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Implementation of advanced methodologies in the commissioning of a
Light Ion Beam Therapy facility

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Radiotherapy plays an important role in the treatment of cancer. If the disease is localized and inaccessible, surgery may not be a viable option and Radiation Therapy is the treatment of choice. After surgery it is the most frequently and most successfully applied form of therapy. More than 50% of all patients with localized malignant tumors are treated with radiation IAEA-TRS461 [1]. In radiotherapy the key problem is to deliver the dose in such a way that ideally the planned target volume receives 100% of the dose needed to kill all cancer cells in the tumor, sparing as much as possible the surrounding normal tissue. In practice, this cannot be achieved because of the unavoidable dose deposition in the entrance channel of the radiation.

After the discovery of X-rays by W.C. Röntgen in 1895, they started to be applied in therapy of malignant tissue. At that time X-rays were first used on a very empirical basis because their physical and biological characteristics were not completely known. In the historical development of radiotherapy two general tendencies are visible: the clinical outcomes are improved by a greater conformity of the applied radiation dose to the target volume and by an increased biological effectiveness of the radiation. In order to overcome the limitations of an exponentially decreasing depth dose distribution of photon radiation and in order to improve the lateral beam scattering, numerous techniques have been developed and applied. To reduce the dose to the healthy tissue in front of the target volume, the energy of the photon was increased to treat deep-seated tumors. The original X-ray tubes (Kilovoltage X-rays) were replaced by high energy γ rays (such as ^{60}Co sources produced in nuclear reactors) and Megavoltage X-ray tubes produced by a *linear accelerator (LINAC)*. For many decades external beam radiotherapy was dominated by the application of ionizing photon radiation, culminating in advanced techniques such as *intensity modulated radiotherapy (IMRT)* or arc-Therapy and innovative delivery devices such as Cyberknife and Tomotherapy. These new treatment

modalities allow improved tumor dose shaping via cross fire techniques and non-uniform partial fields, and *Image-guided radiation therapy (IGRT)* which, using 2D or 3D imaging, increases the accuracy and precision of target localization, thereby reducing the amount of healthy tissue in the treatment field.

The second tendency was to selectively increase the biological effectiveness of the radiation dose delivered to the tumor. Because some tumors contain hypoxic cells that are up to 3 times more radioresistant than the corresponding oxygenated cells, the clinicians tried to decrease the radiotolerance of hypoxic cells by hypoxic sensitizers or by the exposure to hyperbaric oxygen pressure [2].

Ballistics of radiation is also strongly dependent on the particle used. Light Ion Beam Therapy (LIBT) is an advanced technique of external radiation therapy, using light ions such as protons or carbon ions. The application of high-energy beams of light charged particles to radiotherapy was first considered in 1946 when Robert R. Wilson investigated the depth-dose characteristics of proton beams [3]. He recognized the potential benefits of proton beams and predicted “that precision exposures of well-defined small volumes within the body will soon be feasible”. He predicted a steep increase of energy deposition in matter at the end of particle range. This increase had been measured in 1903 for α particles by Bragg and is known as Bragg profile. Charged particles have the advantage of an inverted dose profile, *i.e.* the dose maximum (“Bragg peak”) is at the end of their range, and not close to the tissue surface as with photons.

Charged particles heavier than protons have additional advantages, like the reduced lateral scattering and an increased biological effectiveness at the end of their range, making them well-suited for the treatment of tumors resistant to photon radiation.

Patient treatments started in 1954 at Lawrence Berkeley Laboratory (LBL), Berkeley (US), first with protons and later with helium beams. We have to wait until 1975 for the first patient treated with heavier ions at the Bevalac facility at LBL. There most of the patient treatments were performed with beams of ^{20}Ne 670 MeV/u, which at that time appeared to be most attractive because of their high biological effectiveness in the target volume. These treatments were performed at particle accelerators originally built for nuclear physics experiments and then adapted to tumor therapy. The first hospital-based facility was Loma Linda in California where patients are still treated with protons. In 1994 the *Heavy Ion Medical Accelerator (HIMAC)* dedicated to radiotherapy started with ^{12}C ions at National Institute of Radiological Science (NIRS), Chiba (Japan) using passive systems like in Berkeley.

The first place, where a compact Gantry has been combined with a new active scanning modality (*spot-scanning technique*) for protons, was the experimental therapy center

at Paul Scherrer Institute PSI (Switzerland) [4]. At the same time a new technical solution (*raster scanning technique*) [5] was developed almost in parallel at Gesellschaft für Schwerionenforschung (GSI) in Germany, differing significantly from the previous designs at the Bevalac and HIMAC. There the implementation of a full 2D dimensional scanning combined with active energy variation was first used in patient treatment with ^{12}C ions. The ion beam therapy is becoming increasingly used in recent years with an ever growing number of LIBT facilities being operational or in construction. At the end of 2015 more than 131.240 patients have been treated with protons and 19.376 with ^{12}C ions worldwide (official data from PTCOG website [6]).

The current study is based on collaboration among the Department of Bio-pathology and Medical Biotechnologies, the Department of Physics and Chemistry of University of Palermo (Italy) and the LIBT facility MedAustron (Austria). It is essentially based on the implementation of innovative methodologies related to medical physics support of radiation therapy with active pencil beam scanning (PBS) technique with protons and ^{12}C ions and accomplished into comprehensive Quality Assurance (QA) program. At MedAustron a very complex and innovative treatment technique in external beam radiotherapy has been commissioned and introduced into clinical practice. The active scanning technique with proton and ^{12}C ion beams allows to build-up the dose as a superposition of many thousands of individually placed and weighted pencil beams. In particular, active scanned ion beams represent a novel irradiation technique taking full advantage from the physical interaction properties of these particles with tissues and advanced delivery modality to generate very sharp dose gradients in three dimensions, with many degrees of freedom available at the treatment planning level. Highly conformal dose distributions allow for dose escalation in the target volumes without increasing the dose to surrounding normal tissues. The introduction of new radiation treatment technology into clinical practice requires implementation of several major steps that generally includes acceptance testing and medical commissioning of Beam Delivery System (BDS), Patient Alignment System (PAS), medical software embedded in the Oncology Information System (OIS), Treatment Planning System (TPS) and all needed auxiliary systems. However, before beginning patient treatment of any site, a full simulation of the workflow should be performed that follows every step of the treatment process. The most efficient solution is to use a so-called end-to-end test. The purpose of this test is not just to validate beam line monitor calibration but to confirm that the entire logistic chain of radiation treatment starting from imaging, treatment planning, monitor calibration, patient positioning and verification and beam delivery is efficient and leads to the desired results with sufficient accuracy. The successful completion of end-to-end tests is prerequisite of

starting clinical activity at a LIBT facility. However, site specific end-to-end tests need to be complemented in practical treatments with so-called patient-specific plan verification checks. Conformal treatments always bear the risk that any uncertainty in the delivered dose distribution may lead to a severe underdosage or overdosage of the target volume. Therefore, for a dynamic technique, like a scanned particle beam delivery, special emphasis has to be put on dosimetric verification of planned dose distributions by the TPS. Therefore, the planned dose distribution has to be verified periodically in homogeneous and/or inhomogeneous medium, and patient-specific plan verification is a highly recommended dosimetric procedure within the QA program. This type of measurement is performed as a final check of the accuracy of the dose distribution calculated by the TPS and actually delivered to the individual patient. For any specific plan, the dose distribution from each of the treatment fields is independently measured in a homogeneous water phantom and results are then compared to the corresponding values recalculated by the TPS under the same conditions. For passive beam delivery techniques, it may be sufficient to verify the dose at one single point within the treatment field. In an active scanning system measured dose may perfectly comply with the calculated dose in one point of the field, but can be completely wrong at others. Therefore a simultaneous verification of absorbed dose at many points is required by 2D or better 3D dosimetric systems. The increased complexity related to the technological and process changes places new demands on Quality Assurance (QA) programs, as well as on innovative instrumentation and detectors for beam characterization and phantom/patient specific checks.

The project focused on implementation of innovative methodologies applied to the medical commissioning of a Light Ion Beam Therapy facility consists of three main parts:

- investigation on Integral Depth Dose (IDD) correction factors for plane-parallel ionization chambers in proton beams by Monte Carlo simulations;
- development of the procedures and needed software solution to support the patient-specific plan verification in scanned particle beams;
- development of dosimetric end-to-end test procedures using alanine dosimetry in scanned proton beam therapy.

This thesis is organized in 6 chapters. Chapter 1 briefly summarizes the physical and biological advantages of particle therapy with respect to the standard radiation therapy with photons or electrons. Chapter 2 describes the MedAustron ion beam therapy center and the medical commissioning concept of a LIBT. In Chapter 3 the IDD correction factors for plan-parallel ionization chamber by MC simulations were derived. Corrections were applied to measured depth dose profiles used as basic beam data for the beam

model implemented in the RayStation TPS. Chapter 4 describes the characterization of 24 PinPoint ionization chambers and the implementation in clinical practice of an innovative software solution for patient-specific plan verification in active scanning with particle beams. In chapter 5 the end-to-end test procedures based on alanine dosimetry in scanned proton beams as prerequisite of clinical activity are described. Finally, in Chapter 6 we summarize our results and briefly discuss the perspectives for future works.

CHAPTER 1

LIGHT ION BEAM THERAPY

1.1 Physics of light ion interactions in matter

1.1.1 Classification of Ionizing Radiations

The main distinction among the different radiations able to produce ionization is based on the way they interact with a medium. The charged particles, such as protons or “light ions”¹, because of their electric charge, lose energy and slow down along their path since they continuously interact via Coulomb force with the electrons in the medium. In this process energy is transferred to matter and the main result is ionization and excitation of atoms and molecules. For this reason, charged particles are considered as *directly ionizing radiations*.

Uncharged radiations are not subjected to the Coulomb force. They transfer their kinetic energy to secondary charged particles which then deposit energy in the target material. For this reason uncharged radiations are considered as *indirectly ionizing radiations*. An X- or γ ray, for example, can transfer all or part of its energy to electrons within the medium.

This chapter focuses on interactions of ions with matter in an energy range that is relevant in ion beam therapy.

¹The term “light ions” is used to indicate ions with an atomic mass A heavier than protons. However, in many scientific publications “heavy ions” is commonly used to characterize ions heavier than protons, because of their biological effectiveness increase with respect to protons, although they are relatively light considering the full mass range of nuclei.

1.1.2 Main characteristics

Charged particles interact with matter in three distinct ways [7]:

- 1) electromagnetic interaction with orbital electrons of the medium (*Stopping Power*),
- 2) Multiple Coulomb Scattering (MCS) with atomic nuclei of the medium,
- 3) nuclear interaction with atomic nuclei of the medium (*nuclear fragmentation*).

The *energy loss or Stopping Power* of the particle is primarily due to Coulomb forces between its charge and the negative charge of the orbital electrons within the absorber atoms. The loss of energy to the nuclei of the stopping medium is small in comparison to the energy loss to electrons. A charged particle passing near an atom exerts electrical forces on orbital electrons which feel an impulse from the attractive Coulomb force. In a close encounter, the strength of the forces may be sufficient to cause an orbital electron to be separated from the atom. The direct removal of electrons from neutral atoms by the incident particle is the *primary ionization*. The energy that is transferred to the electron must come at the expense of the kinetic energy of the charged particle, and its velocity is therefore decreased as a result of the encounter. An ionization interaction is a collision between the charged particle and an orbital electron. Part of this energy is used to overcome the binding energy of the electron to the atom, and the remainder is given to the ejected *secondary electron* as kinetic energy. In case these ejected electrons have a kinetic energy large enough to cause further ionization on their own, the consequentially ejected electrons are called *delta (δ) rays*. They represent an indirect means by which the charged particle energy is transferred to the absorbing medium.

For high energy charged particles, an additional energy loss mechanism must be taken into account. When a high energy charged particle passes through the Coulomb field of a nucleus, a more likely result is that the particle will simply be deflected by the strong electrical forces exerted on it by the nucleus (*Scattering*). The particle is rapidly decelerated and loses energy in the “collision”. This energy appears as a continuous X ray spectrum called *bremsstrahlung*. In particular, if a particle of mass M and charge $z \times e$ enters the field of a nucleus of charge Z in an absorber the acceleration produced is proportional to zZ/M . According to classical electrodynamics the resulting radiation would have an intensity proportional to $z^2 Z^2 / M^2$. This radiation of Bremsstrahlung is therefore much smaller for protons and light ions than for electrons. During this interaction the deflection of e.g. a proton or a carbon ion is extremely small, so the observed angular spread of a ion beam leaving a slab of matter is mainly due to the random combination of a lot of deflections. Due to the small deflection angles and

the underlying electromagnetic interaction, this scattering is usually known as *Multiple Coulomb Scattering (MCS)*.

When a particle beam of proton or carbon ions penetrates a thick absorber a small amount of the primary beam will undergo *nuclear interactions*. While the stopping process of high-energy particles penetrating a thick absorber is mainly governed by collisions with atomic electrons, the probability of nuclear interactions is much smaller, but leads to significant effects at large penetration depths. At energies of several hundred MeV/u violent nuclear spallation reactions may result in a complete disintegration of both projectile and target nuclei (not disintegration of the projectile for proton beams) e.g., in central head-on collisions or in partial fragmentations.

1.1.3 Stopping Power and LET

In order to describe the energy losses of a charged particle in passing through a medium the *linear stopping power* S is introduced. The linear stopping power S for charged particles in a given absorber is defined as the ratio of the energy lost dE by a charged particle in traversing a distance dl in the material [8]

$$S = \left(-\frac{dE}{dl} \right). \quad (1.1)$$

Another quantity strictly correlated with the linear stopping power is the *mass stopping power*. The mass stopping power, S/ϱ , for a material of density ϱ , for charged particles, is then [8]:

$$\frac{S}{\varrho} = -\frac{1}{\varrho} \frac{dE}{dl}. \quad (1.2)$$

The SI unit is $\text{J m}^2 \text{ kg}^{-1}$ or in the more common way, such as $\text{MeV cm}^2 \text{ g}^{-1}$.

The *total stopping power* S of a particle in a target material is the sum of the energy loss per distance due to interactions of the projectile ion with electrons in the target, due to interactions with the nuclei and due to radiative energy losses (bremsstrahlung):

$$\frac{S}{\varrho} = -\frac{1}{\varrho} \left(\frac{dE}{dl} \right)_{el} + \frac{1}{\varrho} \left(\frac{dE}{dl} \right)_{nuc} + \frac{1}{\varrho} \left(\frac{dE}{dl} \right)_{rad} \quad (1.3)$$

The electronic stopping power is the dominant term over a wide energy range. Nuclear stopping contributes less than 0.5% to the total stopping power at projectile energies with corresponding particle speeds above the speed of orbital electrons in the target. However, for heavy projectiles, nuclear stopping becomes dominant for projectile speeds around and below the Bohr velocity, which corresponds to a particle energy of 25 keV/u.

Radiative energy loss can be neglected for ions at energies available at medical accelerators.

One of the quantities used to indicate the radiation quality is the *linear energy transfer* (LET) or *restricted linear electronic stopping power*, L_Δ , of a material for charged particles which is [8]

$$L_\Delta = \frac{dE_\Delta}{dl}, \quad (1.4)$$

where dE_Δ is the energy lost by a charged particle due to electronic collisions in traversing a distance dl , minus the sum of the kinetic energies of all the electrons released with kinetic energies in excess of Δ . The SI unit of the LET is J m^{-1} . Usually E_Δ is expressed in eV, or some convenient multiples or submultiples, and L_Δ is often expressed in $\text{keV } \mu\text{m}^{-1}$.

Electronic Stopping Power

The *electronic stopping power* denotes the energy loss of the traversing charged particle due to the interactions with orbital electrons of target material. It can be well described by the Bethe-Bloch formula [9–11]:

$$S_{\text{el}} = \frac{4\pi Z_p^2 e^4 N}{m_e v^2} Z_t \left[\ln \left(\frac{2m_e v^2}{\langle I \rangle} \right) - \ln \left(\frac{1}{1 - \beta^2} \right) - \beta^2 - \frac{C}{Z_t} - \frac{\delta}{2} \right] \quad (1.5)$$

where e is the electron charge, m_e is the electron rest mass, v and $Z_p e$ the speed and the charge of the projectile ion respectively, Z_t and N the average atomic number of the medium atoms and the number of atoms per cubic centimeter respectively and $\langle I \rangle$ is an average value of the excitation and ionization energies of the atoms of the medium, which is a property of the target material.

The first three terms in the brackets are commonly referred to as “Bethe formula”. The $\langle I \rangle$ value can be extracted from penetration depth measurements. Even though the $\langle I \rangle$ value has a non-negligible impact, e.g. on particle range calculations, which vary in the millimeter range for different recommended values [12], it is not well established for all materials. For water, different values are stated in literature [13] ranging from 75 eV to 80.8 eV. The second and third term in the brackets are relativistic corrections. The “shell correction” term $\frac{C}{Z_t}$ becomes relevant for lower energies, it corrects for atomic bindings in the material. The “density effect” $\frac{\delta}{2}$ is due to medium polarization at high particle speeds.

For non relativistic charged particles ($v \ll c$), only the first term in brackets in equation 1.5 remains and it varies slowly with particle energy. Therefore, for a given nonrelativistic particle, the stopping power varies as $1/v^2$ and therefore as $1/E$. A qualitative

explanation of this behavior could be found by noting that when the charged particle has low energy, it spends a larger time in the vicinity of any given electron and the impulse felt by the electron, and hence the energy transfer is larger. As it can be seen from Eq. 1.5, the stopping power increases with the second power of the particle charge $Z_p e$: protons for example will lose energy at a lower rate than “heavy ions” of the same velocity such as carbon ions. The dependence of dE/dx on the different target materials is described by the product $N \times Z$, which is outside the square bracket. Absorbers with high average atomic number and high-density will consequently result in the largest linear stopping power.

Fig. 1.1 shows the LET in water as function of the energy of the particle E for different ion species.

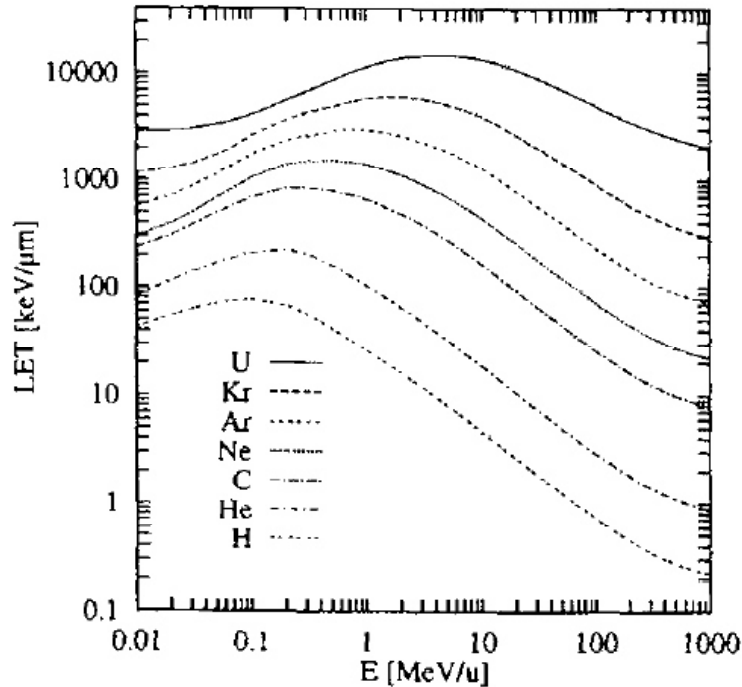


Figure 1.1: Energy loss of different charged particles at various energies calculated with ATIMA [14].

At high velocities the atomic electrons are completely stripped off and the projectile charge is equal to the atomic charge number $Z_p e$. At velocities of light ions below 10 MeV/u, the mean charge state decreases due to the interplay of ionization and recombination processes and Z_p in Eq. 1.5 has to be replaced by the effective charge Z_{eff} , which can be described by the empirical Barkas formula [15]:

$$Z_{eff} = Z_p \left[1 - \exp \left(-125 \beta Z_p^{-\frac{2}{3}} \right) \right] \quad (1.6)$$

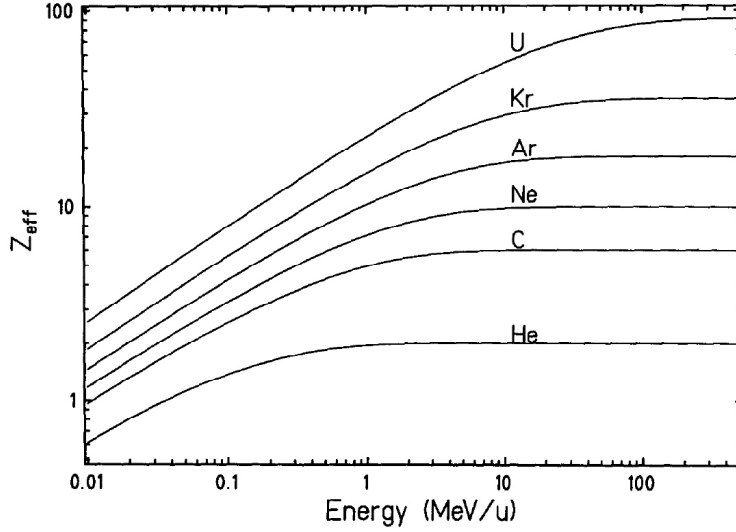


Figure 1.2: Z_{eff} as function of particle energy for different ion species. With increasing particle energy more electrons are stripped off and Z_{eff} approaches the atomic number Z_p [14].

From figure 1.2 it is evident that at low ion energies Z_{eff} in the nominator of the Bethe-Bloch equation 1.5 decrease rapidly, yielding a distinct maximum of energy loss at low energies (fig. 1.1).

Figure 1.3 shows the specific energy losses along the track of various charged particle at various initial energies. Such curves are called *Bragg curves*. For most of the track, the charge on the ions is equal to the nucleus charge, and the specific energy loss increases roughly as $1/E$ as predicted by Eq. 1.5. Near the end of the track, the charge is reduced through electron pick up (see Eq. 1.6) and the curve falls off.

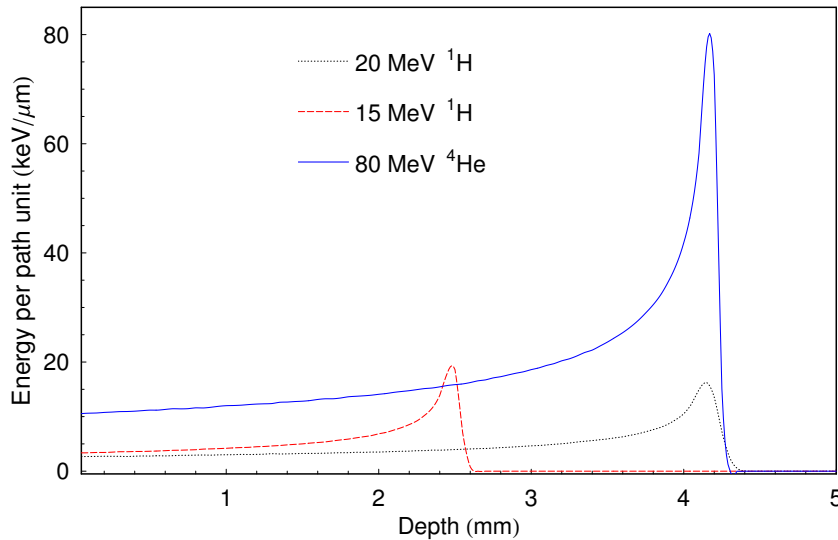


Figure 1.3: Bragg curves of various heavy charged particles at various energies obtained through computer simulation [16]. The position of the peak is dependent on the velocity and charge of the particle and on the properties of medium.

Nuclear Stopping Power

Nuclear stopping power describes the energy loss due to the interaction of the projectile ion with nuclei of the target atoms. This is mainly due to elastic scattering of the projectile on the Coulomb potential of a nucleus. The picture below shows the calculated contributions of the electronic and nuclear stopping power in water for protons and ^{12}C ions. The corresponding dose contribution is, however, very small and can be neglected

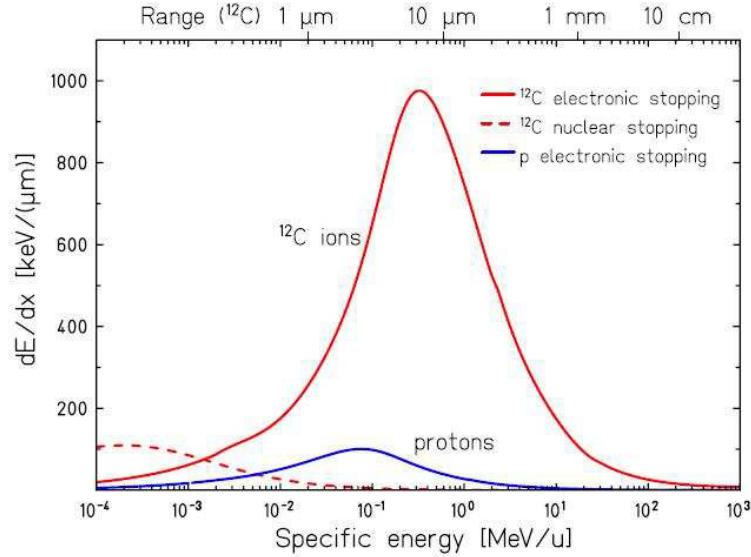


Figure 1.4: Specific energy loss of ^{12}C ions and protons in water. At the top axis the range of ^{12}C ions in water corresponding to their specific energy [17].

in radiotherapy applications [17].

Stopping Power in compounds

The Bethe-Bloch formula Eq. 1.5 is valid only for elemental medium. If the medium is a *mixture* of elements, the atoms act separately, and we can visualize the mixture as a succession of very thin sheets of each constituent element. That picture leads to the Bragg's additivity rule [18], *i.e.* a mass weighted linear combination of the stopping powers of the atomic constituents can be applied:

$$\left(\frac{S}{\rho}\right) = \sum_i w_i \left(\frac{S}{\rho}\right)_i \quad (1.7)$$

where w_i is the fraction by weight of the i_{th} element and $\left(\frac{S}{\rho}\right)_i$ is the mass stopping power of the i_{th} element. *Compounds* are more complicated since their constituent atoms do not act separately, *e.g.* water.

1.1.4 Particles Range

When the incident particle is no longer able to ionize, it has reached the end of its path in the stopping medium and will revert to a neutral atom. Charged particles are therefore characterized by a definite *range* in a given absorber material. The *mean projected range* R_0 is the depth at which half of the particles have stopped. The range of a heavy charged particle depends only on its initial energy and on its average energy loss rate in the medium.

From the total stopping power, the range of the particle in a material can be calculated in its continuous slowing down approximation (CSDA):

$$R_{CSDA} = \int_{E_0}^0 \left(\frac{dE}{dx} \right)^{-1} dE \quad (1.8)$$

where E_0 is the initial kinetic energy of the particle.

For heavy charged projectiles the range calculated in CSDA is nearly the same as the mean range R_0 , *i.e.*, the average traversed absorber thickness, because heavy ions are very little scattered and travel almost on a straight line. Ranges of various ion beams in water are shown in Fig. 1.5. The range of ions with the same specific energy scales with a factor of A/Z^2 , then lower- Z particles have longer ranges than the higher ones. An

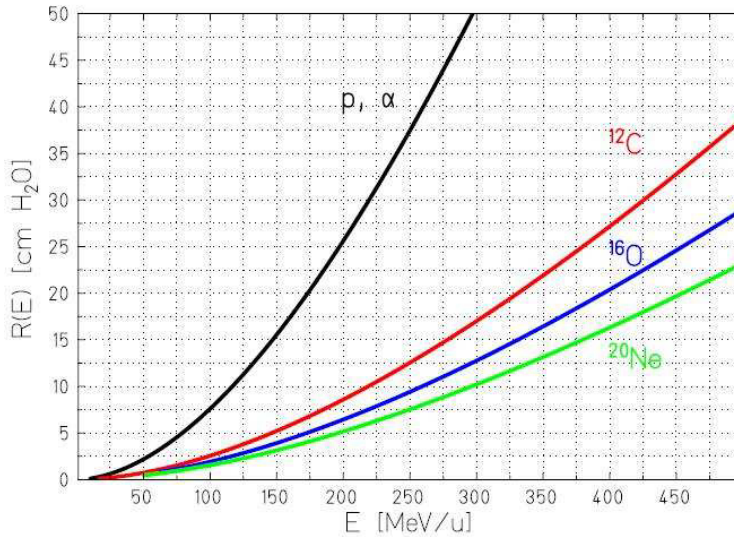


Figure 1.5: Mean range R_0 of heavy ions in water [17].

empirical correlation between the mean projected range R_0 of a particle beam and the parameter R_{80} , *i.e.* the depth of water at the distal 80% point of the Bragg peak, exists $R_0 \approx R_{80}$.

1.1.5 Energy/range straggling

According to Eq.1.5 the energy loss of a single carbon ion plotted as a function of absorber depth would result in a very sharp peak near the stopping point. However, since energy loss occurs as a finite number of individual interactions, it has statistical fluctuations. Therefore, charged particles, even if their initial energy is exactly the same, will not all stop at exactly the same depth in the medium. This is called *range straggling*, or *energy straggling* if we focus on fluctuations in energy loss rather than range. The macroscopic result is a broadening of the Bragg peak for an ion beam consisting of many particles and a changing in the peak-to-plateau ratio.

These fluctuations are described by the asymmetric Vavilov distribution [19] for charged particles passing through a thin layer of matter. In the limit of many collisions the Vavilov distribution becomes a Gaussian [20]:

$$f(\Delta E) = \frac{1}{\sqrt{2\pi}\sigma} \exp \left[-\frac{(\Delta E - \overline{\Delta E})^2}{2\sigma^2} \right] \quad (1.9)$$

with

$$\sigma = 4\pi Z_{eff} Z_t e^4 N \Delta x \left(\frac{1 - \beta^2/2}{1 - \beta} \right) \quad (1.10)$$

From the Eq. 1.10, since the width depends on the penetration depth Δx of the particles, for greater particle energies and longer penetration depth the half width of the Bragg peak becomes larger and the height smaller (see figure 1.6).

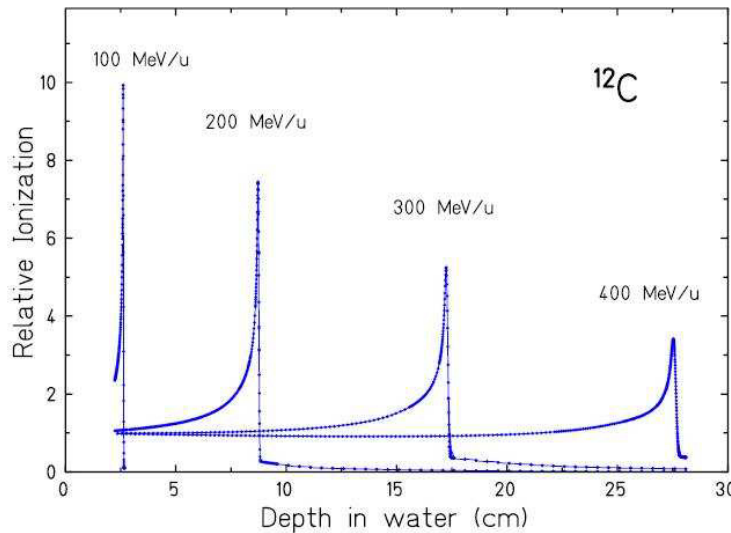


Figure 1.6: Measured Bragg curves for ^{12}C in water [21].

Moreover, because of a dependence of $\sigma \propto \frac{1}{\sqrt{M}}$ the width is smaller for heavier ions than for protons as shown in Fig. 1.7.

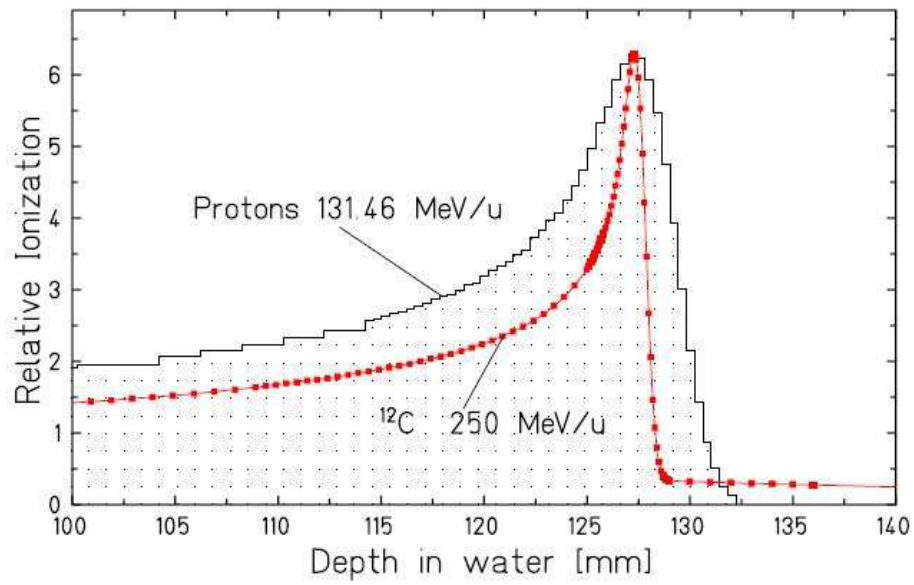


Figure 1.7: Measured Bragg peak for protons and ^{12}C ions having the same mean range in water [21].

1.1.6 Lateral Scattering

The *lateral scattering* of ions is mainly caused by elastic Coulomb interactions with the target nuclei. The angular deflection from a single scatter is almost always negligible. Therefore the main observed effect is the statistical outcome (random walk in the angle) of countless tiny deflections i.e. *Multiple Coulomb Scattering*. The MCS angular distribution is nearly Gaussian, because it is the sum of many small random deflections (the Central Limit Theorem). However, it is not exactly Gaussian because large single scatters in the target, though rare, lead to a Gaussian core distribution with a single scattering tail. The statistical distribution function has been described in the Molière theory [22] and for small angles the higher order terms can be neglected and the angular distribution can be approximated by a Gaussian function with standard deviation [23]

$$\sigma_\theta [\text{rad}] = \frac{14.1 \text{ MeV}}{\beta pc} Z_p \sqrt{\frac{d}{L_{\text{rad}}}} \left[1 + \frac{1}{9} \log \left(\frac{d}{L_{\text{rad}}} \right) \right] \quad (1.11)$$

where d is the target thickness and L_{rad} is the radiation length of the target material (e.g. water 36.08, Al 24.01, Pb 6.37 g/cm²).

Targets containing heavy elements cause an angular spread larger than targets of light elements with the same thickness (in units of g/cm²). Therefore, as we can see in the Fig.1.8, high-Z materials (Pb) are better for scattering whereas low-Z materials (Be, PMMA) are better for stopping particles.

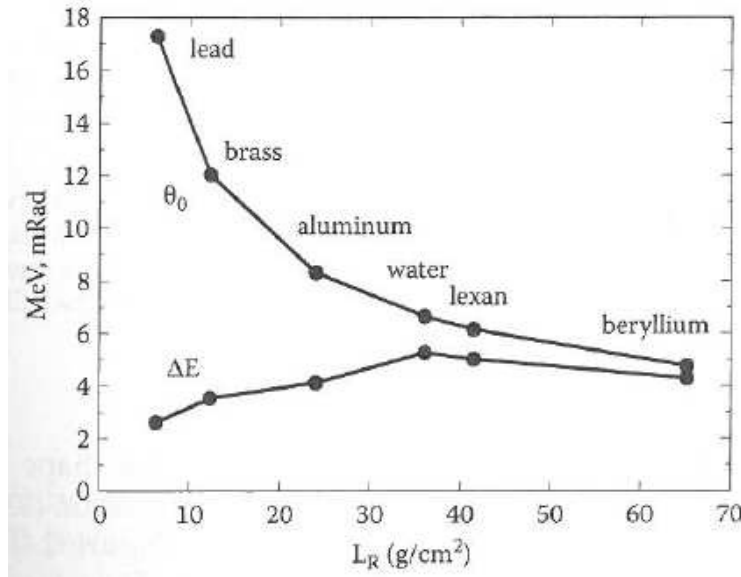


Figure 1.8: Multiple scattering angle and energy loss for 160 MeV protons traversing 1 g/cm² of various materials [13].

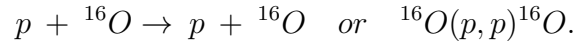
The lateral spread for heavy charged particles is smaller than for protons but it increases significantly towards low energies due to βpc term in the denominator of Eq.

1.11.

1.1.7 Nuclear Interactions

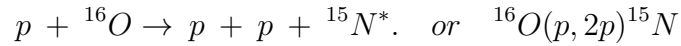
Although electromagnetic interactions of ions dominate, the probability of nuclear reactions is much smaller, but leads to significant effects at large penetration depths. They are far harder to model than stopping and scattering. In particular, in this section we focus only on the nuclear interaction of protons. Following the terminology of ICRU63 [24] we can distinguish among:

- a) *elastic* nuclear interaction, a reaction in which the projectile scatters off the target nucleus, with the total kinetic energy being conserved (the internal state of the target and of the projectile are unchanged)



${}^{16}\text{O}$ is left in its ground state.

- b) *Nonelastic* nuclear reaction, general term referring to nuclear interactions that are not elastic (*i.e.* kinetic energy is not conserved)



is nonelastic because it took energy to remove the target proton from the nucleus.

- c) *inelastic* nuclear reaction is referred to a specific type of nonelastic reaction in which the kinetic energy is not conserved but the final nucleus is the same as the bombarded nucleus



the ${}^{16}\text{O}^*$ is an excited state.

Particles generated by inelastic or nonelastic nuclear reactions are called *secondaries* and the particles in the original proton beam are called *primaries*. Possible secondaries from nonelastic reactions at therapy energies are protons, neutrons, γ rays and alpha particles. Fragments heavier than alphas are rare. The nuclear interactions gradually reduce the number of primary protons in the beam (1% per each cm depth in water) producing a *halo* of secondary protons and adding a tail to the lateral profile of the beam (see chapter 3 for more details). Moreover, nuclear interactions create a fair amount of

heavier particles with high ionization density and then a significant relative biological effect (RBE) (see 1.2). Last effect is the production of neutrons 'aura' [25] that escape the patient without further interactions and are thus responsible for a small contribution to the energy released inside and outside the irradiation area.

The nuclear interaction effect is visible at the interface between different medium such as air and water. The Fig. 1.9 shows a small but definite build up in the entrance region of a proton Bragg curve. A proton beam emerging from air is accompanied by

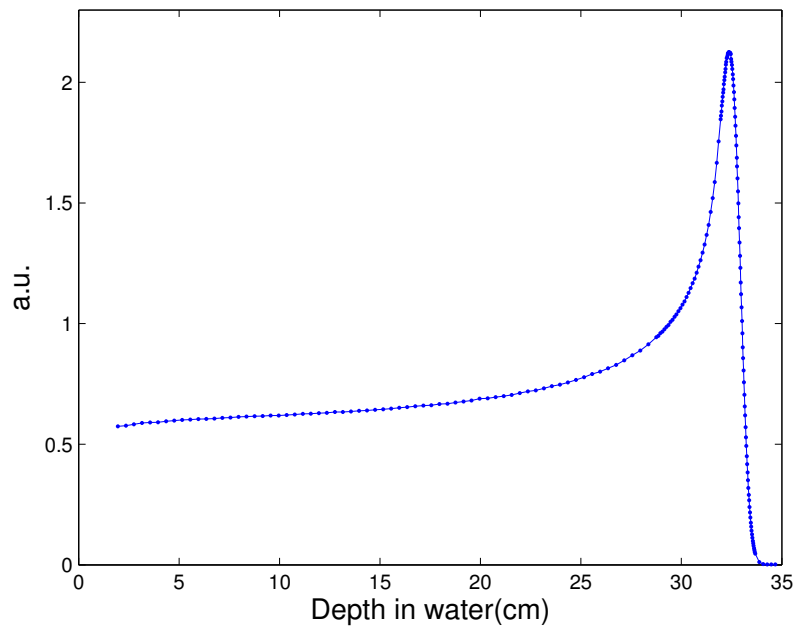


Figure 1.9: Measured depth dose profile for 230 MeV proton in water.

relatively few nuclear secondaries because of the low density of air. Nonelastic reactions increase as soon as the beam hits water, but it takes them one or two centimeters, the characteristic range of secondary protons, to reach the *longitudinal equilibrium*.

The nuclear interactions affect entirely the Bragg curve, each non-elastic reaction removes a proton from the peak and the secondaries, having short ranges and large emitted angles, deposit their energy further upstream. Therefore, nuclear interactions lower the peak and raise the plateau.

1.2 Biological advantages of light ion beam therapy

In addition to the advantageous depth-dose profile (in comparison with photons) and lateral scattering (in comparison with protons) ions heavier than protons offer an even larger efficacy for tumor treatments due to the enhanced biological effect of high-

LET particles. As seen in Eq. 1.5 the LET depends quadratically on the projectile charge Z_p^2 and results in large values for heavy ions. Typically, the large energy deposition in the center of ion tracks result in more severe DNA damage with respect to low-LET irradiation. Since the ionization density of light ions is larger for the low energetic (high-LET) particles as present in the tumor volume relative to the swift ions in the plateau, the biological effect in the target is more pronounced than in the surrounding normal tissue.

The biggest difference between photon and particle irradiation concerns the microscopic spatial energy distribution. In the case of photons the energy is transferred to the cell by photoelectric effect or by Compton effect, depending on the energy of the penetrating photon. Since the cross sections for these processes are rather low, the number of ionization events per incident photon within the volume of a cell is also small. Due to this low number of events, many photons are required to deposit a relevant dose and since these photons are randomly distributed, the resulting ionization density can be assumed to be homogenous over the entire cell volume. Otherwise, for particles the spatial energy distribution is localized around the particle track that results in a typically larger biological effect induced by particles. The radial dose distribution around particles is governed by emission of electrons (δ -rays), which have enough energy to ionize the medium emitting other secondary electrons. Moreover, those electrons are fast enough to leave the track core and undergo a large number of interactions before stopping.

All analytical model calculation [26, 27] and Montecarlo simulation (TRAX code [28]) predict the steep $1/r^2$ decrease of radial dose distribution within the increasing distance r from the center of the particle track and confirm the experimental studies [29] (Fig. 1.10).

The picture in Fig. 1.11 shows the TRAX simulations of δ -rays comparing protons and ^{12}C ions of various energies. The dense emission pattern of electrons from ^{12}C ions at low energies with respect to protons can be noticed. Most electrons have very low energies, below 100 eV.

The typical extension of the track center with the highest “local” dose is on the order of nanometers (see Fig. 1.10 and Fig. 1.11) thus resulting in a large probability of correlated nearby DNA damages (being 2 nm the diameter of DNA) like double strand breaks (DSBs). Moreover, the damages have been created so close to each other (cluster of DSBs) that the cell’s repair capability is reduced and the radiation damage of particles is larger than that of photons.

The Fig. 1.12 shows the different microscopic dose distribution of X ray (practically homogeneous) and ^{12}C ions at different energy and then different LET.

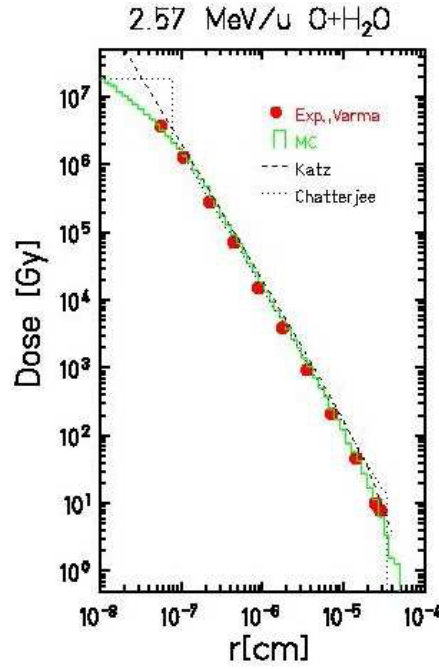


Figure 1.10: Radial dose distribution around the track for ^{16}O ions in water; comparison among different analytical model [26,27], Montecarlo simulation (TRAX code [28]) and experiments [29].

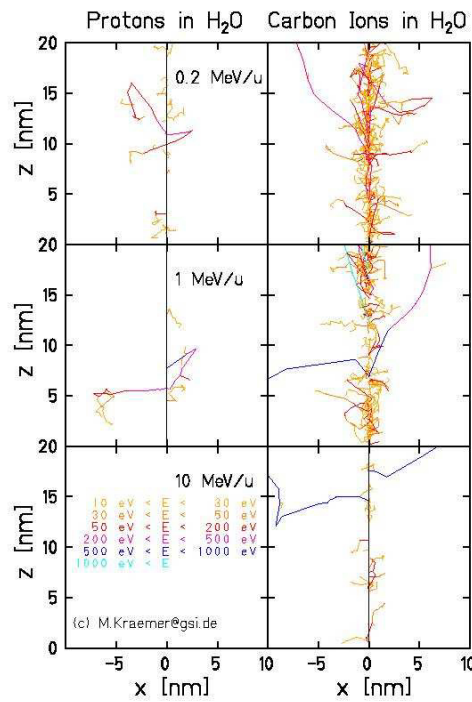


Figure 1.11: Comparison between the ionization patterns created by protons and ^{12}C ions of various energies (TRAX code [28]).

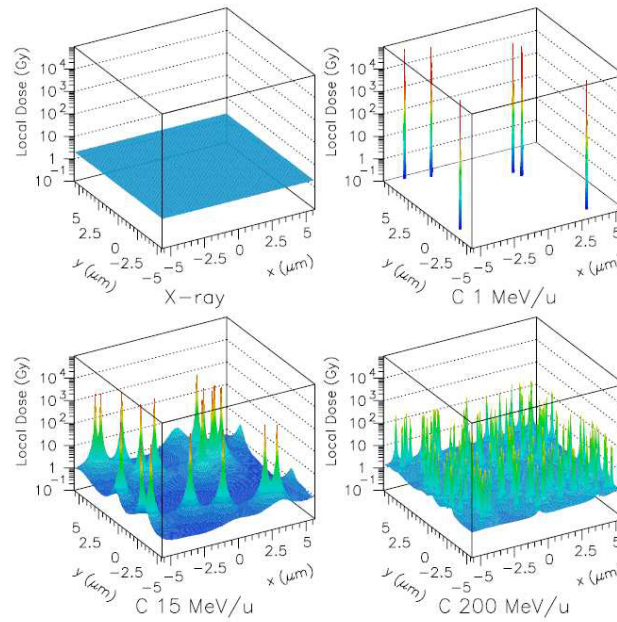


Figure 1.12: Comparison among different microscopic dose distributions for low-LET radiation (X-rays) and high-LET radiation (^{12}C) for the same average macroscopic dose of 2 Gy [30].

1.2.1 Relative Biological Effectiveness RBE

In order to compare the biological effect of photons and particles and show the biological advantages of particles, we have to introduce the concept of cell survival curve. This concept shows the potential of radiation of killing tumor cells and for this reason has a remarkable significance in radiation therapy. There are different biophysical models try to explain the cell survival curve shape. The most common way to parametrize the cell survival S uses the linear-quadratic model [2]

$$S(D) = \exp(-\alpha D - \beta D^2) \quad (1.12)$$

where α and β are parameters measuring the amount of lethal and sub-lethal cell damage, respectively, and D is the dose [2]. The survival curve shows an initial linear decrease (α term) followed by a shoulder determined by the ratio α/β . Smaller values of α/β correspond to a more pronounced shoulder of the dose response curve.

For an accurate estimate of the efficacy of ions, the concept of the *Relative Biological effectiveness (RBE)* must be applied. The RBE is defined as the ratio of the low-LET radiation dose of γ -rays D_γ (for historical reasons ^{60}Co) divided by the dose of particle irradiation which results in the same biological effect (isoeffect).

$$RBE_{isoeffect} = \frac{D_\gamma}{D_{ion}} \quad (1.13)$$

The Fig. 1.13 shows graphically the RBE meaning for heavy ions. As seen in figure. 1.13

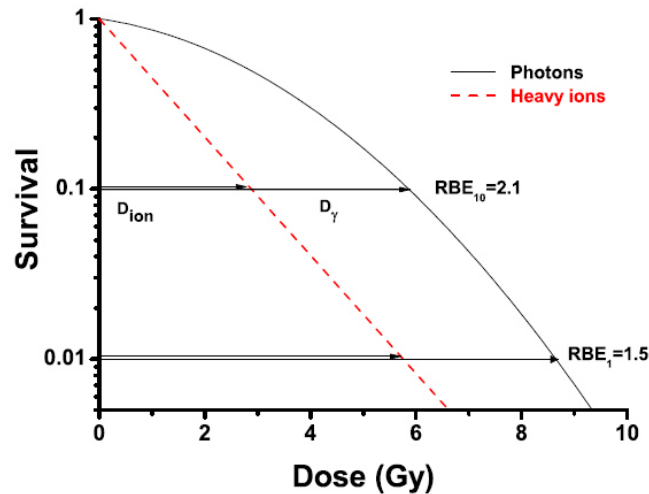


Figure 1.13: Definition of RBE for cell inactivation at 2 different survival level 10% and 1%.

the shoulder in the survival curve for light ions is not present anymore (i.e. the quadratic term) due to the reduced capability of the cell to repair the high LET radiation damage.

The RBE is an important quantity in treatment planning of ion therapy, since it determines the photon-equivalent dose (*biological dose* Gy(RBE)) by weighting with the absorbed (physical) dose. The biological dose quantifies the dose of conventional radiation that would yield the same biological effect as the applied ion radiation. It is used to compare the results of conventional radiation with other radiation qualities such as neutrons, protons, or carbon ions. Equal physical doses of different types of radiation do not produce the same biological effect. The RBE can be used for many biological end points such as DNA strand breaks, mutations, or transformations. In heavy-ion therapy, the RBE for cell killing and normal-tissue complications are most relevant.

The RBE depends on many different parameters related to the particle properties such as dose, ion species, and energy (LET) or to the cell line such as the cell type or tissue.

Although the RBE depends on many different parameters, it was concluded that for proton therapy the magnitude of RBE variation with treatment parameters in clinical situations is only in the order of 10% to 20% (for *in vivo* studies). The average value at mid SOBP overall dose levels was shown to be $RBE = 1.1$ [31]. At almost all institutions, proton therapy is based on the use of a single RBE value ($RBE = 1.1$), which is applied to all proton-beam treatments independent of dose per fraction, position in the SOBP, initial beam energy, or the particular tissue irradiated.

1.3 Accelerators for light ion beam therapy

Until the 1990s particle therapy was performed in nuclear physics laboratories that were equipped with a particle accelerator. At the early stage of ion therapy the Bevalac was the only machine worldwide capable of accelerating ions to kinetic energies of several hundred MeV/u as required for radiotherapy. It was, however, not optimized for the requirements of particle therapy since the design of medical machines has to focus on reliability of the machine operation and extreme care in beam control. Nowadays the *cyclotron* and *synchrotron* are the two types of accelerators that are offered by companies and that have proven to be reliable machines in clinical facilities. In this section a brief description of the currently used accelerators will be reported.

1.3.1 Cyclotrons

The new generation of isochronous cyclotrons for proton therapy can accelerate protons to a fixed energy of 230 or 250 MeV. They are compact with respect to the classical cyclotrons in accelerator laboratories; typical diameter is between 3.5 m (100 tons) and

5 m (200 tons), when equipped with superconducting coils or with room temperature coils, respectively. The Fig. 1.14 shows the design of the first superconducting cyclotron (COMET) of Varian installed by ACCEL at the Paul Scherrer Institute (PSI) in 2007 [32].

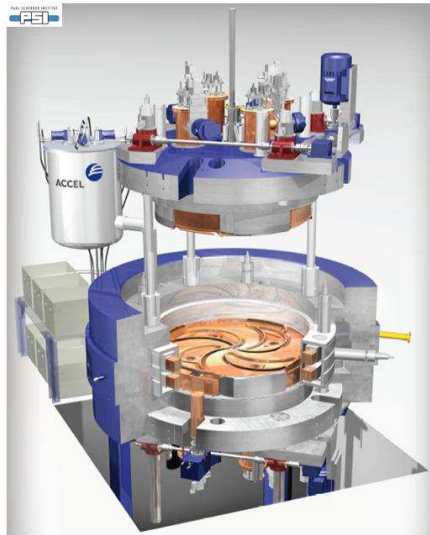


Figure 1.14: The 250 MeV superconducting cyclotron of Varian installed by ACCEL at PSI.

Cyclotrons were considered as easy to operate, highly reliable, and compact machines. They offer extremely stable and regulable beam intensities, but no active energy variation, *i.e.* only by means of passive degraders in the beam line. Nevertheless, the beam energy at the patient can be adjusted very fast and accurately by means of fast degrader (upstream in the beam line or downstream near the nozzle) and an appropriate beam line. The principal components of a cyclotron are:

- A radio frequency (RF) system which provides a strong electromagnetic field by which the protons are accelerated. It consists of two or four electrodes (called “Dee” for the typical shape) that are connected to a RF generator.
- A strong magnet that confines the particle trajectories into a spiral orbit, so that they can be accelerated many times by the RF voltage.
- A proton source in the center of the cyclotron, in which hydrogen gas is ionized and from which the protons are extracted.
- An extraction system that guides the particles that have reached their maximum energy out of the cyclotron into the beam line.

Each “Dee” consists of a pair of copper plates and are placed between the magnet poles which are at ground potential. When the “Dees” are supplied with a positive voltage, the proton crosses the gap between the “Dee” and experiences acceleration toward the grounded region. When the proton approaches the “Dee” at the negative voltage phase, it is accelerated into the gap between the 2 plates. The magnetic field of the iron magnet poles forces the particle trajectory along a circular orbit, so that it crosses the “Dees” and the ground several times during one circumference.

