# Dose Delivery and Image-Based Monitoring Strategies in TERA Linac Complexes for Hadron Therapy 

## THĖSE

présentée à la Faculté des Sciences de l'Université de Genève pour obtenir le grade de Docteur ès Sciences, mention physique

par<br>Caterina CUCCAGNA<br>de Rome (Italie)

Thèse $\mathrm{N}^{\circ} 5541$

## GENÈVE

Atelier d'impression ReproMail
2021

FACULTÉ DES SCIENCES

# DOCTORAT ÈS SCIENCES, MENTION PHYSIQUE <br> Thèse de Madame Caterina CUCCAGNA 

intitulée :

## «Dose Delivery and Image-Based Monitoring Strategies in TERA Linacs Complexes for Hadron Therapy»

La Faculté des sciences, sur le préavis de Monsieur G. IACOBUCCI, professeur ordinaire et directeur de thèse (Département de physique nucléaire et corpusculaire), Monsieur U. AMALDI, professeur et codirecteur de thèse (TERA Foundation, CERN, Suisse), Monsieur S. BRACCINI, professeur (Laboratory of High Energy Physics, Université de Berne, Suisse), Monsieur J. DAMET, docteur (Institut de radiophysique, Centre Hospitalier Universitaire Vaudois, Suisse) et Madame M. KOWALSKA, professeure (Experimental Physics Department, CERN, Suisse), autorise l'impression de la présente thèse, sans exprimer d'opinion sur les propositions qui y sont énoncées.

Genève, le 1 février 2021

Thèse - 5541-


Il n'y a que deux façons de vivre sa vie : l'une en faisant comme si rien n'était un miracle, l'autre en faisant comme si tout était un miracle. (Albert Einstein)

Je suis de ceux qui pensent que la science est d'une grande beauté. Un scientifique dans son laboratoire est non seulement un technicien: il est aussi un enfant placé devant des phénomènes naturels qui l'impressionnent comme des contes de fées. (Marie Curie)

Tout est poison et rien n'est sans poison; la dose seule fait que quelque chose n'est pas un poison. (Paracelse)

## Abstract

Hadron therapy (or therapy with charged particles) is a radiation therapy modality that uses the physical and biological properties of fast hadrons to treat solid tumors. Since the 90s, an increasing number of patients has benefit of hadron treatments, making use of protons especially to cure deep-seated tumours and carbon ions for the ones also radio-resistant. Despite the indisputable superior physical dose distribution of hadrons with respect to photons and the higher radiobiological effectiveness of carbon ions, further clinical studies and research efforts are needed in two main fields: on the one hand, in the development of affordable beam accelerators complexes, able to deliver a precise dose to the patient and, on the other hand, in detector technology allowing to monitor and control the delivered dose.

This thesis aims to contribute to these two main topics.

Regarding the accelerator technology, two new accelerators are presented and further studied, consolidating the bridge between the accelerators physics and the medical physics worlds. The above-mentioned accelerators are TULIP - TUrning LInac for Protontherapy and CABOTO - Carbon BOoster for Therapy in Oncology, both patented by the TERA Foundation, the entity supporting and hosting this thesis work at its laboratories at CERN. For about thirty years, the TERA Foundation, led by professor Ugo Amaldi, has played a major role in the development of new, reliable and compact technologies for hadrontherapy, by introducing for example the linacs, the standard in radiotherapy with photons, in the hadron therapy field where only circular accelerators are used. The first purpose of this thesis is studying the beams generated by a TULIP all-linac and the evaluation of the quality of its treatment capabilities. TULIP is based on a high-frequency linac, mounted on a rotating gantry and allows - as all TERA hadron linacs - a fast active energy modulation, without making use of passive absorbers. The study includes the development of a sophisticated simulation software, based on the Monte Carlo FLUKA code, as well as of 3D particle tracking codes, capable to fully predict the characteristics of the accelerated beams. The system is able to track the particles through the linac and magnetic transport lines of the beam, starting from the ion source and ending in the patient's body. At the author's knowledge, it is the first time that a full simulation package consisting in following the beam, particle by particle, along the beam line until the isocenter has been developed and used for a particle therapy system. The results allow to quantify the effects of the nozzle scattering on the accelerators beam characteristics, demonstrating the possibility of relaxing some beam line optics constraints. This has a strong impact, for example, on the optics design of the beam transport lines as it allows to reduce the number of required focusing
elements. The validity of the results is demonstrated by the author, firstly, by comparing the beam characteristics obtained with TULIP to those of the synchrotron operating at CNAO's facility - the Italian National Center of Oncological Hadron therapy - and secondly by calculating the overall dose distribution delivered by TULIP in a patient scenario by using FLUKA and a commercial Treatment Planning System (TPS), configured ad hoc for TULIP.

As far as the monitoring techniques are concerned, the PET (Positron Emission Tomography) is further explored in real time, during the treatment with hadrons. A first case study evaluates the PET activity generated by the CABOTO linac. Thanks to the low duty cycle (less than $0.1 \%$ ) of the CABOTO pulsed beams, with a PET detector it is possible to record the gamma coincidences during $99.9 \%$ of the treatment time. As a consequence, the in-beam PET measurements with CABOTO produce, in a given time, larger statistics than conventional circular accelerators and allow a more precise determination of the ion range. FLUKA MC simulations, performed by including the CABOTO beam time structure, demonstrates that the PET detector is also sensitive to gamma pairs produced in the $\beta^{+}$decays of isotopes having half-lives $\left(T_{1 / 2}\right)$ in the milliseconds range; the most relevant ones are ${ }^{13} \mathrm{O}\left(T_{1 / 2}=8.6 \mathrm{~ms}\right),{ }^{12} \mathrm{~N}$, $\left(T_{1 / 2}=11 \mathrm{~ms}\right),{ }^{9} \mathrm{C}\left(T_{1 / 2}=126.5 \mathrm{~ms}\right)$ and ${ }^{8} \mathrm{~B}\left(T_{1 / 2}=770 \mathrm{~ms}\right)$. The results of this study suggested a new method to verify the Bragg Peak range for hadron treatments. It consists in the detection of short-lived $\beta^{+}$emitters from a short and low-dose pre-irradiation of a part of the tumour target. Since the PET coincidences are acquired when the beam is off, extending the method also to hadron circular accelerators was a natural further step. In order to demonstrate the feasibility of having a short irradiation run for range verification before a carbon-ion treatment, experiments have been performed at CNAO by using an in-beam PET detector, called INSIDE (INnovative Solutions for In-Beam DosimEtry in hadron therapy). A PMMA target was irradiated with a $220 \mathrm{MeV} / \mathrm{u}$ carbon-ion beam and positron emitter coincidences were acquired when the beam was off. The results show that, with $3 \cdot 10^{7}$ carbon ions, the reconstructed positron emitting nuclei distribution - in 2, 4, 8, 10 and 12 seconds measuring times - is in very good agreement with the predictions of the related FLUKA Monte Carlo simulation. The time-dependence of the measured activity, in the 25 seconds that follow the 0.6 s irradiation, quantitatively agrees with the expected one from MC : the time fit shows that the main contribution of ${ }^{8} \mathrm{~B}$ is well predicted by FLUKA while the ${ }^{10} \mathrm{C}$ yield is $60 \%$ larger than the prediction, probably due to a underestimation of the production cross-section. The main conclusion of the study is that the amount of radio-nuclei, measured in the first 5 s after the irradiation of a target with $3 \cdot 10^{7}$ carbon ions, is sufficiently abundant to determine the average carbon ion range with a sigma of 1 millimetre.

## Résumé

La hadronthérapie (ou thérapie avec des particules chargées) est une modalité de radiothérapie qui utilise les propriétés physiques et biologiques des hadrons rapides pour traiter les tumeurs solides. Depuis les années 90, un nombre croissant de patients bénéficie de traitements avec les hadrons, en utilisant spécialement les protons pour soigner les tumeurs profondes et les ions carbone pour les tumeurs radiorésistantes. Malgré l'indiscutable avantage physique de la distribution de dose délivrée par le hadrons par rapport aux photons et l'efficacité radiobiologique des ions carbone, ultérieures études cliniques et efforts de recherche sont nécessaires dans deux domaines principaux: d'une part, dans le développement de complexes abordables d'accélérateurs des particules, capables de fournir une dose précise au patient et, d'autre part, dans la technologie des détecteurs permettant de surveiller et de contrôler la dose délivrée. Cette thèse vise à contribuer à ces deux thèmes principaux.

En ce qui concerne la technologie des accélérateurs, deux nouveaux accélérateurs sont présentés et étudiés, afin de consolider le lien entre la physique des accélérateurs et le monde de la physique médicale. Les accélérateurs mentionnés ci-dessus sont TULIP - TUrning LInac for Protontherapy et CABOTO - Carbon BOoster for Therapy in Oncology, tous les deux brevetés par la Fondation TERA, l'entité qui a soutenu et hébergé ce travail de thèse dans ses laboratoires au CERN. Depuis une trentaine d'années, la Fondation TERA, dirigée par le professeur Ugo Amaldi, joue un rôle majeur dans la conception de nouvelles technologies fiables et compactes pour la hadronthérapie, en introduisant par exemple les linacs, technologie standard en radiothérapie avec photons, dans le domaine de la hadronthérapie. Le premier objectif de cette thèse est l'étude des faisceaux générés par l'accélérateur TULIP all-linac et évaluer la qualité de son traitement. TULIP est basé sur un linac à haute fréquence, monté sur une structure rotative ( gantry) et permet - comme tous les linacs à hadrons de la Fondation TERA - une modulation rapide et active de l'énergie, sans utiliser des absorbeurs passifs. L'étude inclut le développement d'un logiciel de simulation sophistiqué, basé sur le code FLUKA Monte Carlo, et des codes 3D de suivi des particules, capables de prédire de manière exhaustive les caractéristiques des faisceaux accélérés. Le système suit les particules à travers l'accélérateur et les lignes magnétiques de transport du faisceau, depuis la source d'ions et jusque dans le corps du patient. À la connaissance de l'auteur, c'est la première fois qu'un ensemble complet de simulations permettant de suivre individuellement chaque particule du faisceau tout au long de la ligne jusqu'à l'isocentre, est développé et utilisé pour un système de hadronthérapie. Les résultats ont permis de quantifier les effets de la tête de l'accélérateur (nozzle) sur les caractéristiques
du faisceau des accélérateurs, démontrant ainsi la possibilité d'assouplir certaines contraintes d'optique de la ligne de faisceau. Cela a eu un fort impact, par exemple, sur la conception optique des lignes de transport à haute energie car il a permis de réduire le nombre d'éléments de focalisation requis. La validité des résultats est démontrée, d'une part, en comparant les caractéristiques des faisceaux de TULIP avec celles de l'accélérateur du CNAO (Centre national italien de hadronthérapie oncologique) et, d'autre part, en calculant avec FLUKA la distribution globale de la dose fournie par TULIP pour un cas clinique de traitement d'un patient et un système commercial de planification du traitement (TPS), configuré ad hoc pour TULIP.

En ce qui concerne les techniques de contrôle de la dose, l'utilisation de la TEP (Tomographie par émission de positrons) en temps réel pendant le traitement par hadrons, est investiguée. Un premier cas d'étude évalue l'activité totale de radionucléides d'intérêt pour une mesure par TEP lors d'un traitement par CABOTO. Grâce au rapport cyclique (duty cycle) (moins de $0,1 \%$ ) des faisceaux pulsés CABOTO il est possible d'enregistrer les coïncidences gamma TEP pendant $99,9 \%$ du temps de traitement. Par conséquent, les mesures TEP en temps réel avec CABOTO produisent des statistiques plus importantes que celles disponibles pour les accélérateurs circulaires conventionnels et permettent une détermination plus précise de la position du pic de Bragg des faisceaux. Les simulations FLUKA MC, réalisées en incluant la structure du temps du faisceau CABOTO, démontrent que le détecteur TEP est également sensible aux coïncidences gamma produites dans les $\beta^{+}$-decays des isotopes ayant une demi-vie ( $T_{1 / 2}$ ) dans l'ordre de quelques millisecondes; les plus abondants sont ${ }^{13} \mathrm{O}\left(T_{1 / 2}=8.6 \mathrm{~ms}\right),{ }^{12} \mathrm{~N}$, ( $\left.T_{1 / 2}=11 \mathrm{~ms}\right),{ }^{9} \mathrm{C}\left(T_{1 / 2}=126.5 \mathrm{~ms}\right)$ et ${ }^{8} \mathrm{~B}\left(T_{1 / 2}=770 \mathrm{~ms}\right)$. Cette étude montre l'avantage de la méthode, basée sur la surveillance de la plage de dispersion de la position du pic de Bragg, avec des isotopes TEP d'intérêt. Il était alors naturel de proposer la détection d'émetteurs $\beta^{+}$ de courte durée à partir d'une pré-irradiation à faible dose d'une partie de la cible tumorale étendant également la méthode aux accélérateurs circulaires conventionnels. Afin de démontrer la faisabilité d'avoir une courte période d'irradiation pour la vérification de l'intervalle de distribution de la dose avant un traitement avec ions carbone, des expériences ont été réalisées au CNAO, équipé d'un synchrotron, en utilisant le détecteur TEP INSIDE (INnovative Solutions for In-Beam DosimEtry in hadron therapy). Une cible de PMMA a été irradiée avec un faisceau d'ions carbone de $220 \mathrm{MeV} / \mathrm{u}$ et des coïncidences d'émetteur de positons acquises lorsque le faisceau était à l'arrêt. Les résultats montrent que, avec $3 \cdot 10^{7}$ ions carbone, la distribution des coincidences TEP spatiale, dans un laps de temps de mesure de $2,4,8,10$ et 12 secondes, est en bon accord avec les prédictions d'une étude réalisée avec le code Monte Carlo FLUKA. L' activité mesurée dans les 25 secondes qui suivent une irradiation de 0.6 s est quantitativement en accord avec la prévision du MC: le fit temporel montre que la production de l'isotope ${ }^{8} \mathrm{~B}$ est bien prédite par FLUKA et la production de ${ }^{10} \mathrm{C}$ est $60 \%$ plus grand que la prédiction, probablement en raison d'une sous-estimation de la section efficace. La principale conclusion de l'étude est que la quantité des radionucléides, mesurée dans les premières 5 s après l'irradiation d'une cible avec $3 \cdot 10^{7}$ ions carbone, est suffisant pour déterminer la position moyenne des pics de Bragg des ions carbone avec un sigma de 1 millimètre.

## Contents

Abstract ..... ii
Résumé ..... iv
List of Figures ..... ix
List of Tables ..... xiv
Acronyms ..... xvii
Thesis motivation, structure and personal contributions ..... 1
I GENERAL OVERVIEW ON HADRON THERAPY. THE HADRON LINACS
OF THE TERA FOUNDATION AND THE FLUKA MONTE CARLOCODE.5
1 Hadron therapy ..... 7
1.1 Hadron therapy ..... 7
1.2 Interaction of particles with matter ..... 10
Cross-section, mean free path and range ..... 10
1.2.1 Photon interactions ..... 12
1.2.2 Charged particles interactions ..... 14
Energy losses ..... 14
Multiple Coulomb Scattering ..... 16
Fragmentation ..... 17
Lateral and longitudinal dose profiles ..... 20
SOBP ..... 22
Protons versus ions ..... 22
1.2.3 Biophysical and biological quantities ..... 23
Linear Energy Transfer (LET) ..... 23
Relative Biological Effectiveness ..... 24
Oxygen Enhanced Ratio ..... 25
1.3 State of the art of hadron therapy technology ..... 27
1.3.1 Accelerators ..... 29
Synchrotrons ..... 29
Isochronous cyclotrons and synchrocyclotrons ..... 30
Linacs ..... 31
Other emerging technologies ..... 32
1.3.2 Beam transport and Dose Delivery Systems ..... 33
Beam Transport Systems ..... 33
Dose Delivery Systems ..... 33
1.3.3 Hadron therapy Facilities ..... 35
1.4 Treatment Planning Systems ..... 37
1.5 On-line monitoring techniques ..... 40
1.5.1 PET in hadron therapy ..... 40
PET principle and use in nuclear medicine. ..... 40
PET as monitoring technique in HT ..... 42
1.5.2 Emerging monitoring techniques ..... 44
Prompt gamma detection techniques ..... 44
Secondary particle detection techniques ..... 45
2 Accelerator complexes designed by the TERA Foundation ..... 47
2.1 The TERA Foundation ..... 47
2.2 Cyclinac versus all-linac solutions ..... 50
2.3 TULIP Turning LInac for Protontherapy ..... 51
2.3.1 TULIP accelerator components and beam transport system. ..... 52
2.3.2 TULIP optics and design constraints ..... 54
2.3.3 TULIP Beam Optics Optimization ..... 56
MEBT ..... 56
HEBT ..... 57
2.3.4 TULIP Dose delivery system and the impact on HEBT design ..... 58
Nozzle ..... 58
Orbit Correction ..... 61
2.4 CABOTO CArbon BOoster for Therapy in Oncology ..... 63
2.5 Sparse proportional rescanning. ..... 65
3 The role of Monte Carlo codes for particle transport in hadron therapy ..... 69
3.1 Monte Carlo methods for particle transport ..... 69
3.2 Monte Carlo codes in Medical Physics. ..... 71
3.3 FLUKA ..... 73
Physics models and settings ..... 74
3.4 FLUKA TPS particle therapy tool ..... 75
3.5 FLUKA PET tools ..... 76
II DOSE DELIVERY STRATEGIES FOR A TURNING LINAC FOR PROTON ..... 81
4 Beam characteristics of TULIP predicted with Full Monte Carlo simulations ..... 83
4.1 Rationale ..... 83
Phase-space approach ..... 83
4.2 Simulation workflow ..... 85
4.3 Results along the beam-line ..... 86
Transverse Characteristics ..... 88
Longitudinal Characteristics ..... 90
4.4 Scanning magnet simulation in FLUKA ..... 91
4.5 Predicted beam characteristics of TULIP for a TPS ..... 93
Transverse profiles in water ..... 93
Integrated Depth Dose curves ..... 93
Energy-Range Curve ..... 93
Proton fluence distributions in air ..... 93
4.6 Discussion ..... 97
4.7 Chapter summary ..... 98
5 Dose Distribution using TULIP in a tumour case ..... 99
5.1 Pinnacle $^{3}$ TPS used for TULIP ..... 100
5.1.1 Physics tool ..... 100
Integrated Depth Dose and Lateral Fluence curves. ..... 101
5.1.2 Planning section and DICOM export files ..... 105
5.2 FLUKA TPS simulations for TULIP ..... 106
5.2.1 FLUKA FLAIR DICOM tool ..... 106
$5.2 .2 \quad \mathrm{MC}$ beam model and RTPLAN information ..... 106
5.3 Preliminary comparison Pinnacle TPS - FLUKA MC with TULIP beam model ..... 110
5.3.1 SOBP in water ..... 110
5.3.2 Patient Case with a lung tumour ..... 112
Recalculation in FLUKA/FLAIR ..... 113
5.4 Chapter summary ..... 115
III MONITORING STRATEGIES: FROM THE IN-BEAM PET WITH CABOTO TO THE FAST RANGE VERIFICATION IN HT ..... 117
6 In-beam PET for CABOTO ..... 119
6.1 CABOTO time structure and activity build-up model ..... 120
6.2 FLUKA simulations for in-beam PET with CABOTO ..... 121
Model validation in FLUKA ..... 121
Activity over time with $\beta^{+}$emitter contributions ..... 122
Activity maps and profiles ..... 124
FLUKA simulation with a full-ring PET detector ..... 127
6.3 Chapter summary ..... 128
7 Fast range verification with short-lived $\beta^{+}$emitters: the idea and method ..... 129
7.1 The fast range verification idea ..... 129
7.2 In-beam PET Detectors ..... 132
Short Review on in-beam PET detectors ..... 134
7.3 INSIDE in-beam PET detector ..... 137
General description ..... 137
Data acquisition and processing system ..... 137
7.3.1 FLUKA PET tools for INSIDE ..... 142
7.4 Chapter summary ..... 143
8 Fast range verification experiments with in-beam PET at CNAO ..... 145
8.1 Materials and Methods ..... 145
8.1.1 The experimental set-up and Measurements ..... 145
8.1.2 Background noise ..... 148
8.2 Detailed analysis of Run1 ..... 149
8.2.1 FLUKA Monte Carlo simulations ..... 150
8.2.2 Data Analysis ..... 152
8.3 Results ..... 154
Coincidences evolution versus time and isotopes contribution. ..... 154
Experimental images and profiles along the beam direction. ..... 156
8.4 Discussion and conclusions ..... 160
Summary, conclusions and outlook ..... 163
Appendix A: FLUKA/FLAIR MC TPS tools ..... 167
A. 1 FLUKA/FLAIR DICOM section ..... 167
A. 2 TULIP MC beam Model ..... 169
Appendix B: Additional in-beam PET experiments ..... 181
B. 1 Other experimental runs ..... 182
B.1.1 Second acquisition boro8: run 2 ..... 182
B.1.2 Third acquisition boro8: run 3 ..... 184
B.1.3 Fourth acquisition boro8: run 4 ..... 185
B.1.4 Fifth acquisition boro8: run 5 ..... 186
B.1.5 Sixth acquisition boro8: run 6 ..... 187
Bibliography ..... 189
Acknowledgments ..... 216

## List of Figures

1.1 Example of the 2D dose distribution in a prostate cancer deposited by a protontherapy treatment (left, (a)) versus intensity-modulated radiation treatment withmultiple X-rays fields (right, (b)).8
1.2 Dose distribution versus penetration depth in water: comparison among different ..... 9
1.3 Beam transmission and dose comparisons for protons and photons at different energy values ..... 11
1.4 Interaction of a photon with matter ..... 13
1.5 Stopping power for protons and electrons as a function of kinetic energy ..... 15
1.6 Stopping power for different ions in water as a function of kinetic energy ..... 16
1.7 Multiple Coulomb Scattering in a thin slab ..... 17
1.8 Abrasion-ablation model of nuclear fragmentation ..... 18
1.9 Beam losses of C-ions primary beam at two different energy values $200 \mathrm{MeV} / \mathrm{u}$and $400 \mathrm{MeV} / \mathrm{u}$ and related fragment build-up19
1.10 Typical nuclei of interest in hadron therapy displayed in a portion of the chart of nuclides ..... 19
1.11 2D Dose distribution versus penetration depth in water: comparison between protons and ${ }^{12} C$ ..... 20
1.12 Longitudinal and lateral dose profiles ..... 21
1.13 Calculated beam spread for protons and ${ }^{12} \mathrm{C}$ ions ..... 22
1.14 Spread Out Bragg Peak example ..... 23
1.15 Nanometric secondary electron tracks respectively of protons and ${ }^{12} \mathrm{C}$ ..... 24
1.17 SOBP RBE ..... 26
1.18 High-tech components ..... 27
1.19 CNAO's synchrotron. ..... 29
1.20 Superconductive cyclotrons ..... 30
1.21 LIBO. ..... 32
1.22 Example of beam transfer lines in CNAO facility ..... 33
1.24 HT center ..... 35
1.25 Comparison among proton single-room facilities and ion accelerator complex ..... 36
1.26 Scheme of the treatment planning process ..... 37
1.27 Example of TPS volumes and dose distribution in a patient case ..... 39
1.28 Dose Volume Histogram ..... 39
1.29 HT Monitoring techniques ..... 41
1.30 PET principle ..... 42
$1.31 \beta^{+}$annihilation points distribution compared to dose profile for protons and ${ }^{12} \mathrm{C}$ ..... 43
1.32 PET techniques in hadron therapy ..... 44
1.33 Vertex distribution ..... 46
2.1 Top view of PERLA project layout based on cyclinac project ..... 48
2.2 TULIP and radioisotopes production ..... 49
2.3 TULIP single-room facilities ..... 49
2.4 CABOTO cyclinac ..... 50
2.5 Artistic view of TULIP ..... 51
2.6 TULIP components ..... 53
2.7 The phase space ellipse in the $x-x$ ' plane ..... 54
2.8 MEBT Optics optimization ..... 57
2.9 CNAO's nozzle ..... 58
2.10 Nozzle chambers ..... 59
2.11 TULIP Twiss and dispersion function ..... 60
2.12 Gradients of the TULIP transfer line quadrupoles ..... 61
2.13 HEBT TULIP beam envelope and orbit deviation ..... 62
2.14 TULIP layout magnet lines ..... 62
2.15 CABOTO all-linac layout ..... 63
2.16 Sparse proportional rescanning ..... 66
2.17 Sparse proportional rescanning reduction factor ..... 67
3.1 Monte Carlo versus deterministic analytic methods ..... 71
3.2 FLUKA PET tools workflow ..... 77
3.3 INSIDE in-beam PET detector geometry in FLUKA PET tools ..... 77
3.4 Coincidence events type that can be registered ..... 78
3.5 Count rate of coincidences events type versus activity concentration ..... 79
3.6 Left: FLUKA geometry setup geometry. Right: Example of scoring of gamma produced in in-beam PET Monte Carlo experiment with proton and 3D visual-ization (MATLAB) of gamma production and gamma detection point.79
3.7 FLUKA PET tools results in conventional PET ..... 80
4.1 Beam phase-space parameter representation for a TULIP beam ..... 84
4.2 Simulation work flow and codes ..... 85
4.3 IDD and x profile in water for a TULIP beam $(\mathrm{E}=122 \mathrm{MeV})$ : comparison between86
4.4 Nozzle geometry as designed in FLUKA ..... 87
4.5 Beam size evaluated in air at the isocenter for a parallel pencil beam and zerotransverse dimensions going through the nozzle87
LIST OF FIGURES ..... xi
4.6 Transverse beam sizes at the exit of the BTW Linad ..... 88
4.7 Nozzle effect on beam size variation ..... 88
4.8 Simulated 2D beam profile in vacuum and air ..... 89
4.9 Nozzle effect on energy loss ..... 90
4.10 Nozzle effect on energy spread ..... 90
4.11 Nozzle effect on energy spread in transversal profile ..... 91
4.12 Magnetic field map in FLUKA. ..... 92
4.13 Scanning magnets kicks in FLUKA ..... 92
4.14 2D beam profile in water at $80,210,232 \mathrm{MeV}$ ..... 94
4.15 Integrated Depth Dose curves. ..... 95
4.16 Energy-Range curve for TULIP and the comparison with the CNAO's one ..... 95
4.17 Fluence distribution in air ..... 96
5.1 Simulation work flow ..... 99
5.2 Profile fitting parameter in the TPS ..... 102
5.3 Example of fitted IDD profile in Pinnacle at 211 MeV ..... 103
5.4 Example of TULIP IAF X Profiles ..... 104
5.5 Example of IAF fit parameter results in Pinnacle ..... 104
5.6 FLUKA/FLAIR RTPLAN viewer and MC beam model ..... 107
$5.7 \mathrm{MU} /$ protons curve and stopping power ..... 109
5.8 SOBP with TULIP: comparison between FLUKA and Pinnacle - a 2D view ..... 110
5.9 SOBP with TULIP: comparison between FLUKA and Pinnacle ..... 111
5.10 DVH SOBP with TULIP: comparison between FLUKA and Pinnacle ..... 111
5.11 Dose distribution in Pinnacle for a patient case obtained with the TULIP beam ..... 112
5.12 DVH for a plan calculated with TULIP and comparison with a plan of a cyclotron- ..... 113
5.13 3D visualization of the FLUKA simulation geometry of a Patient case ..... 113
5.14 Preliminary comparison FLUKA -TPS TULIP model in a lung case ..... 114
5.15 Preliminary comparison FLUKA - TPS with TULIP model-DVH for a Lung case ..... 114
6.1 PET simulations for CABOTO: structure and methodology ..... 120
6.2 Simplified CABOTO time structure ..... 121
6.3 Plot of the activity of $\beta^{+}$emitters with short half-life $T_{1 / 2}$ over the irradiation time ..... 123
$6.4 \quad \beta^{+}$emitters activity contribution and variation with target material and beam ..... 123
6.5 Analytical time evolution of the activity during the irradiation ..... 124
6.6 FLUKA Simulation results of ${ }^{12} \mathrm{C}$ SOBP Dose and Ann at rest. ..... 125
6.7 Simulation of the activity 2D maps along the beam direction collected during the irradiation in the first seconds of acquisition times ..... 126
6.8 Activity profiles beta+ emitter contributors during the irradiation ..... 126
6.9 Simulated HT PET images with a full ring scanner ..... 127
6.10 Coincidences growth over time and parent isotope contribution ..... 127
6.11 Activity profiles from FLUKA simulations with full ring detector ..... 128
7.1 Activity trend and corresponding number of decays versus time ..... 131
7.2 Comparison of annihilation at rest: water vs PMMA target ..... 131
7.3 Experimental setup and result BASTEI versus DoPET] ..... 135
7.4 Main components of INSIDE detector ..... 138
7.5 PMMA target position with respect to detector ..... 139
7.6 Single and coincidence event rate ..... 140
7.7 Coincidence event rate zoomed to show the exponential growth during the irra- diation and decay ..... 140
7.8 Experimental PET online images examples-long run ..... 141
8.1 Experimental set-up in CNAO's treatment room with INSIDE detector ..... 146
8.2 An example of a 2D median filter ..... 147
8.3 Median filter effect ..... 147
8.4 Coincidences rate before irradiation ..... 148
8.5 Coincidences rate before irradiation with energy filter ..... 149
8.6 Geometry of the experimental set-up of Run1 ..... 149
8.7 Simulated activity rate and counts with isotope contribution ..... 151
8.8 Simulated annihilation count with isotope contribution ..... 151
8.9 1D profiles of the annihilations produced in the PMMA target ..... 152
8.10 Data analysis workflow ..... 154
8.11 Coincidence rate run1 ..... 154
8.12 Experimental 2D maps of the measured PET Coincidences ..... 156
8.13 Simulation versus experimental data of Longitudinal 1D profiles at 231 s ..... 157
8.14 1D Along z axis before irradiation ..... 157
8.15 Comparison between FLUKA Monte Carlo simulations (black) and experimental results (red) ..... 158
8.16 Longitudinal distribution of six of the fifty runs of FLUKA MC ..... 159
8.17 Distribution of the mean values $z_{\text {mean }}$ at 8 s . ..... 159
8.18 Sigma value in function of acquisition time. ..... 160
A. 1 DICOM CT scans and RT structures in FLUKA/FLAIR ..... 167
A. 2 DICOM RTPLAN in FLUKA/FLAIR ..... 168
A. 3 DICOM RTDOSE in FLUKA/FLAIR ..... 168
B. 1 Experiment 2: coincidence event rate details ..... 182
B. 2 Experiment 2: PET coincidences 2D maps ..... 183
B. 3 Experiment 2: 1D profiles along z axis ..... 183
B. 4 Experiment 3: PET Coincidences 2D maps experiment 3 ..... 184
B. 5 Experiment 3: 1D profiles along z axis ..... 184
B. 6 Experiment 3: 1D profile before irradiation. ..... 185
B. 7 Experiment 4: PET Coincidences 2D maps ..... 185
B. 8 Experiment 4: 1D profiles along z axis ..... 186
B. 9 Experiment 5:PET Coincidences 2D maps experiment ..... 186
B. 10 Experiment 5: 1D profiles along z axis ..... 187
B. 11 Experiment 6: PET Coincidences 2D maps ..... 187
B. 12 Experiment 6: 1D profiles ..... 188

## List of Tables

1.1 Clinical and Beam requirements of an HT facility ..... 28
1.2 Main beam characteristics of HT accelerators. ..... 31
1.3 Main isotopes used in conventional PET ..... 42
2.1 Constraints on the beam parameters ..... 56
4.1 Nozzle elements for TULIP. ..... 87
5.1 TULIP proton machine setting ..... 100
5.2 DVH evaluation for a lung tumour case (Gy). ..... 115
$6.1 \quad \beta^{+}$emitters produced in the interaction of protons ( 206 MeV ) with water ob- ..... 122
7.1 Production of positron-emitting isotopes in the irradiation with carbon ions of water and PMMA phantoms at $400 \mathrm{MeV} / \mathrm{u}$ obtained with FLUKA simulations. The isotopes with production value less than $10^{-3}$ in water are omitted. ..... 130
7.2 Scintillator crystals used for PET ..... 133
7.3 Characteristics of main photo-detectors ..... 134
8.1 Experimental measurements ..... 146
8.2 Production of positron-emitting isotopes in the irradiation with carbon ions of PMMA phantoms. ..... 150
8.3 Fraction of the annihilations inside the target with respect to the total one. ..... 151
8.4 Parameters of the fitting curves, representing the coincidences count rate over time. Simulated data without noise. ..... 155
8.5 Parameters of the fitting curves, representing the coincidences count rate overtime. The parameters fixed in column (d) are taken from column (b) of table8.4 Simulation with noise and experimental data.156
8.6 Look-Up Table (LUT) indicating the intensity in the point P of the images in
156 figure 8.12
8.7 Comparison between the Gaussian parameters in simulated and experimental data for different acquisition times. The errors are 1-sigma values from the 49MC runs.158
B. 1 Experimental runs: background and total coincidences ..... 181
B. 2 Experiment 2: Look-Up Table ..... 183
B. 3 Experiment 3: Look-Up Table ..... 184
B. 4 Experiment 4: Look-Up Table ..... 186
B. 5 Experiment 5: Look-Up Table ..... 187

## Acronyms

AQUA Advanced QUality Assurance in hadrontherapy
CERN European Organization for Nuclear Research
CABOTO CArbon BOoster for Therapy in Oncology
CNAO Centro Nazionale di Adroterapia Oncologica
CPT Charged Particle Therapy
DICOM Digital Imaging and Communication in Medicine
ENLIGHT European Network for LIGht ion Hadron Therapy
ESS Energy Selection System
FBP Filtered Back Projection
FOV Field Of View
FWHM Full Width at Half Maximum
GSI Gesellschaft für Schwerionenforschung-Helmholtz Centre for Heavy Ion Research
HEBT High Energy Beam Transfer line
HIT Heidelberger Ionenstrahl-Therapiezentrum
HT Hadron therapy
IAF In Air Fluence
IDD Integrated Depth Dose
INSIDE Innovative Solutions for In-Beam Dosimetry in Hadrontherapy
PSI Paul Scherrer Institute
IVI Interaction Vertex Imaging
IsoCy Isochronous Cyclotron

LANL Los Alamos National Laboratory
LBNL Lawrence Berkeley National Laboratory
LEBT Low Energy Beam Transfer line
LEM Local Effect Model
LET Linear Energy Transfer
LFS Lutetium Fine Silicate
MCS Multiple Coulomb Scattering
MLEM Maximum-Likelihood Expectation-Maximization
NIRS National Institute Of Radiological Sciences
PET Positron Emission Tomography
PIMMS Proton-Ion Medical Machine Study
PMMA Poly(methyl methacrylate)
SC Superconductive
SCy Synchrocyclotron
SOBP Spread Out Bragg Peak
TERA TErapia con Radiazioni Adroniche
TPS Treatment Planning System
TULIP TUrning LInac for Protontherapy

## Thesis motivation, structure and personal contributions

The research work presented in this thesis was carried out at the TERA Foundation laboratory, located at CERN. The TERA Foundation, as further explained in chapter 2, has been one of the main actors in the development of hadron therapy in Europe, leading many research programs in this field for about 30 years. This thesis work takes place within this context, and, starting from the study of the linacs for hadron therapy, patented by the Foundation, aims to enhance, from different perspectives, the potentialities of the applications of hadrons physics to cancer therapy.

The thesis is structured in the three parts detailed in the following paragraphs, where the author's personal contributions are also underlined.

## PART I - GENERAL OVERVIEW ON HADRON THERAPY. THE HADRON LINACS OF THE TERA FOUNDATION AND THE FLUKA MONTE CARLO CODE.

Chapter 1 gives a broad introduction to hadron therapy and the state of the art of this technology. In order to illustrate through specific examples the physics on which this technology relies, some results of FLUKA Monte Carlo simulations performed by the author are reported.

In chapter 2, after a presentation of the TERA Foundation and its history, the two main TERA linacs are described: TULIP, TUrning LInac for Proton therapy, and CABOTO, Carbon BOoster for Therapy in Oncology. The results presented in this chapter, produced by other researchers of the TERA Foundation, are the starting point of the author's research work on both accelerators, which is described in detail in PART II and PART III. Some of the contents reported in section 2.3 have already been presented by the candidate at the international conference of Monte Carlo for Medical Application (MCMA) in 2017 and published in the European Journal of Medical Physics (EJMP), Physica Medica in the paper Beam parameters optimization and characterization for a TUrning LInac for Protontherapy [1].

Moreover, the last section of chapter 2 focuses on the Sparse Proportional Re-scanning with Hadron Beams [2], a dose delivery technique that is the object of a publication in the European Journal of Medical Physics (EJMP) Physica Medica. It represents a complementary part of this thesis and the author's personal contribution consists in: performing part of the data analysis of the patient cases, constructing the related summary tables, improving the rescanning algorithm
with MATLAB code as well as making the figures reprinted in this thesis.
Chapter 3 presents the chosen physics methods and computing tools: i.e. Monte Carlo for particle transport and interaction, and the FLUKA code. As a member of the FLUKA collaboration, the author has actively contributed to the further development of FLUKA packages dedicated to medical applications. First of all, FLUKA Particle Therapy tools are optimized to support dose delivery, treatment plan calculations and visualization, including in real-patient's scenarios. The details and results are published in the Journal Physics for Medicine and Biology (FLUKA particle therapy tool for Monte Carlo independent calculation of scanned proton and carbon ion beam therapy [3) and summarized in section 3.4. The author has contributed in setting some specific requirements in order to consolidate the integration with HT accelerator beam models and in testing the tools in an agile software development framework. Moreover, the author has used the FLUKA Particle Therapy tools to perform the work described in chapter 5. Another relevant contribution is given by the author in the developments of the FLUKA PET tools, described in section 3.5, in particular in adapting them to in-beam PET scenarios. As for the work on TULIP, the tools have been presented by the candidate at the international conference of Monte Carlo for Medical Application (MCMA) in 2017 and the results published as well in the MCMA focus issue in Physica Medica (An overview of recent developments in FLUKA PET tools [4]).

The thesis core, where the author was the main contributor, consists in PARTS II and III.

## PART II - DOSE DELIVERY STRATEGIES FOR A TURNING LINAC FOR PROTON THERAPY.

Chapter 4 describes the results and simulation work performed to study the beams of TULIP. As for SECTION 2.3, most of this chapter contents were presented by the author at the MCMA 2017, and published in ref. [1]. First of all, the author further developed and automatized the code of the full $3 D$ simulation package for all the 650 energy values of TULIP and integrated it with the FLUKA code. Moreover, the author performed all the full 3D simulations, starting from the high energy beam transport line part up to the patient, as well as the analysis of the results, including the comparison to beams from CNAO, the synchrotron-based Italian National Center of Hadron therapy.

Furthermore, in Chapter 5, the author used the results obtained from the Monte Carlo study of the TULIP beam characteristics to construct the TULIP model in a commercial TPS (Philips' Pinnacle ${ }^{3}$ for protons), as well as the MC beam model in FLUKA. Finally, the author simulated, analysed and compared the dose delivered by TULIP in a patient case, both using the TPS and the FLUKA Particle therapy tool.

## PART III - MONITORING STRATEGIES IN HADRON THERAPY: FROM THE IN-BEAM FOR A CABOTO TO THE FAST RANGE VERIFICATION METHOD.

This part starts with chapter 6 , where the best method to monitor the treatment with the

CABOTO accelerator complex is presented: the in-beam PET. All of this chapter contents are the work of the candidate, receiving support on the FLUKA code by FLUKA collaborators and scientific guidance by the thesis supervisor.

In chapter 7, a new method of monitoring carbon ion treatments with in-beam PET is proposed and called fast range verification. It consists in the detection of short-lived $\beta^{+}$-emitters from a short and low-dose pre-irradiation of a part of the tumour target. The author has performed all the FLUKA simulations mentioned in the chapter, showing the feasibility of the idea. She also presented the obtained results at the ICTR-PHE conference, held in Geneva in 2016. This monitoring method is applicable to treatments carried out not only with CABOTO, but also with circular accelerators. In the same chapter, the author motivates and describes the methods and materials chosen to validate the idea. They consist in irradiating some PMMA targets with the carbon beams generated by the CNAO facility - the synchrotron-based Italian National Center of Hadrontherapy - and in acquiring the PET signal with the in-beam PET detector developed by INSIDE (Innovative Solutions for In-Beam Dosimetry in Hadrontherapy). The author participated in the first ever in-beam PET measurements campaign carried out at CNAO with INSIDE, which used carbon ions beams. The authors analysed the data acquired in some of the experiments, that were performed in the framework of this thesis, and the general results are included in appendix B. Finally in Chapter 8, the author validates the fast range verification idea by analysing in depth the data of one specific experiment and by comparing the results with 49 FLUKA simulation runs, further developing the data analysis and simulation tools from INSIDE collaboration. The main results will be submitted for publication.
Other researchers' contributions to these chapters are reported in footnotes. In line with the vision of the TERA Foundation, all the above-mentioned work, besides the recognized scientific contribution, have the added value of being the result of the fruitful cooperation and exchanges among young and senior researchers and professionals coming from different scientific background and institutions. Example of actors involved come from International Organization such as CERN, Medical companies such as Philips, Clinical institutions mainly CNAO and Clinique de Genolier and Research institutions such as INFN (Refer to Acknowledgements chapter for further details).

Concerning the figures reported in the text, the author drafted all those not explicitly referred, as well as all the figures cited with the wording 'Published in' that are reprinted from the publications by the author.

## Part I

## GENERAL OVERVIEW ON HADRON

## THERAPY. THE HADRON LINACS OF THE TERA FOUNDATION AND THE FLUKA Monte Carlo code.

## Chapter 1

## Hadron therapy

### 1.1 Hadron therapy

Hadron therapy (HT) is a radiation therapy technique mainly used to treat cancer by using hadron beams, i.e. beams of particles made of quarks. It includes all therapies with protons, neutrons, charged pions, antiprotons, as well as light ions, such as helium $\left({ }^{4} \mathrm{He}\right)$, lithium $\left({ }^{6} \mathrm{Li}\right)$, boron $\left({ }^{10} \mathrm{~B}\right)$, carbon $\left({ }^{12} \mathrm{C}\right)$ up to silicon $\left({ }^{28} \mathrm{Si}\right)$ [5]. This technique is also called hadrontherapy, particle therapy, light ion therapy [6], or else heavy ion therapy by GSI (Gesellschaft für Schwerionenforschung-Helmholtz Centre for Heavy Ion Research). More recently, the wording charged particle therapy, CPT, has also been used [7]. Several studies have been developed also for helium [8] and oxygen beams [9, 10] and the first European clinical program using ${ }^{4} \mathrm{He}$ ion beams has been launched at HIT (Heidelberger Ionenstrahl-Therapiezentrum) in 2020 [11]. Moreover, the research on the use of radioactive ions as ${ }^{11} \mathrm{C}$ or ${ }^{15} \mathrm{O}$ [12, 13] is also of interest. The idea of treating cancer with hadron beams, precisely with fast protons, was introduced by Robert Wilson, the founder of Fermilab, in 1946 [14]. The first patients were then treated at the Berkeley National laboratory by Cornelius Tobias, the brothers John and Ernest Lawrence and their collaborators, in September 1954 [15], in the month and year when CERN was founded [16]. For this pioneering application, the beam was accelerated through a cyclotron, the invention for which Ernest Lawrence was awarded the Nobel prize [17]. Afterwards, proton therapy started to be spread to other physics laboratories worldwide. After Berkeley, Uppsala followed in 1957, MGH (Massachusetts General Hospital) in 1961 for neurological radiosurgery and Harvard in 1963. In Russia, fractionated proton therapy started in 1973 in Dubna, and then Moscow (1969) and St. Petersburg (1975). In Japan, the first protontherapy activities were started at Chiba in 1979 and later on in Tsukuba (1983). Finally it was in 1985 that proton therapy was started at the Swiss Institute for Nuclear Research, today known as the PSI (Paul Scherrer Institute). The first hospital-based proton treatment center was built in 1970 at Loma Linda University Medical Center (LLUMC), supported by Fermilab's collaboration under the direction of the Nobel Prize Leon Lederman [18]. Concerning carbon ion therapy, the first patient was treated in 1994 in Japan, at the Heavy Ion Medical Accelerator in Chiba (HIMAC). In Europe, the treatments started at GSI in Germany in 1997. GSI gained experience on carbon
ions through a pilot-project leading to the construction of the first European hospital-based center in Heidelberg (HIT). At this center, a huge gantry for carbon ions weighing 600 tons and 25 meter long was built - and it is still the only one existing in Europe - where the first patient was treated in November 2009 [6]. Moreover, on November $13^{\text {th }} 2012$ the first patient was treated with carbon ions at CNAO, the Italian National Center for Hadron Therapy. The history of this Italian center of excellence started more than twenty years before, when a report titled "For a Centre of Teletherapy with hadrons" by Ugo Amaldi and Giampiero Tosi was published (May 1991) [19].

Nowadays, there are around 100 operational hadron therapy facilities, of which 12 treating also with C-ion and 36 equipped with a rotating gantry 1 . In addition, other 30 facilities, of which 5 for C-ions, are currently under construction [20].
Hadron therapy has been spreading out, thanks to its potential of delivering the dose to the deep-seated tumours more precisely with respect to radiotherapy using photons, thus sparing surrounding healthy tissue. A clinical example is given in figure 1.1, where a comparison between protons and photons of the 2D dose distribution in the central slice of an prostate cancer treatment plan is shown.


Figure 1.1: Example of the 2D dose distribution in a prostate cancer deposited by a proton therapy treatment (left) versus intensity-modulated radiation treatment with multiple X-rays fields (right). The red colour indicates the maximum deposited dose whereas the green one the minimum. The planned dose treatment was around 80 Gy for both treatments. Differently from the proton treatment, photons generate the so-called "low-dose-bath" to the tissues surrounding the prostate. Reprinted from ref. [21].

The dose, or more precisely absorbed dose, is the main physical quantity considered in radiotherapy; it is the energy per unit mass deposited by the beam in matter (e.g. a patient tumour) and it is measured in Gy. Another way to describe from the physicist's point of view the advantage of charged particles with respect to other techniques is by using the 1Drepresentation given in figure 1.2, called longitudinal dose profile, which will be further explained in the following. From this figure it is clear that hadrons are releasing the maximum of dose at the end of their path in matter, exhibiting what is called Bragg peak, differently from other particles releasing the higher dose at the target entrance.

The differences in dose distributions among these particles are due to the physical mechanisms of interaction of radiation with matter typical of hadrons with respect to photons, which

[^0]

Figure 1.2: Dose distribution versus penetration depth in water: comparison among different beam sources. Reprinted from [22].
will be explained in the section 1.2, Another point of strength of hadron beams concerns the radio biological properties. This is particularly evident for carbon and light ions (with $\mathrm{Z} \geq 2$ ), which, having different effects than protons on specific tumour cells, as it will be explained in section 1.2.3, are particularly suitable to control the so-called radio-resistant tumours.

From a clinical perspective, hadron therapy is suited for non-metastasized solid and deepseated tumours. Examples are: ocular melanomas; skull base/spinal cord meningiomas; pediatric cancers; prostate carcinomas. Lungs tumours are indicated as well, but they are technically more complex because the organs move. Moreover, HT treatments, especially the ones with protons, have to compete with more affordable and recently developed techniques with photons. Example are VMAT (Volumetric Modulated Arc Therapy), which can deliver a more conformal dose with respect to conventional techniques with standard RT linacs and faster treatments compared to IMRT (Intensity Modulated Radiation Therapy) [23] or SBRT (Stereotactic Body Radiation Therapy) with photons, today also indicated for metastasis. Several clinical studies have been performed or are ongoing, in order to evaluate the real clinical advantages of therapy with protons with respect to photons. The results are in some cases discordant and dependent by many factors such as cancer type, the body site, the patient history etc. It is out of the scope of this thesis giving a complete overview of all the possible radiotherapy techniques available to treat tumours and the evaluation of the best technique for a specific tumour. Interesting recent papers, comparing the latest radiotherapy techniques with photons and protons in clinical scenarios are for example ref. [21] about prostate cancer, or ref. [24] for skull-base meningiomas.

Concerning the use of carbon ions, encouraging results for the treatment of pancreatic diseases (estimated as the forth cause of death for cancer in Europe [25]) were obtained in Japan [26] and an interesting and promising clinical trial for pancreatic adenocarcinoma, combining
the use of carbon ions and chemotherapy, was recently designed by CNAO [25]. It is relevant to underline that the interest for hadron therapy centers is not only limited to cancer treatments and research studies, but also extended to new clinical applications to be developed in the next future [27]. A concrete example is the treatment of cardiac Arrhythmias with hadron therapy: after experiments with animals described in reference [28], the first patient was treated at CNAO in the same days of the drafting of this thesis (ref. [29], [30]).

### 1.2 Interaction of particles with matter

In many fields of applied physics and in particular in medical physics and radiation protection, the wording "interaction of radiation" instead of "interaction of particles" with matter is more common as well as the classical classification of the radiation in non-ionizing and ionizing, where the boundary between the two is conventionally placed, considering the electromagnetic radiation, at photon energy between 10 eV and 30 eV in the ultraviolet. Non-ionizing radiation indeed does not transport enough energy per quantum to completely remove an electron from an atom, but only to excite the atom or molecule. Non-ionizing radiation will not be treated in this work. Following the same pragmatical approach, the ionizing radiation is classified in:

- direct, such as charged massive particles, whose effects are the ionization and excitation of target atoms (long-range electromagnetic force);
- indirect, such as neutrons and photons (X-rays and gammas). In particular, neutrons interact indirectly via the charged products of their nuclear reactions (interaction is dominated by short-range forces). Photons, although they can ionize atoms directly through the photoelectric and the Compton effects, as it will be reminded later on, are considered as indirect radiation since it is their secondary radiation (i.e. electrons) that ionizes the largest number of target atoms.

In this thesis context, the wording "interaction of particles" instead of "interaction of radiation" is preferred in order to enhance the quantum and probabilistic nature of the described phenomena.

Cross-section, mean free path and range A particle with an energy value $E$ has a certain probability to interact with an atom (or nucleus) with atomic number $Z$ and mass number $A$ quantified by the microscopic cross-section $\sigma$. The cross-section is expressed in barns ( 1 barn $=10^{-24} \mathrm{~cm}^{2}$ ) and can be seen as the effective area of the target in a collision. The cross-section is in relation with another important quantity: the mean free path, $\lambda$, i.e. the average distance between two collisions in a material crossed by a particle, according to the expression:

$$
\begin{equation*}
\lambda=\frac{1}{N \sigma} \tag{1.1}
\end{equation*}
$$

where $N$, is the atomic density of the crossed material, expressed by the relation $\frac{\rho N_{A}}{M}$, with $\rho$, the material density, $M$ molar mass, $N_{A}$, Avogadro's number. For completeness, the inverse
of the mean free path is called macroscopic cross-section $(\Sigma=N \sigma)$.
It can be demonstrated [31, that the mean free path $\lambda$ is in relation with the probability $P(z)$ that a beam particle, impinging perpendicularly to a homogeneous target, experiences a collision in a travelled distance $z$. In particular, this probability can be expressed through the equation 1.2 .

$$
\begin{equation*}
P(z)=\int_{0}^{z} p\left(z^{\prime}\right) d z^{\prime}=1-e^{\frac{-z}{\lambda}} \tag{1.2}
\end{equation*}
$$

whereas the survival probability, $P_{s}(z)$, defined as the probability that the particle does not interact until a distance $z$, can be expressed by equation 1.3 .

$$
\begin{equation*}
P_{s}(z)=e^{\frac{-z}{\lambda}} \tag{1.3}
\end{equation*}
$$

This can be seen as the general Beer-Lambert law describing the attenuation of a radiation in a medium:

$$
\begin{equation*}
I=I_{0} e^{\frac{-z}{\lambda}} \tag{1.4}
\end{equation*}
$$

where $I_{0}$ is the number of particles (or Intensity) in the beam before the interactions, and $I$ can be seen as the surviving beam particles, i.e. the particles that didn't interact with the target.

In medical physics, the mean free path and the law 1.4 are mainly used for indirect radiation, in particular for photon-related studies. As explained later in subsection 1.2.2, the reason resided in the fact that in the energy range used in hadron therapy (ranging from a few tens to a few hundreds of $\mathrm{MeV} / \mathrm{u}$ ), the hadron beam continuously slows down and stops in the target.

Figure 1.3 shows some examples of transmission curves $I / I_{0}$ along $z$ of photons and protons at different kinetic energies interacting with a biological target of 40 cm depth in the $z$ direction.


Figure 1.3: Beam transmission (left) and relative dose (right) distribution along the beam propagation direction $z$ comparisons for protons and photons at different energy values in a human bone-like target (density $1.85 \mathrm{~g} / \mathrm{cm}^{3}$ ). The $\lambda$, the mean free path, is indicated for the photon beam at 500 keV , and the range $R$ for the protons at 200 MeV . Results obtained by FLUKA [32] Monte Carlo simulations performed by thesis's author.

In a separate plot of the same figure, the corresponding dose distributions are also presented. In this example, despite being a good approximation also for protons at 10 GeV , the relation 1.4 is no longer valid for the protons at 200 MeV . In hadron therapy, the concept of range R is used, instead; this corresponds to the distance travelled by the beam before stopping and where the above-mentioned Bragg peak appears in the dose distribution. It has the unit of a length as the mean free path, but it has nothing to do with it neither with the equation 1.4 .

### 1.2.1 Photon interactions

Although they are not hadrons, high-energy photons and their mechanisms of interaction with matter are relevant in hadron therapy for many reasons. First of all, photons are the mostly used particles in conventional radiotherapy, therefore many techniques in hadron therapy have been inherited by photons therapy itself; photons are also at the basis of many of the imaging techniques used in diagnostic such as radiography, CT (Computed Thomography) and PET (Positron Emission Thomography); finally, they are generated as secondary particles from the interaction of hadrons with matter and, as it will be explained later, if from one side photons are an unwanted radiation that needs to be stopped, conversely, secondary photons are detected to retrieve useful diagnostic information.

High-energy photons interact with matter only via electromagnetic processes and, differently from charged particles, the interaction occurs as a single spontaneous localized event where the photon is completed absorbed or re-emitted after the deposition of its energy.

The processes contributing to the absorption or scattering of photons are the following: photoelectric effect, Compton scattering, also called Incoherent scattering, to be distinguished by Coherent scattering or Rayleigh scattering and pair-production, each characterized by a specific cross-section.

In the photoelectric effect the photon having initial energy $E_{\gamma}$, is entirely absorbed by an electron from an atomic shell of the medium. The electron, now called photo-electron is ejected from the atomic shell with a kinetic energy $E_{a}$, which is the difference between the photon energy and the binding energy of the shell. Afterwards, the ion de-excites by either fluorescence of a photon of energy $E_{j}$ or by releasing an Auger electron having kinetic energy $E_{j}$. The photoelectric effect dominates at photon energies in the range of the atomic bounding energies of atoms in the medium. Photons at this energy are called soft $X$-rays. The crosssection decreases rapidly, as the energy $E$ of the photon increases, and increases with the atomic number $Z$, i.e $\sigma_{p h} \propto \frac{Z^{n}}{E^{3}}$, with $n$ equal to 4 or 5 .

At energy values above the highest atomic energy level of the medium, so-called hard Xrays, the Compton scattering dominates. In this process, the incident photon having energy $h \nu$ imparts a portion of it to an atomic electron in the medium. The photon, scattered at an angle of $\theta$, continues with a new energy $h \nu^{\prime}$ following the relation:

$$
\begin{equation*}
\frac{1}{h \nu^{\prime}}-\frac{1}{h \nu}=\frac{1}{m c^{2}}(1-\cos \theta) \tag{1.5}
\end{equation*}
$$

The energy transferred to the atomic electron, $E_{T}=h \nu-h \nu^{\prime}$, can assume any value down to 0 and $\theta \rightarrow 0$ is at a maximum when the scattering angle is $\theta=180^{\circ}$. The maximum transferable energy for the Compton process can be written as:

$$
\begin{equation*}
E_{T(\max )}=h \nu \frac{2 h \nu}{m c^{2}+2 h \nu} \tag{1.6}
\end{equation*}
$$

This maximum appears in the spectrum of energy deposited in the medium, if the Compton scattering is present, and gives rise to a continuous spectrum leading up to an edge lower than the observed or expected position of the photo peak. The cross-section scales approximately with $Z$. Finally, at energy values far above 1.02 MeV , equivalent to two electron rest masses, the electron-positron pair production process dominates: the photon of $\gamma$ rays interacting with a nucleus can create an electron-positron pair. The cross-section scales approximately with $Z^{5}$ [33, 34]. The total cross-section resulting from the sum of the above-mentioned processes as function of the energy is plotted in figure 1.4 for a high $Z$ element, the lead, a material generally used to stop the photons, in order to shield an object from an unwanted radiation. For compounds, instead, it is more common illustrating the dominance of these processes through the mass attenuation coefficient, $\mu_{m}$ given by the expression 1.7 .

$$
\begin{equation*}
\mu_{m}=\frac{1}{\lambda \rho} \tag{1.7}
\end{equation*}
$$

where $\rho$ is the material density of the target.


Figure 1.4: Cross-section (left) for a high Z material in function of the photon energy, and Mass attenuation coefficient (right) for an efficient crystal used for advanced diagnostics. Data extracted from XCOM[35].

Still in figure 1.4 , an example is given of a compound material (a $\mathrm{LaBr}_{3}$ crystal), used as a basic element of a particle detector. In this case, the purpose is to efficiently collect the photons in order to extract useful information. X-rays and PET diagnostic imaging are common
examples of using photons from medical physics.

### 1.2.2 Charged particles interactions

Considering the direct radiation, a charged particle can experience one of the following mechanisms:

1. through the electromagnetic force, collision with the orbital electrons of the target, generating kinetic energy losses;
2. through the electromagnetic and nuclear forces, elastic interaction with a nucleus, resulting in scattering.
3. through the electromagnetic and nuclear forces, non-elastic interaction with a nucleus of the target, causing mainly fragmentation of the target and the primary particle, in the case of an ion; or energy loss (bremsstrahlung), but only for light charged particles like electrons or positrons.

Energy losses In detail, when charged particles interact with the target electrons, they impart to them some energy and thus they ionize and leave the target atoms in an excited state. Meanwhile, the primary radiation gradually looses kinetic energy and, after slowing down and capturing electrons from the target, it stops and becomes neutral. $\delta$-rays, i.e. energetic electrons that can travel through a macroscopic distance, can also be produced by ionizing/exciting surrounding media.

The mean energy loss per unit of path length is called stopping power.
It is measured in $\frac{\mathrm{MeV}}{\mathrm{cm}}$ and is defined as $S(E)=-\frac{d E}{d x}$. Frequently, the mass stopping power is used, measured in $\mathrm{MeV} \cdot \mathrm{cm}^{2} \mathrm{~g}$ and defined as $-\frac{d E}{d x \rho}$, where $\rho$ is the material density [36].

With reference to figure 1.5, representing the stopping power of protons and electrons as function of kinetic energy in PMMA, four regions can be determined and the following considerations can be derived :

- Region I (Linhard-Scharff): at very low kinetic energies, the $S(E)$ rises almost linearly with the energy and the relativistic factor $\beta=v / c$, where $v$ is the velocity of the particle and $c$, the speed of light;
- Region II (Anderson-Ziegler): the $S(E)$ reaches a peak and then starts to decrease;
- Region III (Bethe-Bloch), the most interesting for HT: the stopping power decreases proportionally to $1 / \beta^{2}$, reaches a minimum (MIP - Minimum Ionizing Particles) at $4 \beta \gamma=$ $3-4$; after the MIP, $S(E)$ rises slowly because of relativistic effects;
- Region IV (Radiative): in this region the stopping power increases almost linearly with the energy and the radiative energy losses (bremsstrahlung) are dominant. For electrons, the stopping power becomes important already at relatively low energy ( MeV ).

[^1]

Figure 1.5: Stopping power for protons and electrons as a function of kinetic energy in PMMA. The Roman numerals indicate the regions defined in the text. Data from NIST ${ }^{2}$,

The stopping power at intermediate energies is expressed by the Bethe-Bloch formula, reported in the equation 1.8 .

$$
\begin{equation*}
S(E)=-\frac{d E}{d x}=2 \pi N_{A} m_{e} r_{e}^{2} c^{2} \rho \frac{Z}{A} \frac{z^{2}}{\beta^{2}}\left[\ln \left(\frac{2 m_{e} \gamma v^{2} W_{\max }}{I^{2}}\right)-2 \beta^{2}-\delta-2 \frac{C}{Z}\right] \tag{1.8}
\end{equation*}
$$

where $r_{e}=e^{2} / m_{e} c^{2}=2.818 \cdot 10^{-13} \mathrm{~cm}$ is the classical electron radius; $N_{e}=N_{A} \cdot Z \cdot \rho / A$ is the electron density; $2 \pi N_{A} m_{e} r_{e}^{2} c^{2}=0.1535 \mathrm{MeVg}^{-1} \mathrm{~cm}^{2} ; m_{e}$ electron mass ( $0.511 \mathrm{MeV} / c^{2}$ ); $I$ $=$ mean ionization (excitation) potential of the target; $Z, A$ atomic number and mass number of the absorber medium; $\rho$ material density; ze charge of the incident particle; $\beta=v / c$ of incident particle; $\gamma=1 / \sqrt{1-\beta^{2}} ; \delta$ density effect correction (important at high energy); $C$ shell correction (already important at low energy); $W_{\text {max }}$ maximum kinetic energy imparted to an $e^{-}$in a single collision $\simeq 2 m_{e} c^{2}(\beta \gamma)^{2}$, for $M \gg m_{e}$, where M is the rest mass of the incident particle 34.

