Monte Carlo simulations and analysis of experimental data of a clinical proton therapy system using adaptive aperture.

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Thesis to obtain the Master of Science Degree in Biomedical Engineering

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I declare that this document is an original work of my own authorship and that it fulfills all the requirements of the Code of Conduct and Good Practices of the Universidade de Lisboa.
To...

My mom, for taking me to the library – and everywhere else; My dad, for bringing the library home; My sister, for taking home everywhere else.
Preface

The work presented in this thesis was performed at Maastro Clinic, the radiation oncology clinic of Maastricht, The Netherlands, during the period 02-2019 to 08-2019, under the supervision of Prof. Dr. Frank Verhaegen and Dr. Isabel P. Almeida within the frame of the Erasmus + traineeship program. The thesis was co-supervised at Instituto Superior Técnico by Prof. Dr Patrícia Gonçalves.

For this thesis a non-disclosure agreement was signed with Mevion Medical Systems Inc. stating that the specifications of the hardware and software of the proton therapy system should be kept confidential. The omission of the system detailed specifications has no impact on the understanding of the work described in this thesis.
Abstract

Objective: Radiotherapy aims to destroy tumours with radiation while minimizing dose to healthy tissues. Compared with conventional photon treatments, protons have potentially higher precision. This work explores the potential of Mevion S250i proton therapy system’s dynamic collimator (referred to as adaptive aperture™(AA)), to sharpen the lateral penumbra and to decrease the dose deposition in healthy tissues. This work also aims to validate the Monte Carlo model of the AA.

Methods: Different geometries (regular and irregular) at different depths (shallow and deep) were modelled using the treatment planning system (TPS) including and excluding the AA component. The plans were irradiated with a single-field and a prescribed dose of 2.00 Gy. The measurements were compared against TPS and Monte Carlo (MC) simulations using an in-house developed beam model.

Results: The use of AA allowed to reduce the irradiated field within 13% (shallow plans) and 20% (deeper plans). Lateral penumbra with AA decreased at least 3 mm for the deeper target and 8 mm for the shallower (regular geometry). The relative error between MC simulations and TPS profiles is below 5%. This error is larger when the AA is used. MC simulations present a lower entrance dose compared to the TPS.

Conclusions: The collimating function of the AA allows significant healthy tissue dose sparing in the area surrounding the tumour. MC beam model reveals good agreement with TPS.

Advances in knowledge: The use of dynamic collimators can improve proton pencil scanning techniques.

Keywords

Proton Therapy, Adaptive-Aperture, Monte Carlo Simulations
Resumo

Objetivo: O objetivo da radioterapia é destruir tumores através do uso de radiação, minimizando a dose depositada nos tecidos saudáveis. Comparativamente aos tratamentos com fotões convencionais, protões têm potencialmente maior precisão. Este trabalho visa explorar o potencial do colimador dinâmico presente no sistema clínico Mevion S250i, designado Adaptive Aperture™ (AA), para colimar o feixe de protões. Um segundo objetivo é validar o modelo de Monte Carlo da AA.

Métodos: Diferentes geometrias (regular e irregular) a diferentes profundidades foram modeladas usando o sistema de planimetria de tratamento (SPT), incluindo e excluindo a AA. Os planos foram irradiados (dose prescrita de 2 Gy) e os resultados comparados com o SPT e com as simulações de Monte Carlo (MC) usando o modelo do feixe desenvolvido internamente.

Resultados: O uso da AA permite reduzir as margens do volume irradiado entre 13% (casos mais superficiais) e 20% (casos mais profundos). A penumbra lateral com AA diminuiu entre 3 mm e 8 mm nos volumes mais profundos e superficiais, respectivamente. O erro relativo entre as simulações MC e o SPT foi inferior a 5%, sendo maior o erro nos casos que usam AA. As simulações MC apresentaram uma dose de entrada inferior ao SPT. Estas diferenças foram estudadas neste trabalho.

Conclusões: A função colimadora da AA permite diminuir o campo irradiado e, por conseguinte, a dose nos tecidos saudáveis. O modelo MC revela boa concordância com o SPT.

Avanços no conhecimento: O uso de colimadores dinâmicos permite melhorar a técnica de pencil beam scanning.

Palavras-chave
Terapia com protões, abertura-adaptativa, Simulações Monte Carlo
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At Maastro I learnt more than fits on these pages. Enumerating a few, I learnt that field hockey is a very popular sport in the Netherlands, and so is Korfball; That is ok for a grown-up to eat smarties-cake for lunch and donuts for dinner. That carnival is for everyone. That Belgian people love their country - but only if they are abroad; That Brazilians have a hard time with the Portuguese accent, but that doesn’t come in the way of sharing their incredible energy. That if you are truly passionate about your job, you don’t really need to miss work on a holiday - maybe once every 5 years. For these lessons, I want to thank Agata, Ana, Behzad, Brent, Cecile, Esther, Gabriel, Gloria, Hilaria, Murillo. I cannot help to individually acknowledge Teun, for sharing with me is knowledge for always having time to listen. I Know Porto gained a new supporter.

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Gladly, Técnico also showed me the meaning of a Europe without borders. Here I recognize the importance of my friends that don’t share the same nationality as me. Elena, in particular, for all the moral support to accomplish this work: now I understand why Portuguese call Spanish nuestros hermanos. Talking about international experiences, taking Italian classes during an engineering degree was one of my best decisions. Antônio, Barradas, George, Joana, Mariana, Majó, Renato, Tété, with you it always seems una vita in vacanza. But because life is not just the past 5 years, I also want to leave a note for the friends who grew up with me: Andreia, Bernardo, Chico, Fabinhous, Hélder, Inês, Mongape, Pipoca, Primo, Sara, Toni.

And to my ultimate sponsors to who I dedicated this work: my parents. I hope I can explain you what these pages are about once if you can’t explain it to a six-year-old, you don’t understand it yourself.
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<th>Description</th>
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<td>AA</td>
<td>Adaptive Aperture</td>
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<tr>
<td>AG</td>
<td>Air gap</td>
</tr>
<tr>
<td>CT</td>
<td>Computer tomography</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>EMS</td>
<td>Energy modulation system</td>
</tr>
<tr>
<td>FWHM</td>
<td>Full width at half maximum</td>
</tr>
<tr>
<td>IDD</td>
<td>Integrated depth doses</td>
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<td>LP</td>
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<td>MC</td>
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<td>MCS</td>
<td>Multiple Coulomb Scattering</td>
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<td>MLC</td>
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<tr>
<td>MU</td>
<td>Monitor Unit</td>
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<tr>
<td>OAR</td>
<td>Organ at risk</td>
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<tr>
<td>OF</td>
<td>Objective functions</td>
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<tr>
<td>PBS</td>
<td>Pencil beam scanning</td>
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<tr>
<td>POI</td>
<td>Point of interest</td>
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<tr>
<td>PS</td>
<td>Passive Scattering</td>
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<td>QA</td>
<td>Quality Assurance</td>
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<tr>
<td>ROI</td>
<td>Region of Interest</td>
</tr>
<tr>
<td>RBE</td>
<td>Relative biological effectiveness</td>
</tr>
<tr>
<td>SOBP</td>
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<tr>
<td>TIC</td>
<td>Transmission ion chambers</td>
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This chapter begins describing cancer's impact worldwide. The high incidence of the disease increases the need for better and more efficient radiotherapy treatments. Conventional radiotherapy is discussed and compared to hadron therapy and, in more detail, to proton therapy. The clinical rationale for the former is discussed, before a general thesis overview is presented.
1.1 Cancer

Worldwide, the cancer incidence rate has increased making it the second leading cause of death after cardiovascular disease. The World Health Organization estimated the global cancer burden to have risen up to 17 million new cases and causing 9.5 million deaths in 2018. In Europe, 3.09 million new cancer cases were registered in the past year and it was the cause of death of 1.93 million people. This is particularly alarming considering that Europe contains 9.6% of the world population but has 18% share of the global cancer burden. Also alarming are the prospects for 2030: 24.6 million newly diagnosed patients worldwide and 13 million deaths. The main factors contributing to this scenario is population growth and ageing, which increases the probability of suffering and accumulating genetic mutations. The most common cancers are female breast followed by colorectal, lung and prostate cancer which together represent half of the overall burden of cancer in Europe.

Cancer is a broad term used for a set of diseases in which abnormal cells divide in an uncontrolled way forming a benign, premalignant or malignant tumour. The latter in an advanced stage can spread to other parts of the body through the blood and lymph systems, a process referred to as metastasizing. Cancer has its origins in genetic mutations that affect the way cells function, specially how they grow and divide. What triggers these mutations is not yet fully understood but it is a consequence of the interactions between a person’s genetic factor and three categories of external agents: physical (exposure to UV and ionizing radiation), chemical (consumption of arsenic, tobacco smoke components) and biological (such as infections from certain viruses and bacteria).

Depending on cancer's type and stage, there are several treatments and management (curative or palliative) options including chemotherapy, radiation therapy and surgery. Radiation therapy is an important treatment modality given to approximately 50% of all cancer patients during their course of illness, 40% with curative intent.

1.2 Radiation Therapy

Radiation therapy uses high-energy ionising radiation such as x-rays, electrons or protons to cure or relieve symptoms of cancer and reduce the chance of cancer regrowth after surgery. Radiation effects are mainly attributed to two types of DNA damages at the cell nucleus level: a direct effect in which DNA strand breaks due to the incident particle, and an indirect effect in which DNA strand breaks due to free radicals produced by the incident particle in the cell environment. The main goal of radiation therapy is to maximize the damage to cancerous cells while minimising the damage to the surrounding healthy tissues. This is especially important as the proteins needed to repair and regrow healthy tissue also fuel the growth of cancer cells. The reason radiation therapy can be used to treat cancer cells is an increased radio-sensitivity, compared to healthy tissues, due to their increased multiplication rate. However, not all cancers experience this radio-sensitivity favourable to radiation therapy, in contrast, due to metabolic disorders which can lead to hypoxia, cancers can even be radio-resistant.

Conventional external radiation therapy uses X-rays (high energy photons, typically from 6 MeV to 18 MeV produced by accelerated electrons) or, for some more superficial targets, electrons up to 20 MeV.
Radiation therapy can also be administered internally, by applying radioactive seeds directly in contact with the tumour, which is called brachytherapy.

Nevertheless, from the discovery of X-rays, radiation therapy has quickly evolved. Nowadays, both neutral and charged particles can also be applied to oncological treatments. The use of external beams of charged particles to treat cancer is commonly called hadron therapy. In this case light or heavy ions such as protons or carbon ions are accelerated up to 250 MeV and 430 MeV per nucleon (MeV/n), respectively. These particles can penetrate the tissues with little diffusion and deposit the maximum energy just before stopping, because of their unique physical properties.

1.3 Clinical Rationale

The case of using proton beams to treat tumours is commonly called proton therapy and it will be the main subject of the work presented in this thesis. Protons deposit most of their energy at a given depth, creating a peak of dose called Bragg peak (Figure 1.1), named after William Henry Bragg who first discovered it in 1904. The Bragg peak’s depth depends on the particle energy as well as the traversed medium, therefore in cancer treatments the depth of the particle beam can be tuned so that it deposits most of its energy at the tumour, sparing the healthy tissues behind. Combining beams with different energies results in a set of overlapping Bragg peaks, hence called spread-out Bragg peak (SOBP), a uniform dose can be delivered to a volume as illustrated in (Figure 1.1). The particle irradiation using a SOBP technique has the advantage of decreasing the total volume of healthy tissue irradiated, compared to megavoltage photon beams (detailed explanation presented in Chapter 2).

Figure 1.1 – Relative depth-dose curves for protons (red) vs. photon (black) beam irradiation. The proton curve is the summation of several “Bragg peaks” (red curves) resulting in higher dose deposition over a specific depth in tissue (e.g., the tumour). The beige-shaded regions demonstrate areas of excessive normal tissue irradiation by photons that could otherwise be spared by protons. (Reproduced from 15)

1.4 Thesis Outline

The work described in this thesis focused on performing Monte Carlo simulations to model the proton therapy clinical system at Maastro Clinic, which uses a novel component for beam collimation, called by
its manufacturer *adaptive aperture* and therefore used onwards in this work. The system in question was the first clinical system worldwide to add beam collimation to a pencil beam scanning machine (concept explained in detail in the following sections) and it is, by September 2019, only present in three locations (Maastro Clinic, The Netherlands, the university of Oklahoma Stephenson cancer centre, Oklahoma, U.S.A and MedStar Georgetown University Hospital, Washington, D.C., U.S.A). The innovative component of the adaptive aperture (AA) requires performing experimental validation. In this line of work, measurements were performed to attest the influence of this component using different geometries at different depths. Chapter 3 describes the materials and methods used to perform the measurements, while the results obtained are contemplated in chapter 4. Chapter 5 compares the TOPAS (Monte Carlo code based on Geant4) beam model against Raystation, the treatment planning system (TPS) available at Maastro Clinic and describes the influence of different factors on the deposited dose. Final conclusions are drawn in chapter 6. A personal overview about the prospects of proton therapy in Portugal is given at the end of this work.
Chapter 2

Physics and technology of proton therapy

This chapter describes the physical interactions for the most common particles used in radiation therapy: photons, protons and electrons, explaining the different depth-dose curves for each case. State-of-the-art technology is presented as well as an historical overview of proton therapy, from the discovery of the Bragg peak until nowadays, focusing on the current proton therapy stage in the Netherlands. Challenges in this area are brought-up at the end of the chapter.
2.1 Particle interactions with matter

Different particles deposit dose in tissue in different ways. Figure 2.1 illustrates different depth-dose curves for four different particles used in oncological treatments: electrons, photons, protons and carbon ions. The different ways of depositing energy while traveling through matter comes from the underlying physical interactions of each particle, reviewed next.

![Comparison of depth dose curves for (a) 20 MeV electrons (b) 18 MV photon (c) 130 MeV proton (d) 300 MeV/n carbon ion.](image)

2.1.1. Photons interactions with matter

Photons interact with matter through three different processes: photoelectric effect (Figure 2.2a), Compton scattering (Figure 2.2b) and pair production (Figure 2.2c).

![Photon Interaction mechanisms. (a) Photoelectric effect: material emits electrons when a photon hits its surface; (b) Compton effect: The incident photon hits an electron with a wavelength $\lambda_0$, transfers part of its energy to the electron that is ejected with velocity $v$. The initial photon is scattered with $\lambda > \lambda_0$. (c) Pair production: a photon interacts with a nucleus and its absorbed, resulting in creation of a particle-antiparticle pair, electron-positron.](image)

The photoelectric effect (Figure 2.2a) occurs mainly when the energy of the photon is close to the binding energy of orbital electrons (it can also occur at higher energies, but the probability is lower). In
this case, the photon is absorbed and transfers all its energy to the orbital electron, which is then ejected from the atom. The kinetic energy of the released electron is the difference between the incident photon energy and the binding energy.

