm (Subfigure (d)) depths.

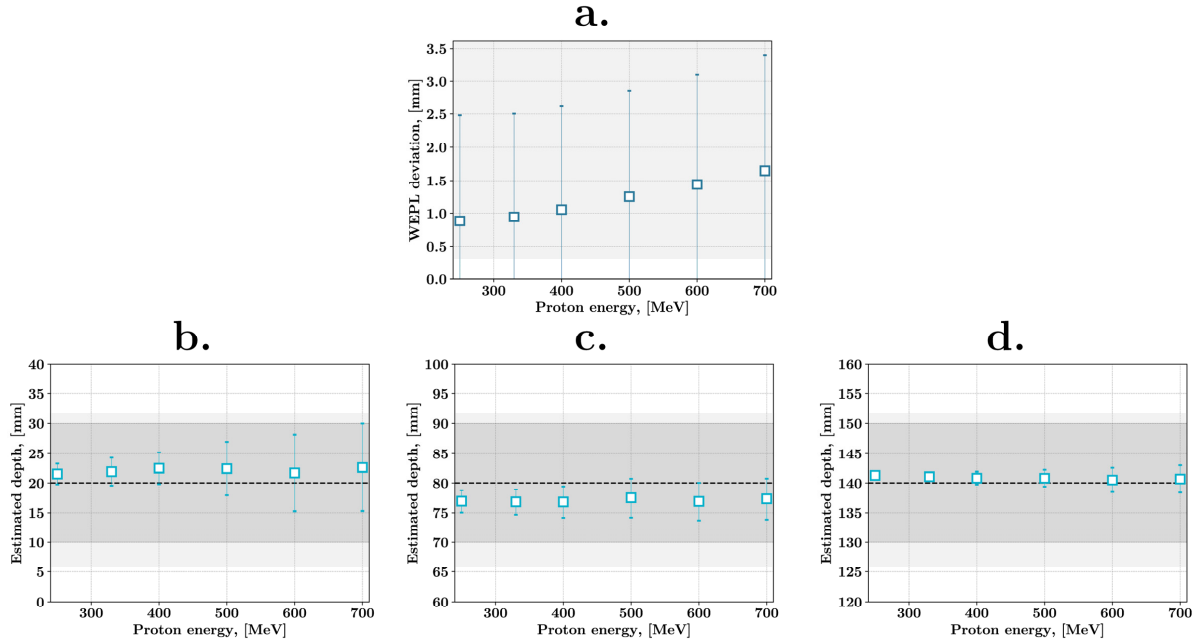


Figure 9.17. Influence of initial proton energy on WEPL value accuracy (*upper line*) and estimated imaged object depth (*lower line*) in focus stacked radiographical images of “multi-depth” phantom in 16 cm test object, using local standard deviation for depth estimation

Upper line: WEPL deviations calculated following formalism given for Figures 9.14. and 9.15, with absolute values used for calculations. Data points correspond to average absolute WEPL deviation value in ring-like ROI around aluminium cubes with 1σ uncertainty given.

Lower line: Data points correspond to average estimated object depth value in ring-like ROI around each aluminium cube with 1σ uncertainty given. Shaded region corresponds to physical extend of aluminium cube, with dashed line indicating middle of each cube. Data given for aluminium cubes located at 20 mm (Subfigure (b)), 80 mm (Subfigure (c)) and 140 mm (Subfigure (d)) depths.

From presented results, it can also be clearly observed that uncertainty of estimated object depth also significantly depends on actual position of the object – decreasing for deeper objects. This is attributable to the underlying physical principles used to estimate a focal depth from a stack of PIB reconstructed radiographs. With principles of both ED-FS and LV-FS approaches based on observable changes of scattering for varying reconstruction plane depth, it becomes clear that precision of these methods depends on MCS amplitude change as function of depth. If the change of MCS amplitude between two adjacent PIB reconstruction plane depths is higher, a higher sensitivity and lower uncertainty can be achieved for estimated object depth via Equations 9.1. and 9.3. As presented in Chapter 2, MCS amplitude change per unit depth is lowest at shallow depths and gradually increases, thus explaining the improved performance of both ED-FS and LV-FS for deeper located imaged objects.

For evaluation of the impact of ion type and ion kinetic energy on estimated object depth accuracy and uncertainty, results with p-Rad were evaluated first. While no clear trends could be observed between proton energy used for imaging and estimated object depth deviation from actual position, clear proton energy influence on associated uncertainty could be observed. As indicated in sub-figures (b), (c) and (d) of Figures 9.16 and 9.17, estimated object depth uncertainty increases with increasing proton energy for both ED-FS and LV-FS approaches in 16 cm test object. Depending on aluminium cube position, estimated position uncertainty with ED-FS increased between 1.2 to 1.5 times for 400 MeV case compared to 250 MeV, while for 700 MeV – between 2.0 to 3.5 times. In case of LV-FS, uncertainty increased between 1.4 to 1.6 times for 400 MeV and 1.9 to 4.1 times for 700 MeV. This is attributable to the impact of MCS amplitude change per unit depth, as discussed for imaged geometry impact. As with increasing proton energy MCS amplitude and amplitude change per unit depth is decreased, the sensitivity of FS approach is decreased, increasing the uncertainty. Slight differences of this phenomenon could be observed in the case of larger anatomies – 32 cm test object thickness. For cube centre depths of 20 and 300 mm, increased uncertainty was observed with 400 and 700 MeV protons with respect to 250 MeV – 1.2 to 1.5 and 1.9 to 2.9 times, respectively. Nevertheless, using ED-FS, for cube centre depth at the middle of test object (160 mm depth), the uncertainty is decreased with higher energy – 1.7 times for 400 MeV with respect to 250 MeV, while for 700 MeV – 1.5 times. This is attributable to lower spatial resolution near the middle of imaged geometry due to limitations of MLP, which in turn reduces sensitivity of FS. Similar trends were observed for LV-FS approach with larger imaged object.

For the studied He-Rad modalities, no significant differences were observed between He3-Rad and He4-Rad. In case of 16 cm test object with ED-FS, estimated object depth deviations varied between -3.7 to 2.7 mm for He3-Rad, while for He4-Rad – from -3.8 to 2.2 mm. Respective uncertainties ranged from 4.0 to 9.9 mm with He3-Rad and 4.8 to 10.6 with He4-Rad. For 32 cm test object, deviations varied between

-6.3 to 4.7 mm with uncertainty between 2.3 and 11.9 mm for He3-Rad, while for He4-Rad -5.7 to 5.1 mm with uncertainty between 2.6 to 12.3 mm. Similarly, as with p-Rad, use of LV-FS with He-Rad resulted in similar estimated depth deviations, while reducing the associated uncertainty by about 1.5 to 3 times, depending on geometry. Following the previously discussed impact of MCS amplitude change per unit depth on estimated depth uncertainty, slightly reduced uncertainty was observed for He3-Rad compared to He4-Rad due to higher scattering. With this rationale in mind, it is also clear that for energies corresponding to same range in water, p-Rad would have lower estimated object depth uncertainty compared to p-Rad. For He3-Rad and He4-Rad energies studied, depth estimation performance of both ED-FS and LV-FS is comparable to that of 400 – 500 MeV p-Rad.

With previous results on depth estimation via ED-FS and LV-FS using the per-pixel object depth estimates in [17], alternative approach was developed for analysis of a particular imaged object to have a more reliable depth uncertainty. Instead of doing per-pixel estimates and analysing information within a ROI around a particular object afterwards, the Author proposed to define the analysis ROI already during the reconstruction process. Thus, in case of ED-FS, after convolution with de-noising and edge detection kernels (or just de-noising kernel in case of LV-FS), a ROI near the boundary of a particular object is defined. Mean and standard deviation of image signal amplitude is extracted and evaluated as function of PIB reconstruction plane depth. Mean image signal amplitude as function of depth is then used to calculate the maximum or minimum of the function for ED-FS and LV-FS respectively, corresponding to estimated depth of a particular object. A visual example of this analysis formalism is given in Figure 9.18.

Use of this formalism for depth estimation via both ED-FS and LV-FS also more clearly visualises the previously described dependencies between depth estimation accuracy and implementation parameters of ED-FS/LV-FS, ion type, ion kinetic energy and the size of imaged test object. One such visualisation is given in Figures A.8.41. and A.8.42. of **Appendix 8.20.**, indicating the impact of ED-FS and LV-FS implementation parameters. Upper line of Figure A.8.41. clearly indicates that an optimum de-noising kernel size needs to be applied to improve the uncertainty of estimated depth with ED-FS. While increasing de-noising kernel size decreases the uncertainty of image signal amplitude, it also reduces the local gradient, thus a compromise between the two effects needs to be considered. On the contrary, with LV-FS only the uncertainty of image signal amplitude is reduced without significant impact on the local gradient, thus suggesting the use of larger de-noising kernel.

Using the proposed analysis method and statistical bootstrapping with 10000 samples as described in **Appendix 8.1.**, estimated depth and associated 95% uncertainty interval for each aluminium cube was calculated. Results with ED-FS approach for different test object thicknesses, ion types and kinetic energies are summarized in Table 9.2., while Table 9.3. summarizes the results with LV-FS approach.

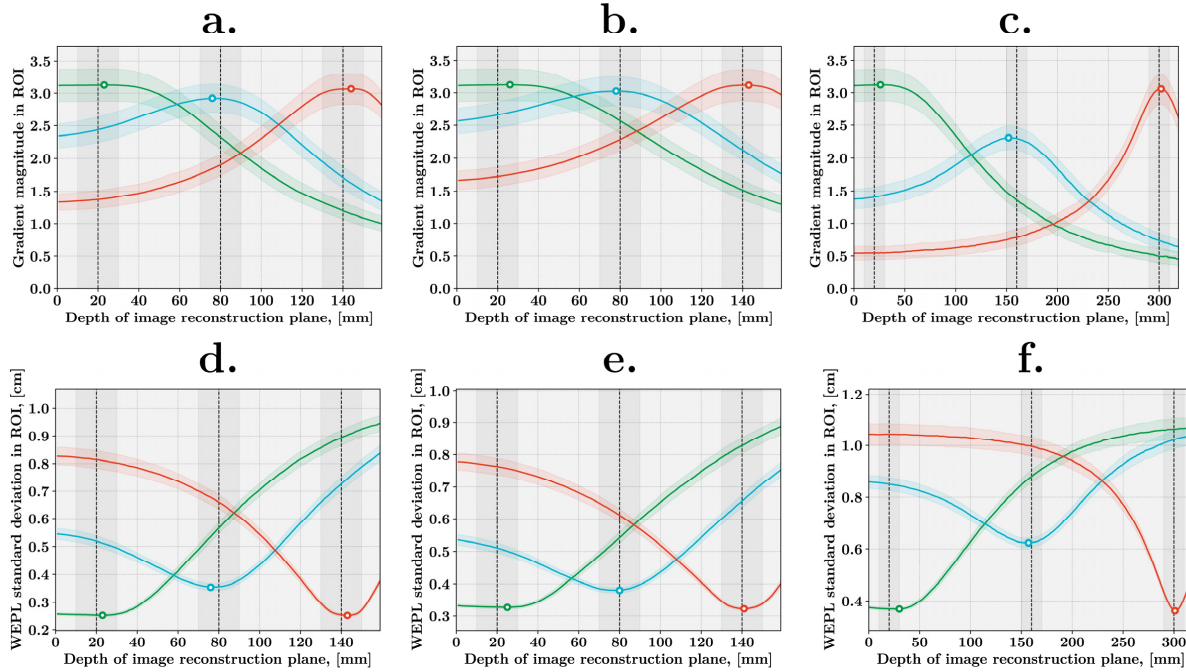


Figure 9.18. Focus stacking metric dependency on image reconstruction plane depth for different test object thicknesses and initial helium-3 ion energies, using Sobel operator (*upper line*) and local standard deviation (*lower line*)

Data binning with pixel size of 0.2 mm. De-noising with Gaussian filter, no data smoothing applied along depth axis - $\sigma = 2$ pixels for Sobel operator and $\sigma = 5$ pixels for local standard deviation. Focus stacking metric given as average (*line*) and 1σ (*shaded region*) in ring-like ROI around each aluminium cube – 20 mm (*green*), 80 or 160 mm (*blue*), 140 or 300 mm (*red*). Maximum or minimum of respective metric depth profile given as a point.

Data given for ^3He ions: 261 MeV/u in 16 cm test object (Subfigure (a),(d)), 364 MeV/u in 16 cm test object (Subfigure (b),(e)) and 364 MeV/u in 32 cm test object (Subfigure (c),(f))

Table 9.2.

Estimated imaged object depth using Sobel operator* for focus stacking with different
test object thicknesses, ion types and initial kinetic energies

Test object thickness	Ion type, kinetic energy	Estimated object depth**		
		z = 20 mm***	z = 80 mm	z = 140 mm
16 cm	Protons, 250 MeV	18.5 ⁺¹⁸ ₋₁₇	76.1 ⁺¹³ ₋₁₄	141.0 ⁺⁸ ₋₉
	Protons, 330 MeV	19.6 ⁺²⁰ ₋₁₈	75.6 ⁺¹⁴ ₋₁₆	140.8 ⁺¹⁰ ₋₁₁
	Protons, 400 MeV	20.3 ⁺²² ₋₁₈	75.6 ⁺¹⁶ ₋₁₈	140.5 ⁺¹² ₋₁₁
	Protons, 500 MeV	21.5 ⁺²³ ₋₂₀	76.0 ⁺¹⁹ ₋₂₀	140.7 ⁺¹³ ₋₁₅
	Protons, 600 MeV	23.0 ⁺²⁶ ₋₂₁	75.2 ⁺²² ₋₂₄	140.1 ⁺¹⁵ ₋₁₇
	Protons, 700 MeV	23.7 ⁺²⁷ ₋₂₂	75.2 ⁺²⁴ ₋₂₆	139.7 ⁺¹⁶ ₋₁₉
	³ He ions, 261 MeV/u	20.6 ⁺²² ₋₁₉	74.9 ⁺¹⁷ ₋₂₀	141.2 ⁺¹² ₋₁₄
	⁴ He ions, 220 MeV/u	22.3 ⁺²⁵ ₋₂₀	75.9 ⁺¹⁹ ₋₂₂	140.3 ⁺¹⁵ ₋₁₆
	³ He ions, 364 MeV/u	21.4 ⁺²³ ₋₁₉	74.5 ⁺¹⁹ ₋₂₁	141.0 ⁺¹³ ₋₁₅
32 cm		z = 20 mm	z = 160 mm	z = 300 mm
	Protons, 250 MeV	20.9 ⁺²³ ₋₁₉	154.5 ⁺²² ₋₂₄	302.1 ⁺⁶ ₋₆
	Protons, 330 MeV	22.9 ⁺²⁶ ₋₂₁	157.8 ⁺¹⁸ ₋₁₉	301.1 ⁺⁷ ₋₇
	Protons, 400 MeV	24.7 ⁺²⁷ ₋₂₃	158.2 ⁺¹⁹ ₋₁₉	301.1 ⁺⁹ ₋₉
	Protons, 500 MeV	25.5 ⁺²⁹ ₋₂₄	156.9 ⁺²⁰ ₋₂₁	300.9 ⁺¹⁰ ₋₁₁
	Protons, 600 MeV	26.7 ⁺³¹ ₋₂₅	154.9 ⁺²¹ ₋₂₄	300.9 ⁺¹² ₋₁₂
	Protons, 700 MeV	27.1 ⁺³³ ₋₂₅	154.8 ⁺²⁶ ₋₂₇	300.7 ⁺¹³ ₋₁₄
	³ He ions, 364 MeV/u	26.6 ⁺³⁰ ₋₂₅	152.7 ⁺²² ₋₂₆	301.1 ⁺¹¹ ₋₁₁
	⁴ He ions, 305 MeV/u	27.6 ⁺³¹ ₋₂₆	154.3 ⁺²³ ₋₂₄	301.0 ⁺¹¹ ₋₁₂

* De-noising with Gaussian filter ($\sigma = 1.5$ pixels for 16 cm test object and $\sigma = 2$ pixels for 32 cm test object)

** Calculated via bootstrapping with 10000 samples for respective metric depth profiles acquired in ring-like ROIs around imaged objects. Uncertainty given as 95% interval.

*** Midplane depth given, physical depth of each aluminium extends ± 10 mm.

Table 9.3.

Estimated imaged object depth local standard deviation* for focus stacking with
different test object thicknesses, ion types and initial kinetic energies

Test object thickness	Ion type, kinetic energy	Estimated object depth**		
		z = 20 mm***	z = 80 mm	z = 140 mm
16 cm	Protons, 250 MeV	20.8^{+6}_{-8}	76.5^{+8}_{-8}	141.1^{+3}_{-3}
	Protons, 330 MeV	20.0^{+9}_{-12}	76.6^{+7}_{-8}	141.1^{+3}_{-3}
	Protons, 400 MeV	20.0^{+11}_{-16}	76.8^{+8}_{-8}	141.0^{+4}_{-4}
	Protons, 500 MeV	20.8^{+12}_{-16}	77.0^{+9}_{-9}	141.0^{+5}_{-5}
	Protons, 600 MeV	19.1^{+16}_{-17}	76.8^{+10}_{-11}	140.3^{+7}_{-6}
	Protons, 700 MeV	19.5^{+18}_{-17}	77.0^{+10}_{-11}	141.4^{+8}_{-7}
	³ He ions, 261 MeV/u	18.5^{+11}_{-16}	77.2^{+9}_{-10}	142.2^{+5}_{-5}
	⁴ He ions, 220 MeV/u	20.4^{+13}_{-16}	77.3^{+9}_{-9}	140.6^{+5}_{-6}
	³ He ions, 364 MeV/u	18.5^{+13}_{-15}	76.6^{+8}_{-10}	142.7^{+5}_{-6}
32 cm		z = 20 mm	z = 160 mm	z = 300 mm
	Protons, 250 MeV	20.3^{+10}_{-14}	150.9^{+21}_{-25}	301.7^{+2}_{-3}
	Protons, 330 MeV	21.7^{+10}_{-16}	154.7^{+16}_{-18}	301.5^{+2}_{-3}
	Protons, 400 MeV	22.7^{+13}_{-18}	156.2^{+15}_{-15}	301.3^{+4}_{-3}
	Protons, 500 MeV	20.2^{+15}_{-18}	157.0^{+13}_{-15}	301.2^{+4}_{-4}
	Protons, 600 MeV	24.1^{+16}_{-21}	157.5^{+18}_{-18}	301.0^{+5}_{-5}
	Protons, 700 MeV	27.1^{+17}_{-24}	156.0^{+16}_{-19}	301.4^{+6}_{-6}
	³ He ions, 364 MeV/u	22.1^{+17}_{-18}	155.1^{+15}_{-16}	301.4^{+3}_{-2}
	⁴ He ions, 305 MeV/u	23.3^{+16}_{-19}	155.7^{+16}_{-17}	301.1^{+3}_{-3}

* De-noising with Gaussian filter ($\sigma = 5$ pixels for 16 cm and 32 cm test objects)

** Calculated via bootstrapping with 10000 samples for respective metric depth profiles acquired in ring-like ROIs around imaged objects. Uncertainty given as 95% interval.

*** Midplane depth given, physical depth of each aluminium extends ± 10 mm.

Results in Tables 9.2. and 9.3. re-iterate the previously identified impact of ion type and kinetic energy on depth estimation accuracy via FS approach due to differences of MCS amplitude change per unit depth. Overall, in the presented high contrast scenario, most favourable imaged object depth estimation performance was observed for 250 MeV protons in 16 cm test object, though He3-Rad and He4-Rad achieves comparable performance for deeper located objects. In case of 32 cm test object, best performance for deeper located objects can be achieved with He3-Rad and He4-Rad, with comparable performance and improved accuracy for shallow objects with 250 – 330 MeV p-Rad. Using LV-FS approach, deviations with respect to aluminium cube centre positions below 2 mm could be achieved for objects near the entrance and exit surface, with deviations below 5 mm for object at the middle of imaged geometry. Associated depth uncertainties below ± 10 mm could be achieved in 16 cm test object, while in case of 32 cm test object – below ± 20 mm. Compared to ED-FS approach, depth estimation uncertainty is reduced 1.5 to 3 times with LV-FS approach.

While all the reported results focused on high contrast scenario, having imaged objects with significantly higher WEPL compared to the surrounding, in clinical scenarios it would be of interest to identify depth position of WEPL value change of about 1 mm. An approach to use FS on WEPL change instead of a particular object was first proposed in [26] and is of great importance for possible clinical importance. While investigation to further optimize proposed ED-FS and LV-FS methods for approach proposed in [26] is out of scope of this work, the Author briefly evaluates the performance of proposed FS approaches in low contrast approaches. For initial assessment, low contrast phantom geometry as described and visualizes in Sections 9.1. and 9.3. was used, having the inserts centred at the middle of the test object. As an example with He3-Rad, mean image signal amplitude and associated standard deviation in ROI near the largest cylindrical inserts of varying contrast level as function of depth is given in Figures 9.19. and 9.20. for ED-FS and LV-FS, respectively. Quantitatively, estimated depth and associated 95% uncertainty interval for each contrast level is given in Tables A.8.13. and A.8.14. of **Appendix 8.21.** for ED-FS and LV-FS, respectively, considering 250 and 400 MeV protons and He3-Rad.

Evaluating the preliminary results on low contrast level impact on ED-FS and LV-FS, it becomes clear as one of the key limitations. In case of ED-FS, decreasing contrast level results in reduced gradient of image signal amplitude after convolution with de-noising and edge detection kernels, thus increasing the uncertainty of estimated object depth as clearly illustrated in Figure 9.19. For example, considering He3-Rad with 16 cm thick test object, the uncertainty interval of [-15 mm; +13 mm] at -2.5% contrast level increases to [-28 mm; +23 mm] and [-39 mm; +41 mm] at -1% and -0.5% contrast levels, respectively. Similar increase of uncertainty interval was observed for inserts with positive contrast level. It should be noted that, in case of p-Rad, precision of object depth estimation clearly decreases with increasing energy (see **Appendix 8.21.**). In comparison, He-Rad performed significantly better in low contrast scenarios, having lower

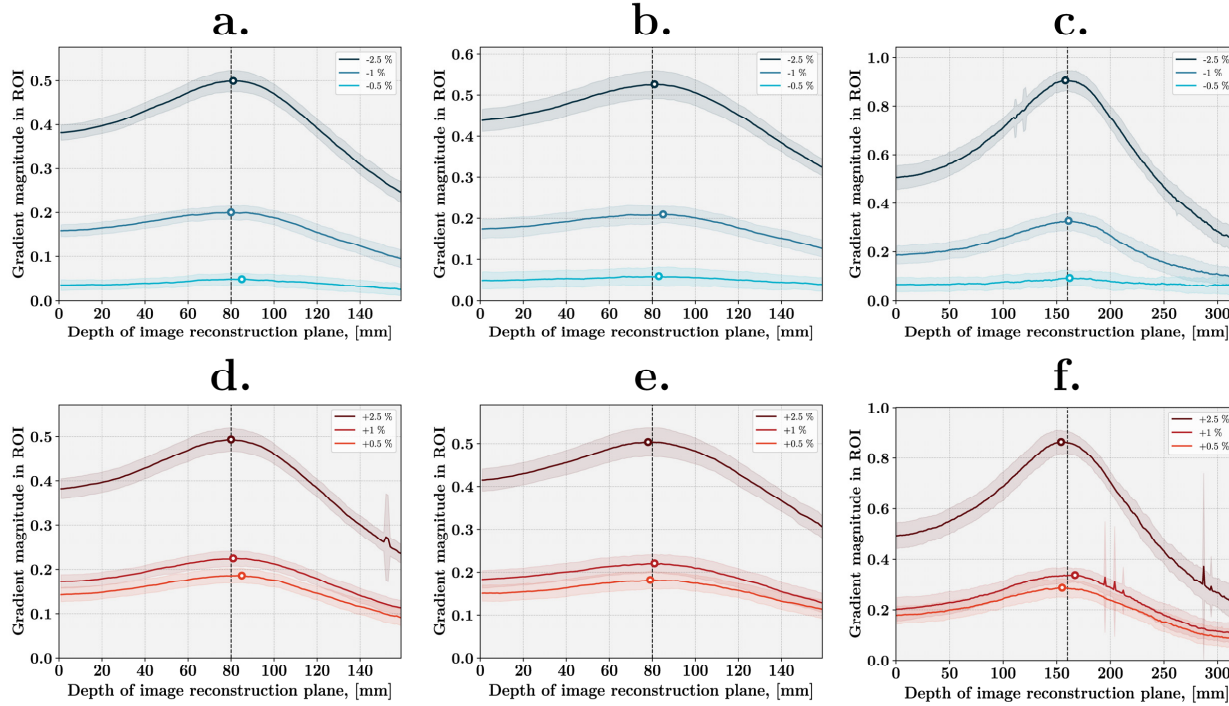


Figure 9.19. Focus stacking metric dependency on image reconstruction plane depth in low contrast scenarios for different test object thicknesses and initial helium-3 ion energies, using Sobel operator

Data binning with pixel size of 0.2 mm. De-noising with Gaussian filter, no data smoothing applied along depth axis, $\sigma = 2$ pixels. Focus stacking metric given as average (*line*) and 1σ (*shaded region*) in ring-like ROI around each cylinder. Maximum of respective metric depth profile given as a point.

Data given for ^3He ions: 261 MeV/u in 16 cm test object (Subfigure (a),(d)), 364 MeV/u in 16 cm test object (Subfigure (b),(e)) and 364 MeV/u in 32 cm test object (Subfigure (c),(f))

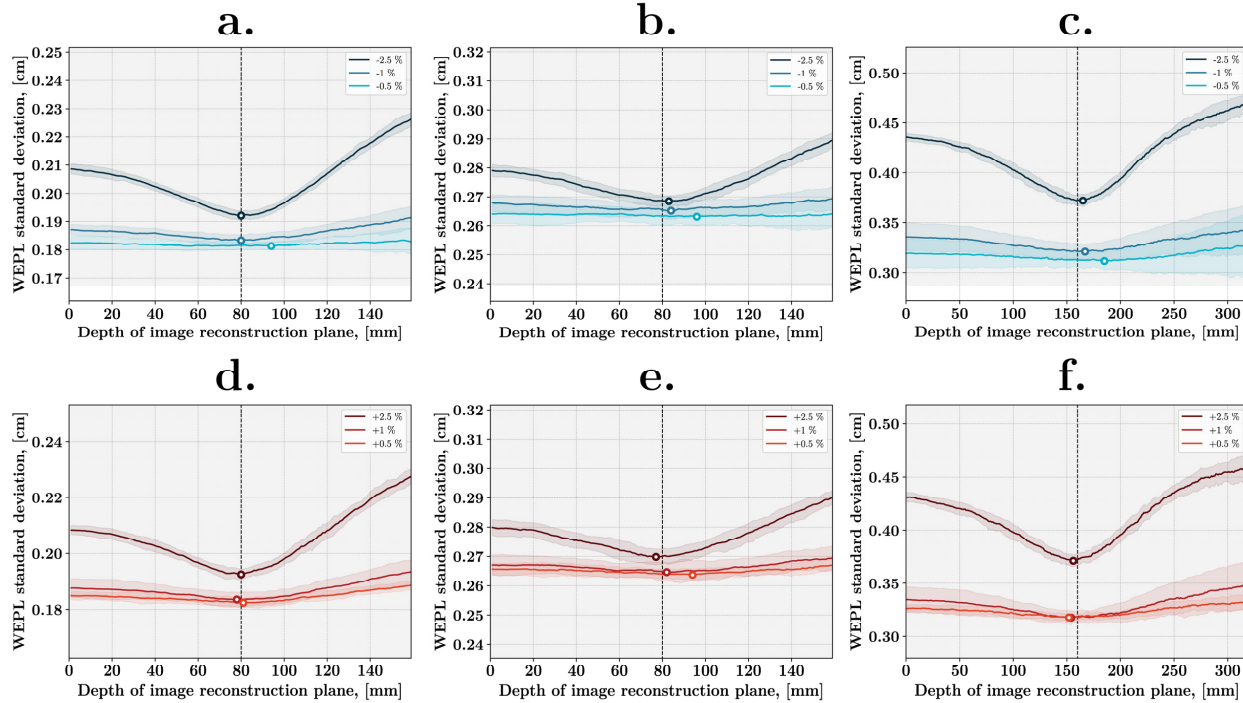


Figure 9.20. Focus stacking metric dependency on image reconstruction plane depth in low contrast scenarios for different test object thicknesses and initial helium-3 ion energies, using local standard deviation

Data binning with pixel size of 0.2 mm. De-noising with Gaussian filter, no data smoothing applied along depth axis, $\sigma = 5$ pixels. Focus stacking metric given as average (line) and 1σ (shaded region) in ring-like ROI around each cylinder. Minimum of respective metric depth profile given as a point.

Data given for ^3He ions: 261 MeV/u in 16 cm test object (Subfigure (a),(d)), 364 MeV/u in 16 cm test object (Subfigure (b),(e)) and 364 MeV/u in 32 cm test object (Subfigure (c),(f))

estimated depth deviation and smaller uncertainty level. This is attributable to increased low contrast resolution and decreased imaging noise of He-Rad compared to p-Rad as discussed previously in Section 9.3. Thus, these initial results suggest that He-Rad could possibly be the i-Rad modality of choice in low contrast imaging with ED-FS.

In case of LV-FS, similar trend could be observed – the uncertainty of estimated object depth significantly increases for lower contrast levels. Considering He3-Rad with 16 cm thick test object, the uncertainty interval of $[-10 \text{ mm}; +9 \text{ mm}]$ at -2.5% contrast level increases to $[-34 \text{ mm}; +21 \text{ mm}]$ and $[-62 \text{ mm}; +81 \text{ mm}]$ at -1% and -0.5% contrast levels, respectively. This and additional results presented in **Appendix 8.21.** suggest, that while for contrast levels higher than $\pm 2.5 \%$, lower uncertainty can be observed with LV-FS compared to ED-FS, for lower contrast levels the advantage of LV-FS is lost with ED-FS indicating lower uncertainty. This is attributable to underlying principle of each method. While in case of ED-FS, change of WEPL values near an object boundary generates the information necessary for Equation 9.1., in case of LV-FS the accuracy of depth estimation via Equation 9.3. depends on the change of WEPL value standard deviation near an object boundary. As homogenous WEPL regions already have an inherent WEPL value standard deviation due to initial energy spread of the beam and energy straggling within the object, the slight increase of local WEPL value standard deviation near a low contrast object boundary is insufficient to register a significant change via Equation 9.3. These preliminary findings on LV-FS limitations in low contrast scenarios need to be further assessed to evaluate the clinical applicability of the proposed method. It should also be noted that the inserts of low contrast phantom were of varying length, thus a methodology introducing narrow slabs of air or high density material (aluminium for example), simulating millimetric shifts should be studied in future work for more unified comparison.

While preliminary results on further extending the capabilities of both p-Rad and He-Rad modalities with LV-FS or ED-FS approach, future work should focus on evaluating possible clinically relevant applications of these methods. One such approach was presented in [26], where FS and depth estimation was used for WEPL change with respect to a reference image rather than evaluating the depth of a specific WEPL region. Such application and further optimization of ED-FS and LV-FS implementation parameters (for example, additional use of Savitzky-Golay filter) in a clinically relevant, complex patient-like geometry would be of high importance in future work.

9.5. Conclusions and discussion

Chapter 9 presented MC simulation-based investigation on two new i-Rad modalities - with high energy protons and helium-3 ions - for patient position verification before the treatment. i-Rad modalities were evaluated in the context of applicability for compact helium ion synchrotron - HeLICS designed by CERN NIMMS. For high energy p-Rad, image quality was evaluated with respect to energy in range from 250 to

700 MeV, with the aim of identifying optimum imaging performance for large anatomies (full-body i-Rad). Contrary, for He3-Rad as an approach proposed by the Author and not yet studied, the aim was to assess if comparable or improved image quality can be reached with respect to He4-Rad. He3-Rad could be an alternative in compact synchrotron scenario, as higher range in water can be obtained for the same magnetic rigidity with respect to He4-Rad - crucial for full-body i-Rad. All results were reported for two test object sizes of 16 and 32 cm - imaging of anatomies like head and pelvis, respectively.

An extensive study on achievable i-Rad image quality in an idealized detector scenario evaluated following parameters: spatial resolution, CNR, imaging dose, correlation between imaging dose and CNR, low contrast resolution, WEPL value uncertainty and accuracy, impact of RSP energy dependency, secondary particle rejection rates and overall uncertainties associated with image reconstruction process.

Finally, the MC simulation-based study focused on development of novel image reconstruction approaches – ED-FS and LV-FS – to further improve p-Rad, He3-Rad and He4-Rad. Achievable image quality improvement and imaged object depth estimation precision was evaluated, considering the impact of imaged geometry and ion type and kinetic energy used for imaging.

Main conclusions from the presented results can be summarized as:

1. Evaluating high energy p-Rad with HeLICS synchrotron, sufficient radiographic image quality ($MTF_{10\%}$ of 1.15 lp/mm, CNR of 24.9) can be achieved with 250 MeV energy in anatomies as head (16 cm test object), while higher energies are necessary for anatomies as pelvis (32 cm test object). Optimum performance in larger anatomical region imaging can be achieved by 330 - 500 MeV protons (compromise between $MTF_{10\%}$ of 0.5 - 0.8 lp/mm and CNR of 9 - 15).
2. Increasing energy for p-Rad results in increased spatial resolution ($MTF_{10\%}$), while decreasing CNR and increasing WEPL value uncertainty. Comparing 250 and 700 MeV energies in 16 cm test object, spatial resolution increases about 2.3 times, with CNR decrease of 2.7 times and WEPL value uncertainty increase of about 2 times.
3. With increasing energy used in p-Rad, higher imaging dose is necessary to achieve the same level of CNR, e.g., for CNR of 10 in 16 cm test object, around 6 times higher imaging dose for 700 MeV p-Rad compared to 250 MeV
4. Due to energy resolution limitation of detection system, higher energy p-Rad have decreased low contrast resolution and reconstructed WEPL value accuracy (uncertainty increase by about 5-6 times, comparing 250 and 700 MeV).
5. Improved CNR and spatial resolution can be observed in smaller object imaging via p-Rad, though WEPL value uncertainties are slightly increased.
6. RSP energy dependency systematically introduces WEPL deviations for high energy p-Rad ($\sim 0.5\%$ higher deviation for 700 MeV compared to 250 MeV), with respect to nominal energy level of 100 MeV/u helium-4 ions for therapy.

7. Evaluating He-Rad with HeLICS synchrotron, maximum range in water of 53 cm can be achieved with helium-3 ions, in comparison with 30 cm of helium-4 ions. Thus, helium-3 ions are possibly suitable alternative for full-body radiography with compact synchrotrons with limited energy reach.
8. He3-Rad has comparable or slightly improved performance with respect to He4-Rad in context of spatial resolution, CNR, WEPL accuracy and uncertainty and low contrast resolution (spatial resolution within 0.2 lp/mm, CNR within 3%, same WEPL accuracy).
9. For scenarios considered, He3-Rad has 11-13% lower imaging dose with respect to He4-Rad for the same number of primary particles. To maintain the same level of CNR, He4-Rad requires 10-15% higher imaging dose with respect to He3-Rad.
10. Use of He3-Rad could lower technical requirements for the detector design, as implementation of $\Delta E - E$ particle identification filter might not be necessary with respect to He4-Rad due to reduced nuclear fragmentation.
11. With respect to p-Rad, He3-Rad and He4-Rad exhibits improved imaging performance. For energies considered, He3-Rad and He4-Rad achieved spatial resolution comparable to 500 - 600 MeV p-Rad, while maintaining high level of CNR, comparable to 250 MeV p-Rad. He3-Rad and He4-Rad has improved low contrast resolution and reduced WEPL value uncertainty, compared to high energy p-Rad.
12. Spatial resolution and local WEPL value standard deviation near an imaged object boundary is dependent on reconstruction plane depth used for PIB approach, thus so-called "focal depth" can be calculated via ED-FS or LV-FS to improved reconstructed image quality and enable object depth estimation.
13. Optimum performance of ED-FS can be achieved by prior Gaussian de-noising with σ of 1.5 - 2.5 pixels and edge detection using Sobel operator, while best performance for LV-FS is achieved by prior Gaussian de-noising with σ of 5 pixels.
14. Both ED-FS and LV-FS can achieve high, object depth independent spatial resolution in final reconstructed image, though LV-FS can achieve up to 2 times higher CNR and WEPL value deviation (with respect to theoretical reference) compared to ED-FS. Highest reconstructed image quality with ED-FS and LV-FS is achieved with 250-330 MeV p-Rad or He-Rad modalities, depending on test object size.
15. In terms of imaged object depth estimation, both ED-FS and LV-FS can achieve mean estimated position accuracy of < 2 mm could for objects near the entrance and exit surface and < 5 mm at the middle of imaged geometry. Nevertheless, compared to ED-FS approach, depth estimation uncertainty is reduced 1.5 to 3 times with LV-FS approach, achieving depth uncertainties $< \pm 10$ mm in 16 cm test object, and in case of 32 cm test object - $< \pm 20$ mm.
16. Depth estimation accuracy of ED-FS and LV-FS is dependent on MCS amplitude change per unit depth, about 2 times lower depth estimate uncertainty can be achieved for objects close to object exit surface compared to entry surface. Similarly,

lower depth estimate uncertainty can be achieved with 250-330 MeV p-Rad or He-Rad modalities, depending on test object size.

Limitations of the performed research. Additional notes and implications of the work.

Considering the methodology and results presented in this Chapter, following limitations and additional implications of the performed study were identified:

- as presented study focused on initial developments of high energy p-Rad, He3-Rad and LV-FS approach and general physical assessment of these imaging methods, an idealized setup was considered with no specific detector setup and associated limitations. Idealized single particle positional and angular data registration was assumed with no detector related spatial resolution limitations. Considering future developments of these i-Rad approaches in context of technological implementation, limitations of different detection systems (as discussed in Chapter 8 and corresponding Appendix) should be evaluated for these approaches, focusing on ion type and kinetic energy dependent characteristics. Even more importantly, future work should evaluate and optimize energy or range detection systems (as discussed in Chapter 8 and corresponding Appendix) necessary for implementation of these i-Rad approaches, as the resolution directly affects WEPL accuracy, image noise and low contrast resolution. While this study provided initial assessment considering a 1% uncertainty in energy detection, further technologically oriented studies should evaluate detection system energy resolution limitations, dependency on ion type and kinetic energy, as well as possibly optimize the system to particular ion type and kinetic energy.
- with the focus on initial development of these i-Rad approaches and general physical assessment, uniform field delivery was considered. In actual implementation scenario, delivery would be realized via PBS, thus further studies should focus on the influence and optimization of spot size, spot spacing and delivery sequence suitable for i-Rad.
- as the study was based on MC-simulations, accuracy of nuclear interaction modelling as relevant for i-Rad has limitations. Thus, in terms of secondary particle rejection and filtering via ΔE -E approach, uncertainties and deviations with respect to measurement data could be expected, prompting necessity for future experimental campaign. Accuracy of used physics model within Geant4 has been outlined in Chapter 4, corresponding Appendix and references benchmarking studies.
- from perspective of FS approach investigation in this study, focus was given on high contrast scenario. As discussed in the final part of Section 9.4., significant impact of contrast level on achievable imaged object depth estimation precision and uncertainty can be observed. This of particular importance for possible clinical application of this approach, as detection of WEPL shifts with magnitude as low as 1 mm is necessary. Further methodological adaptations in terms of imaged setup should be done, with further studies focusing on achievable depth estimation accuracy as function of WEPL shift magnitude, position along depth axis and imaged object size.

- with the focus on initial development of these i-Rad approaches and general physical assessment, simple and standardized phantom geometries were used for quantitative evaluation of image quality. As in a clinical setup, complex anatomies with large spatial WEPL variations and different depths of imaged object features can be expected, additional work should focus on quantitative image quality evaluation in such complex scenarios. Focus should be given on spatial resolution and WEPL value accuracy evaluation, providing additional insights on optimum energy for p-Rad and comparison of both He-Rad modalities with respect to p-Rad. Implementation of such complex geometry scenarios would also be of great importance for further comparison of ED-FS and LV-FS approaches in terms of overall image quality improvement and object depth estimation accuracy.