It is important to notice that the $\mathrm{S}(\mathrm{E})$ is proportional to:

- $Z / A$ that is around $1 / 2$ for the great part of media, hydrogen excluded.
- $z^{2}$ (the atomic number of incident particle) - this means that a C ion loses 36 times more energy than a proton at the same velocity and in the same medium, as it is depicted in figure (1.6).


Figure 1.6: Stopping power for different ions in water as a function of kinetic energy. Reprinted from ref. [37].

Multiple Coulomb Scattering In the interaction with atomic nuclei, with respect to the light charged particles such as electrons, which have a very tortuous path because their mass is the same of the one of the target, the charged hadrons follow a straight path. However, charged hadron beams interact electromagnetically with atomic nuclei and atomic electrons a huge number of times in low-Z materials (for hadronic particles the strong interaction contributes as well). This random process, causing multiple angle deflections of primary charged beam, is called Multiple Coulomb Scattering (MCS). The angular deflection after traversing a length $L$ is well represented by Molière's theory [38]. A complete description of Molière's theory can be found in [39, 40, 41]; in this text, a simple 1D example extracted from [42] is reported.

With reference to figure 1.7, an ideal ion beam (monoenergetic with no transverse or angular spread) is assumed to be impinging on a slab directed along the z axis. Defining a Measuring plane at a distance $L$, the probability per ion of finding $\theta_{x}$ in $d \theta_{x}$ is, with a very good approximation, a Gaussian function:

$$
\begin{equation*}
G_{1 D}\left(\theta_{x} ; \theta_{0}\right) d \theta_{x}=\frac{1}{\sqrt{2 \pi} \theta_{0}} e^{-\frac{1}{2} \frac{\theta_{x}^{2}}{\theta_{0}}} d \theta_{x} \tag{1.9}
\end{equation*}
$$

With reference to the plane MP, each angular deflection $\theta_{x}$ becomes a transverse deflection $\mathrm{x}=$ $\mathrm{L} \theta_{x}$. Therefore the probability of observing an ion at x in dx is :

$$
\begin{equation*}
G_{1 D}\left(x ; x_{0}\right) d x=\frac{1}{\sqrt{2 \pi} x_{0}} e^{-\frac{1}{2} \frac{x_{0}^{2}}{2}} d x \tag{1.10}
\end{equation*}
$$



Figure 1.7: Multiple Coulomb Scattering in a thin slab [42].
with $\sigma_{x}$ :

$$
\begin{equation*}
\sigma_{x}=<x^{2}>^{1 / 2}=\left(\int_{-\infty}^{+\infty} x^{2} G_{1 D}\left(x ; x_{0}\right) d x\right)^{1 / 2}=x_{0} \tag{1.11}
\end{equation*}
$$

For small angles $\left(<10^{\circ}\right)$, the higher-order terms of Molière's theory can be neglected, and the value of $\sigma_{x}$ is well described by the Highland's formula 43], reported in ref. 42]:

$$
\begin{equation*}
\sigma_{x}=\frac{14.1 \mathrm{MeV} \beta c p}{z} \sqrt{\frac{d}{X_{0}}}\left[1+\frac{1}{9} \log _{10}\left(\frac{d}{X_{0}}\right)\right] \tag{1.12}
\end{equation*}
$$

or in the revised form from ref. [44, reported in PDG (Particle Data Group) as well [45]:

$$
\begin{equation*}
\sigma_{x}=\frac{13.6 \mathrm{MeV}}{\beta c p} z \sqrt{\frac{d}{X_{0}}}\left[1+0.088 \log _{10}\left(\frac{d z^{2}}{X_{0} \beta^{2}}\right)\right] \tag{1.13}
\end{equation*}
$$

where $\beta c, p, z$, are the velocity, momentum, and charge number of the incident particle, whereas the absorber material is characterized by the thickness $d$ and the radiation length $X_{0}$ 3. This formula has limitations not only for large angles, but also for targets with large $Z$ and small $\beta$, where the $\beta$-dependence is not well represented [45].

Fragmentation Another process of a charged beam interacting with matter is nuclear fragmentation. It consists in the breakup of the incident particle, as well as the target, into lighter particles or fragments. Therefore two types of fragmentation can be distinguished: the projectile fragmentation and the target fragmentation. Fragmentation increases with the projectile mass, the particle energy and the density of the medium. A model describing well the fragmentation process is the abrasion-ablation model, proposed by Serber [46]. The model applies to peripheral collisions, which account for nearly $90 \%$ of all nuclear events and is a two-step process, illustrated in figure 1.8 .

In the first step, called abrasion, the nucleons included in a zone where the projectile par-

[^2]

Figure 1.8: Abrasion-ablation model of nuclear fragmentation. Reprinted from 47.
ticle is interacting with a target nucleus, are "abraded", forming a fireball, whereas the other nucleons are slightly affected. The second step, the ablation, consists in the de-excitation of the fireball and clusters of the remaining projectiles emitting by evaporation nucleons of fragments. Moreover, peripheral collisions can be classified by charge-changing reactions and non-charge-changing reactions. In charge-changing reactions protons are lost by the nucleus, whereas in non-charge-changing reactions only neutrons are lost [48]. The main characteristics of fragmentation are the following:

1. with the increase of the penetration depth, i.e. the increase of primary particle energy, the primary beam losses are more significant and lower-Z fragments build up;
2. the projectile fragments are moving roughly at the same velocity of the primary projectile whereas the target fragments remain at the interaction point;
3. considering that the range scales with $A / Z^{2}$, a projectile fragment that undergoes a charge-changing reaction has a longer range than the primary particle. For non-chargechanging reactions the fragment has a shorter range [48];
4. the angular distribution of the fragments is forward-directed 47.

In summary, the secondary radiation produced by these non-elastic collision are:

- Charged particles (like protons p, deuterons d, alpha, recoils) and generally the $60 \%$ of this energy is absorbed locally;
- neutral particles like neutrons and gamma;
- unstable recoil particles.

The figure 1.9 clearly shows the first interaction point of a carbon ion beam at two different energy values in water. The main fragments are shown as well. On one side, all these produced secondary fragments travel into the target, or more specifically the patient, thus contributing to an unwanted dose; conversely they can produce a useful signal that can be collected to monitor the primary beam interaction. This is at the basis of a few of the monitoring techniques used in HT as introduced in section 1.5.

In particular, the unstable nuclei can experience decay processes. The main decay processes are: $\alpha$, a nucleus ejects an alpha particle, i.e. a helium nucleus; $\beta^{-}$, the nucleus emits an


Figure 1.9: Beam losses of C-ions primary beam at two different energy values $200 \mathrm{MeV} / \mathrm{u}$ and $400 \mathrm{MeV} / \mathrm{u}$ and related fragment build-up. Reprinted from ref. [49].
electron and an antineutrino in a process that changes a neutron to a proton; $\beta^{+}$, when the nucleus emits a positron and a neutrino in a process that changes a proton to a neutron; $\gamma$, the nucleus after decaying by the emission of an $\alpha$ or $\beta$ particle, produces a daughter nucleus, which can decay to a lower energy state by emitting a gamma ray photon; $p$, proton emission and neutron emission $n$. In figure 1.10 typical nuclei produced by decay processes in hadron therapy displayed in the chart of nuclides are shown with the indication of the main decay mode 50. Nevertheless, the amount of fragments produced in the medium by nuclear reactions increases


Figure 1.10: Typical nuclei of interest in hadron therapy displayed in a portion of the chart of nuclides. The colours in the legend indicates the decay mode of the nuclei. Adapted from [13].
with mass and charge of the primary particle. This fact is no longer an advantage for heavier
ions since the physical selectivity of the beam is deteriorated. This is one of the reasons why the use of Silicon or Argon ended with experiments in Berkeley [51], in addition to the excessive biological effects, as explained in paragraph 1.2 .3 .

Lateral and longitudinal dose profiles The paragraphs above describe three interactions mechanisms of hadron beams with targets. However, one of the quantities to be measured is the absorbed dose, as defined in the introduction, as well as its distributions along the interaction path of the ion beam with the target. A 2D example is represented in figure 1.11 for two different species: protons and ${ }^{12} \mathrm{C}$ ions.


Figure 1.11: 2D Dose distribution versus penetration depth in water: comparison between protons and ${ }^{12} \mathrm{C}$. Results from FLUKA simulations, performed by the author, with impinging p and C beams at 145.75 MeV and $275 \mathrm{MeV} / \mathrm{u}$, respectively, with the same initial beam size of FWHM 4 mm reaching the same range in water of 15 cm .

A more common way of representing the results shown in figure 1.11 is using longitudinal and lateral dose profiles, which are important characteristics in HT. An example where the profiles of three beam species (proton, helium and carbon beams) are present is shown in figure 1.12.

In particular, the longitudinal profile results from inelastic electromagnetic interaction with atomic electrons (mechanisms 1): the curve in 1D (figure 1.2) is called the Bragg curve, from Sir William Henri Bragg, who investigated the slowing down of $\alpha$ particles in air [47], and clearly represents the physical advantage of charged hadrons with respect to other particles.


Figure 1.12: Longitudinal and lateral dose profiles (at Bragg Peak) resulting from the FLUKA simulations as in figure 1.11. Profiles of a helium beam are also added. In the legend the transverse spot size expressed in term of FWHM is also shown.

The length of the average path traveled by the ion in the material before stopping is called mean range and is described by the expression 1.14 .

$$
\begin{equation*}
R=\int_{E_{0}}^{0}\left(\frac{d E}{d x}\right)^{-1} d E \tag{1.14}
\end{equation*}
$$

for a given initial beam energy $E_{0}$. This expression can be derived from the above-described Bethe-Bloch equation 1.8.

The range formula 1.14 is based only on the average energy loss of a single particle. Actually, the statistical fluctuations in the beam energy loss process cause a dispersion of the path length values around the mean $R$. This explains why the real longitudinal width of the Bragg Peak is larger than the one calculated using the range $R$ defined in the mean range formula. This characteristic is called range or energy straggling. It varies approximately as the inverse of the square root of the particle mass but, for the same particle, it is proportional to the increase of the energy [18].

Lateral profile is mostly caused by the elastic scattering on target nuclei which leads to a broadening of the beam (mechanisms 2). This effect, producing an unwanted penumbra, varies inversely to the particle momentum or, in other words, to the atomic mass of the primary beam as shown in figure 1.11. Therefore, the lateral deflection is more pronounced for lighter ions.

Nuclear interactions (mechanisms 3) reduce the intensity of the primary beam and contribute to both longitudinal and lateral profiles [7]. Nuclear interactions, as explained, generate fragments and projectile fragmentation produces fast fragments with lower mass and higher range with respect to the primary ion. This explains the longitudinal tail or distal tail of ${ }^{12} \mathrm{C}$ beam shown in figures 1.2 and 1.11 .

With reference to figure 1.12, it can be noticed that with an initial transverse beam size of 4 mm expressed in Full Width at Half Maximum (FWHM), helium and carbon beams reach the same lateral dose profile of 6 mm FWHM at a depth of 15 cm , with the advantage that
helium beams showcase lower fragmentation tails with respect to carbon ions.
As it will be explained later, in real HT scenarios, the beam, before interacting with the patient, (or water, as in the previous example), crosses several materials for several centimeters, such as some elements in the beamline (the nozzle) and an air gap located between the end of the beam pipe and the patient. Therefore more realistic values of the variation of the beam size along the beam line is presented in figure 1.13 .


Figure 1.13: Calculated beam spread for protons and ${ }^{12} \mathrm{C}$ ions along a typical treatment beam line. The particle beam is parallel with an initial FWHM of 5 mm , and passes through the nozzle, including a thin vacuum window and beam monitors and enters a water tank after traversing 1 m in air. Reprinted from ref. [52].

SOBP In order to cover a target volume (a patient's tumour) by releasing a uniform dose, pristine Bragg curves at chosen different energies and intensities are combined forming what it is called Spread Out Bragg Peak (SOBP) (figure 1.14).

The SOBP width is defined in ref. [53] as the distance between the maxima of the most distal and proximal Bragg peaks used to form the SOBP. This is a more generally valid definition with respect to the one given in ICRU Report 78 [54], where the SOBP was defined as the distance between the distal and proximal $90 \%$ points of the modulated depth-dose curve. Several methods are available in literature on how to choose energy and intensities values. For protons, relevant references are [55], [56] while a more recent one is ref. [57].

Protons versus ions In conclusion, the physical differences in hadron therapy of ions with respect to protons can be summarized in the following features:

1. better lateral dose profile while traversing tissue in depth, due to less scattering;
2. sharper Bragg Peak, although it exhibits a "fragmentation tail";


Figure 1.14: Spread Out Bragg Peak example. Adapted from ref. [7].
3. the generation of secondary particles which can be useful for dose range monitoring purposes.

Besides these physical features, the biological ones are even more important and represent the advantages: (i) ions are more effective because they can determine with higher probability the death of the cancer cells, since they are able to break the double strain of DNA, beyond the repair mechanisms bringing sometimes to unwanted cell mutations; (ii) effectiveness also in absence of Oxygen.

The first characteristic is expressed by two main quantities: a biophysical one called Linear Energy Transfer (LET) and a biological one called Relative Biological Effectiveness (RBE). The second advantage is quantified by the so-called Oxygen Enhanced Ratio (OER). All these quantities are correlated and detailed in the following section 1.2.3).

### 1.2.3 Biophysical and biological quantities

Linear Energy Transfer (LET) The Linear Energy Transfer (LET) is a biophysical quantity used to characterize radiation quality. In the ICRU 70, it is defined as the ratio of the average energy locally imparted to the medium by a charged particle of specified energy, $d \bar{\epsilon}$, to the traversing distance of $d l^{\prime}$ (equation 1.15 )

$$
\begin{equation*}
L_{\Delta}=\left.\frac{d \bar{\epsilon}}{d l}\right|_{\Delta} \tag{1.15}
\end{equation*}
$$

The $\Delta$ refers to the word locally in the definition and indicates the cutoff limit of energy transfer [53]. If all energy values of secondary electrons produced are considered, the LET equals the collisions stopping power and it is called unrestricted LET, $L_{\infty}$. Usually the symbol of infinity is forgotten and radio-biologists call it shortly $L E T$, which is given by equation 1.15 and is nothing else than the stopping power of physicists that is given for different ions by equation 1.8

As shown in figure 1.15, carbon ions, as other ones, produce a higher number of secondary
electrons with respect to protons and this explains why ions are more effective in damaging the DNA.


Figure 1.15: Nanometric secondary electron tracks respectively of protons and ${ }^{12} \mathrm{C}$, simulated by the Monte Carlo code TRAX. The higher DNA damage is caused by carbon ions because of the higher density of the secondary electrons produced. Reprinted from [58].

Moreover, since the rate of energy loss is higher at the end of the particle range, the LET dramatically increases in this region, as shown by the Bragg peak. In addition, the threshold between low- and high-LET radiation is placed at $10 \mathrm{keV}_{\mathrm{Km}}{ }^{-1}$. Typical values for charged particle beams, in the last centimeters of the range, are of the order of a few hundred $\mathrm{keV}_{\mathrm{m}}{ }^{-1}$ [59].

Relative Biological Effectiveness The RBE is defined as the ratio of the absorbed dose of a reference beam of photons, typically 250 kV X-rays or ${ }^{60} \mathrm{Co}$ gamma rays, $D_{\text {photon }}$, to the absorbed dose of any other radiation, notably high LET radiations, $D_{\text {ion }}$, able to produce the same biological effect (equation 1.16).

$$
\begin{equation*}
R B E=\frac{D_{\text {photon }}}{D_{\text {ion }}} \tag{1.16}
\end{equation*}
$$

RBE depends on multiple factors:

- LET
- beam energy
- particle charge
- target volume
- depth
- type and cell cycle of the target cell, which influence the DNA repair capabilities.

Despite several years of studies in physics laboratories and therapy facilities, started in 1970s at Lawrence Berkeley Laboratory (LBL), RBE is one of the most important causes of uncertainties in hadron therapy. In addition, different models are used in European and Japanese HT centers, leading to significant differences in calculated RBE-weighted dose [27].

Therefore, attention needs to be paid in comparing clinical results among different centers. RBE is generally expressed in function of two parameters $\alpha$ and $\beta$ of a Linear Quadratic Model (LQM). Most known RBE models are:

- mixed beam model, used at the National Institute of Radiological Sciences (NIRS) with beam delivery passive-system; it is based on quite simple empirical relations [60];
- local effect model (LEM), used in its version LEM I, in Treatment planning system (TPS) at different carbon-ion therapy centers such as GSI [61], HIT [62] and CNAO [19].
- microdosimetric-kinetic model (MKM) [63] and the modified MKM [64] can be used in beam scanning techniques and introduced in the clinical environment in relatively recent times (2015) in Japan at NIRS. It can also be applied in intensity-modulated particle therapy.

For a detailed description, the reader can refer to ref. [65].

Oxygen Enhanced Ratio OER is the ratio of dose needed to inactivate a cell under hypoxic conditions to the one under aerobic conditions. Studies have demonstrated that OER is lower for high-LET particles with respect to photons. This means that tumours containing hypoxic cells are more effectively treated by high LET irradiation [66].

A relationship among these quantities is reported in figure 1.16 .


Figure 1.16: Relationship among LET, RBE and OER. On the top part the typical LET values of several particles are depicted with the qualitative effect on DNA. Adapted from [67].

Finally, with reference to figure 1.17, although there is a reduction of the average LET over the SOBP, the LET is still much higher than for photons and also for particles in the entrance
region of the beam. Not only does the high LET at the end of particle ranges affect the absorbed dose distribution, but it also has marked consequences for the response of biological systems to that dose.


Figure 1.17: SOBP with dose expressed in several units. The LET curve is also shown. Reprinted from [66].

### 1.3 State of the art of hadron therapy technology

In order to be able to treat a patient with hadrons, specific high technology is needed. The hadron beam needs to be produced with an appropriate intensity; accelerated at kinetic energy values corresponding to ranges compatible with the depth of the tumour to be treated in the patient's body; transported with minimal losses; delivered into the patient in order to guarantee high conform dose distribution, patient's safety and comfort. Therefore, the high-technology core of an HT system consists in the following main components (figure 1.18):

- an ion source to produce the beam: ideally it should be able of varying the intensity.
- an accelerator complex able to reach energy of hundreds on MeV per nucleon and able to modulate it. Typically, it is a synchrotron, for ions and protons, or a cyclotron, only for protons, but other options are under development (subsection 1.3.1;
- a beam transport system made of magnetic elements able to focus and bend the beam to reach the desired direction with respect to the patient (subsection 1.3.2);
- a beam delivery system (subsection 1.3.2) that ensures: the quality of the beam delivered to the patient, with on-board monitoring systems and beam shaping systems;
- one or more patient's treatment rooms which can integrate a complex electro-mechanical rotating structure, called gantry, allowing to irradiate the patient from multiple beam directions.


Figure 1.18: High-tech components of an HT facility. Adapted from [68].

The main requirements of a hadron therapy facility are summarized in table 1.1. to achieve some clinical requirements corresponding beam requirements are needed.
Table 1.1: Clinical and Beam requirements of an HT facility (Adapted from 69 18)

| Clinical Requirements | protons | carbon ions | Beam Requirements | protons | carbon ions |
| :---: | :---: | :---: | :---: | :---: | :---: |
| Treatment field size ( $\mathrm{cm}^{2}$ ) | 30x40 | 20x20 | Scanning magnets/beam spreading |  |  |
| Dose rate | $2 \mathrm{~Gy} /$ (min liter) |  | Beam current | $\sim 1 \mathrm{nA}$ | $\sim 0.1 \mathrm{nA}$ |
| Range in water | $3-32 \mathrm{~g} / \mathrm{cm}^{2}$ |  | Energy | $60-250 \mathrm{MeV}$ | $100-430 \mathrm{MeV} / \mathrm{u}$ |
| Range modulation steps | continuous |  | Beam delivery system | active |  |
| Range adjustment | $0.1 \mathrm{~g} / \mathrm{cm}^{2}$ |  | Energy precision | $5 \cdot 10^{-3}$ |  |
| 80\%-20\% distal fall-off | $<1-6 \mathrm{~mm}$ |  | Range straggling and Acc. energy spread | $1 \%$ or the range$<5 \cdot 10^{-3}$ |  |
| Entrance Lateral Penumbra | $<2 \mathrm{~mm}$ |  | Beam FWHM (mm) | 7 to 22 | 4 to 9 |
| $D_{\text {skin }} / D_{\text {max }}[70$ | <20\% |  | Source to Axis Distance | $>2 \mathrm{~m}$ |  |

### 1.3.1 Accelerators

A complete review of accelerators for HT can be found in ref. 55 or a more recent one in ref. [71]. Here below a short overview will be given.

## Synchrotrons

Synchrotrons in hadron therapy represent the state-of-the-art and are the only mature technology to treat cancer with ions other than protons.

A synchrotron is made of electromagnetic resonant cavities and magnets (quadrupoles, dypoles etc.) arranged in a ring that accelerates particles during each circulation. The strength of the magnetic fields has to be changed at every turn, since the particle increases its energy at every turn, while still moving on the same radius [72]. Synchrotrons required a linac to preaccelerate ions before being injected into the synchrotron ring. In figure 1.19 the synchrotron operated by CNAO is presented. It has the advantage to be the most compact synchrotron treating nowadays patients with C-ions thanks to the fact that the linac has been located inside the 24.5 m diameter ring of the synchrotron.


Figure 1.19: CNAO's synchrotron. Adapted from ref. [19].

In a synchrotron, the beam is delivered in spills lasting few seconds, with pauses of one second, and intensities of $2 \cdot 10^{10}$ protons/cycle or $10^{9} \mathrm{C}$ ions/cycle.

## Isochronous cyclotrons and synchrocyclotrons

Cyclotrons, instead, can be considered the state-of-the-art of proton therapy accelerators. The basic components of a cyclotron are the following:

- a proton source, where hydrogen gas is ionized and protons extracted;
- a Radiofrequency system (RF), providing strong oscillating electric fields, which accelerate protons (30-100 kV);
- a magnet of a few Tesla, allowing the particles to follow a quasi spiral trajectory, being repeatedly accelerated by the RF voltage;
- an extraction system guiding the particles that reached their maximum energy out of the cyclotrons and into a beam transport system (see M. Schippers's chapter in ref. [73]).

Many cyclotrons used today for protontherapy are nowadays superconductive. By using superconductive coils, magnets can achieve high magnetic fields while being very compact and with a total weight that can be reduced below 100 tons [74], against 200 tons of the ones using room temperature coils. Another advantage of SC cyclotrons, and more in general of SC magnets, is that they do not need the cycling procedure of magnetic field, done to reduce the magnetic history [73]. This feature results particularly favourable for the so-called synchrocyclotrons (SCys), which need a variable magnetic field. The more conventional ones are called isochronous cyclotron (IsoCys), because the magnetic field $B$ must be isochronous: at each radius $r$ it must have the appropriate strength to match the time $T$ a proton needs to make one turn according the equation $T=2 \pi m / q B$, where $m$ and $q$ are respectively mass and charge of the particle [73]. In SCys, based on a more recent technology with respect to IsoCys, the frequency of the accelerating electric field is modulated to compensate the decreasing revolution period of the particles. The main elements of a SC cyclotron and two examples of SCys available in the proton therapy market are shown in figure 1.20 .


Figure 1.20: Left: Superconductive cyclotron components [75]; to the right: SCys produced by MEVION [76], mounted directly on a rotating gantry to treat patient(top) and IBA's S2C2 [68](bottom).

## Linacs

Linear accelerators (linacs) represent the state-of-the art technology in conventional radiotherapy. The electron beam is accelerated in small linacs at a few MeV and then hits a tungsten alloy target ${ }_{4}^{4}$, in order to produce X-rays, mainly through bremsstrahlung. The X-ray radiation is then shaped with specific collimators for the treatment. The main elements of a linac are: a charged particle pulsed source; resonant RF cavities assembled and kept under vacuum; RF generators, typically klystrons, at a frequency of 3 GHz , giving an alternated electric field; magnetic elements need to keep the particle beam at the center of the pipe (ex. quadrupoles). The main difference of ion linacs with respect to electron ones consist in the fact that electrons soon approach the upper limit of the speed of light, having a low mass, so accelerating modules can be of the same length. In a proton linac, instead, protons are not relativistic, so that the particle speed increases with the energy and therefore accelerating tanks of different dimensions are needed. Linacs have been proposed for the first time as accelerators for protontherapy by Krandall (ref.[78]) in 1991 and further studied by the TERA Foundation starting from 1994, [79] as further explained in section 2.1 .

An example of a prototype unit of a linac for protontherapy is the LIBO (LInac BOoster) presented in 1.21 Experiments performed in 2011 at the Catania LNS Laboratory 5 used this 3 GHz linac unit as a cyclotron booster to accelerate a proton beam from 62 to 72 MeV , demonstrating for the first time that a high frequency linac coupled with a cyclotron can accelerate protons [80].

The main advantage of linacs is the unique ability to modulate the extracted beam energy without the use of passive absorbers, or Energy Selection System (ESS). Further technical details on linacs for protontherapy will be presented in chapter 2.

The comparison of the main beam characteristics of the above-mentioned accelerator technologies in hadron therapy are summarized in table 1.2.

Table 1.2: Main beam characteristics of HT accelerators.

| Feature | Synchrotron | Cyclotron <br> IsoCy / SCy | Linac |
| :---: | :---: | :---: | :---: |
| Range Mod. Method <br> (Energy variation system) | active | Passive Energy Selection System | active |
| Energy change time | 2 s | 100 ms | $2.5-5 \mathrm{~ms}$ |
| Intensity (ions/s) | $10^{7} \mathrm{C}-10^{9} \mathrm{p}$ | $10^{10}$ | $10^{7} \mathrm{C}-10^{9} \mathrm{p}$ |
| Beam structure | spill/pulsed | continuous $/$ pulsed | pulsed |
| Beam Repetition rate | 0.5 Hz | $\mathrm{~N} / \mathrm{A} / 500-1000 \mathrm{~Hz}$ | $200-400 \mathrm{~Hz}$ |
| Pulse length | $0.5-2 \mathrm{~s}$ | $\mathrm{~N} / \mathrm{A} / 0.5-20 \mu \mathrm{~s}$ | $2-5 \mu \mathrm{~s}$ |
| Beam size (FWHM) 6 | 4 mm |  | 3 mm |

[^3]

Figure 1.21: Linac Booster (LIBO) components: example of a unit of protontherapy linac developed by the TERA Foundation, CERN and INFN [81, 80].

## Other emerging technologies

Fixed-Field Alternating Gradient accelerators (FFAG) is a technology that combines the advantages of a synchrotron, e.g. the possibility to extract ions at several energy values, and the compactness of a cyclotron, as well as the possibility to have a faster repetition rate with respect to SCy. The most significant contribution has been given by Kyoto University Research Reactor Institute in Japan where a proof-of-concept of accelerating protons at 150 MeV in a FFAG machine was given.

Laser-driven accelerators make use of very intense laser pulses impinging on thin solid targets (less than $1 \mu \mathrm{~m}$ ), producing a plasma at the front surface in which the electrons create electric fields of the order of TV $/ \mathrm{m}$. This electric field, $20 \%$ higher than the one in linacs, allows to accelerate ions in shorter length. On the other hand, at the moment of writing, challenges of this technology reside in the huge dimensions of the laser systems, the limited repetition rate of the order of one Hz and high energy spread of the beam. Examples of experimental facilities based on this technology are ELIMAIA in Prague and CALA in Munich ref. [82, 83].

### 1.3.2 Beam transport and Dose Delivery Systems

## Beam Transport Systems

Beam transport systems consist in magnetic lines able to focus and bend the beam, as well as to transport it until a specific point in the treatment room called isocenter. Basic elements are dipoles and quadrupoles, chosen and placed according to a specific optic design, which is compliant to the required beam characteristics and to the physical space constraints of the facility. Generally speaking, beam transport systems consist in different sections, classified according to the beam energy value: as for the example in figure 1.22, Low, Medium and High beam transfer lines are defined (respectively LEBT, MEBT and HEBT).


Figure 1.22: Example of beam transfer lines in CNAO facility. Adapted from courtesy images of CNAO Foundation.

## Dose Delivery Systems

In order to deliver an accurate and homogeneous dose to the tumour, the dose delivery system (DDS) is a crucial aspect in hadron therapy. A DDS consists in ionization and vacuum chambers and, according to the methods used to deliver the dose, other elements are added. The methods that can be employed to deliver the dose are classified in passive and active ones (figure 1.23) 73.

- Passive Methods conform the dose using degraders and compensators, which are generally patient-specific. The most common ones are the Beam-scattering and Layer-stacking, using also a rotating wheel of variable thickness for compensation. A complete description of all passive methods is given by Chu et al in ref. [84.
- Active Methods use magnets to steer the beam in a defined treatment region. Active methods are the spot scanning and the raster scanning. Spot scanning was developed in Japan, but first clinically applied at PSI [85] and used at cyclotron based facility and proposed for linacs. Raster scanning, used mainly with synchrotrons, was developed at

GSI [86] and then applied at HIT, CNAO, MEDAUSTRON. These techniques have the great advantages of not needing patient-specific elements to conform the dose, of having a reduced neutron production and of not delivering extra-dose in the proximal region. On the other hand, they have to be extremely precise, especially with moving organs.

- Wobbling is a combination of the two above-mentioned methods, developed at NIRS.


Raster scanning
Figure 1.23: Scheme of passive and active methods. Reprinted from [7].

The treatment of moving organs represents the biggest challenge in dose delivery. Two types of dose uncertainties are typical: blurring of the edges of the dose distribution and the dose non-homogeneity. The first is the same for active and passive techniques and can be compensated by safety margins or reduced by using tracking or gating. For the treatment of moving organs, passive methods have the advantage that the dose can be quickly delivered and uniformly in the full volume within a fraction of the breathing cycle (less than 200 ms ), reducing dose-homogeneity errors within the target [18].

Moreover, additional strategies can be implemented in the context of spot scanning or raster scanning. Several scientific works have been published on the repainting or rescanning [87] or other methods such as Oblique raster scanning [88]. Moreover, the publications in reference [2] representing a part, albeit minor, of this thesis will be briefly described in chapter 2 .

It is in the context of the active methods that monitoring techniques for hadron therapy became extremely important.

### 1.3.3 Hadron therapy Facilities

As mentioned in the introduction, until 90s hadron therapy treatments were performed only in physics centers. Nowadays, modern facilities for hadron therapy are hospital-based and can be distinguished in: dedicated centers, typically multi-room; single-room (only for protons) and integrated in pre-existing radiotherapy departments. An artistic view of a dedicated HT center, multi-room, is shown in figure 1.24 .


Figure 1.24: Artistic view of a dedicated HT center ${ }^{7}$
Besides the above-mentioned components, a dedicated HT center generally includes: an imaging diagnostic center, anaesthesia rooms (especially used for paediatric treatments), reception and conference rooms, offices, a patient consulting area and a dedicated R\&D beam line department.

In Europe, examples of hospital-based and multi-rooms HT facilities in chronological order of construction and commissioning are: HIT, CNAO, MEDAUSTRON. All synchrotron-based are treating patients with protons and carbon-ions, in fixed horizontal and vertical beam treatment rooms - except for HIT, where a huge rotating gantry of more than 600 tons and 15 m of diameter was installed and is currently in operation. The construction of HIT center, as a more recent one in Marburg, was led by Siemens AG company, industrial player in HT until less than one decade ago. CNAO development and construction instead was led by the non-profit CNAO Foundation.

Single-room facilities are presently proposed only to treat with protons and not with ions, due to the bulky and expensive technology necessary to accelerate ions. As an example, the dimensions of main single-room facilities available on the market are compared with the accelerator (synchrotrons) and three treatment rooms of CNAO are shown in figure 1.25 . The main vendors of cyclotron-based proton therapy facilities are: IBA, MEVION, Varian. IBA

[^4]and Varian have multi-room as well as single-room facilities on the market, whereas MEVION proposes only single-room facility solutions with a synchrocyclotron.


Figure 1.25: Comparison among commercial proton single-room facilities (left) and ion accelerator complex in CNAO (right). Adapted from [89].

As previously explained, until now cyclotrons have been the choice for single-room facilities, because they are based on a well-known technology, they are compact and stable and do not require an injector as it is the case for syncrotrons. Besides these advantages, cyclotrons themselves accelerate the beam at the maximum kinetic energy of 230 MeV , for all the duration of the proton therapy treatment. In addition, the beam current needs to be quite high (reaching 800 nA in the Varian Probeam machine) because the passive energy modulation during the treatment determines a degradation of the beam intensity; this has the disadvantage that lowenergy protons have lower intensity than high-energy protons. These two aspects cause a higher production of secondary radiation (mainly neutrons) that need to be stopped by using several centimeters or sometimes meters of concrete walls. The result is a bulky overall facility. For this reason companies like ProTom, proposing a single-room syncrotron-based facility (Radiance 330), were able to reestablish themselves on the PT market. In a similar way, at the end 2018, Hitachi (ref. [90), leader in the medical technology, made available on the market its singleroom solution, finally chosen by CNAO in its expansion program [91. In conclusion, the linac is the machine producing, in principle, the lowest number of neutrons, since it does not need passive elements and the beam current is less than 1 nA . This is therefore part of the rationale for investing in linacs for hadron therapy.

### 1.4 Treatment Planning Systems

The first treatments in Loma Linda facility showcased that the use of protons was not optimized because of the lack of important supportive instruments: the computer-assisted treatment planning, digital imaging and computer competence [18]. Computer-assisted treatment planning helps the radio-oncologist to predict and to conform the prescribed dose to the tumour, minimizing the dose to the critical organs. With reference to figure 1.26 , the treatment planning process consists in the following steps.


Figure 1.26: Scheme of the treatment planning process. Reprinted from [53].

First of all, the patient is adequately positioned and immobilized for imaging purposes (this can be done either directly in the treatment room or in a CAP (Computer Aided Positioning) room. The patient's imaging consists in CT (Computed Tomography) scans, which can be fused with MR (Magnetic Resonance) or PET (Positron Emission Tomography) scans. These images are imported in a sophisticated software, called Treatment Planning System (TPS), in DICOM (Digital Imaging and Communication in Medicine) format, the standard in transmission of medical images.

In this software, the first operation to be carried out is the contouring of the patients' organs (automatically performed by the software or drawn by the radio technician) followed by the definition and contouring of the treatment volumes to be irradiated. Generally, the following volumes are defined, in order and from the most internal to the most external: a GTV - Gross treatment Volume, i.e. the tumour volume determined by clinical imaging inspection; a CTV Clinical Treatment Volume, including the parts of tissues which could be affected by a tumour spreading; a PTV - Planned treatment Volume, including appropriate margins to ensure target coverage, even in case of tissues movement or patient positioning errors. The volumes to be spared are contoured as well and called OAR - Organs At Risk. After the definition of the prescribed dose to each structure and the number of therapy sessions (called fractions) by the radio-oncologist, the number of proton beams and their orientations (called fields) are then chosen by the medical physicist and appropriately weighed.

Thanks to the algorithms and physical models of the TPS, the dose to the tumour and surrounding tissues is calculated and optimized. An example of TPS volumes, or structures, definition, and dose distribution of one field, is given in figure 1.27. The plan is finally evaluated with a graph, as the one presented in figure 1.28 (relative to the case in figure 1.27) called cumulative DVH - Dose to Volume Histogram. In the DVH, the horizontal axis is the absolute dose in Gy; the upper x-axis is the relative dose in $\%$ with respect to the prescribed dose for each structure; finally on the vertical axis, the fraction of the total volume of the structure (receiving the dose at x -axis) is reported and expressed in \%. The goodness of the plan is assessed following the ICRU recommendations 8 , stating that the whole target volume should receive at least the $95 \%$ of the prescribed dose and not exceed the $107 \%$; the maximum doses for OARs are below the planned dose constraints.

The evaluation of the plan can lead either to an iteration of the process or to the application of the methods and procedures to assure the quality of the treatment plan (Plan QA). The first method of patient-specific QA is the dosimetric verification of the treatment, obtained by delivering the plan first in a homogeneous water phantom equipped with pin-point chambers. This method can be demanding in terms of costs and time for a therapy center, since it should be done for each clinical treatment field. This is one of the reasons justifying the interest in developing specific software packages based on Monte Carlo methods for QA patient verification, as the FLUKA-based one presented in chapter 3.1. the dosimetric plan verification task can be replaced by faster MC forward calculations of the planned treatment field [18].

[^5]

Figure 1.27: Example of TPS volumes (a) and dose distribution in a patient case (b). Published in [2].


Figure 1.28: Example of a cumulative DVH-Dose Volume histogram to evaluate the patient's plan. ${ }^{9}$

In addition to all this, although the TPS used in clinical facilities are commercial software ${ }^{10}$. they need to be customized and commissioned according to the specific accelerator characteristics. As explained in chapter 4 and 5, the modelling of the accelerator machines requires the configuration of a series of machine parameters and the implementation of physical and dosimetric data such as: the Bragg's peak curves, called IDD-Integrated Depth Dose curves, for each particle type, for a set of energy values, and for a single beam size; the transversal beam particle fluence profiles in air at isocenter and other chosen upstream and downstream positions 92 .

[^6]
### 1.5 On-line monitoring techniques

During the several treatment fractions, range deviations can occur because of slightly incorrect positioning or anatomical modifications 93 . Since the treatment plan is defined and optimized only once before the first treatment fraction, these deviations cannot be discovered and corrected. Differently from the conventional radiotherapy, in hadron therapy the penetration depth inside the patient's tumour is a crucial quantity that needs to be known with minimal uncertainties: a few millimeters shift of the penetration depth in fact can determine high dose to the healthy tissue or not enough dose in the tumour.

For these reasons, the development of reliable monitoring techniques is very important for the hadron therapy treatment and has always been of great interest for researchers and clinicians in the field. Nowadays, the main techniques are either based on well-established methods used already in medical imaging field, such as the PET (Positron Emission Thomography), or dedicated detection methods such as prompt gamma imaging and secondary radiation (secondary protons etc.). A complete representation of the different monitoring techniques, with respect to irradiation and acquisition times, is given in figure 1.29 . PET has been the most explored one and further details are given in the next subsection, chapter 3.1 and PART III of this work. In particular, in this thesis, as further developed in PART III, a PET pre-treatment technique is introduced, based on the detection of short $\beta^{+}$emitters called PET fast range calibration or verification.

Finally, the other emerging techniques, in particular prompt gamma imaging and charged secondaries technique, are briefly mentioned in subsection 1.5.2.

### 1.5.1 PET in hadron therapy

PET principle and use in nuclear medicine. PET is an imaging technique consisting in reconstructing tomographic images of a target through the detection of coincidence photons from annihilation events produced by $\beta^{+}$emitting radionuclides. Some prototypes of detector systems, aiming at localizing brain tumours or following brain blood flow with positron emitting radio tracers, were conceived already in the 1960s (namely at MGH and BNL); however, the origins of PET date back to the 1970s, after the developments of mathematical reconstruction algorithms. It happened precisely when Ter-Pogossian, Phelps and Hoffmann proposed a PET system including the employment of the filtered back projection (FBP) method for reconstruction [94, 95].

Nowadays PET is widely used in clinical diagnostics, in the branch called nuclear medicine to detect metabolic cell dysfunctions. Conventional metabolic PET requires the intravenous injection in the patient's body of a tracer, i.e. a chemical compound where some atoms are replaced by a $\beta^{+}$emitter isotope. Tracers are injected in small quantities, as an example 370 MBq of a ${ }^{11} \mathrm{C}$ tracer used for a brain scan correspond to 100 pg of total mass [96]. The chosen chemical substance in the tracer is naturally part of the metabolic process of the specific organ or tissue, so it is more concentrated where the tissue uptake is higher.


Figure 1.29: Representation of the different monitoring techniques in HT on different timescales and delays with respect to the time of irradiation. The arrow on the right suggests when the technique can be used in a clinical treatment, expressed in terms of fractions (FXs). Figure adapted from [73]]-K.Parodi. The PET fast calibration of range proposed in chapter 7 of this thesis is added in the pre-treatment technique.

The most used radiotracer in PET is FDG (fluorodeoxyglucose), a glucose molecule coupled with the $\beta^{+}$emitting isotope ${ }^{18} \mathrm{~F}$, since glucose is at the basis of metabolism of cells and it is known from the 1920s that tumour cells can take up and metabolize more glucose than normal cells [97, 98]. Once the tracer reaches the organ, the molecule is taken up by cells with an increase of its concentration in that site (quantified in term of a ratio unit called standardized uptake value-SUV) and consequently of the specific activity of radioisotope. As depicted in figure 1.30, the unstable isotopes decay, with their half-life $T_{1 / 2}$; each decay process emits a positron, which, after having travelled for a certain range, proportional to its kinetic energy, annihilates with a free electron, producing the gamma pair at 511 keV at $180^{\circ}$ in opposite direction. The annihilation photons are then collected in coincidence by detector rings within a narrow energy and time coincidence window. The final images are then obtained, applying reconstruction algorithms, such as the above mentioned FBP or the more advanced one based on MLEM (Maximum-Likelihood Expectation-Maximization). A good radioisotope for PET diagnostics in nuclear medicine shall have a half-life compatible with treatment time and with small endpoint energy, and consequently short range to avoid the blurring of the image.

Conventional PET is used in three main clinical areas:

- Tumour diagnosis and management: for example to distinguish the cancer from benign tumour; to measure the response to therapy as in the treatment of Hodgkin's lymphoma; to identify the primary tumour when secondary cancers are present etc..
- Cardiology including surgery: in this context PET is particular indicated: to measure the myocardial perfusion using ${ }^{13} \mathrm{~N}$-ammonia and to measure myocardial activity with FDG.


Figure 1.30: PET principle. Left: $\beta^{+}$decay process, right: scheme of the coincidence detection.
Table 1.3: Main isotopes used in conventional PET [99]

| Isotope | $T_{1 / 2}$ <br> $(\mathrm{~min})$ | Endpoint energy <br> $(\mathrm{MeV})$ | Av. range in water <br> $(\mathrm{mm})$ |
| :---: | :---: | :---: | :---: |
| ${ }^{11} \mathrm{C}$ | 20.3 | 0.96 | 1.7 |
| ${ }^{13} \mathrm{~N}$ | 9.97 | 1.19 | 2.0 |
| ${ }^{15} \mathrm{O}$ | 2.03 | 1.70 | 2.7 |
| ${ }^{18} \mathrm{~F}$ | 109.8 | 0.64 | 1.4 |
| ${ }^{68} \mathrm{Ga}$ | 67.8 | 1.89 | 1.7 |
| ${ }^{82} \mathrm{Rb}$ | 1.26 | 3.15 | - |

- Neurology and psychiatry such as management of brain tumours and diagnosis of dementia [100].

PET is characterized by a spatial resolution of the order of 1 mm , worse than other imaging techniques, but conversely, PET has high sensitivity (ranging in commercial detectors from 3 to $20 \mathrm{kcps} / \mathrm{MBq}$ ) with unlimited depth penetration and provides metabolic information. Modern PET systems are therefore integrated with CT scanners or other imaging methods having a better spatial resolution. A complete review of the state-of-the-art of PET combined with other imaging technology in diagnostics can be found in [101]. In addition to commercial solutions, the research and development in PET detectors is very active. Examples come from physics groups from CERN, Universities of Geneva and Bern, such as the TT-PET project, aiming at prototyping a TOF-PET scanner with 30 ps time resolution by replacing scintillators with solid-state technology [102].

PET as monitoring technique in HT Besides its conventional use in nuclear medicine, PET is presently one of the most promising techniques for treatment monitoring and range verification in HT. In this PET application, no radioisotope injection is required as the $\beta^{+}$ activity is generated as a result of fragmentation mechanisms. The $\beta^{+}$emitter distribution, reconstructed with a PET system, can be correlated with Bragg peak position and dose distribution. However, this correlation between activity and dose is complex, requiring models to estimate the magnitude and spatial distribution of those fragments based on the beam and
patient geometry.
Moreover, as presented in figure 1.31 and as can be found in HT literature (e.g. ref. [103]), the shape of the $\beta^{+}$emitter distribution - or more precisely the distribution of annihilation points ${ }^{11}$ - along the beam direction is different for protons and ions: for protons, the emitters only come from the target fragmentation; for ions instead, the emitters also come from the fragmentation of the projectiles and exhibit a peak in the activity distribution in proximity of the Bragg peak. More details about the characteristics of the activities curve and how they vary over time will be detailed in PART III.


Figure 1.31: $\beta^{+}$annihilation points distribution compared to dose profile for protons and ${ }^{12} C$ at $220 \mathrm{MeV} / \mathrm{u}$ impinging on a PMMA target. Results obtained by FLUKA simulations.

Presently, as already mentioned in figure 1.29, PET in HT can be used in three different modalities, by varying the acquisition time:

1. off-room or off-line PET - after the treatment the patient is moved to a separate room and the activity is acquired with a conventional PET detector. Although it can profit of a full-ring, multi-modal and commercially available detection technology, this technique has inconveniences: the mechanical movement of the patient introduces alignment uncertainties and since some time elapses after the end of the treatment, a good part of the decay radiation signal gets lost and deteriorated by biological washout [104. Moreover, in order to have a significant statistic from the remaining long-lived $\beta^{+}$emitters, the acquisition can last up to 30 min , thus prolonging and making uncomfortable the treatment for the patient [105]. This technique started to be used at MGH at the end of 2000's [106, 107] and despite its drawbacks, it remains an accessible monitoring solution for therapy centers not having the means to integrate a dedicated detection system in the treatment room.
2. in-room PET - straight after the treatment, the patient is moved to a conventional fullring PET scanner placed in the treatment room. Re-positioning errors are reduced with

[^7]respect to the off-room solution and some time is saved, since about 5 min are required for the acquisition to have an acceptable image quality. Although the overall patient treatment time is reduced with respect to the off-room solution, the clinical workflow is slowed down since the next patient to be treated has to wait for the end of the previous patient's post-treatment scanning [105].
3. in-beam PET - the acquisition is performed during the treatment time. This technique has several advantages with respect to the previous ones: a higher activity can be detected and the biological washout is practically cancelled. In addition, if combined with a system able to provide the reconstructed PET signal in real time, it could allow the interruption of the beam delivery if any range deviation is detected.
Conversely, a system for in-beam has many challenging requirements to be satisfied, which are further described in section 7.2, the most evident ones are the geometrical integration in the beam line and the dependence of the beam time structure of the accelerator type. In-beam PET has been the most explored and promising technique in HT since the 1990's with many studies performed and further development of the first prototype at GSI in Germany, also tested in clinical scenarios in 2000's-2010's [108, 103, 109]. Other groups worked on the in-PET detector in Japan at HIMAC and National cancer center recently prototyping an innovative geometry and the possibility to be used with radioactive ion $\beta^{+}$emitting beams [110, 13].


Figure 1.32: PET techniques in hadron therapy: in-beam, in-room, off-room. Reprinted from [105].

### 1.5.2 Emerging monitoring techniques

Remaining in the context of particle physics, besides the recent and very promising studies about the use of ultrasounds in HT, based on ionoacustic effect [111, 112], coupled with optoacoustic tomography [113] to measure the Bragg peak position of protons as well as of ions [114], other techniques have been proposed based on the detection of secondary particles. They can be classified in two groups: methods based on prompt gammas detection and on other secondary emitted particles detection.

Prompt gamma detection techniques A limit of PET is that the number of the events is small and the generated signal is slightly delayed by the decay time of the produced $\beta^{+}$isotope during the treatment; prompt gamma radiation instead can in principle provide a response
in real time. Prompt gammas (PG) indeed are more numerous and emitted in a few ns time window and in an energy range of $1-10 \mathrm{MeV}$ from the de-excitation of target nuclei after nuclear interactions. Ion ranges can be correlated with the prompt gamma spatial distribution [115, 116], as well as with their energy distribution as demonstrated in [117] or with TOF (Time of flight) spectrum [118]. The challenges are in developing fast detectors with high count rate capability, which are able to reject the high background produced during the irradiation. An interesting review on prompt gamma monitoring in hadron therapy is published in ref. [119].

Detectors for PG includes Compton cameras [120], collimated (pin hole, single slit, multi slit) scintillator camera [117, 121]. It is worth mentioning that clinical verification was performed with collimated knife-edge camera produced by IBA during protontherapy treatments: in 2016 in Dresden, at a facility based on passive beam delivery, and in 2017 at Philadelphia with pencil beam scanning. The latter experiment allowed to quantify spot by spot range shifts occurring in 6 fractions of a TPS [119]. The absolute amplitude of the average range shift found was of $1-2 \mathrm{~mm}$ better than the 5 mm margin applied clinically in the TPS [122.

PG monitoring cannot be considered yet a real-time in vivo monitoring technique, in part due to the time-consuming reconstruction algorithms, although significant improvements allow now to achieve reconstruction time of less than one minute [123]. Finally, one can consider PG the most promising monitoring technique for proton treatments, thanks to the excellent production yield of PG with respect to other secondary particles.

Secondary particle detection techniques In carbon ions treatments the PG technique is not so used for two main reasons: (i) the PG production is less significant than in protons treatments due to the less primaries needed to release the same dose to the tumour; (ii) a severe background of neutrons covers this PG signal [124]. Conversely, as explained in section 1.2 .2 , due to the fragmentation processes in particular of projectiles, charged fragments are also emitted by the interaction of an ion beam with a target and can be used to retrieve useful information.

A technique based on the detection of secondary charged particles called IVI (Interaction Vertex Imaging) was proposed for application in HT by the TERA Foundation [125; its feasibility was demonstrated with ${ }^{12} \mathrm{C}$ projectiles and emitted secondary protons in [126]. As PG, also this technique can provide a real time response, since the charged particles are produced in a time window of $20-30 \mathrm{~ns}$; the energy ranges are higher with respect to PG and can reach hundreds of MeV . IVI consists in the reconstruction of the trajectories of the secondary charged particles emerging from the patient and the back tracing of their production point. The vertex distribution can be then correlated to ion range. As showed in figure 1.33, in fact, the number of emitted charged particles, mainly protons, increases as the beam interacts with the target and decreases while the ion beam slows down.

More recent studies [127, 124, making use of the Dose Profile, developed within the INSIDE (Innovative Solutions for In-Beam Dosimetry in Hadrontherapy) project, demonstrated that the production point can be measured with a spatial resolution of a few mm [128]. It is difficult to improve this value due to the multiple Coulomb scattering affecting these particles


Figure 1.33: Vertex distributions in a PMMA target of primary, secondary and total protons created by $400 \mathrm{MeV} / \mathrm{u}$ carbon ions and exiting the phantom simulated in GEANT4. The Bragg peak profile is also depicted to show the correlation with the vertex distribution 125.
when interacting with patient's body before emerging. Another limitation of secondary charged particle techniques is linked to the fact that these particles are forward-peaked and the detector cannot be placed at a small angle during the treatment, causing a reduction of the efficiency of the detection system. Finally, also the flux detection of secondary neutrons was explored and some measurements, performed using a dedicated detector [129], reveal how extracting useful correlations for monitoring in HT with neutrons is still challenging, also due to missing cross-section data, necessary to characterize neutron production in tissue-like materials 130 .

Finally, all the above-mentioned monitoring techniques will take advantage of cross-section measurements experiments in HT energy range, as for example the recent results achieved by the FOOT collaboration [131].

## Chapter 2

## Accelerator complexes designed by the TERA Foundation

### 2.1 The TERA Foundation

The TERA Foundation (TErapia con Radiazioni Adroniche), is a non-profit entity created in 1992 in Novara and recognized as a moral entity by the Italian Ministry of Health in 1994, having its research and development site on CERN's premises. In the more than 25 years of its activities, three core programs were developed, employing more than 250 physicists and engineers:

1. In the years 1992-2001, the design and construction approval of CNAO (Italian Center for Hadrontherapy in Oncology, Centro Nazionale per l'Adroterapia Oncologica). The center was built from the 2005, on the basis of the PIMMS study [132], and the first patient was treated in 2011. Nowadays, this facility is a center of excellence in Europe for the treatment with protons and Carbon ions as well as for advanced research activities in medical physics. This result was possible thanks to the fruitful collaboration and sharing of technical competences among several research institutes such as CERN and other prestigious European medical centers, continuously animated by the enthusiasm, vision and perseverance of the TERA Foundation collaborators and its founders Ugo Amaldi and Gaudenzio Vanolo. It is in this CNAO center that the experimental activities presented in this thesis were carried out (see chapter 8).
2. From the nineties until now, the design and development of a compact linac for hadron therapy [79]. This program has provided the following most important outcomes:

- the LIBO, LInac BOoster, project consisting in the design, construction and testing of a high frequency linac unit in collaboration with CERN, the Universities and INFN sections of Milan and Naples [79, presently exposed in the Microcosm permanent exhibition at CERN.
- TOP (Terapia Oncologica con Protoni): this project, initially approved by Italian National Institute of Health (ISS) in 1995 and later led by ENEA (the Italian

National Agency for New Technologies, Energy and Sustainable Economic Development), consists in the development of an all-linac accelerator for proton therapy (Recent beam commissioning results were published in ref. [133]).

- The launch of a spin-off with CERN: ADAM SA (2008), part of AdVanced Oncotherapy (AVO) since 2013, building the LIGHT (Linac for Image-Guided Hadron Therapy) accelerator [134, 71].

Moreover, several conceptual designs and feasibility studies for hadron therapy facilities were carried out, based on the innovative idea of the cyclinac, proposed by Ugo Amaldi himself in 1992: the combination of a low-energy cyclotron, available on the market for radioisotopes production and a LINAC for hadron therapy. The main hardware components of a cyclinac are: (i) a computer-controlled ion source, (ii) a cyclotron, (iii) external beams typically used for producing medical radioisotopes, (iv) a beam transport system, which focuses the particles extracted from the cyclotron into the acceptance of the linac, (v) a linac (sometimes made of two sections) and (vi) a distribution system of the high-energy beam to the treatment rooms.
The main projects based on cyclinac concepts are:

- IDRA and PERLA projects: consisting in the design of advanced protontherapy centers, combining the cyclinac-protontherapy treatment with the production of radiopharmaceuticals in the same facility. An example of layout is represented in figure 2.1.


Figure 2.1: Top view of PERLA project layout based on cyclinac project with the indication of the principal space allocations for the main area. This layout combined a layout of radiopharmacy from ACSI company and the protontherapy area, complete of LINAC and beam transport lines (BTS), designed in detail by the TERA Foundation, and treatment rooms.

[^8]- TULIP, TUrning LInac for Protontherapy, an accelerator system patented by the TERA Foundation ([135,,[136]). It consists of a high gradient Linac mounted on a rotating gantry. TULIP was designed in different configurations: facilities with radioisotope production, one or two rooms (figure 2.2) or in a more compact single room-facility only dedicated to protontherapy (figure 2.3 and ref. [137]). Finally, for the reasons explained later, the most explored solution for TULIP has been the all-linac version, studied in this thesis, also shown in figure 2.3 .


Figure 2.2: A 3D view of the conceptual design of a Cyclinac-TULIP for protontherapy and radioisotopes production in two different configurations: one treatment room (left) and two treatment rooms (right). For the radioisotopes production the ACSI-cyclotron TR24 bunker was chosen.


Figure 2.3: TULIP single-room facilities: cyclinac (left) and all-linac (right). TR24 cyclotron is used as injector.

- CABOTO, CArbon BOoster for Therapy in Oncology, is the main project specifically designed for Carbon ion therapy. The first design was published in [138] and presented in figure 2.4 and its further developed versions studied in 139 and initially proposed in new development programs of new ion accelerators (e.g. Next Ion Medical Machine Study (NIMMS) at CERN [140]).


Figure 2.4: CABOTO cyclinac artistic view [138].

Finally, in parallel to all these efforts in the developments of accelerators and facilities for hadron therapy, in 2008 TERA launched a research program, called AQUA (Advanced Quality Assurance in hadron therapy), dedicated to the development of instrumentation for patient monitoring and quality assurance in hadron therapy, 141. The program, led by Fabio Sauli, the inventor of the GEM detector (Gas Electron Multiplier) [142], aimed at the development of four major monitoring techniques mentioned in the introduction: (i) Proton Range Radiography built upon two prototypes, which were designed and developed (PRR10 and PRR30 [143]); (ii) Interaction Vertex Imaging and Nuclear Scattering Tomography; (iii) in-beam PET with Crystal Detectors and with Multi-gap Resistive Plate Chambers (MRPCs) [144, 99.

### 2.2 Cyclinac versus all-linac solutions

The advantages of cyclinacs are manyfold, in particular:

- the use of small and low-energy (tens of MeV ) cyclotrons, already available on the market, for the production of radiopharmaceuticals, which overcomes the difficulty of building low beta accelerators;
- smaller footprint with respect to an all-linac solution;
- the possibility to construct a multi-purpose medical facility (Radiopharmaceuticals production and hadron therapy).

On the other hand, the cyclinac has still challenges to overcome: such as large transverse emittance [137] of the cyclotron with respect to the linac, very different beam time-structure of
the two accelerators, resulting in a low beam transmission with the need of chopping the beam injected in the cyclotron [145].

Because of these limits, and with the aim of treating patients in the near future with linacs for hadron therapy, companies as AVO-ADAM ${ }^{2}$ and research groups including TERA, have adopted all-linac solutions for their initial projects.

Accordingly, the all-linac solutions for TULIP and CABOTO were chosen as starting point for this thesis work.

### 2.3 TULIP Turning LInac for Protontherapy

As mentioned in the previous section, TULIP ${ }^{3}$ is an innovative single room-facility accelerator system, composed of a high-gradient linac mounted on a rotating frame (gantry) for irradiation of patients from multiple beam directions. In the following paragraphs the main features of the single-room all-linac version as published in ref. [1] will be described. Details about the beam dynamics studies and prototyping of the accelerators can be found in [145] and [139].


Figure 2.5: Artistic view of TULIP and its accelerating sections (the source, the LEBT and nozzle details are not shown). Published in [1].

[^9]
### 2.3.1 TULIP accelerator components and beam transport system.

The TULIP all-linac solution is shown in figure 2.5. It is composed of two main sections. The first one is fixed on the ground and brings the 70 MeV proton beam to the gantry coupling point, where the rotating section starts. The second one is mounted on a rotating frame and brings the $70-230 \mathrm{MeV}$ beam up to the treatment room isocenter. The first section is composed of:

- a proton source;
- a low energy beam transfer line (LEBT);
- a Radiofrequency Quadrupole (RFQ) Linac, accelerating the protons up to 5 MeV [146, 147];
- an Interdigital H-type (IH) cavity, accelerating protons up to 10 MeV [148]
- a Side Coupled Drift Tube Linac (SCDTL) [149] accelerating protons up to 70 MeV ;
- the first part of the Medium energy Beam Transfer line (MEBT), which transports the beam and matches its transverse properties to the gantry coupling point.

The second section is composed of:

- the second part of the MEBT, which transports and matches the beam properties to the following accelerator section;
- the Backward Travelling Wave (BTW) Linac [69, 150, 151, which accelerates the beam up to 230 MeV and runs at the same 3 GHz RF frequency used by all electron Linacs producing X-rays for conventional radiotherapy and by the proton linacs designed by TERA and AVO-ADAM [79];
- the High Energy Beam Transfer Line (HEBT), which transports and matches the beam properties up to the scanning magnets;
- the Beam Delivery System, which matches the beam properties up to the isocenter, through two downstream scanning magnets and a nozzle.

TULIP is still in development phase but some components have already been built, mainly at CERN. Examples are those of figure 2.6.

TULIP, as all the hadron therapy linacs, differs from the current proton therapy centres for the following reasons:

- as far as the time structure and intensity is concerned, it has the publicized advantages of a syncrocyclotron, producing an always-present proton therapy beam, differently from the one extracted from a synchrotron, which cycles with time;
- concerning the energy, it has the advantage of a synchrotron: the output energy is not fixed but can be electronically varied at will without using any passive beam degrader or energy selection systems;
- the energy variation can be electronically achieved in $2.5-5 \mathrm{~ms}$, i.e at least 20 time faster than in cyclotrons and synchrotrons that require more than 100 ms .


Figure 2.6: TULIP prototypes components: A) the RFQ, designed and built by CERN [146, 147, B) One tank of the BTW Linac [151, C) High efficiency Klystron powering one tank of the BTW LINAC (VDBT-I.Siracev), D) FeCo magnet prototype [152]. The position of this components in TULIP are indicated in figure 2.5 .

The main feature and novelty of TULIP is therefore the possibility to perform an active and fast energy variation between 70 MeV and 230 MeV . In particular, the BTW linac energy can be continuously varied by adjusting in a $2-3 \mathrm{~ms}$ time the powers and the phases of the 18 klystrons [79, 145]. The fast energy variation property makes TULIP particularly suited for the volumetric repainting [153], which enables better accuracy in treating moving targets but is today unpractical, because of the slow energy variation of commercial protontherapy systems (from 20 to 200 times slower than TULIP).

Moreover, the TULIP all-linac is characterized by negligible beam losses and small beam emittance thanks to the effective matching of the accelerator sections. This implies that smaller aperture magnets can be used for the beam transport lines.