Compton scattering (also known as incoherent scattering), occurs when the photon has a greater energy than the binding energy of the electron, hence the latter can be ignored, and the electron is a “free electron”. In this case, an electron is scattered away in conjunction with the scattered photon that has a lower energy than the incoming one as seen in Figure 2.2b.

Pair production is the process through which the photon interacts with an electron or a nucleus producing a positron-electron pair as illustrated in Figure 2.2c. Since an electron/positron has a rest mass equivalent to 0.511 MeV of energy, a minimum photon-energy of 1.022 MeV is required for pair production to happen. Pair production only happens close to the nucleus, which can take on the momentum gained by the new particles.

In a radiation therapy treatment with x-rays, the beam enters the patient on the surface, where it delivers a certain surface dose. Beneath the surface, the dose first rises rapidly until reaching a maximum value and then decreases almost exponentially (Figure 1.1, curve b). For 18 MV photon beam, the maximum is reached around 3 cm. The region between the surface and the maximum dose is called build-up region and results from dose deposited by energetic secondary charged particles formed through the processes mentioned before (photoelectric effect, Compton scattering and pair production). Except for a superficial lesion, a higher dose to the tumour as compared to the healthy tissue can only be achieved using multiple beam directions. Standard photon treatment uses, for breast cancer, 6 MV photon beams.

Nowadays, state-of-the-art photon treatments use volumetric modulated arc therapy (VMAT), a fast and precise intensity modulated therapy. VMAT uses a linear accelerator to produce photons. Very small beams with varying intensities are aimed at the tumour during a complete 360 degrees rotation of the system around the patient. This results in attacking the target in a complete three-dimensional manner, maximizing the dose to the target and minimize dose to healthy tissues but at higher costs when compared to typical photon treatments with 2/3 static beams shooting from different directions.

### 2.1.2. Proton interactions with matter

Protons lose energy primarily by inelastic Coulomb interactions with the atomic electrons (Figure 2.3a) resulting in ionization and atom excitation as described by the Bethe Bloch equation (detailed explanation in section 2.1.2ii).

A smaller fraction of protons undergo elastic Coulomb scattering (Figure 2.3b), in which the particles scatter a few degrees due to multiple electromagnetic collisions with atomic nuclei (and, to a smaller degree, electrons). Finally, around 20% of the original protons experience nuclear interactions with the nucleus itself or with constituents of the nucleus - protons, neutrons, or clusters such as alpha particles - where secondary particles are produced (Figure 2.2c).
Theoretically proton bremsstrahlung, the process by which charged particles are deflected by a nucleus, is also possible but as the energy loss in this process is proportional to the inverse square of the particles’ mass, it is mostly relevant in electrons energy loss.

![Figure 2.3 – Proton Interaction mechanisms. (a) energy loss via inelastic Coulombic interactions; (b) deflection of proton trajectory by repulsive Coulomb elastic scattering with nucleus; (c) Interaction of primary proton and creation of secondary particles via inelastic nuclear interaction (p: proton, e: electron, n: neutron, γ: gamma rays). Reproduced from Newhauser and Zhang (2015).](image)

### i. Bethe Bloch theory

The energy loss rate or stopping power, \( S \), due to interactions of charged particles with atomic electrons while traversing a medium is given by the quotient between \( dE \) and \( dx \), where \( E \) is the mean energy loss and \( x \) is the distance. A more useful quantity, which is independent of the medium’s density (apart from the density correction factor), is the mass stopping power, \( S/\rho \), which is expressed by the Bethe-Bloch equation (equation 2.1),

\[
\frac{S}{\rho} = -\frac{1}{\rho} \frac{dE}{dx} = K z^2 Z \frac{1}{\Lambda\beta^2} \left[ 2 \ln \left( \frac{2m_ec^2\gamma^2T_{max}}{I^2} - \beta^2 - \frac{\delta}{Z} \right) - \frac{C}{Z} \right] \,[MeV]
\]

where \( K = 4\pi N_A r_e^2 m_e c^2 \), \( N_A \) being Avogadro’s Number, \( r_e \) and \( m_e \) the radius and mass of the electron, \( c \) the speed of light, \( z \) the charge number of the particle moving in a target material of atomic number \( Z \) and atomic mass \( A \); \( \rho \) is the mass density of the medium and \( I \) the mean ionization potential of the medium. \( \beta \) is the charged particle speed in units of \( c \); \( \gamma \) is the Lorentz factor given by \( (1 - \beta^2)^{-1/2} \). The density effect term, \( \delta/2 \), corrects for the polarization caused by the projectile along its path – relevant only for ultra-relativistic charged particles – and \( C/Z \) is the shell correction term which accounts for the decreased probability interaction for projectiles with velocities similar or smaller than the orbital velocity of bound electrons. The latter is important when the particle velocity becomes closer to the velocity of the atomic electrons. Finally, \( T_{max} \) is the maximum kinetic energy which can be transferred to a free electron in a single collision.

In proton therapy treatments, the velocity of the particles can be easily computed within the clinical ranges of energy (up to 250 MeV) protons experience a maximum velocity around 0.66 times the velocity of light, therefore these are moderately relativistic particles. In this range of energies, excluding the zero
where the Bethe-Bloch equation doesn’t hold, the shell correction and the density effect terms are not relevant and equation 2.1 can be rewritten as equation 2.2

\[
\frac{S}{\rho} = K Z Z_p \left[ 1 - \ln \frac{2m_e c^2 \gamma^2 T_{\max}}{I^2} - \beta^2 \right] \text{[MeV]}
\]

The ratio \(Z/A\) is almost constant for all elements: it varies from 0.5 for biological elements such as carbon and oxygen to 0.42 for high-\(Z\) components such as lead. Hydrogen is an exception since \(Z/A\) ratio is 1, but the concentration of this element is low (around 10%) and nearly uniform through the human body. Therefore, the mass stopping power depends mainly on charge and velocity of the incident particle (not on the particle’s mass, although indirectly, heavier particles move slower for the same kinetic energy). The mass stopping power also depends on the target’s material: linearly with the number of electrons per square centimetre, as the energy loss occurs by Coulomb interactions between the protons and the atomic electrons, and logarithmically through the mean excitation energy, \(I\). The mean excitation energy is a geometric mean value of all ionization and excitation potentials of an atom of the absorbing material. It increases with \(Z\) and binding effects influence its exact value, so calculations are often inadequate to accurately estimate its value. Taking the example of water, its experimentally measured \(I\)-value has been ranging from 67 eV to 78 eV over the last decades, resulting in a 5 to 6 mm difference the range of a particle beam in water. Figure 2.4 plots stopping power of a protons ranging from 1 to \(10^4\) MEV in water, according to the Bethe-Bloch theory.

Figure 2.4 - Stopping power of protons in liquid water (1.00 gcm\(^{-3}\), 75.0 eV) computed using values from NIST database.

Figure 2.4 shows that, when the kinetic energy of the particle decreases – which happens while the particle is penetrating the target medium – the energy loss rate increases. Near the end of the particles’ range, when most of its energy has been lost, there is a steep increase and the energy loss rate \((dE/dx)\) reaches a maximum, corresponding to the peak in energy loss at low energy, and then it drops to zero.
as the particle comes to rest. Peaks for proton beams with different energies are illustrated in Figure 2.5a.

![Figure 2.5](image)

**Figure 2.5** - (a) Depth-dose curves for different energy proton beams in liquid water. (b) Parameters usually used to define the peaks: \( R_{90} \), \( R_{80} \), FWHM, \( l_{8020} \).

Figure 2.5a confirms that increasing the beam energy results in an increased range. Different parameters are used to compare different beam, as defined in Figure 2.5b: \( R_{80} \), the position of the 80% dose in the distal falloff. For mono-energetic proton beams with energies used clinically, the \( R_{80} \) corresponds to the mean projected range of a proton, i.e. the range at which 50% of the protons have stopped. Thus, the \( R_{80} \) is independent of the initial energy spread of the proton beam. Nevertheless, in most proton therapy facilities, the prescribed range is defined at the 90% fall-off, \( R_{90} \). The distal dose fall-off is measured by the difference between the distal \( R_{80} \) and \( R_{20} \) (20% distal falloff) defined by the parameter \( l_{8020} \).

### ii. Multiple Coulomb Scattering

As shown in Figure 2.5a, beams of primary protons with higher energies have broadened peaks. This beam broadening is measured in terms of full width at half maximum (FWHM), defined as the distance between the proximal and distal points where the dose is half the maximum dose., e.g. the peak width measured as the FWHM of the 230 MeV proton beam in Figure 2.5a is broader than the width of the 100 MeV proton beam. This phenomenon is due to multiple Coulomb scattering (MCS). As stated, a proton passing close to the nucleus will be elastically scattered or deflected by the repulsive force from the positive charge of the nucleus. If the number of individual collisions is large enough the MCS angular distribution for small angles is described as a Gaussian, whereas for large angles it follows Rutherford scattering. As a rule of thumb, the contribution to the width of the beam at the Bragg peak due to MCS alone is approximately 2% of the proton range of the Bragg peak in water.

### iii. Nuclear Interactions

In addition to the mechanisms already described, protons may interact with the atomic nucleus producing secondary particles via non-elastic nuclear reactions in which the nucleus is irreversibly transformed.
Paganetti (2002) \(^{21}\) reported that for a 160 MeV proton beam in water, 19.6% of the primary protons undergo a nuclear interaction as they slow down. Neutron’s spectra in water for beam energies of 160, 200 and 230 MeV were dominated by neutrons of energies above (1–10) MeV almost up to the primary beam energy.\(^ {22}\)

On average, the number of secondary particles per primary proton nuclear interaction is 1.80 protons, 0.63 neutrons, 0.38 α-particles, 0.02 deuterons, 0.002 Helium-3 and 0.001 tritons. The energy deposition due to these particles is presented in Figure 2.6.

![Figure 2.6 - Depth-dose distributions (Bragg peak normalized to 100%) for a 160 MeV proton beam incident on a water phantom. (Left) Relative total dose and the relative dose due to primary and secondary protons. (Right) Doses due to different types of particles (solid lines: primary p, secondary α-particles and deuterons (d); dashed lines: secondary protons (p), helium-3 (3He), tritons (t)). The position of the Bragg peak is indicated with the vertical solid. Logarithmic scale on y axis is applied. Reproduced from Newhauser et al (2013) \(^ {21}\).

To account for the dose deposited by secondary particles in the final dose delivered is crucial: despite that the neutron absorbed dose can be neglected (less than 0.7% of the total dose for a passive scattering system\(^ {23}\)), the most common neutron reaction creates secondary protons. These particles present an higher Relative biological effectiveness (RBE), defined as the ratio of the dose of a reference radiation (typically γ-rays or X-rays) and dose of a test radiation (for example, neutrons, protons, heavy ions) that produce the same biological effect.\(^ {24}\) Thus even a small absorbed dose might cause side effects in the patient, the most severe of which is the induction of a second primary cancer\(^ {25}\).

Therefore, the decrease in the primary proton fluence due to nuclear interactions doesn’t translate in a decrease in delivered dose as it is compensated by emission of secondaries that also contribute to energy deposition.

### 2.1.3. Electron interactions with matter

Electrons (and their anti-particle, positrons) fall in the category of light charged particles, that have a high probability of interacting with any particle in their path. They lose energy by two main processes: ionization (electrons interact by inelastic scattering with atomic orbital electrons, leading to excitation and ionization of atoms of the medium) and bremsstrahlung (explained in section 2.1.2). Bremsstrahlung energy loss rate is proportional to electron’s energy, \(E\), while the ionization loss rate varies only logarithmically with the \(E\). Therefore, the former is more important at lower energies while the latter becomes more relevant with increasing energy\(^ {26}\).
A single electron beam dose distribution has a steep dose fall off both laterally and distally after a maximum that is reached at a shallow depth (which increases with energy) as seen in Figure 2.1(curve a). For this reason, electron beams are used clinically to irradiate superficial cancers and diseases.

In the context of proton therapy, the dose produced by secondary electrons is considered negligible at the Bragg peak, as they travel only a few millimetres, even for very energetic protons. For example, at 200 MeV proton energy, the maximum secondary electron energy is around 500 keV, which corresponds to an electron range of approximately 2 mm in water.14

2.2 State of the art

The advantage of proton therapy compared to conventional radiation therapy was first pointed out by Wilson in 194627 when he first presented the idea of using proton beams for treating targets deep within healthy tissue by exploring their characteristic energy deposition (Figure 2.1 curve c). Eight years later, the University of California at Berkeley treated the first patient with metastatic breast cancer to the pituitary gland, using a 184-Inch Cyclotron. However, only in the 1980s the first low energy proton therapy centres started to appear spread around the world: the Paul Scherrer Institute (Switzerland) in 1984, Clatterbridge (UK) in 1989, Orsay (France) in 1991, and iThemba Labs (South Africa) in 1993. This delay in the use of proton therapy was mainly due to lack of technology both at the level of the delivery, and at the imaging and planning. Since the 1990s, commercial entities like IBA (IBA Louvain-la-Neuve, Belgium), or Varian (Palo Alto, CA) began to build cyclotrons or synchrotrons for clinical purposes. Traditional cyclotrons or synchrotrons are very large, typically several meters wide and high, and weigh hundreds of tons. Most existing proton therapy facilities have only one accelerator for multiple treatment room. In recent years, compact systems and single-room solutions have been proposed by several vendors. Mevion Medical Systems (Littleton, MA, USA) developed a compact cyclotron that employs a superconducting magnet, which will be further analysed in this work.

With the technological improvement, by the end of the last century, approximately 25 facilities were in operation. This number exponentially increased in the last decades, with 97 proton therapy centres operating worldwide by September 2019, 43 under construction and 25 in planning stage28-30. As more and more facilities become functional, the number of patients treated with this technology also increased and by December 2018, over 190 000 patients have been treated with proton therapy alone31.

Currently, proton therapy is being used increasingly for the treatment of paediatric32, skull base33,34, hepatocellular35,36, head-and-neck37,38 and brain tumours39 as well as selected breast40 and lung cancers41,42, pancreatic carcinoma43,44, and ocular tumours45. Proton therapy is of greater interest if the target volume is close to critical anatomical structures with important functional properties (commonly called organs at risk, OAR), where a small local overdose can cause significant complications. Proton beams also confer an advantage in otherwise still poorly manageable disease, e.g., for chondrosarcoma of the skull base46 and the spine47,48, the former often cited as the most evident advantage for proton therapy, as shown in Figure 2.7, as the proton plan provides considerable sparing of healthy
tissues anterior to the spinal canal (hearth, stomach), significantly reducing total integral dose to the patient.

**Figure 2.7** - Dosimetric comparison between the use of proton therapy (on the left) and conventional x-ray radiation therapy (on the right) to treat a paediatric medulloblastoma. In both cases, a treatment plan was designed to deliver the same equivalent biological dose to the tumour. Adapted from Eaton et. al. 49

Figure 2.7 highlights the benefits of proton therapy compared to state-of-the-art photon radiation therapy used for craniospinal irradiation in a medulloblastoma patient. Medulloblastoma is a malignant brain tumour that starts in the cerebellum and tends to spread through cerebrospinal fluid to other areas around the brain and spinal cord, hence the need to cover both structures with radiation. Although the target coverage is similar in both plans, on the left image we can notice an absence of dose in the anterior part of the body, sparing OARs such as the heart and stomach.