Future research outlooks

Considering the methodology, results and study limitations presented in this Chapter, following pathways for future additional research were identified:

- MC-based simulation study focusing on implementation of realistic detector technological constraints for i-Rad and evaluating the influence of ion type and ion kinetic energy chosen for imaging;
- experimental campaign, focusing on validation of presented results and evaluation of detection system technological limitations for single-particle tracking;
- MC-based simulation study focusing on quantitative image quality evaluation within anatomically relevant geometry, while also simulating WEPL or geometrical shifts and evaluating detection accuracy with proposed i-Rad methods;
- MC-based simulation study focusing on WEPL or geometrical shift detection and localization along depth axis accuracy with LV-FS and ED-FS approaches. Further optimization of LV-FS and ED-FS mathematical implementation parameters in such complex geometries would also be of significance for future clinical application. Experimental campaign, validating LV-FS and ED-FS approaches would also be a significant milestone towards clinical application.
- from accelerator physics perspective, fast proton or helium-3 beam energy switching via MEE could be explored to enable monitoring of patient position and WEPL changes during the treatment by swift variation between levels necessary for treatment and i-Rad.
- from accelerator physics perspective, design studies on low beam current operation – dedicated beam monitoring instrumentation and adaptations of slow extraction schemes.
- from accelerator physics perspective, evaluation on operation with helium-3 ions – necessary ion source requirements and necessary adaptations for synchrotron injection line (LINAC etc.).
- comparison study, evaluating both reconstructed image quality, detection system and particle accelerator requirements, between single particle tracking and integrating

i-Rad approaches, while assessing the impact of ion type and kinetic energy used for imaging.

- evaluation on achievable image quality with proposed high energy p-Rad and He3-Rad, using compact detection system approaches (such rear-tracker only operation and WEPL evaluation using energy deposition in a thin sensitive layer).

Table 9.4.

- Necessary main RF cavity operation frequencies of NIMMS HeLICS synchrotron for acceleration of proton, helium-3 and helium-4 ion energies investigated

Ion type, initial energy	Corresponding synchrotron RF cavity frequency*
Reference: Helium-4 ion treatment scenario	
helium-4 ions, 220 MeV/u	5.035 MHz
High energy proton radiography scenarios	
protons, 250 MeV	5.256 MHz
protons, 330 MeV	5.763 MHz
protons, 400 MeV	6.108 MHz
protons, 500 MeV	6.492 MHz
protons, 600 MeV	6.788 MHz
protons, 700 MeV	7.022 MHz
Helium-3 ion radiography scenarios	
helium-3 ions, 261 MeV/u	5.339 MHz
helium-3 ions, 364 MeV/u	5.944 MHz

* Necessary RF frequency calculated based on 35 m circumference of HeLICS

9.5.1 Considerations for technological implementation

While the results presented in this Chapter mainly focused on the overall physical feasibility of novel imaging methods as high energy p-Rad, He3-Rad and implementation of ED-FS and LV-FS, following key considerations were identified for technological implementation of these approaches, especially in context of HeLICS system:

- considering HeLICS synchrotron design, operation is optimized for delivering helium-4 ions with energies necessary for treatment delivery. In case of p-Rad and He3-Rad, higher energies would be used, thus necessitating operational RF frequency increase for the main cavity as summarized in Table 9.4. Thus, to accommodate

feasibility of any of the considered i-Rad modalities with HeLICS, main RF cavity should be designed accordingly. Necessary changes in acceleration cycle should also be quantitatively evaluated.

- as i-Rad operation with single particle tracking approach necessitates significantly lower output beam current compared to operating conditions of a treatment beam, slow extraction scheme should be adapted accordingly, while also considering the higher sensitivity requirements of the relevant beam instrumentation for monitoring and control system. Studies on these considerations are provided in Chapter 8 and respective Appendix.
- if monitoring during treatment delivery with proton or helium-3 ion beams is to be considered, feasibility to adapt MEE for fast variation between the two energy levels (treatment and imaging) should be studied.
- if implementation of He3-Rad or He4-Rad is to be considered, detector optimization for these modalities should be done to achieve maximum performance. For implementation of any i-Rad modality, technical integration study with the overall particle accelerator system should be done, considering also the possibilities to integrate beam monitoring system as part of the detection system for single particle tracking.
- specifically for He3-Rad implementation, technical design studies and evaluations should be performed to assess the feasibility of helium-3 ion delivery and compare necessary changes with respect to operation with helium-4 ions.

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Mixed helium-4 ion and deuteron beams for treatment monitoring

By using separate treatment and imaging beam pulses, i-Rad approaches proposed in Chapter 9 could be used for patient position monitoring, though inherent latency of such approach exists. Thus i-Rad approaches would not be efficient to monitor physiological motions such as breathing in real-time. Inspired by the carbon-helium mixing method for carbon IBT as discussed in Chapter 8, this Chapter proposes and investigates a similar method tailored specifically for helium IBT: helium-deuteron (He-D) mixing. Theoretically achievable range shift sensitivity and achievable 2D imaging quality are evaluated for mixed He-D beams.

As in Chapter 9, MC simulated data were used for helium-deuteron mixed beam radiography (He-D-Rad) image reconstruction and range sensitivity evaluation. Section 10.1 outlines methods used for evaluation of two approaches for mixed beam use - range measurement and 2D imaging. Definition of simulation geometry, beam energy choice and physical parameter scoring methods are presented. Methods to choose He-D fluence mixing ratio, assess the additional deuteron imaging beam dose and evaluate range shift sensitivity are also outlined. Reconstruction and image quality metric analysis methods for 2D imaging are adapted from Section 9.2 of Chapter 9.

Results on the proposed He-D-Rad method for treatment monitoring in helium IBT are presented in Section 10.2. Optimum parameters for both range measurement and 2D imaging are evaluated with respect to shift sensitivity and image quality. Conclusions and discussion on the achieved results are outlined in Section 10.3. As provision of He-D beam for the proposed method is complex from accelerator physics perspective, special focus in Subsection 10.3.1 is given for necessities of particle accelerators and detectors for possible future technological implementation.

Contributions of the Author: Work presented in this Chapter has been performed solely by the Author, indicating used literature sources where applicable. MC simulation codes and *python* scripts for 2D image reconstruction developed by both Ilze Baumgarte (RTU) and Aurēlija Viņķe (RTU), under the supervision of the Author, were used as the basis and adapted by the Author for He-D-Rad. MC simulation codes and *python* scripts for range measurement setup were developed solely by the Author.

Approbation of the results presented in this Chapter:

- Oral presentation 5th *CERN Baltic Conference (CBC'25)* in Kaunas, Lithuania, 2025
K.Paļskis, I.Baumgarte, A.Viņķe, T.Torims, M.Vretenar, J.Seco, M.Sapinski “*Towards the last millimeters in helium ion therapy: developing dedicated range verification methods*”
-

10.1. Modelling and analysis methodology

This Section provides brief summary of the modelling and analysis methodology used within the study, while additional methodological details are given in Appendix 9.1.

With p-Rad and He3-Rad in Chapter 9 explored for pre-treatment verification, feasibility of mixed beam approach for helium IBT was evaluated for position monitoring during treatment delivery - general feasibility of mixed helium-deuteron (He-D) beams. No specific beam injection or extraction strategy was considered, assuming same phase space for both particle beams, with simulated beam as for p-Rad and He-Rad. Energy pairs were chosen at same beam rigidity and are summarized in Table 10.1. Range measurement was considered first, with setup adapted from [80]. For the same water test objects as for p-Rad and He-Rad, uniform polystyrene block with dimensions 16×16×19 or 32×32×38 cm was simulated as range detector (see in Figure 10.1).

He-D fluence ratios of 1:500, 1:100, 1:75, 1:50, 1:25 and 1:10 were considered, with the ratio given as imaging beam deuterons per number of treatment beam helium-4 ions. Energy deposition in polystyrene detector was analysed to assess deuteron signal distinguishability, while additional dose contribution and impact on RBE was assessed in water test object. Range sensitivity was assessed by changes in energy deposition profile in polystyrene detector for shifts introduced as material slabs - ± 1 , ± 2 and ± 5 mm.

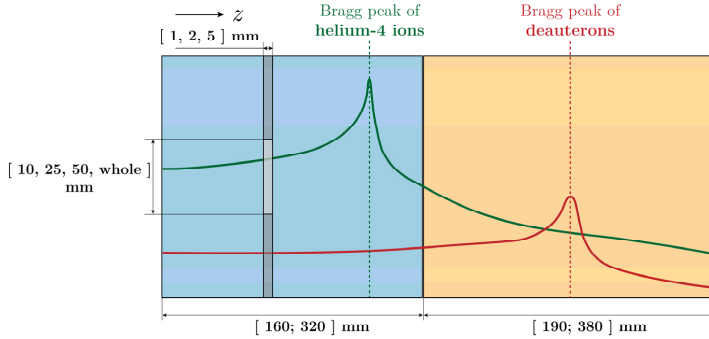


Figure 10.1. Principle of mixed helium-deuteron radiography and corresponding geometry used in MC simulations for range measurement setup

Figure is schematic in nature and not to scale. Blue region corresponds to the water test object, yellow - polystyrene volume. Geometry and dimensions of the introduced materials slabs for range shifts indicated in grey, with the slab centre placed at depth corresponding to the middle of helium-4 ion range

For evaluation of 2-dimensional imaging with mixed He-D beam (He-D-Rad), He-Rad setup was used. Summed datasets of deuteron imaging beam and fragments from helium-4 treatment beam were used in analysis. Novel data filtering routine was developed specific to mixed beams, further discussed in Main Results. Same image

reconstruction formalism was followed, with only high contrast phantom considered - quantitatively evaluating spatial resolution, CNR, imaging dose and WEPL value accuracy. Fluence ratios of 1:100, 1:50 and 1:10 were evaluated.

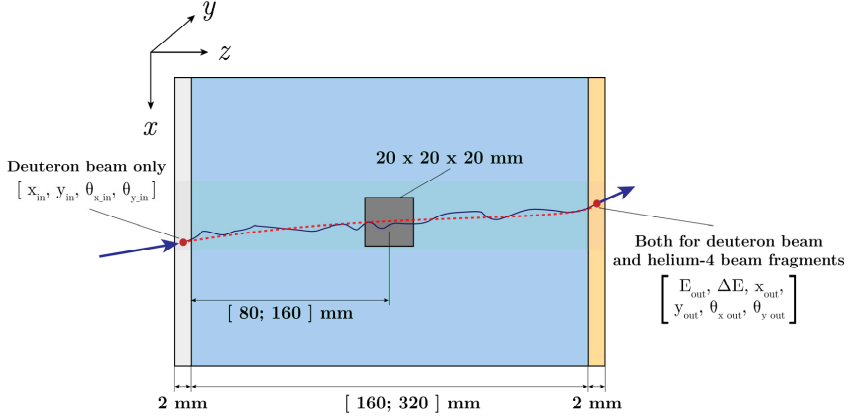


Figure 10.2. Geometry used in MC simulations for 2D imaging of mixed helium-deuteron beams

Light grey region corresponds to idealized air detector, blue region - water test object, yellow region - polystyrene volume. Dark grey volume corresponds to aluminium cube insert. Set of physical parameters registered within each volume indicated for the points in the schematic. True particle trajectory is indicated in blue, most-likely path (MLP) estimate used for image reconstruction - in red.

Table 10.1.

Simulated helium-4 ion and deuteron energy pairs and corresponding ranges in water

Test object thickness	Helium ion range	Helium ion energy	Magnetic rigidity $B\rho$	Corresponding deuteron energy	Corresponding deuteron range
16 cm	9 cm	108.3 MeV/u	3.08 Tm	107.6 MeV/u	17.7 cm
	15 cm	144.8 MeV/u	3.60 Tm	144.0 MeV/u	29.5 cm
32 cm	17 cm	155.6 MeV/u	3.74 Tm	154.7 MeV/u	33.5 cm
	30 cm	216.3 MeV/u	4.48 Tm	215.2 MeV/u	59.2 cm

* All parameters calculated considering Bethe-Bloch equation under CSDA for initial energy-range relationship

10.2. Results of the modelling

Range measurement: Impact of helium-deuteron fluence ratio on energy deposition signal

Of the two simulated scenarios with mixed He-D beams, range measurement was evaluated first. One of the main parameters to assess for the feasibility of mixed He-D beams is the fluence mixing ratio. Figure 10.3 illustrates total energy deposition in simulated polystyrene detector from both deuteron imaging beam and secondary fragments from helium-4 treatment beam.

From data in Figure 10.3, it can be observed that the lowest considered mixing ratio of 1:500 would be insufficient to clearly distinguish Bragg peak of imaging deuterons from secondary fragment background of helium-4 treatment beam. Imaging deuteron Bragg peak can be clearly distinguished already at a fluence ratio 1:100. For this mixing ratio, energy deposition increase of ~50.1-70.4% was observed for lower He-D energy pairs and 36.5-52.6% increase for higher energy pairs at Bragg peak depth with respect to pure helium-4 ion beam fragments for both test object sizes. Deuteron Bragg peak is better discriminated from secondary fragment background of helium-4 ion beam for lower energy pairs energies. This is attributable to increased peak energy deposition of at lower initial energy - reduced loss of primary particle fluence and broadening of the peak due to range straggling. Deuteron Bragg peak intensity relative to helium-4 fragment background increases with increasing deuteron contribution in the beam, reaching 5.5 to 9.2 times higher energy deposition with respect to background at mixing ratio of 1:10. Although increased deuteron contribution in mixed beam could result in higher range sensitivity due to more prominent change in energy deposition profile, it would increase the dose contribution of the imaging beam. Therefore, 1:100 mixing ratio with reduced dose contribution could be more favourable if the achieved range sensitivity is acceptable.

For illustrative purpose, the individual contributions of total energy deposition in polystyrene detector from deuteron imaging beam and secondary fragments from helium-4 ion treatment beam are given in **Appendix 9.2**. As illustrated in Figure A.9.3. of **Appendix 9.2**, deuterons do not have a nuclear fragmentation tail with relatively sharp distal fall-off - improved distinguishability from secondary fragment background of helium-4 beam. This contrast carbon-helium mixing approach for carbon-12 IBT, where helium imaging beam exhibits significant fragmentation tail, possibly reducing peak to distal dose ratio. As the difference of energy deposition levels between deuterons and helium-4 ion fragmentation tail is low, the mixing ratio of 1:100 can be considered. This is not the case for carbon-helium mixing, as the difference is higher, necessitating higher contribution of imaging beam - a ratio of 1:10 typically chosen [9-13].

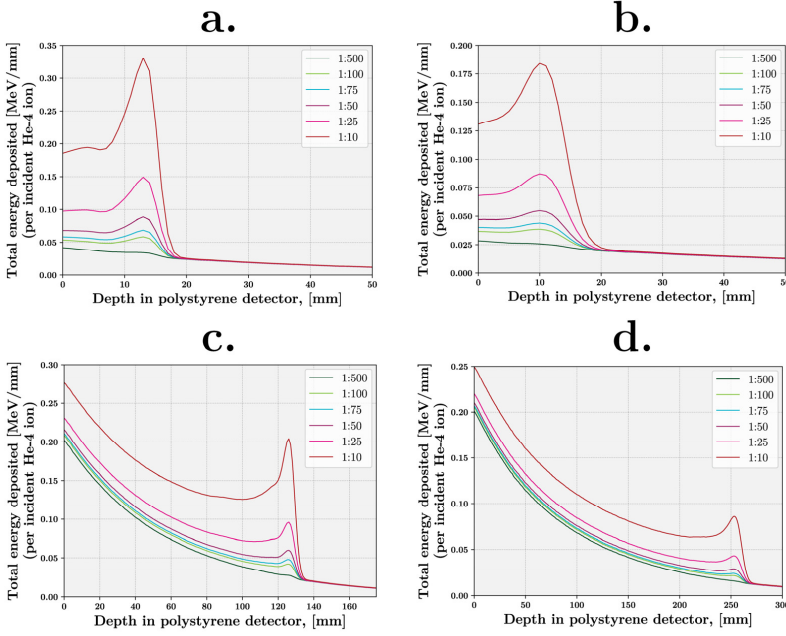


Figure 10.3. Spatial distribution of mixed helium-deuteron beam total energy deposition in simulated polystyrene detector for different fluence ratios and initial particle energy levels

Data given with 1 mm spatial resolution. Helium-deuteron energy pairs as defined in Table 10.1, only deuteron energy levels given here.

Subfigure (a): simulated test object of 16 cm thickness with deuteron energy of 107.6 MeV/u

Subfigure (b): simulated test object of 32 cm thickness with deuteron energy of 154.7 MeV/u

Subfigure (c): simulated test object of 16 cm thickness with deuteron energy of 144.0 MeV/u

Subfigure (d): simulated test object of 32 cm thickness with deuteron energy of 215.2 MeV/u

Range measurement: Deuteron imaging beam contribution to treatment dose distribution. Deuteron imaging beam contribution to relative biological effectiveness

The other factor for choosing fluence ratio of mixed He-D beam is the additional dose contribution of imaging beam delivered to the patient. Lowest possible dose contribution to not perturb treatment dose distribution is desirable, while maintaining acceptable range sensitivity. Figure 10.4 illustrates the relative contribution to physical dose in the irradiated volume by deuteron imaging beam for a fluence ratio of 1:100.

As illustrated in Figure 10.4., for total physical dose distribution normalised to maximum at the Bragg peak, deuteron imaging beam for 1:100 mixing ratio contributes to less than 0.1% throughout the irradiated volume in all geometrical scenarios considered. Contribution only slightly varies with depth, with maximum variation of 0.04% observed for 154.7 MeV/u deuterons in He-D beam for 16 cm test object. Overall,

the additional dose contribution is insignificant, except for scenarios with lower He-D energy pairs (in Figure 10.4.(a) and (b)) - imaging beam contribution becomes relatively significant in the low dose region of treatment beam fragmentation tail. Thus, additional deuteron dose contribution should be considered at treatment planning level.

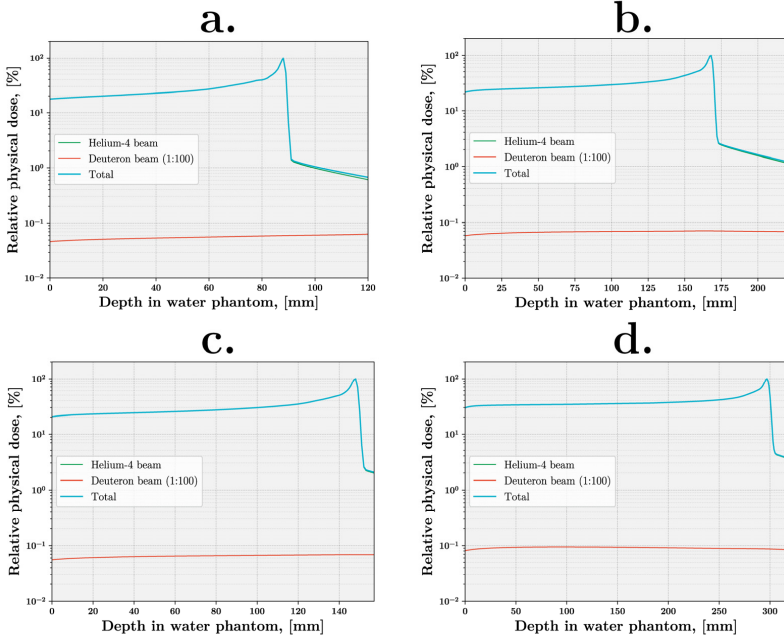


Figure 10.4. Separation of relative physical dose in simulated test object into contributions of helium-4 treatment beam and deuteron imaging beam for fluence mixing ratio of 1:100 and different initial particle energy levels

Data given with 1 mm spatial resolution. Physical doses - total and contributions of helium-4 ions and deuterons - normalized to maximum value of total physical dose. Relative physical dose values given in logarithmic scale. Helium-deuteron energy pairs as defined in Table 10.1, only deuteron energy levels given here.

- Subfigure (a): simulated test object of 16 cm thickness with deuteron energy of 107.6 MeV/u
- Subfigure (b): simulated test object of 32 cm thickness with deuteron energy of 154.7 MeV/u
- Subfigure (c): simulated test object of 16 cm thickness with deuteron energy of 144.0 MeV/u
- Subfigure (d): simulated test object of 32 cm thickness with deuteron energy of 215.2 MeV/u

Dose contribution from deuteron imaging beam scales with fluence ratio of the mixed He-D beam, with this dependency illustrated in **Appendix 9.3**. Maximum physical dose contribution of deuteron imaging beam was observed at fluence ratio of 1:10. In 16 cm test object, the contribution increased from $0.06 \pm 0.01\%$ at 1:100 ratio to $0.60 \pm 0.08\%$ at 1:10 ratio for 107.6 MeV/u deuterons, while for 144.0 MeV/u - from $0.07 \pm 0.00\%$ to $0.65 \pm 0.03\%$. In 32 cm test object, increase from $0.07 \pm 0.01\%$ to

0.71±0.05% and 0.09±0.00% to 0.91±0.03% were observed for mixed He-D beams with deuteron energies 154.7 and 215.2 MeV/u, respectively. With higher impact on treatment dose distribution with 1:10 fluence ratio, the use of lower fluence mixing ratio would be favourable.

As introduced in Chapter 2, physical dose alone is not enough to characterize the biological effect in PT and IBT. Thus, the impact of deuteron imaging beam contribution on RBE and biologically effective dose distribution was also evaluated for He-D mixed beam. Impact of fluence ratio on RBE spatial variation and biologically effective dose distribution is illustrated in Figure 10.5. for 16 cm test object scenario with 154.7 MeV/u deuteron energy in mixed beam. Corresponding numerical data are summarized in **Appendix 9.4** for all investigated scenarios.

As illustrated in Figure 10.5. (a), no significant RBE variation was observed in the entrance plateau for mixed He-D beam. Main impact of He-D mixing was on the peak RBE value near the Bragg peak, with peak RBE values decreased with increasing fluence ratio. For the He-D mixed beam with lowest deuteron energy of 107.6 MeV/u, maximum RBE decreased to 3.92 at 1:100 fluence ratio and 3.68 at 1:10, compared to RBE of 3.95 for pure helium-4 ion beam. Impact was reduced for highest energy pair considered - 215.2 MeV/u deuterons - with pure helium-4 ion maximum RBE of 2.78 decreased to 2.77 and 2.67 for fluence ratios of 1:10 and 1:100, respectively.

Data in Figure 10.5. (a) also illustrate that RBE significantly decreases in the fragmentation tail region with increasing fluence mixing ratio. This is not as significant as the peak RBE decrease, though, due to significantly lower physical dose levels. Throughout the irradiated volume, with respect to pure helium-4 ion beam, average RBE deviation of 0.001 to 0.012 and 0.005 to 0.059 was observed for fluence ratios of 1:100 and 1:10, respectively (see **Appendix 9.4**). RBE decrease with increasing fluence ratio is attributable to the lower LET of imaging beam deuterons compared to helium-4 ions at the Bragg peak. With increasing deuteron contribution, the lower LET contribution increases, effectively reducing total RBE.

Despite the reduction of RBE, Figure 10.5. (b) illustrates that the impact on resulting biologically effective dose distribution is low. The change is minimal because RBE reduction is offset by increased physical dose due to deuteron imaging beam contribution, with quantitative data illustrated in **Appendix 9.4**. Average deviations of biologically effective dose with respect to pure helium-4 ion beams were observed in the range of 0.001 to 0.002 GyRBE for fluence ratio of 1:100, while for ratio of 1:10 - in the range of 0.013 to 0.019 GyRBE. Maximum deviations with respect to pure helium-4 ion beams were in the ranges 0.002 to 0.002 GyRBE and 0.015 to 0.022 GyRBE for fluence ratios 1:100 and 1:10, respectively.

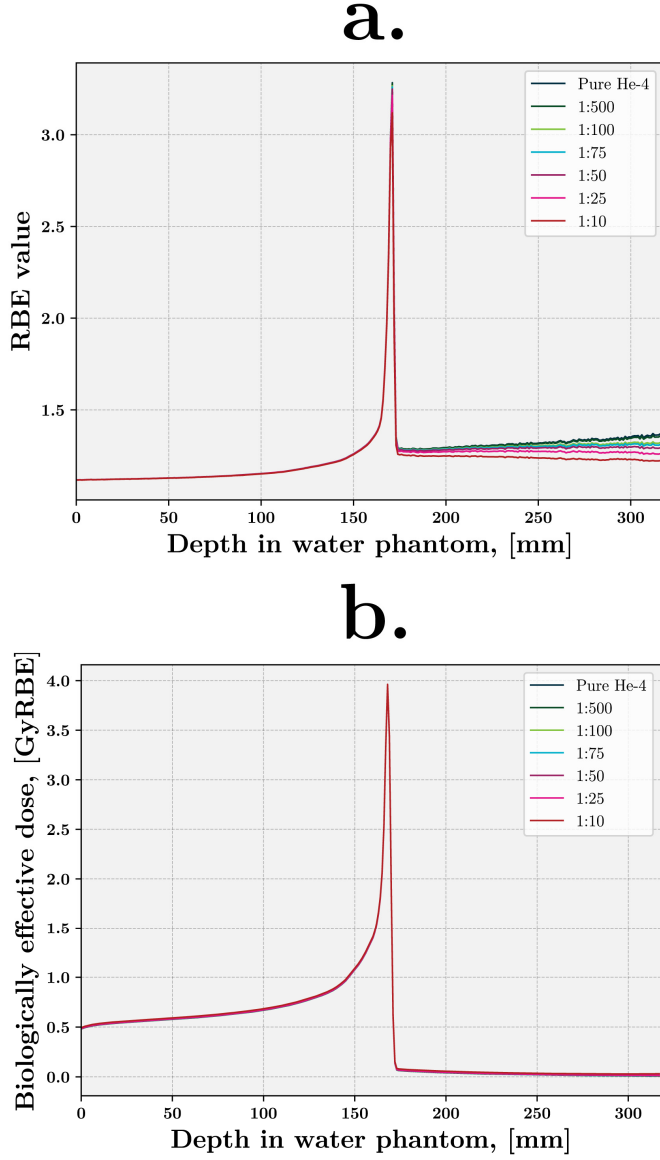


Figure 10.5. Dependency of RBE value (a) and biologically effective dose (b) in simulated test object on fluence mixing ratio for scenario with deuteron energy of 154.7 MeV/u
 Thickness of irradiated test object - 32 cm. Data given with 1 mm spatial resolution. RBE and biologically effective dose values calculated based on 2 Gy absolute dose delivered at the Bragg peak dose maximum, using mMKM parameters for human salivary gland cell line as calculated in Chapter 4.
 Helium-deuteron energy pair as defined in Table 10.1, only deuteron energy level given above.

Range measurement: Mixed helium-deuteron beam sensitivity to range shifts

Finally, range shift sensitivity of range measurement setup was evaluated for mixed He-D beam application. Changes of total energy deposition signal in polystyrene detector were evaluated for introduced shifts of ± 1 , ± 2 and ± 5 mm, additionally considering the impact of insert lateral. Range sensitivity was evaluated for different fluence ratios. Figure 10.6 illustrates sensitivity of energy deposition distribution in 16 cm test object, while Figure A.9.5. of **Appendix 9.5** - in 32 cm test object. Both Figures illustrate the data for fluence ratio of 1:100.

Increasing relative deviation of total energy deposition signal can be observed in both Figures 10.6 and Figure A.9.5. of **Appendix 9.5** for increasing shift magnitude range shift magnitude (Subfigures (a) and (b)). In case of positive shifts (downstream shift), a small decrease in energy deposition with respect to unperturbed reference can be observed first, followed by a major increase at the Bragg peak of imaging deuteron. For negative shifts (upstream shift), the trend is reversed - small initial increase followed by a major decrease in energy deposition. For positive shifts in 16 cm test object, maximum magnitude of initial decrease deviation is -4.6%, -8.8% and -16.2% for shifts +1, +2 and +5 mm, respectively, while peak increase deviation at the deuteron Bragg peak region - +27.1%, +57.8% and +124.2%. Magnitude of energy deposition deviation for positive shifts decreases in 32 cm test object: -2.6%, -3.6% and -7.4% for initial decrease and +10.0%, +22.4% and +57.3% for peak increase of the signal. The absolute magnitude of energy deposition deviation is lower for negative shifts: with an initial increase of +4.1%, +8.1%, +18.9% and peak decrease of -18.4%, -33.5% and -53.5% in 16 cm test object for negative shifts of -1, -2 and -5 mm, respectively, while in 32 cm test object: +1.8%, +3.8% and +8.3% initial increase and -9.1%, -17.3% and -34.6% peak decrease, respectively. The position of peak energy deposition deviation is also affected by the introduced shift magnitude, with more pronounced effect in case of positive shifts. The “the background level” of energy deposition deviation also increases with increasing shift magnitude by about 10% and 5-8% for ± 5 mm shifts for 16 and 32 cm test objects, respectively. Observed energy deposition deviations are clearly distinguishable from the background level even for ± 1 mm shifts.

Apparently higher sensitivity to positive shifts is attributable to the shape of energy deposition signal as indicated in Figure 10.3 and **Appendix 9.3**. Energy deposition difference for deuteron imaging beam depth profile is higher between Bragg peak and distal region, compared to difference between proximal region and Bragg peak. Thus, higher relative deviation of energy deposition is expected for Bragg peak shifts towards distal region - positive ones. Shape of deuteron imaging beam energy deposition profile is also the reason for decreased sensitivity in 32 cm test object (see Figure 10.3 and **Appendix 9.3**).

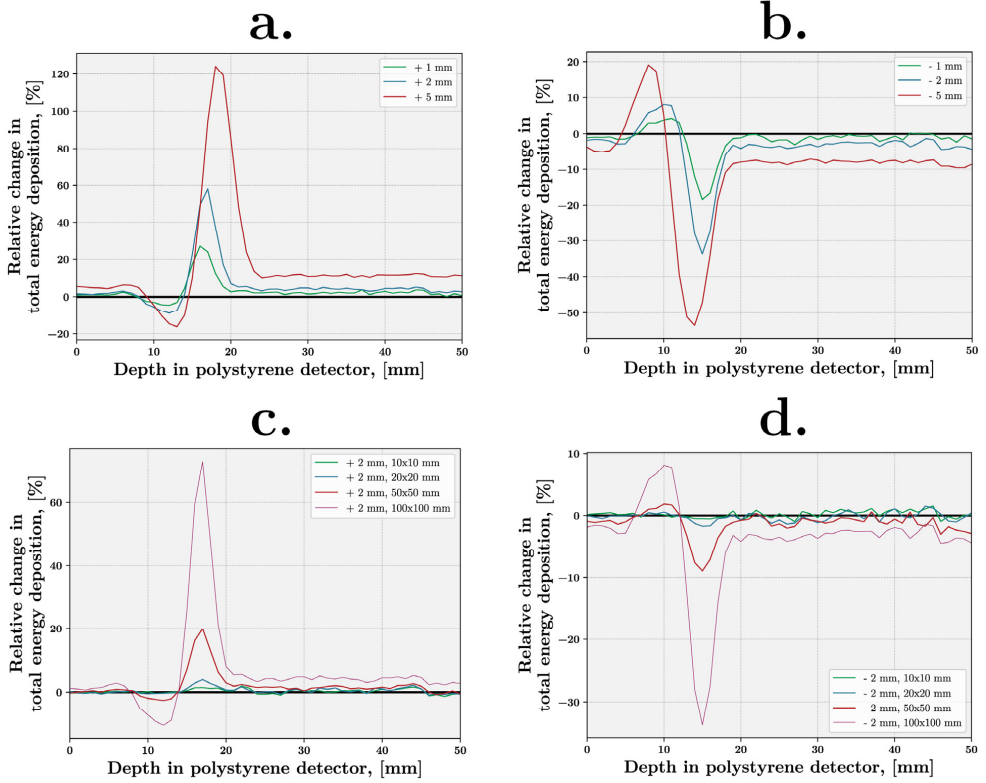


Figure 10.6. Sensitivity of total energy deposition in simulated polystyrene detector to dose maximum shifts in 16 cm simulated test object for mixed helium-deuteron beam with fluence ratio of 1:100

Data given with 1 mm spatial resolution for deuteron energy of 107.6 MeV/u. Helium-deuteron energy pair as defined in Table 10.1. Relative change calculated for each data point with respect to nominal, unperturbed energy deposition curve as $(perturbed - nominal) / nominal$.

Subfigure (a): Sensitivity to positive shifts of 1, 2 and 5 mm, by varying thickness of air insert. Lateral extent of insert: 100×100 mm

Subfigure (b): Sensitivity to negative shifts of 1, 2 and 5 mm, by varying thickness of cortical bone insert. Lateral extent of insert: 100×100 mm

Subfigure (c): Sensitivity to the lateral extent size - 10×10, 20×20, 50×50 and 100×100 of air insert. Thickness of air insert fixed for 2 mm shift.

Subfigure (d): Sensitivity to the lateral extent size - 10×10, 20×20, 50×50 and 100×100 of cortical bone insert. Thickness of cortical bone insert fixed for 2 mm shift.

Data illustrated in Figures A.9.6. and A.9.7. of **Appendix 9.6.** also illustrate the impact of lateral extent of the introduced inserts (Subfigures (c) and (d)) on range sensitivity. For decreasing lateral extent of introduce inhomogeneity, magnitude of initial energy deposition deviation is significantly lower and is almost indistinguishable from background level for 50×50 mm inserts or smaller, compared to nominal 100×100 mm insert (whole irradiation field covered). Thus, only peak magnitude of energy deposition deviation is analysed further. In case of 16 cm test object, for both positive and negative shifts, the magnitude of peak deviation decreases to indistinguishable level from the background if lateral extent of the insert is 10×10 mm (1% of irradiation field area). For positive shifts, magnitude of peak deviation decreases to +16.0% and +3.4% for lateral extents of 50×50 mm (25% of irradiation field area) and 20×20 mm (4% of irradiation field area), respectively, compared to +57.8% for nominal 100×100 mm. For negative shifts magnitude of peak deviation decreases to -8.9% and -1.7% compared to -33.5%. The effect of lateral extent impact is even more pronounced for 32 cm test object, as the magnitude of peak deviation has decreased to indistinguishable level for both 10×10 and 20×20 mm lateral extents of introduced inhomogeneities. In case of 50×50 mm extent, the magnitude of peak deviation has decreased to +6.1% and -4.5% compared to nominal (100×100 mm) of +22.4% and -17.3% for positive and negative shift, respectively.

Change in sensitivity due to lateral extent comes due to smaller number of imaging beam deuterons perturbed with decreasing area of introduced shift with respect to irradiation field size, becoming even more pronounced for larger test object sizes. Even for higher fluence ratio of He-D mixed beam, range sensitivity limitations by lateral extent cannot be fully mitigated: for fluence mixing ratio 1:10, energy deposition deviation introduced by 10×10 mm insert of 2 mm shifts still cannot be identified from background in both 16 cm and 32 cm test objects as indicated in **Appendix 9.6.**

For further quantitative analysis of range sensitivity and impact of fluence mixing ratio, energy deposition deviations were evaluated with respect to the magnitude of introduced Bragg peak position shift. **Appendix 9.7.** illustrates results achieved for three different analyses on energy deposition variation dependency on shift magnitude:

- deviation of the integral energy deposition in whole polystyrene detector, without considering any spatial variations;
- average of point-to-point energy deposition deviations;
- maximum point-to-point variation (data not presented with trends as for average).

Data in Figure A.9.8. of **Appendix 9.7.** illustrate that a simple measurement of integral energy deposition after the irradiated object could provide information to evaluate range shifts. Integral energy deposition in polystyrene detector with respect to the magnitude of introduced range shift follows a linear trend ($R^2 > 0.98$). For 16 cm test object, in case of pure-helium-4 ion beam (measurement of the secondary fragments) sensitivity of 1.92%/mm¹⁵ was observed, with an increase to 2.36%/mm and 3.41%/mm

¹⁵ Relative change of total energy deposition per millimetre of introduced range shift

for mixed He-D beams with ratios of 1:100 and 1:10, respectively. Sensitivities decreased for 32 cm test object: 1.08%/mm, 1.69%/mm and 3.39%/mm for pure helium-4 ion beam and mixed He-D beams of 1:100 and 1:10, respectively. In absolute units, sensitivity corresponds to 0.022 (MeV/ion)/mm¹⁶, 0.035 (MeV/ion)/mm and 0.015 (MeV/ion)/mm for pure helium-4 ion beam and mixed beams of 1:100 and 1:10, respectively, in 16 cm test object. Absolute sensitivity was lower for 32 cm test object: 0.008 (MeV/ion)/mm, 0.020 (MeV/ion)/mm and 0.103 (MeV/ion)/mm, respectively.

Considering the spatial point-to-point variations of energy deposition deviations with respect to nominal case, resulting sensitivities are higher. As indicated in Figure A.9.9. of **Appendix 9.7**, average point-to-point variation of energy deposition does not follow a linear trend with respect to shift magnitude, with similar trend observed for peak variation. Non-linearity is attributable to different response to positive and negative shifts as discussed before. Both approaches presented in **Appendix 9.7** indicate that 1:500 fluence mixing ratio does not provide sufficient range sensitivity improvement, with 1:100 being the minimum from studied values having a significant increase. Although fluence mixing ratio of 1:10 provides best sensitivity, it has increased dose contribution, as discussed before. Without considering any detector limitations in this initial feasibility assessment, 1:100 fluence mixing ratio provides sufficient range shift sensitivity without a significant contribution to treatment dose. Higher deuteron contribution might be necessary, if detector sensitivity and resolution limits are considered in future work.

Range shift sensitivity evaluation was considered for 16 and 32 cm test objects only for scenarios with lower energy pairs of He-D mixed beam. Range sensitivity at higher energies is expected to decrease due to energy deposition profile shape as indicated in Figure 10.3 and **Appendix 9.3**. Fluence mixing ratios with higher deuteron contribution might be favourable for higher energies used, subject to future research work.

Data in **Appendix 9.8**. also indicate the impact of lateral extent of inserts on range sensitivity. A quadratic trend can be observed with respect to lateral dimension of the insert. If this dependency is considered with respect to ratio of insert lateral extent coverage of the irradiation field - a linear dependency can be observed.

2D imaging: Evaluation of approaches for imaging and treatment beam generated deuteron discrimination

With range measurement approach with mixed He-D beams already providing sufficient accuracy that could enable patient position monitoring during the treatment, 2D He-D-Rad imaging was also investigated. For initial feasibility assessment, imaging was considered with a 100×100 mm uniform irradiation field. In a realistic scenario,

¹⁶ Total energy deposited in polystyrene detector (in MeV) per incident particle per millimetre of introduced range shift

image reconstruction should be considered on spot-by-spot basis with modern PBS delivery. Nevertheless, main findings presented below would be also applicable in such a scenario.

First aspect of 2D He-D-Rad imaging to be considered was data filtering approaches to be applied in image reconstruction. As introduced in Chapter 9., data filters on exiting particle kinetic energy and relative angle values are applied, with additional $\Delta E - E$ particle identification filter in He-Rad for rejection of light secondary fragments. In context of 2D d-Rad imaging, it is apparent that data filtering necessary for accurate image reconstruction becomes more complex. Deuterons have significant nuclear fragmentation to protons. With the relatively small difference in mass, kinetic energies of deuterons and protons exiting the imaged object would similar, necessitating to use $\Delta E - E$ particle identification filter to distinguish the two. In mixed He-D beam scenario, helium-4 ion treatment beam would additionally contribute with secondary fragments - protons as well as tritons, re-iterating the necessity to use of $\Delta E - E$ particle identification filter. The main challenge in He-D-Rad after the use of $\Delta E - E$ particle identification filter would be to separate deuterons of imaging beams from deuterons generated as secondary fragments from helium-4 treatment beam. This first subsection on 2D He-D- Rad imaging focuses on approaches developed in this work to distinguish between the two fractions of deuterons, proposing physical characteristics to be used for discrimination of the two.

In all imaging scenarios, data filtering first discriminated deuterons from secondary protons and tritons via the use of $\Delta E - E$ particle identification filter. $\Delta E - E$ distribution of all registered particles at the exit surface of the simulated 32 cm test object are illustrated in Figure 10.7 for He-D beam with deuteron energy of 154.7 MeV/u and in **Appendix 9.9** - for 215.2 MeV/u. Data are given for 1:100 fluence mixing ratio, with Subfigures(a) illustrating $\Delta E - E$ distribution of whole mixed beam, while individual contributions from deuteron imaging beam and helium-4 treatment beam secondary fragments are indicated in Subfigures (b) and (c), respectively.

