

Modelling and simulation of physics processes for in-beam imaging in hadrontherapy

Marco Pinto

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Modelling and simulation of physics processes for in-beam imaging in hadrontherapy

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"Higher-energy machines are now under construction ... and the ions from them will in general be energetic enough to have a range in tissue comparable to body dimensions. It must have occurred to many people that the particles themselves now become of considerable therapeutic interest."

Robert R. Wilson, Radiological Use of Fast Protons, Radiology 47 487-491, 1946

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Résumé

Modélisation et simulation des processus physiques pour l'imagerie en ligne de l'hadronthérapie

par Marco Pinto

L'hadronthérapie joue un rôle de plus en plus important au sein des techniques de radiothérapie grâce aux propriétés balistiques des ions et, dans le cas de ceux plus lourds que les protons, à une augmentation de l'efficacité biologique dans la région tumorale. Ces caractéristiques permettent une meilleure conformation de la dose délivrée au volume tumoral et elles permettent en particulier de traiter des tumeurs radio-résistantes. Elles conduisent cependant à une grande sensibilité du parcours des ions aux incertitudes du traitement. C'est dans ce contexte qu'a été proposée la détection de radiations secondaires émises lors des interactions nucléaires induites par les ions incidents dans le patient. La tomographie par émission de positons et la détection des rayons gamma prompts ont notamment fait l'objet d'une recherche intense ces dernières années. Le réseau de formation européen ENTERVISION, soutenu par la communauté ENLIGHT, a été créé fin 2009 pour développer ce type d'imagerie et, plus généralement, traiter les incertitudes de traitement en hadronthérapie. Le travail présenté dans ce manuscrit et intitulé « Modélisation et simulation des processus physiques pour l'imagerie en ligne de l'hadronthérapie » est l'un des nombreux travaux issus de ce projet. Bien que le sujet soit particulièrement large, le fil conducteur de ce travail a été une étude systématique visant in fine une implémentation d'un dispositif d'imagerie « gamma prompts » utilisable à la fois en faisceau de protons et d'ions carbone. Dans cette optique, le travail a porté essentiellement sur le concept de caméra collimatée multi-fentes qui présente l'avantage d'une relative simplicité et dont l'applicabilité clinique a été en grande partie démontrée par des études antérieures. Il s'agit d'un travail collaboratif initié dans le cadre du projet ETOILE dans le but de fournir des taux fiables d'émission de rayons gamma prompts en cibles homogènes et hétérogènes et d'optimiser la géométrie de la caméra collimatée. Il s'agira également d'étudier la précision, l'amélioration et l'accélération de l'outil de simulations Monte Carlo Geant4. Cela inclut plus précisément l'analyse des données expérimentales obtenues au GANIL (Caen), GSI (Darmstadt), HIT (Heidelberg) et WPE (Essen) et accompagnées des simulations Geant4 correspondantes, mais aussi la proposition de nouvelles approches susceptibles d'être utilisées dans le contrôle de l'hadronthérapie.

Abstract

Modelling and simulation of physics processes for in-beam imaging in hadrontherapy

by Marco Pinto

Hadrontherapy is taking an increasingly important role in radiotherapy thanks to the ballistic properties of ions and, for those heavier than protons, an enhancement in the relative biological effectiveness in the tumour region. These features allow for a higher tumour conformality possible and gives the opportunity to tackle the problem of radioresistant tumours. However, they may lead to a great sensitivity of ion range to treatment uncertainties, namely to morphological changes along their path. In view of this, the detection of secondary radiations emitted after nuclear interactions between the incoming ions and the patient have been long proposed as ion range probes and, in this regard, positron emitters and prompt gammas have been the matter of intensive research. The European training network ENTERVISION, supported by the ENLIGHT community, was created in the end of 2009 in order to develop such imaging techniques and more generally to address treatment uncertainties during hadrontherapy. The present work is one of the many resulting from this project, under the subject "Modelling and simulation of physics processes for in-beam imaging in hadrontherapy". Despite the extensive range of the topic, the purpose was always to make a systematic study towards the clinical implementation of a prompt-gamma imaging device to be used for both proton and carbon ion treatments. In respect to the imaging device design, the focus of this work has been on the multi-slit collimated camera due to its simplicity in concept and proven feasibility from previous studies. This is a collaborative work, initiated within the ETOILE project, with the aim of providing reliable data concerning prompt-gamma emission yields both with homogeneous and heterogeneous targets, Geant4 Monte Carlo simulations accuracy, improvement and acceleration, and camera design optimisation. It comprises experimental data collected at GANIL (Caen), GSI (Darmstadt), HIT (Heidelberg), and WPE (Essen), along with Geant4 simulations and the presentation of novel approaches for the use in hadrontherapy monitoring, in particular background subtraction techniques, new quantities to assess ion ranges based on the prompt-gamma spatial distributions, acceleration schemes to be used in Geant4, and considerable improvements of Geant4 simulations concerning prompt-gamma emission modelling.

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The road leading to this moment started being paved five years ago during my master thesis project, during which I had the opportunity to meet Paulo Crespo. He introduced me to the field of hadron herapy and helped me grow in the world of science. I cannot demonstrate enough how grateful I am to have met him. Muito obrigado por tudo ...

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Abbreviations

\mathbf{BaF}_2	Barium Fluoride scintillator detector
BGO	Bismuth Germanium Oxide
FOV	Field Of View
FWHM	\mathbf{F} ull- \mathbf{W} idth at \mathbf{H} alf \mathbf{M} aximum
GANIL	Grand Accélérateur National d'Ions Lourds (Caen, France)
gFOV	Geometrical Field Of View
GSI	Gesellschaft Helmholtzzentrum für Schwerionenforschung (Darmstadt, Germany)
\mathbf{HF}	High Frequency
HIT	${\bf H} eidelberger \ {\bf I} on enstrahl {\bf \cdot T} herapiezen trum \ (Heidelberg, \ Germany)$
IC	Ionization Chamber
IBA	Ion Beam Applications
LaBr ₃ :Ce	Cerium-Doped Lanthanum(III) Bromide scintillator detector
LYSO:Ce	$Cerium\mbox{-}Doped\mbox{ Lutetium\mbox{-}Yttrium\mbox{ Oxyorthosilicate\mbox{ scintillator\mbox{ detector}}}$
NaI(Tl)	Thallium-Doped Sodium Iodide scintillator detector
NURBS	Non-Uniform Rational \mathbf{B} -Spline
OAR	Organ-At-Risk
PGPL	\mathbf{P} rompt- \mathbf{G} amma \mathbf{P} rofile \mathbf{L} ength
PMMA	Polymethyl Methacrylate
\mathbf{PTV}	Planning Target Volume
$\mathbf{Q}\mathbf{M}\mathbf{D}$	\mathbf{Q} uantum \mathbf{M} olecular \mathbf{D} ynamics
RBE	Relative Biological Effectiveness
\mathbf{rms}	Root Mean Square
SBR	Signal to Background Ratio
SOBP	\mathbf{S} pread- \mathbf{O} ut \mathbf{B} ragg \mathbf{P} eak

TLE	Track-Length Estimator
\mathbf{TMS}	Treatment Monitoring System
TOF	$\mathbf{T}ime \ \mathbf{O}f \ \mathbf{F}light$
\mathbf{TPS}	Treatment Planning System
WPE	$\mathbf{W} est deutsche \ \mathbf{P} rotonen therapiezen trum \ \mathbf{E} ssen \ (Essen, \ Germany)$

Keywords

- Hadrontherapy
- Prompt gammas
- Geant4
- Hadrontherapy monitoring
- Multi-slit collimated camera
- Inelastic hadronic models
- Monte Carlo simulations
- Acceleration of simulations

Mots-Clefs

- Hadronthérapie
- Gamma prompt
- Geant4
- Contrle en ligne de l'hadronthérapie
- Caméra collimatée multi-fentes
- Modèles inélastiques hadroniques
- Simulations de Monte Carlo
- Accélération des simulations

For the one that is always by my side ...

Chapter 1

Résumé substantiel

Chapitre 2 – Introduction

Le traitement des tumeurs cancéreuses avec des faisceaux de particules (appelé hadronthérapie) a été proposé en 1936 par Locher [5] qui pensait tout d'abord à l'utilisation de neutrons. L'utilisation de protons et d'ions lourds a été proposée plus tard, en 1946, par Wilson [6]. Les propriétés physiques de l'interaction des neutrons avec les tissus biologiques ont en fait conduit à de gros problèmes lors de l'application et le développement de la thérapie de neutrons. En conséquence, même si environ 30000 patients ont été traités à ce jour en utilisant ce type de thérapie, son champ d'application est limité et son utilisation est très faible aujourd'hui [2]. Par ailleurs, la radiothérapie utilisant des protons et des ions lourds est de plus en plus répandue. Contrairement aux neutrons dont le profil de dose en profondeur est similaire à celui des photons, les protons et les ions lourds présentent un profil de dépôt d'énergie caractérisé par le pic de Bragg. Le pic de Bragg est un pic étroit et aigu situé à l'extrémité du profil de dose en profondeur dans lequel une partie importante de l'énergie de la particule est déposée. Un tel confinement du dépôt d'énergie donne un profil de dose en profondeur particulièrement intéressant pour la radiothérapie [7]. Par conséquent, une meilleure conformalité de la tumeur est prévue lors de la thérapie par particules.

La figure 2.1 montre une comparaison des profils de dose en profondeur dans l'eau de photons, des protons et des ions carbone avec des énergies pertinentes d'un point de vue clinique. Les propriétés balistiques supérieures des ions par rapport à celles des photons sont mises en évidence, ainsi que le pic de Bragg plus large du faisceau de protons par rapport à celui des ions de carbone. Ce phénomène physique est lié aux processus de perte d'énergie des particules le long de la cible, c'est-à-dire les fluctuations statistiques de



FIGURE 1.1: À gauche: comparaison des profils de dose en profondeur de photons et d'ions carbone. À droite: comparaison des profils profondeur-dose de protons et d'ions de carbone avec la même plage dans l'eau. Adapté de [7].

perte d'énergie lors du grand nombre de collisions entre les ions incidents et les électrons de la cible.

Dans tous les cas, le pic de Bragg est une épée à double tranchant. Il permet en principe d'obtenir un dépôt précis de la dose dans la tumeur mais il rend également la technique plus sujettes à des décalages significatifs entre les distributions de dose planifiée et délivrée. Dans le cadre d'un traitement de radiothérapie, plusieurs aspects physiques et biologiques peuvent conduire à des écarts par rapport au plan de traitement. Parmi ceux-ci, on peut citer, par exemple, les incertitudes associées au faisceau, au positionnement du patient et aux changements morphologiques des patients. Ces incertitudes de traitement conduisent finalement à une incertitude de parcours, car il n'est pas possible de localiser exactement l'endroit où l'ion s'arrête à l'intérieur du patient. Les écarts entre planification et traitement réellement effectué peuvent conduire notamment à un surdosage des tissus sains et à un sous-dosage de la tumeur.

Les incertitudes de cette modalité de radiothérapie rendent donc particulièrement souhaitable une vérification de la conformalité de la dose au cours du traitement. C'est dans ce contexte qu'a été proposée la détection de radiations secondaires émises lors des interactions nucléaires induites par les ions incidents dans le patient. La tomographie par émission de positons (TEP) et la détection des rayons gamma prompts ont notamment fait l'objet d'une recherche intense ces dernières années.

Dans cette optique, le travail a porté essentiellement sur le concept de caméra collimatée multi-fentes qui présente l'avantage d'une relative simplicité et dont l'applicabilité clinique a été en grande partie démontrée par des études antérieures. Il s'agit d'un travail collaboratif initié dans le cadre du projet ETOILE dans le but de fournir des taux fiables d'émission de rayons gamma prompts en cibles homogènes et hétérogènes et d'optimiser la géométrie de la caméra collimatée. Il s'agira également d'étudier la précision, l'amélioration et l'accélération de l'outil de simulations Monte Carlo Geant4. Cela inclut plus précisément l'analyse des données expérimentales obtenues au GANIL (Caen), GSI (Darmstadt), HIT (Heidelberg) et WPE (Essen) et accompagnées des simulations Geant4 correspondantes, mais aussi la proposition de nouvelles approches susceptibles d'être utilisées dans le contrôle de l'hadronthérapie. En particulier, sont décrites des techniques de soustraction de bruit de fond, de nouvelles grandeurs pour estimer le parcours des ions à partir des distributions spatiales de gamma prompts, des méthodes d'accélération de l'outil de simulation Geant4 et une amélioration considérable de cet outil de simulation dans la modélisation de l'émission gamma prompt.

Chapitre 3 – Émission de rayons gamma prompts

Taux absolus d'émission gamma prompts avec des cibles homogènes

Une série d'expériences utilisant des détecteurs collimatés avec une simple fente et des cibles homogènes est présentée ici avec l'analyse des données associée. L'objectif principal est d'obtenir des taux absolus d'émission gamma prompts pour les faisceaux de protons et d'ions carbone. Ces taux absolus sont définis comme le nombre de gamma prompts par ion incident, par l'unité de champ de vue (millimètre), et par l'unité d'angle solide (stéradian). Ces taux seront corrigés de l'efficacité du détecteur et par les photons capables de traverser le collimateur et le blindage. Le but de l'analyse présentée ici est de recueillir des données expérimentales appropriées pour la comparaison avec des simulations et de vérifier la cohérence des différents résultats expérimentaux. Toutes ces expériences et ces analyses de données sont cruciales pour l'utilisation quantitative des informations fournies par l'émission gamma prompts, à savoir guider la construction d'un prototype clinique et de prédire les distributions gamma prompts qui doivent servir de référence au cours du traitement.

Après avoir estimé les facteurs géométriques et le signal gamma prompts à partir de la soustraction de bruit de fond, il est possible d'obtenir les taux absolus avec les données expérimentales des protons (figure 1.2) et des ions carbone (figure 1.3). Les barres d'erreur présentées dans les profils comprennent à la fois les incertitudes statistique (un écart-type) et les incertitudes systématiques (somme quadratique des deux types d'erreur).

Les résultats obtenus avec les données expérimentales des protons et des ions carbone figures 1.2 and 1.3 sont donnés dans le tableau 1.1.



FIGURE 1.2: Profils des taux de γ prompts absolus pour les expériences de protons. Chaque point de données comprend l'incertitude statistique (un écart-type) et les incertitudes systématiques considérées.



FIGURE 1.3: Profils des taux de γ prompts absolus pour les expériences avec des ions carbone. Chaque point de données comprend l'incertitude statistique (un écart-type) et les incertitudes systématiques considérées.

TABLE 1.1: Taux absolus en utilisant le premier point mesuré à l'intérieur de la cible qui n'est pas affecté par l'entrée du profil. La gamme d'énergie indique l'énergie des particules primaires à l'intérieur du champ de vision du premier point après l'entrée de la cible. Elle est estimée avec Geant4. Lorsque les résultats de plusieurs expériences sont combinées, une gamme d'énergie prend en compte les limites d'énergie maximale parmi toutes les expériences considérées.

Material	Gamme d'énergie (MeV/u)	Ion	Taux absolus ($\times 10^{-6}$ gamma prompts ion ⁻¹ mm ⁻¹ sr ⁻¹)
PMMA	[77-90]	Ions carbone	$124 \pm 0.7_{\rm stat} \pm 30_{\rm sys}$
PMMA	[272-310]	Ions carbone	$79 \pm 2_{\mathrm{stat}} \pm 23_{\mathrm{sys}}$
Eau	[264-292]	Ions carbone	$112 \pm 1_{\rm stat} \pm 22_{\rm sys}$
PMMA	[139-156]	Protons	$16~\pm~0.07_{\rm stat}~\pm~1_{\rm sys}$

Comparaison avec des simulations Monte Carlo Geant4

Ensuite, une étude comparative a été effectuée afin d'évaluer la capacité globale de Geant4 à reproduire les taux d'émission gamma prompts. Cette étude vise à analyser les performances de Geant4 et, le cas échéant, à estimer l'ampleur des améliorations nécessaires. Les figures 1.4 et 1.5 montrent la comparaison des taux mesurés et simulés avec différents modèles hadroniques. On constate que, quel que soit le modèle hadronique utilisé, les simulations Geant4 surestiment systématiquement les taux mesurés avec des faisceaux de protons et d'ions carbone.



FIGURE 1.4: Comparaison de données expérimentales en utilisant des protons avec des simulations Geant4 utilisant différents modèles inélastiques hadroniques.



FIGURE 1.5: Comparaison de données expérimentales en utilisant des ions carbone d'énergies différentes avec des simulations Geant4 utilisant différents modèles hadroniques inélastiques. Haut à gauche: 95 MeV/u (irradiation du PMMA). Haut à droite: 310 MeV/u (irradiation du PMMA). Bas à gauche: 300 MeV/u (irradiation de l'eau). Bas à droite: 310 MeV/u (irradiation de l'eau).

Émission gamma prompts avec des cibles hétérogènes

Cette section présente une étude dans laquelle des cibles hétérogènes ont été irradiées avec un faisceau d'ions de carbone de 95 MeV/u. Trois fantômes ont été utilisés: une cible homogène de PMMA, une cible hétérogène de PMMA avec du Téflon et une cible hétérogène de PMMA avec un matériau équivalent poumon. La figure 1.6 montre les trois cibles considérées et la figure 1.7 représente les profils gamma prompts expérimentaux.



FIGURE 1.6: Photos des fantômes utilisé. À gauche: cible homogène de PMMA; au centre: cible hétérogène de PMMA avec du Téflon; à droite: cible hétérogène de PMMA avec un matériau équivalent poumon.

Les profils ont été également simulés avec l'outil Geant4. Les structures mécaniques autour de la cible (par exemple la table mobile et la géométrie de la salle) n'ont pas été prises en compte. Les données simulées ont suivi exactement le même type d'analyse que les données expérimentales. Une évaluation des données de simulation montre une



FIGURE 1.7: Profils de gamma prompts expérimentaux avec les détecteurs BaF_2 (a) et NaI(Tl) (b). Les lignes pointillés représentent le parcours des ions pour chaque fantôme. Ces parcours ont été estimés avec Geant4.

surestimation des taux de gamma prompts par un facteur 2-3 en fonction de la position longitudinale considérée. La figure 1.8 montre cette comparaison.



FIGURE 1.8: Profils gamma prompts mesurés et simulées pour les trois cibles avec le détecteur BaF_2 (a) et le détecteur NaI(Tl) (b).

Chapitre 4 – Optimisation de la géométrie de la caméra collimatée multi-fentes avec temps de vol

Ce chapitre décrit le travail développé pour optimiser une caméra collimaté multi-fentes basé sur la technique du temps de vol et focalisé sur la conception du collimateur. Cette étude était basée avant tout sur une étude Monte Carlo utilisant Geant4. La première étape comprend néanmoins une comparaison des simulations avec les données expérimentales afin de sélectionner les modèles physiques les plus appropriés pour réaliser l'optimisation. Contrairement au chapitre précédent, où la comparaison a été centrée sur les taux gamma prompts, ici, l'analyse comparative portait surtout sur les spectres de temps de vol et, en particulier, l'influence des événements induits par les neutrons. Une discussion approfondie sur les géométries optimisées est proposée à la fin du chapitre.

L'étude comprend trois étapes. La première étape correspond à la comparaison des simulations avec les données expérimentales afin de sélectionner les modèles physiques les plus appropriés pour cette application. La deuxième étape porte sur l'optimisation de la caméra collimatée à l'aide de simulations Geant4. Comme il n'y avait pas de connaissances *a priori* sur les paramètres qui influent le plus sur la performance de l'appareil, il a été décidé de simuler de multiples géométries aléatoires contraintes par des limites significatives. Après cette étape, il a été possible non seulement de déterminer la

la région considérée.

Le tableau 1.2 présente les deux configurations optimisées et la figure 1.9 montre les profils simulés à haute statistique obtenus avec ces deux configurations.

 TABLE 1.2: La conception géométrique des deux caméras optimisées. En ce qui concerne les valeurs de précision, l'incertitude statistique pour un sigma est présenté entre crochets. Toutes les valeurs indiquées sont en millimètres.

Cas	Précision du fall-off	Précision de l'entrée	Précision de la longueur du profil	Champ de vue	Fente	Plaque	Épaisseur	Distance de l'axe du faisceau à collimateur	Distance de l'axe du faisceau au détecteur
a	0.59(0.06)	0.66(0.09)	$\begin{array}{c} 0.88(0.11) \\ 1.12(0.14) \end{array}$	23.6	5.4	2.6	180.2	303.7	485.3
b	0.70(0.08)	0.87(0.12)		13.1	3.0	2.1	190.9	322.3	516.5





FIGURE 1.9: Profils simulés à haute statistique $(4 \times 10^9 \text{ protons})$ obtenus avec les deux configurations optimisées. Le profil à gauche correspond au cas a et le profil à droite au cas b du tableau 1.2.

Chapitre 5 – Amélioration de l'outil de simulations Monte Carlo Geant4

Dans la continuité de la comparaison des données mesurées et simulées proposée au chapitre 2, le chapitre 5 présente l'étude des possibilités d'amélioration des modèles protons de collisions nucléaires inélastiques mises en œuvre dans Geant4. Il commence par une étude préliminaire des différentes options des modèles considérés. Ensuite, les données expérimentales sont comparées avec les données simulées en utilisant l'outil

Geant4 avec les options qui conduisent à une réduction significative des taux d'émission des gamma prompts.

La figure 1.10 montre les profils gamma prompts expérimentaux et simulées avec le modèle nucléaire amélioré qui a donné les meilleurs résultats.



FIGURE 1.10: Profils longitudinales gamma prompts expérimentales et simulées pour une irradiation proton (160 MeV) avec une cible PMMA. Les simulations sont réalisées avec le modèle nucléaire amélioré qui a donné les meilleurs résultats.

Chapitre 6 – Accélération de l'outil de simulations Monte Carlo Geant4

Le flux de travail clinique a des contraintes, notamment en termes de temps disponible pour la planification du traitement. Par conséquent, une stratégie pour l'accélération de la modélisation des émissions gamma prompts est donc particulièrement souhaitable. Ce chapitre présente les principes d'un nouvel algorithme d'accélération appelé pgTLE ainsi que les tests préliminaires de cet algorithme et une estimation des facteurs d'accélération attendus.

L'approche de pgTLE suit deux étapes distinctes. D'une part, il s'appuie sur une base de données d'émission gamma prompts calculée par Monte Carlo, et, d'autre part, il utilise le concept de TLE (« track-length estimator », estimateur de la longueur de la trace de la particule). Bien que le TLE soit un algorithme de réduction de variance relativement standard, il n'est pas mis en œuvre dans Geant4.

La base de données d'émission gamma prompts est un ensemble d'histogrammes 2D de spectres d'énergie gamma prompts en fonction de l'énergie des protons au moment de la réaction nucléaire. Cette étape est effectuée une seule fois pour tous les noyaux atomiques considérés dans la simulation et elle se fait hors-ligne. La figure 1.11 montre un exemple d'histogramme 2D de la base de données.



FIGURE 1.11: L'exemple d'un cas considéré pour la base de données en corrélation l'énergie des protons lors de collisions nucléaires inélastiques avec l'énergie et le nombre des gammas prompt émis par collision nucléaire inélastique. La cible considéré est un matériau équivalent de l'os.

Chapter 2

Introduction

In this chapter an introduction to the subject of the studies conducted is presented. Since the work I have made is focused on the monitoring of hadrontherapy treatments, this topic has more emphasis in this overview. The chapter ends with a description of the work developed and the structure of this manuscript.

2.1 Particle therapy/Hadrontherapy

The form of external beam radiotherapy addressed in the present work does not have a unique designation. Due to different interpretations, several terms exist to refer to the radiotherapy modality using protons and other heavier ions. Terms like particle therapy, hadrontherapy, hadron therapy, heavy-ion therapy, and light-ion therapy are very common and, in some cases, interchangeable. Particle therapy is the broadest one, thus care must be taken to specify the kind of beam being considered. Historically, the radiotherapy modality employing electrons was never considered as particle therapy although they are, in fact, particles. Instead, electron and photon radiotherapies are usually grouped together and designated as conventional radiotherapy (this nomenclature will be used throughout this work in its broad definition of including all forms of radiotherapy using photons and electrons). To address this apparent incoherency, Amaldi coined the term "hadrontherapy" to refer to all radiotherapy modalities using beams of particles made of quarks [1], hence excluding photon and electron radiotherapy. This definition includes neutrons, protons, pions, antiprotons, helium ions, and other heavier ions. Nevertheless, nowadays, particle therapy is very often associated only to therapy with protons and heavier ions since the importance and the use of neutron therapy are gradually decreasing [2] and the application of the other particles is almost negligible. The "hadron therapy" term follows exactly the same logic behind the hadron herapy one, but it is used by some more English-purist

authors by avoiding word compounding (a similar issue exists when confronting the terms radiation therapy and radiotherapy). On the other hand, both heavy-ion and light-ion therapy terms are used to address the same modality: the use of ions heavier than protons to treat tumours. The difference between the use of heavy and light is a matter of perspective. Presently, ions up to oxygen are considered for radiotherapy (although the most common is carbon ion [3]) and these ions heavier than protons are called "heavy ions" in radiobiology terminology due to their increased relative biological effectiveness (RBE). Nevertheless, they are designated as "light ions" when considering the nuclear physics framework [4].

Independently of the preferred term, particle therapy was first proposed in 1936 by Locher [5], who suggested using neutrons in the treatment of tumours. The use of protons and heavier ions was proposed later, in 1946, by Wilson [6]. The physical properties of neutron interaction with biological tissues led to major setbacks in the application and development of neutron therapy. Moreover, in the case of neutron capture therapy, the radiobiological and dosimetry issues are a real obstacle to its clinical use. As a consequence, although about 30 000 patients have been treated to date using this kind of therapy, its field of application is limited and its use has gradually been decreasing [2]. On the other hand, radiotherapy using protons and heavier ions is becoming increasingly widespread. Unlike neutrons, which depth-dose profile is similar to the one of photons, protons and heavier ions show a distinct energy deposition profile, characterised by the Bragg peak. The Bragg peak is a narrow and sharp peak located towards the end of the depth-dose profile and corresponds to a region where a significant part of the energy of the particle is deposited. Such energy deposition confinement within a precise position yields a favourable depth-dose profile to be used in radiation therapy [7]. Hence, a better tumour conformality is expected when considering particle therapy.



FIGURE 2.1: Left: comparison of depth-dose profiles of photons and carbon ions. Right: comparison of depth-dose profiles of protons and carbon ions with the same range in water. Adapted from [7].

Figure 2.1 shows a comparison of depth-dose profiles in water of photons, protons and carbon ions with clinically-relevant energies. The enhanced ballistic properties yielded by ions when compared with photons is shown, as well as the higher broadening of the Bragg peak of proton beams in respect to carbon ion ones. Such a physical phenomenon is related to the energy loss processes of the particles composing the beam along the target, namely to the statistical fluctuations in the energy loss in the large number of collisions of the slowing-down process, which result in a broadening of the Bragg peak for an ion beam consisting of many particles. These fluctuations give origin to the range straggling observed. Proton beams have a higher range straggling when compared with carbon ion beams, since the relationship that governs the range straggling process has a $1/\sqrt{M}$ dependence, where M is the particle mass [8].



FIGURE 2.2: Creation of a SOBP by superimposing several Bragg peaks from carbon ions with different energy and beam intensity. Adapted from [9].

In any case, such sharp peaks cannot provide full tumour volume coverage with the required dose, so the beam delivery system must extend the Bragg peak over a bigger volume, creating the so-called spread-out Bragg peak (SOBP). Figure 2.2 shows how the SOBP can be formed by superimposing several Bragg peaks in the case of carbon ion irradiation. The same procedure is applied for the case of proton beams. There are two main ways to do it (although each approach may have several technical variations). The first is the passive delivery, which employs mechanical structures to shape and tailor the beam to the intended dose distribution. It makes use of one or more scatters (to broaden the beam), range modulators (to produce the actual SOBP), range shifters (to move the SOBP in depth), collimators (to collimate the beam), and compensators (to shape the beam to cope with the distal contour of the tumour volume). Figure 2.3 depicts the different mechanical structures utilised for a passive shaping of the beam, as well as the effects on the transversal and longitudinal profile of the beam. The range modulator, instead of a flat structure as seen in figure 2.3 top, may be a modulator wheel that rotates at a given frequency in order to produce the SOBP, as in figure 2.3 bottom. Furthermore, it can also be observed in the top illustration of this figure that the beam shaping process



makes possible that organs-at-risk (OAR) (magenta structures after the tumour) are not irradiated.

FIGURE 2.3: Mechanical elements of two different designs of a passive shaping delivery system. The top figure is taken from [7] and the bottom one is coming from [10]. Note that in passive mode the shaping system presented at the bottom figure does not make use of the scanning magnets.

The passive delivery has a strong limitation in terms of dose conformality, since a significant dose is deposited in the healthy-tissue regions before the tumour in a longitudinal perspective. This arises from the adjustment of the particle ranges to the distal contour. Figure 2.3 top depicts this situation, where it can be observed that regions before the tumour are being irradiated with high dose (see the region with the check pattern). This issue may be attenuated in favourable cases by employing a variable range shifter and a variable collimator that allow for creating smaller SOBPs that are then stacked together to form an irradiation field that covers the entire target volume [7].

The second mode is active delivery. In this case, the beam is steered by means of magnets to guide it to the desired location – a spot. A spot can be defined as a region of the target volume in which the Bragg peak is located. After a given spot receives the planned dose, the magnets force the beam to move to a different one. If all the spots in an iso-energy layer have been filled, the energy of the particles is modified to allow for the irradiation at a different depth. Despite changing the energy of the particles is a straightforward process with a synchrotron (even though it requires the beam to be switched off), with a cyclotron there is a moderator (usually installed at the accelerator beam exit) that
selects the energy at a given time. In this delivery mode, there are two main technical implementations depending on whether the beam is on or off during the switching between spots in the same energy layer. If the beam is always on, it is called raster scanning [11], otherwise the term spot scanning is used [12]. The term pencil beam scanning is also often employed to refer to active delivery [13]. This delivery mode does not suffer from the high-dose regions proximal to the target volume. Another remark is the fact that, as the Bragg peaks from carbon ions are very sharp, there is the need to include a ripple filter in the nozzle in order to broaden them to allow for a smoother SOBP and, at the same time, optimise the irradiation time [14]. Figure 2.4 depicts a schematic illustration of the active delivery principle.



FIGURE 2.4: Illustration of the active delivery mode principle. Note that other structures that may exist in the nozzle are not shown (e.g. the ripple filter for carbon ion treatments). From [15].

Another important feature of these particles is their enhanced biological effect in the Bragg peak region when compared to photons, which can be quantified through the so-called RBE. For protons, the RBE is assumed to have a constant value of 1.1 along the entire path of the particle [16], although studies have shown that a significant variation may exist (e.g. [17]). In respect to heavier ions, different ions show different and varying RBE along their depth-dose profile. As pointed out by Kraft and Kraft, carbon ions were chosen for radiotherapy because the ratio between the RBE at entrance channel and that at the target volume seems to be optimal for a radioresistant tumour. However, for more superficial tumours, ions heavier than carbon could eventually be more effective [18].

A clinical example showing the advantage of the ballistic properties of ions over some of the most advanced photon therapy solutions is depicted in figure 2.5. In this figure, the treatment plans of two patients using different techniques are compared. Note that this study is very recent [19] and the photon therapy plans should be comparable to the state-of-the-art solutions. The sparing of more healthy tissue is clearly visible for the cases where proton irradiation is considered. In this work, Moteabbed and colleagues state that choosing proton over photon therapy for paediatric patients with brain tumours is highly beneficial regarding secondary malignancies, due to the smaller dose given to the tissues surrounding the tumour [19].



FIGURE 2.5: Treatment plans for two patients, one with a craniopharyngioma (left) and the other with a rhabdomyosarcoma (right), for comparison of several different radiotherapy modalities. The naming convention in the images is the following: passive proton therapy (PPT), pencil-beam scanning protons (PBS), intensity-modulated radiation therapy (IMRT), and volumetric-modulated arc therapy (VMAT). If applicable, the number of fields the treatment plan considers is mentioned. For example, PPT4F means a passive proton therapy plan with four fields. Adapted from [19].

2.2 Hadrontherapy treatment uncertainties

In any case, the Bragg peak is a double-edged sword. Although it allows for a precise local dose deposition, it makes the technique more prone to significant mismatch between the intended and the actually delivered dose distribution. In the course of a radiotherapy treatment, several physical and biological aspects can be associated to deviations from the treatment plan, ergo compromising the precision of dose distribution. Among these it is possible to name, for example, beam-associated uncertainties, imprecisions arising from patient mispositioning and morphological alterations, resulting e.g. from organ movement or biological responses to irradiation in a fractionated scheme. These treatment uncertainties ultimately lead to a range uncertainty, since it is not possible to pin-point exactly the location where the ion will stop inside the patient. On the other hand, the range concept is absent from the radiotherapy using photons, given that photons are expected to come out of the patient. Nevertheless, the aforementioned uncertainties also have a detrimental effect on conventional radiotherapy treatments even though the degree of impact is much smaller due to the different physical interaction properties of the radiations involved.

To address such issues, a common practice is to take uncertainties into account during the treatment planning phase. Concerning proton therapy, Paganetti reports that some treatment centres apply a 3.5% uncertainty on the proton range plus a 3 mm safety margin. He also points out the protocol at Massachusetts General Hospital (Boston, USA), in which 3.5% and 1 mm are employed, respectively. He continues by describing that this results in a 8 mm overshoot for a 20 cm proton range in soft tissue, which, he concludes, is quite substantial [20]. Being so, on the one hand, there is the undoubtedly ballistic advantage provided by ions to treat tumours, but, on the other hand, such an advantage cannot be fully exploited due to the lack of control during treatment.

Nevertheless, range uncertainties are not only attributable to the events occurring during treatment, as listed above. There are also uncertainties related to the dose calculation, namely in the planning computed tomography (CT) and in the dose calculation in the presence of complex geometries. Moreover, all these uncertainties can be exacerbated by the use of analytical approximations present in most of the treatment planning systems (TPS) instead of the use of the more accurate Monte Carlo simulations. Summing most of the possible uncertainty contributions for a proton therapy treatment, Paganetti claims a total of 4.6% range uncertainty plus 1.2 mm of safety margin and 2.4% plus 1.2 mm, respectively for the cases without and with Monte Carlo simulations. There are additional approaches that are clinically followed in order to cope with the uncertainties. For example, it is common practice to avoid having OAR after the distal edge of the ion path in the treatment planning in order to prevent overdosage in more critical structures, in case the actual ion range is greater than the originally planned. One can also prevent treatment scenarios in which the beam must cross highly heterogeneous regions and implants in the patient body.

Moreover, one can perform a so-called dose-error analysis with phantoms [21] and test it against the treatment plan [22]. By assuming a range of values coming from possible uncertainties (e.g. changing the CT calibration curve) it is possible to obtain an estimate of the potential error on the planned dose for each voxel and then better quantify the robustness of the plan in terms of target coverage and dose to healthy tissue. A further step in this approach is to link such analysis to the treatment planning system, for instance, by suppressing pencil beams during the optimisation stage with a higher uncertainty risk [23].

All the aforementioned countermeasures against uncertainties make the plan more robust, as, even if the dose is not delivered as planned due to some unforeseen situation, there is some degree of certainty that the whole target volume receives the intended dose. Usually, several treatment plans are created and tested to assert their robustness against, for example, worst case scenarios that may happen during treatment [24]. The protocol depends on what kind of approach a given clinical facility employs for the optimisation but, in this regard, the work of Unkelbach et al. [25], Pflugfelder et al. [24], and Chen et al. [26] are noteworthy. In the first study, it is proposed a method for treatment plan optimisation based on the worst-case dose distribution by assuming that the proton range may vary within some interval. Pflugfelder et al. extended the concept behind the work of Unkelbach et al. by allowing any type of objective function in the worst-case optimisation (the previous approach was only applicable to linear objective functions) and by including the possibility of setup uncertainties. Finally, Chen et al. developed a multi-criteria optimisation framework, in which the optimisation is performed under several robustness criteria (i.e. several objective functions – in contrast with the other two aforesaid studies, where only one criterion was used). The term robust planning is normally used when these and other principles are considered during the treatment optimisation workflow.

None of these methods allow for monitoring the dose delivered to the patient, however they represent a first approach to address the issue of treatment-associated uncertainties by introducing solutions to account for uncertainties during treatment plan optimisation. They essentially try to accurately estimate the uncertainties in the treatment plan and to develop a plan of action to minimise them in the overall treatment.

2.3 Hadrontherapy monitoring and verification

In face of the uncertainties involved in this radiotherapy modality, it is of utmost importance to ensure dose conformality during treatment. Otherwise, deviations from the treatment plan can produce undesirable effects, such as overdosage in the healthy tissue and underdosage in the tumour. Therefore, monitoring and verification techniques should be considered.

For reducing patient-positioning errors a proper verification protocol can be set to check the position of the patient prior to treatment using, e.g. X-ray imaging techniques [27]. During treatment, fiducial markers or other techniques can be employed. Huber et al. [27] recently suggested that ion-beam radiography could be combined with fiducial markers in order to verify the position of the patient, as well as organ movement. In fact, organ movement is a major concern in particle therapy due to the further uncertainties that arise in that case [28].

The methods just described can help to mitigate some of the treatment-associated uncertainties. However, they do not allow to monitor directly the range of the particles and hence do not provide information neither on overdosage in healthy tissue nor underdosage in the tumour. For that purpose, positron emission tomography (PET) and several other techniques, most of them relying on the detection of events due to inelastic nuclear interactions, have been considered. In the case of light incident ions like carbon ions, such interactions can be well described by the abrasion-ablation model proposed by Serber [7, 29]. Schardt describes it as a two-step process in which the first step comprises the abrasion of the overlapping reaction zone, while the outer nucleons are only slightly affected. The remaining projectile and target fragments then deexcite by evaporation of nucleons or clusters and prompt-gamma emission in the second step [7]. Figure 2.6 depicts an illustration showing the steps of this model. Note that there are no projectile fragments in the case of incident protons.