### 2.2.1. Proton beam delivery techniques

To successfully deliver a certain dose with proton beams to a target volume, two main techniques have been used and are available in clinical systems worldwide: passive scattering (PS) and pencil beam scanning (PBS), schematically shown in Figure 2.8 and described in the following paragraphs.
Passive scattering technique takes advantage of the energy loss that occurs as protons pass through a material to spread the proton beam in the longitudinal direction and scattering it in the lateral direction (due to particle scattering). As Figure 2.8a shows, a modulator system is used to bring the narrow monoenergetic proton beam to the desired energy. Multiple beams of various discrete energies are selected for treatment. A combination of custom-made patient-specific collimators (to shape the beam laterally) and compensators (to shape the beam distally) conform the dose to the target volume.

Pencil Beam Scanning uses magnets to deflect the beam. An energy modulator system (e.g., range shifter) is applied to vary the beam energy (controlling the depth of the beam), delivering dose to the tumour layer by layer over a three-dimensional region (Figure 2.8b). With this technique, there are no modifying devices such as collimators or compensators, decreasing the complexity of the treatment, producing fewer secondary particles such as neutrons, and reducing the integral dose to the patient in comparison with PS systems. Figure 2.8 highlights that the coverage of the tumour achieves very good results on the distal part of the target while, in a proximal part, extra dose is deposited in surrounding tissue.

Increased clinical evidence \(^{41-43}\) report the benefits of PBS over PS in terms of toxicity to the healthy tissues and conformity of the dose distribution to the target. Also, custom-made modifying devices must be manufactured in-house/outsourced and stored for a period of time (ranging from hours to months, depending on the irradiated material)\(^{50}\) after becoming radioactive from contact with the proton beam. These requirements increase the treatment cost when using PS technique (without contributing to revenue) which favours the use of PBS.

### 2.2.2. Treatment planning system

The treatment planning system (TPS) is the general name given to the software where radiation therapy treatment plans are made. Treatment planning requires the acquisition of computer tomography (CT) images. Once this dataset is loaded and tumours are identified, the TPS computes the dose distribution in the patient based on how the therapeutic system will deliver radiation. This allows for iteratively optimize different parameters such as beam number, beam direction, prescribed dose or number of fractions based on the trade-off between maximizing the dose to target and minimizing the dose to healthy tissues.
Until recently, analytical algorithms have represented the state of the art in proton dose calculation for TPS. These algorithms have very fast computational times but are, on the other hand, less accurate. Major limitations are cases with large inhomogeneities and all beams using a range shifter. As the available computational power increases, more systems are moving towards Monte Carlo (MC) methods (see section i).

i. Monte Carlo methods
MC dose methods don’t depend on any external formulas/methods. The algorithm track the paths of individual particles and are specialized to meet the accuracy requirements of radiation therapy for treatment planning, while still implementing approximations to minimize computational time (for instance, nuclear absorption and MCS are neglected for heavier secondaries; Neutrons and gammas are not transported - but their given fractions of the absorbed energy are included in the energy balance and considered to leak out - ; delta electron production is not considered - justified by the fact that released electrons have on average a very short range). The impact of these approximations in dose accuracy is not well known yet and brings up the necessity to benchmarking these algorithms to full MC codes. To address these problem and as typical MC codes have high learning curves, more and more user-friendly MC codes are becoming available in the market. This work uses TOPAS, a Geant4 based Monte Carlo code.

2.2.3. Proton therapy in the Netherlands
In 2009, the Horizon Scanning Report published by the Health council estimating that 5% of patients with breast cancer and 84% of the paediatric tumour, base of skull tumours and ocular melanoma case treated in the Netherlands until 2005 would benefit of using protons. On 2013, the ministry of health issued four permits to build four different centres (Groningen, Amsterdam, Delft and Maastricht, Figure 12) that would cover the Dutch territory considering population density.
Between 2018 and 2019, three of the four Dutch proton therapy centres started treating patients. In particular, the Maastro Clinic, in Maastricht, treated the first patient only 11 months after the arrival of the cyclotron, making it the fastest construction and commissioning of a proton centre ever. The construction of the fourth centre, Amsterdam UMC, in Amsterdam did not come forward yet.

The Healthcare Institute, the Health Council and the Ministry of Health, Welfare and Sports decided that eye melanomas, childhood tumours and tumours in the skull base indications are directly admitted for proton therapy, whereas other indications will have to go through a selection process based on the radiation induced toxicity levels. For these indications (prostate cancer, lung cancer, breast cancer and head and neck tumours), the innovative Dutch model-based approach was introduced, in which a comparison between proton therapy and conventional x-ray radiotherapy treatment plans is made based on predefined models and only patients with a benefit in normal tissue dose according to these models’ thresholds will receive proton therapy treatment. Based on nationally established guidelines and selection criteria, approximately 3% of all irradiated cancer patients are expected to be eligible for the proton therapy.

### 2.2.4. Challenges of proton therapy

Proton therapy faces different challenges that have implications for the widespread clinical adoption of the technique. In this section both physical challenges (range uncertainties) and technical challenges (facility and treatment cost’s) are addressed.

#### ii. Ranges Uncertainties

The accurate range of protons on a target medium is still hard to predict precisely. It is particularly important because, due to the sharp distal dose falloff of protons, a small shift in the SOBP position can cause either irreversible damage to healthy tissues and OAR or it may cause part of the tumour not receiving any dose. The source of this range uncertainties can be due to anatomical changes (e.g., weight loss due to lack of appetite associated to cancer), inaccuracies on dose calculations (e.g., the uncertainty on the water I-value leading to a shift of the SOBP), treatment delivery (e.g., organ motion, especially if the beam crosses the lungs or the bladder) or tumour shrinkage during treatment, as exemplified in Figure 2.10. The magnitude of overdose and undertose within the target will be reduced when more treatment fractions are used, but its nearly around 5%.

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**Figure 2.9** – Prospective proton Therapy centres in the Netherlands, presented in 2013, from which three are already in operation: Holland Particle Therapy Centre (Delft), UMC Groningen Protonen Therapie centrum (Groningen) and ZON-PTC, a joint undertaking between MAASTRO clinic and the Maastricht University Medical centre (Maastricht UMC+).
Figure 2.10 - Range uncertainties due to tumour shrinkage. Dose planned on the CT acquires (left) before treatment starts - beams stops at the distal edge of the tumour and (right) 5 weeks later, were tumour shrinkage during treatment causes beam to overshoot. Image from 56.

Also, Figure 2.10 illustrates the use of computer tomography (CT) data sets for treatment planning and range calculations. Therefore, limitations of CT image acquisitions will affect range predictions.

Current clinical practice handles the proton’s range uncertainty problem including safety margins. An example of a margin recipe is 3.5% + 1 mm, which results in a deliberate overshoot of 8 mm for a 20 cm deep target, introduced at the Harvard Cyclotron Laboratory in 1985 57 and still used by several institutes 19. Applying conservative margin recipes to assure full target coverage may lead to substantial increase in dose deposition and toxicity in the critical structures near the tumour, potentially reducing the leverage of treatment with proton therapy.

iii. Costs

Proton therapy is an expensive technology: initial investment in a facility can cost between €22.5 million and €180 million in terms of construction and equipment expenses 58 and each treatment costs around €36 thousand. However, this technology has been proved cost-effective when compared to photon therapy for cases where patients are carefully selected 59,60.

Peeters et al. 61 compare general (Table 2.1) and treatment costs (Table 2.2) for three different therapy facilities (protons, photons and combined-facilities). From the first, conclusions were that capital, yearly and mean costs per fraction are the most expensive using carbon ions, then using protons and the cheapest using photons, mostly due to the need to accelerate the particles – and carbon-ions are heavier than protons, causing the need for more powerful and more expensive machines. However, Table 2.2 shows that, for some cases, proton and carbon ion treatments can be cheaper than photon treatments, e.g. for prostate cancer, mainly because of a reduced number of fractions when comparing to protons (due to higher RBE).
Table 2.1 - Cost estimation of radiation therapy for combined (proton and carbon), proton-only and photon facilities. Number taken from [22].

<table>
<thead>
<tr>
<th></th>
<th>Combined</th>
<th>Proton-Only</th>
<th>Photon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capital Costs (million €)</td>
<td>138.6</td>
<td>94.9</td>
<td>9.6</td>
</tr>
<tr>
<td>Total cost per year (million €)</td>
<td>36.7</td>
<td>24.9</td>
<td>9.6</td>
</tr>
<tr>
<td>Mean cost per fraction (million €)</td>
<td>1128</td>
<td>743</td>
<td>233</td>
</tr>
</tbody>
</table>

Table 2.2 - Treatment costs for four different tumour sites using carbon ions, protons delivered in proton-only facilities and photons. Different photon techniques exist: IMRT (Intensity Modulated Radiation Therapy), SBRT (Stereotactic body RT), 3DRT (3 dimensional RT), FSRT (Fractionated stereotactic RT). Numbers taken from [22].

<table>
<thead>
<tr>
<th>Tumour Site</th>
<th>Carbon Cost (€)</th>
<th>Fractions</th>
<th>Proton Cost (€)</th>
<th>Fractions</th>
<th>Photon cost (€)</th>
<th>Fractions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>12.530</td>
<td>20</td>
<td>16.090</td>
<td>39</td>
<td>18.160</td>
<td>39 (IMRT)</td>
</tr>
<tr>
<td>Lung</td>
<td>10.030</td>
<td>4</td>
<td>12.380</td>
<td>10</td>
<td>3.720</td>
<td>4 (SBRT)</td>
</tr>
<tr>
<td>Head &amp; Neck</td>
<td>30.080</td>
<td>16</td>
<td>39.610</td>
<td>32</td>
<td>11.520</td>
<td>33 (IMRT)</td>
</tr>
<tr>
<td>Skull-base chordoma</td>
<td>25.070</td>
<td>20</td>
<td>20.530</td>
<td>37</td>
<td>13.970</td>
<td>30 (FSRT)</td>
</tr>
</tbody>
</table>

Similar conclusions were drawn in 2005 when protons were estimated 2.4 times more costly than conventional radiotherapy, in paediatric cancers. This number changes if not only the initial costs are compared but also the total costs of all adverse effects: in this case, a 2.6-fold difference in favour of PBT was obtained, mostly due to late side effects, such as IQ decline, hearing loss, and growth hormone deficiency.

The data presented before is from the past decade. Due to its innovative and rapid evolving character, proton therapy is quickly being optimized, therefore data like this easily becomes obsolete. With further research, proton therapy’s costs are expected to drop. Belgium assessed the viability of building a particle centre in 2013 and the capital cost of a proton-centre was 51.5 million, half the value reported in Table 2.1 mostly because companies are already producing compact systems, which cost much less. Besides, these systems can easily be incorporated in already built medical centres, sharing resources and reducing operating costs. One example is Mevion S250i, the proton therapy system used in Maastro Clinic that will be described in chapter 3.
Chapter 3

Materials and Methods

This chapter will provide a detailed description of the proton therapy system assembled in Maastro Clinic: the in-house beam model developed of this system (Almeida et al. 67) and the method used to perform Monte Carlo simulations. Moreover, this chapter will provide the experimental setup designed for the validation of the model of the novel component for beam collimation, the adaptive aperture, continuing the work described by Almeida et al. 68.
### 3.1 Proton therapy system

Maastro clinic is the first centre in Europe to provide proton therapy using the compact, single-room system, Mevion S250i Proton Therapy System with HYPERSCAN® Pencil Beam Scanning (Mevion Medical Systems Inc., Littleton, MA, U.S.A) illustrated in Figure 3.1a. The nozzle can rotate between -5° and 185° around the patient and extend between 3.6 cm and 33.6 cm towards the isocentre. The nozzle is used to direct the particle beam from different directions to the tumour in a patient, while lying on the treatment table.

In this system protons are accelerated in the gantry-embedded cyclotron producing a pencil beam with a fixed energy of 230 MeV. The protons are conducted from the cyclotron to the patient through the nozzle, also called beam line. Inside the nozzle (Figure 3.1b) a dual axis scanning magnet, which steers the beam in the $x$- and $y$-directions and the dosimetric system composed of six transmission ion chambers (TICs) responsible for measuring the beam spot position, shape and charge.

A fast energy modulation system (EMS) consisting of eighteen lexan plates which, due its low atomic number (Z) aims to minimize neutron production and proton scatter. Through 162 plate-combinations and with optimized thicknesses and air gaps, the EMS provides degradation of the nominal range in water in multiples of 2.1 mm, covering a depth of approximately 32 cm (90% distal falloff) to the surface. Furthermore, the one nominal proton energy combined with this type of EMS, results in Bragg peaks with constant beam widths, e.g. the FWHM in the beam direction is approximately 27 ± 1 mm measured in integrated depth doses (IDDs).

![Figure 3.1](image)

**Figure 3.1** - (a) Mevion S250i Proton Therapy System with HYPERSCAN®, with an inner gantry that rotates from -5 to 185 degrees around the isocentre in the gantry plane with a 0.1 degree accuracy (isocentricity of gantry and couch within 1 mm). (b) Inner gantry with the sketched interior of the nozzle zoomed in. The white arrows refer to the four previously mentioned components: (from left to right): the dual axis scanning magnet, the dosimetric system, the energy modulation system (EMS) and the Adaptive Aperture (AA). [Adapted] 67,69

The AA, used for beam collimation, is located downstream of the beam line. It consists of two opposing blocks of seven dynamic leaves made of Nickel 200 (99.6 % pure) moving in a 20 x 20 cm² treatment field as a block in the $y$-direction and each leaf independently in the $x$-direction. The selected material was used due to minimize neutron production (Nickel's neutron cross section is 4.5 whilst lead neutron's cross section is 0.171) 71). Each block is composed of two larger leaves on the top and bottom with 20.75 mm thickness and five inner leaves 5 mm thick. To simplify, the larger leaves will be called jaws onwards, and the inner leaves just leaves. A detailed representation of the AA can be found in Figure
3.2. The jaws of the AA are the only parts that can close completely and are used to minimize leakage. The five leaves shape the edges of the irradiated volume with a precision of 0.5 mm.

![Image of Mevion's AA](image)

*Figure 3.2: Mevion’s AA opposite to the beam eye view: The AA encompasses two blocks (left and right) of seven parts each, from which you can distinguish two jaws (top and bottom) with increased thickness (y-direction) and five inner leaves. The AA moves as a block in the y-direction but each leaf and jaw can move independently on the x-direction, within a certain range.*

**3.2 Experimental validation of the adaptive aperture**

Target volumes and treatment plans were designed in TPS. The TPS available at Maastro clinic was Raystation version 8B (RaySearch Laboratories, Stockholm, Sweden). In Raystation-8B, two dose calculation approaches are available: pencil beam v4.2 (RS-PBA) and MC v4.1 (RS-MC). The latter algorithm is, as stated by the manufacturer, the only one which computes clinical doses when block apertures/multi-leaf collimators (MLC) are placed in the beamline. Hence, it was the chosen algorithm.