TULIP's mechanical structure design is particularly light, since the linac is directly positioned on the rotating girders, thus reducing the number of supporting parts to the minimum. The four tubular elements of the support girders needed for resistance are also used to support the magnets and to transport ancillaries (cooling, vacuum, electronics). The actuation system foresees the use of counterweights in order to reduce the power needed during rotation. The overall weight of TULIP is about 70 tons, all components included: linac, magnets, support structure, counterweight and ancillaries.

This single-room facility has a footprint of the order of $200 \mathrm{~m}^{2}$.

### 2.3.2 TULIP optics and design constraints

The optics of an accelerator is defined by building the beam transport magnetic line - made of electromagnetic dipoles and quadrupoles.

As a reminder from accelerator physics, dipoles are used to bend the beam and their strength is given by: $1 / \rho=q / p \cdot B_{z 0}$, where $\rho, q, p$ and $B_{z 0}$ are the radius of curvature, the particle electric charge, the momentum and the magnetic field perpendicular to the trajectory. The proton momentum $p=\beta \gamma E_{0}$ is proportional to the rest energy $E_{0}=m c^{2}$ of the particle and the product of the two relativistic parameters $\beta$ and $\gamma$. The relativistic parameters are functions of the particle total energy E : $\gamma=E / E_{0}$ and $\beta=\sqrt{1-1 / \gamma^{2}} . B_{\max } \rho$ is the maximum rigidity of the protons that are transported. For the bending magnets the radius of curvature is: $\rho=p /\left(q B_{\max }\right)$, where the maximum bending field has been chosen to be $B_{\max }=1.8 T$.

Quadrupoles focus and defocus the beam and their effect is described by the quadrupole strength: $k=\frac{q}{p} \frac{d B_{z}}{d x}$, where $d B_{z} / d x$ is the gradient (measured in $\mathrm{T} / \mathrm{m}$ ) and $x$ is a transverse coordinate measured from the centre of the quadrupole. A horizontal focusing quadrupole acts on the $x$ coordinate, thus in the horizontal plane, and defocuses along the vertical $y$ axis; the next quadrupole usually focuses in the opposite direction with an overall focusing effect in both planes. To design a beam transport line, the particle motion is described in the phase space (figure 2.7) - i.e. in the space where one represents the position $x$ (or $y$, depending on which axis is considered) and the divergence $x^{\prime}$ (or $y^{\prime}$ ), measured in mrad - of the trajectory with respect to the particle coordinate $s$, which is measured along the central line of the transport line. The transverse properties of the beam are described by four numbers $(x, x ; y, y$ ) , for


Figure 2.7: The phase space ellipse in the $x-x$ ' plane [154].
each longitudinal position $s$ of the particle along the central line of the magnetic channel. The area of the phase space ellipse, that can be defined in both planes, $x$ and $y$, is a conserved quantity, proportional to the so-called beam emittance $\left(A=\pi \epsilon_{x, y}\right)$; it is measured in mm mrad and is represented by the symbols $\epsilon_{x}$ in $x$ plane and $\epsilon_{y}$ in $y$ plane. It is expressed by the formula $\epsilon_{x, y}=\sqrt{\left\langle x^{\prime \prime 2}\right\rangle\left\langle x^{\prime 2}\right\rangle-\left\langle x x^{\prime}\right\rangle^{2}}$. The emittance in the longitudinal plane $(\epsilon(\phi, E))$ is measured in deg keV . The local properties of a transport beam line are defined by the Twiss
parameters $\alpha, \beta$ and $\gamma$ which are continuous functions of $s{ }^{4}$. As shown in figure 2.7, for a beam of emittance equal to $\epsilon_{x}$, the maximum displacement and the maximum divergence are: $x_{m}=\sqrt{\epsilon_{x} \beta_{x}}, x_{m}^{\prime}=\alpha \sqrt{\frac{\epsilon}{\beta}}$.

In a beam line, each quadrupole is defined by a gradient and a length, or better an effective length, once it is supposed that the magnetic field drop varies sharply at the edge. The same assumption is made for each dipole, which requires the superimposition of three elements: the magnetic field perpendicular to the trajectory, the length and the pole face rotation angle $\psi$. The dipole is a sector magnet, i.e. a magnet that has faces perpendicular to the orbit, $\psi=0$. For a rectangular magnet $\psi$ equals half the bending radius: $\psi=\frac{s}{2 \rho}$, where $s$ is length of the particle trajectory. Further details on beam dynamics can be found in ref. [154].

The TULIP optics design followed precise constraints related to relevant regulations, standards or medical physics considerations. The most peculiar ones are the following:

- a clearance of more than 50 cm is kept between the isocenter plane and the most downstream element of the nozzle;
- the source to axis distance (SAD), i.e. the average distance of the two scanning magnets from the isocenter, is larger than 2 m , in order to reduce the skin dose to the patient [70];
- the scanning field at the isocenter plane is larger than $30 \times 30 \mathrm{~cm}^{2}$, in order to be competitive with existing commercial solutions and to minimize the need for complex 'field-patching';
- given the fast energy adjustment of the linac proton beam and the need to have an optics that is not influenced by momentum mismatches, both the dispersion function and its first derivative at the isocenter are zero;
- the beam size for protons at clinical energy values is mainly characterized by the Multiple Coulomb Scattering through the nozzle elements. The beam size was thus minimized, taking into consideration the limits imposed by the nozzle.

The beam properties of the beamline sections connecting the different accelerators are designed in order to minimize beam losses and optimize the performance of the system for medical therapy. For example, the MEBT optics is adjusted such that the beam properties are not affected by the mechanical rotation of the gantry and the HEBT design ensures that the beam has the appropriate transverse size at the treatment isocenter. In the following section, the beam optics optimization part is reported ${ }^{5}$.

[^10]
### 2.3.3 TULIP Beam Optics Optimization

MEBT The MEBT design and matching was performed considering two main bending sections: the first one covering $180^{\circ}$ in the vertical plane, while the second, starting at the gantry coupling point, covering $26^{\circ}$. This angle was chosen as to obtain the SAD value quoted above. Input and output beam parameters, considered as matching constraints, are those at the end of the SCDTL and at the beginning of the BTW structure, respectively. The matching was performed only considering the transverse plane and using the software Trace3D [155].

In order to keep the Twiss parameters of the beam at the input of the BTW constant with the variation of the gantry angle, the condition of rotational invariance was applied [156]. Given that the emittances in both transverse planes are equal (normalized RMS emittance of $\epsilon=0.03$ $\mu m$ ), this condition is fulfilled if the beam at the coupling point is symmetric (Twiss $\beta_{x}=\beta_{y}$ ) and parallel (Twiss $\alpha_{x}=\alpha_{y}=0$ ). The Twiss parameters of the beam at the end of the SCDTL, at the rotating joint and at the beginning of the BTW are listed in Table 2.1.

Table 2.1: Constraints on the beam parameters used in the matching procedure [1].

| Parameter | Beam at SCDTL end | Beam at BTW entrance |
| :---: | :---: | :---: |
| $\alpha_{x}$ | 1.18 | -0.29 |
| $\alpha_{y}$ | -2.64 | 1.83 |
| $\beta_{x}(m)$ | 1.46 | 0.21 |
| $\beta_{y}(m)$ | 0.22 | 1.48 |

Some further constraints were introduced regarding the magnets. More specifically, the maximum tip field of the PMQs (Permanent Magnet Quadrupoles) was limited to 1 T and the beam-pipe aperture was adjusted to avoid beam losses. A minimum beam pipe radius of 5 mm was chosen in order to prevent beam losses on the pipe wall. It resulted in a maximum gradient of $200 \mathrm{~T} / \mathrm{m}$, the value that was considered as the upper limit in the design procedure. As shown in the results, this value guarantees negligible beam losses along the MEBT.

In the design, 13 quadrupoles, 4 dipoles with $45^{\circ}$ bending angle and 2 dipoles with $26^{\circ}$ bending angle are considered, for a total length of 5 m for the $180^{\circ}$ section and of 2.7 m for the $26^{\circ}$ section respectively. In order to keep the dispersion to zero in the accelerating structures, the choice of using a double-bend achromatic configuration was made, both for the $180^{\circ}$ and the $26^{\circ}$ sections. All the dipoles were considered to have the same radius of curvature $\rho=684.4 \mathrm{~mm}$.

In figure 2.8, the beam envelopes and the dispersion are plotted for the two sections.

[^11]

Figure 2.8: The MEBT beam Envelope as resulting from the code TRACE3D. The blue and red lines describe the beam envelope ( $90 \%$ of the particles) in the horizontal and vertical plane respectively. The two figures show the sections of the transfer line before (top) and after (bottom) the rotating joint. Published in [1] ${ }^{6}$.

HEBT The HEBT consists of two sections separated by bending magnets. In order to contain the dimensions of the last dipole, a downstream scanning system is chosen, composed by two distinct scanning magnets in $X$ and $Y$. These scanning magnets are small dipoles that have two perpendicular transverse fields allowing a fine-grained scan of the treatment area. Beam monitors and vacuum pumps complete the list of components. Particularities of the designed beamline are the choice to use FeCo dipole magnets [152] (figure 2.6, D), enabling a maximum magnetic field of 1.8 T at the center of the magnet. For quadrupole magnets instead, the constraint was using them in single polarity mode. The scanning magnets and the nozzle elements were considered for the magnetic design. The matching of HEBT quadrupole gradients was performed using MADx [157], considering only beam envelopes.

The beam exits the BTW linac with different transverse properties at different energies. An iterative matching algorithm was thus applied to each set of Twiss parameters, in order to evaluate the best quadrupole gradients for each beam energy. Using these results, the PTC module of MADx was used to track the particles from the exit of the BTW linac to the isocenter in vacuum. The results were checked for consistency with the corresponding MADx simulations.

### 2.3.4 TULIP Dose delivery system and the impact on HEBT design

As mentioned, a downstream scanning system has been chosen for this TULIP design. It is composed of two distinct scanning magnets, one for each transverse plane. Realistic dimensions were assumed for the magnets (magnetic lengths of 22.5 cm and 27.5 cm respectively), in order to achieve the maximum beam divergence of 80 mrad and 107 mrad at the maximum beam energy of 232 MeV . An example of the scanned beam with FLUKA simulation is described in chapter 4

Nozzle The final structure of the TULIP accelerator beamline is the nozzle, a combination of a vacuum or helium chamber, detectors used to monitor the beam online. An example on how a nozzle appears in one of the CNAO's treatment rooms is given in figure 2.9. The ionization chambers are also shown. As presented in figure 2.10, these chambers, produced by DE.TEC.TOR s.r.l. 7 , are integrated in two Boxes: the first one (BOX1), includes an integral ionization chamber (with a fully integrating anode) and two segmented strip chambers (stripX and stripY), with vertically- and horizontally-oriented strips; the second box (BOX2) contains an integral ionization chamber and a pixel chamber (with the anode segmented in pixel). The TULIP nozzle was designed starting from the CNAO's and Pyramid's ones [158] and the results are presented in chapter 4.


Figure 2.9: Top: An example of nozzle in one of the CNAO's treatment rooms (Horizontal beam). Bottom: the two images show two views of the ionization chambers produced by DE.TEC.TOR. srl. Courtesy images by CNAO and DETECTOR.

[^12]

Figure 2.10: Drawing of integral (left) and strip (right) chambers made by DE.TEC.TOR. Courtesy images by CNAO and DE.TEC.TOR.

The nozzle design has a huge impact in increasing the final beam spot size, especially at the lower energies required for the treatment (less than 70 MeV ), essentially due to the Multiple Coulomb Scattering of the particles in air and in the chamber materials. In order to mitigate this effect, a Helium chamber could be introduced; however, this solution has firstly the disadvantage of increasing the complexity of the nozzle structure and, secondly it has been shown in ref. 159 that a similar effect can be obtained inserting a range shifter close to the patient.

The results from the nozzle scattering effect were used to define the target beam size at the isocenter in vacuum. In order to linearize as much as possible the variation of the quadrupole gradients along the energy range, a unique value of Twiss $\beta$ function was set as a constraint at the isocenter. Thanks to the slight variation of the beam emittance with the energy, the chosen value of Twiss $\beta$ resulted in a constant beam size in vacuum at the isocenter of about FWHM $=2.5 \mathrm{~mm}$.

Some designs impose to have a beam waist in vacuum (i.e. zero divergence, Twiss $\alpha=0$ ) at the isocenter. A dedicated comparative study has shown that this constraint is not essential to ensure proper clinical parameters for proton beams. Simulations have shown that the influence of a slightly divergent beam at the isocenter in vacuum is not observable for Twiss $\alpha$ values up to $\pm 100$ at high energy, when compared to beams with $\alpha=0$. Indeed, even if $\alpha=0$ in vacuum at the isocenter (i.e. the beam exhibits a waist in vacuum at the isocenter) simulations in air show that the beam is in reality divergent. This is because of the large effect of the nozzle scattering on the beam parameters at the isocenter for proton beams. This has a strong impact on the HEBT optics design, as it allows to reduce the number of required focusing elements.

As shown in figure 2.11, the HEBT line design included the following components:

- 3 quadrupoles for the optics matching;
- one bending section composed by two dipoles of $58^{\circ}$ with an additional quadrupole in between to close the dispersion;
- 3 beam position monitors and 2 combined vertical-horizontal beam orbit correctors able to read and compensate beam orbit errors.

After the bending section, more than 2.7 m of drift have been considered for the scanning magnets, the nozzle and the air gap to the isocenter. The complete spectrum of energy, from 70 to 230 MeV , with a step of 0.5 MeV was analysed. Considering 10 mm of good field region (gfr) for the magnets and a constant 5 -rms normalized emittance of $0.16 \mu \mathrm{~m}$, the limit on the maximum Twiss $\beta$ function is 600 m . As shown in Figure 2.11, the Twiss $\beta$ functions are well below this threshold even for the most critical energy ( 230 MeV ).


Figure 2.11: Twiss $\beta$ and dispersion functions of the transfer line for 230 MeV (MADx output). The centered white rectangles are the dipole magnets; those above (and below) the central line are focusing (defocusing) quadrupoles, called in the following Q1, Q2, Q3 and Q4. Dashed boxes are the monitors and the black ones are the correctors. Published in [1] $\cdot 8$

The quadrupole gradients were matched in order to obtain a fixed value of Twiss $\beta$ at the isocenter and a reduced value of Twiss $\alpha$ functions (less than 100). The process was optimized in order to linearize the values of the gradient to facilitate the power supply and the current variations for different energy values. Starting from the first matching configuration at 70 MeV , the subsequent gradients have been matched starting from the previously found quadrupole gradients. In this way, it was possible to minimize the gradient variation between two adjacent energy values and hence to obtain smooth and linear curves for the quadrupole gradients as a function of the particle momentum. The result of this process is plotted in Figure 2.12. The assumption of 1 T at the gfr ( 10 mm ) results in a maximum gradient of $100 \mathrm{~T} / \mathrm{m}$. As presented in Figure 2.12, the magnitude of all the three gradients is included within the minimum value of 10 and the maximum value of $100 \mathrm{~T} / \mathrm{m}$. The curves are monotonous and smooth among the whole spectrum of momenta. The gradient of the fourth quadrupole of figure 2.11, used to keep the dispersion and its first derivative to zero, is of course independent on the Twiss parameters and it is a linear function of the particle momentum.

[^13]

Figure 2.12: Gradients of the transfer line quadrupoles (Q1,2,3) as a function of the momentum of the particle beam. Published in [1].

The smooth and monotonous gradient variation along the momentum is a crucial characteristic since the HEBT should be able to rapidly change its energy settings following a change in output energy of the Linac.

Orbit Correction In the beamline design process, another important point is the evaluation of errors due to possible misalignment of the magnetic elements. This is critical to ensure that the beam delivery system can position the beam with the correct level of accuracy. The analysis was limited to the 230 MeV kinetic energy case, which represents the worst-case scenario, since the gradients are maximum and the feed-down effects [160] are maximized due to the misalignment.

To evaluate the impact of the quadrupoles misalignment, a Gaussian distribution of 0.5 mm displacement error was applied to the 4 quadrupoles of HEBT. At the isocenter, cumulated errors up to 80 mm are induced. Thanks to the monitors and combined horizontal-vertical correctors, it is possible to cancel the orbit error at the isocenter and to limit the residual error along the line, while keeping corrector kick strengths within the required limits. Figure 2.13 shows the results of this orbit correction procedure, showing the residual orbit deviation on top of the beam envelope. It is worth to note that, even including the residual orbit error, the constraint of 10 mm of good field region is fulfilled. Finally, the corrector kick values, both for the vertical and the horizontal planes, are limited below 10 mrad by choosing appropriate longitudinal positions.

In summary, the beam optics optimization led to the layout of the TULIP magnetic line presented in figure 2.14 .

[^14]

Figure 2.13: Horizontal (blue) and vertical (red) beam envelopes at 5-rms emittance plus the residual orbit deviation after the correction along the transfer line at 230 MeV , for applied misalignment errors of 0.5 mm Gauss (2 $2 \sigma$. Published in [1] ${ }^{9}$.


Figure 2.14: TULIP layout magnet lines Published in [1] ${ }^{10}$.

[^15]
### 2.4 CABOTO CArbon BOoster for Therapy in Oncology

CABOTO, CArbon BOoster for Therapy in Oncology, is an innovative development project of an efficient high-frequency linac for hadron therapy that can accelerate ${ }^{12} \mathrm{C}$ ions and $\mathrm{H}_{2}$ molecules up to $430 \mathrm{MeV} / \mathrm{u}$, bunched in pulses of the order of $2-5 \mu \mathrm{~s}$, with a repetition rate of 360 Hz . With respect to TULIP, CABOTO is four times more challenging because of three main factors:

- In order to achieve the same penetration depth of 32 cm in tissues, a higher kinetic energy is needed ( 220 MeV for protons against $430 \mathrm{MeV} / \mathrm{u}$ for C-ions).
- The ratio $\mathrm{q} / \mathrm{m}$ results in higher accelerating gradients.
- The C-ions have a magnetic rigidity of 6.6 Tm maximum, which is 2.9 larger with respect to the protons (2.3 Tm), because of their mass and energy, resulting in either larger bending magnets or larger magnetic fields.

For the above-mentioned reasons CABOTO is a combination of longer linacs and lower accelerating gradients with respect to TULIP.

The most recent CABOTO design is composed of the following three accelerator sections [139, as presented in figure 2.15 .

- four 750 MHz IH cavities, from $2.5 \mathrm{MeV} / \mathrm{u}$ to $10 \mathrm{MeV} / \mathrm{u}$;
- a 3 GHz DTL, from $10 \mathrm{MeV} / \mathrm{u}$ to $100 \mathrm{MeV} / \mathrm{u}$;
- a 3 GHz HE CCL, from $100 \mathrm{MeV} / \mathrm{u}$ to $430 \mathrm{MeV} / \mathrm{u}$.


Figure 2.15: CABOTO all-linac layout - TERA Foundation.
CABOTO beam is characterized by: repetition rate at $360 \mathrm{~Hz}, \mathrm{RF}$ pulse length $5 \mu \mathrm{~s}$, beam flat top $3 \mu \mathrm{~s}$, overall transmission of about $75 \%$; ion source intensity of about $10^{9} .{ }^{12} \mathrm{C}(6+)$ ions per pulse.

The advantages of CABOTO with respect to syncrontrons are the following :

- CABOTO reaches beam intensities 10 times larger than a synchrotron.
- The spot rate ( 360 Hz ) allows a 10-fold Sparse proportional rescanning and 3D dose distributions for moving organs;
- The emittances of the accelerated beam are 10 times smaller than in synchrotrons, so that the aperture of the HEBT magnets can be definitely smaller.
- The power consumption is about half of that of a synchrotron.

Details studies on CABOTO beam dynamics and accelerator structures can be found in ref. [139].

### 2.5 Sparse proportional rescanning

The Paul Scherrer Institute (PSI) was pioneer in the development of spot scanning and consequently of most of the techniques needed to overcome the challenges of treating moving organs [161, 162]. One of the most explored techniques has been the re-scanning, also called re-painting [163] or multi-painting [79]. As these names suggest, re-scanning consists in visiting N times the tumour volume with many pencil beams or beam spots, distributed according to a spot map covering the tumour and defined by the TPS. Several re-scanning strategies were conceived by research teams, especially at PSI, varying different parameters such as spot size, weight, geometrical distribution, number of rescanning N etc.. [87]. A first classification, according to the order in which the spots are visited in the rescanning process, is the following:

1. repeated delivery, in which the whole dose, corresponding to the weight $P_{i}$ is delivered to each i-th spot in $M_{i}$ visits, before passing to the next spot, with $0 \leq M_{i} \leq N$;
2. layered delivery, in which each layer of the target is scanned $M_{\max }$ times before proceeding to the next layer, where $M_{\max }$ is the maximum multiplicity in the layer;
3. volumetric delivery, in which the whole target is fully scanned once, before repeating the same operation $N-1$ times [2].

Not all these techniques have been applicable until now, due to the limits of the accelerator complex in operation, i.e. cyclotrons or syncrotrons based. In ref. [164 it was demonstrated that volumetric delivery is advantageous only if the time required to change the energy layer is fast enough (of the order of dozens of ms).

Thanks to the fast active energy variation of the order of ms, TERA's linacs can be considered first good candidates for the volumetric rescanning application and, in addition, they have allowed further research on new strategies in dose delivery for spot scanning. For example, in ref. [2], the sparse proportional re-scanning has been introduced and its advantages have been quantified by a reduction factor. The sparse proportional re-scanning aims at reducing the total number of visits necessary for a fast and effective application of repainting technique. In fact, concerning the choice on the number of visits to each spot in each scanning, two first methods were proposed by PSI:

1. scaled re-scanning: for all the S planned spots the numbers of visit is $M_{i}=N$;
2. iso-layered (proportional) re-scanning: in each layer the number of visits $M_{i}$ are scaled (almost) proportionally to the weight $P_{i}$.

In the sparse proportional re-scanning the number of visits $M_{i}$ in the whole target are scaled (almost) proportionally to the weight $P_{i}$. In this method, the total volume is considered, and not a single layer as in the second one, and the same weight quantum $W$ is used for all the S spots by applying the following algorithm: the range between 0 and Pmax - which is the number of particles corresponding to the planned spot with the maximum weight in the whole target - is divided by N to obtain the weight quantum W as: $W=P_{\max } / N$; the weight of each
spot $P_{i}$ of the whole target is compared with the N quantities $\mathrm{W}, 2 \mathrm{~W}, 3 \mathrm{~W} . . \mathrm{NW}$; if $P_{i}$ is in the interval between $(q-1) W$ and $q W$ (with $1 \leq q \leq N)$ then $M_{i}=q$.

An illustration of this algorithm is presented in figure 2.16 in the simple case of a water sphere (representing a homogeneous tumour) and for a central longitudinal slice. Once fixed a $\mathrm{N}=12$ total number of rescanning, the number of visits $M_{i}$ to each spot position are determined according to the above-mentioned algorithm and, as expected, are varying "intra" layer and "inter" layer. Each delivery of the weight quantum $W$ is shown in different colours. This is the case of an equal delivery procedure where, for a given spot position, the W is kept equal at each visit, except for the last one.


Figure 2.16: Illustration of sparse proportional 12 fold-rescanning in a water sphere for a central longitudinal slice. Published in [2].

In ref. [2], the advantages of sparse proportional re-scanning have been proven with a detailed study of 29 proton treatment plans, having different shape and size and treated with a different number of fields for a total of 54 . In particular, comparing for each plan the scaled and sparse rescanning, a reduction factor $\mathrm{RF}(\mathrm{N})$, function of the number of re-scannings N , was defined as:

$$
\begin{equation*}
R F(N)=\frac{V_{N-\text { scaled }}}{V_{N-\text { sparsed }}}=\frac{N S}{V_{N-\text { sparsed }}} \tag{2.1}
\end{equation*}
$$

It has been demonstrated that this factor does not depend neither on the shape and volume of the tumour nor on the distance between the scanned layers within about $\pm 10 \%$. The distribution of the reduction factor for the proton treatment plans is shown in figure 2.17. For $\mathrm{N}=12$ rescannings its value is $R F(12)=3.6 \pm 0.4$. More in general, the $R F(N)$ as function of number of rescanning is plotted in figure 2.17. Of high interest is the $\operatorname{RF}(\mathrm{N})$ for $\mathrm{N}=5$, considered the optimal number of rescanning. Its value is $R F(5)=2.8 \pm 0.3$ These numbers are also applicable in the case of treatments with carbon ion beams.


Figure 2.17: Distribution of reduction factor (left) for $\mathrm{N}=12$ rescanning; Reduction factor RF as a function of number of rescanning N (right). Published in ref. [2].

## Chapter 3

## The role of Monte Carlo codes for particle transport in hadron therapy

### 3.1 Monte Carlo methods for particle transport

In a complex physics problem, where the complexity is measured by the number of dimensions of the variables space, a deterministic analytical approach is not possible. In particle transport, the problem consists in a temporal evolution of an object (the particle) interacting with other objects, which is based upon object-object interaction relationships (cross-sections) [165]. A simple random process repeated several times can well represent a complex problem. This is a typical example where Monte Carlo (MC) methods can be effectively used. The advantage of MC methods for complex problems, in terms of computing time, with respect to analytical approach, is shown in figure 3.1.

The Monte Carlo methods and their application to radiation transport problems were developed by John von Neumann, Stanislaw Ulam and Nicholas Metropolis in the 1947, to model thermonuclear reactions, in parallel with the construction of the first computer: the ENIAC (Electronic Numerical Integrator And Computer). "Monte Carlo" is a code name attributed by N. Metropolis, because the scientists were working under governmental secret and refers to the random nature of the method and the gambling addiction of S. Ulam's uncle.

It has to be underlined that independently, nearly fifteen years earlier, Enrico Fermi, during his research about the moderation of neutrons in Rome, with the other Via Panisperna boys, predicted some experimental results that himself defined "too-good-to-believe" using statistical sampling technique i.e. a Monte Carlo method [166].

Statistical sampling techniques were already known previously, examples are the Buffon's needle problem in 1777 and the $\pi$ determination method proposed by Laplace, but they didn't have success because of the lack of computing power.

The mathematical basis of the MC Methods are random numbers and the Central Limit Theorem. It states that: for large values of N , the distribution of averages (normalized sums SN ) of independent identically-distributed random variables (according to any distribution with mean and variance $\neq \infty)$ tends to a normal distribution with mean $\bar{A}$ and variance $\sigma_{A}^{2} / N$.

This theorem provides the mathematical foundation of Monte Carlo methods in the sense that: given any physical observable A that can be expressed as the result of a convolution of random processes, the average value of A can be obtained by sampling many values of A according to the probability distributions of the random processes.

For particle transport, the MC Methods help solving the Boltzmann transport equation (equation 3.1 in its integro-differential form). It is a balance equation in phase space. At any phase space point, the increment of angular flux $\Psi$ in an infinitesimal phase space volume is equal to: the sum of all "production terms" minus the sum of all "destruction terms". Production terms are: sources, translational motion "in", "Inscattering", Particle Production, Decay "in". Destruction terms are: Absorption, Translational motion "out", "Outscattering", Decay "out". In mathematical form:

$$
\begin{equation*}
\frac{1}{v} \frac{\partial}{\partial t} \Psi(\vec{r}, \vec{\Omega}, E, t)+\vec{\Omega} \cdot \nabla \Psi+\Sigma_{t} \Psi-S=\iint \Psi(\vec{r}, \vec{\Omega}, E, t) \Sigma_{s}\left(\vec{r}, \overrightarrow{\Omega^{\prime}} \rightarrow \vec{\Omega}, E^{\prime} \rightarrow E\right) d E^{\prime} d \overrightarrow{\Omega^{\prime}} \tag{3.1}
\end{equation*}
$$

where on the left side, the first term represents the variation of angular flux; the second one accounts for the flux changes through motion without change of energy/direction (translation term), while the third term denotes absorption by accounting for the total macroscopic crosssection $\Sigma_{t} . S$ is the particle source distribution. On the right side, the term denotes the scattering contribution, where $\Sigma_{s}$ is the macroscopic scattering cross-section, representing the changes in flux due to energy or directional changes of particle position.

The solution of the Boltzmann equation involves complex integration in many variables. Particle non-conserving terms have also to be introduced. The non-homogeneities of the problem further increase the complexity. It is clear that a general analytical or closed-form solutions are out of reach. "Direct" numerical solutions can become prohibitive. However, another way to solve the transport equation is given by the Monte Carlo method where, instead of integrating the probability functions, they are randomly sampled. Therefore the "solution" needs the definition of a "source" as well as of a "detector". The "source" will be a known distribution in the phase space (i.e. a particle beam, a volume filled with $\gamma$ emitters, etc.). The detector or estimator is a region in the phase space, where a solution is searched [167, 168].

The following assumptions are made generally in most Monte Carlo codes:

- Static, homogeneous, isotropic, amorphous media and geometry;
- Markovian process: the fate of a particle depends only on its actual present properties, not on previous events or histories;
- Particles do not interact with one other;
- Particles interact with individual electrons / atoms / nuclei / molecules;
- Material properties are not affected by particle reactions.

In applying the Monte Carlo methods, three aspects have to be considered:

- a large number of events need to be simulated;
- the accuracy depends on the number of events;
- the higher the desired accuracy, the higher the calculation time [73].


Figure 3.1: Monte Carlo versus deterministic analytic methods. Adapted from ref. [165.

### 3.2 Monte Carlo codes in Medical Physics

Monte Carlo codes are used for many purposes in medical physics; the main ones are summarized hereafter:

- Treatment planning optimization and beam model construction;
- Imaging Detector design;
- Nozzle components design or "treatment head" design;
- Quality Assurance for studying clinical scenarios that cannot easily be created in reality;
- LET distribution for radiobiological purposes;
- Model interactions at DNA level;
- Organ motion studies.

A few of the more recent reviews that discuss Monte Carlo for radiotherapy physics and dosimetry are Andreo (1985, 1991), Mackie (1990), Rogers and Bielajew (1990), Ma and Jiang (1999), Verhaegen and Seuntjens (2003), Rogers (2006) [165]. In the context of conventional radiotherapy the most used MC codes are:

EGS (Electron Gamma Shower) initially developed at SLAC (Standford Linear Accelerator Center) in the 1970s and further improved in the version released in 2000 called EGSnrc, able to model complex problems, such as the calculation of the response of ion chambers. Developed in $\mathrm{C}++$, the toolkit is able to model the transport of photons, electrons and positrons at kinetic energies between 1 keV and 10 GeV , in homogeneous materials. It is distributed as free software and open source [169].

PENELOPE (PEnetration and Energy Loss Of Positrons and Electrons), developed in the 1990s in FORTRAN90 [170], was released by NEA (Nuclear Energy Agency) in 2001 and regularly updated [171]. It models all kinds of interactions for electron, positrons and photons, excepts nuclear reactions, in the energy range $50 \mathrm{eV}-1 \mathrm{GeV}$. It is multi-purpose and also used for Electron microscopy.

The drawback of these tools is that they do not manage hadronic interactions. On the other hand, some of the most popular codes that can also be used for hadrons are MCNP, SHIELD-HIT, PHITS and GEANT4 and FLUKA, with only the latter being used in clinical routine for carbon ions.

MCNP, (MOnte Carlo N-Particle) is the first generalized MC radiation particle transport code and was created in 1977 at Los Alamos National Laboratory by merging special-purpose Monte Carlo codes already developed in 1950s and 1960s. Still maintained by LANL (last released version is MCNP6), it is particularly suitable for neutrons interactions thus widely used for reactor simulations, neutron dosimetry, radiation shielding and in medical physics in BNCT (BOron Neutron Capture Therapy) [172].

PHITS (Particle and Heavy Ion Transport code System) was developed in Japan in 2002 [173] and nowadays managed and distributed by JAEA (Japan Atomic Energy Agency), while the developing team comes from different institutions worldwide. It can simulate the transport and collision (even including magnetic field and gravity) of nearly all particles over a wide energy range ( $10^{-4} \mathrm{eV}$ to $1 \mathrm{TeV} / \mathrm{u}$ ) [174]. It has a wide range of applications from accelerator design to the study of cosmic rays. In medical physics, it has been used for several applications ranging from HT facility beam line design (e.g HIMAC) to dose computation in HT including the evaluation of DNA damaging [175].

The SHIELD-HIT code was originally developed in a general-purpose version called SHIELD at JINR (Joint Institute for Nuclear Research in Dubna, Russia) at the end of 1960s. In 1990s the hadron version was then released with the possibility of modelling interactions of hadrons and nuclei in complex geometries up to energy values of $\mathrm{TeV} / \mathrm{u}$. Finally, in 2001 the version dedicated to HT was implemented and today called SHIELD-HIT12A, where HIT stands for Heavy Ion Therapy. The most essential improvements refer to the inclusion of the fluctuations of ionization energy losses and multiple Coulomb scattering of heavy charged particles. Developed in FORTRAN, it was designed for simulating therapeutic beams of ions in biological tissues and interfaced with the treatment planning system for ions (TRiP) [176, 177].

GEANT4 (GEometry ANd Tracking) is an object-oriented MC simulation toolkit developed in $\mathrm{C}++$ able to simulate a wide range of particles with matter over a wide energy range, taking into account electromagnetic, hadronic and optical processes. It was originally designed in its version 3 at CERN for the simulation of particle detectors response and was already able to graphically represent particle trajectories. The first production version was released in 1998 and a worldwide collaboration, still active since 1999, has been maintaining the code [178]. GEANT4 is at the basis of two dedicated tools for medical applications: GATE, specifically designed for conventional PET and SPECT applications, but recently some specific tools were
added for radiotherapy applications [179] and TOPAS (TOol for PArticle Simulation), userfriendly toolbox initially conceived for proton therapy and medical physicists, but now available for use in many other applications in radiation therapy [180].

### 3.3 FLUKA

The FLUKA code is a general-purpose Monte Carlo code, simulating the interaction and transport of hadrons, heavy ions, and electromagnetic particles. It has been jointly developed by CERN and the Italian Institute for Nuclear Physics (INFN) and maintained until 2019 by the FLUKA collaboration [181, [32].

FLUKA can simulate more than 60 particle types and ions over a wide energy range from 1 keV and 20 TeV . Written in FORTRAN 77, its use is made easier by the Flair interface [182. It is one of the few MC codes suitable to simulate hadrons and ions interactions and this fact has permitted its development for hadron therapy applications.

FLUKA has been chosen for all the works presented in this thesis for a combination of reasons. Besides the fact that the code development coordination was at CERN, where this work was mainly performed under the affiliation of the TERA Foundation, at the time of the choice, FLUKA nuclear models were matching experimental data in HT energy range better than other codes [183] and have been widely used in all the topics object of this thesis.

This piece of software indeed represents the standard at CERN for studies on accelerators beam lines (included the ones of the new CERN's ambitious project: the Future Circular Collider (FCC) [184]); therefore its use resulted particularly appropriated in the TULIP's beam characterization studies. Moreover FLUKA has been developed for hadron therapy applications and maintained for almost 20 years [37, [185], with significant improvements in medical applications during the years of 7th European Framework Projects (EC FP7), under the umbrella of the ENLIGHT network (e.g. PARTNER [186], ENTERVISION [16]).

An important outcome of all these research studies was the adoption of FLUKA in clinical facilities. For example, in CNAO and HIT it has been used for: the commissioning phase of the facility; the generation of input data for the TPS, showcasing range agreement within $100 \mu m$ and in the clinical routine, as the core of Quality Assurance Treatment Plan verification systems [187, 188, 185].

Moreover FLUKA has played an important role in the characterization of HT monitoring detectors, such as INSIDE [189], the in-beam PET detector used for the experimental part of this work (chapter 8). In parallel, still at CERN, the heritage of the European projects has been maintained and further developed since 2014 by researchers of FLUKA team, in collaboration with the TERA Foundation and other institutions in the field of the Monte Carlo treatment planning system [3], as well as in on-line monitoring with PET [4, as it will be detailed in the following paragraphs.

The first step for building a FLUKA simulation consists in setting up an input file containing all the input data of the simulation, organized in cards: a beam source, a geometry, some physics
setting and transport thresholds, seed ${ }^{1}$ number, scoring cards or predefined estimators (e.g. FLUENCE, DOSE, activity or annihilation at rest) in a defined mesh (USRBIN card), Energy deposition spectrum (DETECT card), etc.

Setting up a FLUKA simulation is relatively fast, especially in middle-complexity scenarios, thanks to: predefined simple sources and estimators; the Flair platform, developed in Python and Tkinter ${ }^{2}$, where the input file can be edited, compiled, debugged and the simulation runs can be started; the powerful geometry builder GeoViewer, the Flair module allows to create and visualize complex geometries based on combinatorial or voxel geometries.

In more complex scenarios, additional routines (written in Fortran 77) can be customized by the user to set, for example, a complex beam source, as the SOURCE routine used in this thesis to model the TULIP beams, or to include a complex time structure or even a detailed "particle-by-particle" registration of all the phase-space parameters (routine MGDRAW in combination with USERDUMP card), used for analysis of TULIP beam and in beam-PET simulations.

Physics models and settings Although FLUKA is widely used also in high-energy physics, here only main information related to hadron therapy will be described.

Energy losses due to electromagnetic interactions of hadrons in the particle therapy kinetic energy ranges (hundreds of MeV ) are described by Bethe-Bloch theory. This has been implemented in FLUKA taking into account the Barkas $Z^{3}$ and Bloch $Z^{4}$ effects. The Mott cross-section correction is also considered to correct the average stopping power, secondary electron production and energy loss fluctuations.

Multiple Coulomb scattering in FLUKA is based on the Molière theory improved by Bethe taking into account several correlations:

- between lateral and longitudinal displacement and the deflection angle;
- between projected angles;
- between projected step length and total deflection.

Fano correction for heavy charged particle is also modelled. A benchmarking of MCS in FLUKA against experimental data in HT can be found in refs. [190] [32, 185].

Inelastic hadron-nucleus interactions in the particle therapy energy range are described in FLUKA by the PEANUT model. PEANUT includes a Generalized IntraNuclear Cascade (GINC) followed by a pre-equilibrium stage, with standard assumptions on exciton number or excitation energy, and by an equilibrium phase. In the thermally equilibrated system of the produced nuclei, evaporation of nucleons, fragments or $\gamma$-rays, or even fission processes can take place. The evaporation-fission stage of light residual nuclei $(\mathrm{A}<16)$ is modeled by Fermi breakup. [191]. A more complete description can be found in ref. [181]. In order to treat Heavy ion reactions, i.e. nucleus-nucleus interaction, PEANUT is interfaced to different external event generators according the energy range:

[^16]- the BME (Boltzmann Master Equation) model, used for energy value below $125 \mathrm{MeV} / \mathrm{u}$. In this model, nucleons are distributed in binned momentum space according to their energies, and the energy level occupancies follow the Pauli principle. The time evolution is given by the numerical integration of the so-called Boltzmann Master Equation, and a range of mechanisms, depending on the spatial offset of the beam direction to the target particle, may lead to the emission of secondary fragments 192 .
- the rQMD (modified relativistic Quantum Molecular Dynamics) model for energies between $0.1 \mathrm{GeV} / \mathrm{u}$ and $5 \mathrm{GeV} / \mathrm{u}$. In this model projectile and target can be described as two Fermi gases. Details can be found in [13, 193].
- the DPMJET III, an implementation of DUal Parton Model is interfaced in FLUKA for energy $\geq 5 \mathrm{GeV} /$ u. It is not used for particle therapy applications.

BME and rQMD models as well as their transition are particularly relevant in particle therapy, since they finally govern the fragmentation build-up and positron emitters production [13]. Both the BME and the RQMD are interfaced with the PEANUT module, and FLUKA automatically switches between the two depending on the particle energies. Finally FLUKA also considers de-excitation of the remaining equilibrated nucleus via evaporation, fission and fragmentation processes.

In order to ensure and simplify the physics setting of FLUKA simulations the DEFAULTS card is set to the specific physics application (e.g. CALORIME for detector studies, SHIELDIN for radiation protection, etc..) and the best settings are automatically included. A default option called HADROTHE exists for HT studies and it has been used for all the simulations carried out in this thesis work.

### 3.4 FLUKA TPS particle therapy tool

The FLUKA TPS particle therapy tool is a user-friendly MC simulation software specifically designed for HT. It is a quite powerful and flexible tool for the following reasons:

- It is fully integrated in the FLUKA/FLAIR package.
- It uses all the general FLUKA features (physics models, MC features and material properties can be easily adjusted according needs).
- The accelerator beam model can be imported from a commercial TPS model.
- The nozzle geometry design can be included or, as an alternative, the point source approach, generally applied in the commercial TPS, like in ref. [194] can be followed.
- It recognizes images and data formats, according to standards in clinical medical physics (e.g. DICOM - Digital Imaging and Communications in Medicine - and its RT Modules).
- It supports the multiple-field treatment in the same simulation run or allows to perform individual treatment field simulations with the capability of merging the separate field results.
- Besides the dose, other quantities as fluence, activity or related LET quantities can be scored.
- On-the-fly conversion of dose-to-medium to dose-to-water can be performed for both physical and biological calculations, for compatibility with clinical TPS [195].
- The calculation of DVH and the differences between the FLUKA and TPS can be evaluated in the tool.
- The FLUKA results can be exported in DICOM RTDOSE format.

With respect to other MC TPS tools for HT used in medical physics, FLUKA particle therapy tool has the flexibility to simulate novel ions species as primary beam, not only protons or ${ }^{12} \mathrm{C}$, and allows an accurate dose estimation in all kinds of materials, biological or not. Additional details about FLUKA MC TPS tools can be found in ref. [3) and chapter 5 .

### 3.5 FLUKA PET tools

The FLUKA PET tools were originally developed for conventional PET in 2013 [196]; they included a powerful geometric tool integrated in Flair, able to create crystal detectors geometry, layout and material composition. At the beginning, they were only tested in small PET detectors, located in fixed positions, for animal treatment; moreover, they only used point-like radioactive sources and only one image reconstruction algorithm was present (FBP). They were mainly used for inferring the dose map from the $\beta^{+}$emitter distribution and for testing new PET detectors design and options.

The rationale behind the development of PET tools in FLUKA has to be found in the following aspects:

- The pre-existing physics models, bench-marked not only in High Energy Physics but also in Medical Applications, which were able to deal with beam particle as well as with radioactive sources and were also able to follow the on-line evolution of induced radioactivity and dose in the target.
- The native integration with FLAIR and FLUKA tools for QA MC-TPS and thus the easiness in importing DICOM information from clinical images to FLUKA voxel geometry.
- The development of the code to integrate ( $\mathrm{p}, \mathrm{d}$ ), ( $\mathrm{n}, \mathrm{d}$ ) reactions such as Excitation functions ${ }^{12} \mathrm{C}(\mathrm{p}, \mathrm{x}){ }^{11} \mathrm{C}$ and ${ }^{16} \mathrm{O}(\mathrm{p}, \mathrm{x})^{15} \mathrm{O}$, which are very useful features for PET studies in HT: deuteron formation at low energies is treated directly and no longer through coalescence.

The overall workflow of the typical simulation with FLUKA PET tools is shown in figure 3.2, where the main components are described below.

In the context of the author's collaboration with the CERN FLUKA team, PET tools have been improved for different aspects and the main features and results published in ref. 4]. From the geometry point of view, the PET scanners library includes the models of more recent, conventional PET scanners, such as Hi-Rez and Biograph from Siemens or Mosaic from Philips for humans or MicroPET P4 scanner for small animals. Moreover the roto-translations management feature was added, which makes easier to configure a custom detector in specific simulation scenarios. An example of implementation of a custom detector, i.e. the INSIDE in-beam PET detector, is shown in figure 3.3 .


Figure 3.2: FLUKA PET tools workflow describing the simulation setup up to the final image reconstruction. The dashed lines denote optional features, whereas the solid lined functions are automatically handled by the tools. The USERDUMP corresponds to a built-in FLUKA estimator including the necessary output (in ASCII format) from the simulation, which can be processed for the coincidence events information and image reconstruction. Reproduced from [4].


Figure 3.3: INSIDE in-beam PET detector geometry in FLUKA PET tools.

Concerning the sources, non-point-like sources (like NEMA source) were added to the package for conventional studies, whereas for HT applications ion beam sources (including Radioac-
tive ones) can be used with a defined time structure. Important updates about the scoring regards: the introduction of a new USRBIN estimator called ANNIHRST, permitting an easy and fast determination of annihilations at rest points maps and profiles which can be compared with activity or dose maps; the implementation of a new flag (IAZTRK) in order to keep track of parent isotopes. These functionalities were extensively used to achieve the results presented in PART III. The more complex scoring and post-processing routines, allowing to have a more detailed analysis of the secondary particles at the detector were integrated in FLUKA development versions. The raw data output produced by the PET tools consists in a USERDUMP file, containing for each detected particle the following variables: event ID, type of particle identifier, detection position and source position in $\mathrm{x}, \mathrm{y}, \mathrm{z}$ coordinates, production and detection time, particle energy, weight (if a biasing option in FLUKA is used), type of event (if Compton or Raylegh scattering) and the parent isotope identification. This output is then processed by the tools taking into account specific PET parameters in order to generate the coincidences lists. As a reminder, in PET processing different coincidence event types are registered and can be classified in true, random and scatter as described in figure 3.4.


Figure 3.4: Coincidence events type that can be registered: (a)True coincidences, where the green line drawn between the two hit detector elements for that event passes through the point of origin; (b) Scatter coincidences, where one or both $511-\mathrm{keV}$ photons undergo Compton scatter (unwanted); (c) Random coincidences occur when two distinct radionuclei contribute to one detected photon pair (unwanted). The yellow circles indicate the annihilation site and the green ones the detection point; the line in blue indicates the wrongly assigned line of response. Adapted from [13].

The contribution of each coincidence type with the increasing of the activity is not constant but varies as in figure 3.5 .

In addition, the USERDUMP output can be further analysed with external tools producing plots, such as the one in figure 3.6 or the detail time trends as in chapter 6 .

Finally, concerning the image reconstruction, two reconstruction algorithms are now available in the tool: the FBP - Fourier Back-Projection and MLEM - Maximum Likelihood Expectation Maximization. An example of images that can be obtained with FLUKA PET tools are shown in 3.7 4 for a PET conventional setting. They are obtained using a ${ }^{18} \mathrm{~F}$ source, a full-ring MicroPET P4 scanner and the model of a mouse described in refs. 198, 199, and are


Figure 3.5: Count rate of coincidences events type versus activity concentration. Reproduced from [197].


Figure 3.6: Left: FLUKA geometry setup geometry. Right: Example of scoring of gamma produced in in-beam PET Monte Carlo experiment with proton and 3D visualization (MATLAB) of gamma production and gamma detection point.
available in different image formats for download from the Internet [200].
In summary, FLUKA PET tools can be used for two main purposes:

- the design of new PET detectors, in particular for geometry optimization, performance characterization of innovative materials, assessing the effects of different pulse time, deadtime and coincidence timing window to estimate random events impact. Calculation of noise to signal ratio, since all the secondary particles can be scored.
- PET HT studies, to assess the influence of irradiation and acquisition time on PET images in patient-treatment scenarios or in simple geometry to test new monitoring methods in HT or inferring cross-section values from indirect PET measurements.

The ongoing challenges of the FLUKA PET tools consist in implementing a more userfriendly interface to include time structure, attenuation and scatter corrections. For further explanations and details on FLUKA PET tools, reference can be made to [4, 13].


Figure 3.7: FLUKA PET tools result in conventional PET scenario for one slice of the 3D images: a)Reference PET image of the digimouse; b)the Flair visualization of the radioisotope density map in the mouse used as a source in FLUKA; c) and d) PET image reconstruction obtained using respectively the FBP and the best performing MLEM method. Adapted from figure published in ref. (4].

## Part II

## Dose delivery strategies for A TURNING LINAC FOR PROTON THERAPY

## Chapter 4

## Beam characteristics of TULIP predicted with Full Monte Carlo simulations

### 4.1 Rationale

Once the TULIP optics was fixed and the beam transport system was optimized, as explained in chapter 2, the TULIP beams need to be characterized from a medical physics point of view, according to the conventional protocols used in that field [54, 201, 202, 203]. In particular, the beam is characterized in terms of:

- Integrated Depth Dose (IDD) curves in water, in the longitudinal direction, for a set of energy values (the Bragg's curves);
- the beam particle fluence profiles in air, in the transverse directions, at the isocenter and at upstream and downstream positions [92].

The IDD curves allow to take into account the global contribution of the beam energy spread from the accelerator and the straggling contribution from the nozzle materials, air and water target. On the other hand, the transverse beam profiles in air allow to take into account the beam divergence in both transverse directions.

FLUKA Monte Carlo (MC) simulations [186, 32] were made following the approach described in the next paragraph in order to predict the beam characteristics of the TULIP presented in chapter 21 .

Phase-space approach In conventional radiotherapy, two MC simulation approaches have been proposed in literature: the source model and the phase-space approach. The first one, foreseeing the calculation of particle distribution differential in energy, position or angle, is an approximated method, since the information on individual particles is lost; whereas, in the second one, each particle can be followed with all its phase-space parameters (such as: position in space $\mathrm{x}, \mathrm{y}$, phase, $\mathrm{x}^{\prime}$ and $\mathrm{y}^{\prime}$, and kinetic energy) and consequently allows to preserve the correlation among them [165]. Although it requires more computational time and hardware

[^17]to store information, the phase-space approach was chosen for the present study because of the above-mentioned features. An example of beam phase-space representation for a TULIP beam at $142 \mathrm{MeV}{ }^{2}$ is given in figure 4.1. The figures on the top represent the planes where the emittances and Twiss parameters, defined in figure 2.7, can be determined. As a reminder, the relation between the Twiss parameters, beam sizes and divergences, expressed in terms of standard deviations, are: $\sigma_{x}=\sqrt{\beta_{x} \epsilon_{x}}$ and $\sigma_{y}=\sqrt{\beta_{y} \epsilon_{y}} ; \sigma_{x}^{\prime}=\sqrt{\gamma_{x} \epsilon_{x}}$ and $\sigma_{y}^{\prime}=\sqrt{\gamma_{y} \epsilon_{y}}$. At the bottom of the figure 4.1, the energy distribution of the particle is shown, together with the 2 D $(x, y)$ beam profile.


Figure 4.1: Example of the beam phase-space parameter representation for a TULIP beam (Results from the 3D tracking simulation described in the text, extracted at 142 MeV , at 10 cm before the nozzle entrance).

All the TULIP phase-space data, particle by particle, for more than 650 energy values, were made available from the 3D-Tracking analytical study by using 3D tracking codes, combined with the TULIP optics studies. The author first extracted for each energy value the simulated beam characteristics, running and optimizing the 3D-Tracking analytical code; then analysed and integrated the results with the FLUKA Monte Carlo code, according to the workflow presented in the next section.

At the knowledge of the author, this was the first time that a full Monte Carlo simulation was performed tracking the beam particles from the accelerator source until the patient.

[^18]
### 4.2 Simulation workflow

Following the scheme shown in figure 4.2, the first step of the multi-particle simulations consisted in tracking the particles inside the BTW Linac. Using the RFTRACK code [145], 670 Phase-space files, each one containing 20000 particles, were generated 3 , for all kinetic energy values in the clinical therapeutic range ( $70-230 \mathrm{MeV}$ ), in order to have an energy step of 0.5 MeV at most.


Figure 4.2: Simulation work flow and codes. Published in Cuccagna et al. [1].

The energy step was chosen in order to obtain range (penetration depth in water) steps of 1 mm for low beam energies and of 2 mm for high beam energies, required for medical therapy [204]. The second simulation step consisted in tracking the accelerated particles, along the HEBT up to the isocenter, using the PTC package of MADx, as well as the output of RFTRACK as input files. Finally, the tracking output, dumped at 10 cm before the entrance of the nozzle, was used as a source for Monte Carlo simulations with FLUKA.

The integration among the different tracking codes and FLUKA was accomplished through custom MATLAB [205] scripts. Additional FORTRAN user routines were necessary for FLUKA to appropriately read the source phase-space files generated by MADx-PTC (SOURCE routine), as well as to produce particle by particle phase-space results in air (SCORING routines).

Moreover, it was decided to model the nozzle geometry and materials in FLUKA, thus overcoming the water-equivalent approach, following the methods adopted at CNAO [92], but not considering the detector's supports and holders as in 206.

In order to generate the data for the TULIP machine model in the TPS, two other separate sets of FLUKA simulations were performed in water targets for the IDD curves and in air for the beam profile ([203] and [202]), for a set of energy values between 70 MeV and 232 MeV , with an energy step of $10-20 \mathrm{MeV}$. The particles in the initial source file were sampled randomly and used several times using a FLUKA customized source routine. The chosen number of primaries in FLUKA is $4 \cdot 10^{6}$ protons, corresponding to the average number of protons per spot typical of a patient's treatment plan. The results of a simulation, consisting in using only once (no

[^19]sampling) the source particles of a proton beam with kinetic energy of 122 MeV , are compared with the results obtained using the above-described approach (sampling) in the figure 4.3 .


Figure 4.3: IDD (left) and $x$ profile (right) in water for a TULIP beam ( $\mathrm{E}=122 \mathrm{MeV}$ ): comparison between "sampling" and "no sampling" approach. Published in [1].

The results were generated taking advantage of the well-tested FLUKA built-in scoring card (USRBIN), providing, among several other physical quantities, dose and fluence in a threedimensional geometrical domain (such as a voxel map).

In addition, for a more direct comparison with the results obtained from the PTC code, a particle-by-particle scoring was performed using the USRBDX and USRWEIG scoring cards in combination with the flusw FORTRAN routine, properly customized. This method allows to extract not only the beam size $x$ and $y$, but the phase-space information for each particle of the beam (such as position in $x$ and $y, x^{\prime}$ and $y^{\prime}$ and the energy) crossing a defined surface. This method was used to produce results for transverse and longitudinal characteristics (section 4.3).

Finally, by using home-made scripts ${ }^{4}$ developed in Python, all FLUKA beam outputs can be converted to an easy readable format for a Treatment Planning System (e.g. RFA300•ASCII BDS format).

### 4.3 Results along the beam-line

In order to evaluate the minimal beam size achievable in air at the isocenter, the effect of Multiple Coulomb Scattering [38] on the nozzle was determined. The main characteristics of the nozzle are summarized in table 4.1 and presented in figure 4.4 .

The scattering contribution ( $F W H M_{N z l}$ ) of the nozzle to the beam size was obtained by performing some FLUKA simulations $5^{5}$. The nozzle was exposed to monoenergetic parallel (no divergent) proton beams, with different energy values and zero initial transverse Gaussian distribution. The results, as plotted in figure 4.5, allowed to estimate the scattering contribution of the nozzle for any given energy value of the incoming beam.

[^20]Table 4.1: Nozzle elements for TULIP

| Element | Length (cm) |
| :--- | :---: |
| vacuum pipe (VP) and exit vacuum window <br> (including scanning magnets) | 181 |
| exit vacuum window (VW) | 0.08 |
| air gap (AG) 1 | 8.71 |
| ionization chamber (IC)1 | 10.0 |
| $A G$ 2 | 2.00 |
| IC 2 | 10.0 |
| $A G$ 3 | 4.55 |
| nozzle end (NE) to isocenter (ISO) $-A G$ 4 | 54.0 |
| Total size | $\mathbf{2 7 0}$ |



Figure 4.4: Nozzle geometry as designed in FLUKA, the main elements with reference to table 2 , as well as the values of the SAD in $x$ and $y$ are reported. Published in [1].


Figure 4.5: Beam size evaluated in air at the isocenter for a parallel pencil beam and zero transverse dimensions going through the nozzle. The blue points show the results of the simulations and the dotted line is an exponential fit to the simulation results. Published in [1].

These beam sizes arising from scattering add in quadrature to the beam sizes in vacuum without any scattering from the nozzle, as obtained from the HEBT beam dynamics studies (in vacuum). Based on these simulations, it is clear that, with the chosen nozzle, obtaining beam sizes smaller than FWHM $=15 \mathrm{~mm}$ for 70 MeV is not possible. This fact has two main implications. On the one hand, if one wants to profit of the small beam sizes of the linac beams, for example for the mini-beam radiation therapy (pMBRT) [207] applications,
this nozzle design is not adequate and would need to be optimized to reduce the scattering. Conversely, for traditional proton therapy, where slightly higher beam spot sizes could means a reduced number of spots in the treatment plan, the nozzle scattering contribution allow to relax some beam optics constraints, reducing the number of optics elements.

For better understanding, the TULIP results were compared to the available data for protons from CNAO facility, chosen as reference.

## Transverse Characteristics

The beam sizes at the exit of BTW LINAC [145], obtained from the analysis of the RFTRACK files, are plotted in figure 4.6, expressed in FWHM. ${ }^{6}$


Figure 4.6: Transverse beam sizes at the exit of the BTW linac. Published in [1].

Starting from these values, the HEBT was optimized, and the resulting beam sizes at its end before the nozzle are reported in figure 4.7.


Figure 4.7: Nozzle effect on beam size variation with the energy and along the line at three specific points. From the bottom to the top: at 10 cm before the nozzle entrance, at isocenter in vacuum, without considering the nozzle effect, and at isocenter in air, considering all the nozzle elements. The corresponding experimental CNAO curve in air at isocenter as in reference [202] is also plotted. Published in [1].

[^21]Still in figure 4.7, the beam sizes in terms of FWHM evaluated in FLUKA in air at the isocenter, are shown. The results are in agreement with the expected beam sizes, considering the simulated scattering contribution from the nozzle at each energy (figure 4.5) and the vacuum beam size coming from the HEBT beam optics simulations. Moreover, the comparison of the curves of FWHM in air at isocenter for TULIP with the ones obtained from experimental data from CNAO, taken from ref.[202], shows that the beam sizes of TULIP are lower than the ones of CNAO of about $25 \%$ at 70 MeV and of about $20 \%$ at 232 MeV . The 2 D beam profiles for two energy values at the three considered beam line points (before nozzle, at isocenter in vacuum and at isocenter in air with nozzle effect) are reported in figure 4.8, where a symmetrization effect in x and y along the beam line is also shown.


Figure 4.8: Simulated 2D beam profile in vacuum and air for the two different energy values 107 MeV and 210 MeV at the three specific points along the line. Top: at 10 cm before the nozzle entrance, middle: at isocenter in vacuum; bottom: at isocenter in air with nozzle.

## Longitudinal Characteristics

The beam energy loss after the nozzle as a function of the energy, presented in figure 4.9, is consistent with the Bethe-Bloch equation [38].


Figure 4.9: Nozzle effect on energy loss, each \% value is defined normalizing to the kinetic energy value before the nozzle. Published in [1].

Moreover, the beam energy spread is strongly modified by the interaction with the nozzle materials. The energy spread variation as a function of the beam output energy does not exceed 0.26 MeV FWHM ( $\leq 0.1 \% \mathrm{dE} / \mathrm{E}$ ), as shown in figure 4.10. however, it exhibits an oscillating trend, which comes from the energy variation method performed in the BTW Linac. Although the energy spread is increased by a factor 2 , the oscillating effect is reduced after the nozzle due to the statistical nature of the energy loss, as also shown in the same figure 4.10 .


Figure 4.10: Nozzle effect on energy spread. The curves represent the energy spread of the accelerator (dE accelerator), which is the same after the HEBT (dE HEBT), and after the nozzle (dE after nozzle). Published in [1].

The nozzle, combined with scattering in air, has an effect also in the shape of the energy distribution as shown in figure 4.11.


Figure 4.11: Nozzle effect on energy spread in transversal profile of a beam at 232 MeV initial kinetic energy: energy distributions before (top) and after (down) the nozzle. Published in [1].

This result is in agreement with the Landau-Vavilov function [38] for energy losses, that can be obtained by subtracting the energy distribution before and after the nozzle.

### 4.4 Scanning magnet simulation in FLUKA

Scanning magnets were modeled in FLUKA according to different approaches. First of all, a scanning magnet was simulated in detail by importing in FLUKA the magnetic field map obtained from the Opera code, a simulating tool used to design magnets. This was possible by developing a customized FLUKA routine. This was done in the first design of simulation using the TULIP beam, in order to assess the correct scanning magnet behaviour. The comparison of the original magnetic field map in Opera code with the one imported in FLUKA is represented in figure 4.12 .

Afterwards, in order to simulate the magnetic field, a more simplified approach was followed. It required the development of a simpler magnetic field routine, allowing the simulations of the simultaneous action of both $X$ and $Y$ scanning magnets, as if they were thin dipoles. The focusing effects and the fringe fields of the scanning magnets were thus neglected, since they are not affecting the beam significantly. A result for a scanned beam simulation in an extreme point of the scanning field is shown in figure 4.13 .


Figure 4.12: Magnetic field map in Opera (right, courtesy of D. Bergesio) and corresponding magnetic field map imported by the author in FLUKA (left).

$\frac{x}{y} z$


Figure 4.13: Scanning magnets kicks of $B_{x}=0.83 T$ for SMx and $B_{y}=0.90 T$ for SMy on a 232 MeV TULIP beam result in a beam transverse position of $x=-19.0 \mathrm{~cm}$ and $y=17.5 \mathrm{~cm}$ at the isocenter. Published in [1].

### 4.5 Predicted beam characteristics of TULIP for a TPS

The beam characterization mimics the usual medical physics quality assurance protocols as described in [201, 202, 203, [54]. In particular, the beam is characterized in terms of:

- in the longitudinal direction, the Integrated Depth Dose (IDD) curves in water for a set of energy values (the Bragg's curves);
- in the transverse directions, the beam particle fluence profiles, as evaluated in FLUKA [186, 32], in air at the isocenter and at both upstream and downstream positions 92].