FIGURE 2.6: Picture illustrating the abrasion-ablation model proposed by Serber [29]. Adapted from [30].

It is worthwhile to note that this fragmentation process has also an impact on the depthdose profiles of particles that can undergo such a process. These fragments need to be then accounted for during treatment plan since they may deposit dose beyond the target volume. This is commonly designated as the fragmentation (or fragment) tail. Figure 2.7 illustrates the issues involving the fragments produced along the ion path.



FIGURE 2.7: The left figure depicts the depth-dose profile of 330 MeV/u carbon ions and the impact of the different fragments produced along the ion path. The contribution from the different fragments has been estimated by the experimentally-driven model of Sihver et al. [31]. The picture on the right points out the small dose beyond the target volume due to high-energy nuclear fragments (marked by a purple circle and described as fragment tail in the left figure). From [32].

The goal of most of the applied and proposed monitoring techniques for hadrontherapy is to assess the ion range. In fact, there are other approaches that, for example, aim to retrieve the elemental composition of tissues after treatment using PET [33] or even to reconstruct the dose distribution actually delivered [34]. Nevertheless, at this moment, one of the main concerns of hadrontherapy is indeed the range uncertainties. As recently shown in a public survey conducted during the 54th annual meeting of the American Association of Physicists in Medicine, 33% of the attendees selected the range uncertainties associated with proton therapy as the main obstacle to this treatment modality becoming mainstream [35].

In addition, it is important to separate the monitoring modalities into two categories: 1) online and 2) offline. In the first group are included the modalities that are (or can be) employed during treatment. In principle, these modalities can provide real-time information concerning the quality of the treatment being delivered, making possible to, as a last resort, stop the treatment to reassess the treatment plan. Note that the decision of using this last resort may depend on the country rules where the treatment is being carried out. One can even imagine that an online real-time monitoring technique could provide information to guide the particle beam to the right location (e.g. when dealing with fast moving organs) or to perform a low-dose verification with few pencil beams in order to assert the correctness of the planned dose delivery. The second category groups all modalities that are used after the course of the treatment fraction. It does not allow for correcting the treatment just delivered, but it gives the opportunity to adjust and to recalculate the following sessions based on new information.

Another crucial point in hadron herapy monitoring is the workflow leading to the detection of ion range shifts. The measured quantities during irradiation must be then compared with a prediction that can be estimated by analytical methods, Monte Carlo simulations, or a combination of both. The simplest possibility is to have a predicted distribution that is then visually compared to the measured one by superimposing the two cases and eventually by estimating some kind of quantity, like a relative difference per bin/pixel/voxel. As an example, nowadays, the ion range monitoring with PET relies mostly on visual inspection [36]. A more refined approach would be the use of algorithms responsible for estimating some figure of merit (e.g. the prompt-gamma or the positron emitters profiles fall-off position that can be then correlated with ion range) through the application of fitting or other procedures. Finally, the most complex situation is when an automated system is considered. Such a system would be responsible for assessing the existence of ion range shifts based on one or several criteria. In this regard, the work of Kuess et al. [36] presents several statistical methods for automated comparison of in-beam PET images. For one of the considered methods (based on the Pearson's correlation coefficient), they obtained results in terms of sensitivity and specificity comparable to the ones after visual inspections. For the case of prompt-gamma monitoring, Gueth et al. [37] published the study concerning a machine-learning algorithm, in which they show a method to construct a function able to predict ion range shifts based on different prompt-gamma profile features.

The next sections make an overview of different techniques and approaches based on secondary particle emission that are being studied and developed and, in some cases, even applied.

2.3.1 PET

The use of positron emitters to provide information about the ion range was possibly first proposed by Bennett and colleagues in 1975 [38, 39]. They have shown that it was possible to visualise the positron emitters after the irradiation of a plastic target and living animals with 200 MeV protons. These positron emitters are created after inelastic nuclear interactions between the projectile and the target nuclei, thus their production depends on both the projectile and the target. Table 2.1 shows the positron emitters produced in human tissues, as well as their reaction channels and half-life. In this table, the highlighted rows indicate the reaction channels comprising up to 95% of the positron emitters produced in human tissues after proton irradiation [40].

TABLE 2.1: Proton-nuclear reaction channels and β^+ isotopes produced in human tissues. The highlighted rows point to the most abundant reaction channels. Adapted from [40].

Target	Nuclear reaction channels	β^+ isotopes	Half-life (s)
С	${}^{12}C(p,pn){}^{11}C$	$^{11}\mathrm{C}$	1219.80
	${}^{12}C(p,p2n){}^{10}C$	$^{10}\mathrm{C}$	19.29
Ν	$^{14}N(p,2p2n)^{11}C$	$^{11}\mathrm{C}$	1219.80
	${}^{14}N(p,pn){}^{13}N$	^{13}N	587.60
	$^{14}N(p,n)^{14}O$	¹⁴ O	4236.60
0	$^{16}O(p,pn)^{15}O$	¹⁵ O	122.24
	$^{16}O(p,3p3n)^{11}C$	$^{11}\mathrm{C}$	1219.80
	${}^{16}O(p,2p2n){}^{13}N$	^{13}N	587.60
	${}^{16}O(p,p2n){}^{14}O$	^{14}O	4236.60
	$^{16}O(p,3p4n)^{10}C$	$^{10}\mathrm{C}$	19.29
Р	$^{31}\mathrm{P(p,pn)^{30}P}$	³⁰ P	150.00
Ca	$^{40}Ca(p,2pn)^{38}K$	³⁸ K	458.40

Unlike for the proton irradiation case, most of the positron emitters created after carbon ion irradiation originate from projectile fragmentation [41]. This crucial difference in the production of positron emitters after proton and carbon ion irradiation has a significant impact on the corresponding distribution profiles along the depth in a target (or the patient). During proton irradiation, positron emitters are produced along most of the ion path, after nuclear interactions with the target nuclei (figure 2.8, left). In turn, in carbon ion irradiation, since it is mostly the projectile that becomes the positron emitter, there is a cumulative effect towards the end of the ion path (figure 2.8, right). Moreover, the proton-nuclear reactions have a minimum energy threshold. As an example, the two most significant reactions $^{12}C(p,pn)^{11}C$ and $^{16}O(p,pn)^{15}O$ have energy thresholds of 20.3 MeV and 16.6 MeV, respectively [42]. This implies that the production of positron emitters for the case of incident protons will not occur at the very end of the ion path due to insufficient proton energy. Parodi and Enghardt estimate a systematic difference of 6 mm between the 50% level of total activity and the maximum dose in PMMA, but it can be different in other materials [42]. On the contrary, the positron emitter projectile in the case of carbon ion irradiation will travel until very close to the end of the ion range, hence a better correlation with the range itself may be expected [43]. This is also visible in figure 2.8.



FIGURE 2.8: Measured positron emitters depth profiles (solid line) from the irradiation of PMMA targets with 140 MeV protons (left) and 259.5 MeV/u carbon ions (right). The dotted line shows the calculated relative dose distributions. From [44].

The production yields of positron emitters for carbon ion irradiation are higher, per incident particle, than the ones for the proton case. However, since carbon ions have higher stopping power than protons they require a lower particle fluence to deliver the same physical dose. Therefore, it has been estimated that for a given scenario the total activity after proton irradiation is twice the one after carbon ion irradiation [42].

Despite all its advantages, the PET modality has two striking intrinsic issues. The first is the half-life of the different isotopes, in particular ¹⁵O and, notably, ¹⁰C isotopes have short decay times (half-life of 122.24 s and 19.29 s, respectively). In consequence, during treatment, an activity build-up and reduction will happen at the same time. In addition, real-time monitoring with PET is intricate, as the half-lives of positron induced radioisotopes are much longer than the characteristic time in which an iso-energy slice of the tumour is treated. The second issue comes from the fact that positron emitters undergo biological washout, a phenomenon in which the isotopes are taken away from the irradiation region by physiological processes. Figure 2.9 shows a comparison made by Parodi et al. [45] of the TPS and Monte Carlo dose calculation with both the Monte Carlo estimate of the positron emitters distribution and the actual PET measurement. Biological washout effects are clearly visible when comparing the predicted positron emitters distribution and the measured image. Work is currently ongoing to account for this biological washout by modelling it and including the model in the prediction of positron emitters distribution (e.g. see the work of [45, 46] and the result of using one of those models in figure 2.9). Moreover, in PET monitoring, which aims at detecting the position where the annihilation takes place, the positron travels a certain distance before it undergoes annihilation with an electron of the medium. For the ¹⁵O isotope, the positron may travel up to 7.92 mm in water with an average distance of 2.34 mm [47]. Note that these distances depend on the calculation method and its assumptions [47]. The average distance is much smaller than the maximum because 1) the emitted positrons have a continuous energy distribution and 2) the positron paths in matter are not straight [48]). Therefore, this adds an extra uncertainty on the position of the positron emitters.

In any case, PET is currently the only particle therapy monitoring technique in clinical application. PET monitoring can be applied online (it is also called in-beam; the scan is done during treatment), in-room (the scan is performed shortly after the treatment in a PET tomograph installed in the treatment room), or offline (the scan is performed 10-30 minutes after the treatment) [49]. A comparison of the signal measured with the three different approaches is shown in figure 2.10.

An additional issue of PET is the physical difficulty of placing a full-ring tomograph due to external constraints, such as the space for the beam noozle and patient couch, which further reduces the number of measurable decay events [18, 50]. Extensive work has been done to partially overcome such a problem by proposing possible solutions that could be implemented to have an online PET system. In this regard, the work of Crespo and colleagues is noteworthy, since they have made a consistent and comprehensive investigation to allow for exploiting the use of in-beam PET for hadrontherapy monitoring purposes, mainly for carbon ion therapy. They have proposed solutions to optimise the camera geometry and placement and, at the same time, they actively pursued the use of time-of-flight (TOF) PET (TOF-PET) to enhance the signal-to-noise ratios of the device so to achieve a better performance from partial-ring designs [50, 51]. More recently, Surti et al. [52] have made an optimisation study with Monte Carlo simulations in order to design an online PET system for proton therapy monitoring. They found that TOF is needed for the partial ring designs and they state that the minimum timing resolution of the camera must be better or equal to 600 ps for a scanner with an angular acceptance of two-thirds (in respect to a full ring) in order to achieve satisfactory range estimates. They also claim that, based on their study, a two-thirds scanner with 300 ps timing resolution



FIGURE 2.9: Top left: Dose distribution from the TPS. Top right: Dose distribution from Monte Carlo simulations using FLUKA. Middle left: PET measurement. Middle right: PET image simulated by the FLUKA Monte Carlo tool including the effects predicted by a biological washout model. Bottom: PET image predicted by the FLUKA Monte Carlo tool without washout effects. The data presented correspond to the treatment with proton beams of a clival chordoma with two lateral fields of 0.96 GyE each. The measurement was performed 26 min and 16 min after the end of the first and the second field applications, respectively. Range of colour is from blue (minimum) to red (maximum). Adapted from [45].

leads to a bias of 1 mm and a precision of 1.4 mm on the range estimate with realistic positron emitter decays for a clinical fraction [52]. Furthermore, Sportelli and co-workers have reported the first online PET measurement after proton irradiation in a PMMA target with a dual-head PET system that can operate continuously during beam delivery in a cyclotron-based facility [53]. However, this work is still in a preliminary stage and the results presented require that care must be taken. For example, by using only the



FIGURE 2.10: Time-events histogram corresponding the measurement of one irradiation field. From [49].

events measured during beam delivered, the authors were able to reach sub-millimetre range precision with doses higher than 5 Gy, which is much higher than the dose delivery in a typical proton treatment fraction. Nevertheless, they tested the system with a 2 Gy proton irradiation and, by combining the data collected during irradiation plus 60 s acquisition after the end of irradiation, they have shown that the range precision improved by a factor 2 when compared to the case of using only the data from a 60 s acquisition after the end of irradiation [53]. In turn, the feasibility of using a dual-head PET scanner to monitor proton therapy treatments with a synchrotron has been since long demonstrated using the dedicated PET system installed at GSI Helmholtzzentrum für Schwerionenforschung (GSI, Darmstadt, Germany) [43].

2.3.2 Prompt gammas

The use of prompt gammas as a monitoring technique for hadrontherapy was probably first proposed by Stichelbaut and Jongen [54]. Prompt-gamma rays are emitted following the ion beam interaction with the target due to the production of excited nuclei after nuclear fragmentation. As nuclear fragmentation can occur almost all along the entire path of the beam, it allows for the monitoring of the range of its particles, assuming that the nuclear fragmentation can be correlated with the energy deposition profile. Moreover, prompt-gamma emission can be considered to take place at where the nuclear interaction occurs since prompt gammas are emitted almost instantly, thus the emission distribution is not affected by any type of physiological process (e.g. washout) neither by physical processes that may interfere with the determination of the location where the nuclear interaction occurs. Unlike positron emitters monitoring, for which only PET scanners are considered, several possible solutions to exploit the prompt-gamma information are being studied and developed. One can divide the different approaches into three categories: 1) solutions using directly the emission position information, 2) those making use of the energy information from the emitted prompt gammas, and 3) the ones that estimate the ion range based on the time information of prompt gammas. It should be emphasised that, although there are many approaches, none of them are currently being used clinically. This is mainly due to the fact that prompt gammas have a broad energy range and a complex background radiation field that, even for the simplest of the approaches one may consider, requires the development of dedicated devices and extensive research programmes to explore this new field. Notably, prompt gammas are emitted with nuclear interactions along with other particles, hence the detection of those photons must be done in parallel with, e.g. neutron-associated events that may tamper the correlation with the ion range.

Important aspects of prompt-gamma monitoring are the independence of dynamic biological effects (i.e. washout of the observables) and the fact that the maximum in the cross section as a function of energy of prompt-gamma emission is at lower energies in comparison with the PET radioisotope production cross sections, yielding the maximum emission closer to the Bragg peak (in opposition to PET monitoring) [20, 55]. These features suggest that prompt-gamma monitoring can potentially be more advantageous than PET monitoring, as recently pointed out by Moteabbed et al. [55]. The aforementioned study shows that, although the prompt-gamma signal is higher, the PET system provides better detection efficiency, thereby achieving a higher detected signal. However, the detection efficiency considered for the PET system is from a 3D neuroPET scanner, thus very advantageous in terms of solid angle coverage, not available in most of the treatment centres, and only possible to use for brain tumours. Moreover, the detection efficiency considered for prompt-gamma detection is coming from the published data related to Compton camera designs with particularly low detection efficiencies. In fact, the authors state that the detection efficiency assumed for the prompt-gamma case is not optimal and they claim that the difference between PET and prompt-gamma signals can be reduced as the prompt-gamma technology advances towards an optimised system [55]. Finally, this study compares only the positron emitter and the prompt-gamma distributions, not addressing other approaches such as using the energy and time information from prompt gammas.

Based on the proposed ranking, the first category (i.e. solutions using directly the emission position information) comprises gamma cameras with both electronic and passive collimation. The aim of these devices is to provide the emission position by correlating the detected prompt gammas with the longitudinal position along the ion path. In order to maximise this correlation, the cameras are usually assumed to be positioned

at 90° in respect to the beam axis. With this positioning parallax effects are avoided and, for the passive collimation cases, no image reconstruction is required.



FIGURE 2.11: A schematic diagram illustrating the principle of a Compton camera system. It shows the cone produced by one incident gamma ray, which transfers energy E_1 to an electron via Compton scattering at position (x_1,y_1,z_1) in the scatter detector and then deposits its remaining energy E_2 at position (x_2,y_2,z_2) in the absorber detector. From [56].

Compton cameras. The systems with electronic collimation use the Compton scattering process, therefore are named Compton cameras. In the simplest design possible, they comprise one scatter and one absorber detectors. The incident prompt gamma suffers Compton scattering in the former and is then absorbed in the latter. Since the energy of the prompt gamma (its full absorption in the absorber is assumed) and the energy transferred to the electron (thus the scattering angle) in the scatter detector are known, one can create a cone surface of possible locations from where the prompt gamma initially came from. After several registered events, the source of the events can be reconstructed by intercepting the different cones. In a rough approximation, this reconstruction process is similar to the one used for PET imaging but, instead of a line-of-response, there is a cone-of-response. Figure 2.11 depicts the principle of the Compton cameras. However, in such a design, the cone will be wrongly estimated if the photon is not fully absorbed in the absorber detector. To overcome this problem, some authors have proposed solutions where the photon undergoes more than one scattering interaction (e.g. [57-60]). With at least two scatterings, it is then possible to circumvent the need for full absorption. Figure 2.12 illustrates this approach.



FIGURE 2.12: An example of a 3-stage Compton camera with the projected cone created after Compton scattering is illustrated on the left figure, while on the right one an identical Compton camera is depicted with a phantom and a proton beam. The Compton scatter angles (θ_1, θ_2) and the prompt-gamma energy (E_0, E_1, E_2) as it travels through the detectors (D1, D2, D3) are shown. On the right figure, the information available from each detector is presented (position x_i, y_i, z_i and energy deposition ΔE_i in the detector i). From [57].

Several approaches have been proposed concerning the camera design. Roellinghoff et al. [61] published a study analysing the potentialities of a single-scattering Compton camera, while Richard et al. [62] proposed a stack of silicon detectors to act as scatters in order to increase the camera efficiency by allowing double scattering (both used an absorber made of a scintillator crystal). Kormoll et al. studied the performance of some Compton camera solutions for proton therapy monitoring and they found that a design comprising cadmium zinc telluride (CdZnTe) layers as scatters and a LSO absorber could be a good candidate [63]. Llosá et al. have developed a double $LaBr_3$ scintillator (one crystal as scatterer and the other as absorber) Compton camera prototype with promising results for point-like sources [64]. Seo et al. [65] have placed radioactive sources inside an anthropomorphic phantom to then reconstruct them with a double-scattering Compton camera. On the other hand, Thirolf and co-workers [66] have developed Compton camera that also tracks the Compton-scattered electrons, thus increasing the camera efficiency by reducing the Compton cone to a simple arc segment. Finally, it is worthwhile to mention the work of Kurosawa and colleagues [67] in which they presented the very first experimental prompt-gamma distribution after proton irradiation with a Compton camera.

Moreover, to reduce the projected cone from each detected event to two points (or two small regions), the beam information can be included in the reconstruction process, thus only the interception between the projected cone and the beam axis will be accounted for during reconstruction. Also, by including TOF in the design, it is possible to improve the signal-to-background ratio (SBR). This solution needs, however, a particle tagging device such as an hodoscope intercepting the beam [58].

Collimated cameras Studies have shown that the use of a collimated camera makes possible to retrieve information about the ion range during irradiation for both protons [68, 69] and carbon ions [70, 71]. There are two camera design concepts for the collimated cameras. The first one was initially proposed by Bom et al. [69], continued by Smeets et al. [72], and the most recent developments were published by Perali et al. [73]. This system uses a single-slit collimator to retrieve information related to the ion range. The camera is designed in such a way that it allows to monitor the ion range with only one slit. It is a variant of the pinhole camera concept [72] and it is known as knife-edge-shaped slit camera [69]. Figure 2.13 shows the principle of this type of camera. The events cross the slit of the knife-edge collimator and they are detected in a segmented detector. Due to the nature of this technique, the recorded events are reversed in respect to the beam direction, i.e. the most proximal emitted prompt gammas that can go through the slit are detected by the most distal segments of detectors (see figure 2.13 left).



FIGURE 2.13: Left: detection of the prompt gammas (green lines) going through the slit of the knife-edge collimator after being created in the target by incident protons (blue lines). The camera is centred with the expected position of ion stop and the proton beam is coming from the bottom. Right: schematic representation of the knife-edge camera being used in treatment monitoring. Reproduced from [72] (left) and from [73] (right).

The resulting profiles of this system can be observed in figure 2.14. With the most recent prototype, the authors claim that they are able to have a 4 mm precision with a homogeneous target, a clinically-relevant number of incident protons, and with very challenging conditions in terms of counting rates (beam currents of tens of nA at 230 MeV proton beams). Although it is an extremely satisfactory result for a prototype, this precision is still far from the one considered as the end goal, that is at least a 1 mm precision [72]. Nevertheless, from all passive collimation solutions exploiting the information from prompt gammas, this one should be the first to be introduced in a clinical

environment. Furthermore, there is some ongoing research concerning the use of TOF with this type of camera [74]. The initial results from this study demonstrate that TOF clearly improves the SBR, thus potentially improving the precision yielded by such a device.



FIGURE 2.14: Measured entrance (green curve) and fall-off (red curve) prompt-gamma profiles from a knife-edge camera for 100 MeV (left), 160 MeV (middle), and 230 MeV (right) and using a homogeneous PMMA target. The proton range and the target entrance are located at 0 cm for the fall-off and entrance profiles, respectively. From [73].

The second camera design is the multi-slit collimator camera. In this design, a set of slabs of collimating material is placed in front of a detector. The totality of the ion range can be observed if a sufficiently long device is considered. The slabs ensure that a proper angular restriction is applied in order to maximise the correlation with the longitudinal position from where the prompt gammas came. The most straightforward proof of principle of a multi-slit camera is the single-slit collimator camera with a mechanism to move either the device or the target (e.g. moving table). In this regard, the results from several experiments with single-slit cameras have already been published for both proton [68] and carbon ion [70, 71] irradiation along with the feasibility of correlating the detected prompt-gamma events with the ion range. It is noteworthy to refer that, due to the difficulty to discriminate prompt gammas from the extensive background in the case of incident carbon ions, Testa et al. [70] proposed the use of TOF for the case of carbon ion monitoring. Figure 2.15 illustrates the principle of the multi-slit collimator camera.

The use of TOF technique has been shown to be beneficial also for proton therapy monitoring with multi-slit cameras. In a simulation study made by Biegun et al. [75], it was demonstrated that the use of TOF in conjunction with a shifting TOF window based on the position of the prompt-gamma peak can lead to the reduction of the neutron background in more than 99%. Nonetheless, this study was conducted with simulations with a perfect detector (i.e. a plane surrounding the target where the particles are scored as they cross it), so in a real situation this value may not hold for reasons such as the use of too simplistic of an approach (e.g. neutron background created in the collimator device), Monte Carlo modelling inaccuracies, and room background description. Nevertheless, a study performed by Roellinghoff et al. [76] with experimental data based



FIGURE 2.15: The multi-slit collimator camera principle. An ion beam is used to treat a patient and prompt gammas are emitted. These prompt gammas are then collimated and detected. If TOF is of interest, there is maybe the need for a particle tagging device such like a scintillating fibres hodoscope to give the TOF stop signal to the acquisition system. This TOF stop signal should be suitably delayed to come after the TOF start signal from the detectors.

on a single-slit experiment with proton beams has pointed out that TOF potentially enhances the performance of this type of systems by ameliorating the SBR. The same study states that TOF improves the precision in finding ion range shifts by a factor proportional to the background reduction linked to the background statistical fluctuations (*precision* $\propto \sqrt{background/signal}$). Furthermore, it was found that including an energy threshold in the prompt-gamma detection analysis would further improve the SBR by removing the extensive lower energy background components [70].

Both collimated solutions discussed herein have advantages and disadvantages. The knife-edge camera is less bulky and it is lighter but it has a limited field-of-view (FOV) around the expected ion stop position, while the multi-slit camera design allows for monitoring the entire beam path including the position where the beam enters in the patient. In addition, it was found by Roellinghoff that the both camera designs have similar performances in terms of prompt-gamma profile fall-off precision for a spot with 5×10^7 protons (without considering TOF in both cases) [77]. Therefore, it is still unclear which solution may cope better with the clinical requirements. However, in this regard, Bom and colleagues [69] suggested that the prediction of off-beam deviations due to lateral heterogeneities is prone to failure if only the prompt-gamma profile can help overcome such a limitation by using registered correlation based on e.g. the plateau region of the prompt-gamma profile [37]. Hence, by correlating different prompt-gamma profile features with specific morphological situations and/or beam-delivery conditions, it may

be possible to identify those cases in a clinical scenario from the full profile. Since the knife-edge camera has a limited FOV, it is likely that it cannot allow for this kind of assessment. Moreover, based on the information available, only the multi-slit camera is being studied as a possible collimated solution for carbon ion treatment monitoring.

Energy information The exploitation of the energy information of the emitted prompt gammas is a field with growing interest due to the possibility of retrieving both ion range and tissue composition. However, the interest on the energy information is not focused on the energy spectrum as a whole but rather on the discrete gamma decay emission attributed to specific reaction channels. In this application, the work of Polf et al. [78] is noteworthy. In this study they demonstrated that the 6.13 MeV prompt-gamma emission line from the proton on 16 O nucleus reaction is proportional to the concentration of oxygen in tissue irradiated with proton beams, showing that it is possible to determine the concentration of oxygen in tissues irradiated with proton beams by measuring this emission. On the other hand, Verburg and colleagues [79] have been researching and developing a concept in which they correlate the emission yields in water of several discrete gamma decay lines with the proton range. To further improve the SBR, they have also used the TOF technique to make the prompt gamma selection. Figure 2.16 depicts a plot from this study where the experimental profiles obtained from selecting specific gamma lines are compared with the experimental dose-depth curve. For the proton energy considered in this plot (they have also analysed other proton energies with similar conclusions), the correlation with the range is notorious, namely for the ${}^{16}O(p,p'){}^{16}O^*$ (6.13 MeV) and ${}^{16}O(p, p'\alpha){}^{12}C^*$ (4.44 MeV). In these two cases, the prompt-gamma profile fall-off is very close to the dose deposition curve distal edge and a pronounced peak in the prompt-gamma emission near the end of the proton path is observed. Such a pronounced peak is not seen in the total prompt-gamma profile in the same figure and so this feature could be combined with the fall-off information to assist in better determining the ion range. However, this approach alone could probably provide too low prompt-gamma yields. As a comparison, the curves in figure 2.16 were obtained with 1×10^{10} incident protons, while the prostate treatment plan presented in [72] never employs more than 2×10^8 protons per spot and, assuming that the monitoring could be performed at the energy layer scale (46 spots per iso-energy layer [37]), the maximum number of incident protons would be around 9×10^9 . Moreover, the study of Polf et al. [78] has shown that these gamma decay lines are very sensitive to tissue composition, which may interfere with the assessment of correlations with the proton range. On the contrary, Janssen et al. [80] demonstrated with simulations that the use of all prompt-gamma emission information is quite robust, since it leads to an accuracy in the ion range prediction of less than 1 mm when changing tissues and their elemental

composition for irradiations with different proton energies. Nevertheless, as with most of the monitoring and verification techniques proposed so far, only further studies can give an answer to the clinical applicability of the approaches driven by the energy information of prompt gammas.



FIGURE 2.16: Prompt-gamma profiles using all information between 3 to 7 MeV (blue curve) and using the 6.13 MeV (green curve), 4.44 MeV (red curve), and 5.2 MeV (cyan curve) discrete decay lines. These experimental results are from 1×10^{10} incident protons in a water target with a range equal to 9.0 g/cm². The depth-dose curve for the same number of incident protons is also shown for reference. From [79].

Time information Although several hadrontherapy monitoring techniques are being developed with TOF discrimination in order improve the SBR of the retrieved information, there are very recent approaches that go further in the use of TOF. When TOF selection is used, timing is regarded as an effective way to reduce the background, but such an information is only used for the selection of events. Golnik et al. [81] conducted an experimental study in which they measured the time difference between the detection of prompt gammas and the high-frequency (HF) signal from the cyclotron and they demonstrated that these time differences can be correlated with the proton range, mostly due to the different transit times of protons inside the target. Figure 2.17 shows some of the results that they obtained and where the correlation with the mean of the time difference with the proton range can be observed. In addition, they expect a precision of 2 mm on the proton range retrieval within a few seconds, assuming therapeutic proton beams and typical ranges.

In parallel, Testa et al. [84] have shown that it is feasible to verify the proton range with a single measurement point (thus using a single-slit collimator) for passive delivery. This was mostly a simulation study in which they have shown that the prompt-gamma rate detection correlated with the range modulator wheel depends on the position along the SOBP. The monitoring is then possible due to the time pattern in the prompt-gamma



FIGURE 2.17: Left: comparison of experimental (histograms) and modelled (solid lines) time difference profiles of protons impinging a PMMA target with varying thickness. Right: comparison of the experimental (SE, All4440) and modelled (simBox, simG4) mean values of the time difference profiles versus the PMMA thickness. The SE and All4440 use different energy selection criteria and the simBox and simG4 cases are modelled considering the longitudinal prompt-gamma emission profile as a box or simulated by Geant4 [82, 83], respectively. From [81].

signal introduced by the use of the range modulator wheel. According to their study, if the collimator position is carefully chosen to be close to the range of the SOBP, the proton range can be verified up to that point. Then the range uncertainties can only come from the remaining path of the beam, and thus be much limited. They determined the proton range in a water target with a 2 mm accuracy considering a full-ring detector configuration and for a delivered dose of around 2.5 cGy. Figure 2.18 shows the change in the time pattern of the detected prompt gammas by shifting the setup by 2 mm.



FIGURE 2.18: Simulated prompt-gamma rate functions with the detector in different positions with intervals of 2 mm. The inset shows the SOBP and the total number of prompt gamma as function of the depth. From [84].

2.3.3 Interaction vertex imaging

Alternative imaging techniques are based on the detection of secondary protons as recently suggested by Amaldi et al. [85]. While the applicability of this technique to proton beams

is doubtful, the monitoring of carbon ion therapy through the detection of the secondary protons is a promising approach. In order to measure the secondary protons escaping the patient, one or more tracker detectors would be positioned at a given angle from the beam axis. The hits in the detectors are then used to estimate the vertex position of that event. Henriquet et al. [86] carried out a feasibility study with simulations and they were able to correlate the distribution of vertex positions with the ion range, as shown in figure 2.19. Several reconstructed vertex distributions with different incident carbon ion energies are depicted along with the correlation between the inflection point of a complementary error function and the ion range. The results of this study show that this technique is potentially very interesting for carbon ion therapy monitoring, as it yields sufficiently large statistics to be applied at the spot level with a precision around 1 mm.



FIGURE 2.19: Left: reconstructed vertex distributions for carbon ions with 150 (blue), 200 (green), 250 (red), and 300 MeV/u (black) impinging on a head phantom. The histograms correspond to the simulated data while the smooth lines result from fits with a complementary error function. Right: inflection point position of the aforementioned fits as a function of the ion range. These data are for 1×10^6 simulated carbon ions. From [86].

Gwosch et al. [87], on the other hand, published the results from experiments using carbon ion beams and a PMMA target. They have successfully retrieved the fall-off position of the vertex distributions with a precision between 1.3 and 2.8 mm depending on the considered feature of the profiles with 2×10^9 incident carbon ions of energies between 213.41 and 250.08 MeV/u. Additionally, they were able to retrieve information concerning the beam width and position. Figure 2.20 shows one of the results of this study.

More recently, Piersanti et al. [88] have performed the same kind of measurements with a drift camera located at 60° and 90° . The estimated precision on the length of the vertex



FIGURE 2.20: Reconstructed vertex positions after 5×10^4 measured secondary charged particles. The PMMA target dimensions are represented by the black rectangle and the red curve is a depth-dose distribution measured in water and scaled to the target water-equivalent path length. From [87].

distribution (related to the ion range) is estimated to be around 1 mm with 10^3 detected events, which corresponds to about 10^8 incident ions in the target.

2.4 Description of the present work

The work developed during the last three years is a comprehensive and integrated approach towards the clinical implementation of a TOF-based multi-slit collimator device with a single purpose: to provide clearer insights about the applicability of this monitoring technique. This work consists of an in-depth analysis of experimental data of different sorts, a full-size camera design optimisation that is leading to the construction of a full-size prototype, a study of the possibilities to improve Monte Carlo predictions for promptgamma emission yields, and a preliminary investigation of a possible Geant4 acceleration scheme to allow for the use of Monte Carlo simulations to predict the prompt-gamma emission distribution to be compared with a detected distribution in a clinical situation.

Chapter 3 presents most of the experimental data analysed during this work. It includes an extensive analysis of several single-slit experiments with homogeneous targets in order to obtain absolute prompt-gamma emission yields. On the one hand, these yields can be used for Monte Carlo tools assessment by comparing them with the simulation outcomes concerning prompt-gamma emission. On the other hand, they can also be used to estimate the expected performance of any monitoring device, since they are normalized to the geometrical definition of the different experiments. Moreover, the experimental data have been gathered in several facilities with different beam delivery characteristics, thereby contributing to an additional validation of the results in this study. Although there are already in the literature some studies addressing prompt-gamma emission yields, none of them go as far as the present work, which provides an exhaustive cross-check between all the data from ten experiments. Several methods were developed for the analysis of the data. In particular, a TOF-based background subtraction to deal with neutron-associated events and specifically developed for this work should be of great interest. Such method could also be implemented in a monitoring scenario if online background subtraction is needed. Finally, the results obtained were extrapolated to proton and carbon ion therapy treatment scenarios and the feasibility of prompt-gamma monitoring for hadrontherapy was unequivocally shown (without considering heterogeneities issues). After the study to obtain absolute prompt-gamma emission yields, a comparison with Geant4 simulations is performed using the last released version. The chapter ends with the analysis of experimental data concerning inhomogeneous targets. In this study, the results of three different targets irradiated with low energy carbon ion beams are presented and a novel quantity specific to the multi-slit collimator camera is introduced: the prompt-gamma profile length. Since this approach aims at measuring both the entrance position of the incident beam and the prompt-gamma profile fall-off to assess the ion range, this quantity is of great importance to discriminate, for example, between a situation in which the patient was mispositioned and a real ion range shift. Geant4 simulations are also performed in order to verify the accuracy of simulations in describing the different prompt-gamma profile lengths. The work presented in this chapter led to the writing of two articles, one concerning the absolute prompt-gamma emission yields study, and the other the analysis of the experimental data with inhomogeneous targets. At the moment of the writing of this document, they were under review. The content of the articles is included along with additional details and results.

Chapter 4 presents the optimisation study of the design of a multi-slit collimated camera for proton therapy monitoring, mostly focused on the collimating device, since, from a mechanical point of view, it is the most critical part of the camera (i.e. the overall weight will be mainly constrained by the collimator). This chapter begins with a benchmarking of the simulations against the experimental data because, unlike the study undertaken in chapter 3, in which the prompt-gamma emission yields were the primary goal, this study is centred on TOF spectra comparison in order to select an accurate set of Geant4 physics models for TOF information description. The rationale is the need to have a modelling of the camera-dependent interactions as accurate as possible. If there is an under/overestimation of the signal and/or background originated from the target, a detailed analysis of the simulation outcomes can estimate such deviations and envisage methods to correct the precision calculated after simulations, since the precision is proportional to the statistical fluctuations of the background over the signal. Moreover, it is not expected that the signal suffers significant changes due to interactions with the imaging device apart from the attenuation due to septa penetration and the prompt-gamma collimation due to the geometrical constraints. However, the background originated from

the device due to mainly neutron-induced events may be critical. Therefore, there is the need to compare the experimental data with the simulated ones and to find the physics models able to describe the background as accuratly as possible so to have additional confidence in the results when changing the camera geometrical design. After the selection of an adequate set of models, the optimisation is carried out by simulating a multitude of possible configurations. These simulations are then used to give insights about the relationship between the different geometrical parameters of the camera with its expected attainable precision. The chapter ends with a discussion about the solution being currently constructed at the IPNL mechanical workshop. This chapter led to the submission of an article with the title "Design optimisation of a TOF-based collimated camera prototype for online hadrontherapy monitoring" to Physics in Medicine and Biology that is in press at the moment. The content of this article is included along with additional details and results.

In chapter 5 a study concerning the improvement of Geant4 physics models for proton modelling is presented. Such a study aims at obtaining better prompt-gamma emission yields by tuning the built-in options allowed in the implementation of the different models and by testing source code changes following a physical meaning. Significant improvements are achieved, thus paving the way towards more accurate simulations concerning prompt-gamma emission yields. More importantly, the work developed in this chapter may provide clues and opportunities for others to continue to deepen it into similar applications, e.g. the improvement of discrete prompt-gamma decay lines modelling.

Finally, chapter 6 presents a preliminary study of a novel approach to accelerate Geant4 simulations concerning prompt-gamma emission. Monte Carlo simulations are nowadays an important tool in the clinical workflow but its use is very often limited by the considerable computing time required. Notably for the specific application of hadrontherapy and prompt-gamma emission, the simulation of a full treatment plan can take several days, if not weeks. Therefore, it is of utmost importance to ponder the development of analytical alternatives that can be as close as possible to simulations in terms of accuracy or to find means to accelerate Monte Carlo tools. The preliminary study in this chapter addresses the latter by creating the grounds and testing a possible solution for this problem.

A last remark for the fact that, throughout this manuscript, Geant4 is extensively used but not always the same version. The reason for this is the time frame of each task along the three-years period of this work. The intention was to always have the latest and, hopefully, a more accurate version than the previous one when a new study was started. The versions are clearly stated, but it is possible to refer to the appendix C, which contains a summary of the different versions used and the respective sections in this document.

Chapter 3

Prompt-gamma emission

In this chapter, the data from several experiments are presented and analysed. In a first stage, the data from homogeneous targets irradiated with either protons or carbon ions are considered. This is followed by a comprehensive benchmarking with Geant4. Finally, the last section focuses on experimental data from the irradiation of heterogeneous targets with carbon ions, including further simulation work in order to try to reproduce different prompt-gamma profile lengths with distinct ion ranges due to inhomogeneities. It is also important to mention my role in the work presented in this chapter. My task was always centred on the data analysis and I was not directly involved in assembling the detection system. Some of the experiments were even conducted before I started my PhD. Nevertheless, for the ones that were carried out during the period in which I was already an active member of the team, and since I was dealing with the data analysis and simulations, I assisted in the experimental planning by giving inputs concerning e.g. the longitudinal positions to measure and the setup configuration that should be used.

3.1 Prompt-gamma profiles – homogeneous thick targets

In this section ten experiments using single-slit collimated detectors are described. For the sake of simplicity, henceforth experimental data resulting from one detector will be considered as a single experiment. There are some cases for which two detectors were used in parallel in the same measurement but they will undergo independent analysis.