**3.2.1. Geometry and plan design**

Two different volumes were modelled in the TPS (see sections i and ii below). Each volume is placed inside a phantom, as an analogy with a tumour inside the human body. All structures are made of water (12.2% hydrogen, 88.8% oxygen) with density and mean excitation energy values of $\rho_{\text{water}} = 1.00 \text{ g cm}^{-3}$ and $I_{\text{water}} = 75 \text{ e}$, respectively. For each geometry, two clinical plans were made with the same exact configuration. The only difference is the use of the Mevion HYPERSCAN with adaptive aperture (AA): one plan was made with AA (dynamic nickel leaves collimating individual energy layers)
and the other without (nickel leaves are static and fully open) as exemplified in Figure 3.3 for a representative energy layer of one of the geometries designed.

A total of six irradiation plans were designed. In all of them, both a planning imaging set (CT scans) and a proton beam using the pencil beam scanning technique were added. Gantry position and the treatment couch angle were set to 90° and 270°, respectively. The prescribed average dose to the target (average dose) was 2.00 Gy in one fraction with 0.5% MC uncertainty and 10^4 ions per spot.

The specifications for all the plans are summarized in Table 3.1 at the end of this section.

![Figure 3.3 – Beam-eye view: Comparison of designed plans for a sphere (a) without AA - the AA is fully open, without interfering with the beam path and (b) with AA - The AA is placed in beam path.](image)

### i. Geometry 1 - Irregular Geometry

![Figure 3.4 - Different views of the irregular geometry placed within the phantom (green line). (a) Beam eye view (b) Upper view (c) Side view. The phantom (green line surrounding the geometry) is inside the dose grid (grey line).](image)

Three structures with different thicknesses were unified to form an irregular geometry with 106 cm³. Figure 3.4 represent three different views from this structure. Due to its shape, this geometry will be further referred to as hairdryer. The hairdryer was placed 20 cm deep within the external.
For the hairdryer plans, the air gap, i.e., the distance between the exit window and the proximal surface of the phantom was set to 15.1 cm (plan with AA) and 5.0 cm (plan without AA). Plans also differ concerning the number of monitor units (MU). MU are a measure of the machine's output of the proton accelerator. The MUs, in other words, represent the dose delivered by the beam in a reference condition, e.g., 1cGy/MU 72. THE MU are measured by the TICs built into the nozzle. Its value is optimized by the MC-engine in the TPS. Hairdryer plan with AA uses 1202.5 MU while plan without AA uses 1198.3 MU.

ii. Geometry 2 - Regular Geometry

Regular geometry is a 3-cm-radius sphere. To access the behaviour of the AA at different depths, two spheres were designed as illustrated in Figure 3.5: a shallow sphere, placed 10 cm within the phantom and a deep sphere placed 20 cm within the phantom.

For the shallow sphere, the air gap was set for 5.0 cm in both with AA and without AA plans. The number of MU is 1033.6 MU for the plan with AA and 1250.0 MU for the plan without AA.

For the deep sphere, the air gap was set for 15.0 cm in both with AA and without AA plans. The number of MU is 1070.3 MU for the plan with AA and 1168.7 MU for the plan without AA.

![Figure 3.5](image.png)

*Figure 3.5 - Upper view of the designed regular geometry placed within the phantom (green line) which is inside the dose grid (grey line). Two 3-cm-radius spheres were placed (a) 10 cm depth within the phantom (shallow sphere) and (b) 20 cm within the phantom (deep sphere).*
Table 3.1 – General specifications for all irradiated plans: depth of the target within the phantom (depth), use of AA (with AA(✓) and without AA (✓)), air-gap and monitor units (MU) values for both plans of each designed geometry.

<table>
<thead>
<tr>
<th>Geometry</th>
<th>Depth [cm]</th>
<th>AA</th>
<th>Air gap [cm]</th>
<th>MU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sphere (3-cm radius)</td>
<td>10</td>
<td>✓</td>
<td>5.00</td>
<td>1033.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>✕</td>
<td>5.00</td>
<td>1250.0</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>✓</td>
<td>15.1</td>
<td>1070.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>✕</td>
<td>15.1</td>
<td>1168.7</td>
</tr>
<tr>
<td>Hairdryer</td>
<td>20</td>
<td>✓</td>
<td>14.7</td>
<td>1202.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>✕</td>
<td>5.00</td>
<td>1198.3</td>
</tr>
</tbody>
</table>

3.2.2. Plan evaluation

After the plan is designed, the optimization toolbox of the TPS is used together with a set of user-defined objective functions (OF) and their respective weights (which reflect the relative importance of each defined OF) to calculate the plan. The optimal plan is the one who minimizes the value of the OF. The result is a spot-position map with optimized spot weights. In the present work, 4 OFs were used, as defined in Table 3.2.

Table 3.2 – Objective functions description and respective weights for all designed plans. ROI being the target geometry refers to either one of the spheres or the hairdryer. The weights define the relative importance of the objective function: Having all weights at 1 gives the same effect of having all weights at 100.

<table>
<thead>
<tr>
<th>Objective Function</th>
<th>ROI</th>
<th>Description</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum Dose</td>
<td>Target Geometry</td>
<td>2.00 Gy (RBE)</td>
<td>2000.00</td>
</tr>
<tr>
<td>Maximum Dose</td>
<td>Target Geometry</td>
<td>2.02 Gy (RBE)</td>
<td>1000.00</td>
</tr>
<tr>
<td>Uniform Dose</td>
<td>Target Geometry</td>
<td>2.00 Gy (RBE)</td>
<td>300.00</td>
</tr>
<tr>
<td>Dose Fall-Off</td>
<td>External</td>
<td>Dose fall-off [high] 2.00 Gy (RBE) [&lt;br&gt;][low] 0.00 Gy (RBE)&lt;br&gt;Low dose distance 2.00 cm</td>
<td>1.00</td>
</tr>
</tbody>
</table>

The minimum (2.00 Gy) and maximum dose (2.02 Gy) function objectives are met when all parts of the region of interest (ROI) have a dose greater than or equal to 2.00 Gy, in the first case, or less than or equal 2.02 Gy, in the former case. The uniform dose objective is met when the entire ROI volume receives a dose equal to the specified dose level (2.00 Gy).

The dose fall-off function objective is met when all voxel doses within the specified ROI are less than or equal to their respective max dose values. Note that the dose fall-off function is applied to the external. In the cases where it overlaps with a target geometry, the voxels within the latter are disregarded.
The software uses the MC engine to perform dose optimization until changes in the objective value are inferior to a given value, referred to as tolerance level. Raystation recommended a tolerance level between $10^{-5}$ and $10^{-6}$. This work uses $10^{-6}$.  

After objective functions are defined and no further optimization is possible, the final dose is computed with the MC engine, and the final plan is approved. The approved plan is then sent to ARIA (Varian Medical Systems, Inc, Palo Alto, California, U.S.A), the oncology information system which combines medical, surgical and radiation oncology information that manages the patient’s entire journey from initial diagnosis to post-treatment follow-up. After the plan is evaluated and final doses are computed, both plan information and optimized dose are exported in DICOM format.

i. Plan output

For all the spots irradiated, the clinical plan output file (Appendix A) contains information about

- the position of each target spot ($x$ and $y$ coordinates, which together make up the spot map)
- the intensity of each beam pulse per spot (pulse charge)
- the position of the nozzle, treatment couch, nozzle and patient
- the sequence of the range shifter plates

The sequence of range shifter plates is a binary sequence with 1 if the plate is down (intercepting the beam path, causing protons to scatter and lose energy) and 0 otherwise. To a certain combination of plates corresponds a given energy. This conversion is performed using data from the manufacturer. And it is presented on Table 3.3 for the ten selected energies in the deep sphere plan.

<table>
<thead>
<tr>
<th>Energy [MeV]</th>
<th>Plate Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>149.89</td>
<td>1 1 1 1 1 1 1 1 0 0 0 0 0 0 0 0</td>
</tr>
<tr>
<td>154.43</td>
<td>1 1 0 1 1 1 1 0 0 0 0 0 0 0 0 0</td>
</tr>
<tr>
<td>158.87</td>
<td>1 1 1 1 1 1 1 0 0 0 0 0 0 0 0 0</td>
</tr>
<tr>
<td>163.22</td>
<td>1 1 0 1 1 1 0 0 0 0 0 0 0 0 0 0</td>
</tr>
<tr>
<td>167.50</td>
<td>1 1 1 1 1 0 0 0 0 0 0 0 0 0 0 0</td>
</tr>
<tr>
<td>171.70</td>
<td>1 1 0 1 1 0 0 0 0 0 0 0 0 0 0 0</td>
</tr>
<tr>
<td>175.83</td>
<td>1 1 1 1 0 0 0 0 0 0 0 0 0 0 0 0</td>
</tr>
<tr>
<td>179.90</td>
<td>1 1 0 1 0 0 0 0 0 0 0 0 0 0 0 0</td>
</tr>
<tr>
<td>183.91</td>
<td>1 1 1 0 0 0 0 0 0 0 0 0 0 0 0 0</td>
</tr>
<tr>
<td>187.86</td>
<td>1 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0</td>
</tr>
</tbody>
</table>

Table 3.3 - List of 10 energy layers used in the deep sphere plan and corresponding EMS’s plate sequence (1 = in the beam path; 0 - retracted).

3.2.3. Quality-assurance (QA) plan

In order to set-up the measurements, the QA preparation module is used to transfer the clinical plan to a solid phantom (where the QA measurement procedure is simpler) where the final dose is recomputed.

The QA plan uses the RW3 phantom model T29672 (PTW Freiburg, Freiburg, Germany), made of different thicknesses solid-water plates (Figure 3.6a) and the PTW Octavius XDR1500 detector (Figure 3.6b). Solid-water plates have a density of 1.045 $g cm^{-3}$, $(Z/A)_{eff} = 0.536$ and its electronic density is
1.012 times higher than that of water. Solid-Water is a water-equivalent material, meaning that the stopping power and the scattering effect are identical in the measured energy range.

The OCTAVIUS detector has a matrix of 1405 ionization chambers resulting in effective measuring field of 27 cm x 27 cm. The ion chambers are 4.4 mm x 4.4 mm x 3 mm in size, and the centre-to-centre spacing is 7.1 mm. The outer dimensions are 300 mm x 467 mm x 22 mm and the housing frame is made of polycarbonate. The depth measuring plan in the PTW detector is 8 mm under the surface.

The detector measurements absorbed dose or absorbed dose rate with a resolution of 0.1 mGy or 0.1 Gy/min. The QA-Plan selects the phantom (RW3 phantom, Figure 3.6a), the point of interest (zero, which corresponds to the isocentre) and the dose grid resolution (1 mm). Both the gantry and the treatment couch angles are always collapsed to 0 degrees (because this is the defined set-up for patient plan verification in the machine) and the patient position is adjusted to meet the airgap defined in the clinical plan. In the end, a final QA dose is computed after which a QA-plan and QA-dose can be exported in DICOM format.

![Figure 3.6](image)

Figure 3.6 - (a) RW3 phantom consists of individual stackable plates with different thicknesses (1 slab 1 mm thickness, 2 slabs 2 mm, 1 slab 5 mm, 29 slabs 10 mm) made of water-equivalent RW3 material (polystyrene with titanium oxide admixture). (b) PTW Octavius detector

Depth-in-water are selected based on relevant planes in the lateral beam view. To account for the differences between water density and the RW3 density, the selected depths are converted to depth-in-RW3 with equation 3.1.

\[
depth_{RW3} = depth_{Water} \times \frac{\rho_{Water}}{\rho_{RW3}}
\]

Where \(\rho_{Water}\) and \(\rho_{RW3}\) are the water and RW3 phantom density, respectively. \(depth_{Water}\) is the selected depth-in-water and \(depth_{RW3}\) is the depth in the RW3 phantom.

An overview of the entire process described is presented in Figure 3.7: As part of the patient treatments work-flow, an approved clinical plan designed in Raystation, to be delivered to the patient, is sent through ARIA and from there to the treatment control machine (TCM) of the proton system. The plans were first designed in Raystation 8B, exported through ARIA to the TCM. For this unique system, the final positions of the AA are only computed by the TMC at the end of the chain Raystation-Aria-TMC, resulting in a rather complex process. The positions of the AA, as many other parameters, are needed as input to the MC simulations performed in this work.
Figure 3.7 - Workflow of a designed treatment. Target geometries are designed, and their contours can be exported. Each plan requires the input of an imaging dataset (CT scans). For each geometry, two plans are designed: one with AA (w/ AA) and other without AA (wo/ AA), where leaves are completely open and static. Parameters are defined. The optimization toolbox of the TPS is used together with a set of user-defined objective functions (OF) and their respective weights to calculate the plan until no further optimization is possible. At this stage, the final clinical dose is computed and can be exported alongside the clinical treatment plan (clinical plan). To prepare the measurement set-up, one needs to undergo the QA preparation tab. Here, due to different configurations of the system (gantry and couch angles collapsed to zero), a new dose (QA dose) and a new plan (QA plan) can be computed and exported. Files that can be exported are yellow coloured. The ones that will be further used in this work are marked with green background. Software (rounded boxes) used, apart from Raystation, include ARIA and Treatment control machine (TCM).

3.2.4. Measurement set-up

Figure 3.8 - (a) Lateral view of the experimental set-up with 5.00 cm airgap. The OCTAVIUS detector is placed between solid water plates. (b) Lateral view rotated 45º of the experimental set-up from reproduced using the MC model. The CT is given as input and simulates the RW3 phantom. Range shifter plates are positioned in the beam path (plates (1)) or outside of it (plates (0)) according to the clinical plan information.
Measurements were done using the Octavius XDR1500 planar detector and the solid-water equivalent material showed in Figure 3.6. The experimental set-up follows the clinical plan, except that the gantry and the couch angles are manually overridden to 0° and the patient position are adjusted accordingly, to assure that the air gap meets the clinical specifications.