Data in Figure 10.7 and **Appendix 9.9** clearly illustrate that kinetic energy-based filtering alone would not be sufficient to distinguish deuterons from secondary protons and tritons due to similar kinetic energy spectrum. Implementing $\Delta E - E$ filter, deuterons can be clearly distinguished from other light secondary particles, though becomes more complex with higher energy pairs of He-D mixed beam (**Appendix 9.9**). Subfigures (b) and (c) in Figure 10.7 and **Appendix 9.9** clearly illustrate the challenge due deuteron overlap from imaging beam and secondary deuterons generated from the helium-4 treatment beam. Higher energy deuteron fragments from the treatment beam could be removed by using a kinetic energy cut, as imaging beam deuterons have lower expected maximum energy. Nevertheless, the peak intensities in $\Delta E - E$ distribution of imaging beam deuterons to be used for reconstruction overlap secondary deuterons from treatment beam. **Appendix 9.9** illustrates that this becomes even more challenging for higher initial deuteron energies in He-D beam, as imaging beam deuteron intensity

becomes comparable with treatment beam fragment background, fluence ratio of 1:100 is considered. This indicates the need for additional, unconventional data filtering approaches to be implemented for He-D-Rad.

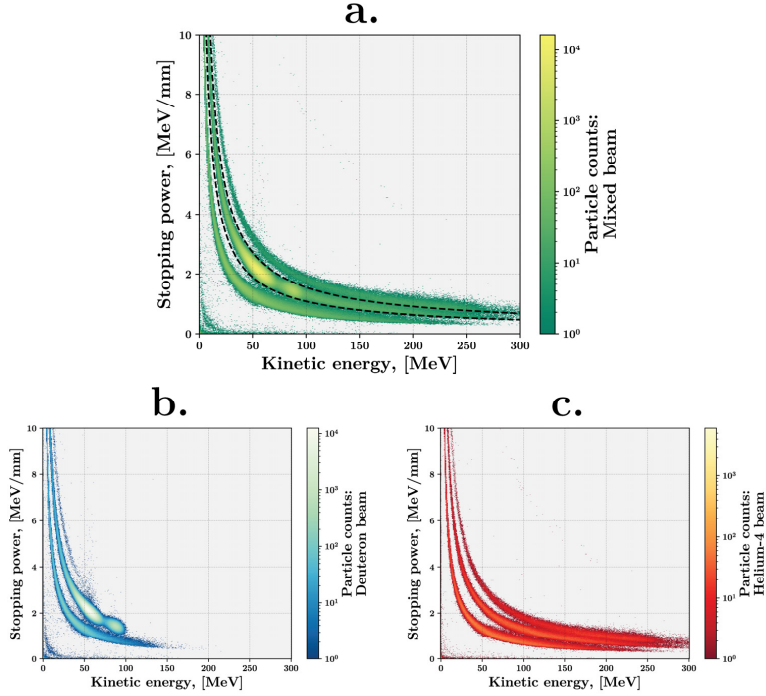


Figure 10.7. Identification $\Delta E - E$ filter - stopping power as function of kinetic energy - for particles registered at the exit surface of 32 cm test object for mixed helium-deuteron beam with initial deuteron energy of 154.7 MeV/u and fluence ratio 1:100

Data given for high contrast phantom in 32 cm test object. Down-sampled 10^6 initial deuteron data were mixed with up-sampled 10^8 initial helium-4 ion data. Registered particle counts given in logarithmic scale. Kinetic energy data grouped in bins of 1 MeV, stopping power - 0.01 MeV/mm. Helium-deuteron energy pair as defined in Table 10.1, only deuteron energy level given above.

Subfigure(a): $\Delta E - E$ filter for all particles registered at test object exit surface. Black lines correspond to nominal stopping power curve in polystyrene as function of kinetic energy with $\pm 3\sigma$ energy straggling uncertainty band for deuterons.

Subfigure(b): $\Delta E - E$ filter for only deuteron imaging beam generated particles registered at test object exit surface.

Subfigure(c): $\Delta E - E$ filter for only helium-4 treatment beam generated fragmentation particles registered at test object exit surface

Only imaging beam deuterons undergoing EM interactions are to be retained for 2D image reconstruction. As introduced in Chapter 2, one of EM interaction mechanisms

- MCS - introduces only minor angular deviations of primary particles from initial direction. On the contrary, all secondary deuteron fragments from helium-4 treatment beam are generated via nuclear interactions. Nuclear interaction processes are characterized by larger angular deviation of secondary fragments with respect to direction of primaries. Thus, if initial primary helium-4 ion angular direction is co-registered with angular direction of outgoing secondary deuteron fragment, observed relative angle would be relatively high. Based on these differences of physical interaction mechanisms for imaging beam deuterons and secondary deuteron fragments from helium-4 treatment beam, the ability to clearly distinguish the two via relative angle was assessed. Mathematical implementation of double Gaussian relative angle filtering approach for mixed beam radiography is presented in **Appendix 9.10**.

For quantitative assessment of the developed data filtering sequence for He-D-Rad, fraction of deuteron imaging beam in the dataset retained for image reconstruction after each data filter was calculated. Resulting data are presented in **Appendix 9.11.**, with fluence ratio of 1:100 considered. Data showcase that the developed data filtering sequence with novel double Gaussian filter could provide significant improvement in discrimination between the primary and secondary deuterons. Limitations do exist, as a fraction of secondary deuterons is still retained after filtering in the dataset to be used for image reconstruction. Discrimination efficiency depends on the deuteron energy level used in the mixed He-D beam and test object size. Better discrimination is achieved for lower energy and smaller test object size, with the latter being main factor.

Quantitatively, for fluence mixing ratio of 1:100 it can be observed that after $\Delta E - E$ filter identification of deuterons, a significant fraction comes from the secondary fragments of helium-4 treatment beam - 66.8% and 92.9% of identified deuterons after in 16 cm test object for low and high He-D beam energy pairs, respectively. In 32 cm test object, secondary fragments constitute 77.9% and 96.3% of identified deuterons, respectively. Addition of 0.1 rad angular cut and double Gaussian relative angle filter significantly reduces the fraction of secondary deuterons in retained data: 35.1% and 54.8% in 16 cm test object for low and high He-D beam energy pairs, respectively, with a fraction of 56.5% and 80.1% in 32 cm test object. After final energy filter, dataset to be used for He-D-Rad image reconstruction has 15.0% (low He-D beam energy pairs) and 14.4% (high He-D beam energy pairs) secondary deuterons for 16 cm test object scenario, and 26.7% and 25.5%, respectively, for 32 cm test object. Such a large fraction of secondary fragments could negatively impact the quality of reconstructed image.

As higher number of deuterons in He-D mixed beam could affect discrimination capabilities of the data filtering sequence, additional evaluation was performed for fluence mixing ratios of 1:50 and 1:10. Comparison of deuteron imaging beam fraction in the dataset retained after filtering for different fluence ratios is illustrated in Figure 10.8.

Data in Figure 10.8. clearly illustrate that increased deuteron contribution in the mixed He-D beam improves discrimination capabilities of the developed data filtering

sequence. In 32 cm test object with high He-D beam energy pairs, after deuteron identification with $\Delta E - E$ filter, secondary deuteron contribution of 96.3% at 1:100 fluence mixing ratio is reduced to 92.8% and 72.1% for 1:50 and 1:10, respectively. Performance of 0.1 rad angular cut and double Gaussian relative angle filter is also significantly improved, lowering the 80.1% secondary contribution at 1:100 to 64.4% and 24.8%, respectively. The overall quality of dataset retained for image reconstruction is improved, increasing the 74.5% contribution of imaging beam deuterons at 1:100 fluence mixing ratio to 86.6% and 97.3% for 1:50 and 1:10, respectively. The significant decrease in fraction of secondary deuteron fragments with increasing fluence mixing ratio, could improve the quality of reconstructed He-D-Rad image. Findings indicate that for the approach of 2D He-D-Rad imaging it could be possibly beneficial to use higher fluence mixing ratios to decrease the number of secondary fragments retained after data filtering.

In the same way as for p-Rad and He-Rad studies of Chapter 9, not just the discrimination capabilities of each data filter were assessed, but also the rejection rate and absolute number of particles retained after each data filter was evaluated. These results are given in **Appendix 9.12**. Main findings presented in **Appendix 9.12** can be summarized as:

- assessing pure d-Rad, for comparable energy levels (same range in water), deuterons exhibit higher data rejection rates with respect to p-Rad, though slightly lower with respect to He3-Rad and He4-Rad. The increase with respect to p-Rad is associated with higher rate of primary deuteron fluence loss, generating secondary protons and neutrons. Relative angle filter has slightly decreased rejection rate due lower MCS;
- retained number of particles for image reconstruction in pure d-Rad is lower than p-Rad and closer to He3-Rad and He4-Rad - possibly compromised CNR performance;
- in mixed He-D beam approach, the number of particles in the dataset retained for image reconstruction is closely related to number of particles used for treatment with helium-4 ion beam. Per spot helium-4 ion beam intensity will be the limiting factor for the number of deuterons available for image reconstruction, possibly limiting reconstructed image quality - highlighting possible benefits of higher fluence ratios.

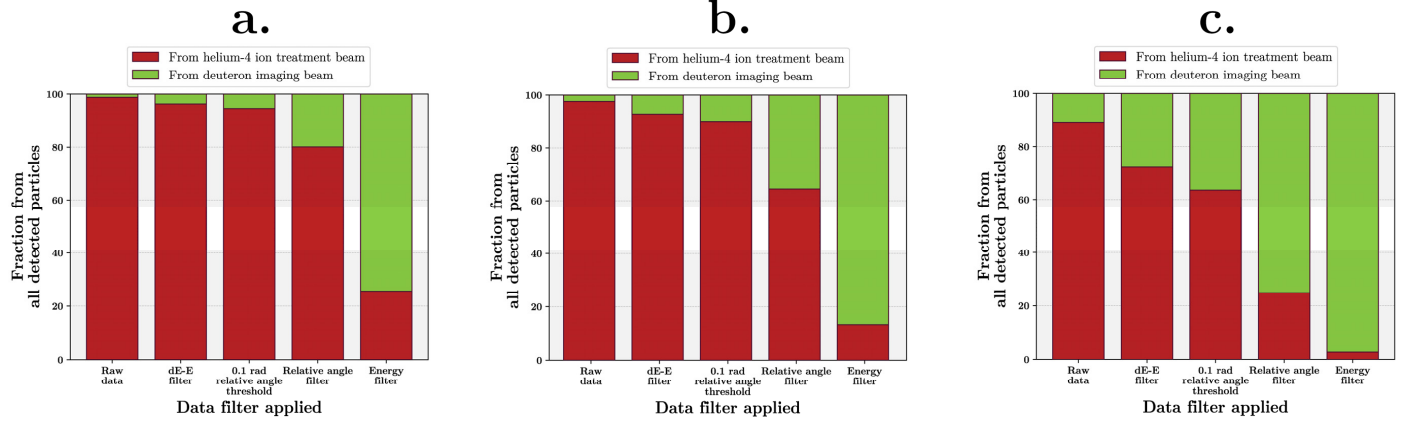


Figure 10.8. Fraction of discriminated imaging beam contribution from all registered particles generated by helium-deuteron mixed beam with varying fluence ratio of 1:100 (a), 1:50 (b) and 1:10 (c)

Data at the exit surface of the test object are given for high contrast phantom embedded in 32 cm test object, irradiated with initial deuteron energy of 215.2 MeV/u. Helium-deuteron energy pairs as defined in Table 10.1, only deuteron energy levels given. Fraction of discriminated imaging beam contribution calculated as the ratio between registered particles at the exit surface of simulated test object from deuteron beam and all mixed-beam particles retained after each data filter.

Subfigure(a): Ratio of 1:100: down-sampled 10^6 initial deuteron data were mixed with up-sampled 10^8 initial helium-4 ion data.

Subfigure(b): Ratio of 1:50: down-sampled 10^6 initial deuteron data were mixed with up-sampled 5×10^7 initial helium-4 ion data.

Subfigure(c): Ratio of 1:10: down-sampled 10^6 initial deuteron data were mixed with up-sampled 10^7 initial helium-4 ion data.

2D imaging: Reconstructed high contrast object radiographs with mixed helium-deuteron beams. Comparison with pure deuteron beams

Retained dataset after the developed data filtering sequence was used for 2D image reconstruction via MLP formalism. Reconstructed image with higher He-D beam energy pair (215.2 MeV/u deuterons) in 32 cm test object is given in Figure 10.9., with additional data for other scenarios given in **Appendix 9.13**. Reconstructed images are provided for whole mixed beam dataset (Subfigures (a)) and by separated contributions of imaging beam deuterons (Subfigures (b)) and helium-4 treatment beam generated deuteron fragments (Subfigures (c)). Data are given for fluence mixing ratio of 1:100.

Data in Figure 10.9 and **Appendix 9.13**. clearly indicate that retained secondary deuterons as fragments from helium-4 treatment beam significantly deteriorate reconstructed image quality. As indicated in Subfigures (b), if only imaging beam deuteron contribution is considered, high quality images with low noise can be reconstructed. Secondary deuterons as fragments from helium-4 treatment beam introduce significant noise (Subfigures (c)), as no direct correlation between their energy, position and angular deviation exists with respect to irradiated object. For data presented in Figure 10.9., the secondary deuterons correspond to 14.4% of particles in reconstruction dataset, while in Figure A.9.18. of **Appendix 9.13** (32 cm test object) - 25.5%. Observed image quality is more deteriorated in the latter scenario.

By increasing contribution of imaging deuterons in the mixed He-D beam, the dataset used for image reconstruction has reduced fraction of secondary deuterons, as discussed. To qualitatively assess the potential impact of fluence mixing ratio on reconstructed image quality, image reconstruction was repeated for datasets with fluence mixing ratios of 1:50 and 1:10 for comparison with 1:100. Reconstructed images for varying fluence ratios and both test object sizes are illustrated in Figure 10.10.

Reduction of secondary deuterons retained from helium-4 ion treatment beam significantly increases the image quality as illustrated in Figure 10.10. Gradual decrease of image noise and better distinguishability of high contrast object boundaries can be observed for increasing fluence ratio to 1:50 and 1:10, with respect to 1:100. Image quality improvement is even more pronounced for 32 cm test object scenario. For reconstructed images at 1:10 fluence ratio, it can be observed that image quality approaches pure deuteron contribution indicated in Subfigures(b) of Figure 10.9 and **Appendix 9.13**.

For qualitative comparison with p-Rad, He3-Rad and He4-Rad reconstructed images in Chapter 9., pure d-Rad were also reconstructed with 0.2 mm resolution and are illustrated in **Appendix 9.14**.

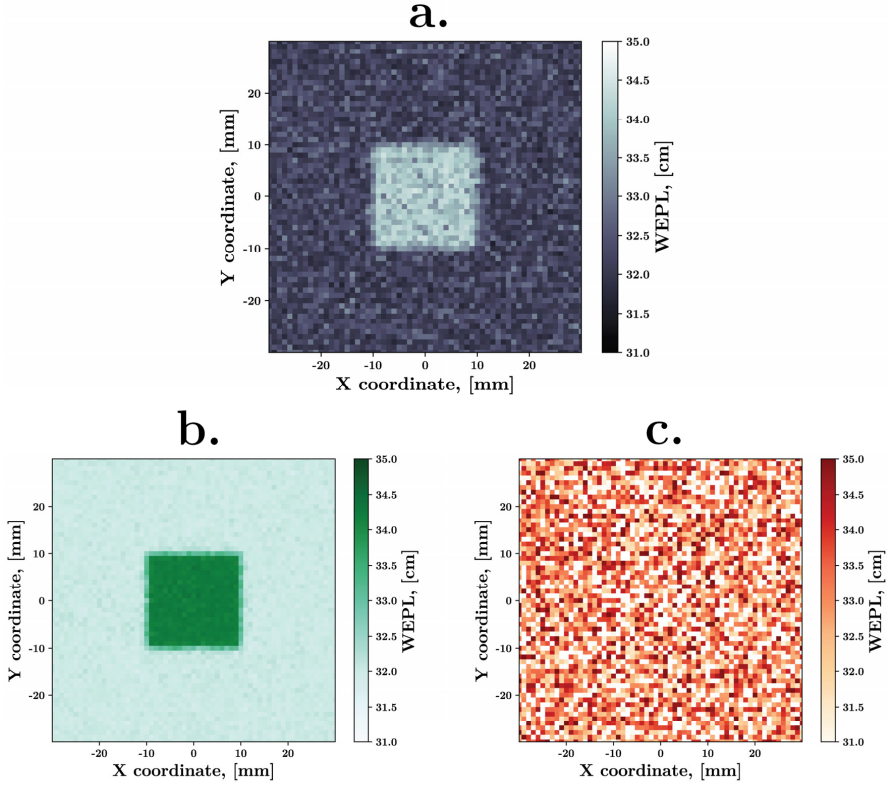


Figure 10.9. Reconstructed radiographic images of high contrast phantom in 32 cm test object for helium-deuteron mixed beams with initial deuteron energy of 215.2 MeV/u and fluence ratio 1:100

Radiographic images reconstructed with pixel size of 1 mm, PIB at test object mid-plane, central 60×60 mm ROI illustrated. Initial data for image reconstruction consisted of down-sampled 10^6 deuteron data mixed with up-sampled 10^8 helium-4 ion data. Helium-deuteron energy pairs as defined in Table 10.1, only deuteron energy levels given.

Subfigure(a): Radiographic image reconstructed based on all mixed-beam particles at test object exit surface retained after data filtering.

Subfigure(b): Radiographic image reconstructed based on only deuteron imaging beam generated particles at test object exit surface retained after data filtering.

Subfigure(c): Radiographic image reconstructed based on only helium-4 treatment beam generated particles at test object exit surface retained after data filtering.

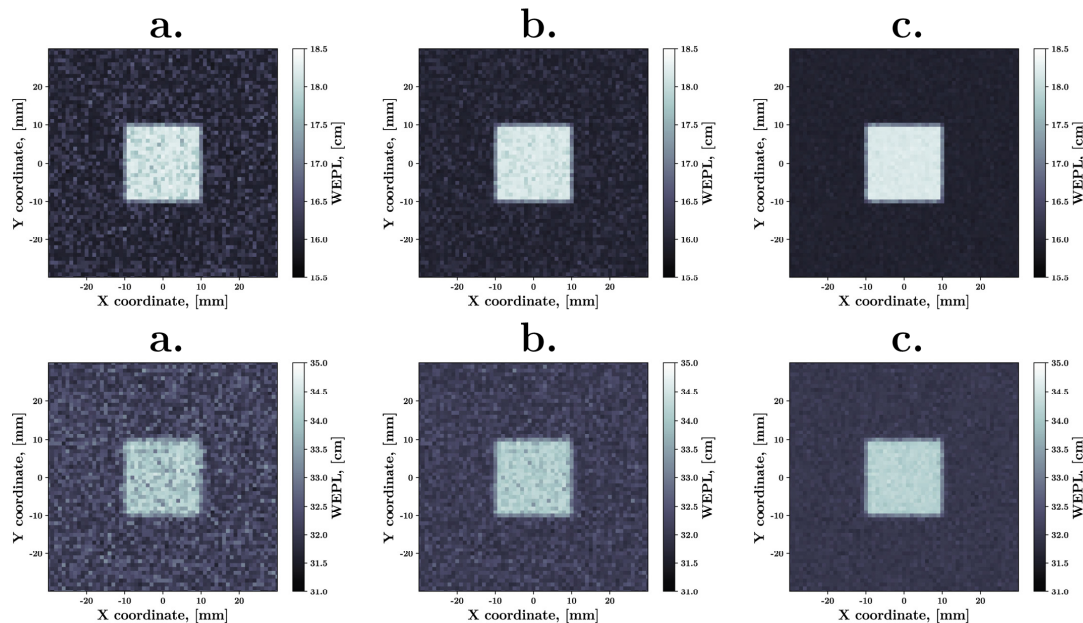


Figure 10.10. Reconstructed radiographic images of high contrast phantom in 16 cm test object for helium-deuteron mixed beams with initial deuteron energy of 144.0 MeV/u and varying fluence ratio of 1:100 (a), 1:50 (b) and 1:10 (c)

Upper line: 16 cm test object with initial deuteron energy of 144.0 MeV/u, lower line: 32 cm test object with initial deuteron energy of 215.2 MeV/u. Radiographic images reconstructed with pixel size of 1 mm, PIB at test object mid-plane, central 60×60 mm ROI illustrated. Radiographic image reconstructed based on all mixed-beam particles at test object exit surface retained after data filtering. Helium-deuteron energy pairs as defined in Table 10.1, only deuteron energy levels given.

Subfigures(a): Ratio of 1:100: down-sampled 10^6 initial deuteron data were mixed with up-sampled 10^8 initial helium-4 ion data.

Subfigures(b): Ratio of 1:50: down-sampled 10^6 initial deuteron data were mixed with up-sampled $5 * 10^7$ initial helium-4 ion data.

Subfigures(c): Ratio of 1:10: down-sampled 10^6 initial deuteron data were mixed with up-sampled 10^7 initial helium-4 ion data.

2D imaging: Quantitative evaluation of radiographic image quality with mixed helium-deuteron beams. Impact of fluence ratio. Comparison with pure deuteron beams

Reconstructed 2D He-D-Rad were assessed quantitatively, extracting main image quality metrics. Spatial resolution was evaluated, extracting spatial frequencies corresponding to 10% of MTF. Figure 10.11 presents spatial resolution in all investigated mixed He-D beam scenarios - varying energy and test object size. Data are presented for 1:100 fluence ratio, comparing to values acquired just from deuteron contribution.

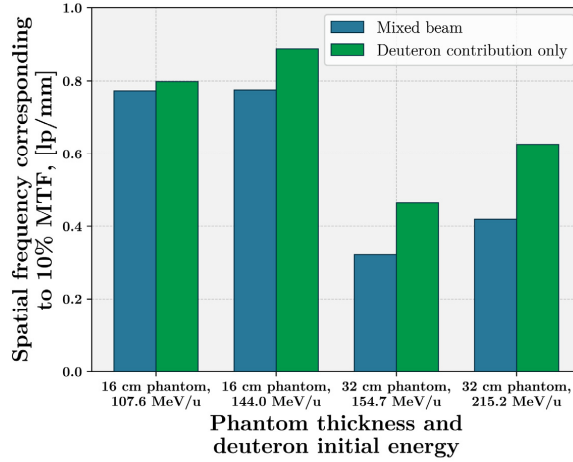


Figure 10.11. Spatial resolution in high contrast phantom radiographic images of helium-deuteron mixed beams with fluence ratio 1:100 for different initial deuteron energies and simulated test object thickness

Spatial resolution defined as spatial frequency corresponding to 10% MTF in reconstructed high contrast phantom radiographic images (pixel size of 1 mm, PIB at test object mid-plane). Images reconstructed based on down-sampled 10^6 initial deuteron data mixed with up-sampled 10^8 initial helium-4 ion data.

Spatial frequency evaluated for images reconstructed based on all mixed-beam particles and only deuteron imaging beam generated particles (at test object exit surface retained after data filtering).

Helium-deuteron energy pairs as defined in Table 10.1, only deuteron energy levels given.

Similarly to p-Rad and He-Rad results presented in Chapter 9., distinguishable spatial frequencies at 10% MTF increase with increasing particle energy and decrease for larger test object size - associated with MCS. In 16 cm test object, 0.772 lp/mm at 10% MTF can be resolved for 106.7 MeV/u deuterons in He-D beam, with negligible increase to 0.775 lp/mm for 144.0 MeV/u He-D beam. Resolvable spatial frequencies decreased by about 2 times in 32 cm test object, with respect to 16 cm scenario: 0.322 lp/mm and 0.419 lp/mm for 154.7 and 215.2 MeV/u deuteron energies in He-D beam, respectively.

Resolvable spatial frequencies were also evaluated for images reconstructed based only on the imaging deuteron contribution. “Idealized He-D-Rad images” had improved spatial resolution, with resolvable spatial frequency increased by 3.3% and 14.5% in 16 cm test object for deuteron energies 106.7 MeV/u and 144.0 MeV/u in He-D beam, respectively. Increase was even higher for 32 cm test object - 44.2% and 49.6% for 154.7 and 215.2 MeV/u in He-D beam, respectively. Noise introduced by secondary deuterons from treatment beam of helium-4 at low fluence ratios (such as 1:100) deteriorates spatial resolution. By increasing fluence ratio to 1:10, spatial resolution comparable to pure d-Rad could be achieved.

As second image quality metric, CNR was evaluated. Figure 10.12 presents CNR in all investigated He-D-Rad scenarios - varying energy and test object size. As discussed before, fluence mixing ratio has significant impact on image noise. Therefore, CNR dependency on fluence ratio (1:100, 1:50 and 1:10) was also evaluated in Figure 10.12, with comparison also including values acquired from only imaging deuteron contribution.

Similar trends of CNR in He-D-Rad can be observed with respect to p-Rad, He3-Rad and He4-Rad presented in Chapter 9. - CNR decreases with increasing particle energy and increasing test object size. This is attributable to higher noise - higher WEPL sensitivity to energy straggling and decreased number of particles retained for image reconstruction (see **Appendix 9.12**) at higher energies.

At fluence ratio of 1:100, low CNR values were observed. For 16 cm test object, CNR of 7.31 and 7.55 was achieved for low and high energy pairs of He-D beam, respectively, while in 32 cm test object CNR was even lower - 4.04 and 4.13, respectively. Values are significantly lower compared to CNR achievable in idealized images with only imaging beam deuteron contribution - 72.43 and 54.63 in 16 cm test object and 31.11 and 23.99 in 32 cm test object - an increase of about 6-10 times.

Image noise is decreased with increasing fluence ratio - a trend which can clearly be observed for CNR values illustrated Figure 10.12. With respect to 1:100 fluence ratio, CNR increase of 1.8 - 1.9 times was observed for 1:50 ratio, while for 1:10 ratio - 4.9 - 6.6 times. Increased CNR at 1:10 is from 61.9% to 92.9% of value achievable with just imaging beam deuteron contribution. Thus, increasing the fluence mixing ratio to 1:10 would significantly improve CNR with values comparable to pure d-Rad.

For direct quantitative comparison with the results presented in Chapter 9., pure d-Rad images were evaluated as p-Rad, He3-Rad and He4-Rad. Results and comparison Additional data are given in **Appendix 9.15**. For comparable energies (with respect to range in water), pure d-Rad provides increased spatial resolution compared to p-Rad due to slightly reduced MCS. In context of CNR, pure d-Rad could have improved performance over p-Rad and both He-Rad approaches.

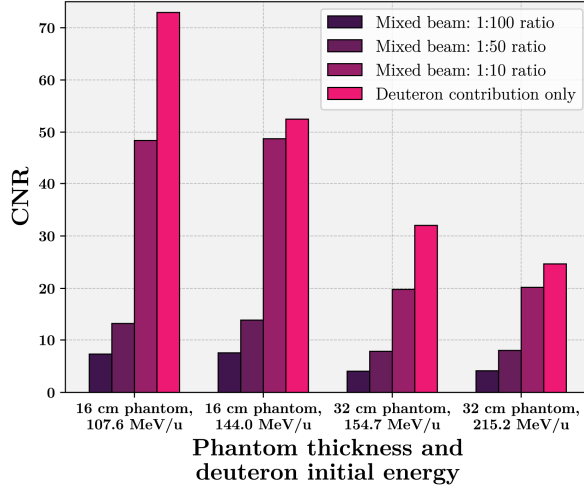


Figure 10.12. CNR in high contrast phantom radiographic images of helium-deuteron mixed beams with varying fluence ratio for different initial deuteron energies and simulated test object thickness

CNR calculated based on reconstructed high contrast phantom radiographic images (pixel size of 1 mm, PIB at test object mid-plane). Images reconstructed based on down-sampled 10^6 initial deuteron data mixed with up-sampled 10^8 initial helium-4 ion data. Only standard deviation of WEPL values within the ROI were used in the calculation, not accounting for intrinsic pixel-level standard deviation. Data given for:

*Ratio 1:100: down-sampled 10^6 deuteron data mixed with up-sampled 10^8 helium-4 ion data.

*Ratio 1:50: down-sampled 10^6 deuteron data mixed with up-sampled 5×10^7 helium-4 ion data.

*Ratio 1:10: down-sampled 10^6 deuteron data mixed with up-sampled 10^7 helium-4 ion data.

*At ratio 1:100, using only deuteron imaging beam generated particles at test object exit surface retained after data filtering for image reconstruction

While relative contribution of deuterons to physical dose in mixed He-D beam was already discussed, data on absolute values for 10^7 initial deuterons are given in Table 10.2. Compared to p-Rad and both He-Rad approaches, an increase of about 1.5 - 2 times can be observed with respect to protons for same number of primaries, while decrease of about 2 -3 times with respect to helium-3 and helium-4 ions, all associated with changes of energy deposition level per particle.

Imaging noise dependency on fluence mixing ratio in He-D-Rad was also evaluated by 1σ WEPL uncertainties - intrinsic and extrinsic. Results are presented in **Appendix 9.16**. Data clearly indicate that increasing fluence ratio from 1:100 to 1:10 significantly reduces relative WEPL value uncertainties - from 2.0-3.4% to 1.4-1.7% intrinsically and 0.8-1.2% to $\sim 0.2\%$ within homogeneous ROI. Relative WEPL value uncertainties at fluence ratio of 1:10 are also comparable to pure deuteron contribution.

Table 10.2.

Calculated imaging dose of pure deuteron radiography scenarios for 16 and 32 cm test objects with embedded high contrast phantom

Initial deuteron energy*	Calculated imaging dose**	
	for 16 cm test object	for 32 cm test object
107.6 MeV/u	0.147 mGy $\pm$ 0.04%	-
144.0 MeV/u	0.109 mGy $\pm$ 0.04%	-
154.7 MeV/u	-	0.107 mGy $\pm$ 0.04%
215.2 MeV/u	-	0.082 mGy $\pm$ 0.04%

* Deuteron initial energies of 107.6 MeV/u and 144.0 MeV/u correspond to 16 cm test object, while 154.7 MeV/u and 215.2 MeV/u - 32 cm test object.

** Imaging dose calculated as total energy deposition within irradiated volume - 10×10×16 or 10×10×32 cm for 16 and 32 cm test objects. Data given for 10⁷ initial particles.

2D Imaging: Accuracy of reconstructed WEPL values. Impact of RSP energy dependency

As last image quality metric, accuracy and uncertainty of reconstructed WEPL values was assessed. Compared to Chapter 9, no low contrast resolution phantom setup was simulated, with evaluation performed for the two regions in high contrast phantom. Results on WEPL value accuracy assessment for He-D-Rad images with varying fluence ratio, as well as pure deuterons beams, are summarized in **Appendices 9.17 and 9.18**.

Overall, WEPL value deviations and uncertainties are higher for lower fluence ratio (1:100) (see **Appendix 9.18**). For lowest investigated fluence ratio of 1:100, average WEPL value deviation (with respect to theoretically expected) of 2.2 mm (range 1.1 to 3.2 mm) was observed, with 1 σ uncertainties in the range of 1.6-3.2 mm. Average WEPL value deviation and uncertainties were reduced to 1.2 mm (range 0.4 to 2.1 mm) and 0.9-2.1 mm, respectively, for ratio 1:50. For ratio 1:10 best performance was observed for WEPL value deviation and uncertainties: 0.7 mm (range 0.3 to 1.5 mm) and 0.2-1.1 mm, respectively. WEPL value accuracy and uncertainty of He-D-Rad with fluence ratio of 1:10 is comparable to pure deuteron contribution. This aspect again underscores the rationale of using higher fluence ratio of 1:10, if a 2D He-D-Rad approach is to be used for patient position monitoring. Additionally, WEPL value accuracy was assessed for pure d-Rad scenario with reconstructed WEPL values summarized in **Appendix 9.17**.

Finally, as in Chapter 9., systematic WEPL value uncertainty due to energy dependency of RSP is evaluated for biologically relevant materials - **Appendix 9.19**. While slight variation is observed, in He-D mixed beam, helium-4 ions for treatment would be at approximately the same energy per nucleon as deuterons for imaging. Thus,

RSP deviation between imaging and treatment contributions is diminished and only deviation for treatment beam energy with respect to nominal needs to be considered.

2D imaging: Possible alternative approaches for imaging and treatment beam generated deuteron discrimination

As discussed throughout the results on 2D imaging with He-D-Rad, use of lower fluence ratios as 1:10 has inherent drawback of not being able to fully discriminate between imaging beam primary deuterons and treatment beam generated secondary deuterons with the currently developed data filtering approach. This drawback can be offset by increasing deuteron contribution in the He-D beam, though alternative approaches would be favourable to limit the contribution of imaging beam to treatment dose distribution. Some alternative approaches are proposed for further discrimination capability improvement at low fluence ratio He-D beams as a possible future research avenue.

Similarly to relative angle differences between deuterons of imaging beam and treatment beam, differences could be expected between the two for time-of-registration - time between primary particle entering the imaged test object and registration of particle exiting the object. Initial results on time-of-registration-based filtering as another approach for discrimination are summarized in **Appendix 9.20**. For such approach, high temporal resolution of detector would be necessary, possibly beyond the typical 100 ps capabilities. Temporal cuts alone are not a sufficient method, though including it as additional parameter in data filtering could improve deuteron discrimination capabilities for low fluence ratio He-D-Rad. Future research on this topic is necessary to assess the sequence of data filters or, possibly, introduction of machine learning based approaches.

10.3. Conclusions and discussion

Chapter 10 presented MC simulation-based investigation on a novel approach for patient position monitoring during helium-4 IBT delivery - mixed He-D beams. As for the same energy per nucleon, deuteron range is about twice that of helium-4 ions, deuteron Bragg peak could be detected outside of the patient for position monitoring purposes in certain anatomies. Proposed approach is similar to carbon-helium mixing for carbon-12 IBT.

MC simulation campaign on mixed He-D evaluated two possible approaches for use - range measurement and 2D imaging via He-D-Rad. All results were reported for two test object sizes of 16 and 32 cm, corresponding to imaging scenarios of anatomies like head and pelvis, respectively. Two energy levels were investigated for each test object size, with Bragg peak positions near the centre of the object and near the exit surface.

In context of range measurement, influence of fluence mixing ratio was evaluated with respect to achievable range sensitivity and in treated volume - contribution to physical dose distribution, RBE value and biologically effective dose distribution. Fluence ratios of 1:500, 1:100, 1:75, 1:50, 1:25 and 1:10 were evaluated.

In context of 2D imaging via He-D-Rad, achievable image quality was assessed with respect to fluence ratio. Additional data filtering approach was developed by the Author to increase the discrimination between primary imaging beam deuterons and deuteron contribution as secondary fragments from the helium-4 treatment beam. Image quality metrics as spatial resolution, CNR, imaging dose, WEPL value uncertainty and accuracy, secondary particle rejection rates, and impact of RSP energy dependency were evaluated.

Main conclusions from the presented results can be summarized as:

1. A novel approach for patient position monitoring during helium-4 ion treatment is proposed, using mixed He-D beams.
2. Deuteron imaging beam contribution to physical dose distribution increases from $\sim 0.06 - 0.07\%$ at fluence ratio 1:100 to $\sim 0.7\%$ at fluence ratio 1:10.
3. Deuteron imaging beam contribution reduces peak RBE value in the irradiated volume with respect to pure helium-4 ion. The reduction is increased for higher fluence ratio, with peak RBE differences of 0.012 and 0.059 in simulated scenario for ratios 1:100 and 1:10, respectively. Reduction of RBE is offset by increase in physical dose, resulting in minimal variation of biologically effective dose values.
4. For idealized range measurement setup, fluence ratio of 1:100 provides sensitivity in total energy deposition profile change for measurement of ± 1 mm range shifts.
5. Range sensitivity with fluence ratio of 1:100 is sufficient to detect range shifts caused by inhomogeneities with lateral extent higher than 25% with respect to irradiation field size.
6. For 2D imaging via He-D-Rad, a novel data filtering approach has been developed. Use of double Gaussian function for relative angle filter can improve discrimination between primary deuterons from imaging beam and deuteron contribution from treatment beam secondary fragments with respect to conventional data filters.
7. For 2D imaging via He-D-Rad, fluence ratio of 1:10 is better suited with respect to 1:100, due to increased reconstructed image quality by reduction of retained secondary deuterons from treatment beam.
8. Increasing fluence ratio from 1:100 to 1:10 results in increased spatial resolution (by ~ 0.2 lp/mm), CNR (by ~ 5 times) and WEPL value accuracy (reduced uncertainty ~ 4 times) in reconstructed 2D He-D-Rad image. At fluence ratio of 1:10, mixed helium-deuteron beams have comparable image quality with pure deuteron beams.
9. For comparable energy levels with p-Rad, He3-Rad and He4-Rad, d-Rad provides slightly increased spatial resolution and CNR in comparison to protons.

Limitations of the performed research. Additional notes and implications of the work.

Considering the methodology and results presented in this Chapter, following limitations and additional implications of the performed study were identified:

- as presented study focused on initial developments of mixed He-D beam usage for range shift monitoring and 2D imaging via He-D-Rad, and general physical

assessment of these imaging methods, an idealized setup was considered with no specific detector setup and associated limitations. With idealized single particle positional and angular data registration assumed, as well as particle energy registration without any resolution limitations, similar considerations on the impact of detection system as discussed in Chapter 9 should be evaluated for technological feasibility assessment.

- another possible limitation from the perspective of detection system for He-D-Ras is the beam intensity. As the helium contribution of the mixed beam needs to be delivered at sufficient DR for treatment, the resulting outgoing beam (deuteron contribution and secondary fragments) intensity should be evaluated. If single particle tracking approach is considered for He-D-Rad, outgoing beam intensity should be on the order of $10^6 - 10^7$ particles per second corresponding to detection system limitations. Due to this, possible reduction of treatment beam DR might be necessary, or the use of either range measurement or integrating He-D-Rad should be considered.
- with the focus on initial development of these i-Rad approaches and general physical assessment, uniform field delivery was considered. In actual implementation scenario, delivery would be realized via PBS, thus further studies should focus on the influence and optimization of spot size, spot spacing and delivery sequence suitable for He-D-Rad.
- as the study was based on MC-simulations, accuracy of nuclear interaction modelling as relevant for i-Rad has limitations. Thus, in terms of secondary particle rejection, filtering via $\Delta E-E$ approach and filtering of nuclear fragment by relative scattering angle, uncertainties and deviations with respect to measurement data could be expected, prompting necessity for future experimental campaign. Accuracy of used physics model within Geant4 has been outlined in Chapter 4, corresponding Appendix and references benchmarking studies.
- with the focus on initial development of these i-Rad approaches and general physical assessment, simple and standardized phantom geometries were used for quantitative evaluation of range sensitivity and image quality. As in a clinical setup, complex anatomies with large spatial WEPL variations and different depths of imaged object features can be expected, additional work should focus on quantitative image quality evaluation in such complex scenarios with He-D-Rad. In case of range sensitivity assessment, capabilities of clinically relevant range shift detection should be evaluated.
- with the focus on initial development of these i-Rad approaches and general physical assessment, no specific methods from accelerator physics perspective were assessed for mixed beam delivery. As outlined in Chapter 8 and corresponding Appendix, several different approaches can be considered for both injection and extraction of mixed ion beam. Each of these approaches would have a clear effect on phase space parameters and output beam intensity variation, which would in turn affect either range sensitivity or achievable He-D-Rad image quality. It should also be noted that

technological feasibility of mixed He-D beam acceleration itself was not considered in this study. Beam dynamics studies and possible technological adaptations should be evaluated for mixed He-D beam acceleration as first crucial step to assess the feasibility of this method. As the charge-to-mass ratio difference between deuterons and helium-4 ions is slightly compared to more actively researched approach of helium and carbon ion mixing, evaluation from accelerator physics perspective is critical.

- with the focus on initial development of these i-Rad approaches and general physical assessment, challenges associated with acceleration of deuterons were not evaluated. As significant fractions of deuterons undergo nuclear fragmentation, resulting neutron contribution should be evaluated from radiation protection perspective. Nevertheless, the decreased mixing ratio of 1:100 compared to helium-carbon mixing should be taken into account as possibility to mitigate radiation safety risks.
- one of the drawbacks of the proposed mixed beam approach is impact of geometrical or WEPL changes beyond the Bragg peak on the registered signal. As such changes would not have as significant effect on the treatment range and delivered dose distribution, approaches to differentiate depth of occurrence for the geometrical or WEPL change should be studied further. As introduced in Chapter 9, one such approach could be the use of either LV-FS or ED-FS, which would enable the possibility to assess the depth, where change has occurred.
- as indicated in the Results section, for 2D imaging via He-D-Rad, the mixing ratio of He-D beam should be increased to maintain adequate image quality. To use lower mixing ratio, additional data filtering routines should be developed and studied to more accurately distinguish deuteron contribution from secondary fragments of helium contribution. One such approach could be the addition of temporal information of particle ToF, though temporal resolution limitations of detection systems need to be considered. Alternatively, machine learning based solutions could also be implemented to improve the data filtering routines.
- while data filtering workflow developed in this study was assessed for He-D-Rad, it can also be applied in the research on carbon-helium mixing to improve reconstructed 2D image quality.