Two of the experiments were carried out at the Grand Accélérateur National d'Ions Lourds (GANIL, Caen, France), another two at the Gesellschaft Helmholtzzentrum für Schwerionenforschung (GSI, Darmstadt, Germany), one at the Heidelberger Ionenstrahl-Therapiezentrum (HIT, Heidelberg, Germany), and the five remaining at the Westdeutsches Protonentherapiezentrum Essen (WPE, Essen, Germany). All the experiments listed were performed using carbon-ion beams, except the ones at WPE, where proton beams were employed.

Before describing each experiment in detail, the common features to all of them are outlined. First, the detection of the prompt gammas emitted from the different targets was performed in all cases at approximately right angles in respect to the beam axis, and using the TOF technique to improve the contrast between the signal and the background, as already demonstrated by Testa et al. [70], thus giving the possibility to discriminate the prompt-gamma events from the background. The time window applied to select the prompt-gamma signal is intrinsically linked to the detector used for each experiment and its time resolution. Herein, the results obtained with five different detectors are presented: a cylindrical thallium-doped sodium iodide [NaI(TI)] detector with 3-inch diameter and 3-inch length, an hexagonally-shaped barium fluoride (BaF₂) detector with 50-mm edge and 140-mm length, two cerium-doped lutetium-yttrium oxyorthosilicate (LYSO:Ce) detectors with $50 \times 40 \times 3 \text{ mm}^3$ and $50 \times 40 \times 5 \text{ mm}^3$, and a cerium-doped lanthanum(III) bromide (LaBr₃:Ce) detector with 1-inch diameter and 2-inch length.

Another common feature to this set of experiments was the use of a VME-based acquisition system with NIM modules and conventional electronics, which was triggered by the OR logical signal of the detectors. An event-by-event acquisition mode was set to allow for TOF information to be stored, thus the trigger was used as the TOF start signal. The TOF stop signal in the carbon ion beam experiments was given by a suitably delayed signal either by a detector intercepting the primary beam or by the high-frequency (HF) signal of the accelerator. In turn, in the proton beam experiments the TOF stop signal was given by the HF signal of the accelerator. It is also noteworthy to refer that dead time correction was applied based on the data from the scalers used during each experiment. In order to prevent binning artefacts in the histograms, the calibration between ADC/TDC channels and energy/time was done by applying the calibration curve for each case and by rebinning channels by an integer number. The histograms are then rescaled by a factor corresponding to the intended binning.

The targets were placed on top of a moving table and acquisitions were carried out at different positions, while the collimator, the shielding and the detectors remained in a fixed position. Afterwards, the events within a region of each measured TOF spectrum (i.e. the time window) were summed to obtain the corresponding yield. The width of the time window is sufficiently large to include all the observable signal. A summary of the detectors and time windows used in each experiment is given in table 3.1.

Experiment	Detector	Time window (ns)
$CANIL_{05} M_{\odot} V/\mu^{-12} C^{6+}$	BaF_2	2.0
GANIL 35 Mev/u C	$\operatorname{NaI}(\operatorname{Tl})$	4.0
GSI 300 MeV/u $^{12}\mathrm{C}^{6+}$	BaF_2	4.5
GSI 310 MeV/u $^{12}\mathrm{C}^{6+}$	BaF_2	3.0
HIT 310 MeV/u $^{12}{\rm C}^{6+}$	LYSO:Ce	3.0
WDF 160 MeV H ⁺ (I)	LYSO:Ce	3.0
WIE 100 MeV II. (1)	${\rm LaBr_3:Ce}$	3.0
WDF 160 MeV H ⁺ (II)	LYSO:Ce	3.0
wind 100 mev II. (II)	${\rm LaBr_3:Ce}$	3.0
WPE 160 MeV H^+ (III)	LaBr ₃ :Ce	4.0

TABLE 3.1: Width values of the time window used for the TOF analysis of each experiment.

Although an absorbed energy threshold of 2 MeV is close to the optimum to enhance the contrast of the prompt-gamma signal for some of the experiments as already suggested elsewhere [89], it was decided to opt for a 1-MeV threshold for all the experiments. This was due to the low statistics obtained for some experiments, where a 2-MeV energy threshold would lead to a reduced statistical significance of the signal. Even though the contrast is enhanced, the use of a threshold also entails discarding some of the signal events, which is critical when the statistics are low. Being consistent in this selection allows for a comparison between data sets. Furthermore, in order to use all the data from the different experiments in an equivalent manner, an upper energy threshold was also considered and set to 7 MeV. The energies considered here were obtained after calibration with gamma sources. It is therefore an absorbed gamma-equivalent energy but, for the sake of simplicity, it will be simply referred to as energy. It is known that scintillator detectors do not have a linear response at higher energies [90, 91]. However, no correction was made to account for this factor since, on the one hand, at energies up to that of the lower threshold the response is expected to be linear and, on the other hand, the fraction of events above 7 MeV is small (vide table 3.2). In consequence, the impact on the results of any possible inaccuracy in selecting exactly 7 MeV is likely to be marginal. Likewise, the use of this high energy threshold should yield a small influence in the absolute yield values presented later in this chapter. Table 3.2 shows the fraction of prompt gammas escaping the target above 1 MeV and between 1 and 2 MeV obtained with Monte Carlo simulations and using the setup of each experiment. This table presents the energy of the prompt gammas escaping the target, which correspond, if no other interactions occur during the photon path, to the energy of the incident prompt gammas in the detectors. Therefore, these data cannot be directly compared with the experimental ones since some photons may have undergone Compton scattering and escaped the detectors, hence not depositing their full energy. However, these numbers are physically more relevant because

they give insights into the (simulated) energy distribution of prompt gammas. Moreover, if one considers the escaping photons in the detectors, the fraction above 7 MeV will be smaller, so confirming the marginal issue of having the high energy threshold.

TABLE 3.2: Fraction of prompt gammas with energies above 1 MeV, between 1 and 2 MeV, and above 7 MeV. Results obtained by simulation with Geant4 and considering the energy spectrum of the photons escaping the target for each experiment.

Experiment	Fraction above 1 MeV	Fraction between 1 and 2 ${\rm MeV}$	Fraction above 7 ${\rm MeV}$
GANIL 95 MeV/u $^{12}\mathrm{C}^{6+}$	49.6%	11.0%	9.4%
GSI 300 MeV/u $^{12}\mathrm{C}^{6+}$	33.7%	7.7%	4.5%
GSI 310 MeV/u $^{12}\mathrm{C}^{6+}$	33.3%	7.5%	4.3%
HIT 310 MeV/u $^{12}\mathrm{C}^{6+}$	33.2%	8.4%	5.2%
WPE 160 MeV $\rm H^+$	39.1%	8.8%	2.1%

Although the nominal particle energy of each experiment is shown, it should be stressed that, in several experiments, detectors were placed in the beam path before the target in order to normalise the data to the number of ions. Hence, the real ion range in the target should correspond to a different particle energy. Table 3.3 shows the projected ion ranges estimated by SRIM 2013 assuming the nominal particle energy in the target.

TABLE 3.3: Projected ion ranges estimated by SRIM 2013.

Experiment	Target	Projected ion range (mm)
GANIL 95 MeV/u $^{12}\mathrm{C}^{6+}$	PMMA	20.99
GSI 300 MeV/u $^{12}\mathrm{C}^{6+}$	Water	174.05
GSI 310 MeV/u $^{12}\mathrm{C}^{6+}$	Water	183.78
HIT 310 MeV/u $^{12}\mathrm{C}^{6+}$	PMMA	163.49
WPE 160 MeV $\rm H^+$	PMMA	154.72

A summary of the experimental details can be found in table A.1.

3.1.1 Experimental data – Proton irradiation

3.1.1.1 WPE 160 MeV H⁺ (I)

For these experiments the LaBr₃:Ce and the $50 \times 40 \times 3 \text{ mm}^3$ LYSO:Ce detectors were used. They were placed at 600 mm from the beam axis behind a tungsten-alloy collimator, which had a slit of 4 mm, and some lead shielding. The LaBr₃:Ce detector was placed on top of the LYSO:Ce. The target used was a cylindrical PMMA phantom with 75-mm radius and 200-mm length. The TOF stop signal was given by the HF of the cyclotron running in pulsed mode with a time structure of approximately 1 ns pulse (FWHM) every 10 ns. The circular beam spot was around 5-mm sigma at isocentre, considering a Gaussian spatial beam distribution [13].

The number of incoming protons was given by the IC placed inside the beam nozzle and by the monitor unit (MU) system. A MU is a measure of the dose being delivered after calibration of the IC inside the beam nozzle under reference conditions. Although the MU system relies on the IC for its calibration, it was used as a second system able to cross-check the results. In turn, the IC was calibrated against a Bragg peak chamber positioned at the target entrance.

> Beam axis Cylindrical PMMA target T5-mm radius, 200-mm length 100 mm 100 mm 200 mm Lead shielding LYSO and LaBr3 detectors

A schematic illustration and a picture of these experiments can be observed in figure 3.1.

FIGURE 3.1: A schematic illustration (left) and a picture (right) of the WPE 160 MeV (I) protons experiments. The schematic illustration is not to scale.

A two-dimensional spectrum (TOF vs energy) is shown herein for illustration purposes, while the energy and TOF spectra for this experiment are shown in appendices B.1 and B.2. The analysis of these experimental data led to the longitudinal profiles presented in figures 3.3 and 3.5 using TOF (if applicable) and energy selection $(1 \le E \le 7 \text{ MeV})$.

During experimental analysis some artefact peaks were observed at the edges of the TOF spectra (see figure 3.6). Moreover, the resulting TOF spectra for the two detectors was different in respect to these artefacts as can be seen in the same figure. In the LYSO:Ce detector data (figure 3.6, bottom), six prompt-gamma peaks are clearly visible but one of them is being affected by the artefact (for the sake of simplicity, this prompt-gamma peak will be referred to as "affected peak"). On the other hand, the LaBr₃:Ce data show only five prompt-gamma peaks. Another striking remark is the fact that, in the LaBr₃:Ce data, two pronounced artefacts are distinguishable, while only one for the LYSO:Ce detector is observed. Since the two detectors follow the same electronics and data acquisition chain, the sixth peak should also be present in the LaBr₃:Ce data, so probably the data from this peak was merged into the artefact. To test this assumption, the two artefact peaks were selected and the energy spectrum was plotted. It was observed that the artefact present



FIGURE 3.2: The two-dimensional spectrum (TOF vs energy) for the WPE 160 MeV H^+ (I) experiment with the LaBr₃:Ce detector, obtained from the measuring position at 145 mm. The TOF axis is relative since no calibration for the axis origin was performed.



FIGURE 3.3: Profiles with and without TOF for the WPE 160 MeV H⁺ (I) experiment with the LaBr₃:Ce detector. The error bars (statistical uncertainty at one standard deviation) are smaller than the markers. An energy selection $(1 \le E \le 7 \text{ MeV})$ was applied to the data.

in both detector data does not contain a meaningful energy spectrum (i.e. the shape of the energy spectrum does not resemble any of the spectra obtained after selecting clear prompt-gamma peaks). However, the artefact that is only observed in the LaBr₃:Ce data does present an energy spectrum that may be correlated with valid events. To address the issues of selecting the affected peak in the LYSO:Ce data with influence of the artefact and the missing prompt-gamma peak in the LaBr₃:Ce ones, it was decided to select five peaks (thus not considering the affected peak) in both set of data and to apply a 6/5



FIGURE 3.4: The two-dimensional spectrum (TOF vs energy) for the WPE 160 MeV H^+ (I) experiment with the LYSO:Ce detector obtained from the measuring position at 145 mm. The TOF axis is relative since no calibration for the axis origin was performed.



FIGURE 3.5: Profiles with and without TOF for the WPE 160 MeV H⁺ (I) experiment with the LYSO:Ce detector. The error bars (statistical uncertainty at one standard deviation) are smaller than the markers. An energy selection $(1 \le E \le 7 \text{ MeV})$ was applied to the data.

factor to account for the sixth peak. This factor assumes that the events are randomly distributed in all peaks. This seems to be a reasonable assumption since, in the data from all the measurement positions, no meaningful difference between prompt-gamma peaks is observed. Nevertheless, by applying this factor, the introduction of a systematic error on this data analysis cannot be excluded.



FIGURE 3.6: Raw TOF spectra considering the LaBr₃:Ce (top) and LYSO:Ce (bottom) detectors data for the WPE 160 MeV H⁺ (I) experiment at the longitudinal position of 145 mm. An energy selection $(1 \le E \le 7 \text{ MeV})$ was applied to the data.

3.1.1.2 WPE 160 MeV H⁺ (II)

These two experiments were performed after the WPE 160 MeV H^+ (I) experiment. The same target and detectors were used, but in a different setup. A schematic illustration and a picture of these experiments can be observed in figure 3.7.



FIGURE 3.7: A schematic illustration (left) and a picture (right) of the WPE 160 MeV (II) proton experiments. The schematic illustration is not to scale.

A two-dimensional spectrum (TOF vs energy) is shown herein for illustration purposes, while the energy and TOF spectra for this experiment are shown in appendices B.3 and B.4. The analysis of these experimental data led to the longitudinal profiles presented in figures 3.9 and 3.11 using TOF (if applicable) and energy selection $(1 \le E \le 7 \text{ MeV})$.



FIGURE 3.8: The two-dimensional spectrum (TOF vs energy) for the WPE 160 MeV H^+ (II) experiment with the LaBr₃ detector obtained from the measuring position at 145 mm. The TOF axis is relative since no calibration for the axis origin was performed.



FIGURE 3.9: Profiles with and without TOF for the WPE 160 MeV H⁺ (II) experiment with the LaBr₃ detector. The error bars (statistical uncertainty at one standard deviation) are smaller than the markers. An energy selection $(1 \le E \le 7 \text{ MeV})$ was applied to the data.

The same issues with the sixth peak as described for the WPE 160 MeV H^+ (I) experiment were also observed in this one. The same 6/5 factor was applied to the data resulting from this experiment. Please refer to section 3.1.1.1 for more information.



FIGURE 3.10: The two-dimensional spectrum (TOF vs energy) for the WPE 160 MeV H^+ (II) experiment with the LYSO:Ce detector obtained from the measuring position at 145 mm. The TOF axis is relative since no calibration for the axis origin was performed.



FIGURE 3.11: Profiles with and without TOF for the WPE 160 MeV H⁺ (II) experiment with the LYSO:Ce detector. The error bars (statistical uncertainty at one standard deviation) are smaller than the markers. An energy selection $(1 \le E \le 7 \text{ MeV})$ was applied to the data.

3.1.1.3 WPE 160 MeV H⁺ (III)

This experiment was performed in different conditions from those of the previous ones (i.e. it was an independent experiment and it took place in a different treatment room). The setup used was similar to the one of WPE 160 MeV H^+ (II) with the LaBr₃:Ce detector, with exception of the target, which was 50 mm longer in this case. Since the data are

similar, consider the figures from WPE 160 MeV H^+ (II) experiment (section 3.1.1.2 and appendix B.3).

3.1.2 Experimental data – Carbon ion irradiation

3.1.2.1 GANIL 95 MeV/u ¹²C⁶⁺

The BaF₂ and the NaI(Tl) detectors were positioned alongside with some additional lead shielding at 605 mm from the beam axis. A 200-mm-thick lead collimator with a 2-mm slit was placed between the detector and the target, which consisted of 27 PMMA slices of $50 \times 50 \times 2 \text{ mm}^3$ each. The monitor for the number of incident ions consisted in a small NaI(Tl) detector placed at a defined distance from the experimental setup and calibrated against a Faraday cup. The influence of the target position on the dose monitor was also checked and it was found to be less than 1%. Nevertheless, the calibration was corrected for this factor. The time structure of the cyclotron at GANIL allowed for the use of the HF signal as TOF stop signal (pulsed beam with a pulse width of approximately 1 ns every 80 ns). The circular beam full-width at half maximum (FWHM) spot size was found to be approximately 5 mm at the target position and the beam was centred with the target cross section, thus ensuring that the entire beam was impinging on the target.

A schematic illustration and a picture of these experiments can be observed in figure 3.12.



FIGURE 3.12: A schematic illustration (left) and a picture (right) of the GANIL $95 \text{ MeV/u} \, {}^{12}\text{C}^{6+}$ experiments. The schematic illustration is not to scale.

A two-dimensional spectrum (TOF vs energy) is shown herein for illustration purposes, while the energy and TOF spectra for this experiment are shown in appendices B.5 and B.6. The analysis of these experimental data led to the longitudinal profiles presented in figures 3.14 and 3.16 using TOF (if applicable) and energy selection ($1 \le E \le 7$ MeV).


FIGURE 3.13: The two-dimensional spectrum (TOF vs energy) for the GANIL 95 MeV/u $^{12}C^{6+}$ experiment with the BaF₂ detector obtained from the measuring position at 16 mm. The TOF axis is relative since no calibration for the axis origin was performed.



FIGURE 3.14: Profiles without (top) and with (bottom) TOF selection for the GANIL 95 MeV/u $^{12}C^{6+}$ experiment with the BaF₂ detector. The error bars (statistical uncertainty at one standard deviation) are smaller than the markers. An energy selection $(1 \le E \le 7 \text{ MeV})$ was applied to the data.



FIGURE 3.15: The two-dimensional spectrum (TOF vs energy) for the GANIL 95 MeV/u $^{12}C^{6+}$ experiment with the NaI(Tl) detector obtained from the measuring position at 16 mm. The TOF axis is relative since no calibration for the axis origin was performed.



FIGURE 3.16: Profiles without (top) and with (bottom) TOF selection for the GANIL 95 MeV/u $^{12}C^{6+}$ experiment with the NaI(Tl) detector. The error bars (statistical uncertainty at one standard deviation) are smaller than the markers. An energy selection $(1 \le E \le 7 \text{ MeV})$ was applied to the data.

3.1.2.2 GSI 300 MeV/u ¹²C⁶⁺

The BaF_2 detector was also used in this experiment. It was positioned at 990 mm from the beam axis. A 200-mm-thick lead collimator with a 15-mm slit was placed between the target and the detector. Some lead shielding was added around the detector and the collimator to improve the SBR. A target composed of five plastic flasks filled with water was used. Each flask had dimensions of $120 \times 250 \times 40 \text{ mm}^3$. Special care was taken to prevent spaces between flasks. Although no measurement before or after the target was made in this experiment, one with a closed collimator was performed. The TOF stop signal was provided by a delayed signal coming from two plastic scintillators intercepting the beam. To avoid losing ion triggering in the plastic scintillators, the beam intensity was kept at low values (i.e. up to a few 10^5 ions/s). However, if an incident ion was missed and its secondary radiation was registered, it would not be taken into account afterwards during the analysis due to the TOF information. These detectors also allowed for retrieving the number of ions hitting the target, thus providing the normalization factor. An ionization chamber (IC) was also used to cross-check the normalization factor provided by the plastic scintillators. The synchrotron at GSI was set to a continuum extraction mode (approximately 8 seconds extraction every 10 seconds) with an elliptical FWHM spot size of ca. 13 mm and 10 mm at the target position, respectively for the Yand the X-axis and considering the beam direction as the Z-axis.

A schematic illustration and a picture of this experiment can be observed in figure 3.17.



FIGURE 3.17: A schematic illustration (left) and a picture (right) of the GSI 300 MeV/u $\rm ^{12}C^{6+}$ experiment. The schematic illustration is not to scale.

A two-dimensional spectrum (TOF vs energy) is shown herein for illustration purposes, while the energy and TOF spectra for this experiment are shown in appendix B.7. The analysis of these experimental data led to the longitudinal profiles presented in figure 3.19 using TOF (if applicable) and energy selection $(1 \le E \le 7 \text{ MeV})$.



FIGURE 3.18: The two-dimensional spectrum (TOF vs energy) for the GSI 300 MeV/u $^{12}C^{6+}$ experiment with the BaF₂ detector obtained from the measuring position at 140 mm. The TOF axis is relative since no calibration for the axis origin was performed.



FIGURE 3.19: Profiles without (top) and with (bottom) TOF selection for the GSI 300 MeV/u ${}^{12}C^{6+}$ experiment with the BaF₂ detector. The error bars (statistical uncertainty at one standard deviation) are smaller than the markers for the case without TOF selection. An energy selection ($1 \le E \le 7$ MeV) was applied to the data.

3.1.2.3 GSI 310 MeV/u ¹²C⁶⁺

This experiment employed the same detector, target and normalization procedure with the information provided by plastic scintillators and an IC as in the GSI 300 MeV/u $^{12}C^{6+}$ one (vide section 3.1.2.2). However, the setup was different. In this case the BaF₂ detector was positioned at a distance of 1345 mm from the beam axis with a 200-mm-thick lead collimator between the target and the detectors. The collimator had a slit of 4 mm. Some lead shielding was added to the setup and several water containers were placed between the collimator and the detector in order to provide shielding against neutrons. A schematic illustration and a picture of this experiment can be observed in figure 3.20.



FIGURE 3.20: A schematic illustration (left) and a picture (right) of the GSI 310 MeV/u $^{12}\mathrm{C}^{6+}$ experiment. The schematic illustration is not to scale.

A two-dimensional spectrum (TOF vs energy) is shown herein for illustration purposes, while the energy and TOF spectra for this experiment are shown in appendix B.8. The analysis of these experimental data led to the longitudinal profiles presented in figure 3.22 using TOF (if applicable) and energy selection $(1 \le E \le 7 \text{ MeV})$.

3.1.2.4 HIT 310 MeV/u ¹²C⁶⁺

A $50 \times 40 \times 5 \text{ mm}^3$ LYSO:Ce detector was positioned at 635 mm from the beam axis. A tungsten-alloy collimator with 100 mm thickness and a 4-mm slit was used. Additional lead shielding was placed surrounding the detector and the collimator. The target was a $100 \times 100 \times 250 \text{ mm}^3$ PMMA phantom positioned on top of a moving table. The TOF stop signal was given by a suitably delayed signal coming from a plastic scintillator intercepting the beam after the beam exit. During this experiment a beam hodoscope being developed in-house was also positioned after the beam exit and hence an additional loss in the beam energy is expected. The beam FWHM spot size was found to be approximately 3.8 mm at the target position.



FIGURE 3.21: The two-dimensional spectrum (TOF vs energy) for the GSI 310 MeV/u $^{12}C^{6+}$ experiment with the BaF₂ detector obtained from the measuring position at 150 mm. The TOF axis is relative since no calibration for the axis origin was performed.



FIGURE 3.22: Profiles without (top) and with (bottom) TOF selection for the GSI 310 MeV/u ${}^{12}C^{6+}$ experiment with the BaF₂ detector. The error bars (statistical uncertainty at one standard deviation) are smaller than the markers for the case without TOF selection. An energy selection ($1 \le E \le 7$ MeV) was applied to the data.



A schematic illustration and a picture of this experiment can be observed in figure 3.23.

FIGURE 3.23: A schematic illustration (left) and a picture (right) of the HIT 310 MeV/u ${}^{12}C^{6+}$ experiment. The schematic illustration is not to scale.

A two-dimensional spectrum (TOF vs energy) is shown herein for illustration purposes, while the energy and TOF spectra for this experiment are shown in appendix B.9. The analysis of these experimental data led to the longitudinal profiles presented in figure 3.25 using TOF (if applicable) and energy selection $(1 \le E \le 7 \text{ MeV})$.



FIGURE 3.24: The two-dimensional spectrum (TOF vs energy) for the HIT 310 MeV/u $^{12}C^{6+}$ experiment with the LYSO:Ce detector obtained from the measuring position at 160 mm. The TOF axis is relative since no calibration for the axis origin was performed.

3.1.3 Experimental data – Discussion

The results presented thus far unequivocally show the possibility of discriminating the prompt-gamma events, for both proton and carbon ion irradiation. The occurrence of those events is most remarkable for the proton and the lower energy carbon ion



FIGURE 3.25: Profiles without (top) and with (bottom) TOF selection for the HIT 310 MeV/u $^{12}C^{6+}$ experiment with the LYSO:Ce detector. The error bars (statistical uncertainty at one standard deviation) are smaller than the markers for the case without TOF selection. An energy selection ($1 \le E \le 7$ MeV) was applied to the data.

experiments due to the lower background, but it is also possible to observe them in the experiments with more energetic carbon ions (refer to the TOF spectra in appendix B for better visualisation). Indeed, the use of the TOF technique has proven to be an efficient way to discriminate prompt gammas (i.e. signal) from neutrons and neutron-induced gammas (i.e. background). Such findings can be confirmed in the figures presented along the previous sections, which show that TOF allows for yielding an improved description of the fall-off in the prompt-gamma longitudinal profile, close to the expected position of the Bragg peak. It was also shown by Roellinghoff et al. that its application improves the precision in finding the proton range in prompt-gamma monitoring by enhancing the SBR [76]. The SBR values for each case are gathered in table 3.4.

There is a slight change in the signal whether TOF selection is or is not applied, but the change (both loss and gain) is, for most cases, within the signal statistical fluctuations. However, even with all the precautions to have a sufficiently large TOF window that includes the entire signal while avoiding an undesirable amount of background, it is not possible to ensure that all prompt-gamma events are taken into account. From the

TABLE 3.4: Experimental results gathered from the prompt-gamma profiles. Maximum and background refer to the maximum point before the prompt-gamma profile fall-off next to the end of the ion range, and to the minimum point after the said fall-off, respectively. In order to estimate the SBR, the signal is calculated by subtracting the background from the maximum. For the carbon ion experiments it was not possible to observe a distinguishable prompt-gamma profile without TOF selection, thus no values are provided. The two GSI experiments have very few points to be considered for such an analysis.

		W	ithout TOF		With TOF		
Experiment	Detector	Maximum	Background	SBR	Maximum	Background	SBR
		$(\times 10^{-9} \text{ con})$	unts per ion)	- ODIC	$(\times 10^{-9} co)$	unts per ion)	obit
$CANIL_{05} MoV/\mu^{12}C^{6+}$	BaF_2				1244	778	0.60
GARTE 35 MEV/U C	$\operatorname{NaI}(\operatorname{Tl})$				1010	696	0.45
GSI 300 MeV/u $^{12}\mathrm{C}^{6+}$	BaF_2		too few	v measu	rement poin	ts	
GSI 310 MeV/u $^{12}{\rm C}^{6+}$	BaF_2		too few	v measu	rement poin	ts	
HIT 310 MeV/u $^{12}\mathrm{C}^{6+}$	LYSO:Ce	_			1056	710	0.49
WPF 160 MeV H^{+} (I)	LYSO:Ce	370	337	0.10	100	75	0.33
WIE 100 MeV II (I)	LaBr ₃ :Ce	531	512	0.04	141	118	0.19
WPF 160 MeV H^+ (II)	LYSO:Ce	741	546	0.36	247	129	0.91
···· E 100 MEV II (II)	LaBr ₃ :Ce	1033	940	0.10	296	222	0.33

data in table 3.4, it is more convenient to have detectors in the slit and not behind the collimator material (see SBR between LYSO:Ce and LaBr₃:Ce for the WPE experiments). This may influence the choice of the detection system in a real monitoring system by favouring designs with segmented detectors centred in the slits instead of monolithic ones. Moreover, the WPE 160 MeV H⁺ (I) uses a setup with better spatial resolution, thus worse efficiency, which is confirmed by the SBR results. Although there is shielding and a reduced background in respect to WPE 160 MeV H⁺ (II), the signal observed in the former experiment suffers a penalty due to the lack of efficiency (i.e. smaller solid angle and FOV) and this is reflected on the SBR.

Nevertheless, the results in table 3.4 show that the TOF technique is, at least, desirable for proton therapy monitoring with prompt gammas in order to improve the SBR, and mandatory for the carbon ion case since it allows for an observable prompt-gamma profile fall-off.

An additional advantage of employing TOF is the possibility to better understand the experimental data and the different types of events detected. Figure 3.26 gives an example of TOF spectra obtained with a 310 MeV/u carbon-ion beam and the relatively large BaF_2 detector: the prompt-gamma peak located around a relative TOF of 5 ns is small



as compared to the secondary-induced events coming from the target (component centred at around 10 ns).

FIGURE 3.26: TOF spectra of the GSI 310 MeV/u ¹²C⁶⁺ experiment for the measurement points at -15 mm (before the target) and 150 mm (inside the target). The TOF components corresponding to the events associated with prompt gammas (a), secondary-induced events from the target ((b), mainly neutron-associated events), and events associated with the surroundings ((c), e.g. walls, ceiling) are pointed out by arrows and have been suggested by Testa et al. [89]. The X-axis is relative since no calibration for the axis origin was performed.

A striking fact is the low number of events available for the high energy carbon ion experiments, notably for the HIT 310 MeV/u $^{12}C^{6+}$ one. The reasons for such lack of statistics is three-fold: 1) the limited amount of time to conduct the experiment and, on the other hand, 2) the need to keep the beam intensity sufficiently low (around few 10^5 ions per second) in order to maintain a high efficiency on the detectors intercepting the beam for particle tagging, and 3) the relatively small detector used for the HIT 310 MeV/u $^{12}C^{6+}$ experiment. Table 3.5 contains the number of incident particles based on the scalers of the detector used as monitor far away from the beam (low energy carbon ion experiment), the scalers of the detector intercepting the beam (high energy carbon ion experiments), or the values yielded by the IC (proton experiments). The dead time is taken into consideration by correcting the *real* number of incident particles (i.e. the raw data from the scalers) to the number of ions responsible for yielding the registered events (i.e. raw data multiplied by the live time). These values correspond to the measurement shown in the previous sections for the 2D spectra and the considered position inside the target (for the results presented in appendix B).

With the analysis carried out up to this point, this set of experiments can already provide several insights concerning prompt-gamma monitoring, namely the feasibility of monitoring ion ranges making use of prompt-gamma information and the advantage of employing the TOF technique in such an application. However, the analysis can go

Experiment	Number of incident ions	Average beam intensity (ions per second)
GANIL 95 MeV/u $^{12}\mathrm{C}^{6+}$	1.22×10^{10}	2.57×10^8
GSI 300 MeV/u $^{12}\mathrm{C}^{6+}$	1.03×10^8	2.50×10^5
GSI 310 MeV/u $^{12}\mathrm{C}^{6+}$	2.73×10^8	2.89×10^5
HIT 310 MeV/u $^{12}\mathrm{C}^{6+}$	3.95×10^8	6.52×10^5
WPE 160 MeV $\mathrm{H^{+}}$ (I)	7.29×10^{11}	2.24×10^9
WPE 160 MeV $\mathrm{H^{+}}$ (II)	3.17×10^{11}	2.16×10^9

TABLE 3.5: Number of incident ions for each experiment at the considered measurement position. The number of incident ions are corrected for the dead time, thus not being the *real* number of incident ions. The average beam intensity results from the number of incident ions divided by the time (both without dead time correction).

even further to estimate absolute prompt-gamma yields. Henceforth, absolute yields will be referred to as the description of the prompt-gamma signal in units of promptgamma counts per incident ion, unit of field of view (millimetre), and unit of solid angle (steradian). These yields will also be corrected for the detector efficiency and for the prompt-gammas able to cross the collimator material and shielding. The rationale for the analysis presented here is to gather experimental data suitable for comparison with simulations and to cross-check such data with other experimental designs. Ultimately, all these experiments and data analyses are crucial for any quantitative use of the information provided by the prompt-gamma emission, in particular to guide the construction of a clinical prompt-gamma camera prototype and to predict the prompt-gamma distributions to be used as a reference during treatment.

3.1.4 Absolute yields

Throughout the process of estimation of absolute yields there was the need to conduct Monte Carlo simulations. The simulations for this work were carried out using Geant4 9.6.p02.

3.1.4.1 Background subtraction

The use of TOF helps in removing most of the background by selecting with a TOF window only the region of interest where the prompt-gamma signal is. Nevertheless, some background events are also present inside the TOF window. One could develop a method based on Monte Carlo simulations in order to estimate the number of those events. However, it is dubious that simulations could yield enough accuracy in such a case since it is virtually impossible to implement a full description of a complex experiment.

Some details are omitted either for simplification (e.g. description of the beam nozzle) or due to unknown parameters (e.g. material composition, distribution of all elements in a room). Our approach is therefore based solely on experimental data. Two different methods were used according to the ion species. Regardless of the two methods and as a fragmentation tail is not expected for the low energy carbon ion and proton experiments, a linear fit is applied using the points before the target and after the ion range. This linear fit is used to further subtract events from the profile after the background subtraction procedures detailed in the following sections. The errors on the fit are also taken into account (summed quadratically with the error bars of the data points).

Carbon ion irradiation data The analysis of these data presented some challenges. On the one hand, the signal is overlapping with the background in a time region where the number of events coming from reactions with fast neutrons is rapidly increasing. This poses some problems mainly in longitudinal positions for which the signal is weaker. On the other hand, the statistics for most of the data with carbon ions are low due to the methods used for the TOF measurement (i.e. when plastic scintillators were used they required a relatively low beam intensity to avoid pile-up). The only exception is the GANIL data for which a different method allowed for a much higher beam intensity at the cost of some loss in accuracy that will be imparted to the data as systematic uncertainty.

One of the most used methods for retrieving signal from background is to use a set of fits that are able to describe the signal and the background. Nevertheless, due to the aforementioned issues the fits have consistently led to yields with large fluctuations, so a different approach was chosen.

The analysis of the data suggests that the background shape in the TOF spectra is the same for every longitudinal position and only its magnitude changes. Such indications were already published by Testa et al. [89]. For example, a higher background (even if slightly) is expected at the very end of the target than at the beginning, since neutron emission is not isotropic and favours forward angles [30, 92]. As a consequence, a spectrum without prompt-gamma signal can be set as reference and used to subtract the background to the spectra containing both signal and background. The condition for this method to work is the application of a scaling factor to the said reference TOF spectrum that reflects the change in the magnitude of the background along the target depth. This factor is estimated based on the ratio of the integrals outside the TOF window for both the reference spectrum and the one to be subtracted.

For most experiments, the reference TOF spectrum was then set to be the one corresponding to a measurement before the target with the use of adequate collimation and shielding. The only exception was the GSI 300 MeV/u $^{12}C^{6+}$ data for which there was

no measurement before the target. For this case a closed-collimator configuration was used as reference.

Proton irradiation data The proton data do not have the issues seen with the carbon ion irradiation. There are both a very distinctive prompt-gamma peak easily separated from the background and very high statistics since it was not necessary to limit the beam intensity to tag the incident protons for TOF measurement. Consequently, it was possible to use a more conventional approach employing fits, resorting to an already available ROOT class called **TSpectrum**. Moreover, the background shape on the TOF spectrum changes along the longitudinal position of the scan. Hence, the assumption used for the carbon ion experiments concerning the background shape does not hold for the proton ones. Although further studies must be performed to give a definitive answer to why this happens, it may be related to the fact that the neutrons that are responsible for most of the background during proton irradiation are emitted by the target nuclei, while for the case of carbon-ion irradiation they come mainly from incident ions. The TOF spectrum of neutron-related events with proton irradiation may therefore be more sensitive to target position than in the carbon-ion irradiation case.

An example of TOF spectra can be seen in figure 3.27, where it is possible to observe the distinct shapes of the background in the TOF spectra of a position before the target and at 145 mm in the target. Another remark concerns the different prompt-gamma peak positions in the TOF spectrum with respect to distinct longitudinal positions. It can be correlated with the different distances travelled by the protons due to both the movement of the moving table and the longitudinal position in the target being measured. Using the proton energy as 160 MeV, the proton transit time between the position -25 mm and 145 mm is around 1.1 ns (see the prompt-gamma peak shift in figure 3.27). Such a shift on the prompt-gamma peak is not clearly observed in the carbon ion experiments due to two combined phenomena related to statistics and signal to background ratio. On the one hand, the experiment that provides the highest statistics (i.e. GANIL 95 MeV/u $^{12}C^{6+}$) was performed with small ion ranges, which entails small changes of the moving table to scan the prompt-gamma profile and therefore small shifts on the prompt-gamma peak position. On the other hand, the carbon ion experiments have an important level of background that may hide the time difference since the signal is less visible.

Although retrieving the signal from protons TOF spectra is easier than from carbon ions TOF spectra, there is no procedure capable of telling if after the fitting procedure only prompt-gamma events remain or if some signal was incorrectly subtracted. To address such an issue, it was decided to vary the input parameters of the routine **TSpectrum** in order to have a set of fits made with different conditions. Three input parameters



FIGURE 3.27: Comparison between two TOF spectra obtained for two longitudinal positions (25 mm before the target and 145 mm inside the target). These data come from the WPE 160 MeV H⁺ (II) experiment using the LaBr₃ detector. The X-axis is relative since no calibration for the axis origin was performed.

were varied: smoothing of the histogram (without or with a third-order filter), clipping window direction (either increasing or decreasing), and clipping window width (between 20 and 60 bins). Such parameters and their variation yielded the most meaningful background subtraction after a preliminary study focused on testing this routine. An histogram with the counts retrieved after each fit is built. Finally, the average of this distribution is used as the number of prompt-gamma events inside the TOF window and the corresponding standard deviation is imparted to the data as systematic uncertainty. Additional information about the TSpectrum method can be found elsewhere [93].

3.1.4.2 Geometrical normalisation

The geometrical parameters of each experiment should be taken into account in order to obtain absolute yields. The parameters that play a role are related to the positioning of each element in the experimental setup and also to other conditions (e.g. collimator slit width). The process for obtaining such parameters to normalise the yields using analytical means is not straightforward. Being so, a Monte Carlo procedure was employed, which allowed to take into consideration the scattering of photons, the collimator absorption and attenuation coefficients, as well as the shadowing effects around the edges of the collimator slit.

For each experiment and detector three parameters were calculated: the detection field of view (FOV), the detection solid angle and a correction factor accounting for the events able to cross the collimator and the shielding and reach the detectors. The simulated energy spectra of the photons escaping the different targets was used as input.