RW3 plates (equivalent to 5 cm thickness) are placed on the table and the PTW detector is placed above them. The detector is positioned using a laser system and corrected for yaw, pitch and roll angles. A certain amount of plates is placed on top of the detector, depending on the defined measured depth. After the airgap is adjusted, the phantom is ready to be irradiated. Figure 3.8a pictures the experimental set-up while Figure 3.8b reproduces it in the MC model, useful in section 3.3

### 3.3 Monte Carlo simulations

Commercial MC treatment plan systems such as Raystation-8B can be benchmarked by measurements but also by comparison with accurate Monte Carlo simulations as the former contains fewer approximations to speed up the calculations. The monte Carlo code used in this work was TOol for PArticle Simulation (TOPAS), based on Geant4 and already validated for proton therapy applications. 73,74

#### 3.3.1. Beam model of the Mevion S250i

The beam model of the Mevion S250i began to be developed at Maastro in October 2017. Increased investigation has improved its accuracy. The main components of a simulated model are the particle source, the nozzle and the target geometry (e.g. a patient or a phantom). Figure 3.9a shows the sketch of the model used in this work:

![Figure 3.9 - (A) Sketch of the beam model developed with TOPAS. The frontal part of the nozzle includes the range shifter plates, the adaptive aperture (AA) and exit window. The magnetic quadrupole and dosimetry system are placed in a fixed position with respect to the beam exit of the cyclotron. The measured virtual source to axis distance to the isocentre for this system is 182.14286 cm. (B) Each component of the AA was independently modelled according to detailed blueprints from Mevion. The AA is positioned according to the centre of the middle leaf and all the other leaves and jaws move as a block with respect to this position, hence the left and right sides have always the same y-coordinate. The magnetic box is not currently used to steer the beam. The beam deflection is defined by a rotational parameter explained in page 35. Following the magnetic box are the ion chambers of the dosimetric](image-url)
system. The EMS (range shifter plates), the AA and the exit window are placed inside the nozzle, that is positioned according to the user-defined air gap. The proton’s source was modelled with a Gaussian distribution. The beam nominal energy and energy spread were set to 228.65 MeV and 0.50 MeV, respectively, using measured IDD curves for fifteen energies measured in air.67.

### 3.3.2. Simulations input

TOPAS is a user-friendly MC code. This feature is derived from the simplicity of specifying the parameters: the software runs a command line program with the name of the top-level text file to build the simulations. Figure 3.10 describes the hierarchical organization of the input files.

![Figure 3.10](image)

**Figure 3.10** - (a) Topas hierarchical organization with respective Input files: from the command line, TOPAS application is initiated running the scoring file. Through the command IncludeFile, the scoring file calls the beam model file, which calls the plan file which finally calls the patient file. The order of the parameters is irrelevant for TOPAS software.

**i. Scorer file**

The top parameter file (scorer file) define the scorer type (Dose to water, $D_w$) and the scoring volume (dose grid). $D_w$ is the fundamental quantity in the dosimetry for radiation therapy and it describes the amount of dose deposited in a specific point if an infinitesimal volume of tissue is replaced by an infinitesimal volume of water. The unit of absorbed dose to water is the Gray (1 Gy = 1 J/kg).

**ii. Beam model file**

The beam model file describes the whole geometry of the Mevion S250i proton therapy system. The most relevant parameters are described below. The code related with beam description can be found in appendix A.

- **Transport cut-off**

  All the particle transport cut-offs are set at 0.5 mm except electrons for which 1 meter was used. Higher cut-offs allow shorter computational times with no impact on the dose. Nevertheless, code optimization in terms of computational speed was not focused on in this work.

- **Physical Settings**

  TOPAS default physics list combining 7 different modules that describe the physical interaction between particles and already validated for proton therapy applications was used\textsuperscript{75}. Each of the modules and its applications is listed on Table 3.4.
Table 3.4 - Physics list's modules and respective description

<table>
<thead>
<tr>
<th>Module</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>g4em-standard_opt4</td>
<td>The best set of electromagnetic physics models selected from the low energy and standard packages. With its concentration on the best possible physics, electromagnetic option 4 is slower than the standard EM package. This module is designed for applications requiring higher accuracy of electrons, hadrons, ion tracking without magnetic field.</td>
</tr>
<tr>
<td>g4h-phy_QGSP_BIC_HP</td>
<td>Identical to QGSP_BIC except that that neutrons of 20 MeV and lower use the High Precision neutron models and cross sections to describe elastic and inelastic scattering, capture and fission.</td>
</tr>
<tr>
<td>g4decay</td>
<td>The decay of all long-lived hadrons and leptons is handled by the G4Decay process. It does not handle the decay of hadronic resonances like deltas, heavy-flavour particles like D and B mesons or charmed hyperons.</td>
</tr>
<tr>
<td>g4ion-binarycascade</td>
<td>The Binary Cascade is an intra-nuclear cascade propagating primary and secondary particles within a nucleus. Interactions are one on one reactions between a primary or secondary particle and a nucleon of the nucleus. Secondary particles can further interact with remaining nucleons. This module includes hadronic inelastic models for ions.</td>
</tr>
<tr>
<td>g4h-elastic_HP</td>
<td>Both are used for high-precision calculation of elastic processes of hadrons and to activate and provide the nuclear capture of negatively charged particles at rest.</td>
</tr>
</tbody>
</table>

iii. Clinical plan file

The clinical plan file encompasses all the information already described from the clinical plan exported from ARIA. Each simulation is divided in time steps: each spot defines one-time step and at each time step, the system loads the entire geometry to reproduce the designed conditions.

a. Beam Rotation

Beam direction is defined by two angles according to equations 3.2 and 3.3.

$$\theta_x = \tan\left(\frac{y}{SVD}\right)$$  \hspace{1cm} 3.2

$$\theta_y = \tan\left(\frac{x}{SVD}\right)$$  \hspace{1cm} 3.3

where $\theta_x$ and $\theta_y$ are, respectively, the angles of the beam relative to the x and y axis. The angles are computed knowing the virtual source virtual distance (SVD, equal to 182.14286 mm) and the y and x positions of each spot, respectively, as explained in Figure 3.11.
Figure 3.11 - Definition of beam’s rotation angle in relation to the x axis (a) and the y axis (b).

b. Particles per spot

Each spot has a weight assigned which depends on the pulse charge, in MU/pC optimized by the MC engine in the TPS algorithm. The higher the weight, the higher the number of protons simulated per spot. From the manufacturer, we know that a pulse charge of 1 pC delivers 0.0693 MU. Therefore, we can compute the charge of each spot and, based on the elementary proton charge, calculate the number (or fraction of the total) of protons hitting one spot. This value depends on the defined initial uncertainty (fraction of the total number of protons that the user chooses to simulate).

iv. Patient file

The patient file contains information for the QA phantom and the dose grid to be loaded. The phantom is reproduced using 60 CT slices (5 mm thick) loaded as input. A material will be assigned to the voxels of the CT based on their Housefield units’ number (#HU) using an extension developed in-house (MyImagingToMaterialConverter). In our case, the #HU is constant through the entire CT and all the voxels will be assigned to water (same specifications as Raystation water). The dose grid is loaded and covers the entire volume of the CT.

3.3.1. Running simulations

TOPAS uses a set of 4 text files describing simulations parameter as input. The simulation’s workflow detailed below is visually described in Figure 3.12.

60 5-cm-thick CT slices and an RTDOSE are placed on a DICOM Directory. The dose grid information is copied from the QA dose (given as input) using TOPAS code line: s:Ge/Patient/CloneRTDoseGrid-From = Ge/Patient/DicomDirectory + "/RTDOSE.dcm". The phantom geometry is defined based on the CT slices volume (60 5-cm-thick slices define a cubic 30 x 30 x 30 cm3 phantom). The My Imaging To Material Converter is a TOPAS extension developed at Maastro, used to assign a material (water, in our case) to each CT voxel. The patient files contain the commands to do so.

The beam model file text file defines the geometry of MEVION S250i components

The plan file contains information, for each spot, regarding coordinates (x and y). Pulse charge delivered to the spot, in MU/pC (which is further converted to the number of protons based on the value of
the elementary charge); Range shifter sequence (a binary sequence which has 1 for the plates that intercept the beam and 0 otherwise) that defines the energy layer. Positioning of the CT(Phantom); Gantry’s angle and treatment couch angle; nozzle distance from the isocentre and AA position. Due to its dynamism, AA positions change very often. At each step of the simulation, the information for each spot is read and the dynamic parameters are considered. TOPAS scores dose-to-water, defined in the Scoring text file. In the end, all simulated doses are summed into a combined DICOM dose file.

Figure 3.12 - Monte Carlo (MC) simulations workflow.

At Maastro clinic, a computer cluster of approximately 600 cores was available at Maastro Clinic. In order to optimize the use of the cluster, the fraction of protons to be simulated (defined by the user) was divided in different independent jobs (with a different random seed number), and the final output files with the scored dose distributions were summed. Due to the multithreaded capabilities of TOPAS and the specificities of the computer cluster, 8-CPU jobs were used to 250 thousand primary protons. Each job last approximately 30 minutes. In this work, for each one of the 6 plans, 300 jobs of 500 thousand primary protons were simulated giving a total of $1.5 \times 10^8$ protons (approximately). The number of protons in each was manually overridden (as each job is designed to run 250 thousand protons, the number of protons per spot was doubled for each spot).

**3.4 Results pre-processing**

**3.4.1. Corrective factors for measured depths**

Measured depths must be corrected to account for the effective point of measurement of Octavius XDR1500 detector, located 8 mm (WET values) below the array surface. As Figure 3.13 illustrates, the zero of the CT (point which is cantered in the isocentre in MC simulations) is shifted 8 mm from the beginning of the external, so experimental depths shall be corrected with an 8 mm shift to match with TPS and TOPAS profiles. From Figure 3.13a we can also notice that the dose grid starts 1 mm before
the external, where the dose is computed. Pre-processing of Raystation data also requires that the first row (zeros) is removed, otherwise a systematic 1 mm shift would be present TPS and TOPAS.

**Figure 3.13** - (a) QA-plan applied shift to account for the OCTAVIUS XDR1500 detector’s effective point of measurement. (b) Nozzle side view: scorer plates (yellow) placed immediately after and before the AA (red rectangle).

### 3.4.2. Phase Space Scorers

Phase space files with information relative to particle’s energy, fluence, creator process and impact position and were analysed to infer the influence of using the AA and the air gap’s influence. For the former, two scorer plates were placed immediately after and immediately before the AA, as illustrated in Figure 3.13b. For the latter, the surface of the CT closest to the nozzle was used to score particles.

### 3.5 Result analysis

The measurements were analysed based on their longitudinal and transversal dose profiles (horizontal and vertical). However, for making it simpler to compare data, from all the irradiated depths, it was chosen the one that is closer from the voxel with maximum dose (Figure 3.14 (a-c)).

AA’s collimating effect was inferred from spot-size analysis, FWHM being the metrics used to quantify this property. Longitudinal and transversal (horizontal and vertical) profiles were taken from planes orthogonal to beam’s direction. The former was analysed based on the width of the SOBP and on the distal dose fall-off (Figure 3.14d). The latter was analysed based on the FWHM, lateral penumbra (LP) and lateral symmetry (LS), defined in equations 3.5 and 3.6, respectively:

\[
LP = \frac{|R_{80_1} - R_{20_1}| - |R_{80_2} - R_{20_2}|}{2}
\]

\[
LS = \frac{D_2 - D_1}{D_2 + D_1} \times 100\%
\]
Where $R_{80,1,2}$ and $R_{80,1,2}$ are the location of the 80% and 20% distal fall-off for each side (1,2) of the lateral profile and $D_1$ and $D_2$ are the integrated doses in each half of the field. These concepts are illustrated in Figure 3.14(e-f).

To attest the proximity of the model with the TPS, integrated depth-dose (IDD) profiles were also studied for all the 6 plans. R90 and R20 were the metrics taken to compare both.

---

**Figure 3.14** - (a-c): Lateral beam view of the three irradiated geometries: (a) shallow sphere, (b) deep sphere and (c) Hairdryer. Vertical lines represent measured depths (white), maximum dose (yellow) and depth used for comparison (green). (d):Metrics used to analyse the longitudinal profiles: SOBP width and distal dose fall-off given by the difference between the distal R10 and R90. (e-f) Metrics used to analyse the transversal beam profiles (e) Left
FWHM (distance between the points where the dose is half the maximum dose, R501 and R502; D1 and D2 correspond to the red and blue area under the curve, respectively.

All DICOM outputs were processed and analysed using MATLAB (R2018b) (The MathWorks, Inc.) program
Chapter 4
Experimental analysis

This chapter presents the results of the measurements and their analysis. Spot Size, longitudinal, transversal and integrated depth dose profiles are used to compare measurements against both TOPAS and TPS. Lateral penumbra, lateral symmetry, FWHM, distal 80%-20% falloff and SOBP width are used to compare the profiles. Discussion of the results is made in parallel with their presentation.
4.1 Proton beam irradiated field

Measurements aim to analyse the performance of the AA at different depths and with different geometries. Figure 4.1 exemplifies the collimating function of this device: The case with AA (Figure 4.1a) decreases the lateral dose spread around the sphere when compared to the one without AA (Figure 4.1b) as already reported by Almeida et. al81 A qualitative map of the dose spread achieved with this device is presented on Figure 4.1c. The dose difference maximum value peaks at 0.45 Gy, which corresponds to 23% of the prescribed dose. Previous results reported a maximum dose difference of 0.6 Gy. The difference is probably explained by the positioning of the water sphere within a phantom (literature scored dose on a 1L-sphere). The physics behind this problem will be further analysed.

![Figure 4.1](image)

**Figure 4.1** - Experimental dose comparison for the deep sphere plan at 209 mm depth (a) with AA and (b) without AA. (c) Dose difference obtained when subtracting the dose given to the target with AA from the one given without the AA. Transversal profiles were taken of each spot as indicated by the red (x-profiles) and the green (y-profiles) line.

The AA blocks mainly primary particles that scatter within the range shifter plates. The dose deposited is reduced in the scoring region since less particles are available to interact with the media. Therefore, less secondaries are produced, and the collimating effect is higher. To quantify the beam width both with AA and without AA, horizontal and vertical values of the FWHM were taken following the dashed lines plotted in Figure 4.1. Figure 4.2 reports the values for the 6 plans, considering all the irradiated depths. The respective horizontal and vertical profiles are presented on Figure 4.3 and will be further analysed in section 4.2.

Analysing Figure 4.2, we infer that the collimating effect of the AA is stronger at shallower depths. For the experimental values, the horizontal FWHM decreases 26 mm for the shallow sphere and only 13 mm and 10 mm for the deep sphere and hairdryer plan, respectively. The vertical-FWHM follow a similar trend, decreasing 26 mm for the shallow sphere and by 15 mm and 8 mm for the deep sphere and hairdryer, respectively. These values are an average of how much de FWHM decreased for all the irradiated depths of each plan (experimental values). This occurs due to the underlying physics processes. In a shallower target, beam spread due to physical interactions with matter is minimized, therefore the collimator effect of the AA is more notorious. For deeper targets, the primary protons that reach the target will scatter and broadening the beam.
Figure 4.2 - Horizontal FWHM (left column) and vertical FWHM (right column), for all irradiated depths in each of the 6 plans. In this work, FWHM is taken as a measure of the spot size. (a,d) - Shallow sphere (b,e) Deep sphere; (c,f) Hairdryer. Data without AA is represented with colour (red for horizontal, green for vertical) while AA data is represented in black.

Figure 4.2 shows a very good agreement of TPS and TOPAS with the experimental values. The higher differences between TOPAS and measurements occur in horizontal shallow sphere plan (1.3 mm). The higher differences between TPS and measurements also occur for the shallow sphere plan (4.4 mm).
The origin of the differences between TPS and measurements can be the underlying physical processes, as RayStation does not simulate neither gamma nor electrons, which contribute to increase the FWHM. However, as these particles are simulated in TOPAS, explanations are still required to justify the agreement between TOPAS and TPS. Extrapolations can suggest that both have an incorrect model for the AA.