Future research outlooks

Considering the methodology, results and study limitations presented in this Chapter, following pathways for future additional research were identified:

- MC-based simulation study focusing on implementation of realistic detector technological constraints for range measurement setup and He-D-Rad;
- experimental campaign, focusing on validation of presented results and evaluation of detection system technological limitations for either range measurement setup or He-D-Rad;
- MC-based simulation study focusing on quantitative image quality evaluation within anatomically relevant geometry, while also simulating WEPL or geometrical shifts

and evaluating detection accuracy with either range measurement setup or He-D-Rad;

- studies accelerator physics perspective aspects on mixed He-D beam delivery – injection, acceleration and extraction;
- study on detection system impact on beam intensity limitations for He-D-Rad and quantitative comparison between single particle tracking and integrating approaches.

10.3.1 Considerations for technological implementation

While the results presented in this Chapter mainly focused on the overall physical feasibility of novel imaging method with He-D, following key considerations were identified for technological implementation of this approach, especially in context of HeLICS system:

- feasibility of whole He-D beam delivery chain – injection, acceleration and slow extraction – should be evaluated with beam dynamics studies. Chapter 8 and corresponding Appendix briefly presents aspects on injection, acceleration and slow extraction of mixed carbon-helium beams, which could be applied for He-D beams. Special focus should be given on evaluating the feasibility of mixed He-D beam acceleration due to slightly higher charge-to-mass ratio of the two beam contributions compared to carbon-helium beams.
- radiation protection considerations should be assessed for the use of high energy deuteron beams necessary for mixed He-D beams, focusing on the additional neutron contribution.
- adequate control and monitoring system should be developed to continuously maintain a constant mixing ratio within the He-D beam, as mixing ratio variations would affect either range sensitivity in range measurement setup or reconstructed image quality in He-D-Rad imaging setup.
- necessary beam intensity limitations should be assessed in the context of feasible readout rate of modern detection systems, if single particle tracking He-D-Rad is considered.

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Helium ion range verification with positron emission tomography

As discussed in Chapters 8, 9 and 10, i-Rad can provide information about changes in patient position or anatomy. To evaluate effects of other uncertainty sources, range verification for Bragg peak localisation can be considered, enabling possibility to assess dose distribution delivered to the patient. Via MC simulations, Chapter 11 investigates *in vivo* range verification using PET - registering e^+e^- annihilation event distribution from β^+ emitter decay. This Chapter identifies nuclear interactions and e^+e^- annihilation event spatial and temporal patterns that are unique to helium-4 ion beams, also assessing correlation between these patterns and spatial dose distribution.

Section 11.1 outlines simulation and data analysis methods used: simulation geometry, scoring of β^+ emitting nuclei and modelling of resulting of e^+e^- annihilation event distribution. A semi-analytical approach developed to incorporate positron range effects is also presented. Approach used for calculation of temporal evolution of e^+e^- annihilation event distribution is given. Methods evaluation of spatial correlation and statistical uncertainty assessment are also discussed.

Section 11.2 presents the findings on spatial e^+e^- annihilation event distribution induced by helium-4 ion beams and its correlation with dose distribution. Temporal evolution is assessed, indicating applicability for in-beam, in-room, and off-line PET registration approaches. With patterns unique to helium-4 ion beams identified, underlying nuclear interaction data are provided. Influence of irradiated material composition is also evaluated. Concluding remarks and discussion on study findings are given in Section 11.3.

Contributions of the Author: All work presented in this Chapter has been performed solely by the Author, indicating used literature sources where applicable.

Approbation of the results presented in this Chapter:

- Oral presentation 5th CERN Baltic Conference (CBC'25) in Kaunas, Lithuania, 2025
K.Paľskis, I.Baumgart, A.Viņķe, T.Torims, M.Vretenar, J.Seco, M.Sapinski “Towards the last millimeters in helium ion therapy: developing dedicated range verification methods”
- Oral presentation at 2nd CERN Baltic conference (CBC'22) in Vilnius, Lithuania, 2022
K.Paľskis, T.Torims, M.Vretenar, J.Seco, M.Sapinski “Physical and biological property comparisons of ^4He and ^3He ion beams for applicability in radiation therapy” - initial results and methodology aspects presented

- Peer-reviewed and accepted, not presented, abstract at *61st Annual Conference of the Particle Therapy Cooperative Group* (PTCOG'23) in Madrid, Spain, 2023
K.Paľskis, T.Torims, M.Vretenar, M.Sapinski, J.Seco, “*Helium-3 and helium-4 ion beam comparison for radiation therapy - achievable signal for treatment range verification*” - initial results and methodology aspects presented
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11.1. Modelling and analysis methodology

This Section provides brief summary of the modelling and analysis methodology used within the study, while additional methodological details are given in Appendix 10.1.

Helium-4 ion beams (115.2, 171.4 and 217.0 MeV/u - range in water of 10, 20 and 30 cm) were simulated as PB impinging on a $\emptyset 30$ cm $\times$ 40 cm cylinder. End of track positions for each relevant β^+ emitting isotope were scored in depth-direction (integrating laterally), calculating production yields P_{β^+} by normalizing per initial particle. IDD's of absorbed dose were also scored for correlation assessment.

A semi-analytical approach to account for positron range effects was developed to decrease statistical uncertainty compared to direct scoring of e^+e^- annihilation event vertexes. Based on the unique positron energy spectrum of each isotope, annihilation point spread functions $aPSF_{sin}$ were calculated in 1-dimension. Results of the approach were validated for β^+ emitters relevant for PET imaging [95], indicating excellent agreement.

From production yields P_{β^+} and β^+ emitter physical characteristics, temporal evolution of β^+ decay spatial distribution was modelled. Following [96], 10 pulses of 10 ms were simulated with 90 ms pause, delivering 10^9 ions (see Table 11.1). β^+ decay was evaluated for both short timescales (integration in beam pause after 1st, 5th and 10th pulse) and long timescales (varying length time windows from 100 ms to 3 hours after irradiation). e^+e^- annihilation event distribution $AE(z, t)$ was calculated as convolution of decayed nuclei $N_{\beta_{decayj}^+}(z, t)$ spatial distribution and annihilation point spread function $aPSF_{sinj}(r)$ of each considered isotope j :

$$AE(z, t) = \sum_{j=iso1}^{iso_{last}} N_{\beta_{decayj}^+}(z, t) \otimes aPSF_{sinj}(r) \quad (11.1)$$

Simulations were performed for different materials - water, soft tissue, adipose tissue and cortical bone - to assess the impact of chemical composition.

Correlation between induced e^+e^- annihilation event distribution and depth dose profile was assessed, by extracting relevant spatial parameters (depth of maximum, 80% and 50% intensity fall-off). Absolute differences between the metrics were calculated, assessing also linear regression between the two. e^+e^- annihilation event distribution range sensitivity and impact of beam intensity was also mathematically evaluated. No specific hardware limitations or imaging artefacts were considered.

Relevant nuclear interaction cross-section data were extracted for validation from *TENDL-2023* and *EXFOR* databases.

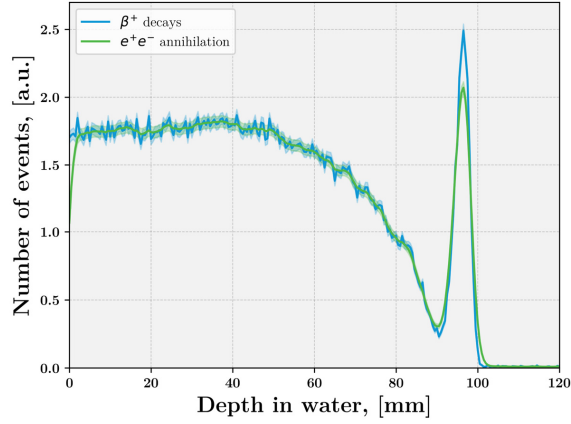


Figure 11.1. Example of spatial distribution of β^+ decays and corresponding e^+e^- annihilation event distribution

Example data are given for ^{13}N nuclei generated by 115.3 MeV/u helium-4 ion beam impinging on water. Solid line corresponds to the mean value, while the shaded bands correspond to $\pm 1\sigma$ uncertainties.

Table 11.1.

Temporal beam characteristics used for simulation of positron emitter decays

	Value of the parameter
Beam current per pulse $I_{0_{pulse}}$	10^{10} ions/s (3.20 nA)*
Average beam current $I_{0_{average}}$	$1.1 \cdot 10^9$ ions/s (0.35 nA)*
Length of irradiation pulse τ_{pulse}	10 ms
Length of pause between pulses τ_{pause}	90 ms
Number of beam pulses for whole delivery m	10 pulses
Total length of irradiation T_{irrad}	910 ms
Total number of primary ions delivered N_0	10^9 ions

* Current calculated for fully stripped helium ions ($z = +2$)

11.2. Results of the modelling

Temporal evolution of β^+ decays: Millisecond timescale

Patterns of helium-4 ion beam induced e^+e^- annihilation event spatial distribution and temporal evolution in this study are evaluated in the context of the various PET-based verification approaches presented in Chapter 8 - in-beam, detecting radioisotopes with millisecond and second half-lives, and in-room and off-line, detecting radioisotopes with half-lives up to several minutes. First two subsections of the Results

focus on temporal evolution of β^+ decays, while the next two - on e^+e^- annihilation event spatial distribution with respect to absorbed dose distribution.

β^+ decay temporal evolution is first presented over short timescale - in-between the beam pulses. Figure 11.2 presents the evolution β^+ decays during the beam pauses after irradiation of water. Data on and soft tissue, adipose tissue and cortical bone are given in **Appendix 10.2**. Water is considered as a reference, while soft tissue and adipose tissue depict oxygen-rich and carbon-rich tissue, respectively. Data are given after first, fifth and last - tenth - beam pulse for lowest considered helium-4 ion energy of 115.3 MeV/u. Sum of β^+ decays is evaluated, identifying also individual isotopic contributions.

Similar trends can be observed in all materials - Figure 11.2 and **Appendix 10.2**. Main isotopic contributions in the millisecond-timescale β^+ decay signal are nitrogen-12 ($T_{1/2}$ of 11 ms) and oxygen-13 ($T_{1/2}$ of 8.58 ms). After first beam pulse, β^+ decay signal is mainly composed of millisecond half-life isotopes, while after 5th and 10th beam pulse - contribution of longer-lived isotopes as oxygen-15 and boron-8 increases.

In water (Figure 11.2), main contribution to β^+ decay comes from nitrogen-12, with notable contribution also from oxygen-13. Oxygen-13 decays to negligible level in first 30 ms after the irradiation pulse, while nitrogen-12 - in first 70 ms. Relative contribution of oxygen-13 to β^+ decay is 11%, 7% and 5% after 1st, 5th and 10th radiation pulse, respectively, while of nitrogen-12 - 73%, 47% and 35%, respectively. With increased background of long-lived isotopes, total number of decays during the beam pause increases 1.5 and 2.1 times after 5th and 10th irradiation pulse, respectively, in comparison with pause after the 1st pulse.

In soft tissue (Figure A.10.4. of **Appendix 10.2**), nitrogen-12 remains the main contribution, with oxygen-13 contribution slightly lower than in water. Oxygen-13 contribution decays to negligible level in first 25 ms after the irradiation pulse, with the nitrogen-12 temporal characteristics same as in water. Relative contribution of oxygen-13 to overall β^+ decay signal is 5%, 4% and 3% after 1st, 5th and 10th irradiation pulse, respectively, while of nitrogen-12 - 84%, 65% and 53%, respectively. With respect to water, total number of β^+ decays is 1.3 - 1.8 times higher.

In adipose tissue (Figure A.10.5. of **Appendix 10.2**), the oxygen-13 contribution is negligible, due to higher fraction of carbon nuclei in material, with nitrogen-12 contribution accounting for majority of decays. Relative contribution of nitrogen-12 to overall β^+ decay signal is 90%, 74% and 65% after 1st, 5th and 10th radiation pulse, respectively. With respect to water, total number of β^+ decays is 1.6 - 2.5 times higher.

Data on cortical bone (Figure A.10.6. of **Appendix 10.2**), indicate significant differences, due to presence of heavier nuclei. While small contribution of the oxygen-13 and significant contribution of nitrogen-12 can be observed, high contribution comes from the background of longer-lived isotopes. Relative contribution of oxygen-13 to overall β^+ decay signal is 3%, 1% and 1% after 1st, 5th and 10th radiation pulse, respectively, while

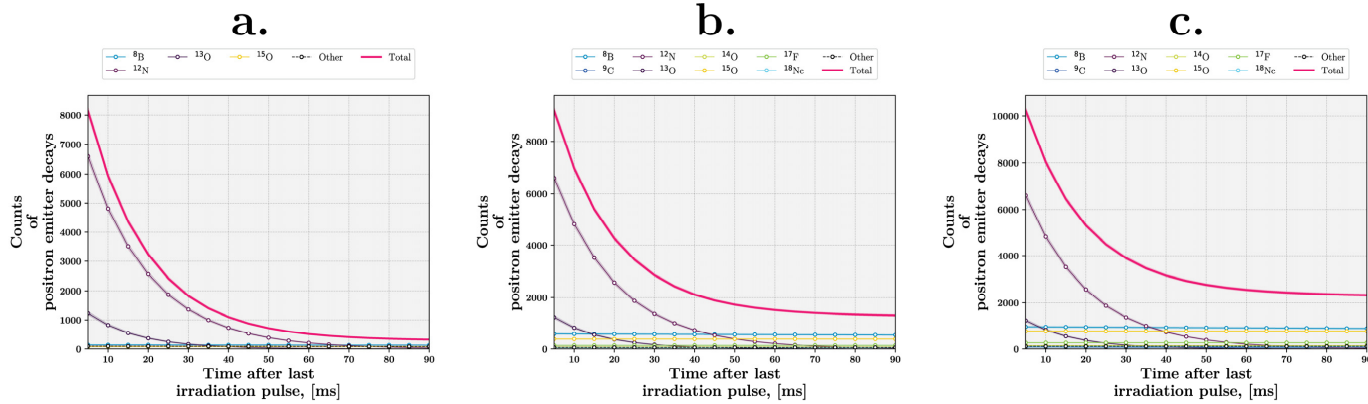


Figure 11.2. Temporal evolution and isotopic separation of β^+ decay counts from irradiated water phantom in 90 ms after 1st (a), 5th (b), and 10th (c) pulse

Data illustrated with 5 ms resolution, corresponding to markers of isotopic contributions. Total β^+ decay counts indicated with pink line, while also indicating most prevalent isotopic contributions in each Subfigure with the sum of other contributing β^+ emitting isotopes indicated as “Other”. 1σ uncertainty of β^+ decay counts indicated for each line as respective shaded region. Note the change of legend and y-axis scale for each Subfigure.

Data given for 115.3 MeV/u helium-4 ion beam (range in water of 100 mm)

of nitrogen-12 - 41%, 15% and 10%, respectively. With respect to water, total number of β^+ decays is 3.1 - 6.2 times higher.

Summarizing the findings, millisecond-timescale β^+ decay is dominated by nitrogen-12, especially in carbon-rich materials such as adipose tissue, though non-negligible contribution also arises from oxygen-13 in oxygen-rich soft tissue. In case of cortical bone, the β^+ decay is dominated by background arising from partial decay of long-lived nuclei. The intensity of β^+ decays registered after each beam pulse is higher due to increasing contribution of long-lived isotope decays - effect of which is evaluated further for spatial distribution of e^+e^- annihilation events. Comparison of presented data with respect to other IBT modalities - protons and carbon-12 ions is of relevance. Therefore, helium-4 ion induced production yield of the main contributions - nitrogen-12 and oxygen-13 - is provided in later subsections.

Temporal evolution of β^+ decays: Second and minute timescale

Significantly more complex β^+ decay temporal evolution patterns can be expected - larger number of different isotopic contributions - for integration time windows after delivery of all beam pulses. Figure 11.3 presents the evolution β^+ decays after delivery of all beam pulses in water. Data for soft tissue, adipose tissue and cortical bone are given in **Appendix 10.3**. Data are given for lowest considered helium-4 ion energy of 115.3 MeV/u. Sum of β^+ decays is evaluated, identifying also individual isotopic contributions.

More in-depth analysis on isotopic contributions is provided afterwards, in context of e^+e^- annihilation event spatial distribution, with data analysis here focusing on main contributions to β^+ decay signal at different time intervals after the irradiation and comparing differences between materials considered.

In case of water, as illustrated in Figure 11.3, main contribution to β^+ decay signal for up to about 800 seconds after irradiation is oxygen-15. Shortly after irradiation up to less than 10 seconds, a significant contribution of boron-8 can also be observed, while up to about 300 seconds after irradiation - fluorine-17 and oxygen-14. Production of fluorine-17 for PET-based verification has not been extensively studied, thus additional focus will be given on the respective contribution to e^+e^- annihilation event spatial distribution in next subsections. Considering longer times after irradiation, main contributions arise from nitrogen-13 and carbon-11. Nitrogen-13 is dominant from about 700 to 2300 seconds after irradiation, with carbon-11 being the dominant afterwards.

The most distinctive characteristic observed in water is the contribution of fluorine-18, also observed in context of early PET verification research [29]. Fluorine-18 as possible contribution to off-line PET verification for helium-4 IBT has not been studied. Fluorine-18 production, as will be discussed later, is unique to helium-4 ion beams compared to other IBT modalities. As fluorine-18 has a relatively long half-life of 109.8 minutes, its contribution is of significance for times higher than ~30 minutes after irradiation and becomes dominant after about 3 hours.

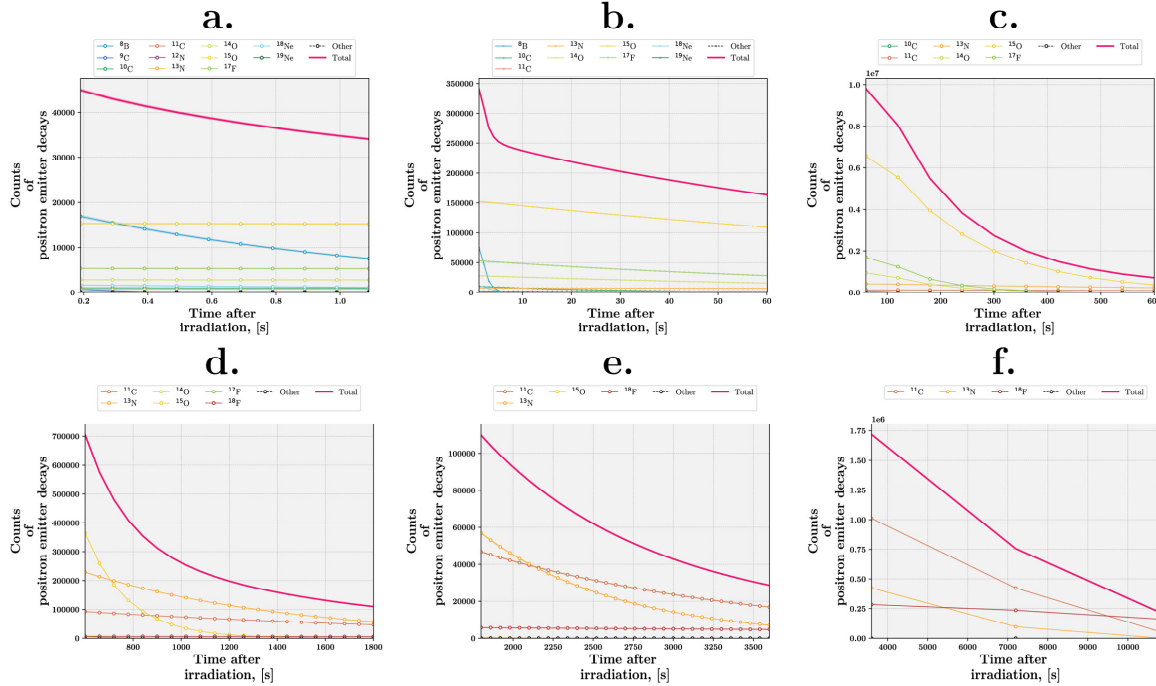


Figure 11.3. Temporal evolution and isotopic separation of β^+ decay counts from water phantom after irradiation

Data illustrated for 115.3 MeV/u helium-4 ion beam (range in water of 100 mm). Total β^+ decay counts indicated with pink line, while also indicating most prevalent isotopic contributions in each Subfigure with the sum of other contributing β^+ emitting isotopes indicated as “Other”. 1σ uncertainty of β^+ decay counts indicated for each line as respective shaded region. Note the change of legend and y-axis scale for each Subfigure.

Data given for following time periods after irradiation: 0.1 to 1 s with 0.1 s resolution (Subfigure (a)), 1 to 60 s with 1 s resolution (Subfigure (b)), 1 to 10 min with 1 min resolution (Subfigure (c)), 10 to 30 min with 1 min resolution (Subfigure (d)), 30 to 60 min with 1 min resolution (Subfigure (e)) and 1 to 3 hours with 1 hour resolution (Subfigure (f)).

For oxygen-rich material as soft tissue, illustrated in Figure A.10.7. of **Appendix 10.3.**, oxygen-15 is the dominant contribution for up to about 600 seconds after irradiation. In shorter timescales, significant contributions of boron-8 (< 10 s) and carbon-10 (< 30 s) can be observed. Similarly to water, up to about 300 seconds after irradiation - fluorine-17 and oxygen-14 can be observed. In contrast to water, when longer times after irradiation are considered, carbon-11 contribution is the dominant from 600 seconds up to 3 hours, with lower contribution of nitrogen-13. At 1 hour after irradiation, contributions of nitrogen-13 and fluorine-18 are similar, though several times lower with respect to carbon-11.

In adipose tissue, illustrated in Figure A.10.8. of **Appendix 10.3.**, higher contributions of carbon-10 and carbon-11 can be observed. Relatively short-lived carbon-10 is the dominant signal contribution to about 20 seconds after irradiation, while carbon-11 - dominant after 300 seconds. Considering longer timescales after irradiation, the contribution of fluorine-18 is almost negligible in adipose tissue compared to water and soft tissue, signifying the role of oxygen concentration for fluorine-18 production.

In addition to previously discussed, several contributions from interactions with heavier nuclei can be observed for cortical bone, illustrated in Figure A.10.9. of **Appendix 10.3.**, such as calcium-39, ground state chlorine-34, scandium-41 and ground state scandium-42, phosphorus-30 and others. Considering long-term timescales of about 30 minutes after irradiation, in addition to fluorine-18, nitrogen-13 and carbon-11, contributions of ground state potassium-38 and metastable chlorine-34 can be observed.

Observed β^+ decay temporal evolution after irradiation illustrates complex dependency on different isotopic contributions, significantly impacting also variation of e^+e^- annihilation event spatial distribution due to differences in underlying nuclear interaction threshold energies and cross-sections, as discussed in later subsections.

In context of long timescales for in-room or off-line PET verification, significantly higher dependency on tissue material was observed in contrast to short timescale in-beam approach, as larger number of isotopes are of relevance with variation of temporal window.

Based on findings in water and soft tissue, one of the key focal points in the presented study is on fluorine-18 as a unique isotope produced in biological tissue after irradiation with helium-4 ion beams. It can be observed that the relative contribution of fluorine-18 in timescales above 30 minutes to overall β^+ decay signal is in competition with nitrogen-13 and carbon-11, depending on the abundance of oxygen nuclei in the biological material. Quantitatively, fluorine-18 contributes to 9%, 3%, 1% and 3% of overall β^+ decay in time interval 30 - 60 minutes after irradiation for water, soft tissue, adipose tissue and cortical bone, respectively, while in time interval 1 - 3 hours: 40%, 15%, 5% and 17%, respectively.

For additional quantitative comparison of the different β^+ decaying isotope contributions for PET verification approaches, MC simulated production yields of the respective isotopes in various materials are provided in **Appendix 10.4.** Table A.10.6.

of **Appendix 10.4** provides the data on light β^+ decaying nuclei up to neon-19, while Table A.10.8. of **Appendix 10.4** provides the data on heavier nuclei from sodium-20 up to titanium-45.

Focusing on fluorine-17 and fluorine-18, data in **Appendix 10.4** indicate that the production yield for both isotopes is proportional to the relative oxygen nuclei mass contribution of the investigated material - 88.8%, 63.0%, 44.6% and 23.3% for water, soft tissue, cortical bone and soft tissue, respectively. Compared to water, production yield of fluorine-17 decreases by 33%, 45% and 70% for soft tissue, cortical bone and soft tissue, respectively, while production of yield fluorine-18 decreases by 31%, 25% and 69%, respectively.

As all results presented in first two subsections correspond to lowest energy of helium-4 ions studied, additional data to assess the impact of helium-4 ion energy on β^+ decaying isotope production yield are provided in Table A.10.7. of **Appendix 10.4**. For light β^+ decaying nuclei in the range from boron-8 to oxygen-15, with respect to 115.3 MeV/u energy, an increased isotope production yield was observed of about 1.6 to 2.6 times for energy of 171.4 MeV/u, while for 217 MeV/u - an increase of about 2.1 to 4.1 times. In contrast, for heavier nuclei as fluorine-17, fluorine-18, neon-18, and neon-19 a decrease in production yield was observed for higher initial beam energies. With respect to 115.3 MeV/u decrease by 6%, 19%, 8% and 21%, respectively, was observed for 171.4 MeV/u and for 217 MeV/u - by 22%, 35%, 14% and 36%, respectively. As discussed later in this Chapter, this is attributable to cross-sections of nuclear interactions producing respective nuclei. Cross-section of respective interactions is highest for low particle kinetic energies [26-28]. Thus, as higher initial helium-4 ion energies result in increased primary particle fluence loss, the number of residual low-energy helium-4 ions is decreased near the Bragg peak, attributing to the decreased production yield.

Spatial distribution of e^+e^- annihilation events from β^+ decays: Millisecond timescale

With β^+ decay temporal evolution evaluated, corresponding e^+e^- annihilation event spatial distributions and their inherent temporal variation, is of highest relevance with respect to PET-based range verification. e^+e^- annihilation event spatial distributions were calculated based β^+ decay distributions, accounting to positron range effects via the method developed by the Author. No additional biological washout kinetics were accounted for in this initial assessment study, though this aspect is of great significance and is slightly discussed at the end of this Chapter. Figure 11.4 presents e^+e^- annihilation event spatial distribution observed during pauses in-between the beam pulses after irradiation of water and soft tissue, respectively. Data on soft tissue, adipose tissue and cortical bone are given in **Appendix 10.5**. Sum of e^+e^- annihilation event spatial distribution is evaluated with respect to absorbed dose distribution, while also separating the individual isotopic contributions.

Data presented in Figure 11.4 and **Appendix 10.5** illustrate that in millisecond-timescale, induced e^+e^- annihilation event spatial distribution does not have

a prominent peak in proximity of the absorbed dose distribution maximum. This is mainly attributable to nitrogen-12 as main contribution of millisecond-timescale β^+ decays. As nitrogen-12 decay emits relatively high energy positrons (average energy of 7.7 MeV, maximum - 16.3 MeV) [1-2], they have a long range in material before annihilating with electrons and producing PET-detectable photons. The long range effectively “smears-out” e^+e^- annihilation event spatial distribution with respect to β^+ decay distribution.

By qualitative evaluation, the lack of e^+e^- annihilation event spatial distribution peak is most prominent for registration after 1st irradiation pulse in all materials as the background from long-lived isotope decays is not as prominent. For water and soft tissue (Figure A.10.10 of **Appendix 10.5**), background signal generated primarily by slightly longer-lived fluorine-17 decays spatially exhibits higher correlation with the Bragg peak position. This is attributable to lower positron range effects of fluorine-17 due to decreased emission energies (average energy of 0.735 MeV, maximum - 1.738 MeV) and characteristics of the underlying nuclear interactions. With lower energy threshold and increased cross-section for lower particle energies, fluorine-17 production is increased near the Bragg peak. This could possibly improve the correlation between Bragg peak position and e^+e^- annihilation event spatial distribution in oxygen-rich tissue for in-beam PET verification. Nevertheless, in carbon-rich material - adipose tissue (Figure A.10.11 of **Appendix 10.5**) - the lack of e^+e^- annihilation event spatial distribution peak is observable for intervals after all beam pulses as nitrogen-12 is the dominant contribution.

As illustrated in Figure A.10.12 of **Appendix 10.5**, in cortical bone, due to presence of heavy nuclei, significantly different e^+e^- annihilation event spatial distributions can be observed. With scandium-41 and ground-state scandium-42 decays having significantly lower energy positron emissions with respect to nitrogen-12, e^+e^- annihilation event spatial distribution is less affected by positron range effects. Additionally, nuclear interactions for production of these isotopes have favourable energy threshold and cross-section characteristics, increasing the production yield near the Bragg peak. Thus, e^+e^- annihilation event spatial distribution in cortical bone could exhibit prominent fall-off region in correlation with the Bragg peak position.

Quantitative evaluation of the presented e^+e^- annihilation event spatial distributions was performed, by assessing correlation with the Bragg peak position, and is provided in Table 11.2 and **Appendix 10.6**. Table 11.2 provides the comparison of spatial metrics for different irradiated materials, while **Appendix 10.6** provides data on the impact of helium-4 ion energy. In addition to assessing deviations between e^+e^- annihilation event and absorbed dose spatial dose distributions, linear regression fit between respective metrics was performed. Coefficient of determination and sensitivity - spatial change in e^+e^- annihilation event distribution with respect to change in absorbed dose distribution (ideally a value of 1 is to be expected) - were evaluated.

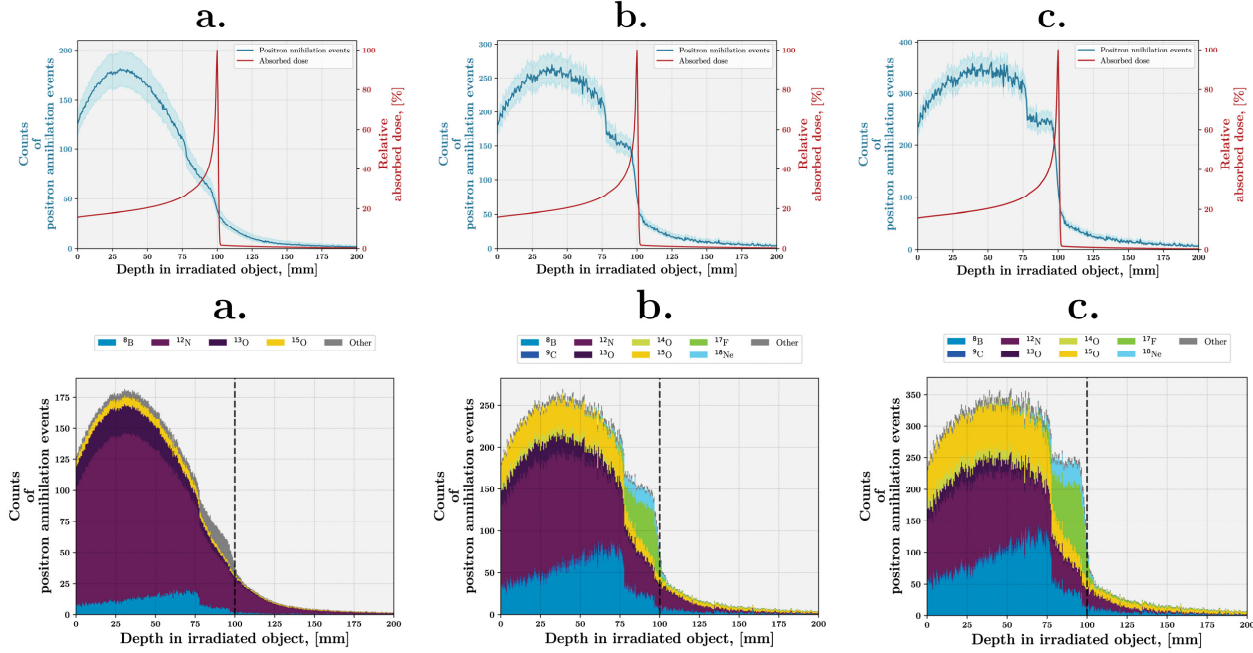


Figure 11.4. Spatial distribution and isotopic contributions of e^+e^- annihilation events in irradiated water phantom in 90 ms after 1st (a), 5th (b), and 10th (c) irradiation pulse

Data illustrated as sum of all β^+ decays and corresponding e^+e^- annihilation events over 90 ms period, with spatial depth resolution of 0.5 mm. *Upper line*: total positron annihilation event distribution given, with 1σ uncertainty indicated as shaded region. Relative (normalized to maximum) depth dose distribution given for comparison, statistical uncertainty below 0.1% not illustrated. *Lower line*: Stacked histogram of e^+e^- annihilation event isotopic contributions, indicating most prevalent in each Subfigure, with the sum of other contributing β^+ emitting isotopes indicated as “Other”. Black dashed line indicates position of absorbed dose maximum. No uncertainties indicated for visual clarity, note the change of legend and y-axis scale for each Subfigure.

Data given for 115.3 MeV/u helium-4 ion beam (range in water of 100 mm)

Table 11.2

Metrics of e^+e^- annihilation event spatial distribution for millisecond detection timescales in water, soft tissue, adipose tissue, and cortical bone after irradiation with helium-4 ions* and correlation of these metrics with absorbed dose distribution

Time interval **	Irradiated material	Absorbed dose distribution***			e^+e^- annihilation event distribution****			Statistical metrics for correlation of parameters for varying beam range*****		
		$R_{D_{\max}}$	$R_{D_{80\%}}$	$R_{D_{50\%}}$	$R_{AE_{\max}}$	$R_{AE_{80\%}}$	$R_{AE_{50\%}}$	$k_{\max} (R^2)$	$k_{80\%} (R^2)$	$k_{50\%} (R^2)$
Pulse #1	water	100.0	100.5	100.8	30.5	61.5 ± 7.2	78.9 ± 3.0	0.145 (0.81)	0.680 (1.00)	0.888 (1.00)
	soft tissue	96.5	97.1	97.4	38.0	70.0 ± 4.5	83.8 ± 3.3	0.247 (-)	0.870 (-)	0.964 (-)
	adipose tissue	102.0	102.6	102.9	50.0	78.5 ± 1.8	91.6 ± 2.5	0.312 (-)	0.889 (-)	1.005 (-)
	cortical bone	58.5	59.2	59.3	25.5	54.5 ± 1.8	61.2 ± 0.8	0.508 (-)	0.802 (-)	0.971 (-)
Pulse #5	water	100.0	100.5	100.8	39.0	75.3 ± 5.2	96.0 ± 1.0	0.190 (0.93)	0.676 (1.00)	0.914 (1.00)
	soft tissue	96.5	97.1	97.4	38.0	73.4 ± 5.3	87.6 ± 4.3	0.531 (-)	0.852 (-)	0.962 (-)
	adipose tissue	102.0	102.6	102.9	45.5	77.4 ± 1.8	90.0 ± 2.3	0.61 -0 (-)	0.957 (-)	0.991 (-)
	cortical bone	58.5	59.2	59.3	44.0	57.3 ± 0.3	61.6 ± 0.3	0.195 (-)	0.948 (-)	0.999 (-)
Pulse #10	water	100.0	100.5	100.8	52.5	77.5 ± 6.0	98.3 ± 0.3	0.228 (0.96)	0.872 (1.00)	0.996 (1.00)
	soft tissue	96.5	97.1	97.4	38.0	72.9 ± 1.8	92.4 ± 1.3	0.531 (-)	0.861 (-)	0.939 (-)
	adipose tissue	102.0	102.6	102.9	39.0	77.1 ± 1.5	90.3 ± 2.0	0.693 (-)	0.931 (-)	0.992 (-)
	cortical bone	58.5	59.2	59.3	44.0	57.3 ± 0.3	61.4 ± 0.3	0.195 (-)	0.964 (-)	1.005 (-)

* Data given only for helium-4 ion energy of 115.3 MeV/u.

** Time interval corresponds to 90 ms after delivery of 1st, 5th and 10th radiation pulse

*** Absorbed dose spatial distribution evaluated with 0.5 mm resolution. Extracted metrics: depth of maximum dose ($R_{D_{\max}}$), depth corresponding to 80% distal dose fall-off ($R_{D_{80\%}}$) and depth corresponding to 50% distal dose fall-off ($R_{D_{50\%}}$). Statistical uncertainty not given, lower than resolution.

**** e^+e^- annihilation event spatial distribution evaluated with 0.5 mm resolution. Extracted metrics: depth with maximum e^+e^- annihilation intensity ($R_{AE_{\max}}$), depth corresponding to 80% fall-off of e^+e^- annihilation peak intensity ($R_{AE_{80\%}}$) and depth corresponding to 50% fall-off of e^+e^- annihilation peak intensity ($R_{AE_{50\%}}$). Statistical uncertainty not given for $R_{AE_{\max}}$, while extracted for $R_{AE_{80\%}}$ and $R_{AE_{50\%}}$, based on 1σ uncertainties of e^+e^- annihilation event intensity.

***** k corresponds to slope (sensitivity) of linear fit using least-squares linear regression between spatial metrics absorbed dose and e^+e^- annihilation event distributions evaluated for all helium-4 energies. Coefficient of determination R^2 for linear fit given in parentheses for water (2 energies evaluated for other materials).

Analysing the data presented in Table 11.2, correlation between positions corresponding to maximum in absorbed dose and e^+e^- annihilation event distributions is comparatively weak - spatial deviations of the respective peak positions are larger than 10 mm (range from 14 to 70 mm) and observed sensitivity (slope of the linear fit) is low - 0.15 to 0.23, 0.25 to 0.53, 0.31 to 0.69 and 0.20 to 0.50 mm/mm for water, soft tissue, adipose tissue and cortical bone, respectively. Slightly increased performance can be observed in oxygen-rich materials (water and soft tissue) after 5th and 10th pulse with respect to 1st pulse, attributable to the previously discussed fluorine-17 contribution.

Analysing 80% and 50% intensity fall-off positions as metrics for correlation, improved performance was observed. With 80% intensity fall-off position as comparison metric observed deviations between absorbed dose and e^+e^- annihilation event distributions were in ranges 23 to 39, 24 to 27, 24 to 26 and 2 to 5 mm for water, soft tissue, adipose tissue and cortical bone, respectively, with decreased deviations and improved sensitivity observed after 5th and 10th pulse with respect to 1st pulse. Observed sensitivities were lowest in water phantom (0.68 to 0.86 mm/mm), while sensitivities above 0.85 mm/mm were observed after 1st pulse and above 0.9 mm/mm - after 5th and 10th pulse - for soft tissue, adipose tissue, and cortical bone.

50% intensity fall-off position as comparison metric illustrated the best performance with deviations between the two distributions in ranges 3 to 22, 5 to 14, 11 to 13 for water, soft tissue, and adipose tissue, while for cortical bone - around 2 mm. Similarly, decreased deviations and improved sensitivity was observed after 5th and 10th pulse with respect to 1st pulse. Observed sensitivities were lowest in water phantom (0.888 to 0.996 mm/mm), while sensitivities above 0.96 mm/mm were observed in all scenarios for soft tissue, adipose tissue, and cortical bone.

Data in **Appendix 10.6** illustrate that deviation between the two spatial distribution metrics are higher for increased initial helium-4 ion beam energy, attributing to the relatively low sensitivities as discussed before.

Spatial distribution of e^+e^- annihilation events from β^+ decays: Second and minute timescale

Figure 11.5 presents the e^+e^- annihilation event spatial distributions for long integration time windows in water respectively. Data for soft tissue, adipose tissue and cortical bone are presented in **Appendix 10.7**.

Qualitative properties of the e^+e^- annihilation event spatial distribution were first evaluated. Firstly, results with water presented in Figure 11.5 were evaluated. While the main contributions from oxygen-15, nitrogen-13 and carbon-11 exhibit only a prominent fall-off upstream to the Bragg peak position, as discussed in Chapter 8, two isotopic contributions stand out. For time windows up to 10 minutes, a prominent peak close to the Bragg peak position is observed by fluorine-17 contribution, while for timescales above 30 minutes - a significant peak is formed by fluorine-18 contribution with position of less than 2 mm upstream of the Bragg peak. Thus, both contributions

could significantly improve the correlation between absorbed dose and e^+e^- annihilation event spatial distributions.

Comparing results of oxygen-rich material - soft tissue - in Figure A.10.13. of **Appendix 10.7**, slight differences can be observed with respect to water. With respect to overall signal, amplitudes of fluorine-17 and fluorine-18 peaks are lower in comparison to water, attributable to reduced production yield due to lower oxygen nuclei mass fraction in soft tissue. In time window from 10 to 60 minutes after irradiation, non-negligible contribution to the observable peak is associated with nitrogen-13.