Each photon emitted isotropically along a line source is propagated across the simulated experimental setup and if the total energy deposition in the detector is within the energy thresholds used for the experimental data, the axial position z of the emission point is registered in order to build a histogram. Figure 3.28 depicts an ideal case of such a photon emission profile. The line sources had dimensions corresponding to the ion range for each case. A possible definition of the FOV is the FWHM of this distribution (as shown in equation (3.1)). In order to keep the detection efficiency constant inside the FOV, it is assumed that the events outside the FWHM (red region in figure 3.28) are included in this distribution (grey region in figure 3.28), thus approximating this distribution to a rectangular function.



 $FOV \approx FWHM = |z_5 - z_3| \tag{3.1}$

FIGURE 3.28: Ideal case of longitudinal distribution of emitted photons after detection in a single-slit experiment.

In turn, the total detection efficiency ε is estimated using equation (3.2) and it includes both geometrical and intrinsic efficiencies. The calculation consists in considering an isotropic point-like source centred in front of the slit, where N_d and N_e are the number of detected and emitted gammas, respectively. In order to estimate the yields for emitted energies above 1 MeV, only gammas with energies above this threshold are considered. Consequently, N_d accounts solely for events that have an energy deposition between 1 and 7 MeV in the detector (i.e. the experimental energy thresholds).

$$\varepsilon = \frac{N_{d_{[1 \le E \le 7 \text{ MeV}]}}}{N_{e_{[E \ge 1 \text{ MeV}]}}} \tag{3.2}$$

With these considerations, the final absolute yields correspond to absolute yields of prompt gammas with energy higher than 1 MeV.

Finally, the correction factor κ is the ratio between detected events from inside the FOV and all detected events. It estimates the ratio of prompt gammas being observed inside the signal peak that corresponds to events coming from the slit opening. The photons able to cross the collimator and shielding, thus originating from a different longitudinal position than the one being observed can be obtained through the relationship $(1 - \kappa)$. However, due to the approximation to a rectangular function, κ cannot be estimated using the FOV as presented in equation (3.1) since events outside the FWHM are being considered. On the other hand, by approximating the distribution to a ramp function, the events in the red region in figure 3.28 between z_1 and z_2 compensate the lack of events in the green region of the same figure. Therefore, κ can be approximated by equation (3.3), where f(z) corresponds to the function depicted in figure 3.28.

$$\kappa = \int_{z_2}^{z_6} f(z) dz \times \left(\int_{-\infty}^{+\infty} f(z) dz \right)^{-1}$$
(3.3)

Although equation (3.3) is the correct analytical expression for the aforementioned geometrical considerations, its implementation with real cases is not straightforward. Thus, it was decided to use for the integral in the numerator the z_1 and z_7 as limits of integration. It is assumed that any impact on the final result should be negligible given that there are very few events in this region in respect to the total number of events.

3.1.4.3 Systematic errors

An estimation of the systematic uncertainties is crucial to obtain absolute yields. Although it is not possible to rule out other possible sources of systematic uncertainties, three main sources are assumed: 1) normalization in respect to the number of ions, 2) background subtraction procedure, and 3) geometrical description of each experimental setup. The systematic errors were rounded up to the next integer (in percentage) and they are shown in table 3.7. The systematic uncertainty shown in this table concerning background subtraction is a weighted average using the data points inside the ion range. It is the average of the absolute number of events left inside the TOF window after background subtraction. The calculation method of the systematic uncertainty depends on the ion species and it is presented in section 3.1.4.3. Nevertheless, it should be noted that, for further analysis, each individual data point is assigned with a specific systematic uncertainty due to background subtraction and only one value is given in the aforementioned table for simplicity purposes.

Number of ions In order to retrieve the number of ions for posterior normalization, two methods were used in most of the experiments.

For the proton irradiation experiments, one method consisted in retrieving the number of particles by using the integrated current in the IC available at the beam nozzle and calibrated against a Bragg peak chamber detector. The other one used the MU system of the treatment system.

For the carbon ion cases, distinct approaches were applied in different experiments. For those at GANIL, a distant detector was calibrated using a Faraday cup. In the HIT $310 \text{ MeV/u}^{12}\text{C}^{6+}$ experiment and the ones at GSI, plastic scintillators were used, which also tagged the particle by yielding a TOF stop signal. In the experiments at GSI, a second method was implemented, consisting of an independent IC (i.e. plugged to a distinct electronics chain and acquisition system) calibrated by the plastic scintillators.

For all the experiments using two methods, only the results from one of them was used to normalise the data. The systematic error on the number of ions was assumed to be the maximum difference between the two methods considering all acquisition runs. Concerning the systematic error for the data from the GANIL experiments, the error on the calibration curve was used. For the HIT 310 MeV/u $^{12}C^{6+}$ experiment it was not possible to obtain an estimation of the systematic error on the number of ions since only one beam monitoring was used.

Background subtraction As already detailed in section 3.1.4.1, two distinct background subtraction procedures were used according to the ion species. Consequently, different considerations were made to cope with the systematic error of each background subtraction method.

• Carbon ion irradiation data

The rationale for subtracting the data of a given measurement with a reference TOF spectrum is to get a subtracted TOF spectrum in which only the prompt-gamma events are present. However, such a spectrum may be subjected to both statistical fluctuations and systematic uncertainties imparted by the method. If the method performs a good subtraction all bins except the ones corresponding to prompt-gamma events should yield an average value of zero. Therefore, in order to estimate

the systematic uncertainties of the method, the ten bins immediately before and after the TOF window for the prompt-gamma peak were used to make a linear fit and the contribution inside the TOF window was extrapolated. The contribution of those events was compared with the total number of events inside the TOF window and this corresponds to the systematic uncertainties of the method. Only ten bins were used from each side because for some experiments the number of bins with meaningful data before the prompt-gamma peak is limited.

• Proton irradiation data

The systematic uncertainty on the background subtraction method for proton irradiation data has been already described in section 3.1.4.1 and it is defined as the standard deviation of the number of counts retrieved by different approaches for background subtraction.

Experimental setup From the systematic uncertainties considered, the ones related to the experimental setup are the most difficult to quantify. They are related to the accuracy of the measurements for each meaningful geometrical element in the experimental setup. The procedure was then to stipulate some reasonable assumptions related to the accuracy of the measurements and analytically estimate the change on the FOV and solid angle. After iterating along all possibilities considered for a given experiment, the maximum deviation was used as systematic uncertainty.

Monte Carlo simulations were not used to perform this estimation due to the CPU time needed. It is acknowledged that simulations are more accurate but the interest for this estimation is the variation yielded by changing geometrical dimensions rather than absolute values. The analytical procedure was verified with Monte Carlo simulations for the GSI 300 MeV/u $^{12}C^{6+}$ experiment. In this verification the slit width was varied and the difference in FOV and solid angle between simulations and the analytical approach was within $\pm 13\%$.

Table 3.6 presents the tolerance values considered for the geometrical dimensions. It should be stressed that some items are only applicable to specific experiments (e.g. the use of lead and tungsten collimators).

3.1.4.4 Absolute yields normalization

The absolute prompt-gamma yields $Y_{i,j}$ for a given experiment *i* and for a given longitudinal position along the target *j* in units of counts ion⁻¹ mm⁻¹ sr⁻¹ are then obtained using equation (3.4) in which $S_{i,j}(t)$ corresponds to the TOF spectrum after subtraction

Geometrical element	Tolerance (mm)
Distance beam axis to collimator front face	± 2.5
Distance collimator back face to detector	± 2.5
Lead collimator thickness	± 1.0
Tungsten collimator thickness	± 0.25
Collimator slit with $guide^1$	± 0.1
Collimator slit without $guide^1$	± 1.0

TABLE 3.6: Tolerances assumed for the geometrical description.

 1 For all experiments, except for the GSI 300 MeV/u $^{12}{\rm C}^{6+},$ an aluminium piece was used along the slit to ensure a constant and fixed slit width.

			Systematic uncertainty	r	
Experiment	Detector	Number of ions	Background subtraction	Experimental setup	
			Sachground Subtraction	FOV	Solid angle
GANIL 05 MeV/11 12C6+	BaF_2	20%	5%	7%	8%
GARANE 55 MeV/u C	$\operatorname{NaI}(\operatorname{Tl})$	20%	7%	7%	8%
GSI 300 MeV/u $^{12}\mathrm{C}^{6+}$	BaF_2	10%	14%	8%	9%
GSI 310 MeV/u $^{12}\mathrm{C}^{6+}$	BaF_2	10%	39%	5%	5%
HIT 310 MeV/u $^{12}\mathrm{C}^{6+}$	LYSO:Ce	_	33%	4%	2%
WPF 160 MeV H^{+} (I)	LYSO:Ce	3%	5%	3%	2%
WIE 100 MeV II (I)	${\rm LaBr_3:Ce}$	3%	4%	3%	2%
WPF 160 MeV H^{+} (II)	LYSO:Ce	3%	2%	5%	3%
VVI 12 100 IVIEV II (II)	LaBr ₃ :Ce	3%	3%	4%	5%
WPE 160 MeV H^+ (III)	LaBr ₃ :Ce	3%	8%	4%	5%

TABLE 3.7: Estimated systematic uncertainties.

for a given experiment *i* and longitudinal position *j* along the target, and N_{ions} to the estimated number of ions during the experiment. Variables κ , FOV, and ε are given in equations 3.1 to 3.3. The yields are estimated inside the TOF window $[t_1, t_2]$.

$$Y_{i,j} = \frac{\kappa}{N_{\text{ions}} \times FOV \times 4\pi\varepsilon} \times \int_{t_1}^{t_2} S_{i,j}(t) \,\mathrm{d}t \tag{3.4}$$

3.1.4.5 Results

Background subtraction

• Carbon ion irradiation data

Herein, the steps of the background subtraction procedure for the carbon ion data are shown for the GSI 300 MeV/u $^{12}C^{6+}$ experiment as an example. In figure 3.29 (a) two TOF spectra are depicted, the reference spectrum and the one that will undergo the background subtraction (measurement at 160 mm inside the target). Afterwards, in figure 3.29 (b) the reference spectrum is scaled using a factor based on the integral outside the TOF window for both spectra in order to account for the difference in background magnitude. The spectrum at a given position is then subtracted using the scaled reference TOF spectrum. Finally, in figure 3.29 (c) the TOF region around the prompt-gamma peak after background subtraction is shown along with the linear fit used to estimate the systematic uncertainty on the background subtraction procedure. For this specific case it can be observed that the systematic uncertainty is relatively small since the linear fit obtained with the points around the prompt-gamma peak is almost constant and equal to zero.



FIGURE 3.29: Different steps of the background subtraction procedure using the GSI $300 \text{ MeV/u}^{12}\text{C}^{6+}$ experiment and the measurement at 160 mm inside the target as an example. (a) TOF spectrum to be subtracted and the reference one. (b) reference TOF spectrum scaled in order to account for the difference in background magnitude. (c) TOF region around the prompt-gamma peak after background subtraction.

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• Proton irradiation data

Concerning the proton experiments, the **TSpectrum** routine was used in order to estimate the background superimposed with the prompt-gamma peak. Figure 3.30 (left) depicts one case for which the aforementioned routine estimates the background based on some initial parameters. The routine is repeatedly applied with different initial parameters and the number of events inside the TOF window for each case is used to produce a distribution like the one shown in figure 3.30 (right). The average

value is considered as the number of prompt gammas inside the TOF window and the standard deviation of such a distribution is imparted to the results as systematic uncertainty.



FIGURE 3.30: (Left) Example of a TOF spectrum undergoing subtraction for the WPE 160 MeV H⁺ (II) experiment using the LYSO detector. The background estimation was performed using the ROOT routine **TSpectrum** and all estimated backgrounds for this specific case by such a routine are depicted in the figure. (Right) Distribution of integral values inside the TOF window retrieved after the application of the **TSpectrum** routine with different parameters. For this specific case, the average value and the standard deviation are, respectively, 0.136×10^{-6} and 0.002×10^{-6} counts inside TOF window per incident proton.

Geometrical normalization Each experiment was simulated and the FOV, ε and κ were estimated. Figure 3.31 depicts some of the profiles used to estimate the FOV and κ and table 3.8 contains the outcomes of this analysis for all experiments.



FIGURE 3.31: Simulated profiles used to estimate the FOV and κ . Each profile represents the emission axial position of a gamma that had an energy deposition inside the detector between 1 and 7 MeV. The profiles of some experiments are omitted since they are similar to, at least, one of the depicted.

Absolute yields After estimating the geometrical factors and the prompt-gamma signal from the background subtraction, it is possible to obtain the absolute yields for

Experiment	Detector	FOV (mm)	$\varepsilon \\ (\times 10^{-6})$	κ
GANIL 95 MeV/u $^{12}\mathrm{C}^{6+}$	BaF_2 NaI(Tl)	4.3 4.2	48 28	0.80 0.83
GSI 300 MeV/u $^{12}{\rm C}^{6+}$	BaF_2	25.1	215	0.90
GSI 310 MeV/u $^{12}{\rm C}^{6+}$	BaF_2	6.7	54	0.90
HIT 310 MeV/u $^{12}{\rm C}^{6+}$	LYSO	20.0	21	0.92
WPE 160 MeV H ⁺ (I)	LaBr ₃ LYSO	$7.5 \\ 6.0$	14 15	0.95 0.94
WPE 160 MeV H^+ (II)	LaBr ₃ LYSO	27.1 19.3	16 22	0.84 0.89
WPE 160 MeV H^+ (III)	$LaBr_3$	27.1	16	0.84

TABLE 3.8: Geometrical normalization of the data.

each experiment for both proton (figure 3.32) and carbon ion (figure 3.33) data set. The error bars presented in the profiles include both statistical (one standard deviation) and systematic uncertainties after a quadratic sum.



FIGURE 3.32: Profiles of the proton experiments after full normalization. Each data point includes both statistical (one standard deviation) and the considered systematic uncertainties.



FIGURE 3.33: Profiles of the carbon ion experiments after full normalization. Each data point includes both statistical (one standard deviation) and the considered systematic uncertainties.

The results gathered from both figures 3.32 and 3.33 are shown in table 3.9. In order to avoid the pile-up of events coming from secondary particles increasingly produced downstream along the beam path with the ones originated from incident ions, the results presented use the data from the first measured point inside the target not affected by the prompt-gamma profile entrance rise (i.e. after half FOV centred at target entrance). This assumption was verified with Geant4 (using reference physics list QGSP_BIC_HP) and it was found that for all carbon ion experiments at least 90% of the particles at the point considered are primary particles (electrons are disregarded). For the proton irradiation, this percentage is of at least 97%.

For the cases where there is data from more than one experiment, the standard weighted least-squares formula [94] is used. Only statistical uncertainties are considered for error propagation. Regarding the systematic uncertainties, most of them should be correlated at some extent but their error propagation proved to be extremely difficult. As such, when results are combined in any way and systematic uncertainties are stated, it was decided to use the largest systematic uncertainty amongst all results to be combined.

TABLE 3.9: Absolute yields using the first measured point inside the target not affected by the prompt-gamma profile entrance rise with both statistical and systematic uncertainties. The energy range row shows the energy range of the primary particles inside the FOV of the first point after the target entrance estimated by Geant4. When the results of more than one experiment are combined, the energy range considers the maximum energy limits amongst all the experiments considered.

Material	Energy range (MeV/u)	Ion species	Absolute yield ($\times 10^{-6}$ counts ion ⁻¹ mm ⁻¹ sr ⁻¹)
PMMA	[77-90]	Carbon ions	$124 \pm 0.7_{\rm stat} \pm 30_{\rm sys}$
PMMA	[272-310]	Carbon ions	$79 \pm 2_{\text{stat}} \pm 23_{\text{sys}}$
Water	[264-292]	Carbon ions	$112 \pm 1_{\rm stat} \pm 22_{\rm sys}$
PMMA	[139-156]	Protons	$16~\pm~0.07_{\mathrm{stat}}~\pm~1_{\mathrm{sys}}$

3.1.5 Discussion

Absolute prompt-gamma yields are presented in this section. They include both statistical and systematic uncertainties. Although it is not possible to rule out other sources of systematic uncertainties, the ones considered should have the highest impact. To some extent, the good agreement for both proton and carbon ion irradiation found among different experimental conditions (i.e. targets, detectors, setup geometries, facilities, and energy in the case of carbon ions) acts as a validation of the results. For the proton case, the same energy and target composition is used, thus the same absolute yields are expected. For the carbon ion experiments, each type of experiments (lower and higher energy) follow the trend published by Kox et al. [95], which shows a total reaction cross sections for ${}^{12}C{}^{-12}C$ experiments of 965 mb and 858 mb for 83 and 300 MeV/u projectile energy, respectively. Assuming a similar trend for the present cases, the lower energy experiments should express an increased prompt-gamma emission, which is actually verified. Moreover, the results show a higher prompt-gamma emission when using a water target in respect to a PMMA one (vide e.g. table 3.9 for the two highest energy ranges of carbon ions). It has been suggested that the target composition plays an important role on the prompt-gamma emission for proton irradiation, namely the oxygen content [78, 79]. The present work shows the same tendency when irradiating with carbon ions since the absolute yield with the PMMA target was lower than the one with the water target (a factor of $0.71 \pm 0.02_{\text{stat}} \pm 0.25_{\text{sys}}$).

Comparing the prompt-gamma yields of two different ion species with the same range in water, i.e. 160 MeV protons and 310 MeV/u carbon ions, the latter shows a value about six times greater than the former. Although there was no clear idea about how much the yield for carbon ions would be, the increased emission is expected since in a carbon ion

irradiation both target nuclei and projectile contribute for such an emission, while in a proton irradiation only the target nuclei may emit prompt gammas.

Recently Agodi et al. 2013 published prompt-gamma absolute yields of 80 MeV/u carbon ions impinging on a PMMA target. They found a yield of $(2.32 \pm 0.01_{stat} \pm 0.15_{sys}) \times 10^{-3}$ counts $ion^{-1} sr^{-1}$ for energies above 2 MeV and considering the full ion range. The comparison between the results presented herein and the aforementioned study is not direct since some considerations must be applied. Only the results of the GANIL 95 MeV/u experiment are suitable for such a comparison due to the similar energy range. However, the results shown in table 3.9 only consider a point after the entrance with a single-slit collimator while Agodi et al. published the integrated emission for the entire ion range. As such, if an average value between the entrance and the maximum yield immediately upstream of the prompt-gamma falloff is used, conditioned by a 2-MeV energy threshold (i.e. all steps described in the present work are repeated with 2 MeV as lower energy threshold instead of 1 MeV), an absolute yield of $(174 \pm 0.9_{\text{stat}} \pm 50_{\text{sys}}) \times 10^{-6}$ counts $ion^{-1} mm^{-1} sr^{-1}$ is obtained. The corresponding value published by Agodi and colleagues after considering the projected ion range of 80 MeV/u carbon ions in PMMA (15.42 mm, estimated with SRIM 2013) is $(150 \pm 0.6_{\text{stat}} \pm 10_{\text{sys}}) \times 10^{-6}$ counts ion^{-1} mm⁻¹ sr⁻¹. Although the outcome from our collaboration suffer from a higher systematic uncertainty, the agreement with previously published results from independent collaborations is remarkably good. Further experiments aiming at confirming these results with lower systematic uncertainties may provide additional information.

The outcomes presented herein use the data from two experiments already published by our collaboration [89, 97]. The present study provides slightly different results from the ones that can be found in those articles. Such a difference is the consequence of a review process of most of the single-slit collimator data of our collaboration, namely in terms of background subtraction methods, dead time correction and error estimation. Therefore, the results presented here should be seen as an updated and more accurate set of data and should be considered instead. In addition, the work presented so far in this manuscript, led to the submission of an article that is currently being reviewed.

Finally, it is possible to use the experimental results to make some considerations about prompt-gamma monitoring in a treatment scenario. For proton irradiation, and based on other studies [37, 72] in which the number of protons for a given spot used for a prostate tumour treatment is considered, it was decided to use 5×10^7 protons per spot and 46 spots per energy slice. On the other hand, Krämer et al. [98] states a total of 7×10^8 carbon ions in the target volume (around 120 cm³) to deliver an absorbed dose of 1 Gy using around 10 000 raster positions with 39 energy slices. Hence, as an approximation, 1×10^5 and 1×10^7 carbon ions will be considered in this analysis, respectively per spot and per energy slice. Table 3.10 shows the extrapolation of the absolute yields in table 3.9 to a given treatment scenario in the aforementioned conditions, considering the PMMA target for both cases, and using the data from the higher energy carbon ion irradiation.

		Number of prompt gammas (counts $mm^{-1} sr^{-1}$)
Protons	Spot Energy slice	$\begin{array}{l} 800 \pm 4_{\rm stat} \pm 50_{\rm sys} \\ 36800 \pm 161_{\rm stat} \pm 2300_{\rm sys} \end{array}$
Carbon ions	Spot Energy slice	$8 \pm 0.2_{\rm stat} \pm 2_{\rm sys}$ $790 \pm 20_{\rm stat} \pm 230_{\rm sys}$

TABLE 3.10: Number of prompt gammas estimated using the absolute yields shown in table 3.9 and taking into account the number of ions used for two treatment scenarios.

On the other hand, a precise estimation concerning the background events in a treatment scenario may be extremely difficult with the available data. The number of background events depends on, for example, the treatment room dimensions and materials, the specifications of the monitoring camera (namely the collimating and detection devices), and the beam time structure (e.g. if the particle bunches have a sufficiently large period, the background events originated after one particle bunch will not overlap with the prompt-gamma events of the next one). Moreover, it is not possible to simply apply the normalization factors used to obtain the absolute prompt-gamma emission yields to background events, since all the assumptions rely on prompt-gamma interactions. However, one can extrapolate the background events observed in the experimental data and infer some conclusions concerning those in a treatment scenario. As described before, the number of prompt-gamma events is obtained through the integration of the events inside the time window after background subtraction. In turn, the background events can be estimated by subtracting the number of prompt-gamma events from the integral inside the time window before background subtraction. Using the experimental data from the HIT 310 MeV/u $^{12}C^{6+}$ and the WPE 160 MeV H⁺ (II) with the LYSO:Ce detector experiments, respectively for carbon ions and protons, it is possible to retrieve a ratio of prompt-gamma to background events inside the TOF window and it was found to be around 1:1. Assuming that the same relationship holds for a treatment scenario and for a full-size camera, these results associated with the ones from table 3.10 unequivocally demonstrate the feasibility of discriminating the prompt-gamma signal from the background. Indeed, the number of prompt gammas is always at least 3σ of the background statistical fluctuations, except for the case of monitoring a carbon ion treatment at spot level. In fact, the aforementioned situation is the only one that poses more challenges due to the low signal available.

3.2 Comparison with Monte Carlo simulations

This section describes a benchmarking study carried out in order to evaluate the overall Geant4 performance in reproducing prompt-gammas emission yields. Such a study aims at analysing Geant4 performance and, if any, what is the extent of the improvement needed.

Four hadronic inelastic models were considered for proton modelling: Binary Cascade, Bertini Cascade, Precompound and Intra-Nuclear Cascade of Liège (INCL). Although a recent study has shown that INCL is not predictive enough for ion beam therapy applications yet [99], it was still considered, given that prompt-gamma emission was not taken into account in the said study. After assessing the proton modelling against the experimental irradiation data gathered at WPE, one of those models was used for protons while testing Quantum Molecular Dynamic (QMD), Binary Light Ion Cascade (BLIC), and INCL models for heavier ions. This work focused on the primary particle modelling, although it is acknowledged that other particles may play a role on the prompt-gamma emission, in particular neutrons. In a later chapter (chapter 4), a study comprising a benchmarking of different models for neutron interactions in the context of proton irradiation, shows no compelling evidence that neutron modelling impacts prompt-gamma emission. As such, G4NeutronHPInelastic (less than 20 MeV) and Bertini Cascade (higher than or equal to 20 MeV) were used for neutrons since they are in accordance with the findings of that study.

A dedicated Geant4 simulation code was developed to carry out this work. It describes the experimental setups and allows for switching between hadronic inelastic models for protons and ions depending on the test case. All simulations were performed using Geant4 version 10 patch 02 and a summary of the common physics models can be found in table 3.11. To have a meaningful comparison, the simulated data were selected based on the same energy thresholds applied to the experimental data $(1 \le E \le 7 \text{ MeV})$.

TABLE 3.11: Other Geant4 simulation settings common to the physical models tested

EM	Hadronic inelastic neutrons		Hadronic elastic	Other processes
1.1.11	$< 20 { m ~MeV}$	$>= 20 { m MeV}$	Harrome elastic	Other processes
G4EmStandardPhysics	G4NeutronHPInelastic	G4BertiniNeutronBuilder	G4HadronElasticPhysicsHP	G4DecayPhysics G4EmExtraPhysics G4RadioactiveDecayPhysics

It should be stressed that when there were more than one experimental data set in the same conditions (notably for the proton experiments), only one case was simulated in order to save computation resources. In fact, there are only two cases in such a situation: the experiments using proton beams and the low energy carbon ion ones. For the former, it was decided to use the data from the WPE 160 MeV H^+ (I) experiment with the

LaBr₃:Ce detector. The rationale for this choice is the better spatial resolution of the setup used in this case and the better detection properties of the LaBr₃:Ce detector. On the other hand, for the low-energy carbon ion beams experiments, the choice was to use the data from the BaF₂ detector since it has a bigger volume and thus a higher detection efficiency that is then useful to have more events in the simulations.

3.2.1 Proton irradiation

Table 3.12 shows the four physics lists selected for the Geant4 simulations. For proton irradiation, the modelling of ions heavier than protons was done by BLIC, as it is regarded as the Geant4 standard ion model for the energy ranges used in hadrontherapy treatments. All Geant4 hadronic inelastic models normally employed for proton modelling were included in the study described herein. Although QMD can model protons as well, it is, on the one hand, more often utilised for heavier ions and, on the other hand, a very computationally demanding model. Hence, it was not taken into account. It should also be noted that Bertini Cascade model was considered in this comparison, although it is known for being less accurate for proton dose calculations than Binary Cascade (see e.g. [100]) and for having too simplistic of an approach for modelling prompt-gamma emission [101]. Nevertheless, such a model was included in this benchmarking in order to verify to what extent these issues may affect the longitudinal prompt-gamma emission profiles. In addition, Precompound model was also tested since 1) it is a viable proton model for the energy range and 2) it has been considered for studies related with prompt-gamma emission with reasonable results (see e.g. [102]).

Physics list $\#$	Hadronic inelastic protons	Hadronic inelastic ions
1 – Bertini Cascade	G4BertiniProtonBuilder	
2 – Binary Cascade	G4BinaryProtonBuilder	C 4 Ion Pinamy Cagoodo Dhyrrigg
3 - INCL	G4INCLXXProtonBuilder	G410IIDIIIaryCascader hysics
4 – Precompound	G4PrecoProtonBuilder	

TABLE 3.12: Geant4 simulation settings specific for proton irradiation benchmarking.

Figure 3.34 shows the comparison between the experimental data and the simulation results of the different hadronic inelastic models. It is possible to observe that all the models used overestimate the experimental data, the Bertini cascade model being the worst case. The data show that the overestimation can vary approximately from 92% (Precompound) to 470% (Bertini cascade). Table 3.13 summarises these discrepancies. In addition, it includes a column (*Improvement needed*) that already introduces a quantity used in a later chapter (chapter 5), where the models are investigated and changes in



FIGURE 3.34: Comparison of proton irradiation experimental data with simulations using different Geant4 inelastic hadronic models (see table 3.12).

Geant4 parameters with physical meaning are tested to attain a reduction. Apart from obvious prompt-gamma emission overestimation and contrarily to the experimental data, it is noteworthy that the simulated prompt-gamma profiles show an increased detection of prompt gammas after around 100 mm. The reason for this behaviour is unknown at this moment but it will be investigated in chapter 5.

TABLE 3.13: Comparison of proton irradiation experimental data with simulations using different Geant4 inelastic hadronic models. The comparison is made with the data from the measurement position closer to half proton range, i.e. 70 mm in this case. The error stated is an approximation and it results from the quadratic sum of the error bars of figure 3.34, thus including both statistical and systematic uncertainties.

Inelastic hadronic model	Overestimation $(\%)^1$	Improvement needed $(\%)^2$
Bertini Cascade	470 ± 54	82 ± 9
Binary Cascade	193 ± 23	66 ± 8
INCL	173 ± 21	63 ± 8
Precompound	92 ± 11	48 ± 6

1 (simulation - experimental)/experimental

 2 (simulation – experimental)/simulation

An additional set of simulations was also carried out in order to test a remark made by Verburg et al. [101], claiming that the Tripathi light ion cross section approach is better than the default one (G4ProtonInelasticCrossSection) for proton irradiation at lower energies. The test comprised the change of the class responsible for estimating cross sections for the Precompound model. The result of this test is shown in figure 3.35. No meaningful difference is found in respect to the yields. However, instead of the relatively fast change of the prompt-gamma profile slope at around 100 mm, a steady increase of the yield on the plateau is now observed. With the information available, it is not possible to state that such a change is better regarding the objective of this work. This would require further studies, namely the irradiation of different target materials and the use of different projectile energies in order to assert the advantage of its use.



FIGURE 3.35: Comparison of proton irradiation experimental data with simulations using different Geant4 inelastic hadronic models (see table 3.12) and testing the use of Tripathi light ion cross section approach (G4TripathiLightCrossSection) with the Precompound model.

3.2.2 Carbon-ion irradiation

In this section, the experimental data concerning carbon ion irradiation are compared with the outcomes of simulations making use of different Geant4 hadronic models. The purpose of the benchmarking described in this section is to verify the agreement between simulations and experimental data using the latest release of Geant4 and the default implementation of each hadronic model. A similar study has been done by Dedes et al. [103], who found that tuning one parameter of the QMD model yielded a better agreement with experimental data. Table 3.14 shows the three hadronic inelastic models considered for the simulations with carbon ions while the figures 3.36 to 3.38 depict the comparison between the prompt-gamma longitudinal profiles. Finally, table 3.15 summarises the discrepancies observed in the comparison.

Physics list $\#$	Hadronic inelastic protons	Hadronic inelastic ions
1 – BLIC 2 – INCL	G4BinaryProtonBuilder	G4IonBinaryCascadePhysics G4IonINCLXXPhysics C4IonOMDRhusics

TABLE 3.14: Geant4 simulation settings specific for carbon ion irradiation benchmarking.



FIGURE 3.36: Comparison of experimental data from a 95 MeV/u carbon ion irradiation of a PMMA target with simulations using different Geant4 inelastic hadronic models (see table 3.14).



FIGURE 3.37: Comparison of experimental data from a 310 MeV/u carbon ion irradiation of a PMMA target with simulations using different Geant4 inelastic hadronic models (see table 3.14).



FIGURE 3.38: Comparison of experimental data from a 300 (top) and a 310 MeV/u (bottom) carbon ion irradiation of a water target with simulations using different Geant4 inelastic hadronic models (see table 3.14). Note that both x- and y-axis scales are different for the two plots.

TABLE 3.15: Comparison of experimental data concerning carbon ion irradiation with simulations using different Geant4 inelastic hadronic models. The comparison is made with the data from the measurement position closer to half ion range. The error stated is an approximation and it results from the quadratic sum of the error bars shown in figures 3.36 to 3.38, thus including both statistical and systematic uncertainties.

Inelastic hadronic model	Experiment	Overestimation $(\%)^1$	Improvement needed $(\%)^2$
BLIC	GANIL 95 MeV/u $^{12}\mathrm{C}^{6+}$	129 ± 35	56 ± 15
	GSI 300 MeV/u $^{12}\mathrm{C}^{6+}$	67 ± 15	40 ± 9
	GSI 310 MeV/u $^{12}\mathrm{C}^{6+}$	165 ± 125	62 ± 47
	HIT 310 MeV/u $^{12}\mathrm{C}^{6+}$	346 ± 140	78 ± 31
INCL	GANIL 95 MeV/u $^{12}\mathrm{C}^{6+}$	90 ± 24	47 ± 13
	GSI 300 MeV/u $^{12}\mathrm{C}^{6+}$	84 ± 18	46 ± 10
	GSI 310 MeV/u $^{12}\mathrm{C}^{6+}$	158 ± 120	61 ± 46
	HIT 310 MeV/u $^{12}\mathrm{C}^{6+}$	417 ± 169	81 ± 33
QMD	GANIL 95 MeV/u $^{12}\mathrm{C}^{6+}$	140 ± 38	58 ± 16
	GSI 300 MeV/u $^{12}\mathrm{C}^{6+}$	67 ± 15	40 ± 9
	GSI 310 MeV/u $^{12}\mathrm{C}^{6+}$	166 ± 126	62 ± 48
	HIT 310 MeV/u $^{12}\mathrm{C}^{6+}$	387 ± 157	79 ± 32

1 (simulation - experimental)/experimental

 2 (simulation – experimental)/simulation

The comparison for carbon ion irradiation produced mixed results. On the one hand, the overestimation observed for GANIL 95 MeV/u $^{12}C^{6+}$, GSI 300 MeV/u $^{12}C^{6+}$, and GSI 310 MeV/u $^{12}C^{6+}$ experiments are relatively consistent (considering the error bars for each case). However, there is an excessive overestimation for the HIT 310 MeV/u $^{12}C^{6+}$ experiment when compared with the other cases. Even though there is no clear idea why, it may be related with a larger discrepancy in Geant4 outcomes for the PMMA target at higher carbon ion energy and/or some factor not considered during experimental analysis that could increase the experimental yields. In fact, considering figure 3.33 (page 74), this experiment is the one presenting the lowest yields (although it is a small difference to the other high energy experiments with water targets). An additional study with PMMA targets and high energy carbon ions should be performed to cross check these experimental values.

3.2.3 Discussion

The main conclusion of this study comparing experimental data with the outcome of Geant4 simulations is that there is a systematic overestimation of the prompt-gamma emission yields by the Monte Carlo code Geant4, regardless of the primary particle species, energy, and target considered. This fact has been long observed by numerous published studies (e.g. [97, 101, 103, 104]) for both total prompt-gamma emission and discrete

prompt-gamma emission lines. The distinguishing aspect of the study presented herein is the comprehensive comparison against an extensive set of different experiments and the testing of all possible hadronic inelastic models available in Geant4 within the context of hadrontherapy. However, it is somewhat surprising that the prompt-gamma emission overestimation for the case of incident protons seem higher than the ones estimated for the carbon ion case. Both Binary Cascade and INCL models show an overestimation around 180%, while for the carbon ion cases the overestimation is in the range of 67%-166% (excluding HIT 310 MeV/u $^{12}C^{6+}$ data). One would expect a reversed situation since the prompt-gamma profile for carbon ion irradiation is more affected by the modelling of the other secondaries than the proton case. This issue definitely deserves further studies, namely by assessing the Geant4 modelling of the other particles created after both proton and carbon ion interactions in PMMA and water targets.

3.3 Prompt-gamma profiles – heterogeneous targets

3.3.1 Material and Methods

The experiment was performed at the GANIL facility (Caen, France) using a ¹²C beam of 95 MeV/u. Three phantoms were irradiated: a homogeneous PMMA phantom ($\rho = 1.165 \pm 0.046 \text{ g/cm}^3$) consisting of 27 adjacent slices of $50 \times 50 \times 2.1 \text{ mm}^3$ each, a PMMA phantom in which the sixth slice was replaced by a teflon piece with a thickness of 2.0 mm ($\rho = 2.150 \pm 0.153 \text{ g/cm}^3$) and a PMMA phantom with a 5.6-mm-thick section of lung-equivalent tissue ($\rho = 0.207 \pm 0.005 \text{ g/cm}^3$, CIRS Inc, Norfolk, VA, USA – lung inhale) at the position of the fourth PMMA slice. The average density values were determined by measuring the dimensions and the mass of the slices, while the uncertainties were derived from the uncertainties associated to the measuring devices. The homogeneous case has been already presented in a previous section (section 3.1.2.1) and the setup and acquisition system used was the same of that experiment.



FIGURE 3.39: Pictures of the phantoms used (after irradiation as the yellowing of the PMMA slabs shows evidence of it). Left: homogeneous PMMA phantom; centre: PMMA phantom with the Teflon inserts; right: PMMA phantom with the lung-equivalent material insert.

To distinguish prompt-gamma events from the extensive background of neutrons and scattered photons, TOF discrimination was once more used as in the absolute yields study. This implied an event-by-event registration of the time difference between the detected secondary radiation and the delayed signal of the incoming ion given by the high-frequency pulse of the cyclotron (~ 12.5 MHz). In the TOF domain, events were accepted when they appeared in a time window of 2.67 ns and 3.44 ns centred at the prompt-gamma peak, respectively in the BaF₂ and NaI(Tl) spectrum. These time windows were chosen in order to include all distinguishable events related to prompt-gamma emission (see figure 3.40) and they correspond to, at least, approximately $\pm 2\sigma$ of the prompt-gamma peak. In terms of energy selection, lower limits of 1 MeV and 0.6 MeV were imposed on the BaF₂ and NaI(Tl) spectrum, respectively, a compromise to include as many valid data as possible and to avoid interference with the hardware threshold and the 511-keV annihilation photons. The energy resolution $\Delta E/E$ with a Cs-137 source (662 keV) was estimated to be around 22.2% and 9.2% for the BaF₂ and NaI(Tl) detectors, respectively.

Nonetheless, even considering these conditions, the background events in the promptgamma profiles are still significant [105, 106]. Therefore, the same background subtraction method utilised for the absolute yields study for carbon ion experiments was used (see section 3.1.4.1, page 62).



FIGURE 3.40: TOF spectra from the measurements at two positions: one before the phantom (-9.6 mm, red dashed line) and another inside it (16 mm, blue solid line). These TOF spectra were obtained with the NaI(Tl) detector for the homogeneous phantom and a lower energy threshold of 600 keV was used. For this specific case, the TOF spectrum at -9.6 mm is the reference spectrum for background subtraction for homogeneous phantom (no scaling factor was applied in this figure). The X-axis is relative since no calibration for the axis origin was performed.