Furthermore, FWHM-values are higher for the shallow sphere than for the deeper sphere, when no AA is used (coloured markers from Figure 4.2). To decrease beam’s nominal energy (230 MeV), lexan plates are placed within the beam path. To reach shallower depths, the plate’s thickness increases. Alongside, increased MCS of primary protons on the range shifter plates will broaden the beam, increasing the FWHM. The AA, placed after the energy modulated system, blocks the passage of these particles and therefore, with AA, the FWHM of deeper plans is higher.

4.1.1. Airgap influence on spot size

As different air gaps (AG) were used in the measurements, we design two different plans to understand the influence of this factor. For both deep sphere plans, with and without AA (original AG of 15.1 cm), the AG was set to 0.3 cm (minimum allowed by TPS). These plans will be further referred as “without AG”. Table 4.1 presents values of the FWHM for the different measured depths of these plans 4 plans.

<table>
<thead>
<tr>
<th>Measured Depth [mm]</th>
<th>FWHM w/o AA [mm]</th>
<th>Δw/oAA [mm]</th>
<th>FWHM w/ AA [mm]</th>
<th>Δw/AA [mm]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>w/o AG</td>
<td>w/ AG</td>
<td>w/o AG</td>
<td>w/ AG</td>
</tr>
<tr>
<td>31</td>
<td>77.1</td>
<td>77.0</td>
<td>-0.1</td>
<td>65.8</td>
</tr>
<tr>
<td>73</td>
<td>79.1</td>
<td>79.0</td>
<td>-0.1</td>
<td>67.3</td>
</tr>
<tr>
<td>115</td>
<td>81.2</td>
<td>81.0</td>
<td>-0.2</td>
<td>69.3</td>
</tr>
<tr>
<td>168</td>
<td>83.4</td>
<td>83.4</td>
<td>0.0</td>
<td>72.9</td>
</tr>
<tr>
<td>188</td>
<td>86.8</td>
<td>86.5</td>
<td>-0.3</td>
<td>73.7</td>
</tr>
<tr>
<td>209</td>
<td>87.3</td>
<td>87.5</td>
<td>0.2</td>
<td>74.8</td>
</tr>
</tbody>
</table>

From Table 4.1, no general trend could be observed, with all differences below 1 mm: for the plan without AA, increasing the airgap reduced the spot size in 67% of the cases. However, with AA, increasing the airgap increased the spot size in 83% of the cases. Titt et. al. showed the behaviour of the lateral-FWHM for a proton beam in air, confirming that the airgap plays a role in shaping the beam, as protons’ interactions with air will increase beam broadening.
4.2 Transversal Profiles

Figure 4.3 represents transversal profiles for the measured depth closer to the Bragg peak (green lines from Figure 3.14 a-c) according to the horizontal and vertical lines plotted on Figure 4.1. FWHM values are present in the caption of each plot.

**Figure 4.3** - Transversal profiles Black lines indicate data with AA (w/ AA). Coloured lines indicate data without AA, as indicated by the dotted lines of Figure 4.1 (red indicate horizontal profiles w/o AA and green indicate vertical profiles w/o AA). Plots compare TOPAS (solid lines), TPS (dotted lines) and experimental measurements (scatter points). (a,b,c) x-profiles for the measured depths closest to the Bragg peak. (d,e,f) y-profiles for the measured depths closest to the Bragg peaks. Each figure’s caption compares the values of full width at half maximum (FWHM) for the plotted curves.
Considering data without AA, transversal-FWHM of the deeper is 2/3% higher than for the shallower sphere. Considering data with AA, the difference reaches 8-9%. This highlighted the important role of the AA, for shallow targets. The need to trim the lateral field edge and avoid irradiating critical anatomic structures reflects the importance of analysing the LP when performing proton plans. Values are presented on Table 4.2. Lateral symmetry was also analysed. Values are presented on Table 4.3.

**Table 4.2** · Lateral Penumbra (LP), in mm, for x and y profile of each irradiated plan considering the experimental measurements (exp), RayStation output (TPS) and TOPAS simulations (top). Results are taken in concerning the experimental depths closest to the Bragg peak’s depth.

<table>
<thead>
<tr>
<th>Plan</th>
<th>x-profile LP</th>
<th>y-profile LP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$LP_{\text{EXP}}$</td>
<td>$LP_{\text{TPS}}$</td>
</tr>
<tr>
<td>Shallow Sphere</td>
<td>18.2</td>
<td>17.0</td>
</tr>
<tr>
<td>Shallow Sphere w/AA</td>
<td>10.1</td>
<td>7.2</td>
</tr>
<tr>
<td>Deep Sphere</td>
<td>17.7</td>
<td>17.1</td>
</tr>
<tr>
<td>Deep Sphere w/ AA</td>
<td>13.4</td>
<td>11.6</td>
</tr>
<tr>
<td>Hairdryer</td>
<td>15.6</td>
<td>14.7</td>
</tr>
<tr>
<td>Hairdryer w/ AA</td>
<td>12.2</td>
<td>11.2</td>
</tr>
</tbody>
</table>

**Table 4.3** · Lateral Symmetry, in %, for x and y profile of each irradiated plan considering the experimental measurements (exp), RayStation output (TPS) and TOPAS simulations (top). Results are taken in concerning the experimental depths closest to the Bragg peak’s depth.

<table>
<thead>
<tr>
<th>Plan</th>
<th>x-profile LS</th>
<th>y-profile LS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$LS_{\text{EXP}}$</td>
<td>$LS_{\text{TPS}}$</td>
</tr>
<tr>
<td>Shallow Sphere</td>
<td>-0.2</td>
<td>-0.4</td>
</tr>
<tr>
<td>Shallow Sphere w/AA</td>
<td>0.1</td>
<td>-0.2</td>
</tr>
<tr>
<td>Deep Sphere</td>
<td>2.1</td>
<td>0.5</td>
</tr>
<tr>
<td>Deep Sphere w/ AA</td>
<td>-1.9</td>
<td>-3.1</td>
</tr>
<tr>
<td>Hairdryer</td>
<td>0.1</td>
<td>-1.1</td>
</tr>
<tr>
<td>Hairdryer w/ AA</td>
<td>4.1</td>
<td>1.9</td>
</tr>
</tbody>
</table>

For all the plans, the use of AA decreased the LP both on x-profiles (8.1 mm for the shallow sphere, 4.3 mm for the deep sphere and 3.3 mm for the hairdryer plan) and for y-profiles (where the reduction was 9.4 mm, 4.9 mm and 2.8 mm, in the same order).

MC simulations present the same trend, with the x-profile LP decreasing 9.8 mm for the shallow sphere, 5.5 mm for the deep sphere and 3.5 mm for the hairdryer. The y-profile LP decreased 9.6 mm, 5.1 mm and 4.0 mm, in the same order.

TPS usage of AA decreased x-profiles LP in 8.7 mm, 4.5 mm and 1.8 mm and y-profiles LP in 9.3 mm, 4.8 mm and 3.7 mm, for the shallow sphere, deep sphere and hairdryer, respectively.

The aperture to the scanning proton beam can sharpen the lateral penumbras. The collimating effect of the AA is stronger at shallower depths because of the underlying physics processes: in a shallower target, beam spread due to physical interactions with matter is minimized, therefore the collimator effect...
of the AA is more notorious. For deeper targets, the primary protons that reach the target will scatter and broadening the beam.

Almeida et. al. simulated an 1L-sphere (6.2 cm radius) reported an average difference in LP of 4.5 mm and 4.1 mm between plans with and without AA for the measurements and simulations, respectively. Results in this work, for a 3-cm-radius sphere, show an average decrease of 4.6 mm and 5.3 mm showing that the AA also performs well for smaller targets. This is important to achieve better results for treatment of paediatrics and brain tumours where shallower and smaller spot sizes have been difficult to achieve.

Regarding lateral symmetry (LS), no significant trend was observed when comparing data with and without AA. The increased values of the hairdryer y-profiles comparing to the remaining cases are due to its anisotropy, as the increased volume in the left side (beam eye view, Figure 3.4a) increased the dose scored on that side.

This metric is, however, important to compare different beams (experimental, TPS and MC model). The higher differences when compared to the measurements for both TPS and TOPAS are registered when the AA is used. The difference reaches 3.2% between TPS and measurements and 4.9% between TOPAS and measurements. Maximum differences reported are for deep plans with AA (sphere and hairdryer, respectively). This might suggest that the AA model might be improved.

i. Airgap influence on lateral penumbra

To understand the effect of the air gap in the lateral penumbra, data from Table 4.1 was used to compute the lateral penumbra in 4 different situations: with and without airgap, both using with AA and without AA. Results are shown in Figure 4.4 and reflect an increase in lateral penumbra with increasing airgap.

![Figure 4.4](image)

**Figure 4.4** - FWHM for the two deep sphere plans (a) w/o AA and (b) w/AA. For each of the mentioned plans, the air gap (AG) was different: the designed plan considered a 15.1 cm distance between the exit window and the patient (w/ AG). This distance was set to 0.3 cm, the minimum allowed by the TPS (w/o AG).

A clear trend is seen in figure 4.4: increased air gap increases the lateral penumbra due to proton’s interactions with air. These results were expected and already reported by Rana et.al.83
4.3 Longitudinal Profiles

The longitudinal pencil beam profiles are obtained by taking the dose at each voxel in the middle line of the yz-plane. Results for the six irradiated plans are plotted in Figure 4.5. As explained in section 3.4, the experimental depths were shifted 8 mm to account for the effective measurement point of the detector.

![Figure 4.5 - Longitudinal profiles for the 6 designed plans: (a) shallow sphere; (b) deep sphere; (c) Hairdryer. Figure compares data with AA (black line) and without AA (purple line) for TPS (dotted line), TOPAS (solid line) and experimental data (dots).](image)

Qualitatively, it is possible to distinguish one peak at proton’s end range in both sphere plans (Figure 4.5a,b). These peaks are a result of small weighting coefficients defined when designing the plan (Table 3.2). A posteriori, it was recognized that the uniform dose weight should be higher to avoid these features in the longitudinal profiles.

Measurements of the shallow sphere with AA (Figure 4.5a, black markers), don’t match Raystation nor TOPAS longitudinal profile for the depths of 11 mm, 25 mm and 42 mm. The origin of this high error traces back to beam delivery, probably due to an error on the experimental setup. Using the PTW software to run a gamma analyses comparing irradiated with TPS-QA doses revealed that measurements were not clinically acceptable (gamma pass rate below 80%, appendix D). The low gamma pass rate was potentially caused by the reduction of cross-sectional area of the target at these depths, already reported by Kim et.al83. SOBP width and distal fall-off values for the above plotted longitudinal profiles
are presented on Table 4.4. As no measurements were taken in the distal fall-off, results below only compare TPS with TOPAS. Values concerning the spherical geometry revealed that the SOBP is independent of the depth measured. These results confirms a characteristic of the mechanical EMS, which produces shifted Bragg peaks with equal widths for the whole energy range. The SOBP width of the hairdryer is higher than the SOBP width of the spheres. This is because the hairdryer (Figure 3.4) is longer than the sphere considering the beam axis (z-axis).

Table 4.4 - Longitudinal Profiles analysed metrics: SOBP width (SOBP) and distal 90%-10% fall-off ($l_{90,10}$) presented for the six irradiated plans. The difference between the TPS and TOPAS is given by $\Delta$.

<table>
<thead>
<tr>
<th>Plan</th>
<th>SOBP$_\text{TPS}$ [mm]</th>
<th>SOBP$_\text{TOP}$ [mm]</th>
<th>$\Delta$ [mm]</th>
<th>$l_{90,10}$$_\text{TPS}$ [mm]</th>
<th>$l_{90,10}$$_\text{TOP}$ [mm]</th>
<th>$\Delta$ [mm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shallow Sphere</td>
<td>72.18</td>
<td>72.16</td>
<td>0.02</td>
<td>15.17</td>
<td>14.51</td>
<td>0.66</td>
</tr>
<tr>
<td>Shallow Sphere w/AA</td>
<td>71.78</td>
<td>72.61</td>
<td>-0.83</td>
<td>12.96</td>
<td>13.08</td>
<td>-0.12</td>
</tr>
<tr>
<td>Deep Sphere</td>
<td>73.64</td>
<td>70.54</td>
<td>3.10</td>
<td>9.15</td>
<td>9.94</td>
<td>-0.79</td>
</tr>
<tr>
<td>Deep Sphere w/ AA</td>
<td>71.02</td>
<td>70.45</td>
<td>0.57</td>
<td>12.17</td>
<td>11.68</td>
<td>0.49</td>
</tr>
<tr>
<td>Hairdryer</td>
<td>85.01</td>
<td>80.41</td>
<td>4.60</td>
<td>8.01</td>
<td>8.11</td>
<td>-0.09</td>
</tr>
<tr>
<td>Hairdryer w/AA</td>
<td>86.88</td>
<td>80.71</td>
<td>6.17</td>
<td>8.78</td>
<td>9.63</td>
<td>-0.85</td>
</tr>
</tbody>
</table>

The 90%-10% distal dose falloff is smaller for the deepest geometries and, in these cases, higher when the AA is used. Sharper distal dose falloff was expected. That was not accomplished due to the defined objective functions (Table 3.2): The OF concerning the dose fall off has an assigned weight of 1.00. This weight is 2000 times smaller than the one defined for the prescribed dose. As the weights are relative, this one was neglectable for the TPS as it was 0.0005 times smaller.

Longitudinal profiles in Figure 4.5 also show that plans using the AA have a higher entrance dose. Important is to mention that plans were optimized using the same constraints. During clinical routine, a plan with AA would be optimized independently from the one with the AA and lower entrance doses are achieved when using this device. TPS compensates the higher entrance dose by lowering the number of MU in AA plans, which can be noticed in Table 3.1.
Chapter 5

Beam model analysis

To access the accuracy of TOPAS beam model, IDD profiles were compared with TPS. Differences were found and analysed. Several properties of the MC model were revised: Energy, spread, physic list, air gap influence and others described further in this chapter.
5.1 Energy and Spread

The energy value previously defined for the beam model, 228.65 MeV, was tuned based on the IDD profiles of proton range in water. The mean excitation energy of water used in these simulations was 78 eV, the most recent value reported\(^{84}\). However, experimental values for the mean excitation energy of water range between 75 eV and 81.8 eV\(^{85}\). Raystation-8B uses 75 eV\(^{72}\) and does not allow the user to change it. Therefore, as our study aims to compare TOPAS with Raystation, a new energy tune using \(I_{\text{water}} = 75 \text{ eV}\) had to be performed. The primary proton energy was tuned to 229.4 MeV. The R90 for this energy is 218.87 mm, reported in Figure 5.1a and presents a relative error of 0.08% when compared to 218.89 mm reported on Table 5.1. Therefore, all the further simulations presented in this work use a nominal beam energy of 229.4 MeV.