With significantly reduced oxygen nuclei mass fraction in adipose tissue - carbon-rich material - as illustrated in Figure A.10.14. of **Appendix 10.7**, both fluorine-17 and fluorine-18 peaks are significantly reduced in amplitude. Nevertheless, in the carbon-rich adipose tissue, production of nitrogen-13 is more prominent and with favourable nuclear interactions characteristics - low energy threshold and high cross-section at low kinetic energies -, increasing production in proximity to the Bragg peak. From 1 to 60 minutes after irradiation, peak in e^+e^- annihilation event spatial distribution is primarily formed by nitrogen-13, with fluorine-18 contribution significant only after 1 hour.

In cortical bone (Figure A.10.15. of **Appendix 10.7**), similar phenomena to soft tissue can be observed, with additional contributions of ground state potassium-38 and phosphorus-30 to peaks in e^+e^- annihilation event spatial distribution in timescale from 10 to 60 minutes. Fluorine-18 remains as main contribution after 30 minutes.

Quantitative evaluation of the presented e^+e^- annihilation event spatial distributions was performed in the same approach as for short timescales, with respective data provided in Table 11.3 and **Appendix 10.8**. Table 11.3 provides the comparison of spatial metrics for different irradiated materials, while **Appendix 10.8** provides data on the impact of helium-4 ion energy. Further data evaluation was performed in the same fashion as for millisecond-timescale.

Analysing data presented in Table 11.3, correlation between absorbed dose and e^+e^- annihilation event distributions is significantly improved with respect to millisecond detection timescale. Analysing positions corresponding to maxima in both distributions - average spatial deviations among studied materials of -43, -29, -26, -18, -12 and -1.4 mm were observed for integration time windows after irradiation of 100 ms to 1 s, 1 s to 1 min, 1 min to 10 min, 10 min to 30 min, 30 min to 1 h and 1 h to 3 h, respectively. For oxygen-rich materials (water and soft tissue) lower deviations were observed in comparison to adipose and cortical bone - less than 3 mm in timescales from 1 s to 30 minutes after irradiation and lower than 1.5 mm - from 30 minutes onwards. Analysing the sensitivity and correlation metrics, best performance was observed in water. Ideal sensitivity of unity was achieved for integration time windows of 1 to 3 hours after irradiation in all materials studied, except adipose tissue.

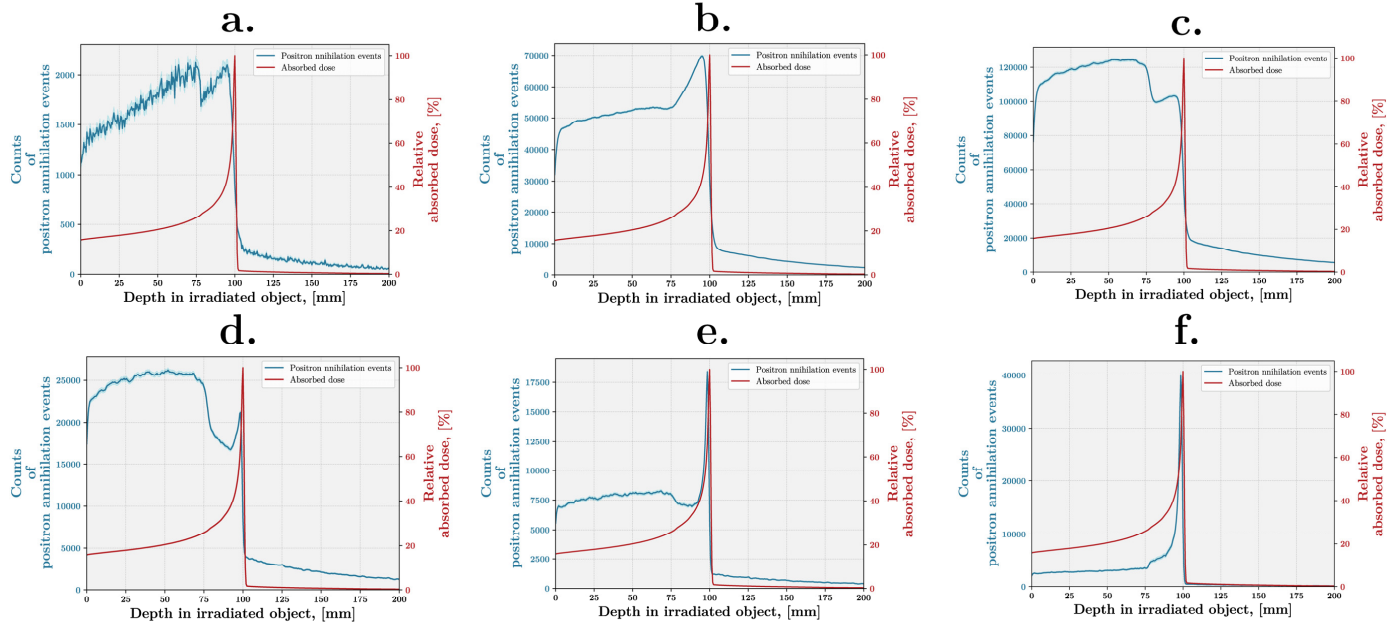


Figure 11.5. Spatial distribution and isotopic contributions of e^+e^- annihilation events in water phantom after irradiation. Data illustrated as sum of all β^+ decays and corresponding e^+e^- annihilation events over specified time interval in each Subfigure, with spatial depth resolution of 0.5 mm. Data given for 115.3 MeV/u helium-4 ion beam (range in water of 100 mm)

First page: total positron annihilation event distribution given, with 1σ uncertainty indicated as shaded region. Relative (normalized to maximum) depth dose distribution given for comparison, statistical uncertainty below 0.1% not illustrated.

Data given for following time periods after irradiation: 0.1 to 1 s with 0.1 s resolution (Subfigure (a)), 1 to 60 s with 1 s resolution (Subfigure (b)), 1 to 10 min with 1 min resolution (Subfigure (c)), 10 to 30 min with 1 min resolution (Subfigure (d)), 30 to 60 min with 1 min resolution (Subfigure (e)) and 1 to 3 hours with 1 hour resolution (Subfigure (f)).

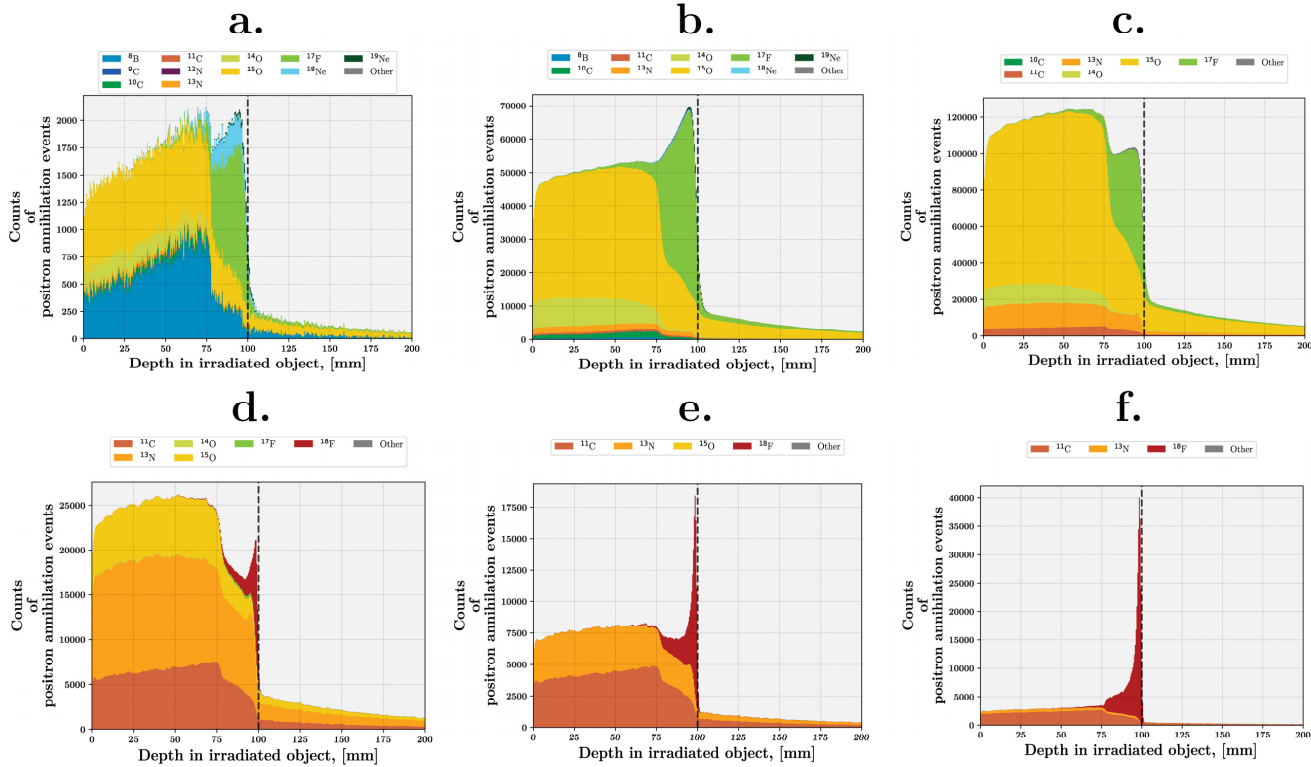


Figure 11.5. cont. Spatial distribution and isotopic contributions of e^+e^- annihilation events in water phantom after irradiation
Second page: Stacked histogram of e^+e^- annihilation event isotopic contributions, indicating most prevalent in each Subfigure, with the sum of other contributing β^+ emitting isotopes indicated as “Other”. Black dashed line indicates position of absorbed dose maximum. No uncertainties indicated for visual clarity, note the change of legend and y-axis scale for each Subfigure.

Table 11.3

Metrics of e^+e^- annihilation event spatial distribution for second and minute detection timescales in water, soft tissue, adipose tissue, and cortical bone after irradiation with helium-4 ions* and correlation of these metrics with absorbed dose distribution

Time interval	Irradiated material	Absorbed dose distribution**			e^+e^- annihilation event distribution***			Statistical metrics for correlation of parameters for varying beam range****		
		$R_{D_{\max}}$	$R_{D_{80\%}}$	$R_{D_{50\%}}$	$R_{AE_{\max}}$	$R_{AE_{80\%}}$	$R_{AE_{50\%}}$	$k_{\max} (R^2)$	$k_{80\%} (R^2)$	$k_{50\%} (R^2)$
100 ms	water	100.0	100.5	100.8	74.5	78.0	99.5	0.975 (1.00)	1.094 (1.00)	1.003 (1.00)
	soft tissue	96.5	97.1	97.4	61.5	92.5	95.6	0.289 (-)	0.983 (-)	1.008 (-)
	adipose tissue	102.0	102.6	102.9	8.5	58.0	97.3	0.400 (-)	0.951 (-)	0.829 (-)
	cortical bone	58.5	59.2	59.3	40.0	57.0	60.7	0.263	0.980	1.013
1 s	water	100.0	100.5	100.8	95.0	98.2	99.6	1.000 (1.00)	1.000 (1.00)	1.004 (1.00)
	soft tissue	96.5	97.1	97.4	92.0	95.0	96.4	0.995 (-)	1.003 (-)	1.009 (-)
1 min	adipose tissue	102.0	102.6	102.9	23.5	92.3	101.8	0.844 (-)	0.804	1.005 (-)
1 min	water	100.0	100.5	100.8	52.5	81.5	99.3	0.583 (0.98)	0.984 (1.00)	1.001 (1.00)
	soft tissue	96.5	97.1	97.4	61.5	95.0	96.3	0.567 (-)	0.997 (-)	1.007 (-)
	adipose tissue	102.0	102.6	102.9	99.0	100.7	101.7	1.000 (-)	1.005 (-)	1.010 (-)
10 min	cortical bone	58.5	59.2	59.3	39.5	56.7	58.4	0.949	0.997	1.008
10 min	water	100.0	100.5	100.8	52.0	97.7	99.5	0.830 (0.99)	0.898 (1.00)	1.000 (1.00)
	soft tissue	96.5	97.1	97.4	94.0	95.4	96.2	0.562 (-)	0.861 (-)	1.007 (-)
	adipose tissue	102.0	102.6	102.9	99.0	100.6	101.5	1.000 (-)	1.005	1.010 (-)
30 min	cortical bone	58.5	59.2	59.3	39.5	53.0	58.5	0.949	1.067	1.005
30 min	water	100.0	100.5	100.8	98.5	99.3	99.7	1.003 (1.00)	1.001 (1.00)	1.003 (1.00)
	soft tissue	96.5	97.1	97.4	95.0	95.9	96.3	0.552 (-)	0.964 (-)	1.009 (-)
	adipose tissue	102.0	102.6	102.9	58.5	100.5	101.5	0.859 (-)	0.797 (-)	1.007 (-)
1 h	cortical bone	58.5	59.2	59.3	57.5	58.3	58.7	0.517	0.802	1.003

Table 11.3 continued

Metrics of e^+e^- annihilation event spatial distribution for second and minute detection timescales in water, soft tissue, adipose tissue, and cortical bone after irradiation with helium-4 ions* and correlation of these metrics with absorbed dose distribution

Time interval	Irradiated material	Absorbed dose distribution**			e^+e^- annihilation event distribution***			Statistical metrics for correlation of parameters for varying beam range****		
		$R_{D_{\max}}$	$R_{D_{80\%}}$	$R_{D_{50\%}}$	$R_{AE_{\max}}$	$R_{AE_{80\%}}$	$R_{AE_{50\%}}$	$k_{\max} (R^2)$	$k_{80\%} (R^2)$	$k_{50\%} (R^2)$
1 h	water	100.0	100.5	100.8	98.5	99.4	99.7	1.005 (1.00)	1.001 (1.00)	1.001 (1.00)
	soft tissue	96.5	97.1	97.4	95.0	95.8	96.3	1.000 (-)	1.004 (-)	1.008 (-)
3 h	adipose tissue	102.0	102.6	102.9	100.5	101.3	101.8	0.449 (-)	0.983 (-)	1.010 (-)
	cortical bone	58.5	59.2	59.3	57.5	59.1	58.6	1.000 (-)	0.986 (-)	1.001 (-)
1 s										
-	cortical bone	58.5	59.2	59.3	25.5	52.4	58.5	0.669 (-)	0.922 (-)	1.006 (-)
10 s										
10 s										
-	cortical bone	58.5	59.2	59.3	54.0	57.4	58.7	1.000 (-)	1.001 (-)	1.009 (-)
1 min										

* Data given only for helium-4 ion energy of 115.3 MeV/u.

** Absorbed dose spatial distribution evaluated with 0.5 mm resolution. Extracted metrics: depth of maximum dose ($R_{D_{\max}}$), depth corresponding to 80% distal dose fall-off ($R_{D_{80\%}}$) and depth corresponding to 50% distal dose fall-off ($R_{D_{50\%}}$). Statistical uncertainty not given, lower than resolution.

*** e^+e^- annihilation event spatial distribution evaluated with 0.5 mm resolution. Extracted metrics: depth with maximum e^+e^- annihilation intensity ($R_{AE_{\max}}$), depth corresponding to 80% fall-off of e^+e^- annihilation peak intensity ($R_{AE_{80\%}}$) and depth corresponding to 50% fall-off of e^+e^- annihilation peak intensity ($R_{AE_{50\%}}$). Statistical uncertainty not given, lower than resolution.

**** k corresponds to slope (sensitivity) of linear fit using least-squares linear regression between spatial metrics absorbed dose and e^+e^- annihilation event distributions evaluated for all helium-4 energies. Coefficient of determination R^2 for linear fit given in parentheses for water (2 energies evaluated for other materials).

As observed in Figure 11.5 and **Appendix 10.7**, fluorine-17 and fluorine-18 peak intensities could be lower than plateau intensity of e^+e^- annihilation event distributions. 80% and 50% intensity fall-off positions were also considered as metrics for correlation analysis. Improved performance was achieved, with respect to maximum intensity position as a metric and with respect to millisecond detection timescales, also. With 80% intensity fall-off position as comparison metric, observed deviations between absorbed dose and e^+e^- annihilation event distributions were less than 5 mm in timescales up to 30 minutes, and less than 1.5 mm for timescales from 30 minutes onwards. Observed sensitivities were above 0.8 mm/mm in all investigated scenarios.

Similarly to millisecond detection timescale, 50% intensity fall-off position as comparison metric illustrated the best performance with deviations between the two distributions in the range of 1 to 2 mm for all irradiated material and integration time window combinations, with ideal sensitivity of 1 mm/mm observed for timescales above 1 s after irradiation.

Data in **Appendix 10.8** illustrate that deviations between the two spatial distribution metrics are slightly higher for increased initial helium-4 ion beam energy if maximum intensity or 80% intensity fall-off position is considered as a metric of comparison. For integration timescales above 30 minutes dependency on initial helium-4 ion energy was not observed. If 50% intensity fall-off position is considered, no influence of varying initial helium-4 ion energy was observed on deviations between the spatial distribution metrics for all integration time windows considered.

As can be observed for both millisecond and second/minute detection timescales, significant contribution in the e^+e^- annihilation event spatial distributions induced by helium-4 ion beams comes from fluorine-17 and fluorine-18 nuclei. This is attributable to corresponding production nuclear interactions - discussed further in this Chapter.

Sensitivity of e^+e^- annihilation event spatial distribution to range shifts. Influence of primary beam intensity

Sensitivity of calculated e^+e^- annihilation event spatial distributions was evaluated with respect to range shifts. Sensitivity assessment was performed using statistical bootstrapping method. Registered shifts and associated uncertainties were evaluated with respect to the magnitude of introduced shift. Summary of quantitative evaluation is provided in **Appendix 10.9**. Additionally, impact of primary beam intensity on range shift uncertainty was quantitatively evaluated, with results provided in Appendices **10.10** and **10.11**.

Analysis of underlying nuclear interactions. Comparison of β^+ emitter production yield in water between therapeutically used ions: helium-4 ions, protons and carbon-12 ions

As indicated for the analysis of the e^+e^- annihilation event spatial analysis, unique contributions of fluorine-17 and fluorine-18 can be observed for helium-4 ion beam irradiation, especially for oxygen-rich materials - water and soft tissue. To analyse the

underlying mechanisms of production for these nuclei, Table 11.4 provides summary of main nuclear interactions relevant for fluorine-17 and fluorine-18 production by helium-4 ion beam interactions with oxygen-16 nuclei. As helium-4 ion beams undergo fragmentation in the irradiated tissue, Table 11.4 presents possible interaction not just by primary helium-4 ions, but also helium-3, triton, and deuteron fragments. Nitrogen-14 nuclei, present in biological tissue, were also considered in case of fluorine-17 production.

Table 11.4

Main physical characteristics for nuclear interactions of fluorine-17 and fluorine-18 production in oxygen-rich material by helium-4 ion beams

β^+ decaying nucleus	Nuclear interactions for possible production	Threshold energy $E_{\text{threshold}}$	Maximum production cross-section σ_{max}	Respective kinetic energy $E_{\sigma_{\text{max}}}$
^{17}F	$^{16}\text{O}(\alpha, 2n + p)^{17}\text{F}$	34.6 MeV	15.2 mb	60 MeV
	$^{16}\text{O}(\alpha, d + n)^{17}\text{F}$	31.8 MeV	8.0 mb	50 MeV
	$^{16}\text{O}(^3\text{He}, n + p)^{17}\text{F}$	8.5 MeV	89.9 mb	19 MeV
	$^{16}\text{O}(^3\text{He}, d)^{17}\text{F}$	18.3 MeV	6.1 mb	80 MeV
	$^{16}\text{O}(t, 2n)^{17}\text{F}$	9.4 MeV	42.1 mb	22 MeV
	$^{16}\text{O}(d, n)^{17}\text{F}$	1.8 MeV	218.9 mb	9 MeV
	$^{14}\text{N}(\alpha, n)^{17}\text{F}$	6.1 MeV	120.4 mb	9 MeV
^{18}F	$^{16}\text{O}(\alpha, n + p)^{18}\text{F}$	23.2 MeV	137.0 mb	40 MeV
	$^{16}\text{O}(\alpha, d)^{18}\text{F}$	20.4 MeV	18.1 mb	30 MeV
	$^{16}\text{O}(^3\text{He}, p)^{18}\text{F}$	2.0 MeV	399.2 mb	7 MeV
	$^{16}\text{O}(t, n)^{18}\text{F}$	0 MeV	387.4 mb	5 MeV
	$^{16}\text{O}(\alpha, 2n)^{18}\text{Ne} \rightarrow ^{18}\text{F}$	29.7 MeV	1.7 mb	55 MeV
	$^{16}\text{O}(^3\text{He}, n)^{18}\text{Ne} \rightarrow ^{18}\text{F}$	3.8 MeV	44.7 mb	11 MeV

* Data have been extracted from TENDL-2023 database [26-27]

Table 11.4 illustrates, that several nuclear interaction pathways exist for production of fluorine-17 and fluorine-18 in oxygen-rich tissue. In case of fluorine-18 production on oxygen-16, significant contributions by both primary helium-4 ions via $(\alpha, n + p)$ or (α, d) and secondary fragments - helium-3 ions via $(^3\text{He}, p)$ and tritons via (t, n) - can be observed. All the identified nuclear interactions have relatively low energy

threshold and have highest cross-section at low energies, attributing to the observed fluorine-18 peak proximity to the Bragg peak.

For fluorine-17 production on oxygen-16, while contributions from primary helium-4 ions are relatively low via $(\alpha, 2n + p)$ and $(\alpha, d + n)$, significantly higher contributions can be observed from secondary fragments - helium-3 ions via $(^3\text{He}, d)$, tritons via $(t, 2n)$ and deuterons (d, n) .

From secondary fragments, helium-3 ions have relatively high cross-section for both fluorine-17 and fluorine-18 production. Due to differences in charge-to-mass ratio with respect to helium-4 ions, largest portion of secondary helium-3 nuclei stop proximal to primary helium-4 ion Bragg peak. This further attributes to the observed spatial distribution of e^+e^- annihilation events from fluorine isotopes. In addition to oxygen-16 nuclei, nitrogen-14 was also evaluated. Nitrogen-14 has a relative mass contribution of 2.5%, 0.7% and 4.2% in soft tissue, adipose tissue, and cortical bone. While this is a relatively low contribution, primary helium-4 ion interaction with nitrogen-14 nuclei could produce non-negligible additional contribution of fluorine-17 via (α, n) .

For evaluation of the observed spatial e^+e^- annihilation event patterns induced by helium-4 ions with respect to other IBT modalities - protons and carbon-12 ions - production yields and respective spatial distributions of relevant β^+ emitting isotopes were compared. Quantitative data are summarized in **Appendix 10.12**.

Analysing data in **Appendix 10.12**, a higher production yield of relevant isotopes can be observed for helium-4 ions with respect to protons:

- **for nitrogen-12:** about 3 - 6 times higher yield spatially;
- **for nitrogen-13:** about 1.5 - 2 times higher yield, though more prominent peak in production yield distribution can be observed for protons.
- **for fluorine-17 and fluorine-18:** unique for helium-4 ions, as only a negligible contribution of fluorine-17 can be observed with protons, while fluorine-18 can be produced only by helium-4 ions.

In contrast to protons and helium-4 ions, projectile fragmentation-based generation of β^+ emitting nuclei can be observed for carbon-12 ions (boron-8, carbon-10 and carbon-11 contributions). Nevertheless, carbon-12 ions have about 4 - 8 times higher production yield of nitrogen-12 with respect to helium-4 ions. Nitrogen-13 production yield is about 2 - 4 times with carbon-12 ions with a clearly distinguishable peak near the Bragg peak position.

Focusing on fluorine-17 and fluorine-18, helium-4 ions exhibited the highest yield of fluorine-17 and fluorine-18 for all ion types considered in IBT, also indicating favourable spatial characteristics.

β^+ emitter production yields and spatial distributions of e^+e^- annihilation events: comparison between helium-3 and helium-4 isotopes in water

As indicated in Table 11.4, helium-3 ions could possibly have favourable e^+e^- annihilation event spatial distribution characteristics with respect to helium-4 ions.

As nuclear reactions underlying fluorine-17 and fluorine-18 production have lower threshold energies and higher interaction cross-sections, increased number of e^+e^- events could be expected in spatial proximity to the Bragg peak position. Experimental studies have evaluated potential of helium-3 beams [30], while possible fluorine contributions have been identified in earlier MC simulation studies [31]. Thus, in the scope of the Thesis, main characteristics relevant to PET-based range verification were also compared between helium-3 and helium-4 ions. Relevant data and respective analysis are summarised in **Appendix 10.13**.

Overall, the presented results on helium-3 ions indicate a highly attractive performance in oxygen-rich tissue, due to significant contributions of fluorine-17 and neon-18, improving spatial correlation and sensitivity to range shifts over helium-4 ion beams. Nevertheless, helium-3 ion delivery is more challenging from technical perspective and clinical use, with additional discussion provided at the end of this Chapter.

Theoretical assessment of PET system resolution impact on detectable e^+e^- annihilation event spatial distribution

As mentioned before, the study presented was limited to assessing just the e^+e^- annihilation event spatial distribution itself, not accounting for technical limitations associated with the PET system itself. In a realistic scenario, all observed e^+e^- annihilation event spatial distributions in this study would be significantly perturbed by the limitations of the volumetric coverage and the spatial resolution of PET detector. While assessment with a specific PET hardware was not in the scope of this Thesis, possible effects of limited PET system spatial resolution were briefly evaluated. Illustrative data of e^+e^- annihilation event spatial distribution convolution with Gaussian kernel corresponding to typical PET resolutions is given in **Appendix 10.14**.

No significant impact was observed for millisecond detection timescale as no prominent spatial characteristics are present in the distribution. Nevertheless, slight changes in the fall-off of the signal can be observed, possibly impacting achievable range sensitivity.

On the contrary, as prominent peaks exist in e^+e^- annihilation event spatial distributions for second/minute detection timescales, introduction of PET system spatial resolution limit impacts the shape of detectable signal. Magnitude of peaks associated with fluorine-17 and fluorine-18 is decreased, approaching a level comparable with the intensity at the plateau. While spatial peaks could still be distinguishable with FWHM spatial resolution of 5 mm, the reduction in peak magnitude with FWHM of 10 mm results in loss of respective peaks. For time integration window of 1 to 10 seconds, fluorine-17 peak could still be distinguished, while in the case of fluorine-18 peak - only in timescales above 30 or 60 minutes. Nevertheless, fall-off positions are unaffected and could still be used as relevant metric for range shift detection.

Overall, the brief theoretical investigation on PET system spatial resolution impact, illustrates possibly significant limitations on the approaches discussed before. Nevertheless, presented results provide important insights for PET-based range

verification method development in helium-4 IBT. Unique characteristics in e^+e^- annihilation event spatial distributions have been identified with respect to other therapeutically relevant ion beams - protons and carbon-12 ions.

11.3. Conclusions and discussion

Chapter 11 presented MC simulation-based investigation on unique patterns within spatial distribution and temporal evolution of e^+e^- annihilation events induced by irradiation of helium-4 ions. Induced patterns were evaluated in the context of range verification using PET.

For calculation of e^+e^- annihilation events from spatial distribution of β^+ decays, semi-analytical approach was developed and implemented by Author based on convolution with positron annihilation point spread function (aPSF), which accounts for finite range effects of positrons emitted during β^+ decay. Method for calculation of aPSF for any arbitrary β^+ decaying isotope was developed.

Temporal evolution of β^+ decays and correlation of e^+e^- annihilation event and absorbed dose spatial distributions was evaluated for varying helium-4 ion energies and different materials: water as reference and soft tissue, adipose tissue and cortical bone, reflecting patient anatomy. Correlation of spatial metrics was quantitatively evaluated, presenting also mathematical evaluation of range shift sensitivity and the impact of primary beam intensity. β^+ decaying isotope production yields for helium-4 ions were compared with respect to protons and carbon-12 ions. Finally, possible helium-3 ion beam use in context of PET-based range verification was evaluated.

Main conclusions from the presented results can be summarized as:

1. A semi-analytical approach for calculation of e^+e^- annihilation events from spatial distribution of β^+ decays has been developed. Furthermore, a method for aPSF calculation for any arbitrary β^+ decaying isotope has been developed.
2. After helium-4 ion beam irradiation of oxygen-rich material, such as soft tissue, significant contributions of fluorine-17 and fluorine-18 isotopes are produced. Corresponding main nuclear interactions are $^{16}\text{O}(\alpha, 2n + p)^{17}\text{F}$ and $^{16}\text{O}(\alpha, d + n)^{17}\text{F}$ for fluorine-17, $^{16}\text{O}(\alpha, n + p)^{18}\text{F}$ and $^{16}\text{O}(\alpha, d)^{18}\text{F}$ for fluorine-18, with additional contributions from secondary fragments.
3. For an in-beam approach, fluorine-17 contribution can be observed after sufficient accumulation - in presented work, after 5th irradiation pulse, improving correlation of the distribution with respect to the Bragg peak position.
4. For in-room and off-line approaches, significant fluorine-17 contribution can be observed in timescales up to 10 minutes, with peak of e^+e^- annihilation event spatial distribution < 10 mm upstream of the Bragg peak position, improving correlation of the distribution with respect to absorbed dose.
5. For in-room and off-line approaches, significant fluorine-18 contribution can be observed in timescales after 30 minutes, with peak of e^+e^- annihilation event spatial

distribution < 1.5 mm upstream of the Bragg peak position, improving correlation of the distribution with respect to absorbed dose.

6. For all PET verification approaches, 50% e^+e^- annihilation event intensity fall-off position provided best agreement with corresponding absorbed dose distribution metrics, indicating suitability for use in range verification.
7. For in-beam approach, helium-4 ion induced e^+e^- annihilation event spatial distribution sensitivity to range shifts is increased for lower initial helium-4 beam energies and beam pauses after later irradiation pulses due to fluorine-17 contribution.
8. For relatively long integration time windows considered in this work, helium-4 primary beam intensity has more significant impact on range sensitivity for in-beam approach (millisecond timescale) compared to in-room and off-line approaches (second/minute timescale).
9. Induced fluorine-17 and fluorine-18 contributions are unique and with highest production yield for helium-4 ions, compared to proton and carbon-12 ion beams.
10. Use of helium-3 ion beams could improve range sensitivity of in-beam PET approach due to production fluorine-17 and neon-18 in close proximity (< 1 mm upstream) to the Bragg peak.

Limitations of the performed research. Additional notes and implications of the work.

Considering the methodology and results presented in this Chapter, following limitations and additional implications of the performed study were identified:

- as presented study focused on initial developments and general physical assessment on using helium ion induced e^+e^- annihilation for detection with PET, an idealized setup was considered, evaluating the ideally detectable signal with no specific detector setup and associated limitations. While at the end of the Result section and corresponding signal, brief theoretical evaluation on PET spatial resolution impact on detectable signal was provided, further work should be done to assess the impact of detection system limitations. Special focus should be given to assess the spatial coverage differences for various PET geometry implementations specific to in-beam, in-room or off-line verification approaches. Evaluation of PET geometry and other detection system limitations is crucial to assess the achievable spatial resolution and detectable signal magnitude per dose. Additionally, detectable signal should also be further re-evaluated for clinically relevant integration time windows.
- with the focus on initial development of PET-based verification for helium ion beams, uniform field delivery was considered with a single energy level. In actual implementation scenario, delivery would be realized via PBS, thus further studies should focus on the influence of spot size and spot spacing impact on detectable signal by PET. Additional focus should be given on detectable signal level for a single energy layer and how accuracy of PET-based verification with in-beam, in-room or off-line approaches would be influenced by multiple energy layer delivery.

- as the study was based on MC-simulations, accuracy of nuclear interaction modelling has limitations as relevant for β^+ emitter production yield and spatial distribution calculations. As parameters used in calculations are directly influenced nuclear interaction cross-section data, accuracy of these data are crucial. Accuracy of used physics model within Geant4 has been outlined in Chapter 4, corresponding Appendix and references benchmarking studies. Nevertheless, as discussed in Chapter 8 and corresponding Appendix, accurate, experimentally verified nuclear interaction data as relevant for therapeutical energy levels are relatively limited and several initiatives are working towards expanding the dataset. Thus, experimental validation of presented findings and further re-evaluation of simulation results, while implementing experimentally derived nuclear interaction cross-section data, would be of high importance.
- with the focus on initial development of PET-based verification for helium ion beams, simple phantom geometries, uniformly consisting of tissue-like materials, were used for quantitative evaluation of resulting signal for detection via PET and achievable range sensitivity. As in a clinical setup, complex anatomies with large tissue elemental composition variations can be expected, additional work should focus on quantitative evaluation on achievable PET signal in such complex scenarios. Special focus should be given on range sensitivity assessment, evaluating the capabilities of clinically relevant range shift detection, while also considering detection system limitations.
- only gamma photons generated via e^+e^- annihilation were considered in the presented results. Nevertheless, signal detected by PET could also be influenced by gamma photon emissions due to nuclear decay and possibly secondary neutrons. Thus, additional considerations on the background signal contribution in the detection system should be done in further work.
- as discussed in Chapter 8 and corresponding Appendix, one of the key challenges for PET-based range verification is the impact of biological washout on detectable signal and associated modelling. This aspect was not modelled and evaluated in the presented study, though must be taken into account within further work necessary for possible clinical implementation. Nevertheless, focusing on the fluorine-18 contribution induced by helium ion beams, as presented in [32,34] fluorine has different kinetics within human cells [33] comparing to isotopes of other elements as relevant for PET-based verification. Results of [32,34] suggested that biological washout for fluorine-18 could be limited, though further experimental validation is necessary to validate this.

Future research outlooks

Considering the methodology, results and study limitations presented in this Chapter, following pathways for future additional research were identified:

- MC-based simulation study focusing on implementation of realistic PET detector technological constraints and re-evaluating the achievable signal and range

sensitivity, while also evaluating the necessary deliver dose level to achieve helium beam range estimate with clinically relevant uncertainty;

- experimental campaign, focusing on validation of presented results and evaluation of detection system technological limitations for PET-based verification of helium ion range;
- MC-based simulation study focusing on detectable signal by PET system and achievable range sensitivity within anatomically relevant geometry;
- algorithm development for helium ion beam range assessment via PET-based verification on spot-by-spot or layer-by-layer basis to achieve feasibility of clinically relevant workflow;
- studies on biological washout modelling for fluorine-17 and fluorine-18 contributions with further validation studies via experimental *in-vivo* campaign.

11.3.1 Considerations for technological implementation

While the results presented in this Chapter mainly focused on the overall physical feasibility of using helium beam induced fluorine-17 and fluorine-18 signals for detection with PET, following key considerations were identified for technological implementation of this approach:

- necessities to adapt beam temporal structure to allow in-beam or in-room verification should be evaluated from accelerator physics perspective, as optimization of slow extraction scheme would be necessary.
- as already discussed in the review of Chapter 8 and corresponding Appendix – optimization and integration of suitable PET detection system.

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Oxygen-18 as prompt gamma contrast agent for helium ion range verification

Chapter 12 focuses on another range verification method for Bragg peak localisation - PG photon detection. Detection of PG photons could provide real-time dose delivery verification, also compatible with the millisecond scale of *FLASH* therapy. Practical implementation of PG photon verification is limited by relatively low emission counts and high energy of emitted photons, complicating construction of a suitable detector. To address these issues, Chapter 12 proposes and evaluates the feasibility of oxygen-18 as a contrast agent via MC simulation study. Use of oxygen-18 could increase the number of PG photon emissions, especially at lower energy range, improving detected signal characteristics. Theoretically detectable PG photon signal spatial and temporal characteristics and respective correlation with dose distribution are evaluated for oxygen-18 enriched water, comparing to reference scenario of oxygen-16 water.

Used MC simulation and data analysis methods are outlined in Section 12.1: simulation geometry, definition of isotopically enriched oxygen-18 water, parameter scoring routines for emitted and detectable PG photons and neutrons. Additionally, methods to assess spatial and temporal suppression of neutron background are also presented. In addition to general characteristic evaluation, clinically relevant geometry is also simulated. For this scenario, methods imitating virtual PG photon detection systems (spatial, temporal, and spectral) are presented, along with approaches to evaluate range sensitivity, correlation with spatial dose distribution and impact of primary beam intensity. Uncertainty assessment is also discussed.

Simulation results are summarised in Section 12.2, focusing on PG photon signal characteristic improvement provided by oxygen-18 enriched water. In addition to general characteristics, signal improvements with oxygen-18 enriched tumour geometry are discussed for various virtual detection approaches. Correlation with absorbed dose distribution and range sensitivity is reported, providing comparison with reference oxygen-16 water. Results on neutron background suppression are also given. Conclusions and discussion on the study are given in Section 12.3, with possible technological implementation aspects discussed specifically in Subsection 12.3.1.

Contributions of the Author: Majority of the work presented has been performed solely by the Author, indicating used literature sources where applicable. Basis of the *python* scripts for PG photon spectrum and spatial distribution evaluation was created by Liga Rubene (RTU), under the supervision and further development by the Author. Initial basis of the *python* script for PG photon spectral line identification was created by Konstantinos Kostakis (DKFZ at time), under the supervision and further development by the Author.

Student research work supervised related to the results presented in this Chapter:

- Bachelor thesis:
Liga Rubene “*Dependence of correlation between Bragg peak position and gamma photon emission on helium-3 and helium-4 ion beam parameters*”, Riga Technical University, Submission: May 2023, Supervisor: **K.Paļskis** - thesis presents initial results in reference oxygen-16 conditions, analysis methodology is developed
- Master’s thesis:
Liga Rubene “*The impact of ^4He ion energy on gamma photon emission depending on irradiated tissues with varying ^{18}O concentration*”, Riga Technical University, Submission: May 2025, Supervisor: **K.Paļskis** - thesis presents results on oxygen-18 in localized tumour geometry condition

Approbation of the results presented in this Chapter:

- Oral presentation 5th CERN Baltic Conference (CBC’25) in Kaunas, Lithuania, 2025
K.Paļskis, I.Baumgarte, A.Viņķe, T.Torims, M.Vretenar, J.Seco, M.Sapinski “*Towards the last millimeters in helium ion therapy: developing dedicated range verification methods*”
 - Oral presentation at 2nd CERN Baltic conference (CBC’22) in Vilnius, Lithuania, 2022
K.Paļskis, T.Torims, M.Vretenar, J.Seco, M.Sapinski “*Physical and biological property comparisons of ^4He and ^3He ion beams for applicability in radiation therapy*” - initial results and methodology aspects presented
 - Peer-reviewed and accepted, not presented, abstract at 61st Annual Conference of the Particle Therapy Cooperative Group (PTCOG’23) in Madrid, Spain, 2023
K.Paļskis, T.Torims, M.Vretenar, M.Sapinski, J.Seco, “*Helium-3 and helium-4 ion beam comparison for radiation therapy - achievable signal for treatment range verification*” - initial results and methodology aspects presented
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12.1. Modelling and analysis methodology

This Section provides brief summary of the modelling and analysis methodology used within the study, while additional methodological details are given in Appendix 11.1.

Water cylinder, with same geometry as for PET verification, was used, considering the same helium-4 ion energy levels. Two MC simulation campaigns were conducted: firstly, assessing general impact of ^{18}O on PG photon characteristics, and secondly, evaluating clinically relevant scenario and impact of ^{18}O on the signal registered with various PG photon detection approaches. Following [97-98], ^{18}O nuclei as contrast agent were considered in ^{18}O -water. ^{18}O -water had density of 1.1093 g/cm³, with regular ^{16}O -water considered for comparative reference (0.9982 g/cm³) – both considered at temperature of 20 °C. Mean excitation energy for both was set to 78 eV.

Table 12.1.

Physical characteristics used in simulations for water molecules with ^{16}O and ^{18}O enrichment

	^{16}O -water	^{18}O -water
Mean excitation energy I	78 eV	
Atomic number to mass ratio Z/A	0.5552	0.4996
Density ρ^*	0.9982 g/cm ³	1.1093 g/cm ^{3**}

* Density values indicated at temperature of 20 °C

** Calculated based on Z/A ratio differences, validated with data in [8]

For first part of campaign, two ideal detection volumes of air (2 mm thickness) were considered around cylinder - cylindrical (90 and 120 cm long with 70 and 130 cm inner diameter, respectively) and spherical (70 cm inner radius). Emission depth positions, energy and emission times were scored for all generated photons, with same characteristics scored at detection volume crossing points. With secondary neutrons as prominent background in realistic detection system, relevant parameters at neutron crossing points with detection volume were scored in the same manner. IDDs were scored for correlation assessment. Emitted and detected PG photon energy spectra, time-of-flight (ToF) and spatial distributions were evaluated. Correlation between spatial and temporal metrics was assessed with respect to absorbed dose distribution.