The IDD curves allow to consider the global contribution of the beam energy spread from the accelerator and the straggling contribution from the nozzle materials, air, and water target. On the other hand, the transverse beam profiles in air allow to consider the beam divergence in both transverse directions.

Integrated Depth doses curve are "measured" in clinical environment with a parallel-plate ion chamber with a surface larger enough to collect the total integrated dose from the pencil beam, including the lateral spreading part.

Monte Carlo simulations, impinging the beam in a water tank, and propagating along the longitudinal axis, as in [203] and [202], were performed to determine the IDD curves for a set of energy values between 70 MeV and 232 MeV , with an energy step of $10-20 \mathrm{MeV}$.

Transverse profiles in water The beam size in water was assessed and shown in the following examples in figure 4.14.

Integrated Depth Dose curves The IDD curves are shown in figure 4.15.

Energy-Range Curve The Energy-Range curve of TULIP, with the range determined as the distal $90 \%$ of the Bragg peak of the proton beam in water, is plotted in figure 4.16. As reference, the CNAO's curve is also reported.

## Proton fluence distributions in air

The beam transverse distributions in air, at the isocenter and at the longitudinal boundaries of the treatment volume, are necessary parameters to quantify the nozzle scattering and the divergence of the beam. Generally, commercial TPSs use this data to model the beam as a spatial cone-shaped distribution with the vertex at the average SAD [194]. The results of the FLUKA simulations are presented in figure 4.17 and compared with experimental data from the CNAO facility taken from ref. [202].


Figure 4.14: 2D beam profile in water at $80,210,232 \mathrm{MeV}$ : on the left, the 2 D profile in $\mathrm{y}, \mathrm{z}$. Published in [1].


Figure 4.15: Integrated Depth Dose curves. Image published in [1].


Figure 4.16: Energy-Range curve for TULIP and the comparison with the CNAO's one, the kinetic energy is defined as mean value. (CNAO's curve built from courtesy measurements by A. Mirandola-CNAO Foundation). Published in [1].


Figure 4.17: Top: Proton fluence distribution in air for three z values (for clearness of the figure, only three energy values are reported). Bottom: the TULIP beam widening in air, expressed in terms of FWHM, is compared with CNAO one as reference (CNAO measured values courtesy of CNAO Foundation [202] ). Published in [1].

### 4.6 Discussion

The results of this study show that some constraints on the beamline can be relaxed, because their effects are averaged out by the nozzle properties. This is the case for the Twiss $\alpha=0$ constraint generally imposed in designing beam lines for ion therapy. Another interesting result concerns the variation of the energy spread and distributions along the complete beamline. It was shown that the nozzle contribution dramatically reduces the amplitude variation of the wave-like behavior energy spread with the energy, typical of linacs. Defining a variation rate percentage as $(\max -\min ) / \max$, the variation decreases from $68 \%$ to $25 \%$, as shown in figure 4.10. Thanks to the chosen phase-space approach, the beam energy distribution from the accelerator line is known and its variation along the nozzle elements can be evaluated. This approach is presently not available in commercial TPSs, although it can provide valuable information for discrepancies in dose distributions between treatment plan and measurements.

In addition, the study showcases how the developments of thin nozzles and monitoring chambers is crucial in order to benefit of the small emittance of Linacs. The beam sizes achievable with TULIP in air at the isocenter are, in fact, smaller with respect to those typically found in proton therapy synchrotrons, such as CNAO, as reported in figure 4.7 [202].

Also the beam widening in air is compatible with measurements performed at CNAO, although the TULIP beams showcase a higher beam widening in air with respect to CNAO, as shown in figure 4.17 .

In addition, the proposed design of the TULIP gantry (figure 2.5 satisfies the requirements of a single-room facility for proton therapy. The footprint ( $200 \mathrm{~m}^{2}$ ) is in line with single-room facilities already available in clinics such as Mevion S250 and IBA Proteus One [5]. Finally, the TULIP gantry radius, although higher than the IBA Proteus One, is small enough for a gantry with a downstream scanning system, in spite of the fact that the average Source to Axis Distance is larger than 2 m . The gantry is in principle more affordable because of the small number and reduced dimensions of the magnetic elements.

Another important potentiality of TULIP consists in the short time required for a treatment. Besides the physical position and dimensions of the tumor target and planned dose, proton beam treatment time with spot scanning depends on very different aspects of the overall facility, summarized below:

- the optimization of the treatment plan in terms of the number of beam direction fields, resulting number of energy layers per field, number of spots per layer and repainting technique.
- the design of the dose delivery system in terms of speed of the scanning magnets and detection area of ionization chambers, influencing the size of irradiation field.
- at the accelerator complex level, it depends on the proton current available from the source, beam time-structure, energy variation system, magnetic line characteristics.


### 4.7 Chapter summary

A Monte Carlo based 3D simulation package for a TUrning LInac for Protontherapy was developed allowing to study for the first time the proton beams particle by particle from the accelerator to the patient target. The presented results are relevant for the following reasons and from different physics branch perspectives:

- from the accelerator physics and beam dynamics point of view, they highlight the beam properties of linacs for proton therapy, showing the differences and advantages with respect to other accelerators for proton therapy already present in clinics;
- from the methodological point of view, they test a simulation process for the study of new accelerators that can be easily translated to other accelerators for particle therapy such as linacs for Carbon ion therapy (e.g. CABOTO [138]);
- from the point of view of medical physics, they allow to generate the machine-specific parameters in order to configure a Treatment Planning System to predict dose distributions using TULIP as shown in chapter 5


## Chapter 5

## Dose Distribution using TULIP in a tumour case

The optimization and study of the TULIP beams resulting from the full MC simulations allowed the construction of a TULIP beam model in a commercial Treatment Planning System, in order to evaluate the dose distribution that can be achieved with a TULIP.

The TPS Pinnacle ${ }^{3}$ for protons by Philips was used; it was installed and made available at the Clinique Génolier in Switzerland. As shown in figure 5.1, the output of TULIP full MC simulations described in chapter 4, were converted in a suitable data format (IBA RFA-300 ASCII data file format) and imported in the physics module of the TPS.

The TULIP beam model was configured, validated and virtually commissioned in the TPS.
In parallel, an MC beam model was built in FLUKA for TULIP, based on the phase-space results of the full MC simulations.


Figure 5.1: TULIP dose distribution simulation work flow and files.
Afterwards, a SOBP and the proton Treatment plan of a patient case, already used in 88,
using a different accelerator model and TPS, were recalculated in Pinnacle as well as with the FLUKA Particle Therapy Tool and the results were compared.

### 5.1 Pinnacle ${ }^{3}$ TPS used for TULIP

Pinnacle ${ }^{3}$ Radiation Therapy Planning software for proton has been developed by Philips. This software supports the medical personnel in creating a treatment plan for patients, maximizing the dose delivered to the treatment tumour volume while minimizing the dose delivered to the surrounding healthy tissues. The system is capable of operating in the forward planning as well as in the inverse planning modes, both for conventional radiation therapy (using photons/electron) and proton therapy [208]. It is a complex software including: a physics tool, where the accelerator machine parameters are modelled, and a planning section, where the patient images are imported in DICOM format, the treatment plan is created and optimized. The physics and dose calculations algorithms implemented by Philips in Pinnacle are based on these main references [209, 210, 211]. Pinnacle resulted particularly advantageous because the physics model was flexible enough to allow the configuration of a new proton machine. With the aim of studying the TULIP beam model properties, in fact, this functionality was an essential requirement in the choice of the TPS.

### 5.1.1 Physics tool

In the proton physics tool of Pinnacle, the TULIP proton machine was configured. The main configuration parameters are summarized in the table 5.1.

Table 5.1: TULIP proton machine setting

| SETTING | VALUE |
| :---: | :---: |
| Couch rotation angle | $0^{\circ} / 360^{\circ}$ |
| Gantry angle | $-20^{\circ} /+200^{\circ}$ |
| Delivery type | Spot Scanning |
| Nominal SAD $(\mathrm{cm})$ | 196.30 |
| SAD X $(\mathrm{cm})$ | 216.30 |
| SAD Y (cm) | 176.30 |
| Max. deflection from z axis to ISO in X $(\mathrm{cm})$ | 19 |
| Max. deflection from z axis to ISO in Y $(\mathrm{cm})$ | 17.5 |
| Gaussian model | double |
| Energy spectrum | Continuous |
| 1 |  |
| Minimum/Maximum energy $(\mathrm{MeV})$ | $73 / 232$ |

[^22]The 'Nominal SAD' is the average between the 'SAD X ' and 'SAD Y ' values defined in chapter 4 and represents the distance between a nominal origin of the beam source and the isocenter. The 'Max. deflection parameters' are the maximum deflection in $x$ and $y$ of the proton beam from the propagation axis $z$, achievable respectively from the scanning magnets in X and Y from a central spot and it is related to the transverse treatment field size of $38 \times 35$ $\mathrm{cm}^{2}$ defined in chapter 4. The 'Gaussian model' parameters refer to the modality chosen (single or double) for the modelling of the traversal profiles in air. The 'Energy spectrum' parameter specifies if the set of energy values can be considered continuous or discrete.

Integrated Depth Dose and Lateral Fluence curves. The Integrated Depth Dose (IDDs) and the in-air lateral fluence (IAFs) curves simulated in FLUKA and shown in chapter 4 have been imported in Pinnacle, after conversion in the RFA-300 data format, using some scripts in Python ${ }^{2}$. The imported IDDs are between the minimum ( 73 MeV ) and maximum energy value ( 232 MeV ) with energy step of $10-20 \mathrm{MeV}$.

The IAFs were imported at 5 different positions along the $z$ beam axis (in cm ): $-25,12.50$, $0,12.50$ and 25 . The beam sizes were considered asymmetric, therefore two 'Profile Group lists' were created in $x$ and $y$ direction.

Afterwards, all the profiles were fitted by adjusting the parameters for IDD and Fluence in air. The IDD fitting parameters are divided in 'basic' and 'advanced'.

The basic ones are:

- 'RZero' is the fitting parameter that represents the range used in the model for the depth dose distribution of the Bortfeld Bragg peak. The RZero parameter equals the water equivalent distance of the distal $80 \%$ value of the Bragg peak.
- 'SigmaZero' and 'SigmaOne' are two parameters that represent the width of the Gaussian range straggling, where 'SigmaOne' adds a depth dependence to the model.
- 'Epsilon' is the fitting parameter from the Bortfeld Bragg peak depth dose distribution model representing the fraction of primary fluence contributing to the "tail" of the energy spectrum.

The advanced ones are enumerated below and each one of them has an impact in the part of the curve represented by the corresponding number shown in figure 5.2. They need to be adjusted if the differences between the computed and measured profile exceed $2 \%$ :

1. 'Sharpen Distal Edge Factor': parameter acting on the distal edge of the profile. The higher the value, the sharper the distal edge will be;
2. 'Increase Build Up Factor': parameter correcting the underestimation of dose that can occur at the entrance region of the IDD. It decreases linearly as the range decreases.
3. 'Reduce distal edge weighting during fit?': if this parameter is set to "yes", a better fit is obtained at the proximal side of the peak.

[^23]

Figure 5.2: Profile fitting parameter in the TPS. The meaning of the numerical callouts is described in the text ${ }^{3}$.
4. 'Gaussian build up': the software introduces a Gaussian function to the (proximal) tail of the curve in order to improve the fitting accuracy at shallow depths for high energies [208].

An example of the results obtained for a fitted TULIP IDD profile at 211 MeV is given in figure 5.3.

The main fitting parameters for the IAFs are: the gaussian center, center of the gaussian profile (the initial value is the peak value), the Sigma, standard deviation of the gaussian curve and the normalization factor, affecting the height of the fitted curve. They are optimized by the software for each energy value and for each defined z position (field Profile). An example of the IAF results obtained at 211 MeV is plotted in figures 5.4 .

The beam widening along the z axis is modeled in the TPS in terms of the Sigma of the Gaussian with the quadratic function:

$$
\begin{equation*}
\text { Sigma }=\left(10^{-4} \cdot \text { Alpha } \cdot Z^{2}\right)+\left(10^{-2} \cdot \text { Beta } \cdot Z\right)+\text { Gamma } \tag{5.1}
\end{equation*}
$$

where $Z$ is the distance along the central axis from the midpoint between the $X$ and $Y$ scanning magnets and Alpha, Beta, Gamma, three parameters optimized by the software.

The TPS offers the option to adopt a single or double gaussian model. The Gaussian

[^24]

Figure 5.3: Example of fitted IDD profile in Pinnacle for a TULIP beam. The figure is divided in four parts: In A, 'Profile' indicates the selected file for the specific energy value ( 210 MeV ); in B the data of the IDD profiles at 211 MeV of the FLUKA ('Measured' column) and TPS fit ('Computed' column) are shown and the differences calculated in 'Error(\%)' column; in C the formula and plot of the 'Error(\%)' are shown; in D the 'Measured' and 'Computed' IDD curves are plotted.

One component models the small-angle MCS scattering of the primary beam whereas the Gaussian Two accounts for the additional broadening due to the so called nuclear halo, i.e. the contribution from nuclear products and large-angle MCS [18, 212].

If a double gaussian model is chosen, as for TULIP, all the above mentioned quantities are defined for Gaussian One and Gaussian Two curves and an Average Gaussian Ratio is defined as the ratio of the Gaussian One and Gaussian Two Normalization factor. This factor should be constant by varying the energy as it is verified for TULIP model, as shown in the table in figure 5.5. In this figure, the sigma at 73 MeV (the most divergent beam) of Gaussian One varying along z , fitted with equation 5.1, is plotted on the right.

After modelling the proton machine, the next step consisted in the validation of the model accuracy for spot scanning. To this aim, at least one computed depth profile and a lateral profile needed to be compared with measured depth-dose profile and cross-beam profile. Since real measurements could not be performed with TULIP, additional MC simulations ${ }^{T}$ including SOBP and single spot profiles were needed and the output was imported in the validation section of the TPS.

[^25]

Figure 5.4: Example of TULIP IAF Profiles in X position: comparisons between FLUKA ('Measured') and TPS fit ('Computed') at 211 MeV . The profiles are given at the different 'Z' positions highlighted with green squares in the figure. (The profile at the isocenter - ' $\mathrm{Z}=0$ $\mathrm{cm}^{\prime}$ - is repeated to facilitate the reading of the figure.)


Figure 5.5: Left: IAF fit parameters defined in the text and calculated in Pinnacle for all the energy values included in the model. Right: The sigma of the Gaussian One variation at 73 MeV versus z direction is plotted.

### 5.1.2 Planning section and DICOM export files

The planning section of Pinnacle allows to perform all the operations described in chapter 1 in section 1.4

Once the plan is optimized in the TPS, the results can be exported in several files in the DICOM format. DICOM - Digital Imaging and Communication in Medicine - is the standard used for the transmission and management of medical images and related information among different systems. It was developed by ACR (American College of Radiology) and NEMA (National Electrical Manufacturers Association) starting from 1983 and regulated now in the ISO standard 12052:2017. DICOM-RT is the radiotherapy extension of the DICOM, coding some specific information peculiar to radiotherapy. Additional information for hadron therapy was added in 2006 and published in the report supplement $1025^{5}$. In particular, the DICOM output files that can be generated are:

- RT image or the CT scans DICOM files including the patient geometry subdivided in VOXELS, each characterized by a HU (Hounsfield Unit) value.
- RTSTRUCTURE is the DICOM file containing the structures i.e. the organs and treatment volumes defined and drawn during the planning phase.
- RTDOSE contains the three-dimensional dose map made of voxel. The dose voxel grid can have a different dimension and spacing from the CT voxel grid used to model the patient geometry.
- RTPLAN contains information of the beam plan itself and is the most specific file for HT. The most important attributes are:
- The introductory Ion Beam Sequence section including for example, the ion type, the delivery modality, the number of irradiation fields and fractions, the irradiation angles, geometrical information and many other parameters.
- The subsection Ion Control point sequence containing other sub-attributes such as the number of Control points, corresponding to the number of energy layers, including for each value the Nominal Beam Energy and the Scan Spot Position Map.
- For each Control point, in addition to the spot positions, the Scan Spot Meterset Weights are defined; they can be expressed in terms of number of particles or Monitor Unit $\left.{ }^{6}\right]$ according to what is defined in the attribute (Primary Dosimetric Unit attribute).

The text below explains how, starting from this quantity, the following relation 5.2 permits to extract the correct weight to be associated to each spot of the plan, by using the attributes extracted from the RT plan:

$$
\begin{equation*}
\text { SpotWeight }=\text { BeamMeterSet } \cdot \frac{\text { ScanSpotMetersetWeights }}{\text { FinalCumulativeMetersetWeight }} \tag{5.2}
\end{equation*}
$$

[^26]In the output of the RTPLAN, also the beam sizes in $x$ and $y$ in air at isocenter are present and expressed in terms of FWHM of a Gaussian distribution.

### 5.2 FLUKA TPS simulations for TULIP

### 5.2.1 FLUKA FLAIR DICOM tool

DICOM files can be read and further analysed in several commercial software platforms (such as in MATLAB or Python and their built-in DICOM routines ${ }^{7}$ ) and thanks to the recent developments of the FLUKA MC TPS, mentioned in chapter 3.1, they can be imported in FLUKA.

In the context of the FLUKA particle therapy tool development project, a dedicated DICOM section was developed in the FLAIR interface of FLUKA ${ }^{8}$ In particular, besides the functionalities of importing, visualizing and editing the DICOM files, the tool allows to retrieve some useful information from DICOM files and makes it available for the MC simulation input file:

- From the CT Scans DICOM, the patient geometry can be automatically integrated in the FLUKA input file with a specific geometry card called VOXEL. The conversion of the HU in FLUKA material is obtained with a look-up table based on the work by ref. [213].
- From the RTDOSE, the dose VOXEL map is extracted and converted in the scoring binned map of the USRBIN card in the FLUKA input file. The RTDOSE DICOM, converted in the FLUKA bnn format (the FLUKA output of the USRBIN card), is also used in FLAIR for the comparison with the MC DOSE result in RTViewer section.
- From the RTSTRUCTURE, the different contoured organs and regions are imported in FLUKA and are used for the calculation of the DVH, the graphical plot used to evaluate the goodness of a treatment plan that has been described in chapter 1.
- From the RTPLAN, the information about the beam fields orientation, the beam source position, the energy values for each fields, the spot maps and weights are extracted and used to fill in the dedicated FLUKA beam cards, as described in the next paragraph.

Some images showing the FLAIR DICOM tools are included in appendix A.

### 5.2.2 MC beam model and RTPLAN information

Although all the information extracted from the DICOM file is fundamental to set up a FLUKA simulation for TPS recalculation, it is not sufficient for example to fully characterize the initial spot beams. Therefore the DICOM FLAIR menu called RTPLAN offers the option of combining

[^27]the DICOM RTPLAN information with a MC beam model of the accelerator and importing the resulting spot beam map in the FLUKA input file.

The above-mentioned MC beam model does not consist in the same characteristics and quantities defined to configure the TPS beam model in TPS physics tool. The Monte Carlo does not use the analytical pencil beam algorithm implemented in the TPS and only few beam characteristics are indeed needed at a certain distance from the isocenter before the nozzle.

Similarly to what was already done in ref. [194], the MC beam model implemented in FLAIR includes a Look-Up-Table consisting of a set of energy values and for each energy value, a momentum spread, beam spot sizes in $x$ and $y$, beam angular spread in $x$ and $y$, and the number of protons per monitor unit at the beam source position (figure 5.6).


Figure 5.6: RTPLAN viewer in FLUKA/FLAIR DICOM menu. Left (A): the list of the imported DICOM files in FLUKA from the TPS. Center (B): Import section and visualization of part of the MC beam model for TULIP. Right (C): Visualization of the RT Plan infomation imported from the DICOM RT Plan.

As mentioned in chapters 3.1 and 4 , different approaches can be followed in designing MC simulations for TPS recalculations and the above-mentioned MC beam model parameters can have different meanings. Staying focused on the HT spot scanning techniques 9 , some authors (as in reference [214], [215], [194]) do not model the geometry of the nozzle elements and materials crossed by the beam before reaching the patient, such as the air gap between the end of the nozzle and the patients.

For example, in ref. [194], the effects of these elements are taken into account correcting the MC beam model quantities. In particular, what is defined energy spread in 194 does

[^28]not correspond to the energy spread of the accelerator, but it is a tuned value from range measurements and MC iterations, at the end including the accelerator energy spread, as well as the energy straggling of nozzle materials. In a similar way, the quantities called beam angular spread in $x$ and $y$ are not the divergences of the beam $x^{\prime}$ and $y^{\prime}$ before the nozzle, but angle values obtained as the $\operatorname{arctg}$ of the ratio of the measured spot size in air at the isocenter and the SAD value. This approach has two main advantages: it does not require the knowledge of the characteristics of the beam from the accelerator and the nozzle geometry; the MC simulation is less time-consuming. The drawbacks are that it requires measurements at the facility and the tuning of the parameters.

The approach followed for TULIP is more similar to the one used in ref. [186, 190]: the nozzle geometry and materials are included in the beam line. As already mentioned in chapter 4 , one of the advantages of having a full simulation from the accelerator is that the characteristics of the beam are known also at the exit of the HEBT before the nozzle: in particular the beam spread for each energy value is known, therefore no tuning or indirect estimation is needed and the same applies to the divergences of the beam $x^{\prime}$ and $y^{\prime}$.

This means that, for TULIP, the characteristics defined in the MC beam model, differently from the approach of ref. [194], directly represent the physical quantities characterizing the accelerator line. The Look-Up-Table extracted for the TULIP beam model from the full MC simulations is added in the appendix A.

Once that the MC beam model is imported, it is combined with the RTPLAN information and the FLUKA input file is updated with some developed ad hoc beam cards called: SPOTBEAM, SPOTPOS, SPOTDIR and SPOTTRANS. External source routines are no longer needed as in [187] and these cards fully define the beam spot plan, the beam spot orientation position and physics characteristics before the isocenter. The spot scanning map position is simulated by calculating the geometrical deflection of each spot position. This methodology is considered equivalent to the full modelling of the scanning magnets [18].

Another parameter of the MC beam model is the ratio number of protons over the so called MU, Monitor Unit. The Monitor Unit is a quantity introduced and used in conventional radiotherapy and it is proportional to the electric charges produced by an ionization chamber irradiated by a beam. In details, the monitor chamber reads 100 MU when an absorbed dose of 1 Gy is delivered to a point at a given depth in the phantom, where the surface of the phantom is positioned so that the specified point is at the isocentre of the machine, and the field size is $10 \mathrm{~cm} \times 10 \mathrm{~cm}$ at the isocentre [216].

In some TPSs, such as the Syngo from Siemens and Raystation from Raysearch company, the spot weight is expressed directly in terms of number of protons. Other TPSs, instead, such as Eclipse from Varian medical system and Pinnacle, use the Monitor Unit. This information as already mentioned is called in DICOM standard Primary Dosimetric Unit.

A calibration curve Monitor Unit over number of protons (MU/protons) versus energy is generally built starting from measurements with monitor chambers for a set of energy values following a conventional procedure developed in the IAEA TRS-398 report [217] and improved
by other authors [218]. This curve is specific for every facility. In the case of TULIP, instead of real measurements, an additional set of FLUKA simulations was performed ${ }^{10}$ to build the curve MU over Number of protons versus Energy. It is worth noting that in a first approximation the $\mathrm{MU} /$ protons ratio is proportional to the electronic stopping power of protons in air [219]. In figure 5.7 the interpolation of the $\mathrm{MU} /$ protons ratio obtained for all the energy in the TULIP beam model is compared to the stopping power in air data downloaded from PSTAR website: the approximation is quite good. In the same figure, for completeness, the calibration curve from the TIPFA facility in Trento ${ }^{11}$ is also shown.


Figure 5.7: Relation MU/protons curve and stopping power.

[^29]
### 5.3 Preliminary comparison Pinnacle TPS - FLUKA MC with TULIP beam model

### 5.3.1 SOBP in water

A Spread Out Bragg Peak was planned in Pinnacle ${ }^{12}$ using the TULIP machine model prescribing 1 GyE in a region of $10 \times 10 \times 6 \mathrm{~cm}^{3}$ of a water phantom and positioned in order to obtain a maximum range of 27 cm and a modulation of 10 cm . The results were exported in DICOM formats and imported in FLUKA. The comparison between the FLUKA simulations using the TULIP MC beam model and the TPS are shown in figures 5.8 (2D results) and 5.9 .


Figure 5.8: An example of a Spread Out Bragg Peak (SOBP) calculated with Pinnacle using the TULIP machine and comparison with FLUKA simulations with the TULIP MC beam model a 2D view from FLAIR.

Although some discrepancies are present in the entrance region, a uniform dose is obtained in the TPS and the flat region of the SOBP is well reproduced in FLUKA, as presented in the Dose volume histogram comparison in figure 5.10.

[^30]

Figure 5.9: An example of a Spread Out Bragg Peak (SOBP) calculated with Pinnacle using the TULIP machine model and comparison with FLUKA simulations with the TULIP MC beam model-1D profile along the beam propagation direction.


Figure 5.10: DVH for a SOBP with TULIP: comparison between Pinnacle (planned) and FLUKA (calculated).

### 5.3.2 Patient Case with a lung tumour

The patient test case mentioned in chapters 1 (figure 1.27) and 2 was recalculated using the TULIP model first of all in the Pinnacle TPS and then in FLUKA. The geometry and dose calculated as in the Planning section of Pinnacle, is shown in figure 5.11.


Figure 5.11: Dose distribution in Pinnacle in the three reference planes for a patient case obtained with the TULIP model. In the bottom-right part of the figure the 3D geometry setup is shown.

As a first step, the results obtained from Pinnacle were exported in DICOM files and compared with another TPS ${ }^{13}$ configured for a commercial Isocyclotron-based proton therapy machine produced by Varian. The DVH - Dose Volume Histogram - of the plans calculated in the two TPSs are shown in figure 5.12 .

[^31]

Figure 5.12: DVH for a plan calculated with TULIP and comparison with a plan of a Isocyclotron-based proton therapy machine model (IsoCy-PT).

The steepness of the curves of the PTV and CTV indicated that a good dose conformity can be obtained with TULIP beam model, comparable with the one obtained for a model of a cyclotron-based proton therapy facility.

Recalculation in FLUKA/FLAIR The plan was finally imported in FLUKA/FLAIR for MC recalculation. A 3D view of the geometrical setup in FLUKA, including the nozzle materials, is presented in figure 5.13 .


Figure 5.13: 3D visualization of the FLUKA simulation geometry of a Patient case (lung tumour). The nozzle model, the patient geometry imported by CT scan in DICOM format (A), and external elements like a detector (B) are visible.

The preliminary results obtained with FLUKA with the TULIP model and the comparison with the commercial Pinnacle TPS are presented in figures 5.14 and 5.15 .


Figure 5.14: Preliminary comparison FLUKA -TPS TULIP model in a lung case


Figure 5.15: Preliminary comparison TPS (planned) and FLUKA (calculated) with TULIP model: DVH for a Lung case.

The DVH in figure 5.15 showcases consistent differences between the FLUKA and the TPS. In detail, as reported in table 5.2, the dose differences between MC and the commercial TPS in the PTV accounts for about $10 \%$ for $D_{5 \%}{ }^{14}$ value and more than $25 \%$ for $D_{95 \%}$ value. Considering the organs at risk (OAR): for the bone marrow ('MOELLE' in figure 5.15) the

[^32]dose predicted by FLUKA is $25 \%$ higher for $D_{5 \%}$ and $17 \%$ for $D_{10 \%}$; for the heart ('COEUR' in figure 5.15) instead the FLUKA predictions are 5 times lower than the one of the TPS for $D_{5 \%}$ and 14 times lower for $D_{10 \%}$

Table 5.2: DVH evaluation for a lung tumour case (Gy).

|  | PTV |  | bone marrow |  |  | heart |  |  |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- |
|  | $D_{5 \%}$ | $D_{95 \%}$ | $D_{5 \%}$ | $D_{7.5 \%}$ | $D_{10} \%$ | $D_{5 \%}$ | $D_{7.5 \%}$ | $D_{10 \%}$ |
| TPS | 52.0 | 48.5 | 0.65 | 0.55 | 0.48 | 49.5 | 43.6 | 35 |
| MC | 58.2 | 35.5 | 0.86 | 0.70 | 0.58 | 10.7 | 4.8 | 2.5 |

These huge differences are probably due to the air-cavities as it was shown for other patient cases in ref. [3] but further investigations and recalculations in other patient scenarios are needed in order to state that this patient case is an example, where the physics implemented in the Monte Carlo helps to provide more realistic dose distributions than the pencil beam algorithm implemented in the TPS [220].

### 5.4 Chapter summary

In this chapter, starting from the TULIP full MC simulations results, the steps performed to virtually commission the TULIP machine in a commercial TPS are described. The goodness of the results is evaluated with the Dose Volume Histogram, one of the tool used in clinical medical physics.

The results are then compared to FLUKA simulations, which allow a more complete characterization of the beam parameters from the accelerator and of the nozzle geometry. A $M C$ beam model for the FLUKA TPS tools is then defined for TULIP.

The dose distribution of a SOBP in water calculated with the TPS matches the dose obtained with FLUKA in the target volume.

Moreover, a patient plan for a lung tumour case has been calculated, first with the commercial TPS using the configured TULIP machine and then recalculated with FLUKA. Thanks to the new functionalities of the FLUKA/FLAIR DICOM tools, the two plans were compared, quantifying the dose differences using images and the DVH. The results show that the dose differences between Monte Carlo and the TPS for this patient case are of the order of the 25 \%.

Further investigations and recalculations in patient cases other than lung tumours would help to confirm that the differences in dose distributions between MC and the TPS are only due to the presence of air cavities where MC had already demonstrated better agreement with measured doses [220].

Despite the discrepancies with respect to the FLUKA recalculations, the study shows that the TULIP linac complex, on the basis of the model reconstructed with MC studies, can be modelled in commercial TPS and potentially achieve the same dose distribution of a cyclotronbased proton therapy system.

## Part III

Monitoring strategies: from the in-beam PET with CABOTO to the fast range verification in HT

## Chapter 6

## In-beam PET for CABOTO

In chapter 1, the main methods for beam monitoring in HT have been presented. The suitability and efficacy of these methods depend on the type of treatments, the particle species used for the treatment (protons or ions), the geometrical constraints and, last but not least, on the properties of the beams produced by the accelerator. In particular, a very important characteristic is the beam time structure which, as already mentioned in table 1.2, varies significantly according to the accelerator type. The beam duty cycle - DC ${ }^{1}$ - is the parameter used to quantify the above-mentioned differences: for synchrotrons, the duty cycle can vary from 10 to $90 \%$, moreover IsoCys deliver continuous wave beams ( $\mathrm{DC}=100 \%$ ), while for new SCys it is of the order of $0.1 \%$ [221, 119].

For linacs, and in particular for CABOTO, the beam duty cycle is also $0.1 \%$, resulting from the fact that the beam is bunched in pulses of the order of 2-5 $\mu \mathrm{s}$, with a repetition rate of 360 Hz . This low DC means that the beam is off during $99.9 \%$ of the treatment time. This feature suggests that CABOTO would be well suitable for in-beam PET monitoring techniques, because the acquisition can be performed during the pauses of the micro-bunches; in this way, the suppression of random coincidences is not needed as in the case of cyclotrons [222, 221]; finally, $\gamma$-pairs produced in the $\beta^{+}$decays of isotopes having half-lives $\left(T_{1 / 2}\right)$ in the ms range can also be detected.

The interest from the scientific community in short-lived $\beta^{+}$emitters for PET in HT is quite recent, due to the impossibility of detecting them with the HT technology available until less than ten years ago and because their longer range could blur the images. As far as the author knows, when the analysis contained in this thesis started, there were no available publications in medical physics journals focused on this theme. It is worth mentioning that the reference paper from Dendooven et al. [223] was published just a few months after the beginning of this analysis for CABOTO. By a mere coincidence, the work published by him and his team about fast emitters in protontherapy and the preliminary results about in-beam PET for CABOTO and fast range verification [224] were presented at the same conference in Geneva (ICTR-PHE 2016). This chapter reports on the simulation work prepared and presented by the author at the

[^33]above-mentioned meeting in Geneva. With reference to the scheme in figure 6.1, simulations were carried out, by using the FLUKA MC code together with MATLAB routines, written to take into account analytically the CABOTO time structure. A first set of simulations identified the $\beta^{+}$emitter isotopes, produced by the interaction of a pencil beam (protons or ${ }^{12} \mathrm{C}$-ions) with phantoms of different materials. Considering the CABOTO time structure, the $\beta^{+}$activity versus time was extrapolated for all produced $\beta^{+}$emitters at different irradiation and acquisition time windows.

A second set of simulations including a conventional PET detector was performed, by using the development version of the FLUKA PET tools. The scoring and analysis of gamma pair coincidences arrival times on the PET detector verified their correspondence to the beam irradiation profile. Tracing of the history of each coincidence allowed the identification of the parent isotope contribution.


Figure 6.1: PET simulations: structure and methodology.

### 6.1 CABOTO time structure and activity build-up model

In order to reduce the computational time, and for the sake of simplicity, the variation in time of the activity was implemented analytically. A simple MATLAB model was built to predict the activity and the influences of a pulsed beam structure. The CABOTO time structure is shown in figure 6.2. Since the pulse length $t_{\text {pulse }}$ is three orders of magnitude smaller than the distance between the two pulses $\Delta t$, the pulse was approximated as a Dirac-delta-like pulse.

As a reminder, the time evolution of each nuclide $N$ produced during the irradiation with a continuous beam is given by the relation:

$$
\begin{equation*}
N(t)=N_{\infty}\left(1-e^{-\lambda t}\right) \tag{6.1}
\end{equation*}
$$

where $\mathrm{N}(\mathrm{t})$ is the number of isotopes produced at a certain irradiation instant $t, N_{\infty}$ is the total amount of nuclei produced during the total irradiation time; $\lambda$ is the decay constant


Figure 6.2: Simplified CABOTO time structure with the calculation of the duty cycle.
linked to the half-life $T_{1 / 2}$ via the formula $\lambda=\ln (2) / T_{1 / 2}{ }^{\dagger}$. The time evolution of the nuclides production $N$ with a pulsed beam, made of identical pulses can be calculated with the formula:

$$
\begin{align*}
& N_{n}=N_{0}\left(e^{-n \lambda\left(\Delta t+t_{p u l s e}\right)}+e^{-(n-1) \lambda\left(\Delta t+t_{p u l s e}\right)}+e^{-(n-2) \lambda\left(\Delta t+t_{p u l s e}\right)}+\cdots+1\right)= \\
& \quad N_{0} \sum_{k=0}^{n} e^{-k \lambda\left(\Delta t+t_{p u l s e}\right)}=N_{0} \frac{1-\left(e^{\left.-\lambda\left(\Delta t+t_{\text {pulse }}\right)\right)^{n+1}}\right.}{1-e^{-\lambda\left(\Delta t+t_{p u l s e}\right)}} \tag{6.2}
\end{align*}
$$

where $\Delta t$ is the inverse of Pulse Repetition Rate and $N_{0}$ is the number of nuclides added in each beam pulse and n is the total number of pulses. The continuous and pulsed approaches converge to the same values for $n \rightarrow \infty$ :

$$
\begin{equation*}
N_{\infty}=N_{0} \sum_{k=0}^{\infty} e^{-k \lambda\left(\Delta t+t_{p u l s e}\right)}=N_{0} \sum_{k=0}^{\infty}\left(e^{-\lambda\left(\Delta t+t_{p u l s e}\right)}\right)^{k}=N_{0} \frac{1}{1-e^{-\lambda\left(\Delta t+t_{p u l s e}\right)}} \tag{6.3}
\end{equation*}
$$

Expanding according the Taylor's series and by approximating at the $1^{\text {st }}$ order the result is:

$$
\begin{equation*}
N_{\infty}=\frac{N_{0}}{\lambda\left(\Delta t+t_{\text {pulse }}\right)} \tag{6.4}
\end{equation*}
$$

So, it is mathematically demonstrated that the two time evaluations converge to the same limit value. The validation of the MATLAB analytical model with FLUKA simulations is presented in the next section and results for a study case are plotted in figure 6.3.

### 6.2 FLUKA simulations for in-beam PET with CABOTO

Model validation in FLUKA The pulsed model defined by equation 6.2 was verified by means of some simple FLUKA simulations using built-in cards, neither requiring programming of customized routines in FORTRAN 77, nor long computing times. In details, in this simulation, the time structure of the beam, impinging on a water tank of $10 \mathrm{x} 10 \mathrm{x} 30 \mathrm{~cm}^{3}$, was modelled by using irradiation profile (IRRPROFI) cards and the activity was scored via the predefined RESNUCLEI card at several cooling times (DCYSCORE and DCYTIMES cards), isotope by isotope.

[^34]From this RESNUCLEI output file, the $\beta^{+}$emitters are selected, according to the information found in Nuclear DataBases like RIPL[225] and ENSDF ${ }^{2}$. From this simulation, ten $\beta^{+}$emitters are found and reported in table 6.1 together with their half-life $T_{1 / 2}$, decay constant $\lambda$, branching ratid $3^{3}$ and the endpoint energy $Q_{\text {dec }}$. Moreover the FLUKA output files were further

Table 6.1: $\beta^{+}$emitters produced in the interaction of protons $(206 \mathrm{MeV})$ with water obtained by FLUKA simulations.

| Isotope | $T_{1 / 2}(\mathbf{s})$ | $\lambda(\mathbf{1} / \mathbf{s})$ | Branching $(\%)$ | $Q_{d e c}(\mathbf{M e V})$ | $N_{0}$ (nuclei/proton) |
| :---: | :---: | :---: | :---: | :---: | :---: |
| ${ }_{8}^{13} \mathrm{O}$ | 0.00858 | 80.78638 | 89.1 | 16.74796 | $6.60 \mathrm{E}-05$ |
| ${ }_{7} \mathrm{~N}$ | 0.011 | 63.01338 | 96.5 | 16.31607 | $4.44 \mathrm{E}-04$ |
| ${ }_{6}^{9} \mathrm{C}$ | 0.1265 | 5.479424 | 61.5997 | 15.65833 | $1.06 \mathrm{E}-04$ |
| ${ }_{5}^{8} \mathrm{~B}$ | 0.77 | 0.900191 | 99.552 | 16.95791 | $1.10 \mathrm{E}-03$ |
| ${ }_{6} \mathrm{C}$ | 19.29 | 0.035933 | 99.9671 | 2.62607 | $1.57 \mathrm{E}-03$ |
| ${ }_{6}^{17} \mathrm{~F}$ | 64.49 | 0.010748 | 99.854 | 1.73847 | $2.00 \mathrm{E}-06$ |
| ${ }_{8}{ }_{8} \mathrm{O}$ | 70.606 | 0.009817 | 99.878 | 4.12204 | $9.02 \mathrm{E}-04$ |
| ${ }_{8} \mathrm{O}$ | 122.24 | 0.00567 | 99.9003 | 1.73217 | $3.39 \mathrm{E}-02$ |
| ${ }_{7} 3 \mathrm{~N}$ | 597.9 | 0.001159 | 99.8036 | 1.19847 | $2.80 \mathrm{E}-03$ |
| ${ }_{7}^{11} \mathrm{C}$ | 1221.84 | 0.000567 | 99.7669 | 0.96041 | $1.83 \mathrm{E}-02$ |

analysed to retrieve the activity value of each $\beta^{+}$emitter at the defined cooling times; in parallel, the analytical curves were calculated with the MATLAB model for each $\beta^{+}$emitter. The starting values $N_{0}$ (column 6 table 6.1) were retrieved by a RESNUCLEI card, which gives in output the number of each nuclei species produced per primary beam particle. The results are summarized in figure 6.3. For each isotope, each activity point determined through FLUKA simulations lies on the analytically calculated curve ${ }_{4}^{1}$. These results can now be compared to a very recent study, published by Bongrand et al. [226] on short-live $\beta^{+}$emitter production in protontherapy, based on GEANT4 MC simulations, and the experimental results in ref. [223]. Although the results were obtained in different conditions and a quantitative validation cannot be performed, the $\beta^{+}$emitters found from FLUKA simulations reported in table 6.1 are the same as the ones predicted by GEANT4, and the two $\beta^{+}$emitters with the highest production rates in the experimental data $\left({ }^{11} \mathrm{C},{ }^{15} \mathrm{O}\right)$ from ref. [223] are also the ones with the highest production rate in both Monte Carlo codes.

Activity over time with $\beta^{+}$emitter contributions With the purpose of a preliminary characterization of the emitters contribution over time, the FLUKA simulation was therefore further simplified by removing the time structure and leaving only the RESNUCLEI card that gives in output the $N_{0}$ values defined above, and the time behaviour calculated analytically. Simulations were performed in different scenarios for proton and ${ }^{12} \mathrm{C}$ beams and with different homogeneous materials such as water and skeletal muscle. The results about the different $\beta^{+}$ emitters contribution to the overall activity are shown in figure 6.4.

[^35]

Figure 6.3: Plot of the activity of $\beta^{+}$emitters with short half-life $T_{1 / 2}$ over the irradiation time: the saw-tooth curves represent the behaviour with a pulsed irradiation beam; the dashed curves represent the behaviour with a continuous irradiation beam. The circles represent the results of FLUKA simulations obtained with the DCYTIME cards for different cooling times, including the irradiation profile card. Top: short-lived produced $\beta^{+}$emitters showcasing a saw-tooth behaviour. Bottom: Long-lived isotopes showcase a stairs behaviour.


Figure 6.4: $\beta^{+}$activity contribution and variation with target material and beam. The call-outs indicate the half-life $T_{1 / 2}$.

The analytical time evolution of the activity during the irradiation with ${ }^{12} \mathrm{C}$ of a water target is presented in figure 6.5. This is the scenario further analysed in the following paragraphs.


Figure 6.5: Analytical time evolution of the activity produced by dominant emitters during the irradiation ( $\log$ scale) of a water phantom with a ${ }^{12} \mathrm{C}$ beam.

In order to determine the activity maps in space at different times, a similar simplified simulation approach was finally followed.

Activity maps and profiles In order to determine the activity maps and the contribution from the produced isotopes, FLUKA simulations were made by using the new USRBIN estimator, called ANNIHRST, and a customized FORTRAN routine, called comscw [13], which allows the scoring of the contributions of selected isotope types to the annihilation point distribution.

Here below the results obtained with a more complex beam source consisting in a ${ }^{12} \mathrm{C}$ SOBP are presented. The SOBP was imported in FLUKA from DICOM RTPLAN ${ }^{5}$ and used as beam source. Concerning the time, the scoring was performed in FLUKA in the so-called semi-analogue modality, set in the DCYSCORE card, providing the maximal $\beta^{+}$distribution that can be obtained acquiring for an infinite acquisition time irradiating instantaneously, with the number of primary particles defined in the SOBP plan. The results of the physical dose, annihilation point maps and profile along beam direction are shown in figure 6.6.

In order to determine the influence of the acquisition time on the shape of the profile, simulations with FLUKA IRRPROFI and DCYTIME scoring cards were first performed to verify the analytical model, in a similar way to the methods described before. The results of 2D maps and profiles in the first seconds of irradiation are presented in figures 6.7 and 6.8.

The simulations confirm that the most relevant $\beta^{+}$emitters in irradiation time less than

[^36]

Figure 6.6: FLUKA simulation results of ${ }^{12} \mathrm{C}$ SOBP in water. Top: 2D map of the Physical Dose. Center: 2D map of the annihilation at rest. Bottom: Annihilation profile along z. The black curve is the sum of all contributions. On the right scale the Dose profile is expressed in arbitrary unit.
one second are ${ }^{13} \mathrm{O}\left(T_{1 / 2}=8.6 \mathrm{~ms}\right),{ }^{12} \mathrm{~N}\left(T_{1 / 2}=11 \mathrm{~ms}\right),{ }^{9} \mathrm{C}\left(T_{1 / 2}=126.5 \mathrm{~ms}\right),{ }^{8} \mathrm{~B}\left(T_{1 / 2}=770 \mathrm{~ms}\right)$, with a non-negligible contribution from ${ }^{10} \mathrm{C}\left(T_{1 / 2}=19 \mathrm{~s}\right)$. In particularly, the peak of ${ }^{8} \mathrm{~B}$ found in the figure at 1 s is at the basis of the ideas and studies developed in next chapters.


Figure 6.7: Activity 2D maps along the beam direction at the specific times $110 \mathrm{~ms}, 1 \mathrm{~s}, 10 \mathrm{~s}$ during the first seconds of irradiation of a water target with a ${ }^{12} \mathrm{C}$ beam.


Figure 6.8: Activity profile of the maps in figure 6.7 with the detail of $\beta^{+}$emitter contributors.

FLUKA simulation with a full-ring PET detector Going towards a real experiment and in order to explore the more advanced FLUKA functionalities, some simulations were performed including both the time-structure and detector geometry, by making use of the FLUKA PET tools. A scenario of a single ${ }^{12} \mathrm{C}$ pencil beam irradiating for 3 minutes a tissue-like tank was considered. The commercial full-ring HiRez scanner model was also used. The geometrical layout is the one shown in figure 3.6 and the results are shown below.

The PET images with the built-in FBP algorithm of FLUKA PET tools are shown in figure 6.9


Figure 6.9: Simulated HT PET images with a full ring scanner.

From the analysis of coincidences files from PET tools, the temporal trend of the coincidences, generated from the decay of each emitter, is shown in figure 6.10. As expected, the number of coincidences per time unit for each isotope $i$ increases as $\left(1-e^{-\lambda_{i} t}\right)$ when the beam is on, reaches a maximum at the end of irradiation and starts decaying according the law $e^{-\lambda_{i} t}$.


Figure 6.10: Coincidences growth over time and parent isotope contribution.

From the analysis of profiles along $z$ over time, the peak from ${ }^{8} \mathrm{~B}$ is also found in this scenario, during the first seconds of irradiation. The increasing contribution from ${ }^{15} \mathrm{O}$, fragment of the target, is covering the activity peaks produced by projectile fragments. The isosceles triangle shape of the ${ }^{15} \mathrm{O}$ is due to the variable sensitivity of the coincidence along beam axis. This explored scenario, as it will be further explained in next chapter, is only a starting point study, since conventional full-ring PET scanners are not suitable for the use in HT for in-beam PET studies.


Figure 6.11: Activity profiles from FLUKA simulations with full ring detector at different acquisition times generated in the interaction of a ${ }^{12} \mathrm{C}$ beam with a water phantom.

### 6.3 Chapter summary

This chapter describes different FLUKA simulation approaches and advantages related to inbeam PET, arising from a low duty-cycle beam structure as the one of the CABOTO accelerator. The $\beta^{+}$activity collected during the irradiation with a single pencil beam has been computed together with the estimation of the short half-life $\beta^{+}$emitters contribution. The obtained results, and in particular the peak in the activity distribution, already detectable after one second of irradiation due to ${ }^{8} \mathrm{~B}$, suggested the new method to verify the range in HT, proposed in the next chapters.

## Chapter 7

## Fast range verification with short-lived $\beta^{+}$emitters: the idea and method

### 7.1 The fast range verification idea

The results obtained in the simulations studies for CABOTO suggested a new potential method to calibrate the Bragg Peak range. The idea consists in irradiating the patient for a time of about one second, delivering a small percentage of the total dose in one fraction and reconstructing the activity peak generated from the acquisition of the PET signal for a few seconds after the irradiation. If the position along the $z$ axis of this activity peak can be estimated with an accuracy of 1 mm , then it can be correlated with the Bragg Peak position and the beam energy corrected at the next delivery.

For an accelerator having a time structure similar to that of CABOTO, even an in-beam signal could be considered; however, since nowadays the only accelerator type in use for C-ions therapy is the synchrotron, this method has been experimentally studied by considering only the off-line PET signals obtained with the CNAO syncrotron. In this way, the calibration proposal could be verified experimentally and is applicable to existing synchrotrons, without the need of complex synchronization methods depending on the specific accelerator time structure; it can also be applied to other accelerator types that will be possibly developed in the future.

For the preparation of the calibration proposal, two sets of FLUKA simulations were performed, both in water and in PMMA, with a ${ }^{12} \mathrm{C}$ pencil beam at $400 \mathrm{MeV} / \mathrm{u}$. The simplified approach described in chapter 6, including the analytical evaluation of the irradiation and acquisition time, was followed. More specifically, the output values of the FLUKA RESNUCLEI scoring card, representing the nuclei produced per primary particle, were first obtained and then reported in table 7.1.

Table 7.1: Production of positron-emitting isotopes in the irradiation with carbon ions of water and PMMA phantoms at $400 \mathrm{MeV} / \mathrm{u}$ obtained with FLUKA simulations. The isotopes with production value less than $10^{-3}$ in water are omitted.

| Isotope | $T_{1 / 2}(\mathrm{~s})$ | nuclei $/{ }^{12} \mathrm{C}$ <br> ( $400 \mathrm{MeV} / \mathrm{u}$ ) <br> Water tank $\mathrm{V}=10 \times 10 \times 40 \mathrm{~cm}^{3}$ | $\begin{gathered} \text { nuclei } /{ }^{12} \mathrm{C} \\ (400 \mathrm{MeV} / \mathrm{u}) \end{gathered}$ <br> PMMA phantom $\mathrm{V}=10 \times 10 \times 40 \mathrm{~cm}^{3}$ |
| :---: | :---: | :---: | :---: |
| O-15 | 122.24 | $1.59 \mathrm{E}-01$ | $8.70 \mathrm{E}-03$ |
| O-14 | 70 | $4.48 \mathrm{E}-03$ | $3.99 \mathrm{E}-04$ |
| N-13 | 597.9 | $1.60 \mathrm{E}-02$ | $1.37 \mathrm{E}-03$ |
| N-12 | 0.011 | $1.51 \mathrm{E}-03$ | 4.32E-04 |
| C-11 | 1221.84 | $1.14 \mathrm{E}-01$ | 7.24E-02 |
| C-10 | 19.29 | $1.22 \mathrm{E}-02$ | $5.34 \mathrm{E}-03$ |
| C-9 | 0.1265 | $1.68 \mathrm{E}-03$ | $7.79 \mathrm{E}-04$ |
| B-8 | 0.77 | $9.34 \mathrm{E}-03$ | $3.40 \mathrm{E}-03$ |

For each isotope $i$, the nuclei $i_{i} /{ }^{12} \mathrm{C}$ quantity was corrected according to the equation 7.1, in order to determine the trend in time before and after the irradiation as well as the produced number of nuclei $N d_{i}$.

$$
\begin{equation*}
N d_{i}=\text { nuclei } i_{i} /{ }^{12} \mathrm{C} \cdot I \cdot\left(1-e^{-\lambda_{i} t_{i r r}}\right) \cdot \lambda_{i}^{-1} \cdot\left(1-e^{-\lambda_{i} t_{a c q}}\right)=n u c l e i_{i} /{ }^{12} \mathrm{C} \cdot F_{i t I} \tag{7.1}
\end{equation*}
$$

where $I$ is the ions current defined as the number of ions per second, $t_{i r r}$ the irradiation time and $t_{\text {acq }}$ is the offline acquisition time. The chosen values for the proposal were: $I=5.3 \cdot 10^{7}$, i.e. $3.2 \cdot 10^{7}$ in a $t_{i r r}=0.6 \mathrm{~s}, t_{\text {acq }}=1.4 \mathrm{~s}$, in order to have a calibration run lasting 2 s in total.

The results of the activity and the number of decays over time produced by each $\beta^{+}$emitter in this scenario in water are shown in figure 7.1. In order to determine the profiles along $z$ in the considered time, each annihilation (at rest) curve, obtained by FLUKA ANNIHREST for each emitter, was multiplied by the factor $F_{i t I}$, in the equation 7.1 determined analytically. The resulting profiles for water and PMMA are shown in figure 7.2 ,

From the comparison of the two materials in the same simulated scenario, PMMA showcases a lower production of ${ }^{15} \mathrm{O}$ with respect to water as well as a slightly higher production of boron 8: a definite advantage for the proposal, since the material composition of PMMA is closer to biological tissues with respect to water.

In 2 s , the number of ${ }^{8} \mathrm{~B}$ events predicted by FLUKA is close to $1.5 \cdot 10^{5}$ so that a PET detector having a $2 \%$ total efficiency would collect around 3000 coincidences, arising from a restricted spatial region, which can be sufficient to determine the carbon range with a 1 mm precision.

With the aim to validate this conclusion against measurements, the first step consisted in the choice of the detector and of the facility where the experiment had to be performed. In the next section, an overview on the PET detectors characteristics as well as a review of the ones operating in Europe is presented.


Figure 7.1: Activity trend (top) and corresponding number of decays (bottom) versus time from the interaction in water of $3.2 \cdot 10^{7}{ }^{12} \mathrm{C}$ ions at $400 \mathrm{MeV} / \mathrm{u}$, irradiation time of 0.6 s and acquisition time of 1.4 s .


Figure 7.2: Comparison of annihilation at rest: water vs PMMA target from a $400 \mathrm{MeV} / \mathrm{u}{ }^{12} \mathrm{C}$ and irradiation time of 0.6 s and acquisition time of 1.4 s .

### 7.2 In-beam PET Detectors

In order to be used during a hadron therapy treatment, a PET detector needs to be specifically designed and satisfy more stringent requirements than a conventional PET system used in diagnostics. A first difference is the space constraint: the geometrical design of the PET detector for HT shall allow the passage of the beam and irradiation of the patient in different directions. For this reason, a full ring system for in-beam PET is not suitable, so a dual-head compact design has to be preferred.

Another difference is the intensity of the radioactive source, i.e. the activity produced by secondary particles, during a complete HT treatment, which is around $200 \mathrm{~Bq} \cdot \mathrm{GyE}^{-1} \cdot \mathrm{~cm}^{-3}$, i.e. two orders of magnitude smaller than in conventional PET [125, 104]. Moreover, the range of some of the produced $\beta^{+}$emitters during the treatment (such as ${ }^{13} \mathrm{O},{ }^{12} \mathrm{~N}$ ) can reach a few millimeters, one order of magnitude larger than ${ }^{18} \mathrm{~F}$ isotope used in conventional PET. Another aspect is the background noise due to neutrons and charged particles which, albeit peaked in the forward direction, is relatively large over the full solid angle, thus limiting the detectable true PET signal.

Finally, the large flux of secondary particles may cause radiation-damage to detector elements, suggesting the choice of a detector, and of the overall electronic system, which is robust to radiation-induced aging problems and able to work when the beam is on.

In summary, the above-mentioned aspects indicate the use of a detector with the following properties. First of all, the artifacts linked to the limited angular coverage of the scanner can be reduced increasing the detector front area [227. The efficiency can be also increased by using a detector thickness between two and three absorption lengths. Some methods, aiming at determining in an approximate way the depth of interaction, may be needed, to reduce the parallax error. In order to optimize the SNR (Signal-to-Noise Ratio) or NEC (Noise Equivalent Count), the detector elements shall have short intrinsic dead time 1 , allowing a coincidence width of the order of nanoseconds to discriminate the true coincidence from scatter events and not correlated background. A high light output (number of photons per MeV ) of the scintillator in the photoemission zone is also required, implying a more linear response, a better energy resolution, and a more accurate spatial resolution [228]. Unfortunately, fast emission is often coupled to a low light yield, and vice-versa [197].

Scintillator materials characterized by a short decay constant and light output are Lutetiumbased like LSO or LYSO, they are commercially available in large quantities and more performing than the classic system based on BGO. The drawback of the Lutetium-based materials is that they produce an intrinsic background due to the ${ }^{176} \mathrm{Lu}$ that is an isotope emitting a beta particle and three gamma photons at 307, 207 and 86 keV [73, 229].
$\mathrm{LaBr}_{3}$ could be a good candidate: this crystal has an excellent light yield and a fast decay time ( 15 ns ), but unfortunately it is hygroscopic, expensive and it has a small attenuation

[^37]length ( 2.2 cm ).
A relatively new material, LFS, is particularly suitable for PET applications since it is comparable to LSO and LYSO for density and light yield ( $80 \%$ with respect to $\mathrm{NaI}: \mathrm{Tl}$ ) and has improved time performances [230]. The main scintillator crystal properties are summarized in table 7.2

Table 7.2: Scintillator crystals used for PET [197, 230.

| Material | Density $\left(\mathrm{g} / \mathrm{cm}^{3}\right)$ | Light yield ( $N_{p h} / \mathrm{MeV}$ ) | Decay time ( $n s$ ) | $\begin{gathered} \mu 511 \mathrm{keV} \mathrm{~V} \\ \left(\mathrm{~cm}^{-1}\right) \end{gathered}$ | Ph fraction at 511 keV (\%) |
| :---: | :---: | :---: | :---: | :---: | :---: |
| $\mathrm{NaI}: \mathrm{Tl}$ <br> (Sodium iodide) | 3.67 | 41000 | 230 | 0.34 | 17 |
| BGO <br> (Bismuth germanate) | 7.13 | 8200 | 300 | 0.96 | 40 |
| LSO:Ce <br> (Lutetium oxyorthosilicate) | 7.4 | 30000 | 40 | 0.87 | 32 |
| LYSO:Ce <br> (Lutetium yttrium oxyorthosilicate) | 7.1 | 32000 | 40 | 0.82 | 30 |
| GSO:Ce <br> (Gadolinium oxyorthosilicate) | 6.71 | 8000 | 60 | 0.7 | 25 |
| $\begin{aligned} & \text { YAP:Ce } \\ & \text { (Yttrium aluminum perovskite) } \end{aligned}$ | 5.37 | 21000 | 27 | 0.46 | 4.20 |
| LuAP:Ce <br> (Lutetium aluminum perovskite) | 8.3 | 12000 | 18 | 0.95 | 30 |
| BaF2 -fast | 4.89 | 1400 | 0.6 | 0.43 |  |
| BaF2 -slow <br> (Barium fluoride) | 4.89 | 9500 | 630 | 0.43 |  |
| LaBr3:Ce <br> (Lanthanum bromide) | 5.08 | 63000 | 16 | 0.47 | 15 |
| LFS <br> (Lutetium Fine Silicate) | 7.35 | 32800 | 33 |  |  |

To complete the properties of a basic detector system, the scintillator crystal geometry and photon wavelength have to match the properties of a photocathode system, in order to collect the light produced by the scintillation process and convert it into an electric current pulse.

Conventional photomultiplier tubes (PMTs) have been the most adopted system since 1948; they are characterized by high quantum efficiency, high signal amplification factor (order of $10^{6}$ ) and low noise. The most common detector configuration used in commercial scanners couples each detector block to four PMTs with light sharing, providing the position of the conversion with an accuracy of a few mm or better. More recently, position Sensitive PMTs (PSPMTs), coupled with pixelated scintillators, were developed in order to increase the spatial resolution to $1-2 \mathrm{~mm}$ [231]. Moreover, the requirement to determine the depth of interaction, considerations of cost and commercial availability indicated a preference for the readout of multi-anode photomultipliers (MAPM) or solid-state Avalanche Photodiodes (APD) arrays. The latter have high temperature sensitivity, a complex readout circuit and a small detection area.

A solid-state solution overcoming these limits, developed in 2000s, is called Silicon Photo-
multipliers (SiPM) and represents a valid alternative owing to their large gain, which eliminates the need of using channel amplifiers, their low cost, compactness and their possibility to operate in presence of magnetic fields. Known drawbacks of this solution are: dark counting rate increasing with temperature, limited dynamic range and limited size.

In table 7.3 the technical characteristics of photodetectors are summarized.
Table 7.3: Characteristics of main photo-detectors 101].

|  | PMT | APD | SiPM |
| :--- | :---: | :---: | :---: |
| Gain | $10^{5}-10^{6}$ | $10^{2}$ | $10^{5}-10^{6}$ |
| Dynamic range | $10^{6}$ | $10^{4}$ | $10^{3}$ |
| Excess noise factor | $0.1-0.2$ | $>2$ | $1.1-1.2$ |
| Risetime (ns) | $<1$ | $2-3$ | 1 |
| Time jitter (ns FWHM) | 0.3 | $>1$ | 0.1 |
| Dark current | $<0.1 \mathrm{nA} / \mathrm{cm}^{2}$ | $1-10 \mathrm{nA} / \mathrm{mm}^{2}$ | $0.1-1 \mathrm{MHz} / \mathrm{mm}^{2}$ |
| Photon detection efficiency at $420 \mathrm{~nm}(\%)$ | 25 | $60-80$ | $<40$ |
| Bias-voltage(V) | $1,000-2,000$ | $100-1,500$ | $>100$ |
| Power consumption | $100 \mathrm{~mW} / \mathrm{ch}$ | $10 \mu \mathrm{~W} / \mathrm{mm}^{2}$ | $<50 \mu \mathrm{~W} / \mathrm{mm}^{2}$ |
| Gain dependence with temperature $(\% / C)$ | $<1$ | $2-3$ | $3-5$ |
| Gain dependence with voltage $(\% / V)$ | $<1$ | 10 | 100 |
| Magnetic susceptibility | Very $\operatorname{high}(\mathrm{mT})$ | $\mathrm{No}(\mathrm{up}$ to 9.4 T$)$ | $\mathrm{No}(\mathrm{up}$ to 15 T$)$ |
| Radiation hardness | good | acceptable | acceptable |
|  |  | with cooling | with cooling |
| Large area | Yes | No | Scalable |
| Ambient light immunity | No | Yes | Yes |
| Readout circuit | Simple | Complex | Simple |

Finally, besides the scintillators and the photodetector unit, the performance of a detector is influenced by the choice of good electronic systems and performing reconstruction algorithms.