1.3.2 Synchrotrons

For proton therapy cyclotron and synchrotron are competitive but for ions heavier than protons synchrotrons are currently the only accelerators in operation. The main advantage of a synchrotron is that particles are accelerated until the desired energy, almost no radioactivity is created due to the beam losses in the beam line and the intensity (particle current) of the low energy particles is the same as for high energy particles. The latter is due to the absence of transmission loss in a degrader used in a cyclotron to change passively the particle energy. The synchrotron requires a larger space with respect to a compact cyclotron, usually a ring of magnets 6-8 m diameter for protons and a ring of 20-25 m for light ions (accelerating from proton to ^{16}O in clinical energy range). The Fig. 1.15 compares two different designs of synchrotron accelerator dedicated to protons only or to proton and heavier ions. The beam line before the synchrotron ring is

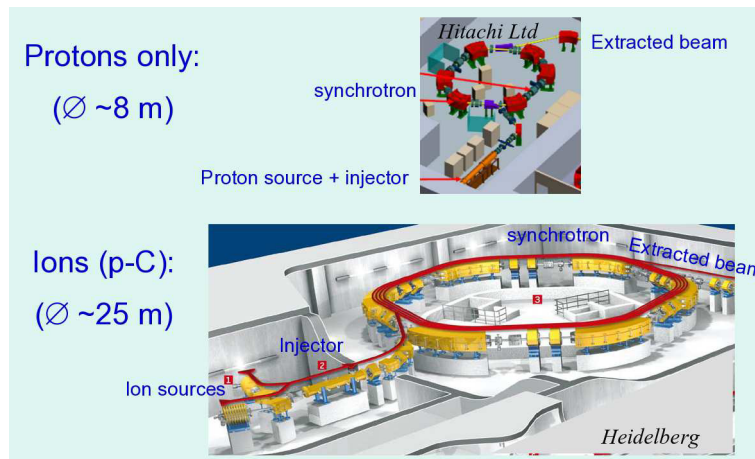


Figure 1.15: Schematic comparison between a dedicated synchrotron for protons of Hitachi company and the synchrotron installed at “Heidelberg Ion Beam Therapy Center” (HIT) for light ions.

the injector system that consists of:

- Several ion sources for ion medical accelerator. All the desired ions can be obtained from gas (usually hydrogen or carbon dioxide) with the specified ion currents in the required charge states.

- A low energy beam transport line (LEBT) isolates the correct charge state of the ions.
- A RFQ (Radio Frequency Quadrupole) transforms the DC ion beam to the RF time structure of the LINAC at 216 MHz. The output energy of the RFQ beam is near 400 keV/u .
- A compact LINAC (Linear Accelerator) accelerates particles up to 7 MeV/u .
- A medium energy beam line (MEBT) that contains a stripper foil and analysis system to strip electrons from the ions up to the charge state selected for synchrotron injection (e.g. for ^{12}C the MEBT strips the ions in order to have a charge of $+6e$). Now particles are ready to get into the ring of the synchrotron where it will be accelerated up to 430 MeV/u .

The energy of the circulating particle bunch is increased in an RF cavity located in the ring. The increase of particle momentum p is synchronous with the magnet fields increase in the ring (see Eq. 1.14) because the particles must remain in an orbit with a constant average radius (different from a cyclotron where the orbit increases up to the maximum extraction radius).

$$\frac{p}{Bq} = r = \text{const} \quad (1.14)$$

Instead of fast extraction in a single turn from the ring, a slow extraction scheme is necessary for accurate dose application of active scanning beam delivery techniques (see section 1.4.2). The last part is the High Energy Beam Transport Line (HEBT) from the synchrotron to the treatment rooms. The beam transport has to take place without transmission losses for all ion species and beam energies and must focus the beam to the different required beam sizes (*foci*) at the isocenter.

1.4 Beam delivery systems

As it was mentioned in the previous section, after the acceleration (via a cyclotron or a synchrotron) the beam is transported into the treatment rooms by the HEBT transport line. The task of a *beam delivery system* is to transport the particle beams to the treatment area and distribute the beam over the planning target volume (PTV) according to the treatment plan. The particle beam that reaches the treatment room is mono-energetic and has a lateral spread of only a few millimeters depending on energy, ion species and beam optic. Without any modification this beam would give a dose distribution on the patient that is not clinically useful because the dimensions of tumors are of the order of

few centimeters in lateral and depth direction. For this purpose it is needed to spread the beam to a useful uniform area in lateral direction as well as to create a uniform dose distribution in depth direction. In general, two methods were followed:

- the *passive scattering delivery systems*;
- the *active scanning delivery systems*.

In the first case, the particle beam is adapted in three dimensions to the target volume only by passive field shaping elements. In the second case, the target volume is dissected in small volume elements (voxels) and a pencil-like beam is used to fill the voxels with the appropriate dose, ideally without any material in the beam path.

1.4.1 Passive scattering delivery system

In a passive system the initially narrow beam delivered by the accelerator is first broadened by a scattering device, normally a double-scattering system which generates a flat transversal dose profile. The Fig. 1.16 shows the principle of a fully passive system.

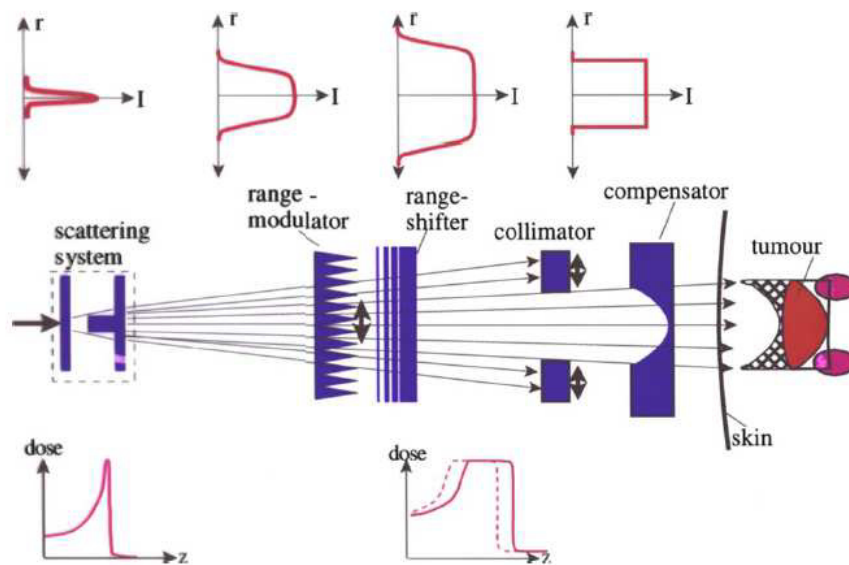


Figure 1.16: A passive beam shaping system where the initial narrow beam is broadened by scattering system and adapted to the target volume by various passive devices.

The Spread Out Bragg Peak SOBP is created by a range modulator (“wheel modulator”) in order to cover the entire length of the target volume. The SOBP can be shifted in depth by absorber plates “range shifter” usually made by plastic material, *i.e.* low- Z materials because they provide the least amount of scattering per unit of range shift (see Fig. 1.8). Clearly something is needed to conform the dose to the target. As in conventional external beam radiotherapy, a block or collimator shapes the dose laterally.

Regarding the material high-Z material are the obvious choice as they stop the particles in the shortest physical distance (usually the two materials are brass and cerrobend). To conform the dose to the distal part of the target one needs the range compensator that takes into account also the complex target shape. To reduce the lateral penumbra the air gap between the patient and the compensator is minimized by moving the snout closer to the patient. The collimator and compensator are both patient-specific and it is extremely time consuming to build these devices for each patient.

1.4.2 Active scanning delivery system

For fully active beam delivery the target volume is divided in layers of equal beam energy (iso-energetic slices) and each layer is covered by a grid of spots (voxels). The scanning beam system delivers the dose sequentially to these voxels. The particles are deflected when a magnetic field has been applied and this feature allows to spread the beam laterally. Regarding the spread out of the beam in depth the Bragg peaks are stacked by changing the particle energy through the accelerator (synchrotron) or through a passive system placed inside the beam line (cyclotron). The active scanning has several advantages:

- neither field-specific nor patient-specific hardware is needed, as collimator or compensator for passive scattering techniques;
- the dose can be varied from voxel to voxel allowing to compensate for pre-irradiation of proximal subvolumes, dose contributions from secondary fragments, and variations of biological effectiveness (RBE);
- the material in the beam line can be minimized, increasing the beam transmission and reducing the production of secondary particles like neutrons in front of the patient;
- it is more efficient than passive scattering because less particles need to be delivered in order to achieve the same total dose to the target volume and therefore it spares better the surrounding normal tissues;
- an Intensity Modulated Particle Therapy (IMPT) can be achieved similar to IMRT with X-ray. Each individual field of a treatment plan delivers an optimized and inhomogeneous fluence pattern such that the desired dose distribution in the patient is achieved when all fields are combined [33].

The main disadvantage is the demand on the complicated control and safety systems and the requirements on the stability and reproducibility of the beam position. Three main different techniques have been introduced worldwide during the last two decades:

- the discrete scanning or “*spot scanning*”;
- the quasi-discrete scanning;
- the continuous scanning or “*raster scanning*” [34].

The first *spot scanning* system was developed at the National Institute of Radiological Science (NIRS) in Japan for 70 MeV protons by Kanai in 1983 [35]. From this experience the world’s first spot scanning Gantry (the so called ‘Gantry 1’ located at PSI) was built in 1992 [4] and the first patient was treated in 1996. The *spot scanning* is applied as a step-and-shoot technique where the beam is switched off in between spots “*discrete spot scanning*” by a fast “kicker magnet” (the beam can be switched on and off in 50 μ s). In this way the unwanted dose between spots is avoided. The spot scanning delivery is usually coupled with a cyclotron accelerator therefore the energy needs to be tuned via a passive system (e.g. from 70 MeV up to 230 MeV by a “fast degrader” placed after the cyclotron in the beam line and consisting in a series of opposed carbon wedges). Lateral scanning is performed by two sweeper magnets (X and Y direction) placed upstream the last 90°bending magnet (upstream scanning).

The “*quasi-discrete scanning*” [5] was developed at the Gesellschaft für Schwerionenforschung (GSI) in the early 1990s and later adopted by HIT (Heidelberg, Germany), CNAO (Pavia, Italy) and MedAustron (Wiener Neustadt, Austria). The quasi-discrete scanning technique is coupled with a synchrotron accelerator which allows a dynamic variation of the ion beam energy. The technique is based on the virtual dissection of the tumor in slices of equidistant particle ranges and each iso-energetic slice is subdivided into a large number of voxels. When the desired particle fluence in one voxel is reached by measuring the number of particles released, the beam is moved to the next raster without turning it off. The pencil beam is moved in horizontal and vertical direction along an iso-energetic slice by fast magnetic scanners (see Fig. 1.17).

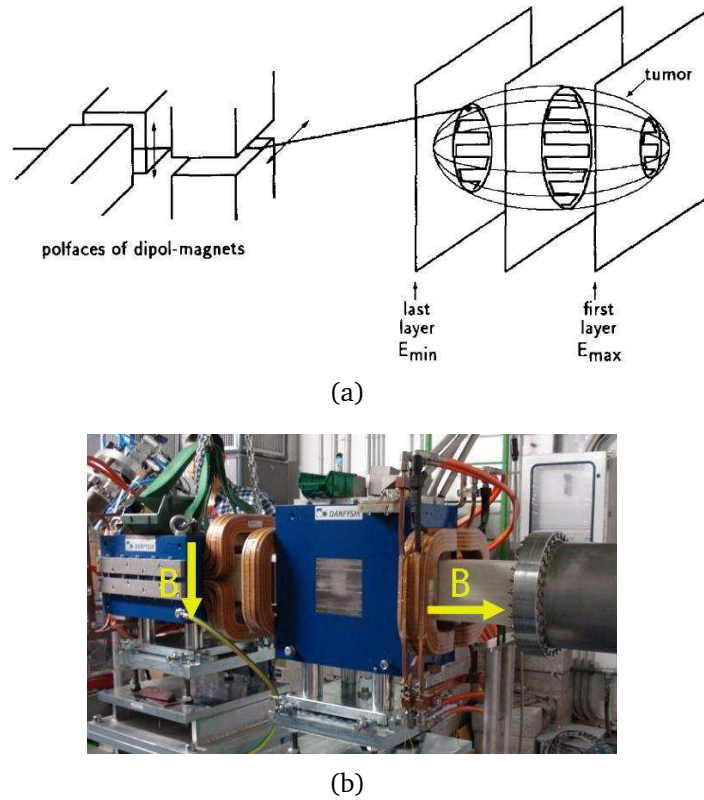


Figure 1.17: (a) The target volume is irradiated by moving a pencil-like ion beam with fast magnets over thin slices in depth. The irradiation starts from the distal slice to the proximal slice [5]. (b) The scanning magnets placed into the beam line at the CNAO facility.

The *raster scanning* is a method in which a pencil beam of particles is scanned continuously across the cross-section of the beam in a raster pattern. Variation in intensity as a function of beam position is achieved by continuous control of the particle-beam intensity and/or the scanning speed. Between two iso-energetic layers the beam is turned off.

1.5 Dosimetry in light ion beams

1.5.1 Introduction

The passage of ionizing radiations through matter induces processes of ionizations and excitations of the medium atoms and molecules. These microscopic processes are the origin of macroscopic directly or indirectly measurable effects.

The primary target of dosimetry is the determination or the calculation of the dose absorbed by the irradiated matter.

Any effect which causes the variation of a physical and/or chemical parameter as a function of the energy absorbed per unit mass of a medium could be exploited to carry out a determination of the absorbed dose. The various measurement methods can be distinguished in *absolute methods* which allows to obtain the dose value directly from the measure of physical or chemical parameter and *relative methods* which need an intercalibration with some absolute equipment. Some absolute methods are: the *calorimetric method* based on the measure of the temperature variation induced by ionizing radiation in graphite or water, the *chemical method* based on the oxidation of ferrous ions into ferric ions (*Fricke dosimetry*) and the *ionometric method* based on the measure of ionization in a gas (ionization chamber dosimetry). Among the relative methods the *photographic method* (based on the formation of a latent image after the ionizing radiation passage) and the *thermoluminescence method* (based on the luminescence in solids induced by heating) can be counted. The Electron Paramagnetic Resonance *EPR* dosimetry is also a relative method and is based on the detection of the free radicals produced by ionizing radiation in passing through matter.

The energy imparted by ionizing radiation to matter with the volume V and the mass m is defined as a stochastic quantity ϵ . Considering particles interacting with volume V , the energy imparted to it is the sum of energies (without the rest mass energy) from all charged and uncharged particles entering the volume $\epsilon_{i,in}$, minus the energy of those leaving the volume $\epsilon_{i,out}$, plus $\sum Q$ of all changes of the rest energy of nuclei and elementary particles which occur in the volume ($Q > 0$: decrease of rest energy; $Q < 0$: increase of rest energy) from any nuclear reactions involved. Thus

$$\epsilon = \sum_i \epsilon_{i,in} - \epsilon_{i,out} + \sum Q. \quad (1.15)$$

The most important dosimetric quantity is the *absorbed dose*. The *absorbed dose* is the mean energy imparted in an infinitely small amount of matter [8]

$$D = \frac{d\bar{\epsilon}}{dm}. \quad (1.16)$$

Dose is a macroscopic non-stochastic quantity. The SI unit of the absorbed dose is Gray (Gy) and $1 \text{ Gy} = 1 \text{ J kg}^{-1}$.

1.5.2 Solid State Detectors in Particle Therapy

Solid state detectors provide information about the absorbed dose to a medium based on energy deposition in an active volume of condensed matter. The advantage of solid

state detectors is their higher signal due their ionization density, thus the possibility to achieve smaller detectors and higher spatial resolution for dosimetry. The higher ionization density, however, is also the reason for saturation effects, which can be observed for all solid-state detectors in high-LET beams (such as ^{12}C ion beam) as well as at the distal edge of a proton Bragg peak. The solid state detectors irradiated with particle beams show that the response depends not only on the applied dose, but also on the nature of the radiation field. For all this detectors we can observe a “quenching” in the signal response near the Bragg Peak with respect to the plateau region. This phenomenon is evident for most solid state detectors such as diamond detectors, diodes [36], films [37], thermoluminescent dosimeters (TLDs) [38], optical stimulated luminescence (OSL) detectors and alanine EPR dosimeter [39,40]. These effects of reduced effectiveness strongly depends on ion species Z , energy ion E and, for some detectors, also the fluence ϕ is expressed as a *Relative Effectiveness (RE)* $\eta(Z, E, \phi)$. In literature the RE definition is not unique. There is the iso-response definition similar to the RBE definition:

$$\eta_{iso-response}(Z, E, \phi) = \frac{D_X}{D_{particle}}|_{iso-response} \quad (1.17)$$

the ratio of the dose to low-LET radiation D_X (^{60}Co radiation) and the dose to particle radiation $D_{particle}$, which yields the same detector response. The second definition is the ratio of the response of the detector irradiated with reference radiation $S(D_X)$, to the response after irradiation with particle irradiation $S(D_{particle})$, at the same nominal dose:

$$\eta_{iso-dose}(Z, E, \phi) = \frac{S(D_X)}{S(D_{particle})}|_{iso-dose} \quad (1.18)$$

In order to exploit the power of solid state detectors it is needed to know the relative effectiveness to be able to correct the signal measured and accomplish the right dose value.

CHAPTER 2

MEDAUSTRON LIGHT ION BEAM THERAPY (LIBT) FACILITY

2.1 The MedAustron project

MedAustron is a LIBT and research facility in Wiener Neustadt in the county of Lower Austria (Austria). MedAustron is designed as a dual-particle facility using proton and carbon ion beams for clinical and nonclinical research [41]. The first patient with protons has been treated in December 2016 and it is planned to treat up to 1000 patients per year in full operation (2020). The building was constructed within 18 months with the sandwich method (patented Forster Sandwich Construction) that uses thick concrete panels between which the excavated soil is loosely placed and subsequently compacted to the density of concrete 2.1. The 'Forster Sandwich' technology allowed saving 25000 tons of the concrete, 7500 tons of steel and shortening construction time by 6 months. The development of the equipment installed at MedAustron was performed within a cooperation of several industrial and scientific partners. The accelerator has been developed in collaboration with the European Organization for Nuclear Research (CERN) in Geneva (Switzerland) and in collaboration with CNAO (Italy). Four irradiation rooms (IR1 - IR4) are available (see figure 2.2). Three rooms (IR2 - IR4) will be used for clinical purposes. The IR1 is dedicated to NCR (non-clinical research) where protons up to 800 MeV can be used. IR3 is equipped with a fixed horizontal beam line (HBL) for carbon ion and proton beams. IR2 is equipped with a horizontal and a vertical beam line (VBL) for both particles. In IR4 a proton gantry which allows irradiation from various angles (from -10 to 185) is installed. The Gantry has been developed in collaboration with the Paul Scherrer Institut (PSI) in Villigen (Switzerland) based on the design of PSI Gantry



Figure 2.1: Accelerator building construction applying Forster Sandwich Construction technology.

2 [42]. All IRs are supplied with quasi-discrete spot scanning delivery systems developed in cooperation with CNAO Foundation [43, 44] in Pavia (Italy).

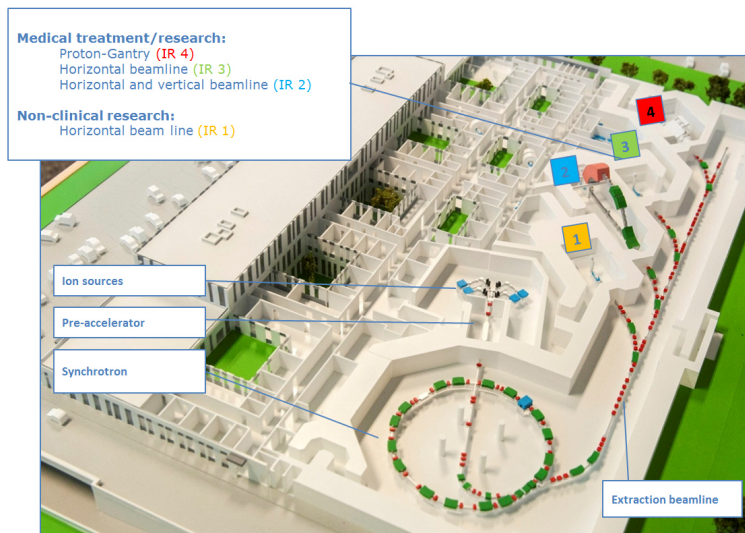


Figure 2.2: MedAustron layout with accelerator components and Irradiation Rooms (IR1-IR4) indicated.

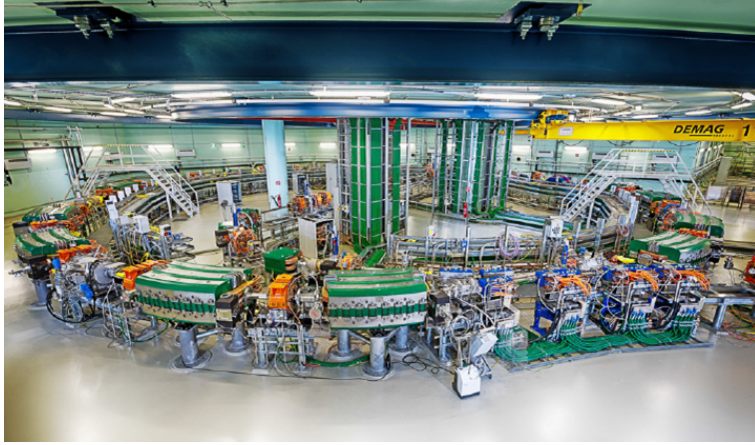
Each irradiation room is equipped with a Patient Alignment System (PAS) composed by a ceiling-mounted robot and a couch-based imaging ring system equipped with an independently movable X-ray source and flat panel detector. The PAS has been developed within a cooperation between MedAustron, Buck Engineering and Consulting GmbH in Reutlingen (Germany) and medPhoton GmbH in Salzburg (Austria). The ceiling-mounted robot (Examove 7C) has 7 degrees of freedom and facilitates non-isocentric treatments to reduce the air gap (mainly for protons). The ImagingRing system provides planar and cone-beam computed tomography (CBCT) imaging [45, 46] for accurate inter-fraction patient positioning and adaptive radiotherapy. A comprehensive im-

age, data and patient information management software that centralizes the ion beam therapy process and is accessible by a multi-disciplinary team across multiple locations will give to the MedAustron the flexibility to choose the optimal treatment solutions. The Institute for research and development on advanced radiation technologies (radART) of the PMU (Salzburg, Austria) established a scientific collaboration with MedAustron in the field of developing, integrating and commissioning an open source software suite for MedAustron. The open-radART software suite provides a framework to cover a large number of software components and tasks. In principal, it unifies capabilities in the context of Defining, Recording and Verifying patient treatments, controlling the MedAustron Particle Therapy Accelerator (MAPTA) as well as handling patient data in terms of being an Oncology Information System (OIS). The main key components are Patient Study Record (PSR), Treatment Operation Editor (TO-ED) and the Radiotherapy Software system (RTSS) suite with the purposes explained in the following. Taking care of the OIS addressing part, PSR collects all patient related data from anamnesis to treatment as well as scheduling related information. TO-ED is capable to prospectively plan an entire therapy course in a granular manner based on a DICOM prescription provided by the Treatment Planning system (TPS). More specifically, it defines a linear chronological sequence of actions, named treatment operation. Such a Treatment Operation provides the basis of single fractions grouped in a patient's therapy course including all required steps from patient positioning, patient positioning verification as well as runfile generation for MAPTA. Last but not least, RTSS orchestrates all low-level in-room software and hardware components, which are required to execute the above mentioned treatment operation. Moreover, RTSS monitors the treatment by means of Logfiles, which are received by the Dose Delivery System (DDS). All three Modules are highly synced and read from and write to the open-radART file system which can also be seen as a fully DICOM compatible Picture and Archiving and Communication System (PACS).

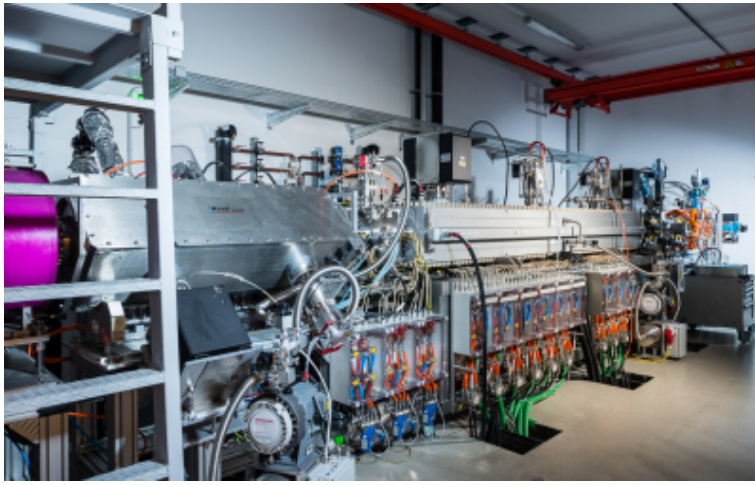
2.2 Accelerator at MedAustron

MedAustron is equipped with a synchrotron accelerator able to accelerate for medical and research purpose ions from protons up to Neon. The facility can deliver proton in an energy range of 60 to 250 MeV (from 3 to 38 cm in water) and carbon ions in a range of 120 to 430 MeV/u (from 3 to 27 cm in water) [47]. The accelerator design is based on the Proton-Ion Medical Machine Study (PIMMS) [48] and is a further development of the machine installed at CNAO [49].

In general, the beam transport line is a central vacuum pipe system of a total length



(a)



(b)

Figure 2.3: (a) MedAustron synchrotron with dipole magnets in green and quadrupole magnets in orange. (b) MedAustron RFQ and IH-mode drift-tube LINAC.

of around 400 m from the sources to the irradiation room. More than 130 pumps are necessary to maintain a pressure down to 5×10^{-9} mbar and about 300 magnets are needed to bend and focus the beam. Beam diagnostics equipment is distributed through the accelerator complex to control and guarantee that the nominal characteristics of the beam (e.g. mean kinetic energy, energy spread, intensity, transversal shape, beam divergence and emittance) are maintained during acceleration and transport. In total 153 monitors of 16 different species (e.g. Faraday cups) are used in the accelerator complex. The whole system consists of more than 8000 different components supplied by more than 220 vendors from 23 countries, none of these items being off-the-shelf. The beam produced by one of the three ion sources is selected and transported by the LEBT system to the LINAC. The LINAC consists of a radio frequency quadrupole (RFQ) and an IH-mode drift-tube LINAC. The RFQ accelerates the particles to 400 keV/u, the injection energy into the synchrotron of 7 MeV/u is achieved by a LINAC. After the LINAC, the

particles C^{+4} or H_3^+ are totally stripped with a thin carbon foil and guided by the MEBT to the synchrotron. Before entering to the synchrotron a degrader might be inserted in order to reduce the transmission. In particular four degrader settings are available: 100%, 50%, 20%, and 10% transmission. The synchrotron is a ring (approximately 25 m in diameter) accelerating particles by means of oscillating, high-frequent (radio-frequency) electromagnetic fields. In the first phase, the synchrotron accumulates the particles coming from the injector. This process is performed in several cycles in which the particles in the synchrotron keep orbiting while more particles are accumulated. Subsequently, the particles are captured and accelerated by means of an RF cavity to the final energy required for the specific iso-energetic layer irradiation. Finally, the particles are extracted from the synchrotron and guided to the HEBT, using a method called 'slow extraction' (spill length from 1 s to 10 s). The maximum number of particles extracted are 2×10^{10} and 4×10^8 for proton and ^{12}C ions, respectively.

2.3 Active scanning beam delivery system at MedAustron.

At MedAustron the quasi-discrete spot scanning technique has been implemented (see paragraph 1.4.2). Main tasks of the Beam Delivery System (BDS) are to steer the pencil beams at the correct position (via scanning magnets upstream in the beam line), to verify the beam parameters (intensity, position and shape) and correct in real time, to stop the beam if necessary (sending an interlock). The main BDS components are the scanning magnets, the beam monitors and the passive elements (ripple filters (RiFis) and range shifter (RaShi))

The scanning system consists of two power supplies connected to two identical dipole magnets for horizontal and vertical beam deflections placed at the end of the HEBT at distances 6.70 m (Y horizontal scanning) and 7.42 m (X vertical scanning) upstream to the isocenter. The scanning magnets allow a maximal scanning field size at isocenter of 200×200 mm in IR2 and IR3, while the maximal field size in the gantry room (IR4) is 120×200 mm.

In order to verify the delivered number of particles, position and shape per spot and the total number of particles, three redundant measurement devices are placed in the nozzle:

- the *Independent Termination System* (ITS) box, equipped with an integral plane-parallel ionization chamber filled with N_2 gas. The electrodes dimension are 211×211 mm and the gap between electrodes is 5 mm.

- the *DDS Box1* equipped with an integral chamber (IM) and 2 strip ionization chambers. The IM measures the beam fluence at high speed (1 MHz), sensitive area of $211 \times 211 \text{ mm}^2$ and filled with N_2 gas. The two strip chambers measure the beam position and shape with an accuracy of $100 \mu\text{m}$ every $80\text{-}100 \mu\text{s}$. Their anodes are made by kapton foils covered by 128 aluminum strips of 1.55 mm wide and with a pitch of 1.65 mm. The two strip chambers are rotated by 90° in order to measure the profiles in both planes (sensitive area of electrodes $211 \times 211 \text{ mm}^2$). Strip chambers also provide a beam fluence measurement and are also used as ‘redundant’ fluence monitors for safety reasons.
- the *DDS Box2* is identical to *Box1* as redundant system. Box1 and Box2 are contiguous and totally separate ($\approx 2 \text{ cm}$).

To start and stop the beam quickly, in the HEBT a fast chopper is installed. The chopper is a set of four identical fast magnets powered in series. The beam can be interrupted between spots (within $300 \mu\text{s}$) for two different reasons:

- an interlock has been sent to the DDS Interlock Gateway (DIG);
- the distance between spots in the iso-layer is larger than a set threshold by the user; in this case a so called ‘island jump’ occurred.

At low energies, Bragg peak widths¹ are lower than 1 mm (down to about 0.3 mm for 120 MeV/u carbon ions) and the Bragg peak width has to be increased artificially in order to reduce the number of energy steps required to deliver a homogeneous SOBP. Ripple filters (RiFis) are used to enlarge pristine Bragg peaks only by 2-3 mm in order to reduce the treatment time [50, 51]. The minimum extracted beam energies (60 MeV and 120 MeV/u respectively for protons and ^{12}C ions) is a limitation for superficial tumor volumes. Therefore, a range shifter (Rashi) (slab of PMMA of physical dimensions $210 \times 210 \times 30 \text{ mm}^3$) housing in the nozzle is automatically inserted in the beam when needed. The schematic of the nozzle for the HBL in IR3 is reported in figure 2.4.

2.4 Treatment Planning System (TPS) for ion beam therapy

Treatment planning is a process to design radiation beams which optimize the dose to the target volume and spare the surrounding normal tissues. Treatment planning for

¹The Bragg peak width corresponds to the Bragg peak thickness measured at a given dose level. At MedAustron, the Bragg peak width is referred to the width at the 80% dose level $\text{BP}_{w,80}$

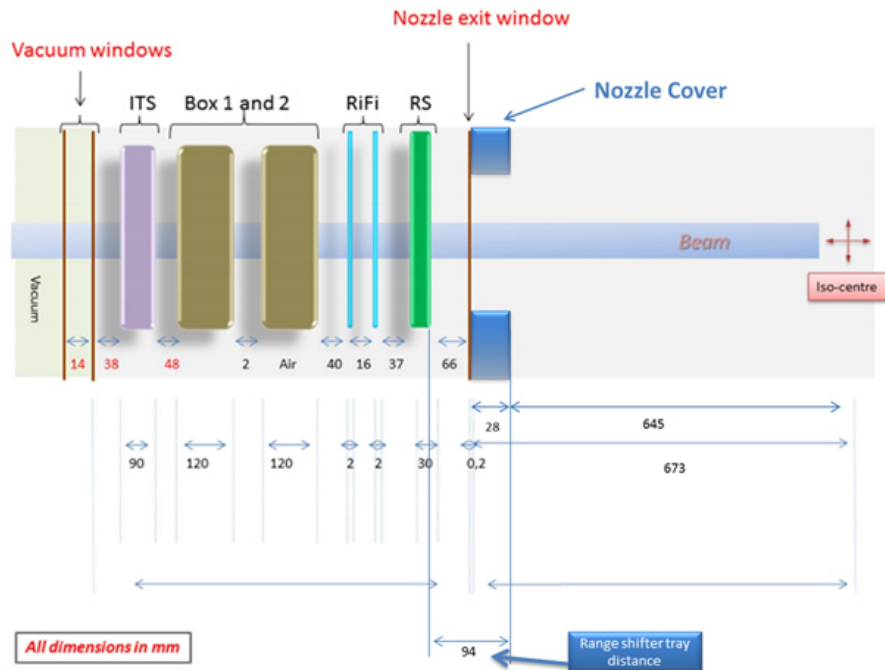


Figure 2.4: Schematic drawing of nozzle elements for the fixed HBL with approximate dimensions in mm. In particular the ITS, Box1, Box2 and the passive elements are in evidence.

proton radiotherapy and ions heavier than protons, are mainly different in the larger variability of RBE for ions with respect to protons, which implies the use of appropriate biophysics models.

At MedAustron, treatment planning is accomplished with the TPS RayStation (RS) developed in cooperation with RaySearch Laboratories, Stockholm (Sweden). RS has been extended and customized by the MedAustron specifications to include scanned proton and carbon ion beams as new treatment modalities. At the time of writing this thesis RayStation v5.0 was installed for clinical purpose and RayStation v6.1 was prepared for clinical commissioning.

The proton planning module allows optimising spot weights and the scanning pattern for the quasi-discrete active scanning implemented at MedAustron. For dose calculation two algorithms are used, pencil beam and Monte Carlo engine (MC is available only in the non-clinical RSV4.99). The module includes a multi-criteria optimization for selecting the best clinical compromise for each patient. Additionally robust optimization, which includes the uncertainties in range and patient position during the optimization, was implemented.

The carbon ion planning module uses for physical dose calculation the pencil beam algorithm. Since RBE depends on different parameters (see section 1.2.1) biophysical models have been developed during last decades in order to predict the complex behavior of different irradiated tissues. Two different models are world-wide used in clinic: the

Microdosimetric Kinetic Model (MKM) adopted at the National Institute of Radiological Science (NIRS), Chiba (Japan) and the *Local Effect Model (LEM)* [52–55] successfully applied in the carbon pilot project at GSI. In the first commercial TPS for carbon ions treatment Siemens *SYNGOTM PT planning*, currently used in clinic at the *Ion Beam Center (HIT)* (Heidelberg, Germany) and at *CNAO* (Pavia, Italy), the first version of the Local Effect Model (LEM I [53]) has been implemented and used for all the clinical cases. In RS multiple relative-biological-effectiveness models are available, such as two versions of LEM (LEM I and LEM IV [55]). In figure 2.5 a comparison of two dose distributions computed with two proton and ^{12}C ion beams for a typical skull base chordoma tumor: the comparison view shows the carbon plan spares better the optical nerves, the chiasm and the brain stem compared to the proton plan.

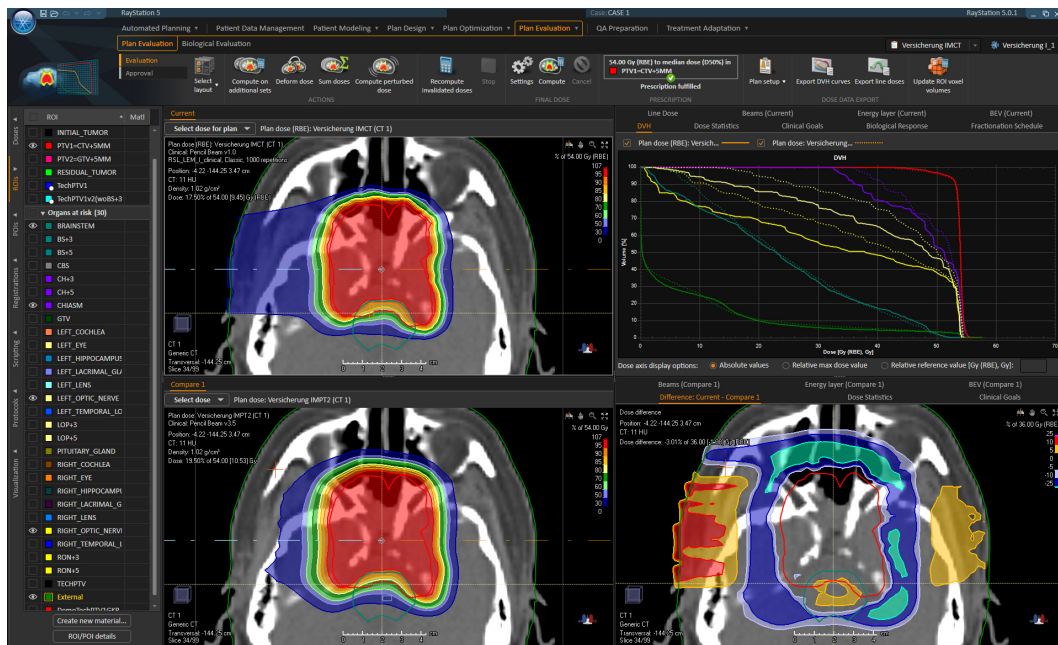


Figure 2.5: On the top-left the dose distribution for the carbon plan, on the bottom-left the dose distribution for the proton plan. Comparison of the DVH for the tumor and different OARs are also shown on the top-right part.

The treatment workflow of adaptive re-planning as well as 4D treatment planning (e.g. re-painting technique) are additional key features of RS. The TPS supports fall-back planning: after the plan has been approved, the system can generate back-up plans using alternative machines and treatment techniques. Furthermore, a scripting interface in ironpython language is embedded in RS in order to automatize and speed up the treatment workflow (see chapter 4).

2.5 Medical commissioning at MedAustron

A process of the implementation of radiotherapy equipment into clinical practice should be supported by the comprehensive QA programme of medical systems that includes several steps [56]:

- specifications;
- acceptance testing;
- commissioning for clinical use;
- quality control (QC) tests;
- preventive maintenance programme;
- education and training of staff.

Acceptance testing by definition is verifying that the components of ion beam therapy equipment are functioning as specified and can be calibrated for clinical implementation.

Following acceptance of accelerator and of all medical equipment at LIBT facility, a full characterization of its performance for clinical use over the whole range of possible operation must be undertaken. This process is called medical commissioning. The major tasks for medical commissioning at MedAustron were: the calibration of the BDS, PAS and medical software and testing these systems under varying clinical conditions, determination of appropriate intervention thresholds, acquirement of data for entry into the TPS and execution of end-to-end tests for planned patient treatments. Medical commissioning involves a variety of measurements that are performed in order to characterize the complete irradiation system and, as a result, gives confidence that not only the characteristics of the beam delivered to the patient comply with clinical requirements but also the resulted dose distribution is in agreement with the prescribed treatment plan. MedAustron is a dual particle facility, thus the commissioning contained the actions that are common for both protons and carbon ions, however, the majority of measurements and calibrations should be performed as a separate action for each particle type and in each medical irradiation room (IR). It is common practice at many LIBT facilities to start treatment operation in one room while continuing parallel commissioning work in other rooms. If one or more of the rooms have the same design, then detailed measurements may only need to be performed for one room and then just validated in the other rooms. This practice was applied to the MedAustron fixed beam irradiation rooms (IR3 and IR2). The results of medical commissioning served as base-line data for the set-up

of the QA program, including periodic QC checks that should include the BDS, PAS, TPS and all related steps of the treatment process (patient positioning, treatment planning and dosimetry). The QA program that was established at MedAustron used medical commissioning data to define functional performance characteristics and their constancy checks, the frequencies and action levels for the constancy checks. As the experience with ion beam treatment commissioning is limited, the procedures and tolerances will likely change as the experience at the MedAustron will increase.

CHAPTER 3

INVESTIGATION ON IDD CORRECTION FACTORS FOR PLANE-PARALLEL IONIZATION CHAMBERS BY MONTE CARLO SIMULATIONS IN PROTON BEAMS.

3.1 Introduction

Among the different basic beam data needed to model a pencil beam scanning (PBS) system, pristine integral depth dose curves in water have to be measured for the entire range of available beam energies. At MedAustron, 20 “major” proton energies (out of the total 255) have been selected for the beam modeling in the TPS. However, the measurement of integral depth dose (IDD) by using commercially available large area plane-parallel ionization chambers PPICs (e.g. PTW Bragg Peak ionization chamber TM 34070) have to be corrected for a systematic offset due to their finite radius. The dose components of a monoenergetic pencil beam in water can be subdivided in three different parts: *core*, *halo* and *aura* [25]. The core consists of primary protons and is broadened by multiple Coulomb scattering (MCS) and slow down by multiple collisions with atomic electrons (Bethe-Bloch theory). Their number slowly decreases because of nuclear interactions, which feed the halo and aura. The halo consists of charged secondary particles, secondary protons and target fragments, from elastic interactions with H, elastic and inelastic interactions with O, and non-elastic interactions with O (see section 1.1.7). Applying energy and momentum conservation it is possible to show that the most energetic secondaries charged reach a radius equal to approximately $1/3$ of the range of the incident beam at the mid-range [25]. Therefore, for the highest energy available at MedAustron $252.7\text{ MeV}/u$ physical range $R_{80\%} \approx 380.0\text{ mm}$ the beam halo extends up to a radius of $\approx 127\text{ mm}$ which is much larger than the radius of the PTW

plane-parallel chamber (TM 34070, diameter 81.6 mm). The aura, with extents in the scale of meters, consists of neutral secondaries (neutrons and gamma) and the charged particles they set in motion 3.1.

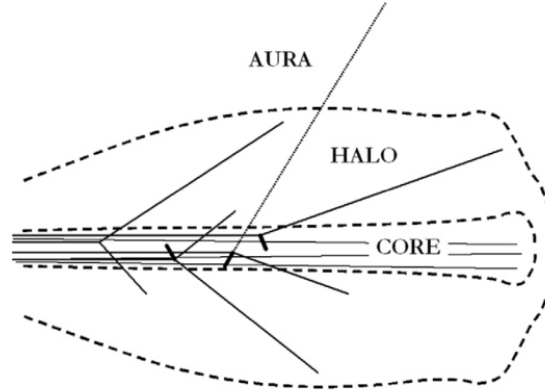


Figure 3.1: Schematic view of core, halo and aura components along the propagation of a proton pencil beam [25].

Because of the finite size of the chambers, some dose in the long tail region of the transverse dose profiles (low-dose envelope), may not be accounted for [57, 58]. Monte Carlo simulations can be used to evaluate the dose reduction due to escaping secondaries from finite size PPICs and predict correction factors applied to measured depth-dose profiles for Treatment Planning System (TPS) commissioning support [59]. These chamber size correction factors were provided to RaySearch Laboratories in order to create a beam model for protons in the TPS RayStation v5.0. The Monte Carlo simulations have been performed with Gate a toolkit of Geant4 code. A preliminary sensitivity study on the IDD correction factors for PPICs is reported in this work. In order to compute IDD correction factors the choice of the correct nuclear model for the description of non-elastic and elastic nuclear interactions is a crucial point. For that reason a benchmarking of nuclear models in Gate/Geant4 was performed with measurements carried out at MedAustron Horizontal Beam Line (HBL) with protons. The study described in this work focuses on benchmarking Gate/Geant4 nuclear models for proton pencil beams within transverse dose profiles measured in water. Three different physics builders (QBBC, QGSP_BERT_HP, QGSP_BIC_HP) suggested by the Geant4 community for medical applications were evaluated. Additional measurements in a large scanned field were carried out in order to validate the simulated IDD correction factors. Finally, the IDD correction factors applied to the measured depth dose profiles for the 20 “major” proton energies are reported.

3.2 Materials and methods

3.2.1 Measurements

The measurements presented in this work were performed at the fixed beam line (HBL) with proton beams. Measurements of transverse dose profiles were carried out at four energies (62 MeV, 123.5 MeV, 187 MeV and 250.3 MeV) in order to cover the whole clinical energy range. At each energy, transverse dose profiles were measured in water at four different depths (20 mm and 50%, 80%, 97.5% of the physical range R_{80}). Measurements were carried out with a 1D Linear Array Holder which can host up to 24 PinPoint ionization chambers (see chapter 4). The PinPoint chambers are equally spaced (distance between two consecutive chambers centers 10 mm) inside the linear array holder. The holder was mounted to the moving mechanism of PTW *MP3-PL* customized MP3-P water phantom in order to provide larger scanning dimensions. The in-house software (“Plan Verificator” described in section 4) allows to remotely control the whole equipment from the Local Control Room and to acquire the measured raw data. A plane parallel ionization chamber TM 34080 (diameter 81.6 mm, PTW-Freiburg) was fixed at the water phantom entrance as integral beam monitor (reference chamber) and connected to a Unidos Webline electrometer (see figure 3.2). The MP3-PL water

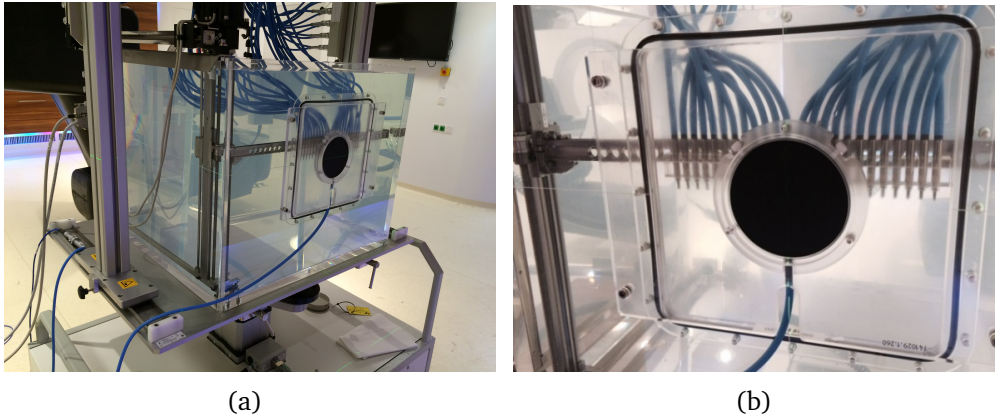


Figure 3.2: Experimental setup for the transverse dose profile measurements. The linear array holder with the 24 PinPoint chambers (field chambers) and the PPIC TM34080 (reference chamber) are shown.

phantom was positioned with its thin window at the irradiation room isocenter (67.8 cm air-gap). At each depth two transverse dose profiles were acquired in order to have a lateral resolution of 5 mm. At the time of measurements the beam monitors inside the Nozzle were not calibrated in terms of absolute dose, therefore the estimation of delivered number of protons was done by the charge collected in the PPIC TM 34080 fixed

at the water phantom entrance. Then each PinPoint measurement was normalized to absorbed dose to water per incident proton (Gy/p).

Validation of IDD correction factors was performed with measurements in a single-layer scanned field (diameter $\phi = 160$ mm) with a Roos ionization chamber (TM34001, PTW-Freiburg). The aim was to directly derive from measurements the IDD correction factors for the Bragg peak chamber TM34070 as ratio between measurements in a single-layer scanned field and measurements in a pristine pencil beam with the Bragg peak chamber TM34070. The Roos chamber is a plane-parallel chamber of 15.6 mm diameter and the reference point is situated on the inner side of the entrance window at 1.12 mm behind the entrance plane. The Roos was mounted in the MP3-PL water phantom and connected to a UNIDOS WebLine electrometer. An operating voltage +200 V was applied. Considering the WET of the thin window of the MP3-PL and the reference point of the Roos the first measurement point is in a WED = 7.5 mm. In figure 3.3 the experimental setup used for the measurements with the Roos chamber and with the Bragg peak chamber in the MP3-PL water phantom is shown. For the Bragg peak

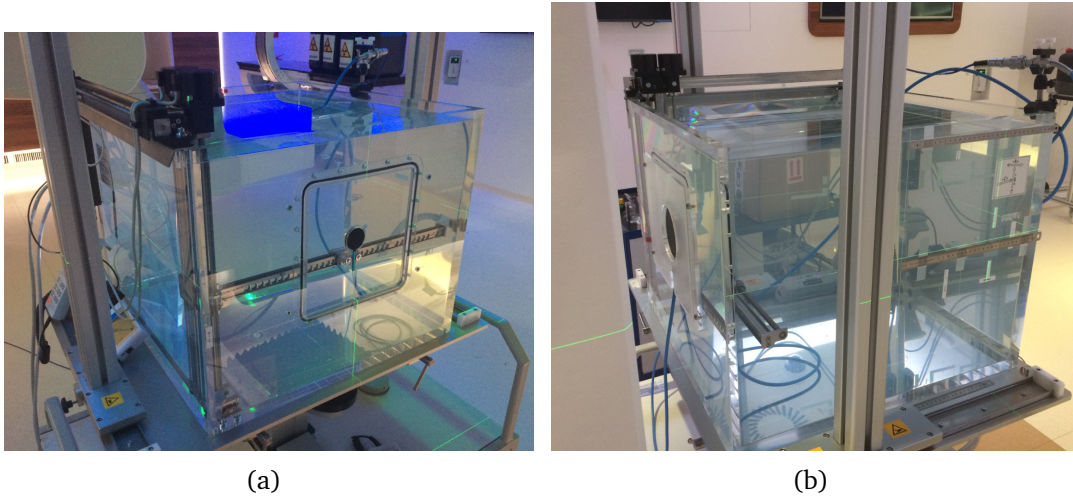


Figure 3.3: Experimental setup for the validation of IDD correction factors. In (a) the setup for measurements with the Roos chamber, in (b) the setup for measurements with the Bragg peak chamber TM34070 (b).

chamber measurements depth dose profiles with a single-energy pencil beam at 198 MeV and 252.7 MeV (largest energy available) were carried out. Regarding the Roos chamber measurements at different depths in water were carried out with a single-layer circular field of diameter $\phi = 160$ mm for 198 MeV and 252.7 MeV (see figure 3.4). The Roos chamber was positioned at the center of the scanned circular field. In addition for energy 252.7 MeV measurements with Roos chamber at the center of a single-layer scanned field $192 \times 192 \text{ mm}^2$ were carried out at two depths in order to verify if there was still a contribution of peripheric spots to the central dose.

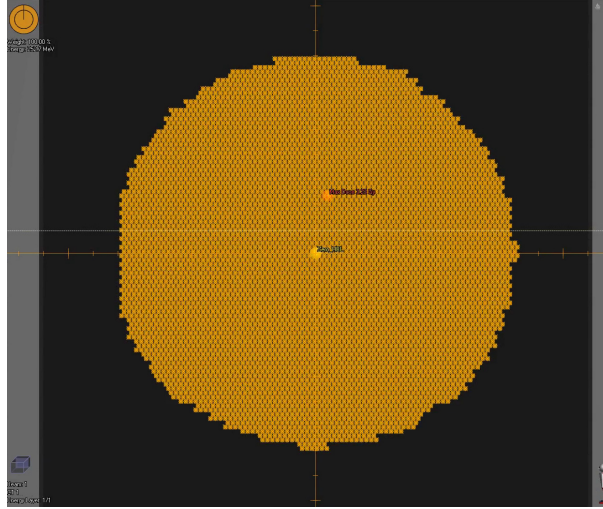


Figure 3.4: Spot positions in BEV for the circular field at 252.7 MeV measured with the Roos chamber at different depths in water.

3.2.2 Monte Carlo simulation environment.

The latest version Gate v7.1 Geant4 v10.01.02 has been used in order to benchmark the nuclear models of Geant4 with the measured transverse dose profiles and to simulate the final IDD correction factors. The full design of the nozzle has been implemented in the simulation. The proton source of the simulation has been placed at $SAD = 1300$ mm upstream from the isocenter in vacuum at the Nozzle entrance in order to take fully into account the transport of the beam through the nozzle and the air gap before the water phantom/patient. The approach used is slightly different from the simplified method described by L. Grevillot et al. [60], in which the proton source was placed at the nozzle exit. In figure 2.4, a schematic view of the nozzle with all its components is given. The main parameters in the simulation have been fixed as described in [61] and reported in 3.1:

Step limiter	0.1 mm
range cut	0.1 mm
tracking cut	0.1 mm
$\langle I \rangle$ value water	78 eV

Table 3.1: Parameters selected in the simulation.

Impact of different physics processes on the IDD correction factors for differently-sized PPICs.

In order to evaluate the impact of different physics interactions on the correction factors for differently-sized PPICs Monte Carlo simulations were based on Gate/Geant4 previous

version (Gatev7.0 [62] built on Geant4v9.05.02 [63]). In this version of MC code the user could easily activate or deactivate different interaction processes and could select different models for each process by a “Physics list.mac” macro without changing the C++ source code and recompiling. The nozzle was excluded from the simulation setup to highlight only the impact of the single interaction processes. The proton beam propagates in air before impinging on a water phantom. Full integrated IDDs were scored on the whole diameter of a water cylinder ($\phi = 1000$ 1000 mm) and depth-dose profiles were scored in two differently-sized PPICs (see figure 3.5):

- a PPIC ROOS type (TM 34073, PTW-Freiburg) diameter 39.6 mm (named 'PPIC PTW_S' in this work)
- a PPIC (Bragg peak chamber TM34070, PTW-Freiburg) diameter 81.6 mm (named 'PPIC PTW_B' in this work)

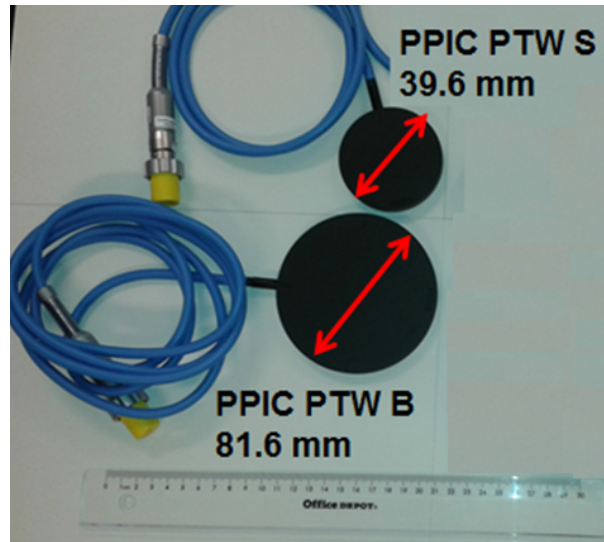


Figure 3.5: The two different sized PPICs.

The longitudinal scoring resolution along the beam axis was 0.1 mm. The six optics parameters were set to fix values for all the energies simulated (optics was not tuned with experimental data in this case). The $\langle E \rangle$ was not tuned as the energy spread ΔE was set to 0. Different simulations were performed with and without Multiple Coulomb Scattering (MCS) activated, with and without elastic nuclear interaction activated and with and without the non-elastic nuclear interactions activated. Moreover, when non-elastic nuclear interaction was activated we tested three different hadronic models: the “precompound” model suggested by Grevillot et al. [61], the “Binary Cascade” model and the “Bertini cascade” [64] model suggested in literature [65, 66].