![Diagram of depth-dose curves and energy spread influence.](image)

**Figure 5.1** - (a) Beam energy tuning: Depth-dose curves for different nominal beam energies and respective R90 values: 228.65 MeV (black line, R90 = 217.11 mm), 229.4 MeV (blue line, R90 = 229.4 MeV) and 229.5 MeV (cyan line, 229.5 MeV). The R90 value is taken to compare with RayStation R90 value and select the best energy. (b) Energy spread influence: the blue line is our current model; black and orange vary \(\pm 0.1\%\). (c) Raystation definition of beam energy and energy spread: to some discrete energy values, the TPS assigns weights that correlate with the number of protons having that energy. (d) Hairdryer without AA simulated using the nominal energy of the beam and energy spread (blue) and comparing to using TPS’s energy spectra.

Regarding the beam energy spread, TOPAS defines this parameter as a percentage of the energy. The present beam model of Maastro clinic uses 0.21\%, similar to energy spread values found in literature\(^{86,87}\). Figure 5.1b aims to understand the impact of this parameter on the depth-dose curves. As there was no significant difference when varying the spread \(\pm 0.1\%\), no change was applied to this
parameter. Note that, increasing the beam energy spread increases broadening of the beam in the beam direction and increases the entrance dose as more particles with lower energies (traveling only few mm in depth) are produced.

Raystation doesn’t model their beam with a nominal energy and spread. Instead, they use a discrete energy spectrum where to each specified energy they assign a weighting factor (Figure 5.1c). This weighting factor correlates with the number of protons having a specific beam energy. To understand the impact of this difference, we replaced our gaussian source model by Raystation's spectrum. Figure 5.1d presents the results for the hairdryer plan without AA. As seen, this change did not present a higher entrance dose, so the source model was kept as described by Almeida et. al.67.

5.2 Integrated depth-dose (IDD) profiles

To assess the validation of the beam model, simulated IDD profiles (blue) are compared with TPS IDD profiles (red) in Figure 5.2. Two situations are analysed: (a,c,e) refers to plans without the AA.(b,d,f) refers to plans with AA.

In the first case, a low entrance dose problem can be noticed when comparing TOPAS simulations with Raystation-TPS. To characterize the difference, the relative error between TPS and TOPAS is plotted (yellow line). In all plans, the error value is maximum at the entrance and decreases with depth until reaching a minimum at the depth where the dose is maximum. At the end range, the relative error increases. This is because Raystation stops tracking particles after the phantom while topas keeps considering the secondary (and other generation) particles, preventing the scored dose of reaching zero. With AA, no low entrance dose is observed. A higher entrance dose with AA was already mentioned in section 4.3. On theory, the Nickel material used in AA’s leaves was chosen to minimize proton interactions/secondary productions. However, under the defined constrains, the plan optimization was not ideal and higher dose than clinical achievable was delivered. Efforts were made to try to access the nature of this lower dose and hypothesis were tested. Section 5.3 discuss this problem further.

Overall, Figure 5.2 reveals a good agreement between TOPAS MC model and Raystation. Despite the relative error reaching 5% at the entrance of the phantom (for the deeper targets without AA), it quickly decreases and remains below 2%.

Almeida et al.81 reported a close agreement in the plateau region for experimental and simulated IDD with the system nominal energy of 230 MeV. These results might suggest that further optimization of the range shifter plates shall be performed. One the other hand, an incomplete description of the scattering processes in the lexan plates by the TPS due to dose calculations approximations shall also be considered.

Further analyses can be performed comparing the R90 and R10 values for each irradiated plan. The difference between TPS and TOPAS values is denoted by Δ. Results are presented in Table 5.1 and reveal a close agreement between simulations and TPS. For all cases, differences stay below 0.2 mm, except for the R90 values in the hairdryer plan with AA. For this plan, the simulated entrance dose using TOPAS is higher (see section 5.3),
Figure 5.2 - Integrated depth dose (IDD) profiles for the 6 plans comparing TPS (red line) with TOPAS (blue line). The relative error between the two is presented on the left y-axis (yellow line). Upper row - Shallow Sphere; Middle Row - Deep Sphere; Bottom row - Hairdryer. (a,c,e) plans without the AA. (b,d,f) plans with AA. Profiles normalized to the maximum value.

Table 5.1 - R90 and R20 values for the 6 plans irradiated compared between TOPAS (TOP) and TPS. Delta describes the difference between TPS and TOPAS.

<table>
<thead>
<tr>
<th>Plan</th>
<th>$R_{90}^{TOP}$ [mm]</th>
<th>$R_{90}^{TPS}$ [mm]</th>
<th>$\Delta R_{90}$ [mm]</th>
<th>$R_{20}^{TOP}$ [mm]</th>
<th>$R_{20}^{TPS}$ [mm]</th>
<th>$\Delta R_{20}$ [mm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shallow Sphere</td>
<td>121.7</td>
<td>121.5</td>
<td>-0.20</td>
<td>141.2</td>
<td>141.1</td>
<td>-0.10</td>
</tr>
<tr>
<td>Shallow Sphere w/AA</td>
<td>121.6</td>
<td>121.6</td>
<td>0.00</td>
<td>136.6</td>
<td>136.4</td>
<td>-0.20</td>
</tr>
<tr>
<td>Deep Sphere</td>
<td>220.9</td>
<td>220.7</td>
<td>-0.20</td>
<td>240.7</td>
<td>240.7</td>
<td>0.00</td>
</tr>
<tr>
<td>Deep Sphere w/AA</td>
<td>223.1</td>
<td>223.2</td>
<td>0.10</td>
<td>238.3</td>
<td>238.2</td>
<td>-0.10</td>
</tr>
<tr>
<td>Hairdryer</td>
<td>218.9</td>
<td>218.7</td>
<td>-0.20</td>
<td>228.9</td>
<td>228.9</td>
<td>0.00</td>
</tr>
<tr>
<td>Hairdryer w/AA</td>
<td>219.9</td>
<td>219.5</td>
<td>-0.20</td>
<td>229.0</td>
<td>229.0</td>
<td>0.00</td>
</tr>
</tbody>
</table>
5.3 Low entrance dose

Figure 5.2 highlighted the low entrance dose problem of TOPAS when compared to RayStation for the plans without AA. Figure 2.6 plots the contributions of the different proton generations. The dose deposited by secondary protons increases within the first phantom’s centimetres, stabilizing almost until the Bragg peak. After, the energy deposited by the particles drops (Figure 2.6). Contributions are below 5% of the total dose (Figure 2.6). Knowing this, different hypothesis could be brought up: One of possible explanations might be that MC model was losing/not scoring particles, causing dose in TOPAS to be lower than in TPS. Another possible explanation is that the TPS inadequately modelled in-phantom interactions, including multiple-Coulomb scattering and secondary particles originated from nuclear interactions. Nuclear interactions are more important for the high energy proton beams in water which would explain why the error is higher for the deepest geometries.

Note that the low entrance dose problem was not posed for the plans with the AA. It seems to be due to the higher entrance dose reported in the longitudinal profiles of Figure 4.5. In particular, the deep sphere plan with the AA observes a higher entrance dose. This seems to be related with the number of particles simulated, as lowering the number of particles decreases the difference between TOPAS and Raystation. The full comprehension of this phenomena and why it only affects the deep sphere plan was not analysed in this work. However, we focused our efforts in describing the low entrance dose problem reported in the simulated IDD profiles without the AA. A qualitative analyses aiming to understand is described in sections 5.3.1-5.3.5.

5.3.1. Physic List

Topas default physics list is validated for proton therapy and the included modules handle protons and all secondary particles (neutrons, helium ions, deuterons, tritons, photons, electrons, etc.) This section tested the influence of each one of these models (described in Table 3.4) in depth-dose curves by removing one-at-a-time of the default physics list. The results are presented in Figure 5.3, where they are compared against TPS (red curve) and TOPAS using the default physics list (blue curve).

The module g4em-standard_opt4 is fundamental for the physics accuracy of the simulations. Without the information regarding electromagnetic interactions, the resultant depth-dose curve doesn’t describe proton’s physics (black line in Figure 5.3a). Comparing the influence of the remaining modules, we can infer that the ones which affect the secondary particles are the g4h-phy_QGSP_BIC_HP and g4h-elastic_HP (Figure 5.3b and e, respectively). Without them the depth-dose curves differ from the blue one, representing TOPAS using default physics list. Contributions from the modules deleted in Figure 5.3 c,d were not relevant for the present work as the black line always overlaps the blue one.

Figure 5.3b reveals that the g4h-phy-QGSP-BIC-HP module strongly influences secondary particles, as lower dose is observed when it is removed from physics list. This module describes elastic and inelastic scattering, capture and fission. Therefore, as these processes are not considered, less secondaries are produced, and the dose drop in the shallow region (where most of these particles deposit energy). The importance of elastic processes is highlighted in Figure 5.3e, by removing g4m-elastic_HP module.
In these conditions, the dose also dropped, although the reduction was less when compared to Figure 5.3b.

**Figure 5.3** - Influence of each module in the default physics list compared against TPS (red) and TOPAS using the default physics list (blue). Black curves represent the depth-dose curves while removing from the default physics list the module (a) g4em-standard-opt4; (b) g4h-phy-QGSP-BIC-HP; (c) g4stopping; (d) g4decay; (e) g4h-elastic-HP; (f) g4ion-binary-cascade.

Further tests were performed to understand the influence of the inelastic and elastic processes and see if their incomplete description was the origin of the low entrance dose problem. On one hand, the default module for elastic processes, g4h-elastic_HP, was replaced for other elastic modules available on topas: g4h-elastic or g4h-elastic_D. On the other hand, the module g4h-inelastic-QBBC, which contains hadronic inelastic models for protons and neutrons was added to the default physics list. No differences were observed in any of the cases mentioned before. Therefore, and knowing that the default physics list has already been validated for protons, no module changes were performed on the simulations presented in this work.

### 5.3.2. Scorer

TOPAS model is defined to score dose to water in the dose grid. This enables the physician to define a dose grid covering only a region of interest in the CT instead of scoring particles in the whole CT volume, significantly decreasing the computational time. In our simulations, this is not relevant as the dose grid covers the whole target volume. If a part of the CT was out of the dose grid (due to bad positioning, for instance), one could think that a set of particles were not being scored causing dose discrepancies,
possibly at the entrance region. To analyse this, the dose was scored on the CT and results were compared to the default settings of scoring dose in the dose grid. Figure 5.4a concludes that no dose difference was found.

### 5.3.3. AA-positioning

One other factor thought that could be causing some particles to miss the target in TOPAS model was the AA positioning: If it would be positioned erroneously, particles would be wrongly blocked which might cause the low entrance dose problem. Figure 5.4b is a boxplot which compares the AA position of plan files with log files from the treatment machine. x-axis considers 15 positions, the y-position of the centre leaf and x-positions of all the 14 leaves (note that, as the AA moves as a block in the y-axis, only one y-position is required to place the AA correctly). The blue rectangle defines the interquartile range. The median corresponds to the horizontal bar within the rectangle. Red dots are outliers. As shown, both the median and outliers are within the AA’s 1 mm tolerance, revealing a good position of the AA in for the analysed positions.

### 5.3.4. Particle Cut-off

General principles in Geant4 (and, therefore, in TOPAS) assume that all particles produced (and accepted) will be tracked up to zero range. TOPAS uses a default of cut in range (cut-off) of 0.05 mm for all particles. This means that particles will only be accepted if they have enough energy to travel 0.05 mm. The lower this value, the higher the computational power required (as more particles are produced). Our MC beam model uses a default threshold for production of 0.5 mm for all particles. Different cut-off simulations were made to understand if the value was too high (hence, particles were not being produced). As shown in Figure 5.4c, even smaller cut-offs (for all particles) than reported default value lead to the same depth-dose curves.

#### i. Decreasing computational time

As seen in section 2.1.3, even the most energetic electrons within the proton therapy clinical energy range travel a maximum of 2 mm in water. However, they scatter intensively having random trajectories. Simulating these interactions requires high computational power. Therefore, we investigate the influence of higher cut-off for electrons. We assess the impact of higher electron cut-offs on deposited dose and computational time.

As seen before, our MC model uses 0.5 mm cut-off for all particles. For electrons only, this value was replaced by 1 m. No significant difference in deposited dose was observed (Figure 5.4d). Dose uncertainty was compared and, with the 1 m electron cut off, the simulation’s uncertainty decreased 0.04% (neglectable). Figure 5.4e compares the computational time for 3 different electron’s range cut-offs (0.5 mm, 3 mm and 1 m) for each computer available to run jobs at Maastro’s cluster. With 1 m cut-off, and comparing with the value of 0.5 m, computational times dropped around 30% (Figure 5.4e). Therefore, further simulations were computed using 1 m electron cut-off and 0.5 mm cut-off for all the other particles.
Figure 5.4 - Different simulations to try to assess the nature of the low entrance dose. (a) Scorer-volume comparison: dose grid vs CT. (b) Boxplot comparing the positions of the AA from the plan file with Mevion S250i log files. (c) Particle transports’ cut-off between 1 μm and 1 mm were tested. (d) Electron transport cut-off influence. (e) Computational time per job when compare simulations using three different electron cut-offs: 0.5 mm (red); 3 mm (green) and 1 m (blue).
5.3.5. Air gap influence

The present section describes the air gap (AG) influence on the results. When reducing the AG, TOPAS low entrance dose increases. If the AG is set to 0 cm, the dose difference between TOPAS and Raystation vanishes (Figure 5.5a). The effect also goes in the opposite direction: increasing the AG lowers the entrance dose (black line, Figure 5.5a).

Figure 5.5a plots, on the right y-axis, the relative error between TOPAS simulation without AG and TPS with 15 cm AG. Compared with Figure 5.2, the relative error drops and remains below 1%. The higher relative error value at the entrance in this case is probably due to the fact that the minimum achievable AG by the TPS is 0.3 cm while TOPAS simulates no AG (0 cm).

Figure 5.5b scored individually primary and secondary protons with and without air gap. Its analysis revealed that primary protons’ IDD profiles with and without AG overlap, hence these particles are not influenced by the air gap. However, IDD concerning secondary protons revealed a dose difference in the initial build-up region, which accounts for the same dose difference observed between TOPAS and TPS IDD profiles scoring the contribution of all particles.

To better understand this issue, both primary and secondary proton’s impact positions on the most proximal surface of the phantom were analysed using phase space files. Figure 5.5c,d compares situations with and without 15 cm airgap, respectively. The output corroborated the results from Figure 5.5b, proving that primary protons are not significantly affected by the AG’s size: 99.9% hits the target when no AG is used and 99.7% does it if the target is 15 cm apart from the exit window. On the other hand, only 50.2% of the secondary protons hit the target with 15 cm AG compared with 72.2% when the AG is zero.