Short Review on in-beam PET detectors LBNL (Lawrence Berkeley National Laboratory) was the pioneer in the use of an in-beam PET system but soon the experiment was abandoned due to the detector ${ }^{2}$ activation, coming most probably by the passive beam spreading system installed in the facility [232, 227].

The first working system was installed at GSI, where a raster scanning system was available. The detector was a dual head system called BASTEI (Beta Activity Measurements at the Therapy with Energetic Ions). Consisting of two heads having a $42 \times 21 \mathrm{~cm}^{2}$ area each, and placed at a distance of around 40 cm from the isocenter, it was built from block detectors of the ECAT EXACT tomograph from CTI PET Systems Inc. The block units of this detector were made of BGO crystals coupled to PMTs. Each block consisted in $8 \times 8$ BGO with $6.75 \times 6.75 \mathrm{~mm}^{2}$ front surface each and 20 mm depth and was read by four PMT. Each head consisted of $8 \times 4$ block detectors. This detector configuration allowed to reach about 4.2 million lines of response (LOR) crossing the field of view (FOV) of the scanner [233]. This scanner was fully integrated in the GSI treatment room and equipped with an electronic system synchronized with a beam delivery system; moreover, it was optimized for the inter-spill coincidences acquisition.

[^38]The system was used in many research and clinical studies at GSI, it demonstrated the feasibility of the technique and showed valuable results [234, 222, 103]. Its main features are the following: total detection efficiency at the center of the positron camera was approximately $2.3 \%$ in the fixed energy window $(250,850) \mathrm{keV}$. The energy resolution was about $16 \%$ at 511 keV , the spatial resolution varies between 5 and 7 mm (FWHM) in the central plane parallel to detector heads [235].

Another detector for in-beam PET is DoPET (Dosimetry with a Positron Emission Tomography), developed in Italy by INFN and University of Pisa. A first prototype was build in 2008 and it consisted in two planar detector heads placed 38 cm apart, having an active area of about $4.5 \times 4.5 \mathrm{~cm}^{2}$. Each head was made up of $21 \times 21$ LYSO square crystals ( 2 mm size, 2.15 mm pitch) coupled to one squared multianode PMT (Hamamatsu H8500), active area of $49 \times 49 \mathrm{~mm}^{2}$.

The energy resolution was less than $16 \%$ at 511 keV and the detection efficiency measured at the center of the field of view (FoV) with a ${ }^{22} \mathrm{Na}$ point source of 150 kBq was about $1 \%$ in the full energy window ( $150-850 \mathrm{keV}$ ) [235, [236]. An interesting preliminary experiment, aimed at comparing the performances of this prototype with BASTEI, was performed at GSI and the related results are published in [235]. The experimental setup, showed in figure 7.3 , consisted in irradiating a PMMA phantom with a $116 \mathrm{MeV} / \mathrm{u}{ }^{12} \mathrm{C}$ beam with the two detectors acquiring coincidences simultaneously for during about 30 min .



Figure 7.3: Left: Setup of the BASTEI and DoPET combined experiment; right: Comparison between the BASTEI and DoPET detector of reconstructed activity profile from a 3 min-long irradiation with ${ }^{12} \mathrm{C}$ at $116.6 \mathrm{MeV} / \mathrm{u}$ for a beam-off PET acquisition of the order of 30 min in a PMMA target (figure from ref. [235]).

As depicted in figure 7.3, BASTEI and DoPET showcases similar performances for the range determination, whereas DoPET showcased a better spatial resolution with respect to BASTEI, mainly due to the smaller crystal: FWHM of the peak was 6 mm for DoPET and 14 mm for

## BASTEI.

An improved larger DoPET version, based on this first prototype, and with an active area of $10 \mathrm{x} 10 \mathrm{~cm}^{2}$, was developed in 2012 and described in [237]. Several experiments were performed especially with proton beam in the CATANA facility (Sicily, Italy) [104, 238 providing a coincidence resolution of 3 ns , the maximum data collection rate for detected coincidences is about 1 million counts per second (cps).

Further experiments were done at CNAO in 2015 and published in ref. [239], using a second improved version of the detector, called DOPET-L and characterized by a surface area of $15 \times 15$ $\mathrm{cm}^{2}$. Homogeneous and patient-like phantoms were irradiated with proton as well as with ${ }^{12} \mathrm{C}$ beams with long irradiation of 1-2 minutes and acquisition time of 10 minutes. The results suggested that monitoring of proton treatment were feasible but for carbon treatment some improvements were needed on dead-time and pile-up effects. Two other experimental studies, including comparison with FLUKA MC simulations, were done in 2017 at the ATREP proton therapy center in Trento (Italy) [240].

The above-mentioned system, although different in the geometry and readout electronics, are all based on PMT technology [197]; moreover, they have the drawback that they cannot operate when the beam is on. On the other hand, a detector based on solid-state photodetector, which can also acquire when the beam is on, was developed within the INSIDE project and is in operation since 2016 at CNAO. With respect to other more recent solid-state solutions proposed by Shao et al. [241] or [242, allowing to reach sub mm-activity ranges during irradiation with protons on homogeneous phantoms, this detector has still the advantage of combining inbeam PET with a tracking system for IVI, the Interaction Vertex Imaging method mentioned in chapter 1 [231.

INSIDE was finally chosen for the experimental part of this thesis, since at the time of the choice it had already demonstrated its performances also in clinical scenarios, although only for proton beams [243] and it had the indisputable advantage of being installed at CNAO, the HT facility son of the TERA Foundation, as explained in the previous chapters.

### 7.3 INSIDE in-beam PET detector

In the next paragraphs the INSIDE in-beam detector is described. The data acquisition and processing system is explained making use of experimental data acquired in the framework of a experimental campaign performed in CNAO with INSIDE where the author actively took part.

General description The INSIDE project (INnovative Solutions for In-beam DosimEtry in hadron therapy) has been led by a wide Italian collaboration established among several Italian Universities $3^{3}$, INFN and CNAO since 2010, following a MIUR ${ }^{4}$ Italian fund.

The in-beam PET detector was built in 2015 in Torino and consists in two planar heads having a surface of $26.6 \times 11.25 \mathrm{~cm}^{2}$ each (included gaps) of 300 kg weight (electronics included) [128]. With reference to figure 7.4, each head is made of $16 \times 16$ matrices of segmented Lutetium Fine Silicate (LFS) scintillating crystals coupled to Hamamatsu Silicon PhotoMultipliers (SiPMs) distributed in $2 \times 5$ modules, with 3.3 mm gaps in between. The distance between the two heads can be adjusted between 50 and 65 cm , thanks to a movable support integrated on a mechanical cart of aluminum alloy profiles.

2560 detector channels are available for each head (i.e. $2560 \times 2$ Line of Responses-LORwithin the Field of View - FOV). All the signals coming from the $2 \times 2560$ detectors are acquired by a complex Front End electronics TOFPET ASIC, based and processed by 20 Xilinx SP605 FPGA (Field Programmable Gate Array) boards [243, 230]. The front-end boards are mounted on a cooling plate where water flows to maintain the system at a stable temperature around 18 ${ }^{\circ} \mathrm{C}$. In particular, one detection module requires four ASICs for the readout and each of them can sustain input event rate up to 100 kHz per channel. Time-to-digital converter has 50 ps resolution to perform time and energy measurements.

The Energy in fact is measured in Time Over Threshold (TOT) unit. The TOT methods, now used also in PET for conventional application, consists in applying a threshold crossing the rising edge as well as the falling edge of the pulse generated in the analog stage of the front-end signal. The difference between the two time-stamps, fixed by the intersection of the threshold and each of the two edges, established the duration of the pulse and provides a measurement of the energy released in the detector. The use of two threshold levels allows the suppression of dark counts.

Data acquisition and processing system The Data AcQuisition (DAQ) system of the INSIDE PET detector receives the data from the FGPA readout transmitted via a UDP ${ }^{5}$ based GB Ethernet protocol. The DAQ is installed on a server with 32 hyper threaded cores and 128 GB RAM, placed in the control room of a treatment room in CNAO, and controlled by a sophisticated software developed with ROOT [245] and BOOST ${ }^{6}$ ibraries. DAQ system com-

[^39]

Figure 7.4: Main components of INSIDE detector. Left: detector overview with the indication of the head aluminum box (A), the detection modules surface (B) and the FGPA readout (C). Center-top: details of the aluminum box (A) containing the front-end electronics boards (a1) installed on the cooling plates; center-bottom: PET detection modules of one head (B) configured in $2 \times 5$ array included in a glass fiber support. Right-top: one of the front-end boards (a1) based on the 64 -channels ASIC TOFPET; right-bottom: one of the detection modules (b1) with the detail of the $16 \times 16$ LFS crystal matrix. Figure built with pictures taken at CNAO and from ref. 2447.
municates also with a GUI $]^{7}$ to monitor online the coincidences during the treatment. Finally a Labview-based software with a user interface allows the calibration and monitoring of the overall system, including power supply, cooling and read-out electronics.

The data processing system was developed by the INSIDE collaboration to work with the CNAO synchrotron and mainly designed to monitor in real time the patient's dose via the detection of PET activity.

As already mentioned, synchrotrons have a macro-time structure consisting in spills of the order of 1 second and, in addition, the spill itself has a sub- $\mu$ s time structure that generates many random events during the irradiation. Moreover, these events cannot be suppressed by techniques used in conventional PET, such as the delayed-coincidence method or the singles count rates method, because the intensity during the micro-bunch time structure is not constant. Two techniques were proposed in literature to suppress in-beam PET random events: synchronization with the radiofrequency signal of accelerator and gating with a fast particle detector [221]. The first technique has the disadvantage that it cannot be applied online and the second one requires that the facility has a fast particle detector available and can be integrated in the treatment room. Further details on techniques able to select in-beam data can be found in ref. [246, 128, 247] and the patent ref. [248]. Since these techniques were not yet

[^40]fully developed at the time of the experiments, the data analysis of the fast range verification experiments did not include the in-spill data which were rejected by filtering in time.

From the DAQ and GUI, the system raw data are converted in usable data which can be used not only for an immediate online feedback, but also for further offline analysis.

Examples are the single and coincidence rate data, which allow - for example - to: count the produced coincidences, distinguish the inter-spill information from in-spill ones and detect any beam interruption.

As an example, the output obtained for a long acquisition performed by the author in CNAO (run 6 online) ${ }^{8}$ are described in the following. A PMMA phantom made of 3 modules of dimensions, $x, y, z$, in cm, respectively $15 \times 15 \times 20,15 \times 15 \times 5,15 \times 15 \times 5$, was irradiated with $2 \cdot 10^{10}{ }^{12} \mathrm{C}$-ions at $398.84 \mathrm{MeV} / \mathrm{u}$, distributed in a $2 \times 2 \mathrm{~cm}^{2}$ field of 100 spots, and the INSIDE detector placed as in the scheme in figure 7.5 .


Figure 7.5: Geometry of the experimental set-up of run 6: the expected position of the Bragg Peak (BP) is indicated with the dotted line in red. The PMMA target position with respect to the detector is shown. The used reference system is at the bottom left of the figure.

In details, with reference to the figure 7.6, showing the single event rate and coincidence event rate over time, the phantom was irradiated for almost 33 min , in 500 spills of 2 s each, and the PET acquisition stopped after 18 min . As shown in figure 7.7 the irradiation was interrupted after 43 spills for 17 s .

[^41]

Figure 7.6: Single and coincidence event rate.



Figure 7.7: Coincidence event rate or run 6 online zoomed to show the exponential growth during the irradiation and decay, once ended. In the bottom part the 17 s irradiation pause is shown.

The PET output are images of dimensions $224 \times 112 \times 264(x \times y \times z) \mathrm{mm}^{3}$, corresponding to the FOV of the detector, and voxel dimension of 1.6 mm , corresponding to the size of the squared crystal, that can be reconstructed at different acquisition times with specific filtering tools. These are generated in NIfTI ${ }^{9}$ format and read by a software application for medical imaging called ITK-SNAP ${ }^{10}$. An example is provided in figure 7.8 , where six images reconstructed at the time intervals indicated in figures 7.6 and 7.7 (before, during and after irradiation, during the beam pause and total acquisition time) are compared and visualized in three different planes: axial, sagittal, coronal.


Figure 7.8: Experimental PET online images examples for a long ${ }^{12} \mathrm{C}$ irradiation. The images are related to the time period of acquisition defined in figures 7.6 and 7.7 .

From figure 7.8, it is evident that INSIDE, as all the two-heads detectors, showcases elongated artifacts and distortion in the Axial and Coronal transverse planes, due to the reduced geometrical coverage. Only in the sagittal plane, parallel to the detector surfaces, the images well reproduce the reality. For an in-depth analysis of these artifacts in INSIDE, the reader can find more details in ref. [128].

As it will be explained and shown in the next chapter, other routines allow the filtering of images and extraction of the profiles. The 1D-profile from the sagittal plane ( $z$ axis) is the most interesting one, because it showcases the activity peak correlated to the Bragg Peak.

[^42]
### 7.3.1 FLUKA PET tools for INSIDE

The FLUKA PET tools for INSIDE were developed by the INSIDE collaboration, already before (and further improved in parallel) the FLUKA PET tools described in chapter 3.1.

The FLUKA package for INSIDE integrates and is fine-tuned on the beam characteristics of CNAO, including nozzle geometry and Dose Delivery System (DDS) information. In details, the DDS file, specific for each irradiation, includes all the information deriving from RT plan DICOM files (particle type, spot positions, energy values and weight, i.e. the number of particles per spot) combined with the beam time structure. Moreover, it integrates the analysis tools developed for the experimental apparatus, thus enabling a fast comparison of experimental measurements with simulated data. The simulations can be performed before the experiment: to predict the expected results, and in this case the a priori DDS information will be the ideal one coming from the planned treatment. Of course, it can be also performed a posteriori, especially if used during the clinical treatment so as to apply a treatment correction (in the so-called on the fly response). In this case, in the simulation the real DDS file can be included, thus taking into account possible - although rare - delivery errors, such as a delayed spill from the accelerator or a spot position deviation.

The tools were optimized to simulate real-patient scenarios and for clinical applications; therefore, in order to significantly reduce the computational time, a two steps approach was preferred.

In the first step of the simulation, the primary beam is reproduced with reduced statistics (1/100), but all the process of interactions with the target (MCS, fragmentation of target and projectiles) are taken into account, and DDS information is included. In this first step, the 3 D endpoint position, production time and energy of each $\beta^{+}$isotope during the irradiation is scored on a file that is then used as an input for the second step. This file is used to reconstruct the activity profile in the target, discriminating each radioisotope contribution.

In the second step, the full detector geometry with the actual time and energy resolution is included, but only the $\beta^{+}$activity is considered as primary beam; all the other secondaries produced in the primary interaction, especially during the spill, are not modelled. Finally, the output of the second step is a file containing the time and the deposited energy of each event in the specific detector element. This file can be analyzed with a C++ software developed ad hoc, in which the detector energy and the time resolution are included. Events registered within 3 times the scintillator decay time are merged; if instead they have energy values outside the energy window (that can be adjusted) they are discarded. From the resulting events the coincidences are extracted and saved in a list-mode file. Afterwards, the reconstruction algorithm, the MLEM, is applied and the PET images reconstructed in the same way as the experimental data. The robustness of this two-step approach and biasing is proven in Pennazio et al. [249] [128].

FLUKA PET tools for INSIDE are the ones used for the comparison with the experiment presented in chapter 8 .

### 7.4 Chapter summary

This chapter introduces the method of fast range verification for ${ }^{12} \mathrm{C}$ ions with the in-beam PET technique and presents the results of the MC simulations showing the feasibility of the idea. A brief overview of the existing in-beam PET detectors is presented after detailing the related requirements. Finally, the one chosen to perform the experiment aimed at validating the fast range verification idea is the INSIDE two-head detector. The description includes the general characteristics, the data acquisition and processing tools of the system that were used, together with the dedicated FLUKA simulation tool, in the experiment as presented in chapter 8.

## Chapter 8

## Fast range verification experiments with in-beam PET at CNAO


#### Abstract

In order to demonstrate the feasibility of the fast range verification method just before the Carbon ion treatments described in chapter 7, $\beta^{+}$coincidence events from a short irradiation of ${ }^{12} \mathrm{C}$ ion beam in PMMA phantoms were acquired at the CNAO facility with the INSIDE in-beam PET detector. The experimental results show that the reconstructed PET signal from a short irradiation of less than one second, with $3 \cdot 10^{7}$ Carbon-ions at $220 \mathrm{MeV} / \mathrm{n}$, in a measurement time of 6 seconds, can be correlated with the position of the Bragg peak, with an accuracy of one millimeter. Although similar experiments were performed at CNAO with the INSIDE detector, this is the first time, to the knowledge of the author, that such a short ${ }^{12} \mathrm{C}$ irradiation in time was performed and carefully analyzed at short times in order to extract a meaningful measurement of the particle range.


### 8.1 Materials and Methods

### 8.1.1 The experimental set-up and Measurements

Homogeneous phantoms of different sizes were placed on the coach of the first treatment room of CNAO, where a horizontal beam is available. As in figure 8.1, the in-beam INSIDE PET detector system, described in chapter 7, was positioned and aligned with the target and the beam axis, keeping the distance between the two detector heads to the default value of 50 cm .

Concerning the irradiating targets, the PMMA - Poly(methyl methacrylate) material, widely used for phantoms in medicine, was preferred to water for the following reasons:

1. its stochiometric composition $\left(\mathrm{C}_{5} \mathrm{O}_{2} \mathrm{H}_{8}\right)$ and its density $\left(1.18 \mathrm{~g} / \mathrm{cm}^{3}\right)$ are closer to those of the human body than water;
2. it is easy to handle.

Different experimental runs with ${ }^{12} \mathrm{C}$ beams were performed, with the parameters summarized in table 8.1.


Figure 8.1: Experimental set-up in CNAO's treatment room with INSIDE detector.

Table 8.1: Experimental measurements

| $\begin{gathered} \mathbf{N} \\ \text { Exp. } \end{gathered}$ | Phantom dim. $\left(\mathrm{cm}^{3}\right)$ | $\begin{aligned} & \text { Iso Pos } \\ & (\mathrm{cm}) \end{aligned}$ | Beam Ek ( $\mathrm{MeV} / \mathrm{u}$ ) | Range in PMMA (cm) | $\mathbf{N}^{12} \mathrm{C}$ | $\begin{gathered} \text { Spill } \\ \text { duration (s) } \end{gathered}$ | Field Dim ( N of spots) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | $4.9 \times 4.9 \times 20$ | 10 | 221.45 | 9.3 | $3 \times 10^{7}$ | 0.6 | 1 |
| 2 | $\begin{aligned} & 4.9 \times 4.9 \times 34 \\ & (4.9 \times 4.9 \times 20 ; 4.9 \times 4.9 \times 7 ; 4.9 \times 4.9 \times 7) \end{aligned}$ | 20 | 398.84 | 22.3 | $3 \times 10^{8}$ | 6 spills | 1 |
| 3 | $4.9 \times 4.9 \times 34$ <br> (same phantom run 2, active) | 20 | 398.84 | 22.3 | $3 \times 10^{7}$ | 1 spill | 1 |
| 4 | $\begin{aligned} & 8 \times 8 \times 26 \\ & (8 \times 8 \times 14 ; 8 \times 8 \times 12 \text {-stairs }) \end{aligned}$ | 15 | 300 | 15 | $4.5 \times 10^{7}$ | 1 spill | $3 \times 3 \mathrm{~cm}^{2}$ <br> ( 225 spots) |
| 5 | $\begin{aligned} & 8 \times 8 \times 26 \\ & \text { (same phantom run } 4, \text { active) } \end{aligned}$ | 15 | 349.91 | 19 | $4.5 \times 10^{7}$ | 1 spill | $\begin{aligned} & 3 \times 3 \mathrm{~cm}^{2} \\ & (225 \text { spots }) \end{aligned}$ |
| 6 | $\begin{aligned} & 15 \times 15 \times 30 \\ & (15 \times 15 \times 20 ; 15 \times 15 \times 10) \end{aligned}$ | 23 | 400 | 22.3 | $2 \times 10^{10}$ | 7 spills | $\begin{aligned} & \hline 2 \times 2 \mathrm{~cm}^{2} \\ & (100 \text { spots }) \end{aligned}$ |

Run1 is the one used for the verification of the particle range, described in details in the rest of this chapter. The results of the other runs are reported, for completeness, in the appendix B.

As described in chapter 7, the data acquisition and the 4D PET image processing systems, developed by the INSIDE collaboration, allow the collection of PET coincidences and the
optimal reconstruction of PET images with five iterations of the MLEM algorithm, without exploiting the Time of Flight information. Moreover, the obtained images of sizes in voxel of $140 \times 70 \times 165$ can be smoothed with a three-dimensional 'median filter', with a 5 cm wide kernel corresponding to $7 \times 7 \times 7$ voxels. The median filter is widely used in image processing and has the effect to remove salt-and-pepper noise while preserving edges [250, 251, 252].

The Median Filter replaces the central value of a predefined 3D parallelepiped window with the median value of the voxels contained in the window. The window is moved, voxel by voxel, over the entire image. An example of the effect of the 2D median filter is shown in figure 8.2.

| Input |  |  |  |  |  |  | Output |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | 4 | 0 | 1 | 3 | 1 | 1 | 4 | 0 | 1 | 3 | 1 |
| 2 | (2) | 4 | 2 | 2 | 3 | 2 | 1 | 1 | 1 | 1 | 3 |
| 1 | 0 | 1 | 0 | 1 | 0 | 1 | 1 | 1 | 1 | 2 | 0 |
| 1 | 2 | 1 | 0 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 2 |
| 2 | 5 | 3 | 1 | 2 | 5 | 2 | 2 | 2 | 2 | 2 | 5 |
| 1 | 1 | 4 | 2 | 3 | 0 | 1 | 1 | 4 | 2 | 3 | 0 |

Figure 8.2: An example of a 2D median filter ${ }^{1}$

The effect of the median filter on PET image, extracted from the experimental data collected in 231 s with a $222 \mathrm{MeV} / \mathrm{u}$, is shown in the figure 8.3. It can be seen that, after the treatment, the sparse hits disappear and the borders of the Bragg spot are much better defined. These features greatly improve the determination of the particle range.


Figure 8.3: Median filter effect on the experimental data from Run1 acquired up to 231 s after irradiation: image without (left) and with (right) the application of the median filter.

The last operation on the image consists in regulating the contrast and setting a color map. Besides the images, the tools allow the extraction of 1D profile along the three axis $x, y, z$.

The output of 1D profile along the beam direction $z$ is the most interesting one because it shows the activity peak correlated to the Bragg Peak. The 1D profile is given by default in the reference system of the field of view of the detector ( $0-26.4 \mathrm{~cm}$ ).

Filtering options are available both at events level as well as at image level. In particular, for the analysis of coincidences over time, no energy filter was applied, whereas for the reconstruction of profiles an energy window of $\pm 25$ TOT (Time-Over-Threshold) ${ }^{2}$ around the

[^43]channel photo peak was chosen in order to reject background noise and mainly acquire events in the photo peak.

### 8.1.2 Background noise

The background noise to the PET signal of the experimental acquisition with INSIDE is mainly produced, as mentioned in chapter 7, by ${ }^{176} \mathrm{Lu}$, which is a $\beta^{+}$emitter present in the LFS material of the detector. This background was measured in each experimental run by analyzing the (fake) PET signals before the starting of the beam irradiation. The detailed background noise trend for Run1 is shown in figure 8.4 and corresponds to a rate of 52 coincidences per second. By applying the above-mentioned energy filter, the resulting background noise is presented in figure 8.5. the filter is effective since it reduces the background by a factor of about 4 (from $52.0 \mathrm{~s}^{-1}$ to $12.4 \mathrm{~s}^{-1}$ ), while cutting only $50 \%$ of the good events.

## Coincidence event rate



Figure 8.4: Coincidences rate before the irradiation without energy filter. The number of coincidences is 772 , the average count rate is $52.0 \mathrm{~s}^{-1}$

To reduce the statistical error on this number for the present analysis the background measurements made before the other runs, described in the appendix B, have been added. The final results of the background level without energy filter is $51.0 \pm 0.9$ events/s.

Coincidence event rate


Figure 8.5: Coincidences rate before irradiation with energy filter. The number of coincidences is 186 , the average count rate is $12.4 \mathrm{~s}^{-1}$.

### 8.2 Detailed analysis of Run1

To understand the results, 49 identical Montecarlo simulations $3^{3}$ were performed with INSIDE FLUKA PET Tools in the same experimental condition of Run1. The geometry of the experimental setup is presented in figure 8.6.


Figure 8.6: Geometry of the experimental set-up of Run1: the expected position of the Bragg Peak is indicated with the dotted line in red. The isocenter position is also indicated (ISO).

[^44]
### 8.2.1 FLUKA Monte Carlo simulations

The $\beta^{+}$emitters followed in the MC are summarized in table 8.2 , where the production rates per primary ${ }^{12} \mathrm{C}$ are also given for the energy ( $222 \mathrm{MeV} / \mathrm{u}$ ) used in Run1. These results are obtained with the same FLUKA simulation discussed in chapter 7 and reported in table 7.1 in water and PMMA at $400 \mathrm{MeV} / \mathrm{u}$.

Table 8.2: Production of positron-emitting isotopes in the irradiation with carbon ions of PMMA phantoms.

| Isotope | T1/2 (s) | $\begin{gathered} \text { nuclei } /{ }^{12} \mathrm{C} \\ (222 \mathrm{MeV} / \mathrm{u}) \\ \text { PMMA phantom } \\ \mathrm{V}=4.90 \times 4.90 \times 20 \mathrm{~cm}^{3} \end{gathered}$ |
| :---: | :---: | :---: |
| O-15 | 122.24 | $1.27 \cdot 10^{-2}$ |
| O-14 | 70 | $3.47 \cdot 10^{-4}$ |
| N-13 | 597.9 | $1.80 \cdot 10^{-3}$ |
| N-12 | 0.011 | $3.17 \cdot 10^{-4}$ |
| C-11 | 1221.84 | $7.52 \cdot 10^{-2}$ |
| C-10 | 19.29 | $3.93 \cdot 10^{-3}$ |
| C-9 | 0.1265 | $5.03 \cdot 10^{-4}$ |
| B-8 | 0.77 | $3.58 \cdot 10^{-3}$ |

In addition, by analysing the particle-by-particle annihilation events output files of the 49 MC runs ${ }^{7}$, the temporal and spatial distributions of the simulated events were reconstructed, with the discrimination of the parent isotopes.

As it is clear in figures 8.7, where the activity rate and annihilations count integrated over time are shown, four isotopes are the main contributors to the measured coincidences event rate: i.e. ${ }^{8} \mathrm{~B},{ }^{10} \mathrm{C},{ }^{15} \mathrm{O},{ }^{11} \mathrm{C} .{ }^{12} \mathrm{~N}$ and ${ }^{9} \mathrm{C}$ give minor contributions.

Since the range of short $\beta^{+}$emitters is longer, with respect to the $\beta^{+}$emitters used in conventional PET, there is a percentage of positrons generated from the $\beta^{+}$decay of nuclei produced in the PMMA target, which annihilates in the surrounding air. The results in figure 8.8 and table 8.3 show that, for the isotope of interest, this percentage is less than $5 \%$.

In addition, the annihilation at rest profiles along $z$, reconstructed at different acquisition times (figure 8.9), show the isotopes that give the largest contributions to the measured activity peak. The results confirmed what was obtained from the preliminary simulations presented in chapter 7, in particular the dominance of ${ }^{8} \mathrm{~B}$ nuclei produced during the short irradiation and its main contribution to the activity peak in the first 10 s .

[^45]

Figure 8.7: Simulated activity rate of radioisotopes produced by $3 \cdot 10^{7}$ Carbon ions during the first 0.6 s of irradiation and the first 5 s of acquisition, binning of 0.05 (left). Integrated number of counts for 231 s of acquisition from the end of the irradiation (offline signal) (right).


Figure 8.8: Simulated annihilation count, with isotope contribution in the target in the first 24 s (left). Zoom of the first 2 s in $\log$ scale to show the shorter half life emitters (right). The dotted curves represent the total number of annihilations including the positrons annihilating outside the PMMA target.

Table 8.3: Fraction of the annihilations inside the target with respect to the total one.

| isot | B-8 | C-9 | C-10 | C-11 | N-12 | N-13 | O-13 | O-14 | O-15 | TOT |
| ---: | ---: | ---: | ---: | ---: | ---: | ---: | ---: | ---: | ---: | ---: |
| Ratio | 0.962 | 0.970 | 0.967 | 0.976 | 0.946 | 0.715 | 0.767 | 0.894 | 0.947 | 0.954 |



Figure 8.9: 1D profiles of the annihilations produced in the PMMA target at different acquisition times from the end of the irradiation. Binning of 1.6 mm .

### 8.2.2 Data Analysis

The experimental fractions of the different $\beta^{+}$emitters have been estimated from the exponential fits of the coincidences rate over time. In particular - starting from the end of the 0.6 s irradiation with $3 \cdot 10^{7}$ carbon ions - the total gamma-gamma coincidence rate, $C_{r}(t)$, as a function of the elapsed time $t$, while the beam is off, is proportional to the sum of the number of produced $\beta^{+}$nuclei, multiplied by the relevant exponential function, as shown in equation 8.1 .

$$
\begin{equation*}
C_{r}(t)=\sum_{i=i}^{M} C_{r o_{i}} e^{-\lambda_{i} t_{o f f}} \tag{8.1}
\end{equation*}
$$

The quantities $\lambda_{i}$ are the decay constants of each isotope $i ; M_{i}$ is the number of different nuclei species produced, which are included in the fit because they contribute by more than $3 \%$ to the total rate; $C_{r o_{i}}$ are the coincidence rate due to each isotope at the end of the 0.6 s time. Each value $C_{r o_{i}}$ is proportional to the total number of $\beta^{+}$nuclei of the relative isotope according to the equation 8.2.

$$
\begin{equation*}
C_{r o_{i}}=\epsilon_{i} \cdot \frac{n u c l e i_{i}}{p} \cdot I \cdot\left(1-e^{-\lambda_{i} t_{i r r}}\right)=\epsilon_{i} \cdot \text { annrate } \tag{8.2}
\end{equation*}
$$

Where: $\epsilon_{i}$ is the coincidence efficiency, nucle $i_{i} / p$, is the number of isotopes $i$ produced per primary particle $p$ of ${ }^{12} \mathrm{C}, I$ the number of incident ${ }^{12} \mathrm{C}$ per second and annrate the number of annihilations per second produced in step 1 of the simulation. The equation 8.1 is used to fit the simulated and experimental rate, where $C_{r o_{i}}$ are the fitting parameters.

In order to compare the data with the output of the 49 MC runs, the measured constant rate due to the decay of lutetium, contained in the LSF detector, has to be considered [253]. The background distribution, determined by measurements done before irradiation, can be assumed as Poisson-like with mean value $51.0 \pm 0.9$ coincidences per each second, as shown at the beginning of section 8.1.2.

As a first step, a fit of the average values of the 49 FLUKA runs was performed to obtain the fit parameters, without including the background. Five isotopes were considered in the fit: ${ }^{9} \mathrm{C}$, ${ }^{8} \mathrm{~B},{ }^{10} \mathrm{C},{ }^{15} \mathrm{O}$ and ${ }^{11} \mathrm{C}$ and the binning step was 0.2 s . As generally used in count experiments with relatively low count rate, where the Gaussian approximation of the Poisson statistics is no longer valid, a binned likelihood fitting method was applied [245, 254, 255]. Moreover, in order to evaluate the goodness of fit, the reduced $\chi^{2}$ has been calculated with two methods: Pearson's chi-square, $\chi_{r}^{2}$, and the Baker-Cousins, $\chi_{r L}^{2}$ [256].

In order to quantify the precision of the estimated parameters, the 49 runs were fitted separately, obtaining the averaged fitting parameters with related errors.

As a second step, a background Poisson noise - with a mean value constant in time of ( $5.1 \pm 0.09$ ) events per bin of 0.1 seconds - was added to each of the bins of the 49 simulation runs. Each run was then fitted with a corrected equation with respect to 8.1, adding a constant value $K=5.1$ events $/ 0.1 \mathrm{~s}$.

As a final step, the same fitting equation (that includes the term $K$ ) was applied to the experimental data, by keeping the less sensitive parameters fixed at the values determined with the Monte Carlo.

The comparison of the output of these three fits to the data and to the MC outputs allows an estimate of the production rates of the different beta-emitters.

For the most important measurement - i.e. the estimation of the range of the $222 \mathrm{MeV} / \mathrm{u}$ carbon ions - the procedure shown in figure 8.10 was applied:

- The experimental data and the MC data were summed up at various time intervals after the end of the irradiation and filtered in energy.
- The median filter was applied to each data set.
- The 1D profiles along the $z$ direction were extracted from the 3D images, summing the signal intensity in a volume of $56 \mathrm{~mm} \times 11 \mathrm{~mm} \times 260 \mathrm{~mm}$.
- The experimental 1D $z$-profile plots were translated by 3.2 cm , in order to have the zero of the reference system in correspondence to the proximal face of the target.
- The parameters resulting from the Gaussian fits of the data and the MC were compared.


Figure 8.10: Data analysis workflow. On the left in the squares, the used INSIDE tools scripts.

### 8.3 Results

Coincidences evolution versus time and isotopes contribution. The coincidence decay rate, expressed in number of events per bin of 0.2 s , is shown in figure 8.11 including a zoom in the first 24 s of acquisition.


Figure 8.11: Left : Experimental (red) versus the simulated (black) coincidence count (bin $=0.2 \mathrm{~s}$ ), starting from the end of the irradiation during the next 231 s of acquisition. The simulation curve with added noise is depicted in blue. The related fitting curves are also shown. Right: zoom of the first 26 s .

Three coincidence rate histograms are plotted: simulation, simulation with added noise (both simulated averaged curves from the 49 runs) and experimental data. The corresponding fitting curves are also indicated.

The first very important observation is that the experimental data are about only $15 \%$ larger than the MC predictions. In particular, the fitted parameters of equation 8.1, corresponding to the fractions of coincidences due to the main $\beta^{+}$nuclei, are presented in table 8.4 and permit to quantify these differences.

Table 8.4: Parameters of the fitting curves, representing the coincidences count rate over time. Simulated data without noise.

|  | (a) Average of 49 runs <br> without noise <br> parfit | (b)Distribat$\pm\left(\sigma_{\text {parfit }} \pm \sigma_{\text {sigmaparfit }}\right)$ <br> without noise |
| :---: | :---: | :---: |
| parfit $_{\text {mean }}^{2}$ | $\mathbf{1 . 1 0 6}$ | $\mathbf{1 . 2 1 0} \pm \mathbf{0 . 0 5 8}$ |
| $X_{r L}^{2}$ | $\mathbf{1 . 0 8 3}$ | $\mathbf{1 . 1 1 8} \pm \mathbf{0 . 0 4 3}$ |
| $\mathbf{B - 8}$ | $12.718 \pm 0.314$ | $(12.707 \pm 2.394) \pm(2.195 \pm 0.087)$ |
| C-10 | $2.254 \pm 0.04$ | $(2.255 \pm 0.256) \pm(0.278 \pm 0.005)$ |
| O-15 | $0.901 \pm 0.033$ | $(0.901 \pm 0.23) \pm(0.229 \pm 0.004)$ |
| C-11 | $0.613 \pm 0.016$ | $(0.613 \pm 0.111) \pm(0.111 \pm 0.002)$ |
| C-9 | $22.760 \pm 2.089$ | $(22.884 \pm 14.945) \pm(14.596 \pm 0.892)$ |

Column (a) is the overall fit of the sum of the 49 runs, giving small errors due to high statistics. The $\chi^{2}$ is close to of 1.0 , thus indicating a good fit. Since in this case the statistics are high, and therefore the Poisson distribution can be approximated with a Gaussian, also the Pearson's $\chi^{2}$ is performing well.

Column (b) shows the fit parameters and their sigmas obtained by fitting separately each one of the 49 runs. The central values match the ones in column (a) and the statistical errors are roughly 7 times larger as expected because the MC runs are 49.

Columns (c), (d) and (e) of table 8.5 are fitted with the modified fitting equation 8.1, in order to take into account the constant Poisson noise contribution. The resulting averaged parameters from the 49 separated fits of the simulation curves with added noise are shown in column (c). In column (d), the parameters coming from the same fits of column (c) are presented, but fixing the two parameters for ${ }^{15} \mathrm{O}$ and ${ }^{9} \mathrm{C}$. In this way, the fitting parameters of curves with noise are closer to the values in column (b). Finally, the results obtained by fitting the experimental data with the same equation are reported in column (e).

By comparing the experimental data with the simulation ones, the fit confirms the production of the considered isotopes. The experimental contributions of ${ }^{8} \mathrm{~B}$ and ${ }^{11} \mathrm{C}$ agree with the MC predictions within the errors. Instead, the comparison of column (e) with column (a) shows that FLUKA underestimates the ${ }^{10} \mathrm{C}$ contribution by a factor $1.65 \pm 0.15$, close to the factor 2 mentioned in ref. [185.

Table 8.5: Parameters of the fitting curves, representing the coincidences count rate over time. The parameters fixed in column (d) are taken from column (b) of table 8.4. Simulation with noise and experimental data.

|  | (c) MC with noise | (d) MC with noise | (e) Experimental |
| :---: | :---: | :---: | :---: |
| $X_{r}^{2}$ | $\mathbf{1 . 2 1 7} \pm \mathbf{0 . 0 7 6}$ | $\mathbf{1 . 2 1 8} \pm \mathbf{0 . 0 7 5}$ | $\mathbf{1 . 1 8 1}$ |
| $X_{r L}^{2}$ | $\mathbf{1 . 0 1 0} \pm \mathbf{0 . 0 4 5}$ | $\mathbf{1 . 0 1 7} \pm \mathbf{0 . 0 4 7}$ | $\mathbf{1 . 0 0 8}$ |
| $\mathbf{B - 8}$ | $(12.682 \pm 2.951) \pm(2.866 \pm 0.082)$ | $(12.806 \pm 2.482) \pm(2.137 \pm 0.072)$ | $13.562 \pm 2.332$ |
| $\mathbf{C - 1 0}$ | $(2.281 \pm 0.511) \pm(0.533 \pm 0.004)$ | $(2.272 \pm 0.312) \pm(0.301 \pm 0.003)$ | $3.740 \pm 0.318$ |
| O-15 | $(.853 \pm 0.52) \pm(0.523 \pm 0.003)$ | $\boldsymbol{0 . 9}$ | $\boldsymbol{0 . 9}$ |
| $\mathbf{C - 1 1}$ | $(.638 \pm 0.264) \pm(0.265 \pm 0.002)$ | $(0.608 \pm 0.069) \pm(0.065 \pm 0)$ | $0.606 \pm 0.066$ |
| $\mathbf{C - 9}$ | $(24.298 \pm 18.45) \pm(17.215 \pm 0.953)$ | 22.5 | 22.5 |

Experimental images and profiles along the beam direction. The reconstructed PET images, after a 0.6 s irradiation time with $3 \cdot 10^{7}$ ions and in time intervals equal to $2,4,8,10$, 12, 24 seconds respectively, are presented in figure 8.12.


Figure 8.12: 2D maps of the measured PET coincidences reconstructed with the median filter in $2,4,8,10,12,24 \mathrm{~s}$ after the end of the irradiation.

The intensities I of the images of figure 8.12 , in the point P (crossing of the two axis), and expressed in arbitrary unit (a.u.), are reported in Table 8.6.

Table 8.6: Look-Up Table (LUT) indicating the intensity in the point P of the images in figure 8.12

| $\mathrm{t}(\mathrm{s})$ | 2 | 4 | $\mathbf{8}$ | 10 | 12 | 24 | 231 |
| ---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| $\mathrm{I}(\mathbf{a . u})$ in $\mathbf{P}$ | 0.01 | 0.13 | 0.86 | 1.07 | 1.41 | 4.65 | $3.30 \mathrm{E}+04$ |

Although the intensities are different, the images in figure 8.12 show that, by reducing the acquisition time, the region with the maximum intensity of the signal is always the same.

The longitudinal profile of the image reconstructed in 231 s following a 0.6 second irradiation, is represented by the red curve of figure 8.13 . The FLUKA prediction, obtained from the sum of the 49 simulations and normalized to the peak value, is shown in black. The excess in the experimental curve in the portion of the curve (due to the target fragments) before the peak is
not fully understood. It could be due to a residual lutetium background not properly filtered by the applied median filter in that region.


Figure 8.13: Longitudinal 1D profiles of the reconstructed images at 231 s for the experimental (red) and Montecarlo (black) data. The vertical dotted line represents the expected position $(9.3 \mathrm{~cm})$ of the Bragg Peak (BP) at $222 \mathrm{MeV} / \mathrm{u}$ in PMMA. The target begins at the origin of the axis.

In order to be sure that the background noise or residual activity from a previous run is not correlated with the range determination, a profile before irradiation is extracted.

The comparison of the peak positions in figure 8.14 with the ones in figures 8.13 and 8.15 confirms that the activity peak obtained in the Run1 is not due to a previous irradiation of the target.


Figure 8.14: The spatial distribution of the coincidences before the irradiation. PET FOV reference system.

Similarly to figure 8.13, in figure 8.15, the longitudinal distributions of the events collected in $2,4,810,12,24$ are shown and compared to the FLUKA predictions. It is worth noting that, at these short times, the production of target fragmentation nuclei is negligible.


Figure 8.15: Comparison between FLUKA Monte Carlo simulations (black) and experimental results (red) of longitudinal activity profiles (with the energy filter) in $2,4,8,10,12,24 \mathrm{~s}$. The results in z axis are shown in the range $3-13 \mathrm{~cm}$, the target starts in $\mathrm{z}=0$. The MC results are normalized to the experimental data at the peak. The normalization factor is about 2.5 (sim/exp).

The experimental and simulations profiles are in very good agreement. The agreement between simulated and experimental profiles can be quantified by comparing the parameters of their Gaussian fits, shown in table 8.7.

Table 8.7: Comparison between the Gaussian parameters in simulated and experimental data for different acquisition times. The errors are 1-sigma values from the 49 MC runs.

|  | Acquisition time (s) |  |  |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Fitted param. | $\mathbf{2}$ | $\mathbf{4}$ | $\mathbf{6}$ | $\mathbf{8}$ | $\mathbf{1 0}$ | $\mathbf{1 2}$ | $\mathbf{2 4}$ |
| $z_{\text {mean }}(\mathrm{mm})$ sim. | $76.5 \pm 2.6$ | $76.9 \pm 1.2$ | $76.7 \pm 1.0$ | $76.8 \pm 0.7$ | $77 \pm 0.7$ | $76.9 \pm 0.7$ | $77.1 \pm 0.5$ |
| $z_{\text {mean }}(\mathrm{mm})$ exp. | 77 | 76.8 | 76.9 | 77.2 | 76.7 | 76.1 | 75.6 |
| $\sigma_{\text {peak }}(\mathrm{mm})$ sim | $4.6 \pm 1.8$ | $4.3 \pm 0.6$ | $4.4 \pm 0.6$ | $4.3 \pm 0.5$ | $4.3 \pm 0.4$ | $4.4 \pm 0.4$ | $4.5 \pm 0.3$ |
| $\sigma_{\text {peak }}(\mathrm{mm}) \exp$. | 4 | 3.9 | 4.5 | 4.4 | 4.3 | 4.4 | 4.8 |

The excellent agreement demonstrates that the MC simulations accurately predicts the carbon ion range.

As a first step towards the determination of the accuracy with which the centre of the zdistribution can be experimentally determined, figure 8.16 shows the longitudinal distributions
of 6 runs of FLUKA Monte Carlo at 8 s . The numbers of coincidences for each run are shown in the insets. Figure 8.17 gives the distribution of $z_{\text {mean }}$ at 8 s , i.e. the fitted mean value of each simulation run $i$. The shape is Gaussian with a mean value of 76.8 mm and a sigma equal to 0.7 mm .


Figure 8.16: Longitudinal distribution of six of the fifty runs of FLUKA MC Simulations for the 8 s acquisition and $3 \cdot 10^{7}$ carbon ions. The red lines represent the mean values of the Gaussian fits.


Figure 8.17: Distribution of the mean values $z_{\text {mean }}$ at 8 s . The Gaussian has a mean $\mu=76.8$ mm and a standard deviation $\sigma=0.7 \mathrm{~mm}$. Distribution of the mean values $z_{\text {mean }}$ at 8 s . The Gaussian has a mean $\mu=76.8 \mathrm{~mm}$ and a standard deviation $\sigma=0.7 \mathrm{~mm}$.

The measured position of the peak $z_{\text {mean }}$ stays in the distributions of the simulated runs, as well as the width of the activity peak $\sigma_{\text {peak }}$. Finally, the sigma value of the Gaussian fit of $z_{\text {mean }}$
decreases as $1 / \sqrt{t}$ with the increasing of the coincidence number, as expected from Poisson's statistics, describing this process (Figure 8.18). This proves that with an acquisition time of 6 s , the range can be determined with a precision of 1 mm .


Figure 8.18: Left: Sigma values obtained from the Gaussian fit of $z_{\text {mean }}$ in function of acquisition times: $2,4,6,8,10,12,20,24 \mathrm{~s}$. The best fitting curve is proportional to $1 / \sqrt{t}$. Right: the increase of number of coincidences in time.

### 8.4 Discussion and conclusions

A PMMA phantom was irradiated at CNAO with $3 \cdot 10^{712} \mathrm{C}$ ions for 0.6 s and the 4D-PET signal was collected by the INSIDE detector for about 250 s . The INSIDE double-head PET detector registered, without energy filter, 15700 coincidences in 231 s . In this numbers, the intrinsic LFS - related random background is included. From the experimental runs with no beam the background noise rate is $(51.0 \pm 0.9)$ coincidences/s, corresponding to 11800 coincidences in 231 s , leaving a signal of 3900 true coincidences, only the $25 \%$ of the total number of coincidences. With the energy filter, the total number of coincidences in 231 s is about 5600 and the background noise rate decreases by a factor 4 , corresponding to about 2800 coincidences in 231 s . The true coincidence number in this case increases to $50 \%$ of the total number of coincidences.

In spite of the lutetium background, the results collected in table 8.7 show that in a few seconds it is possible to reconstruct a Gaussian-shaped activity distribution with FWHM $\simeq 10$ mm along the beam direction, coming from the short-lived $\beta^{+}$emitters fragments of the ${ }^{12} \mathrm{C}$ projectiles. The good agreement of the data with the MC predictions allows to conclude that the statistical error on the range measurement can be obtained from the distribution of the 49 identical MC runs, as shown in figure 8.17.

The analysis of the distributions of experimental and FLUKA MC simulated coincidences as a function of time shows that the two isotopes ${ }^{8} \mathrm{~B}$ and ${ }^{10} \mathrm{C}$ are the main contributors to the very narrow and clear signal shown in figures 8.16 and 8.17. Although the INSIDE detector has
not been optimized for measurement of cross-sections, the fitting analysis allowed to quantify the fact that FLUKA underestimates the ${ }^{10} \mathrm{C}$ production with respect to ${ }^{8} \mathrm{~B}$ by about $60 \%$.

In addition, as confirmed by 49 runs of FLUKA simulations, performed in the same experimental scenario, the statistical contribution given by the low number of coincidences accounts for 1 mm sigma for a measurement time of 5 seconds.

It is worth mentioning that promising results have already been obtained with INSIDE in clinical scenarios using inter-spill data at CNAO [249], but the development of a dedicated synchronization system, based on CNAO synchrotron time structure is required. The new rapid range verification method could be performed with a two-head detector with any type of ion accelerator, following the modality chosen in this thesis.

In conclusion, the experiment proves that a PET detector, having similar performances as the ones of INSIDE, can verify the particle range with a 1 mm error, in less than 10 seconds, with a number of carbon ions equal to $3 \cdot 10^{7}$. In order to give low doses to the target during this verification run, which typically will precede the irradiation run, the spot can be moved along a $3-5 \mathrm{~cm}$ segment located at the centre of the tumour and aligned along the axis of the PET detector.

The range position resulting from the verification run can then be used to correct the carbon ion range during the much longer treatment run by applying a correction to the Treatment Plan, that has to take into account the delivered small dose due to the calibration run. Further studies are needed at different energy values of the primary beam in order to assess the impact of the different fraction of fragment production (see figure 1.9) and in more complex experimental scenarios, in order to consider, for example, the inhomogeneities of a real target. However this work opens a very interesting perspective for the in-vivo verification of range during a patient treatment.

## Summary, conclusions and outlook


#### Abstract

Hadron therapy is a technique which kills tumor cells through hadrons ionizing radiations. The indisputable superior physical dose distribution of hadrons with respect to photons and the higher radiobiological effectiveness of carbon ions justify the development of this technique.

However, the further spreading of this therapy requires, on the one hand, affordable accelerators equipped with precise dose delivery technologies and, on the other hand, methods to monitor the dose assuring a treatment of high quality. This thesis aims to respond to these two general requirements.


Concerning the accelerator technology and dose delivery, two accelerators for HT are presented and further studied: TULIP and CABOTO. They are based on the linac technology that is the standard in radiotherapy with photons and has been introduced by the TERA Foundation in the field of Hadron therapy (HT), where so far only circular accelerators have been used. As far as accelerators and dose delivery are concerned, in this thesis three original contributions are detailed.

Firstly, for TULIP - the new single-room facility for proton therapy based on a linear accelerator mounted on a rotating gantry - the beam optics of the magnetic transport lines has been designed and optimized with the development of a 3D particle transmission code, combined with the well-known FLUKA Monte Carlo code. The results allowed to quantify the effects of the nozzle scattering on the accelerator beam characteristics, demonstrating the possibility of relaxing some beam line optics constraints. This had a strong impact, for example, on the HEBT optics design as it allowed to reduce the number of required focusing elements. In addition, the comparison of the predicted TULIP beam characteristics to the measured ones of CNAO's synchrotron facility showed compatible results for cancer treatment.

The second contribution consists in the development of a new full 3D simulation tool. This integrated simulation approach, consisting in following the protons, particle by particle, from the source through the linac and the beam lines to the patient, has never been adopted before in HT. This is a simulation methodology that can be easily translated into other ion beams medical accelerators, leading to a direct determination of quantities such as the energy spread and divergence of the beams, that are only indirectly determined in clinical facilities and Treatment Planning Systems (TPS). From a medical physics perspective, the study allowed the extraction of machine-specific parameters in order to configure a Treatment Planning System to predict dose distributions using TULIP.

The third achievement concerns the computation of the dose delivered by TULIP beams in a patient-like scenario. In particular, the simulated TULIP beams were integrated in a commercial TPS, using the simulated beam characteristics. Furthermore, a patient proton plan was calculated, optimised in the TPS and recalculated for quality assurance purposes using the FLUKA Monte Carlo Particle Therapy Tool, coupled with the TULIP MC beam model. This is the first time that results about the dose distribution of a hadron linac are obtained by applying a full Monte Carlo phase-space model and using a commercial TPS. Although further studies are needed, the preliminary TULIP dose calculations and comparisons between FLUKA and the commercial TPS show the feasibility to obtain the same optimized dose distribution presently achieved in clinical context with other proton therapy systems. Future studies could cover the analysis of additional tumour cases, taking also into account the accelerator time structure and rescanning techniques such as the sparse proportional rescanning.

Linacs in HT can open a new era of HT treatment. First of all, profiting of the fast energy variation that needs only 5 milliseconds instead than the about 100 ms of circular accelerators, linacs can reduce the irradiation time in a treatment to a few seconds per fraction. Moreover, their active energy variation would make the linacs more efficient with respect to cyclotrons, not requiring passive energy degraders, and make the overall facility less bulky. Finally, thanks to their reduced beams size, linacs for HT could represent a valid option for the mini-beam radiation therapy ( pMBRT ) techniques [207]. It is worth to mention that some companies such as AVO-ADAM, starting from the TERA works, have further studied and developed a linacbased protontherapy system, called LIGHT, expected to treat the first patient in the near future.

Concerning the monitoring techniques, treatments with the carbon ion beams accelerated by the TERA linac - called CArbon BOoster for Therapy in Oncology (CABOTO) - have been simulated by taking into account the very special time structure of all linac beams, which are "off" about 99.9 \% of the time. Firstly, FLUKA MC simulations have been performed to evaluate the PET activities generated during a target irradiation with a ${ }^{12} \mathrm{C}$-beam made of microsecond pulses separated by a few milliseconds. This allows the accidental-free measurement of $\beta^{+}$ emitters that have milliseconds lifetimes, which is not possible with circular accelerators, due to the less favourable time structure of their beams. As a consequence, the in-beam PET measurements with CABOTO produce, in a given time, larger statistics than conventional accelerators that can lead to a more precise determination of the ion range.

This study made clear the great advantage of the fast range verification method based on the PET in-beam monitoring of the position of the Bragg peak. It was then natural to propose the detection of short-lived $\beta^{+}$emitters from a pre-irradiation short and low-dose of a part of the tumour target, which is also possible with conventional circular accelerators. As a second step, to quantify the precision of the method, experiments have been performed with the INSIDE detector at CNAO, the Italian Centre for Oncological Hadron Therapy in Pavia. In this thesis the detailed PET analysis of an experiment performed at $222 \mathrm{MeV} / \mathrm{u}$ with $3 \cdot 10^{7}$ carbon ions impinging for 0.6 s on a PMMA homogeneous phantom is presented.

The comparison of the measured longitudinal $\beta+$ activity distributions with the predictions of 49 runs of complete FLUKA simulations has brought to four main conclusions:

- the time-dependence of the measured activity, in the 25 seconds following the 0.6 s irradiation quantitatively agrees with the expected one;
- the time fit shows that the main contribution of ${ }^{8} \mathrm{~B}$ is well predicted by FLUKA while the ${ }^{10} \mathrm{C}$ yield is $60 \%$ larger than the prediction, probably due to an underestimation of the production cross-section;
- once the image reconstruction and processing techniques used by the INSIDE team including a "median filter" - were applied to the data, the longitudinal z-distributions of the activities in $2,4,8,10,12$ and 24 seconds were almost perfectly Gaussian with $F W H M \simeq 10 \mathrm{~mm}$, in very good agreement with FLUKA predictions;
- from the distribution of the average peak positions of the 49 FLUKA runs it could be concluded that, with an acquisition time of 5 s , the carbon ion range can be determined with a precision of $\sigma=1 \mathrm{~mm}$.

In order to apply - as a fast range monitoring technique - the very good results obtained in this work to clinical treatments, further studies are needed first in non-homogeneous phantoms and then in patients.

## Appendix A: FLUKA/FLAIR MC TPS tools

This appendix includes in section A.1 some figures of the FLUKA/FLAIR MC TPS tools and, in section A. 2 the summary parameters of the TULIP MC beam model, defined in chapter 5 obtained from the full MC simulations discussed in chapter 4

## A. 1 FLUKA/FLAIR DICOM section



Figure A.1: DICOM CT scans and RT structures in FLUKA/FLAIR.


Figure A.2: DICOM RTPLAN in FLUKA/FLAIR.


Figure A.3: DICOM RTDOSE VIEWER in FLUKA/FLAIR: Comparison TPS vs FLUKA of the lung tumour case in chapter 5 (Sagittal view).