Validation of IDD correction factors based on Roos chamber measurements in a single-layer scanned field.

The MC simulations were performed with Gate v7.1 [62] built on Geant4 v10.01p02 [67], so the latest version of Gate/Geant4 at the time of the performed experiments. Specified MedAustron beam optics parameters were inserted as input in the Gate code as an initial guess. These parameters were the expected ones at the source position SAD=1300 mm upstream to isocenter in order to reproduce 4 mm of spot size in terms of $FWHM$ at isocenter in vacuum. However, these parameters needed to be tuned in order to match the measured values in air at isocenter and at different air gaps. A similar approach as described in [60] was used for the tuning of the beam model. Nevertheless, in [60] the optics parameters were estimated at nozzle exit, while with the integration of the full nozzle they were predicted at the nozzle entrance. The full MC beam modeling was developed based on measured spot sizes in air and depth dose profiles in water for the 20 'major' energies. The outcome of the beam modeling was the selection of the eight parameters needed to describe the proton source phase space. The six optics parameters spot size (σ_x and σ_y), the beam divergence (σ_ϑ and σ_φ) and the beam emittance ($\epsilon_{\vartheta,x}$ and $\epsilon_{\varphi,y}$) at the nozzle entrance were tuned with measurements of transverse dose profiles in air. $\langle E \rangle$ and the energy spread ΔE were tuned based on measurements of depth dose profiles with the Bragg peak chamber PTW_B ($\phi = 81.6$ mm). More details are reported in Elia et al. [68]. In the simulation a water cylinder of $\phi = 1000$ mm has been placed with its surface at isocenter position (678mm air gap from the nozzle exit window). The dose was scored in several volumes built inside the water cylinder:

- a cylinder of $\phi = 400$ mm representing the full integrated IDD;
- a box of 192×192 mm² representing the measurements in a single-layer scanned field of the same lateral dimensions;
- a cylinder of $\phi = 160$ mm representing the single-layer scanned circular field of diameter $\phi = 160$ mm;
- a cylinder of $\phi = 81.6$ mm representing the active diameter of the Bragg peak chamber TM34070.

The longitudinal scoring resolution along the beam axis was 0.1 mm. Since correction factors mainly depends on the elastic and non-elastic nuclear interactions (see section 3.3.1). Therefore, in order to validate the IDD correction factors three different physics builders (QGSP_BIC_HP, QGSP_BERT_HP and QBBC) were compared. The electromag-

netic interactions were described by the standard model (G4EmStandardPhysics_option4) which can be activated for each builder adding the suffix 'EMZ'.

Benchmarking nuclear models in Gate/Geant4 using measurements of transverse dose profiles.

The goal was to simulate full transverse dose profiles (25 cm laterally) in water at different depths. A water cylinder of $\phi = 1000$ mm has been placed with its surface at isocenter position (678 mm air gap from the nozzle exit window). In order to have enough statistics mainly in the tails of the dose transverse profiles (low-dose envelope) we built inside the water cylinder concentric hollow cylinder one inside the other. The external hollow cylinders (from 125 mm down to 30 mm) have a difference between the internal and external radius of 5 mm, the internal ones (from 30 mm down to 2 mm) a difference between the internal and external radius of 2 mm. In this way we can set the lateral resolution of the simulated transverse dose profiles.

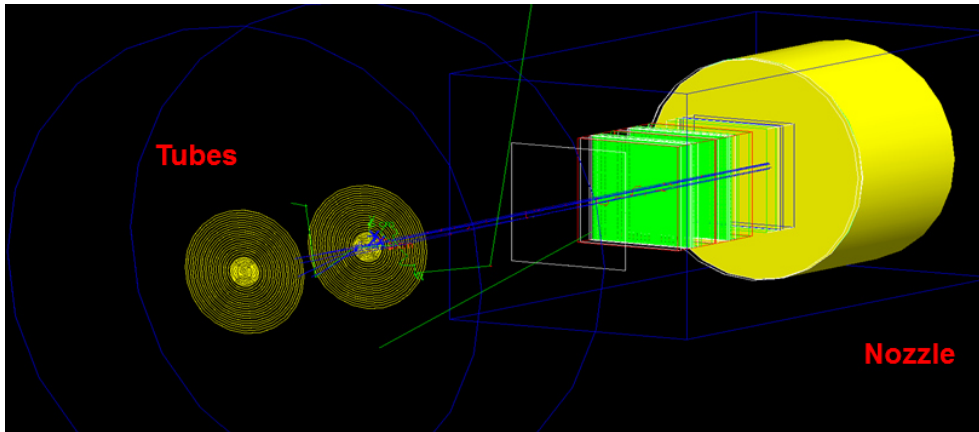


Figure 3.6: Simulation setup used for the study of the transverse dose profiles in water. In the picture the structure of the nozzle and the dose scoring approach based on concentric hollow cylinders.

Exploiting the symmetry of the simulation in X and Y (same initial beam optics parameters) we summed up the energy deposited in each annulus in order to get the energy deposited in one point of the lateral profile. In order to compare the transverse dose profiles at the same depth we interpolate the MC data at the same relative R_{80} of the measurements (50%, 80%, 97.5%). In order to get rid of the binning artifacts the energy deposited in each annulus has been divided by the geometrical area of the annulus itself (so the units are MeV/cm^2). The scoring resolution in depth was set to 1 mm. Moreover using filters, attached to all actors, the energy deposited by primary protons and all secondary particles has been separately stored. The number of particles simulated was 10^7 protons distributed on 10 CPUs (10^6 protons for each CPU). The

simulation time was around 12 hours and we avoided the use of any variance reduction technique as in Sawakuchi et al. [69]. Initial energy spread was set to $\Delta E = 0.0 \text{ MeV}$ and the beam optics parameters were tuned on experimental data as reported in section 3.2.2. Simulations were performed with three different physics builders (QGSP_BIC_HP, QGSP_BERT_HP, QBBC) and were compared with measurements of the low-dose envelope.

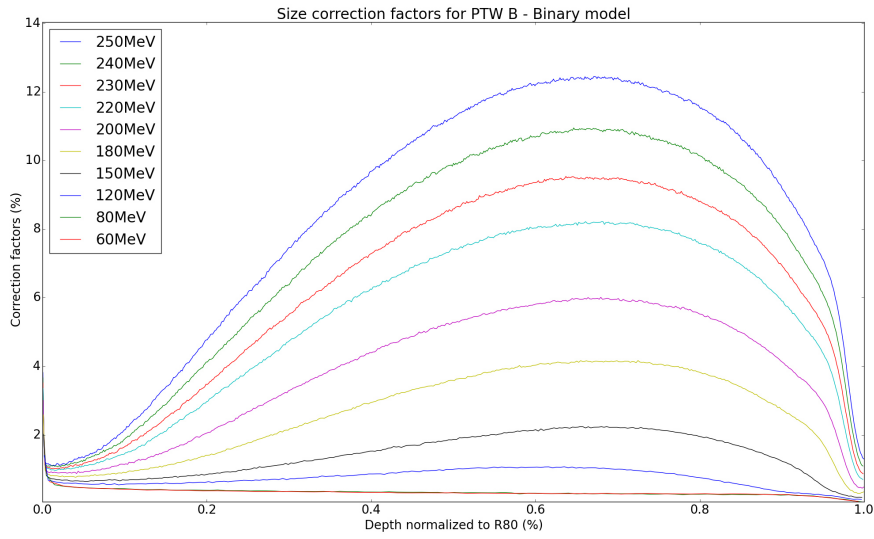
3.3 Results

3.3.1 Impact of different physics processes on correction factors for differently-sized PPICs

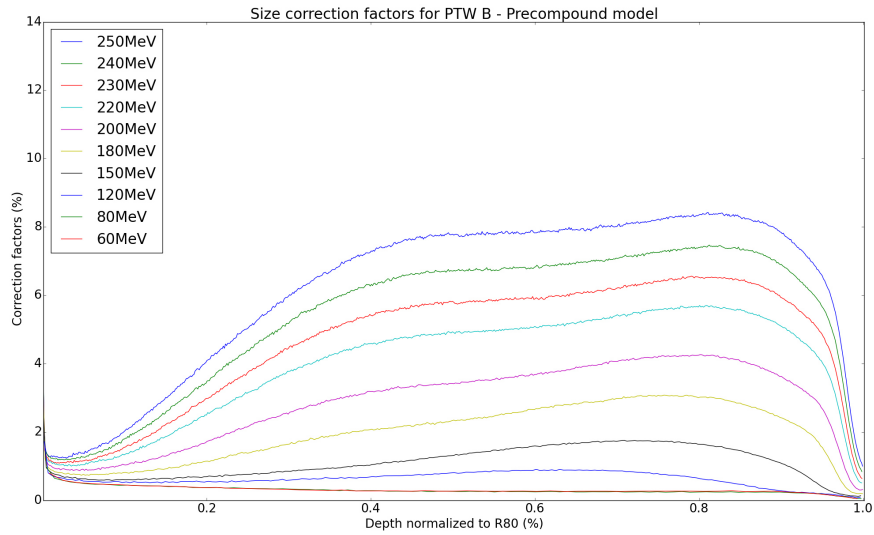
Correction factors for differently-sized PPICs were computed based on simulated depth dose profiles scored in different volumes (see section 3.2.2). In depth for each bin the correction factors were computed in percentage as:

$$\text{Correction factors } [\%] = \frac{(E_{IDD} - E_{PTW_X})}{E_{PTW_X}} \times 100 \quad (3.1)$$

where E_{IDD} is the full energy [MeV/u] deposited in the whole water cylinder ($\phi = 1000$ mm) and E_{PTW_X} is the energy [MeV/u] deposited in the PPIC chamber volume ($\phi = 81.6$ mm for the PTW_B and $\phi = 39.6$ mm for the PTW_S). *Correction factors* as function of energy and depth in water were computed for two different non-elastic hadronic models ('Precompound' [61] and 'Binary Cascade' [65]) and reported in figure 3.7. The correction factors, plotted as function of depth normalized to R_{80} , show the same behavior at different energies. One can see in figure 3.7 the correction factors in terms of shape and absolute values are strongly dependent on the non-elastic hadronic physics set in the simulation. For the 'Binary Cascade' model, the correction factors are up to 12% for the highest energy available 250 MeV/u and the maximum is reached around $\approx 70\%$ of R_{80} for all the energies. For the 'Precompound' model as already reported by Grevillot et al. [61], the maximum is around 8% at 250 MeV/u and is located $\approx 85\%$ of R_{80} for all the energies. We investigated also the impact of MCS on the correction factors for different energies and differently-sized PPICs 3.8. The impact of MCS on correction factors is more visible at high energies (250 MeV) close to the Bragg peak (see picture 3.8 (a)). That behavior can be explained from the MCS theory which predicts an increase of the scattering component with depth in the medium (water). As is shown 3.8 (b) the



(a)



(b)

Figure 3.7: Correction factors as function of depth normalized to the physical range (R_{80}) at different clinical energies [from 60 to 250 MeV/u] for the PPIC PTW_B. In (a) the 'BinaryCascade' non-elastic hadronic model was set, in (b) the 'Precompound' non-elastic hadronic model was set.

impact of MCS is negligible for the larger area PPIC (PTW_B) and more evident for the small volume PTW_S up to 1.5% close to the Bragg peak.

Furthermore, we investigated the impact of non-elastic and elastic hadronic processes on the correction factors. Figure 3.9 plots the correction factors as function of the three different main processes (MCS, non-elastic and elastic nuclear interactions) for the PPIC PTW_B at the highest energy 250MeV.

As already seen in figure 3.8 the contribution of MCS is almost negligible also in fig-

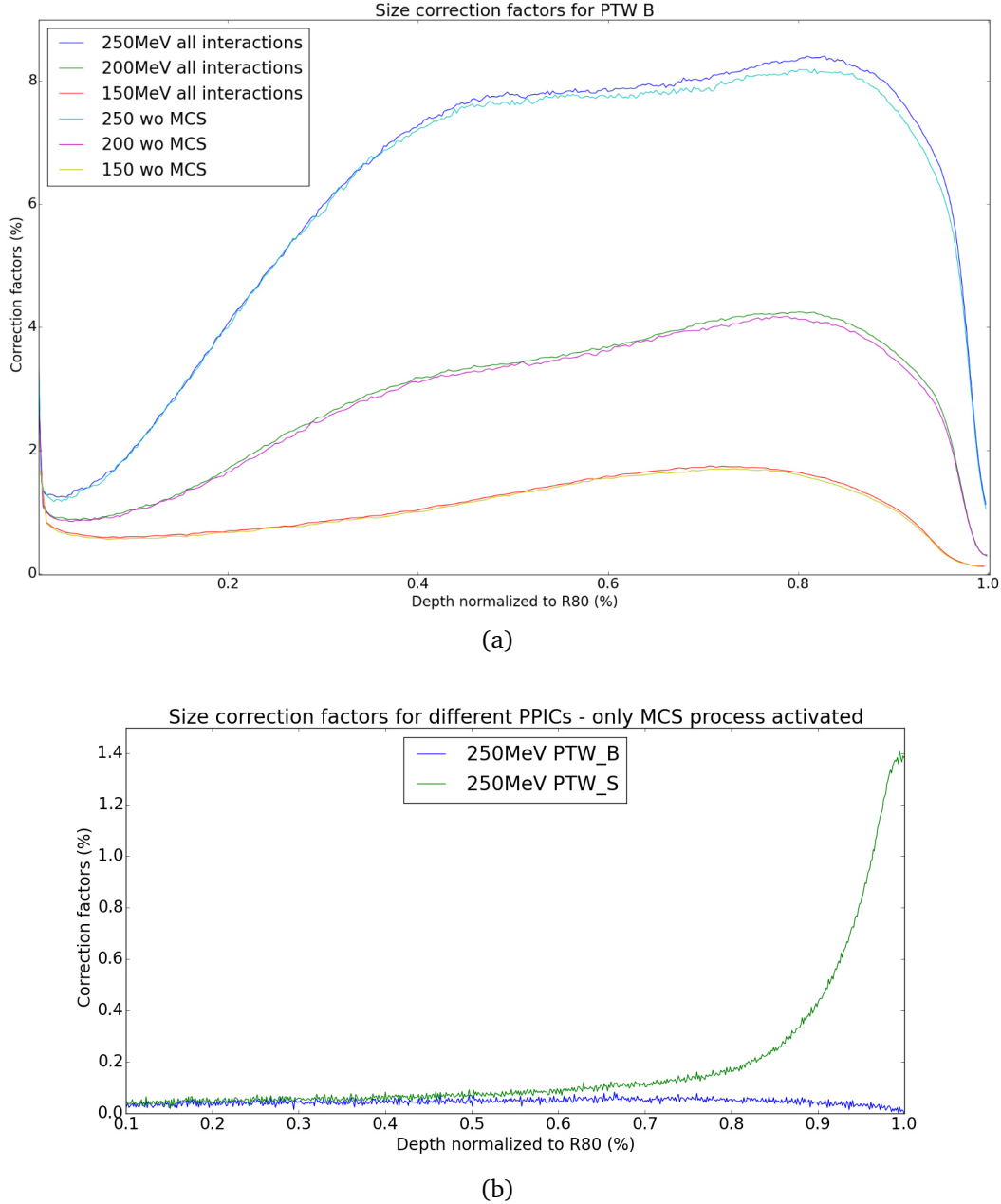


Figure 3.8: Correction factors as function of depth normalized to R_{80} . In (a) correction factors for the PPIC PTW_B at three different energies with and without the MCS activated. In (b) correction factors for the two PPICs at 250MeV: non-elastic and elastic hadronic processes are deactivated and MCS is activated.

ure 3.9 for the large area PPIC. Moreover, the secondary protons and fragments due to non-elastic nuclear interactions contribute at the entrance of the phantom with the maximum at the mid-range of the Bragg peak, while the elastic scattered protons contribute mostly close to the Bragg peak region.

Furthermore, a study with different non-elastic hadronic models was performed deactivating the elastic hadronic process in the simulations. Therefore, we compared the impact of three different non-elastic nuclear models ('Precompound', 'Bertini Cascade'

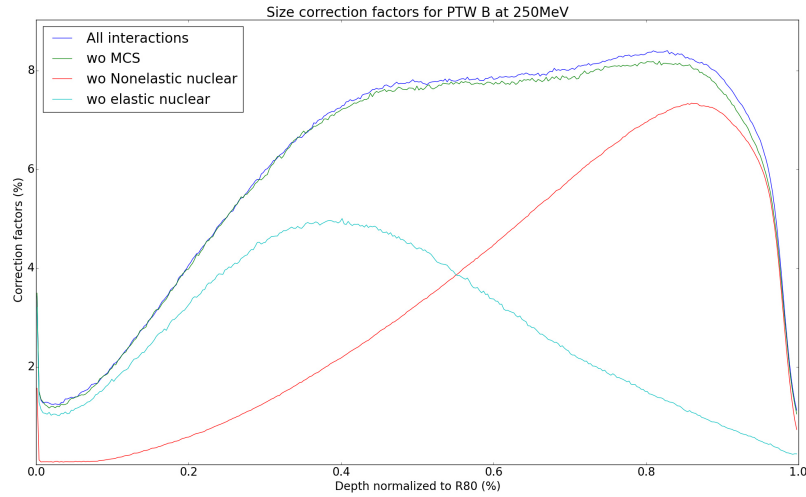


Figure 3.9: Correction factors as function of depth normalized to R_{80} for the PTW_B. Correction factors for the 'Precompound' model with all the interactions activated, with MCS deactivated, with non-elastic nuclear interactions deactivated and with elastic nuclear interactions deactivated.

and 'Binary Cascade') on correction factors for the highest energy 250 MeV/u. At this energy we have the maximum difference among the different models being our worst case scenario.

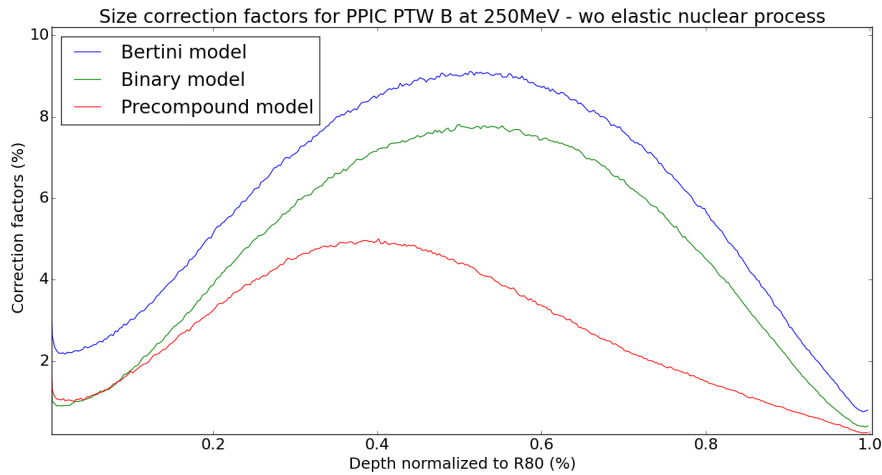


Figure 3.10: Correction factors as function of depth normalized to R_{80} for the PTW_B at 250MeV. The elastic nuclear interaction was deactivated and three different non-elastic hadronic models ('Precompound', 'Bertini Cascade' and 'Binary Cascade') are plotted.

As it is shown in picture 3.10 the main influence on the correction factors for PPICs is due to the non-elastic hadronic interactions of primary protons with the medium. Therefore, the implementation in MC simulation of different non-elastic hadronic models leads to a different description of non-elastic scattering of protons off nuclei in water medium (e.g. $^{16}\text{O}(p, 2p)^{15}\text{N}$). Depending on the selected hadronic model secondary charged par-

ticles are created with different energy and angular distribution spectra which lead to a different amount of energy deposition outside of the PPICs volume. That is directly reflected on the shape and absolute values of *correction factors* for each specific PPICs.

3.3.2 Validation of IDD correction factors based on Roos chamber measurements in a single-layer scanned field

In the figure 3.11 depth dose profiles measured with the Bragg peak chamber TM34070 (ϕ 81.6 mm) in a single pencil beam and with a Roos chamber at the center of single-layer scanned field are shown.

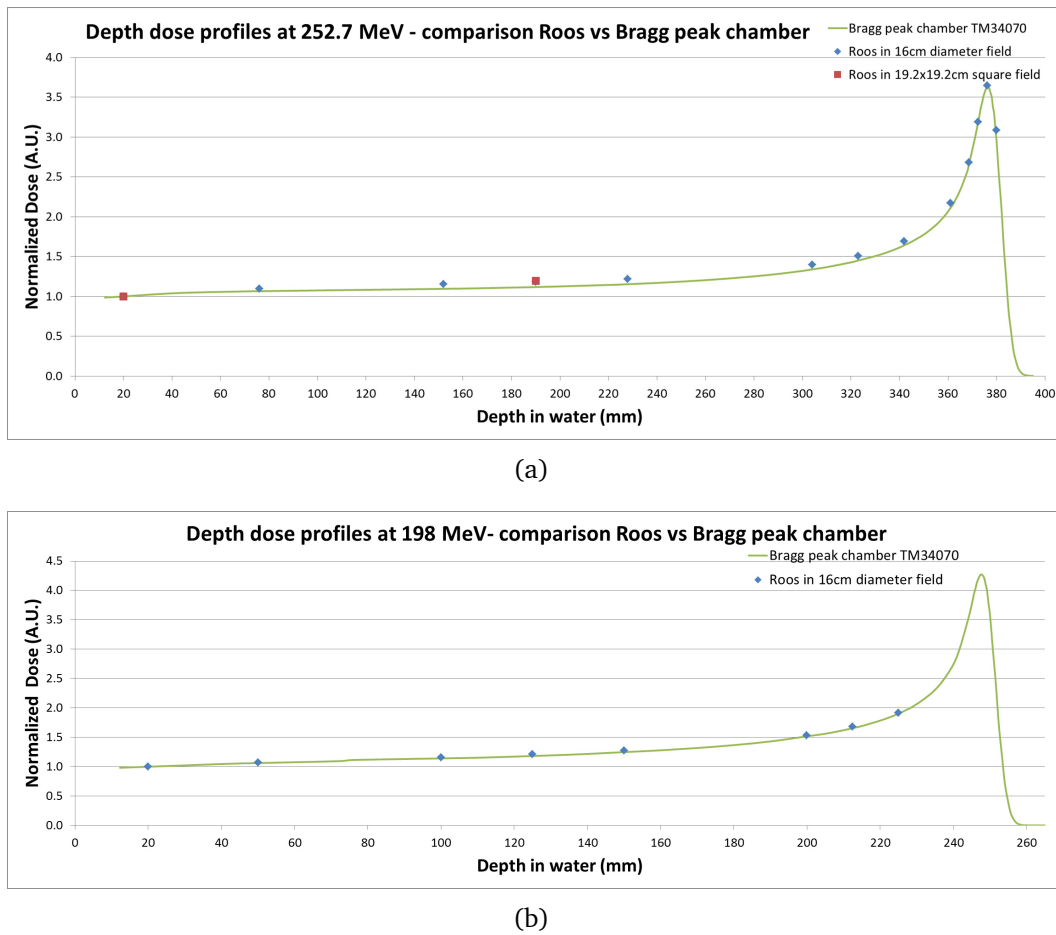


Figure 3.11: Comparison depth dose profile measured with Bragg peak chamber TM34070 ($\phi = 81.6$ mm) and the Roos chamber for 252.7 MeV and 198 MeV. In green the depth dose profile measured with the Bragg peak chamber in a single pencil beam. In blue the measurements with the Roos chamber at the center of a single-layer circular field ($\phi = 160$ mm) at several depths in water. In red the measurements with the Roos chamber at the center of a single-layer field ($192 \times 192 \text{ mm}^2$) of 252.7 MeV at two depths in water.

Under the assumption that the contribution of elastic and non-elastic nuclear interaction in the water phantom is not so relevant in the plateau region, all the measurements

are normalized to a WED of 20 mm. Since the measurements with the Roos chamber were performed in water at different depths downstream to the isocenter we needed to take into account the geometrical divergence of the pencil beam scanning at the HBL. The scanning magnets central positions relatively to isocenter are placed at 7420 mm in X and 6700 mm in Y scanning direction. Therefore we needed to correct the Roos readings M_{Roos} up to +11% for the different lateral spacing of spots with depth in water downstream to the isocenter.

Then, we derived correction factors based on the measurements with the Bragg peak chamber TM34070 in a single pencil beam and with Roos chamber in a circular single-layer field ($\phi = 160$ mm) 3.2:

$$\text{Correction factors measured [\%]} = \frac{(M_{Roos} - M_{PTW_B})}{M_{PTW_B}} \times 100 \quad (3.2)$$

where M_{PTW_B} is the corrected reading for the Bragg peak chamber TM34070. Same correction factors have been derived from MC simulation with the three different physics builders (QGSP_BIC_HP, QGSP_BERT_HP and QBBC) and the results are shown in figure 3.12.

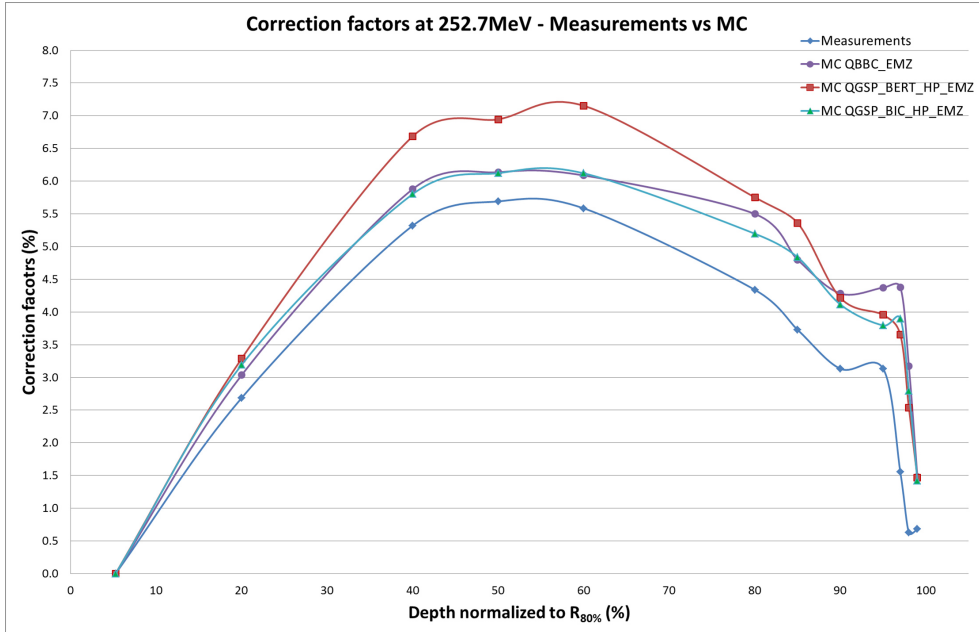


Figure 3.12: Correction factors as function of depth normalized to R_{80} for the PTW_B at 252.7 MeV. Comparison between the measurements with Roos/Bragg peak chamber and the MC with different physics builders activated. All the data are normalized to 20 mm in WED.

The QGSP_BERT_HP shows the largest differences with the measurements up to 1.5% at the mid-range of the Bragg peak (at 50% of R_{80}). Both QGSP_BIC_HP and QBBC shows similar behavior overall the depths and a 0.5% differences at the mid-range. Both

shape of the curves quite well reproduce the measured values even in the high gradient dose region (Bragg peak region $\geq 90\%$ of R_{80}) where the uncertainties due the positioning of the two detectors are higher. Similar results have been found for the energy 198 MeV. As reported in [70] the Binary cascade (QGSP_BIC_HP) shows better results for low-energy protons and neutrons in comparison to Bertini cascade (QGSP_BERT_HP) in terms of differential cross-sections. Moreover, the implementation of the two physics builders QGSP_BIC_HP and QBBC is very similar in the Geant4 code. The only difference is that the QBBC has higher precision than the others for many hadron-ion and ion-ion interactions in a wide energy range.

3.3.3 Benchmarking nuclear models in Gate/Geant4 using transverse dose profiles

The plot in figure 3.13 shows the transverse dose profile measured with the method described in section 3.2.1 for the highest energy available 250 MeV.

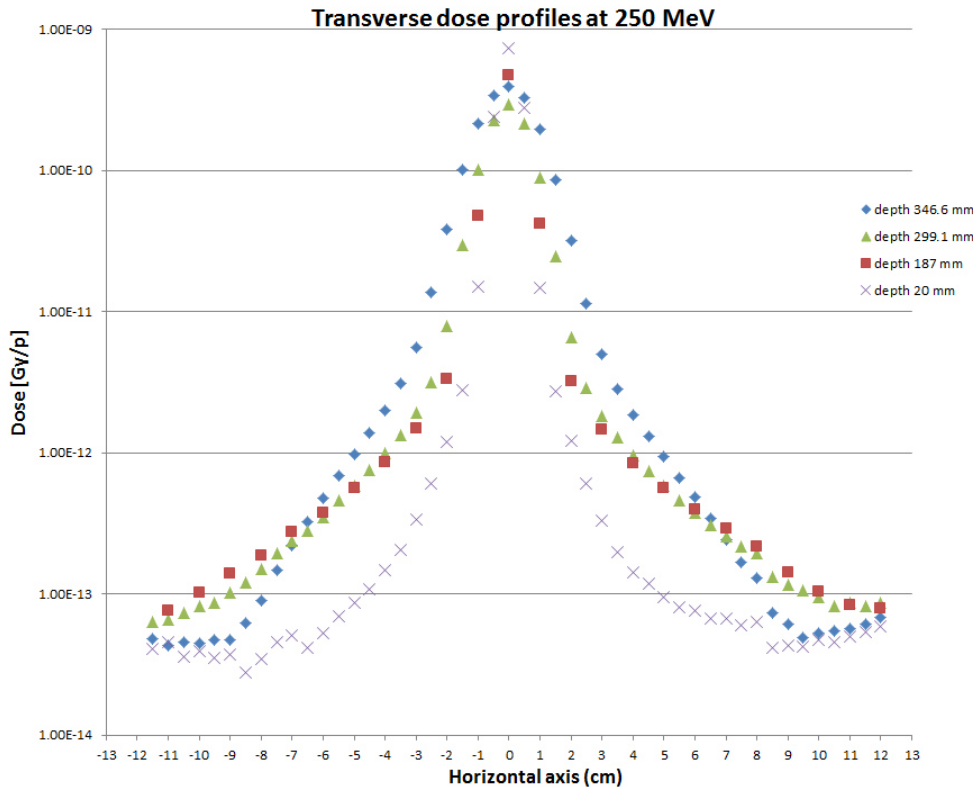


Figure 3.13: Transverse dose profiles at four depths for 250MeV proton beam. The plot shows transverse dose profiles at four depths (20 mm, 187 mm $\approx 50\%$ of R_{80} , 299.1 mm $\approx 80\%$ of R_{80} , 346.6 mm $\approx 97.5\%$ of R_{80}). The measurements are normalized to the number of protons.

Dose levels 4 orders of magnitude lower than the central axis dose can be measured with PinPoint chambers as already reported by Sawakuchi et al. [57]. In order

to characterize the transverse dose profiles we extracted from the measurements some parameter as the FWHM, full width at 1% level (FW0.01M) and full width at 0.1% level (FW0.001M) and they are displayed in figure 3.14.

The data plotted in figure 3.14 show a similar behavior as the experimental data reported by Sawakuchi et al. [57] measured at MD Anderson (PTCH). Our measurements in terms of FWHM, FW0.01M and FW0.001M at the water phantom entrance (20 mm depth) are lower than the measurements reported by Sawakuchi et al. [57]. The higher FW0.01M and FW0.001M found at PTCH are due to the so-called 'spray' component [25] coming from a Beam Profile Monitor (BPM tungsten wire chambers) located about 310 cm upstream of the isocenter [58], in which protons passing through the tungsten scatter more, especially at low energies, and contribute to the low-dose envelope in the water phantom. The 'spray' component is minimized within MedAustron nozzle design.

In order to compare the measurements with the simulations with different physics builders the simulated and measured data at all depths were normalized to the integral under the simulated and measured curves at a fixed depth in the plateau region (at 20 mm depth for 123.5, 187 and 250.3 MeV and at 17.2 mm depth for 61.9 MeV). This normalization approach (instead of normalizing to the maximum for instance) is more robust and closer to what usually is done for clinical applications. The comparison MC-measurements for 250.3 MeV and 61.9 MeV with the normalization at the integral is reported in the plots 3.15.

The shape of the MC simulations for all the physics builders is in a good agreement with the measurements down to dose levels of four orders of magnitudes of the central dose. The main deviations of simulations from the measurements are at very low dose levels $\approx 10^{-4}$ in which the noise of the PinPoint chambers is reached. In order to quantify the agreement among simulations with different physics builders and the measurements the relative variation ΔFWHM , $\Delta\text{FW0.01M}$ and $\Delta\text{FW0.001M}$ in % have been calculated. Moreover the agreement between simulated and measured transverse dose profiles in shape was quantified using a figure-of-merit (FOM). The FOM is defined as dose-weighted average point-to-point dose differences:

$$FOM[\%] = \frac{\sum_i D_{meas}^i \times \frac{|D_{meas}^i - D_{MC}^i|}{D_{meas}^i}}{\sum_i D_{meas}^i} \times 100 \quad (3.3)$$

The impact of different physics builders is mostly relevant at large radii. The agreement between simulations and measurements in the core region is mainly influenced by the MC tuning. Therefore we excluded from the analysis the 'core' region of the pencil beam and we analyzed only the tails. A criteria to select the 'core' region was the

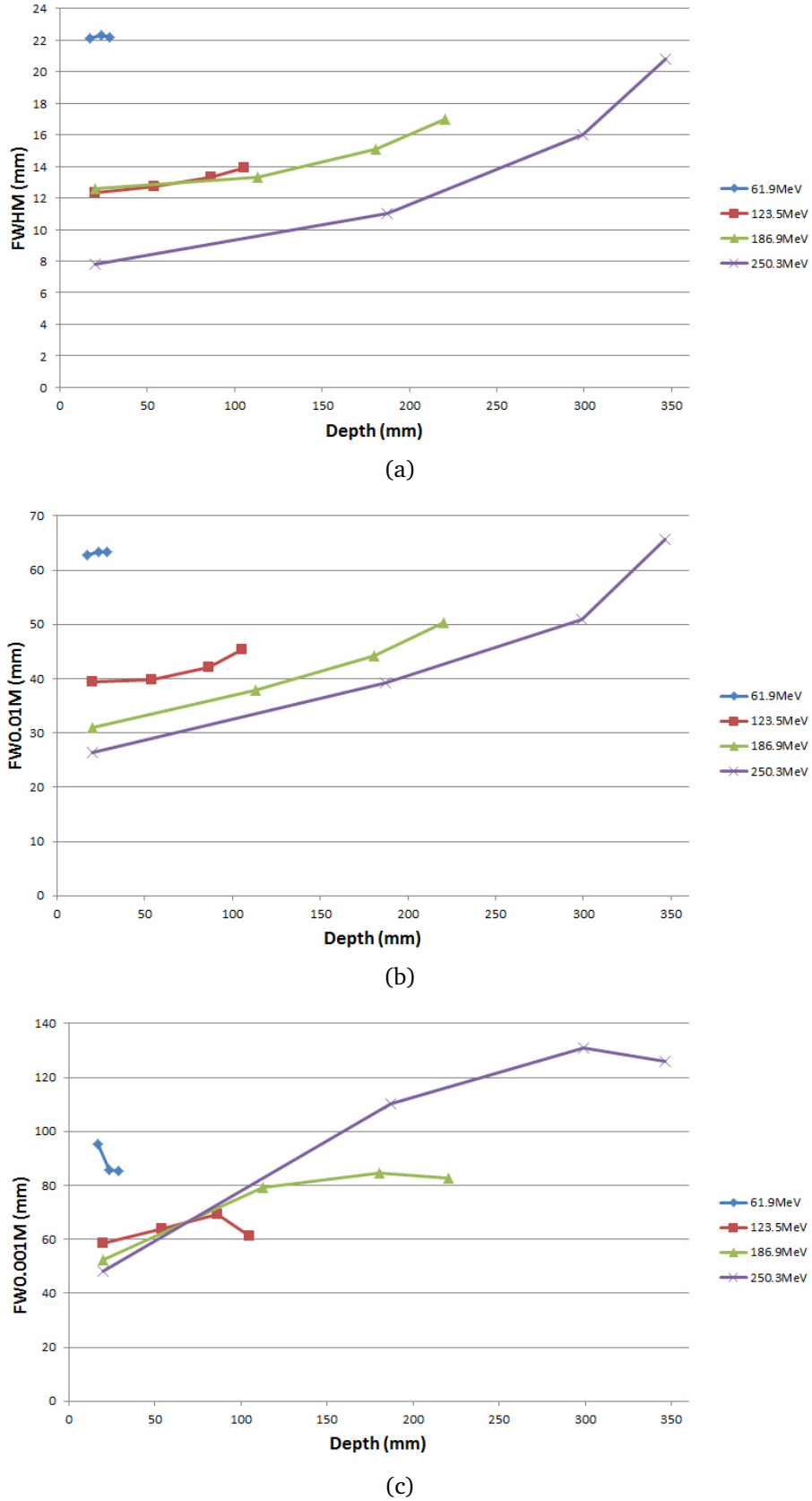


Figure 3.14: FWHM (a), FW0.01M (b) and FW0.001M (c) of transverse dose profiles as a function of depth in water for the 4 energies. Solid lines represent linear interpolations of the data for better visualization.

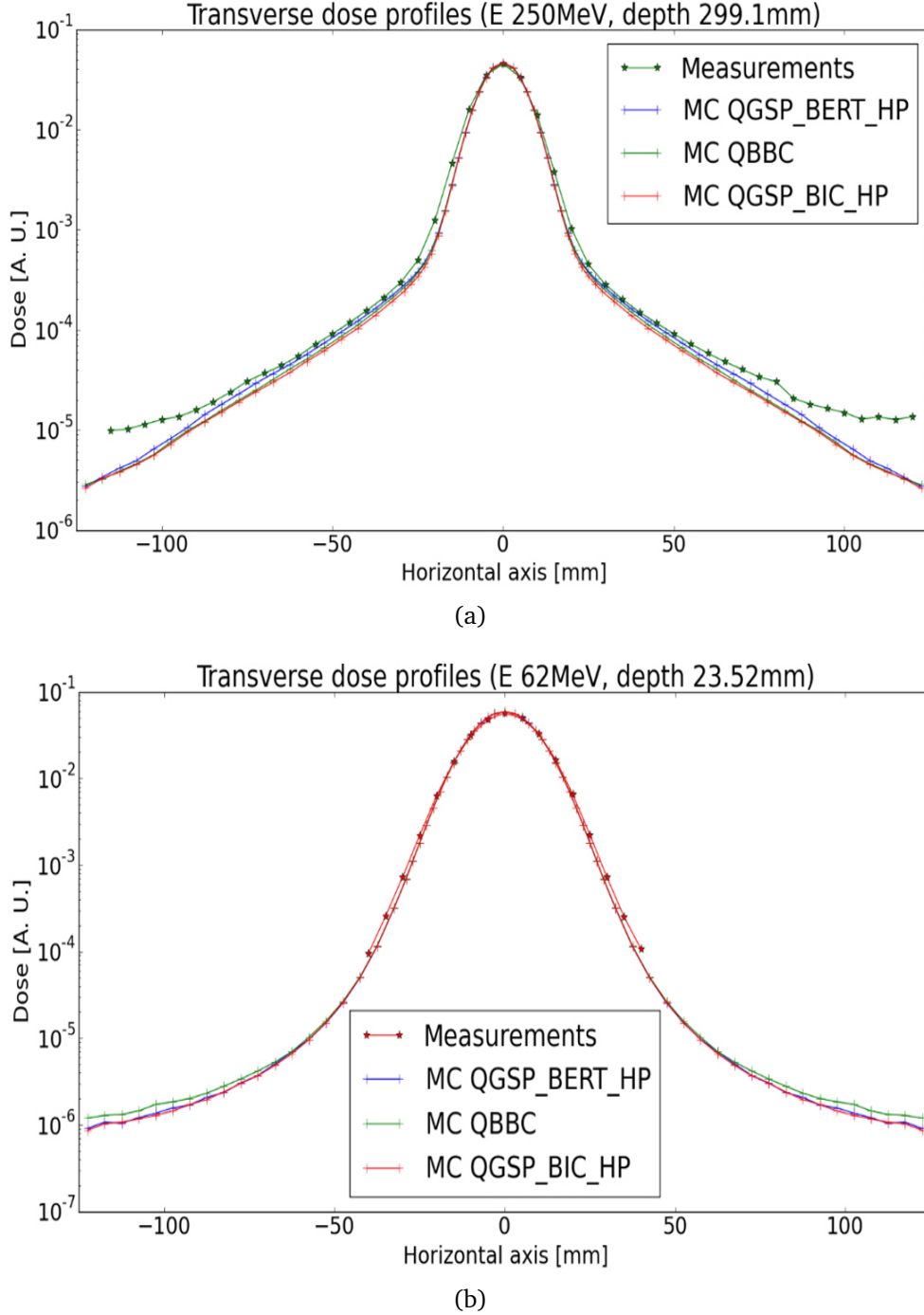


Figure 3.15: Comparison between the simulated transverse dose profiles for different physics builders and the measured ones in water at two different energies: (a) energy 250 MeV and (b) energy 62 MeV.

measured FW0.01M at 1% level for different energies and depths. Therefore, we considered in the analysis of the FOM only the data in the tails outside the FW0.01M. In order to have a better picture for the four energies we compute the average values for all measurements-simulation comparison quantities ($\Delta FWHM$, $\Delta FW0.01M$, $\Delta FW0.001M$ and FOM(%)) for each physics builder. Data are reported in table 3.2. As reported in table 3.2 the simulation with the QBBC physics builder active shows slightly better

Physics Builder	$\Delta FWHM$	$\Delta FW0.01M$	$\Delta FW0.001M$	FOM [%]
QBBC	3.6 ± 0.2	9.3 ± 0.4	8.7 ± 0.4	21.2 ± 0.6
QGSP_BIC_HP	3.8 ± 0.2	9.9 ± 0.4	9.3 ± 0.4	21.8 ± 0.4
QGSP_BERT_HP	3.6 ± 0.2	9.7 ± 0.4	8.8 ± 0.4	22.2 ± 0.7

Table 3.2: Average values of $\Delta FWHM$, $\Delta FW0.01M$, $\Delta FW0.001M$ and FOM(%) for the four energies and all depths in water. The uncertainties reported are standard deviation of the mean.

agreement in terms of FWHM, FW0.01, FW0.001M and FOM. Those results confirm the outcome of measurements in the single-layer scanned field reported in section 3.3.2.

3.3.4 IDD correction factors for the 20 ‘major’ energies over the whole clinical energy range.

In this section we report on the IDD correction factors simulated for the 20 ‘major’ energies at MedAustron among the whole clinical range for protons [from 62.4 to 252.7 MeV/n]. Based on the validation of different physics builders with the low-dose envelope measurements reported in section 3.3.3 and with the Roos/Bragg peak chamber measurements reported in section 3.3.2, we selected the QBBC physics builder to perform simulations in order to compute the IDD correction factors. The dose was scored in several cylinders:

- a cylinder of diameter $\phi = 1000$ mm representing the full integrated IDD;
- a cylinder of diameter $\phi = 200$ mm representing the full integrated IDD but closer to the clinical scenario (maximum field size for HBL is 200×200 mm);
- a cylinder of diameter $\phi = 81.6$ mm representing the active diameter of the Bragg peak chamber TM34070.

The longitudinal scoring resolution along the beam axis was 0.1 mm. The beam model was tuned based on measurements of depth dose profiles in water and transverse dose profiles in air at different air gaps as reported in section 3.2.2. Based on simulation in different volumes IDD correction factors are computed as follow:

$$CF [A.U.] = 1 + \frac{(E_{IDD} - E_{PTW_X})}{E_{PTW_X}} \quad (3.4)$$

In particular, the $CF_{\phi 200}$ are computed with IDD integrated over a cylinder of $\phi = 200$ mm diameter and the $CF_{\phi 1000}$ are computed with IDD integrated over a cylinder of $\phi = 1000$ mm diameter.

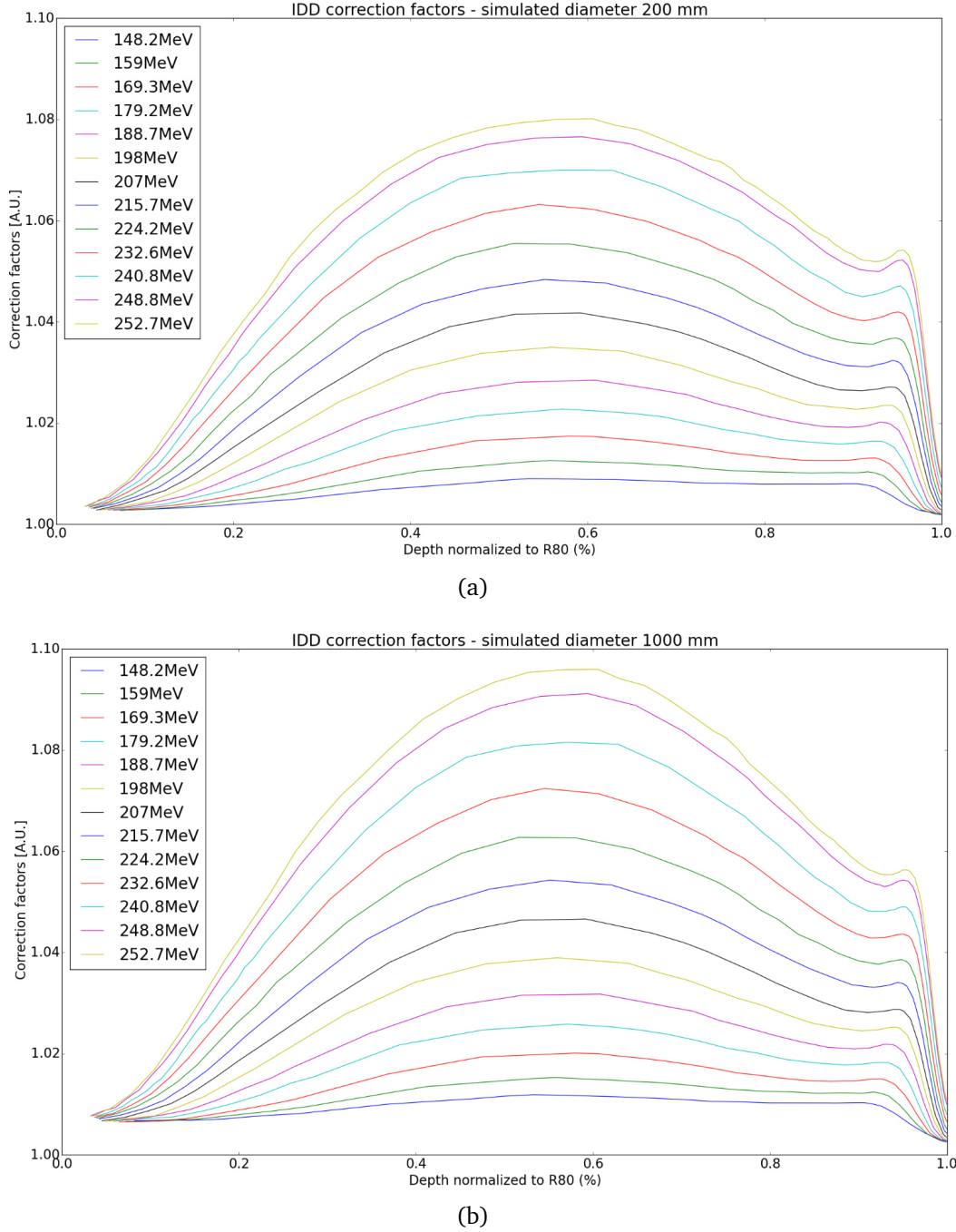


Figure 3.16: IDD's correction factors as function of depth normalized to R_{80} for different energies. In (a) correction factors $CF_{\phi 200}$ for the the PPIC PTW_B scoring the full integrated IDD's in a cylinder of $\phi = 200$ mm. In (b) correction factors $CF_{\phi 1000}$ for the the PPIC PTW_B scoring the full integrated IDD's in a cylinder of $\phi = 1000$ mm.

One can see in picture 3.16 the corrections based on IDD's scored in $\phi = 1000$ mm are up to 2% larger than the corrections based on IDD's scored in $\phi = 200$ mm. This is mainly due to the dose additional dose deposited by the neutrons in the larger volume. Both IDD corrections show similar shape as function of energy and depth in water, with a maximum at the $\approx 60\%$ of the R_{80} . Since cylinder of diameter $\phi = 200$ mm is closer to

the clinical scenario as maximum field size we corrected all the 20 measured depth dose curves with $CF_{\phi 200}$. In figure 3.17 the raw data and the data corrected with $CF_{\phi 200}$ for depth dose profiles at 252.7 MeV is shown. As one can see in figure 3.17 the corrections

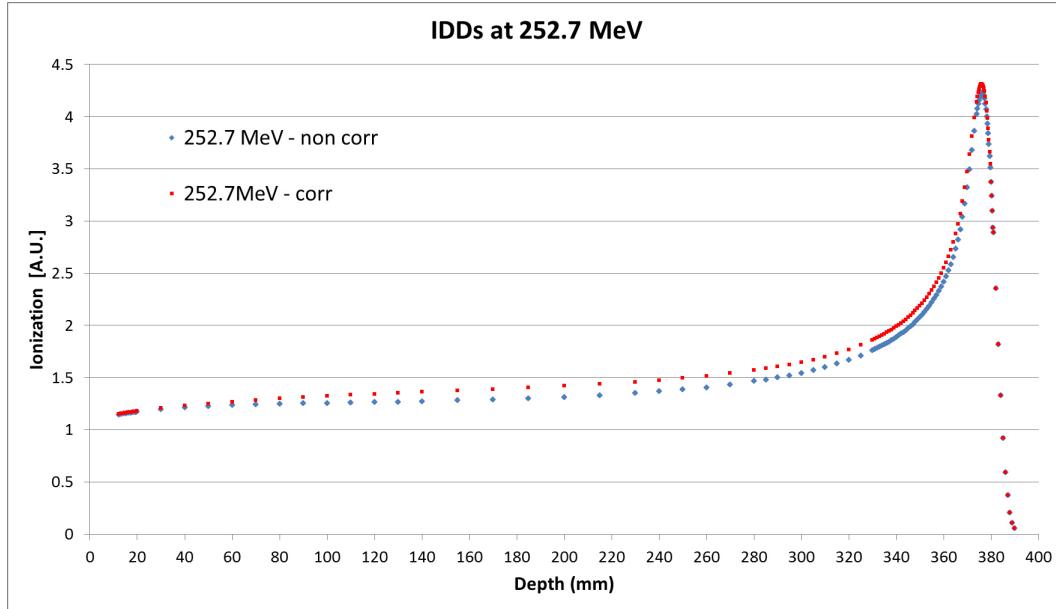
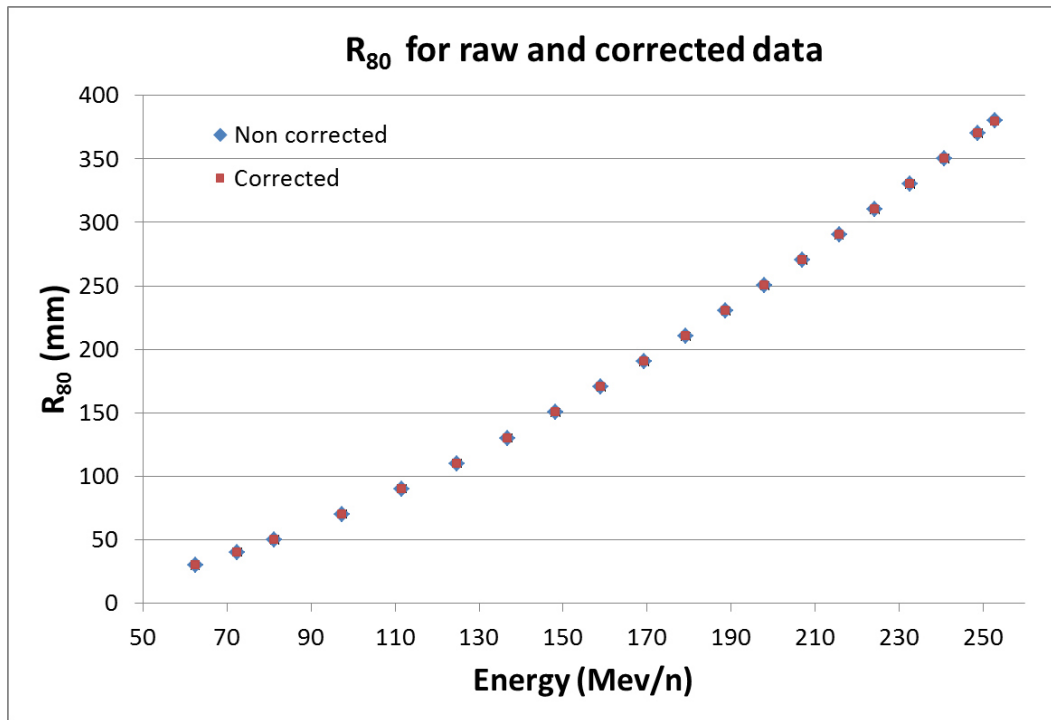
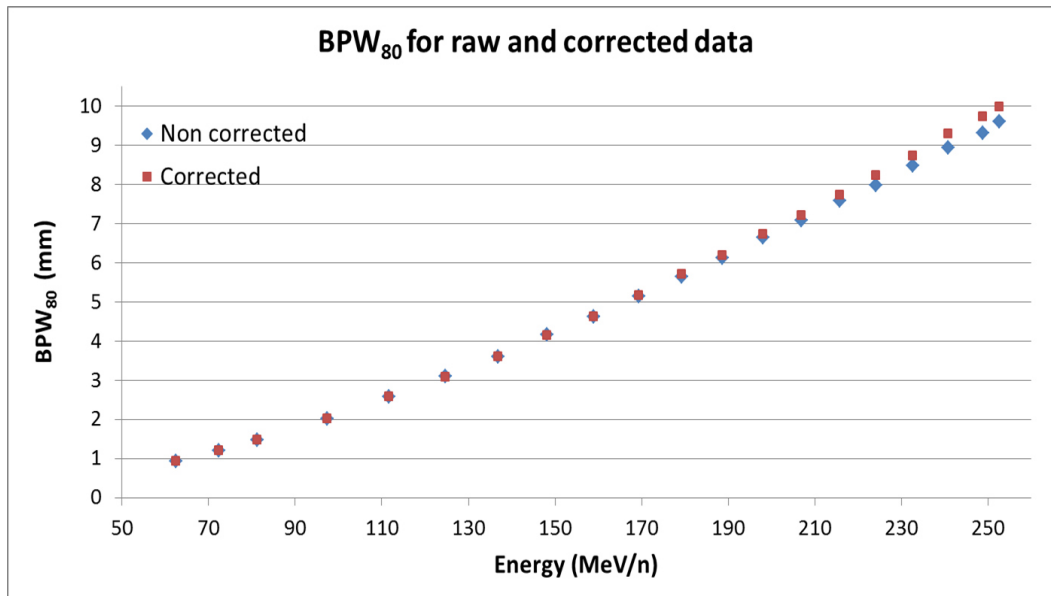


Figure 3.17: Depth dose profiles at 252.7 MeV with and without the correction factors $CF_{\phi 200}$ applied.

are mainly applied at the mid-range of the R_{80} and in the Bragg peak region ($\approx 97\%$ of R_{80}) as expected from figure 3.16 (a). We investigated the impact of corrections on parameters as R_{80} and Bragg peak width at 80% level ($BP_{w,80}$). In the figure 3.18 the R_{80} and the $BP_{w,80}$ are shown as function of proton energy for the measured depth dose profiles and for the data corrected by $CF_{\phi 200}$. Regarding the R_{80} the non-corrected and corrected data show similar behavior with maximum deviation of 0.03% at 252.7 MeV/n. The BPW_{80} is the most influenced parameter by the $CF_{\phi 200}$ corrections mainly due to the elastic nuclear interaction of primary protons which scatter out of the chamber volume close to the Bragg peak region (see figures 3.9 and 3.16). Deviation between the raw data and the corrected one was found up to 4.6 % at 248.8 MeV/n.