As the experimental ion range cannot be directly extracted from the PG profile, the prompt-gamma profile length (PGPL) is proposed as figure of merit. The PGPL is defined as the distance between the positions marking 50% of the PG profile rise and 50% of the PG profile fall-off. The goal of this quantity is to have an absolute measure of the ion range. If only the PG profile fall-off is used, it is not possible to attribute a

detected PG profile fall-off deviation to an ion range shift since the patient may have been mispositioned.

By randomly sampling the yields of the points comprising the rise and fall-off regions within their error bars, the 50% positions are determined using a set of linear fits through the three most relevant data points weighted with their statistical errors. This procedure is repeated several times in order to obtain a distribution of the depths corresponding to the 50% position. The mean and standard deviation of this distribution are then used as the depth of either the entrance rise or the fall-off and the corresponding uncertainty, respectively. Since the PG profiles are not continuous distributions, their lengths depend on the points selected to retrieve the 50% positions. Therefore, three approaches were employed in order to study the impact of the 50% positions retrieval method on this quantity. They rely on the same random sampling but they differ on where the minimum position is. Method 1 uses the minimum yield in the data, method 2 considers the minimum as zero, and method 3 employs as minimum the average of the three profiles. The maximum position is always the maximum yield in the 4-mm range of points considered for the profile entrance rise and fall-off in each profile. The positions of these points are shown in table 3.16. Figure 3.41 shows a schematic representation of this fitting process and the retrieval of the position of the target entrance by means of the data points available. The same principle applies to the retrieval of the position of the prompt-gamma profile fall-off. In the right part of this figure is shown a case where the target entrance position is miscalculated because the measurement points are not in the correct position to allow for a proper position retrieval.

Profile rise	PMMA PMMA-Teflon PMMA-lung	-2, 0, 2 mm -2, 0, 2 mm -0.5, 1.5, 3.5 mm
Profile fall-off	PMMA PMMA-Teflon PMMA-lung	20, 22, 24 mm 18, 20, 22 mm 23.5, 25.5, 27.5 mm

TABLE 3.16: Longitudinal positions considered for the linear fit to estimate either the 50% profile rise or the 50% profile fall-off. Note that the points for the PMMA-lung prompt-gamma profile already include a longitudinal shift that will be discussed in the next section (section 3.3.2).


FIGURE 3.41: Schematic representation of the process used to retrieve the position of the entrance and the fall-off of the prompt-gamma profile (for the sake of simplicity, only the case of the target entrance retrieval is shown). Three points (red circles) are used to make a linear fit (blue line) and the intersection of this function with the 50% height gives the 50% position on the horizontal axis. The illustration on the left represents a case where the 50% position on the profile entrance rise is accurately calculated, while the one on the right shows how a bias d can be introduced in the PGPL estimation when the three points describing the entrance rise are not centred in respect to the target entrance.

In addition, a second method to retrieve the 50% positions was tested. It relies on the fit of the four-parameter sigmoid function first proposed by our collaboration for ion range retrieval in interaction vertex imaging [86] and then also adapted by Janseen et al. [80] to find correlations in simulated data between proton range and the PG profile fall-off. The function is as follows: $a + b \times \operatorname{erfc}[c(z - d)]$, where z is the longitudinal position, a is the minimum, b is the half-maximum, c defines the steepness, and d is the position of the inflection point. The parameter d corresponds then to the 50% position. In order to assure a consistent fitting procedure for the three profiles, a was fixed to zero (it is then assumed that no background remains after background subtraction) and b for the fit of the PG profile fall-off for the PMMA-teflon and PMMA-lung cases was fixed to the PMMA one since there is no physical reason for the prompt-gamma emission to not be the same for the three profiles and the PMMA one has more data points in this region. The entrance rise fit does not include any restriction on b because there are observable differences in the detected yields between the three profiles immediately proximal to the entrance rise that can be attributed to some systematic uncertainty introduced by the background subtraction procedure. The difference between the parameters d after fit on the PG profiles entrance and fall-off is then defined as PGPL. By using a second method, it is possible to compare the outcomes from both methods and discuss the usefulness of each.

A typical number of carbon ions delivered to the phantom for each measurement position is 1×10^{10} with a beam intensity of 2×10^8 ions s⁻¹ (see GANIL 95 MeV/u ${}^{12}C^{6+}$ case in table 3.5, page 62). As comparison, Krämer et al. [98] states a total of 7×10^8 carbon ions in a target volume (around 120 cm³) to deliver an absorbed dose of 1 Gy.

The gathered experimental data were also used to benchmark Geant4 toolkit (version 9.6.p02) using the QMD model for ions heavier than protons and the Binary Cascade model for nucleons. Contrarily to what was done in section 3.2, the purpose herein is not to assess yields. Simulations were used in an attempt to reproduce the experimental prompt-gamma profile length. The profile length is of utmost importance for the prompt-gamma monitoring modality considered in this work, since it may be one of the main quantities to verify during treatment. Thus, with the increasingly growing use of Monte Carlo simulations in the clinical environment and with the experience already obtained from PET ion range monitoring modality may use them as well at some extent. The Geant4 version used in this section corresponds to the latest release available at the time this work was performed.

The ion range was estimated based on a procedure with Geant4 simulations. The density value for each material and the associated uncertainty were used to randomly assign density values to the simulated materials following a Gaussian distribution. Several hundreds of simulations were performed and, for each simulation, the mean projected ion range was retrieved and used to fill a histogram. From this histogram, the mean and the standard deviation were calculated and used as ion range and its uncertainty. Ideally, the different ion ranges should be experimentally estimated using a plane-parallel ionization chamber in water. However, this was not possible due to the nature of the facility where this experiment was conducted.

3.3.2 Results

Figure 3.42 shows the experimental prompt-gamma profiles after a first analysis. The results do not consider background subtraction or any other analysis apart from energy, time calibration and selection of the events inside the TOF windows.

For each detector and for every phantoms, the longitudinal prompt-gamma profile are then reconstructed based on the aforementioned analysis conditions concerning background subtraction. However, after background subtraction, yields up to 5×10^{-8} (BaF₂) and 1×10^{-7} (NaI(Tl)) counts per ion showed up in the profiles while prompt-gamma rays due to secondary nuclear reactions are negligible at this beam energy. It is then assumed that the background subtraction procedure did not subtract all background events, so each profile was corrected with a linear function the first and the last point in order to have a longitudinal profile baseline around zero as it was done in the study for the retrieval



FIGURE 3.42: Experimental prompt-gamma profiles obtained for the PMMA, PMMA-Teflon and PMMA-lung phantoms using the BaF_2 (a) and the NaI(Tl) detector (b). These are the prompt-gamma experimental yields before background subtraction.

of absolute yields (see section 3.1.4.1, page 62). The error propagation due to the two aforementioned procedures was taken into account. The results are shown in figure 3.43 and it is also possible to verify the potentiality of the background subtraction when comparing the profiles of figures 3.42 and 3.43. The profiles are smoother and follow the expected behaviour in the latter better (e.g. there are no significant fluctuations between data points where they should not occur). The zero position corresponds to a first on-line estimate of the phantom entrance centred in front of the collimator opening. After an off-line analysis to refine the positioning of the phantoms based on the position of the profile entrance rise, it was verified that the prompt-gamma profile for the PMMA-lung phantom was shifted in respect to the others. Such a shift can only be attributed to a misposition of the phantom during the experiment. It was found that applying an offset of 1.5 mm on this profile leads to a good agreement on the profile entrance rise position in respect to the other profiles. Hence, hereafter this profile will have this offset (see figure 3.44). This finding emphasizes the ability of the collimated-camera technique to detect such small phantom-positioning errors. Note that only statistical errors are shown to preserve the figure quality. The systematic errors on each data point are of the order of 20% and originate from uncertainties on the calibration of the small NaI(Tl) detector, used for the normalization to the number of primary ions.



FIGURE 3.43: Experimental prompt-gamma profiles obtained for the PMMA, PMMA-Teflon and PMMA-lung phantoms using the BaF₂ (a) and the NaI(Tl) detector (b). The rectangles represent the phantoms with or without inserts (shaded areas). Note a slight shift of the PMMA-lung phantom in respect to the other two profiles.

The impact of the 95 MeV/u 12 C ions was also simulated with the Geant4 toolkit with the same experimental setup. Mechanical structures further away from the setup (e.g. moving table and room geometry) were not taken into account. The simulated data



FIGURE 3.44: Experimental prompt-gamma profiles obtained for the PMMA, PMMA-Teflon and PMMA-lung phantoms using the BaF₂ (a) and the NaI(Tl) detector (b) with the PMMA-lung phantom position corrected with an offset of 1.5 mm. The rectangles represent the phantoms with or without inserts (shaded areas) and the dashed lines show the ion range for each phantom estimated with Geant4.

followed exactly the same analysis conditions and background subtraction procedure as the experimental ones. An evaluation of the simulated data shows an overestimation of the experimental prompt-gamma yields by a factor 2-3 depending on the longitudinal position considered, an effect which was expected after the results presented in section 3.2. Figure 3.45 depicts the direct comparison between experimental and simulated data. An extensive comparison in terms of yields was already performed in this chapter (see section 3.2). The main rationale for having this study here as well is the comparison between experimental and simulated prompt-gamma profile lengths. This is of great interest since it may be one of the main quantities if only ion range is to be considered.



FIGURE 3.45: Comparison of the experimental and simulated prompt-gamma profiles for the PMMA, PMMA-Teflon and PMMA-lung phantoms using the BaF_2 (a) and the NaI(Tl) detector (b).

To allow for a better comparison of the experimental and simulated profile shapes and lengths, the simulated prompt-gamma yields were rescaled using the same factor for the three profiles. This factor was defined in respect to the highest-lying data point just before the fall-off of the PMMA profile. In order to better understand each profile shape behaviour, some positions were simulated without the respective experimental data point. An overview of the comparison between prompt-gamma profiles is given in figure 3.46.

Geant4 simulations were also used to determine the ion range of the 95 MeV/u 12 C beam for the PMMA, PMMA-Teflon and PMMA-lung phantoms. The results are presented in figure 3.43 using dashed lines. For the homogeneous PMMA phantom a range of 20.5 mm was calculated, while for the Teflon and lung inserts ranges of 19.5 mm and 25.1 mm were obtained.



FIGURE 3.46: Comparison of the experimental and simulated prompt-gamma profiles for the PMMA, PMMA-Teflon and PMMA-lung phantoms using the BaF₂ (a) and the NaI(Tl) detector (b). Each simulated profile is rescaled using the same factor for the three profiles. This factor is defined in respect to the highest-lying data point just before the fall-off of the PMMA profile.

A comparison of the simulated ion range and the measured versus simulated promptgamma profile lengths is presented in table 3.17. The data shown in this table take only into consideration the method 1 using the linear functions to estimate the 50% position and then the prompt-gamma profiles length. Nevertheless, the three approaches using the linear function were employed and the difference in regard to the ones of table 3.17 is discussed in the next section (section 3.3.3).

Taking the homogeneous PMMA prompt-gamma profile as a reference profile, it is possible to study the impact of the density changes on the profile lengths. Ultimately, a difference in the profile lengths may be correlated with an ion range shift. Table 3.18 gives the

Ion range (mm)		Prompt-gamma profile length (mm)					
1 Hantom	Simulation	Experiment (BaF_2)	Simulation (BaF_2)	Experiment $(NaI(Tl))$	Simulation (NaI(Tl))		
PMMA	20.75 ± 0.79	21.8 ± 0.2	20.8 ± 0.6	21.9 ± 0.3	20.7 ± 0.8		
PMMA-Teflon	19.39 ± 0.69	19.9 ± 0.2	20.3 ± 0.8	19.6 ± 0.3	19.9 ± 1.2		
PMMA-lung	25.32 ± 0.75	23.9 ± 0.2	25.5 ± 0.9	23.9 ± 0.3	26.6 ± 1.1		

TABLE 3.17: Simulated ion ranges and experimental versus simulated prompt-gamma profile lengths of a 95 MeV/u ¹²C ion beam in the PMMA, PMMA-Teflon and PMMA-lung phantoms and using the linear function to retrieve the PGPL. Only the statistical uncertainties are given.

variations of the simulated ion ranges and the prompt-gamma profile lengths for the PMMA-Teflon and PMMA-lung cases.

TABLE 3.18: Variations of the simulated ion ranges and the prompt-gamma profile lengths with the Teflon and lung-equivalent inserts (the reference case is the homogeneous PMMA phantom). Ion ranges and prompt-gamma profile lengths are given in table 3.17.

Phontom	Ion range (mm)	Prompt-gamma profile length (mm)						
1 nantom	Simulation	Experiment (BaF_2)	Simulation (BaF_2)	Experiment $(NaI(Tl))$	Simulation $(NaI(Tl))$			
PMMA-Teflon	-1.36 ± 1.05	-1.9 ± 0.3	-0.5 ± 1.0	-2.3 ± 0.4	-0.8 ± 1.4			
PMMA-lung	4.57 ± 1.09	2.1 ± 0.3	4.7 ± 1.1	2.0 ± 0.4	5.9 ± 1.4			

The results of the second approach using the sigmoid functions can be seen in the next figures and table. Figure 3.47 depicts the several fits to the data using the sigmoid function, figure 3.48 presents the relation between ion range and PGPL, and table 3.19 shows the outcomes after the fits. For this case, there was no comparison with simulated data since the previous results with the linear fits have demonstrated that the simulations follow quite well the experiments outcomes.

TABLE 3.19: Absolute and relative measurements of the PGPL of a 95 MeV/u 12 C ion beam in the phantoms considered and using the sigmoid function to retrieve the PGPL. The relative measurement is the variation with respect to the homogeneous PMMA phantom. Only statistical uncertainties are given.

	Absolute measurement			Relative measurement		
	Ion range	Profile length (mm)		Ion range	Profile ler	ngth (mm)
Phantom	(mm)	BaF_2	NaI(Tl)	(mm)	BaF_2	NaI(Tl)
PMMA	20.75 ± 0.79	21.16 ± 0.39	20.77 ± 0.63	_		
PMMA-teflon	19.39 ± 0.69	19.23 ± 0.43	18.93 ± 1.10	-1.36 ± 1.05	-1.93 ± 0.58	-1.84 ± 1.27
PMMA-lung	25.32 ± 0.75	25.26 ± 0.37	25.16 ± 0.50	4.57 ± 1.09	4.10 ± 0.54	4.39 ± 0.80

3.3.3 Discussion

When evaluating the prompt-gamma profiles in figure 3.44, a good agreement between the three curves was obtained for the points at the phantom entrance. Furthermore,



FIGURE 3.47: Experimental prompt-gamma profiles for the PMMA, PMMA-Teflon and PMMA-lung phantoms using the BaF_2 (a) and the NaI(Tl) detector (b) and the fits using the sigmoid function.



FIGURE 3.48: PGPL in function of ion range when using the sigmoid functions.

at positions that were not affected by the inserts, e.g. in the plateau and just before the fall-off, similar prompt-gamma yields were recorded. At the inserts positions, clear variations are observed between the different longitudinal prompt-gamma profiles. An increase in the prompt-gamma yield is visible at the position of the Teflon while an explicit dip is present at the position of the lung-equivalent tissue. However, the quantification of the correlation of the prompt-gamma emission with density and material composition is outside the scope of the present study and requires a different approach such as the one followed by Polf et al. [108]. Table 3.17 demonstrates a strong correlation between the ion range and the prompt-gamma profile length since both observables express the same trend when varying the phantom composition, turning the prompt-gamma profile length into an excellent probe for ion range studies.

Concerning the comparison between experimental and simulated data, it is possible to observe that simulations reproduced the general experimental profile shape of the prompt-gamma fall-off. Likewise, the experimentally observed behaviour between the prompt-gamma yield in the position of the inserts was correctly simulated, showing an increase of the prompt-gamma yield at the position of the Teflon insert and a dip for the lung-equivalent tissue. However, simulation results display large discrepancies for the individual data points, thus being inappropriate to predict absolute prompt-gamma yields. Moreover, for all the cases considered, the distal part of the simulated prompt-gamma profiles is always more pronounced than the experimental one when compared with a plateau region. Although the use of Monte Carlo simulations may not be mandatory for a clinical implementation of prompt-gamma monitoring, these findings for Geant4 data may rise some concerns and further studies concerning an hypothetical clinical implementation of this technique are needed. As already briefly discussed in section 3.3.1, the implementation of PET monitoring in a treatment scenario relies on Monte Carlo data, either by using full simulations for estimating the positron emitters distribution or by creating, for example, look-up tables that are then used to estimate such a distribution analytically or to accelerate its calculation.

Even though simulations were not able to predict the absolute yields of the experimental data as expected from the study in section 3.2 (page 78 and thereafter), they do predict with a reasonable accuracy the experimental prompt-gamma profiles length. When comparing the ion ranges and the experimental and simulated prompt-gamma profile lengths, an agreement of around 1 mm is found (vide table 3.17). However, when considering the variation on the ion range and the corresponding variation on the experimental profile lengths in respect to the homogeneous phantom (i.e. a reference profile), disagreements up to 2.6 mm are seen for the PMMA-lung case with the NaI(Tl) detector (vide table 3.18).

Although it may be difficult to deal with such a disagreement in an hadrontherapy treatment monitoring scenario, all indicates that it may result from the method for estimating the prompt-gamma profiles length and, ultimately, from the discrete nature of the experimental data. In the PMMA-lung experimental profile lengths, discrepancies up to 1.7 mm and 0.6 mm (BaF₂ and NaI(Tl), respectively) among the three methods for estimating the profiles length can be found. Furthermore, while for the PMMA and PMMA-Teflon profiles there is a symmetry around zero on the points used to retrieve the 50% position of the phantom entrance, the PMMA-lung one had to be shifted. The phantom entrance is at zero and thus it is expected that the 50% position roughly corresponds to it. By having a symmetry at the position 1.5 mm for the PMMA-lung profile, a bias of the order of this shift is introduced on the method (see table 3.16 for profile rise and the figure 3.41 to look to a case where a bias is introduced). Therefore, the discrepancy on the three methods for estimating the profile length and the bias on the PMMA-lung profile length demonstrate how critical it is to have a convenient data sampling and a robust estimation method of rise and fall-off positions. It may be that the method of the three points with the linear fit is not robust enough and further studies are mandatory to assess other possibilities.

On the other hand, the outcomes of using the sigmoid function are much more satisfactory. For the cases considered, it is possible to observe a strong correlation between ion range and PGPL and no bias is perceived in these results. Figure 3.48 visually shows the strong correlation found. It is then clearly demonstrated that the selection of an appropriate function for the fit is of utmost importance. The present work cannot assert that the sigmoid function used is the most adequate one, but at least shows that this issue requires a dedicated and in-depth study of possible applicable functions.

It should also be stressed the importance of doing this study with a relatively low-energy carbon-ion beam. In these conditions it is possible to study the prompt-gamma profile due mostly to primary particles only, since in this energy range the production of secondary particles is small when compared to higher energies. This allows to understand its impact when higher energies are used and to separate it from the prompt gammas produced by secondaries. In addition, the ion range at this energy is around 2 cm in PMMA, thus, in a clinical situation, it may mean that such a monitoring is already made inside the planning target volume (PTV). Considering the possible systematic errors of these results, the prompt-gamma monitoring with the collimated-camera technique potentially allows for detecting ion range variations as small as 1-2 mm situated at a distance less than 2 cm from the Bragg peak. Further supporting such a claim, for the conditions of the present study, was the observation off-line of a 1.5 mm shift on the PMMA-lung profile in respect to the other two profiles (see figure 3.43). Moreover, a 1 mm ion range shift was clearly visible on the registered prompt-gamma profiles (PMMA vs PMMA-Teflon phantoms, e.g. figure 3.44).

Finally, these measurements were performed with a tightly collimated setup, thus with a high spatial resolution. Camera-design optimizations reported elsewhere [109, 110] show a compromise between spatial resolution and detection efficiency and it is expected that an eventual clinical device may have a poorer spatial resolution. It is then foreseen that a smoother profile is retrieved with unpredictable consequences to the ability of detecting ion range shifts at the scale presented herein.

Chapter 4

Multi-slit collimated camera optimisation

This chapter describes the work developed to optimise a full-size multislit collimated camera based on the TOF technique and focused on the collimator design. It was mainly a Monte Carlo study using Geant4, however, the first step comprised a simulation benchmarking in order to select the most adequate physical models to carry out the optimisation. Contrarily to the previous chapter, where the comparison was centred on the prompt-gamma yields, herein the benchmarking targeted the experimental and simulated TOF information and, in particular, the influence of the neutron-induced events. An extensive discussion concerning the solutions found and the design being constructed is presented.

4.1 Introduction

The use of passive collimating devices for medical imaging is an established procedure for the cases where there is the need to collimate either emitted or transmitted radiation, mainly for diagnostic purposes. As an example, for nuclear medicine imaging, the optimisation of passive collimators relies on geometrical and photon attenuation considerations, since the energy of the incoming particle is known. In any case, it is not possible to have energies higher than the one characteristic of the radioisotope injected in the patient. Moreover, there is no concern about the background since the only source of radiation is the patient. A comprehensive overview on this topic was made by Donald Gunter [111]. The use of passive collimating systems in hadrontherapy, however, needs to respect different conditions in order to be able to take advantage of the information provided by prompt gammas. The energy of the emitted prompt gammas is not fixed and the energy spectrum ranges up to more than 10 MeV [102]. On the other hand, the treatment room contributes with radiation background due to e.g. inelastic interactions of charged particles and interactions of neutrons in the delivery machine nozzle and room walls. In that sense, even the collimator itself may act as a secondary source of radiation.

A key aspect of hadrontherapy monitoring is to be able to find the ion range inside the patient. This means that the aim of the prompt-gamma camera is to detect edges corresponding to the entrance rise and to the fall-off in the prompt-gamma longitudinal profile. For this purpose, unlike for nuclear medicine imaging, a good spatial resolution is not *a priori* required. Likewise, it is not mandatory to have three-dimensional information, given that essentially the longitudinal ion path is relevant. One may consider the potential usefulness of retrieving three-dimensional images, however such a task is outside the scope of this work. Therefore, there is no need to ponder about a multi-hole collimator system as often used in nuclear medicine, but rather focus on a multi-slit one with parallel slabs and positioned orthogonally to the beam axis.

This work was based on Monte Carlo simulations, thus there was the need to verify their accuracy in this context, which was achieved by a benchmarking with experimental data. In the optimisation process, the TOF technique was used in order to achieve a better camera performance due to the improved SBR. Moreover, this study aimed not only at finding a solution that yields a good performance, but also at understanding the trends of the camera geometry that drive its performance. The following sections present the methods employed to optimise a parallel multi-slit camera, with emphasis on the collimator, the expected performance based on Monte Carlo simulations, and a discussion about the potentiality and possible limitations of using such a collimated camera for hadrontherapy monitoring purposes. Although this work was mainly focused on proton therapy monitoring and on data coming from experiments with protons, all the procedures followed should also be applicable to other ion species, namely carbon ions.

4.2 Methods

The optimisation of a parallel multi-slit camera is not a trivial procedure mainly due to the complexity of the physical processes taking place during a hadrontherapy treatment, as shown in the previous section. The most adequate strategy to optimise a device in this scenario is based on Monte Carlo tools. However, only if the trends in the optimisation process are understood, i.e. how the variation in each parameter influences the final design and its performance, it is possible to drive further developments.

Assuming that the physical models implemented in Monte Carlo tools are accurate enough, one could attain a high level of accuracy in the expected performance. Nevertheless, Monte Carlo simulations require large amounts of computing time, which leads to a lack of flexibility of the optimisation process for e.g. the fine tuning of the camera geometrical parameters. Such a flexibility is crucial if e.g. some mechanical constraints are met during the construction phase and a fast adjustment of the camera design is needed.

In this context, the present work comprised three stages. The first addressed a benchmarking of the Monte Carlo tool chosen in order to select the best physical models for this application. The second stage focused on the optimisation by means of Monte Carlo simulations. Since there was no *a priori* knowledge about the parameters that influence the camera performance the most, it was decided to simulate multiple random geometries constrained by meaningful boundaries. After this point, it was possible not only to choose the camera geometry with the best performance among the ones simulated, but also to understand the trends in the geometrical parameters that impact its performance the most. Finally, the third stage used all these simulations as a training data set for a multivariate regression analysis in order to have an analytical tool able to predict camera performances. Such a tool is not intended for further optimisation of the device but rather to provide fast and accurate results within the region considered in the training. One could argue that this parametrisation could be used to achieve better camera performances, however it would be at the cost of extrapolation and it would always require simulations to cross-check the result.

The Monte Carlo simulations were carried out with the Geant4 toolkit [82], version 9.6.p01, and the regression analysis was made using a built-in library in ROOT framework [112] called TMultiDimFit. The Geant4 version used in this chapter corresponds to the latest release available at the time the present work was performed.

Unless otherwise stated, all results presented herein only consider events with an energy deposition higher than 1 MeV in order to improve the signal to background ratio of prompt gammas.

4.2.1 Geant4 benchmarking

The Geant4 benchmarking comprised two steps, the first one to rule out the most inaccurate hadronic physics models and the second one to make an in-depth study of the Geant4 model outcomes. The decision to do the first step was to avoid spending too much computing resources with models that could be excluded in a more simplistic analysis.

Geant4 is a toolkit in which the user is responsible for selecting the most appropriate physics models for the given problem. The electromagnetic models available should not have a critical impact on the results since their overall precision is around a few percent [113, 114]. On the other hand, the hadronic models, especially those concerning the prompt-gamma emission, may influence significantly the outcome, as already demonstrated in chapter 3. Although these studies deal essentially with carbon ions, the latter also suggests an overestimation of prompt-gamma yields for proton irradiation. Therefore, a comprehensive study about Geant4 limitations pertaining to protons as primary particles is essential to not only be able to select the most adapted set of physical models for the simulations, but also to discuss more thoroughly the expected camera performance.

User-defined physics lists were utilized in order to test a broad set of physics models, raising questions concerning user-related errors in the physics list definition. As a consequence, each step of Geant4 benchmarking also included two built-in reference physics lists (i.e. defined by the Geant4 developers) to ensure the absence of physics models inconsistencies that could be explained by user-related errors.

First selection of physical models.

A 160 MeV proton beam impinging on a cylindrical PMMA target was simulated for several hadronic physics models (tables 4.1 and 4.2). The target had a radius of 75 mm and a length of 200 mm. The same target was used throughout this study for both simulations and experiments. In this simulation the information concerning all photons able to escape the target was stored in a file for further analysis. By applying an angular acceptance constraint on the data, one is able to select only the photons that have the highest probability of being detected by a hypothetical collimated camera. These prompt gammas are, in the context of this monitoring technique, the signal of interest and it is utterly fundamental to have the best description of the signal. The outcomes of the simulations with the different models were then compared and those considered the best for this application were selected for the next step.

Among the hadronic physics models selected for this first selection, the Bertini Cascade model with its own pre-equilibrium and de-excitation implementations was not considered herein due to its excessive overestimation, already demonstrated in chapter 3. However, the combination of the Bertini Cascade with the Precompound model (BERT+PRECO in table 4.1) was tested to verify if the use of a different pre-equilibrium and de-excitation models has an effect on the outcomes.

Contrarily to the study performed in chapters 3 and 5, here the aim was to carry out an in-depth study of the impact of selecting different physics lists on the TOF spectra. This is the reason why the neutron models assume a special importance in this chapter.

TABLE 4.1: Naming conventions for each set of Geant4 physics models tested. For simplicity reasons the designation of each model in this table was abbreviated, thus *QMD* corresponds to G4QMDReaction, *BC* to G4BinaryCascade, and *BERT+PRECO* to G4CascadeInterface using G4PreCompoundModel for pre-equilibrium instead of the built-in implementation in the G4CascadeInterface. By default, BC is followed by the G4PreCompoundModel while QMD has no equilibrium phase. The de-excitation phase is common to all the collision model. Apart from the ones described here, the reference physics list QGSP_BIC_HP was also used.

	Hadronic inelastic									
Name	Protons	N	leutrons	Othera						
	FIOTOHS	$> 20 { m ~MeV}$	$< 20 { m ~MeV}$	Others						
phys1	BC	BC								
phys2	BERT+PRECO	BERT+PRECO								
phys3	QMD	BC								
phys4	BERT+PRECO	BERT+OWN								
phys5	QMD	BERT+OWN	G4NeutronHPInelastic	QMD						
phys6	QMD	QMD								
phys7	BC	BERT+OWN								
phys8	BC	BERT+PRECO								
phys9	BERT+PRECO	BC								

 TABLE 4.2: Other Geant4 simulation settings common to all user-defined sets of physical models tested.

EM	Hadronic elastic	Other processes
G4EmStandardPhysics_option4	G4HadronElasticPhysicsHP	G4DecayPhysics G4EmExtraPhysics G4RadioactiveDecayPhysics

In-depth study of selected physics lists.

After selecting the most promising sets of physical models, Geant4 simulation outcomes were compared with experimental data. For a more thorough analysis, TOF data was used, which allowed for the analysis of both background and signal behaviours by comparing an experimental TOF spectrum with a simulated one.

The experimental data selected to pursue this work was the WPE 160 MeV H^+ (II) already described in section 3.1.1.2. The rationale for the choice of this data set was the setup configuration that resembles a possible clinical camera the most, i.e. no shielding. This issue is of utmost importance due to the focus on the TOF technique. Only the data from the LaBr₃:Ce detector was considered. The other detector is too thin to provide a good insight regarding background behaviour.

4.2.2 Simulation of random camera geometries

The purpose of simulations was to obtain the longitudinal profile resulting from a given set of geometrical parameters and to estimate the corresponding precision. This allows for 1) finding a camera design able to yield a good performance (precision), 2) trying to understand the trends that drive precision, and 3) yielding the input for the regression analysis by relating the precision obtained for a given simulated profile and the different geometrical parameters. The simulations of the random geometries were carried out with only the most accurate set of physical models among the tested ones.

The concept of precision in this context was developed by Roellinghoff et al. [76] and it is related to the uncertainty in finding the true value of the position of the prompt-gamma profile fall-off close to the end of the ion range. It is also intrinsically associated with the overall performance of the camera in estimating the ion range for a given number of ions. The method for retrieving the precision relies on having a reference profile with high statistics which, in turn, is fit by a non-uniform rational B-spline (NURBS) function in the region of the profile fall-off. The high statistics profile is then sampled into lower statistics profiles corresponding to the expected statistics of a given number of incoming protons and the NURBS function is used to fit such a low-statistics profile. This function has only one degree of freedom that corresponds to the beam axis direction, thus yielding a deviation from the reference profile mainly driven by statistical fluctuations. The process is repeated multiple times and a histogram of these deviations is built. Afterwards, the standard deviation of this histogram is stored in a second one and the process is repeated through several iterations. The precision is then the mean value of the second histogram and the precision error (statistical) corresponds to one standard deviation.

Although the notion of precision was described in terms of the fall-off position, the same method can be applied to the prompt-gamma profile entrance rise, thus retrieving the target entrance position. With the combined information from the entrance and fall-off positions it is possible to estimate the prompt-gamma profile length. All these quantities are essential to understand how to use this technique in a clinical scenario. Ultimately, the goal is to determine the ion range inside the target, which is correlated to the prompt-gamma profile length, but a reference measurement of the point where the incoming beam enters the patient is also mandatory. Unless stated otherwise, precision refers to the precision in finding the position of the prompt-gamma profile fall-off.

The detector considered for simulations was a bismuth germanium oxide (BGO) monoblock with dimensions of $50 \times 100 \times 250 \text{ mm}^3$ (x,y,z and considering the beam axis as the z-axis). This kind of scintillator presents the following advantages: a relatively good timing resolution with high energy photons (around 3 ns FWHM), no intrinsic radioactivity, and moderate cost. For simulations, a TOF selection window of 4 ns centred on the prompt-gamma peak was applied. The position of each event in the scintillator was estimated by the energy-weighted position of interaction. The collimator material was set to be the tungsten alloy used for some of the experiments (DENSIMET[®] 185). In order to avoid any edge effect in the detected events, the collimator was higher and longer than the detector. Care was taken to always have slits with the same size even at the borders. That is the reason why, in figure 4.1, the collimator length has a minimum of 300 mm and not a fixed value. The length of the collimator and the number of slits depend on the randomly sampled width of slits and slabs. The ranges for the random sampling of each geometrical parameter are presented in table 4.3.

TABLE 4.3: Ranges of values considered for each geometrical parameter.

Geometrical parameter	Range (mm)
Slit width	[0.5 - 7.5]
Slab width	[0.5 - 7.5]
Collimator thickness	[50-200]
Distance from beam axis to collimator front face	[300 - 1000]
Distance from beam axis to detector front face	[360 - 1060]

Another important remark is the potential influence of the spatial resolution on the camera performance. This point is not well known yet and requires an extensive study to understand it, which is outside the scope of the present work. However, it may play an important role in the camera performance (further discussion in section 4.4). In this context, it is also not clear how spatial resolution should be defined. Again, a detailed study would probably be needed for determining the most meaningful quantity and the retrieval method. Nevertheless, such a quantity should be correlated with the geometrical field of view (gFOV) of the collimator on the target (slit width plus two penumbra regions estimated by the geometrical parameters of the camera). Thus, the optimisation includes a constraint on the gFOV, which cannot be greater than 25 mm. The decision to take this value was a choice based on the ultimate goal of this camera: to be able to monitor ion ranges as short as a few centimetres. The main reason for not using the FOV as described in chapter 3 (see page 66) was the time needed to estimate it for each random camera geometry. In addition, the definition given for FOV in chapter 3 could not be directly applied herein since it concerns single-slit experiments, in which the collimator penetration is not a critical issue.

Additional constraints were implemented in order to ensure that the gFOV from neighbouring slits overlaps in the target. Such a constraint guarantees that the entire target around the beam range is seen through the slits of the collimator. The study of an optimal overlap was considered as being outside the scope of this work.



FIGURE 4.1: Schematic representation of the geometry used for the simulations (not at scale). The designations used in this figure are self-descriptive except for the geometrical parameter P that refers to the geometrical penumbra of a slit.

During the analysis of the simulated geometries a binning equal to the slit width plus the slab width (i.e. the collimator pitch) was considered for the longitudinal profiles.

In total, 14730 random geometries were simulated. A schematic representation of the geometry used for the simulations can be seen in figure 4.1.

4.2.3 Monte Carlo data analysis

The Monte Carlo data were analysed in terms of the device geometrical parameters and their relation with the precision. In order to further understand the trends driving the precision, four additional parameters were used: 1) the gFOV, 2) the collimator pitch, 3) the collimator weight, and 4) the collimator fill factor. All the definitions except that of the collimator weight can be seen in equations 4.1 to 4.3. In these equations, the naming of the parameters follows the same convention as for figure 4.1 except for axisColl which refers to the axis-collimator distance.

$$gFOV = slit + 2P = slit + 2\left(axisColl \times \frac{slit}{thickness}\right)$$
(4.1)

$$pitch = slit + slab \tag{4.2}$$

$$fill \ factor = \frac{slab}{pitch} \tag{4.3}$$

The calculation of the weight of the collimator assumed a device with at least 30 cm width, but in a way that slabs always have the same size (i.e. the slabs at the extremities are not cut to obtain exactly a 30-cm-long collimator).

Finally, this analysis assumed the expected statistics for a hypothetical distal pencil beam in an active delivery system with 5×10^8 protons, which somewhat overestimates what can be expected during a real treatment. The number of protons of a typical spot in a distal layer for a prostate treatment is of the order of a magnitude of 1×10^8 ([72, 76, 115]). The relatively large number of protons chosen had the intention of completely avoiding the issue of outliers due to low-statistic profiles [76] or other statistical artefacts. Nevertheless, as already discussed by Roellinghoff and colleagues, the precision in an outliers-free region is proportional to the inverse of the square root of the number of protons, so any camera optimised for high statistics should remain optimal for lower statistics at least down to a number of protons for which statistical artefacts are negligible. By comparing the height of the experimental [76] and simulated detectors (this work), we estimate that the minimum number of protons for an outliers-free region for the present work is around 4×10^7 protons.

4.2.4 Multivariate regression analysis

The regression analysis was performed using a built-in routine available in the ROOT framework called TMultiDimFit. This routine addresses the problem of multidimensional fits in physical sciences and it is an extension of the least squares fitting to higher orders by relying on polynomials [116, 117]. In order to use it, one needs to select appropriate initial parameters. When it is expected that the data should follow a given theoretical description, the parameters may be defined accordingly. However, for this application there was no clear idea of a mathematical model that could be used. The most problematic parameters in this case are the maximum number of polynomials in the final function and the maximum order of each polynomial. Therefore, it was decided to randomly select those parameters based on meaningful ranges inferred from the documentation and examples [117]. Those ranges are shown in table 4.4.

TABLE 4.4: Ranges of values considered for the two TMultiDimFit parameters studied.

Parameter	Range
Maximum number of terms in each polynomial	[50-150]
Maximum polynomial order	[3-10]

The inputs for the multivariate regression analysis were the five independent variables corresponding to the different geometrical parameters considered (table 4.3) and the

precision obtained with such geometrical parameters as a dependent variable. The routine is expected to yield a function describing the relationship between precision and the camera geometry. In order to avoid introducing a bias in the procedure, only 35% of the results coming from simulations (randomly selected) were used for the TMultiDimFit training, while all data were used for the goodness of fit. The selection of the best model was made by considering the function yielding the minimum error (i.e. sum of squared residuals) among those with a reduced χ^2 over the testing sample in the range [0.99-1.01]. Hence, this selection procedure avoids model over-fitting and, at the same time, only models fitting the data properly are chosen. In turn, the minimum-error criterion helps in the selection among the possible functions by giving an indication about the accuracy of the function in following the data.

The parametrisation was then tested against new Monte Carlo simulations (i.e. different from the ones used for training and goodness of fit) of camera geometries with parameters around some selected cases. The selection of the cases to test is the result of a cluster analysis of the Monte Carlo data assisted by the silhouette method [118] in order to assert the robustness of the clustering. The cluster analysis partitions the data into several groups (i.e. clusters) based on dissimilarities and similarities among them. Usually, this grouping method uses a measure of distance between each datum to assign a given datum to a given cluster. In turn, the silhouette method relies on calculating an average distance between a datum and all the other data inside the same cluster and then comparing it with an average distance between the same datum and all the other data in the other clusters. After the clustering, each selected case corresponds to a centroid (i.e. mean position of all the data inside a cluster). An upper limit of 1.5 mm on the allowed precision was applied for this test, since the goal is to obtain a camera design with a precision better than that value. This analysis was done using MATLAB^(R).