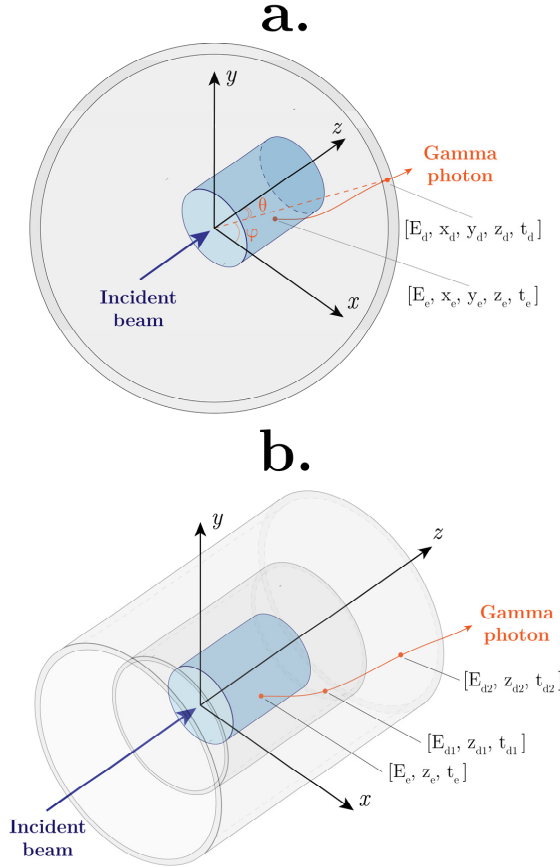


Figure 12.1. Geometries used for gamma photon and neutron scoring in MC simulations: spherical (a) and cylindrical (b)

Only gamma photons indicated, parameter scoring for neutrons was performed in the same manner.

Subfigure (a): Inner radius of spherical detector volume - 70 cm, centre of the water cylinder face coincided with the centre of the sphere. φ defined between momentum direction and X-axis, θ - between momentum direction and Z-axis. Physical parameters scored at position of creation (e) and crossing detector volume (d)

Subfigure (b): Inner radii of the cylindrical detector volumes - 35 and 65 cm, with centres of all volumes coincident. Parameters scored at position of creation (e) and crossing each detector volume (d1 and d2)

The second part of the campaign used clinically relevant scenario - 100×100×100 mm cubic “tumour” volume with ^{18}O -water embedded in a ^{16}O -water cylinder, similarly as [99]. For comparative reference, “tumour” volume with ^{16}O -water was considered. Irradiation field size was 100×100 mm with uniform intensity throughout, only helium-4 ion energy of 171.4 MeV/u was considered. Same idealized detector volumes were used, scoring energy, ToF and position at detector crossing points, with

additional scoring of angle of momentum with respect to z-axis for implementation of virtual collimators. Idealized conditions with no material budget imitated main PG photon detection approaches: multi-slit collimator, knife-edge slit, PG timing and PG spectroscopy - using dedicated data filters. Such idealized approach imitates general trends of real detector systems, though is limited in accurate estimation of detectable PG photon counts. For each method, sensitivity to introduced range shifts (± 1 , ± 2 , ± 5 and ± 10 mm) was evaluated: re-simulated and compared with unperturbed reference, using statistical bootstrapping. To assess the impact of primary beam intensity, calculations were repeated for different number of primaries (based on calculated PG photon yield), estimating number of particles necessary to achieve a particular level of registered shift uncertainty.

12.2. Results of the modelling

General ^{18}O contrast agent characteristic evaluation: Spectral properties of PG emissions

First part of MC simulation campaign on ^{18}O -based contrast agent evaluation on general impact on physical properties of emitted PG photons, by comparison of ^{18}O and ^{16}O water. As one of the main parameters for comparison, spectral characteristics of emitted and detected PG photons were evaluated. Figure 12.2 illustrates energy spectra of emitted (*upper line*) and detected (*lower line*) of PG photons as generated in whole irradiated object volume. Energy spectra are illustrated for varying helium-4 ion beam ranges in water.

Analysing emitted PG photon energy spectra, ^{18}O water has higher magnitude of PG photon emissions with respect to reference of ^{16}O in the energy range 0 - 4 MeV. Furthermore, the higher magnitude also corresponds to significantly increased number of discrete spectral lines unique for ^{18}O with respect to ^{16}O . In the energy range above 4 MeV, shapes of energy spectra for ^{18}O and ^{16}O water are comparable, while ^{18}O spectra exhibit a few unique discrete spectral lines also in this higher energy range. Increasing initial energy of helium-4 ions does not affect the general shape of emitted PG photon energy spectrum for both water types, though overall intensity increases.

Comparing the spectra of emitted and detected PG photon spectra, the overall intensity decreases for the latter. Additionally, significant differences in ^{18}O water can be observed for detected PG photons in 0 - 1 MeV range with respect to emission. While several discrete spectral lines can be distinguished within this range in the emission spectrum, respective detected intensity is significantly lower with majority of spectral lines not distinguishable from continuum background. This is attributable to significantly higher attenuation of lower energy PG photons via mechanisms discussed in Chapter 2. Due to higher attenuation, only clearly distinguishable spectral lines in detected PG photon spectrum of ^{18}O water in the range 0 - 1 MeV are the ones with highest emission intensity - 0.51, 0.82 and 0.87 MeV.

For quantitative evaluation, absolute PG photon yield comparison between ^{16}O and ^{18}O water is summarized in Table 12.2.

Table 12.2.

Comparison of emitted and detected PG photon yield between ^{16}O and ^{18}O enriched water phantoms irradiated with helium-4 ions of varying energy

Irradiated material	Beam energy	PG photons emitted (per incident particle)*		PG photons detected (per incident particle)**	
		0 - 10 MeV	0 - 4 MeV	0 - 10 MeV	0 - 4 MeV
^{16}O enriched water	115.3 MeV/u	$0.447 \pm 0.02\%$	$0.310 \pm 0.03\%$	$0.358 \pm 0.02\%$	$0.266 \pm 0.03\%$
	171.4 MeV/u	$1.037 \pm 0.01\%$	$0.787 \pm 0.02\%$	$0.657 \pm 0.02\%$	$0.507 \pm 0.02\%$
	217.0 MeV/u	$1.600 \pm 0.01\%$	$1.270 \pm 0.01\%$	$0.911 \pm 0.01\%$	$0.690 \pm 0.02\%$
^{18}O enriched water	115.3 MeV/u	$0.770 \pm 0.02\%$	$0.632 \pm 0.02\%$	$0.614 \pm 0.02\%$	$0.521 \pm 0.02\%$
	171.4 MeV/u	$1.617 \pm 0.01\%$	$1.364 \pm 0.01\%$	$1.129 \pm 0.01\%$	$0.959 \pm 0.01\%$
	217.0 MeV/u	$2.355 \pm 0.01\%$	$2.006 \pm 0.01\%$	$1.495 \pm 0.01\%$	$1.268 \pm 0.01\%$

* Temporal cut of ≤ 50 ns applied, scoring PG photons emitted from whole phantom volume. PG photon emission given for 2 energy ranges: 0-10 and 0-4 MeV. 1σ binomial uncertainty given as relative value, calculated for 5×10^7 primary particles.

** Temporal cut of ≤ 50 ns applied, scoring PG photons detected by idealized spherical detector. Detected PG photons given for 2 energy ranges: 0-10 and 0-4 MeV. 1σ binomial uncertainty given as relative value, calculated for 5×10^7 primary particles.

Data in Table 12.2. quantitatively illustrate the increase of emitted and detected PG photon yield in ^{18}O water with respect ^{16}O water. For PG photon energy range up to 10 MeV, emitted PG photon yield increased by 72.3%, 55.9% and 47.2% for ^{18}O water with respect to ^{16}O water for helium-4 ion energies of 115.3, 171.4 and 217.0 MeV/u, respectively. Similarly, the detected PG photon yield increased respectively by 71.5%, 71.8% and 64.1%. Although absolute PG photon yield increases with increasing helium-4 ion energy, the relative increase for ^{18}O water with respect to ^{16}O water is lower for higher energies.

Majority of unique PG photon discrete energy lines for ^{18}O water are in the energy range 0 - 4 MeV. Comparing ^{18}O water with respect to ^{16}O in this energy range, emitted PG photon yield was increased by 103.9%, 73.3% and 58.0%, respectively, while detected PG photon yield - by 95.9%, 89.2% and 83.8%.

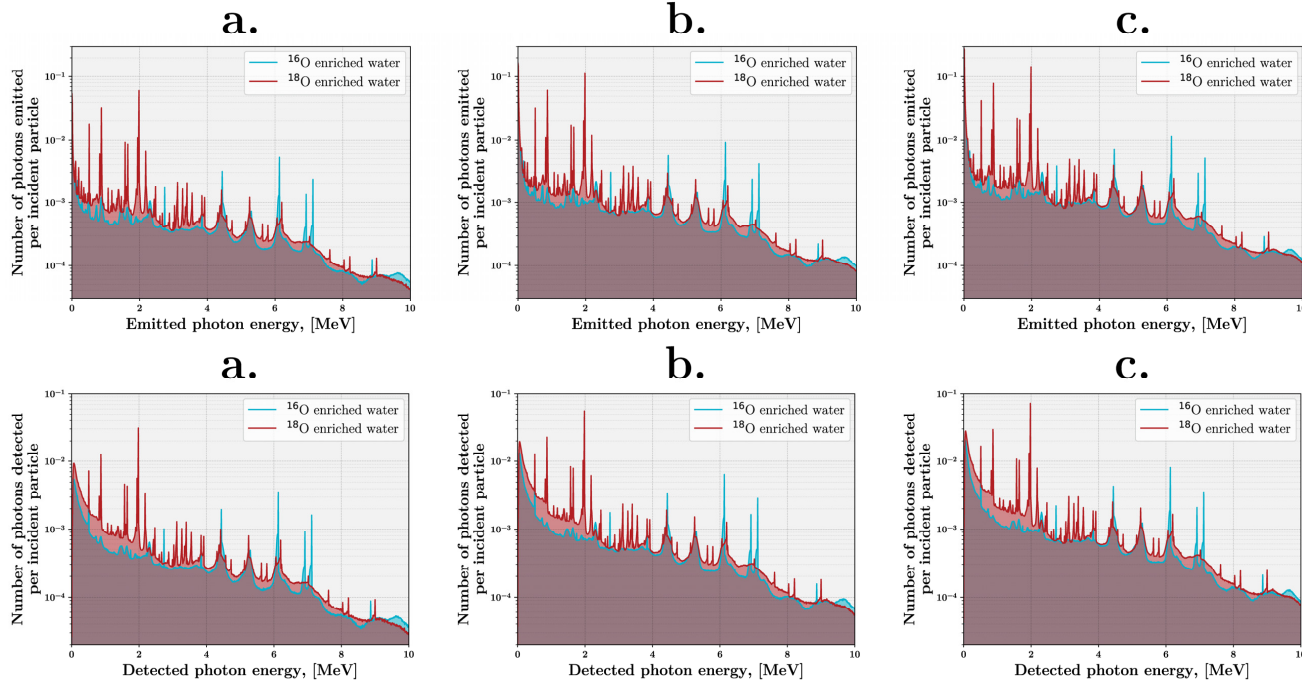


Figure 12.2. Comparison of energy spectra for emitted and detected PG photons for ^{16}O and ^{18}O enriched water for different helium-4 ion energies

Data illustrated for energy range 0-10 MeV with data grouped in bins of 10 keV, with temporal cut of ≤ 50 ns applied in both scenarios to distinguish delayed emissions. Number of PG photons per bin normalized by number of incident particles - $5 \cdot 10^7$ - and given in logarithmic scale. Statistical uncertainty per bin not illustrated for visual clarity - 1σ binomial uncertainty in the range from 0.02% (0.3 per incident particle) to 3.16 % ($2 \cdot 10^{-5}$ per incident particle). *Upper line* - data on PG photons emitted in whole water phantom volume, *lower line* - data on PG photons detected by idealized spherical detector.

Data given for helium-4 ions of energies 115.3 MeV/u (100 mm range in water, Subfigures (a)), 171.4 MeV/u (200 mm range in water, Subfigures (b)) and 217.0 MeV/u (300 mm range in water, Subfigures (c)).

Increase of unique PG photon spectral lines corresponds to de-excitation of several nuclei - ^{18}O , ^{19}F , ^{19}Ne , ^{20}Ne and ^{21}Ne - produced via unique interactions of helium-4 ions with target ^{18}O atoms, which have small reaction cross-section or are not kinematically possible in the reference scenario with ^{16}O atoms. **Appendix 11.2.** summarizes data on main nuclear de-excitations contributing to unique PG photon emissions in ^{18}O water.

Data illustrated in Figure 12.2 correspond to PG photons only, using 50 nanosecond temporal cut. Via processes of delayed photon emission or secondary photon generation from nuclear decay, photons could be also detected at larger timescales (microseconds up to several seconds or minutes). Relevant data on this aspect are provided in **Appendix 11.3.**

General ^{18}O contrast agent characteristic evaluation: Temporal properties of PG emissions and neutron background

After comparison of spectral properties, other physical characteristics relevant for range verification - temporal and spatial properties of PG emission - were evaluated and compared. Comparison of temporal energy spectra between ^{16}O and ^{18}O is presented in **Appendix 11.4** for emitted and detected PG photons, respectively. Data are given for different initial helium-4 ion energies.

Data in Figure A.11.3. of **Appendix 11.4.** illustrate that the highest number of emitted PG photons for all relevant spectral lines in both ^{16}O and ^{18}O scenarios can be observed for emission times < 1 ns, < 1.7 ns and < 2.2 ns for initial helium-4 energies of 115.3, 171.4 and 217.0 MeV/u, respectively. Increased intensity corresponds to the contribution of primary helium-4 ions, while for emission times larger than indicated values - contribution from secondary particles. For primary particle emission time distribution, no significant differences were observed between ^{16}O and ^{18}O water. Analysing whole temporal PG photon energy distribution - higher intensities are observed for longer emission times in case of ^{18}O water, with most of the PG emissions observed for < 6 ns in ^{16}O water and $< 8 - 10$ ns in ^{18}O water. As higher emission time contributions arise from secondary particles, the observed difference in ^{18}O water could be attributable to changes in generated secondary particle energy spectrum. Higher kinetic energies of secondary particles would result in longer particle trajectories (and time) for interactions with matter, slightly delaying PG photon emission. For ^{16}O water, a decreasing intensity for main PG photon spectral lines can be observed with increasing emission time after primary helium-4 ion contribution. While in ^{18}O water similar trend can be observed for most of the PG photon spectral lines, in the energy range of 0 - 2 MeV several discrete spectral lines with highest intensity are rather constant up to 6 nanosecond emission time. This signifies the role PG photon generation by secondary particles in the low energy - 0 to 2 MeV - range for ^{18}O water.

Similar trends can be observed for detected PG photons, as illustrated in Figure A.11.4. of **Appendix 11.4.** Highest intensity of detected PG photons, corresponding to primary particle interactions, can be observed in the detection time range from 2.4 ns to

about 3.7, 4.6 and 5.3 ns for initial helium-4 energies of 115.3, 171.4 and 217.0 MeV/u, respectively. Though, in contrast, to spectra for emission, detected PG photon temporal energy spectra illustrate higher values of detection time for lower PG photon energies in the range 0 - 2 MeV. This can be attributed to higher scattering and other interactions at low energies, increasing PG photon trajectory length and subsequently - detection time. This is even more prominent in ^{18}O water, compared to ^{16}O water.

Figure 12.3 illustrates PG photon emission time distributions for ^{16}O and ^{18}O water, separating contributions generated by primary or secondary particle interactions. Data given for photons with energy above 0.5 MeV.

Data in Figure 12.3 illustrates the increase of maximum emission time for PG photons emitted by primary particles with increasing initial helium-4 ion energy. The shape of emission time distribution for PG photons generated by primary particles is comparable between ^{16}O and ^{18}O water - as the emission time in interactions by primaries is proportional to velocity profile in irradiated material, no significant differences are expected between as the energy loss is the same in both materials. On the contrary, significant differences can be observed in the contribution from secondary particles - relatively higher magnitude and emission time range can be observed in the case of ^{18}O water. Nevertheless, if all PG photons in the energy range 0.5 - 10 MeV are considered, resulting emission time distribution has more prominent peak in ^{18}O water scenario. Contrary to ^{16}O water, the peak emission time of all PG photons corresponds closely to peak emission time of primary particle generated photons for ^{18}O water (higher by about 1.4 to 1.8 ns) - important for range verification. PG photon yield at peak emission time is about 1.5 times higher for ^{18}O water.

Figure A.11.5 of **Appendix 11.5** illustrates PG photon detection time distributions for ^{16}O and ^{18}O water. As generated neutrons could significantly affect detected signal in realistic scenario, differences in neutron production between the ^{18}O water and ^{16}O water are also illustrated. As photons and neutrons have different energy loss characteristics in detectors, and idealized air detector was considered in this work -neutron data presented in Figure A.11.5 of **Appendix 11.5** do not have any energy cut applied.

Considering all PG photons with energies above 0.5 MeV, similarly to emission time, no significant differences between ^{16}O and ^{18}O can be observed for detection time distributions corresponding to photons generated by primary particles. The contribution of PG photons generated by secondary particles is of higher magnitude and longer detection times for ^{18}O water, effectively extending maximum detection time of significant PG photon signal ($> \sim 1\%$ of maximum) from about 7.5 to 10 ns.

Analysing the detection time distributions for neutrons, contrasting characteristics can be observed with respect to PG photons, with more details given in **Appendix 11.5**.

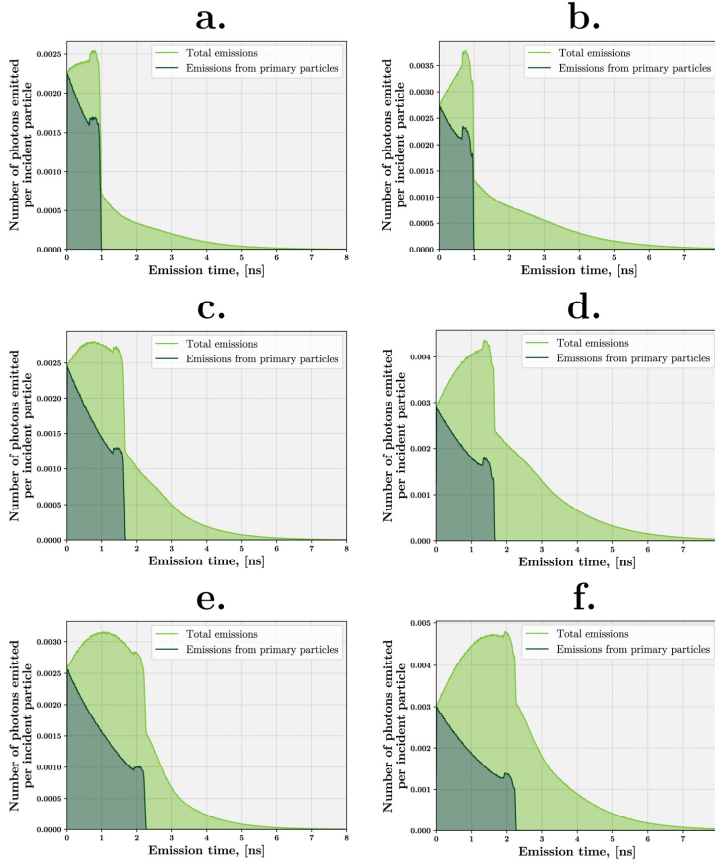


Figure 12.3. Comparison of PG photon emission time distributions for ^{16}O and ^{18}O enriched water for different helium-4 ion energies

Data given for PG photons with energy above 0.5 MeV. PG photon emission times (with respect to primary particle impinging on phantom) grouped in bins of 0.01 ns (range 0-8 ns). Number of PG photons per each bin normalized by number of incident particles - 5×10^7 . Data given for all PG photon emissions and separately - PG photons emitted by primary particle interactions. Statistical uncertainty per bin not illustrated for visual clarity - 1σ binomial uncertainty in the range from 0.20% (5×10^{-3} per incident particle) to 4.47% (1×10^{-5} per incident particle).

Data for ^{16}O enriched water given in left column (Subfigures (a), (c) and (e)), for ^{18}O - in right column (Subfigures (b), (d) and (f)). Data given for helium-4 ions of energies 115.3 MeV/u (100 mm range in water, Subfigures (a),(b)), 171.4 MeV/u (200 mm range in water, Subfigures (c),(d)) and 217.0 MeV/u (300 mm range in water, Subfigures (e),(f))

General ^{18}O contrast agent characteristic evaluation: Spatial properties of PG emissions and neutron background

In addition to temporal property comparison between ^{18}O and ^{16}O water, spatial properties of PG emission were also evaluated. Continuing previously discussed PG photon signal and neutron background distinguishability, spatial emission property differences between the two could be used in addition to detection time-based cuts. Differences of both temporal and spatial properties of detected PG photons and secondary neutrons in ^{18}O water and ^{16}O water are illustrated in **Appendix 11.6**.

Data in Figure A.11.6. of **Appendix 11.6**. illustrate, that PG photons are predominantly detected perpendicularly with respect to primary beam propagation. With additional quantitative data provided in later paragraphs, highest PG photon yield was observed at azimuthal emission angles in the ranges of $45^\circ - 115^\circ$, $55^\circ - 120^\circ$ and $50^\circ - 120^\circ$ for initial helium-4 energies of 115.3, 171.4 and 217.0 MeV/u, respectively. No significant differences between ^{18}O and ^{16}O water can be observed with respect to azimuthal detection angle distribution and correlation with detection time for primary particles (highest intensity in the distribution), while having differences for larger detection times as discussed before.

With PG photons isotropically emitted via nuclear de-excitation in “centre-of-mass” frame, the resulting azimuthal angle distributions, as discussed, are attributable to Doppler shift only from recoil momentum of target nuclei [17]. In contrast, secondary neutrons generated via nuclear interactions retain a significant fraction of momentum from the projectile particle [18]. As illustrated in Figure A.11.7. of **Appendix 11.6**., resulting azimuthal angle distributions for secondary neutrons are rather “forward peaked” - largest fraction of neutrons are generated angularly close to beam propagation axis. In ^{16}O water, highest secondary neutron yield was observed in azimuthal angle ranges from 0° up to 31° , 25° and 24° for initial helium-4 energies of 115.3, 171.4 and 217.0 MeV/u, respectively. For comparison, in ^{18}O water azimuthal angle ranges with highest secondary neutron yield were from 0° up to 35° , 30° and 29° , respectively. In both ^{16}O and ^{18}O water, time with highest neutron yield was 5.2 ns, 4.4 ns and 4.0 ns, respectively.

Overall, comparison between azimuthal angle and detection time distributions for PG photons and neutrons in **Appendix 11.6** clearly indicates that both contributions to detected signal could be sufficiently distinguishable if adequate temporal cut and detector location (based on azimuthal angle with respect to Bragg peak) is chosen.

Data presented in Figure 12.4. illustrate the correlation between absorbed dose and PG photon emission point spatial distributions for both ^{18}O and ^{16}O water for varying initial helium-4 ion beam energies. No significant qualitative differences be observed in PG photon emission point spatial distributions between ^{18}O and ^{16}O water. In both scenarios, peak of the distribution closely corresponds to the position of dose maximum. In case of ^{18}O water, the PG photon yield at peak position was about 1.5 times higher compared to ^{16}O water. Data on in-depth quantitative analysis for spatial parameter

deviations between absorbed dose and PG photon emission point spatial distributions are summarized in Table 12.3.

Table 12.3.

Comparison of emitted PG photon* spatial distribution metrics between ^{16}O and ^{18}O enriched water phantoms irradiated with helium-4 ions of varying energy and correlation of these metrics with absorbed dose distribution

Irradiated material	Beam energy	Absorbed dose distribution**			PG photon emission distribution***		
		$R_{D_{\max}}$	$R_{D_{80\%}}$	$R_{D_{50\%}}$	$R_{PG_{\max}}$	$R_{PG_{80\%}}$	$R_{PG_{50\%}}$
^{16}O enriched water	115.3 MeV/u	100.0	100.4	100.8	98.7 ± 0.2	100.2 ± 0.0	100.9 ± 0.0
	171.4 MeV/u	200.0	201.0	201.8	197.3 ± 0.5	200.8 ± 0.0	202.2 ± 0.0
	217.0 MeV/u	300.0	301.6	302.8	298.9 ± 0.8	301.7 ± 0.1	304.2 ± 0.1
^{18}O enriched water	115.3 MeV/u	100.0	100.4	100.8	99.7 ± 0.1	100.5 ± 0.0	101.1 ± 0.0
	171.4 MeV/u	200.0	201.0	201.7	199.5 ± 0.2	201.2 ± 0.0	203.2 ± 0.0
	217.0 MeV/u	300.0	301.5	302.5	298.5 ± 1.0	302.0 ± 0.0	303.8 ± 0.1

* Data given for PG photons with energy above 0.5 MeV, with temporal cut of ≤ 50 ns applied

** Absorbed dose spatial distribution evaluated with 0.5 mm resolution. Extracted metrics: depth of maximum dose ($D_{\max}$), depth corresponding to 80% distal dose fall-off ($D_{80\%}$) and depth corresponding to 50% distal dose fall-off ($D_{50\%}$). Statistical uncertainty not given, lower than resolution.

*** PG photon emission spatial distribution evaluated with 1 mm resolution. Extracted metrics: depth with maximum emitted PG photon intensity ($PG_{\max}$), depth corresponding to 80% fall-off of emitted PG photon peak intensity ($PG_{80\%}$) and depth corresponding to 50% fall-off of emitted PG photon peak intensity ($PG_{50\%}$). Statistical uncertainty given based on 1σ uncertainties of emitted PG photon intensity distribution.

Comparing spatial deviation between positions corresponding to maxima of absorbed dose and PG photon emission point distributions, slightly increased performance can be observed for ^{18}O water with respect to ^{16}O water. Deviations of -1.3 and -2.7 mm were observed in ^{16}O water, while only 0.3 and 0.5 mm in ^{18}O water for helium-4 ion energies of 115.3 and 171.4 MeV/u. At energy level of 217.0 MeV/u, observed deviation were higher and comparable - 1.1 and 1.5 mm for ^{16}O and ^{18}O water, respectively. For the other considered spatial distribution metrics:

- **for 80% fall-off position:** deviations of -0.2, -0.2 and +0.1 mm for ^{16}O water, for ^{18}O water - +0.1, +0.2 and +0.5 mm;
- **for 50% fall-off position:** deviations of +0.1, +0.4 and +1.4 mm for ^{16}O water, for ^{18}O water - +0.3, +1.5 and +1.3 mm.

Slight variations and dependency of initial kinetic energy of helium-4 ions are attributable to contribution of secondary particle generated PG photons. Nevertheless, relatively low deviations between absorbed dose and PG photon emission distribution are observed. This could be attributable to relatively low energy thresholds for PG photon generation nuclear interactions. Summarizing, ^{18}O water provides comparable or slightly improved

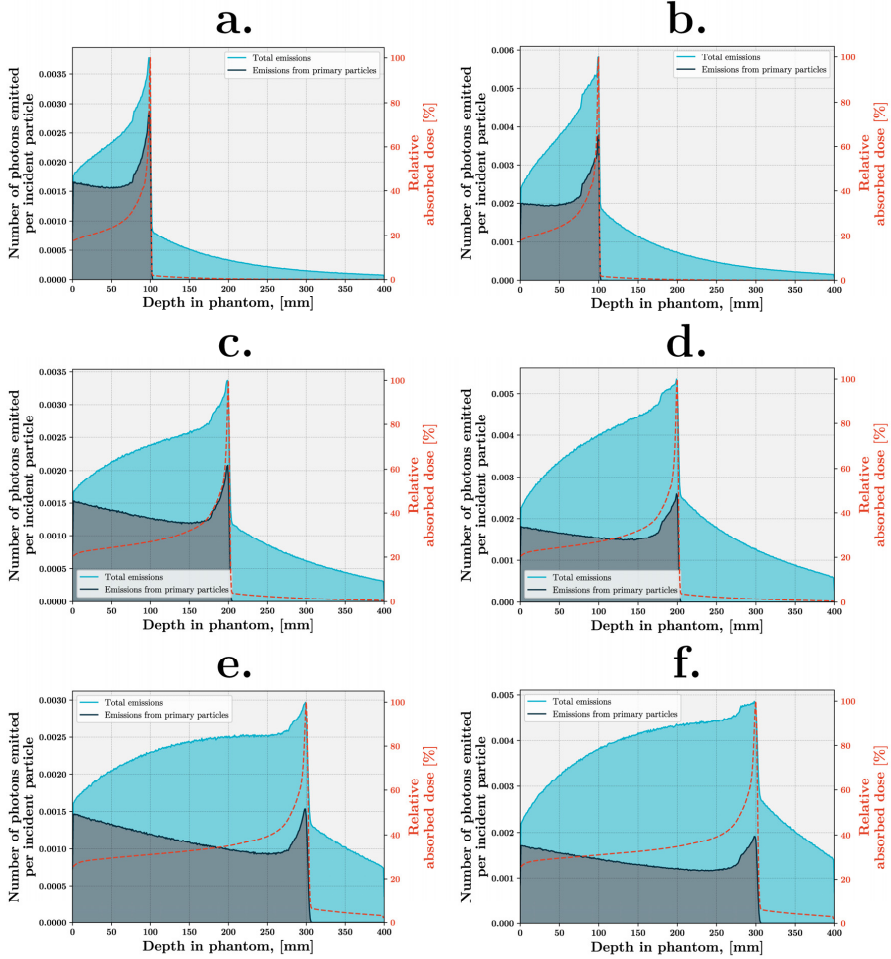


Figure 12.4. Comparison of PG photon emission position distribution along beam axis for ^{16}O and ^{18}O enriched water for different helium-4 ion energies

Data given for PG photons with energy above 0.5 MeV, with temporal cut of ≤ 50 ns applied. PG photon emission point coordinates along beam axis (depth) grouped in bins of 1 mm (range 0-400 mm). Number of PG photons per each bin normalized by number of incident particles - 5×10^7 . Data given for all PG photon emissions and separately - PG photons emitted by primary particle interactions. Statistical uncertainty per bin not illustrated for visual clarity - 1σ binomial uncertainty in the range from 0.18% (6×10^{-3} per incident particle) to 4.47% (1×10^{-5} per incident particle). Relative (normalized to maximum) depth dose distribution given for comparison, statistical uncertainty below 0.1% not illustrated.

Data for ^{16}O enriched water given in left column (Subfigures (a), (c) and (e)), for ^{18}O - in right column (Subfigures (b), (d) and (f)). Data given for helium-4 ions of energies 115.3 MeV/u (100 mm range in water, Subfigures (a),(b)), 171.4 MeV/u (200 mm range in water, Subfigures (c),(d)) and 217.0 MeV/u (300 mm range in water, Subfigures (e),(f))

performance with respect to ^{16}O , depending on the initial helium-4 ion energy and spatial distribution parameter considered.

It is also important to note that data in Table 12.3 illustrate no impact of ^{18}O enrichment on absorbed dose distribution - an important characteristic for contrast agent to be used therapeutically. For materials with different isotopic composition, differences of atomic number to mass ratio are offset by change in density, thus the overall energy loss is not impacted.

In context of range verification, PG photon spatial characteristics outside the irradiated volume - in the detector volume - are of even higher importance. PG photon yield in detector volume as function of position along beam axis is presented in Figure A.11.8. of **Appendix 11.7** for ^{18}O and ^{16}O water. With respect to emission point distribution, detection point distribution does not have a prominent peak due to isotropic nature of PG photon emission. Therefore, as introduced in Chapter 8 and discussed in next subsections, in realistic scenarios hardware with limited angular or spatial acceptance needs to be introduced for signal detection suited for range shift registration. For un-filtered PG photon spatial signal in detector volume, no significant differences of distribution shape can be observed for the ^{18}O and ^{16}O water. Negligible deviation between spatial position with maximum detected PG photon intensity and Bragg peak can be observed for lowest helium-4 ion energy of 115.3 MeV/u. For higher helium-4 ion energies, significant upstream shift can be observed for PG photon distribution maximum with respect to Bragg peak position. Comparing PG photon maximum intensity, 1.6 times higher yield was observed for ^{18}O in comparison to ^{16}O .

For quantitative evaluation, data on position of detected PG photon yield maximum and associated uncertainty for both ^{16}O and ^{18}O water are summarized in Table A.11.3. of **Appendix 11.7**.

Analysing data in Table A.11.3. of **Appendix 11.7**, no significant differences can be observed between ^{16}O and ^{18}O water, though ^{18}O water indicated decreased uncertainty of maximum intensity position, attributable to higher PG photon yield.

Finally, the distinguishability of PG photon and secondary neutron distributions were evaluated with respect to detection time and detection position along beam propagation axis. Resulting distributions are illustrated in Figures A.11.9 and A.11.10 of **Appendix 11.8** for PG photons and secondary neutrons, respectively. Due to differences of physical mechanisms for production, as discussed previously, similar differentiability between PG photons and secondary neutrons can be observed if Z-axis position instead of azimuthal angle is considered. Slight differences between ^{16}O and ^{18}O water are similar as in the evaluations with respect to azimuthal angle. Data illustrated in Figures A.11.9 and A.11.10 of **Appendix 11.8** re-iterate the feasibility of distinguishability between PG photon signal and neutron background if suitable detection time window and detector position is used.

General ^{18}O contrast agent characteristic evaluation: Evaluation of spatial and temporal PG characteristic correlation with absorbed dose distribution

As the final aspect of first MC simulation, quantitative correlation between spatial and temporal characteristics of PG photons was assessed. Correlation was assessed comparatively between ^{18}O and ^{16}O water, with PG photons above 0.5 MeV considered.

Data in **Appendix 11.9** illustrate correlation between Bragg peak position and position with maximum emitted and detected PG photon intensity. In both ^{16}O and ^{18}O water, high Pearson correlation coefficient was observed ($r > 0.999$) between Bragg peak position and position with maximum emitted PG photon intensity. Ideal sensitivity was observed, with slope of the linear fit equal to 1 - 1 mm change in Bragg peak position corresponds to 1 mm shift in PG photon emission maximum position. Similarly, high Pearson correlation coefficient ($r > 0.991$) was also observed for Bragg peak position correlation with position of maximum detected PG photon intensity, though the sensitivity was reduced with linear fit slope of 0.52 and 0.50 for ^{16}O and ^{18}O water, respectively. This is attributable to the shape of unfiltered PG photon spatial distribution, as discussed before.

Emission and detection time distribution characteristic parameters as function of the Bragg peak position are presented in **Appendix 11.10**. Quantitative analysis of correlation for illustrated data was as follows:

- **emission time distribution maximum:** Pearson correlation coefficients of 0.834 and 1.000, linear fit slopes (sensitivity) of 1 and 6 ps/mm for ^{16}O and ^{18}O respectively;
- **emission time distribution FWHM:** Pearson correlation coefficients of 0.999 and 0.999, linear fit slopes (sensitivity) of 6 and 8 ps/mm;
- **emission time distribution integral:** Pearson correlation coefficients of 0.975 and 0.969, linear fit slopes (sensitivity) of 2 and 2 ps/mm;
- **detection time distribution maximum:** Pearson correlation coefficients of 0.812 and 1.000, linear fit slopes (sensitivity) of 2 and 6 ps/mm;
- **detection time distribution FWHM:** Pearson correlation coefficients of 0.994 and 0.992, linear fit slopes (sensitivity) of 7 and 8 ps/mm;
- **detection time distribution integral:** Pearson correlation coefficients of 0.973 and 0.967, linear fit slopes (sensitivity) of 2 and 2 ps/mm.

Summarizing, comparable or even improved temporal characteristic correlation and associated sensitivity can be achieved with ^{18}O with respect to ^{16}O . Time distribution FWHM and integral are more reliable descriptors, though maximum of the time distribution can also be considered for ^{18}O water scenario.

Overall, summarizing the results of first part of the MC simulation campaign, assessing the general ^{18}O contrast agent characteristics - clear potential can be observed. Introduction of ^{18}O nuclei significantly increase the overall yield of PG photons, especially in the lower energy range of 0 - 4 MeV. Furthermore, the presence of several spectral lines unique to ^{18}O and other nuclei produced via interactions with helium-4 ion beams, that are not present for ^{16}O nuclei could enable PGS approaches. ^{18}O water as a contrast

agent exhibits comparable or even improved spatial and temporal characteristic correlation with absorbed dose distribution with respect to ^{16}O . This aspect is crucial to range verification. In context of secondary neutron generation - source of background in signal registration - ^{18}O does exhibit increased production yield with respect to ^{16}O . Nevertheless, the increase in PG photon yield is higher with respect to secondary neutron increase, thus comparable or even improved neutron background rejection could be expected for ^{18}O contrast agent, though this topic is just briefly introduced in the scope of the Thesis and needs further studies. Finally, with respect to ^{16}O water, introduction of ^{18}O contrast agent does not perturb the absorbed dose distribution - crucial aspect in IBT treatment planning. Of course, the level of perturbation would need to be assessed also in biological tissue, though it is beyond the initial characterization presented in the Thesis.

All the aforementioned characteristics in idealized phantom (whole volume enriched) do indicate ^{18}O as extremely attractive contrast agent for PG photon signal enhancement for helium-4 IBT. Thus, the second part of presented results briefly focuses on clinically relevant scenario with simulated tumour volume enriched with the contrast agent and evaluates the ideally detectable PG photon signal.

General ^{18}O contrast agent characteristic evaluation: Impact of ^{18}O contrast agent concentration

Before further investigations, brief discussion and quantitative results are provided on the role of ^{18}O contrast agent concentration. Throughout this section, all the reported results have been considered for 100% enrichment of ^{18}O nuclei in water. In a realistic, clinical scenario this could possibly be infeasible as well as being associated with higher costs of the contrast agent. Although investigation on optimum concentration of ^{18}O contrast agent to be used for PG photon signal enhancement is beyond the scope of this Thesis, initial data are provided in **Appendix 11.11**.

Data illustrated in **Appendix 11.11** indicate the naturally expected unique spectral line intensity decrease for lower ^{18}O concentrations. It can be observed that distinguishable intensity level of most of ^{18}O unique spectral lines with respect to ^{16}O reference can be observed at 10 % concentration, though highest intensity spectral peaks, such as 1.98 MeV, could still be distinguished at lowest considered concentration - 1 %. Additionally, data in **Appendix 11.11** indicates several low energy (< 500 keV) emission spectral lines unique to ^{18}O , not discussed before. Apparent reduction of their intensity can be observed for detected PG photon signal, due to photon attenuation and scattering. Nevertheless, it would be of further research interest to investigate these spectral lines for use in approaches as PGS. This aspect though it is for future research pathways as focus in this study has been on energy range 0 - 4 MeV.

Concentration effects on detectable unique ^{18}O contrast signal are also largely dependent on tumour geometry as illustrated in Master's thesis supervised by the Author on this topic [13]. Considering a tumour volume enriched with ^{18}O , the size of the tumour and depth of the tumour (corresponding to relative volume with ^{18}O with respect to

irradiated volume) significantly impact the achievable overall increase of PG signal intensity and distinguishability of unique spectral lines.

PG detection with ^{18}O as a contrast agent: Evaluation of PG spectral characteristics

The second part of MC simulation campaign focuses on more clinically relevant scenario - $100 \times 100 \times 100$ mm tumour enriched with ^{18}O contrast agent embedded in ^{16}O water volume. This part of the work addresses how PG photon signal spectral, spatial, and temporal characteristics are impacted by only a limited part of the irradiated volume filled with ^{18}O contrast agent - a clinically relevant scenario.

With a lower fraction of irradiated volume enriched with ^{18}O , significant changes in PG photon energy spectrum could be expected, as large fraction of the volume would correspond to the reference medium - ^{16}O . Additionally, as the presence of ^{18}O nuclei is limited to a local region, the unique PG photon spectral line intensity could also be impacted by the energy dependency of cross-section for the nuclear interactions. Illustrative example for change in the detected PG photon energy spectrum in “enriched tumour” scenario is given in Figure 12.5.

Figure 12.5 clearly illustrates that in the case of contrast agent localized only in the tumour region, the impact of ^{18}O nuclei presence is significantly reduced. Almost no difference can be observed between for PG photon energy spectra of ^{18}O enriched tumour and reference scenario - regular ^{16}O water filled tumour - in the energy range above 4 MeV. Prominent spectral lines in the energy range up to 2 MeV can still be observed, especially 1.98 MeV, though respective intensities are lower as discussed before. Additionally, the example of varying virtual multi-slit collimator angular acceptance also signifies the impact of detected PG photon count - for lower number of PG photons detected (due to detector acceptance, hardware limitations or number primary particles used for irradiation) the spectral differences are less distinguishable.