(a)



(b)

Figure 3.18: R_{80} and the BPW_{80} as function of energy for all the 20 major proton energies. The parameters are extracted for the measured depth dose profiles (non corrected) and for the data corrected by $CF_{\phi 200}$.

3.4 Discussion and Conclusion.

In a scanned proton beam it is important to consider that the primary core of each pencil beam is laterally surrounded by a low-dose envelope due to the scatter of secondary particles produced in the interactions of the primary protons with matter. To correctly calculate absolute dose in scanned proton beams, as required when commissioning the TPS, it is necessary to model the low-dose envelope with sufficient accuracy. In this work we have investigated and validated the IDD correction factors to be applied to a finite size plane-parallel ionization chamber (PPIC). Previous works of Grevillot et al. [60] and Clasio et al. [59] simply quantify the corrections to be applied scoring the dose in the finite volume of the PPIC [60] or parametrize the correction factors as function of energy and depth [59]. Other work from Anand et al [71] corrects for the missing dose experimentally. However, no sensitivity studies were performed in order to investigate the sources of IDD correction factors. Plotted as function of depth normalized to the physical range R_{80} , IDD correction factors show a similar shape regardless the selected energy (at least above 120 MeV/u). The shape and the absolute values strongly depend on the non-elastic hadronic models selected with difference up to 4% for the highest energies (see figure 3.7 and 3.10). The contribution of MCS to the correction factors is negligible for the Bragg peak chamber (TM34070, $\phi = 81.6$ mm) but starts to be significant (up to 1%) for smaller volume PPIC (TM34073, $\phi = 39.6$ mm). Since we observed substantial deviations among different non-elastic nuclear models in the Monte Carlo a validation of the physics (the so called physics builders in Gate v7.1 Geant4 v10.01.02) with measurements was performed. Two different experiments have been designed for the validation purpose.

Measurements of transverse dose profiles with 24 PinPoint ionization chambers were carried out in a single pencil beam at four energies spread over the whole clinical energy range (see section 3.3.3). Differently from the previous works done by Sawakuchi et al [57] at MD Anderson Cancer Center and Gottschalk et al [25] at Massachusetts General Hospital's Francis H. Burr Proton Therapy Center, in this work we used a 1D Linear Array Holder with 24 PinPoint ionization chambers instead of a single small volume thimble chamber. A similar approach was used also at HIT and reported in the work of Schwaab et al [72]. In this way we speed up the measurements sparing beam time highly precious during medical commissioning of LIBT. We measured transverse dose profiles over 4 orders of magnitude lower than the central axis dose at four different depths for each energy. The experimental results were comparable to Sawakuchi et al [57], Schwaab et al [72] and Gottschalk et al [25] with the advantage to have characterized the low-dose envelope up to 252.7 MeV/u (the highest energy available

at our facility) and above the range of energies used in the previous works. Regarding MC simulations, previous work of Hall et al [73] compare MC Geant4 v10.01p2 with the experimental results reported in Gottschalk et al [25] at only one energy (177 MeV/u) and only one physics builder (QGSP_BIC_HP). In Sawakuchi et al [69] the inelastic nuclear interactions were treated with a single default option in the MC code MCNPX, which considers the pre-equilibrium model after the Bertini intra-nuclear cascade model [64]. In Schwaab et al [72] the MC FLUKA code [74] was selected for the simulations with a fixed physics model (PEANUT Pre-Equilibrium Approach to Nuclear Thermalization [75]). No comparison of different hadronic models with low-dose envelope measurements was found in literature. In our work MC Gate/Geant4 v10.01p2 was compared with low-dose envelope measurements at four different energies using three different physics builders (QGSP_BIC_HP, QGSP_BERT_HP, QBBC). The shape of the MC simulations for all the physics builders was found in a good agreement with the measurements down to dose levels of four orders of magnitudes of the central dose. Since the impact of different physics builders is mostly relevant at large radii we excluded from the analysis the 'core' region of the pencil beam analyzing only the tails (outside the FW0.01M at 1% level). The average values for all measurements-simulation comparison quantities (Δ FW0.01M, Δ FW0.001M and FOM(%)) for each physics builder showed a slightly better agreement for the QBBC physics builder. However, the differences found were not statistically significant.

As second experiment a validation of IDD correction factors was performed with measurements in a single-layer scanned field (diameter $\phi = 160$ mm) with a Roos ionization chamber (TM34001, see section 3.2.1). The aim was to directly derive from measurements the IDD correction factors for the Bragg peak chamber TM34070 as ratio between measurements in a single-layer scanned field and measurements in a pristine pencil beam with the Bragg peak chamber TM34070. This innovative method is not reported in literature. MC simulation was performed for all three physics builders (QGSP_BIC_HP, QGSP_BERT_HP, QBBC). For each physics builders IDD correction factors were derived at two energies 198 MeV/u and 252.7 MeV/u and compared with the measurements. The shape of simulated IDD correction factors as function of depth normalized to R_{80} is in quite good agreement with the measurements mainly for the QGSP_BIC_HP and the QBBC models. Larger deviations have been observed close to the Bragg peak region due to high gradient and positioning uncertainties of the ionization chambers (see figure 3.12). Both QGSP_BIC_HP and QBBC shows similar behavior overall the depths and a 0.5% differences at the mid-range. At the same depth the QGSP_BERT_HP shows larger deviations up to 1.5%.

As reported in Ivantchenko et al [70] the implementation of the two physics builders QGSP_BIC_HP and QBBC is very similar in the Geant4code. The only difference is that the QBBC has higher precision than the other for many hadron-ion and ion-ion interactions in a wide energy range. So the similar results found in this work are expected. Moreover, the Binary cascade (QGSP_BIC_HP) and the QBBC shows better results for protons and neutrons at the clinical energy range in comparison to Bertini cascade (QGSP_BERT_HP) in terms of differential cross-sections [70]. The results of this work goes to the same direction of the suggestions of Geant4 developers, which are reported in [70]. Moreover, our studies have more clinical relevance since they are based on dosimetric comparison and not on pure fundamental physics (double cross-sections comparison) as reported in Ivantchenko et al [70].

Based on those results we selected the QBBC physics builder to derive IDD correction factors for the 20 “major” energies at MedAustron among the whole clinical range for protons [from 62.4 to 252.7 MeV/u]. The correction factors for IDD scored in a cylinder of 1000 mm diameter ($CF_{\phi 1000}$) shows larger deviations up to 2% for high energies in comparison to correction factors for IDD scored in a cylinder of 200 mm diameter ($CF_{\phi 200}$). The differences are due to the integration of dose deposited by neutrons and gamma in the larger volume. Our choice was to restrict the integration volume to $\phi = 200$ mm which is closer to our maximum field size $200 \times 200 \text{ mm}^2$ at the HBL. Though for our clinical application this choice is reasonable, further investigations could be done in order to assess the maximum integration radius at which the contribution of neutrons and gamma is still relevant. Based on the computed $CF_{\phi 200}$ the experimental depth dose profiles acquired with the Bragg peak chamber were corrected. “Corrected” and “raw” depth dose profiles have been provided to RaySearch laboratories and, based on those data, two different beam models for the TPS were developed. A detailed validation of both beam models with measurements was performed at MedAustron. The details of validation are not reported as they are out of the scope of this work. Based on results of the validation the “corrected” beam model was selected for clinical treatment with protons at the HBL.

CHAPTER 4

PATIENT-SPECIFIC PLAN VERIFICATION IN ACTIVE SCANNING WITH PARTICLE BEAMS.

4.1 Introduction

In the last decades new technologies have been introduced in radiotherapy with the aim of improving treatment outcome by means of dose distributions which conform more closely to the target volumes. Highly conformal dose distributions allow for dose escalation in the target volumes without increasing the dose to surrounding normal tissues. At MedAustron a very complex and innovative treatment technique in external beam radiotherapy has been implemented. The active scanning technique with proton and ^{12}C ion beams allows to build-up the dose as a superposition of many thousands of individually placed and weighted pencil beams. In particular, active scanned ion beams represent a novel irradiation technique taking full advantage from the physical interaction properties of these particles with tissues and advanced delivery modality to generate very sharp dose gradients in three dimensions, with many degrees of freedom available at the treatment planning level. The increased complexity related to the technological and process changes places new demands on Quality Assurance (QA) programs, as well as innovative instrumentation and detectors for beam characterization and checks. Quality Assurance processes are defined as “all those planned and systematic actions necessary to provide adequate confidence that a product or process will satisfy given requirements for quality” (INTERNATIONAL ORGANIZATION FOR STANDARDIZATION 1994 [56]). In particular a QA programme is needed in principal for two reasons:

- to ensure a high degree of accuracy in the whole radiation therapy process. The ICRU 83 [76] recommends that the overall accuracy in the radiation dose delivered

to the patient must be within $\pm 5\%$;

- to reduce/avoid treatment errors. New approaches of safety culture are required, since complexity may also increase the sensitivity to uncertainties and risk for accidental exposures.

Conformal treatments always bear the risk that any uncertainty in the delivered dose distribution may lead to a severe underdosage or overdosage of the target volume. Therefore, for a dynamic technique, like a scanned particle beam, special emphasis has to be put on dosimetric verification of planned dose distributions by the TPS. In the treatment planning phase, two different optimization strategies can be typically applied:

- The Single Field Optimization (**SFO**) is a direct active scanning equivalent of open-field photon plans (3D-CRT) or passive scattered proton treatments, in which the optimization process is restricted to each field individually. This is easy, fast and robust because it ensures that a homogeneous dose is delivered to the target by every field individually;
- For the Multiple Field Optimization (**MFO**) the optimization of each spot is performed over all fields in parallel. Each individual field can deliver a highly inhomogeneous dose distribution to the target, with all fields combined ensuring the planned homogeneous target dose. This technique is less robust and very sensitive to delivery uncertainties [33].

In both cases, very sharp dose gradients (more in ^{12}C ion than in proton beams), which can be achieved on a spot-to-spot basis, make scanned particle therapy quite complex and sensitive to planning and delivery uncertainties. Therefore, the planned dose distribution has to be verified periodically in homogeneous and/or inhomogeneous medium, and patient-specific plan verification is a highly recommended dosimetric procedure within the QA program. The aim of patient-specific QA (PSQA) is twofold:

- to verify that each field of a composite patient plan is deliverable without triggering any interlocks or accelerator failures;
- the measurements are performed as a final check of the accuracy of the dose distribution calculated by the TPS and actually delivered to the individual patient. For any specific plan, the dose distribution from each of the treatment fields is independently measured in a homogeneous water phantom and results are then compared to the corresponding values recalculated by the TPS under the same conditions.

For *passive beam delivery techniques*, the relative dose distribution is defined by a few mechanical components, i.e. the ridge filter (or modulator wheel) defining the SOBP, the range shifter defining the energy of the beam, the collimator defining the treatment field and the compensator adjusting the dose distribution to the distal edge of the target volume (see figure 1.16). For a given setting of these devices, it may therefore be sufficient to verify the dose at one single point within the treatment field. In an *active scanning system* measured dose may perfectly comply with the calculated dose in one point of the field, but can be completely wrong at others. Therefore a simultaneous verification of absorbed dose at many points is required by 2D or better 3D dosimetric systems.

After evaluating and comparing different techniques for the PSQA used at different particle therapy facilities worldwide, a commercial equipment based on the use of multiple ionization chambers (PTW, Freiburg, Germany) has been acquired at MedAustron. The system is the commercial version of the 3D dosimetric system originally described by Karger et al in 1999 [77] and developed at GSI. The Heidelberg Ion-Beam Therapy Center (HIT, Germany) and the Centro Nazionale di Adroterapia Oncologica (CNAO, Italy) have implemented in their clinical workflow the 3D Detector block with the 24 PinPoint chambers. However, no specific software to support this equipment and interface it to the RayStation TPS is commercially available. In this chapter we present an innovative, in-house developed software that makes the treatment plan verification workflow efficient, reliable and fast. Moreover, the full characterization of the 24 PinPoint ionization chambers in proton beam is reported in this work as preliminary step for further commissioning work. Furthermore, we will report on some examples of the entire workflow implemented in clinical practice in the context of the first patient treatments with protons at MedAustron.

4.2 Materials and methods

Two different sized water phantoms MP3-P and MP3-PL from PTW are available for the verification measurements at MA. The MP3-PL is a customization of the commercially available MP3-P in order to measure dose distributions at the highest energy available at MA (252.7 MeV/u which corresponds to 380 mm penetration depth in water). Based on measurements in our proton beam the Water Equivalent Thickness (WET) of the entrance windows of the two water phantoms are slightly different:

- $WET = 5.84$ mm for the MP3-P water phantom;
- $WET = 5.87$ mm for the MP3-PL water phantom.

The measured values have been taken into account in the implementation of the plan verification workflow. The water phantoms are equipped with a motorized arm that can be moved in three dimensions (A, B, C axes). Two different ionization chamber arrays for dosimetric verification in 3D can be attached to this arm and remotely be positioned in the phantoms:

- the *1D linear array* holder;
- the *3D detector block* holder.

Both systems fix up to 24 PinPoint ionization chambers model TM31015, volume = 0.03 cc and inner diameter of 2.9 mm. Both holders can be rotated by 90° and are therefore prepared to be used for Horizontal (HBL) and Vertical (VBL) beam lines. The 3D detector Block is a commercial holder (PTW-Freiburg) based on the original design developed at GSI [77] and the PinPoint chambers are distributed in different planes, allowing a quasi-three dimensional dosimetric verification of dose delivery in actively scanned particle beams for HBL and VBL. Figure 4.1 shows technical drawings of the 3D detector block and 1D linear array holders. The use of ionization chambers requires two

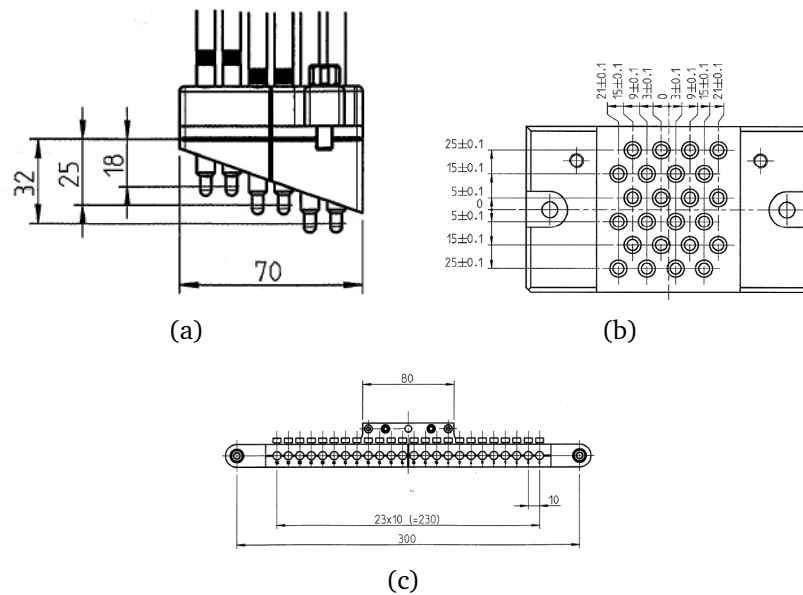


Figure 4.1: Technical drawings of the 3D detector Block (a,b) and the 1D linear array holders (c).

PTW-10004 MULTIDOS 12-channel electrometers, two 12-connector boxes, a control unit and a ComServer. The whole system is shown in figure 4.2. The two 12-channels Multidos electrometers provide a fix high voltage supply (+400 V) and read-out the signals of the 24 Pinpoint chambers. A Control Unit (TBA Control Unit) controls the moving mechanism that positions the two chamber arrays in the water phantom. A

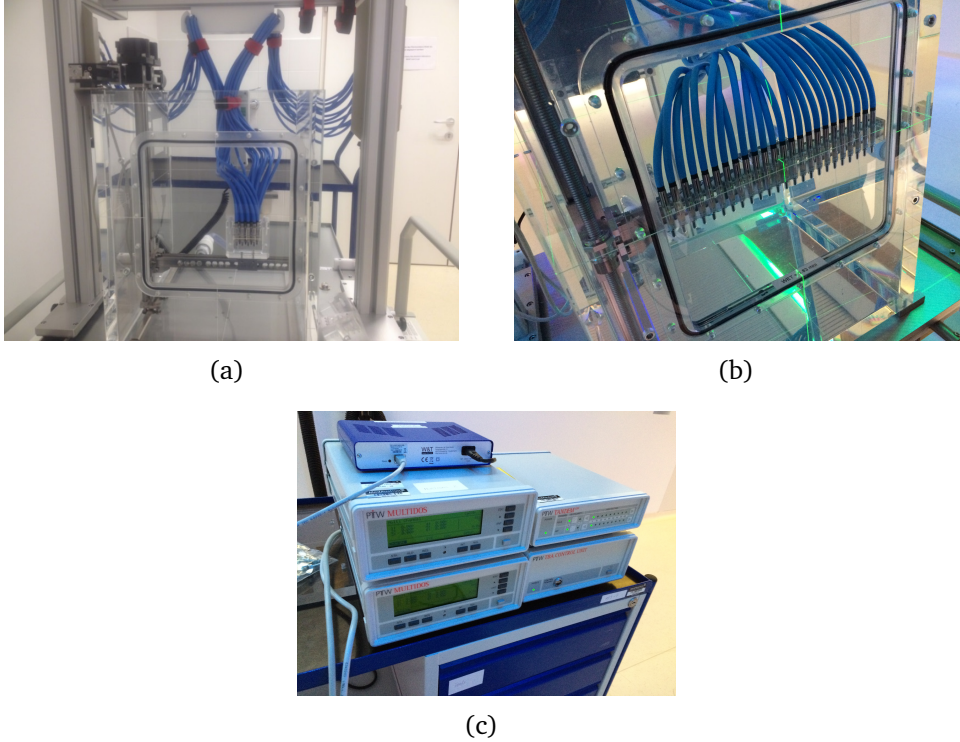


Figure 4.2: (a) The PTW 3D detector Block and (b) the 1D linear array holder with the 24 PinPoint ICs mounted into the MP3-P water phantom. (c) The related electronics consisting of two MULTIDOS electrometers, TBA control unit and a ComServer port.

ComServer connects the serial RS-232 interface of the two Multidos and TBA control unit to the IP network. However, the lack of commercial software prevents the remote control of all the equipment via the network.

4.2.1 Characterization of PinPoint ionization chambers in actively scanned proton beam

In order to use the 24 PinPoint ionization chambers for the dosimetric TPS commissioning and patient-specific plan verification we need to characterize them and establish for them a Quality Assurance program. The commissioning of dosimetry equipment is a necessary pre-requisite to acceptance testing, commissioning and further QA checks of a LIBT facility. The commissioning methods developed allowed determining the accuracy of the QA devices in clinical conditions and better define the QA tolerances for periodic quality assurance. Below a list of tests which have been carried out on the PinPoint chambers:

1. X-ray check was carried out for each Pinpoint chamber to verify the integrity of their construction;

2. check source readings in ^{90}Sr to monitor the stability of Pinpoint chamber response to ionising radiation;
3. cross-calibration and ion recombination study in a stable 6MV photon beam;
4. ion recombination and polarization study in actively scanned proton beam;
5. cross-calibration of Pinpoint chambers in actively scanned proton beam.

The X-ray of the 24 PinPoint chambers was performed with the Imaging Ring system [46] installed on the treatment couch (see section 2 for more details). The pixel size of the flat panel is 0.4 mm and the 24 PinPoint chambers were positioned close to the X-ray source on the table top in order to achieve a larger magnification. The central electrode (material Al, diameter 0.3 mm) was visible on the images and no bending was visually detected. No faults (cracks, deformations) were visible in the insulators and proper connection of wiring to electrodes were observed. In figure 4.3 the setup used and the X-ray image of a sample of six PinPoint chambers is shown.

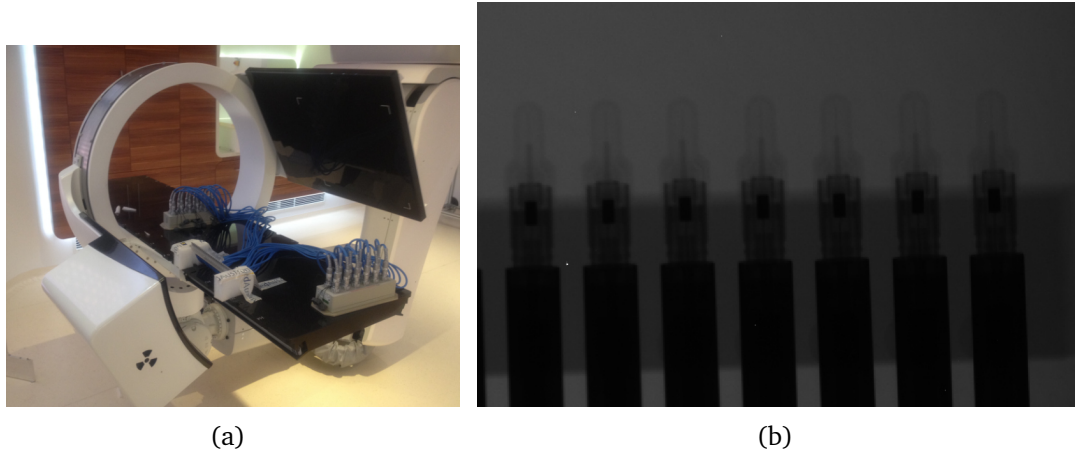


Figure 4.3: (a) Setup of the 24 PinPoint chambers for the X-ray image at the Imaging Ring system [46]. (b) X-ray image of a sample of six PinPoint chambers.

To monitor the stability of PinPoint chambers response to ionising radiation we performed reading in a check source of ^{90}Sr . This test is part of the QA program for the 24 PinPoint chambers. For each PinPoint chamber a maximum deviation of 0.5 % has been observed over one year. In the section 4.3 we report the results of the characterization of the chambers in the proton beam.

Ion recombination and polarization study in proton beams.

The incomplete collection of charge in an ionization chamber cavity due to the recombination of ions requires the use of a correction factor k_s . The recombination con-

sists of a dose rate independent contribution from initial (columnar) recombination and a dose rate or dose per pulse dependent contribution from volume (general) recombination. Both effects depend on the chamber geometry and on the applied polarizing voltage. Since ion recombination has been reported to be a complex phenomenon in Pinpoint chambers [78, 79], a study of the saturation behavior of these chambers is needed during the commissioning phase of these instruments. The idea is to study the ion recombination and polarity of 24 Pinpoint chambers simultaneously in a mono-energetic proton beam. In the 3D detector block every row of four chambers will be at a different depth and thus being at a different LET. In this way a representative sample for each of six LETs is obtained. Moreover, we use the highest intensity available at the energy applied (degrader setting 50% see section 2.2) in order to measure ion recombination in the worst case scenario. In clinical application a maximum degrader setting 80% (see section 2.2) is foreseen with a reduction of the intensity (number of protons per spill). The two Multidos electrometers supply a fixed voltage (+400 V) to the whole set of PinPoint chambers. Therefore, in order to change the voltage for the 24 PinPoint ICs simultaneously we used an external HV supply (ORTEC 428) adapting the electronics of the output channels (see figure 4.4).

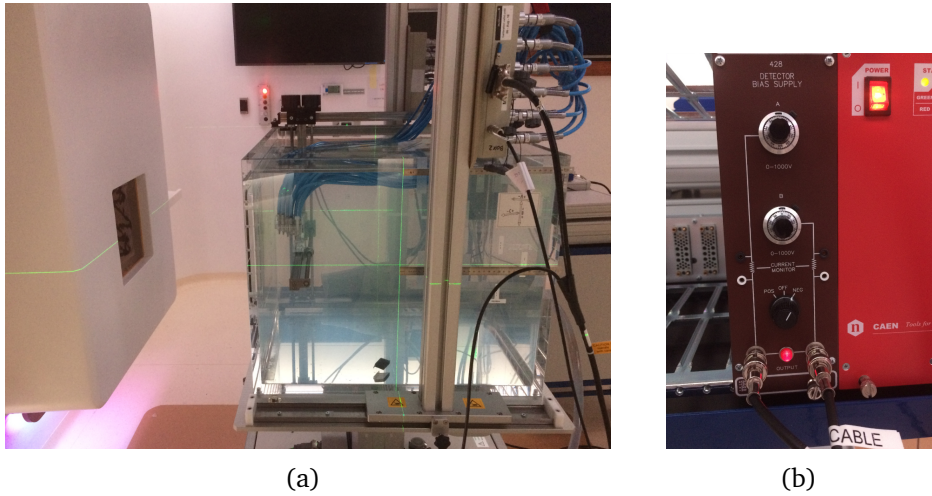


Figure 4.4: (a) Experimental setup for the ion recombination and polarity study and (b) the High Voltage supply ORTEC428.

In particular, the measurements were carried out at 8 voltage points ± 400 V, ± 300 V, ± 200 V, ± 100 V. Measurements were carried out in a mono-energetic field at 111.6 MeV/u ($R_{80} \approx 90$ mm) and the 6 rows of PinPoint ICs were placed at depth of 36.8 mm (plateau region) to 86.8 mm (peak region). After the change of the voltage the PinPoint ICs were pre-irradiated with a dose between 7 Gy and 22 Gy depending on the position of the Pinpoint IC in depth. The readings of each PinPoint IC has been corrected for temperature and pressure $k_{T,P}$. For each voltage point five readings have been acquired

in order to have a good statistics.

Cross-calibration of PinPoint ionization chambers in a proton beam.

The aim of the cross-calibration is to determine the calibration coefficient in terms of absorbed dose to water in the beam quality Q_{cross} (proton beam):

$$N_{D,W,Q_{cross}}^{PinPoint} = \frac{M_{Q_{cross}}^{ref}}{M_{Q_{cross}}^{PinPoint}} \times N_{D,W,Q_0}^{ref} \times k_{Q_{cross},Q_0}^{ref} \quad (4.1)$$

where $M_{Q_{cross}}^{ref}$ and $M_{Q_{cross}}^{PinPoint}$ are the dosimeter readings for the reference chamber (Farmer chamber) and the PinPoint chamber, respectively, corrected for the influence quantities temperature and pressure $k_{T,P}$, polarity effect k_{pol} and ion recombination k_s . The N_{D,W,Q_0}^{ref} is the calibration factor in terms of absorbed dose to water for the Farmer chamber at quality Q_0 (^{60}Co) and k_{Q_{cross},Q_0}^{ref} is the beam quality correction factor for the Farmer chamber. The cross-calibration was performed in a stationary water phantom MP1 (PTW, Freiburg) with a 3 mm PMMA thin entrance window. The only movable axis of the MP1 water phantom is in depth with 0.1 mm resolution. The phantom was set up with the outer surface of the thin window at the irradiation room isocenter. The idea was to cross-calibrate the 24 PinPoints two-by-two against two Farmer chambers calibrated in ^{60}Co at the Seibersdorf Laboratories (Austria). The figure 4.5 shows the experimental setup used for the cross-calibration. A Farmer chamber was always positioned in the middle as beam monitor chamber. All the ionization chambers (Farmer and PinPoint) were positioned at

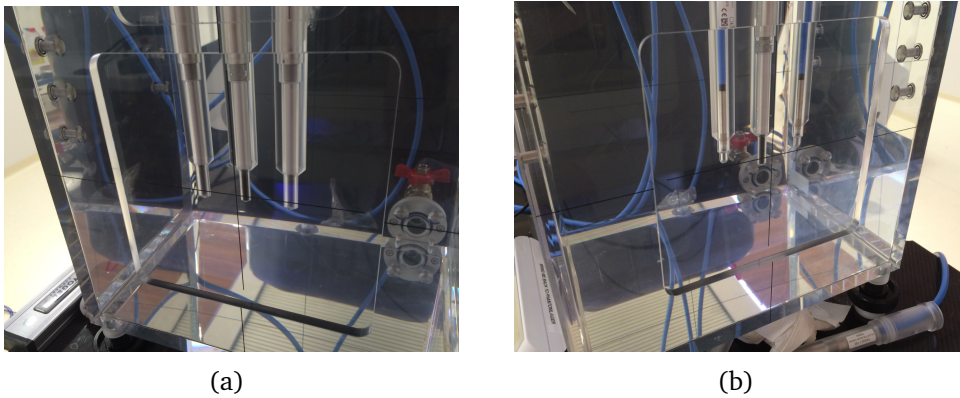


Figure 4.5: (a) Experimental setup for the measurements with the Farmer chambers. (b) Experimental setup for the PinPoint chamber measurements. The two lateral PinPoint and the Farmer in the middle as monitor chamber.

the water-equivalent reference depth, $z_{ref} = 20$ mm, in the MP1 water phantom on the beam axis. In order to position the effective point of measurement of the chambers at the reference depth [80] we applied a shift of:

- for the Farmer $0.75 \times r_{cyl} = 2.3$ mm away from the source;
- for the PinPoint $0.75 \times r_{cyl} = 1.1$ mm away from the source;

where in both cases r_{cyl} is the inner radius of the chambers. A mono-energetic square field of size 12×12 cm² with lateral spot spacing of 2 mm at isocenter for 179.2 MeV/u protons has been delivered. Degradar has been set to 80% as in clinical applications. Each Farmer chamber reading has been corrected for the corresponding temperature and pressure ($k_{T,P}$) factors. No corrections for polarity (k_{pol}) and ion recombination (k_s) have been applied since they have been measured and found to be negligible for this specific degrader setting in proton beam. The N_{D,W,Q_0}^{ref} value in eq. 4.1 corresponds to the calibration factor at ^{60}Co reported in the corresponding calibration certificate provided by Seibersdorf Laboratories (Farmer *SN7778* $N_{D,W,Q_0}^{ref} = 5.387 \times 10^{-2} [Gy/nC]$, Farmer *SN7777* $N_{D,W,Q_0}^{ref} = 5.351 \times 10^{-2} [Gy/nC]$). The k_{Q_{cross},Q_0}^{ref} in (Eq. 4.1) has been taken from the values reported in the TRS-398 calculated as a function of the corresponding beam quality ($k_{Q_{cross},Q_0}^{ref} = 1.029 \pm 0.017$ for a residual range $R_{res} \geq 15g \times cm^{-2}$). In order to minimize the effect of any variation of the accelerator output the readings of the Farmer $M_{Q_{cross}}^{ref}$ are normalized as $M_{Q_{cross}}^{ref} / M_{Q_{cross}}^{SN7779}$ with respect to the middle Farmer beam monitor *SN7779*. The measurements with the three Farmer ICs were repeated 4 times during the cross-calibration procedure (16 hours beam time) in order to check the stability of the beam delivery (see figure 4.5(a) for the setup). Regarding the PinPoint chamber measurements each reading has been corrected for the corresponding temperature and pressure ($k_{T,P}$) factors. No corrections for polarity (k_{pol}) and ion recombination (k_s) have been applied (see section 4.3.1). In order to minimize the effect of any variation of the accelerator output the reading of each Pinpoint chamber $M_{Q_{cross}}^{PinPoint}$ is normalized as $M_{Q_{cross}}^{PinPoint} / M_{Q_{cross}}^{SN7779}$ with respect to the Farmer beam monitor chamber *SN7779*.

4.2.2 A new software solution to support PSQA workflow.

For the Patient Specific Quality Assurance (PSQA), an approach similar to GSI, HIT and CNAO with 24 PinPoint ionization chambers in a three-dimensional array (3D detector block) in a water phantom was implemented at MedAustron. However, no software to support this equipment and interface it to the RayStation TPS is commercially available. In order to support plan QA workflow two software solutions were developed in-house within this study:

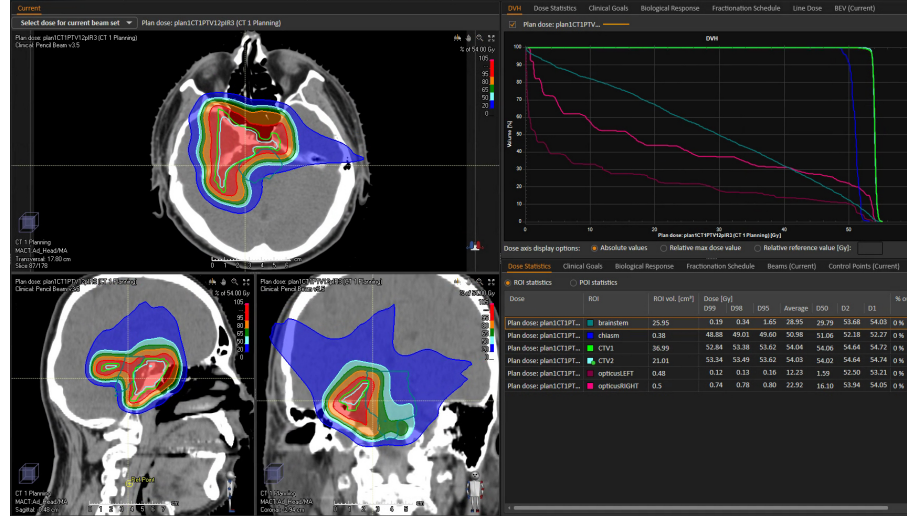
- exploiting the RayStation TPS scripting interface a script *MA_QA_v3_scale_factor.py* in ironpython language was developed;

- a software called “Plan Verificator” in C# language was developed in collaboration with a software engineer in the framework of his master thesis [81].

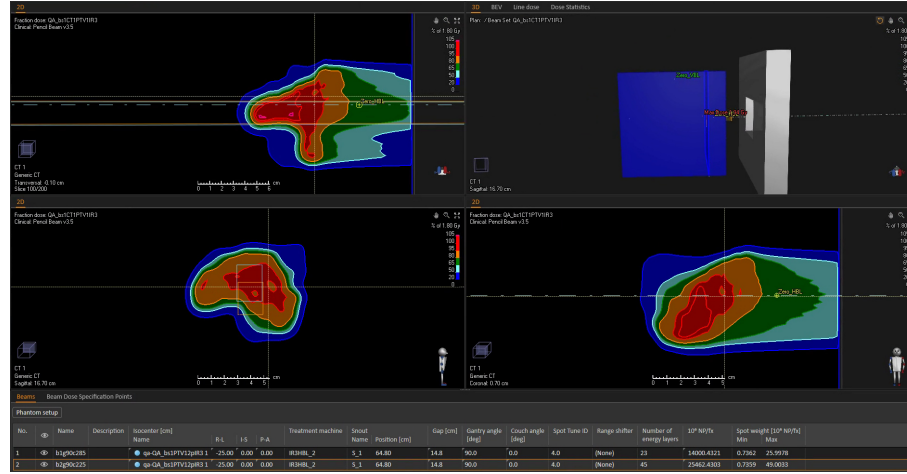
One of the aim of PSQA is to verify that the dose measured in a water phantom matches the dose that the treatment plan foresees to be delivered to the patient. However, the patient’s geometry and density are quite different to that of the water phantom. For this reason the patient treatment plan is re-computed with the same beam energies, the same scan pattern and spot weights into the water phantom geometry. The new recomputed plan is called *QA plan*. The beam data of the QA plan and the clinical plan are the same. A $2 \times 2 \times 2 \text{ mm}^3$ voxel size is selected as reasonable compromise between calculation speed and dose calculation accuracy. The virtual water phantom contains two marker points (*Zero_HBL* and *Zero_VBL*) for the setup in HBL and VBL. The dimensions of the virtual water phantom make it suitable for verification in both the MP3-P and MP3-PL water phantom. The figure 4.6 shows a patient treatment plan and the re-computation in the virtual water phantom in the “QA preparation” module of RS. In RayStation terminology a treatment plan is composed of “Beam-Sets”. For instance in case of a prostate treatment plan, a first Beam-Set is planned to the prostate gland and seminal vesicles (54 Gy) and a second Beam-Set is the sequential boost to the prostate gland only (up to 79 Gy). Each Beam-Set is usually composed of two beams. The couch angle for all the beams composing each Beam-Set is set to 0 and recomputed into the virtual water phantom. Since, at MedAustron the nozzle is fixed (no movable snout) the patient is moved closer to the nozzle to reduce air-gap (non-isocentric treatments). Therefore, also the PSQA is performed in so-called non-isocentric configuration with the water phantom positioned closer to the nozzle in order to reproduce as close as possible the patient treatment setup. The distance between nozzle cover and the entrance window of the water phantom is called *gap*. Different gaps have been implemented in the workflow depending on the specific patient treatment:

- gap of 14.8 cm;
- gap of 24.8 cm;
- gap of 34.8 cm;
- gap of 64.8 cm (isocenter setup).

After re-computing the treatment plan in the virtual water phantom with a specific gap, the user runs the script *MA_QA_v3_scale_factor.py* in the “QA preparation” module of RS. The script has an own user interface in which the beam, the beam line (horizontal or vertical), the ionization chamber array to be used for the measurements (linear array



(a)



(b)

Figure 4.6: (a) Dose distribution in transversal, coronal and sagittal view for a clinical case. (b) Dose distribution recomputed in virtual water phantom.

holder or 3D detector block, see figure 4.2), the water phantom (MP3-P or MP3-PL) and the measurement position of the holder in terms of water phantom coordinates (A,B,C) can be selected. In the figure 4.7 an example of the GUI of the script is shown. After inserting the position A,B,C of the holder via the “Align points and compute dose” button the script virtually places the ionization chamber array in the dose distribution of the selected beam in the QA plan. In the figure 4.8 a screenshot of the GUI and the ionization chamber positions overlaid as 24 green POIs (Point Of Interest) to the dose distribution of the QA plan. The script uses a reference point on the holder called Holder Reference Point (HRP) and layout information of the bore holes (see figure 4.1) in the arrays to determine the position of the central electrode of each ionization chamber. In addition, two additional offsets are taken into account:

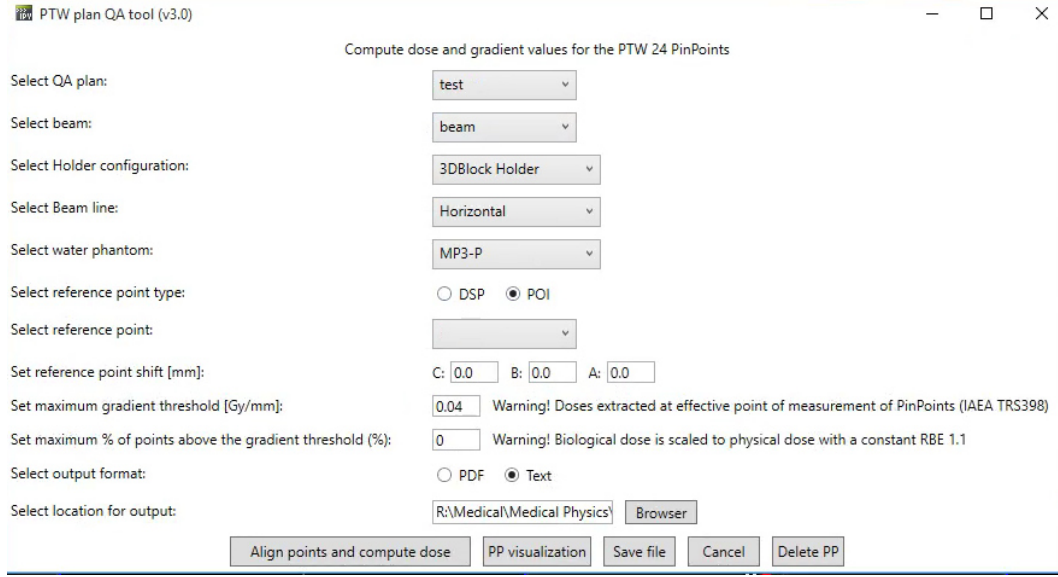


Figure 4.7: GUI of 'MA_QA_v3_scale_factor.py' script.

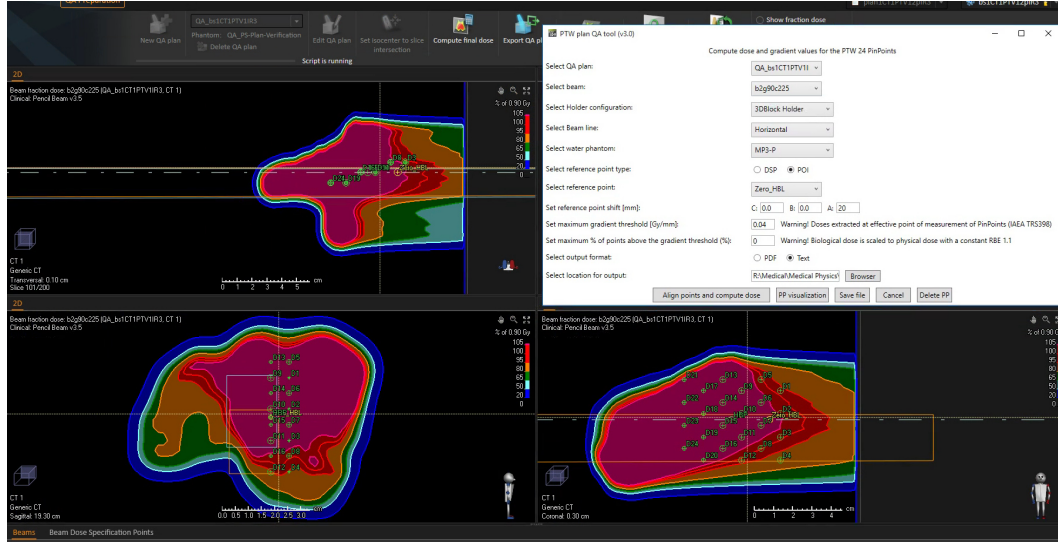


Figure 4.8: The 24 PinPoint chambers (green POIs) overlaid on the dose distribution recomputed in the water phantom in transversal, coronal and sagittal view.

- the effective point of measurement following TRS-398 [80], $0.75 \times r_{cyl} = 1.1$ mm;
- a different WET of the PMMA beam entrance window for the water phantom ($WET_{MP3-P} = 5.84$ mm, $WET_{MP3-PL} = 5.87$ mm)

When the ionization chamber array has been positioned, the script determines the physical dose (in Gy) at the specific POIs and the dose gradients (in Gy/mm). The dose is tri-linearly interpolated among the closest eight dose voxels at the effective point of measurement for each of the 24 Pinpoint chambers. Moreover, the displayed biological dose is scaled to physical dose for protons by dividing with the constant RBE factor of 1.1. As safety measure, depending on the selected holder (3D detector block or Linear

Array holder) and the water phantom selected (MP3-P or MP3-PL), the limits in A,B,C are hardcoded in order to prevent collisions with the water phantom walls. Moreover, shifts more than one digit after comma (in mm units), are not allowed as they are not processed by the MP3-P/PL water phantom stepping motors. The option to visualize the extracted dose (Gy) and dose gradient (Gy/mm) values at each effective point of measurement of the 24 PinPoint chambers is implemented via the button “PP visualization”, as shown in figure 4.9. Via the “Save” button, a text file (“QA plan” file) which contains

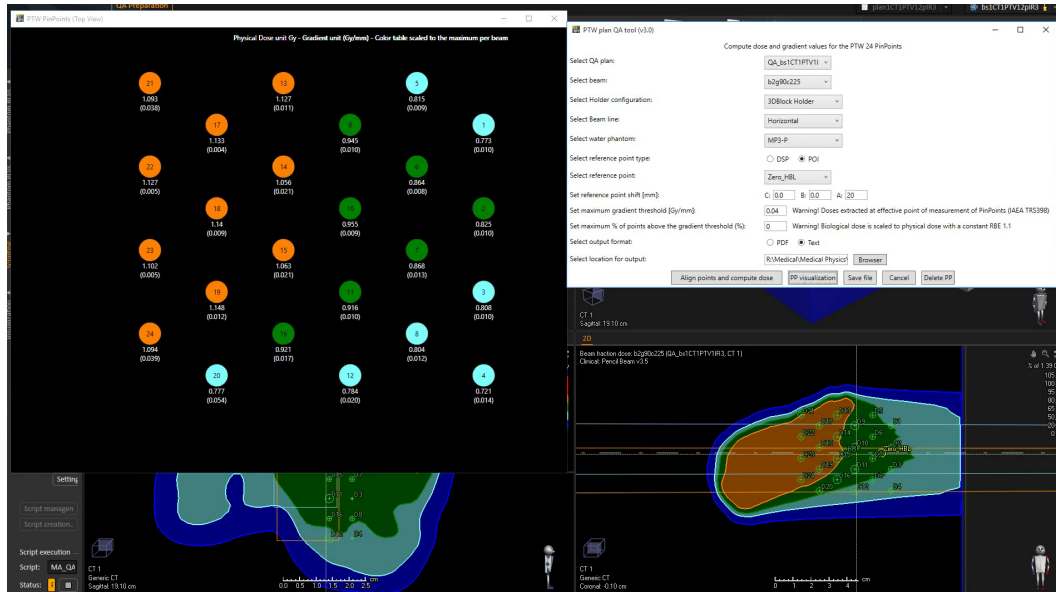


Figure 4.9: For each PinPoint chamber, the dose (Gy) and dose gradient (Gy/mm) values are shown. Each chamber is represented by a color based on the selected “color table” for the current dose displayed. The color table is scaled to the maximum dose per beam.

the dose, dose gradient data and also information about the patient and the treatment plan is stored in the selected folder (see figure 4.10). The verification workflow requires a lot of interaction with the measurement equipment, for example to position the ionization chamber array and instruct the two Multidos electrometers. PTW does not provide any software tool for an efficient execution of the verification measurements. In this context we developed and integrated in the clinical workflow a software called “Plan Verificator” [81]. The *Plan Verificator* is developed in C# and with the user interface technology Windows Presentation Foundation (WPF). It can be executed on any Windows computer with a .Net runtime environment and an installed Microsoft Excel. The *Plan Verificator* supports the execution of the entire verification workflow, from the measurement acquisition, to the dose computation, to the analysis of the differences and the creation of a QA report in pdf format. In software development the interactions between users and software systems are often expressed as use-cases. The use-cases for the *Plan Verificator* give a good overview of the functionality of the program:

```

# Patient ID: 1479451499
# Patient Name:
# Plan name: plan1CT1PTV12pIR3
# Beam Set Name: bs1CT1PTV12pIR3
# Prescribed biological dose (Gy[RBE]): 25.2
# Particle Type: Protons
# Machine Name: IR3HBL_2
# Beam Line: Horizontal
# Beam Name: blg90c285
# Couch Angle (deg): 0.0
# Gantry Angle (deg): 90.0
# RaShi: Out
# SpotTuneID: 4.0
# Gap (cm): 14.8
# Dosegrid (cm): {'R-L': 0.20000000000000001, 'I-S': 0.20000000000000001, 'P-A': 0.20000000000000001}
# Threshold maximum gradient (Gy/mm): 0.04
# Maximum % of points above the threshold gradient (%): 0.0
# Holder type: 3DBlock Holder
# Phantom type: MP3-PL
# QA plan name: QA_bs1CT1PTV1IR3
# QA plan modification time: 07.12.2016 16:39:08

# Reference POI: Zero_HBL
@ HRP Shift:
@C (mm) B (mm) A (mm)
0.0 0.0 0.0

#Maximum physical dose per beam (Gy): 0.607

@ IC Pos in Dicom coordinates:
@IC Posx Posy Posz Physical Dose (Gy) Gradient (Gy/mm)
1 230.2 -7.0 15.0 0.320 0.002
2 230.2 -7.0 3.0 0.336 0.003
3 230.2 -7.0 -9.0 0.334 0.006
4 230.2 -7.0 -21.0 0.320 0.007
5 220.2 -7.0 21.0 0.314 0.009
6 220.2 -7.0 9.0 0.341 0.002
7 220.2 -7.0 -3.0 0.351 0.006
8 220.2 -7.0 -15.0 0.332 0.009
9 210.2 0.0 15.0 0.361 0.006
10 210.2 0.0 3.0 0.363 0.001
11 210.2 0.0 -9.0 0.369 0.004
12 210.2 0.0 -21.0 0.362 0.006
13 200.2 0.0 21.0 0.322 0.013
14 200.2 0.0 9.0 0.378 0.003
15 200.2 0.0 -3.0 0.378 0.003
16 200.2 0.0 -15.0 0.381 0.004
17 190.2 7.0 15.0 0.378 0.009
18 190.2 7.0 3.0 0.402 0.003
19 190.2 7.0 -9.0 0.368 0.004
20 190.2 7.0 -21.0 0.361 0.005
21 180.2 7.0 21.0 0.336 0.009
22 180.2 7.0 9.0 0.416 0.002
23 180.2 7.0 -3.0 0.410 0.006
24 180.2 7.0 -15.0 0.377 0.007

```

Figure 4.10: An example of the ASCII file generated by the script. The header part contains information about the patient, plan, Beam-Set, Beam, Gap, Beam line, detector holder used. Moreover, the shift to be applied in the water phantom in terms of A,B,C coordinates, the maximum physical dose per beam, the dose and the dose gradient values extracted at each PinPoint chamber position.

- control the two Multidos electrometers and the MP3-P/PL controller;
- control the position of the ionization chamber array (3D detector block or linear array holder) in the water phantom;
- load and view the “QA plan” files exported via the *MA_QA_v3_scale_factor.py* script from the TPS;
- zeroing both Multidos electrometers simultaneously;
- acquire measurements with both Multidos and all 24 ionization chambers simultaneously;

- store the acquired measurement data;
- enter air pressure and water temperature in the GUI ($k_{T,P}$), in order to derive dose from the ionization chamber readings;
- view the measurement data in (nC) and the derived absorbed dose to water in (Gy);
- view a comparison of the dose differences between the TPS planned dose and the measured one including a statistical analysis;
- exclude PinPoint chambers from the analysis either manually or via a dose gradient threshold;
- generate and store a QA report in pdf format for documentation purpose.

On the lowest level, the *Plan Verificator* communicates with the two Multidos electrometers and the TBA Control Unit via RS-232 telegrams. However, the software is not connected via RS-232 to the devices directly but via Ethernet to a ComServer (see figure 4.2). The ComServer wraps the RS-232 telegrams of devices into TCP/IP messages and sends them via the network. In the other direction, the ComServer unwraps the data sent by the *Plan Verificator* and passes it on via RS-232. The connection of the software to the measurement equipment is shown in figure 4.11. The *Plan Verificator* requires some

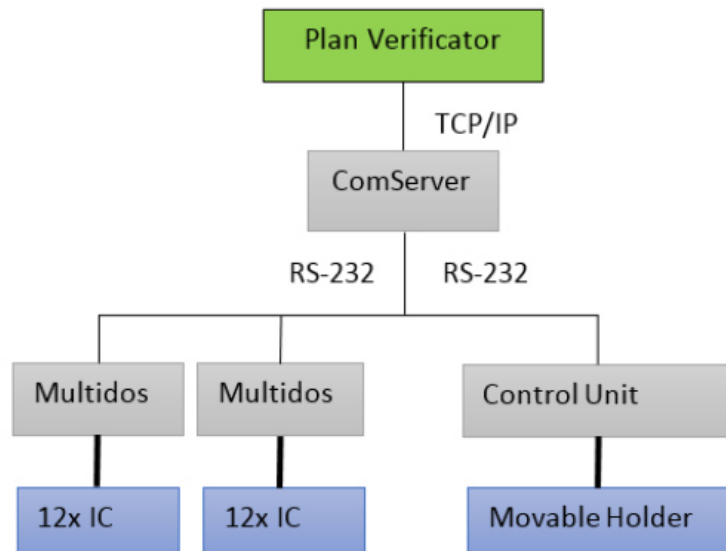


Figure 4.11: Connections of the *Plan Verificator* to the two Multidos and the TBA control Unit via the ComServer. Each Multidos electrometer connect 12 PinPoint chambers and the TBA control unit controls the movement of the holder inside the water phantom.

information about its environment. For this reasons a configuration and a calibration file

are created. Changes in the configuration data of those two files can prevent the *Plan Verificator* from working correctly. The configuration must be changed only by expert users. Technically, this is done by storing both files in a dedicated directory with specifically managed access rights. Write access to the directory is only granted to expert users. The configuration file (xml format) contains important settings for the *Plan Verificator*. Storing the settings in a file has the advantage that new values can be set by authorized users without changes in the code of the *Plan Verificator* software. The file contains the following information:

- connection settings, such as the ComServer address and the ports that the two different Multidos electrometers and the TBA Control Unit are connected to;
- the path to the QA database;
- measurement settings for the Multidos like the range to be used;
- a threshold for the dose gradients (0.04 Gy/mm) in order to deactivate ionization chambers in high dose gradient regions;
- the holder position for the pre-irradiation of the 24 PinPoint chambers;
- action levels and thresholds for the statistical analysis of the difference between planned and measured dose.

The calibration file is an Excel file which contains the following information:

- the serial number of each PinPoint chamber;
- the calibration factor $N_{D,W,Q_{cross}}^{PinPoint}$ for each pinpoint;
- the ion recombination factor k_s , the polarity factor k_{pol} and the beam quality factor $k_{Q_p,Q_{cross}}$;
- the serial numbers of the two Multidos electrometers.