4.3 Results

4.3.1 Geant4 benchmarking

First selection of physical models.

The proposed camera aims at detecting gammas emitted perpendicularly to the beam axis after traversing a collimating device. Hence, as a first selection, it is important to verify how each set of physical models behave constrained by a similar angular restriction along the beam axis. From the simulated data on the particles escaping the target after



FIGURE 4.2: Longitudinal profile of the photons induced by an irradiation with 160 MeV protons and escaping the target after a polar angular selection considering the range [89°-91°]. No energy selection was applied.

irradiation, gammas were selected and an angular constraint was defined. The outcome can be seen in figure 4.2, where the longitudinal profile of the escaping gammas after being constricted to a polar angle in the range $[89^{\circ}-91^{\circ}]$ is shown.

The results show unequivocally that all sets of physical models produce similar profiles. These results were already partially expected based on the simulations performed in chapter 3. However, including the Bertini cascade with the G4PreCompoundModel has shown that the extremely high yields observed when using the default Bertini cascade model can be reduced to a level for which the yields are comparable to those of the other models tested. The results are also important in demonstrating that neither the neutron nor the GenericIon modelling seem to have a significant impact, otherwise it would be possible to distinguish the outcomes of those three cases. Such observation was already expected since a primary proton in this energy range does not create a significant amount of those particles. Thus, for selection purposes in this context, only the proton modelling should be of interest.

In table 4.5 the different physics lists are compared regarding their CPU time. One could argue that neither the results of the test used nor the CPU time are good quantities to discard some of the physics lists. However, the next stage is the benchmarking with experimental data, for which simulations with a sufficient number of events are required in order to allow for a meaningful comparison. In face of the available computing resources, only a few should undergo such benchmarking.

The reference physics list QGSP_BIC_HP should be selected to assert the absence of user-related errors. From the remaining lists it is reasonable to exclude those based on the Binary Cascade as it is already included in the reference physics list. Both the QMD-based and the ones with Bertini Cascade with G4PreCompoundModel are still a possibility. However, the CPU time required for the former is three-fold that for the latter without obvious advantages for the test considered. The selection at this point was somewhat arbitrary because the CPU time differences are of the order of a few percent (e.g. around 2% between *phys4* and *phys9*). Nevertheless, due to the lack of other criteria, *phys4* was selected since it was the fastest among the sets of physics lists using the Bertini Cascade with G4PreCompoundModel for proton modelling.

TABLE 4.5: CPU time needed for each set of physical models averaged over ten independent simulations. Although these values are machine-dependent, they should give a relative measure of comparison since the time estimations were made in the same machine.

Name	Average CPU time per primary (ms)
phys1	2.807
phys2	2.731
phys3	7.456
phys4	2.670
phys5	7.469
phys6	7.692
phys7	2.811
phys8	2.876
phys9	2.719
QGSP_BIC_HP	2.181

In-depth study of the selected physics lists.

The experimental data reflect the beam time structure of the cyclotron installed at WPE, which has a high-frequency (HF) signal around 106 MHz, thus consisting of proton bunches with a period of 9.4 ns. The procedure to obtain the simulated data followed several steps. First, the experimental setup was simulated in Geant4 and the energy deposition and TOF of each event with energy deposition in the detector was recorded. No beam time structure was considered at this stage. During the experiment, the electronics were tuned to use as a STOP signal one in every five HF pulses, thus allowing for a TOF spectrum range of around 47 ns. To emulate the beam time structure, the simulated recorded events were then randomly assigned to one of the possible five proton bunches. Finally, the experimental number of incident protons (using the ionisation chamber and with dead time correction) and the number of protons are used to normalise experimental and simulated data, respectively. The results of such a treatment are shown in the figures comparing experimental and simulated TOF spectra (figures 4.3 and 4.4).

By analysing figure 4.3, it is possible to find three TOF components (indicated by arrows). The most obvious one corresponds to prompt-gamma events (brown arrow) since before and after the target this component is almost negligible but for a measurement position inside the target and the proton range it becomes prominent. Note that this component is shifting along the target since the distance travelled by protons is different for the

different longitudinal positions (the TOF STOP signal is always fixed since it is defined by the cyclotron HF and only the target moves on top of the moving table). A second component is the neutron-associated events coming from the target. This component is pointed out by a green arrow in figure 4.3. It can be seen that this component increases along the target and it is explained by the fact that neutrons are preferably emitted forward due to momentum conservation. Finally, there is a component for which its contrast (i.e. difference between its maximum and minimum before the prompt-gamma events) and time position remain constant (magenta arrows). We realised that the time between the prompt gammas and this component should correspond to events coming from inside the nozzle (that was not included in the simulations). In the sequence of such a finding, IBA provided the full details of the nozzle in terms of geometry and materials. Note that this component is difficult to be observed in the simulations, mainly due to lower statistics.

Another remark for figure 4.3 is the fact that the simulated TOF spectrum baseline is lower than the experimental one. There are two possible explanations: 1) the simulations underestimate the background and 2) the geometry is not simulated with enough detail (e.g. the room was not simulated, the composition of the materials may in reality be different from those used in Geant4). Although it is reasonable to consider that the two hypotheses are playing a role, the fact that the simulated baseline is always the same relatively to the experimental one, regardless the target position, is an indication that the most critical aspect is the definition of the geometry. Henceforth this underestimation will be called room component.

In figure 4.4 it is possible to visualise the effect on the TOF spectra of applying a constant function to the simulated data. The results of the simulations with the nozzle description are also depicted in this figure. One can see that the TOF spectrum component is now present in the simulations, thus validating the assumption of the detection of nozzle-related events.

The finding of the room component is indeed very important since the aim of using TOF is to improve the SBR. It is of uttermost importance to have a good description of both the signal and the background or at least to be aware of the limitations of the simulations and then conclude based on that. Therefore, a constant function was applied to the simulated data used in the optimisation since it is a reasonable approach to compensate, at least partially, this effect. The room component was assumed to be linearly dependent with the detector volume and it was added to the simulated data for the optimisation.



FIGURE 4.3: Experimental and simulated TOF spectra for three target positions. The position zero corresponds to the target entrance and the target has a length of 200 mm. Note that the projected range of 160 MeV protons in PMMA is 152 mm. The arrows point to different TOF components. For simplicity reasons, the arrows consider only the TOF components of a single proton bunch.



FIGURE 4.4: Experimental and simulated TOF spectra for three target positions for which the nozzle was simulated and an offset was applied to the simulated data. The offsets used were 6.2×10^{-10} and 3×10^{-10} counts per proton per 0.1 ns, respectively for *phys4* and QGSP_BIC_HP. The position zero corresponds to the target entrance and the target has a length of 200 mm.

Globally, Geant4 was able to describe the TOF spectra background shape with a reasonably good agreement for both physics lists (*phys4* and QGSP_BIC_HP). However, the reference physics list showed a higher discrepancy in terms of background shape for the positions inside and especially after the target when comparing the relative amplitude of prompt-gamma and neutron-related TOF components. The prompt-gamma signal is

overestimated in both cases, although a better agreement is found for the reference physics list. Concerning the *phys4* case, the disagreement is approximately 38% for the point measured at 100 mm, therefore any precision values stated herein should be addressed with some caution since they may also be overestimated. In fact, all the results presented in the work of Roellinghoff and colleagues [76] show that the precision as defined for this study is inversely proportional to the signal, hence if the signal is reduced by some factor, the same detrimental factor in the precision is expected.



FIGURE 4.5: Experimental and simulated longitudinal prompt-gamma profiles after applying the offset to the simulated data and using a TOF window of 4 ns centred on the TOF prompt-peaks. The error bars due to the statistical error are not visible since they are within the markers. The position zero corresponds to the target entrance and the target has a length of 200 mm.

Despite the better agreement regarding the signal yield for the reference physics list, *phys4* shows a better description of the background shape. Since the impact of the signal on the precision is known but not the possible effect of a worse background description, *phys4* was selected for use in this work. This issue is more critical if one compares TOF and non-TOF data. Even if an in-depth study of the origin of the overestimation by simulations is outside the scope of the present investigation, it is reasonable to assume that the problem may be related to the Binary Cascade physics description since it is the critical change concerning hadronic physics between the QGSP_BIC_HP and *phys4* for this energy range. This issue is partially studied in chapter 5.

4.3.2 Monte Carlo data analysis

Figure 4.6 depicts the behaviour of the precision for each geometrical parameter.

Although the results shown in figure 4.6 can be used to verify some possible trends, each plot shows only how the precision changes for a single parameter. It is reasonable to



FIGURE 4.6: Precision versus a single geometrical parameter: a) slit width, b) slab width, c) thickness, d) distance from beam axis to collimator front face, and e) distance from beam axis to detector front face. Each entry is normalised to the histogram binning. Camera height: 100 mm.

assume that a combination of parameters may also play a role in the precision behaviour. Hence, figure 4.7 depicts some other design parameters that feature a combination of single geometrical parameters.

Table 4.6 presents several camera configurations following three different cases (endpoints). The next list describes each case considered.

Case 1: best precision on the fall-off position

Case 2: best precision on the profile length

Case 3: best precision on the fall-off position with a gFOV lower than 15 mm

Figure 4.8 depicts the simulated longitudinal prompt-gamma profiles from the two geometries presented in table 4.6. In order to better understand the shape of the profiles, each one was divided in a stack of two components according to the particles exiting the target: the detected events due to photons and the neutron-related events.



FIGURE 4.7: Properties of the camera design and their relation with precision: a) gFOV, b) collimator pitch, c) collimator weight per centimetre height, and d) collimator fill factor. All these parameters except the collimator weight were defined in equations 4.1 to 4.3. Each entry is normalised to the histogram binning. Camera height: 100 mm.

 TABLE 4.6: Several camera configurations based on different endpoints. Concerning the precision values, the statistical uncertainty for one sigma is presented inside brackets.

 All the values presented are in millimetres. Camera height: 100 mm.

Case	Precision fall-off	Precision entrance	Precision profile length	gFOV	Slit	Slab	Thickness	Distance axis-collimator	Distance axis-detector
1	0.59(0.06)	0.66(0.09)	0.88(0.11)	23.6	5.4	2.6	180.2	303.7	485.3
2				- sar	ne as	case 1	_		
3	0.70(0.08)	0.87(0.12)	1.12(0.14)	13.1	3.0	2.1	190.9	322.3	516.5

4.3.3 Multivariate regression analysis

After selecting the best parametrisation following the method detailed in section 4.2.4, a cluster analysis was carried out on the Monte Carlo data. The clustering served as a method to select geometries to be tested against the parametrisation. The minimum number of clusters considered was three and the maximum ten. The silhouette method always yielded three clusters with the highest silhouette value. Hence, a three-cluster approach was followed for the input data. Table 4.7 presents the three centroids found. Around each centroid several Geant4 simulations were performed for which only one geometrical parameter was changed. Figure 4.9 shows the result of such a benchmarking.



FIGURE 4.8: Prompt-gamma profiles from the configurations presented in table 4.6, respectively a) and c) cases 1 and 2, and b) and d) case 3. The top profiles are separated in photons and neutron-induced events and correspond to the maximum simulated statistics $(4 \times 10^9 \text{ protons})$. The distinction between types of events considers the particle exiting the target. The bottom profiles use a clinically-relevant amount of incident protons $(1 \times 10^8 \text{ protons})$ as already discussed in section 4.2.3 and the error bars shown are for one standard deviation. The precision obtained for this statistic is $1.30 \pm 0.18 \text{ mm}$ and $1.66 \pm 0.23 \text{ mm}$, respectively for the cases depicted in c) and d). The bin size is equal to the collimator pitch. The dashed line represents the proton projected range in the PMMA target. It should be noted that the bottom profiles result from the scaling of the data from the top ones and not new simulations corresponding to the considered number of protons. The purpose was to estimate the average number of counts in each bin along with the expected 1σ error bars.

TABLE 4.7: Centroids retrieved after clustering. All the values presented are in millimetres.

	Slit	Slab	Thickness	Distance axis-collimator	Distance axis-detector
Centroid cluster 1	3.22	2.11	170.5	421.2	813.3
Centroid cluster 2	3.55	5.49	155.6	377.2	723.9
Centroid cluster 3	2.32	2.60	112.2	384.6	646.8

4.4 Discussion

The present work followed three main stages: 1) comparison of Geant4 simulations with experimental data and 2) camera design study for online monitoring in proton therapy based on Geant4 simulations, and 3) parametrisation of the simulation results in order



FIGURE 4.9: Precision values obtained using the parametrisation and corresponding to the variation of a single geometrical parameter while keeping the others constant: varying a) slit width, b) slab width, c) thickness, d) distance from beam axis to collimator front face, and e) distance from beam axis to detector front face. Geant4 simulations are also plotted. The curve coming from the parametrisation is only plotted for the combination of geometrical parameters for which it was trained.

to have a fast and accurate tool that can replace the time-consuming simulations for preliminary studies (given that the camera geometrical parameters to test are inside the range considered for the parametrisation training, otherwise all simulations must be done).

The dimensions of the camera considered for optimisation should also be carefully examined. The camera for optimisation in this work has a height of 10 cm, but most likely a final device will be higher, thus increasing the amount of signal detected. On the other hand, the number of protons per spot considered in this optimisation may be considered as large, even for a distal one. Ultimately, these questions may only be answered with e.g. the study of several treatment plans to verify what is a reasonable spot dose to monitor and to have a camera with dimensions matching that requirement.

Due to the complex nature of the problem addressed in this work, Monte Carlo simulations were used to find a set of camera geometries able to provide millimetric precision. Table 4.6

presents the geometrical parameters that allow for yielding two complementary solutions: one aiming to obtain the best precision and another considering the best precision achievable with a gFOV lower than 15 mm. Although gFOV is not directly spatial resolution, it should have a similar tendency. However, these results are affected by the inaccuracy of Geant4 in predicting prompt-gamma emission yields. The inelastic hadronic model used herein was the Bertini Cascade with the Precompound model, which predict similar yields to the Binary Cascade (see figure 4.2). Based on the results of the Binary Cascade presented in chapter 3 (section 3.2.1, page 79) and assuming that no significant modelling changes occured between Geant4 versions, it is therefore possible to assume that the simulated longitudinal profiles have a signal overestimation of 193%, thus a signal reduction of 66% is expected in a real situation. Such a reduction will necessarily have a negative effect on the precision. In any case, the quantification of this effect cannot be performed without further experiments since the neutron-associated events may also have different yields in respect to the simulated ones, which will affect the real precision attainable with the multi-slit device.

Another goal proposed in this study was to obtain meaningful information about the geometrical parameter trends driving the precision. It can be observed in figure 4.6 that thicker collimators seem to slightly favour better precisions. However, the geometrical parameters that influence the precision the most are the slit width and the distances from the beam axis to the collimator and to the detector. For those three parameters, the precision is improved by changing them towards a higher camera efficiency, thus making it the most important camera characteristic driving the precision. In any case, such a finding must be treated with reservation since increasing the slit width will inevitably worsen the expected spatial resolution with an as yet unpredictable impact in face of heterogeneities or ion range shifts due to unexpected morphological changes near the end of the ion path. Moreover, the ability to position the camera closer to the patient is limited by the treatment being considered (e.g. a head vs. a prostate treatment), by the treatment room configuration and by the TOF-capabilities from both detectors and signal processing modules. In addition, a higher background is expected as the distance between the patient and the camera decreases. In order to fully address these issues, further experimental work with a full-size prototype is needed. Figure 4.9 also supports these findings, except for the case of the distance from the beam axis to the collimator, where no significant variation is observed. It is not clear why, but it is reasonable to assume that this parameter does not have an impact on the precision for the range of parameters considered.

Figure 4.7 provides further insights regarding the trends in the geometrical parameters. The most striking information comes from the quantities that correlate slab and slit widths (i.e. collimator pitch and fill factor). While the slab width alone does not produce a significant effect on the precision, it can be seen that the best precision values are obtained for a collimator pitch between 6 and 8 mm, and for fill factors between 0.3 and 0.6 mm. An important and interesting remark is that the camera design that corresponds to the best precision has a collimator pitch and a fill factor of 8 mm and 0.325, respectively. Furthermore, a high collimator fill factor (> 0.7) shows a strong detrimental effect on the precision. Concerning gFOV, the trend is to have better precisions with a better camera efficiency, while the collimator weight does not have an obvious impact on the precision, except for very light (< 2 kg/cm) and very heavy (> 7 kg/cm) collimators for which the precision is generally worse.



FIGURE 4.10: Entrance and fall-off precisions from the simulated camera geometries. Each entry is normalised to the histogram binning.

Although most of the discussion is centred on the precision in finding the prompt-gamma fall-off position, the precision in the retrieval of the entrance position is also of utmost importance. The device being developed aims at registering all events along the ion path, thereby providing a full prompt-gamma profile. With such a profile it is possible to retrieve the ion range by making use of both the entrance and the fall-off positions. Due to the lower number of events at the entrance (see the profiles shown in figure 4.8) a worse precision is expected for this position. Figure 4.10 supports this claim since it shows that the precision for the entrance position is systematically worse than the one for the fall-off for the simulated geometries.

However, the measurement of the entrance position by means of prompt gammas may not be mandatory. It can be retrieved with e.g. the data provided by an optical surface imaging system intersected with the information of the beam position coming from the treatment planning system (TPS). The optical system provides information that is independent of the statistics (i.e. spot size) with a relatively good precision. For example, Schöffel et al. [119] found an accuracy of 1.02 ± 0.51 mm (with a maximum deviation of 2.86 mm) on retrieving the thorax surface of healthy volunteers for a commercially-available system (accuracy estimated considering the deviations between volunteer displacements and recommended couch transformations calculated by a 4 degrees-of-freedom registration using the optical system). On the other hand, a full prompt-gamma profile can potentially attain a better precision for the entrance position (see table 4.6, but notice that those results are from Geant4 simulations considering a homogeneous target with a very well defined target entrance) and the entire measurement is made with a single device. Additionally, it was suggested elsewhere [69] that the prediction of off-beam deviations is prone to failure if only the prompt-gamma fall-off position is known, while having more information about the prompt-gamma profile can help overcome such a limitation by using registered correlation [37]. In any case, the precision on the retrieval of a given position with this camera intrinsically depends on the spot statistics.

Concerning the parametrisation, figure 4.9 shows an overall good agreement between parametrisation and Monte Carlo simulations. The final result is an analytical tool based on Monte Carlo simulations that can assist on further developments of the camera in situations where one must deal with mechanical constraints like having the exact dimensions of the slabs from a supplier or in the positioning of the camera inside the treatment room. The striking advantage of this tool is to possess the capacity to roughly estimate the precision for different geometries very rapidly. However, the clear disadvantage is the inability to accurately predict the precision for sets of geometries that were almost absent during the training.

Although this study is focused on proton therapy monitoring, it is important to note that all the procedures followed in this work should also be applicable to other ion species, namely carbon ions. However, care must be taken since the proposed solutions herein should not be directly usable in different treatment scenarios. For example, a higher background in a carbon ion irradiation is expected, thus it is reasonable to presume that the camera should be placed in a more distant position in respect to the beam axis in order to benefit from a better separation of signal and background components in TOF spectra.

Other studies before have focused on the optimisation of multi-slit collimated cameras. Min et al. [120] have presented an optimisation study in which a camera without TOF with 2, 2, and 150 mm, respectively slit width, slab width, and collimator thickness, was proposed. Their criterion for the optimisation was a quantity that they have called as background fraction and it is essentially the contrast between the maximum signal and the background after the prompt-gamma profile fall-off. Therefore, it is not possible to directly compare the designs herein and the one from the aforesaid study due to the different criteria. However, the simulation of their design is planned for the near future using the precision criterion for a meaningful comparison. In addition, the doctoral studies of Roellinghoff [77] led to the optimisation of a multi-slit collimated camera without TOF based on the same precision criterion as presented here. It was found that the optimised solution has a precision on the retrieval of the fall-off position of about 3 mm for 5×10^7 incident protons and a detector with a height of 20 cm. Since the precision is proportional to the ratio $\sqrt{background/signal}$ and both *background* and *signal* are proportional to the number of protons, N, it follows that the precision is then proportional to $1/\sqrt{N}$ [76]. Furthermore, by assuming that the precision is also inversely proportional to the square root of the height of the detector, it is feasible to estimate the precision of the optimised designs herein for the conditions followed by Roellinghoff. Table 4.8 presents this comparison.

TABLE 4.8: Comparison between the optimised design of Roellinghoff [77] and the optimised designs of the present study. It is assumed 5×10^7 protons and a detector with a height of 20 cm for all cases. Note that the numbers in this table are not in conflict with the numbers given in the caption of figure 4.8 since the detector in the aforementioned figure has a height of 10 cm.

Design	Precision (mm)
Roellinghoff (without TOF)	3.0
Best precision	1.3
Best precision with gFOV $<15~\mathrm{mm}$	1.6

The comparison shown in table 4.8 is essentially showing the impact of using TOF. With these numbers, it is clear that employing TOF allows for a substantial improvement on the retrieval precision of the fall-off position. Note, however, that the advantage provided by applying TOF is inherently dependent of the beam time structure and timing performance of the detectors. In a first approximation, the gain factor in the precision when using TOF corresponds to the square root of the background reduction. As an example, with the IBA C230 cyclotron (period of 9.4 ns between proton bunches) and assuming a time window of 4 ns, the precision should improve by a factor around $\sqrt{2.4}$.

4.5 Solution being developed

The device currently being constructed within our collaboration, and to which the present work has contributed, is also worthwhile to discuss. A drawing of the collimator can be seen in figure 4.11. It comprises two collimator heads with a modular approach. Each slab will have dimensions of $170 \times 120 \times 1.5$ mm³ with a maximum tolerance of 0.15 mm and several slabs can be combined together to form wider slabs. The material considered for the slabs is a tungsten alloy with a density higher than 18 g/cm³ in order to maximise the collimation of photons.

The collimator was divided in two parts mainly in order to make the transportation easier, but also to test the influence of having measurements with a different arrangement



FIGURE 4.11: Drawing of the collimator being constructed with its size and weight. The figure is to scale.

of slabs and slits between collimator heads. For example, it would be possible to test the impact of offsetting the configuration in one of the collimator heads. Although all geometries considered must have the gFOV of neighbouring slits overlapping in the target, it may not be enough to provide a full and sufficient coverage of the target.

The design of the collimator being constructed makes it versatile and, although it is not exactly neither of the ones found in the sequence of this optimisation study, this work had a strong impact on the choice of the design. The present investigation showed the very significant influence of the relation between collimator efficiency and spatial resolution. This is the main reason why the solution being pursued allows for the possibility of rearranging the configuration of slabs and slits, thus studying cameras with higher efficiency and with better spatial resolution. This is an utterly important feature as already pointed out before. A more efficient camera may yield better precisions but, on the other hand, a camera with better spatial resolution may find potential ion range shifts due to heterogeneities in the end of the ion path more easily and also provide better information for off-beam deviations. The thickness of 170 mm was selected in order to permit a very small gFOV without the need to reduce the slit width to extremely low values.

Chapter 5

Improvement of Geant4 simulations for prompt-gamma emission in the context of proton therapy

In the sequence of the findings from the comparison between data from experiments and Monte Carlo simulations in chapter 3, in the present chapter the study of the possibilities of improvement of the proton nuclear inelastic collision models implemented in Geant4 are described. It begins with a preliminary test on the effect of changing the options of the models considered, followed by a comparison with experimental data for the cases yielding a significant prompt-gamma yield reduction on the test. Finally, an energy deposition and positron emitters distribution comparison between tuned and a reference models is performed.

5.1 Introduction

The Monte Carlo simulation code Geant4 has been developed as a toolkit, i.e. a flexible code that allows the user to have increased control over some key aspects of the simulations, as it is the set of physics models selected for a particular application. Such a development policy has been kept since the first Geant4 release [82]. Essentially, it is the user responsibility to opt for the most appropriate physics models for his/her own application, which brings along clear advantages, but also some drawbacks. The benefits come from the fact that, when choosing the models to use for the intended purpose, the user may disregard the physical processes that are unnecessary in the context, thereby deciding on the level of accuracy desired. This may have a strong impact on the CPU time needed as
well. On the other hand, being able to select the most adequate set of physics models for a given application, demands of users a high level of understanding in respect to physics and models implementation, which is not, in many cases, a requirement easy to fulfil. Therefore, in the past years, in an attempt to partially circumvent this issue, Geant4 developers have created the so-called *reference physics lists*. These are sets of physical models that gather the most common models and that can be called in the code with a single line. Moreover, a list of specific applications and the corresponding recommended reference physics lists (i.e. expected to cope with the level of accuracy required) was made available, thus providing a ready-to-use solution for the physical models complexity and their application limits. At a smaller scale, the so-called *builders* classes have also been implemented, allowing for setting all the definitions and parameters mandatory to call a physical model. The alternative is for the user to define all the said definitions and parameters him/herself. A more recent development has been the *helper* class G4PhysListFactory, that makes possible to call the full set of physical models with a simple string. Nevertheless, independently of how many user-friendly approaches are available to the user, Geant4 is definitely a very flexible toolkit, since the user continues to have full control of most of the details from his/her simulation. Besides, the source code is always available, making it possible to tune the application further by implementing corrections and improvements. In this context, our collaboration has recently developed an in-depth study of one of the physics models implemented in Geant4 (the QMD) and by changing some parameters constrained by a range with physical meaning it was possible to improve Geant4 predictions for prompt-gamma emission in respect to experimental data for carbon ion irradiation [103].

The rationale for the need of improving the Geant4 nuclear models was already extensively shown throughout this manuscript with the several benchmarks performed. In any case, this issue must not be taken lightly, given that Geant4 accuracy for dose calculations is relatively good, as it can be found in the literature (e.g. [121] and [114, 122] for proton and carbon ion therapy, respectively). It is possible that an improvement in the promptgamma emission may disturb the dose estimation accuracy. In a scenario like this, few options are available. On the one side, one can put aside such an improvement, since the priority is to keep dose accuracy as high as possible. On the other side, one may prefer to decouple the two simulations (i.e. dose and prompt-gamma emission) in order to have the best modelling possible for both. The former allows for a single simulation where one would obtain an accurate dose, but an overestimated prompt-gamma emission yield, which could be overcome by applying correction factors afterwards or by using only the prompt-gamma profile length (as shown for the heterogeneous targets study in chapter 3, section 3.3). The latter would provide the most accurate results for both quantities but at the expense of repeating the simulation. Ultimately, it will depend on the available resources and how each solution copes with the hypothetical clinical workflow when using prompt-gamma monitoring devices.

Globally, a nuclear inelastic interaction in Geant4 with incident protons may be divided in three stages: 1) the collision between the proton and the nucleons in the target nucleus, 2) a pre-equilibrium stage in which the highly excited fragments are de-excited through the creation of other fragments (in the case of Precompound model – the most widely used pre-equilibrium model in Geant4 – only neutrons, protons, deuterons, thritium, and helium nuclei can be emitted) until a equilibrium state is reached (i.e. if any, the excitation energy is shared by many nucleons among the fragments created), and 3) an equilibrium stage that further de-excites the fragments through the ejection of nucleons, light fragments, and photons. The equilibrium concept in this context usually refers to a low excited nuclear state without the possibility to continue to break the fragment. For the case of light nuclei, this excitation energy per nucleon is often comparable to the nucleon binding energy. However, it can still emit light particles [123]. Moreover, it can happen that fragments reach the equilibrium stage with a relatively high excitation energy. For those cases, the multifragmentation model is employed. Each hadronic inelastic model uses its own approach and assumptions, making it more or less suitable depending on the application and the required accuracy. As an example, a model like Binary Cascade treats the intra-nuclear cascade during collision at each step as a binary system between the projectile and a single nucleon. The possible effects of all other nucleons forming the nucleus on this step are not taking into account. In turn, QMD takes the interaction between nucleons within the target and other nucleons within the projectile into account, thus making it the most descriptive and exhaustive collision model implemented in Geant4.

A full description of each approach can be found in the Geant4 Physics Manual and the references cited therein available in the Geant4 website [123].

There are at least five ways to test and then improve Geant4 outcomes: 1) test several physics models and decide which one to use, 2) if better cross sections for a given application are available, input those instead of using the default ones, 3) implement an user-defined physics model and replace the one from Geant4 (this is possible without changing the source code: the user can call an external C++ class and associate it with a given physics process), 4) test the built-in options included in the implementation of several models, and 5) change the source code. Apart from 2) and 3), this chapter will cover the different options to test and improve Geant4 outcomes for prompt-gamma emission. The quantity to improve in this work is the total emission yield of prompt gammas and not, for example, the analysis and use of specific gamma lines for monitoring, like other collaborations are pursuing (e.g. [78, 79]). Nevertheless, it should provide

references to others working on prompt-gamma emission with Geant4 about some existing possibilities to improve the simulation outcomes.

Before performing this assessment, it was decided to only look for parameters that could allow for changes with physical meaning. A clear example is the nuclear radius that has a range of accepted values depending on the assumptions taken. The rationale is the need to preserve the physical modelling nature of the code, since for different cases (e.g. different materials and projectile energy) it would not be possible to assert the reliability of Geant4 results. This is even more crucial when dealing with medical physics, namely hadrontherapy, for which a wide range of complex scenarios is viable. It is true that, at this moment, Geant4 overestimates the prompt-gamma emission yields, thus not being fully reliable. However, its behaviour is limited by the models and their implementation and it can be reproduced by any Geant4 user. On the other hand, if one implements non-physical improvements, such as randomly discarding prompt gammas after their creation by a given factor in order to cope with the overestimation, this would require a complete awareness of all possible scenarios. Considering this example, the user would need to have the data to estimate correction factors for the different energies, materials, and particles (including prompt-gamma emission coming from secondaries). Although such an endeavour is feasible, the goal of this study is to provide solutions attainable within the framework of the current Geant4 implementation and that could be easily put in place in both Geant4 and Geant4-based tools developed with the aim of medical in general and, more particularly, hadrontherapy research (e.g. GATE, TOPAS, GAMOS).

The study undertaken and presented herein was not exhaustive, since several options and parameters may have been overlooked. However, it is definitely a comprehensive investigation that, above all, aims to demonstrate that there is room for improvement with the available models and implementation in Geant4 concerning prompt-gamma emission. All simulations performed in this chapter were done using Geant4 version 10 patch 02.

5.2 Test of several physics models

To avoid CPU-intensive simulations, it was decided to use a simple setup in a first stage to test for any change on the prompt-gamma emission yields in the sequence of changing parameters or options. The setup consisted of a 1-cm thick PMMA target surrounded by a spherical detector in order to detect all gammas in 4π created after inelastic processes. The target was placed in vacuum and a 160-MeV proton beam was used. Choosing a PMMA target allows for a direct comparison with the overestimation observed when testing against the experimental data. In order to estimate statistical effects, each case is simulated five times with different seeds and the yields given correspond to the average and the standard deviation after those simulations. The events reaching the spherical detector are then selected by particle (only gammas are accepted), by energy (only between 1 to 7 MeV so to match the energy values used in the experimental data analysis), and by time of flight (to select only prompt gammas).

As in chapter 3, Binary Cascade, Bertini Cascade, Precompound and INCL will be used. The study of the hadronic inelastic models for neutrons and ions will not be carried out. This follows one of the conclusions of the work developed in chapter 4, according to which, the modelling of those particles does not seem to play a meaningful role on the prompt-gamma emission yields for proton irradiation. The emission yields obtained by changing either built-in options or parameters will be compared with those resulting from the default implementation. Although the QMD model was used in the benchmarking presented in chapter 4, the outcome was similar to that of other models, but with a much higher need for computing time. Therefore, it was not included in the first part of the study but rather at a later stage, after verifying that the other models have not yielded satisfactory results. At this later stage, the impact of the free QMD parameter found by Dedes et al. [103] showing a more accurate modelling of prompt-gamma emission yields for carbon ions will be assessed for the case of proton irradiation. In addition, knowing that they may also have an impact on the prompt-gamma yields, the models comprising the equilibrium stage will be assessed.

It should be stressed that most of the built-in options, hard-coded parameters, and free parameters are neither documented nor the reason why they were assigned their value is explained. A typical hard-coded parameter that can vary within an accepted physical range is the nuclear radius. On the other hand, a built-in option may be the way the cross sections are parametrised to be utilised afterwards by the models. Very often, these built-in options can be selected by simply writing a command line in an external file (a macro file) that will then be read by Geant4. Finally, there are other parameters that seem to be an implementation choice. For instance, the hard-coded threshold in the Binary Cascade concerning the lower limit of excitation energy that a fragment may have in order to be treated by Binary Cascade. Below this limit, the fragment is sent to Precompound to be further de-excitated. However, there is no clear idea about the value that this threshold should take (section 32.1.15 of Geant4 physics manual [123]), which makes it an implementation choice.

5.2.1 Assessment of built-in options

In this section, only built-in options accessible to all end-users are presented. Moreover, it is important to remind that the results presented in this section correspond to a perfect detection of prompt gammas in 4π after protons with 160 MeV impinge into a 1-cm thick PMMA target.

Binary Cascade

No Binary Cascade built-in options were found. Table 5.1 shows the yield obtained with the default implementation for comparison purposes.

TABLE 5.1: Yields obtained with the default implementation of Binary Cascade model.

Option	Yield $(\times 10^{-4} \text{ counts per proton})$	Difference in yield (%)
DEFAULT	46 ± 0.2	not applicable

Bertini Cascade

The Bertini Cascade implementation allows for the use of several built-in options. For some of them, the user must provide a value for the quantity at hand. As an example, the user can define a "*maximum momentum for p-n clusters*" (from class G4CascadeParamMessenger). The options of this model requiring an input value will not be considered due to the lack of time to investigate the meaningful physical ranges for each case. Table 5.2 shows the yields after changing each built-in option and their difference in respect to the default implementation of Bertini Cascade model.

TABLE 5.2: Yields obtained with different built-in options of Bertini Cascade. The default implementation considers all the options shown as false. Highlighted is an option resulting in a significant reduction in the prompt-gamma emission yields in respect to the default implementation.

Yield $(\times 10^{-4} \text{ counts per proton})$	Difference in yield (%)
96 ± 0.4	not applicable
96 ± 0.7	0
45 ± 0.4	-53 ± 0.5
96 ± 0.5	0
96 ± 0.4	0
96 ± 0.4	0
96 ± 0.4	0
	Yield $(\times 10^{-4} \text{ counts per proton})$ 96 ± 0.4 96 ± 0.7 45 ± 0.4 96 ± 0.5 96 ± 0.4 96 ± 0.4 96 ± 0.4

The only option that yields an expressive reduction in the prompt-gamma emission yields is the use of the Precompound model for the pre-equilibrium stage instead of the Bertini pre-equilibrium approach.

Precompound

TABLE 5.3: Yields obtained with different built-in options of Precompound model. The default Precompound model uses OPTxs = 3. Except for the OPTxs option, that expects an integer between 1 and 4, and the useCEMtr one, that is defined as true, the default implementation considers the remaining options shown as false. Highlighted are the two options yielding a significant reduction in the prompt-gamma emission yields in respect to the default implementation.

Option	Yield $(\times 10^{-4} \text{ counts per proton})$	Difference in yield (%)
DEFAULT	25 ± 0.5	not applicable
useHETCEmission = true	24 ± 0.1	-4 ± 0.07
useGNASHT ransition = true	14 ± 0.2^{-1}	-44 ± 1
OPTxs = 1	23 ± 0.2	-8 ± 0.2
OPTxs = 2	26 ± 0.3	$+4\pm0.08$
OPTxs = 4	24 ± 0.4	-4 ± 0.1
useSICB = true	25 ± 0.3	0
useNGB = true	26 ± 0.3	$+4\pm0.08$
useSCO = true	15 ± 0.2	-40 ± 1
useCEMtr = false	25 ± 0.3	0

¹ This result comes from the fact that Geant4 contains a bug in the GNASHTransition method. After the bug corrected, the yield is equal to 15 ± 0.1 counts per proton (-40 ± 0.8 percentage difference). The wrong value is kept herein for consistency purposes, since this is the one yielded by anyone running the Geant4 version 10 patch 2. Nevertheless, it is also important to analyse what the bug is introducing in the code for such a substantial reduction. Further discussion in section 5.2.3.

There are two options that yield a significant reduction of prompt-gamma emission in respect to the default implementation. Table 5.3 presents the yields after changing each built-in option and their difference in respect to the default implementation of Precompound model. The option *useGNASHTransition* activates the use of an alternative method based on the standalone GNASH code [124] to estimate the probability of the different types of emission that can occur during the pre-equilibrium stage. The result shown in table 5.3 for the use of the *useGNASHTransition* option contains a bug. When the bug is corrected, the yield reduction continues to be quite substantial, thus this option is worthwhile to be further considered. On the other hand, the *useSCO* option is defined as "*soft cutoff from pre-equilibrium to equilibrium*" (from G4PreCompoundModel class). It is a pragmatic procedure to share the fragments close to the equilibrium between

pre-equilibrium and equilibrium stages. It samples a random value that is then compared with the value of an empirical function. The result of this comparison determines the use of the pre-equilibrium or equilibrium stages. Instead of a fixed value to make the transition between models, this implementation allows for a smoother transition. Considering the rationale of such a parameter, it is surprising that this option is not activated by default. Nevertheless, the results of using this parameter suggest that the less the Precompound model is used, the better the prompt-gamma emission yields become. This indicates that the yield overestimation may be more related with the Precompound model rather than with the de-excitation stage. Note that the Precompound model does not emit photons, thus the overestimation is always caused by the de-excitation. However, the kind of fragments sent to the de-excitation will inevitably affect its accuracy of modelling photon emission.