For quantitative analysis of ^{18}O contrast agent effect on the number of detected PG photon count in “enriched tumour” scenario, data in Table 12.4 provide comparison with respect to a reference scenario. Data are provided for 0 - 10 MeV range and for low energy range - 0.5 and 3 MeV. The low energy range of 0.5 - 3 MeV was chosen as largest impact of ^{18}O could be observed in Figure 12.5. All subsequent results are provided in this lower energy range unless specified otherwise.

Data in Table 12.4 indicate that in “enriched tumour” scenario, an increase of detected PG photon yield by 13 % and 16 % was observed with ^{18}O contrast agent with respect to ^{16}O reference for energy ranges 0 - 10 MeV and 0.5 - 3 MeV, respectively. This indicates the expected decrease in overall PG photon yield, when only a limited part of the irradiated volume is filled with the contrast agent. Nevertheless, the increase is significant, more-so for lower energy range, prompting further investigations.

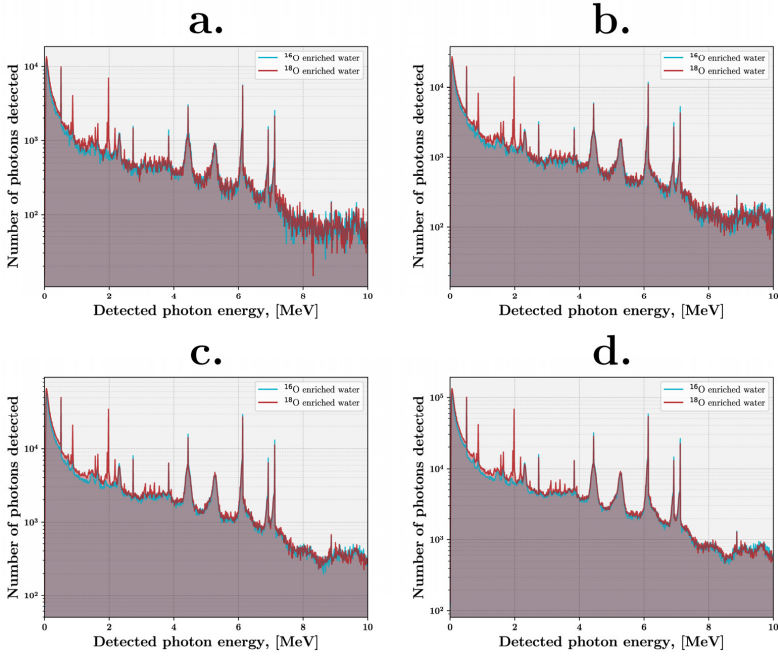


Figure 12.5. Example comparison of energy spectra for detected PG photons for ^{16}O and ^{18}O enriched tumour scenario for virtual multi-slit collimator with different angular acceptance

Data illustrated for energy range 0-10 MeV with data grouped in bins of 10 keV, with temporal cut of ≤ 50 ns applied. Number of PG photons per bin given in logarithmic scale. Statistical uncertainty per bin not illustrated for visual clarity - 1σ binomial uncertainty in the range from 0.32% (10^5 photons) to 22.36 % (~ 20 photons). Helium-4 ions with energy 171.4 MeV/u (200 mm range in water) used.

Data given for virtual multi-slit collimators with angular acceptances of $\pm 1^\circ$ (Subfigure (a)), $\pm 2^\circ$ (Subfigure (b)), $\pm 5^\circ$ (Subfigure (c)) and $\pm 10^\circ$ (Subfigure (d)).

Table 12.4.

Comparison of detected PG photon yield between ^{16}O and ^{18}O enriched simulated tumour scenario

Material of simulated tumour	Beam energy	PG photons detected (per incident particle)*	
		0 - 10 MeV	0.5 - 3 MeV
^{16}O enriched water	171.4 MeV/u	$0.527 \pm 0.03\%$	$0.437 \pm 0.04\%$
^{18}O enriched water	171.4 MeV/u	$0.598 \pm 0.03\%$	$0.507 \pm 0.03\%$

* Temporal cut of ≤ 50 ns applied, scoring PG photons detected by idealized cylindrical detector (70 cm diameter). Detected PG photons given for 2 energy ranges: 0-10 and 0.5-3 MeV. 1σ binomial uncertainty given as relative value, calculated for 5×10^7 primary particles.

PG detection with ^{18}O as a contrast agent: Sensitivity of PG emission spatial and temporal characteristics to range shifts

Before detectable PG photon signal evaluation with virtual detectors, the range sensitivity for emitted PG photons was assessed, using spatial and temporal features. The impact of introduced range shifts of ± 1 , ± 2 , ± 5 and ± 10 mm on emission spatial and temporal distributions for ^{18}O enriched tumour with respect to ^{16}O reference scenario are illustrated in **Appendix 11.12**.

Evaluating only emission characteristics, adequate range sensitivity could be observed in both ^{18}O enriched tumour scenario and ^{16}O water reference. Nevertheless, ^{18}O enrichment indicates improved PG photon count with respect to reference, favourable for detection. Considering spatial distribution of emission points, ^{18}O had 56% higher PG photon yield at the Bragg peak position with respect to reference. Similarly, about 58% higher peak PG photon yield was also observed in the emission time distribution.

One of the key advantages of tumour enrichment by ^{18}O - by observing PG photon emission point spatial distribution, tumour region can be clearly identified with a significant increase of PG photon yield. In the illustrated tumour depth extent from 150 to 250 mm, an increase of PG photon yield by up to 67% can be observed. Similarly, an increased PG photon yield by up to 67% in the emission time distribution can be observed for times corresponding to approximately primary particle travel times to depths within the “enriched tumour” extent - from about 1.05 to 1.65 nanoseconds.

Evaluating spatial and temporal characteristics of PG photon emission, an increased signal statistics could be achieved by using ^{18}O contrast agent with suitable detection methods. Additionally, as the contrast agent is localized, unique features in detectable signal shape are expectable further improving detection capabilities. To quantitatively assess these aspects, the next subsections present results on idealized detection of spatial characteristics via virtual multi-slit collimator and knife-edge slit, as well as temporal characteristic detection for PG timing approaches. Lastly, detection of unique spectral lines of ^{18}O contrast agent is briefly presented for possible implementation as PGS approach.

PG detection with ^{18}O as a contrast agent: PG spatial distribution detection with virtual multi-slit collimator

A virtual multi-slit collimator with varying angular acceptance of $\pm 1^\circ$, $\pm 2^\circ$, $\pm 5^\circ$ and $\pm 10^\circ$ was considered first for PG photon spatial distribution detection. Figure 12.6 illustrates the comparison of detectable signal for ^{18}O enriched tumour and ^{16}O water reference with a virtual multi-slit collimator of varying angular acceptance. For ^{18}O enrichment, clear increase for the number of detected PG photons can be observed in the region corresponding to the tumour. With respect to ^{16}O reference, an average increase of about 63% for the number of detected PG photons was observed in the tumour region. Additionally, detected PG photon spatial distribution for ^{18}O enriched tumour scenario has more prominent characteristics, possibly improving the sensitivity to range shifts. This is noticeably observable in Subfigure (c) for $\pm 5^\circ$ angular acceptance of the

virtual multi-slit collimator. While for ^{16}O reference no distinguishable peak can be observed due to large variation of PG photon momentum direction, a clear peak is observed for ^{18}O due to spatially localized increase of PG photon emission from the tumour region. This is only partially observable for $\pm 10^\circ$ angular acceptance. While an increase of the virtual multi-slit collimator angular acceptance proportionally increases the number of detected PG photons, loss of distinct distribution shape can be observed.

Figure A.11.16. of **Appendix 11.13** presents qualitative illustration of changes in PG photon spatial distribution by introduction of range shifts as detected by virtual multi-slit collimator of varying angular acceptance. Corresponding quantitative evaluation of range sensitivity is presented in Figure A.11.17. of **Appendix 11.13** - magnitude of registered shift magnitude with respect to actual shift introduced. Qualitatively, in data presented in Figure A.11.16. of **Appendix 11.13**, a distinguishable difference of detected PG photon spatial distribution can be observed for a minimum of ± 2 mm shift for angular acceptances of $\pm 1^\circ$ and $\pm 2^\circ$, with significantly worse distinguishability for $\pm 5^\circ$ and $\pm 10^\circ$ - respectively, only ± 5 mm and ± 10 mm. Furthermore, qualitatively improved distinguishability can be observed for ^{18}O enriched tumour with respect to ^{16}O reference.

Quantitative evaluation presented in Figure A.11.17. of **Appendix 11.13** will be further discussed only for $\pm 1^\circ$, $\pm 2^\circ$ and $\pm 5^\circ$ angular acceptances. For ^{16}O reference scenario, average deviations of registered shift with respect to nominal were 0.6, 0.6 and 1.0 mm for virtual angular acceptances considered, with associated uncertainties of 2.4, 2.4 and 2.1 mm, respectively. Comparatively, for ^{18}O enriched tumour scenario: average deviations of 0.8, 0.6 and 1.2 mm, with associated uncertainties of 2.1, 1.6 and 1.5 mm, respectively. Additional statistical analysis was performed by a linear regression - slope of the fit should equal to 1 - 1 mm introduced shift corresponds to 1 mm registered shift. For lowest virtual multi-slit collimator angular acceptance considered - R^2 of 0.988 and slope of 0.93 ± 0.04 was observed for ^{16}O water reference. A slightly improved performance was observed for ^{18}O enriched tumour scenario with R^2 and slope of the fit of 0.990 and 1.01 ± 0.04 .

^{18}O had a slightly improved performance with respect to ^{16}O , having linear fit slopes closer to ideal unity and comparable registered deviations. Nevertheless, the most significant aspect is the reduced registered shift uncertainty due to the increased number of PG photons detected. The number of PG photons detected is the key aspect for assessing overall achievable uncertainty of the method. The minimum number of primary helium-4 ions to achieve a certain level of uncertainty is directly affected by this, indicating minimum dose to be delivered per spot. Uncertainty level estimation was done via bootstrapping for varying number of primary helium-4 ions with results presented in Figure 12.7.

Data in Figure 12.7 illustrate that to achieve the same level of registered range shift uncertainty, ^{18}O enriched tumour scenario requires smaller number of primary helium-4 ions with respect to ^{16}O water reference. This a favourable aspect as a smaller

number of particles per spot could be delivered in this scenario, not necessitating special treatment planning strategies. Number of primary helium-4 ions necessary for the same uncertainty level also decreases with increasing angular acceptance up to $\pm 5^\circ$, decreasing afterwards due to limited sensitivity. The absolute numbers illustrated correspond to an idealized scenario of full volumetric coverage, with no absorption and geometry effects of the multi-slit collimator, thus significantly higher number of helium-4 ions necessary is expected in a realistic scenario. Nevertheless, the relative scaling between ^{18}O enriched tumour and ^{16}O water reference is of relevance, with the former requiring around 1.5 - 2.5 times less helium-4 ions delivered to achieve registered shift uncertainty of ± 1 mm.

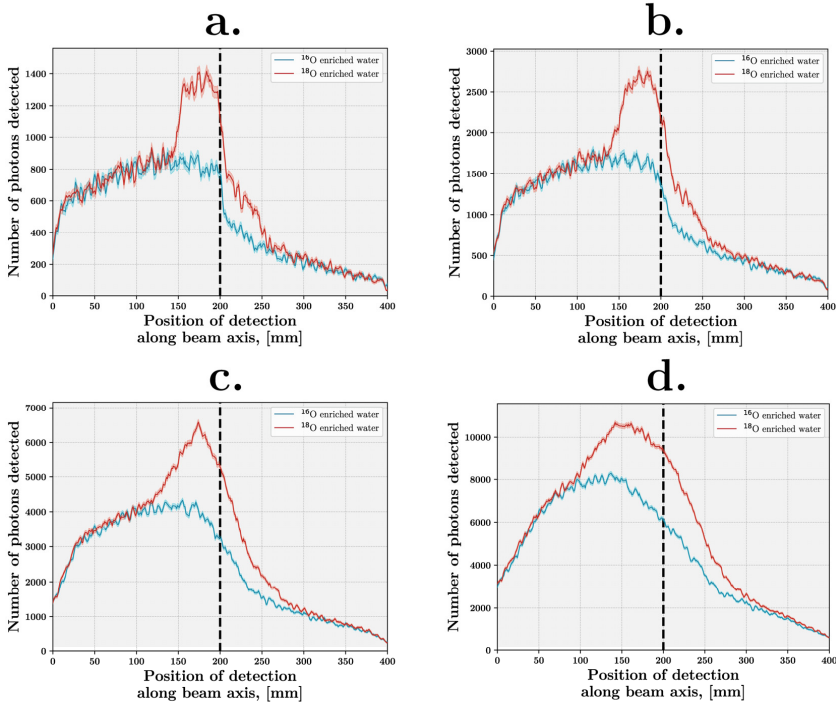


Figure 12.6. Comparison of PG photon spatial distributions detected with virtual multi-slit collimator for ^{16}O and ^{18}O enriched tumour scenario

Data detected with idealized cylindrical detector (70 cm diameter) given. Energy filter of 0.5 to 3 MeV and temporal cut of ≤ 50 ns applied for PG photon data. Spatial data grouped in bins of 1 mm. 1σ binomial uncertainty per bin illustrated as shaded region for each respective line, number of incident particles - 5×10^7 . Helium-4 ions with energy 171.4 MeV/u (200 mm range in water) used. Position of absorbed dose maximum position indicated as dashed black line.

Data given for virtual multi-slit collimators with angular acceptances of $\pm 1^\circ$ (Subfigure (a)), $\pm 2^\circ$ (Subfigure (b)), $\pm 5^\circ$ (Subfigure (c)) and $\pm 10^\circ$ (Subfigure (d)).

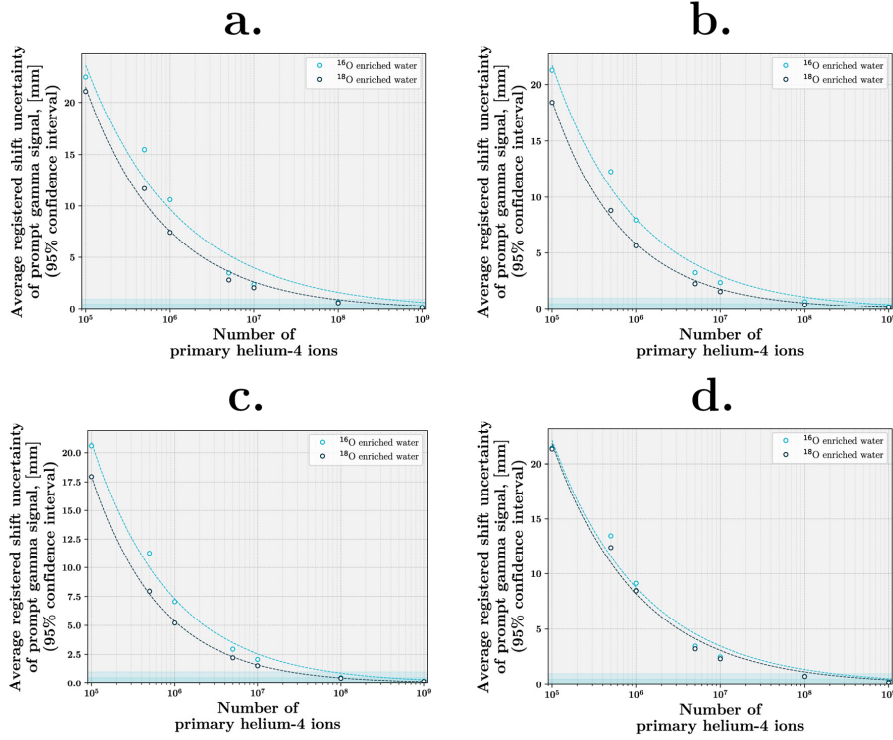


Figure 12.7. Influence of primary beam intensity on shift uncertainty registered with virtual multi-slit collimator in ^{16}O and ^{18}O enriched tumour scenario

Uncertainty defined as single sided 95% confidence interval. Data given for PG photons detected with idealized cylindrical detector (70 cm diameter), energy filter of 0.5 to 3 MeV and temporal cut of ≤ 50 ns applied. Data points correspond to average of all considered shift scenarios (± 1 , ± 2 , ± 5 and ± 10 mm) as calculated from 1000 bootstrapped samples, no error bars indicated. Data points given for 10^5 , 5×10^5 , 10^6 , 5×10^6 , 10^7 , 10^8 and 10^9 primary helium-4 ions, while dashed lines correspond to a fitting function of form $a/\sqrt{N}$ (N - number of primary ions) to reflect the Poissonian nature of uncertainty dependency on primary beam intensity. Shaded regions correspond to 0.5 and 1 mm uncertainty.

Data given for virtual multi-slit collimators with angular acceptances of $\pm 1^\circ$ (Subfigure (a)), $\pm 2^\circ$ (Subfigure (b)), $\pm 5^\circ$ (Subfigure (c)) and $\pm 10^\circ$ (Subfigure (d)).

PG detection with ^{18}O as a contrast agent: PG spatial distribution detection with virtual knife-edge slit

A virtual knife-edge slit with varying openings of 1, 2 and 5 mm was considered as the second approach for PG photon spatial distribution detection, with the virtual slit centred at the Bragg peak position. Figure 12.8 illustrates the comparison of detectable signal for ^{18}O enriched tumour and ^{16}O water reference with a virtual knife-edge slit. Similarly to multi-slit collimator, with ^{18}O enrichment clear increase of the number of detected PG photons can be observed in the tumour region. With respect to ^{16}O reference,

an average increase in the number of PG photons detected of about 57%, 69% and 77% was observed for slit opening of 2, 5 and 10 mm, respectively. Additionally, detected PG photon spatial distribution for ^{18}O enriched tumour scenario has prominent peak, possibly improving range sensitivity. Larger slit results in an increase of the number of detected PG photons proportionally, though decreased signal shape quality is to be expected.

Figure A.11.18. of **Appendix 11.14** presents qualitative illustration of range shift induced changes in PG photon spatial distribution as detected by virtual knife-edge slit of varying opening. Corresponding quantitative evaluation of range sensitivity is presented in Figure A.11.19. of **Appendix 11.14**. Qualitatively, in data presented in Figure A.11.18. of **Appendix 11.14**, a distinguishable difference can be observed in detected PG photon spatial distribution for a minimum of ± 2 mm shift for all slit openings considered.

Quantitative evaluation presented in Figure A.11.19. of **Appendix 11.14**. is done in the same manner as for multi-slit collimator, though indicating results for 10^8 primary particles considered due to reduced signal (compared to 10^7 of the former). For ^{16}O reference, average deviations of registered shift with respect to nominal were 1.8, 0.4 and 0.9 mm for virtual slit openings considered, with associated uncertainties of 1.6, 1.3 and 0.9 mm, respectively. Comparatively, for ^{18}O enriched tumour scenario: average deviations of 1.4, 0.9 and 0.8 mm, with associated uncertainties of 1.0, 0.7 and 0.6 mm, respectively. Additional statistical metrics were evaluated as for multi-slit collimator. For 2 mm slit - R^2 of 0.971 and slope of 0.95 ± 0.03 was observed for ^{16}O water reference. A slightly improved performance was observed for ^{18}O enriched tumour scenario with R^2 and slope of the fit of 0.982 and 1.02 ± 0.02 .

Similarly to virtual multi-slit collimator, ^{18}O had a slightly improved performance with respect to ^{16}O , having linear fit slopes closer to ideal unity and comparable registered deviations, with, reduced registered shift uncertainty due to the increased number of PG photons detected. To evaluate the minimum number of primary helium-4 ions to achieve a certain level of registered shift uncertainty approach as in multi-slit collimator scenario was considered, with data presented in Figure 12.9.

As for multi-slit collimator, data in Figure 12.9, illustrate that to achieve the same level of registered range shift uncertainty, ^{18}O enriched tumour scenario requires smaller number of primary helium-4 ions with respect to ^{16}O water reference. Number of primary helium-4 ions necessary for the same uncertainty level also decreases with increasing slit opening. The relative scaling between ^{18}O enriched tumour and ^{16}O water reference is of relevance, with the former requiring around 2.5 - 3 times less helium-4 ions delivered to achieve registered shift uncertainty of ± 1 mm. Though once again, several factors affecting the absolute number of primary helium-4 ions necessary are not considered in the current work with virtual, idealized detector.

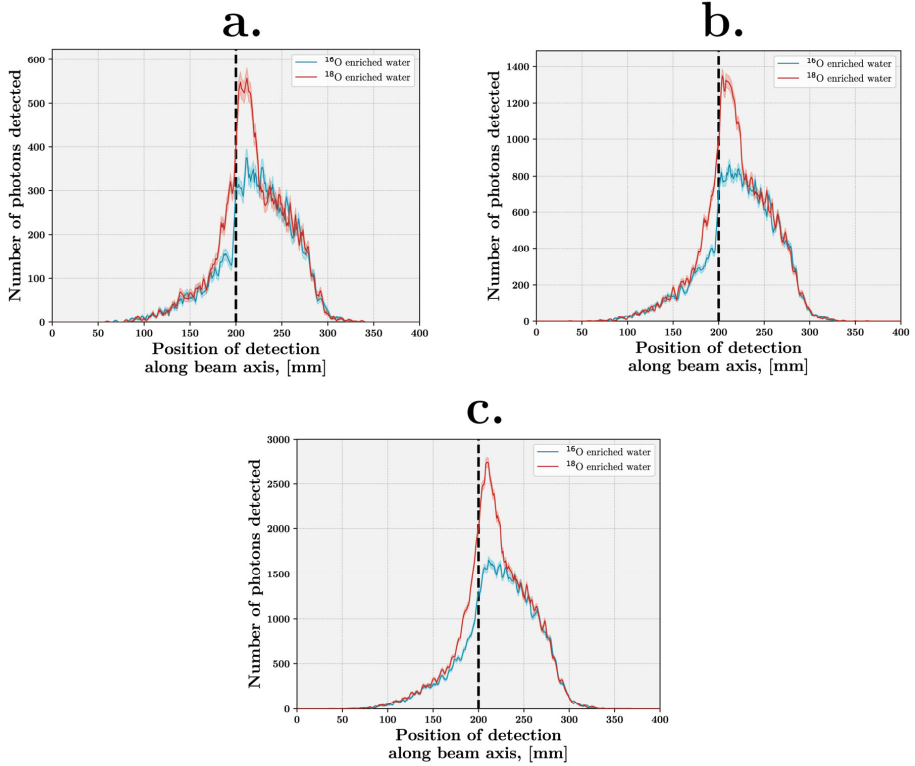


Figure 12.8. Comparison of PG photon spatial distributions detected with virtual knife-edge slit for ^{16}O and ^{18}O enriched tumour scenario

Data detected with idealized cylindrical detector (70 cm diameter) given. Energy filter of 0.5 to 3 MeV and temporal cut of ≤ 50 ns applied for PG photon data. Spatial data grouped in bins of 1 mm. 1σ binomial uncertainty per bin illustrated as shaded region for each respective line, number of incident particles - 5×10^7 . Helium-4 ions with energy 171.4 MeV/u (200 mm range in water) used. Position of absorbed dose maximum position indicated as dashed black line.

Data given for virtual knife-edge slit with opening of 1 mm (Subfigure (a)), 2 mm (Subfigure (b)) and 5 mm (Subfigure (c)). Virtual knife-edge slit centred at absorbed dose maximum position.

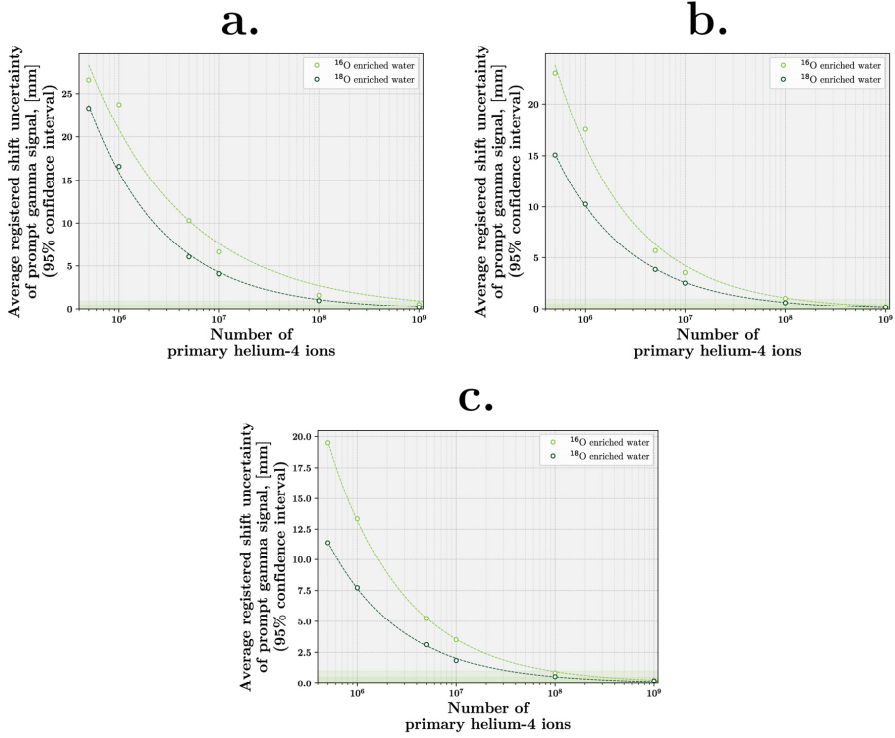


Figure 12.9. Influence of primary beam intensity on shift uncertainty registered with virtual knife-edge slit in ^{16}O and ^{18}O enriched tumour scenario

Uncertainty defined as single sided 95% confidence interval. Data given for PG photons detected with idealized cylindrical detector (70 cm diameter), energy filter of 0.5 to 3 MeV and temporal cut of ≤ 50 ns applied. Data points correspond to average of all considered shift scenarios (± 1 , ± 2 , ± 5 and ± 10 mm) as calculated from 1000 bootstrapped samples, no error bars indicated. Data points given for 10^5 , 5×10^5 , 10^6 , 5×10^6 , 10^7 , 10^8 and 10^9 primary helium-4 ions, while dashed lines correspond to a fitting function of form $a/\sqrt{N}$ (N - number of primary ions) to reflect the Poissonian nature of uncertainty dependency on primary beam intensity. Shaded regions correspond to 0.5 and 1 mm uncertainty.

Data given for virtual knife-edge slit with opening of 1 mm (Subfigure (a)), 2 mm (Subfigure (b)) and 5 mm (Subfigure (c)). Virtual knife-edge slit centred at absorbed dose maximum position.

PG detection with ^{18}O as a contrast agent: Temporal characteristic detection for PG timing approach

In addition to spatial characteristic-based PG detection, PG timing approach was also investigated for the ^{18}O enriched tumour scenario. Initially, comparison was performed by scoring all PG photon timing data irrespective of the position, considering idealized full volumetric coverage of the detector, with data summarized in **Appendix 11.15**.

As indicated in **Appendix 11.15**, a significant difference in PG photon detection time distributions can be observed. With respect to ^{16}O water reference, ^{18}O enriched tumour scenario has 30% increase of peak PG photon yield, while having a fall-off shift by about 0.4 ns. The peak increase is attributable to the increased PG photon production, while the fall-off shift is attributable to the increased contribution for longer detection times of PG photons generated by secondary particles, as demonstrated before. The shape of detection time distribution is significantly affected by the introduced shifts. Qualitatively, clear differences can be observed for shifts of at least ± 2 mm both for the rising and fall-off portions of the distribution.

For further quantitative evaluation, an additional spatial cut was added for the detected PG photons, to reflect a more realistic detection scenario - limitation of detector size. Resulting detection time distributions are illustrated in Figure 12.10. No significant changes of the distribution shape can be observed with respect to increasing detector length - only an increase in absolute magnitude of detected number of PG photons. Around 41% increase of peak PG photon yield was observed for ^{18}O enriched scenario with respect to ^{16}O water reference, with a fall-off shift by about 0.4 ns.

Figure 12.11 presents qualitative illustration of range shift changes in PG photon detection time distribution as obtained by virtual cylindrical detector of varying length. Corresponding quantitative evaluation of range sensitivity is presented in Figure A.11.21. of **Appendix 11.16**. Qualitatively, with respect to nominal, unperturbed scenario, Figure 12.11 indicates distinguishable differences in the PG photon detection time distribution, as discussed previously, with more pronounced differences observable for ^{18}O enriched tumour scenario. Positive range shifts decrease the magnitude of the rising part of the distribution and increase detection times for the fall-off section, with reversed effect observed for negative shifts.

For quantitative evaluation, parameters characterizing the detection time distribution were calculated - time with maximum intensity, FWHM, mean integral and times corresponding for certain fall-off value in PG photon detection time distribution. Corresponding quantitative evaluation of range sensitivity is presented in Figure A.11.21. of **Appendix 11.16**. presents changes in the mean integral of the distribution. Calculated values of integral of the detection time distribution had a positive correlation with respect to introduced range shift magnitude. For ^{16}O water reference, R^2 values of 0.980, 0.981 and 0.984 were observed between time distribution integral and introduced shift magnitude for cylindrical detector length of 20, 50 and 100 mm, respectively. Corresponding slopes of linear fits were 9.3 ± 0.5 , 9.2 ± 0.3 and 9.2 ± 0.2 ps/mm, respectively. In case of ^{18}O enriched tumour, observed R^2 values were 0.963, 0.972 and 0.977, respectively, while linear fit slopes - 9.8 ± 0.4 , 9.4 ± 0.3 and 9.0 ± 0.2 ps/mm. The average uncertainties of registered detection time distribution integral values were, respectively, ± 14.1 , ± 9.0 and ± 6.3 ps for ^{16}O water reference, while for ^{18}O enriched tumour - ± 12.3 , ± 7.8 and ± 5.7 ps.

^{18}O had a slightly improved performance with respect to ^{16}O , having slightly higher or sensitivity for detection time distribution characteristic parameters with reduced uncertainty of the calculated parameters due to the increased number of PG photons detected.

Evaluation for the minimum number of primary helium-4 ions to achieve a certain level of registered shift uncertainty is more complex for PG timing approach. Figure A.11.22. of **Appendix 11.16.** provides data temporal distribution characteristic parameter uncertainty scaling with beam intensity, indicating favourable performance of ^{18}O .

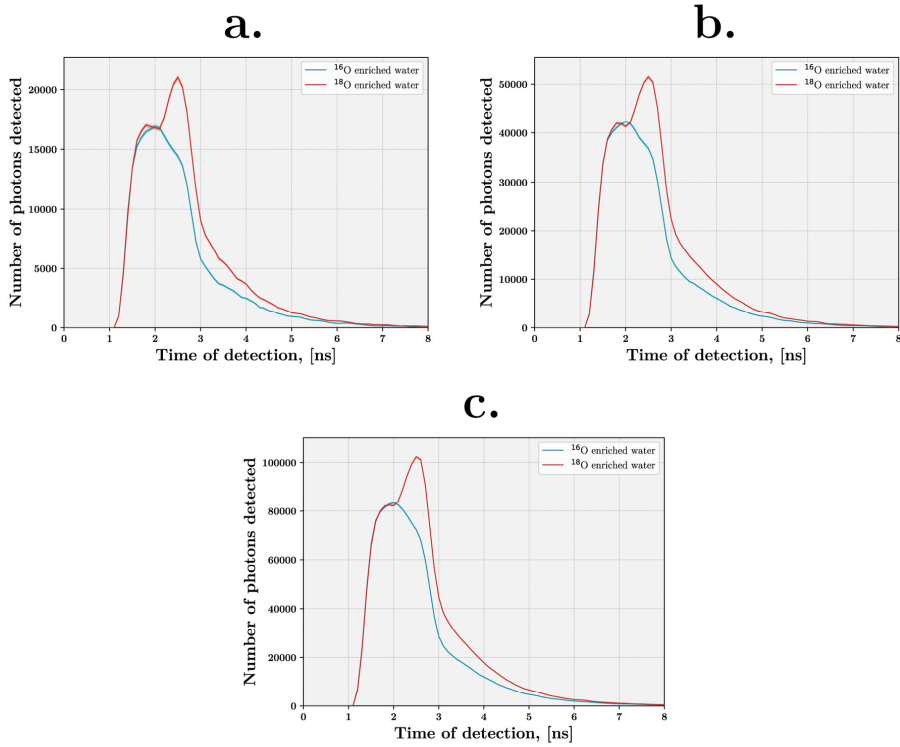


Figure 12.10. Comparison of PG photon time distributions detected with virtual detector of varying size for ^{16}O and ^{18}O enriched tumour scenario

Data detected with idealized cylindrical detector (70 cm diameter) given, with energy filter of 0.5 to 3 MeV applied. Detection times given with respect to primary particle impinging on phantom. Temporal data grouped in bins of 0.01 ns. 1σ binomial uncertainty per bin illustrated as shaded region for each respective line, number of incident particles - 5×10^7 . Helium-4 ions with energy 171.4 MeV/u (200 mm range in water) used.

Data given for virtual cylindrical detector with length of 20 mm (Subfigure (a)), 50 mm (Subfigure (b)) and 100 mm (Subfigure (c)). Virtual detector centred at absorbed dose maximum position.

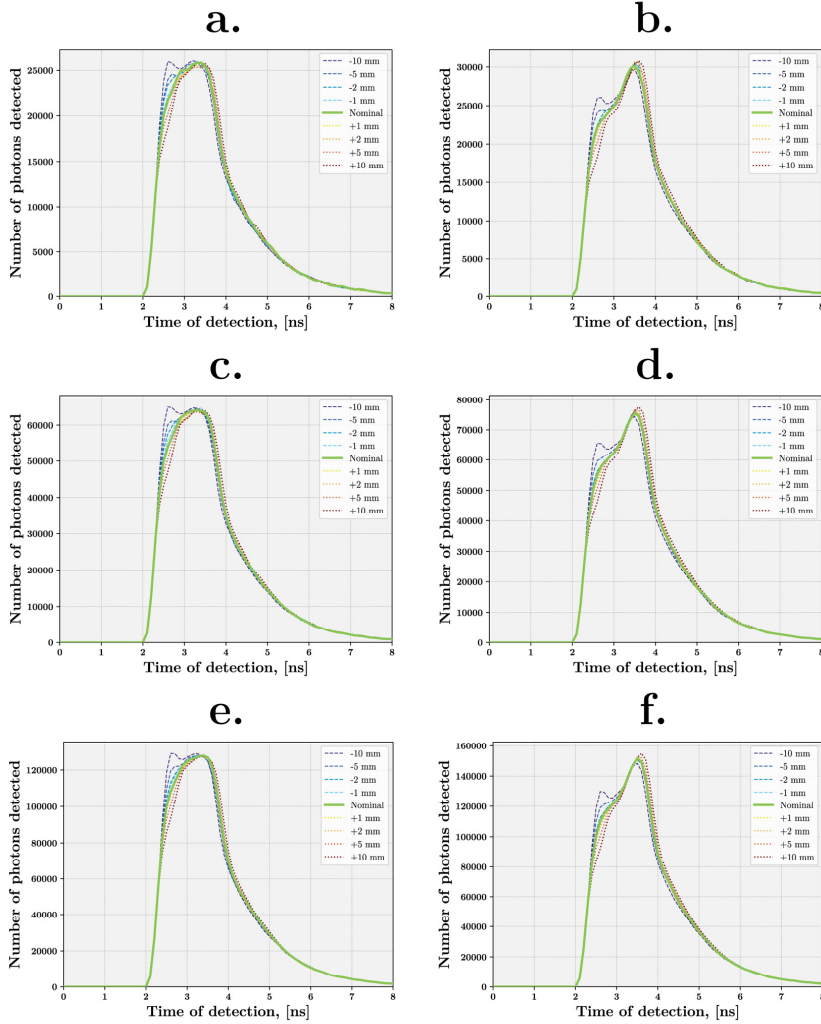


Figure 12.11. Changes of PG photon time distributions detected with virtual detector induced by range shifts in ^{16}O and ^{18}O enriched tumour scenario

Data detected with idealized cylindrical detector (70 cm diameter) given, with energy filter of 0.5 to 3 MeV applied. Detection times given with respect to primary particle impinging on phantom. Temporal data grouped in bins of 0.01 ns. Statistical uncertainty per bin not illustrated for visual clarity - 1σ binomial uncertainty in each bin in the range from 0.25% (1.6×10^5 photons) to 10.00% (~ 100 photons), number of incident particles - 5×10^7 . Nominal, unperturbed scenario given as thick green line. Helium-4 ions with energy 171.4 MeV/u (200 mm range in water) used. Data for ^{16}O enriched water given in left column (Subfigures (a), (c) and (e)), for ^{18}O - in right column (Subfigures (b), (d) and (f)). Virtual cylindrical detector with varying length illustrated: 20 mm (Subfigure (a)), 50 mm (Subfigure (b)) and 100 mm (Subfigure (c)). Virtual detector centred at absorbed dose maximum position.

PG detection with ^{18}O as a contrast agent: Energy spectrum characteristic detection for PG spectroscopy

Lastly, the unique spectral characteristics of ^{18}O contrast agent were evaluated for possible detection via PGS. Several characteristic spectral peaks were evaluated, comparing changes in detected PG photon intensity with respect to the magnitude of the introduced shift. Resulting data are given in **Appendix 11.17**.

Appendix 11.17 presents only six spectral lines with the highest Pearson correlation coefficient between relative change of spectral line intensity and the magnitude of the introduced Bragg peak position shift - 0.82, 0.87, 1.65, 1.94, 1.98 and 2.18 MeV. Provided data are given for full volumetric coverage - idealized spherical detector. Good correlation was observed with Pearson correlation coefficient values of the six spectral lines, respectively: 0.892, 0.973, 0.895, 0.937, 0.991 and 0.954. The calculated sensitivities (slope of linear fit) for each spectral line expressed as percent relative change of intensity per millimetre of range shift introduced were respectively: 0.28 ± 0.01 , 0.51 ± 0.00 , 0.23 ± 0.01 , 0.44 ± 0.01 , 0.70 ± 0.00 and 0.39 ± 0.01 %/mm. Based on the reported statistical analysis, the best performance with respect to range sensitivity in PGS approach, are 0.87, 1.94 and 1.98 MeV spectral lines.

As illustrated in **Appendix 11.18**, introduced Bragg peak position shift directly corresponds to a relative change of the integral absorbed within the tumour. Thus, the sensitivity of unique ^{18}O spectral lines was also evaluated with respect to absolute change in the integral absorbed dose within the enriched tumour volume, for a 2 Gy integral dose for the tumour volume from single energy level. Figure 12.12 illustrates the number of detected PG photons of respective energy as a function of absolute change in tumour integral dose. Summary of the observed coefficient of determination values of the linear approximation and corresponding absolute sensitivity is provided in Table 12.5.

Similar trends as discussed before can be observed in Figure 12.12. Table 12.5 illustrates that high values for coefficient of determination can be observed from 0.783 to 0.990 depending on the spectral line considered. In the idealized 2 Gy integral dose scenario from single helium-4 ion energy level delivery, the observed sensitivity as counts per Gray integral dose change is the range from $8.74 \cdot 10^6$ to $9.09 \cdot 10^7$ PG photons per Gray, if an idealized spherical detector volumetric coverage is considered. Highest sensitivity and coefficient of determination was observed for 1.98 MeV spectral line.

To briefly investigate the impact of detector size and volumetric coverage, evaluations as indicated in Figure 12.12 and Table 12.5 were repeated with idealized cylindrical detector of varying length - 20, 50 and 100 mm, centred around Bragg peak position. Summary of the observed results is provided in **Appendix 11.19**. Data indicate decreased PGS sensitivity with reduced detector volumetric coverage, though sufficient performance is retained 0.87, 1.94 and 1.98 MeV spectral lines.

Lastly, the impact of the number of primary helium-4 ions used for irradiation on statistical uncertainty in PGS methods was briefly evaluated, with results given in **Appendix 11.20**.