Each of the factor stored in the configuration excel file has been determined with measurements as preliminary step to the PSQA. In particular, in the sections 4.3.2 and 4.3.1 more details on those factors are reported. Based on the information stored in this file the *Plan Verificator* determines on-the-fly the absorbed dose to water for each PinPoint chamber as following:

$$D_{w,Q_p}^{PinPoint} = M_{raw}^{PinPoint} \times k_{pol} \times k_s \times k_{T,P} \times N_{D,W,Q_{cross}}^{PinPoint} \times k_{Q_p,Q_{cross}} \quad (4.2)$$

Detector set EBG Configuration of detector set from date: 2016-09-03							
PinPoint number	SN	$N_{D,W,Q_{cross}}$ (Gy/nC)	Electrometer	k_s	k_{pol}	$k_{q,q0}$	
	1	566	1.20571	Multidos 1 SN 001595	1	1	1
	2	567	1.20531	Multidos 1 SN 001595	1	1	1
	3	568	1.20107	Multidos 1 SN 001595	1	1	1
	4	569	1.21343	Multidos 1 SN 001595	1	1	1
	5	570	1.19831	Multidos 1 SN 001595	1	1	1
	6	571	1.19286	Multidos 1 SN 001595	1	1	1
	7	572	1.19385	Multidos 1 SN 001595	1	1	1
	8	573	1.20630	Multidos 1 SN 001595	1	1	1
	9	574	1.22195	Multidos 1 SN 001595	1	1	1
	10	575	1.19973	Multidos 1 SN 001595	1	1	1
	11	576	1.19355	Multidos 1 SN 001595	1	1	1
	12	577	1.22922	Multidos 1 SN 001595	1	1	1
	13	578	1.21474	Multidos 2 SN 001586	1	1	1
	14	579	1.22891	Multidos 2 SN 001586	1	1	1
	15	580	1.20336	Multidos 2 SN 001586	1	1	1
	16	581	1.22162	Multidos 2 SN 001586	1	1	1
	17	582	1.20395	Multidos 2 SN 001586	1	1	1
	18	583	1.21022	Multidos 2 SN 001586	1	1	1
	19	584	1.22600	Multidos 2 SN 001586	1	1	1
	20	585	1.19790	Multidos 2 SN 001586	1	1	1
	21	586	1.20635	Multidos 2 SN 001586	1	1	1
	22	587	1.21327	Multidos 2 SN 001586	1	1	1
	23	588	1.20483	Multidos 2 SN 001586	1	1	1
	24	589	1.22053	Multidos 2 SN 001586	1	1	1

Figure 4.12: An example of the calibration file. The cross-calibration and correction factors are assessed in sections 4.3.2 and 4.3.1.

where the $k_{T,P}$ is re-computed by the software each time the user inserts the water temperature and air pressure in the GUI (see figure 4.13) and $M_{raw}^{PinPoint}$ is the reading (nC). If the values are not set the text fields are displayed with a red frame and the dose



Figure 4.13: The tool bar at the top of the *Plan Verificator* contains all tools required to execute a verification. In evidence the temperature and pressure text fields.

is not computed. This safety mechanism ensures that the user enters values. When the values were set once they are kept for the next verifications to speed up the process of executing multiple verifications after each other. In the figure 4.14 the complete GUI of *Plan Verificator* is shown. As one can see in the figure 4.14 the Plan Verificator GUI is subdivided in four tabs:

1. The *QA Plan tab* displays the data of the loaded “QA plan” files exported by the *MA_QA_v3_scale_factor.py* script. It represents the interface between the data extracted from the TPS and those acquired during the measurements. This includes beam and patient data of the treatment plan, the machine name, the beam line but also QA plan specific information like the phantom type.
2. In the *Holder Position tab* all information related to the position of the holder with the ionization chamber array are displayed. The holder can be moved to a predefined pre-irradiation position, the position planned via the *MA_QA_v3_scale_factor.py*

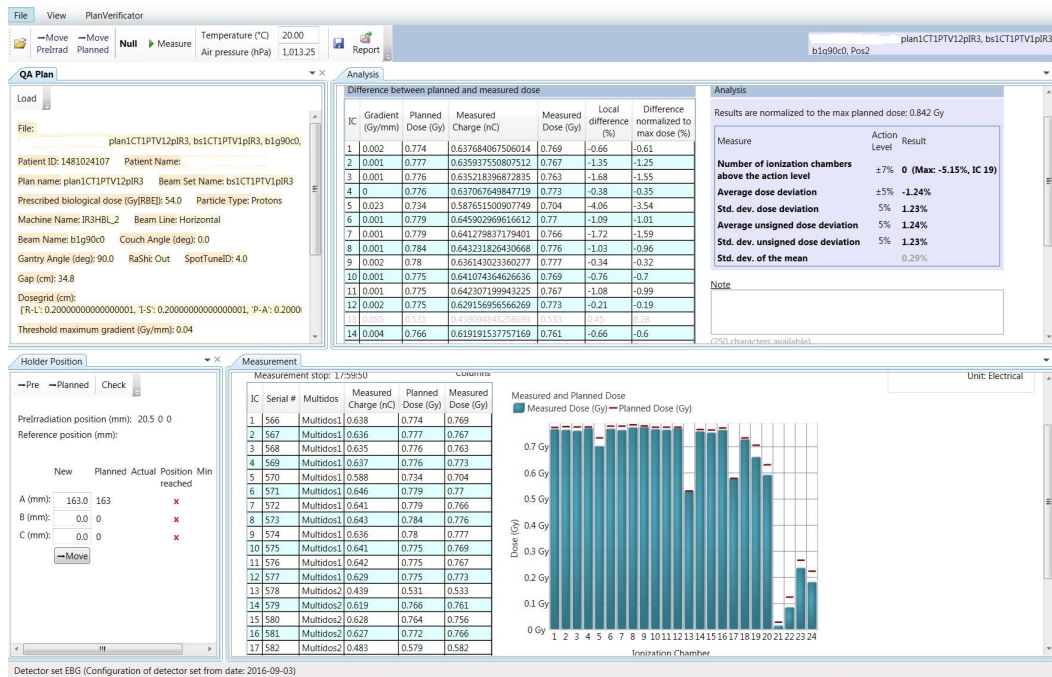


Figure 4.14: GUI of *Plan Verificator*. On the top-left part - QA plan information imported from the TPS, on the bottom-left part - “Holder position” tab to move the holder with the 24 PinPoint ionization chambers inside the water phantom, on the top-right part - “Measurement tab” to remotely control the two Multidos electrometers and acquire the measurements, on the bottom-right part - “Analysis tab” to compare measurement results with the planned dose and create a QA report for documentation.

script and an ad-hoc movement entered manually by the user. If the ionization chamber array is requested to move to a position that is outside the defined limits the Control Unit ignores the command and answers with an error. In this case the Plan Verificator displays an error dialog.

3. The *Measurement tab* displays the measured charge and the computed dose of each PinPoint chamber in a table. The latest ionization chamber readings are acquired and displayed every 5 seconds. A plot displays the latest measured dose values and the planned dose values (see figure 4.15). Moreover The *Measurement Setup* box on the right side of the tab displays which Multidos electrometers are used for the measurement and the settings of the electrometers. It is possible to execute measurements with only 12 ionization chambers. The Multidos settings are read from the configuration xml file. As safety measure, the settings cannot be changed in the user interface 4.15.
4. The *Analysis tab* shows the planned and measured dose values per ionization chamber and in addition, the local and the global relative differences between TPS and measurements. The latter are differences normalized to the maximum dose of the beam. The differences are computed every time when dose values change, i.e. after

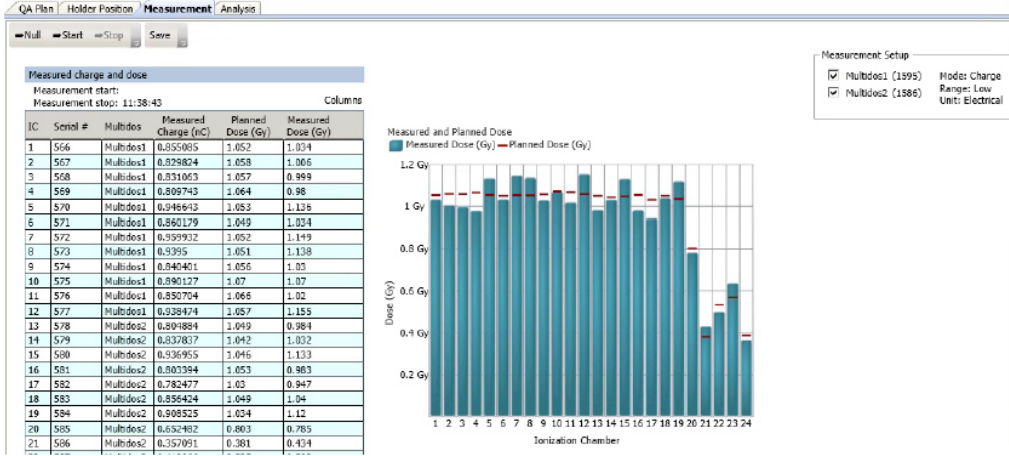


Figure 4.15: *Measurement tab* of the GUI *Plan Verificator*. The table with the SN of PinPoints, the measured charge, measured dose and the planned one is reported. On the top right- the *Measurement Setup* box containing the Multidos SN and the configurable settings of the electrometers.

a measurement update (5 seconds) has been received or when water temperature or air pressure are changed by the user. If the global difference for a PinPoint exceeds the action level threshold, set in the configuration file, the according display is highlighted with a red background. When the measurement is stopped four statistical measures are computed. The analysis is displayed next to the table with the differences (see figure 4.16). If the result of a measure exceeds the configured action level, it is highlighted. Ionization chambers can be deactivated automatically via the gradient threshold (0.04 Gy/mm) but also manually.

The agreement between the planned dose and the measured one is judged based on statistical measures of the overall global deviations. If N PinPoint chambers are positioned in a dose gradient $\leq 0.04 \text{ Gy/mm}$ five action levels are taken into account:

- the *signed mean* $\langle \Delta \rangle$ is the average value of the global relative differences defined as:

$$\langle \Delta \rangle = -5\% \leq \sum_i^N \frac{1}{N} \frac{D_{meas}^i - D_{TPS}^i}{D_{max}} \leq +5\% \quad (4.3)$$

- the *unsigned mean* $\langle \Delta_{ABS} \rangle$ is the average of the absolute value of global relative differences defined as:

$$\langle \Delta_{ABS} \rangle = \sum_i^N \frac{1}{N} \frac{|D_{meas}^i - D_{TPS}^i|}{D_{max}} \leq 5\% \quad (4.4)$$

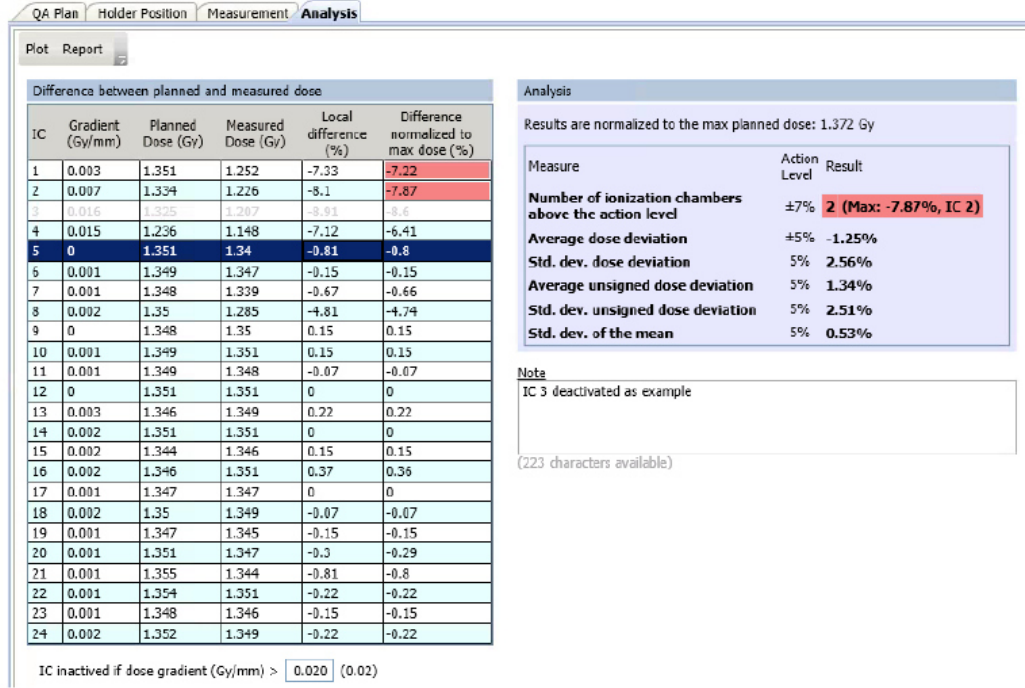


Figure 4.16: Analysis tab of the GUI Plan Verificator. For each PinPoint the local difference and the global difference between planned dose and measured one are computed and displayed. On the right the statistical measures with the respective action levels.

- the standard deviation s of global relative differences defined as:

$$s = \sqrt{\frac{1}{N-1} \sum_i^N (\Delta_i - \langle \Delta \rangle)^2} \leq 5\% \quad (4.5)$$

where $\Delta_i = \frac{D_{meas}^i - D_{TPS}^i}{D_{max}}$

- the standard deviation s_{ABS} of the absolute value of global relative differences defined as:

$$s_{ABS} = \sqrt{\frac{1}{N-1} \sum_i^N (\Delta_i - \langle \Delta_{ABS} \rangle)^2} \leq 5\% \quad (4.6)$$

where $\Delta_i = \frac{D_{meas}^i - D_{TPS}^i}{D_{max}}$

- for each pinpoint active $\Delta_i = -7\% \leq \frac{D_{meas}^i - D_{TPS}^i}{D_{max}} \leq +7\%$

Chambers in a higher gradient region $> 0.04 \text{ Gy/mm}$ are excluded from the analysis, since their response is not accurate enough due to the finite size of the detector sensitive volume and experimental set-up uncertainties. After acquiring the measurements the user can save the raw data into an excel file and also to generate a QA report in pdf format for documentation purpose. The QA pdf report contains :

- General information about the verification, like the name of the user and the date and time of the verification;
- the patient and beam data (as read from the “QA plan” file extracted via the script from the TPS);
- a measurement log including the name of the calibration file used, the used measurement settings, the holder position at which the measurement was executed, the serial numbers of the Multidos electrometers, temperature and pressure;
- plots of comparison planned dose with measured one and local and global relative differences;
- the results of the analysis including the information whether or not an action level was exceeded;
- the section for the date and signature of the QA report by the user.

4.3 Results

4.3.1 Ion recombination and polarization study in proton beams

Figure 4.17 displays the saturation curves for four PinPoint ICs at a depth of 36.8 mm (plateau region) and for four ICs at 86.8 mm (peak region) in water.

A significant asymmetry is visible between positive and negative polarities that was also noticed for the irradiation in a stable 6MV photon beam and already mentioned in the papers by Le Roy et al. [78] and Miller et al. [79]. In order to evaluate the ion recombination, the average values of the reading at the positive and negative polarities were calculated $\langle M(V) \rangle$. In the plot of figure 4.18 the $\langle 1/M(V) \rangle$ as function of the inverse square voltage $1/V^2$ for a sample of 6 PinPoint ICs placed at different depths in water is shown.

As shown in figure 4.18 the measurements deviate from the expected linear behavior already at 300 V where another process, that can play a role, is the charge multiplication. In order to assess the ion recombination correction factors k_s , at each voltage point the average of the positive and negative polarity has been calculated and the saturation current M_{sat} for each PinPoint has been linearly extrapolated taking into account only the 100V and 200V points. The k_s , at the operating voltage of +400V, has been computed as the ratio $\frac{M_{sat}}{M(400V)}$ where $M(400V)$ is the value interpolated at +400V (see figure 4.19).

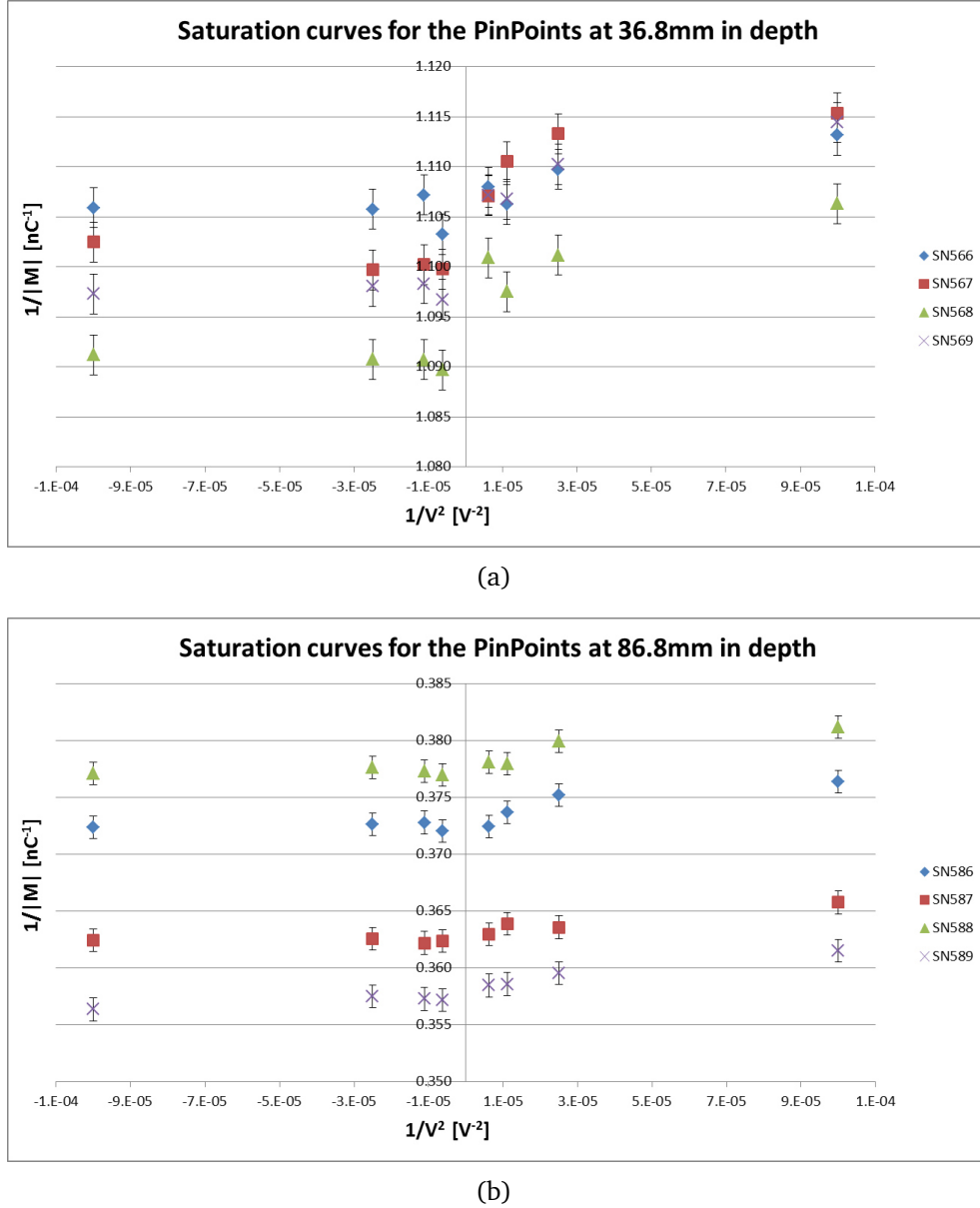


Figure 4.17: Saturation curves of eight Pinpoint ICs. (a) Four Pinpoint ICs are placed at a depth of 36.8mm (plateau region) and (b) four Pinpoint ICs at a depth of 86.8mm (peak region).

In figure 4.19 one can see that the standard two-voltage method applied at 100V and 400V slightly overestimates the ion recombination for the PinPoint chambers. Both methods show that ion recombination is negligible in a synchrotron based actively scanned proton beam with this beam intensity and degrader setting. Therefore, the k_s was set equal to unity for all the PinPoint chambers (see the calibration file in figure 4.12).

In order to assess the polarity correction factors k_{pol} for each PinPoint IC the approach recommended in TRS 398 [80] has been followed. However, as already shown in figure 4.17, the asymmetric behavior of the PinPoints response at positive and negative polarity affects the k_{pol} determination. The plot of figure 4.20 displays the k_{pol} at

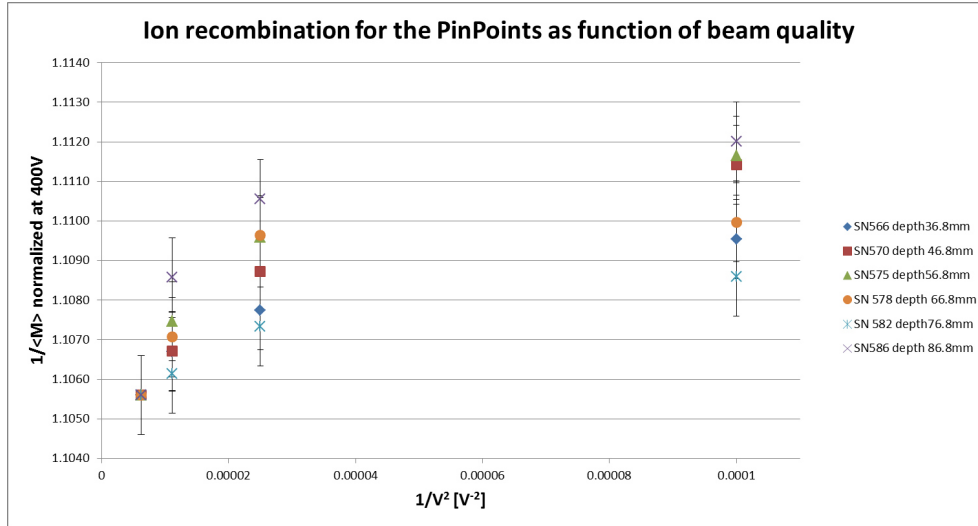


Figure 4.18: Ion recombination behavior for 6 PinPoint chambers at 400 V, 300 V, 200 V and 100 V. Data at each point is calculated as the average between the positive and negative polarity for the same voltage. Data at different depths are normalized to 400V.

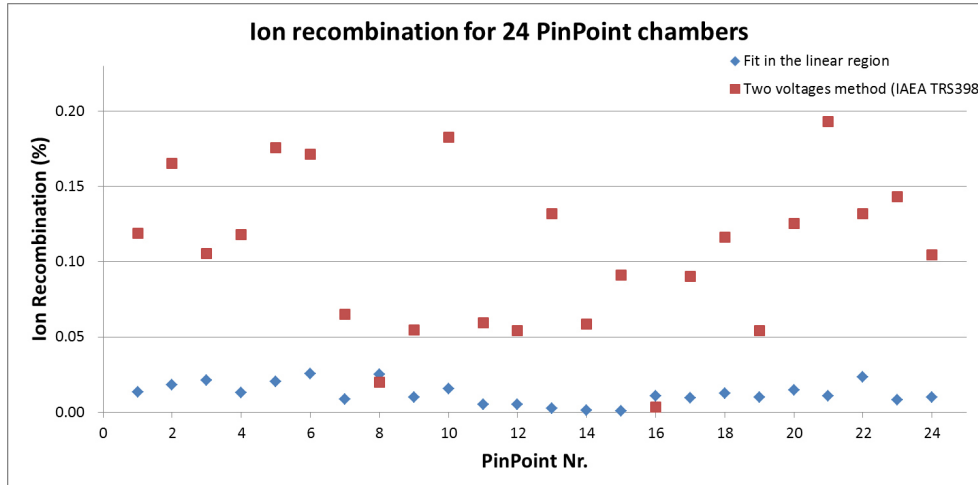


Figure 4.19: Ion recombination of 24 PinPoint ICs determined with a fit in the linear region and with the standard two voltage method proposed by TRS398 [80].

different voltages for the 24 PinPoint ionization chambers.

From the plot in figure 4.20 the increasing polarity correction factor at lower voltage reflects the significant asymmetry of the saturation curves of figure 4.17. Regarding the operating voltage $+400V$ the maximum polarity correction is 0.8% with an average of $1.003\% \pm 0.002\%$. Under the assumption that the polarity does not strongly depend on the beam quality then we correct neither the cross-calibration data (see chapter 4.3.2) nor the plan-verification measurements for polarity. However, we needed to verify this assumption with measurements in a SOBP. Therefore, we delivered a homogeneous physical dose of 1 Gy into a box of 8 cm side centered at a Water Equivalent Depth (WED) of 15 cm in the water phantom. A clinical degrader setting of 80% has been selected. The

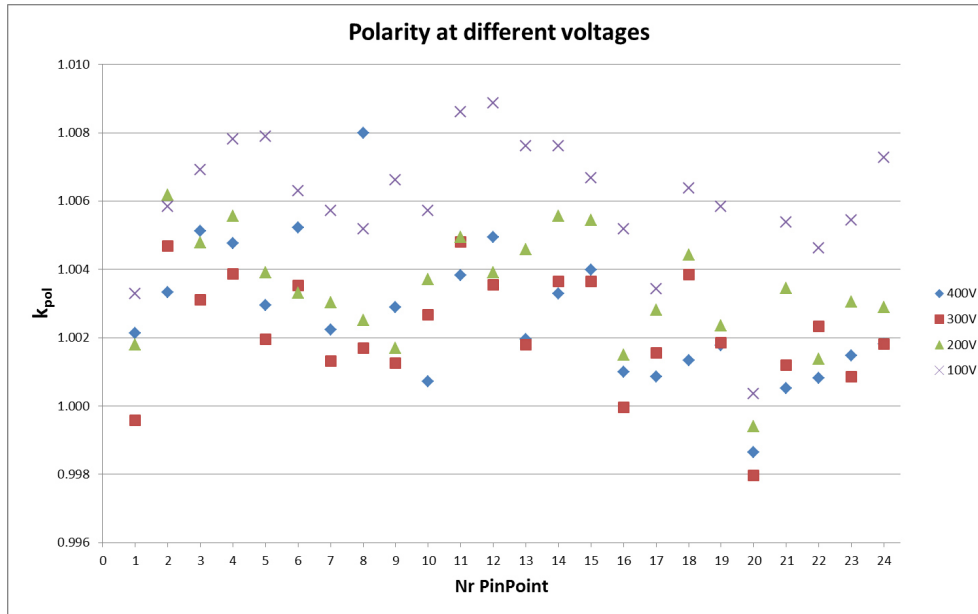


Figure 4.20: Polarity correction factors as function of the applied voltage for the 24 PinPoints.

24 PinPoints inserted inside the 3D detector Block were placed in the SOBP. Figure 4.21

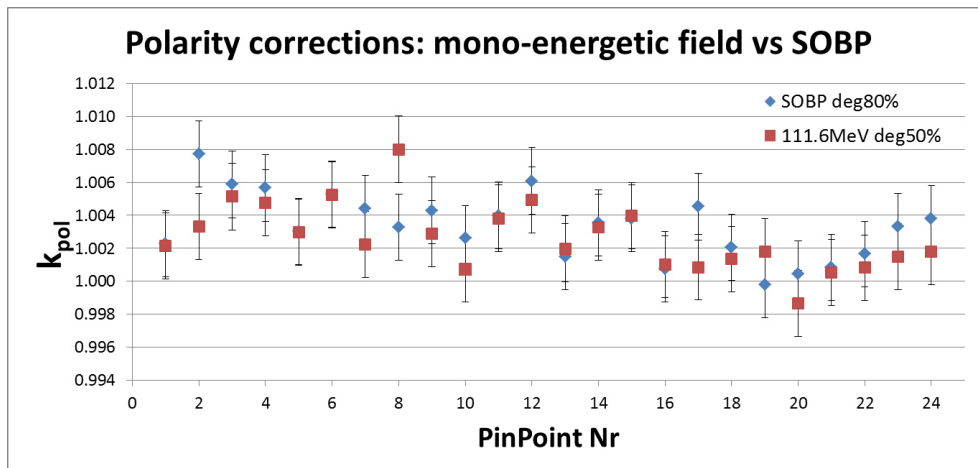


Figure 4.21: Polarity correction factors measured in the SOBP and in a mono-energetic field for the 24 PinPoints.

shows no significant differences between the polarity corrections in a mono-energetic beam and in SOBP. Therefore, no dependency of polarity on the beam quality has been measured and we can avoid to correct the plan-verification measurements for polarity effect. Therefore, the k_{pol} was set to unity for all the PinPoint chambers (see the calibration file in figure 4.12).

4.3.2 Cross-calibration of PinPoint ionization chambers in proton beam

The measurements with the three Farmer chambers were repeated four times during the 16 hour measurement session in order to check the stability of the beam delivery (see figure 4.5(a) for the setup). The table 4.1 shows a very good reproducibility of the Farmer measurements SN7777 and SN7778 normalized to the monitor chamber SN7779 with a standard deviation of the mean of 0.08%. In figure 4.22 the cross calibration

	Farmer SN7778 (Gy/nC)	Farmer SN7777 (Gy/nC)
1 st measurement	0.0557	0.0554
2 nd measurement	0.0557	0.0554
3 rd measurement	0.0556	0.0552
4 th measurement	0.0555	0.0554
Mean	0.0556	0.0553
stdev	0.0001	0.0001
stdom	0.09%	0.07%

Table 4.1: Measurements with the two calibrated Farmer chambers normalized to the monitor Farmer chamber. Four measurements have been acquired in total at the beginning, two intermediates and one at the end of the measurement session.

factors $N_{D,W,Q_{cross}}^{PinPoint}$ of the 26 Pinpoint chambers are displayed (beside the 24 PinPoint chambers dedicated for patient-specific QA we characterize other two spare PinPoint chambers). The error bars reported in the plot are estimated following the uncertainty budget calculation reported below in the text. In the table below the cross-calibration factors $N_{D,W,Q_{cross}}^{PinPoint}$ measured in a proton beam and the calibration factors $N_{D,W,Q_0}^{PinPoint}$ measured in ^{60}Co beam by PTW-Freiburg are shown. In TRS 398 [80] the beam quality correction factors k_{Q_{cross},Q_0} in a proton beam for the PinPoint type TM31015 are not reported, therefore a calculation has been done and details are reported below (theoretical value $k_{Q_{cross},Q_0}^{PinPoint} = 1.020 \pm 0.017$ for a residual range $R_{res} = 19g \times cm^{-2}$). Moreover, it is possible to extract the $k_{Q_{cross},Q_0}^{PinPoint}$ from the measurements as ratio of the calibration factors in a proton beam and in ^{60}Co beam:

$$k_{Q_{cross},Q_0}^{PinPoint} = \frac{N_{D,W,Q_{cross}}^{PinPoint}}{N_{D,W,Q_0}^{PinPoint}} \quad (4.7)$$

As it is shown in figure 4.23 the measured beam quality factors are in very good agreement with the computed $k_{Q_{cross},Q_0}^{PinPoint} = 1.020 \pm 0.017$ with a maximum deviation of 0.6% and a standard deviation of 0.24%.

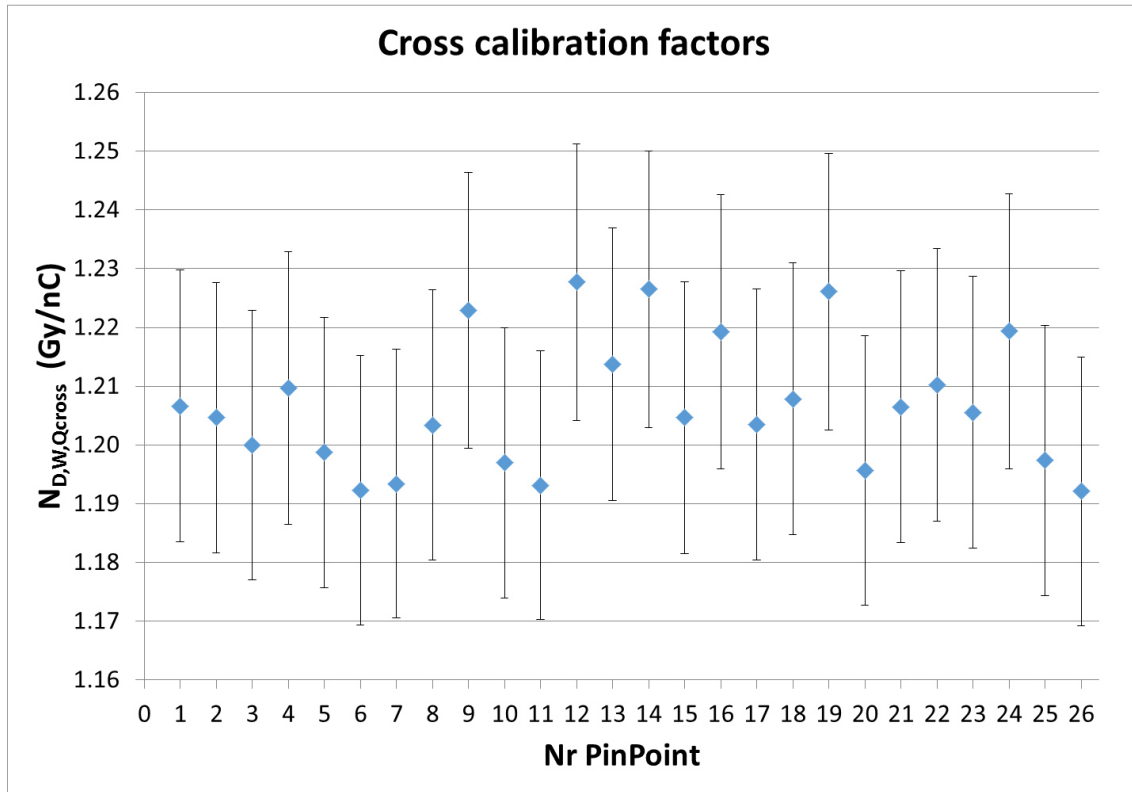
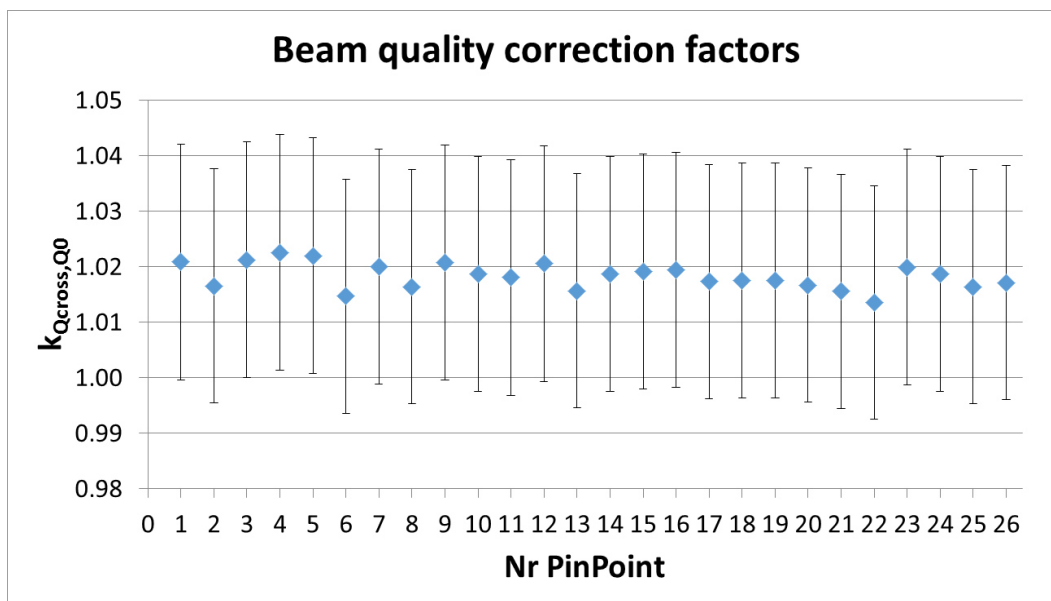


Figure 4.22: Cross calibration factors for the 26 PinPoint ICs.

Figure 4.23: Measured $k_{Q_{cross},Q_0}^{PinPoint}$ for the 26 PinPoint chambers.

Nr. PinPoint	SN	$N_{D,W,Q_{cross}}^{PinPoint}$ (Gy/nC)	$N_{D,W,Q_0}^{PinPoint}$ (Gy/nC) from PTW
1	566	1.207	1.182
2	567	1.205	1.185
3	568	1.200	1.175
4	569	1.210	1.183
5	570	1.199	1.173
6	571	1.192	1.175
7	572	1.193	1.17
8	573	1.203	1.184
9	574	1.223	1.198
10	575	1.197	1.175
11	576	1.193	1.172
12	577	1.228	1.203
13	578	1.214	1.195
14	579	1.227	1.204
15	580	1.205	1.182
16	581	1.219	1.196
17	582	1.204	1.183
18	583	1.208	1.187
19	584	1.226	1.205
20	585	1.196	1.176
21	586	1.207	1.188
22	587	1.210	1.194
23	588	1.206	1.182
24	589	1.219	1.197
25	512	1.197	1.178
26	513	1.192	1.172

Table 4.2: Cross-calibration factors in proton beam at the beam quality Q_{cross} and calibration factors provided by PTW-Freiburg in ^{60}Co beam.

Uncertainty budget.

The error bars shown in this chapter have been estimated with a detailed analysis of the uncertainties for each step of the measurement and are reported in the table below. The final combined standard uncertainty has the character of a standard deviation which

Farmer ionization chamber		
	Type A (%) k=1	Type B (%) k=1
M (reading)	0.1	
k_{pol}		0.16
k_s		0.13
$k_{T,P}$		0.15
N_{D,W,Q_0}^{Farmer}		0.7
k_{Q,Q_0}		1.7
z_{ref}		0.1
combined standard uncertainty $D_{w,Q}^{Farmer}$	1.86	
PinPoint TM31015		
M (reading)	0.2	
k_{pol}		0.2
k_s		0.1
$k_{T,P}$		0.15
z_{ref}		0.1
$D_{w,Q}^{Farmer}$	1.86	
combined standard uncertainty $N_{D,W,Q_{cross}}^{PinPoint}$	1.9	
combined standard uncertainty $k_{Q_{cross},Q_0}^{PinPoint}$	2.0	

Table 4.3: Uncertainties estimation for the cross calibration of PinPoint in proton beam.

corresponds to a confidence limit of 68%. As one can see from the table 4.3 the uncertainty in the cross-calibration is dominated by the uncertainty on the k_{Q,Q_0} of the Farmer chamber [80]. For the measurements of plan verification with PinPoint ionization chambers in the 3D block holder, beside the uncertainty on $N_{D,W,Q_{cross}}^{PinPoint}$, the uncertainty related to the absolute positioning of the chambers on the dose distribution needs to be added. The uncertainty on the positioning is a sum of different contributions:

Uncertainty	MP3-PL (mm)	MP3-P (mm)
Water phantom with in-room lasers	0.5	0.5
Scanning mechanism of the water phantom	0.3	0.2
Pinpoint chamber in the 3D detector block holder	0.5	0.5

Table 4.4: Uncertainties estimation on the positioning of the 24 PinPoint chambers in the MP3-P/PL water phantoms.

Overall we can estimate an uncertainty of the order of $\Delta \vec{r} = \pm 1$ mm for the chamber positioning for both water phantoms. The uncertainty in the positioning $\Delta \vec{r}$ shall be translated in an uncertainty in dose $\Delta \vec{D}$ depending on the local dose gradient G_D (Gy/mm) where the PinPoint chamber is positioned. In particular based on dose gradient the dose distribution can be subdivided in three different regions:

- homogeneous region - local dose gradient $G_D < 0.01$ (Gy/mm);
- low dose gradient region - local dose gradient 0.01 (Gy/mm) $< G_D < 0.04$ (Gy/mm);
- high dose gradient region - local dose gradient $G_D > 0.04$ (Gy/mm).

In a clinical situation one single portal deliver around ≈ 1 Gy physical dose therefore we can derive a different uncertainty depending on the positioning of the chamber.

Uncertainties on PSQA		
	Type A (%) k=1	Type B (%) k=1
M (reading)	0.5	
k_{pol}		0.2
k_s		0.1
$k_{T,P}$		0.15
$N_{D,W,Q_{cross}}^{PinPoint}$		1.9
$k_{Q,Q_{cross}}^{PinPoint}$		0.2
$\vec{r}(x, y, z)$ for $G_D < 0.01$ (Gy/mm)		$\delta < 1$
$\vec{r}(x, y, z)$ for 0.01 (Gy/mm) $< G_D < 0.04$ (Gy/mm)		$1 < \delta < 4$
$\vec{r}(x, y, z)$ for $G_D > 0.04$ (Gy/mm)		$\delta > 4$
homogeneous region $D_{w,Q}^{PinPoint}$	u = 2.2 %	
low dose gradient region $D_{w,Q}^{PinPoint}$	2.2% < u < 4.5%	
high dose gradient region $D_{w,Q}^{PinPoint}$	u > 4.5 %	

Table 4.5: Uncertainties estimation for PSQA.

From the table 4.5 it is evident that in homogenous dose regions the uncertainty is mainly dominated by the cross-calibration factor of the pinpoint $N_{D,W,Q_{cross}}^{PinPoint}$. Increasing the dose gradient the uncertainty in the positioning dominates the whole uncertainty budget. Measurements with PinPoints placed in a dose gradient $G_D > 0.04$ (Gy/mm) shall be evaluated considering a total uncertainty of more than 4.5%.

Theoretical calculation of k_{Q,Q_0} for PinPoint TM31015 ionization chamber in proton beam.

Under the condition that the Bragg-Gray cavity theory with fluence correction factors is valid, the k_{Q_p,Q_0} can be calculated as:

$$k_{Q_p,Q_0}^{PinPoint} = \frac{(s_{w,air})_p}{(s_{w,air})_{^{60}Co}} \times \frac{(W_{air})_p}{(W_{air})_{^{60}Co}} \times \frac{[p_{dis}p_{wall}p_{cav}p_{cel}]_p}{[p_{dis}p_{wall}p_{cav}p_{cel}]_{^{60}Co}} \quad (4.8)$$

In the table 4.6 the main information about the dimensions and the material of the chamber, extracted from the data sheet of the PinPoint TM31015, are reported.

Inner radius of cavity (mm)	1.45
Thickness sleeve of PMMA (mm)	0.57
Thickness wall of graphite (mm)	0.09
Mass density PMMA (g/cm^3)	1.19
Mass density graphite (g/cm^3)	1.84
Central electrode diameter (Aluminium) (mm)	0.3

Table 4.6: Dimensions and materials of the PinPoint TM31015

Following the Appendix B of TRS398 [80] the different factors of equation 4.8 have been computed. For the ^{60}Co calibration beam, the Spencer-Attix stopping-power ratios $s_{med,air}$, are taken from the calculations of Andreo [82, 83]. These calculations were performed by using the electron stopping-power data tabulated in the ICRU Report 37. The ratios of photon mass energy-absorption coefficients are taken from literature [84]. For protons the water to air stopping power ratios are taken from TRS398 [80]. In the table 4.7 the coefficients used in the calculation of equation 4.8 are reported:

	^{60}Co	Proton
$s_{w,air}$	1.133	$1.137 - 4.3 \times 10^{-5} \times R_{res} + 1.84 \times 10^{-2} / R_{res}$
$s_{PMMA,air}$	1.102	—
$s_{graphite,air}$	1.002	—
$\mu_{W,PMMA}$	1.03	—
$\mu_{W,graphite}$	1.113	—
$p_{dis}p_{wall}p_{cav}p_{cel}$	0.99025	1
W_{air}	33.97	34.23

Table 4.7: Coefficients used for the calculation of $k_{Q_p,Q_0}^{PinPoint}$.

Regarding the p_{cel} in ^{60}Co a value of 0.993 (reported in TRS398) shall be used for chambers with an aluminum central electrode of 1 mm diameter, essentially for a Farmer chamber. The electrode of the PinPoint TM31015 is smaller (0.3 mm in diameter) that is why we used the value 0.998 taken from the paper of Crop et al. [85]. The computed

value of $k_{Q_p, Q_0}^{PinPoint}$ as function of the residual range for the PinPoint TM31015 are reported in table 4.8 and in the plot of figure 4.24:

Beam Quality index	$R_{res} (g/cm^2)$	$(s_{w,air})_p$	$k_{Q_p, Q_0}^{PinPoint}$
	0.25	1.1443	1.028
	0.5	1.1407	1.024
	1	1.1388	1.023
	1.5	1.1382	1.022
	2	1.1378	1.022
	2.5	1.1376	1.022
	3	1.1375	1.022
	3.5	1.1374	1.022
	4	1.1373	1.021
	4.5	1.1372	1.021
	5	1.1372	1.021
	7.5	1.1369	1.021
	10	1.1368	1.021
	15	1.1365	1.021
	20	1.1362	1.020
	30	1.1358	1.020

Table 4.8: Computed $(s_{w,air})_p$ and $k_{Q_p, Q_0}^{PinPoint}$.

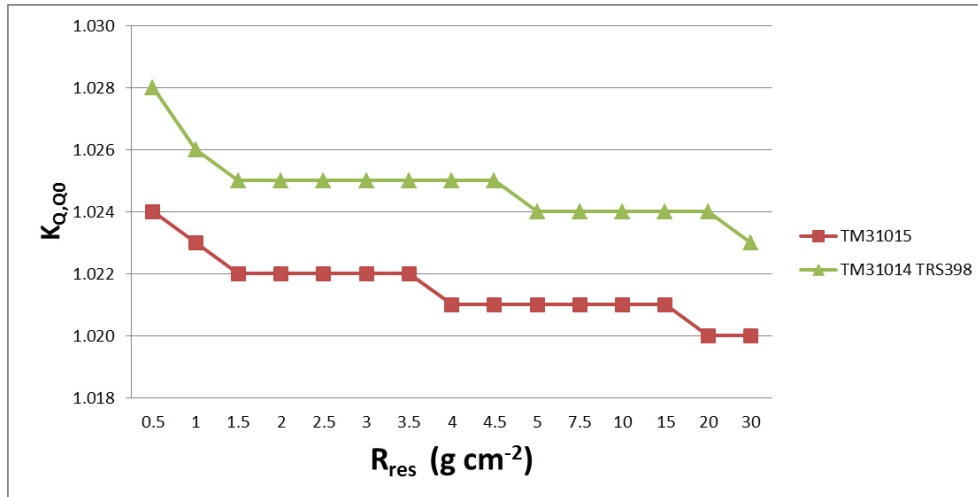


Figure 4.24: $k_{Q_p, Q_0}^{PinPoint}$ as function of the residual range for the PinPoint model TM31015 and the PinPoint model TM31014. The data for the PinPoint model TM31014 are tabulated in TRS 398 [80].

4.3.3 Application in clinical practice.

In order to fully implement the PSQA process in the clinical workflow, the software solution described in 4.2.2 was validated according to *IEC 62304:2006* related to Medical Device Software Lifecycle [86]. The validation of the software component is not included in this manuscript and we report here only some examples of the entire implemented workflow in the context of the first PSQA in active scanned proton beams at MedAustron. Before starting the patient plan verification procedure the plan has been reviewed and approved by a Radiation Oncologist (RO). As described in 4.2.2 the user needs to re-compute the dose in the virtual water phantom and extract the dose of the 24 PinPoints for different positions of each beam. In the initial phase of starting up of the facility two/three different holder positions for each beam of a composite patient plan are extracted via script. With the export of the dose information from the TPS in the “QA plan” files, the preparation of the plan QA is completed and the verification measurements can be executed (see section 4.2.2). For the execution of the PSQA measurements in order to speed up the setting up procedure a dedicated trolley was developed in-house for reproducible positioning the MP3-P water phantom on the robotic couch in the treatment room. Indeed, for both MP3-P/PL water phantoms the standard/commercial solution provided by PTW-Freiburg is set for the measurements with the *scanlift*. The *scanlift* supports the MP3-M phantom tank for height adjustment and also supplies water pumping. The carriage is provided with a mechanical support to accommodate the MP3-P/PL positioning device with three-point mounting for leveling. The MP3-P water phantom has been removed from the *scanlift* and fixed on the in-house developed trolley as shown in figure 4.25. In order to speed-up the setup procedure in-room, the water phantom is filled with water in the phantom lager and moved with the trolley to the IR. In the treatment room a dedicated workflow is implemented in the Record & Verify System (*RTSS* see chapter 2) to set up the MP3-P for measurements execution. A reproducible positioning of the MP3-P water phantom on the robotic couch is assured by two lock bars. The two lock bars are always placed at the same table top indices (H3-F3) and customized polyoxymethylene bars are mounted on their top. The two plastic bars have four plugs of cuneiform shapes which fit exactly on the four holes made in the metallic base plate on which the MP3-P is mounted. The user slides the trolley on the couch table top until the four holes in the metallic base plate match with the four cuneiform plugs of the two plastic bars placed in H3-F3. Then, the couch grabs the metallic base plate and the MP3-P water phantom. In the figure 4.26 the different steps of the workflow in order to position the MP3-P on the table top of the robotic couch are shown.

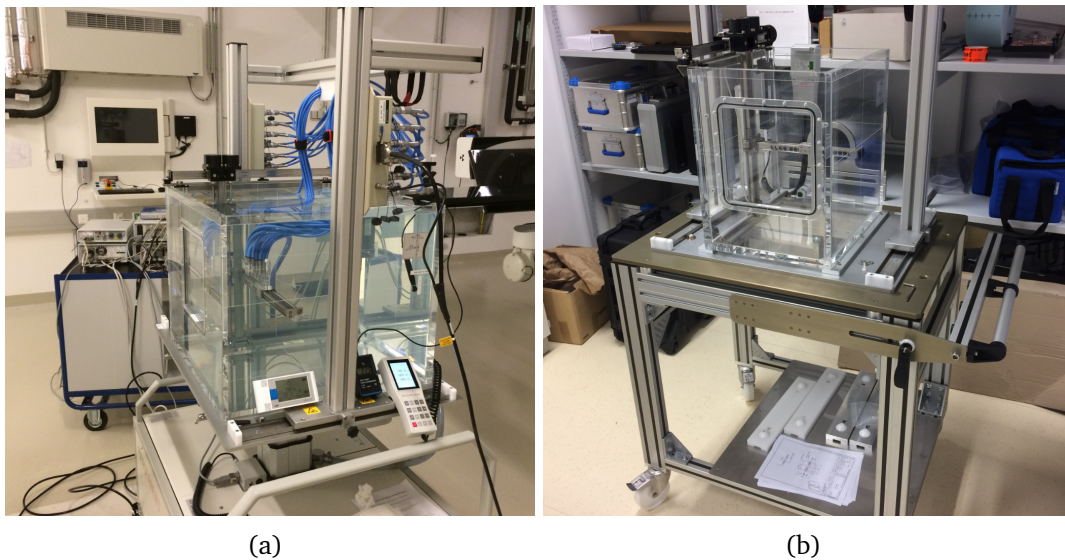


Figure 4.25: (a) Setup of the MP3-PL with PTW-Freiburg commercial solution scanlift at isocenter in IR1.
(b) MP3-P water phantom on the dedicated trolley.

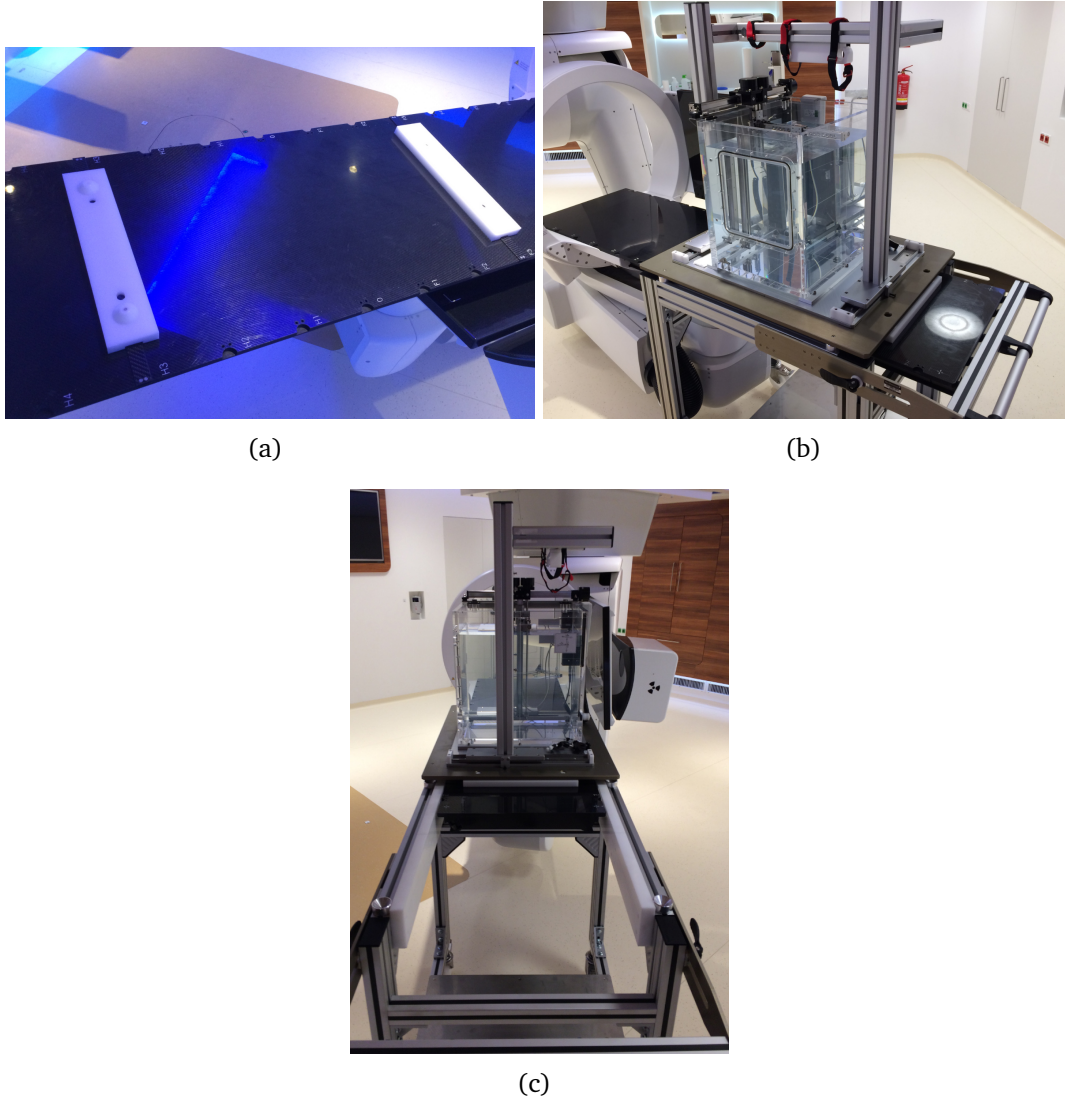


Figure 4.26: (a) Polyoxymethylene bars mounted in H3-F3 of the table top. (b) Trolley slides on the table top. (c) MP3-P positioned on the couch and the trolley is removed.