The results presented in this section suggest that TOPAS and Raystation aren’t modelling the distribution of the secondary protons in the same way, with Raystation underestimating the scatter angle. In this situation, more particles hit the target which lead to dose increase. As the contribution of the secondaries becomes less relevant, so does the error between TPS and TOPAS. A further analysis would be to directly compare Raystation phase space files with TOPAS, however this scorer is only available with Raystation research license, and this work was performed using only the clinical one (which doesn’t allow to extract phase space information). Zhang et. al. reported similar results and conclusions for calculations performed using a TPS-analytical method and developed a correction factor dataset for different air gaps which increased the accuracy of calculated dose. At Maastro research to understand this problem is still being conducted.
Figure 5.5 - (a) Influence of air gap (AG) in TOPAS simulations (red) Raystation plan with 15 cm AG; TOPAS simulations (green) without AG; (blue) with 15 cm AG; (black) with 20 cm AG. (b) Analysis of primary and secondary protons depth-dose curves with AG (blue) and without AG (green). (c-d) Comparison of TPS depth-dose curves with and without AG for the deep sphere with AA (c) and without AA (d). (e-f) Impact positions of primary (blue) and secondary (red) protons on target's proximal surface without airgap (e) and with airgap (f).
5.4 Influence of the AA

To analyse the AA influence, phase space files were scored immediately before and after the multi-leaf collimator (Figure 3.13b) in two different situations: with AA and without it - once again, without AA means that the AA is fully open. For this purpose, 5000 particles were simulated. The goal was to confirm if the AA was creating particles that would deposit dose within the first cm depth, increasing the entrance dose. What we saw meets our expectations. For the same number of particles simulated, the number of primary protons hitting the target immediately after the AA represents a lower fraction of the total when the device is in use, as other secondary particles are created (the percentage of primaries drops from 84% to 57%). The major sources of these particles are inelastic scattering of protons (32.41%) and neutrons (7.47%). Annihilation can be distinguished as well when the AA is present, as it creates 1.3% of the particles. Without AA, its contribution is irrelevant (0.1%). Scoring the energy of the secondary particles originated from neutron and proton inelastic processes, the values don’t exceed 15 MeV for the former case. For the latter (Figure 5.6b,c), energy spectra comparison revealed that although more particles are created, their spectra is shifted for the low energies it is less probable that they hit the target.

Besides the impact position, also the difference between the incident angle and initial angle (with respect to the x and y axis) are analysed in Figure 5.7. Comparing the difference between Figure 5.7 (b-c) and (e-f), both situations with AA scored less protons with zero angle difference, increasing the contribution of the higher angular difference values. Once the nickel leaves of the AA aim to reduce proton interactions with the material, further investigation for the increased angle of particles when hitting the scorer shall be pursued. Contributions shall also be analysed concerning particles hitting the target.
Figure 5.7 - Different between incident cosine and initial cosine for the same situations described in Figure 5.6.
Chapter 6

Conclusions

This chapter sums up the results and discussion of chapters 4 and 5. Limitations to the present work are discussed and future challenges are defined. An overview of the current state of proton therapy in Portugal is also made on the last section, with a final personal comment.
Growing clinical evidence has been proving Proton-therapy as a ground-breaking technology to treat cancer. A careful selection of patients can lead to increased health benefits when compared to conventional photon treatments. The present work aimed to explore the potential of the innovative Adaptive Aperture™ proton multi-leaf collimator (pMLC) of Mevion S250i with HYPERSCAN proton therapy system. By October 2019, Maastro Clinic is the only European proton-therapy centre to use this device. Therefore, there is the need to clinical validate the AA and its MC model.

The need of a MC model was discussed in chapter 2. The higher computational power lead to replacement of analytical algorithms for MC based computation algorithms in TPS. However, the high computational time of MC still requires that smaller approximations are performed. The impact of these in dose calculations is not yet fully understood and brings the need of benchmarking TPS against MC codes. MC codes, such as Geant4, have a steep learning curve. To spread MC within the proton therapy community, more user-friendly codes are becoming available. TOPAS, the MC-code used in these simulations is one example.

Chapter 3 characterizes MEVION S250i with HYPERSCAN, which presents an innovative dynamic multi-leaf collimator that adapts to each patient needs using pencil beam scanning technique. This multi leaf collimator is designed to reduce dose to healthy tissues and minimise neutron dose (produced by protons interacting with high atomic number materials such as patient apertures typically used in passive scatter beam delivery technique). Currently, Maastro uses the AA in all patient plans. Therefore, there is the need to characterize both its performance and MC model.

Chapter 4 evidenced that using AA increases dose sparing in healthy tissues compared with conventional proton beam scanning techniques. Transversal-FWHM decreases around 20% for plans at 10 cm depth from target’s surface and 10% for targets 20 cm deep within the phantom. Lateral penumbra decreased, on average, 8.8 mm for the shallow plans and 3.8 mm for the deeper ones. Raystation overpredicts this value by 0.7 mm while TOPAS underestimates it by 0.1 mm.

The collimating effect of the AA is stronger at shallower depths because of the underlying physics processes: in a shallower target, beam spread due to physical interactions with matter is minimized, therefore the collimator effect of the AA is more notorious. For deeper targets, the primary protons that reach the target will scatter and broadening the beam. Lateral symmetry suggested that further work shall be performed when using AA both in TPS and MC model, as difference between both and the experimental measurements reached 3.2 % for TPS and 4.9 % for TOPAS

Despite the AA evidently reducing the lateral dose, longitudinal profiles suggest that the use of the device increased the entrance dose when compared to no-AA plans. This was due to poor definition of treatment objective functions and assigned weights. Raystation compensates the higher entrance dose by decreasing the number of MU. Nevertheless, to understand if/which particles were being produced with AA, phase space files were scored in two surfaces placed immediately before and after the pMLC. Comparing data without AA to data with AA revealed that the percentage of primaries drops from 84% to 52%. Therefore, it would be legit to assume that the AA is creating secondary particle (decreasing the percentage of the primaries in the scorer region). However, energy spectra of the particles originated by proton inelastic processes with AA is shifted to the lower energies, comparing with no AA case. Further tests should be performed to test the influence of these particles on the target.
Chapter 5 dives into the MC beam model, comparing it to TPS. Differences of 5% between both were reported for plans without AA. Several tests were performed, and it was found that decreasing the airgap decreased the relative error below 1%, suggesting that the model of secondary particles in Raystation was incomplete and explaining the better agreement between the shallow sphere simulated and Raystation IDD profiles, as in this plan the airgap was set to 5 cm.

In any case, the AA confers a dynamical collimation of the beam in real time for a wide range of energies and different thicknesses targets, decreasing the need for patient-specific collimators and increasing the efficiency of pencil beam scanning but further work shall be performed to access TPS and MC-code model of the AA.

6.1 Limitations

Limitation to this work comprise the use of the same constrains in plan optimization and the blocked access to Raystation physics, a license independent from the clinical one that allows for exploring the underlying physics in the Raystation model. Comparing Raystation files with TOPAS phase space files would allow to fully characterize the differences.

Monte Carlo will always be slow. Despite the increased computational power, further improvements to speed up the MC code can be studied. Scoring dose-to-media instead of dose to water, for instance, saves computational time and in a work where all the media voxels are water could have been used.

6.2 Future work

Further work concerning the AA aims to explore its collimating function from different angles, and for targets with different sizes.

Further work concerning the TOPAS MC model requires simulations with inhomogeneous media and measurements off-axis. In order to treat lung patients, integrating target motion in the code is required. Lung plans are relevant due to the relative movement of the tumour caused by breathing. Another challenge is modelling the magnets and steer the beam accordingly.

The present code dose scoring depends on the number of particles. MC dose should be normalized nor to depend on it. Increasing the number of particles on a MC simulation shall only reduce the uncertainty. Once the code is fast and accurate enough, the final goal would be to incorporate MC in the clinical routine.

6.3 Final considerations

This section consists on an overview about the current state of proton therapy in Portugal.
All over the world the number of proton therapy centres continues to rise. While the Netherlands presents 3 proton centres serving a population of 17 million people, in Portugal the debate continues about whether money should be spent in bringing this technology inside our borders.

In 2018, Portuguese government approved the creation of a working group focused on defining a strategy of national interest for the establishment of a national healthcare system (NHS) integrated health unit for particle beam therapies with a strong research component. This project represented an investment of €100 million in 5 years (with community funds and reimbursed funds from European investment bank) and combined the force of major Portuguese hospitals and oncological centres, Instituto Superior Técnico (IST), Lisbon faculty of medicine (FMUL) and foundation for science and technology (FCT). Yearly, 700 patients are expected to be recommended for proton treatments, according to 2018 prospects. 1 year later, this number has increased to 750.

In 2017, 50 thousand new oncological cases were reported in Portugal. The cancer incidence in our country has been increasing 3%-4% each year and is predicted to reach 60 thousand new cases by 2030. To prepare for this scenario, government must ensure that clinical services are able to respond to this need, with more facilities or increasing the throughput in already existent facilities. With different treatment options, the efficiency of the treatments also plays a role and treatments proven to reduce the probability of secondary cancers will decrease healthcare costs in the long-term. Despite the increased clinical evidence favouring protons over photons, scepticism is still present, and many issues concern some opinions.

Several issues were criticized regarding the approval of a proton facility in Portugal: lack of qualified manpower (which was addressed with opening of more vacancies in higher education physics); The need of investment in other medical devices, such as magnetic resonance imaging (MRI) or CT systems; The lack of support to master students with scholarships from FCT. These issues are concerning the physicist, who may be overlooking the fact that a proton therapy centre can bring innovation and capital investment. Regardless, they claim that establishing a collaboration protocol with a foreign operating unit may be a more cost-effective measure.

Between 2014-2015, UK sent abroad 400 patients at the cost of €30 million, funding not only the patient but one or two caregivers depending on the age of who is receiving treatment. Today, three proton centres are running in the UK. Canada and the Netherlands also started by funding out-of-country treatments and nowadays both have more than one fully operating centre. A report concerning the clinical indications, patient selection criteria, prospect of capital costs was not found for the Portuguese situations. However, a main factor also plays an important role: patients’ ability and willingness to travel and live abroad up to 7 weeks.

Regarding the incorporation of the treatments in the national healthcare service, foreign models reporting good results in patient selection can serve as example: The Dutch model-based approach has presented evidence about its efficiency and could be implemented as a model of selection.

As a personal reflection, throughout the biomedical engineering degree, we felt the incredible energy of many physicians, who tried to enclose the relationship between medicine and technology. But sadly, we also come across conservatives’ mentalities, focusing on practicing medicine as it has been practiced in the last 20 years and ignoring the technological revolution that we are living in. For me it’s
impossible to overlook the ground-breaking potential of proton technology, when we know that conventional radiotherapy can lead to an IQ drop in children below 90 points\(^9\). And note that, per year, around 400 new cases of paediatric cancers are register in Portugal.

Summing up, we all know budgets and financial constrains are always on the menu for Portugal. But if more and more Portuguese demonstrate great mastery abroad, why can't they do so at home? Portugal can be a small country - size wise - but is full of big people able to fight against cancer, the lack of progress, and most important, for each-other... if only they realize the importance of looking to the bigger picture.
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Appendix A

Plan excel file

Appendix A contains the excel plan file extracted from the DICOM output file.
The DICOM Plan file exported from treatment control machine (TCM) is read using MATLAB and copied to an excel file. This excel file will be further read by MATLAB again and parameters are reorganized in a text file (plan file) which will be used as TOPAS INPUT.

Figure A.1 - Excel plan file extracted from DICOM output from treatment control machine using MATLAB. (Upper row) First columns. (bottom row) last columns. The total number of lines is the same as the total number of spots.
Appendix B

Beam Model text file (excerpt)

Appendix B contains the part of the Beam Model text file used as TOPAS input which defines the beam source.
# Beam Model of the Mevion S250i Hyperscan System
# Isabel P. Almeida
# Started: October 2017
# This file contains the information of the beam line:
# Dipole magnet, beam monitors, range shifter, adaptive aperture, exit window
# Version 2: all components are placed inside the “Gantry” so that we can
# change the rotation angle, as in the real treatment room
# Version ZonPTCv1: specific data from ZonPTC

includeFile = Plan.txt

d:Ph/Default/CutForAllParticles = 0.5 mm # single range cut to use for all particles
d:Ph/Default/CutForElectron = 1 m # overrides CutForAllParticles for Electron

d:Ge/World/HLX = 3 m
d:Ge/World/HLY = 3 m
d:Ge/World/HLZ = 3 m
b:Ge/World/Invisible = "False"
s:Ge/World/Color = "black"
s:Ge/World/Material = "G4_AIR"
s:Ge/myBeamPosition/Parent = "Gantry"
s:Ge/myBeamPosition/Type = "Group"
d:Ge/myBeamPosition/TransZ = Ge/MagneticFieldBox/TransZ + 2.85714 cm # Virtual axial distance = -182.14286 cm (measured by ZonPTC)

d:Ge/myBeamPosition/TransX = 0 mm
d:Ge/myBeamPosition/TransY = 0 mm
d:Ge/myBeamPosition/RotX = Ge/RotSpotX deg
d:Ge/myBeamPosition/RotY = Ge/RotSpotY deg

# --- Beam
s:So/myBeam/Component = "myBeamPosition"
s:So/myBeam/BeamParticle = "proton"
d:So/myBeam/BeamEnergy = 228.65 MeV
u:So/myBeam/BeamEnergySpread = 0.2174

#----- Primary: Emittance beam
s:So/myBeam/Type = "Emittance"
#1. Bivariate Gaussian: X,X,correlation and Y,Y,correlation
s:So/myBeam/Distribution = "BiGaussian"

# Data from the emittance fit:

d:So/myBeam/SigmaX = 1.5228329 mm
u:So/myBeam/SigmaXPrime = 0.00152599549557624
u:So/myBeam/CorrelationX = 0.10735935090014787

d:So/myBeam/SigmaY = 1.793950320 mm
u:So/myBeam/SigmaYprime = 0.001456750827832650
u:So/myBeam/CorrelationY = 0.135731996511997262
Appendix C

Plan text file (excerpt)

Appendix C contains part of the Plan text file used as TOPAS input which defines the beam source.
includeFile = Patient.txt
i:Ts/Cpus = 8

dv:Tf/SpotRotX/Values = 3135  1.1246  1.1246  1.1246  1.044  1.044  ...  -0.77617 deg
dv:Tf/SpotRotY/Values = 3135  0.78511 -0.33293 -0.61243 -0.75218 -0.47269  ...  -0.18437 deg

d:Ge/RotSpotX = -1 * Tf/SpotRotX/Value deg
d:Ge/RotSpotY = 1 * Tf/SpotRotY/Value deg
Appendix D

Gamma analysis

Appendix D presents a qualitative gamma analyses map for the shallowest measurements in the shallow sphere plan.
Gamma passing rates were below 75% at the depths of 11 mm, 26 mm, and 42 mm. For all the other depths, gamma passing rates reached 98.8% at 68 mm, 97.8% at 94 mm, and 100% at both 105 mm and 115 mm. Due to an error, the data pictured doesn’t report gamma passing rates, which are also an output nor the qualitative analyses for the shallowest depth.