## A. 2 TULIP MC beam Model

The following pages report the file with the summary values of the full MC simulations of TULIP beams for each simulated kinetic energy used to define the MC beam model. The name of the columns of the file are defined below:

- Emeantot(MeV): Kinetic energy mean value of the proton beam expressed in MeV .
- $\mathbf{N p} / \mathbf{M U}:$ number of protons per Monitor Unit.
- $\mathbf{D p}(\mathbf{M e V} / \boldsymbol{c})$ : Momentum spread $\Delta p$ expressed in terms of FWHM in $\mathrm{MeV} / c$.
- dphix(mrad): angular spread $\Delta \Phi_{x}$ in $x$ direction expressed in terms of FWHM in mrad.
- dphiy (mrad): angular spread $\Delta \Phi_{y}$ in $y$ direction expressed in in terms of FWHM in mrad.
- $\mathbf{x F W H M}(\mathrm{cm})$ : beam size in $x$ in FWHM in cm .
- yFWHM(cm): beam size in $y$ in FWHM in cm .

| Emeantot (MeV) | $\mathrm{Np} / \mathrm{MU}$ | Dp (Mev/c) | dphix (mrad) | dphiy (mrad) | xFWHM (cm) | yFWHM (cm) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 70.12640788 | 690402.2716 | 0.219159485 | 1.010270357 | 0.709628161 | 0.0395 | 0.1732 |
| 70.34479333 | 690935.1824 | 0.219944326 | 1.151652739 | 0.737357502 | 0.0314 | 0.1697 |
| 70.47189219 | 691263.7051 | 0.220311065 | 1.220058746 | 0.751173901 | 0.0343 | 0.1695 |
| 70.61530001 | 691650.4211 | 0.220926658 | 1.284294724 | 0.76455242 | 0.0408 | 0.1691 |
| 70.72545768 | 691958.9152 | 0.221316173 | 1.326093377 | 0.773985136 | 0.0461 | 0.1686 |
| 70.81839595 | 692226.8527 | 0.22200118 | 1.354880608 | 0.7809637 | 0.0507 | 0.168 |
| 70.97438951 | 692692.2089 | 0.222868315 | 1.394169103 | 0.791703124 | 0.0579 | 0.1668 |
| 71.10602585 | 693100.0034 | 0.223768379 | 1.418057505 | 0.800028108 | 0.0633 | 0.1656 |
| 71.22208498 | 693470.8926 | 0.22441814 | 1.43239668 | 0.807245333 | 0.0675 | 0.1646 |
| 71.32705874 | 693815.4383 | 0.225353646 | 1.43970926 | 0.813355183 | 0.0707 | 0.1634 |
| 71.51346159 | 694448.2961 | 0.226984331 | 1.441852522 | 0.822836779 | 0.0752 | 0.1611 |
| 71.67775403 | 695028.1585 | 0.228102693 | 1.432005092 | 0.829209282 | 0.078 | 0.1592 |
| 71.82632931 | 695570.1326 | 0.229781579 | 1.417284009 | 0.835499384 | 0.0797 | 0.1573 |
| 71.96297842 | 696083.1795 | 0.230935237 | 1.399355197 | 0.841645599 | 0.0807 | 0.1555 |
| 72.09013726 | 696573.0103 | 0.232639987 | 1.379385447 | 0.846470959 | 0.0814 | 0.1541 |
| 72.20954128 | 697043.7574 | 0.234084143 | 1.357019106 | 0.850734051 | 0.0816 | 0.1526 |
| 72.32246815 | 697498.4943 | 0.235804967 | 1.335177932 | 0.854997733 | 0.0816 | 0.1513 |
| 72.58205967 | 698578.4868 | 0.239727741 | 1.282769564 | 0.863653589 | 0.0799 | 0.1485 |
| 72.81653374 | 699594.846 | 0.243944803 | 1.237968143 | 0.872320342 | 0.0785 | 0.1459 |
| 73.03189945 | 700561.9083 | 0.2484475 | 1.199294964 | 0.878524451 | 0.0775 | 0.1441 |
| 73.23207436 | 701489.0428 | 0.252962413 | 1.169818946 | 0.883713474 | 0.0766 | 0.1426 |
| 73.4198488 | 702383.1022 | 0.258021044 | 1.149632409 | 0.889568328 | 0.0758 | 0.1412 |
| 73.59715663 | 703248.6298 | 0.263085331 | 1.135687353 | 0.894767669 | 0.0755 | 0.14 |
| 73.92612505 | 704908.2157 | 0.274024635 | 1.125134428 | 0.902538305 | 0.0757 | 0.1385 |
| 74.22759151 | 706488.926 | 0.285235341 | 1.128747982 | 0.907365764 | 0.0767 | 0.1373 |
| 74.50715803 | 708004.5754 | 0.296977002 | 1.141953186 | 0.910116521 | 0.0779 | 0.1363 |
| 74.76869065 | 709464.6785 | 0.308979084 | 1.151913418 | 0.912479836 | 0.0782 | 0.1354 |
| 75.0150859 | 710876.6654 | 0.320973781 | 1.154694655 | 0.914533175 | 0.0774 | 0.135 |
| 75.24846916 | 712245.8428 | 0.332960097 | 1.155901969 | 0.915389994 | 0.0765 | 0.1345 |
| 75.47053662 | 713576.6243 | 0.345201443 | 1.161019386 | 0.914771864 | 0.0758 | 0.1342 |
| 75.68259259 | 714872.2785 | 0.357432697 | 1.167195435 | 0.91343754 | 0.0753 | 0.1343 |
| 75.88575153 | 716135.8222 | 0.369390131 | 1.171783991 | 0.911951984 | 0.0743 | 0.1347 |
| 76.08092259 | 717369.7121 | 0.380811369 | 1.175341676 | 0.91116389 | 0.0731 | 0.135 |
| 76.26884004 | 718575.857 | 0.392486794 | 1.178203484 | 0.909213602 | 0.0735 | 0.1354 |
| 76.45019815 | 719756.3612 | 0.403627579 | 1.182262627 | 0.909234223 | 0.072 | 0.1361 |
| 76.62548459 | 720912.3526 | 0.414497838 | 1.18613528 | 0.910431787 | 0.0706 | 0.1371 |
| 76.7951871 | 722045.2494 | 0.425098326 | 1.185699231 | 0.908301001 | 0.0693 | 0.1378 |
| 76.95974669 | 723156.4141 | 0.435429741 | 1.187732281 | 0.901211658 | 0.0683 | 0.1381 |
| 77.18729521 | 724712.7997 | 0.436428514 | 1.185354087 | 0.894309635 | 0.0683 | 0.138 |
| 77.31981835 | 725629.5983 | 0.436880337 | 1.184281906 | 0.89099229 | 0.0684 | 0.1382 |
| 77.46939578 | 726673.308 | 0.437811285 | 1.183891703 | 0.887508744 | 0.0686 | 0.1384 |
| 77.58433176 | 727481.5974 | 0.4380453 | 1.182876929 | 0.884945215 | 0.0687 | 0.1386 |
| 77.68133217 | 728167.9293 | 0.438584913 | 1.182295939 | 0.883176217 | 0.0689 | 0.1389 |
| 77.84422558 | 729328.9065 | 0.439219817 | 1.181743894 | 0.880486709 | 0.0693 | 0.1394 |
| 77.98174689 | 730317.0742 | 0.440177845 | 1.180476088 | 0.878515714 | 0.0697 | 0.1399 |
| 78.10302809 | 731194.489 | 0.440655174 | 1.179992624 | 0.877090676 | 0.0702 | 0.1404 |
| 78.21276304 | 731993.0603 | 0.441420982 | 1.179391948 | 0.875937777 | 0.0705 | 0.141 |
| 78.40776495 | 733422.8314 | 0.441973026 | 1.177050606 | 0.87443378 | 0.0713 | 0.1421 |
| 78.57977423 | 734695.0107 | 0.442841431 | 1.175573286 | 0.873267811 | 0.072 | 0.1433 |
| 78.73538917 | 735854.4896 | 0.443490486 | 1.173804165 | 0.872493525 | 0.0727 | 0.1445 |
| 78.87858981 | 736928.3984 | 0.444169862 | 1.171547326 | 0.872002554 | 0.0734 | 0.1457 |
| 79.01193156 | 737934.1427 | 0.444614349 | 1.16880002 | 0.871730082 | 0.0739 | 0.1467 |
| 79.13718465 | 738883.7812 | 0.445078676 | 1.166221278 | 0.871725279 | 0.0745 | 0.1475 |
| 79.2557083 | 739786.6331 | 0.445559422 | 1.163581091 | 0.871553585 | 0.075 | 0.1514 |
| 79.52842619 | 741878.978 | 0.44668938 | 1.155665517 | 0.870980672 | 0.0764 | 0.1521 |
| 79.77500435 | 743787.6001 | 0.44762464 | 1.147109857 | 0.870689798 | 0.0775 | 0.1528 |
| 80.00172529 | 745555.5414 | 0.448607818 | 1.137620663 | 0.869521174 | 0.0786 | 0.1532 |
| 80.21265557 | 747210.6837 | 0.449371632 | 1.127439932 | 0.867695469 | 0.0795 | 0.1534 |
| 80.41067597 | 748772.8681 | 0.449909717 | 1.119738828 | 0.865996589 | 0.0807 | 0.1537 |
| 80.59783519 | 750256.1831 | 0.450474248 | 1.115237657 | 0.863811542 | 0.0822 | 0.1537 |
| 80.94550429 | 753027.198 | 0.451411574 | 1.108900546 | 0.858637671 | 0.0854 | 0.154 |
| 81.26459099 | 755585.535 | 0.451906801 | 1.099276101 | 0.854017092 | 0.0881 | 0.1542 |


| 81.56100109 | 757972.3475 | 0.424386578 | 1.083617783 | 0.850222537 | 0.09 | 0.1547 |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 81.83861066 | 760214.5234 | 0.428338069 | 1.068551981 | 0.844465022 | 0.0919 | 0.1551 |
| 82.10050248 | 762333.8378 | 0.431806787 | 1.059809319 | 0.836213807 | 0.0941 | 0.1556 |
| 82.34890034 | 764345.9758 | 0.435298494 | 1.054216243 | 0.829657539 | 0.0965 | 0.1564 |
| 82.58555464 | 766263.3731 | 0.439063383 | 1.049807417 | 0.826110002 | 0.0987 | 0.1575 |
| 82.81185521 | 768095.9578 | 0.442590742 | 1.041972677 | 0.824901919 | 0.1002 | 0.155 |
| 83.0289366 | 769851.8896 | 0.446638802 | 1.032483891 | 0.823325002 | 0.1012 | 0.1537 |
| 83.23771197 | 771537.7591 | 0.45019242 | 1.023944596 | 0.821608401 | 0.1019 | 0.1525 |
| 83.43898442 | 773159.4344 | 0.453756995 | 1.021855918 | 0.820665826 | 0.1029 | 0.1514 |
| 83.63337956 | 774721.4802 | 0.457331338 | 1.018008086 | 0.820401433 | 0.1034 | 0.1505 |
| 83.82152389 | 776228.5658 | 0.461166372 | 1.010390446 | 0.82078915 | 0.103 | 0.1496 |
| 84.00388265 | 777684.141 | 0.465008615 | 1.007466182 | 0.820896512 | 0.0998 | 0.1486 |
| 84.18087116 | 779091.3185 | 0.468605662 | 1.015271419 | 0.820204942 | 0.0997 | 0.1478 |
| 84.4184764 | 780970.7236 | 0.468528827 | 1.0230176 | 0.823352396 | 0.0983 | 0.147 |
| 84.5567434 | 782058.6916 | 0.468192389 | 1.027167016 | 0.824829288 | 0.0977 | 0.1464 |
| 84.71271403 | 783280.4465 | 0.468064878 | 1.032485247 | 0.826382586 | 0.0966 | 0.1456 |
| 84.83250445 | 784214.5464 | 0.468025592 | 1.03670496 | 0.827690048 | 0.0957 | 0.145 |
| 84.93354154 | 784999.3718 | 0.467530585 | 1.039396667 | 0.82891322 | 0.095 | 0.1444 |
| 85.10314944 | 786310.2298 | 0.467372159 | 1.044844697 | 0.831226803 | 0.0937 | 0.1437 |
| 85.24622784 | 787409.424 | 0.466777746 | 1.048725244 | 0.833171735 | 0.0925 | 0.143 |
| 85.37232828 | 788373.0959 | 0.466475363 | 1.051861801 | 0.835178669 | 0.0914 | 0.1424 |
| 85.48638725 | 789240.5955 | 0.465952481 | 1.054492226 | 0.836779631 | 0.0904 | 0.1419 |
| 85.68897532 | 790771.5854 | 0.447240193 | 1.059902532 | 0.839523767 | 0.0885 | 0.141 |
| 85.86753138 | 792110.3882 | 0.445335599 | 1.064358558 | 0.841460114 | 0.0868 | 0.1402 |
| 86.02897581 | 793312.2386 | 0.443722958 | 1.068396067 | 0.842680189 | 0.0852 | 0.1394 |
| 86.17747709 | 794410.3899 | 0.441644321 | 1.07195941 | 0.842946372 | 0.0837 | 0.1386 |
| 86.3157153 | 795426.2478 | 0.440089931 | 1.075523538 | 0.842735989 | 0.0824 | 0.1379 |
| 86.44552409 | 796374.4849 | 0.438308018 | 1.078127893 | 0.841920522 | 0.0812 | 0.1372 |
| 86.56827873 | 797266.085 | 0.43654431 | 1.081142663 | 0.840667259 | 0.0801 | 0.1365 |
| 86.85052294 | 799297.0197 | 0.432199376 | 1.086185677 | 0.836808477 | 0.0778 | 0.1352 |
| 87.10554076 | 801108.8025 | 0.428422482 | 1.091975443 | 0.832474456 | 0.0759 | 0.1347 |
| 87.33983792 | 802753.5681 | 0.424205109 | 1.097493004 | 0.828830793 | 0.0744 | 0.135 |
| 87.55770529 | 804265.6941 | 0.420527708 | 1.101701627 | 0.826688722 | 0.0734 | 0.1364 |
| 87.76211439 | 805669.0214 | 0.416639886 | 1.106669323 | 0.82344097 | 0.0728 | 0.1385 |
| 87.95523235 | 806980.9528 | 0.412783788 | 1.112090725 | 0.818511327 | 0.0723 | 0.1412 |
| 88.3137473 | 809380.1391 | 0.405643895 | 1.120659973 | 0.811902051 | 0.0716 | 0.1469 |
| 88.64251945 | 811537.9498 | 0.398835651 | 1.123886385 | 0.809515821 | 0.0707 | 0.1499 |
| 88.94766608 | 813503.6928 | 0.392342139 | 1.117751076 | 0.809250936 | 0.0697 | 0.1494 |
| 89.23339325 | 815311.4221 | 0.386151354 | 1.112679644 | 0.813050104 | 0.069 | 0.147 |
| 89.50279879 | 816986.226 | 0.380499231 | 1.114092582 | 0.819935387 | 0.0691 | 0.1446 |
| 89.7582128 | 818547.0392 | 0.37513311 | 1.117394399 | 0.829333914 | 0.0696 | 0.1426 |
| 90.00144468 | 820008.6089 | 0.370047401 | 1.1177118 | 0.837717146 | 0.0701 | 0.1408 |
| 90.23396815 | 821383.2069 | 0.365237458 | 1.116486296 | 0.843663242 | 0.0705 | 0.1392 |
| 90.45694016 | 822681.6975 | 0.360943346 | 1.11419489 | 0.849374109 | 0.071 | 0.1376 |
| 90.67135739 | 823913.5114 | 0.356673735 | 1.111018691 | 0.853978753 | 0.0717 | 0.136 |
| 90.87801624 | 825086.2723 | 0.352913362 | 1.107543757 | 0.859127692 | 0.0725 | 0.1345 |
| 91.0775851 | 826206.3629 | 0.349415943 | 1.106206376 | 0.863601807 | 0.0735 | 0.133 |
| 91.27069095 | 827279.5147 | 0.346422199 | 1.105967185 | 0.867768986 | 0.0748 | 0.1316 |
| 91.45783424 | 828310.4104 | 0.343201437 | 1.103638464 | 0.872405218 | 0.0759 | 0.1302 |
| 91.63944511 | 829303.0669 | 0.340480761 | 1.093777389 | 0.877038592 | 0.0781 | 0.1291 |
| 91.88640579 | 830642.082 | 0.339114203 | 1.096446423 | 0.879989234 | 0.0793 | 0.1277 |
| 92.03006923 | 831415.9937 | 0.338400181 | 1.097057962 | 0.881687134 | 0.0799 | 0.1269 |
| 92.19208524 | 832284.9488 | 0.337174453 | 1.097870396 | 0.883410453 | 0.0807 | 0.1259 |
| 92.31647296 | 832949.6882 | 0.336010313 | 1.098041941 | 0.884606204 | 0.0812 | 0.1253 |
| 92.42139279 | 833508.9837 | 0.335119929 | 1.098166117 | 0.885986624 | 0.0817 | 0.1247 |
| 92.59746419 | 834445.1382 | 0.333394896 | 1.097940399 | 0.887973872 | 0.0825 | 0.1237 |
| 92.74595346 | 835232.757 | 0.331957085 | 1.0973809 | 0.889814451 | 0.0832 | 0.1229 |
| 92.87681495 | 835925.8346 | 0.330548722 | 1.096547113 | 0.891134917 | 0.0837 | 0.1222 |
| 92.99514774 | 836551.9947 | 0.328920529 | 1.095467819 | 0.892248516 | 0.0841 | 0.1215 |
| 93.20529279 | 837663.4189 | 0.326432353 | 1.093016318 | 0.894555185 | 0.0849 | 0.1205 |
| 93.39045891 | 838643.0379 | 0.32398707 | 1.089918489 | 0.896532927 | 0.0855 | 0.1196 |
| 93.55786238 | 839529.7321 | 0.321572809 | 1.086883794 | 0.898389172 | 0.0861 | 0.1188 |
| 93.71179368 | 840346.5572 | 0.319422633 | 1.083593884 | 0.900179093 | 0.0866 | 0.1181 |


| 93.85504866 | 841108.4974 | 0.317291399 | 1.080252322 | 0.901860015 | 0.087 | 0.1176 |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 93.98958036 | 841825.9925 | 0.315175865 | 1.076740594 | 0.903589961 | 0.0873 | 0.117 |
| 94.11678195 | 842506.4694 | 0.313073697 | 1.073192191 | 0.905420926 | 0.0876 | 0.1165 |
| 94.40921784 | 844080.244 | 0.308344626 | 1.064597371 | 0.910183159 | 0.0882 | 0.1154 |
| 94.67336605 | 845515.5576 | 0.303668333 | 1.055689961 | 0.914451853 | 0.0887 | 0.1147 |
| 94.9160316 | 846848.1906 | 0.299510966 | 1.046857926 | 0.918411183 | 0.089 | 0.1142 |
| 95.14166875 | 848101.4002 | 0.295386215 | 1.038221562 | 0.922932043 | 0.0893 | 0.1138 |
| 95.35332843 | 849290.978 | 0.291288857 | 1.030640069 | 0.926882852 | 0.0896 | 0.1133 |
| 95.55327013 | 850428.0683 | 0.287691304 | 1.025052424 | 0.929638468 | 0.0899 | 0.113 |
| 95.92441386 | 852572.9634 | 0.28079083 | 1.018341423 | 0.932355176 | 0.091 | 0.1124 |
| 96.26478849 | 854578.3085 | 0.274664589 | 1.01662005 | 0.931974293 | 0.0923 | 0.1115 |
| 96.5806841 | 856471.4464 | 0.269061519 | 1.018874551 | 0.929320252 | 0.0916 | 0.1105 |
| 96.87650285 | 858271.5955 | 0.263972133 | 1.019217299 | 0.92689071 | 0.0922 | 0.1098 |
| 97.15543113 | 859992.6573 | 0.259389174 | 1.015905312 | 0.927724636 | 0.0924 | 0.1096 |
| 97.41991752 | 861645.4113 | 0.25530681 | 1.012466147 | 0.929691708 | 0.0924 | 0.1095 |
| 97.67182027 | 863237.9738 | 0.251720317 | 1.011591306 | 0.929643775 | 0.0927 | 0.1093 |
| 97.91263741 | 864776.9353 | 0.248390045 | 1.011579977 | 0.927944433 | 0.0932 | 0.1097 |
| 98.14361589 | 866267.8594 | 0.245548695 | 1.011345046 | 0.926274883 | 0.0933 | 0.11 |
| 98.36575935 | 867715.1888 | 0.243193275 | 1.011556372 | 0.924810848 | 0.0933 | 0.1101 |
| 98.57989585 | 869122.574 | 0.24132117 | 1.012689823 | 0.922784374 | 0.0932 | 0.1103 |
| 98.78674156 | 870493.2115 | 0.239460502 | 1.01184833 | 0.92497372 | 0.0928 | 0.1112 |
| 98.98690836 | 871829.8385 | 0.237844951 | 1.009539284 | 0.929035333 | 0.0919 | 0.1126 |
| 99.18094047 | 873134.9328 | 0.23694187 | 1.01073411 | 0.927798177 | 0.0914 | 0.1132 |
| 99.36929281 | 874410.5317 | 0.236046377 | 1.019537736 | 0.91505225 | 0.0915 | 0.112 |
| 99.62398861 | 876148.7774 | 0.235085371 | 1.025033875 | 0.912470166 | 0.0915 | 0.1125 |
| 99.7721857 | 877167.1012 | 0.234467914 | 1.027894391 | 0.911939685 | 0.0915 | 0.1128 |
| 99.93935312 | 878321.7496 | 0.234065955 | 1.030869799 | 0.91159264 | 0.0914 | 0.1133 |
| 100.0677253 | 879212.6582 | 0.233470157 | 1.033005763 | 0.912465658 | 0.0912 | 0.1137 |
| 100.1760087 | 879966.9578 | 0.233128521 | 1.034755739 | 0.913362931 | 0.091 | 0.114 |
| 100.3577705 | 881238.7845 | 0.232247828 | 1.037346247 | 0.914123687 | 0.0908 | 0.1147 |
| 100.5111056 | 882317.1369 | 0.231163755 | 1.039347308 | 0.915453069 | 0.0905 | 0.1151 |
| 100.6462678 | 883271.7256 | 0.230564856 | 1.040787729 | 0.9160782 | 0.0902 | 0.1157 |
| 100.7685147 | 884138.3003 | 0.229746631 | 1.042029618 | 0.916682654 | 0.09 | 0.1161 |
| 100.9856711 | 885685.0009 | 0.228604607 | 1.043854714 | 0.917058844 | 0.0894 | 0.1169 |
| 101.1770806 | 887055.9094 | 0.227489796 | 1.044998846 | 0.916949145 | 0.0889 | 0.1177 |
| 101.3501847 | 888301.664 | 0.226162346 | 1.045904087 | 0.91597606 | 0.0884 | 0.1183 |
| 101.5094025 | 889452.3435 | 0.22531429 | 1.046399096 | 0.915199633 | 0.0879 | 0.1188 |
| 101.6576298 | 890527.6717 | 0.224477929 | 1.046702323 | 0.913681812 | 0.0875 | 0.1192 |
| 101.7968512 | 891541.161 | 0.223419459 | 1.046767021 | 0.911972048 | 0.087 | 0.1195 |
| 101.9285351 | 892502.8206 | 0.222601025 | 1.047387313 | 0.909193598 | 0.0864 | 0.1197 |
| 102.2313942 | 894725.3776 | 0.220236685 | 1.046720512 | 0.90097157 | 0.0854 | 0.1206 |
| 102.5051272 | 896746.6259 | 0.218367534 | 1.045392894 | 0.891266442 | 0.0845 | 0.1213 |
| 102.75674 | 898614.3874 | 0.216753872 | 1.043743045 | 0.880142593 | 0.0837 | 0.122 |
| 102.9908019 | 900359.8823 | 0.215159641 | 1.041904059 | 0.868560855 | 0.083 | 0.123 |
| 103.2104926 | 902004.8593 | 0.213811943 | 1.041490546 | 0.85858443 | 0.0824 | 0.1243 |
| 103.4181343 | 903565.2214 | 0.212707761 | 1.04329926 | 0.851008077 | 0.0822 | 0.1277 |
| 103.8038429 | 906477.1249 | 0.210761273 | 1.049145732 | 0.840996527 | 0.0822 | 0.1299 |
| 104.1578965 | 909164.0129 | 0.209307911 | 1.050687077 | 0.83522154 | 0.0818 | 0.1326 |
| 104.4867902 | 911670.552 | 0.20856842 | 1.043295739 | 0.832827176 | 0.0807 | 0.1358 |
| 104.7950417 | 914027.8834 | 0.208306804 | 1.036708617 | 0.814390974 | 0.0795 | 0.1372 |
| 105.0859513 | 916258.8117 | 0.208518295 | 1.035598388 | 0.787317798 | 0.0792 | 0.1386 |
| 105.3620052 | 918380.5528 | 0.209655842 | 1.038013507 | 0.774445325 | 0.0793 | 0.1424 |
| 105.6251444 | 920406.5884 | 0.211258547 | 1.041113916 | 0.779861756 | 0.0796 | 0.1446 |
| 105.8769158 | 922347.6892 | 0.213551715 | 1.043263857 | 0.785347631 | 0.0794 | 0.1442 |
| 106.1185797 | 924212.6606 | 0.216304741 | 1.044483124 | 0.779193175 | 0.0786 | 0.1419 |
| 106.3511601 | 926008.664 | 0.21997065 | 1.045514839 | 0.770580296 | 0.0777 | 0.1389 |
| 106.5755335 | 927741.8637 | 0.224091942 | 1.04575363 | 0.766067224 | 0.0771 | 0.1369 |
| 106.7924232 | 929417.3465 | 0.2288942 | 1.047399291 | 0.761979822 | 0.0766 | 0.1352 |
| 107.0024669 | 931039.6261 | 0.229383946 | 1.050730212 | 0.756255305 | 0.0764 | 0.1332 |
| 107.2062098 | 932612.5692 | 0.233506166 | 1.051472642 | 0.755369519 | 0.0762 | 0.1321 |
| 107.4041281 | 934139.5659 | 0.237627471 | 1.04541624 | 0.764960176 | 0.0757 | 0.1324 |
| 107.6675092 | 936169.549 | 0.238285838 | 1.044341109 | 0.773137952 | 0.076 | 0.1326 |
| 107.8207439 | 937349.2116 | 0.239046765 | 1.043347939 | 0.777384662 | 0.0761 | 0.1326 |


| 107.9935732 | 938678.259 | 0.239336472 | 1.042053947 | 0.781815607 | 0.0761 | 0.1325 |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 108.1262833 | 939697.6017 | 0.239663661 | 1.040906962 | 0.785246299 | 0.0762 | 0.1324 |
| 108.2382224 | 940556.5122 | 0.240235926 | 1.039815978 | 0.787501325 | 0.0763 | 0.1323 |
| 108.4260998 | 941996.082 | 0.240736288 | 1.037945916 | 0.791460256 | 0.0763 | 0.1319 |
| 108.584585 | 943208.2824 | 0.241489281 | 1.036246467 | 0.794589118 | 0.0764 | 0.1315 |
| 108.7242877 | 944275.0273 | 0.241808511 | 1.034532854 | 0.79660237 | 0.0765 | 0.1312 |
| 108.8506239 | 945238.1499 | 0.253852933 | 1.033269939 | 0.79902193 | 0.0764 | 0.1218 |
| 109.0750495 | 946945.1011 | 0.255207011 | 1.030231656 | 0.802011918 | 0.0765 | 0.121 |
| 109.272851 | 948444.9927 | 0.256810399 | 1.027585716 | 0.804449885 | 0.0765 | 0.1204 |
| 109.4517423 | 949797.4877 | 0.25820576 | 1.025100678 | 0.805657226 | 0.0766 | 0.1285 |
| 109.6162717 | 951037.7952 | 0.259838373 | 1.022871167 | 0.807622482 | 0.0766 | 0.1189 |
| 109.7694376 | 952189.1352 | 0.261256096 | 1.020744537 | 0.808475901 | 0.0768 | 0.1181 |
| 109.913309 | 953267.5461 | 0.262457374 | 1.018935681 | 0.808777896 | 0.0769 | 0.1263 |
| 110.0493752 | 954284.5839 | 0.264113778 | 1.01713835 | 0.809957202 | 0.077 | 0.1255 |
| 110.3623465 | 956612.6321 | 0.267827832 | 1.013337838 | 0.810409811 | 0.0773 | 0.1238 |
| 110.6452317 | 958702.3049 | 0.271341153 | 1.010426364 | 0.810065659 | 0.0777 | 0.1222 |
| 110.9052518 | 960609.8239 | 0.274871369 | 1.00824989 | 0.810762954 | 0.0781 | 0.1204 |
| 111.1471597 | 962372.3882 | 0.278414221 | 1.006795086 | 0.810552671 | 0.0787 | 0.1188 |
| 111.3742426 | 964016.2592 | 0.281966814 | 1.004882771 | 0.81099101 | 0.0791 | 0.1174 |
| 111.5888798 | 965560.5727 | 0.285749991 | 1.002377398 | 0.813477754 | 0.0796 | 0.1163 |
| 111.9876487 | 968405.4452 | 0.293110076 | 0.996610031 | 0.822230201 | 0.0804 | 0.1144 |
| 112.3537623 | 970989.7732 | 0.300486045 | 0.992144786 | 0.831669975 | 0.0815 | 0.113 |
| 112.6939357 | 973367.5468 | 0.308094593 | 0.990241003 | 0.837797836 | 0.0828 | 0.1118 |
| 113.0128311 | 975576.2638 | 0.315488009 | 0.98854323 | 0.841895439 | 0.0839 | 0.1104 |
| 113.3138529 | 977643.3023 | 0.372714193 | 0.98552811 | 0.846745583 | 0.0851 | 0.1093 |
| 113.599575 | 979589.3611 | 0.379398751 | 0.982718798 | 0.851259822 | 0.0862 | 0.1082 |
| 113.8719999 | 981430.5441 | 0.386309885 | 0.9813145 | 0.854983146 | 0.0872 | 0.1072 |
| 114.1327223 | 983179.6758 | 0.393445554 | 0.980355297 | 0.858029924 | 0.0882 | 0.1063 |
| 114.3830373 | 984847.1683 | 0.400583488 | 0.979260886 | 0.861287325 | 0.089 | 0.1054 |
| 114.6240136 | 986441.6139 | 0.408163641 | 0.978287872 | 0.864740437 | 0.0895 | 0.1047 |
| 114.8565621 | 987970.3107 | 0.415743793 | 0.977509932 | 0.867633574 | 0.0919 | 0.1039 |
| 115.0814206 | 989439.2153 | 0.423543497 | 0.976140792 | 0.870957752 | 0.0915 | 0.1034 |
| 115.2992294 | 990853.4856 | 0.431561838 | 0.973805605 | 0.875060698 | 0.0909 | 0.1029 |
| 115.510561 | 992217.7022 | 0.439797981 | 0.973688694 | 0.877840662 | 0.0904 | 0.1023 |
| 115.7159037 | 993535.7861 | 0.448031676 | 0.978712366 | 0.876907489 | 0.0904 | 0.1015 |
| 115.9885805 | 995274.8199 | 0.44868637 | 0.979173344 | 0.880113827 | 0.0898 | 0.1014 |
| 116.14715 | 996280.2694 | 0.4490871 | 0.979568724 | 0.881722874 | 0.0896 | 0.1014 |
| 116.3259358 | 997408.7971 | 0.449673944 | 0.980135164 | 0.883442041 | 0.0892 | 0.1014 |
| 116.4631749 | 998271.4322 | 0.450327626 | 0.980519191 | 0.884637506 | 0.0888 | 0.1014 |
| 116.5789039 | 998996.4214 | 0.450578033 | 0.980951895 | 0.885323128 | 0.0885 | 0.1013 |
| 116.7730966 | 1000207.971 | 0.451576255 | 0.981686691 | 0.886720534 | 0.0882 | 0.1013 |
| 116.9368534 | 1001224.828 | 0.451967116 | 0.982335983 | 0.887889855 | 0.0878 | 0.1013 |
| 117.0811528 | 1002117.251 | 0.45260769 | 0.982985291 | 0.888586058 | 0.0874 | 0.1012 |
| 117.2116261 | 1002921.278 | 0.453270186 | 0.98357887 | 0.889182737 | 0.0871 | 0.1012 |
| 117.4433112 | 1004342.319 | 0.454423063 | 0.984730544 | 0.889814396 | 0.0865 | 0.1011 |
| 117.647441 | 1005587.333 | 0.455183202 | 0.985862778 | 0.890170703 | 0.0859 | 0.101 |
| 117.8319837 | 1006707.298 | 0.45641006 | 0.986824689 | 0.890429691 | 0.0855 | 0.1009 |
| 118.0016737 | 1007732.5 | 0.457442008 | 0.987782328 | 0.890528534 | 0.085 | 0.1008 |
| 118.1595967 | 1008682.673 | 0.458274484 | 0.988776553 | 0.890179435 | 0.0846 | 0.1007 |
| 118.3078964 | 1009571.527 | 0.459339375 | 0.98973944 | 0.88974133 | 0.0843 | 0.1006 |
| 118.4481342 | 1010409.047 | 0.459981699 | 0.990617394 | 0.889265494 | 0.0839 | 0.1005 |
| 118.7705666 | 1012323.703 | 0.46228271 | 0.992904576 | 0.887690766 | 0.083 | 0.1003 |
| 119.0618715 | 1014040.63 | 0.464630255 | 0.995113031 | 0.885806191 | 0.0822 | 0.1 |
| 119.3295499 | 1015607.756 | 0.466795734 | 0.997350478 | 0.883336459 | 0.0816 | 0.0997 |
| 119.5784922 | 1017056.318 | 0.468988537 | 0.999542981 | 0.88068418 | 0.0809 | 0.0995 |
| 119.8120976 | 1018408.017 | 0.470986967 | 1.001629472 | 0.878523773 | 0.0803 | 0.0992 |
| 120.0328422 | 1019678.659 | 0.473003828 | 1.003506614 | 0.877542374 | 0.0797 | 0.0993 |
| 120.4428159 | 1022021.846 | 0.430452971 | 1.006592353 | 0.877131559 | 0.0787 | 0.0995 |
| 120.8190571 | 1024153.742 | 0.434206334 | 1.008771142 | 0.87748289 | 0.0777 | 0.0997 |
| 121.1685098 | 1026118.581 | 0.437776244 | 1.010023656 | 0.877174437 | 0.0767 | 0.1 |
| 121.4959892 | 1027947.016 | 0.440941743 | 1.011521007 | 0.876136097 | 0.0757 | 0.1003 |
| 121.8050446 | 1029661.589 | 0.444129081 | 1.013581776 | 0.874954891 | 0.075 | 0.1005 |
| 122.0983233 | 1031279.122 | 0.447334614 | 1.015659807 | 0.873329727 | 0.0727 | 0.1007 |


| 122.3778954 | 1032812.728 | 0.450126628 | 1.017077096 | 0.872229221 | 0.0719 | 0.101 |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 122.6454095 | 1034272.767 | 0.452932573 | 1.018309074 | 0.870539451 | 0.0712 | 0.1012 |
| 122.9022038 | 1035667.625 | 0.455750616 | 1.019640484 | 0.86929681 | 0.0706 | 0.1016 |
| 123.1493828 | 1037004.219 | 0.458151476 | 1.020849993 | 0.867757993 | 0.0701 | 0.1019 |
| 123.3878615 | 1038288.281 | 0.460348672 | 1.021831097 | 0.86624405 | 0.0696 | 0.1022 |
| 123.6184407 | 1039524.802 | 0.462555144 | 1.022900781 | 0.865799416 | 0.0692 | 0.1026 |
| 123.8417813 | 1040717.918 | 0.464769972 | 1.024040641 | 0.866114911 | 0.0688 | 0.1032 |
| 124.0584622 | 1041871.24 | 0.466565877 | 1.024764627 | 0.864619945 | 0.0683 | 0.1035 |
| 124.2689876 | 1042987.911 | 0.468369243 | 1.024662715 | 0.859892203 | 0.068 | 0.1034 |
| 124.5493792 | 1044469.373 | 0.467932409 | 1.027475208 | 0.859942938 | 0.0683 | 0.1036 |
| 124.7124357 | 1045327.919 | 0.467466322 | 1.028542045 | 0.85976859 | 0.0684 | 0.1037 |
| 124.8962823 | 1046293.378 | 0.467181473 | 1.029500398 | 0.859473514 | 0.0685 | 0.1038 |
| 125.0374082 | 1047032.691 | 0.466538176 | 1.02996782 | 0.858958996 | 0.0686 | 0.1038 |
| 125.1564166 | 1047654.944 | 0.466354641 | 1.030201664 | 0.858758406 | 0.0687 | 0.1039 |
| 125.3561165 | 1048696.702 | 0.46541032 | 1.030232691 | 0.858020858 | 0.0687 | 0.1039 |
| 125.5245228 | 1049572.92 | 0.464939884 | 1.030114658 | 0.857486018 | 0.0688 | 0.104 |
| 125.6729241 | 1050343.355 | 0.464288687 | 1.02962444 | 0.857011327 | 0.0688 | 0.104 |
| 125.8071106 | 1051038.654 | 0.463659975 | 1.029223397 | 0.856260695 | 0.0688 | 0.104 |
| 126.0454012 | 1052270.318 | 0.462662133 | 1.027907213 | 0.855381073 | 0.0688 | 0.104 |
| 126.255365 | 1053352.42 | 0.461497442 | 1.026570371 | 0.854316155 | 0.0687 | 0.104 |
| 126.4451946 | 1054328.301 | 0.460365011 | 1.025240001 | 0.853419382 | 0.0687 | 0.1039 |
| 126.6197579 | 1055223.708 | 0.459257162 | 1.02382171 | 0.852627754 | 0.0687 | 0.1039 |
| 126.7822272 | 1056055.415 | 0.458380215 | 1.022255069 | 0.85190032 | 0.0686 | 0.1038 |
| 126.9348065 | 1056835.075 | 0.457096682 | 1.02087412 | 0.851305309 | 0.0686 | 0.1038 |
| 127.0791011 | 1057571.171 | 0.456249143 | 1.019413579 | 0.850659582 | 0.0686 | 0.1038 |
| 127.4108999 | 1059259.437 | 0.423279977 | 1.016014265 | 0.849565557 | 0.0686 | 0.1038 |
| 127.7107181 | 1060780.03 | 0.422870145 | 1.012962277 | 0.848741548 | 0.0687 | 0.1037 |
| 127.9862661 | 1062173.654 | 0.42249484 | 1.010062007 | 0.848373801 | 0.0687 | 0.1036 |
| 128.2425707 | 1063466.832 | 0.4221469 | 1.00749425 | 0.848263434 | 0.0688 | 0.1037 |
| 128.4831254 | 1064677.983 | 0.42182135 | 1.005326892 | 0.848297264 | 0.069 | 0.1036 |
| 128.7104754 | 1065820.52 | 0.421514563 | 1.003600888 | 0.847858662 | 0.0692 | 0.1036 |
| 129.132813 | 1067937.938 | 0.420946949 | 1.000697007 | 0.847107024 | 0.0697 | 0.1033 |
| 129.5205316 | 1069876.686 | 0.420218984 | 0.997997512 | 0.846409476 | 0.0702 | 0.103 |
| 129.880773 | 1071674.288 | 0.4197397 | 0.99499371 | 0.846327284 | 0.0708 | 0.1028 |
| 130.2184836 | 1073356.701 | 0.419292316 | 0.991838418 | 0.845970478 | 0.0714 | 0.1025 |
| 130.5373247 | 1074943.098 | 0.418871627 | 0.988807916 | 0.845936214 | 0.072 | 0.1022 |
| 130.8399589 | 1076447.425 | 0.418473838 | 0.985908654 | 0.846199168 | 0.0725 | 0.102 |
| 131.1285395 | 1077880.923 | 0.418304311 | 0.98298568 | 0.846380775 | 0.0731 | 0.1016 |
| 131.4047685 | 1079252.467 | 0.418151844 | 0.980127364 | 0.846709294 | 0.0738 | 0.1013 |
| 131.6700153 | 1080569.187 | 0.417806442 | 0.977349915 | 0.846849597 | 0.0744 | 0.1011 |
| 131.9254132 | 1081836.976 | 0.417682819 | 0.974450869 | 0.84744431 | 0.0751 | 0.1008 |
| 132.1719108 | 1083060.755 | 0.397004455 | 0.971632465 | 0.847815056 | 0.0758 | 0.1005 |
| 132.4103058 | 1084244.656 | 0.393597794 | 0.970910284 | 0.847574654 | 0.0766 | 0.1 |
| 132.6412915 | 1085392.265 | 0.390620367 | 0.971462255 | 0.846649325 | 0.0776 | 0.0994 |
| 132.8654672 | 1086506.673 | 0.387655685 | 0.969065751 | 0.84698085 | 0.0784 | 0.0991 |
| 133.0833446 | 1087590.516 | 0.384910052 | 0.960562965 | 0.850361082 | 0.0786 | 0.0992 |
| 133.3708567 | 1089022.131 | 0.383328736 | 0.955479665 | 0.851775322 | 0.0789 | 0.0992 |
| 133.5380546 | 1089855.498 | 0.382305019 | 0.952571459 | 0.852719073 | 0.0791 | 0.0993 |
| 133.7265724 | 1090795.967 | 0.381050951 | 0.949326846 | 0.853793468 | 0.0793 | 0.0994 |
| 133.871286 | 1091518.567 | 0.380055984 | 0.946953821 | 0.854406629 | 0.0796 | 0.0994 |
| 133.9933214 | 1092128.408 | 0.379088234 | 0.945021811 | 0.854949332 | 0.0797 | 0.0993 |
| 134.1981052 | 1093152.825 | 0.37761318 | 0.941813628 | 0.855915478 | 0.0801 | 0.0994 |
| 134.3708037 | 1094017.851 | 0.376383249 | 0.939282902 | 0.856880553 | 0.0804 | 0.0994 |
| 134.5229919 | 1094781.05 | 0.374971889 | 0.937205899 | 0.85744382 | 0.0806 | 0.0995 |
| 134.6606067 | 1095471.943 | 0.373578478 | 0.935415007 | 0.857871574 | 0.0809 | 0.0994 |
| 134.9049963 | 1096700.836 | 0.371448129 | 0.932434482 | 0.858779312 | 0.083 | 0.0993 |
| 135.1203472 | 1097785.913 | 0.369353671 | 0.930168597 | 0.859340065 | 0.0834 | 0.0993 |
| 135.3150594 | 1098768.904 | 0.367490827 | 0.928421379 | 0.859488337 | 0.0836 | 0.0992 |
| 135.4941236 | 1099674.61 | 0.365441964 | 0.927009465 | 0.859816081 | 0.084 | 0.0991 |
| 135.6607922 | 1100519.231 | 0.363614585 | 0.925921198 | 0.859667305 | 0.0842 | 0.0989 |
| 135.817325 | 1101314.025 | 0.361800208 | 0.925132004 | 0.859586643 | 0.0846 | 0.0988 |
| 135.9653718 | 1102067.204 | 0.360202196 | 0.92469983 | 0.8592396 | 0.0849 | 0.0987 |
| 136.3058251 | 1103805.193 | 0.355937775 | 0.924278307 | 0.858079503 | 0.0856 | 0.0983 |


| 136.6135112 | 1105383.826 | 0.352126968 | 0.924904268 | 0.856553354 | 0.0864 | 0.0978 |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 136.8963341 | 1106842.296 | 0.348349435 | 0.926404445 | 0.854279339 | 0.0873 | 0.0973 |
| 137.1594461 | 1108206.099 | 0.344803481 | 0.928619673 | 0.851217592 | 0.0881 | 0.0966 |
| 137.4064285 | 1109492.924 | 0.34148422 | 0.929821965 | 0.849239704 | 0.0887 | 0.0962 |
| 137.6398887 | 1110715.622 | 0.338183655 | 0.929115123 | 0.848445648 | 0.0891 | 0.0958 |
| 138.0736858 | 1113005.231 | 0.332037528 | 0.925194724 | 0.849158287 | 0.0895 | 0.0957 |
| 138.4720458 | 1115129.909 | 0.326553473 | 0.921003214 | 0.851126509 | 0.0896 | 0.0957 |
| 138.8422788 | 1117125.361 | 0.320905829 | 0.919171703 | 0.852044911 | 0.0899 | 0.0956 |
| 139.1894678 | 1119016.306 | 0.315902518 | 0.918374075 | 0.852408742 | 0.0902 | 0.0954 |
| 139.5173233 | 1120820.713 | 0.311537062 | 0.917176686 | 0.85268334 | 0.0903 | 0.0952 |
| 139.8286349 | 1122552.021 | 0.307195181 | 0.916539531 | 0.852583268 | 0.0903 | 0.095 |
| 140.1255816 | 1124220.685 | 0.302874179 | 0.91629976 | 0.85282487 | 0.0883 | 0.0948 |
| 140.4099039 | 1125835.023 | 0.299179973 | 0.916522068 | 0.852459707 | 0.0878 | 0.0947 |
| 140.6829982 | 1127401.661 | 0.295501748 | 0.916621305 | 0.852358453 | 0.0872 | 0.0946 |
| 140.9460301 | 1128926.117 | 0.292040462 | 0.91684187 | 0.852723674 | 0.0865 | 0.0945 |
| 141.1999706 | 1130412.96 | 0.288996706 | 0.917483161 | 0.852587371 | 0.0859 | 0.0943 |
| 141.4456416 | 1131866.038 | 0.286166522 | 0.916996834 | 0.852943459 | 0.0851 | 0.0942 |
| 141.6837466 | 1133288.629 | 0.283346697 | 0.915858699 | 0.853607356 | 0.0841 | 0.0942 |
| 141.9148934 | 1134683.548 | 0.280738333 | 0.916537462 | 0.853611847 | 0.0835 | 0.094 |
| 142.1396109 | 1136053.233 | 0.278542108 | 0.921223128 | 0.852955935 | 0.0831 | 0.0938 |
| 142.4346562 | 1137871.667 | 0.27730148 | 0.920197131 | 0.851144255 | 0.0825 | 0.0939 |
| 142.6061907 | 1138938.427 | 0.276361149 | 0.919856779 | 0.850296642 | 0.0822 | 0.0938 |
| 142.7995603 | 1140148.515 | 0.275606195 | 0.919513825 | 0.849208404 | 0.0819 | 0.094 |
| 142.9479719 | 1141082.178 | 0.27468584 | 0.919339078 | 0.848782941 | 0.0816 | 0.0941 |
| 143.0731083 | 1141872.428 | 0.273985467 | 0.919246902 | 0.84854065 | 0.0814 | 0.0942 |
| 143.2830606 | 1143203.827 | 0.272818358 | 0.919198236 | 0.848066627 | 0.081 | 0.0943 |
| 143.4600846 | 1144331.107 | 0.271677933 | 0.919338167 | 0.847477958 | 0.0807 | 0.0945 |
| 143.61606 | 1145327.354 | 0.270554746 | 0.919480952 | 0.847407953 | 0.0803 | 0.0948 |
| 143.75708 | 1146230.105 | 0.269644709 | 0.919716306 | 0.84710904 | 0.0801 | 0.0949 |
| 144.0074729 | 1147836.682 | 0.267850734 | 0.920215386 | 0.846497308 | 0.0797 | 0.0952 |
| 144.2280687 | 1149254.676 | 0.266282163 | 0.92074611 | 0.846142924 | 0.0794 | 0.0955 |
| 144.4274881 | 1150537.498 | 0.26493174 | 0.921329895 | 0.845640433 | 0.0791 | 0.0957 |
| 144.6108528 | 1151716.969 | 0.26359475 | 0.921948383 | 0.845251541 | 0.0787 | 0.096 |
| 144.7815006 | 1152813.881 | 0.262268522 | 0.922640436 | 0.844324638 | 0.0785 | 0.0962 |
| 144.9417504 | 1153842.718 | 0.260951195 | 0.923267545 | 0.843827941 | 0.0783 | 0.0964 |
| 145.0932909 | 1154814.054 | 0.259841438 | 0.92392726 | 0.843083653 | 0.0781 | 0.0967 |
| 145.4417272 | 1157039.154 | 0.256793352 | 0.925486014 | 0.84065981 | 0.0775 | 0.097 |
| 145.7565578 | 1159036.053 | 0.254174427 | 0.927069749 | 0.837621283 | 0.0771 | 0.0973 |
| 146.0458929 | 1160856.58 | 0.251578051 | 0.928631509 | 0.834235275 | 0.0767 | 0.0976 |
| 146.3150189 | 1162536.672 | 0.249398639 | 0.930093637 | 0.830524666 | 0.0763 | 0.0977 |
| 146.5676096 | 1164102.033 | 0.247034679 | 0.931239715 | 0.827435627 | 0.0758 | 0.0981 |
| 146.8063409 | 1165571.379 | 0.244882576 | 0.932189566 | 0.825115177 | 0.0755 | 0.0984 |
| 147.2498593 | 1168275.414 | 0.241007324 | 0.933496276 | 0.822355184 | 0.0747 | 0.0993 |
| 147.6570711 | 1170729.149 | 0.237364105 | 0.934766627 | 0.820429252 | 0.0739 | 0.1004 |
| 148.0354741 | 1172984.969 | 0.23414457 | 0.936143159 | 0.817302051 | 0.0732 | 0.1014 |
| 148.3902808 | 1175079.274 | 0.23114504 | 0.937581572 | 0.813994653 | 0.0727 | 0.1023 |
| 148.72529 | 1177038.572 | 0.228559932 | 0.939006477 | 0.811050056 | 0.0721 | 0.1033 |
| 149.0433721 | 1178882.882 | 0.225990112 | 0.940136326 | 0.808136611 | 0.0715 | 0.1044 |
| 149.3467591 | 1180627.756 | 0.223829247 | 0.940985822 | 0.805492327 | 0.071 | 0.1076 |
| 149.6372276 | 1182285.568 | 0.221877404 | 0.942002564 | 0.802465888 | 0.0705 | 0.1084 |
| 149.9162194 | 1183866.349 | 0.219935578 | 0.943119932 | 0.799805578 | 0.07 | 0.1092 |
| 150.1849239 | 1185378.369 | 0.218397416 | 0.944377575 | 0.796878943 | 0.0696 | 0.11 |
| 150.4443358 | 1186828.537 | 0.217064171 | 0.945353792 | 0.793938151 | 0.0692 | 0.1107 |
| 150.6952975 | 1188222.701 | 0.215540771 | 0.945942302 | 0.793461917 | 0.0687 | 0.112 |
| 150.9385297 | 1189565.856 | 0.214614639 | 0.94619605 | 0.794505455 | 0.0682 | 0.1133 |
| 151.1746547 | 1190862.314 | 0.21369388 | 0.947116668 | 0.791922803 | 0.0678 | 0.1141 |
| 151.4042145 | 1192115.826 | 0.212778112 | 0.949181917 | 0.782872243 | 0.0676 | 0.1141 |
| 151.7061552 | 1193754.44 | 0.21221634 | 0.950052963 | 0.775829948 | 0.0676 | 0.114 |
| 151.881666 | 1194701.746 | 0.211725851 | 0.950796862 | 0.771680009 | 0.0677 | 0.1138 |
| 152.0794903 | 1195765.013 | 0.211223568 | 0.951416292 | 0.76730538 | 0.0678 | 0.1138 |
| 152.2313015 | 1196577.807 | 0.210747263 | 0.952079305 | 0.764003669 | 0.0679 | 0.1138 |
| 152.3592917 | 1197260.963 | 0.210480643 | 0.952554739 | 0.76150268 | 0.068 | 0.1138 |
| 152.5740069 | 1198402.772 | 0.209774612 | 0.953234855 | 0.757267291 | 0.0681 | 0.114 |


| 152.7550228 | 1199361.315 | 0.209087845 | 0.953851007 | 0.753896973 | 0.0683 | 0.1141 |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 152.9144979 | 1200202.772 | 0.208609367 | 0.954298971 | 0.751135501 | 0.0683 | 0.1142 |
| 153.0586684 | 1200961.084 | 0.20813963 | 0.954642629 | 0.748811202 | 0.0684 | 0.1144 |
| 153.3146244 | 1202301.885 | 0.207414453 | 0.955019195 | 0.745140529 | 0.0685 | 0.1148 |
| 153.54009 | 1203477.29 | 0.206511167 | 0.955108694 | 0.742272613 | 0.0686 | 0.1151 |
| 153.7438874 | 1204535.283 | 0.205816041 | 0.954874987 | 0.740283157 | 0.0687 | 0.1156 |
| 153.9312584 | 1205504.363 | 0.205130453 | 0.954430841 | 0.738852889 | 0.0688 | 0.1161 |
| 154.1056188 | 1206403.095 | 0.20464775 | 0.953787966 | 0.737752403 | 0.0687 | 0.1166 |
| 154.2693415 | 1207244.375 | 0.20397596 | 0.952964647 | 0.737181395 | 0.0688 | 0.1171 |
| 154.4241546 | 1208037.59 | 0.203309463 | 0.952025697 | 0.736807774 | 0.0688 | 0.1176 |
| 154.7800754 | 1209853.057 | 0.202149238 | 0.948740079 | 0.737386069 | 0.0686 | 0.119 |
| 155.1016241 | 1211483.809 | 0.201203901 | 0.944772701 | 0.739240881 | 0.0684 | 0.1204 |
| 155.3970992 | 1212974.852 | 0.200273708 | 0.939915937 | 0.742280808 | 0.0682 | 0.1219 |
| 155.6719097 | 1214355.497 | 0.199550123 | 0.934480219 | 0.74624081 | 0.0679 | 0.1235 |
| 155.9298142 | 1215646.095 | 0.198641918 | 0.929961171 | 0.747389963 | 0.0676 | 0.1246 |
| 156.1735506 | 1216861.456 | 0.198324914 | 0.927261002 | 0.744236732 | 0.0676 | 0.1254 |
| 156.6263287 | 1219108.676 | 0.197515844 | 0.925193567 | 0.732871653 | 0.0678 | 0.1262 |
| 157.0419951 | 1221160.607 | 0.197115171 | 0.925761456 | 0.722734083 | 0.0682 | 0.1228 |
| 157.428239 | 1223058.677 | 0.197117571 | 0.925745292 | 0.717585638 | 0.0686 | 0.1218 |
| 157.7903757 | 1224831.487 | 0.197712613 | 0.92506953 | 0.711940093 | 0.069 | 0.1208 |
| 158.1323011 | 1226499.95 | 0.198510211 | 0.92404861 | 0.703790074 | 0.0689 | 0.1195 |
| 158.4569449 | 1228079.768 | 0.200087864 | 0.922746146 | 0.696586153 | 0.0689 | 0.119 |
| 158.7665893 | 1229583.145 | 0.201863742 | 0.921051151 | 0.692442016 | 0.0689 | 0.1192 |
| 159.0630505 | 1231019.775 | 0.203836638 | 0.920005351 | 0.688991945 | 0.0689 | 0.1198 |
| 159.3478025 | 1232397.51 | 0.20658366 | 0.919643572 | 0.684825614 | 0.0689 | 0.1204 |
| 159.6220574 | 1233722.794 | 0.209332454 | 0.919044196 | 0.681498317 | 0.0691 | 0.1213 |
| 159.8868389 | 1235001.05 | 0.212660037 | 0.916989344 | 0.680754183 | 0.0691 | 0.1218 |
| 160.1430043 | 1236236.819 | 0.216180378 | 0.915557755 | 0.680978396 | 0.0693 | 0.1221 |
| 160.3912901 | 1237433.949 | 0.220085145 | 0.915346404 | 0.680846905 | 0.0697 | 0.1222 |
| 160.6323258 | 1238595.636 | 0.224181407 | 0.914161904 | 0.681211515 | 0.07 | 0.1221 |
| 160.8666777 | 1239724.737 | 0.228660713 | 0.910044592 | 0.683808512 | 0.0702 | 0.1217 |
| 161.1744891 | 1241207.342 | 0.230023746 | 0.909727363 | 0.683623231 | 0.0705 | 0.121 |
| 161.3534369 | 1242069.108 | 0.230690531 | 0.909337549 | 0.683658 | 0.0707 | 0.1205 |
| 161.5551576 | 1243040.464 | 0.231919026 | 0.90856635 | 0.683873401 | 0.0708 | 0.12 |
| 161.7099756 | 1243785.942 | 0.232598193 | 0.907944203 | 0.684187549 | 0.071 | 0.1195 |
| 161.8405122 | 1244414.504 | 0.23329066 | 0.907294045 | 0.684545768 | 0.0711 | 0.1191 |
| 162.0595233 | 1245469.137 | 0.234698329 | 0.906044109 | 0.685393113 | 0.0713 | 0.1183 |
| 162.2441916 | 1246358.485 | 0.235741557 | 0.904892518 | 0.686591455 | 0.0715 | 0.1177 |
| 162.4068975 | 1247142.168 | 0.236796513 | 0.903815133 | 0.687618967 | 0.0715 | 0.1171 |
| 162.5540042 | 1247850.826 | 0.23785967 | 0.902737781 | 0.688726223 | 0.0717 | 0.1166 |
| 162.8152102 | 1249109.456 | 0.239620815 | 0.900866979 | 0.691007918 | 0.0719 | 0.1157 |
| 163.0453408 | 1250218.772 | 0.241397977 | 0.899142275 | 0.693454236 | 0.072 | 0.1149 |
| 163.2533885 | 1251222.052 | 0.242995334 | 0.89754162 | 0.695861969 | 0.0722 | 0.1144 |
| 163.444696 | 1252145.006 | 0.244601039 | 0.896103738 | 0.69835417 | 0.0724 | 0.1138 |
| 163.6227449 | 1253004.383 | 0.246213194 | 0.894732871 | 0.700836814 | 0.0726 | 0.1133 |
| 163.7899538 | 1253811.816 | 0.247639854 | 0.893589325 | 0.703231124 | 0.0727 | 0.1128 |
| 163.948084 | 1254575.775 | 0.249070857 | 0.892438804 | 0.705631167 | 0.0728 | 0.1124 |
| 164.3117091 | 1256334.02 | 0.252853446 | 0.890124321 | 0.711064337 | 0.0733 | 0.1115 |
| 164.6403143 | 1257924.96 | 0.256651241 | 0.888330669 | 0.715801436 | 0.0737 | 0.1107 |
| 164.9423571 | 1259389.219 | 0.260269724 | 0.887140731 | 0.719517834 | 0.0741 | 0.11 |
| 165.2233535 | 1260753.28 | 0.26389645 | 0.886316719 | 0.722542758 | 0.0746 | 0.1093 |
| 165.4871265 | 1262035.484 | 0.267529485 | 0.885444346 | 0.724793123 | 0.075 | 0.1085 |
| 165.7364695 | 1263249.228 | 0.271167439 | 0.884128719 | 0.726981834 | 0.0753 | 0.1079 |
| 166.1998241 | 1265509.475 | 0.278264691 | 0.88106389 | 0.731545901 | 0.076 | 0.1067 |
| 166.6254007 | 1267591.41 | 0.285751185 | 0.878243208 | 0.735615747 | 0.0766 | 0.1055 |
| 167.0210131 | 1269532.409 | 0.292865513 | 0.876344417 | 0.739027444 | 0.0772 | 0.1045 |
| 167.3920927 | 1271358.422 | 0.299984383 | 0.874636837 | 0.742263667 | 0.0778 | 0.1034 |
| 167.7425969 | 1273088.334 | 0.307483862 | 0.87268066 | 0.745804575 | 0.0784 | 0.1025 |
| 168.0755155 | 1274736.392 | 0.314418235 | 0.87086883 | 0.749302681 | 0.0789 | 0.1016 |
| 168.393182 | 1276313.709 | 0.321730827 | 0.869378678 | 0.75295432 | 0.0794 | 0.1006 |
| 168.6974281 | 1277828.987 | 0.328854794 | 0.868151569 | 0.755908281 | 0.0799 | 0.0997 |
| 168.9897638 | 1279289.397 | 0.335790002 | 0.866787557 | 0.758846185 | 0.0803 | 0.0988 |
| 169.271427 | 1280700.81 | 0.342724615 | 0.865545239 | 0.761780143 | 0.0807 | 0.0981 |


| 169.543453 | 1282068.129 | 0.34947021 | 0.86452283 | 0.764823483 | 0.0811 | 0.0973 |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 169.8067182 | 1283395.497 | 0.362793999 | 0.863198383 | 0.76790048 | 0.0814 | 0.0965 |
| 170.0619723 | 1284686.456 | 0.368218524 | 0.861678375 | 0.770503349 | 0.0816 | 0.0958 |
| 170.3098626 | 1285944.059 | 0.373831034 | 0.860782975 | 0.773289004 | 0.0818 | 0.095 |
| 170.5509527 | 1287170.959 | 0.379630994 | 0.861248176 | 0.775718502 | 0.0822 | 0.0943 |
| 170.8650236 | 1288775.07 | 0.381235496 | 0.859533645 | 0.777973436 | 0.0819 | 0.0941 |
| 171.0475967 | 1289710.679 | 0.382202387 | 0.858744066 | 0.779147339 | 0.0819 | 0.0939 |
| 171.2533928 | 1290768.125 | 0.383148487 | 0.858189338 | 0.78011013 | 0.0817 | 0.0938 |
| 171.411331 | 1291581.742 | 0.384135426 | 0.857853807 | 0.781040463 | 0.0816 | 0.0936 |
| 171.5444935 | 1292269.159 | 0.384768839 | 0.857678529 | 0.781683522 | 0.0815 | 0.0935 |
| 171.7679009 | 1293425.444 | 0.386072094 | 0.857593747 | 0.782473999 | 0.0814 | 0.0932 |
| 171.9562608 | 1294403.319 | 0.38721775 | 0.857634827 | 0.783153377 | 0.0813 | 0.093 |
| 172.1222191 | 1295267.21 | 0.388382148 | 0.857842629 | 0.783780664 | 0.0812 | 0.0929 |
| 172.2722619 | 1296050.153 | 0.389372791 | 0.858110246 | 0.784247548 | 0.0811 | 0.0927 |
| 172.5386714 | 1297444.86 | 0.391008275 | 0.858784233 | 0.78506317 | 0.0828 | 0.0923 |
| 172.7733773 | 1298678.526 | 0.392856689 | 0.85949277 | 0.785611546 | 0.0825 | 0.0921 |
| 172.9855546 | 1299797.858 | 0.394350008 | 0.860303884 | 0.78590517 | 0.0824 | 0.0917 |
| 173.1806547 | 1300830.597 | 0.395857191 | 0.861091504 | 0.786562166 | 0.0822 | 0.0916 |
| 173.3622297 | 1301794.816 | 0.39718873 | 0.861915038 | 0.786839688 | 0.0821 | 0.0912 |
| 173.5327475 | 1302703.065 | 0.398715547 | 0.862706635 | 0.787047362 | 0.0819 | 0.091 |
| 173.6940048 | 1303564.481 | 0.400063235 | 0.863550458 | 0.787381892 | 0.0818 | 0.0908 |
| 174.064815 | 1305554.708 | 0.403271471 | 0.86538348 | 0.788267738 | 0.0814 | 0.0903 |
| 174.3999093 | 1307364.842 | 0.406321106 | 0.867122824 | 0.788898843 | 0.081 | 0.0899 |
| 174.7079159 | 1309038.688 | 0.409205273 | 0.868606994 | 0.789970181 | 0.0807 | 0.0895 |
| 174.9944581 | 1310604.775 | 0.412291224 | 0.869847126 | 0.790756922 | 0.0803 | 0.0892 |
| 175.2634434 | 1312082.911 | 0.415018298 | 0.870995638 | 0.791946666 | 0.0799 | 0.0889 |
| 175.5177177 | 1313487.513 | 0.417755957 | 0.8720196 | 0.792813106 | 0.0796 | 0.0886 |
| 175.9902504 | 1316117.195 | 0.42325633 | 0.874053159 | 0.794677429 | 0.0788 | 0.0881 |
| 176.4242795 | 1318555.627 | 0.428597126 | 0.87605062 | 0.796115536 | 0.0781 | 0.0876 |
| 176.8277741 | 1320843.046 | 0.43377243 | 0.878191416 | 0.797066019 | 0.0773 | 0.0871 |
| 177.2062735 | 1323007.371 | 0.438963198 | 0.880265513 | 0.798285194 | 0.0767 | 0.0866 |
| 177.5638133 | 1325068.914 | 0.444166249 | 0.882306507 | 0.799526408 | 0.076 | 0.0862 |
| 177.9034421 | 1327042.994 | 0.449194597 | 0.884294063 | 0.800842462 | 0.0753 | 0.0859 |
| 178.2275298 | 1328941.499 | 0.454231318 | 0.88642521 | 0.801842491 | 0.0746 | 0.0855 |
| 178.5379625 | 1330773.877 | 0.459274984 | 0.888455112 | 0.802720482 | 0.074 | 0.0852 |
| 178.8362703 | 1332547.777 | 0.464324457 | 0.890492157 | 0.803705033 | 0.0733 | 0.0848 |
| 179.1237151 | 1334269.5 | 0.469378811 | 0.892470091 | 0.804863324 | 0.0726 | 0.0846 |
| 179.4013521 | 1335944.059 | 0.474253256 | 0.894493168 | 0.805557079 | 0.072 | 0.0842 |
| 179.6700747 | 1337574.974 | 0.479131404 | 0.895830091 | 0.807170839 | 0.0713 | 0.084 |
| 179.9306468 | 1339165.139 | 0.472431704 | 0.896810337 | 0.80860409 | 0.0706 | 0.0839 |
| 180.1837281 | 1340717.073 | 0.475668408 | 0.898704794 | 0.809603813 | 0.07 | 0.0836 |
| 180.4298719 | 1342232.859 | 0.479092621 | 0.90181078 | 0.809002121 | 0.0695 | 0.0831 |
| 180.7504519 | 1344215.395 | 0.479134446 | 0.902600923 | 0.809456182 | 0.0692 | 0.0833 |
| 180.9367652 | 1345371.415 | 0.479129177 | 0.903156965 | 0.809443887 | 0.0691 | 0.0833 |
| 181.1467395 | 1346677.164 | 0.479100161 | 0.903731078 | 0.809452484 | 0.0688 | 0.0833 |
| 181.3078575 | 1347680.941 | 0.478937415 | 0.904192039 | 0.809274673 | 0.0687 | 0.0834 |
| 181.4436834 | 1348528.237 | 0.478983638 | 0.904477685 | 0.809086597 | 0.0685 | 0.0835 |
| 181.6715233 | 1349951.431 | 0.478937242 | 0.905106113 | 0.808977161 | 0.0684 | 0.0836 |
| 181.8635859 | 1351152.657 | 0.478927107 | 0.905672878 | 0.808558112 | 0.0682 | 0.0836 |
| 182.032781 | 1352211.728 | 0.478940123 | 0.906072457 | 0.808106299 | 0.068 | 0.0835 |
| 182.18573 | 1353169.608 | 0.478786614 | 0.906523884 | 0.807734368 | 0.0679 | 0.0836 |
| 182.4572529 | 1354870.722 | 0.478514614 | 0.907212471 | 0.807066904 | 0.0676 | 0.0836 |
| 182.6964153 | 1356369.127 | 0.478275579 | 0.90781118 | 0.806382999 | 0.0674 | 0.0836 |
| 182.9125834 | 1357722.922 | 0.478059965 | 0.908357551 | 0.805594872 | 0.0672 | 0.0837 |
| 183.1113217 | 1358966.67 | 0.477862102 | 0.908832884 | 0.8049717 | 0.0669 | 0.0837 |
| 183.2962564 | 1360122.92 | 0.477678298 | 0.909251528 | 0.804478638 | 0.0667 | 0.0838 |
| 183.4699065 | 1361207.357 | 0.477505984 | 0.909665015 | 0.803771994 | 0.0665 | 0.0838 |
| 183.6341062 | 1362231.418 | 0.477343294 | 0.909918799 | 0.803227834 | 0.0663 | 0.0839 |
| 184.0116108 | 1364579.569 | 0.476605641 | 0.910697264 | 0.801714281 | 0.0659 | 0.0838 |
| 184.3526715 | 1366691.766 | 0.475905598 | 0.911363769 | 0.800228022 | 0.0656 | 0.084 |
| 184.666095 | 1368623.26 | 0.475416141 | 0.911788782 | 0.799074921 | 0.0652 | 0.0841 |
| 184.9576208 | 1370410.179 | 0.474585341 | 0.9121172 | 0.798126794 | 0.0648 | 0.0842 |
| 185.2312371 | 1372077.704 | 0.473955136 | 0.912533115 | 0.796961216 | 0.0645 | 0.0843 |