As already described in section 4.2.2 the PSQA can be performed at different *gaps* which are patient specific. In particular four gaps are implemented in the workflow. Therefore after grabbing the MP3-P water phantom, the robotic couch is moved to the selected position depending on chosen air gap. A tracking camera system to correct for any table top bending due to the MP3-P water phantom weight is active for a reproducible positioning. The figure 4.27 shows the setup of the MP3-P with the robotic couch for two different *gaps*.

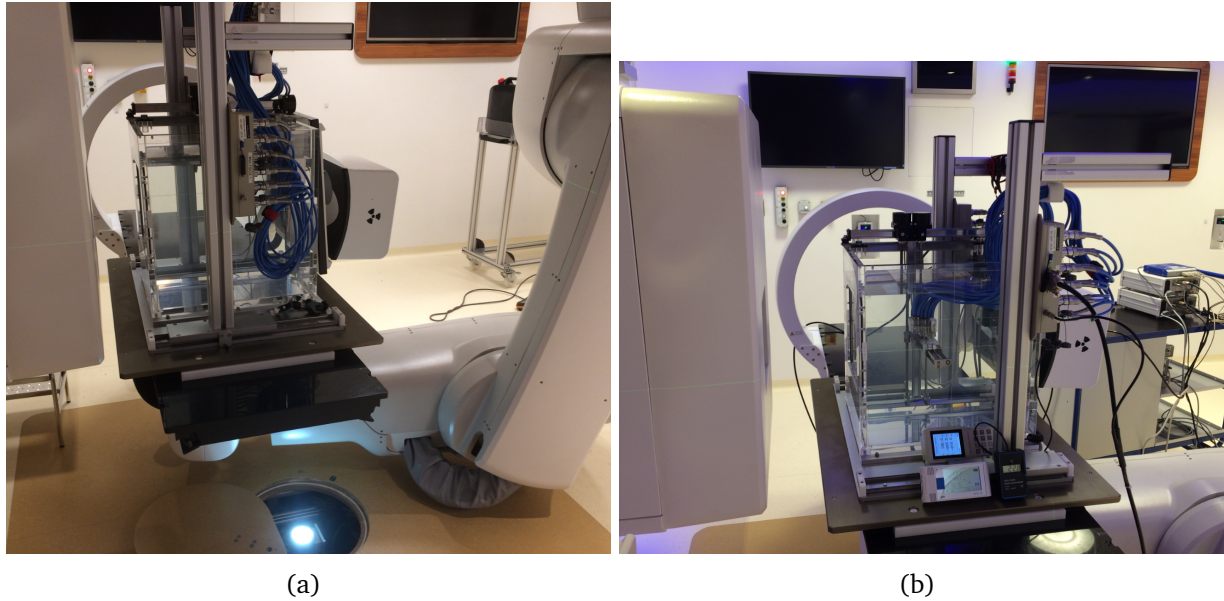


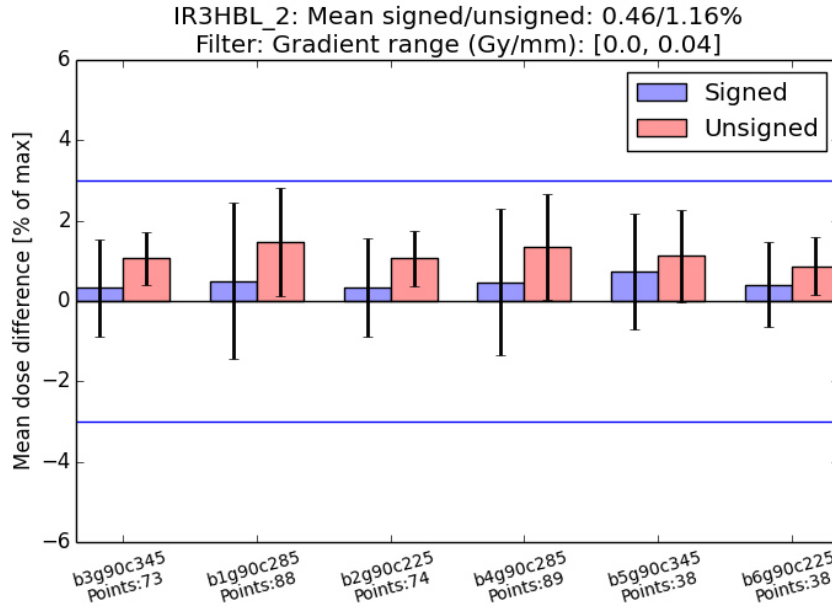
Figure 4.27: (a) The MP3-P set up at $gap = 14.8$ cm. Tracking camera is active in order to correct for the bending. (b) The MP3-P set up at $gap = 24.8$ cm. The electronics, thermometer and barometer are also visible.

After positioning the water phantom at a predefined gap, the 24 PinPoint chambers placed on the *3D detector block* holder are aligned following an ad-hoc procedure inside the MP3-P water phantom. Before starting the patient specific verification measurements the 24 PinPoint chambers are pre-irradiated with a minimum dose of ≈ 8 Gy in order to settle the readings. For each beam of a composite plan the dose is measured in two/three holder positions. For each position a QA report in pdf is created by *Plan Verificator* software and stored in the OIS for documentation purpose. Two examples of patients treated at MedAustron with protons are reported here: a meningioma of base of skull and a prostate patient. Before starting the treatment the PSQA was performed. Three Beam-Sets have been planned for the meningioma patient:

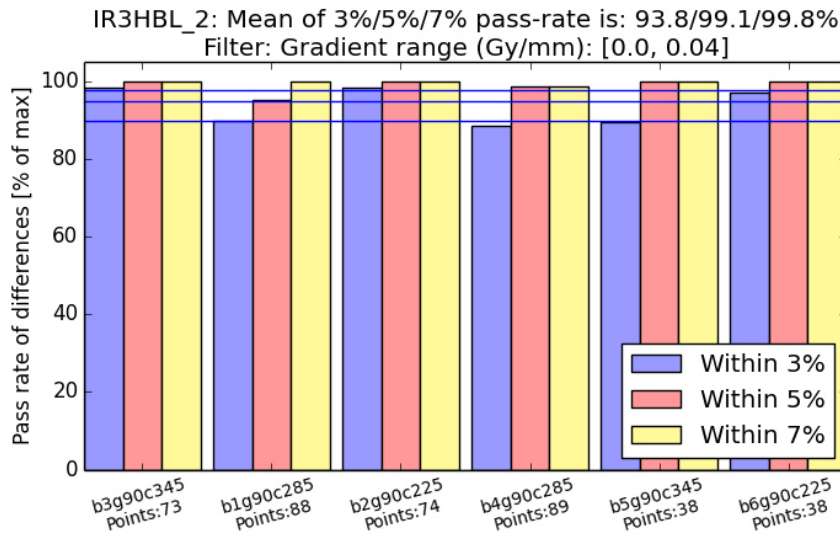
- BeamSet_1, composed of two beams, delivers 25.2 Gy (RBE) in 14 fractions;
- BeamSet_2, composed of two beams, delivers 25.2 Gy (RBE) in 14 fractions and it is alternated day-by-day with BeamSet_1 in order to smooth the uncertainties, deliver a more robust plan and reduce toxicities;
- BeamSet_3, composed of two beams, delivers 3.6 Gy (RBE) in 2 fractions as sequential boost to a smaller target volume.

The plots in figure 4.28 show the mean signed and unsigned of global relative differences (see eq. 4.3 and 4.4) for each beam of the composite plan and the pass-rates of global relative differences at 3%, 5% and 7%. The error bars are the overall standard deviations

calculated as reported in eq. 4.5. Only the PinPoint chambers positioned in a gradient region $G_D < 0.04$ Gy/mm are taken into account in the analysis. More than 400 readings



(a)



(b)

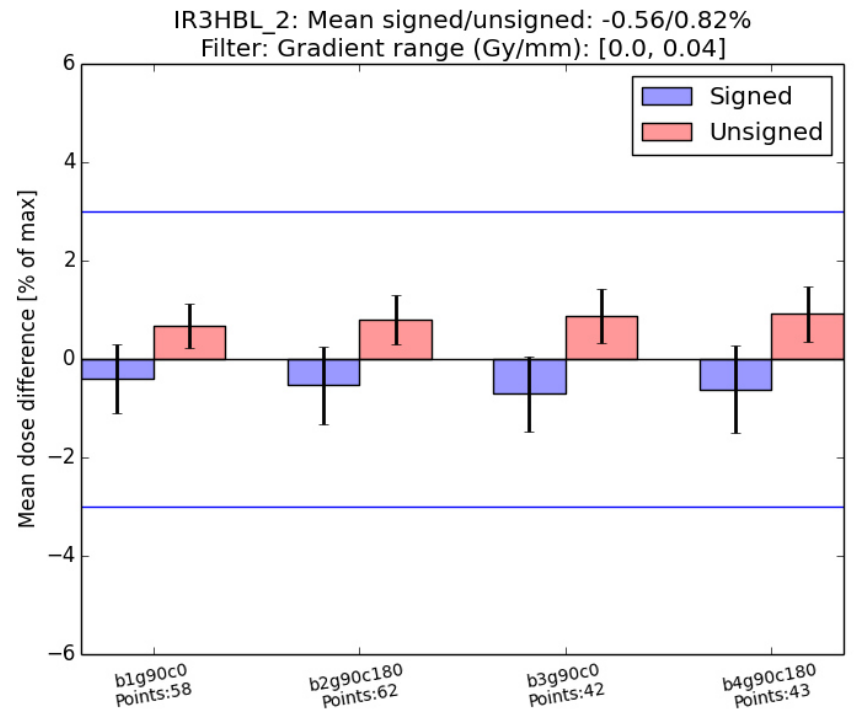
Figure 4.28: (a) The mean of the global relative differences for all the six beams composing the Meningioma patient plan. (b) The pass-rates of global relative differences at 3%, 5% and 7% deviations.

are part of the analysis. The patient planned dose is in a very good agreement with the measurements for all the six beams. The average value of the signed mean is 0.46 ± 0.06 % and the average value of the unsigned mean is 1.16 ± 0.09 % for all the six beams. Overall the 400 measured points included in the analysis 99.1% are within 5% deviation.

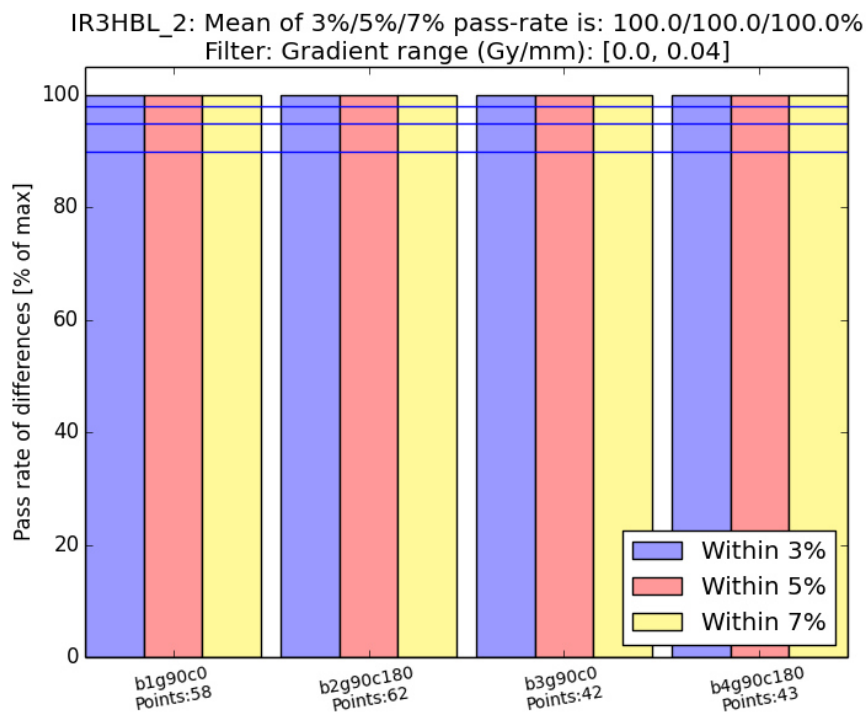
Two Beam-Sets have been planned for the prostate patient:

- BeamSet_1, composed of two opposite beams, delivers 54 Gy (RBE) in 30 fractions to the prostate gland and seminal vesicles;
- BeamSet_2, composed of two opposite beams, delivers 25.2 Gy (RBE) in 14 fractions as sequential boost to the prostate gland.

The plots in figure 4.29 show the mean signed and unsigned of global relative differences (see eq. 4.3 and 4.4) for each beam of the composite plan and the pass-rates of global relative differences at 3%, 5% and 7% deviations. The error bars are the overall standard deviations calculated as reported in eq. 4.5. Only the PinPoint chambers positioned in a gradient region $G_D < 0.04$ Gy/mm are taken into account in the analysis as for the meningioma case. More than 200 readings were taken into account in the analysis. The patient planned dose is in a very good agreement with the measurements for all the four beams. The average value of the signed mean is -0.56 ± 0.07 % and the average value of the unsigned mean is 0.82 ± 0.05 % for all the six beams. Overall the 200 measured points included in the analysis 100% are within 3% deviation.



(a)



(b)

Figure 4.29: (a) The mean of the global relative differences for all the six beams composing the prostate patient plan. (b) The pass-rates of global relative differences at 3%, 5% and 7% deviations.

4.4 Discussion and Conclusion.

In December 2016 patient treatments started in the HBL with protons at MedAustron. The very high degree of complexity related to this advanced technology places new demands on Quality Assurance (QA) programs. Therefore, patient-specific plan verification is a highly recommended dosimetric procedure within the QA program. This type of measurement is performed as a final check of the accuracy of the dose distribution calculated by the TPS and actually delivered to the individual patient. Moreover, the correct deliverability of the treatment plan through the whole treatment chain needs to be verified for each patient before starting the treatment. At MedAustron, a commercial equipment based on the use of 24 PinPoint ionization chambers (PTW, Freiburg, Germany) has been acquired. The system originally was developed at GSI [77] and nowadays, used at Heidelberg Ion-Beam Therapy Center (HIT, Germany) and the Centro Nazionale di Adroterapia Oncologica (CNAO, Italy) [87]. However, no specific software to support this equipment and interface it to the RayStation TPS is commercially available. This chapter reported on the full characterization of the 24 PinPoint ionization chambers in proton beams and the description of an innovative, in-house developed software that makes the treatment plan verification workflow more efficient, reliable and faster.

In order to check the integrity of the 24 PinPoint ionization chambers, X-ray images of all chambers were acquired in a Imaging Ring system [46]. No bending of central electrode was visually detected for each PinPoint. To monitor the stability of PinPoint chambers response to ionizing radiation check source reading in ^{90}Sr was performed. This test is part of the QA program for the 24 PinPoint chambers. For each PinPoint chamber a maximum deviation of 0.5 % has been observed over one year. Due to the small volume of the PinPoint chambers in comparison to the Farmer a pre-irradiation larger than 10 Gy was needed to settle the chambers. Regarding the investigation of the PinPoint chambers in proton beams no data in literature have been found. A study in photon beams is already reported by Le Roy et al. [78] and Miller et al. [79] but it is based on the characterization of few small volume chambers. In this study a more systematic investigation over 24 PinPoint chambers was conducted in proton beam with high consistency of the results in comparison to the available literature data in photon beams.

Regarding ion recombination behavior in proton beams, a significant asymmetry between positive and negative polarities was found for the whole set of 24 PinPoint chambers. Similar asymmetry was also noticed for the irradiation in a stable 6 MV photon beam but not reported in this manuscript. This behavior for small volume chambers

was already reported in literature [78, 79] but based on measurements of one single chamber in photon beam. Those asymmetric behaviors are due to the leakage currents generated in the stems which are added or subtracted depending on the polarity applied (overestimation at positive polarities and underestimation at negative polarities). This prevents the calculation of the ion recombination correction factors using the standard two-voltage method [80] which overestimates recombination. Moreover, at 300 V charge multiplication processes start to play a role in small volume ionization chambers due to the high electric field strength close to the central electrode. This process may occur in the chamber volume when the electric field strength close to the central electrode becomes too high. No clear dependence of the saturation behavior as function of the depth (beam quality) can be detected from the data. Unfortunately the Multidos electrometers, controlling 12 PinPoints at once, do not allow reducing the operating voltage to lower values than +400 V. Same behavior has been observed for the measurements carried out in the 6 MV photon beam but not reported in this thesis. Ion recombination was found negligible in scanning proton beams (within 0.03%) and therefore the k_s corrections were set to unity. Polarity is a more complex phenomenon for small volume PinPoint chambers. No data in proton beams are available in literature. Variability of the polarity corrections within 0.8% from chamber to chamber were observed in proton beams. An investigation of polarity at different beam quality (R_{res}) was performed but no significant dependency of polarity corrections with the R_{res} was detected. As consequence, we correct neither the cross-calibration data (see section 4.3.2) nor the plan-verification measurements for polarity ($k_{pol} = 1$ for all the 24 PinPoint chambers).

A cross-calibration of the whole set of PinPoints in the proton beam was carried out. In the TRS-398 [80] the beam quality factors $k_{Q_p, Q_0}^{PinPoint}$ as function of R_{res} in proton beam are not reported for the PinPoint chamber (TM31015). So a full calculation of $k_{Q_p, Q_0}^{PinPoint}$ was done for the first time and details are described in this manuscript. The measured beam quality factors $k_{Q_p, Q_0}^{PinPoint}$ are in very good agreement with the computed $k_{Q_p, Q_0}^{PinPoint} = 1.020 \pm 0.017$ based on TRS-398 [80] with a maximum deviation of 0.6% and a standard deviation of 0.24%.

The interface between the RayStation TPS and the PTW-equipment has been developed based on a script plug-in “MA_QA_v3_scale_factor.py” running on the “QA preparation” module of RayStation and the “Plan Verificator” software. The entire software component has been verified and validated according to the international standard IEC 62304 [86]. An in-house dedicated trolley has been developed and implemented into the clinical workflow to set up the MP3-P water phantom on the robotic couch. This solution makes the equipment setup by a factor of 2 faster. Moreover, it is necessary for

the measurements in IR4 (room equipped with the proton Gantry) in which, due to the rolling-floor, the setup with the water phantom mounted on the scan lift (PTW, Freiburg) is not a suitable option. The implemented workflow chain (software and hardware components) for plan verification was extensively used for the Beam Delivery System (BDS) and TPS commissioning in IR3. Moreover, the results of a prostate and a skull base tumor are reported in this manuscript as representatives of the first PSQA measurements with protons at MedAustron. The higher modulation scanning pattern for the meningioma case in comparison to the prostate is reflected by the better results of PSQA found for the prostate case.

Commercially available programs for verification measurements with 2D ionization chamber arrays extract the planned dose information from TPS data in DICOM format and can thus process data from every TPS. The *Plan Verificator* relies on the script plug-in “*MA_QA_v3_scale_factor.py*” for the RayStation TPS to extract the required data. In this context a further development of *Plan Verificator* could be the integration of a DICOM module in order to make it independent of the specific TPS used. Moreover, an analysis tool to compute the 3D gamma index [88] for the 24 measured points could be integrated in the “Analysis tab” of the *Plan Verificator* and the results documented in the QA pdf report. In this way the software could become a suitable commercial solution not only for other Light Ion Beam Therapy facilities but also extended to the more complex photon techniques. Trend lines of PSQA results grouped in different anatomical sites (head, H&N, prostate), different modalities (protons and carbon ions), planning techniques (SFO and MFO), use of the passive elements (range shifter for protons and ripple filters for carbon ions) in the planning will be evaluated in order to re-assess tolerances and action levels based on the gained experience at MedAustron.

CHAPTER 5

DOSIMETRIC END-TO-END TEST PROCEDURES IN SCANNED PROTON BEAM THERAPY.

5.1 Introduction.

The introduction of new radiation treatment technology into clinical practice requires implementation of several major steps that generally includes acceptance testing and medical commissioning of beam delivery system, patient alignment system, medical software, treatment panning system and all needed auxiliary systems. The increased complexity related to implementation of active scanning light ion beam delivery into clinical practice places new demands on QA programs as well as on new instrumentation and detectors for beam characterization and beam delivery checks. The control of the dose delivered with a scanned beam needs quite a different approach to dosimetry and dose delivery verification than used for passive scattering methods. Therefore, a simultaneous determination of absorbed dose at many points is required by the dynamic delivery mode. This requirement is also important for the realization of the final step in medical commissioning of LIBT facility and it shall be performed before beginning patient treatments. Follow this action a full simulation of the workflow shall be performed that includes every step of the treatment process. The most efficient solution for this simulation is to use a so-called end-to-end test. The purpose of this test is not just to validate beam line monitor calibration but to confirm that the entire logistic chain of radiation treatment starting from imaging, treatment planning, monitor calibration, patient positioning and verification and beam delivery is efficient and leads to the desired results with sufficient accuracy. End-to-end tests are usually performed in the anthropomorphic phantoms that allow to place detectors in different locations and thus perform simultaneous verification

of accuracy in delivery of planned absorbed dose at many points. Since the first patients selected for treatments at MedAustron included patients with brain tumors and patients with prostate cancer, the developed end-to-end tests were focused on these anatomical sites. The successful completion of end-to-end tests is a prerequisite of starting clinical activity at a LIBT facility. In addition, in this work, we want to show the opportunity to extend the possible applications of the Alanine Electron Paramagnetic Resonance (EPR) dosimetry in light ion beams [40, 89, 90].

5.2 Materials and methods

5.2.1 Phantoms preparation.

In order to perform the end-to-end test at MedAustron different phantoms have been designed. In particular one homogeneous phantom and two anthropomorphic phantoms (head and pelvis) have been customized to comply with MedAustron specifications for end-to-end test. The homogeneous polystyrene phantom (named in this work “**homogeneous phantom**”) was already used to test the feasibility of an audit procedure with protons and carbon ions at the HIT facility, as reported in literature [90]. The mass density of the material is close to water. The phantom was designed in such a way that its dimensions represent a head phantom. Seven plates, each with a size of $20 \times 20 \times 3$ cm³, were stacked together to form a 21 cm long phantom 5.1. The phantom can host

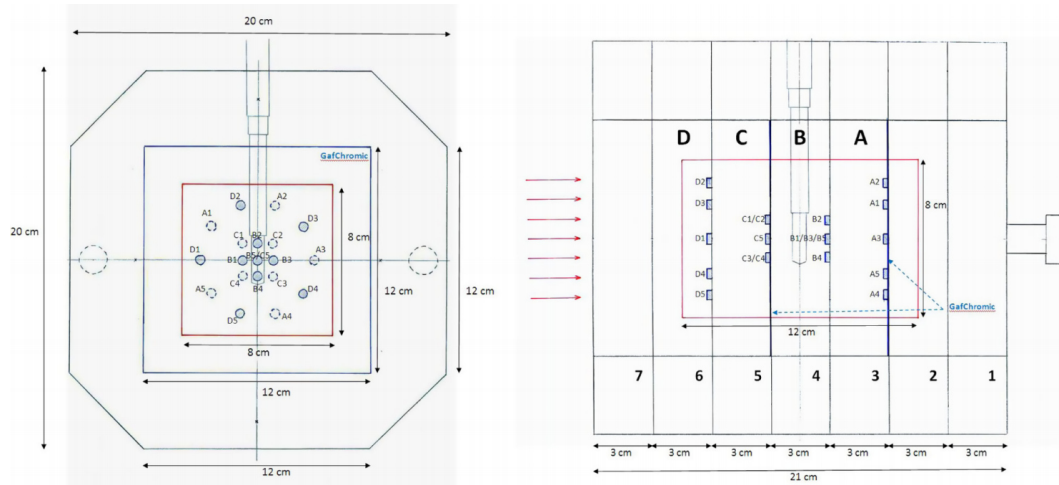


Figure 5.1: Drawings of the phantom design in transversal (on the left) and sagittal view (on the right). Red lines inside the phantom represent the target volume and the arrows outside show the beam direction. A Farmer chamber indicates the additional plate which can be placed in the centre of the phantom (instead of plate B holding 5 Alanine pellets) [90].

a set of 20 Alanine pellets; the specific pattern of detector placement allows good cov-

erage of the target volume and minimises the shadowing of the detectors in the Beam's Eye View. Four plates, labelled A, B, C and D, hold these dosimeters. In addition to the cavities for the Alanine pellets, plates A and C were manufactured with a depression to place a radiochromic film just upon the pellets and perpendicular to the beam direction. In this way the “quenching” effect on the film is minimized. Another plate with the same dimensions was prepared to allocate different kind of inserts for ionisation chambers (Farmer 0.6 cm³ TM30013, Semiflex 0.3 cm³ TM31013, Semiflex 0.125 cm³ TM31010). White marking lines on the surface of the assembled phantom allow an accurate positioning during the alignment process for the planning CT and the alignment on the robotic couch with in-room lasers in the Irradiation Room.

The Proton Therapy Dosimetry head phantom model 731 HN (named in this work “**Head phantom**”) used at the PSI facility [91] has been customized in collaboration with CIRS (Tissue Simulation & Phantom Technology). The head phantom is close to the real patient head geometry and reproducing different tissue heterogeneities. It allows the verification of correct dose delivery for complicated geometries due to the entrance surface and irregular internal structures such as bone (see figure 5.2). This phantom

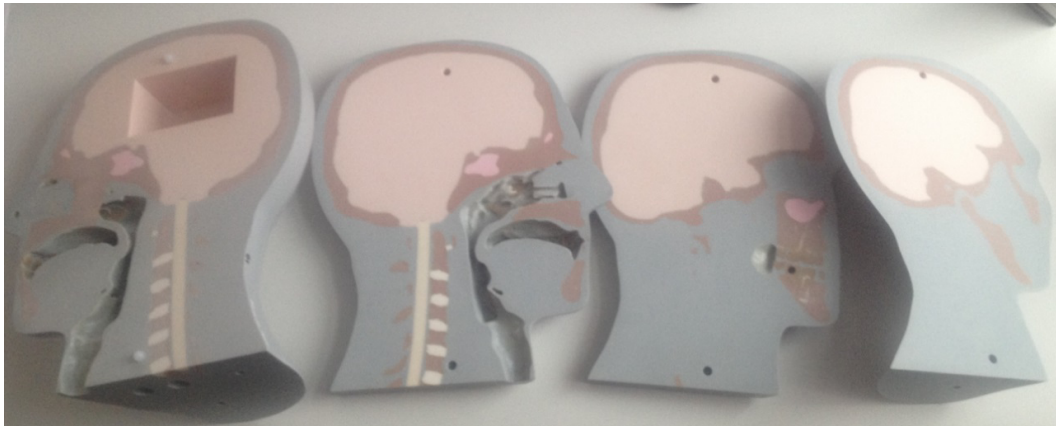


Figure 5.2: The MedAustron customized head phantom and the four different slices in which the phantom is subdivided. In the half bulk part of the head on the left the customized cavity to allocate different types of detectors is visible.

is already customized for particle therapy and presents the advantage (with respect the most common Alderson phantom) to be cut in the sagittal direction avoiding air gaps between the different slices along the beam axis direction through which particles could “tunnel”. The phantom is sectioned in 20 mm increments for three EBT film locations in the cranio-caudal direction starting from the approximate center of the sagittal plane. The main advantage of this sectioning for film placement is the possibility to evaluate the effect of heterogeneities in the head-neck region on the dose distribution. The disadvantage is that the available commercial version of the phantom is limited to film dosimetry only. To overcome this disadvantage and allow absolute measurements with ion cham-

bers and Alanine detectors, we customized the phantom in collaboration with CIRS. In particular, in the half bulk part of the head a rectangular brain cavity has been created for placement of interchangeable dosimetry inserts. Cubic brain tissue equivalent inserts of the size $5 \times 5 \times 8 \text{ cm}^3$ were customized to allow measurements with Alanine pellets and different ionization chambers (two Farmer TM30013, two Semiflex 0.125 cm^3 TM31010 and two PinPoint 0.03 cm^3 TM31015) 5.3. As the phantom was designed, one Alanine

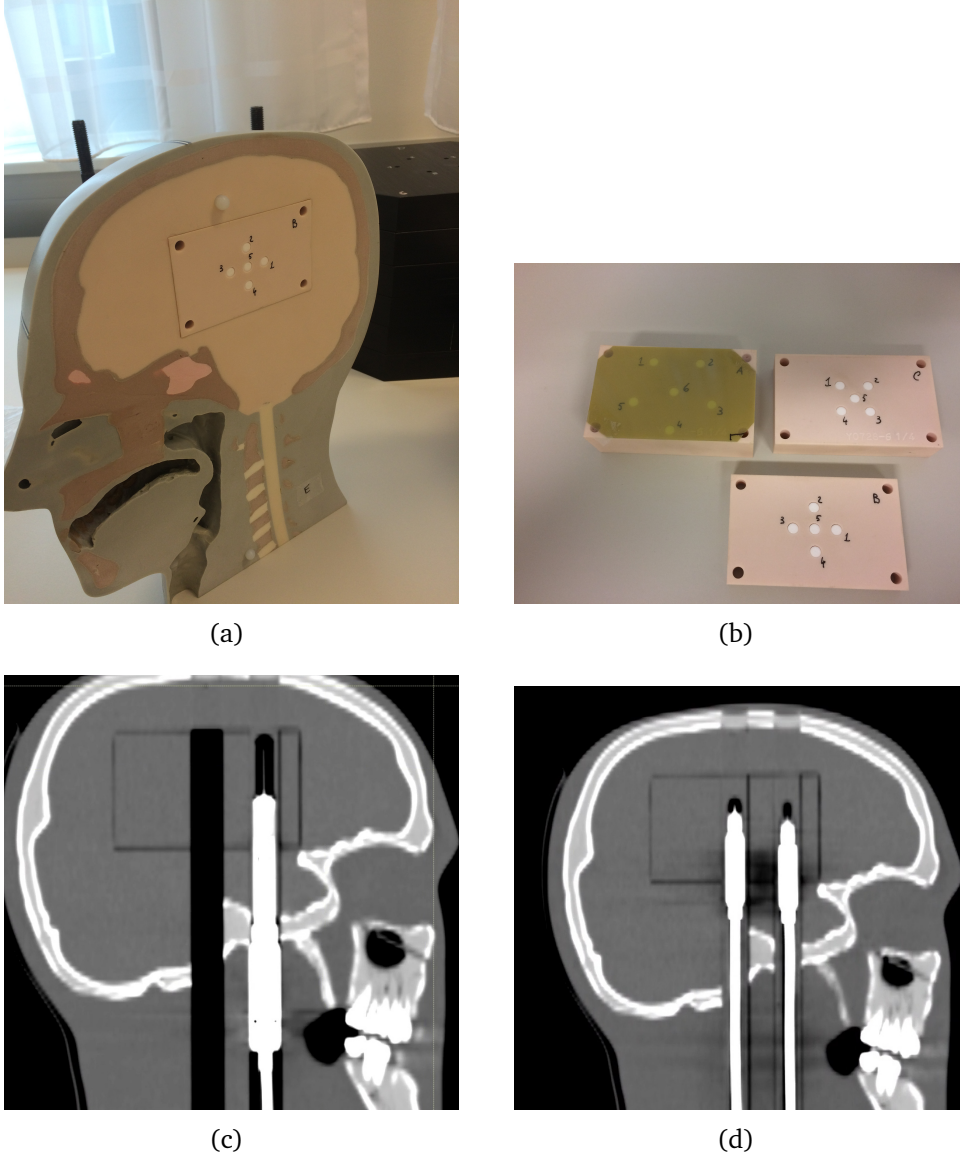


Figure 5.3: (a) Half bulk part of the head with Alanine pellets inside. (b) Alanine pellets places inside the cubic brain tissue equivalent insert. Each cubic insert is subdivided in three slices. (c) CT scan of the head with one Farmer chamber placed in the brain cavity. The second cavity is not filled in this image but during measurements it was filled either with a second chamber or substitute material. (d) CT scan of the head with a Semiflex and a Pinpoint chamber in the brain cavity.

pellet is at the same position of the effective point of measurement of the ionization chamber. The brain cubic insert for Alanine pellets has been subdivided in three slices

to allocate up to 22 Alanine pellets for single plan irradiation (see figure 5.3(b)). The pattern of detector placement was customized in order to have good coverage of the target volume and minimize the shadowing of the detectors in the Beam's Eye View. All the ionization chambers have customized brain tissue equivalent sleeve to ensure that the effective point of measurement is at the center of the brain cubic insert in superior-inferior direction. Moreover, the corresponding WET in proton beam was measured for each phantom material component and the values were compared with the values computed by the TPS.

The CIRS Dynamic Pelvis Phantom (named in this work '**pelvis phantom**') is designed for end-to-end analysis of image acquisition, planning and dose delivery in image-guided radiation therapy. However, we have purchased only the static part of the phantom without any 2D motions. The integration of the motion control can be done in the future upgrade. In the phantom there is the possibility to allocate different water-equivalent interchangeable cubes with side of 6.35cm . The cubes accommodate ionization chambers, films or Alanine pellets. The film stack cubic insert accommodates 13 radiochromic films with 4 mm spacing. The cube features grooves that enable easy orientation of film scans in the TPS. The ionization chamber cubes are designed for target acquisition and quantitative dose measurements. Each cube allows to outline a 50 cc prostate gland volume and is machined to receive the chamber at the center of the prostate target volume. In particular, a Farmer TM30013, a Semiflex 0.125cm^3 TM31010 and a PinPoint 0.03cm^3 TM31015 chamber can be placed inside the phantom (see figure 5.5). For the Alanine pellet measurements (nominal dimensions of Alanine pellets are 5 mm diameter and 2.3 mm thickness) water-equivalent cubic inserts have been sliced in three parts and can allocate up to 22 Alanine pellets for single plan irradiation (see figure 5.4). The pattern of detector placement was customized in order to have a good

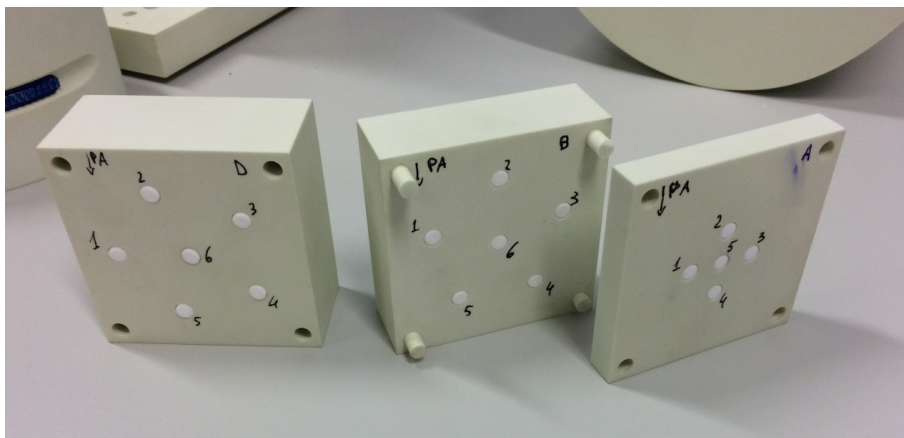


Figure 5.4: Alanine pellets placement inside the cubic tissue-equivalent insert to modeling prostate volume. Each cubic insert is subdivided in three slices.

coverage of the target volume and minimize the shadowing of the detectors in the Beam's Eye View.

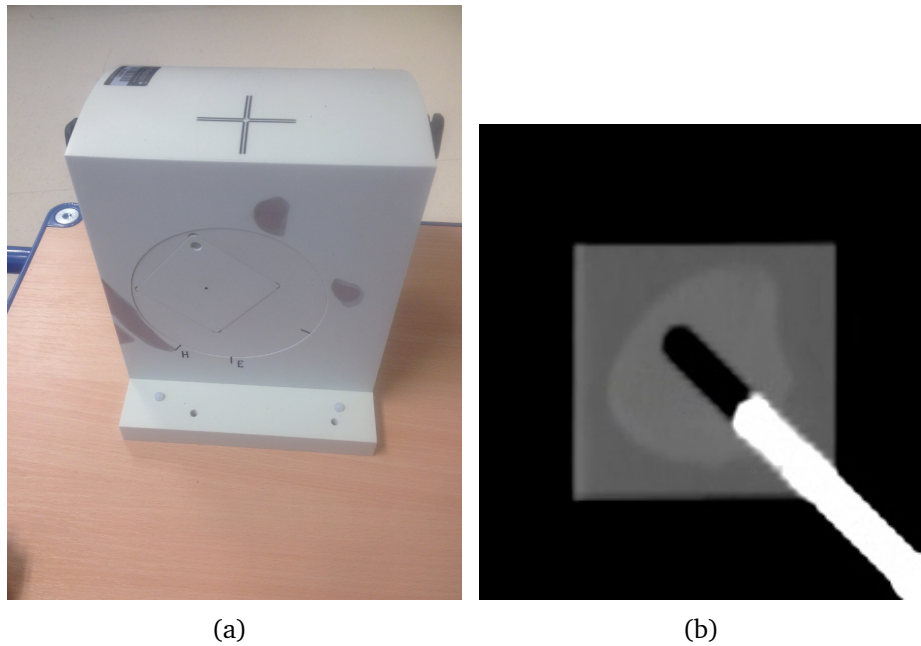


Figure 5.5: (a) Half bulk part of the pelvis phantom with the rotating cylinder to simulate the prostate movement and the cube insert for the chambers. (b) CT scan of the cubic insert with the Farmer chamber inside.

5.2.2 Alanine Electron Paramagnetic Resonance (EPR) dosimetry

The choice of a dosimetric technique for a specific dose distribution measurement is a challenge in light ion beam therapy. In the following paragraphs we will focus on the features of Alanine Electron Paramagnetic Resonance (EPR) dosimetry for end-to-end test available at MedAustron and its implementation in the clinical practice.

The EPR dosimetry provides information about the absorbed dose to a medium through measuring the concentration of the free radicals produced by ionizing radiation. Up to now, there are three internationally recognized applications of the EPR technique: Alanine/EPR dosimetry [92–96] (see figure 5.6), the procedures for identification of irradiated foodstuffs containing cellulose and bone material. Since the early works by Box and Freund in 1959 [97], Bradshaw *et al.* 1962 [98], Rotlab and Simmons in 1963 [99], the development of Alanine/EPR dosimetry has reached a level that makes it competitive with classical methods of dosimetry such as thermoluminescence, chemical and ionization methods, at least at the higher dose range (above 10 Gy). Thus, they opened the possibility to use Alanine as a dosimetric material.

The EPR signal from powders of Alanine irradiated with photon beams consists of

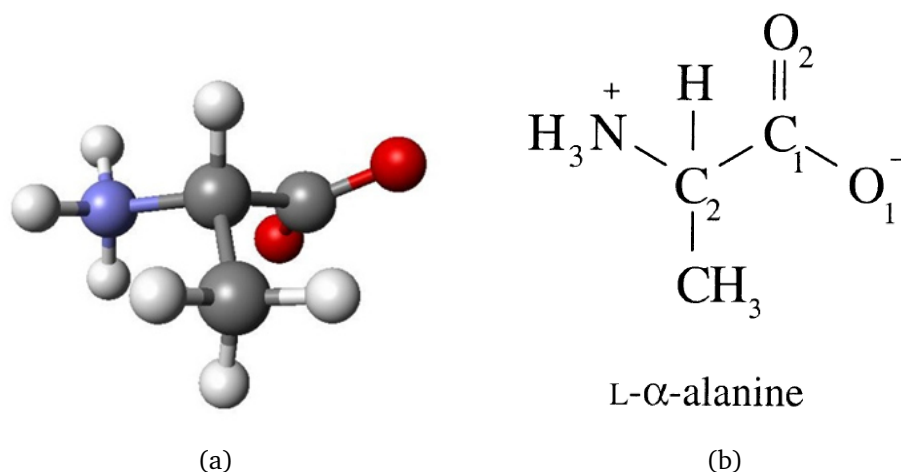


Figure 5.6: 3D and schematic representation of the Alanine molecule.

components from at least three different radical species. The main radical species is the product denoted **R1** (also known as **SAR**, *Stable Alanine Radical*), formed by deamination from a protonated Alanine radical anion. The second species, **R2**, is stabilized by net hydrogen abstraction from the central carbon atom, while **R3** is probably another oxidation product. The first two radical species **R1** and **R2** appear to occur in comparable relative amounts (55-60 and 30-35%, respectively), whereas the third species is a minority species (5-10%) (see figure 5.7).

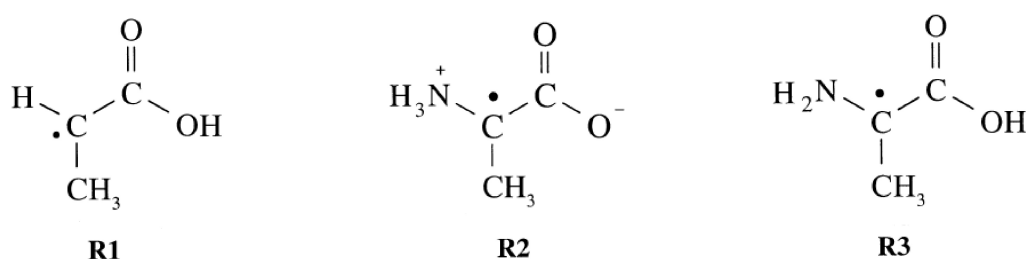


Figure 5.7: Radical species forms in Alanine after photon irradiation.

Up to now, Alanine can be considered to be the best studied material in the field of Solid State/EPR dosimetry and at present it is formally accepted by PTB (Physikalisch-Technische Bundesanstalt, Germany), NIST (National Institute for Standards and Technology, USA) [95] and NPL (National Physical Laboratory, UK) [96] as a secondary reference and transfer dosimeter for high (industrial) dose irradiation. The Alanine/EPR dosimetry has many advantages such as:

- the linearity of the EPR response in a wide range of doses - from 10 up to 5×10^4 Gy;

- high stability of the radiation induced free radicals (mainly **R1** and **R2**) under normal conditions;
- long shelf life and low background signal;
- tissue-equivalence *i.e.* simulation of biological tissue in terms of radiation absorption properties (for low-LET radiation);
- ruggedness and ease of handling;
- no sample treatment before EPR measurement of the signal;
- low cost for individual dosimeter samples;
- absence of dose rate dependence of response;
- sufficiently small size for use in mapping radiation dose distribution;
- much more simplified modeling as compared to TLD detectors and this facilitate the use of Alanine detectors also for particle beams [100].

One of the disadvantages is the sensitivity (at least 10 Gy is needed for a 0.5% reproducibility). The Alanine detectors in form of pellets are provided for the current study by NPL. The detectors have a nominal diameter of 5.0 mm and a thickness of about 2.3 mm. The NPL Alanine detectors consist of 90.9% by weight L- α -Alanine and 9.1% high



Figure 5.8: Example of Alanine pellets.

melting point paraffin wax. On average the weight of the pellets is 54.5 mg and varies in the order of ± 1 mg. The average density is around 1.22 g/cm³ actually close to PMMA (density 1.19 g/cm³), but varies slightly from batch to batch. Thus in PMMA phantoms

the perturbation can be regarded relatively small. In water equivalent phantoms, like the phantoms used in this work, the perturbation will be larger. The pellets have to be handled with care; they are reasonably solid thanks to 10% of paraffin binder but still they can break or be crushed quite easily. The temperature during irradiation influences the response. At normal room temperatures, the variation is about 0.14% per °C so an accuracy of better than 0.5 °C in temperature measurement should be aimed for. Since plastic phantoms may have a small thermal diffusivity they were left in the treatment room for 8 hours before the irradiation packed with Alanine pellets. Moreover, there is a risk of cross contamination among pellets. Indeed, small grains of Alanine could remain in the hole accommodating the pellet be irradiated multiple times and then stick to a subsequent pellet contaminating the signal of that pellet. Therefore, the holes were always cleaned up carefully with a dry tissue or cotton bud after each change of pellets in a cubic insert. The pellets were provided by NPL in a bulk with a series of numbered bags. The pellets were handled with care with a vacuum-tweezer and after irradiation stored individually in each bag and all the bags were sent together to NPL for the read-out (see picture 5.9). We carefully recorded the NPL's pellet numbers connected to the positioning of the pellet in the irradiation area. NPL supplied both irradiated and non-irradiated



Figure 5.9: (a) Handling of the Alanine pellets with a dedicated vacuum tweezers. (b) Numbered bags containing individually irradiated Alanine pellets. In the picture also the control dosimeters encapsulated in a Delrin container are shown.

control dosimeters, which were stored and transported with the pellets at all times. The dosimeters were conditioned at 55% relative humidity for ten weeks prior to use in order to reduce post-irradiation fading. After each irradiation the pellets were shipped to the NPL in block of 40 pellets, where they were evaluated following the standard procedure [101].

5.2.3 Corrections for Alanine pellet dose response.

Background

As we underlined in section 1.5.2, unlike ionization chambers, the dose response of solid state detectors like films or Alanine (as well as the surviving fraction of exposed biological cells) depends explicitly on the charge, the fluence and the energy E of the particles which constitute the mixed radiation field. Hence, the *Relative Effectiveness* (RE, symbol η) for these kind of detectors must be computed ([100, 102]). In this work the iso-response definition similar to the RBE definition has been adopted (see equation 1.17). Many models aim at describing the efficiency of detectors when exposed to heavy charged particles:

- Microdosimetric Models;
- Amorphous Track Models (or Track Structure Models).

Amorphous track models are based on three main assumptions:

- the energy deposition around a particle track can be described by a continuous, averaged radial dose profile $D_r(r; E; Z)$. The stochastic processes of secondary electron emission is neglected;
- the detector responds locally in the same manner to energy deposited by secondary electrons, regardless of their origin;
- convolution of low-LET dose response and radial dose distribution RDD yields the absorbed dose response to heavy ion irradiation.

Averaging over many particle tracks of an average dose distribution around a single particle track is assumed. Figure 5.10 (a) shows one history of Monte Carlo simulation of a single ^{12}C traversing water and figure 5.10 (b) shows the radial dose distribution (RDD) $D_r(r; E; Z)$ for the same ^{12}C averaged over many particle histories. The first approach to the track structure model was developed by Butts and Katz in 1967 [103] and the model was first designed for explaining the RBE behavior of enzymes and viruses. In target theory a system is considered to consist of sensitive, spherical, active elements, also called targets. These elements need to be activated by a “hit” which describes a single event with sufficient energy transfer to change the state of the element. Once activated, the element will stay in this mode, regardless if it is hit multiple times afterward. Some detectors are “multi-hit detectors”, which means, a sensitive element needs multiple hits in

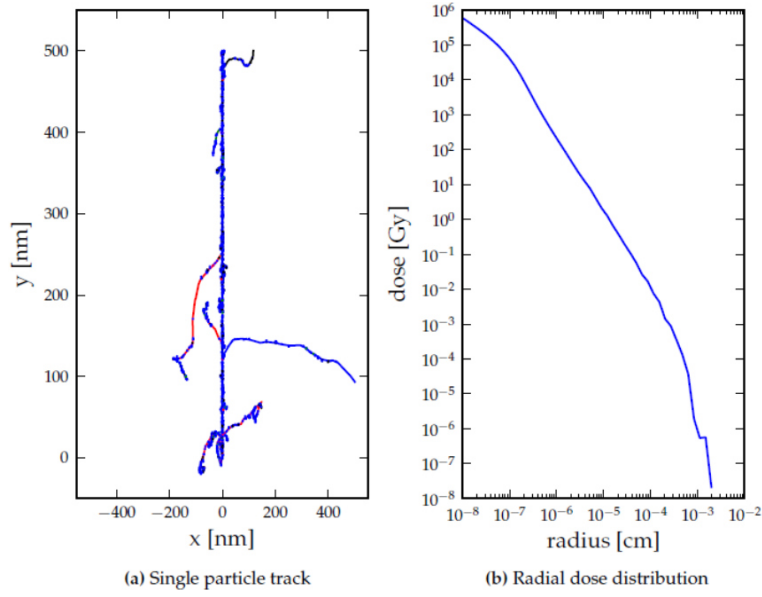


Figure 5.10: (a) Single ion track of a $100\text{MeV/u } ^{12}\text{C}$ ion in water. (b) The corresponding radial dose distribution (M. Kraemer et al. [28]). .

order to get activated. Because the hits are independently distributed the law describing the probability of a target being hit is a Poisson distribution. The probability P of exactly n hits with $\bar{N}$, the average number of affected targets which depend on the applied dose, is given by:

$$P(n) = \frac{\bar{N}^n e^{-\bar{N}}}{n!} \quad (5.1)$$

If a target required n hits to be activated, targets with $n - 1$ hits or less are not affected. If N_0 is the total number of targets then the fraction of affected targets can be expressed in function of the sum over all targets receiving less than n hits:

$$\frac{N}{N_0} = 1 - e^{-\bar{N}} \sum_{i=0}^{n-1} \frac{\bar{N}^i}{i!} \quad (5.2)$$

Considering a one-hit detector exposed to gamma radiation, where the elements on average experience $\bar{N}$ hits, the probability P_1 for an activation of one element is:

$$P_1(\bar{N}) = 1 - e^{-\bar{N}} \quad (5.3)$$

The dose response for single hit detector can be expressed in terms of the dose that is $\bar{N} = D / D_{37}$ where D_{37} is the dose at which $\approx 63\%$ of the saturation signal is reached and where all elements on average experience 1 hit. The Alanine EPR detector is a good example of a one-hit detector. J. W. Hansen and K. J. Olsen adapted the track-structure model for one-hit detectors to Alanine dosimeters [89]. The model is different from

the Katz' model because it adopts a different radial dose distribution $D_r(r; E; Z)$. In particular the assumption is valid that the integral of the RDD should be identical with the stopping power which is not the case in the Katz model. The difference between the LET and the integral of the RDD around the track is added to the top of the central core part [100]:

$$D_r(r) = \begin{cases} D_{core} & \text{if } r < a_0 \\ D(r) & \text{if } a_0 \leq r \leq r_{max} \\ 0 & \text{if } r > r_{max} \end{cases} .$$

with D_{core} chosen in such a way that:

$$D_{core} = \frac{1}{\varrho} \left(\frac{dE}{dx} \right) - 2\pi \int_{a_0}^{r_{max}} r D(r) dr \quad (5.4)$$

The r_{max} is the maximum radius of the ion track which depends on the maximum energy of the secondary electrons produced. Regarding the NPL Alanine pellets the dose response curve at Low-LET radiation (^{60}Co) is reported in figure 5.11 (b). From the figure the one-hit detector behavior of Alanine dosimeters is clear with the characteristic D_{37} resulting from the fit is 63.1 kGy. To compute the $RE(E, Z)$ as function of energy and ion species, the RDD in Alanine (figure 5.11(a)) is folded with the Alanine dose response at low-LET radiation (^{60}Co) (figure 5.11(b)). Figure 5.11(c) shows the computed $RE(E, Z)$ of Alanine EPR detectors for different incident ions as function of Energy [104].

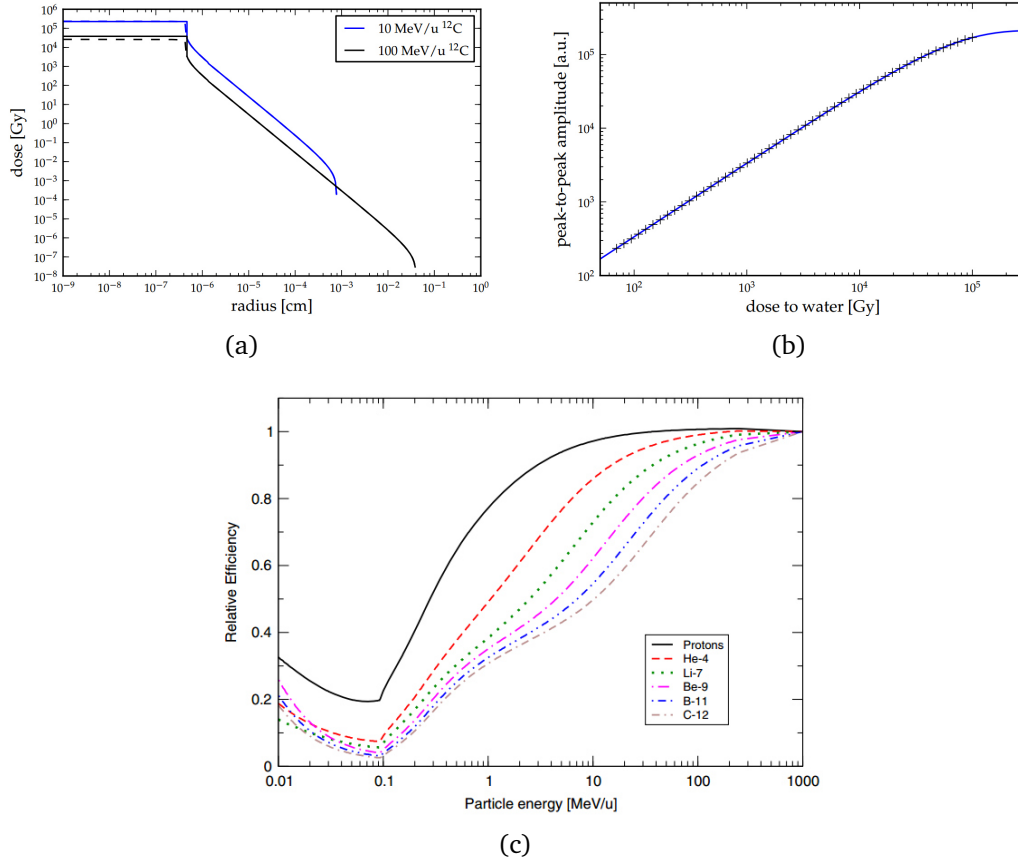


Figure 5.11: (a) RDD as a function of the distance from the particle track for carbon ions at two different energies in Alanine, showing the constant core part and the penumbra of the RDD. (b) Amplitude of Alanine EPR Signal as function of the absorbed dose to water for ^{60}Co . In black the experimental points, in blue the fit. (c) $RE(E, Z)$ of Alanine dosimeters as function of the ion's energy. At high energy all the RE tend to unity [104].

Implementation of corrections for alanine pellet dose response in the Monte Carlo algorithm of RayStation TPS.