INCL

For INCL model, all built-in options require a value provided by the user. However, contrarily to the options in Bertini Cascade model, these have a straightforward meaning. The *accurateNucleus* options allows for selecting which nucleus should be accurately described, either the one of the projectile or that of the target. In turn, the *maxClusterMass* option gives the user the possibility to choose the maximum mass number of the nucleon clusters created after collision. The two extreme cases will be tested to assess the impact of this parameter. Finally, the *cascadeMinEnergyPerNucleon* option is used to set the lower energy threshold for the INCL model. When the excitation energy per nucleon is below this value, the fragment is sent to Precompound for further de-excitation. Table 5.4 presents the yields after changing each built-in option and their difference in respect to the default implementation of INCL model.

TABLE 5.4: Yields obtained with different built-in options of INCL model. The INCL model uses accurateNucleus = projectile, maxClusterMass = 8, and cascadeMinEnergyPerNucleon = 1 MeV by default.

Yield $(\times 10^{-4} \text{ counts per proton})$	Difference in yield (%)
38 ± 0.5	not applicable
38 ± 0.5 39 ± 0.5 28 ± 0.5	$ \begin{array}{c} 0 \\ +3 \pm 0.05 \\ 0 \end{array} $
38 ± 0.5 38 ± 0.5 38 ± 0.5	0 0 0
	Yield (×10 ⁻⁴ counts per proton) 38 ± 0.5 38 ± 0.5 38 ± 0.5 38 ± 0.5 38 ± 0.5 38 ± 0.5 38 ± 0.5

Equilibrium stage

This is the final step on an inelastic hadronic interaction. It further de-excites the nucleus using different models: multifragmentation, Fermi break-up, evaporation, and photon evaporation. The selection of the models depends on several factors, such as the mass and atomic number, and excitation energy. Table 5.5 presents the yields obtained with different built-in options available in the Geant4 managing class of the equilibrium stage (G4ExcitationHandler) and their difference in respect to its default implementation.

Class	Option	Yield $(\times 10^{-4} \text{ counts per proton})$	Difference in yield (%)
	DEFAULT	46 ± 0.2	not applicable
G4ExcitationHandler	OPTxs = 1 OPTxs = 2 OPTxs = 4 useSICB = true	$ \begin{array}{r} 46 \pm 0.2 \\ 46 \pm 0.2 \\ 46 \pm 0.2 \\ 46 \pm 0.2 \\ \end{array} $	0 0 0 0

TABLE 5.5: Yields obtained with different built-in options available in the Geant4 managing class of the equilibrium stage (G4ExcitationHandler). The inelastic hadronic model used was the Binary Cascade.

5.2.2 Testing source code changes with physical meaning

In this section, several parameters that require a re-compilation of Geant4 will be tested. This study considers only the parameters that may be changed according to a physical or a model-dependent range of possible values. Moreover, it is important to remind that the results presented in this section correspond to a perfect detection of prompt gammas in 4π after protons with 160 MeV impinge into a 1-cm thick PMMA target.

Binary cascade

The first parameter in test, the BCminP, is the minimum kinetic energy that a nucleon must have to be treated by Binary Cascade. Below this value, the nuclear interaction is sent to Precompound model. The default value is equal to 45 MeV. In order to estimate the impact parameter of a collision, Binary Cascade uses the nuclear radius and adds a margin of 3 fm. However, the reason for this choice is never stated but it can probably be related with the need to have a nuclear radius larger than the nucleon diameter (~1 fm). Test A and test B consider 0 and 6 fm margin, respectively. After estimating the impact parameter of a collision, the model calculates the position in the nucleus (considered as a sphere) where the first interaction (if any) will occur. However, such a calculation assumes the radius of the nucleus plus 10%. Again, there is no information explaining the reason for this choice. In consequence, test C and test D try to assess the effect of this larger nuclear radius by considering no extra margin and a 20% margin, respectively. Table 5.6 shows the results of these tests.

Class	Option	Yield $(\times 10^{-4} \text{ counts per proton})$	Difference in yield (%)
	DEFAULT	46 ± 0.2	not applicable
G4BinaryCascade	theBCminP = 15 MeV test A test B test C test D	$ \begin{array}{r} 46 \pm 0.1 \\ 47 \pm 0.5 \\ 45 \pm 0.2 \\ 46 \pm 0.3 \\ 46 \pm 0.2 \end{array} $	$\begin{array}{c} 0 \\ +2 \pm 0.02 \\ -2 \pm 0.01 \\ 0 \\ 0 \end{array}$

TABLE 5.6: Yields obtained with different changes in the source code of Binary cascade model.

Bertini cascade

No obvious parameters suitable to be changed within physical boundaries were found.

Precompound

 fR_0 , or more commonly referred to as r_0 , is the empirical constant used to calculate the nuclear radius and its value varies according to the nucleus and the method used to measure the nuclear radius. For example, Blatt and Weisskopf state r_0 values ranging from 1.17 to 1.71 fm for beryllium and carbon nuclei, respectively [125]. The current value defined in Precompound model is 1.5 fm. Table 5.7 shows the yields after changing this parameter within those values.

 TABLE 5.7: Yields obtained with different changes in the source code of Precompound model.

Class	Option	Yield $(\times 10^{-4} \text{ counts per proton})$	Difference in yield (%)
_	DEFAULT	25 ± 0.5	not applicable
G4PreCompoundParameters	$fR_0 = 1.17$ $fR_0 = 1.71$	26 ± 0.4 25 ± 0.5	$+4\pm0.1$ 0

INCL

No obvious parameters suitable to be changed within physical boundaries were found.

Equilibrium stage

The first parameter in test is κ and it is used to calculate the Coulomb energy for the Fermi break-up model. The current value defined is equal to 6 (it is dimensionless, since it is a ratio between nuclear volumes), although the initial implementation used κ equal to 1 (until Geant4 version 9.4). According to a developer comment in the G4FermiConfiguration class, there is no theoretical constraint for κ values below 10. Therefore, the first test will verify the yields for the extreme cases allowed. The parameter r_0 is the empirical parameter used to calculate the radius of the nucleus, as already described in the Precompound model subsection of the present section, and it is also used by the Fermi break-up model. The last study for the equilibrium stage will focus on the selection of evaporation models. Initially, Geant4 only had the evaporation model following the original description of Weisskopf and Ewing [123, 126]. However, an alternative model called generalised evaporation model (GEM) was also included [123, 127] and the current implementation uses a mixture of the two approaches. Therefore, the use of only one approach is tested in order to check the impact of each evaporation model on the prompt-gamma emission. Table 5.8 shows the yields after the aforementioned changes and their difference in respect to the default implementation.

Class	Option	Yield $(\times 10^{-4} \text{ counts per proton})$	Difference in yield (%)
	DEFAULT	46 ± 0.2	not applicable
G4FermiConfigurationList	$\kappa = 1 \ \kappa = 10 \ r_0 = 1.17 \ r_0 = 1.71$	$\begin{array}{l} 49 \pm 0.3 \\ 44 \pm 0.3 \\ 46 \pm 0.4 \\ 44 \pm 0.3 \end{array}$	$+7 \pm 0.04$ -4 ± 0.03 0 -4 ± 0.03
G4Evaporation	Only default evaporation Only GEM evaporation	$46 \pm 0.2 \\ 46 \pm 0.2$	0 0

TABLE 5.8: Yields obtained with different changes in the source code from the models comprising the equilibrium stage. The inelastic hadronic model used was the Binary cascade.

5.2.3 Discussion

The first global impression is that each Geant4 hadronic model offers several built-in options to allow for a fine tuning of simulations. Several options are kept for historical reasons even after the developers considered that a given approach is not adequate for some reason. The source code is full of comments from the developers pointing in this direction and even some contradictory comments exist where further changes are not documented. However, Geant4, as well as several other Monte Carlo codes, was originally developed for high energy experiments, so it is expected that some features are not

tailored for hadron herapy applications [20]. As an example, one can refer the work of Dedes and colleagues [103], in which it was seen that a parameter in QMD model was not optimised for lighter systems (as the ones related to hadrontherapy). Another example is the presentation given at the 2008 Geant4 hadronic group meeting, stating that a given choice for the option *OPTxs* in Precompound model "seems to describe rightly the behaviour of reaction cross sections at barrier energies for medium and heavy targets", but "Problem: for incident protons and light system (²⁷Al) at Coulomb barrier energies, Wellisch's parameterization works better" and the decision was to use the worse option for light systems although with some corrections (quotes and information taken from [128]). The "Wellisch's parameterization" is the OPTxs = 2, while the default one is the OPTxs= 3. Although the Geant4 hadronic group has been addressing several issues affecting Geant4 performance for hadrontherapy purposes, such as the improvement of the Fermi break-up model and photon evaporation [129], and Geant4 developers have been seeking new solutions specially dedicated to medical physics [130], the possibilities for fine tuning of the simulation as well as the advantages/disadvantages of each approach should be more clearly stressed. Moreover, the development of new models (or at least alternative fine-tuned versions of the existing ones) for the medical community should be a priority. For example, the Geant4 electromagnetic physics group seems to have acknowledged this and their efforts are turning to the improvement of lower energy models, of which the Geant4 DNA project and the very recent G4EmStandardPhysics option4 reference physics list are clear signs. This is even more important when statistics show an increasing use of Geant4 for medical applications, as a quick survey in PubMed [131] database demonstrates (see table 5.9). As a term of comparison with other Monte Carlo codes, the number of entries in this database for FLUKA, MCNP, and GEANT4 keywords are 280, 583, and 466, respectively. In any case, these built-in options give the possibility to try to improve the simulation outcomes. Furthermore, they are useful, not only for the present study, but also to improve the Geant4 accuracy in similar applications, e.g. the hadron promotion for the specific prompt-gamma lines (e.g. [78, 79]).

The considered changes to the source code, on the other hand, did not have a meaningful impact on the prompt-gamma emission, hence not being further studied. Additionally, as it was verified in chapter 4, Bertini Cascade model coupled with Precompound also shows a significant decrease in the yields. Nevertheless, such an improvement is not sufficient, in view of the very high yields obtained with the default Bertini model in respect to the other models. As so, the only model showing the potentiality for improvement is the Precompound model, namely with the *useGNASHTransition* and *useSCO* options allowing for the reduction necessary to achieve comparable yields with experimental data already presented in chapter 3, section 3.2.1.

Publication year	Number of entries
2004	19
2005	19
2006	23
2007	23
2008	36
2009	54
2010	50
2011	67
2012	82
2013	82

TABLE 5.9: Number of entries per year in the PubMed database after querying for the GEANT4 keyword.

The results shown in the said chapter pointed out that a reduction between 40% and 50% in the prompt-gamma yields would be required for the Precompound model. The only options able to attain such reduction values are the aforesaid ones. However, as already stated in section 5.2.1 the option useGNASHTransition triggers a bug in Geant4, more precisely in the G4PreCompoundModel class. The Precompound model follows the approach proposed by Gudima et al. [132], in which it is assumed that transitions in terms of number of excitons (excitons in this model is equal to the sum of excited particles and holes inside the excited nucleus) can only be made in a very specific way. At some point in the code, the transition probabilities are calculated along with a logical test to verify if the excited nucleus is in an adequate configuration state to be sent to the de-excitation models (i.e. multifragmentation, Fermi break-up, evaporation, and photon evaporation). However, the concept of these transitions is not implemented in the GNASH transitions class. Therefore, the return value is always zero for the transition probabilities when using the useGNASHTransition option and the nucleus is immediately sent to the de-excitation models, thus no Precompound model treatment is done on this excited nucleus. The following sections will focus on the results from a corrected version of Precompound model and the useGNASHTransition option will continue to be considered, since after correction it still leads to a significant reduction of the prompt-gamma emission (see the value at the footnote of table 5.3). A bug report to Geant4 developers has been filed.

5.3 Final benchmarking

The final benchmarking includes the comparison of simulations with experimental proton and carbon ion data. For the proton case, in accordance with what was discussed in the previous section, a corrected and tuned version of the Precompound model is used to compare simulated and experimental data.

5.3.1 Experimental proton data

The comparison between experimental and simulated data with the tuned version of the Precompound model is depicted in figure 5.1. Note the use of Tripathi light ion cross section approach for testing purposes.



FIGURE 5.1: Experimental and simulated prompt-gamma profiles from the proton irradiation experiments. Except for the default case (red circles), the simulated data was retrieved using a tuned version of Precompound model with a given parameter change.

After analysing the results from figure 5.1 the conclusions that can be drawn are rather unsatisfactory. On the one hand, the goal of reducing the prompt-gamma yield was partially accomplished with the considered options. All the cases tested show a substantial prompt-gamma emission yield reduction along the plateau. However, on the other hand, there is a steep increase for all cases in the prompt-gamma yields towards the end of the proton range, namely after around an average primary energy of 40 MeV. There are, at least, three reasons that may explain this phenomenon: 1) the hadronic inelastic cross section in Geant4 is overestimated for this energy range, 2) the prompt-gamma energy is not being accurately calculated by the models, and 3) the photon evaporation model in de-excitation phase is emitting more prompt-gammas than it should and/or the input fragment data in the photon evaporation model are not correct. It should be noted that, for this last reason, it does not necessarily mean that the problem is in the de-excitation models, it can also be in Precompound model.

One of the best approaches to test the first hypothesis is to simply compare the Geant4 cross sections with experimental ones. In this case, the overestimation would not be entirely due to a wrong modelling but rather, at least partially, to an excessive number of hadronic inelastic interactions, thus more prompt gammas per unit of distance. Geant4

provides a feature to directly extract its cross sections with a function call (through the class G4HadronicProcessStore and by calling the GetInelasticCrossSectionPerAtom method). This functionality was thus used to retrieve the total inelastic cross section as estimated by Geant4. The compiled data of incident protons from Carlson [133] concerning targets of carbon and oxygen nuclei were selected for this test and the results are shown in figure 5.2.



FIGURE 5.2: Comparison between experimental and simulated total inelastic cross sections with incident protons. This comparison is made considering targets of carbon (left) and oxygen (right) nuclei. The experimental data were retrieved from the tables of compiled data by Carlson [133].

As it can be observed from the comparison in figure 5.2, the Geant4 total proton inelastic cross sections for both targets is in good agreement with the experimental data. Although there is a consistent slight overestimation of the Geant4 cross section in respect to the oxygen data, it does not seem high enough to justify the observed excess of prompt-gamma emission.

A simple test can be done to give an indication on whether the second hypothesis can be accepted as an explanation. Assuming that the problem could derive from the energy selection cuts due to a wrong sampling of prompt-gamma energy, if one changes the energy thresholds it would be expected to see a different behaviour towards the distal part of the prompt-gamma profiles. Since few events exist next to the high energy cut (7 MeV), this threshold was not considered. Figure 5.3 depicts the simulated prompt-gamma profiles with a lower energy threshold of 2 and 3 MeV.

The results shown in figure 5.3 indicate that the problem may not reside in the energy thresholds applied since, regardless of the cut used, the behaviour is the same for lower primary energies corresponding to the energy range of around 40 MeV down to zero (after about 100 mm of path travelled by 160 MeV protons inside a PMMA target). Hence, the second hypothesis is not verified. However, it is surprising that the agreement in the plateau region between the experimental data and the default Precompound model is better for the 3 MeV energy threshold, thus indicating that the problem might be energy-dependent. Consequently, the simulated detected energy spectra from different longitudinal positions along the target were analysed. The results are shown in figure 5.4.



FIGURE 5.3: Simulated prompt-gamma profiles with a lower energy threshold of 2 (left) and 3 MeV. The higher energy cut of 7 MeV is kept constant. Note that the Y-axis range is different for the two plots and that the corresponding axis scale does not provide units. This is intentional since, in order to compare all profiles using the simulated data from the different proton experiments, the absolute normalisation factor had to be applied. However, this factor is estimated in respect to a lower energy threshold of 1 MeV (see section 3.1.4), thus not having a physical meaning if the energy selection is different. Nevertheless, regarding the comparison of the profile shapes, such an approach is adequate and reasonable.



FIGURE 5.4: Averaged experimental (top) and simulated (bottom) energy spectra from positions inside the target before and after 100 mm using the WPE 160 MeV H^+ (I) with the LaBr₃ detector. Note that the scale is the same for both pictures for a better comparison.

When comparing the difference between the experimental and simulated energy spectra depicted in figure 5.4, one can see some differences. However, part of these differences

(e.g. the energy spectra baseline) can be attributed to the background events inside the TOF window in the experimental data. It is not possible, or at least it is not a straightforward procedure, to fully simulate this behaviour, thus it is difficult to analyse the Geant4 modelling of the continuum gamma emission with the available data. Still, there are some features that seem to point out inaccurate modelling in the simulations. For example, in the simulated data, the difference in the integral of the data before and after 100 mm is quite pronounced (as already expected due to the results from the prompt-gamma profiles). Although the simulated energy spectra in figure 5.4 suffer from some lack of statistics that partially prevents a proper and careful analysis, it seems that the characteristic gamma lines are quite exaggerated after 100 mm when comparing with the experimental case. As such, the problem seems to be related to the third hypothesis, which suggests that there is a prompt-gamma emission overestimation originated from the models, namely for the discrete gamma emission. This issue has been already studied and discussed by Verburg et al. [101] and Polf et al. [104]. However, the available data and subsequent analysis cannot explain why the agreement in the plateau region between experimental and simulated data with the default Precompound model is better when using a higher energy threshold. Nevertheless, it is possible to suggest an explanation for the simulation behaviour based on all these findings. From the results presented in section 5.2.1, one can consider that sending fragments as soon as possible to the deexcitation stage (i.e. by using the useSCO and the bugged useGNASHTransition options) reduces the prompt-gamma emission. Since the excitation energy of those fragments will, in average, be higher, the Fermi break-up model can be applied more often (the use of this model is energy-dependent). Therefore, this model may predict the state of the fragments that undergo photon evaporation in a more accurate way. The pronounced peak towards the end of the prompt-gamma profile may be explained by the lower excitation energy of the fragments in this region, which will then cause a decrease in the use of Fermi break-up model. Such an issue definitely deserves a dedicated study that, due to lack of time, could not be performed here.

The considered hadronic models have not so far yielded a satisfactory agreement with the experimental data. Despite that, there is a last option that was discarded in the initial benchmarking in chapter 3: the use of QMD model. Usually, this model is never used for incident hadrons, since there is a variety of alternative models providing reasonable results with much less computing resources needed. Still, employing QMD may provide better outcomes and, on the other hand, there is already some expertise concerning the said model after the work of Dedes et al. [103]. Nonetheless, the initial attempts to use the QMD model with Geant4 version 10 patch 2 were fruitless, since no matter the interaction considered, QMD model was always producing fragments without respecting the energy conservation law by more than 1 GeV. A first bug causing such an issue was found.

When the simulation of primary protons was requested, the code implementation was adding twice the primary particle as "participant" in the G4QMDGroundStateNucleus class, thus the extra proton was the responsible for the excess of energy in the energy conservation check (the rest mass of one proton plus its kinetic energy). This bug was introduced in Geant4 version 10 after some code cleaning. A second bug was also found. Although the model and the code implementation consider incident protons, when an incident proton interacts with a hydrogen nucleus, the code enters into a infinite loop. All attempts to fix this problem using the code implementation logic, thus not changing any of the model physics features, have turned out to be futile. Therefore, a strategy to bypass this issue was implemented, which consisted of calling Precompound model when a hydrogen nucleus is the target with a proton as projectile. Bug reports have been filed for the QMD model issues found.

The previous work of Dedes et al. [103] for carbon ions has shown that the QMD model has a parameter L that allows for reducing the prompt-gamma emission yields. QMD approximates each nucleon state to a Gaussian function and this parameter describes the width of such a Gaussian, thus being related to the effective interaction range between nucleons. In the same study, it was stated that, after some literature review, this parameter is in fact free in the QMD model and it should be tuned accordingly to the intended system. As an example, Hartnack and colleagues state that a parameter L equal to 2.165 fm² may be used for Au+Au interactions [103, 134], while for Ca+Ca and lighter systems a value equal to 1.08 fm² may be applied instead. Since the default value in Geant4 is 2 fm², one can easily infer that this parameter is not optimised to model the possible nuclear interactions in Monte Carlo simulations for hadrontherapy purposes.

Figure 5.5 depicts the comparison between experimental and simulated data using the QMD model to model proton nuclear inelastic collisions with different L values. The results shown demonstrate that the parameter L is an effective parameter to tune in order to improve the prompt-gamma emission modelling for protons, following the same findings as the study of Dedes et al. [103] for carbon ions. The best agreement is found for a parameter L equal to 0.9 fm² but 1.0 fm² yields also a reasonable agreement. Contrary to the study undertaken by Dedes et al., the results obtained with 0.8 fm² for proton beams underestimate the prompt-gamma yields. Nevertheless, for the tested values of L, which are less or equal to 1.0 fm², it seems there is an overestimation on the entrance rise. After the entrance, the yields decrease slightly and the agreement is better. The origin of this issue remains unknown.

Apart from the prompt-gamma yields, other quantities should also be checked due to their importance when performing Monte Carlo simulations in the context of hadrontherapy. The energy deposition and the positron emitters production are definitely two of them



FIGURE 5.5: Experimental and simulated longitudinal prompt-gamma profiles for the WPE 160 MeV H⁺ (I) experiment. All simulated profiles use the QMD physics model for proton hadronic inelastic interactions with different L parameters.

because of dose calculations and PET monitoring, respectively. The rationale for keeping an acceptable agreement before and after tuning these two quantities is to ensure that a single Monte Carlo simulation can be used to score the three quantities, thus maintaining the simulation workflow as simple as possible. However, the comparison is done with the default implementation of the model, hence assuming that the default implementation yields accurate results. Such an assumption seems to be reasonable based on several studies that have been performed testing the Geant4 accuracy for dose and positron emitters distributions calculation (see e.g. [41, 135]). For positron emitters production, the comparison is made with the ¹¹C and ¹⁵O production, since these are the ones that contribute the most for the shape of the activity profile that allows for PET monitoring [43, 44]. Figure 5.6 shows the comparison of the longitudinal energy deposition in the target and the longitudinal isotope production obtained with the default QMD implementation against QMD simulations with L parameters equal to 1.0 fm^2 and 0.9 fm^2 (using the target and beam characteristics of the WPE 160 MeV H⁺ (I) experiment). In this figure, the results from Binary Cascade are used to assess the performance of the QMD model since it has been acknowledged as reliable for dose calculations in Geant4 [100]. Moreover, the results obtained herein with Binary Cascade for longitudinal profiles of isotope production rates agree well with the work of Seravalli et al. [136], where they used a PMMA target being irradiated by a 160 MeV proton beam. While using experimental cross sections coupled with GATE, the same study states a total yield of 0.032 and 0.011 nuclei per proton, respectively for ¹¹C and ¹⁵O. According to the results depicted in figure 5.6, Binary Cascade yields 0.037 and 0.012 nuclei per proton, respectively for the same nuclei.



FIGURE 5.6: Results of energy deposition, ¹¹C and ¹⁵O production rate. Each case on the left depicts the different longitudinal profiles and, on the right, the percent error on the different quantities using the Binary Cascade model as reference ($(|test - reference|/reference) \times 100$). Except for the hadronic inelastic physics, all other physical parameters and models are the same. **TOP**: energy deposition. **MIDDLE**: ¹¹C production rate. **BOTTOM**: ¹⁵O production rate.

The results from figure 5.6 show that any of the QMD model cases tested can be employed in dose calculations since the percent error in respect to the Binary Cascade model is always below 3% along the proton range. After the Bragg peak there is a larger inconsistency, which can be attributed to different secondary yields produced by the primary proton, but its impact should be small in terms of dose. The positron emitters production rate is, on the other hand, a quite different scenario, as it is always underestimated regarding the Binary Cascade model estimate, while the tuning of QMD improves the outcome by reducing this underestimation. Nevertheless, the most problematic issue is the difference in ¹¹C and ¹⁵O production maximum range when compared with the Binary Cascade prediction, mainly in the case of ¹⁵O. While under/overestimation can be partially accounted for if one is aware of it, this range is more troublesome since it is correlated with the proton range. Although the reason for such a discrepancy is still unknown, the QMD model (even in its default implementation) does not seem suited for the estimation of positron emitters production when applied to proton irradiation. It should be noted that QMD was recommended after the study of Böhlen et al. [137] and it was the preferred model in the work of Robert and colleagues [92] concerning carbon ion hadronic inelastic modelling. Furthermore, after the study presented herein, it was the only hadronic inelastic model among the tested and tuned ones obtaining a good prediction of prompt-gamma emission yields along the entire proton range.

Chapter 6

Acceleration of Geant4 simulations for prompt-gamma emission in the context of proton therapy

The clinical workflow has some constraints, namely in terms of the time available for treatment planning. Therefore, a strategy for the acceleration of prompt-gamma emission modelling will be presented, discussed, and analysed in this chapter. First, a Geant4 profiling considering different primary particles, physical processes, and geometrical complexity will be performed in order to increase the awareness concerning CPU time bottlenecks in analogue simulations. Afterwards, the presentation of a novel approach for an acceleration scheme will follow along with some preliminary tests and expected acceleration factors.

6.1 Introduction

The use of Monte Carlo simulations for medical applications, namely in proton and carbon ion therapy calculations, is progressively becoming the state of the art, either due to its adoption in a full replacement of analytical tools, or due to its use to validate and build analytical methods. This increasingly adoption of Monte Carlo codes in the clinical workflow and medical radiation research is mainly led by the smaller uncertainties and better accuracy associated with its use [20, 138, 139]. Moreover, the major drawback of Monte Carlo simulations – the calculation time needed, is being overcome by the development of faster hardware along with innovative solutions, like heterogeneous systems and computational grids or farms (see e.g. [140–142]). However, even with all these new solutions, there is still some room left to explore and refine older approaches, like biasing (e.g. [143]), optimisation of simulation code (e.g. [144]), and the use of pre-calculated data (e.g. [145]).

This chapter deals with a new approach for estimating prompt-gamma emission. It relies on Monte Carlo simulations to first build a database, which will be used afterwards during further simulations. In this sense, it may be categorised as a "pre-calculated data approach", but the striking difference is the second set of simulations, since it employs a track-length estimator (TLE) coupled with an analytical approach based on the pre-calculated data to estimate the aforementioned emission.

TLE is a known fluence scorer in Monte Carlo simulations and it is established as a powerful tool to accelerate them [146, 147]. It relies on the knowledge of the track length between successive collisions or structure boundary (e.g. boundary of a voxel) in order to estimate a particle fluence. This fluence will be equal to the step length divided by the volume of the considered structure. The fluence can then be used to calculate, for example, the dose in the medium. When considering voxelized structures, this approach allows for assigning the quantity in study to all voxels between physical interaction, thus providing a significant variance reduction [147]. A schematic representation comparing analogue Monte Carlo and the TLE approach is depicted in figure 6.1.



FIGURE 6.1: Schematic representation of the TLE principle. The red line represents an arbitrary particle track while the yellow star indicates an interaction. The figure on the left shows the schematic illustration of the analogue Monte Carlo scoring, in which only the pixel where the interaction occurs stores information about the intended quantity. On the other hand, the figure on the right illustrates the TLE principle for which the scoring happens in all pixels crossed by the particle track and each scored pixel quantity is proportional to the track length inside the considered pixel.

The approach discussed herein is innovative since, on the one hand, Geant4 does not provide a TLE implementation, hence there is the need to develop it, and, on the other hand, it should allow for a substantial reduction of the CPU time due to the joint use of both TLE and pre-calculated data. To note the specificity to prompt gammas of the TLE implementation, it was decided to use the acronym pgTLE for this algorithm.

6.2 Code profiling

As discussed in the previous section, several options may be implemented in order to accelerate Monte Carlo simulations. However, no matter which acceleration strategy one may adopt, it is important to understand which processes have a major impact on the calculation time for the intended application. Ultimately, knowing this, one may develop approaches that target those bottlenecks.

For proton therapy applications, there is the need to work with voxelized geometries and to have an accurate modelling of electromagnetic (EM) processes to account for most of the dose deposited. In addition, the hadronic processes must also be considered to model the interactions with the target nuclei. In this section, the steps leading to a Geant4 profiling and the results are described. It was decided not to perform a code profiling as it is usually done, for example, by describing in detail the calculation time needed for each class and function in the code. Such an approach would be cumbersome since Geant4 is currently a toolkit with around 750,000 lines of code [148] and the analysis of a typical profiling would overwhelm this entire work. Being so, the methodology used was very pragmatic. The first step was to employ a simple homogeneous phantom being irradiated by a proton beam and increasingly activating the different physical processes (i.e. transportation, EM, hadronic elastic, and hadronic inelastic processes). In the subsequent steps, the procedure was the same, but with phantoms of growing complexity in terms of geometry and material. For each case, the process was repeated five times with different seeds to reduce statistical fluctuations. The average time per primary particle is presented. The number of primaries is large enough to discard the Geant4 initialisation time as a factor. The use of a computed tomography (CT) scan image as the most complex case was pondered, but there would be no added value in introducing that much complexity. Eventually, the goal of this pragmatic code profiling is to be aware of the bottlenecks present in Geant4 simulations when the modelling needs of proton therapy are taken into account.

The phantoms were built with a cubic geometry (600-mm side) and for all cases their dimensions were kept constant. The particle source is placed in the centre of the cube and it is modelled as isotropic. The geometry is always defined using G4VNestedParameterisation since Schümann et al. have demonstrated that it provides an efficient navigation through highly voxelized structures, namely CT images [149]. In order to assess the performance of modelling only the primary particle, a specific case will be considered, in which every new particle created is immediately killed. Such a study gives an indication of the cost of only propagating a given particle with a given set of physics processes activated. The impact of modelling electrons will also be checked by changing the corresponding production cut with a full simulation. It should be stressed that any profiling approach in a code as large and as complex as Geant4 inevitably creates some bias on the analysis and it may thus hinder important details. Nevertheless, the methodology followed should at least give some hints concerning performance bottlenecks. A remark for the fact that the transportation-only CPU time values have a bias. Since for this case the primary particle will not interact, the track length will be longer than when considering EM and hadronic interactions. Hence, more navigation-associated computations for the primary particle will be performed. It was considered a normalisation regarding the primary track length, but such an approach would only work when the secondary particles are not propagated. As so, it was decided not to apply any normalisation but, instead, to be aware of this issue.

It should be stressed that for all cases the default production cut value of 0.7 mm was used (default when considering the QGSP_BIC_HP reference physics list).

Material	Density (g/cm^3)
Lung inhale	0.217
Lung exhale	0.508
Adipose tissue	0.967
Breast	0.990
Water	1.000
Muscle	1.061
Liver	1.071
Trabecular bone	1.159
Dense bone	1.575

TABLE 6.1: Material defined in the Geant4 DICOM example taken from the ICRU report 46 [150].

The code to perform this study was based on the DICOM example of Geant4. The materials considered were the ones defined in this example taken from the International Commission on Radiation Units and measurements (ICRU) report 46 [150] (table 6.1). The following list describes the increasing complexity of the phantoms used, table 6.2 shows the specifications of the computer used for this profiling, and table 6.3 presents the physics list used for this study. It should be noted that the meaning of "randomly

heterogeneous" in the following list of test cases is a random selection of the materials constituting each voxel.

- homo1: monolithic and homogeneous water target
- homo10: homogeneous water target divided in 10 voxels in each direction (voxel size: 60×60×60 mm³)
- homo100: homogeneous water target divided in 100 voxels in each direction (voxel size: 6×6×6 mm³)
- homo600: homogeneous water target divided in 600 voxels in each direction (voxel size: 1×1×1 mm³)
- hetero10: randomly heterogeneous target divided in 10 voxels in each direction (voxel size: 60×60×60 mm³)
- hetero100: randomly heterogeneous target divided in 100 voxels in each direction (voxel size: 6×6×6 mm³)
- hetero600: randomly heterogeneous target divided in 600 voxels in each direction (voxel size: 1×1×1 mm³)

TABLE 6.2: Specifications of the computer used for the code profiling.

Brand and model	CPU	RAM	Hard drive
Dell M3800	Intel [®] Core TM i7-4702HQ CPU @ 2.20GHz	$16 \text{GB} \ 1600 \text{MHz} \ \text{DDR3L}$	500GB 5400rpm SATA 6Gb/s

TABLE 6.3: Physics list defined for the profiling. Note that the use of each process depends on the considered test case.

Process	Models
EM	$G4EmStandardPhysics_option4$
Hadronic elastic	G4HadronElasticPhysicsHP
Hadronic inelastic	G4HadronPhysicsQGSP_BIC_HP (proton and neutron) G4IonBinaryCascadePhysics (others)

6.2.1 Primary particle: proton

The first test was to simulate protons as primary particles. Their energy was fixed at 160 MeV, given that this value is a representative energy of the ones used clinically. Table 6.4 shows the results from the different test cases with and without simulation of secondaries.

6.2.2 Primary particle: gamma

In this section, the results of the simulation of gammas as primary particles is presented. The energy of the gammas was randomly assigned between 1 and 10 MeV, since it is a representative range of the energy of prompt gammas emitted in the context of proton therapy. Table 6.5 shows the results from the different test cases with and without secondaries.

TABLE 6.4: Results of the code profiling when using 160 MeV protons as primary particles. Five tests are considered: transportation only (transportation), addition of electromagnetic processes (EM), addition of elastic hadronic processes (Elastic), and addition of inelastic hadronic processes (Inelastic).

	CPU time per primary (μs)								
	No secondaries					With secondaries			
Case	Transportation	EM	Elastic	Inelastic	EM	Elastic	Inelastic		
homo1	3	56	82	143	68	97	617		
homo10	11	67	97	159	95	128	670		
homo100	84	156	215	279	268	325	964		
homo600	505	741	991	1018	1024	1261	2241		
hetero10	12	79	221	292	156	310	1712		
hetero100	111	252	542	761	455	881	3813		
hetero600	739	1294	2805	3085	1697	3460	16368		

TABLE 6.5: Results of the code profiling when using gammas as primary particles. The gammas were simulated with a random energy between 1 and 10 MeV. Two tests are considered: transportation only (transportation) and addition of electromagnetic processes (EM).

	CPU time per primary (μs)					
	No secondaries		With secondaries			
Case	Transportation	EM	EM			
homo1	3	19	76			
homo10	12	34	199			
homo100	91	164	642			
homo600	661	992	2280			
hetero10	12	33	180			
hetero100	109	197	634			
hetero600	544	926	1954			

6.2.3 Discussion

The results for protons as primary particles follow what was initially expected: the growing complexity, of either physics or geometry, tends to drive an increasing higher need for CPU time. Taking into consideration the *no secondaries* cases, the geometry has a substantial impact on the proton tracking time, going up to a factor around 246 when comparing the most complex heterogeneous target with the homogeneous one with only transportation activated. However, since the other processes overwhelm transportation, this factor is reduced to a value around 21 when comparing the same cases with all processes in the physics list activated.

When comparing the results from tables 6.4 and 6.5, it is observed that, without propagation of secondaries, the tracking of protons is more CPU time consuming. However, when secondaries are propagated, the simulation with gammas is more time demanding for all geometrical cases used. The reason for this is the tracking of electrons, given that, in a homogeneous water target with the primary particle energy range considered for the profiling study, the gammas create around four times more electrons per primary particle. Although the proton ionisation process should correspond to a *de facto* higher number of electrons being produced in respect to the Compton, photoelectric, and pair production processes for gammas, in reality many of the electrons created by the proton ionisation are below the production cut. As already stated, the production cut was set to 0.7 mm since it is considered as the default value for the reference physics lists recommended for medical physics applications (e.g. QGSP_BIC_HP).

It is also worthwhile to estimate the time needed to propagate the number of protons for a typical pencil-beam spot and the expected number of prompt gammas that results from the proton interactions. Assuming that 5×10^7 protons are needed to fill a spot, this would require, for the most complex geometry (i.e. hetero600), around 43 h and 227 h, respectively without and with the propagation of secondaries (using a single CPU of the machine considered), a time frame usually not compatible with the clinical workflow. In turn, for the gamma propagation, following the data shown in table 3.10(page 77), the number of protons to deliver a spot would be responsible for emitting around 550 prompt gammas mm⁻¹ sr⁻¹, thus about 6900 prompt gammas mm⁻¹ in 4π (assuming an isotropic emission). Using the CPU time without secondaries for gammas from table 6.5 and the projected proton range in PMMA (table 3.3, page 44), one would obtain a total of around 989 s. Although about 15 min of calculation time for the tracking of all gammas may seem relatively fast, such a calculation time seems excessive to cope with the clinical workflow because of all other spots in the treatment plan. It is then advisable to also envisage procedures to circumvent this issue, like analytical solutions (e.g. ray tracing algorithms as the one in [151]) or faster calculation methods

(e.g. calculation on a graphics processing unit, for instance following the approach of Bert and colleagues [152]). However, the investigation of this problematic is outside the framework of the research project herein and should be therefore considered elsewhere.

6.3 pgTLE approach

Herein, the concept and details about the pgTLE algorithm are provided. It is important to note that this approach addresses the prompt-gamma emission, thus the goal is to accelerate its modelling to allow for a substantial reduction of the computational resources needed. Ultimately, the aim is to develop a solution that can be applicable within the context of hadrontherapy monitoring with prompt gammas and that is able to cope with the clinical workflow constraints, namely the time spent to prepare and validate both the treatment and monitoring planning. Although at this moment the procedure required to employ prompt-gamma monitoring in therapy is unknown, it is expected that it may utilize at some extent Monte Carlo-based solutions, considering the strategy being followed so far for hadrontherapy monitoring with PET systems [153], even if it is only as validation.

6.3.1 Concept

The pgTLE approach follows two distinct concepts. On the one hand, it relies on a database of prompt-gamma spectrum emission calculated *a priori* by Monte Carlo in order to replace CPU expensive calculations, and, on the other hand, it uses the concept of TLE. Although TLE is a relatively standard variance reduction technique algorithm, it is not implemented in Geant4. The method is separated into three different steps:

- 1. Prepare the prompt-gamma emission database.
- 2. Run a low statistics simulation in order to identify which voxels are hit by incident ions. For each of these voxels, a full prompt-gamma energy spectrum is calculated.
- 3. Propagate prompt gammas through the geometry.