| 185.4898482 | 1373644.235 | 0.473158824 | 0.91308978 | 0.796105777 | 0.0642 | 0.0844 |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 185.9703391 | 1376527.002 | 0.471605002 | 0.914423494 | 0.794522936 | 0.0636 | 0.0847 |
| 186.4115673 | 1379138.107 | 0.470092833 | 0.91589092 | 0.792856211 | 0.0632 | 0.085 |
| 186.8216649 | 1381529.81 | 0.434546032 | 0.917017141 | 0.791315523 | 0.0628 | 0.0852 |
| 187.206284 | 1383738.682 | 0.435655908 | 0.91794933 | 0.789780892 | 0.0623 | 0.0855 |
| 187.569542 | 1385791.547 | 0.436964448 | 0.919049377 | 0.788311593 | 0.0619 | 0.0858 |
| 187.9145491 | 1387708.812 | 0.438287732 | 0.919940397 | 0.787084883 | 0.0615 | 0.0861 |
| 188.2437231 | 1389506.449 | 0.439623662 | 0.920854077 | 0.785418954 | 0.0611 | 0.0864 |
| 188.5589878 | 1391197.262 | 0.440790001 | 0.921661262 | 0.784186687 | 0.0607 | 0.0866 |
| 188.861904 | 1392791.711 | 0.441966202 | 0.922594933 | 0.782719509 | 0.0604 | 0.0869 |
| 189.1537588 | 1394298.489 | 0.443331515 | 0.923346552 | 0.781433542 | 0.0601 | 0.0872 |
| 189.4356282 | 1395724.917 | 0.444524183 | 0.924101198 | 0.779966025 | 0.0598 | 0.0874 |
| 189.7084233 | 1397077.239 | 0.445904054 | 0.924721193 | 0.779166829 | 0.0595 | 0.0879 |
| 189.9729232 | 1398360.837 | 0.44711004 | 0.925303552 | 0.778452445 | 0.0592 | 0.0882 |
| 190.2298005 | 1399580.393 | 0.448321828 | 0.926085002 | 0.777194464 | 0.0588 | 0.0885 |
| 190.4796406 | 1400740.017 | 0.44953892 | 0.927077294 | 0.774633641 | 0.0587 | 0.0887 |
| 190.8056329 | 1402212.842 | 0.44906926 | 0.926801857 | 0.775194724 | 0.0587 | 0.089 |
| 190.9950928 | 1403048.448 | 0.448541814 | 0.926541359 | 0.775332502 | 0.0587 | 0.089 |
| 191.2086151 | 1403972.955 | 0.447993657 | 0.926229755 | 0.775447792 | 0.0588 | 0.0893 |
| 191.372457 | 1404670.389 | 0.447669487 | 0.925933475 | 0.775301695 | 0.0588 | 0.0893 |
| 191.5105806 | 1405250.525 | 0.447368271 | 0.925699559 | 0.775136377 | 0.0589 | 0.0894 |
| 191.7422776 | 1406208.153 | 0.446805657 | 0.925277865 | 0.774733912 | 0.0589 | 0.0896 |
| 191.9375952 | 1407000.865 | 0.446454992 | 0.924809743 | 0.774219865 | 0.059 | 0.0897 |
| 192.1096608 | 1407688.627 | 0.445766454 | 0.924512029 | 0.773615198 | 0.059 | 0.0897 |
| 192.2652073 | 1408302.152 | 0.44527215 | 0.924123881 | 0.773220596 | 0.0591 | 0.0898 |
| 192.5413485 | 1409373.007 | 0.444673397 | 0.923282803 | 0.772318246 | 0.0592 | 0.0899 |
| 192.784587 | 1410297.876 | 0.443925026 | 0.922626384 | 0.7711724 | 0.0592 | 0.0899 |
| 193.0044467 | 1411119.949 | 0.443376782 | 0.921816987 | 0.770337599 | 0.0593 | 0.09 |
| 193.2065858 | 1411864.813 | 0.442665541 | 0.921111785 | 0.769391619 | 0.0594 | 0.0901 |
| 193.3946914 | 1412549.097 | 0.442145935 | 0.920422416 | 0.768584719 | 0.0595 | 0.0901 |
| 193.5713246 | 1413184.319 | 0.441636682 | 0.919720624 | 0.767902945 | 0.0595 | 0.0902 |
| 193.7383506 | 1413778.842 | 0.440957375 | 0.919032859 | 0.767069402 | 0.0595 | 0.0902 |
| 194.1223749 | 1415125.029 | 0.439736526 | 0.917283291 | 0.765597236 | 0.0597 | 0.0904 |
| 194.4693542 | 1416319.384 | 0.438370919 | 0.915562565 | 0.764258665 | 0.0597 | 0.0905 |
| 194.7882424 | 1417401.487 | 0.437388004 | 0.913907204 | 0.762946877 | 0.0599 | 0.0907 |
| 195.0848751 | 1418396.942 | 0.416101623 | 0.912162295 | 0.762155029 | 0.06 | 0.0908 |
| 195.3633068 | 1419323.405 | 0.413384646 | 0.910595705 | 0.761477304 | 0.0601 | 0.091 |
| 195.6264901 | 1420193.634 | 0.411039029 | 0.909305547 | 0.760838305 | 0.0602 | 0.0911 |
| 196.1155338 | 1421801.448 | 0.406384577 | 0.907237696 | 0.75949275 | 0.0606 | 0.0915 |
| 196.5646866 | 1423274.187 | 0.402125706 | 0.905466175 | 0.757974751 | 0.061 | 0.0916 |
| 196.982215 | 1424646.354 | 0.397898701 | 0.903427146 | 0.756927972 | 0.0613 | 0.0919 |
| 197.3738641 | 1425941.527 | 0.394053287 | 0.901412057 | 0.755693557 | 0.0616 | 0.092 |
| 197.7438187 | 1427176.587 | 0.390407461 | 0.899417974 | 0.754698322 | 0.0619 | 0.0923 |
| 198.0952401 | 1428364.059 | 0.386957957 | 0.897538742 | 0.75386453 | 0.0622 | 0.0925 |
| 198.4305853 | 1429513.505 | 0.383702171 | 0.895709914 | 0.752736193 | 0.0625 | 0.0926 |
| 198.7518093 | 1430632.392 | 0.380637983 | 0.893784237 | 0.752048951 | 0.0628 | 0.0929 |
| 199.0604982 | 1431726.66 | 0.377763626 | 0.891955709 | 0.751239289 | 0.0631 | 0.093 |
| 199.3579597 | 1432801.115 | 0.374900765 | 0.890330724 | 0.750246058 | 0.0634 | 0.0931 |
| 199.6452874 | 1433859.694 | 0.372048404 | 0.888493302 | 0.749475862 | 0.0638 | 0.0932 |
| 199.9234066 | 1434905.66 | 0.369735653 | 0.8874291 | 0.748907562 | 0.0641 | 0.0933 |
| 200.193109 | 1435941.749 | 0.36707816 | 0.886681007 | 0.748512641 | 0.0645 | 0.0935 |
| 200.4550778 | 1436970.264 | 0.364781745 | 0.884992349 | 0.74797943 | 0.0648 | 0.0936 |
| 200.7099079 | 1437992.531 | 0.362668965 | 0.881613611 | 0.746782125 | 0.065 | 0.0935 |
| 201.0412353 | 1439352.833 | 0.360683629 | 0.883123238 | 0.745405108 | 0.0656 | 0.0932 |
| 201.2338098 | 1440159.065 | 0.359497886 | 0.883544696 | 0.744929023 | 0.0658 | 0.093 |
| 201.450855 | 1441080.992 | 0.357944609 | 0.883697428 | 0.744532254 | 0.0661 | 0.0929 |
| 201.6174097 | 1441797.694 | 0.356778079 | 0.883579741 | 0.74418003 | 0.0662 | 0.0927 |
| 201.7578268 | 1442407.984 | 0.355981571 | 0.883397913 | 0.744152947 | 0.0664 | 0.0927 |
| 201.9933852 | 1443443.872 | 0.354419468 | 0.882835959 | 0.743872347 | 0.0666 | 0.0925 |
| 202.1919719 | 1444328.56 | 0.352882836 | 0.882052216 | 0.74402597 | 0.0668 | 0.0924 |
| 202.3669284 | 1445116.303 | 0.351714384 | 0.881246297 | 0.744032259 | 0.0669 | 0.0923 |
| 202.5250972 | 1445834.956 | 0.350557555 | 0.880380773 | 0.744115108 | 0.067 | 0.0922 |
| 202.8059157 | 1447125.487 | 0.348444466 | 0.878639741 | 0.744612941 | 0.0673 | 0.092 |


| 203.0532981 | 1448277.146 | 0.346354923 | 0.876934776 | 0.744963417 | 0.0674 | 0.0919 |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 203.2769232 | 1449329.505 | 0.344633487 | 0.875182688 | 0.745407626 | 0.0675 | 0.0919 |
| 203.4825413 | 1450306.122 | 0.343100342 | 0.873473579 | 0.746112702 | 0.0676 | 0.0917 |
| 203.6738994 | 1451222.38 | 0.341577326 | 0.871930789 | 0.746546863 | 0.0678 | 0.0916 |
| 203.8536004 | 1452088.985 | 0.340062675 | 0.870365754 | 0.747028186 | 0.0678 | 0.0916 |
| 204.0235397 | 1452913.75 | 0.338730429 | 0.868964172 | 0.747453476 | 0.0679 | 0.0915 |
| 204.4143089 | 1454828.266 | 0.335336848 | 0.865619002 | 0.74876957 | 0.0681 | 0.0913 |
| 204.7674405 | 1456578.018 | 0.332321236 | 0.862730378 | 0.749723954 | 0.0684 | 0.0911 |
| 205.0920333 | 1458200.885 | 0.329501738 | 0.860284952 | 0.750756334 | 0.0686 | 0.0909 |
| 205.3940173 | 1459721.677 | 0.326874004 | 0.858253487 | 0.751387053 | 0.0688 | 0.0907 |
| 205.6775124 | 1461157.72 | 0.324434938 | 0.856494755 | 0.752151396 | 0.0691 | 0.0905 |
| 205.9455189 | 1462521.693 | 0.322182229 | 0.854927316 | 0.752607182 | 0.0695 | 0.0902 |
| 206.4436234 | 1465069.813 | 0.317530821 | 0.85209287 | 0.753680041 | 0.07 | 0.0897 |
| 206.9012152 | 1467421.121 | 0.3136086 | 0.84945679 | 0.754742705 | 0.0705 | 0.0893 |
| 207.3266931 | 1469611.89 | 0.309885268 | 0.846903326 | 0.755849847 | 0.071 | 0.0888 |
| 207.7258937 | 1471667.582 | 0.306356445 | 0.844453511 | 0.756980534 | 0.0715 | 0.0883 |
| 208.1030687 | 1473606.932 | 0.303018854 | 0.842116814 | 0.758379201 | 0.072 | 0.088 |
| 208.4614293 | 1475444.233 | 0.300043886 | 0.839857292 | 0.759302447 | 0.0725 | 0.0875 |
| 208.8034715 | 1477190.709 | 0.297255357 | 0.837645992 | 0.760537391 | 0.0729 | 0.0871 |
| 209.1311812 | 1478855.379 | 0.294477881 | 0.835495194 | 0.761823857 | 0.0734 | 0.0867 |
| 209.4461693 | 1480445.635 | 0.292057638 | 0.833509472 | 0.762822254 | 0.0738 | 0.0863 |
| 209.749764 | 1481967.635 | 0.289646075 | 0.831557687 | 0.763892474 | 0.0742 | 0.0859 |
| 210.043076 | 1483426.581 | 0.287589358 | 0.829519038 | 0.765407697 | 0.0747 | 0.0855 |
| 210.327045 | 1484826.921 | 0.285366228 | 0.828158749 | 0.765957561 | 0.0751 | 0.085 |
| 210.6024751 | 1486172.498 | 0.283496264 | 0.827196317 | 0.766558466 | 0.0756 | 0.0845 |
| 210.87006 | 1487466.666 | 0.281632104 | 0.82551839 | 0.767574806 | 0.076 | 0.0841 |
| 211.1304037 | 1488712.52 | 0.279946479 | 0.822233904 | 0.770094076 | 0.0762 | 0.0839 |
| 211.4668867 | 1490303.248 | 0.278225775 | 0.822762985 | 0.770443413 | 0.0765 | 0.0836 |
| 211.6624321 | 1491217.781 | 0.277266663 | 0.822830326 | 0.770855214 | 0.0766 | 0.0834 |
| 211.8828037 | 1492239.844 | 0.275950611 | 0.822674721 | 0.77137957 | 0.0768 | 0.0833 |
| 212.0518956 | 1493018 | 0.275005698 | 0.822490309 | 0.771693203 | 0.0769 | 0.0832 |
| 212.1944415 | 1493669.948 | 0.274246764 | 0.822251424 | 0.77193372 | 0.0769 | 0.0831 |
| 212.4335503 | 1494755.341 | 0.272924495 | 0.821683894 | 0.77228748 | 0.077 | 0.0828 |
| 212.6351106 | 1495662.434 | 0.271793669 | 0.821100411 | 0.772779983 | 0.077 | 0.0826 |
| 212.8126722 | 1496455.667 | 0.270674882 | 0.820555896 | 0.773135202 | 0.0771 | 0.0826 |
| 212.9731846 | 1497168.083 | 0.269737315 | 0.819985035 | 0.773443153 | 0.0771 | 0.0824 |
| 213.2581379 | 1498422.116 | 0.268225444 | 0.818925196 | 0.774132603 | 0.0773 | 0.0822 |
| 213.5091356 | 1499515.603 | 0.266730723 | 0.817904746 | 0.774655961 | 0.0773 | 0.082 |
| 213.7360077 | 1500495.227 | 0.265420706 | 0.816992552 | 0.775287609 | 0.0774 | 0.0817 |
| 213.9445941 | 1501388.706 | 0.264120057 | 0.81614601 | 0.775796151 | 0.0774 | 0.0816 |
| 214.1387001 | 1502214.094 | 0.262999145 | 0.815370633 | 0.776191048 | 0.0774 | 0.0814 |
| 214.3209694 | 1502983.923 | 0.261884332 | 0.814720888 | 0.776730209 | 0.0775 | 0.0812 |
| 214.4933266 | 1503707.316 | 0.260946805 | 0.814147437 | 0.777168413 | 0.0775 | 0.0811 |
| 214.8896173 | 1505354.131 | 0.258534832 | 0.812937385 | 0.778108208 | 0.0777 | 0.0807 |
| 215.2476946 | 1506823.071 | 0.256314897 | 0.812152749 | 0.779152131 | 0.0762 | 0.0803 |
| 215.5767984 | 1508157.801 | 0.25428216 | 0.811846919 | 0.779662133 | 0.0763 | 0.08 |
| 215.8829506 | 1509386.738 | 0.252433385 | 0.811816449 | 0.780470189 | 0.0764 | 0.0797 |
| 216.1703346 | 1510529.597 | 0.250766259 | 0.811810498 | 0.781225227 | 0.0766 | 0.0794 |
| 216.4419973 | 1511600.713 | 0.249279049 | 0.811554974 | 0.781903927 | 0.0766 | 0.0791 |
| 216.9468479 | 1513568.537 | 0.246325 | 0.810548116 | 0.78343063 | 0.0766 | 0.0786 |
| 217.4105846 | 1515351.561 | 0.243735709 | 0.809683779 | 0.785112901 | 0.0767 | 0.0781 |
| 217.8417351 | 1516989.655 | 0.241506241 | 0.80926346 | 0.786311795 | 0.0766 | 0.0777 |
| 218.2462253 | 1518510.441 | 0.239461964 | 0.809019262 | 0.78762803 | 0.0767 | 0.0773 |
| 218.6283716 | 1519933.976 | 0.237429529 | 0.808736638 | 0.788964648 | 0.0766 | 0.0768 |
| 218.9914338 | 1521275.359 | 0.235749029 | 0.808619701 | 0.790086832 | 0.0766 | 0.0764 |
| 219.3379459 | 1522546.289 | 0.234247913 | 0.808553741 | 0.791444357 | 0.0764 | 0.076 |
| 219.6699237 | 1523756.042 | 0.232924941 | 0.808696148 | 0.792515619 | 0.0763 | 0.0756 |
| 219.9890022 | 1524912.117 | 0.231779072 | 0.808787201 | 0.79392152 | 0.0762 | 0.0752 |
| 220.2965296 | 1526020.677 | 0.230638954 | 0.808938107 | 0.794843458 | 0.0761 | 0.0748 |
| 220.5936331 | 1527086.857 | 0.229504069 | 0.809136583 | 0.796316467 | 0.0759 | 0.0745 |
| 220.8812666 | 1528114.986 | 0.22871458 | 0.808951259 | 0.7963938 | 0.0757 | 0.074 |
| 221.1602459 | 1529108.753 | 0.227758971 | 0.808442263 | 0.796019496 | 0.0753 | 0.0734 |
| 221.4312749 | 1530071.332 | 0.227147599 | 0.808722426 | 0.797071284 | 0.0751 | 0.073 |


| 221.6949668 | 1531005.475 | 0.226539596 | 0.810777768 | 0.80058164 | 0.075 | 0.0731 |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 222.0363257 | 1532211.807 | 0.225563686 | 0.80909444 | 0.803076194 | 0.0746 | 0.0734 |
| 222.2346894 | 1532911.532 | 0.224981108 | 0.808463053 | 0.804337379 | 0.0744 | 0.0736 |
| 222.4582242 | 1533699.139 | 0.224389791 | 0.807912677 | 0.805571935 | 0.0742 | 0.0737 |
| 222.6297342 | 1534302.908 | 0.223817871 | 0.807601386 | 0.806274752 | 0.074 | 0.0738 |
| 222.7743125 | 1534811.583 | 0.223256061 | 0.807514442 | 0.806586893 | 0.0739 | 0.0739 |
| 223.0168189 | 1535664.372 | 0.222659232 | 0.807464075 | 0.807198133 | 0.0737 | 0.0739 |
| 223.2212321 | 1536382.95 | 0.222076639 | 0.807586436 | 0.807424255 | 0.0735 | 0.0739 |
| 223.4012987 | 1537015.881 | 0.221503204 | 0.807811077 | 0.80741402 | 0.0734 | 0.0739 |
| 223.5640694 | 1537588.059 | 0.221105878 | 0.808117365 | 0.807585157 | 0.0733 | 0.0739 |
| 223.8530172 | 1538604.134 | 0.220155477 | 0.808872328 | 0.807228707 | 0.0731 | 0.0737 |
| 224.107519 | 1539499.754 | 0.219387644 | 0.809612655 | 0.806721168 | 0.073 | 0.0736 |
| 224.3375472 | 1540310.056 | 0.21862913 | 0.810430083 | 0.806367924 | 0.0728 | 0.0735 |
| 224.5490265 | 1541055.894 | 0.218047031 | 0.811211876 | 0.805605017 | 0.0727 | 0.0733 |
| 224.7458174 | 1541750.843 | 0.217470511 | 0.812029717 | 0.805091062 | 0.0726 | 0.0732 |
| 224.9306016 | 1542404.324 | 0.217067769 | 0.812810426 | 0.804200232 | 0.0725 | 0.073 |
| 225.1053318 | 1543023.19 | 0.216499659 | 0.813603142 | 0.803608102 | 0.0725 | 0.0729 |
| 225.5070604 | 1544450.064 | 0.215346556 | 0.815278719 | 0.802295179 | 0.0722 | 0.0726 |
| 225.8700312 | 1545744.916 | 0.214377316 | 0.816746669 | 0.800657317 | 0.072 | 0.0723 |
| 226.2036176 | 1546940.472 | 0.213588194 | 0.817980681 | 0.799486718 | 0.0717 | 0.072 |
| 226.513928 | 1548058.006 | 0.212976686 | 0.818914607 | 0.798518556 | 0.0714 | 0.0718 |
| 226.8052062 | 1549112.26 | 0.212372316 | 0.819651855 | 0.798020476 | 0.0712 | 0.0716 |
| 227.0805427 | 1550113.94 | 0.211773961 | 0.820313138 | 0.797877864 | 0.0709 | 0.0715 |
| 227.5922044 | 1551990.019 | 0.210929027 | 0.821634254 | 0.79810343 | 0.0704 | 0.0714 |
| 228.0621828 | 1553731.938 | 0.210267936 | 0.822884036 | 0.798170052 | 0.0699 | 0.0714 |
| 228.4991272 | 1555369.321 | 0.209955451 | 0.824150197 | 0.798396597 | 0.0695 | 0.0713 |
| 228.9090478 | 1556922.643 | 0.209652521 | 0.825401578 | 0.79811932 | 0.0691 | 0.0711 |
| 229.2963221 | 1558406.735 | 0.209693657 | 0.82663977 | 0.798090119 | 0.0687 | 0.071 |
| 229.6642564 | 1559832.738 | 0.209909194 | 0.827822154 | 0.79837102 | 0.0682 | 0.0709 |
| 230.01542 | 1561209.261 | 0.210465819 | 0.829048126 | 0.798145518 | 0.0678 | 0.0707 |
| 230.3518572 | 1562543.116 | 0.210859077 | 0.83019432 | 0.798279689 | 0.0674 | 0.0707 |
| 230.6752259 | 1563839.796 | 0.211591682 | 0.831347999 | 0.797963038 | 0.067 | 0.0705 |
| 230.9868932 | 1565103.804 | 0.21249512 | 0.832528593 | 0.798288167 | 0.0666 | 0.0705 |
| 231.288002 | 1566338.885 | 0.213736307 | 0.833662312 | 0.798229811 | 0.0662 | 0.0704 |
| 231.5795192 | 1567548.186 | 0.214979642 | 0.834826996 | 0.798087084 | 0.0659 | 0.0703 |
| 231.8622721 | 1568734.385 | 0.216559606 | 0.835940043 | 0.797942983 | 0.0655 | 0.0701 |
| 232.1369743 | 1569899.78 | 0.218141003 | 0.837076522 | 0.798101014 | 0.0651 | 0.0701 |
| 232.4042473 | 1571046.358 | 0.21989089 | 0.838182625 | 0.798246154 | 0.0647 | 0.07 |

## Appendix B: Additional in-beam PET experiments

This appendix reports the analysis results of the other experimental acquisitions presented in table 8.1. These acquisitions come from the first experimental session performed using the detector INSIDE with ${ }^{12} \mathrm{C}$ beams to which the author participated in person. This means that some runs were performed to prove that INSIDE system was able to acquire a useful signal and to reconstruct PET images from ${ }^{12} \mathrm{C}$ ion beams. The following scenarios are quite different from Run1, analysed in chapter 8. In particular, they differ for energy, current, irradiation and acquisition time as well as for type of phantom. In some conditions phantoms irradiated in previous runs were used.

Table B. 1 summarizes the pre-irradiation background noise for each run, with and without filter in energy spectrum, and the total number of collected coincidences at the end of irradiation.

Table B.1: Experimental runs: background and total coincidences

|  | BKG | BKG noise wo filter in Energy |  | BKG with filter in Energy |  | Total |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | bins (0.1s) | Coinc | Coinc/bin | Coinc | Coinc/bin | coincidences |
| Run1 | 148 | 772 | 5.22 | 186 | 1.26 | 21548 |
| run 2 | 272 | 1359 | 5 | 316 | 1.16 | 541978 |
| run 3 | 193 | 1002 | 5.19 | 253 | 1.31 | 71450 |
| run 4 | 142 | 611 | 4.3 | 183 | 1.28 | 38684 |
| run 5 | 200 | 1026 | 5.13 | 351 | 1.7 | 44753 |
| run 6 | 203 | 871 | 4.2 | 272 | 1.34 | 381372 |
|  |  |  |  |  |  |  |

In the following sections, for each experiment, the figures and profiles along $z$ direction at four times after the irradiation are shown. The used reference system is the one of the detector, as described in figure 7.5.

## B. 1 Other experimental runs

## B.1.1 Second acquisition boro8: run 2

Run 2 consists in irradiating the target with $3 \cdot 10^{8}{ }^{12} \mathrm{C}$ at $399 \mathrm{MeV} / \mathrm{u}$ distributed in 6 spills. As shown in figure B.1, they correspond to 22 s of irradiation, of which 10 s when the beam is on.


Figure B.1: Experiment 2. PET coincidences event rate. Top: total coincidence event rate during the spills and interspills (IS) time. Bottom: coincidence event rate during the first two interspills. The inspill component is suppressed.

The irradiation is followed by an offline acquisition time 268 s long. For the reasons explained in chapter 7 the signal acquired during the spills (when the beam is on) is not considered to reconstruct the PET images. For this long run, as well as for the experiment number 6, the shown images were reconstructed collecting the PET signal in the interspill periods, indicated
in figure B.2. The position of the activity peak, shown in figures B. 2 and B.3, is compatible with the expected BP position of 22.3 cm in PMMA for a beam $399 \mathrm{MeV} / \mathrm{u}$. (Corresponding to $\mathrm{z}=15.6 \mathrm{~cm}$ in the detector reference system).


Figure B.2: Experiment 2. PET Coincidences 2D maps reconstructed, during the beam-off time, respectively after $1,2,3$ spills, in the interspill ( $I S$ ) beam pauses. The bottom - right image shows the total interspill acquisition ( 5 interspills) plus an offline time of 268 s after irradiation.

Table B.2: Experiment 2. Look-Up Table (LUT) indicating the intensity in the point P of the images in figure B.2.

| IS | $\mathbf{1}$ | 2 | 3 | 5ISs $+268 s$ |
| ---: | :---: | :---: | :---: | :---: |
| $\mathbf{I}(\mathbf{a} . \mathbf{u})$ in $\mathbf{P}$ | 0.13 | 1.73 | 5.20 | 2665 |



Figure B.3: Experiment 2. 1D profile along z axis reconstructed during the beam-off time, respectively after $1,2,3$ spills and total ( 5 interspills plus an offline time of 268 s ), with the application of the median filter. The origin of the target is positioned at $z=-6.7 \mathrm{~cm}$. The BP position is expected at $z=15.6 \mathrm{~cm}$.

## B.1.2 Third acquisition boro8: run 3

In this scenario, the same setup as experiment 2 was maintained but already irradiated phantoms were used. In details, the 20 cm phantom was the one used in the Run1.


Figure B.4: Experiment 3. PET Coincidences 2D maps reconstructed, during the beam-off time, in $2,5,15,317 \mathrm{~s}$ with the application of the median filter. The contribution from a previous irradiation can be observed.

Table B.3: Experiment 3. LUT indicating the intensity in the point P of the images in figure B. 4 .

| $\mathrm{t}(\mathrm{s})$ | 2 | 5 | 15 | 317 |
| ---: | :---: | :---: | :---: | :---: |
| $\mathrm{I}(\mathrm{a} . \mathrm{u})$ in P | 0.0002 | 0.08 | 0.86 | 44.28 |



Figure B.5: Experiment 3. 1D profile along z axis reconstructed at 2, $5,15 \mathrm{~s}$ from the end of 1 s of irradiation with $3 \cdot 10^{7}$ at $399 \mathrm{MeV} / \mathrm{u}$.

The peak at 6 cm in figure B.5 is compatible with the residual activity of the phantom used in Run1.

The $z$ - profile extracted before this run, when the beam is off, presented in figure B.6, clarifies this statement.

Image profile along $z$ axis


Figure B.6: Experiment 3: 1D profile along z axis reconstructed before the irradiation at 399 $\mathrm{MeV} / \mathrm{u}$.

## B.1.3 Fourth acquisition boro8: run 4

In this experiment a squared field of $3 \mathrm{x} 3 \mathrm{~cm}^{2}$ inside the PMMA target was irradiated with $4.5 \cdot 10^{7}{ }^{12} \mathrm{C}$ ions at $300 \mathrm{MeV} / \mathrm{u}$.


Figure B.7: Experiment 4. PET Coincidences 2D maps reconstructed, during the beam-off time, in $2,5,15,238 \mathrm{~s}$, with the application of the median filter-experiment $4-2 \mathrm{D}$ images reconstructed after $2,5,15,238 \mathrm{~s}$ from the end of 1 s of irradiation with $4.5 \cdot 10^{7}$ at $300 \mathrm{MeV} / \mathrm{u}$, the contribution of the target fragments are visible.

Table B.4: Experiment 4. LUT indicating the intensity in the point P of the images in figure B. 7

| $\mathbf{t}(\mathbf{s})$ | 2 | 5 | 15 | 317 |
| ---: | :---: | :---: | :---: | :---: |
| $\mathbf{I}(\mathbf{a} . \mathbf{u})$ in $\mathbf{P}$ | 0.02 | 0.19 | 0.57 | $2.53 \mathrm{E}+4$ |



Figure B.8: Experiment 4. 1D profiles along z axis reconstructed after 2, 5, 15, 238 s from the end of 1 s of irradiation with $4.5 \cdot 10^{7}$ at $300 \mathrm{MeV} / \mathrm{u}$. The contribution of the target fragments are visible. The z-axis limits correspond to the detector geometry (FOV). The phantom (total z length $=26 \mathrm{~cm}$ ) is positioned with its origin in correspondence of $\mathrm{z}=-2.3 \mathrm{~cm}$. Expected position of the Bragg Peak is at $\mathrm{z}=12.7 \mathrm{~cm}$ ( 15 cm in the PMMA phantom).

## B.1.4 Fifth acquisition boro8: run 5

Experiment 5 used the same phantoms of run 4 but the energy of the ${ }^{12} C$ beam was $350 \mathrm{MeV} / \mathrm{u}$.


Figure B.9: Experiment 5: PET Coincidences 2D maps reconstructed, during the beam-off time, in $2,5,15,164 \mathrm{~s}$, with the application of the median filter.

Although the residual activity peak of run 4 is evident, the activity peak at 17 cm is compatible with the expected BP position of the $350 \mathrm{MeV} / \mathrm{u}$.

Table B.5: Experiment 5. LUT indicating the intensity in the point P of the images in figure B. 9 .

| $\mathrm{t}(\mathrm{s})$ | $\mathbf{2}$ | $\mathbf{5}$ | $\mathbf{1 5}$ | $\mathbf{1 6 4}$ |
| ---: | :---: | :---: | :---: | :---: |
| $\mathrm{I}(\mathrm{a} . \mathbf{u})$ in P | 0.0002 | 0.025 | 0.22 | 7.70 |



Figure B.10: Experiment 5. 1D profiles along $z$ axis reconstructed after 2, 5, 15, 164 s from the end of irradiation; the pre-irradiation profile is also shown. The inset reports the intensity profiles in log scale.

## B.1.5 Sixth acquisition boro8: run 6

Run 6 consists in irradiating a PMMA target of $15 \times 15 \times 30 \mathrm{~cm}^{3}$ in a field of $2 \times 2 \mathrm{~cm}^{2}$ with $2 \cdot 10^{10}{ }^{12} \mathrm{C}$ at $400 \mathrm{MeV} / \mathrm{u}$ distributed in 7 spills. This run has been used in chapter 7 to describe the data acquisition and analysis system of INSIDE.


Figure B.11: Experiment 6. PET Coincidences 2D maps.


Figure B.12: Experiment 6: 1D profiles along $z$ axis.

## Bibliography

[1] Cuccagna C, Bencini V, Benedetti S, Bergesio D, Carrio Perez P, Felcini E, et al. Beam parameters optimization and characterization for a TUrning LInac for Protontherapy. Phys Medica 2018;54:152-65. URL: https://www.sciencedirect.com/science/article/ pii/S1120179718311608, doi 10.1016/J.EJMP.2018.08.019.
[2] Amaldi U, Cuccagna C, Lo Moro A, Rizzoglio V, Bernier J, Bulling S. Sparse proportional re-scanning with hadron beams. Phys Medica 2019;65:200-8. URL: http://www.ncbi. nlm.nih.gov/pubmed/31505371, doi 10.1016/j.ejmp.2019.07.022.
[3] Kozłowska WS, Böhlen TT, Cuccagna C, Ferrari A, Fracchiolla F, Georg D, et al. FLUKA particle therapy tool for Monte Carlo independent calculation of scanned proton and carbon ion beam therapy. Phys Med Biol 2019;URL: http://iopscience.iop.org/ article/10.1088/1361-6560/ab02cb, doi:10.1088/1361-6560/ab02cb.
[4] Augusto RS, Bauer J, Bouhali O, Cuccagna C, Gianoli C, Kozłowska WS, et al. An overview of recent developments in FLUKA PET tools. Phys Med 2018;0(0). URL: http: //www.ncbi.nlm.nih.gov/pubmed/30017561. doi 10.1016/j.ejmp.2018.06.636.
[5] Degiovanni A, Amaldi U. History of hadron therapy accelerators. Phys Medica 2015;31(4):322-32. URL: http://www.sciencedirect.com/science/article/pii/ S1120179715000629, doi:10.1016/j.ejmp.2015.03.002.
[6] Amaldi U, Bonomi R, Braccini S, Crescenti M, Degiovanni A, Garlasché M, et al. Accelerators for hadrontherapy: From Lawrence cyclotrons to linacs. Nucl Inst Methods Phys Res A 2010;620:563-77. doi:10.1016/j.nima.2010.03.130.
[7] Durante M, Paganetti H. Nuclear physics in particle therapy: a review. Rep Prog Phys 2016;79(9):096702. URL: http://www.ncbi.nlm.nih.gov/pubmed/27540827. doi:10.1088/0034-4885/79/9/096702.
[8] Tessonnier T, Mairani A, Brons S, Sala P, Cerutti F, Ferrari A, et al. Helium ions at the heidelberg ion beam therapy center: comparisons between fluka monte carlo code predictions and dosimetric measurements. Phys Med Biol 2017;62(16):6784803. URL: http://stacks.iop.org/0031-9155/62/i=16/a=6784?key=crossref. 680e67f4fcdda6be76d5d74411709fd3, doi:10.1088/1361-6560/aa7b12.
[9] Kurz C, Mairani A, Parodi K. First experimental-based characterization of oxygen ion beam depth dose distributions at the Heidelberg Ion-Beam Therapy Center. Phys Med Biol 2012;57(15):5017-34. URL: http://stacks.iop.org/0031-9155/57/i=15/a= 5017?key=crossref.e81b061231bb81ae55cd55eed94ef4b9, doi:10.1088/0031-9155/ 57/15/5017.
[10] Kopp B, Mein S, Dokic I, Harrabi S, Böhlen TT, Haberer T, et al. Development and validation of single field multi-ion particle therapy treatments. Int J Radiat Oncol 2019;URL: https://www.sciencedirect.com/science/article/pii/ S0360301619338799, doi:10.1016/J.IJROBP.2019.10.008.
[11] Mein S, Dokic I, Klein C, Tessonnier T, Böhlen TT, Magro G, et al. Biophysical modeling and experimental validation of relative biological effectiveness (RBE) for 4 He ion beam therapy. Radiat Oncol 2019;14(1):123. URL: https://ro-journal.biomedcentral. com/articles/10.1186/s13014-019-1295-z, doi:10.1186/s13014-019-1295-z.
[12] Chacon A, Safavi-Naeini M, Bolst D, Guatelli S, Franklin DR, Iwao Y, et al. Monte Carlo investigation of the characteristics of radioactive beams for heavy ion therapy. Sci Rep 2019;9(1):6537. URL: http://www.nature.com/articles/s41598-019-43073-1. doi:10.1038/s41598-019-43073-1.
[13] Dos Santos Augusto R. On the feasibility of using radioactive ion beams in hadrontherapy: dosimetric and imaging studies. Ph.D. thesis; Ludwig-Maximilians-Universitat Munchen; 2018.
[14] Wilson RR. Radiological Use of Fast Protons. Radiology 1946;47(5):487-91. URL: http://pubs.rsna.org/doi/10.1148/47.5.487, doi:10.1148/47.5.487.
[15] Tobias CA, Lawrence JH, Born JL, McCombs RK, Roberts JE, Anger HO, et al. Pituitary irradiation with high-energy proton beams a preliminary report. Cancer Research 1958;18(2):121-34. URL: https://cancerres.aacrjournals.org/content/18/2/121. arXiv:https://cancerres.aacrjournals.org/content/18/2/121.full.pdf.
[16] Dosanjh M. From Particle Physics to Medical Applications. 2399-2891; IOP Publishing; 2017. ISBN 978-0-7503-1444-2. URL: http://dx.doi.org/10.1088/ 978-0-7503-1444-2, doi:10.1088/978-0-7503-1444-2.
[17] Lawrence JH, TOBIAS CA, BORN JL, McCOMBS RK, ROBERTS JE, ANGER HO, et al. Pituitary irradiation with high-energy proton beams: a preliminary report. Cancer Res 1958;18(2):121-34. URL: http://www.ncbi.nlm.nih.gov/pubmed/13511365.
[18] Linz U. Physical and Biological Rationale for Using Ions in Therapy. 2011. URL: http://link.springer.com/10.1007/978-3-642-21414-1\{_\}4. doi:10.1007/ 978-3-642-21414-1_4.
[19] Rossi S. The National Centre for Oncological Hadrontherapy (CNAO): Status and perspectives. Phys Medica 2015;31(4):333-51. URL: http://www.sciencedirect.com/ science/article/pii/S1120179715000617. doi:10.1016/j.ejmp.2015.03.001.
[20] PTCOG. Particle therapy co-operative group. https://www.ptcog.ch; 2020. Accessed: 2020-01-12.
[21] Kamran SC, Light JO, Efstathiou JA. Proton versus photon-based radiation therapy for prostate cancer: emerging evidence and considerations in the era of value-based cancer care. 2019. URL: https://pubmed.ncbi.nlm.nih.gov/30967625/, doi:10.1038/ s41391-019-0140-7.
[22] Amaldi U, Kraft G. Particle-accelerators-take-up-the-fight-against-cancer. https: //cerncourier.com/particle-accelerators-take-up-the-fight-against-cancer; 2006. Accessed:2020-01-15.
[23] Teoh M, Clark CH, Wood K, Whitaker S, Nisbet A. Volumetric modulated arc therapy: A review of current literature and clinical use in practice. 2011. URL:/pmc/articles/PMC3473700/?report=abstracthttps://www.ncbi.nlm. nih.gov/pmc/articles/PMC3473700/. doi 10.1259/bjr/22373346.
[24] Florijn MA, Sharfo AWM, Wiggenraad RG, van Santvoort JP, Petoukhova AL, Hoogeman MS, et al. Lower doses to hippocampi and other brain structures for skull-base meningiomas with intensity modulated proton therapy compared to photon therapy. Radiother Oncol 2020;142:147-53. URL: https://doi.org/10.1016/j.radonc.2019.08.019. doi:10.1016/j.radonc.2019.08.019.
[25] Vitolo V, Cobianchi L, Brugnatelli S, Barcellini A, Peloso A, Facoetti A, et al. Preoperative chemotherapy and carbon ions therapy for treatment of resectable and borderline resectable pancreatic adenocarcinoma: A prospective, phase II, multicentre, single-arm study. BMC Cancer 2019;19(1):922. URL: https://bmccancer.biomedcentral.com/ articles/10.1186/s12885-019-6108-0. doi:10.1186/s12885-019-6108-0.
[26] Shinoto M, Yamada S, Terashima K, Yasuda S, Shioyama Y, Honda H, et al. Carbon Ion Radiation Therapy with Concurrent Gemcitabine for Patients with Locally Advanced Pancreatic Cancer. Int J Radiat Oncol Biol Phys 2016;95(1):498-504. doi:10.1016/j. ijrobp. 2015.12.362.
[27] Durante M. New challenges in high-energy particle radiobiology. 2014. URL: http:// www.birpublications.org/doi/10.1259/bjr.20130626, doi:10.1259/bjr.20130626.
[28] Lehmann HI, Graeff C, Simoniello P, Constantinescu A, Takami M, Lugenbiel P, et al. Feasibility Study on Cardiac Arrhythmia Ablation Using High-Energy Heavy Ion Beams. Sci Rep 2016;6. doi:10.1038/srep38895.
[29] ANSA . Protons treat heart arrhythmia. http://www.ansa.it/english/ news/science_tecnology/2020/01/22/protons-treat-heart-arrhythmia_ f0ff4012-e8c8-49b7-b624-a5c25062e44c.html; 2020. Accessed:2020-01-25.
[30] CERN . Protons herald new cardiac treatment. https://cerncourier.com/a/ protons-herald-new-cardiac-treatment/; 2020. Accessed:2020-03-25.
[31] Lechner A. Particle Interactions with Matter. In: Proc. of the CAS-CERN Accelerator School:Beam Injection, Extraction and Transfer, Erice, Italy, March 2017. 2018, p. 47-68.
[32] Ferrari A, Sala PR, Fasso A, Ranft J. FLUKA: A multi-particle transport code (Program version 2005). 2005.
[33] Amaldi U. Fisica delle radiazioni ad uso di radiologi, radiobiologi e protezionisti. Testi e manuali della sienza contemporanea; serie di biologia e medicina; Turin: Boringhieri; 1971. URL: http://cds.cern.ch/record/108615.
[34] Braibant S, Giacomelli G, Spurio M. Particles and fundamental interactions: supplements, problems and solutions : a deeper insight into particle physics. Undergraduate Lecture Notes in Physics; Dordrecht: Springer; 2012. URL: https://cds.cern.ch/ record/1453314, doi:10.1007/978-94-007-4135-5.
[35] IAEA . Nist-xcom: Photon cross sections database. https://physics.nist.gov/ PhysRefData/Xcom// 2020. Accessed:2020-02-07.
[36] Podgorsak EB. Radiation Physics for Medical Physicists; 2nd ed. Biological and Medical Physics, Biomedical Engineering; Berlin, Heidelberg: Springer; 2010. URL: https:// cds.cern.ch/record/1338976, doi:10.1007/978-3-642-00875-7.
[37] Parodi K. On the feasibility of dose quantification with in-beam PET data in radiotherapy with 12C and proton beams. Ph.D. thesis; Technischen Universitat Dresden; 2004.
[38] Patrignani C, et al. (Particle Data Group). Review of Particle Physics. Chin Phys 2016;C40(10):100001. doi $10.1088 / 1674-1137 / 40 / 10 / 100001$.
[39] Bethe HA. Moliere's theory of multiple scattering. Phys Rev 1953;89:1256-66. doi:10. 1103/PhysRev.89.1256.
[40] Gottschalk B, Koehler A, Schneider R, Sisterson J, Wagner M. Multiple coulomb scattering of 160 mev protons. Nuclear Instruments and Methods in Physics Research Section B: Beam Interactions with Materials and Atoms 1993;74(4):467 90. URL: http://www.sciencedirect.com/science/article/pii/0168583X9395944Z. doi:https://doi.org/10.1016/0168-583X(93)95944-Z.
[41] Moliere G. Theorie der Streuung schneller geladener Teilchen I. Einzelstreuung am abgeschirmten Coulomb-Feld. Zeitschrift für Naturforsch A 1947;2(3):13345. URL: http://www.degruyter.com/view/j/zna.1947.2.issue-3/zna-1947-0302/ zna-1947-0302.xml. doi 10.1515/zna-1947-0302.
[42] Gottschalk B. Radiotherapy Proton Interactions in Matter. 2018. URL: https://www.semanticscholar.org/paper/
Radiotherapy-Proton-Interactions-in-Matter-Gottschalk/ c8b5a6d73f51ebed1fb0311606107e545a8f9cc5.
[43] Highland VL. Some practical remarks on multiple scattering. Nuclear Instruments and Methods 1975;129(2):497-9.
[44] Lynch GR, Dahl OI. Approximations to multiple Coulomb scattering. Nucl Inst Methods Phys Res B 1991;doi:10.1016/0168-583X (91)95671-Y.
[45] Tanabashi M, et al. (Particle Data Group). Review of Particle Physics. Phys Rev 2018;D98(3):030001. doi:10.1103/PhysRevD.98.030001.
[46] Serber R. Nuclear reactions at high energies. Phys Rev 1947;72:1114-5. URL: https: //link.aps.org/doi/10.1103/PhysRev.72.1114. doi:10.1103/PhysRev.72.1114.
[47] Schardt D, Elsässer T, Schulz-Ertner D. Heavy-ion tumor therapy: Physical and radiobiological benefits. Rev Mod Phys 2010;82(1):383-425. URL: https://link.aps.org/ doi/10.1103/RevModPhys.82.383. doi:10.1103/RevModPhys.82.383.
[48] Sommerer F. Experiments and FLUKA simulations of O beams for therapy monitoring by means of in-beam Positron Emission Tomography. Ph.D. thesis; Technischen Universitat Wien; 2007.
[49] Haettner E, Iwase H, Krämer M, Kraft G, Schardt D. Experimental study of nuclear fragmentation of 200 and $400 \mathrm{MeV} / \mathrm{u}(12) \mathrm{C}$ ions in water for applications in particle therapy. Phys Med Biol 2013;58(23):8265-79. URL: http://www.ncbi.nlm.nih.gov/ pubmed/24216465. doi:10.1088/0031-9155/58/23/8265.
[50] IAEA . Iaea live chart of nuclides. https://www-nds.iaea.org/relnsd/vcharthtml/ VChartHTML.html; 2020. Accessed:2020-02-07.
[51] Castro JR, Linstadt DE, Bahary JP, Petti PL, Daftari I, Collier JM, et al. Experience in charged particle irradiation of tumors of the skull base: 1977-1992. Int J Radiat Oncol Biol Phys 1994;29(4):647-55. doi:10.1016/0360-3016(94)90550-9.
[52] Weber U, Kraft G. Comparison of carbon ions versus protons. Cancer J 2009;15(4):325-32. URL: http://www.ncbi.nlm.nih.gov/pubmed/19672150 doi:10. 1097/PPO.0b013e3181b01935.
[53] Charlie Ma CM, Lomax AJ. Proton and carbon ion therapy. Imaging in medical diagnosis and therapy; Boca Raton, FL: CRC Press; 2013. URL: https://cds.cern.ch/record/ 1529898, doi $10.1201 / \mathrm{b} 13070$.
[54] DeLuca PM, Wambersie A, Whitmore G. ICRU Report 78 Prescribing, recording, and reporting proton-beam therapy. 2007. URL: http://jicru.oxfordjournals.org/cgi/ doi/10.1093/jicru/ndm021. doi:10.1093/jicru/ndm021.
[55] Bortfeld T, Schlegel W. An analytical approximation of depth-dose distributions for therapeutic proton beams. Phys Med Biol 1996;41(8):1331-9. doi:10.1088/0031-9155/ 41/8/006
[56] Lu HM, Kooy H. Optimization of current modulation function for proton spread-out Bragg peak fields. Med Phys 2006;33(5):1281-7. doi $10.1118 / 1.2188072$.
[57] Yokokawa K, Furusaka M, Matsuura T, Hirayama S, Umegaki K. A new SOBP-formation method by superposing specially shaped Bragg curves formed by a mini-ridge filter for spot scanning in proton beam therapy. Phys Medica 2019;67:70-6. doi:10.1016/j.ejmp. 2019.10 .036
[58] Amaldi U, Kraft G. Radiotherapy with beams of carbon ions. Reports Prog Phys 2005;68(8):1861-82. URL: http://stacks.iop.org/0034-4885/68/i=8/a=R04?key= crossref.9a0f1e1c20da5f308fd7ce9a8adad161. doi $10.1088 / 0034-4885 / 68 / 8 /$ R04
[59] Park SH, Kang JO. Basics of particle therapy I: physics. Radiat Oncol J 2011;29(3):135. doi:10.3857/roj.2011.29.3.135.
[60] Hirao Y, Ogawa H, Yamada S, Sato Y, Yamada T, Sato K, et al. Heavy ion synchrotron for medical use -HIMAC project at NIRS-Japan-. Nucl Physics, Sect A 1992;538(C):541-50. doi $10.1016 / 0375-9474(92) 90803-\mathrm{R}$.
[61] Krämer M, Scholz M. Rapid calculation of biological effects in ion radiotherapy. Phys Med Biol 2006;51(8):1959-70. URL: https://iopscience.iop.org/article/10.1088/ 0031-9155/51/8/001https://iopscience.iop.org/article/10.1088/0031-9155/ 51/8/001/meta. doi $10.1088 / 0031-9155 / 51 / 8 / 001$.
[62] Combs SE, Jäkel O, Haberer T, Debus J. Particle therapy at the Heidelberg Ion Therapy Center (HIT) - Integrated research-driven university-hospital-based radiation oncology service in Heidelberg, Germany. 2010. doi:10.1016/j.radonc. 2010.02.016.
[63] Kase Y, Kanai T, Matsumoto Y, Furusawa Y, Okamoto H, Asaba T, et al. Microdosimetric Measurements and Estimation of Human Cell Survival for Heavy-Ion Beams. Radiat Res 2006;166(4):629-38. URL: http://www.bioone.org/doi/10.1667/RR0536.1. doi:10.1667/RR0536.1.
[64] Inaniwa T, Furukawa T, Kase Y, Matsufuji N, Toshito T, Matsumoto Y, et al. Treatment planning for a scanned carbon beam with a modified microdosimetric kinetic model. Phys Med Biol 2010;55(22):6721-37. URL: https://iopscience.iop.org/article/10.1088/0031-9155/55/22/008https:
//iopscience.iop.org/article/10.1088/0031-9155/55/22/008/meta. doi:10.1088/ 0031-9155/55/22/008.
[65] Karger CP, Peschke P. RBE and related modeling in carbon-ion therapy. Phys Med Biol 2017;63(1):01TR02. URL: http://stacks.iop.org/0031-9155/ 63/i=1/a=01TR02?key=crossref.56daddOf285482f7b131497402432ed9, doi:10.1088/ 1361-6560/aa9102.
[66] Suit H, Delaney TF, Trofimov A. Physical and Biological Basis of Proton and of Carbon Ion Radiation Therapy and Clinical Outcome Data. Rev Accel Sci Technol 2009;02(01):115. URL: https://www.worldscientific.com/doi/abs/10.1142/S179362680900017X. doi:10.1142/s179362680900017x.
[67] Hall E, Giaccia A. Radiobiology for the Radiologist. Wolters Kluwer Health; 2018. ISBN 9781496395139. URL: https://books.google.ch/books?id=rcNVDwAAQBAJ.
[68] IBA. Ion beam application. https://iba-worldwide.com/; 2020. Accessed:2020-02-07.
[69] Degiovanni A. High gradient proton linacs for medical applications. Ph.D. thesis; SB; Lausanne; 2014. doi•10.5075/epfl-thesis-6069.
[70] Pullia M, Necchi M, Savazzi S, Viviani C, Osorio Moreno J, Collaboration UW. ULICE Union of Light Ion Centres in Europe JRA6.1 Functional Specifications. Tech. Rep.; CNAO; 2009. URL: https://espace.cern.ch/ULICE-results/SharedDocuments/ DeliverableJRA\{_\}6.1\{_\}public.pdf.
[71] Myers S, Degiovanni A, Farr JB. Future Prospects for Particle Therapy Accelerators. Rev Accel Sci Technol 2019;10(01):49-92. doi:10.1142/s1793626819300056.
[72] Bortfeld T, Paganetti H, Kooy H. MO-A-T-6B-01: Proton Beam Radiotherapy - The State of the Art. Med Phys 2005;32(6Part13):2048-9. URL: http://doi.wiley.com/ 10.1118/1.1999671, doi:10.1118/1.1999671.
[73] Paganetti H. Proton Therapy Physics, Second Edition. Series in Medical Physics and Biomedical Engineering; CRC Press; 2018. ISBN 9781351855747. URL: https://books. google.ch/books?id=DDd7DwAAQBAJ.
[74] Zhang T, Wang C, Li M, Cui T, Yin Z, Ji B, et al. Developments for 230 MeV superconducting cyclotrons for proton therapy and proton irradiation. Nucl Instruments Methods Phys Res Sect B Beam Interact with Mater Atoms 2017;406:244-9. doi:10.1016/j.nimb.2016.11.010.
[75] Zhang Y, Huth I, Wegner M, Weber DC, Lomax AJ. Surface as a motion surrogate for gated re-scanned pencil beam proton therapy. Phys Med Biol 2017;62(10):404661. URL: http://stacks.iop.org/0031-9155/62/i=10/a=4046?key=crossref. 440900e9b1253b8c4cdc6d4f99f2729a. doi:10.1088/1361-6560/aa66c5.
[76] MEVION. Mevion medical systems. https://www.mevion.com/; 2020. Accessed:2020-02-07.
[77] Sedlatschek K, Machenschalk R, Natter B. Tungsten alloy x-ray target. 1973. URL: https://patents.google.com/patent/US3719854A; US-3719854-A.
[78] Hamm R. W. CKR, M.I PJ. Conference record of the 1991 IEEE Particle Accelerator Conference : accelerator science and technology, May 6-9, 1991, San Francisco, California. In: IEEE Nucl. Plasma Sci. Soc. Lawrence Berkeley Lab. Stanford Linear Accel. Center. Los Alamos Natl. Lab. Nucl. Plasma Sci. Soc. Lawrence Berkeley Lab. Stanford Linear Accel. Center. Los Alamo. IEEE. ISBN 0780301358; 1991, p. 3283.
[79] Amaldi U, Braccini S, Puggioni P. High Frequency Linacs for Hadrontherapy *. Reviews of Accelerator Science and Technology 2009;2:111-31.
[80] De Martinis C, Giove D, Amaldi U, Berra P, Crandall K, Mauri M, et al. Acceleration tests of a 3 GHz proton linear accelerator (LIBO) for hadrontherapy. Nucl Instruments Methods Phys Res Sect A Accel Spectrometers, Detect Assoc Equip 2012;681:10-5. doi:10.1016/j.nima.2012.04.017.
[81] Amaldi U, Berra P, Crandall K, Toet D, Weiss M, Zennaro R, et al. LIBO - A linacbooster for protontherapy: Construction and tests of a prototype. Nucl Instruments Methods Phys Res Sect A Accel Spectrometers, Detect Assoc Equip 2004;521(2-3):51229. doi:10.1016/j.nima.2003.07.062.
[82] Verdú-Andrés S, Amaldi U, Faus-Golfe Á. Literature review on linacs and FFAGs for hadron therapy. Int J Mod Phys A 2011;26(10-11):1659-89. URL: Www. worldscientific.com doi:10.1142/S0217751X11053109.
[83] Dosanjh M, Bernier J. Advances in Particle Therapy: A Multidisciplinary Approach by Manjit Dosanjh and Jacques Bernier Free for the next 60 days, the full text of "Advances in Particle Therapy" https://rdcu.be/4ftt. 2018. ISBN ISBN 9781138064416.
[84] Chu WT, Ludewigt BA, Renner TR. Instrumentation for treatment of cancer using proton and light-ion beams. 1993. URL: http://aip.scitation.org/doi/10.1063/1.1143946. doi:10.1063/1.1143946.
[85] Pedroni E, Bacher R, Blattmann H, Böhringer T, Coray A, Lomax A, et al. The 200MeV proton therapy project at the Paul Scherrer Institute: Conceptual design and practical realization. Med Phys 1995;22(1):37-53. URL: http://doi.wiley.com/10.1118/ 1.597522. doi:10.1118/1.597522.
[86] Haberer T, Becher W, Schardt D, Kraft G. Magnetic scanning system for heavy ion therapy. Nucl Instruments Methods Phys Res Sect A Accel Spectrometers, Detect Assoc Equip 1993;330(1-2):296-305. URL: https://www.sciencedirect.com/science/ article/pii/016890029391335K, doi:10.1016/0168-9002(93)91335-K.
[87] Knopf AC, Lomax AJ. In the context of radiosurgery - Pros and cons of rescanning as a solution for treating moving targets with scanned particle beams. Phys Medica 2014;30(5):551-4. URL: http://www.ncbi.nlm.nih.gov/pubmed/24767870. doi:10.1016/j.ejmp.2014.03.010.
[88] Amaldi U. Oblique raster scanning: An ion dose delivery procedure with variable energy layers. Phys Med Biol 2019;64(11). URL: https://iopscience.iop.org/article/10. 1088/1361-6560/ab0920 doi:10.1088/1361-6560/ab0920
[89] Amaldi U, Cuccagna C, Garonna A, Vazirisereshk MR. DEVELOPMENT PLANS OF CNAO. Tech. Rep.; TERA Foundation; 2017.
[90] Hitachi . Hitachi website. http://www.hitachi.com/businesses/healthcare/ products-support/pbt// 2020. Accessed:2020-02-25.
[91] ANSA . Hitachi signs agreement to provide CNAO with proton therapy system. https://www.news-medical.net/news/20191209/ Hitachi-signs-agreement-to-provide-CNAO-with-proton-therapy-system.aspx 2020. Accessed:2020-01-25.
[92] Molinelli S, Mairani A, Mirandola A, Vilches Freixas G, Tessonnier T, Giordanengo $S$, et al. Dosimetric accuracy assessment of a treatment plan verification system for scanned proton beam radiotherapy: one-year experimental results and Monte Carlo analysis of the involved uncertainties. Phys Med Biol 2013;58(11):3837-47. URL: http://stacks.iop.org/0031-9155/58/i=11/a=3837? key=crossref.bcb7d6d706a08547338115de2defe809, doi:10.1088/0031-9155/58/11/ 3837.
[93] Knopf AC, Lomax A. In vivo proton range verification: A review. 2013. URL: http://stacks.iop.org/0031-9155/58/i=15/a=R131?key=crossref. a4dce585277cdd2c3b0331cb1d3e7322, doi:10.1088/0031-9155/58/15/R131.
[94] Wagner HN. A brief history of positron emission tomography (PET). Semin Nucl Med 1998;28(3):213-20. doi:10.1016/S0001-2998(98)80027-5.
[95] Ter-Pogossian MM, Phelps ME, Hoffman EJ, Mullani NA. A positron-emission transaxial tomograph for nuclear imaging (PETT). Radiology 1975;114(1):89-98. arXiv:https://doi.org/10.1148/114.1.89.
[96] ETH-PS-USZI RS. Pet and spect: Physical principles and basic strategies of radiotracer development forpre-clinical and clinical use. 2016.
[97] Warburg O, Wind F, Negelein E. The metabolism of tumors in the body. J Gen Physiol 1927;8(6):519-30. URL:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2140820/. doi:10.1085/jgp.8.6.519.
[98] Fadaka A, Ajiboye B, Ojo O, Adewale O, Olayide I, Emuowhochere R. Biology of glucose metabolization in cancer cells. J Oncol Sci 2017;3(2):45-51. doi:10.1016/j.jons. 2017. 06.002 .
[99] Watts D, Borghi G, Sauli F, Amaldi U. The use of multi-gap resistive plate chambers for in-beam PET in proton and carbon ion therapy. J Radiat Res 2013;54(suppl_1):i13642. URL: https://academic.oup.com/jrr/article-abstract/54/suppl\{_\}1/i136/ 919110. doi:10.1093/JRR.
[100] Bailey DL, Townsend DW, Valk PE, maisey Editors MN. Positron emission tomography. Basic sciences. J Neuroradiol 2008;doi:10.1016/s0150-9861(06)77283-2.
[101] Cal-Gonzalez J, Rausch I, Sundar LK, Lassen ML, Muzik O, Moser E, et al. Hybrid imaging: Instrumentation and data processing. 2018. doi 10.3389/fphy.2018.00047.
[102] Bandi Y, Benoit M, Cadoux FR, Forshaw D, Hänni R, Hayakawa D, et al. The TT-PET project: a thin TOF-PET scanner based on fast novel silicon pixel detectors. J Instrum 2018;13(01):C01007-. URL: https://doi.org/10.1088/1748-0221/13/01/ C01007https://iopscience.iop.org/article/10.1088/1748-0221/13/01/C01007. doi:10.1088/1748-0221/13/01/C01007.
[103] Enghardt W, Parodi K, Crespo P, Fiedler F, Pawelke J, Pönisch F. Dose quantification from in-beam positron emission tomography. Radiother Oncol 2004;73:S96-8. URL: http://linkinghub.elsevier.com/retrieve/pii/S0167814004800240. doi:10.1016/ S0167-8140(04)80024-0.
[104] Sportelli G, Belcari N, Camarlinghi N, Cirrone GAP, Cuttone G, Ferretti S, et al. First full-beam PET acquisitions in proton therapy with a modular dual-head dedicated system. Phys Med Biol 2014;59(1):43-60. URL: https://iopscience.iop.org/article/10. 1088/0031-9155/59/1/43. doi:10.1088/0031-9155/59/1/43.
[105] Shakirin G, Braess H, Fiedler F, Kunath D, Laube K, Parodi K, et al. Implementation and workflow for PET monitoring of therapeutic ion irradiation: a comparison of inbeam, in-room, and off-line techniques. Physics in Medicine \& Biology 2011;56(5):1281. URL: http://stacks.iop.org/0031-9155/56/i=5/a=004.
[106] Parodi K, Paganetti H, Cascio E, Flanz JB, Bonab AA, Alpert NM, et al. PET/CT imaging for treatment verification after proton therapy: A study with plastic phantoms and metallic implants. Med Phys 2007;34(2):419-35. URL: http://doi.wiley.com/10. 1118/1.2401042, doi:10.1118/1.2401042.
[107] Parodi K, Paganetti H, Shih HA, Michaud S, Loeffler JS, DeLaney TF, et al. Patient Study of In Vivo Verification of Beam Delivery and Range, Using Positron Emission Tomography and Computed Tomography Imaging After Proton Therapy. Int J Radiat Oncol 2007;68(3):920-34. URL: http://linkinghub.elsevier.com/retrieve/ pii/S036030160700377X. doi 10.1016/j.ijrobp.2007.01.063.
[108] Enghardt W, Fromm WD, Manfrass P, Schardt D. Limited-angle 3D reconstruction of PET images for dose localization in light ion tumour therapy. Phys Med Biol 1992;37(3):791-8. URL: http://stacks.iop.org/0031-9155/37/i=3/a=021?key= crossref.acf812fb8c34d06d2222e24cead5a00b, doi 10.1088/0031-9155/37/3/021.
[109] Crespo P, Shakirin G, Fiedler F, Enghardt W, Wagner A. Direct time-of-flight for quantitative, real-time in-beam PET: a concept and feasibility study. Physics in Medicine \& Biology 2007;52(23):6795. URL: http://stacks.iop.org/0031-9155/52/i=23/a=002.
[110] Tashima H, Yoshida E, Inadama N, Nishikido F, Nakajima Y, Wakizaka H, et al. Development of a small single-ring OpenPET prototype with a novel transformable architecture. Phys Med Biol 2016;61(4):1795-809. URL: https://iopscience.iop.org/article/10. 1088/0031-9155/61/4/1795. doi:10.1088/0031-9155/61/4/1795.
[111] Assmann W, Kellnberger S, Reinhardt S, Lehrack S, Edlich A, Thirolf PG, et al. Ionoacoustic characterization of the proton Bragg peak with submillimeter accuracy. Med Phys 2015;42(2):567-74. URL: http://doi.wiley.com/10.1118/1.4905047https://aapm. onlinelibrary.wiley.com/doi/full/10.1118/1.4905047, doi:10.1118/1.4905047.
[112] Lehrack S, Assmann W, Bertrand D, Henrotin S, Herault J, Heymans V, et al. Submillimeter ionoacoustic range determination for protons in water at a clinical synchrocyclotron. Phys Med Biol 2017;62(17):L20-30. URL: https://iopscience.iop.org/ article/10.1088/1361-6560/aa81f8https://doi.org/10.1088/1361-6560/aa81f8. doi:10.1088/1361-6560/aa81f8.
[113] Kellnberger S, Assmann W, Lehrack S, Reinhardt S, Thirolf P, Queirós D, et al. Ionoacoustic tomography of the proton Bragg peak in combination with ultrasound and optoacoustic imaging. Sci Rep 2016;6(1):1-7. URL: www.nature.com/scientificreports. doi:10.1038/srep29305.
[114] Lehrack S, Assmann W, Bender M, Severin D, Trautmann C, Schreiber J, et al. Ionoacoustic detection of swift heavy ions. Nucl Instruments Methods Phys Res Sect A Accel Spectrometers, Detect Assoc Equip 2019;950. URL: http://arxiv.org/abs/1903. 12170http://dx.doi.org/10.1016/j.nima.2019.162935, doi:10.1016/j.nima. 2019. 162935, arXiv:1903.12170.
[115] Min CH, Kim CH, Youn MY, Kim JW. Prompt gamma measurements for locating the dose falloff region in the proton therapy. Appl Phys Lett 2006;89(18):183517. URL: http://aip.scitation.org/doi/10.1063/1.2378561. doi 10.1063/1.2378561.
[116] Testa E, Bajard M, Chevallier M, Dauvergne D, Le Foulher F, Freud N, et al. Monitoring the Bragg peak location of 73 MeVu carbon ions by means of prompt $\gamma$-ray measurements. Appl Phys Lett 2008;93(9):093506. URL: http://aip.scitation.org/doi/10.1063/1. 2975841. doi:10.1063/1.2975841 arXiv:0809.0185
[117] Verburg JM, Seco J. Proton range verification through prompt gamma-ray spectroscopy. Physics in Medicine \& Biology 2014;59(23):7089. URL: http://stacks.iop. org/0031-9155/59/i=23/a=7089
[118] Golnik C, Hueso-González F, Müller A, Dendooven P, Enghardt W, Fiedler F, et al. Range assessment in particle therapy based on prompt $\gamma$-ray timing measurements. Phys Med Biol 2014;59(18):5399-422. URL: https://iopscience.iop.org/article/ 10.1088/0031-9155/59/18/5399, doi•10.1088/0031-9155/59/18/5399,
[119] Krimmer J, Dauvergne D, Létang JM, Testa . Prompt-gamma monitoring in hadrontherapy: A review. 2018. doi $10.1016 / \mathrm{j}$. nima.2017.07.063
[120] Fontana M, Ley JL, Dauvergne D, Freud N, Krimmer J, Letang JM, et al. Monitoring Ion Beam Therapy With a Compton Camera: Simulation Studies of the Clinical Feasibility. IEEE Trans Radiat Plasma Med Sci 2019;4(2):218-32. doi:10.1109/trpms. 2019. 2933985.
[121] Park JH, Kim SH, Ku Y, Kim CH, Lee HR, Jeong JH, et al. Multi-slit promptgamma camera for locating of distal dose falloff in proton therapy. Nucl Eng Technol 2019;51(5):1406-16. doi:10.1016/j.net.2019.03.008.
[122] Xie Y, Bentefour EH, Janssens G, Smeets J, Vander Stappen F, Hotoiu L, et al. Prompt Gamma Imaging for In Vivo Range Verification of Pencil Beam Scanning Proton Therapy. Int J Radiat Oncol Biol Phys 2017;99(1):210-8. doi:10.1016/j.ijrobp.2017.04.027.
[123] Yao Z, Xiao Y, Chen Z, Wang B, Hou Q. Compton-based prompt gamma imaging using ordered origin ensemble algorithm with resolution recovery in proton therapy. Sci Rep 2019;9(1):1-15. URL: https://doi.org/10.1038/s41598-018-37623-2. doi:10.1038/ s41598-018-37623-2.
[124] Traini G, Battistoni G, Bollella A, Collamati F, De Lucia E, Faccini R, et al. Design of a new tracking device for on-line beam range monitor in carbon therapy. Phys Medica 2017;34:18-27. URL: http://dx.doi.org/10.1016/j.ejmp.2017.01.004. doi:10.1016/j.ejmp.2017.01.004.
[125] TERA Foundation . SISTEMA AQUA, Advanced quality assurance for CNAO. Tech. Rep.; TERA Foundation; 2008.
[126] Henriquet P, Testa E, Chevallier M, Dauvergne D, Dedes G, Freud N, et al. Interaction vertex imaging (IVI) for carbon ion therapy monitoring: a feasibility study.