In order to perform dosimetry with Alanine pellets in a proton beam one needs to know $\bar{\eta}_{aln}$ at each detector position in the mixed field. In collaboration with RaySearch laboratories we implemented the correction for the “quenching” of Alanine pellet directly into the MC platform available in an evaluation/research version of RayStation (RS v4.99). In case that track overlapping effects on a microscopic level can be neglected, the relative effectiveness $\bar{\eta}_{aln}$ for the field can be calculated from the binned energy spectra of all ions in the radiation field as a dose weighted average of the relative effectiveness [105], $\eta_{aln}(E_j, Z_i)$, of each ion type:

$$\bar{\eta}_{aln} = \frac{\sum_{i=1}^{n_{proj}} \sum_{j=1}^{n_{bin}} \phi(E_j, Z_i) \times \left(\frac{S_{col}}{\rho}\right)_{aln}(E_j, Z_i) \times \eta_{aln}(E_j, Z_i)}{\sum_{i=1}^{n_{proj}} \sum_{j=1}^{n_{bin}} \phi(E_j, Z_i) \times \left(\frac{S_{col}}{\rho}\right)_{aln}(E_j, Z_i)} \quad (5.5)$$

where the $\eta_{aln}(E_j, Z_i)$ is the relative effectiveness of the particle Z_i with the energy E_j (as shown in the figure 5.11(c)), $\phi(E_j, Z_i)$ is the fluence, $\left(\frac{S_{col}}{\rho}\right)_{aln}(E_j, Z_i)$ is the mass collision stopping power in pure alanine and the denominator of the equation is the total dose deposited in the volume of interest. ICRU report 49 [13] presents the most comprehensive set of stopping power data available in literature. However, no stopping power data for pure alanine and alanine pellet composition are reported. In previous work Onori et al. [106] calculated stopping powers for alanine by applying Bragg’s rule to the stopping powers of the elementary constituents (see equation 1.7). However, this rule does not account for the influence of chemical binding effects. Based on the report published by NPL in 2006 [107] the mass collision stopping power in pure alanine and in the alanine pellet material (90.9% by weight L- α -Alanine and 9.1% paraffin wax) have been computed. In the plot 5.12 the mass collision stopping powers for the pure alanine and the alanine pellets are reported as function of the energy. Larger deviations (up to $\approx 3.4\%$) between the stopping power in pure alanine and in alanine pellet were found for energies below 0.1 MeV. Those data were implemented in the MC code of RS4.99. In particular both stopping powers were used in the simulation:

- since the ranges of produced electrons are smaller than the alanine grain dimensions (from 5 to 200 μm), all electrons that contribute to the total dose originate in the alanine grains. Therefore, to compute the dose weighted RE as reported in equation 5.5 we use the mass collision stopping power for pure alanine;
- for macroscopic transport in the MC code every step (on average) takes the proton

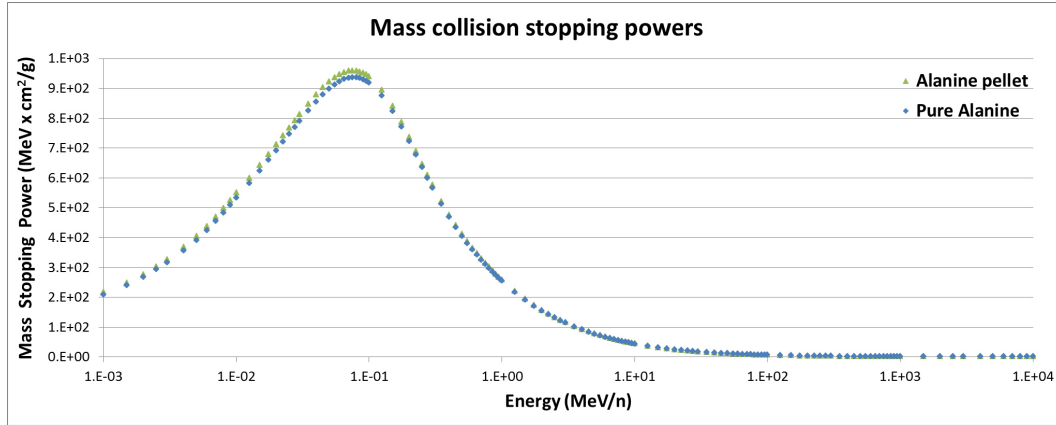


Figure 5.12: Mass collision stopping power for pure alanine and alanine pellets as function of the energy of the primary protons [107].

through a mix of the alanine and paraffin binder and thus to calculate the mean energy loss the mass stopping power of the mixture (alanine pellet) needs to be considered.

Regarding the RE a look-up table for protons based on the Hansen-Olsen model [89] that was lately reviewed by Herrmann [104] has been hardcoded in the MC code. In the plot of figure 5.13 the $\eta_{aln}(E_j, Z = 1)$ as function of energy for protons is shown. The plot shows that the largest variation of RE is at low energy (from 10 keV to 1 MeV).

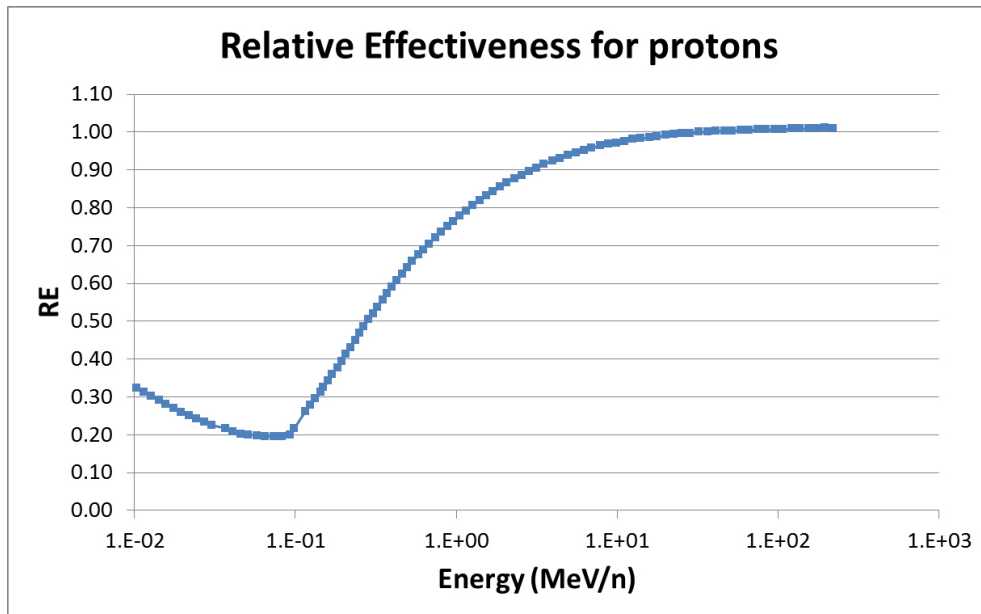


Figure 5.13: $\eta_{aln}(E_j, Z = 1)$ of alanine dosimeters as function of the proton energy [104].

Therefore, it is crucial to track primary and secondary protons in that energy range. In first instance the contribution of particles heavier than protons (e.g. deuterium and alpha particles) has been neglected. Moreover, as first implementation the $\eta_{aln}(E_j, Z = 1)$ table

for protons is hardcoded with the option to read an external look-up table (e.g. in future a table $\eta_{EBT}(E_j, Z = 1)$ for EBT films could be provided as input for the EBT correction factors).

For each beam alanine dose weighted average RE $\bar{\eta}_{aln}$ is scored in each voxel of the whole dose grid (3D $\bar{\eta}_{aln}$ distribution), as shown in picture 5.14: Based on the CT



Figure 5.14: 3D $\bar{\eta}_{aln}$ distribution for one lateral beam in the head phantom.

images of the phantoms the alanine pellets are contoured as cylinder of dimension 5 mm diameter and 2.5 mm length. The calculation of 3D RE corrections was performed in a dose grid of $1 \times 1 \times 1 \text{ mm}^3$ and an average value of $\langle \bar{\eta}_{aln} \rangle_{\text{pellet}}$ is extracted at each pellet position. In case the plan is composed of more than one beam, the RE at each pellet position is weighted by the dose contribution to the pellet given by each beam 5.6.

$$\langle \bar{\eta}_{aln} \rangle_{\text{pellet,plan}} = \frac{\sum_{i=1}^n \langle \bar{\eta}_{aln} \rangle_{\text{pellet},i} \times D_i}{\sum_{i=1}^n D_i} \quad (5.6)$$

where the n is the number of the beams composing the plan, $\langle \bar{\eta}_{aln} \rangle_{\text{pellet},i}$ is the average of RE contributions to the pellet computed for i -th beam and D_i is the dose contribution to the pellet for i -th beam. In the plot of figure 5.15 the RE computed at each alanine pellet position for a plan composed by two opposite beams in the pelvis phantom (see section 5.2.6).

Alanine pellets: how to derive absorbed dose to water in proton beams.

The relative effectiveness derived from MC calculations as reported in section 5.2.3 is given in terms of absorbed dose to alanine but for comparison with the TPS a conversion

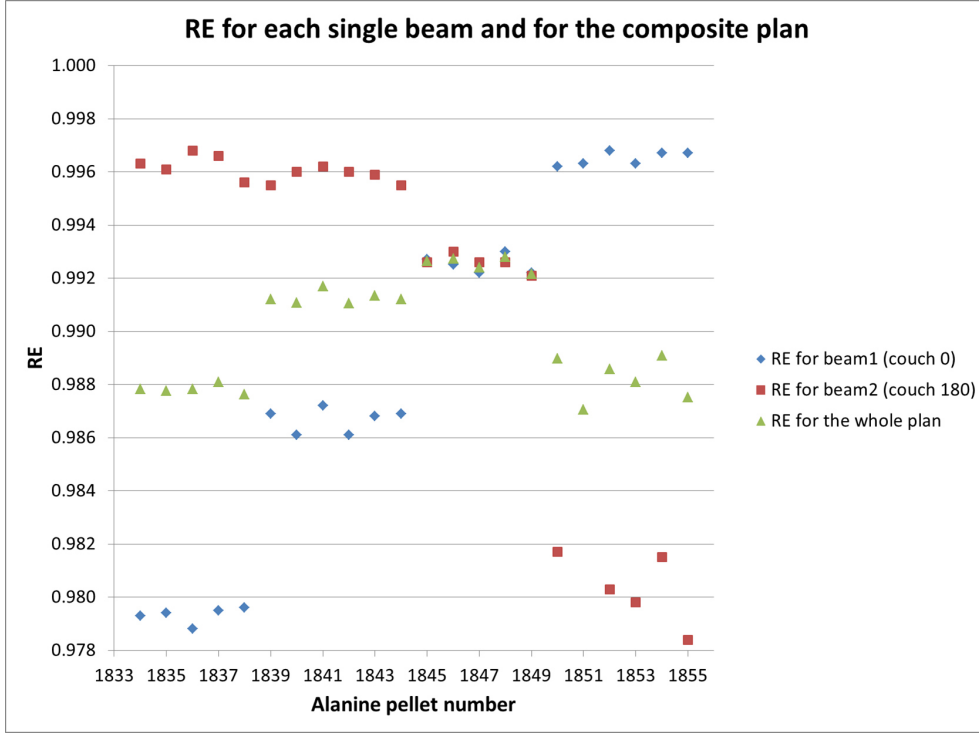


Figure 5.15: RE computed for each single beam and for the composite plan in the pelvis phantom.

into absorbed dose to water has to be performed. In the following the dose is denoted by D_{aln} and D_w to distinguish between absorbed dose to alanine and to water. Then Eq. 1.17 can be reformulated to:

$$D_{aln,p} = \frac{D_{aln,60Co}}{\langle \bar{\eta}_{aln} \rangle_{pellet,plan}} \quad (5.7)$$

where $D_{aln,60Co}$ is the absorbed dose to alanine in ^{60}Co , $D_{aln,p}$ is the absorbed dose to alanine in proton beam and $\langle \bar{\eta}_{aln} \rangle_{pellet,plan}$ is the RE computed at each pellet position for a generic composite treatment plan (see section 5.2.3). In order to convert dose to alanine in dose to water the mass stopping power ratio water to alanine $\left(\frac{S_{col}^p}{\rho} \right)_{aln}^w$ for proton beam has to be computed. The value $\left(\frac{S_{col}^p}{\rho} \right)_{aln}^w = 1.024$ was derived by Monte Carlo simulation as reported in [90] based on stopping power values from tables in ICRU report 73 [108] and ICRU report 49 [13]. Then the dose to water in a proton beam is:

$$D_{w,p} = \frac{D_{aln,60Co}}{\langle \bar{\eta}_{aln} \rangle_{pellet,plan}} \times \left(\frac{S_{col}^p}{\rho} \right)_{aln}^w \quad (5.8)$$

The read out of pellets was provided by NPL in terms of the equivalent absorbed dose to water in ^{60}Co . Therefore, we need to relate absorbed dose to water in ^{60}Co to absorbed dose to alanine in ^{60}Co . The Bragg-Gray cavity theory is not valid in the alanine pellet since the main condition (that no electrons generated in the cavity contribute to the

charged particle spectrum in the cavity) is not fulfilled. Applying the Burlin cavity theory:

$$D_{aln,^{60}Co} = D_{w,^{60}Co} \left[d \times \left(\frac{S_{col}^{^{60}Co}}{\rho} \right)_w^{aln} + (1 - d) \times \left(\frac{\mu_{en}^{^{60}Co}}{\rho} \right)_w^{aln} \right] \quad (5.9)$$

where d is the fraction of dose deposited in the detector coming from electrons generated outside the detector and $\left(\frac{\mu_{en}^{^{60}Co}}{\rho} \right)_w^{aln}$ is the ratio of mass energy absorption coefficients of water and the pellet's alanine/paraffin wax mixture for ^{60}Co . Since the alanine to water ratios of stopping powers and mass energy absorption coefficients are close to each other in ^{60}Co [90, 109], the following simplifying assumption can be made:

$$D_{aln,^{60}Co} \approx D_{w,^{60}Co} \times \left(\frac{\mu_{en}^{^{60}Co}}{\rho} \right)_w^{aln} \quad (5.10)$$

Therefore, based on eq. 5.10 the eq. 5.8 can be written as:

$$D_{w,p} \approx \frac{D_{w,^{60}Co}}{\langle \bar{\eta}_{aln} \rangle_{pellet,plan}} \times \left(\frac{S_{col}^p}{\rho} \right)_{aln}^w \times \left(\frac{\mu_{en}^{^{60}Co}}{\rho} \right)_w^{aln} \quad (5.11)$$

For the ratio of the mass energy absorption coefficients of water and the pellet's alanine/paraffin wax mixture $\left(\frac{\mu_{en}^{^{60}Co}}{\rho} \right)_w^{aln}$ a constant value 0.976 was recommended by NPL. An analysis of the uncertainties related to all involved parameters is reported in section 5.3.3.

5.2.4 Ionization chambers.

As mentioned above, all the anthropomorphic phantoms were designed in such a way that different ionization chamber inserts can be placed perpendicular to the beam direction. This enables the use of ionization chambers calibrated in terms of absorbed dose to water which are the most commonly recommended reference dosimeters for clinical dosimetry. In this study an assembly of PTW Unidos Weblin electrometer and PTW Farmer chambers (Type TM30013) were used. In order to avoid signal saturation due to the high dose rate the range of the electrometer was set to medium. A voltage of +400V was applied to the chamber. The correction factors for recombination and polarity effects were set to unity, since measurements carried out in our synchrotron-based proton beam show a negligible contribution of those two effects on the response of the Farmer chambers. The chambers have been calibrated in terms of absorbed dose to water N_{D,w,Q_0} in ^{60}Co at the Secondary Standard Dosimetry Laboratory (SSDL) of

Seibersdorf Laboratories (Austria). The $k_{Q_p, Q_0} = 1.03 \pm 0.02$ is the beam quality correction factor derived from TRS 398 [80] as the average value over the range of beam qualities encountered in the end-to-end tests. The absorbed dose to water in proton beam was derived as:

$$D_{w, Q_p} = M_{Q_p} \times k_{T, P} \times N_{D, w, Q_0} \times k_{Q_p, Q_0} \quad (5.12)$$

where M_{Q_p} is the collected charge of the Farmer chamber and $k_{T, P}$ is the coefficient to correct for temperature and pressure differences in comparison to the reference.

5.2.5 EBT3 radiochromic films.

In order to check the homogeneity of the 2D dose distribution the plastic phantoms were loaded with GafChromic EBT3 films in addition to the Alanine pellets. These films are sensitive for doses up to 10 Gy [110, 111]. As all the solid state detectors also EBT3 films are effected by “quenching” effects [110, 112]. Thus, in order to use them for absolute measurements we would need to predict RE corrections based on a model [102] as it is done for the Alanine. In this work the focus was rather on an evaluation of their relative dose response. To characterize transverse dose profiles measured with films the parametrization was taken from Gall et al [113] as recommended by ICRU78 [34]. The lateral field homogeneity (in percent) was defined as in eq. 5.13:

$$HI = \frac{Max - Min}{Max + Min} \times 100 \quad (5.13)$$

where Max and Min are respectively the maximum and minimum doses evaluated in the treatment width. Moreover, the lateral penumbra of a transverse profile is the distance between two dose points measured in the lateral fall-off between the 80% and 20% dose levels (LP_{80-20}). Treatment width is defined as the distance between two lateral penumbra LP_{80-20} widths ($2 \times LP_{80-20}$) from the 50 percent isodose levels of the lateral-beam profile (see picture 5.16).

For each plan films were irradiated in different depths and then scanned with Epson Expression 11000XL Pro in transmission mode after 24 h. The read-out procedure was based on Dreindl et al. [114].

5.2.6 End-to-end test procedures.

During testing, the three phantoms were transferred through the workflow as real patients to simulate the entire clinical procedure. First step was the registration of the test patients (phantoms) in the *Oncology Information System (OIS)* with demographics data

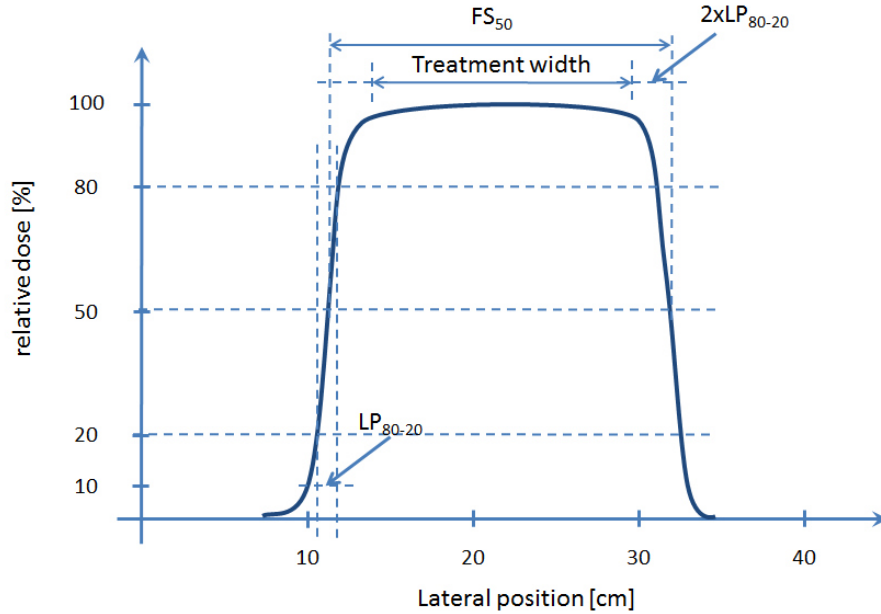


Figure 5.16: Transverse dose profile indicating several parameters [34, 113].

(Name, Surname, Gender, date of birth, etc.). A bar code bracelet was created, printed and assigned to the phantom. The three phantoms (*homogeneous phantom*, *Head phantom*, *Pelvis phantom*) were prepared with dummy pellets made of same tissue-equivalent materials of the cubic inserts (see figure 5.17).

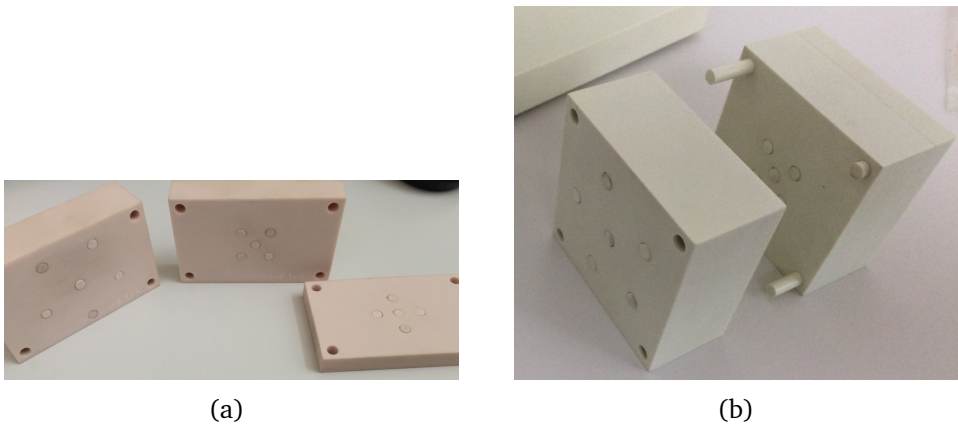


Figure 5.17: Cubic targets to allocate Alanine detectors filled with (a) brain tissue equivalent and (b) prostate tissue equivalent dummy pellets.

In the figure 5.18 the alignment of the three phantoms on the CT couch with the in-room laser system is shown. The *head phantom* was immobilized (with a thermo-plastic mask) on the Base of Skull (BoS) extension plate for typical head and head&neck cases. The mask was left on the phantom over one night in order to minimize the shrinkage.

The CT scans were acquired with pre-defined scan protocols used at MA for cranial and pelvic treatments. However, a slice thickness of 1 mm has been selected instead

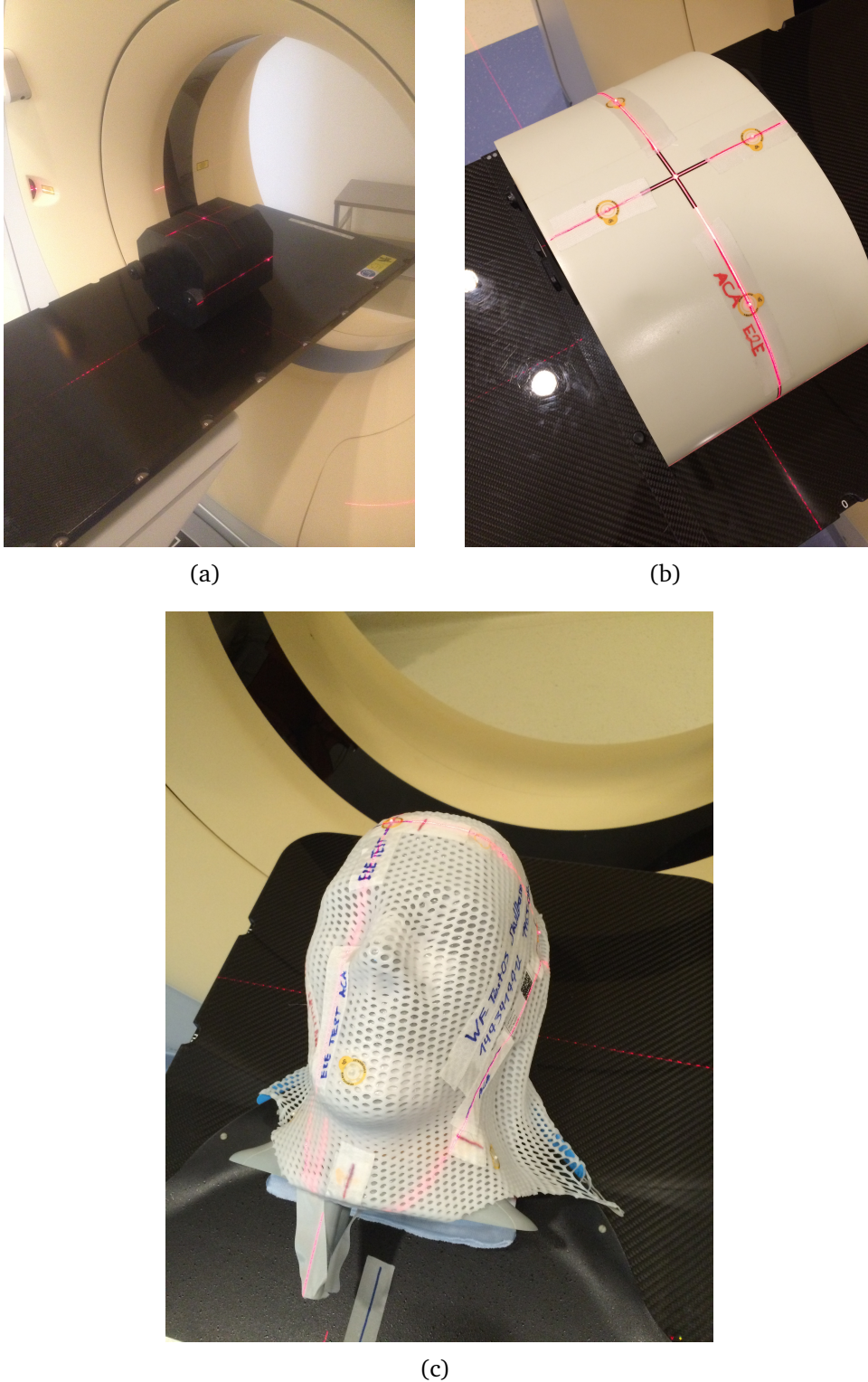


Figure 5.18: The alignment of the *homogeneous phantom* (a), the *Pelvis phantom* (b) and the *Head phantom* immobilized in the BoS frame (c).

of the clinical 2 mm for Head and 3 mm for pelvis protocol in order to have a better resolution at the Alanine pellet positions. The CT images were exported from the CT console to the *Picture Archiving and Communication System (PACS)* and imported to the

TPS RayStation v5.0.2.

Regarding the *homogeneous phantom* a target of $8 \times 8 \times 12 \text{ cm}^3$ located symmetric around isocenter has been outlined. Moreover, at the position of each Alanine pellet a Region of Interest (ROI) was drawn. A physical dose of 10 Gy was planned to the target volume (figure 5.19) in order to achieve a reproducibility better than 0.5% on the dose delivered to the Alanine pellets.

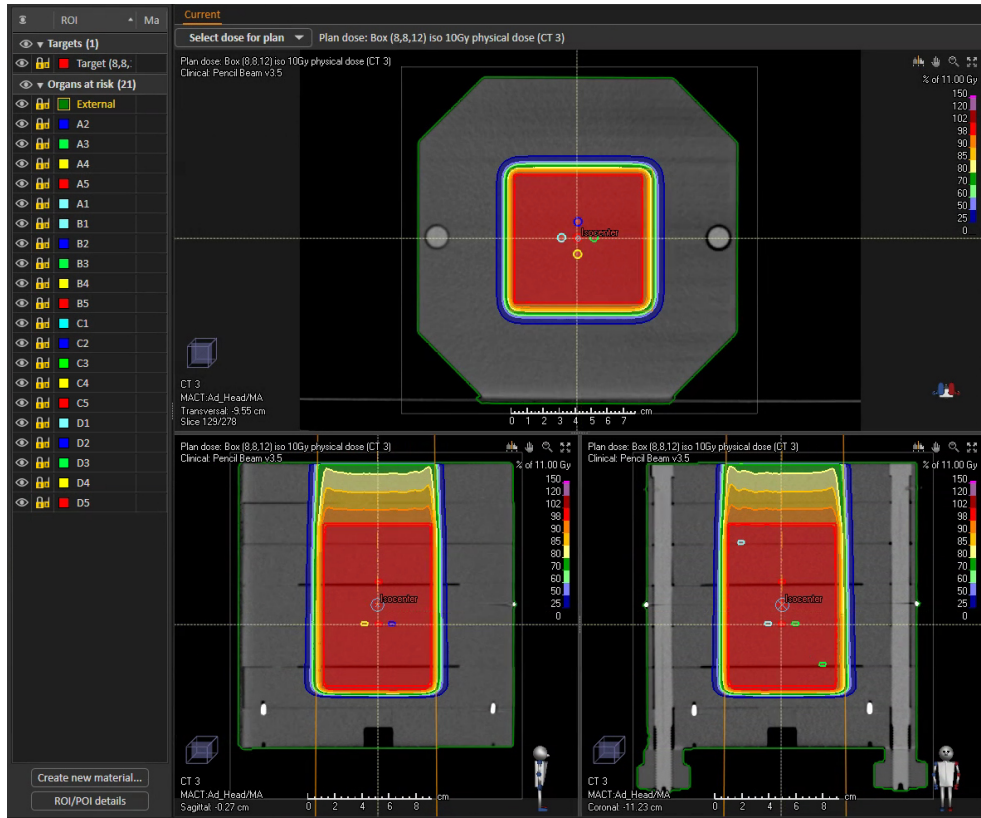


Figure 5.19: Transversal, Sagittal and coronal views of dose distribution of the plan in the *homogeneous phantom*, where ROIs representing the pellet positions in the phantom are shown.

Concerning the *Head phantom*, three different clinical scenarios of increasing complexity were simulated.

1. The first scenario was a configuration with a single beam (Gantry 90° , couch 0°) in isocenter condition (isocenter at the center of the target volume and large air gap $\approx 60 \text{ cm}$). A cylindrical target of 7 cm in diameter and 6.5 cm in height ($\approx 250 \text{ cc}$) was delineated on the CT scan in order to cover homogeneously all the pellets. A physical dose of 10 Gy was planned to the target volume (see figure 5.20 (a)).
2. The second scenario was a configuration with two oblique beams (both beams at Gantry 90° , with couch tilted 350° and 190°). In order to be closer to a real patient treatment scenario, the irradiation was performed in non-isocentric condition for

both beams. Therefore, the head phantom was moved toward the nozzle in order to minimize the air gap (≈ 15 cm). The planning technique was SFO (see 4) for both beams. A physical dose of 10 Gy was planned to the target volume (see figure 5.20 (b)). A weight of 104 kg was placed on the table top to simulate the real patient weight.

3. The third scenario was very similar to the second one. The main difference was that one of the two beams needed the range shifter inserted in the beam line as the target volume was extended to the phantom surface (see figure 5.20 (c)).

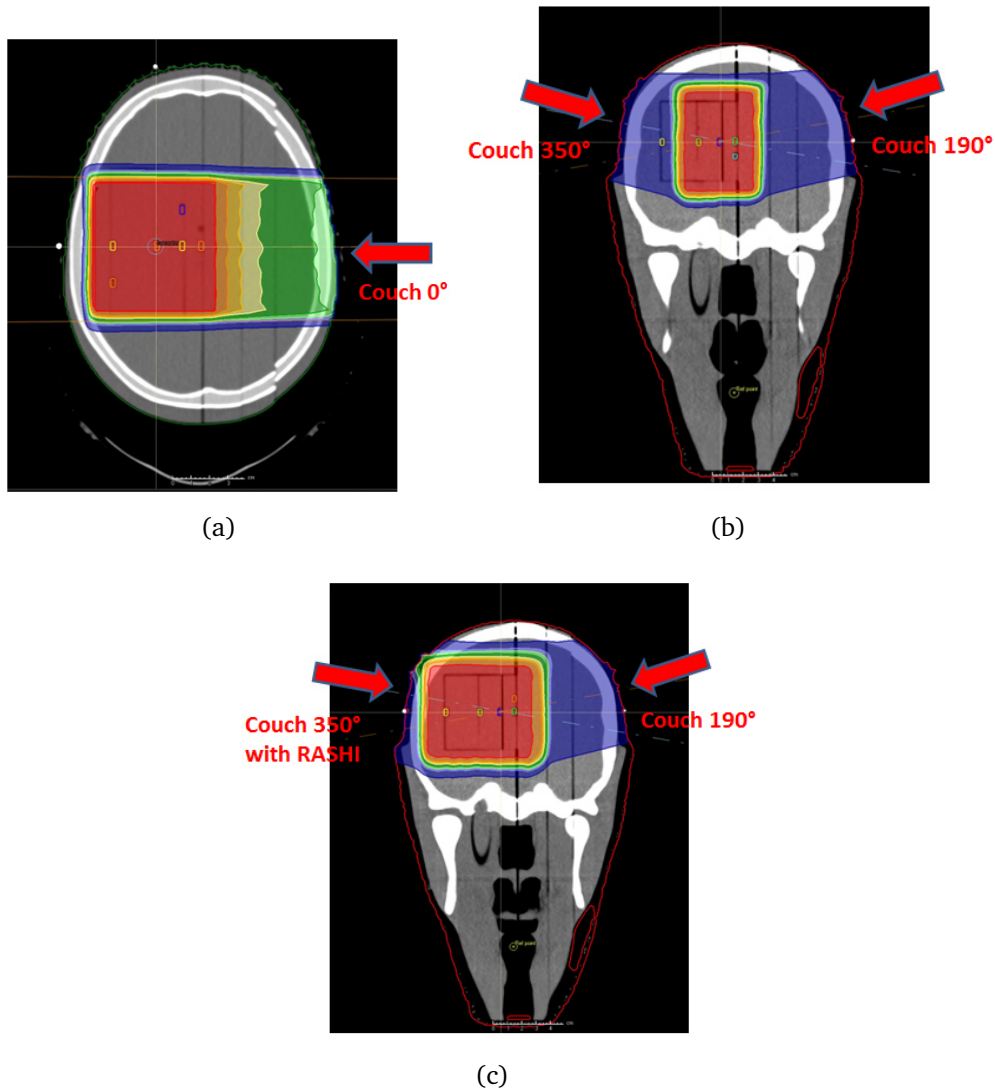


Figure 5.20: Dose distributions for the three clinical scenario in the *Head phantom*. the red arrows represents the beams' direction. The first scenario with one beam in (a), in (b) the second scenario with two oblique beams and in (c) the third scenario with two oblique beams and range shifter.

Regarding the *Pelvis phantom*, as for the *Head phantom*, a cylindrical target of 7cm in diameter and 6.5cm in height (≈ 250 cc) was delineated on the CT scan. Two treatment

plans were created: one plan consists of a “single beam” (Gantry 90°, couch 0°) and the other plan consists of two “opposite beams” (Gantry 90°, couch 0° and 180°). A physical dose of 10 Gy was planned to the target volume (see figure 5.21) for both treatment plans. In order to compute correction factors for the “quenching” of Alanine pellets, all

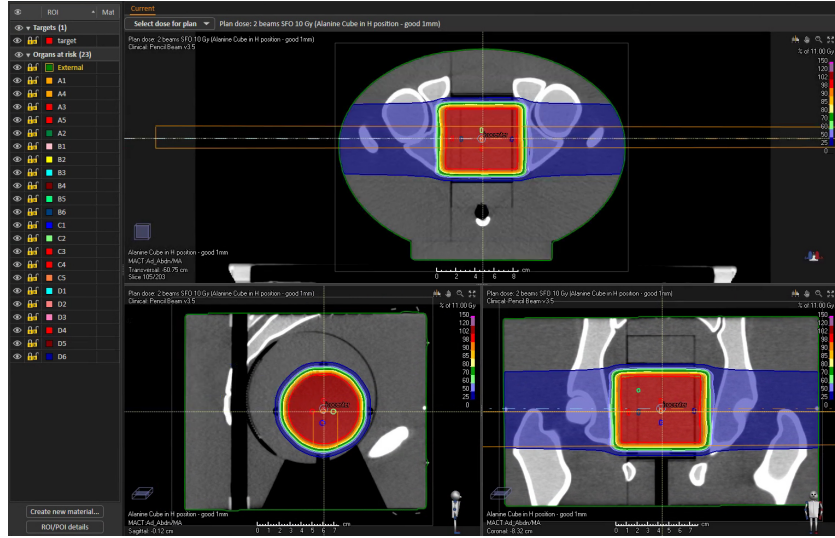


Figure 5.21: Transversal, Sagittal and Coronal views of dose distribution of the treatment plan in the *Pelvis phantom*, where the ROIs representing the pellet positions in the phantoms are shown.

the plans were exported to the evaluation version RayStation v4.99. There, the plans were recomputed with the Monte Carlo (see section 5.2.3) dose algorithm. For each voxel in the dose grid the correction factors in 3D were displayed overlaid to the CT scan of the phantoms 5.22. The dose weighted average relative effectiveness $\bar{\eta}$ for each pellets (ROI) have been extracted via scripting.

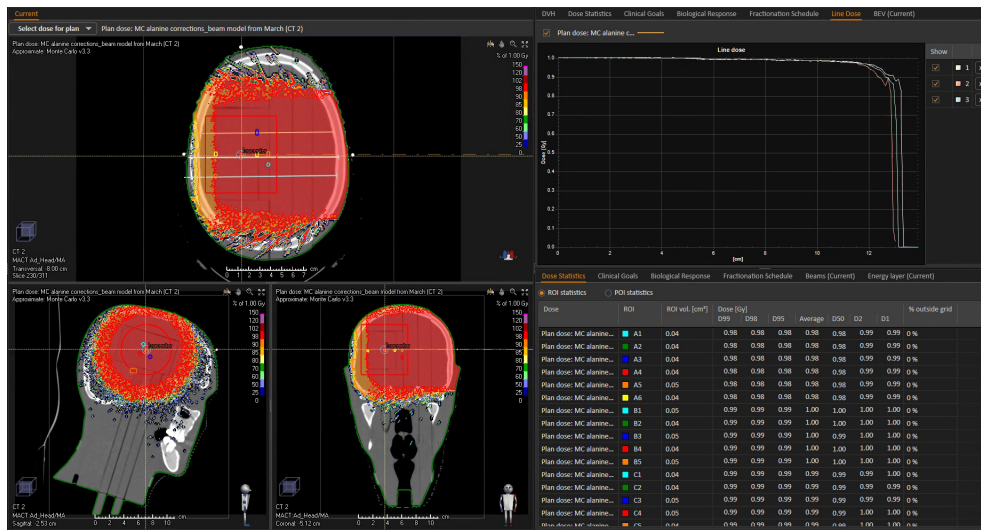


Figure 5.22: 3D map of correction factors for Alanine pellets “quenching” for the Head phantom. On the top-right three profiles of correction factors are shown.

After the approval of the treatment plans they were exported to the *PACS*. The *Treatment to Machine (T2M)* module provides conversion of the DICOM RT Ion Plan into the machine file structure “Run files” depending on the treatment plan, the IR and the associated beamline characteristics. All the plans were irradiated in the Horizontal Beam Line (HBL) of Irradiation room 3 at MedAustron. The entire in-room workflow was managed by the software *Radiation Treatment Software System (RTS²)* (see section 2). The *homogeneous phantom* was loaded with 20 Alanine pellets and two EBT films for the first irradiation and with Farmer chamber (TM30013) and dummy pellets for the second irradiation. The *homogeneous phantom* has been aligned with in-room lasers for both irradiations (see figure 5.23).

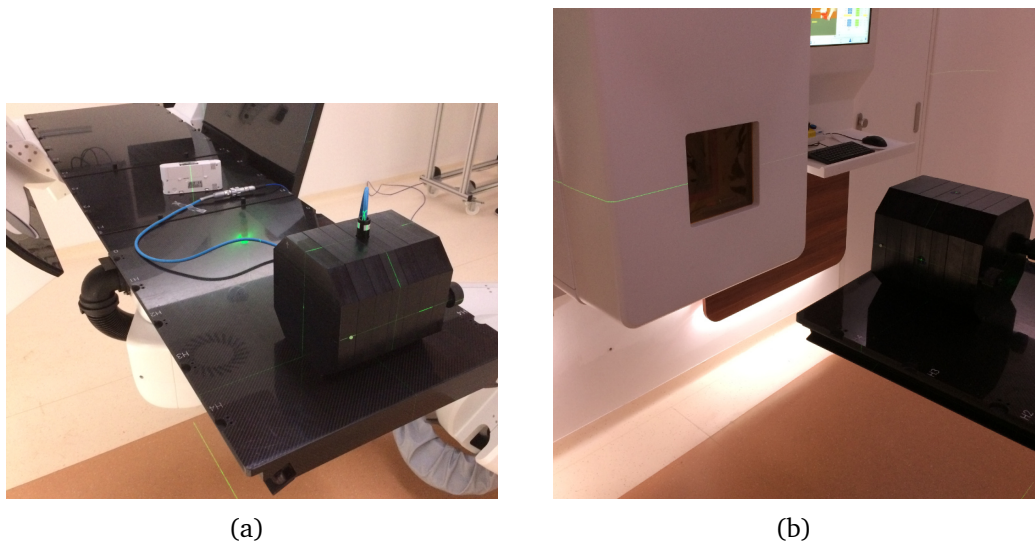


Figure 5.23: The alignment of the *homogeneous phantom* loaded with the Farmer chamber (a) and loaded with the Alanine pellets and EBT films (b).

The *Head phantom* was loaded with 22 Alanine pellets and two EBT films for the first irradiation and with two Farmer chambers (TM30013) for the second irradiation. The *Head phantom* on the BoS frame was positioned on the robotic couch in IR3. Two X-ray images (one A-P projection and one lateral projection) were acquired with the Imaging Ring system. A 2D/3D imaging registration with on-the-fly Digitally Reconstructed Radiographs (DRRs) reconstructed from the CT scan was performed. A setup correction vector based on the imaging registration was applied. The robotic couch moved to the treatment position after applying setup correction (see figure 5.24). An infrared camera installed on the floor correct on line the treatment position of the phantom depending on the weight placed on the table top. Regarding the *Pelvis phantom* two irradiations were performed:

- irradiation of a plan with a “single beam”. The phantom was loaded with 22 Ala-

nine pellets and two EBT films;

- irradiation of a composite plan made of two “opposite beams”. The phantom was loaded with 22 Alanine pellets and two EBT films.

The in-room workflow has been performed in a similar way as for the head phantom 5.24. All the error bars reported in the plots and tables of this chapter are expressed



(a)



(b)

Figure 5.24: (a) The experimental setup of the *Head phantom* fixed with the thermo-plastic mask on the BoS frame and loaded with Alanine pellets and EBT films. A patient weight of 104 kg was placed on the table top and the infrared camera corrects for the bending of the couch in comparison to the planning CT. (b) The experimental setup of the *Pelvis phantom* loaded with Alanine pellets and EBT films.

as a standard deviation which corresponds to a confidence limit of 68%.

5.2.7 Comparison of alanine dosimetry with ionization chamber dosimetry in water.

IAEA TRS 398 [80] recommends water as the reference medium for the determination of absorbed dose with proton beams. Plastic phantoms should not be used for absolute dosimetry in proton beams since the required water-to-plastic fluence correction factors, h_{pl} , are not known for plastics. The anthropomorphic phantoms used in this work are made by plastic materials which are tissue-equivalent only for photon beams. There are no data on their tissue-equivalence in proton beams.

Therefore, in addition to the comparison in the anthropomorphic phantoms the idea was to compare the response of the Alanine pellets with the ionization chambers in water. The comparison was performed in a stationary water phantom MP1 (PTW, Freiburg) with a 3 mm PMMA thin entrance window. The only movable axis of the MP1 water phantom is in depth with 0.1 mm resolution. The phantom was set up with the outer surface of the thin window at the in-room isocenter. Since Alanine pellets are hygroscopic they need to be waterproofed before inserting them into the water phantom. Customized holders were provided together with the Alanine pellets by NPL. The holders (F-type) have the same outer dimensions (7 mm diameter) as the Farmer chamber and can be placed inside the same plastic holder commercial designed for the Farmer. In each F-type holder nine Alanine pellets can be positioned as shown in figure 5.25. An additional plastic rod of 15 cm can be screwed on the F-type holder in order to easily insert and remove it from the plastic Farmer holder. The same commercial Farmer holder was used for accurately positioning the stack of nine Alanine pellets and the Farmer ionization chamber (TM30013) at the same measurement depths in water. A semiflex chamber placed on the left side in beam eye's view was used as additional beam monitor chamber. The figure 5.26 shows the setup of measurement with the Farmer and the Alanine pellets encapsulated inside the T-type holder. Two different plans were irradiated:

1. a single-layer scanned field $7 \times 7 \text{ cm}^2$ of energy 179.2 MeV. Measurements were carried out at the clinical reference depth z_{ref} of 20 mm in water. Both detectors were irradiated with a physical dose of 10 Gy;
2. a fully modulated scanned field of $6 \times 6 \times 6 \text{ cm}^3$ with the center of SOBP positioned at the WED of 15 cm. Measurements were carried out at two different residual range: $R_{res} = 2 \text{ cm}$ and $R_{res} = 4 \text{ cm}$. A physical dose of 10 Gy was delivered to the target volume.

However, the effective point of measurement is different for Alanine and Farmer chamber:

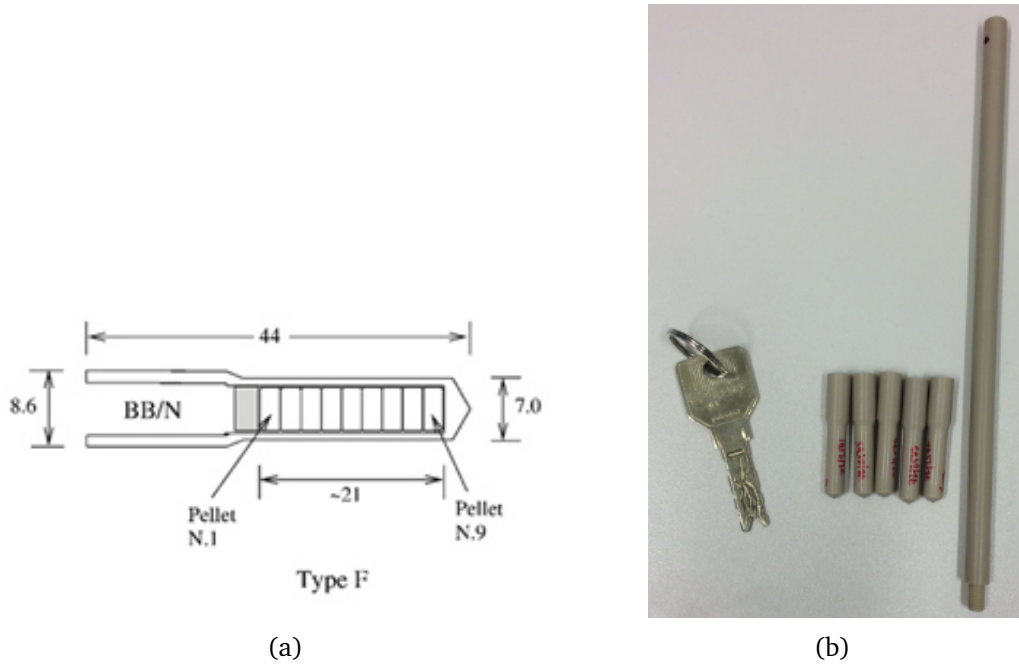


Figure 5.25: (a) The drawing of the customized F-type holder with the nine Alanine pellets encapsulated inside. (b) Five F-type holders used for the measurements in the water phantom. A rod can be screwed on the F-type holder in order to easily insert and remove from the plastic Farmer holder.

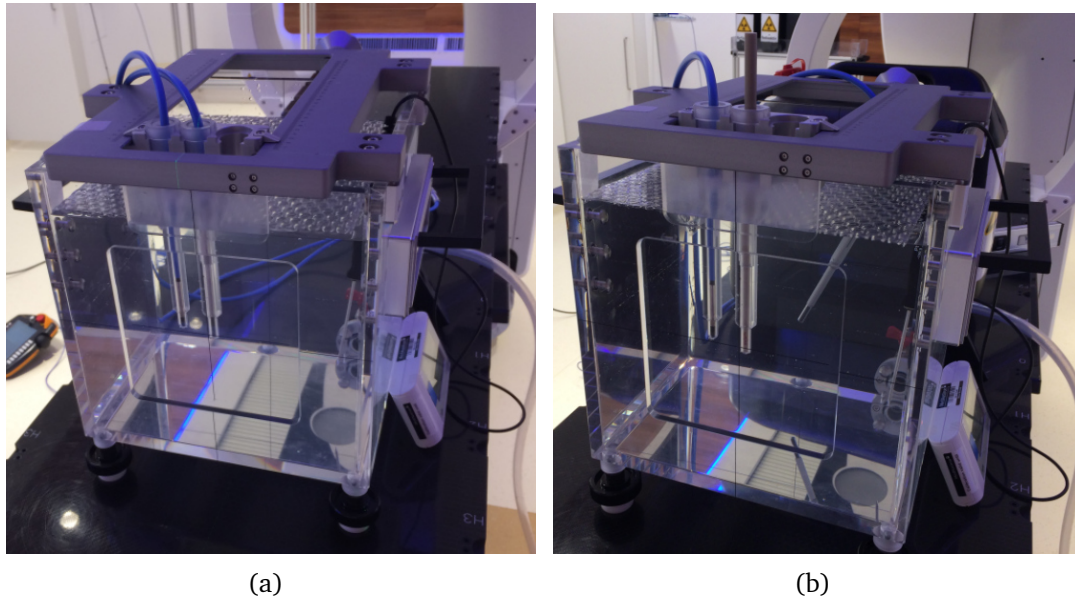


Figure 5.26: (a) Setup of the MP1 water phantom at isocenter with the Farmer chamber positioned along the central beam axis. A semiflex chamber positioned on the left side in BEV has been used as beam monitor chamber. (b) Setup of the MP1 water phantom at isocenter with the F-type holder containing nine Alanine pellets. A semiflex chamber positioned on the left side in BEV has been used as beam monitor chamber.

- for the Farmer chamber the reference point, located on the central axis at the centre of the cavity volume, shall be positioned a distance $0.75 \times r_{cyl} = 2.3 \text{ mm}$ away from the source (i.e. deeper in water).

- for the Alanine pellet the reference point, corresponding to the center of mass of the detector, shall be positioned at the reference depth z_{ref} .

The readings of the Farmer and Semiflex chamber were corrected for the water temperature and air pressure. The Alanine pellet readings were corrected for the water temperature.

5.3 Results

5.3.1 Measurements in plastic phantoms

Regarding the *homogeneous phantom* the idea was to reproduce the same setup described in the previous paper [90] in order to benchmark our data with a reference. Measurements were carried out in two sessions over one month. In the figure 5.27 the deviations between the Alanine pellets' readings and the planned dose with the TPS (RayStation v5.0) are reported. The data reported in the plot are not corrected for the “quenching” effect. As one can see in plot 5.27 the measurements over one month

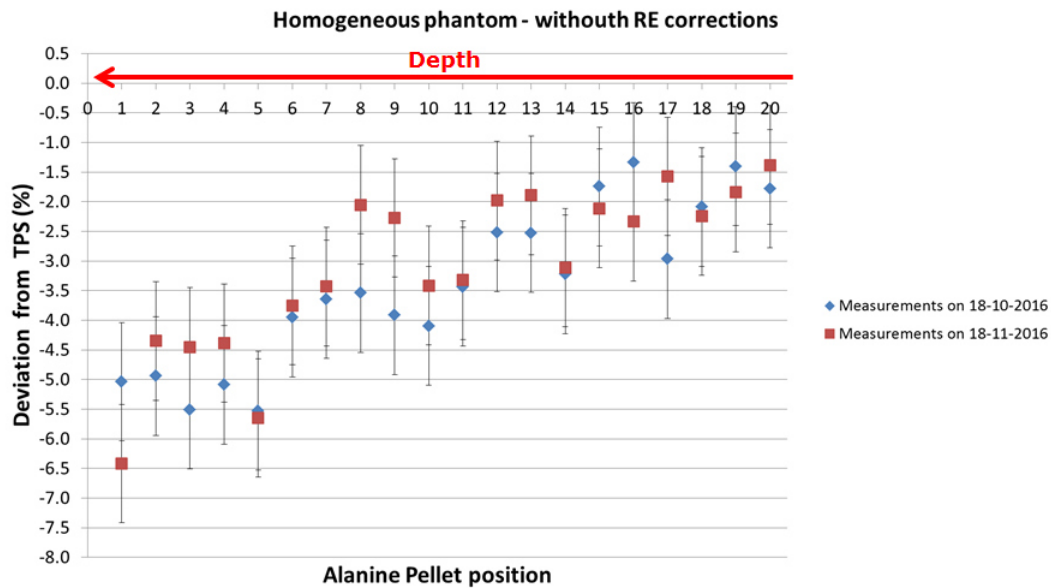


Figure 5.27: Deviations between Alanine pellets' readings and planned dose with RayStation v5.0. The data reported in the plot are not corrected for the “quenching” effect. In blue the data measured on 18-10-2016 and in red the data measured exactly one month after (18-11-2016). The error bars are one standard deviation of $\pm 1\%$.

are very reproducible with all the pellets within one standard deviation. Due to the “quenching” effect deviations up to 6.4% at large depth ($WED \approx 15$ cm) were measured. Therefore, corrections for the relative effectiveness were applied to the measurements

as reported in the paper [90]. In the picture 5.28 the data with and without RE corrections are shown as function of WED in the *homogeneous phantom*.

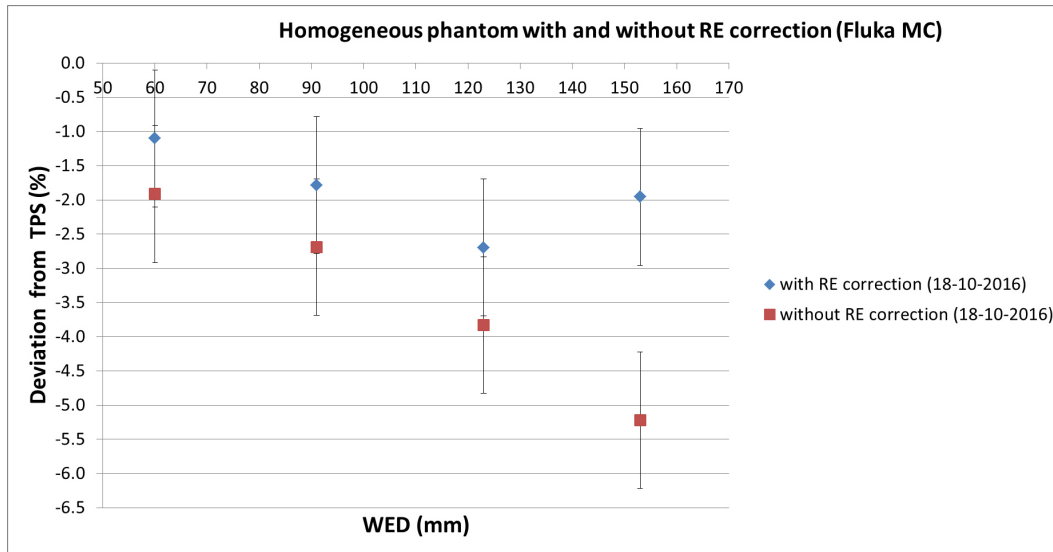


Figure 5.28: Deviations between Alanine pellets' readings and TPS planned dose as function of WED in the *homogeneous phantom*. In blue the data with the RE corrections applied based on Fluka MC and reported in [90] and in red the data without RE corrections. Each point in the plot is the average of 5 Alanine pellets at the same WED.