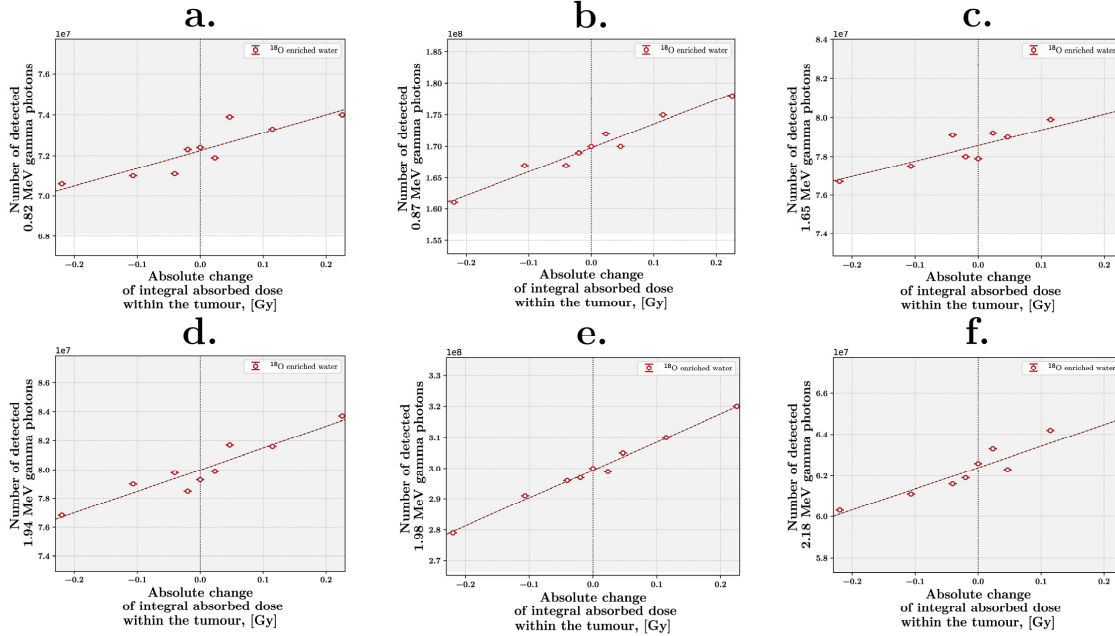


Figure 12.12. Sensitivity of ^{18}O specific spectral line absolute intensity to introduced integral absorbed dose changes in the simulated tumour

Data given for PG photons detected with idealized spherical detector, with a temporal cut of ≤ 50 ns applied and **all PG photons scored irrespective of their spatial position**. Data points for introduced shifts of ± 1 , ± 2 , ± 5 and ± 10 mm given as absolute change of spectral line intensity, error bars indicate the calculated 1σ binomial uncertainty of PG photon count. Coloured dashed line indicates linear fit using least-squares linear regression, with shaded region corresponding to 95% confidence interval of the fit. Helium-4 ions with energy 171.4 MeV/u (200 mm range in water) used. Number of incident particles - 5.3×10^{10} , corresponding to 2 Gy integral absorbed dose in the tumour from the single energy Bragg peak. Note the change of y-axis scale in each Subfigure.

Data for six ^{18}O specific spectral lines, having indicated the highest Pearson correlation coefficient with respect to introduced shift magnitude: 0.82 MeV (Subfigure (a)), 0.87 MeV (Subfigure (b)), 1.65 MeV (Subfigure (c)), 1.94 MeV (Subfigure (d)), 1.98 MeV (Subfigure (e)) and 2.18 MeV (Subfigure (f)).

PG photon intensity for each spectral line taken with margin of ± 5 keV.

Table 12.5.

Sensitivity of ^{18}O specific spectral line intensity to changes in integral absorbed dose in simulated tumour scenario

PG photon energy*	Sensitivity to change of absorbed dose**, [counts/Gy]	Coefficient of determination R^2
0.82 MeV	$8.74 \cdot 10^6 \pm 0.3\%$	0.783
0.87 MeV	$3.79 \cdot 10^7 \pm 0.1\%$	0.956
1.65 MeV	$7.99 \cdot 10^6 \pm 0.3\%$	0.812
1.94 MeV	$1.51 \cdot 10^7 \pm 0.2\%$	0.885
1.98 MeV	$9.09 \cdot 10^7 \pm 0.1\%$	0.990
2.18 MeV	$1.04 \cdot 10^7 \pm 0.2\%$	0.900

* Spectral lines, having indicated the highest Pearson correlation coefficient with respect to introduced shift magnitude were analysed.

** Data for sensitivity assessment: number of detected PG photons by idealized spherical detector with temporal cut of ≤ 50 ns applied. Intensity for each spectral line taken with a margin of ± 5 keV. Sensitivity and corresponding 1σ uncertainty extracted based on linear fit using least-squares linear regression. Coefficient of determination R^2 additionally given.

PGS approach, detecting the intensity of 0.87, 1.94 or 1.98 MeV spectral lines, is another addition to possible detection approaches using ^{18}O as a contrast agent. All the results presented in the second part of the MC simulation campaign indicate significant potential of ^{18}O , providing improved accuracy for all the main PG photon detection methods.

12.3. Conclusions and discussion

Chapter 12 presented MC simulation-based investigation on a novel approach proposed by the Author for PG photon signal enhancement via the use of ^{18}O enriched contrast agent - in this study ^{18}O water. Presented work develops on initial nuclear property study presented S. España et al. in [8]. MC simulation campaign was done in two parts - general physical characteristic evaluation and clinically relevant “enriched tumour” geometry. All results were compared with respect to ^{16}O water as reference.

MC simulation campaign on general physical characteristic evaluation focused on main parameters relevant for PG photon-based range verification in geometries, where whole irradiated volume consists of respectively ^{18}O or ^{16}O water. ^{18}O impact on PG photon emission spectra, spatial emission point and emission time distributions was evaluated, while also assessing these characteristics as registered by an idealized detector. Correlation of PG photon characteristics with respect to the Bragg peak position was

evaluated. Impact of ^{18}O on neutron production was also evaluated as a potential source of background noise in a realistic detection scenario.

The second part of MC simulation campaign - “enriched tumour” scenario - focused on assessing ^{18}O impact on PG photon signal if contrast agent is localized within a simulated tumour region. Different signal registration approaches were evaluated using virtual, idealized detectors corresponding to methods of multi-slit collimator, knife-edge slit and prompt gamma timing. For both spatial and temporal characteristic detection methods, achievable range sensitivity was evaluated for ^{18}O enriched tumour with respect to nominal ^{16}O water, while also assessing and comparing the impact of primary beam intensity on registered range shift uncertainty. Lastly, possibility of unique ^{18}O induced spectral line intensity monitoring was assessed as PGS approach for Bragg peak position and integral tumour dose monitoring.

Main conclusions from the presented results can be summarized as:

1. A novel approach of using ^{18}O -based contrast agent for increased PG photon production in low energy range after irradiation with helium-4 ion beams has been proposed and developed conceptually.
2. ^{18}O -enriched water as a contrast agent increases PG photon emission in energy range of 0 - 4 MeV: by about 58% - 104% (in the simulated scenario) with respect to normal water (^{16}O).
3. Majority of unique discrete PG photon emission energies for ^{18}O -enriched water correspond to de-excitation ^{18}O and ^{19}F nuclei. Most prominent spectral peak is 1.982 MeV from de-excitation of ^{18}O .
4. Use of ^{18}O -enriched water contrast agent does not perturb dose distribution with respect to normal water (^{16}O) due to same EM energy loss characteristics.
5. For general scenario, PG photon emission time and detection time distributions are comparable between ^{18}O -enriched water and normal water (^{16}O), with higher secondary contribution to former. This indicates maintained correlation with the Bragg peak position with increased photon count.
6. For general scenario, PG photon emission and detection spatial location distributions are comparable between ^{18}O -enriched water and normal water (^{16}O), with higher secondary contribution to former. This indicates maintained correlation with the Bragg peak position with increased photon count.
7. Use of ^{18}O -enriched water contrast agent increases secondary neutron production with respect to normal water (^{16}O) by about 5 - 10%. As increase in PG photon production by ^{18}O is higher, comparable or increased performance of secondary neutron rejection as background noise in realistic detection scenario can be expected for ^{18}O -enriched water.
8. For localized tumour region with ^{18}O -enrichment, significant increase of PG photon production can be observed in energy range up to 3 MeV - by about 16% in investigated geometric scenario. The increase is dependent on the simulated tumour size and depth in the irradiated object [14].

9. For localized tumour region with ^{18}O -enrichment and idealized virtual detectors for registration of PG photon spatial distribution (multi-slit collimator and knife-edge slit), a peak increase of 60-80% of detected photons was observed with respect to normal water (^{16}O). ^{18}O -enrichment improves range sensitivity and decreases the number of primary helium-4 ions necessary to achieve 1 mm uncertainty of registered range shift by 2 - 3 times compared to normal water (^{16}O).
10. For localized tumour region with ^{18}O -enrichment and idealized virtual detectors for registration of PG photon ToF distribution (prompt gamma timing), a peak increase of 30% of detected photons was observed with respect to normal water (^{18}O). ^{18}O -enrichment improves range sensitivity and decreases the number of primary helium-4 ions necessary to achieve certain level of uncertainty compared to normal water (^{16}O).
11. With presence of discrete PG photon energies unique for ^{18}O , PGS approach can be used with the proposed ^{18}O -enriched water contrast agent. By registering intensities of 0.87, 1.94 and 1.98 MeV PG photons for localized tumour region with ^{18}O enrichment, Bragg peak position shifts and integral tumour dose changes can be monitored. For idealized scenario with 2 Gy delivery, integral tumour dose could be monitored with a sensitivity of $8 * 10^6$ to $9 * 10^7$ counts per Gray.

Limitations of the performed research. Additional notes and implications of the work.

Considering the methodology and results presented in this Chapter, following limitations and additional implications of the performed study were identified:

- as presented study focused on initial developments and general physical assessment on using ^{18}O contrast agent for PG-based range verification, an idealized setup was considered, evaluating the detectable signal with no specific detector setup and associated limitations. While virtual implementation of collimation or detector sensitive area was considered, further work on the impact of collimation and detector geometry should be done in order to evaluate achievable signal. Special focus should be given to assess the impact of spatial coverage differences for different PG detection systems. Such additional studies on detection system limitations are crucial to assess the achievable spatial resolution and detectable signal magnitude per dose.
- with the focus on initial development of using ^{18}O contrast agent for PG-based range verification, uniform field delivery was considered with a single energy level. In actual implementation scenario, delivery would be realized via PBS, thus further studies should focus on the influence of spot size, spot spacing and delivery sequence impact on detectable PG signal. Additional focus should be given on detectable signal level for a single spot depending on the dose level, so that the feasibility of spot-by-spot range shift analysis could be achieved.
- as the study was based on MC-simulations, accuracy of nuclear interaction modelling has limitations as relevant for PG emission production yield and spatial distribution calculations. As parameters used in calculations are directly influenced nuclear

interaction cross-section data, accuracy of these data are crucial. Accuracy of used physics model within Geant4 has been outlined in Chapter 4, corresponding Appendix and references benchmarking studies. Nevertheless, as discussed in Chapter 8 and corresponding Appendix, accurate, experimentally verified nuclear interaction data as relevant for therapeutical energy levels are relatively limited. Thus, experimental validation of presented findings and further re-evaluation of simulation results, while implementing experimentally derived nuclear interaction cross-section data, would be of high importance.

- with the focus on initial development of using ^{18}O contrast agent for PG-based range verification, simple phantom geometries, uniformly consisting of water and injected ^{18}O contrast agent, were used for quantitative evaluation of resulting PG signal. As in a clinical setup, complex anatomies with large tissue elemental composition variations, contributing to PG signal, can be expected, additional work should focus on quantitative evaluation on achievable PG signal in such complex scenarios. Special focus should be given on range sensitivity assessment, evaluating the capabilities of clinically relevant range shift detection, while also considering detection system limitations. Evaluation should also focus further on evaluating the necessary minimum concentration of ^{18}O contrast agent within the region of interest to achieve clinically relevant improvement, while also focusing on the impact of volume containing ^{18}O contrast agent.
- although considerations on secondary neutrons and possible filtering approach were presented to minimize the impact of the background signal, these aspects need to be further re-evaluated with realistic detector and collimation setup.
- it should be noted that the presented results on using ^{18}O contrast agent for PG-based range verification are not limited to only helium ion beams, as this approach could also be used to enhance PG signal for proton and carbon ion therapy.

Future research outlooks

Considering the methodology, results and study limitations presented in this Chapter, following pathways for future additional research were identified:

- MC-based simulation study focusing on implementation of realistic PG detector technological constraints and re-evaluating the achievable signal and range sensitivity, while also evaluating the necessary delivered dose level to achieve helium beam range estimate with clinically relevant uncertainty;
- experimental campaign, focusing on validation of presented results and evaluation of detection system technological limitations for PG-based verification with ^{18}O contrast agent of helium ion range;
- MC-based simulation study focusing on detectable signal by using ^{18}O contrast agent for PG-based range verification and achievable range sensitivity within anatomically relevant geometry;
- algorithm development for spot-by-spot analysis of ^{18}O contrast agent enhanced PG signal to achieve feasibility of clinically relevant workflow;

11.3.1 Considerations for technological implementation

While the results presented in this Chapter mainly focused on the overall physical feasibility of novel range verification method by using oxygen-18 as PG contrast agent, following key considerations were identified for technological implementation of this approach

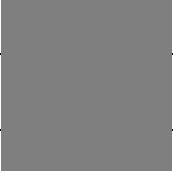
- necessities to adapt beam temporal structure to allow PG detection and analysis on spot-by-spot based should be evaluated from accelerator physics perspective, as optimization of slow extraction scheme would be necessary.
- as already discussed in the review of Chapter 8 and corresponding Appendix – optimization and integration of suitable PG detection system.
- implementation of oxygen-18 contrast agent injection should also be considered, focusing on how the contrast agent would be delivered to the region of interest. Additionally, methods for quantifying the concentration and spatial distribution of the contrast agent within the region of interest should also be developed to allow accurate calculation of reference PG signal for range shift evaluation.

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Conclusions of the Thesis



In the Doctoral Thesis research, two innovative approaches to improve light ion beam therapy for cancer treatment were explored - application of *FLASH* effect via ultra-high dose rate delivery and development of range verification methods to achieve necessary precision for high dose delivery required for *FLASH* effect use. Results of the Thesis presented novel experimental findings on role of radiochemistry under ultra-high dose rate for *FLASH* effect, modelled scaling of *FLASH* effect dosimetric conditions for different ion types, analysis of technological ultra-high dose rate delivery methods with ion beams and development of computational tools for quantitative comparison of these methods. With *FLASH* effect requiring high dose levels, new range verification methods to enable necessary delivery accuracy were proposed and evaluated via Monte Carlo simulations - high energy proton and helium-3 ion radiography for pre-treatment anatomy verification, mixed helium-deuteron beams for anatomy monitoring during delivery and *in-vivo* dose verification via detection of unique positron-electron annihilation patterns induced by helium-4 ions and use of ^{18}O -enriched water for prompt gamma photon signal enhancement.

The results achieved in the Thesis can be translated into new ion beam therapy clinical delivery methods to improve sparing of normal tissue, reduce treatment uncertainties and overall increase treatment outcomes. With focus on helium ion beam therapy, results contribute to future developments of this novel modality and technical design of dedicated particle accelerators for delivery, as CERN NIMMS HeLICS synchrotron. With detailed discussion provided in Thesis document, main findings and conclusions of presented research are:

1. Hydrogen peroxide production in aerated water has a statistically significant ($p < 0.05$) decrease with increasing dose rate - up to 38% with average dose rate increasing up to 100 Gy/s compared to 0.1 - 1 Gy/s. Observed dose rate dependency is diminished by addition of solvated scavengers - nitrous oxide or sodium nitrate with concentrations $> 250 \mu\text{M}$ - or decrease of partial oxygen pressure - from 21% to 4%.
2. For pulsed beam delivery, influence on hydrogen peroxide production in pure water is best parametrized by beam microstructure via pulse and bunch dose rates compared to average dose rate - linear regression analysis indicating coefficients of determination R^2 of 0.93 and 0.92 compared to 0.55, respectively.
3. Experimental findings indicate the role of temporal beam microstructure, solvated electrons and molecular oxygen level as key determinants of ultra-high dose rate induced radiochemical changes. Findings contribute to future developments of radical-

radical recombination hypothesis of *FLASH* effect and serve as benchmark for Monte Carlo model improvements.

4. Following experimental validation measurements (Points 1. - 3.), a theoretical model has been developed to estimate *FLASH* effect dose threshold using solvated electron concentration as surrogate metric. Developed model enables evaluation of dosimetric parameter threshold scaling between different ion types to achieve *FLASH* effect.
5. Based on developed model (Point 4.) and comparative analysis for 12 ion types, higher dose levels are predicted for increasing mass of the ion due to decrease of solvated electron production yield and interplay with physical dose distribution. As example, 1.2 - 1.3 times and 2 - 2.5 times higher *FLASH* effect dose threshold levels are predicted for helium-4 and carbon-12 ions, respectively, compared to protons. Consecutively, higher biologically effective dose would be delivered in the tumour - 1.1 - 1.4 times for helium-4 ions and 1.8 - 3.0 times for carbon-12 ions - possibly limiting clinical applicability.
6. Considering predicted increase of *FLASH* effect dose threshold for heavier ions, differential of relative biological effectiveness is decreased, thus increasing entrance dose (48-62% for protons to 56-80% for carbon-12 ions in simple geometry). Optimum dose conformality of high, intermediate and low isodose levels is observed for ions between helium and boron. Optimum performance for *FLASH* effect application, considering threshold conditions and dose conformality, could be achieved for helium and lithium ions.
7. A pencil-beam algorithm has been developed, employing novel parametrization function for lateral dose profile - sum of a Gaussian and two logistic distributions - and three term approach for linear energy transfer (and associated parameter) parametrization. Developed algorithm reproduces Monte Carlo reference data with deviations <1% in region of interest, for protons, helium, lithium and carbon ions in energy range relevant for clinical use. Algorithm is suited for dose rate calculation in active pencil beam scanning.
8. Comparative analysis of ultra-high dose rate delivery methods with light ion beams indicated proton transmission beams and use of 3-dimensional range modulators with proton or helium-4 ion beams as most suited for technological implementation with particle accelerator design considered within the Thesis - CERN NIMMS HeLICS synchrotron.
9. Several range verification methods, focusing on helium-4 ion therapy delivery with compact synchrotrons as CERN NIMMS HeLICS synchrotron, have been proposed and quantitatively evaluated to ensure delivery accuracy necessary for light ion *FLASH* therapy:
 - 9.1. At same beam rigidity, helium-3 ions can achieve higher range in tissue in contrast with helium-4 ions, enabling full-body radiography for particle accelerators as CERN NIMMS HeLICS. For same range in tissue, helium-3 ions can achieve comparable image quality (spatial resolution within 0.2 lp/mm, contrast-to-noise ratio

within 3%, same water equivalent path length accuracy) and dose reduction of 10-15% (at same contrast-to-noise ratio) with respect to helium-4 ions. Considering higher range at same beam rigidity, helium-3 ions would outperform helium-4 for radiographical position verification.

9.2. Considering high energy proton radiography enabled by CERN NIMMS HeLICS, 330 to 500 MeV proton energy could achieve optimum image quality (compromise between spatial resolution of 0.5 - 0.8 lp/mm and contrast-to-noise ratio of 9 - 15) for full-body imaging (anatomy thickness > 32 cm).

9.3. By using reconstruction plane depth dependent physical parameters (spatial resolution or local water equivalent path length variation), focus stacking can be implemented in image reconstruction to improve spatial resolution and water equivalent path length value precision and enable depth estimation of imaged object.

9.4. Local water equivalent path length variation based focus stacking enables reconstruction plane independent spatial resolution, improved contrast-to-noise ratio and mean water equivalent path length accuracy within 1 - 1.5 mm, outperforming edge detection based focus stacking. Furthermore, under high contrast conditions the method enables imaged object depth estimation with deviations of ± 5 mm and significantly decreased estimated depth uncertainty compared to edge detection based focus stacking.

9.5. With helium-3 ion and high energy proton radiography as methods for patient position verification before treatment with CERN NIMMS HeLICS design, mixed helium-deuteron beams could be used for position monitoring during helium-4 ion therapeutical delivery.

9.6. Mixed helium-deuteron beams with a fluence ratio of 1:100 can be used for range measurement and position monitoring during treatment, detecting range shifts of ± 1 mm (if inhomogeneity lateral extent is > 20% of the beam size), with < 0.1% contribution to treatment physical dose and negligible impact on biologically effective dose distribution.

9.7. Using double Gaussian relative angle filtering and a fluence ratio 10:1, mixed helium-deuteron beams can be used for 2-dimensional radiographical image acquisition during treatment delivery. Proposed approach provides adequate image quality - spatial resolution of 0.4 - 0.6 lp/mm, contrast-to-noise ratio of 20 and water equivalent path length accuracy < 1.5 mm. Double Gaussian relative angle filtering could also be used for carbon-helium mixed beams in carbon ion therapy.

9.8. Uniquely to helium-4 ion beams, fluorine-18 (^{18}F) and fluorine-17 (^{17}F) is induced and corresponding β^+ decay signals can improve Bragg peak localization with positron emission tomography in oxygen-rich tissue. ^{18}F peak in electron-positron annihilation event spatial distribution is closely correlated with Bragg peak with deviations < 1.5 mm for timescales above 30 minutes, while ^{17}F : < 3 mm for timescales below 10 minutes.

9.9. ^{18}O enriched water can be used as contrast agent in helium-4 ion beam therapy (as well as other ion beam therapy modalities) to enhance prompt gamma production yield - by 84-96% in energy range < 4 MeV compared ^{16}O water (whole object enriched with contrast agent). ^{18}O enriched water would have comparable or decreased secondary neutron background.

9.10. For 100% concentration of ^{18}O enriched water in localized geometry, detectable number of prompt gamma photons is increased by $> 20\%$ for energies 0.5 - 3 MeV compared ^{16}O water as reference (depending on tumour geometry). This leads to decreased number of primary particles necessary to reach range uncertainty < 1 mm for idealized spatial detection approaches - about 2 - 4 times. Performance is also improved for temporal characteristic detection approaches as prompt gamma photon timing.

9.11. ^{18}O enriched water contrast agent also enables spectroscopic prompt gamma detection approach - by monitoring the intensity of specific spectral lines - 0.87, 1.94 and 1.98 MeV -, delivered integral tumour dose could be monitored with a sensitivity of $8 \cdot 10^6$ to $9 \cdot 10^7$ counts per Gray (for 2 Gy delivery and idealized volumetric acceptance for detection).

- 10.** Results presented in the Thesis serve as physics foundation for future developments and technical implementation of helium-4 ion *FLASH* therapy (dosimetric thresholds and considerations for technological delivery) and corresponding dedicated range verification methods.

With broader discussion provided in respective Chapters of the Thesis. Main recommendations for future research and practical implementation can be summarized as follows:

1. Presented findings on dose threshold level scaling for different ion types should be experimentally validated via *in-vitro* or *in-vivo* studies. Proposed scaling model does suggest possible dose rate threshold increase for increasing linear energy transfer (heavier ions) - radiochemistry kinetics simulations would be beneficial for initial assessment, followed by experimental validation via *in-vitro* or *in-vivo* studies.
2. With current experimental validation campaign (hydrogen peroxide production dose rate dependency) performed with low linear energy transfer ionizing radiation types - X-rays and electrons - further measurements with high LET radiation (proton or ion beams) would enable additional verification of proposed radiochemical change mechanism under ultra-high dose rate. Systematic studies on role of molecular oxygen concentration would also provide further insights on presented theoretical basis of experimental findings. Validation with radiochemistry kinetics simulations would be necessary for Monte Carlo simulation model adaptations based on experimental findings.
3. Presented pencil-beam dose and dose rate calculation algorithm should be expanded further to account for tissue heterogeneity as relevant in realistic clinical patient case. Quantitative evaluation studies of ultra-high dose rate delivery method comparison

for light ion beam delivery (as presented in Chapter 7) would be relevant to assess technical implementation into particle accelerator systems and characterize necessary dosimetric parameter space.

4. With high energy proton and helium-3 ion radiography presented with idealized setup, limitations of realistic detector design and achievable output beam current should be explored. Further comparative studies should focus on image reconstruction in complex, patient-like anatomies and implementation of novel reconstruction approaches such rear-tracker only radiography. Further assessment of technical parameters for high energy proton and helium-3 ion radiography implementation in a synchrotron is necessary. Focus stacking approach for 3-dimensional feature acquisition should be further studied in complex, patient-like anatomies, giving the focus to feasibility of clinically significant range shift detection (low contrast scenarios). Further optimization of de-noising kernel size or use of smoothening via Savitzky-Golay filter for focus stacking as impact factors on image quality improvement and estimated depth accuracy should be considered with complex, patient-like anatomies.
5. Similar aspects as for high energy proton and helium-3 ion radiography, should be further evaluated for mixed helium-deuteron beams. Additional data filtration methods via machine learning could be explored for 2-dimensional image acquisition. Special focus should be given to assess mixed helium-deuteron beam injection, acceleration and extraction.
6. Findings on induced fluorine-17 and fluorine-18 signals for positron emission tomography-based verification need further Monte Carlo simulation-based and experimental validation with realistic detector setup, patient anatomy and beam delivery limitations. Aspects of biological washout due to physiological processes need to be considered and evaluated.
7. Findings on ^{18}O based contrast agent enhancement need further Monte Carlo simulation-based and experimental validation with realistic detector setup, patient anatomy and beam delivery limitations.
8. Given the uncertainties and accuracy limitations of nuclear interaction models in Monte Carlo simulations, Points 4. - 7. would benefit from experimental verification studies, validating observed phenomena.

Research presented in the Thesis provides a significant step towards implementation of light ion *FLASH* therapy and dedicated range verification methods, outlining strong foundational basis and general feasibility assessment for several new treatment delivery approaches. With majority of research performed as Monte Carlo simulation studies, next steps should focus on experimental validation based on current findings. Furthermore, additional technical implementation and design studies are necessary to evaluate integration of developed methods into particle accelerator (as CERN NIMMS HeLICS synchrotron) systems.

Approbation of the Thesis results

Scientific publications

Full length articles (direct Thesis topicality):

- **Paļskis, K.**, Korobeinikova, E., Bogorada-Saukuma, D., Camarda, A., Taylor, R., Benedetto, E., Mamis, E., Radziņa, M., Ērglis, A., Adliene, D., Dosanjh, M., Vretenar, M., Torims, T. “*Particle Therapy - Future for the Baltic States?*” - *Synthesis of the Expert Workshop Report*. Health and Technology, 2024, Vol. 14, No. 1, pp.965-972. ISSN 2190-7188. e-ISSN 2190-7196. Available: doi:10.1007/s12553-024-00875-2 (*Full length article indexed in Web of Science/Scopus*)
- Zhang, T., Stengl, C., Derksen, L., **Paļskis, K.**, Koritsidis, K., Zink, K., Adeberg, S., Major, G., Weishaar, D., Theiß, U., Jin, J., Spadea, M., Theodoridou, E., Hesser, J., Baumann, K., Seco, J. Analysis of Hydrogen Peroxide Production in Pure Water: Ultrahigh Versus Conventional Dose-Rate Irradiation and Mechanistic Insights. Medical Physics, 2024, Vol. 51, No. 8, pp.1-14. ISSN 0094-2405. e-ISSN 2473-4209. Available: doi:10.1002/mp.17335 (*Full length article indexed in Web of Science/Scopus*)

Conference proceedings:

- Vretenar, M., Angoletta, M., Bisoffi, G., Borburgh, J., Bottura, L., **Paļskis, K.**, Taylor, R., Tranquille, G., Benedetto, E., Sapinski, M. *A Compact Synchrotron for Advanced Cancer Therapy with Helium and Proton Beams*. Journal of Physics: Conference Series, 2023, Vol. 2420, Article number 012103. ISSN 1742-6588. e-ISSN 1742-6596. Available: doi:10.1088/1742-6596/2420/1/012103 (*Conference proceedings indexed in Web of Science/Scopus*)
- Vretenar, M., Tranquille, G., Borburgh, J., **Paļskis, K.**, Bottura, L., Angoletta, M., Taylor, R., Torims, T., Adliene, D., Benedetto, E., Sapinski, M., Gershkevitch, E., Korobeinikova, E., Radziņa, M., Kalniņa, M. *Conceptual Design of a Compact Synchrotron-Based Facility for Cancer Therapy and Biomedical Research with Helium and Proton Beams*. In: 14th International Particle Accelerator Conference (IPAC '23): Conference Proceedings, Italy, Venice, 7-12 May, 2023. Geneva: JACoW Publishing, 2023, pp.5024-5027. e-ISBN 978-3-95450-231-8. e-ISSN 2673-5490. Available from: doi:10.18429/JACoW-IPAC2023-THPM058 (*Conference proceedings not indexed in Web of Science/Scopus*)
- E. Benedetto, M. E. Angoletta, F. Asvesta, J. Borburgh, L. Bottura, A. Cassar, G. W. D. Flier, L. Garolfi, P. Gruebling, H. Huttunen, A. Kolehmainen, V. Korchevnyuk, **K. Paļskis**, P. Panttaja, V. Sansipersico, M. Sapinski, R. Taylor, G. Tranquille, S. Van der Schueren, M. Vretenar *A compact synchrotron for cancer therapy with helium ions*. In: 16th International Particle Accelerator Conference (IPAC '25): Conference Proceedings, Taiwan, Taipei, 1-6 June, 2025. Geneva: JACoW Publishing, 2025, pp.5024-5027. e-ISBN 978-3-95450-248-6. e-ISSN 2673-5490. Available from: doi:10.18429/JACoW-IPAC25-TUPB105 (*Conference proceedings not indexed in Web of Science/Scopus*)

Published abstracts:

- **Paļskis, K.**, Torims, T., Vretenar, M., Sapinski, M., Seco, J. *P 342 - FLASH-RT Dose Threshold Effect Estimation for Particle Beams by Modelling Solvate Electron Production Dependency on Particle LET 3D Distribution*. International Journal of Particle Therapy, 2023, Vol. 10, No. 2, 388-389.lpp. e-ISSN 2331-5180. Available: doi:10.14338/IJPT-23-PTCOG61-10.2
- Dosanjh, M., Facchetti, A., Necchi, M., Sammut, N., Bateman, J., **Paļskis, K.**, Taylor, R., Robertson, C. *P 231 - Training the Future in HITRIplus Project: A Report on Specialised Course on Heavy Ion Therapy Research*. International Journal of Particle Therapy, 2023, Vol. 10, No. 2, pp.335-335. e-ISSN 2331-5180. Available: doi:10.14338/IJPT-23-PTCOG61-10.2
- Korobeinikova E, **Paļskis K**, Gershkevitch E, Dosanjh M. 4294 *Advances in Radiotherapy Treatment in the Baltic States from 2016 to 2023 as seen through the lens of technology, delivery techniques and*

capacity. Radiotherapy and Oncology 2025 (Abstract book of 2025); 206: S2335-S2336. Available: doi:10.1016/S0167-8140(25)03283-9

- Torims T., Adliene D., **Paļskis K.**, Vretenar M. *STATUS REPORT AND CONCEPT OF AN INNOVATIVE PARTICLE THERAPY CENTER IN THE BALTIC STATES*, 19th Nordic-Baltic Conference on Biomedical Engineering and Medical Physics Book of Abstracts, RTU Press (Latvia), 2023, ISBN 978-9934-22-919-0, Available: <https://ebooks.rtu.lv/product/19th-nordic-baltic-conference-on-biomedical-engineering-and-medical-physics/?lang=en>

Full length articles (not direct Thesis topicality):

- Radziņa, M., Saule, L., Mamis, E., Koester, U., Cocolios, T., Pajuste, E., Kalniņa, M., **Paļskis, K.**, Sawitzki, Z., Talip, Z., Jensen, M., Duchemin, C., Leufgen, K., Stora, T. *Novel Radionuclides for Use in Nuclear Medicine in Europe: Where do We Stand and Where Do We Go?*. EJNMMI Radiopharmacy and Chemistry, 2023, Vol. 8, Article number 27. ISSN 2365-421X. Available: doi:10.1186/s41181-023-00211-5 (Full length article indexed in Web of Science/Scopus)
- Radziņa, M., Saule, L., Mamis, E., Pajuste, E., Koester, U., Cocolios, T., Proskurins, J., Kalniņa, P., Zabolockis, R., **Paļskis, K.**, Talip, Z., Jensen, M., Duchemin, C., Baatout, S., Leufgen, K., Stora, T. *Novel Radionuclides: Demand, Production and Distribution for Translational Research in Europe*. EJNMMI Radiopharmacy and Chemistry, 2024, Vol. 9, Article number 85. ISSN 2365-421X. Available: doi:10.1186/s41181-024-00318-3 (Full length article indexed in Web of Science/Scopus)
- Dosanjh, M., Gershan, V., Wendling, E., Khader, J., Ige, T., Ristova, M., Hugtenburg, R., Georgieva, P., Coleman, C., Pistenmaa, D., Hovhannisyann, G., Saghatelian, T., Kazimov, K., Rzayev, R., Babayev, G., Aliyev, M., Gershkevitch, E., Khomeriki, I., Petriashvili, L., Topeshashvili, M., Zakirova, R., Rakhimova, A., Karnakova, N., Rakhatbek, A., Kazybaev, N., Bondareva, O., **Paļskis, K.**, Boka, G., Korobeinikova, E., Kudrevicius, L., Apostol, I., Eftodiev, L., Rosca, A., Rusnac, G., Khikmatov, M., Luchkovskiy, S., Severyn, Y., Alimov, J., Ismailova, M., Talibova, S. *Access to Diagnostic Imaging and Radiotherapy Technologies for Patients with Cancer in the Baltic Countries, Eastern Europe, Central Asia, and the Caucasus: A Comprehensive Analysis*. The Lancet Oncology, 2024, Vol. 25, No. 11, pp.1487-1495. ISSN 1470-2045. e-ISSN 1474-5488. Available from: doi:10.1016/S1470-2045(24)00452-2 (Full length article indexed in Web of Science/Scopus)

Contributions in scientific conferences (direct Thesis topicality)

- **3rd FLASH Radiotherapy and Particle Therapy conference (FRPT)**, 2023, Toronto, Canada
Poster: “The best particle for ion-beam based FLASH: investigating the compromise between threshold dose and dose conformality” **Paļskis, K.**, Torims, T., Vretenar, M., Sapinski, M., Seco, J.
- **2nd FLASH Radiotherapy and Particle Therapy conference (FRPT)**, 2022, Barcelona, Spain
Poster: “Assessing particle FLASH-RT effectiveness by modelling solvate electron production dependency on particle LET” **Paļskis, K.**, Torims, T., Vretenar, M., Sapinski, M., Seco, J.
- **61st Annual PTCOG Conference**, 2023, Madrid, Spain
 - Poster: “FLASH-RT dose threshold effect estimation for particle beams by modelling solvate electron production dependency on particle LET 3D distribution” **Paļskis, K.**, Torims, T., Vretenar, M., Sapinski, M., Seco, J.
 - Accepted, peer-reviewed abstract (not presented): “Helium-3 and helium-4 ion beam comparison for radiation therapy - achievable signal for treatment range verification” **Paļskis, K.**, Torims, T., Vretenar, M., Sapinski, M., Seco, J.
- **5th CERN Baltic Conference**, 2025, Kaunas, Lithuania
 - Oral presentation “Towards the last millimeters in helium ion therapy: developing dedicated range verification methods” **Paļskis, K.**, Baumgarte, I., Viņķe, A., Torims, T., Vretenar, M., Sapinski, M., Seco, J.
 - Poster (I.Baumgarte presenting): “Enabling the Third Dimension in Planar Radiographic Imaging - Feasibility of Focus Stacking with Helium Ion Radiography” Baumgarte, I., **Paļskis, K.**

- **4th CERN Baltic Conference**, 2024, Tallinn, Estonia
 - Oral presentation “*Experimental studies of radiochemical changes at ultra-high dose rates (UHDR) in perspective of FLASH therapy*” **Paļskis, K.**, Torims, T., Vretenar, M., Sapinski, M., Seco, J.
 - Poster (I.Baumgarte presenting): “*Investigation of Helium-3 Usage in Radiography for Patient Position Verification in Particle Therapy*” Baumgarte, I., **Paļskis, K.**, Vretenar, M.
 - Poster (A.Vinke presenting): “*Simulation-Based Assessment of Proton Radiography Across Energy Levels: Investigations on optimum imaging energy*” Vinke, A., **Paļskis, K.**, Vretenar, M.
- **3rd CERN Baltic Conference**, 2023, Riga, Latvia

Oral presentation “*Analytical pencil beam dose and dose-rate engine development for FLASH therapy studies of heavy ion and very high energy electron beams*” **Paļskis, K.**, Torims, T., Vretenar, M., Sapinski, M., Seco, J.
- **2nd CERN Baltic Conference**, 2022, Vilnius, Lithuania

Oral presentation “*Physical and biological property comparisons of ⁴He and ³He ion beams for applicability in radiation therapy*” **Paļskis, K.**, Torims, T., Vretenar, M., Sapinski, M., Seco, J.
- **66th RTU Student Scientific conference**, 2025, Riga, Latvia

Poster (I.Baumgarte presenting): “*Jonu radiogrāfijas attēlu kvalitātes raksturlielumu atkarība no izmantotā hēlija izotopa*” Baumgarte, I., **Paļskis, K.**
- **Rīga Stradiņš University International Research Conference on Medical and Health Care Sciences “Knowledge for Use in Practice”**, 2025, Riga, Latvia

Poster (A.Vinke presenting): “*Simulation-Based Assessment of Proton Radiography Across Energy Levels: Investigations on Optimum Imaging Energy*” Vinke, A., **Paļskis, K.**, Vretenar, M.

Contributions in scientific seminars

- **CERN Medical Applications Forum (MAPF) meeting**, July 12, 2024, online: <https://indico.cern.ch/event/1346852/> “*Ultra high dose rate and ion beams for cancer therapy: biophysics perspective*”
- **CERN Medical Applications Forum (MAPF) meeting**, May 10, 2023, online: <https://indico.cern.ch/event/1217563/> “*Dose threshold modelling studies for ion beam FLASH therapy*”
- **CERN EP-SFT Group: Detector simulation bi-weekly meeting**, May 30, 2023, online: <https://indico.cern.ch/event/1291255/> “*Dose threshold modelling studies for ion beam FLASH therapy*”
- **Joint NIMMS-SEEIIST Meeting #90**, February 10, 2023, online: <https://indico.cern.ch/event/1252418/> “*FLASH effect dose threshold modelling for heavy ion beams*”
- **Joint NIMMS-SEEIIST Meeting #80**, April 8, 2022, online: <https://indico.cern.ch/event/1147665/> “*Ions for radiotherapy: biological modelling and FLASH aspects*”
- **Joint NIMMS-SEEIIST Meeting #70**, September 17, 2021, online: <https://indico.cern.ch/event/1076571/> “*Physical and biological effectiveness studies on protons and heavy ions for use in FLASH radiotherapy*”
- **NIMMS Internal Meeting #56**, February 7, 2025, online: <https://indico.cern.ch/event/1511121/> “*FLASH effect application for light ion therapy and development of range verification methods*”
- **NIMMS Internal Meeting #51**, September 27, 2024, online: <https://indico.cern.ch/event/1460836/> “*Radiography at HeLICS*”
- **NIMMS Internal Meeting #50**, September 20, 2024, online: <https://indico.cern.ch/event/1457427/> “*Summer student presentations: Investigation on novel radiography approaches with helium synchrotron, high energy proton and helium-3 radiography*” (as supervisor)

- **NIMMS Internal Meeting #50**, May 17, 2024, online: <https://indico.cern.ch/event/1416936/>
“Radiochemistry studies under UHDR irradiation: experimental experience at DKFZ”
- **NIMMS Internal Meeting #42**, January 19, 2024, online: <https://indico.cern.ch/event/1370083/>
“Highlights from the FLASH conference” (as relevant for literature review in Chapters 3 and 7)

Supervision of student work

Bachelor Thesis:

- **L.Rubene** *Dependence of correlation between Bragg peak position and gamma photon emission on helium-3 and helium-4 ion beam parameters*, 2023 (defended 9/10)
- **I.Baumgarte** *Dependence of ion radiographic image quality characteristics on the utilized helium isotope*, 2025 (defended 10/10)

Engineering qualification work:

- **L.Rubene** *Multi-functional phantom for daily quality assurance checks in ion therapy*, 2024 (defended 9/10)

Master Thesis:

- **L.Rubene** *The impact of ^4He ion energy on gamma photon emission depending on irradiated tissues with varying ^{18}O concentration*, 2025 (defended 9/10)

CERN Summer studentships:

- **I.Baumgarte** *Investigation of helium-3 ion usage in radiography for patient position verification in particle therapy* (co-supervised with Maurizio Vretenar)
- **A.Vinke** *Simulation-Based Assessment of Proton Radiography Across Energy Levels: Investigations on optimum imaging energy* (co-supervised with Maurizio Vretenar)

Other

Candidate has **2 entries** in **The Latvian National Encyclopedia** on PhD topicality (theoretical background, literature review):

- **physics of radiation therapy**: <https://enciklopedija.lv/skirklis/256202-radi%C4%81cijas-terapijas-fizika>
- **particle therapy**: <https://enciklopedija.lv/skirklis/256687-da%C4%BCi%C5%86u-terapija>

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