Phys Med Biol 2012;57(14):4655-69. URL: https://iopscience.iop.org/article/ 10.1088/0031-9155/57/14/4655, doi:10.1088/0031-9155/57/14/4655
[127] Piersanti L, Bellini F, Bini F, Collamati F, De Lucia E, Durante M, et al. Measurement of charged particle yields from PMMA irradiated by a $220 \mathrm{MeV} / \mathrm{u}<$ sup $>12</$ sup $>$ $<\mathrm{i}>\mathrm{C}</ \mathrm{i}>$ beam. Phys Med Biol 2014;59(7):1857-72. URL: http://stacks.iop.org/ $0031-9155 / 59 / \mathrm{i}=7 / \mathrm{a}=1857$ ? $\mathrm{key}=\mathrm{crossref} .48 \mathrm{e} 3199 \mathrm{e} 7 \mathrm{dOf4cf91c11f8b7e4e230ea}$. doi:10.1088/0031-9155/59/7/1857.
[128] Ferrero V. Online range monitoring in particle therapy with the INSIDE PET detector. Phd thesis; Università degli Studi di Torino; 2019.
[129] Traini G, Battistoni G, Giacometti V, Gioscio E, Marafini M, Mirabelli R, et al. Preliminary test of the MONDO project secondary fast and ultrafast neutrons tracker response using protons and MIP particles. J Instrum 2018;13(04):C04014-. URL: https://iopscience.iop.org/article/10.1088/1748-0221/13/04/C04014https:// doi.org/10.1088/1748-0221/13/04/C04014 doi:10.1088/1748-0221/13/04/C04014.
[130] Patera V, Mattei I. Nuclear interactions and medicine. Eur Phys J Plus 2019 1341 2019;134(1):1-19. URL: https://link.springer.com/article/10.1140/epjp/ i2019-12484-6. doi:10.1140/epjp/i2019-12484-6.
[131] Mattei I, Alexandrov A, Alunni Solestizi L, Ambrosi G, Argiro S, Bartosik N, et al. Measurement of 12 C Fragmentation Cross Sections on C, O, and H in the Energy Range of Interest for Particle Therapy Applications. IEEE Trans Radiat Plasma Med Sci 2020;4(2):269-82. doi $10.1109 /$ trpms.2020.2972197.
[132] Badano L, Benedikt M, Bryant PJ, Crescenti M, Holy P, Maier AT, et al. (CERNTERA Foundation-MedAustron Oncology-2000 Collaboration). Proton-Ion Medical Machine Study (PIMMS), 1. 1999. URL: https://cds.cern.ch/record/385378.
[133] Picardi L, Ampollini A, Bazzano G, Cisbani E, Ghio F, Montereali RM, et al. Beam commissioning of the 35 mev section in an intensity modulated proton linear accelerator for proton therapy. Phys Rev Accel Beams 2020;23:020102. URL: https://link.aps. org/doi/10.1103/PhysRevAccelBeams.23.020102. doi:10.1103/PhysRevAccelBeams. 23.020102
[134] Degiovanni A, et al. Status of the Commissioning of the LIGHT Prototype. In: Proc. 9th International Particle Accelerator Conference (IPAC'18), Vancouver, BC, Canada, April 29-May 4, 2018. No. 9 in International Particle Accelerator Conference; Geneva, Switzerland: JACoW Publishing. ISBN 978-3-95450-184-7; 2018, p. 425-8. URL: http://jacow.org/ipac2018/papers/mopml014.pdf. doi doi:10.18429/ JACoW-IPAC2018-MOPML014; https://doi.org/10.18429/JACoW-IPAC2018-MOPML014.
[135] Amaldi U, Braccini S, Magrin G, Pearce P, Zennaro R. Ion acceleration system for medical and/or other applications. 2010. URL: https://www.google.ch/patents/EP2106678B1. EP Patent 2,106,678.
[136] Amaldi U, Braccini S, Magrin G, Pearce P, Zennaro R. Ion acceleration system for medical and/or other applications. 2013. URL: https://www.google.ch/patents/US8405056; US Patent 8,405,056.
[137] Degiovanni A, Amaldi U, Bergesio D, Cuccagna C, Moro A, Magagnin P, et al. Design of a fast-cycling high-gradient rotating linac for trotontherapy. Proc of IPAC2013 2013;:3642-4URL: https://accelconf. web.cern.ch/accelconf/IPAC2013/ papers/thpwa008.pdf.
[138] Verdu-Andres S, Amaldi U, Faus-Golfe A. CABOTO, a high-gradient linac for hadrontherapy. J Radiat Res 2013;54(SUPPL.1). doi:10.1093/jrr/rrt053.
[139] Benedetti S. High-gradient and high-efficiency linear accelerator for hadron therapy. Ph.D. thesis; EPFL; 2018. URL: http://infoscience.epfl.ch/record/253063. doi:10.5075/epfl-thesis-8246.
[140] Sapinski M, Benedetto E, Vretenar M. New ion therapy machine design study. https://indico.cern.ch/event/824363/contributions/3447777/attachments/ 1856881/3051289/2019June05_SlowExtractionWG.pdf 2019. Accessed:2020-02-07.
[141] TERA Foundation . Sistema AQUA, Advanced Quality Assurance. http:// project-aqua.web.cern.ch/; 2008. Accessed:2020-02-07.
[142] Sauli F. GEM: A new concept for electron amplification in gas detectors. Nucl Instruments Methods Phys Res Sect A Accel Spectrometers, Detect Assoc Equip 1997;386(2-3):531-4. doi:10.1016/S0168-9002(96)01172-2.
[143] Bucciantonio M, Amaldi U, Kieffer R, Sauli F, Watts D. Development of a fast proton range radiography system for quality assurance in hadrontherapy. Nucl Instruments Methods Phys Res Sect A Accel Spectrometers, Detect Assoc Equip 2013;732:564-7. doi:10.1016/j.nima.2013.05.110.
[144] Amaldi U, Borghi G, Bucciantonio M, Kieffer R, Samarati J, Sauli F, et al. Development of TOF-PET detectors based on the Multi-Gap Resistive Plate Chambers. Nucl Instruments Methods Phys Res Sect A Accel Spectrometers, Detect Assoc Equip 2015;778:85-91. doi:10.1016/j.nima.2015.01.018.
[145] Benedetti S, Grudiev A, Latina A. High gradient linac for proton therapy. Phys Rev Accel Beams 2017;20(4):40101. URL: https://journals.aps.org/prab/pdf/ 10.1103/PhysRevAccelBeams.20.040101https://link.aps.org/doi/10.1103/ PhysRevAccelBeams.20.040101, doi 10.1103/PhysRevAccelBeams.20.040101.
[146] Vretenar M, Dallocchio A, Dimov V, Garlaschè M, Grudiev A, Lombardi A, et al. A Compact High-Frequency RFQ for Medical Applications. In: Proc., 27th Linear Accelerator Conference, LINAC2014: Geneva, Switzerland, August 31-September 5, 2014. 2014, p. THPP040. URL: http://jacow.org/LINAC2014/papers/thpp040.pdf.
[147] Lombardi AM, Dimov VA, Garlasche M, Grudiev A, Mathot S, Montesinos E, et al. Beam Dynamics in a high frequency RFQ. In: Proc. of IPAC2015, Richmond, VA, USA. ISBN 9783954501687; 2015, p. 2408-12. URL: http://accelconf.web.cern.ch/AccelConf/ IPAC2015/papers/weyb2.pdf
[148] Benedetti S, Grudiev A, Latina A. Design of a 750 MHz IH Structure for Medical Applications. In: Proc., 28th Linear Accelerator Conference, LINAC16: East Lansing, MI, USA, 25-30 September 2016. 2017, p. MOPLR049.
[149] Ronsivalle C, Picardi L, Ampollini A, Bazzano G, Marracino F, Nenzi P, et al. First acceleration of a proton beam in a side coupled drift tube linac. EPL (Europhysics Lett) 2015;111(1):14002. URL: http://stacks.iop.org/0295-5075/111/i=1/a=14002?key= crossref.8e6b645e37e24dc49cab855d9696ba3c. doi 10.1209/0295-5075/111/14002.
[150] Benedetti S, Amaldi U, Degiovanni A, Grudiev A, Wuensch W. RF Design of a Novel S-Band Backward Traveling Wave Linac for Proton Therapy. In: Proc., 27th Linear Accelerator Conference, LINAC2014: Geneva, Switzerland, August 31-September 5, 2014. 2014, p. THPP061. URL: http://jacow.org/LINAC2014/papers/thpp061.pdf.
[151] Benedetti S, Argyropoulos T, Lasheras NC, Degiovanni A, Garlasché M, Navarro JG, et al. Fabrication and testing of a novel S-band backward travelling wave accelerating structure for proton therapy linacs. In: Proc., 28th Linear Accelerator Conference, LINAC16: East Lansing, MI, USA, 25-30 September 2016. 2017, p. MOPLR048.
[152] Lopez R. Conceptual Design Report: FeCo dipole magnet. Tech. Rep.; CERN; 2014. URL: https://edms.cern.ch/ui/\{\#\}!master/navigator/document?D: 1857470122:1857470122:subDocs.
[153] Zhang Y, Huth I, Wegner M, Weber DC, Lomax AJ. An evaluation of rescanning technique for liver tumour treatments using a commercial pbs proton therapy system. Radiotherapy and Oncology 2016;121(2):281 -7. URL: http: //www.sciencedirect.com/science/article/pii/S016781401634333X. doi:https:// doi.org/10.1016/j.radonc.2016.09.011.
[154] Wiedemann H. Particle Accelerator Physics. 2015 ed.; Springer, Cham; 2015. ISBN 9783319183176. doi $10.1007 / 978-3-319-18317-6$.
[155] Rusthoi D, Lysenko W, Crandall K. TRACE 3-D. 1997. URL: http://laacg.lanl. gov/laacg/services/download\{_\}trace.phtml\{\#\}ps0.
[156] Pavlovic M, Griesmayer E, Seemann R. Beam-transport study of an isocentric rotating ion gantry with minimum number of quadrupoles. Nuclear Instruments and Methods in Physics Research, Section A: Accelerators, Spectrometers, Detectors and Associated Equipment 2005;545(1-2):412-26. URL: http://www.sciencedirect.com/ science/article/pii/S0168900205005176. doi:10.1016/j.nima.2005.01.322.
[157] Laurent Deniau . MAD-X Methodical Accelerator Design. 2017. URL: http://mad.web. cern.ch.
[158] ANSA. Proton Therapy. http://www.ptcusa.com/particle_therapy.html 2020. Accessed:2020-03-27.
[159] Palm M, Benedikt M, Fabich A. DESIGN CHOICES OF THE MedAustron NOZZLES AND PROTON GANTRY BASED ON MODELING OF PARTICLE SCATTERING. In: Proceedings of IPAC2011, San Sebastián, Spain . 2011, p. THPS081. URL: https: //inspirehep.net/literature/1182672.
[160] Russenschuck S. Field computation for accelerator magnets: Analytical and numerical methods for electromagnetic design and optimization. Weinheim: Wiley-VCH; 2010. ISBN 9783527407699. URL: http://eu.wiley.com/WileyCDA/WileyTitle/ productCd-3527407693.html.
[161] Phillips MH, Pedroni E, Blattmann H, Boehringer T, Coray A, Scheib S. Effects of respiratory motion on dose uniformity with a charged particle scanning method. Phys Med Biol 1992;37(1):223-34. URL: http://stacks.iop.org/0031-9155/37/i=1/ a=016?key=crossref.0bd4565d1a410ea062eaf3817ecddd83, doi:10.1088/0031-9155/ 37/1/016.
[162] Lomax AJ, Böhringer T, Bolsi A, Coray D, Emert F, Goitein G, et al. Treatment planning and verification of proton therapy using spot scanning: Initial experiences. Med Phys 2004;31(11):3150-7. URL: http://www.ncbi.nlm.nih.gov/pubmed/15587667http:// doi.wiley.com/10.1118/1.1779371, doi:10.1118/1.1779371.
[163] Zenklusen SM, Pedroni E, Meer D. A study on repainting strategies for treating moderately moving targets with proton pencil beam scanning at the new Gantry 2 at PSI. Phys Med Biol 2010;55(17):5103-21. URL: http://stacks.iop.org/0031-9155/55/i=17/ a=014?key=crossref.d0ca0d1844900f9343adfdece5d00937. doi:10.1088/0031-9155/ 55/17/014.
[164] Bernatowicz K, Lomax AJ, Knopf A. Comparative study of layered and volumetric rescanning for different scanning speeds of proton beam in liver patients. Phys Med Biol 2013;58(22):7905-20. URL: http://stacks.iop.org/0031-9155/58/i=22/a=7905? key=crossref.29da1b637911c66ea9a5c7f1405afd66, doi:10.1088/0031-9155/58/22/ 7905.
[165] Seco J, Verhaegen F. Monte Carlo Techniques in Radiation Therapy. Imaging in medical Diagnosis A; Taylor \& Francis; 2013. ISBN 1098-6596. URL: https://books.google. ch/books?id=rGc879Q1haUC. doi $10.1017 /$ CB09781107415324.004.
[166] Metropolis N. The beginning of the Monte Carlo Methods. Los Alamos Sci Spec Issue 1987;15(1):125-30.
[167] Fassò A, Ferrari A, Sala PR. Principles of Monte Carlo Calculations and Codes; chap. -. Berlin, Heidelberg: Springer Berlin Heidelberg. ISBN 978-3-642-11327-7; 2011, p. 35-57. URL: https://doi.org/10.1007/978-3-642-11327-7_4. doi:10.1007/ 978-3-642-11327-7_4.
[168] Razani A. A monte carlo method for radiation transport calculations. Journal of Nuclear Science and Technology 1972;9(9):551-4. doi:10.1080/18811248.1972.9734896.
[169] Townson R, Tessier F, Mainegra E, Walters B. EGSnrc Toolkit for Monte Carlo simulation of ionizing radiation transport. https://nrc-cnrc.github.io/EGSnrc/; 2020. Accessed:2020-05-07.
[170] Baró J, Sempau J, Fernández-Varea JM, Salvat F. PENELOPE: An algorithm for Monte Carlo simulation of the penetration and energy loss of electrons and positrons in matter. Nucl Inst Methods Phys Res B 1995;100(1):31-46. doi:10.1016/0168-583X (95)00349-5.
[171] Nuclear Energy Agency . PENELOPE 2018: A code system for Monte Carlo simulation of electron and photon transport. 2019. URL: https:// www.oecd-ilibrary.org/content/publication/32da5043-en. doi/https://doi.org/ https://doi.org/10.1787/32da5043-en.
[172] Los Alamos National Laboratory: MCNP Home Page. https://mcnp.lanl.gov/\} 2020. Accessed:2020-05-07.
[173] Iwase H, Niita K, Nakamura T. Development of general-purpose particle and heavy ion transport monte carlo code. J Nucl Sci Technol 2002;39(11):1142-51. doi:10.1080/ 18811248.2002 .9715305 .
[174] Sato T, Iwamoto Y, Hashimoto S, Ogawa T, Furuta T, Abe Si, et al. Features of Particle and Heavy Ion Transport code System (PHITS) version 3.02. J Nucl Sci Technol 2018;55(6):684-90. URL: https://www.tandfonline.com/doi/full/10.1080/ 00223131.2017 .1419890 , doi:10.1080/00223131.2017.1419890.
[175] PHITS Particle and Heavy Ion Transport code System. https://phits.jaea.go.jp/ Reference.html; 2020. Accessed:2020-05-07.
[176] Bassler N, Hansen DC, Lühr A, Thomsen B, Petersen JB, Sobolevsky N. SHIELDHIT12A - a Monte Carlo particle transport program for ion therapy research. J Phys

Conf Ser 2014;489:012004. URL: https://iopscience.iop.org/article/10.1088/ 1742-6596/489/1/012004, doi $10.1088 / 1742-6596 / 489 / 1 / 012004$.
[177] SHIELD-HIT12A. https://shieldhit.org/; 2020. Accessed:2020-05-07.
[178] Agostinelli S, Allison J, Amako K, Apostolakis J, Araujo H, Arce P, et al. GEANT4 A simulation toolkit. Nucl Instruments Methods Phys Res Sect A Accel Spectrometers, Detect Assoc Equip 2003;506(3):250-303. doi:10.1016/S0168-9002(03)01368-8.
[179] GATE - Simulations of Preclinical and Clinical Scans in Emission Tomography, Transmission Tomography and Radiation Therapy. http://www.opengatecollaboration.org/ home; 2020.
[180] Perl J, Shin J, Schümann J, Faddegon B, Paganetti H. TOPAS: An innovative proton Monte Carlo platform for research and clinical applications. Med Phys 2012;39(11):681837. URL: https://pubmed.ncbi.nlm.nih.gov/23127075/. doi:10.1118/1.4758060.
[181] Battistoni G, Böhlen T, Cerutti F, Chin PW, Esposito LS, Fassò A, et al. Overview of the FLUKA code. Annals of Nuclear Energy 2015;82:10 - 8. doi $10.1016 / \mathrm{j}$.anucene. 2014.11.007.
[182] Vlachoudis V. FLAIR: A Powerful But User Friendly Graphical Interface For FLUKA. Proc Int Conf on Mathematics, Computational 2009;:1-11.
[183] Böhlen TT, Cerutti F, Dosanjh M, Ferrari A, Gudowska I, Mairani A, et al. Benchmarking nuclear models of FLUKA and GEANT4 for carbon ion therapy. Phys Med Biol 2010;55(19):5833-47. URL: http://iopscience.iop.org/0031-9155/55/19/ 014https://iopscience.iop.org/article/10.1088/0031-9155/55/19/014 doi:10. 1088/0031-9155/55/19/014.
[184] Zimmermann F, Benedikt M, Capeans Garrido M, Cerutti F, Goddard B, Gutleber J, et al. Future Circular Collider. Tech. Rep. CERN-ACC-2018-0059; CERN; Geneva; 2018. URL: https://cds.cern.ch/record/2651305; submitted for publication to Eur. Phys. J. ST.
[185] Battistoni G, Bauer J, Boehlen TT, Cerutti F, Chin MPW, Dos Santos Augusto R, et al. The FLUKA Code: An Accurate Simulation Tool for Particle Therapy. Front Oncol 2016;6:116. URL: http://journal.frontiersin.org/article/10.3389/fonc. 2016.00116/abstract doi:10.3389/fonc.2016.00116.
[186] Böhlen TT, Bauer J, Dosanjh M, Ferrari A, Haberer T, Parodi K, et al. A Monte Carlo-based treatment-planning tool for ion beam therapy. J Radiat Res 2013;54 Suppl 1(suppl_1):77-81. URL: http://jrr.oxfordjournals.org/cgi/content/long/ 54/suppl_1/i77. doi:10.1093/jrr/rrt050.
[187] Böhlen T, Cerutti F, Chin M, Fassò A, Ferrari A, Ortega P, et al. The FLUKA Code: Developments and Challenges for High Energy and Medical Applications. Nuclear Data Sheets 2014;120:211-4. URL: http://linkinghub.elsevier.com/retrieve/pii/ S0090375214005018, doi:10.1016/j.nds.2014.07.049.
[188] Mairani A, Böhlen TT, Schiavi A, Tessonnier T, Molinelli S, Brons S, et al. A Monte Carlo-based treatment planning tool for proton therapy. Phys Med Biol 2013;58(8):247190. URL: http://www.ncbi.nlm.nih.gov/pubmed/23514837. doi:10.1088/0031-9155/ 58/8/2471.
[189] Fiorina E. An integrated system for the online monitoring of particle therapy treatment accuracy. Nucl Instruments Methods Phys Res Sect A Accel Spectrometers, Detect Assoc Equip 2016;824:198-201. URL: https://www.sciencedirect.com/science/article/ pii/S0168900215013911?via\{\%\}3Dihub, doi:10.1016/J.NIMA.2015.11.029.
[190] Parodi K, Mairani A, Sommerer F. Monte Carlo-based parametrization of the lateral dose spread for clinical treatment planning of scanned proton and carbon ion beams. J Radiat Res 2013;54(suppl_1):i91-6. URL: https://academic.oup.com/jrr/ article-abstract/54/suppl\{_\}1/i91/919436, doi:10.1093/JRR.
[191] Arico G. Ion Spectroscopy for improvement of the Physical Beam Model for Therapy Planning in Ion Beam Therapy. Ph.D. thesis; University of Heidelberg; 2016. doi:https: //doi.org/10.11588/heidok.00022292.
[192] Cerutti F, Battistoni G, Capezzali G, Colleoni P, Ferrari A, Gadioli E, et al. Low energy nucleus-nucleus reactions: The bme approach and its interface with fluka. In: 11th International Conference, Varenna, Italy, June 12-16, 2006. 2006, p. -.
[193] Sorge H, Stöcker H, Greiner W. Poincaré invariant Hamiltonian dynamics: Modelling multi-hadronic interactions in a phase space approach. 1989. doi:10.1016/ 0003-4916(89) 90136-X.
[194] Fracchiolla F, Lorentini S, Widesott L, Schwarz M. Characterization and validation of a Monte Carlo code for independent dose calculation in proton therapy treatments with pencil beam scanning. Phys Med Biol 2015;60(21):860119. URL: http://stacks.iop.org/0031-9155/60/i=21/a=8601?key=crossref. 66920c51466c3210b0355303054a3bb3. doi:10.1088/0031-9155/60/21/8601.
[195] Bauer J, Sommerer F, Mairani A, Unholtz D, Farook R, Handrack J, et al. Integration and evaluation of automated Monte Carlo simulations in the clinical practice of scanned proton and carbon ion beam therapy. Physics in Medicine and Biology 2014;59(16):463559.
[196] Ortega PG, Torres-Espallardo I, Cerutti F, Ferrari A, Gillam JE, Lacasta C, et al. Noise evaluation of compton camera imaging for proton therapy. Physics in Medicine \& Biology 2015;60(5):1845. URL: http://stacks.iop.org/0031-9155/60/i=5/a=1845.
[197] Del Guerra A, Belcari N, Bisogni MG. Positron Emission Tomography: Its 65 years. La Rivista del Nuovo Cimento 2016;39(4):155-223. URL: https://www.sif.it/riviste/ sif/ncr/econtents/2016/039/04/article/0, doi:10.1393/ncr/i2016-10122-6.
[198] Stout D, Chow P, Silverman R, Leahy RM, Lewis X, Gambhir S, et al. Creating a whole body digital mouse atlas with PET, CT and cryosection images. Molecular Imaging and Biology 2002;4(4):S27.
[199] Dogdas B, Stout D, Chatziioannou AF, Leahy RM. Digimouse: a 3D whole body mouse atlas from CT and cryosection data. Phys Med Biol 2007;52(3):577-87. URL: https://iopscience.iop.org/article/10.1088/0031-9155/52/3/003. doi:10.1088/ 0031-9155/52/3/003.
[200] Biomedical Imaging Group . Digimouse: 3D Mouse Atlas. https://neuroimage.usc. edu/neuro/Digimouse_Download 2012. Accessed:2020-02-20.
[201] Giordanengo S, Manganaro L, Vignati A. Review of technologies and procedures of clinical dosimetry for scanned ion beam radiotherapy. Phys Medica 2017;43:79-99. URL: https://www.sciencedirect.com/science/article/pii/S1120179717304854? via\{\%\}3Dihub, doi:10.1016/J.EJMP.2017.10.013.
[202] Mirandola A, Molinelli S, Vilches Freixas G, Mairani A, Gallio E, Panizza D, et al. Dosimetric commissioning and quality assurance of scanned ion beams at the Italian National Center for Oncological Hadrontherapy. Med Phys 2015;42(9):5287-300. URL: http://doi.wiley.com/10.1118/1.4928397. doi 10.1118/1.4928397.
[203] Giordanengo S, Garella MA, Marchetto F, Bourhaleb F, Ciocca M, Mirandola A, et al. The CNAO dose delivery system for modulated scanning ion beam radiotherapy. Med Phys 2014;42(1):263-75. URL: http://doi.wiley.com/10.1118/1.4903276. doi:10.1118/1.4903276.
[204] Garonna A, Farinon F, Kronberger M, Kulenkampff T, Kurfürst C, Myalski S, et al. Status of proton beam commissioning of the Medaustron particle therapy accelerator. Proc of IPAC2016, Busan, Korea 2016;:3176-9URL: http://accelconf.web.cern.ch/ accelconf/ipac2016/papers/thoab01.pdf.
[205] MATLAB version 8.5.0.197613 (R2015a). The Mathworks, Inc.; Natick, Massachusetts; 2015.
[206] Lima TVM, Dosanjh M, Ferrari A, Molineli S, Ciocca M, Mairani A. Monte Carlo Calculations Supporting Patient Plan Verification in Proton Therapy. Front Oncol 2016;6:62.

URL: http://www.ncbi.nlm.nih.gov/pubmed/27047796http://www.pubmedcentral. nih.gov/articlerender.fcgi?artid=PMC4796019, doi:10.3389/fonc.2016.00062,
[207] Lansonneur P, Mammar H, Nauraye C, Patriarca A, Hierso E, Dendale R, et al. First proton minibeam radiation therapy treatment plan evaluation. Sci Rep 2020;10(1):1-8. URL: https://doi.org/10.1038/s41598-020-63975-9. doi:10.1038/s41598-020-63975-9.
[208] Pinnacle3 16.0 Physics Instructions for Use. Philips; 5520 Nobel Drive Fitchburg, WI 53711 USA; 2016.
[209] Bortfeld T. An analytical approximation of the Bragg curve for therapeutic proton beams. Med Phys 1997;24(12):2024-33. doi:10.1118/1.598116.
[210] Soukup M, Fippel M, Alber M. A pencil beam algorithm for intensity modulated proton therapy derived from Monte Carlo simulations. Phys Med Biol 2005;50(21):5089-104. URL: http://stacks.iop.org/0031-9155/50/i=21/a=010? key=crossref.d26e45f94e710de832fca244a5dcd17b. doi:10.1088/0031-9155/50/21/ 010.
[211] Kooy HM, Clasie BM, Lu HM, Madden TM, Bentefour H, Depauw N, et al. A Case Study in Proton Pencil-Beam Scanning Delivery. Int J Radiat Oncol Biol Phys 2010;76(2):62430. doi:10.1016/j.ijrobp. 2009.06.065.
[212] Saini J, Cao N, Bowen SR, Herrera M, Nicewonger D, Wong T, et al. Clinical Commissioning of a Pencil Beam Scanning Treatment Planning System for Proton Therapy. Int J Part Ther 2016;3(1):51-60. URL: http://theijpt.org doi:10.14338/ijpt-16-0000.1.
[213] Schneider W, Bortfeld T, Schlegel W. Correlation between CT numbers and tissue parameters needed for Monte Carlo simulations of clinical dose distributions. Physics in Medicine and Biology 2000;45(2):459-78. doi:10.1088/0031-9155/45/2/314.
[214] Grevillot L, Bertrand D, Dessy F, Freud N, Sarrut D. A Monte Carlo pencil beam scanning model for proton treatment plan simulation using GATE/GEANT4. Phys Med Biol 2011;56(16):5203-19. URL: https://iopscience.iop.org/article/10.1088/ 0031-9155/56/16/008https://iopscience.iop.org/article/10.1088/0031-9155/ 56/16/008/meta. doi:10.1088/0031-9155/56/16/008.
[215] Grassberger C, Lomax A, Paganetti H. Characterizing a proton beam scanning system for Monte Carlo dose calculation in patients. Phys Med Biol 2015;60(2):633-45. URL: https://iopscience.iop.org/article/10.1088/0031-9155/60/2/633https: //iopscience.iop.org/article/10.1088/0031-9155/60/2/633/meta. doi:10.1088/ 0031-9155/60/2/633.
[216] Mayles P, Nahum A, Rosenwald JC, editors. Handbook of Radiotherapy Physics: Theory and Practice; vol. 35. CRC Press; 2008. URL: http://doi.wiley.com/10.1118/1. 2969650, doi $10.1118 / 1.2969650$.
[217] Andreo P, Burns DT, Hohlfeld K, Huq MS, Kanai T, Laitano F, et al. Absorbed Dose Determination in External Beam Radiotherapy: an International Code of Practice for Dosimetry Based on Standards of Absorbed Dose to Water. Tech. Rep. 398; International Atomic Energy Agency; 2000.
[218] Jäkel O, Hartmann GH, Karger CP, Heeg P, Vatnitsky S. A calibration procedure for beam monitors in a scanned beam of heavy charged particles. Med Phys 2004;31(5):100913. URL: http://doi.wiley.com/10.1118/1.1689011, doi•10.1118/1.1689011.
[219] Gomà C, Lorentini S, Meer D, Safai S. Proton beam monitor chamber calibration. Phys Med Biol 2014;59(17):4961-71. URL: https://iopscience.iop.org/article/ 10.1088/0031-9155/59/17/4961https://iopscience.iop.org/article/10.1088/ 0031-9155/59/17/4961/meta. doi 10.1088/0031-9155/59/17/4961.
[220] Taylor PA, Kry SF, Followill DS. Pencil Beam Algorithms Are Unsuitable for Proton Dose Calculations in Lung. Int J Radiat Oncol Biol Phys 2017;99(3):750-6. doi:10.1016/ j.ijrobp.2017.06.003.
[221] Crespo P, Barthel T, et al. HFK. Suppression of random coincidences during in-beam pet measurements at ion beam radiotherapy facilities. IEEE Transactions on Nuclear Science 2005;52(4):980-7. doi $10.1109 /$ TNS. 2005.852637.
[222] Enghardt W, Crespo P, Fiedler F, Hinz R, Parodi K, Pawelke J, et al. Charged hadron tumour therapy monitoring by means of PET. Nucl Instruments Methods Phys Res Sect A Accel Spectrometers, Detect Assoc Equip 2004;525(1-2):284-8. URL: http:// linkinghub.elsevier.com/retrieve/pii/S0168900204004218 doi:10.1016/j.nima. 2004.03.128.
[223] Dendooven P, Buitenhuis HJT, Diblen F, Heeres PN, Biegun AK, Fiedler F, et al. Shortlived positron emitters in beam-on PET imaging during proton therapy. Phys Med Biol 2015;60(23):8923-47. URL: http://stacks.iop.org/0031-9155/60/i=23/a=8923? key=crossref.8976067304f2e5a0efda9c42424e628a. doi:10.1088/0031-9155/60/23/ 8923.
[224] Cuccagna C, Augusto R, Kozlowska W, Ortega P, Vlachoudis V, Ferrari A, et al. Evaluation study of in-beam PET performances with a Carbon ion linac (CABOTO). Radiother Oncol 2016;118:S28-9. URL: https://www.sciencedirect.com/science/ article/pii/S0167814016300585, doi $10.1016 / \mathrm{S} 0167-8140(16) 30058-5$.
[225] Capote R, Herman M, Obložinský P, Young PG, Goriely S, Belgya T, et al. RIPL Reference Input Parameter Library for Calculation of Nuclear Reactions and Nuclear Data Evaluations. Nucl Data Sheets 2009;110(12):3107-214. doi 10.1016/j.nds. 2009. 10.004
[226] Bongrand A, Busato E, Force P, Martin F, Montarou G. Use of short-lived positron emitters for in-beam and real-time $\beta+$ range monitoring in proton therapy. Phys Medica 2020;69:248-55. doi:10.1016/j.ejmp.2019.12.015.
[227] Crespo P, Shakirin G, Enghardt W. On the detector arrangement for in-beam PET for hadron therapy monitoring. Phys Med Biol 2006;51(9):2143-63. URL: https://iopscience.iop.org/article/10.1088/0031-9155/51/9/002. doi:10.1088/ 0031-9155/51/9/002.
[228] Humm JL, Rosenfeld A, Del Guerra A. From PET detectors to PET scanners. 2003. URL: https://link.springer.com/article/10.1007/s00259-003-1266-2. doi:10.1007/s00259-003-1266-2.
[229] Yamamoto S, Horii H, Hurutani M, Matsumoto K, Senda M. Investigation of single, random, and true counts from natural radioactivity in LSO-based clinical PET. Ann Nucl Med 2005;19(2):109-14. URL: http://link.springer.com/10.1007/BF03027389. doi:10.1007/BF03027389,
[230] Bisogni MG, Attili A, Battistoni G, Belcari N, Camarlinghi N, Cerello P, et al. INSIDE in-beam positron emission tomography system for particle range monitoring in hadrontherapy. J Med imaging (Bellingham, Wash) 2017;4(1):011005. URL: http://www.ncbi.nlm.nih.gov/pubmed/27981069http://www.pubmedcentral. nih.gov/articlerender.fcgi?artid=PMC5133454 doi:10.1117/1.JMI.4.1.011005.
[231] Bisogni MG, Del Guerra A, Belcari N. Medical applications of silicon photomultipliers. 2019. doi:10.1016/j.nima.2018.10.175.
[232] Kapusta M, Crespo P, Wolski D, Heidel K, Heinrich L, Hutsch J, et al. The LSO/APD array as a possible detector for in-beam PET in hadron therapy. In: IEEE Trans. Nucl. Sci.; vol. 51. 2004, p. 1389-94. doi 10.1109/TNS.2004.832318.
[233] Pawelke J, Byars L, Enghardt W, Fromm WD, Geissel H, Hasch BG, et al. The investigation of different cameras for in-beam PET imaging. Physics in Medicine \& Biology 1996;41(41):279-. URL: http://iopscience.iop.org/article/10.1088/0031-9155/ 41/2/006/pdf.
[234] Enghardt W, Debus J, Haberer T, Hasch BG, Hinz R, Jäkel O, et al. Positron emission tomography for quality assurance of cancer therapy with light ion beams. Nucl Phys A 1999;654(1 SUPPL. 1):1047c-50. URL: https://www. sciencedirect.com/science/article/pii/S0375947400885978?via\{\%\}3Dihub. doi:10.1016/S0375-9474(00)88597-8.
[235] Attanasi F, Belcari N, Del Guerra A, Enghardt W, Moehrs S, Parodi K, et al. Comparison of two dedicated 'in beam' PET systems via simultaneous imaging of 12 C-induced $\beta$

+ -activity. Phys Med Biol 2009;54(2):N29-35. URL: https://iopscience.iop.org/ article/10.1088/0031-9155/54/2/N01. doi:10.1088/0031-9155/54/2/N01.
[236] Vecchio S, Attanasi F, Belcari N, Camarda M, Cirrone GA, Cuttone G, et al. A PET prototype for in-beam monitoring of proton therapy. IEEE Trans Nucl Sci 2009;56(1):516. doi:10.1109/TNS.2008.2008306,
[237] Rosso V, Battistoni G, Belcari N, Camarlinghi N, Ferrari A, Ferretti S, et al. A new PET prototype for proton therapy: comparison of data and Monte Carlo simulations. J Instrum 2013;8(03):C03021-. URL: https://iopscience.iop.org/article/10.1088/ 1748-0221/8/03/C03021. doi:10.1088/1748-0221/8/03/C03021.
[238] Rosso V, Belcari N, Bisogni M, Camarlinghi N, Cirrone G, Collini F, et al. DoPET: an intreatment monitoring system for proton therapy at 62 MeV . Journal of Instrumentation 2016;11(12):C12029. URL: http://stacks.iop.org/1748-0221/11/i=12/a=C12029.
[239] Sportelli G, Belcari N, Camarlinghi N, Ciocca M, Collini F, Molinelli S, et al. Inbeam PET data characterization with the large area DoPET prototype. J Instrum 2016;11(02):C02089-. URL: https://iopscience.iop.org/article/10.1088/ 1748-0221/11/02/C02089. doi $10.1088 / 1748-0221 / 11 / 02 / \mathrm{C} 02089$.
[240] Muraro S, Battistoni G, Belcari N, Bisogni MG, Camarlinghi N, Cristoforetti L, et al. Proton therapy treatment monitoring with the DoPET system: activity range, positron emitters evaluation and comparison with Monte Carlo predictions. J Instrum 2017;12(12):C12026-. URL: https://doi.org/10.1088/1748-0221/12/12/ C12026https://iopscience.iop.org/article/10.1088/1748-0221/12/12/C12026. doi:10.1088/1748-0221/12/12/C12026.
[241] Shao Y, Sun X, Lou K, Zhu XR, Mirkovic D, Poenisch F, et al. In-beam PET imaging for on-line adaptive proton therapy: an initial phantom study. Phys Med Biol 2014;59(13):3373-88. URL: https://iopscience.iop.org/article/10.1088/ 0031-9155/59/13/3373, doi:10.1088/0031-9155/59/13/3373.
[242] Cambraia Lopes P, Bauer J, Salomon A, Rinaldi I, Tabacchini V, Tessonnier T, et al. First $<\mathrm{i}>$ in situ $</ \mathrm{i}>$ TOF-PET study using digital photon counters for proton range verification. Phys Med Biol 2016;61(16):6203-30. URL: https://iopscience.iop.org/ article/10.1088/0031-9155/61/16/6203. doi:10.1088/0031-9155/61/16/6203.
[243] Ferrero V, Cerello P, Fiorina E, Monaco V, Rafecas M, Wheadon R, et al. Innovation in online hadrontherapy monitoring: An in-beam pet and prompt-gamma-timing combined device. Nucl Instruments Methods Phys Res Sect A Accel Spectrometers, Detect Assoc Equip 2018;URL: https://www.sciencedirect.com/science/article/ pii/S0168900218310234. doi 10.1016/J.NIMA.2018.08.065.
[244] Ferrero V. The INSIDE project: in-beam PET scanner system features and characterization. J Instrum 2017;12(03):C03051-. URL: http://stacks.iop.org/ $1748-0221 / 12 / \mathrm{i}=03 / \mathrm{a}=\mathrm{C} 03051$ ? key=crossref.96f0a8541181dbbc0bfc6ae4e7c1fb76. doi:10.1088/1748-0221/12/03/C03051.
[245] Brun R, Rademakers F. ROOT - An object oriented data analysis framework. Nucl Instruments Methods Phys Res Sect A Accel Spectrometers, Detect Assoc Equip 1997;389(1-2):81-6. URL: https://root.cern.ch/, doi:10.1016/S0168-9002(97)00048-X.
[246] Piliero MA, Belcari N, Bisogni MG, Camarlinghi N, Cerello P, Coli S, et al. First results of the INSIDE in-beam PET scanner for the online monitoring of particle therapy treatments. J Instrum 2016;11(12):C12011URL: http://stacks.iop.org/1748-0221/11/i=12/a=C12011?key=crossref. c6926f4b65e7bed78ac27625bfe98164. doi:10.1088/1748-0221/11/12/C12011.
[247] Kostara E, Sportelli G, Belcari N, Camarlinghi N, Cerello P, Del Guerra A, et al. Particle beam microstructure reconstruction and coincidence discrimination in PET monitoring for hadron therapy. Phys Med Biol 2019;64(3):035001. URL: http://stacks.iop.org/ $0031-9155 / 64 / \mathrm{i}=3 / \mathrm{a}=035001$ ?key=crossref.743d6321dc205b81e8a7bad53ee46d92. doi:10.1088/1361-6560/aafa28.
[248] Sportelli G, Bisogni MG, Morrochhi M, Camarlinghi N. Method and apparatus for acquiring positron emission tomography data in full beam hadron therapy. 2019. URL: http://hdl.handle.net/11568/10; WO 2019138384 A1.
[249] Pennazio F, Battistoni G, Bisogni MG, Camarlinghi N, Ferrari A, Ferrero V, et al. Carbon ions beam therapy monitoring with the INSIDE in-beam PET. Phys Med Biol 2018;63(14):145018. URL: http://stacks.iop.org/ $0031-9155 / 63 / \mathrm{i}=14 / \mathrm{a}=145018$ ?key=crossref.978bf5a8c52480db190d547ccab6c6f7. doi:10.1088/1361-6560/aacab8.
[250] Evans JR. Running median filters and a general despiker. Bulletin of the Seismological Society of America 1982;72:331-8.
[251] Lim J. Two-dimensional Signal and Image Processing. Prentice-Hall international editions; Prentice Hall; 1990. ISBN 9780139353222. URL: https://books.google.ch/ books?id=6PRsAAAAIAAJ.
[252] Justusson BI. Median Filtering: Statistical Properties; chap. 5. Berlin, Heidelberg: Springer Berlin Heidelberg. ISBN 978-3-540-38446-5; 1981, p. 161-96. URL: https: //doi.org/10.1007/BFb0057597, doi:10.1007/BFb0057597.
[253] Wei Q. Intrinsic Radiation in Lutetium Based PET Detector: Advantages and Disadvantages. Chinese Physics C Supported by China Postdoctoral

Science Foundation 2015;URL: https://arxiv.org/ftp/arxiv/papers/1501/1501. 05372.pdf. arXiv:1501.05372.
[254] James F. Statistical Methods in Experimental Physics. WORLD SCIENTIFIC; 2006. ISBN 978-981-256-795-6. URL: https://www.worldscientific.com/worldscibooks/ 10.1142/6096, doi:10.1142/6096.
[255] Behnke O, Kröninger K, Schott G, Schörner-Sadenius T, editors. Data Analysis in High Energy Physics. Weinheim, Germany: Wiley-VCH Verlag GmbH \& Co. KGaA; 2013. ISBN 9783527653416. URL: http://doi.wiley.com/10.1002/9783527653416. doi:10. 1002/9783527653416.
[256] Baker S, Cousins RD. Clarification of the use of CHI-square and likelihood functions in fits to histograms. Nucl Instruments Methods Phys Res 1984;221(2):437-42. doi:10. 1016/0167-5087(84)90016-4.

## Acknowledgements

The accomplishment of this work would have not been possible without Prof. Ugo Amaldi: first of all, he gave me the opportunity to work as a scientific collaborator and engineer at the TERA Foundation, where I could provide significant contributions to the design of new hadron therapy facilities. Moreover, and perhaps more importantly, he has awakened my passion for the "beautiful and useful" physics by guiding me through a scientifically-challenging landscape with his engaging vision and "energizing" enthusiasm for research. Prof. Amaldi encouraged my "reborn" interests in physics applied to medicine and my aspiration to pursue my scientific studies with a PhD, by accepting the thesis supervision and co-direction. These few lines are certainly not enough to express my immense gratitude to him.

I am also grateful to Prof. Giuseppe Iacobucci who supported my enrollment at the University of Geneva as a PhD student and assisted me as thesis director, motivating me to arrive at the end of this path, and helping me to overcome expected and unexpected difficulties.

As the methods and materials are fundamental to achieve the results, I warmly thank the authors and developers of the FLUKA software, in particular: Alfredo Ferrari, Giuseppe Battistoni, Francesco Cerutti thanks to whom I discovered the applications of Monte Carlo methods in particle physics. I am very grateful to them not only for their support and advice on FLUKA, but also for having introduced me to the team at CERN, working (also) on medical applications. First of all, I warmly thank Vasilis Vlauchodis for his continuous help in finding solutions in FLUKA/FLAIR medical application projects and for supporting me in adapting the software to the TERA projects. Moreover my sincere gratitude goes to Ricardo Dos Santos Augusto, Wioletta Kozlowska and Pablo Garcia Ortega for the many fruitful exchanges throughout my PhD study. In particular, I thank them all for the many long hours spent together at CERN, or remotely, in developing the FLUKA medical application tools.

Moreover, I would like to address a heartfelt word of gratitude to all my colleagues of the TERA Foundation. First of all, the accelerator and beam optics team, in particular for providing the results that started off my work on TULIP: Stefano Benedetti, Daniele Bergesio, Enrico Felcini, Vittorio Bencini and Mohammad Varasteh. A special thank goes to Adriano Garonna, at the time technical director of the TERA team at CERN, who not only supported me from the technical standpoint but also encouraged me during the most critical moments. In addition, starting from the first period at TERA, my thankful thoughts go to: Alberto De Giovanni, who introduced me to the world of the linacs for hadrontherapy, Valeria Rizzoglio who introduced me to the Treatment Planning Systems and repainted grey days with her
friendliness. I acknowledge the AQUA group, in particular Prof. Fabio Sauli and Martina Bucciantonio for their teachings on imaging techniques in hadron therapy.

I also acknowledge some outstanding engineers like: Paolo Magagnin, who introduced me to the CAD software in use at CERN, Alessandra Lo Moro, Giovanni Porcellana, Mohammad Vasiri, Sonia Allegretti and Vanja Ljubicic for sharing many convivial moments at the Foundation. Moreover, a though of warm gratitude goes to the memory of the Engineer Pierluigi Riboni who led the engineering group with enthusiasm and creativity.

Finally, the TERA Foundation could not exist without the dedication and hardworking of Maria di Rosa, whom I thank for her daily support in my integration at CERN and with languages, Gaudenzio Vanolo for his activity in funding our research, and Emanuela Rodini and Elena Santoro for the administrative supports.

My gratitude goes to some brilliant people from CNAO Foundation: Marco Pullia and Sandro Rossi in particular for the beam time I could benefit from during the experiments with INSIDE, for providing some important data on that facility and for allowing me to spend some time at CNAO, to learn the basis of clinical medical physics. I also kindly thank Alfredo Mirandola for providing information on CNAO's beam characteristics.

Furthermore, I am extremely grateful to the INSIDE collaboration members. First of all to Prof. Giuseppina Bisogni and Piergiorgio Cerello for allowing to perform the experiment with the INSIDE detector and to use the data acquisition/analysis tools. I also warmly thank Elisa Fiorina, Francesco Pennazio and Veronica Ferrero for valuable input on the data analysis and simulations with INSIDE.

I also address a special thank to the people from Clinique Genolier: Prof. Jacques Bernier and Shelley Bulling for allowing to use the Pinnacle TPS platform by Philips as well as Gregory Bolard, now at L'Hopital de la Tour, and Laertes Papaspyrou from Philips for valuable support with the TPS.

I thank also Marco Schwarz and Francesco Fracchiolla for hosting me to visit the proton therapy center in Trento (TIFPA) and for providing some useful data on that facility. I also acknowledge Prof. Vincenzo Patera, from La Sapienza University in Rome, who supported me behind the scenes by facilitating my networking with FLUKA and INSIDE collaborations.

Moreover, I cannot forget all the colleagues, supervisors and friends whom I have met around Europe also during my work experiences in the industry, who indirectly contributed to reach this objective, with their pragmatic, "straight to the point" advices. I thank them for this and also for the happy moments spent together during social occasions or even during "virtual" coffee breaks in the course of the COVID 19 Pandemic.

My immense gratitude goes to my loving husband Saverio and my sons, Federico and Lorenzo, whose love, patience and in some occasions sacrifices were fundamental to achieve this result. Last, but not least I thank other members of my family, coming to our "rescue" from Italy in challenging moments, such as my parents in law, my mother who always believed in me together with my sister who has been the first person teaching me the word "physics", when I was a small child.


[^0]:    ${ }^{1}$ all for protons, excepted 2 also for carbon ion; see section 1.3

[^1]:    ${ }^{2}$ PSTAR and ESTAR: https://www.nist.gov/pml/stopping-power-range-tables-electrons-protons-and-helium-ions

[^2]:    ${ }^{3}$ Until 2016 in the PDG only the expression in $\ln$ instead of $\log _{10}$ was reported, so the parameter is 0.038 instead of 0.088 and the factor $z^{2} / \beta^{2}$ was absent.

[^3]:    ${ }^{4}$ The tungsten alloy is generally obtained by mixing tungsten with other transition metals with high melting point and atomic number such as rhenium, osmium, iridium and platinun 77.
    ${ }^{5}$ Laboratori Nazionali del Sud
    ${ }^{6}$ Without considering scattering in the nozzle elements, see chapter 4 for further details.

[^4]:    ${ }^{7}$ from ENLIGHT CERN website: https://enlight.web.cern.ch/.

[^5]:    ${ }^{8}$ International Commission of Radiation Units and Measurements, published several reports with recommendations in radiation therapy: REPORT 50,78 and 93 are the most important in HT, https://icru.org/home/reports/

[^6]:    ${ }^{9}$ Courtesy of V. Rizzoglio and Clinique Genolier
    ${ }^{10}$ Varian, Siemens, Philips and Raysearch companies are the main vendors.

[^7]:    ${ }^{11}$ For PET in HT, as it will be shown in the following, since the contributions to the activity is given by different radioisotopes having different $\beta^{+}$range, that can be also of several millimeters, it is important especially in the simulation to distinguish between the production position distribution of isotopes and the annihilation points of the produced positron.

[^8]:    ${ }^{1}$ https://www.advancedcyclotron.com/

[^9]:    ${ }^{2}$ https://www.avoplc.com/en-gb/
    ${ }^{3}$ The following sections about TULIP are part of the work published in ref. [1].

[^10]:    ${ }^{4}$ the Twiss parameters $\beta$ and $\gamma$ should not be confused with the homonyms relativistic parameters.
    ${ }^{5}$ These optics simulation studies, which are published in [1] , were performed by other authors of the publications (V. Bencini, A. Garonna for MEBT and E. Felcini and D. Bergesio for HEBT). The automation of the 3D particle tracking codes integration and a large part of the FLUKA-based beam characterization were instead mainly performed by the candidate and, for this reason, reported in the separate chapter 4 .

[^11]:    ${ }^{6}$ V. Bencini author

[^12]:    ${ }^{7}$ https://detector-group.com, spin-off Turin University and INFN

[^13]:    ${ }^{8}$ E. Felcini's authored.

[^14]:    ${ }^{9}$ E. Felcini's authored.

[^15]:    ${ }^{10}$ D. Bergesio's authored.

[^16]:    ${ }^{1}$ The seed is an initial number of the pseudorandom number generator which guarantees the reproducibility of the random sequence
    ${ }^{2}$ "Tool kit interface"-Python Graphical User Interface

[^17]:    ${ }^{1}$ Most of the contents of this chapter has been published in the paper [1].

[^18]:    ${ }^{2}$ The data in this example are the results at 142 MeV obtained from the 3D simulation tracking at 10 cm before the nozzle entrance

[^19]:    ${ }^{3}$ Courtesy of S. Benedetti

[^20]:    ${ }^{4}$ Courtesy of W. Kozlowska
    ${ }^{5}$ M. Varasteh Anvar's contribution

[^21]:    ${ }^{6} F W H M=2 \sqrt{2 \ln 2} \sigma \approx 2.355 \sigma$. It is reminded that this relation is valid only for gaussian beams.

[^22]:    ${ }^{1}$ the TULIP linac cannot generate the same continuous energy spectrum as a cyclotron; however, also considering the fact that the TPS approximates to the 0.1 MeV the imported energy, defining the TULIP spectrum continuous is considered an acceptable approximation for the scope of this work.

[^23]:    ${ }^{2}$ Pinnacle scripts coded by W. Kozlowska

[^24]:    ${ }^{3}$ Figure adapted from Pinnacle TPS and its manual.

[^25]:    ${ }^{4}$ Performed in collaboration with W. Kozlowska

[^26]:    ${ }^{5}$ https://www.dicomstandard.org/News/ftsup/docs/sups/sup102.pdf
    ${ }^{6}$ defined in subsection 5.2 .2

[^27]:    ${ }^{7}$ RT DICOM files were, for example, analysed with MATLAB routines to achieve the results presented in the ref. Sparse proportional re-scanning with hadron beams [2].
    ${ }^{8}$ The most recent FLAIR DICOM interface and integration with FLUKA code was developed and authored by V. Vlachoudis and W. Kozlowska; the Author's contribution to the tools consisted in defining some requirements, testing and providing feedback.

[^28]:    ${ }^{9}$ In scattering techniques the modelling of passive elements, such as modulators or compensators present on the beam line, is mandatory [18.

[^29]:    ${ }^{10}$ Performed in collaboration with W. Kozlowska
    ${ }^{11}$ Data from TIPFA facility are courtesy of F. Fracchiolla

[^30]:    ${ }^{12}$ Acknowledgements to Gregory Bolard and Laertes Papaspyrou for their support and training on planning with Pinnacle TPS.

[^31]:    ${ }^{13}$ the Treatment plan, courtesy of the Clinique Genolier, was calculated with the Eclipse TPS from the company Varian and part of the work published in ref. [2].

[^32]:    ${ }^{14} D_{5 \%}$ and $D_{95 \%}$ indicate the values of the DVH corresponding to the Dose in Gy respectively at volume value of $5 \%$ and $95 \%$

[^33]:    ${ }^{1}$ The percentage of beam-on time with respect to overall irradiation time; it can be obtained by multiplying pulse length by repetition rate.

[^34]:    ${ }^{\dagger}$ for the sake of clarity, we remind that the mean lifetime $\tau=1 / \lambda$

[^35]:    ${ }^{2}$ https://www.nndc.bnl.gov/ensdf/
    ${ }^{3}$ The branching ratio is the fraction of atoms that decay by the emission of a particular radiation, whereas decay by electron capture EC does not emit a positron [100].
    ${ }^{4}$ The isotope ${ }_{9}^{17} \mathrm{~F}$ is omitted because its contribution is negligible

[^36]:    ${ }^{5}$ DICOM data courtesy of CNAO Foundation

[^37]:    ${ }^{1}$ the dead time of a detector is the time after the detection of an event when the system is not able to detect another event. To the total dead time both the intrinsic dead time due to the physical properties of the detector as well as the data acquisition system contribute.

[^38]:    ${ }^{2}$ called PEBAII and BGO based

[^39]:    ${ }^{3}$ Torino, Pisa, Roma La Sapienza and Polytechnic University of Bari
    ${ }^{4}$ Italian Ministry of Schooling, University and Research
    ${ }^{5}$ User Datagram Protocol
    ${ }^{6}$ https://www.boost.org/

[^40]:    ${ }^{7}$ Graphical User Interface

[^41]:    ${ }^{8}$ This acquisition was performed at the end of the measurement session described in the chapter 8 and appendix B.

[^42]:    ${ }^{9}$ Neuroimaging Informatics Technology Initiative- https://nifti.nimh.nih.gov/
    ${ }^{10}$ http://www.itksnap.org/pmwiki/pmwiki.php

[^43]:    ${ }^{1}$ https://www.cs.auckland.ac.nz/courses/compsci373s1c/PatricesLectures/
    ${ }^{2}$ for the photo peak at 511 keV , it corresponds to an energy window of 56 keV FWHM, i.e. to an energy resolution of $11 \%$

[^44]:    ${ }^{3}$ Courtesy of F. Pennazio, INSIDE collaboration

[^45]:    ${ }^{4}$ from the Step 1 of the simulation tool described in the chapter 7