The estimated number of prompt gammas per energy bin and per voxel, $dN_{\gamma}/dE_{\gamma}(x, y, z)$, normalised to the number of incident protons is calculated with equation (6.1), where each symbol represents the following quantities:

• $\mu(m, E_i)$, proton inelastic attenuation coefficient of a given material m and for the proton i entering the (x, y, z) voxel with an energy E_i

- L_i , track length of the proton *i* inside the (x, y, z) voxel
- $dN_{\gamma}/dE_{\gamma}(m, E_i)$, prompt-gamma energy spectrum per proton inelastic interaction for a given material m and for the proton i entering the (x, y, z) voxel with an energy E_i
- *n*, number of primary protons used in step 2

$$\frac{\mathrm{d}N_{\gamma}}{\mathrm{d}E_{\gamma}}(x,y,z) = \sum_{i=1}^{n} \mu(m,E_i) L_i \frac{\mathrm{d}N_{\gamma}}{\mathrm{d}E_{\gamma}}(m,E_i)$$
(6.1)

The proton energy is therefore assumed constant along the track length inside voxels.

Step 1 – prepare the prompt-gamma emission database

The prompt-gamma emission database is a set of 2D histograms correlating a promptgamma energy spectrum with a given proton energy for each material considered. This step is performed only once for all materials and it is done off-line. A proton impinges a homogeneous target of the given material and every time a prompt gamma is emitted (Geant4 condition: a gamma emitted from a fHadronicInelastic process with a proton as parent) both the energies of the prompt gamma and of the proton at the time of prompt gamma creation are recorded in a file. This procedure is repeated for a given number of protons, to which the histogram is then normalised. There is no theoretical limit for the number of primary protons needed to create this database, but it should have enough statistics in order to not contain artefacts. It should be noted that the incident protons should have an energy higher than the one used clinically so to fill all the meaningful energy range and that the target should be big enough to allow for the complete stop of protons inside.

Step 2 – low statistics simulation

The purpose of the "relatively" low statistics simulation is to create a 3D prompt-gamma emission map in the voxelized geometry. Each simulated proton will be subjected to a simulation for which, every time a proton traverses a given voxel, the energy spectrum $dN_{\gamma}/dE_{\gamma}(x, y, z)$ scaled by the proton inelastic cross section and by the track length to account for the emission probability (equation (6.1)), is summed to it. This process is repeated up to a given number of incident protons depending on the size of the geometry,



FIGURE 6.2: Example of one case considered for the database correlating the proton energy during inelastic nuclear collisions with the energy and number of the prompt gammas emitted per inelastic nuclear collision. The target considered for this plot is the bone equivalent material as described in [44].

beam properties (namely dimension and divergence), and voxel size. In this method, there is no problem with low statistics per voxel since, every time a proton hit a given voxel, a full prompt-gamma energy spectrum is assigned to that voxel. Although the energy spectrum assigned to a given voxel does not show the effects of low statistics if few protons hit it, the resulting prompt-gamma emission from that voxel will inherently have a higher systematic uncertainty because a representative average track length was not properly estimated. Nevertheless, this approach has the advantage of not requiring any de-biasing technique afterwards, since all the scaling factors imparted to the energy spectrum should make the average voxel prompt-gamma emission equivalent to an analogue Monte Carlo simulation.

In the end, the 3D map should be a representative distribution of the prompt-gamma emission in the geometry. The reason why, in the beginning of this section, the word relatively is between quotes is due to the fact that enough protons must be simulated in order to achieve the aforementioned representative distribution. A rule to estimate such number of protons is still unknown. In order to have an idea of the time gained by this algorithm (assuming step 2 as the sole responsible for the time gain), a test case was implemented. First, the typical number of protons composing a pencil beam (i.e. 5×10^7 protons, see section 3.1.5 in page 75) was fully simulated in a complex water target (1 mm³ voxels) with an energy of 160 MeV. To further emulate a clinical proton spot irradiation, the lateral beam spatial spread distribution was defined as Gaussian with 5 mm sigma, a value close to the one found by Grevillot et al. [13]. The outcome of this simulation is a list of voxels where prompt gammas were emitted, along with their number per voxel. The results from this simulation are depicted in figure 6.3.

To avoid considering voxels that contribute very little to the total prompt-gamma emission, the data was projected in each of the target axis and a voxel selection was made. In the transversal axes, a Gaussian fit was carried out and the sigma value retrieved for each one. Subsequently, a criterion based on the sigma value (transversal axes) and on a given percentage of the prompt-gamma profile fall-off was implemented to select voxels (see table 6.6). The index numbers of the selected voxels are then written to a second list.

In a second simulation, the list of selected voxels is used as input. When all voxels of such a list are hit by at least one proton, the simulation code prints the number of primary protons. This test is repeated several times with different seed numbers to verify the consistency of the result. The outcomes are presented in table 6.6.



FIGURE 6.3: Prompt-gamma emission distribution in a voxelized homogeneous water target (1 mm³ voxels) in axial (left) and longitudinal (right) views.

In order to make this process clearer, the following list summarises it.

- 1. 100 simulations were performed, each with 5×10^5 incident protons the voxel numbers where prompt gammas are emitted are saved into a file
- 2. the 100 files are read and several files are created based on different criteria for voxel selection (see table 6.6) and where there is no duplicate voxels
- 3. five simulations are launched with a given input file and the simulation stops when all voxels in the file are hit
- 4. this process is repeated for all files with different voxel selection criteria
- 5. the number of primary protons needed to hit all listed voxels is printed

Given that the prompt-gamma profile obtained with these criteria is representative of the prompt-gamma distribution, this means it is possible to reach a significant number of

Stopping condition	Voxel selection criteria	Number of primaries $(\times 10^4)$	
Full simulation	not applicable	5000	
	$\pm 3\sigma$ (x,y) and 5% fall-off (z)	2150 ± 867	
All listed versels are hit at least once	$\pm 2.5\sigma$ (x,y) and 5% fall-off (z)	71.4 ± 10.1	
All listed voxels are lift at least once	$\pm 2\sigma$ (x,y) and 5% fall-off (z)	6.6 ± 1.0	
	$\pm 2.5\sigma$ (x,y) and 1% fall-off (z)	96.6 ± 37.4	

TABLE 6.6: Results from the test cases with voxel selection criteria in order to estimate the number of primary particles needed to hit all listed voxels after a given voxel selection criterion. Each case is simulated five times to estimate the uncertainty.

hit voxels with prompt-gamma emission (for the spot considered) with only 6.6×10^4 primary protons. By taking into consideration the prompt-gamma emission probability per voxel, following equation (6.1), it may then be possible to use a number of protons as low as this one to estimate the distribution of prompt gammas, thus a reduction factor in the number of simulated protons of around 750. However, this reduction factor for a real application might be different, since the test cases do not take into account any other effects besides the voxel hit. Moreover, additional studies are needed to verify if less strict criteria can be applied with good prompt-gamma distribution accuracy, thereby further increasing this factor. It should also be noted that the geometry in test has an extremely fine description and it can be seen as a worst case scenario. Hence, the use of more common voxel dimensions (e.g. [154, 155], where voxels with 2 mm^3 and $2.73 \times 2.73 \times 3.27$ mm³ are reported, respectively) can further reduce the amount of particles needed for the considered stopping condition. Nevertheless, one issue not considered so far is the overhead introduced by the use of the pgTLE algorithm. For example, the need to keep track of the energy spectrum $dN_{\gamma}/dE_{\gamma}(m, E_i)$ for each voxel may be cumbersome due to memory limits and input/output operations on the disk. These factors will have an impact on the simulation time and it is expected that, for the same amount of primaries, this step 2 will be more time consuming than an analogue simulation.

Ultimately, a more thorough analysis must be conducted in order to estimate the amount of primary protons mandatory to yield a prompt-gamma profile within a given accuracy in respect to the one retrieved from a full Monte Carlo simulation.

Up to this moment, no other particle other than protons is being simulated. Every time a particle is created, it is killed, a situation analogous to the "no secondaries" cases tested during the profiling. It is assumed that most of the useful information for proton range purposes is coming from the proton inelastic interactions and few other particles are created that can undergo interactions with a meaningful contribution to the prompt-gamma emission. If this assumption is not true, a bias is inevitably introduced on the results of the hybrid approach. The assumption will be tested and the results presented in section 6.3.2.

Step 3 – propagation of prompt gammas

After the selection of the number of incident protons, prompt gammas are created for each voxel (x, y, z) in the geometry (each voxel in the geometry will act as a gamma source). The number of simulated prompt gammas can be larger than the expected prompt-gamma emission since it is always possible to normalise it to the expected one afterwards. The energy of the gammas will be randomly sampled, following the energy spectrum calculated during the low statistics simulation and the emission is considered to be isotropic. To avoid binning artefacts, the emission position is also randomly sampled inside the given voxel. The gammas are then propagated through the geometry using only electromagnetic interactions. If there is the need to further accelerate the process, this Monte Carlo propagation may also be replaced by analytical methods, like ray-tracing techniques.

6.3.2 Preliminary study of assumptions bias

So far, the hybrid approach only contemplates prompt gammas originated from proton inelastic processes. However, such a simplification may render the method inaccurate for clinical applications by introducing some bias. Therefore, the purpose of this section is to perform a preliminary work on this assumption, by comparing all sources of prompt gammas in cases with a typical clinical proton energy of 160 MeV.

The first test comprises a homogeneous cylindrical PMMA target with 200 mm length and 75 mm radius. In order to study the effect of heterogeneities, a second test with an arbitrarily complex target is performed. The target is a PMMA block of 250 mm length and 75 mm radius, with several cylindrical pieces of different materials inside. Each of these cylinders has 10 mm length and 65 mm radius. The materials are the same used in the code profiling. Figure 6.4 depicts a schematic illustration of the heterogeneous target defined for the Geant4 simulations.

Gammas are scored at the target border and the information concerning position, momentum, energy, TOF, the creator process, and the particle that created them are stored in a file (a phase space) for posterior analysis. In order to approximate the distribution of the recorded gammas to a case where a monitoring device is present, gammas are selected according to a polar angular acceptance in the range $[89^{\circ}-91^{\circ}]$ (similar to what was done in chapter 4, section 4.3.1). Since it is reasonable to use an energy threshold



FIGURE 6.4: Illustration of the geometry implemented in Geant4 for the test with an arbitrarily complex heterogeneous target. The target is made of PMMA (number 11 in the figure) with several cylindrical slabs of different materials inside. The definition of the materials was taken from the ICRU report 46 [150]. Using the numbers shown in the figure, the complete material list is: 1) air, 2) trabecular bone, 3) water, 4) liver, 5) lung inhale, 6) dense bone, 7) breast, 8) lung exhale, 9) muscle, and 10) adipose tissue.

on the detected gammas in a real scenario in order to improve the signal contrast, the same energy threshold applied to the experimental data presented in chapter 3 was used $(1 \le E \le 7 \text{ MeV})$. Moreover, in order to use only the information provided by prompt gammas, TOF selection is employed to select them. This study was performed using the QGSP BIC HP reference physics list.

The results shown in figures 6.5 and 6.6 demonstrate that the assumptions for this acceleration scheme have a not negligible effect on the prompt-gamma profile, namely on its amplitude. The difference is always greater than approximately 5%, which may be considered excessive. However, by considering the 80% prompt-gamma fall-off (assuming the maximum before the fall-off), the prompt-gamma profile length difference is up to 1 bin, thus the length difference is at maximum equal to 1 mm for both homogeneous and heterogeneous case. Being so, if the quantity of interest is the measurement of the proton range using only the prompt-gamma fall-off position, such an approach for fast computation of the prompt-gamma emission may be extremely useful.

It is likewise important to note that the neutron-associated processes are the second most common to contribute to the prompt-gamma emission. In a later stage of this hybrid algorithm, it may be worthwhile to consider the implementation of those processes in the method, namely the neutron inelastic interactions, knowing that it is the one that contributes to the emitted prompt gammas the most, with 99.9% of the total prompt gammas, while the remainder 0.1% results from the neutron capture process (both homogeneous and heterogeneous target cases show the same numbers).



FIGURE 6.5: Longitudinal profile (top) and relative difference between gammas created by all processes and gammas originated from proton inelastic only (bottom) for the homogeneous target.

The events identified as "Gammas from other processes" represent less than 0.3% of the total number of prompt gammas. They are the result of inelastic interactions of secondary nuclei created after a proton inelastic process (0.01% of the total prompt gammas), and of Bremsstrahlung process from either electrons (0.2%) or positrons (0.02%). These numbers demonstrate that these processes are not meaningful for the prompt-gamma emission for the cases considered, thus not deserving special treatment in respect to the hybrid approach.



FIGURE 6.6: Longitudinal profile (top) and relative difference between gammas created by all processes and gammas originated from proton inelastic only (bottom) for the heterogeneous target.
Chapter 7

Conclusions and outlook

This manuscript provides an insight in several steps of the research and development towards the construction and application of a multi-slit collimator camera. It began by describing a comprehensive and extensive experimental work focused on demonstrating the feasibility of the prompt-gamma monitoring with such a device. The confidence in the data presented is clearly enhanced after the absolute yields study. Even with different setups, irradiation facilities, detectors, as well as different people in charge of the electronics and acquisition chain, the data agree remarkably well after the normalisation. It may be that some systematic uncertainties were not accurately estimated or some of them were not considered, but there are no indications that this may have a significant impact.

The study with inhomogeneous targets is also noteworthy. To my knowledge, this study is the very first to address the prompt-gamma monitoring with inhomogeneous targets with carbon ions. There was already some analysis performed on these data during the course of the doctoral studies of Testa [156] within our collaboration but it was a preliminary study, thus with some inconsistencies that have been corrected and presented herein. These data were also used to create a prompt-gamma profile length quantity, which is a striking quantity in the multi-slit collimated camera, as it allows for distinguishing this technique from the other collimated camera design, the knife-edge collimator camera. This approach assumes that the position where the beam enters the patient is known to then estimate the ion range based on the position of the prompt-gamma fall-off. In fact, this is partially true, given that it is possible to use the information from the beam delivery system to know which pencil beam is being delivered at that moment and then estimate the entrance point in the patient. To further extend the accuracy of this entrance point retrieval, it may be possible to use optical systems to identify the location of the patient skin surface. However, even if one assumes that the entrance retrieval precision of the multi-slit collimated camera is worse than the combination of TPS, information of the patient position, and optical systems (yet to be proven), the clinical integration alone of all these different systems plus the monitoring device itself into a single "treatment monitoring system" (TMS) may be extremely difficult. This may be eased if one considers that all these systems are provided by the same vendor, who can then make a real full TMS integration, or if clear industry-based standards for the TMS exist. By providing the measurement of the full ion range with the prompt-gamma profile length quantity, the multi-slit collimated camera avoids all this hassle, not to mention that such a quantity can potentially be directly correlated with the ion range. Moreover, the multi-slit collimated camera does not assume an *a priori* knowledge of the Bragg peak position, while the knifeedge camera does due to a better precision of the fall-off position retrieval. Nevertheless, the knife-edge solution is less bulky and less heavy, hence easier to implement in a clinical scenario, and possibly less expensive for the same set of features (e.g. scintillating crystal, TOF). Concerning the other techniques exploiting prompt gammas (i.e. the ones using energy and time information), although very promising, at the moment of writing only one article for each case was available [79, 81].

The collimator optimisation study allows for a better understanding of the attainable performance of the multi-slit collimated camera. It is based on Monte Carlo simulations, thus with potential inaccuracies due to the physical models and simplifications. However, it was a good starting point for the construction of the device that may have a precision between 1 and 2 mm at the level of a typical pencil beam distal spot. Moreover, the discussion concerning the advantage of using TOF is extremely importance since it shows the impact of using it in a device such as this one. When comparing optimised multi-slit collimated cameras with and without TOF, it is possible to attain a fall-off retrieval precision of 1.3 and 3 mm, respectively, for a clinically-relevant number of incident protons and homogeneous PMMA targets. Although this improvement depends on the time structure of the beam and further studies using inhomogeneous targets are needed, TOF is definitely a feature that should be considered when developing hadrontherapy monitoring solutions using prompt gammas. The final device is being currently constructed and I hope some results may come out soon and that the entire community focused on hadron provide monitoring may profit from them, notably from the potentialities of the multi-slit collimated camera to detect ion range shifts due to lateral inhomogeneities and other complex cases that may rely on the information provided by the full profile and not only from the fall-off position. In my opinion, such studies must have priority since they may provide further results about the distinct characteristics of this camera: the ability to monitor by means of the prompt-gamma emission the full ion range and the better spatial resolution when compared with the knife-edge approach. Furthermore, the simulation study should be extended to carbon ion beams (and why

not also to helium and oxygen ion beams due to the growing interest in these two ion species) to assess the feasibility of using the optimised design with them. In any case, the use of this device in a clinical scenario with carbon ions may be limited, given that the expected number of prompt-gammas emitted for a spot and iso-energy layer may be too low to have the multi-slit collimated camera as a viable solution. Likewise, the need to increase the distance to the beam axis to allow for a better use of TOF to separate prompt gammas from neutron-induced events further reduces the amount of signal available. In this regard, interaction vertex imaging may be more advantageous due to the number of protons leaving the patient but, so far, the studies have been focused on relatively small phantoms and proton scattering and stopping in the patient may be decisive factors for the future of this technique. For additional information concerning the applicability of interaction vertex imaging to carbon ion therapy monitoring, the studies of Henriquet et al. [86], Gwosch et al. [87], and the forthcoming doctoral thesis manuscript of Reithinger [157] (in French but an English article should be published soon) should be given due consideration. A hybrid solution may also be considered, in which prompt gammas and secondary charged particles are detected to complement each other information. However, if translating to the clinical practice a single monitoring device has proven to be a difficult task due to the intrinsics of hadrontherapy monitoring, to integrate two devices in one may be extremely challenging. Therefore, I would propose that the research of the multi-slit collimated camera for proton beams be continued, while putting all the efforts on the interaction vertex imaging when considering carbon ion treatment monitoring.

The improvement of Geant4 inelastic hadronic models and the simulation acceleration studies (for the sake of simplicity, hereafter the former is simply referred to as *improvement* study and the latter as *acceleration study*) can be considered as being in a preliminary stage. However, both of them show the potentialities allowed by the Geant4 toolkit with its open-source approach: an end-user can always improve the built-in functionalities and add new ones. The improvement study demonstrated that the possibilities to tune Geant4 to a specific application are not only the selection of a set of physical models comprising a physics list and the choice of cuts. In fact, there are several free, model-specific quasi-free (i.e. bounded by a given range), and physics-specific quasi-free (i.e. bounded by a given physical range, e.g. r_0 in the nuclear radius equation) parameters that can be tuned according to the user application. Several of these parameters in different hadronic models were tested and the results were then compared with experimental data. This study led to the proposal of a tuned version of QMD model to be used as proton hadronic inelastic model when prompt-gamma emission is to be considered, thus showing its capabilities. Nevertheless, the groups focusing in gamma spectroscopy should verify if this model is more accurate when dealing with discrete prompt-gamma decay lines. In any case,

I would strongly recommend that the developers take a closer look at this model, as during this work several bugs were found and the code implementation does not seem very refined. With the proper developments and improvements, I do believe that this model has the potential to be among the strongest ones built-in in Geant4 due to the better overall accuracy already pointed out by the present study and several others. Still, this can only happen if the computing time needed by QMD is dramatically reduced. One cannot expect that a much more descriptive model as QMD will be as fast as, for example, Binary Cascade but, when the computing time difference between them can be a factor ten (or even more) higher for the same application, it can be difficult to justify its use except for very specific scenarios. On the other hand, the acceleration study described a method to be implemented in Geant4 in order to accelerate its computing time for prompt-gamma emission estimation. Although it is still in a very preliminary stage, it already demonstrated that it may possibly have a great impact on the acceleration of simulations. Other approaches with the same goal exist. The group of IBA has recently presented a novel method based on look-up tables and pencil-beam algorithms to predict the prompt-gamma distribution that is then detected by the knife-edge camera they are developing [158]. In this work, they claim less than 2 s calculation time in a yet non-optimised module to obtain the expected prompt-gamma distribution after detection for a full treatment. The usefulness of this tool, however, can only be assessed in a clinical situation, as relying on pencil-beam algorithms also carries the limitations of such approaches, namely the lateral beam penumbra and the behaviour in highly heterogeneous media (in this regard, the work of Egashira et al. [159] shows a good overview). Therefore, a method that does not rely on pencil-beam algorithms as the one presented in chapter 6 may be advantageous. Again, only the clinical use of these tools may prove their utility and applicability.

Herein an extensive, comprehensive, and systematic work was performed concerning the research and development of a TOF-based multi-slit collimated camera. It is my belief that the present study will contribute to the development of this monitoring solution and its translation into clinics. In addition, the studies focusing on Geant4 improvements and its acceleration may be used by others in different fields but dealing with the same difficulties.

Appendix A

Summary of the experiments

TABLE A.1: Summary of the features of the targets, detectors and collimators used in each experiment.

Carbon-ion experiments				
	GANIL 95 MeV/u	GSI 300 MeV/u	GSI 310 MeV/u	HIT 310 MeV/u
Target-detector distance (mm)	605	990	1345	635
Target material	PMMA	Water	Water	PMMA
Target longitudinal dimension (mm)	54	200	200	250
Target transversal dimensions (mm^2)	50×50	120×250	120×250	100×100
Detector	BaF_2 NaI(Tl)	BaF_2	BaF_2	LYSO:Ce
Collimator material	Lead	Lead	Lead	Tungsten
Collimator thickness (mm)	200	200	200	100
Collimator slit (mm)	2	15	4	4

Proton experiments			
	WPE		
	160 MeV (I)	160 MeV (II)	160 MeV (III)
Target-detector distance (mm)	600	505	505
Target material	PMMA	PMMA	PMMA
Target radius (mm)	75	75	75
Target length (mm)	200	200	250
Detector	LYSO:Ce	LYSO:Ce	LoPresCo
	$LaBr_3:Ce$	LaBr ₃ :Ce	Labr3:Ce
Collimator material	Tungsten	Tungsten	Tungsten
Collimator thickness (mm)	100	100	100
Collimator slit (mm)	4	4	4

Appendix B

Experimental data analysis

B.1 WPE 160 MeV H^+ (I) – LaBr₃ detector



FIGURE B.1: Energy spectra obtained from the measurement positions before and inside the target within the proton range with error bars (one standard deviation) associated to each bin (**top**) and with area filling for visualisation purposes (**bottom**). The energy spectra presented are the result of summing the data from the respective positions in order to improve the statistics and by considering only the events inside the prompt-gamma TOF window.



FIGURE B.2: TOF spectra obtained from measurement positions before and inside the target with error bars (one standard deviation) associated to each bin (**top**) and with area filling for visualisation purposes (**bottom**). The TOF axis is relative since no calibration for the axis origin was performed.

B.2 WPE 160 MeV H^+ (I) – LYSO detector



FIGURE B.3: Energy spectra obtained from the measurement positions before and inside the target within the proton range with error bars (one standard deviation) associated to each bin (**top**) and with area filling for visualisation purposes (**bottom**). The energy spectra presented are the result of summing the data from the respective positions in order to improve the statistics and by considering only the events inside the prompt-gamma TOF window.



FIGURE B.4: TOF spectra obtained from measurement positions before and inside the target with error bars (one standard deviation) associated to each bin (**top**) and with area filling for visualisation purposes (**bottom**). The TOF axis is relative since no calibration for the axis origin was performed.

B.3 WPE 160 MeV H^+ (II) – LaBr₃ detector



FIGURE B.5: Energy spectra obtained from the measurement positions before and inside the target within the proton range with error bars (one standard deviation) associated to each bin (top) and with area filling for visualisation purposes (bottom). The energy spectra presented are the result of summing the data from the respective positions in order to improve the statistics and by considering only the events inside the prompt-gamma TOF window.



FIGURE B.6: TOF spectra obtained from measurement positions before and inside the target with error bars (one standard deviation) associated to each bin (**top**) and with area filling for visualisation purposes (**bottom**). The TOF axis is relative since no calibration for the axis origin was performed.

B.4 WPE 160 MeV H^+ (II) – LYSO detector



FIGURE B.7: Energy spectra obtained from the measurement positions before and inside the target within the proton range with error bars (one standard deviation) associated to each bin (**top**) and with area filling for visualisation purposes (**bottom**). The energy spectra presented are the result of summing the data from the respective positions in order to improve the statistics and by considering only the events inside the prompt-gamma TOF window.



FIGURE B.8: TOF spectra obtained from measurement positions before and inside the target with error bars (one standard deviation) associated to each bin (**top**) and with area filling for visualisation purposes (**bottom**). The TOF axis is relative since no calibration for the axis origin was performed.





FIGURE B.9: Energy spectra obtained from the measurement positions before and inside the target within the proton range with error bars (one standard deviation) associated to each bin (**top**) and with area filling for visualisation purposes (**bottom**). The energy spectra presented are the result of summing the data from the respective positions in order to improve the statistics and by considering only the events inside the prompt-gamma TOF window.



FIGURE B.10: TOF spectra obtained from measurement positions before and inside the target with error bars (one standard deviation) associated to each bin (**top**) and with area filling for visualisation purposes (**bottom**). The TOF axis is relative since no calibration for the axis origin was performed.

B.6 GANIL 95 MeV/u ${}^{12}C^{6+}$ – NaI(Tl) detector



FIGURE B.11: Energy spectra obtained from the measurement positions before and inside the target within the proton range with error bars (one standard deviation) associated to each bin (top) and with area filling for visualisation purposes (bottom). The energy spectra presented are the result of summing the data from the respective positions in order to improve the statistics and by considering only the events inside the prompt-gamma TOF window.



FIGURE B.12: TOF spectra obtained from measurement positions before and inside the target with error bars (one standard deviation) associated to each bin (**top**) and with area filling for visualisation purposes (**bottom**). The TOF axis is relative since no calibration for the axis origin was performed.





FIGURE B.13: Energy spectra obtained from the measurement positions before and inside the target within the proton range with error bars (one standard deviation) associated to each bin (**top**) and with area filling for visualisation purposes (**bottom**). The energy spectra presented are the result of summing the data from the respective positions in order to improve the statistics and by considering only the events inside the prompt-gamma TOF window.



FIGURE B.14: TOF spectra obtained from measurement positions before and inside the target with error bars (one standard deviation) associated to each bin (**top**) and with area filling for visualisation purposes (**bottom**). The TOF axis is relative since no calibration for the axis origin was performed.





FIGURE B.15: Energy spectra obtained from the measurement positions before and inside the target within the proton range with error bars (one standard deviation) associated to each bin (**top**) and with area filling for visualisation purposes (**bottom**). The energy spectra presented are the result of summing the data from the respective positions in order to improve the statistics and by considering only the events inside the prompt-gamma TOF window.



FIGURE B.16: TOF spectra obtained from measurement positions before and inside the target with error bars (one standard deviation) associated to each bin (**top**) and with area filling for visualisation purposes (**bottom**). The TOF axis is relative since no calibration for the axis origin was performed.





FIGURE B.17: Energy spectra obtained from the measurement positions before and inside the target within the proton range with error bars (one standard deviation) associated to each bin (**top**) and with area filling for visualisation purposes (**bottom**). The energy spectra presented are the result of summing the data from the respective positions in order to improve the statistics and by considering only the events inside the prompt-gamma TOF window.



FIGURE B.18: TOF spectra obtained from measurement positions before and inside the target with error bars (one standard deviation) associated to each bin (**top**) and with area filling for visualisation purposes (**bottom**). The TOF axis is relative since no calibration for the axis origin was performed.

Appendix C

Geant4 versions used

TABLE C.1: Geant4 versions used throughout the manuscript. The reason for the use of different Geant4 versions is the time frame of each task. As a principle, at the beginning of each task, the latest Geant4 release available at that moment was chosen.

Chapter	Section	Section name	Geant4 version
	Section 3.1.4 and subsections therein	Absolute yields	9.6.p02
Chapter 3	Section 3.2 and subsections therein	Comparison with Monte Carlo simulations	10.00 p02
	Section 3.3 and subsections therein	Prompt-gamma profiles – heterogeneous targets	9.6.p02
Chapter 4	All sections and subsections therein	_	9.6.p01
Chapter 5	All sections and subsections therein	_	10.00 p02
Chapter 6	All sections and subsections therein	_	10.00 p02

Appendix D

Curriculum Vitae

MARCO PINTO

PERSONAL INFORMATION

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Professional email

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Phone +351 967566194

PROFILE

Results-driven researcher in the field of medical physics with proven working efficiency. My research track record, with several articles in renowned journals, oral communications, and posters, demonstrates a great dedication and commitment to the projects I am involved in. Proficiency in GEANT4, C/C++, and ROOT with working knowledge in FLUKA, MCNP/X, and other programming languages.

RESEARCH INTERESTS

Medical physics (radiation physics) Monte Carlo simulation (Geant4, FLUKA, MCNP/X) Monitoring techniques and adaptive strategies for hadrontherapy Parallel architectures (many-core CPU, GPU)

EDUCATION

December 2014 Université Claude Bernard Lyon 1 (UCBL), France

PhD in Medical Physics Marie Curie network ENTERVISION Hosting institutes: IPNL and CREATIS

PhD thesis

Modeling and simulation of physics processes for in-beam imaging Supervisor: Dr. Étienne Testa Co-supervisor: Dr. Jean Michel Létang

September 2010

Universidade de Coimbra (UC), Portugal

Integrated master in Biomedical Engineering Specialization: Radiation and Medical Imaging Grade: 15/20 (1st position in Radiation and Medical Imaging specialization) **Master thesis** *Implementation of a Cyclotron-Based Neutron Beamline: A Viability Study* Grade: 19/20 Supervisor: Prof. Dr. Rui Ferreira Marques Co-supervisors: Dr. Francisco Alves, Dr. Paulo Crespo

WORK EXPERIENCE

January 2015–present

Postdoc, Ludwig-Maximilians-Universität (LMU)

Munich, Germany Postdoc position in the experimental medical physics group of the LMU (link) focused on research in the field of ion radiography/tomography and aiming at the development of a fast Monte Carlo-based treatment planning system for carbon ion beams.

October 2011–December 2014 PhD student, IPNL and CREATIS

Lyon, France PhD project in the framework of the Marie Curie network ENTERVISION dedicated to the development of novel solutions in the field of particle therapy. The context of my project was particle therapy monitoring with prompt gammas and its goal was three-fold: 1) extensive and comprehensive experimental data analysis, 2) benchmarking, assessment and improvement of GEANT4 simulations, and 3) design and optimization of a collimated camera for prompt-gamma monitoring.

November 2010–September 2011

Researcher, LIP COIMBRA

Coimbra, Portugal Research and development of a novel monitoring system for X-ray radiotherapy treatments. My tasks were to make a feasibility study with Monte Carlo simulations of such a system and to perform the design and optimization work of a prototype camera to be tested in a clinical environment. This work led to the construction of a prototype and the results obtained were published and also presented at the 2011 IEEE NSS/MIC conference.

September 2009–September 2010

Master thesis, Universidade de Coimbra

Coimbra, Portugal Feasibility study of the implementation of a neutron beamline using a proton cyclotron dedicated to radioisotope production. This work was carried out by means of GEANT4 simulations.

TEACHING EXPERIENCE

2013/2014

Nondestructive	Practical course on radiography, ultra-sounds, and eddy current.
testing	2 nd semester, 1 st master year of Mechanical Engineering, INSA Lyon, France
GEANT4 workshop	Invited lecturer for introductory course on GEANT4. International School on Subatomic Physics, IPNL 28 October – 2 November 2013. School webpage: <i>link</i>
Introduction to	Introductory course on FLUKA.
FLUKA	1 st semester, 2 nd master year of "Environnement, Atmosphère, Radioprotection" and "Synthèse, Vieillissement et Caractérisation des matériaux du nucléaire".

Université Claude Bernard Lyon 1, Lyon, France

SKILLS

Programming	C/C++, Python, Java, Matlab Parallel programming: CUDA, C++ AMP, directives, task-based
Monte Carlo	GEANT4, FLUKA, MCNP/X
Data analysis	ROOT
Computer	LaTeX, Productivity Suits, Linux, Windows
Soft skills	Leadership skills

WORKSHOPS/TUTORIALS/SPECIALIZED SCHOOLS

Workshop on Range Assessment and Dose Verification in Particle Therapy, 29 - 30 September 2014 2014, Dresden, Germany Monte Carlo methods in Radiation Therapy, 4 - 6 September 2014, Oxford, United Kingdom Introduction to MCNP/X using the Visual Editor, 24 - 28 March 2014, Nuclear Energy Agency (NEA), Issy-les-Moulineaux, Paris, France ENTERVISION/IBA Industrial Course, 14 - 18 October 2013, IBA headquarters, Belgium 2013 ENTERVISION Detectors and Electronics Course, 9 - 13 September 2013, Valencia, Spain Programming Heterogeneous Parallel Architectures, 24 June - 5 July 2013, CEA computer science summer school, Cadarache, France 2012 ENTERVISION Leadership Course, 12 - 16 November 2012, Surrey, United Kingdom ENTERVSION Summer School, 25 - 29 June 2012, Lyon, France ENTERVISION Basic Training Course, 19 - 20 March 2012, HIT and GSI, Germany DoReMi-EURATOM course on Modelling Radiation Effects From Initial Physical Events, 30 2011 May – 10 June 2011, Pavia, Italy

10th Fluka Course, 28 March – 1 April 2011, Heidelberg, Germany

PATENTS

2014 A patent has been filed for which I am co-inventor (filing date 9th May 2014, still under confidentiality)

PUBLICATIONS

2015

M. Pinto, M. De Rydt, D. Dauvergne, G. Dedes, N. Freud, J. Krimmer, J. M. Letang, C. Ray, E. Testa, M. Testa. *Experimental carbon ion range verification in inhomogeneous phantoms using prompt gammas*, Medical Physics, 2015, *under review*

J. Krimmer, M. Chevallier, J. Constanzo, D. Dauvergne, M. De Rydt, G. Dedes, N. Freud, P. Henriquet, C. La Tessa, J. M. Létang, R. Pleskač, **M. Pinto**, C. Ray, V. Reithinger, M. H. Richard, I. Rinaldi, F. Roellinghoff, C. Schuy, E. Testa, M. Testa. *Collimated prompt gamma TOF measurements with multi-slit multi-detector configurations*, Journal of Instrumentation, 2015 (*link*)

M. Pinto, M. Bajard, S. Brons, M. Chevallier, D. Dauvergne, G. Dedes, M. De Rydt, N. Freud, J. Krimmer, C. La Tessa, J. M. Létang, K. Parodi, R. Pleskač, D. Prieels, C. Ray, I. Rinaldi, F. Roellinghoff, D. Schardt, E. Testa, M. Testa. *Absolute prompt-gamma yield measurements for ion beam therapy monitoring*. Physics in Medicine and Biology, 2015 (*link*)

J. Krimmer, J.-L. Ley, C. Abellan, J.-P. Cachemiche, L. Caponetto, X. Chen, M. Dahoumane, D. Dauvergne, N. Freud, B. Joly, D. Lambert, L. Lestand, J.M. Létang, M. Magne, H. Mathez, V. Maxim, G. Montarou, C. Morel, **M. Pinto**, C. Ray, V. Reithinger, E. Testa, Y. Zoccarato. *Development of a Compton Camera for Medical Applications based on Silicon Strip and Scintillation Detectors*. Nuclear Instruments and Methods in Physics Research Section A: Accelerators, Spectrometers, Detectors and Associated Equipment, 2014 (*link*)

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2013 M. Cunha, M. Pinto^{*}, H. Simões, B. Ferreira, M. do Carmo Lopes, P. Fonte, P. Crespo, Dose-Free Monitoring of Radiotherapy Treatments With Scattered Photons: Concept and Simulation Study, IEEE Transactions on Nuclear Science, 2013, *<u>note</u>: M. Cunha and M. Pinto contributed equally to this work (<u>link</u>)

H. Simões, M. Cunha, **M. Pinto**, J. Gonçalves, L. Sampaio, R. J. Ferreira, H. M. Saraiva, A. R. Barbeiro, M. Capela, B. Ferreira, P. Fonte, S. Ghithan, A. Leal Plaza, M. d. C. Lopes, P. Martins, P. Crespo, *Dose-Free Monitoring of Radiotherapy Treatments With Scattered Photons: First Experimental Results at a 6-MV Linac*, IEEE Transactions on Nuclear Science, 2013 (*link*)

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- 2011 M. Cunha, M. Pinto, B. Ferreira, P. Fonte, M. C. Lopes, P. Crespo. Dose-Free Monitoring of Radiotherapeutic Treatments with Scattered Photons: Concept and Simulation Study. 2011 IEEE NSS/MIC, 23 – 29 November 2011, Valencia, Spain

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M. Pinto, D. Dauvergne, M. De Rydt, G. Dedes, N. Freud, J. Krimmer, J. M. Letang, C. Ray, E. Testa. *Online particle therapy prompt-gamma monitoring with a collimated camera: heterogeneous phantom study.* 52nd Annual Conference of the Particle Therapy Co-Operative Group (PTCOG), 2 – 8 June 2013, Essen, Germany

P. Cambraia Lopes, **M. Pinto**, H. Simões, A. K. Biegun, P. Dendooven, D. C. Oxley, K. Parodi, D. R. Schaart, P. Crespo. *Monte-Carlo study on prompt-gamma imaging through multi-slat collimators: intrinsic performances with simple and anthropomorphic phantoms*. 52nd Annual Conference of the Particle Therapy Co-Operative Group (PTCOG), 2 – 8 June 2013, Essen, Germany

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OTHER INFORMATION

Grants	2011–2014 · Marie Curie fellowship
Memberships	2014–present \cdot IEEE Engineering in Medicine and Biology Society
	2011–present \cdot Portuguese Physical Society and Medical Physics Division
	2010–present \cdot IEEE Nuclear and Plasma Sciences Society
Languages	Portuguese · Mother tongue
	ENGLISH · Working proficiency
	FRENCH · Intermediate

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