As expected the RE corrections are bigger (up to 3.5%) for larger depths close to the distal part of the SOBP. The plot in figure 5.29 shows the same data of figure 5.27 after RE corrections applied as reported in [90].

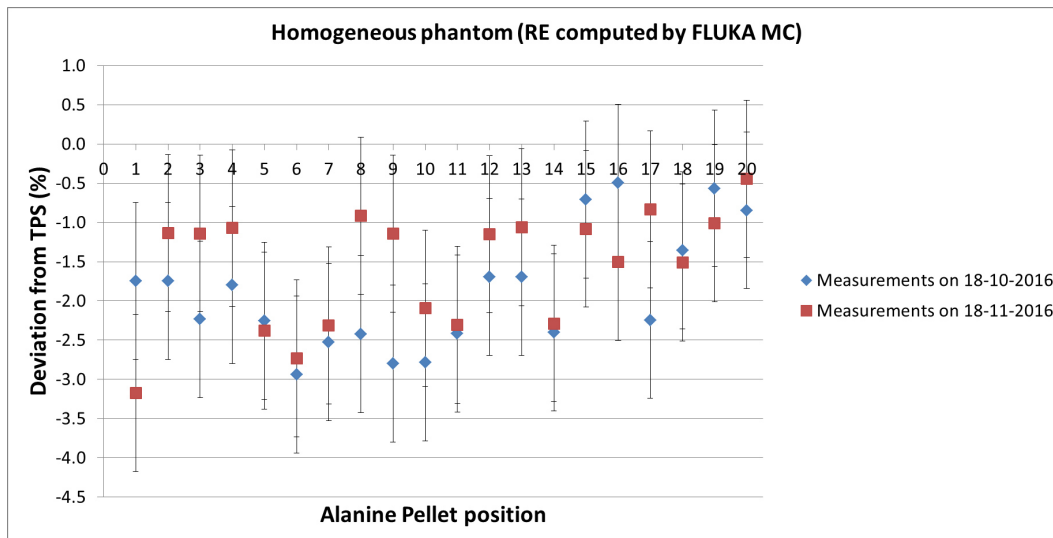


Figure 5.29: Deviations between Alanine pellets' readings and TPS planned dose. The data are corrected for the RE. In blue the data measured on 18-10-2016 and in red the data measured one month after (18-11-2016).

Table 5.1 shows the overall mean of deviations of Alanine pellets from TPS planned dose. The data in the table shows a very good reproducibility of the measurements

	Deviations [%] (data 18-10-2016)	Deviations [%] (data 18-11-2016)
Mean	-1.9	-1.6
Standard deviation	0.8	0.7
Minimum deviation	-0.5	-0.4
Maximum deviation	-2.9	-3.2

Table 5.1: Overall mean deviations of Alanine pellets from TPS planned dose. RE corrections derived from [90]).

within 0.3% over one month. Moreover, the Alanine pellets, after correction for quenching, underestimate the planned dose on average around -2%. Similar behavior was found and reported in the paper [90]) with measurements carried out at HIT. Regarding the measurements acquired with the Farmer chamber at the center of the target volume a very good reproducibility of the beam delivery was measured as for the Alanine pellets (within 0.3%). However, as one can see in table 5.2 the data for Alanine pellets systematic deviate from the Farmer chamber measurements up to 2.9%. Regarding the

	Deviations [%] (data 18-10-2016)	Deviations [%] (data 18-11-2016)
Mean	-2.9	-2.3
Standard deviation	0.7	0.7
Minimum deviation	-1.7	-1.1
Maximum deviation	-3.9	-3.6

Table 5.2: Overall mean deviations of Alanine pellets from Farmer chamber measurements. RE corrections derived from [90]).

film measurements two EBT3 films have been irradiated with the Alanine pellets. For each of the two EBT films different transverse dose profiles have been analyzed at 10 mm distance. For the two EBT3 film the average homogeneity HI was respectively 2.5 ± 0.3 % and 2.3 ± 0.4 % and therefore within our 5% clinical tolerance level.

Concerning the measurements in the *head phantom* in the plot of figure 5.30 we report the measurements of Alanine pellets in the simplest clinical scenario with a single beam in isocentric condition (see picture 5.20 (a)). The table 5.3 shows the overall mean of deviations of Alanine pellets from TPS planned dose and from the Farmer measurements.

From the plot 5.30 and the table 5.3 the Alanine pellets measurements were reproducible within 0.4% on average. A systematic underestimation of $\approx 2\%$ of Alanine pellets results in comparison to the TPS planned dose was found as in the homogeneous phantom. Moreover, a systematic deviation between the Farmer chamber measurement at the center of the volume with the Alanine pellets was confirmed also in the *head phantom*.

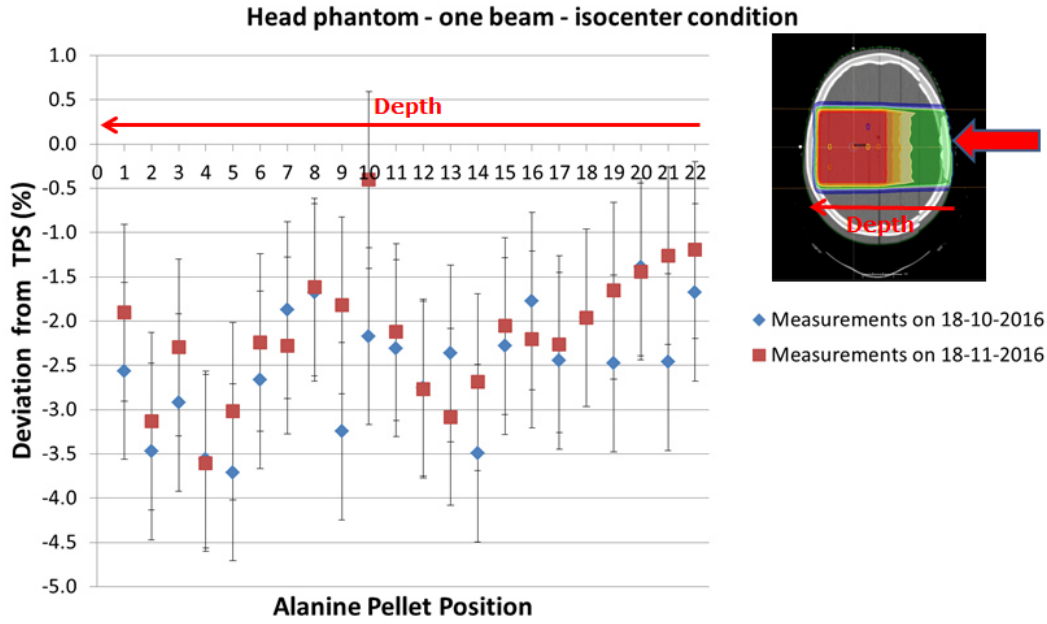


Figure 5.30: Deviations between Alanine pellets' readings and TPS planned dose. The data are corrected for the RE as described in section 5.2.3. In blue the data measured on 18-10-2016 and in red the data measured one month after (18-11-2016).

	Deviation Alanine-TPS on 18-10-2016 [%]	Deviation Alanine-Farmer on 18-10-2016 [%]	Deviation Alanine-TPS on 18-11-2016 [%]	Deviation Alanine-Farmer on 18-11-2016 [%]
Mean	-2.5	-3.6	-2.1	-3.2
Stdev	0.7	0.6	0.7	0.7
Min dev.	-1.4	-2.4	-0.4	-1.9
Max dev.	-3.7	-4.9	-3.6	-4.4

Table 5.3: Overall mean deviations of Alanine pellets from TPS planned dose and from the Farmer measurements for the single beam irradiation in the *head phantom*. RE corrections derived as described in section 5.2.3

For the irradiated EBT3 film the homogeneity HI along the central cross-sectional profile in PA direction was 2.3%, so also within our 5% clinical tolerance level.

Measurements in a more complex clinical scenario with two oblique beams in non isocentric condition (small air gap) were carried out as described in section 5.2.6 (see picture 5.20 (b)). As it is shown in the plot of figure 5.31 the Alanine pellets systematic underestimate the planned TPS dose $\approx 2\%$ as in the previous experiments. The pellets number from 2050 to 2055 were exposed to a dose level lower (≈ 4 Gy) than the suggested 10Gy by NPL. However, as one can see in the plot, the deviations from the TPS planned dose are comparable to the pellets positioned in the target. This is a very good indication for further application of Alanine pellet dosimetry at lower dose level closer to the prescription dose used for patient treatments (2 - 3 Gy/fraction). For the irradiated

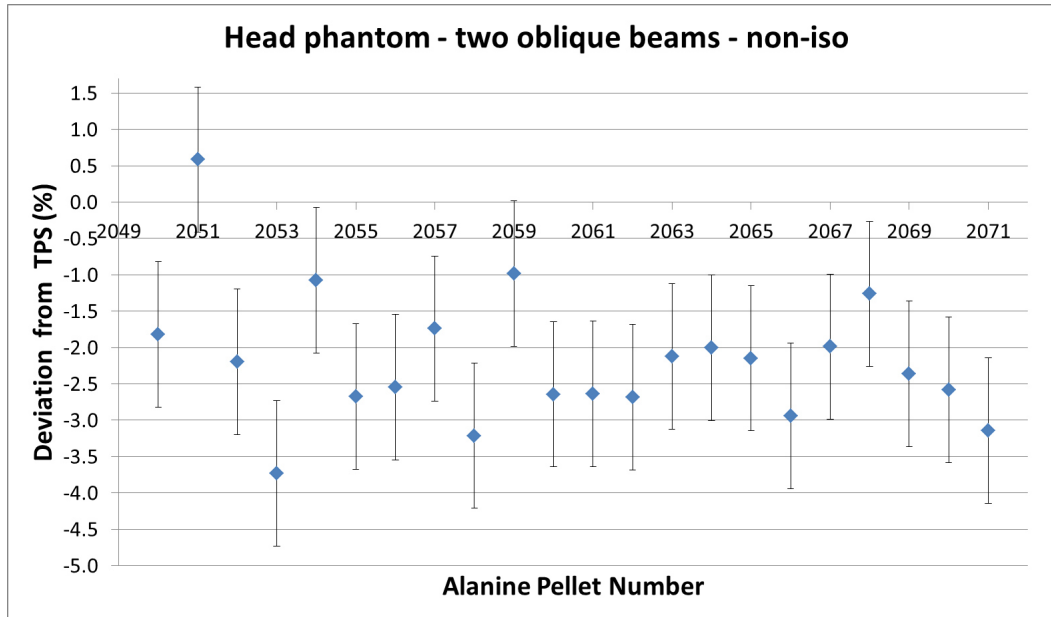


Figure 5.31: Deviations between Alanine pellets' readings and TPS planned dose. The data are corrected for the RE as described in section 5.2.3.

EBT3 film the homogeneity HI along the central cross-sectional profile in PA direction was 3% within our 5% clinical tolerance level.

As last step in order of clinical case complexity we carried out measurements in the head phantom with two oblique beams in non isocentric condition (small air gap) and one of the two beams with range shifter (see picture 5.20 (c)). Based on data acquired during the commissioning of the TPS, the Pencil Beam (PB) algorithm of RayStation v5.0 has some limitations and deficiencies in the dose calculation in presence of range shifter and large air gaps. Therefore, we recalculated the plan with the Monte Carlo (MC) algorithm v4.0 implemented in a research version of the TPS.¹ The plot in the figure 5.32 shows the deviations of Alanine pellets in comparison to the PB and MC algorithm of RayStation. As expected, due to the limitations of PB, the MC algorithm shows less deviations in comparison to PB. In table 5.4 the overall mean of the deviations from PB and MC are reported. For the MC algorithm average deviations $\approx -2\%$ have been found as for the other experiments in the homogeneous and the head phantom. No measurements with ionization chambers were performed within this particular setup. For the irradiated EBT3 film the homogeneity HI along the central cross-sectional profile in PA direction was 2.6% and therefore within our 5% clinical tolerance level.

As described in section 5.2.6 measurements with Alanine pellets have been carried out also in the *Pelvis Phantom*. In figure 5.33 the Alanine deviations to the TPS planned dose for the plan consisting of a “single beam” (Gantry 90°, couch 0°) and the plan

¹At the time of writing this manuscript the MC algorithm was not fully validated for clinical applications but it was good enough for our evaluations.

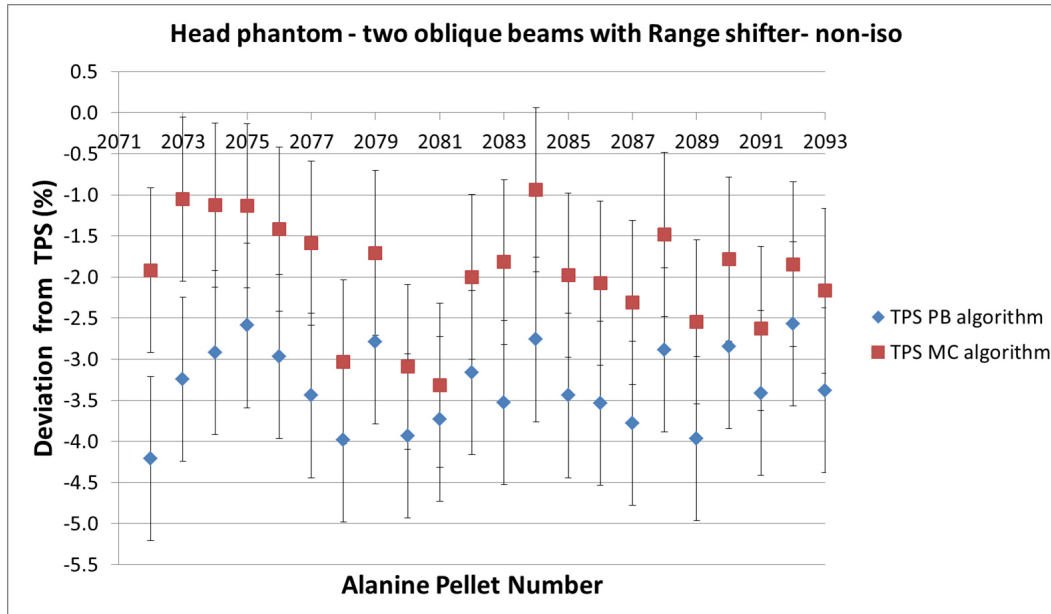


Figure 5.32: Deviations between Alanine pellets' readings and TPS planned dose with the PB and MC algorithm. The data are corrected for the RE as described in section 5.2.3. The MC algorithm is not fully validated for clinical applications.

	Deviation of Alanine from PB algorithm [%]	Deviation of Alanine from MC algorithm [%]
Mean	-3.3	-2.0
Standard deviation	0.5	0.7
Minimum deviation	-2.6	-0.9
Maximum deviation	-4.2	-3.3

Table 5.4: Overall mean deviations of Alanine pellets from PB and MC algorithms implemented in RayStation TPS. The data are corrected for the RE as described in section 5.2.3.

consisting of two “opposing beams” (Gantry 90°, couch 0° and 180°). In comparison to the measurements in the *homogeneous* and in the *head phantom* larger deviations were found in the *pelvis phantom*. Therefore, the plans were recomputed with MC v4.0 algorithm as for the plan with range shifter in the *head phantom*. The table 5.5 reports the overall mean of the deviations from PB and MC for both plans. As shown in table 5.5 the plan computed with MC algorithm partly reduces the deviations. For the *Pelvis Phantom* a larger underestimation of about $\approx 4\%$ has been found. For the two EBT3 films the average homogeneity HI along the central cross-sectional profile in PA and SI directions was respectively 2.8% and 2.9% for the “single beam” plan and the “opposing beams” plan. Both values are within our 5% clinical tolerance level.

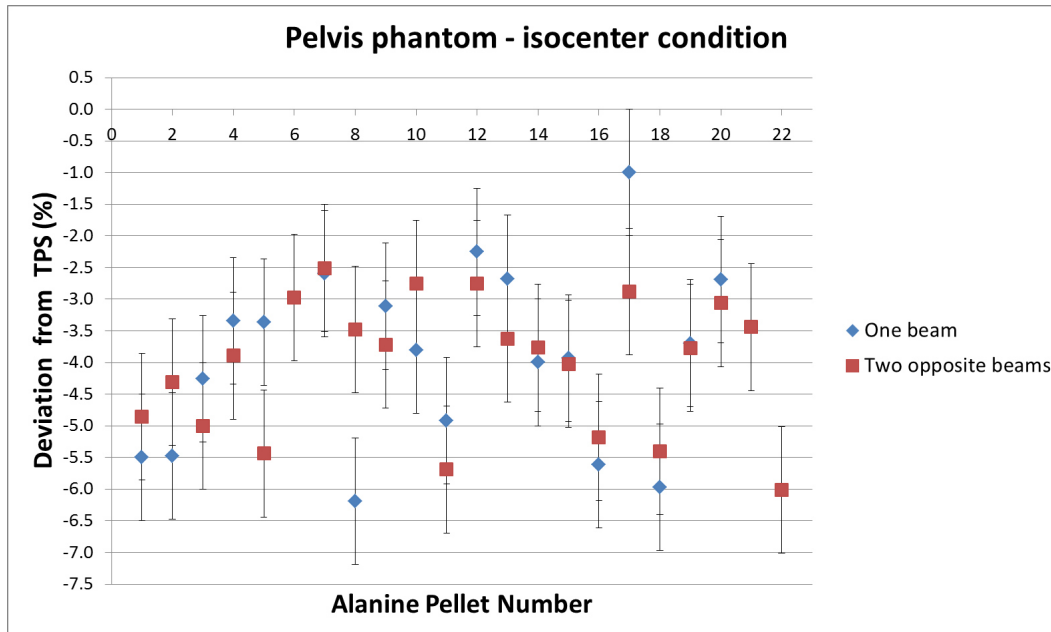


Figure 5.33: Deviations between Alanine pellets' readings and TPS planned dose for a “single beam” plan and two “opposing beams” plan. The data are corrected for the RE as described in section 5.2.3.

	Deviation Alanine-PB “single beam”[%]	Deviation Alanine-PB “opposing beams”[%]	Deviation Alanine-MC “single beam”[%]	Deviation Alanine-MC “opposing beams”[%]
Mean	-3.9	-4.0	-3.4	-3.5
Stdev	1.4	1.1	1.4	0.7
Min dev.	-1.0	-2.5	-0.3	-2.3
Max dev.	-6.2	-6.0	-6.4	-5.0

Table 5.5: For the “single beam” plan and the “opposing beams” plan the overall mean deviations of Alanine pellets from PB and MC algorithms implemented in RayStation TPS. RE corrections derived as described in section 5.2.3

5.3.2 Measurements in water phantom: Alanine pellets versus Farmer chamber.

In order to minimize the “quenching” effect of the Alanine pellets we carried out measurements in the plateau region ($z_{ref} = 20$ mm in water) in a single-layer scanned field 7×7 cm² of energy 179.2 MeV. At $z_{ref} = 20$ mm in water nine Alanine pellets and the Farmer chamber (TM30013) were irradiated with a setup described in the section 5.2.7. In the plot of figure 5.34 the deviations of Alanine pellets from the Farmer chamber measurements are shown. The measurements in plot are corrected as reported in the

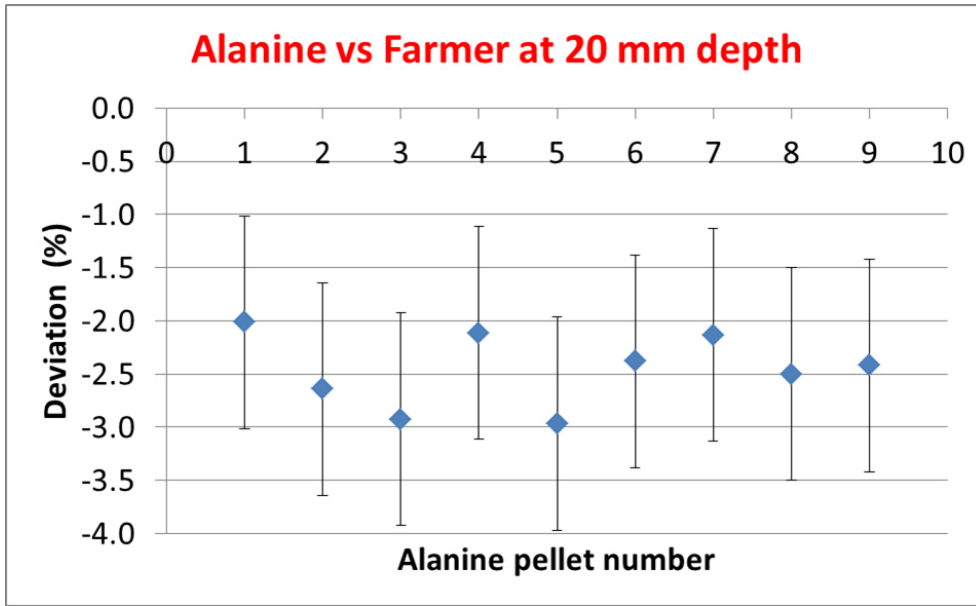
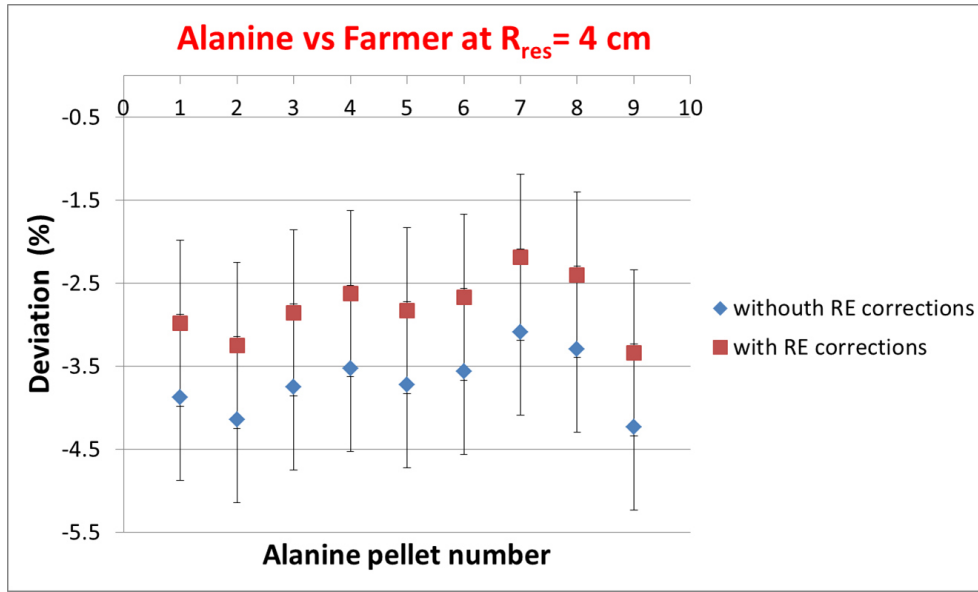


Figure 5.34: Deviations between Alanine pellets’ readings and Farmer chamber measurements at $z_{ref} = 20$ mm in water for a single-layer scanned field of energy 179.2 MeV.

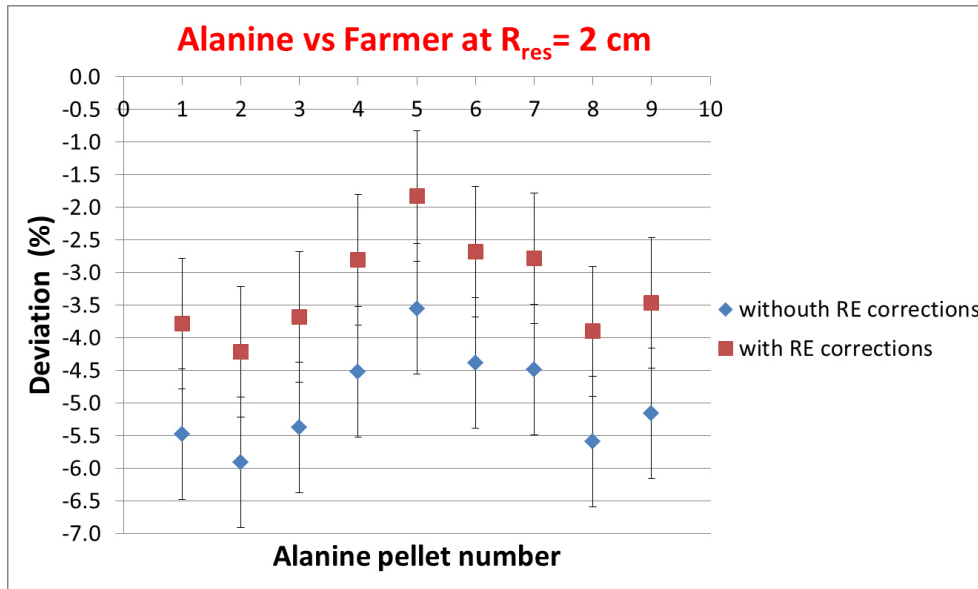
section 5.2.3 with RE set to unity. The plot of figure 5.34 shows that the Alanine pellets assess a lower absorbed dose to water in comparison to the Farmer chamber of -2.5 ± 0.3 %.

In addition a comparison Alanine versus Farmer was performed in a fully modulated scanned field of $6 \times 6 \times 6$ cm³ with the center of SOBP positioned at the WED of 15 cm. Measurements were carried out at two different residual ranges ($R_{res} = 4$ cm close to the center and $R_{res} = 2$ cm close to the distal part of the SOBP). In the plot of figure 5.35 the deviations of Alanine pellets from the Farmer chamber measurements (with and without RE corrections) are shown at the two R_{res} .

Plots in figure 5.35 show the quenching effect increase close to the distal part of the SOBP $R_{res} = 2$ cm as expected. Average deviation of -2.8 ± 0.4 % was found at $R_{res} = 4$ cm and -3.2 ± 0.8 % was found at $R_{res} = 2$ cm.



(a)



(b)

Figure 5.35: Deviations between Alanine pellets' readings and Farmer chamber measurements in water for a fully modulated SOBP are displayed. In (a) the measurements were carried out at $R_{res} = 4\text{ cm}$ and in (b) at $R_{res} = 2\text{ cm}$.

5.3.3 Uncertainty budget.

The overall uncertainty on absorbed dose to water determined with thimble chambers in proton beams at MedAustron is 2% ($k=1$) based on the guidance of TRS 398 [80]. The uncertainties are dominated by the k_{Q,Q_0} contribution $\approx 1.7\%$. In the table 5.6 the estimated uncertainties of Alanine measurements are reported. The combined uncertainty for the Alanine pellet measurements are defined as the root mean square

of the underlying initial components like NPL readout, MC simulation, stopping power ratio (uncertainty based on TRS-398), ratio of the mass energy absorption coefficients and phantoms setup. The uncertainty of the RE corrections derived by MC is dominated by the uncertainty of the Hansen and Olsen model itself. For the mass energy ratios for ^{60}Co the uncertainty is typically much smaller than 0.5% but the simplifying assumption made in eq. 5.11, that this ratio is sufficient, also involves some uncertainty which is part of this estimate. For the phantom setup the largest dose deviation inside a pellet given by the TPS was assumed.

Physical quantity	Relative Standard Uncertainty [%]
NPL readout	1
RE corrections derived by MC	2
$(S^p/\rho)_{al}^w$	2
$(\mu_{en}^{Co}/\rho)_w^{al}$	0.5
Phantom setup	0.5
Combined standard uncertainty in D_{w,Q_p}	3.1

Table 5.6: Estimated relative standard uncertainty of D_{w,Q_p} measured with Alanine pellets. The combined uncertainty for the Alanine pellet measurements are defined as the root mean square of the different components.

5.4 Discussion and Conclusion.

In order to validate beam monitor calibration several dosimetry intercomparisons for proton and carbon ion beams for passive scattering delivery systems are reported in literature [115–117]. In scanning ion beams due to facility-specific beam monitor calibration procedures it is not feasible to apply similar method and provide such inter-comparison. The Radiological Physics Center (RPC) is auditing proton facilities in US using OSLDs (Optical Stimulated Luminescence Dosimeters) and TLDs [118]. However, these detectors used by RPC for dosimetry measurements do not provide suitable accuracy for scanned proton and carbon beams as the “quenching” effect of TLD detectors is not well understood and evaluation of correction factors is a challenge [38, 119]. Contrary to TLDs, where the correction factors for quenching in scanning proton and carbon beams are not accurate, previous studies showed the feasibility of alanine EPR dosimetry in Light Ion beam therapy [40, 90, 100, 104]. Moreover, dosimetric audits with alanine detectors to verify the dosimetric accuracy of conventional photon and electron beams for IMRT plans are well established in Belgium [120] and the UK [121]. A strong motivation to use alanine as dosimeter for end-to-end tests is the very stable post-irradiation

signal and the non-destructive readout process which make them suitable for archiving and possible future analysis (opposite to TL technique where the readout delete the stored dose information). Moreover, alanine detectors have a linear dose response up to high dose levels $\approx 10^5$ Gy and they are dose rate independent up to extremely high dose rates. The latter is a very positive feature in scanning beams with high dose rate. A weakness of the alanine dosimeters might be the rather high dose prescription of 10 Gy which is needed for an acceptable reproducibility of 0.5 %. However, in this work some of the alanine pellets were irradiated at 4 Gy dose level and showed comparable agreement with the TPS planned dose as for the pellets irradiate with 10 Gy.

Overall more than 230 Alanine pellets were irradiated during the end-to-end testing at MedAustron and all the results are reported in this work. No comparable set of data for consistency on reproducibility of results can be found in literature. Regarding the measurements carried out in plastic phantoms the setup of the experiment performed at the Heidelberg Ion-Beam Therapy Center (HIT) and reported in Ableitinger et al. [90] was reproduced at MedAustron in order to have a benchmark. The measurements were acquired in two sessions at one month of distance. Average deviations of alanine pellets with respect to the planned dose were -1.9 ± 0.8 % and -1.6 ± 0.7 % and maximum deviation of -3.2 %. So all the measured pellets were within 5 % and very reproducible within 0.3 % over one month. Those results are in very good agreement ($k=1$) with the measurements carried out at HIT in which an average deviation of -2.4 ± 0.9 % and a maximum deviation of -3.6 % was found for proton beams [90]. The high reproducibility of those measurements and the excellent agreement with the results obtained at HIT was the basis for further investigations with more complex anthropomorphic phantoms. Therefore, we went through the whole treatment radiation chain with a customized *head phantom*. As first step, a treatment plan with a single beam was delivered two times over one month to check the reproducibility. Alanine pellets measurements were found very reproducible within 0.4% after one month. Average deviations of alanine in comparison to the planned dose were -2.5 ± 0.7 % and -2.1 ± 0.7 % and maximum deviation of -3.7 %. Deviations are slightly larger than the measurements in the *homogeneous phantom* but still within the uncertainty. The aim of the work was to increase the complexity of clinical cases step-by-step. Indeed, a treatment plan made of two oblique beams in non-isocentric technique (smaller air gap than at isocenter) was planned and delivered to the *head phantom*. Average deviation of alanine in comparison to the planned dose was -2.2 ± 0.9 % and maximum deviation of -3.7 %. Deviations are in agreement with the clinical case of one single beam and with the experiment performed in the *homogeneous phantom*. Moreover, for this specific indication, six alanine pellets were exposed

to ≈ 4 Gy dose level and still the deviations from the planned dose were comparable to the pellets exposed to 10 Gy. That is a very good indication for further application of Alanine pellet dosimetry at lower dose level closer to the prescription dose used for patient treatments (2 - 3 Gy/fraction). However, more detailed investigations at dose levels lower than 10 Gy would be needed. As last step of clinical case complexity for the *head phantom*, a treatment plan made of two oblique beams in non-isocentric condition and range shifter was delivered to the *head phantom*. Since the PB algorithm installed in the TPS RS v5.0 has some well known deficiencies and limitations in the dose calculation in presence of range shifter and large air gaps, the plan was recomputed with a MC algorithm installed in RS v6.0. As expected the average deviation of alanine pellets from the PB algorithm were larger than the previous clinical cases (-3.3 ± 0.5 % and maximum deviation of -4.2 %). However, the comparison with the MC shows similar behavior as the other measurements with an average of -2.0 ± 0.7 % and maximum deviation of -3.3 %.

Concerning the measurements in the *pelvis phantom* two clinical scenarios were planned: a simple one with a plan made of one single beam and a complex one with a plan made of two opposing beams. In both cases the deviations of alanine in comparison to the planned dose were larger than the measurements carried out in the homogeneous and head phantom. Average deviation of -4.0 ± 1.1 % and maximum deviation of -6.0 % were detected in the plan with two opposing beams. The recalculation with the MC algorithm in RS v6.0 helped to reduce the differences down to -3.5 ± 0.7 % on average and -5.0 % as maximum deviation. The larger deviations for the pelvis phantom may be due to the non-tissue equivalence of bone materials (femoral heads) placed on the beam axis direction. The PB algorithm in the TPS consider the nuclear interaction in different materials as in water. Therefore, the amount of high Z materials (e.g. ^{40}Ca in the bones) could result in a larger attenuation of primary proton fluence in the SOBP. This could be the reason why the measurements are much lower than the planned dose. The primary proton fluence attenuation is partly predicted by the MC algorithm but still the large uncertainties in the total cross-section data (up to 20% [24]) might explain the observed deviations. Further investigation on the fluence correction factors in different plastic materials needs to be carried out based on Monte Carlo simulations.

For the measurements with EBT3 films only the relative dose response was considered. For each end-to-end test the plastic phantom was loaded with Alanine pellets and EBT3 films in order to check the homogeneity of the 2D dose distribution. For all the films irradiated the homogeneity index HI (see eq. 5.13) was always better than 3% and within 5% clinical tolerance level established at MedAustron.

It was observed that, in all experiments carried out in plastic phantoms, alanine pellets assess a systematic lower dose than the Farmer ionization chamber. The systematic deviation between the two dosimetric techniques was around $\approx 3\%$. The monitor chambers of BDS and the beam model of TPS are calibrated against ionization chamber dosimetry. Therefore, a 2% systematic deviation found between Alanine and TPS planned dose can be attributed to the discrepancy between the two dosimetric techniques. Similar systematic deviation between alanine and Markus-type plane-parallel ionization chamber in PMMA phantom was found by Fattibene et al. [122, 123] and Onori et al. [124] in a 60 MeV proton beam. An overview of the literature regarding the use of alanine as a dosimeter in clinical proton beams was presented by Palmans [125]. Similar underestimation was found also from other authors [40, 90, 126] but not enough statistics was acquired in these papers in order to draw clear conclusions. More than 200 Alanine pellets irradiated in this study shows a consistent underestimation of alanine in comparison to ionization chambers in plastic phantoms.

In this work, in addition to the measurements in plastic phantoms, a comparison alanine versus Farmer chamber in water was performed. In table 5.7 the deviations between the absorbed dose to water determined with alanine pellets and ionization chambers are reported for each experiment in the scanned proton beams at MedAustron.

Phantom type	Field	Measurement point	Mean [%]	St. Dev. [%]	Min. Dev. [%]	Max. Dev. [%]
Water phantom	Square field $7 \times 7 \text{ cm}^2$ E 179.2MeV	$R_{res} = 19 \text{ cm}$	-2.5	0.3	-2.0	-3.0
Water phantom	box $6 \times 6 \times 6 \text{ cm}^3$	$R_{res} = 4 \text{ cm}$	-2.8	0.4	-2.2	-3.3
Water phantom	box $6 \times 6 \times 6 \text{ cm}^3$	$R_{res} = 2 \text{ cm}$	-3.2	0.8	-1.8	-4.2
Homogenous phantom (18-10-2016)	box $8 \times 8 \times 12 \text{ cm}^3$	$R_{res} = 6 \text{ cm}$	-2.9	0.7	-1.7	-3.9
Homogenous phantom (18-11-2016)	box $8 \times 8 \times 12 \text{ cm}^3$	$R_{res} = 6 \text{ cm}$	-2.3	0.7	-1.1	-3.6
Head phantom (18-10-2016)	cylinder 270 cm^3	$R_{res} = 3.5 \text{ cm}$	-3.6	0.6	-2.4	-4.9
Head phantom (18-11-2016)	cylinder 270 cm^3	$R_{res} = 3.5 \text{ cm}$	-3.2	0.7	-1.9	-4.4

Table 5.7: The results of the comparison of alanine dosimetry and ionization chamber dosimetry. For each irradiation some information about the phantom, the characteristic of the irradiated field, the measurement point are reported. Moreover, four statistic measures (mean, standard deviation, minimum and maximum deviations) of the overall deviations between dose determined with Alanine pellets and ionization chambers are shown.

As one can see from table 5.7 a systematic mean deviation of $\approx 3\%$ between the two dosimetric techniques was found for all the experiments performed in different materials (water and plastic) and different irradiation fields. Considering the overall uncertainties of the two dosimetric techniques they agree within uncertainty of measurement techniques (see section 5.3.3). The systematic deviation is at present not understood and it could be related to the uncertainty on the k_{Q,Q_0} for the ionization chambers and RE, stopping power ratio water to alanine, perturbation factors for Alanine pellets in proton beams or a combination of a number of these components. One source of uncertainty may be hidden on beam quality correction factors k_{Q,Q_0} tabulated in TRS-398 for Farmer chamber [127]. This is mainly an indication that perturbation factors in protons are not unity as assumed in TRS-398 and they could be easily add up to 1% corrections. Stopping powers for alanine and alanine pellet mixture have an uncertainty up 2%. Measurements of stopping power for the alanine pellet mixture have been carried out in proton beam at MedAustron. As preliminary result we found a value for stopping power ratio water-to-alanine pellet material slightly higher ($\approx 1.5\%$) than the calculated one. This could be an indication that also the stopping ratio water-to-pure alanine could be slightly higher than the value 1.024 [90] used for our end-to-end tests. Further investigations based on Monte Carlo simulation need to be done. The Hansen-Olsen model [89] used to derive RE corrections in proton beams presents several uncertainties mainly related to the selected radial dose distribution in the track structure model (see section 5.2.3). Most of the data in literature validate the model for heavier ions than proton [100,104] (e.g. ^{12}C ions). The model may deviate substantially for proton beam as it is based on amorphous track structure models which may work better for the densely ionizing carbon ion track than for the more sparsely ionizing track of a proton. Further validation in proton beam is necessary. Perturbation factors of alanine in proton beams are not known and might be an additional source of uncertainty. An estimation of those factors can be assessed by Monte Carlo simulation.

In conclusion, as end-to-end tests are prerequisites of clinical operation they shall be performed as last step of medical commissioning of LIBT facility. Since MedAustron started clinically with head and pelvis treatments end-to-end tests described in this work were carried out in proton beam for those two body sites. The results reported here based on Alanine pellet and ionization chamber measurements are within the uncertainties of both dosimetric methods. As final result, the new scanned proton beam technology has been properly implemented and integrated in clinical practice at MedAustron and the decision to start with patient treatments was taken.

CHAPTER 6

DISCUSSION AND CONCLUSIONS

This Thesis reports the description and the results related to the innovative methodologies applied to the medical commissioning of a Light Ion Beam Therapy facility. Here the main experimental results obtained in this work are collected along with some suggestions for further investigations.

Regarding the first topic of this study, Monte Carlo (MC) simulation is a very useful tool in order to support and speed up the medical commissioning of a LIBT facility. At MedAustron the MC particle transport code Gate v7.1 toolkit of Geant4 v10.01p02 is implemented. In a scanned proton beam it is important to consider that the primary core of each pencil beam is laterally surrounded by a low-dose envelope due to the energy deposited by scattered secondary particles produced in the interactions of the primary protons with matter. To correctly calculate absolute dose in scanned proton beams, as required when commissioning the TPS, it is necessary to model the low-dose envelope with sufficient accuracy. In this work we have investigated and validated the IDD correction factors to be applied to a finite size plane-parallel ionization chamber PPIC (TM34070, PTW-Freiburg). Previous works of Grevillot et al. [60] and Clasié et al. [59] simply quantify the corrections to be applied scoring the dose in the finite volume of the PPIC. In this work we performed a sensitivity study of the impact of the elemental physics processes (non-elastic nuclear interactions, elastic nuclear interactions and MCS) on IDD correction factors. From this study a substantial deviations among different non-elastic nuclear models was observed, thus a validation of the physics (the so called physics builders in Gatev7.1) with measurements was performed. The validation was carried out with two different methods. Transverse dose profiles were measured in water with 24 PinPoint ionization chambers in a single pencil beam at four energies spread over the whole clinical energy range. Similar experiments characterizing the low-dose

envelope surrounding the core of the pencil beam have been performed by other groups and reported in Sawakuchi et al [57], Gottschalk et al [25], Schwaab et al [72]. The main innovative features of our approach are:

- the use of 1D linear array holder with 24 PinPoint chambers (e.g. in Sawakuchi et al [57] and Gottschalk et al [25] only a single small volume chamber has been used) which speed up the measurements allowing us to increase the statistics and the number of energies measured. Beam time is highly precious during medical commissioning of a LIBT facility;
- the measurement of the low-dose envelope for the 252.7 MeV/u ($R_{80} \approx 38$ cm in water) where the *halo* contribution is more prominent. This energy range was not investigated so far;
- the benchmarking of the Gate/Geant4 code evaluating three different physics builders (QGSP_BIC_HP, QGSP_BERT_HP, QBBC) with the measured transverse dose profiles. Hall et al [73] reported the comparison of Geant4 v10.01p2 with a single physics builder (QGSP_BIC_HP) for one single energy 177 MeV/u [25]. Sawakuchi et al [69] reported a comparison of MC code MCNPX with a single default inelastic nuclear interactions, which considers the pre-equilibrium model after the Bertini intra-nuclear cascade model [64]. In Schwaab et al [72] the MC FLUKA code [74] was selected for the simulations with a fixed physics model (PEANUT Pre-Equilibrium Approach to NUClear Thermalization [75]). No comparison of different hadronic models with low-dose envelope measurements was found in literature.

The results showed a good agreement in terms of shape between MC simulations and measured transverse dose profiles. The QBBC physics builder was in slightly better agreement with measurements however, no statistical significant differences were found between the three non-elastic nuclear models. Future work on the improvement of the measurement outcome based on the estimation of the number of protons N_p delivered by the DDS will allow us to compare the simulated and measured transverse dose profiles in absolute terms as Gy/ N_p . Moreover, a better tuning of the MC beam model with the detailed description of the Nozzle, as reported in Elia et al. [68], could improve the outcome of the benchmarking. The second experimental method consisted in deriving experimentally IDD correction factors for the Bragg peak chamber TM34070 as ratio between measurements in a single-layer scanned field with a Roos ionization chamber (TM34001, see section 3.2.1) and measurements in a pristine pencil beam with the Bragg peak chamber TM34070. This approach is innovative and no similar data were

found in literature. We reproduce the same experimental setup in the MC Gate/Geant4 simulation evaluating again the three physics builders (QGSP_BIC_HP, QGSP_BERT_HP, QBBC). Both QGSP_BIC_HP and QBBC shows similar behavior overall the depths and a 0.5% differences at the mid-range with the measurements. At the same depth the QGSP_BERT_HP shows larger deviations up to 1.5%. The mid-range was shown in our study to be the part where the largest corrections appears independent on the applied physics builder. Ivantchenko et al [70] described the similarity of the implementation of the two physics builders QGSP_BIC_HP and QBBC in the Geant4 code, therefore the similar behavior of the hadronic models found in this work is expected. Moreover, the Binary cascade (QGSP_BIC_HP) and the QBBC shows better results for protons and neutrons at the clinical energy range in comparison to Bertini cascade (QGSP_BERT_HP) in terms of differential cross-sections [70]. The results of this work goes to the same direction and add a clinical relevance since they are based on dosimetric comparison and not on pure fundamental physics (cross-sections comparison) as reported in Ivantchenko et al [70]. Based on our results we selected the QBBC physics builder to derive IDD correction factors for the 20 “major” energies at MedAustron among the whole clinical range for protons [from 62.4 to 252.7 MeV/u]. The correction factors for IDD scored in a cylinder of 1000 mm diameter ($CF_{\phi 1000}$) show a larger deviations up to 2% for high energies in comparison to correction factors for IDD scored in a cylinder of 200 mm diameter ($CF_{\phi 200}$). This is mainly due to the energy deposited by neutrons and gamma. Further investigations could be addressed on the experimental investigations of the neutron-gamma component at large scattered angles in order to improve the knowledge on total nuclear cross-sections and the hadronic interaction models implemented in different MC codes used in clinical application (e.g. FLUKA, Geant4, MCNPX). The corrected prediction of out-of-field fluences of charged fragments and neutrons in the patient geometry could be beneficial for secondary cancer risk estimation (mainly for the increasing population of pediatric patients treated with proton therapy) and, out of patient geometry, for better assessment of the shielding. Based on the computed $CF_{\phi 200}$ the experimental depth dose profiles acquired with the Bragg peak chamber were corrected. “Corrected” and “raw” depth dose profiles have been provided to RaySearch Laboratories (Sweden) and, based on those data, two different beam models for the TPS RSV5.0 were developed. A detailed validation of both beam models with measurements was performed at MedAustron. The details of validation are out of the scope of this work. Based on results of the validation the “corrected” beam model was selected for clinical treatment with protons at the HBL.

Due to the complexity of the scanning technique with proton and ^{12}C ion beams the agreement between the delivered and the computed dose in the TPS has to be verified

in different points of the treatment volume prior to each patient irradiation. Therefore, patient-specific plan verification (PSQA) is a highly recommended dosimetric procedure within the QA program. Moreover, the correct deliverability of the treatment plan through the whole treatment chain needs to be verified for each patient before starting the treatment. A commercial dosimetry solution, originally developed at GSI [77] and today commercialized by PTW-Freiburg, based on the use of multiple ionization chambers (PinPoint ionization chambers) for a quasi-three dimensional dosimetric verification, has been acquired at MedAustron. However, no specific software to support the selected dosimetric equipment and interface it to the TPS is commercially available. Therefore, at the TPS level we developed a script in ironpython language in order to extract dose and dose gradient values at the effective point of measurement for each PinPoint ionization chamber. From the measurements side, the “Plan Verificator” software has been integrated in the plan verification workflow. The “Plan Verificator” supports the verification by remotely controlling the PTW equipment, carrying out measurements, comparing the measurement results with the planned dose and exporting the data into a pdf QA report for documentation. The entire software component has been verified and validated according to the international standard IEC 62304 [86]. An in-house dedicated trolley has been developed and implemented into the clinical workflow to set up the MP3-P water phantom on the robotic couch. This solution makes the equipment setup faster by a factor of 2 for PSQA. Moreover, it is necessary for the measurements in IR4 (room equipped with the proton Gantry) in which, due to the rolling-floor, the setup with the water phantom mounted on the scan lift (PTW-Freiburg) is not a suitable option. Moreover, a full characterization of the 24 PinPoint ionization chambers in proton beams was done before starting to use them for plan verification. Studies in photon beams concerning the characterization of few small volume ionization chambers have been conducted by Le Roy et al. [78] and Miller et al. [79]. However, any systematic investigation of 24 PinPoint chambers in scanning proton beams is reported in literature. Regarding ion recombination behavior in proton beams, a significant asymmetry between positive and negative polarities was found for the whole set of 24 PinPoint chambers. Similar asymmetry was also noticed for the irradiation in a stable 6 MV photon beam but not reported in this manuscript. This behavior for small volume chambers was already reported in literature [78,79] but based on measurements of one single chamber in photon beam. The asymmetry of the ionization chambers’ response at different polarity prevents the determination of the ion recombination correction factors using the standard two-voltage method [80] which would overestimate recombination. Moreover, at 300 V charge multiplication processes start to play a role in small volume ionization chambers due to

the high electric field strength close to the central electrode. Unfortunately, the Multidos electrometers, controlling 12 PinPoints at once, do not allow reducing the operating voltage to lower values than +400 V. The results of this work could suggest to the vendor (PTW-Freiburg) a reduction of the operating voltage for such small volume chambers. Ion recombination was found negligible in scanning proton beams (within 0.03%) and therefore the k_s corrections were set to unity. Polarity is a more complex phenomenon for small volume PinPoint chambers. No data in proton beams are available in literature. Variability of the polarity corrections within 0.8% from chamber to chamber were observed in proton beams. An investigation of polarity at different beam quality (R_{res}) was performed but no significant dependency of polarity corrections with the R_{res} was detected. As consequence, we correct neither the cross-calibration data nor the plan-verification measurements for polarity ($k_{pol} = 1$ for all the 24 PinPoint chambers). A cross-calibration of the whole set of PinPoints in the proton beam was carried out. In the TRS-398 [80] the beam quality factors $k_{Q_p, Q_0}^{PinPoint}$ as function of R_{res} in proton beam are not reported for the PinPoint chamber (TM31015). So a calculation of $k_{Q_p, Q_0}^{PinPoint}$ was done for the first time and details are reported in chapter 4. The measured beam quality factors $k_{Q_p, Q_0}^{PinPoint}$ are in very good agreement with the computed $k_{Q_p, Q_0}^{PinPoint} = 1.020 \pm 0.017$ based on TRS-398 [80]. The implemented workflow chain (software and hardware components) for plan verification was extensively used for the Beam Delivery System (BDS) and TPS commissioning in IR3. Moreover, the results of the PSQA for the first 25 patients treated at MedAustron, partly reported in this manuscript, are very encouraging. Regarding the clinical indications, we started with treatment of head tumors (mainly Meningiomas), paranasal tumors, head and neck and prostate tumors. Patient plans composed by fields without Range Shifter show on average a very good agreement with the measurements within $\pm 1\%$ and, in most of the cases, the 95% of measured points are within 5% dose deviation. A systematic overestimation of the dose on average $\approx +2\%$ by the TPS in comparison to the measurements was found for beams with Range Shifter due to the well known deficiencies of pencil beam algorithm PBv3.5 of RSv5.0 in presence of Range Shifter, large air gaps, shallow targets in water and small field sizes (below $4 \times 4 \text{ cm}^2$). The issue is related to the modeling in PBv3.5 of the large angle scattering component mainly due to the nuclear interactions (*halo*) in inhomogeneous systems. The sandwich Range Shifter, large air column and patient/phantom surface represents an highly inhomogeneous system in which the lateral spread of the nuclear halo is underestimated by the PB algorithm, which lead to an overestimation of the dose level, especially at shallower depth targets and small field sizes. However, none of the PSQA performed was out of the our clinical action levels (the $\pm 5\%$ criteria for the mean

global dose differences and the $\pm 7\%$ criteria for a single point measurement) and all the plans were deliverable without major issues for the quality of the treatment and the patient safety. Furthermore, the hardware and software components described in this manuscript can be easily adapted for the upcoming vertical beam line (VBL) and ^{12}C ion commissioning. Commercially available programs for verification measurements with 2D ionization chamber arrays extract the planned dose information from TPS data in DICOM format and can thus process data from every TPS. The *Plan Verificator* relies on the script plug-in “MA_QA_v3_scale_factor.py” for the RayStation TPS to extract the required data. In this context a further development of *Plan Verificator* could be the integration of a DICOM module in order to make it independent of the specific TPS used. Moreover, an analysis tool to compute the 3D gamma index [88] for the 24 measured points could be integrated in the “Analysis tab” of the *Plan Verificator* and the results documented in the QA pdf report. In this way the software could become a suitable commercial solution not only for other Light Ion Beam Therapy facilities but also extended to the more complex photon techniques.

Regarding the third topic of the project, end-to-end tests were performed at the Horizontal Beam Line (HBL) with proton beams in order to confirm that the entire logistic chain of radiation treatment works as intended. Especially for new treatment techniques implemented in a cancer treatment facility, the end-to-end test can help to detect and eliminate any possible systematic errors occurring in the treatment chain or dosimetry process. Anthropomorphic phantoms (head and prostate) have been customized in order to allocate different detectors such as ionization chambers, Alanine pellets and radiochromic films. One of the challenges of alanine for dosimetry in particle beams is the known response dependency (quenching) on the charge, the fluence and the energy of the particles constituting the mixed radiation field. However, contrary to TLDs, where the correction factors for quenching in scanning proton and carbon beams are not accurate [38, 119], previous studies showed the feasibility of alanine EPR dosimetry in Light Ion beam therapy [40, 90, 100, 104]. Corrections for the quenching were implemented in the Monte Carlo dose calculation platform of a non-clinical version of RayStation TPS. A previous attempt to implement quenching corrections on a TPS was done at GSI with the experimental TPS TRiP98 [128]. In TRiP98 RE corrections only for radiographic film dosimetry [37, 102] and TL dosimetry [38, 119] were implemented. For the first time we implemented the RE corrections of Alanine pellets on a commercial TPS. Since the corrections are integrated in the same TPS this makes the entire workflow much easier and faster without Dicom formatting issues. Among the positive features of alanine as dosimeter for end-to-end tests it is worth to mention the very stable post-irradiation sig-

nal and the non-destructive readout process which make them suitable for archiving and possible future analysis (opposite to TL technique where the readout delete the stored dose information). Moreover, alanine detectors have a linear dose response up to high dose levels $\approx 10^5$ Gy and they are dose rate independent up to extremely high dose rates. The latter is a very positive feature in scanning beams with high dose rate. Overall more than 230 Alanine pellets were irradiated during the end-to-end testing in proton beams within three different phantoms (homogeneous polystyrene phantom, head and pelvis phantom) and different clinical cases. No comparable set of data for consistency on reproducibility of results can be found in literature. In order to have a benchmark we reproduced the setup of the experiment performed at the Heidelberg Ion-Beam Therapy Center (HIT) and reported in Ableitinger et al. [90]. The high reproducibility of those measurements (within 0.3% based on two measurement sessions over one month) and the excellent agreement with the results obtained at HIT (see chapter 5 for more details) was the basis for further investigations with more complex anthropomorphic phantoms. Similar results to the homogeneous phantom were found also for the customized head phantom (average deviations of alanine pellets in comparison to the planned TPS dose was $\approx -2\%$) in different clinical cases (one single beam, two oblique beams, two oblique beams with Range Shifter). Larger deviations were found for the pelvis phantom (on average $\approx -4\%$). They may be explained by the non-tissue equivalence of bone materials (femoral heads) placed on the beam axis direction. Further investigation on the fluence correction factors in different plastic materials needs to be carried out based on Monte Carlo simulations. Regarding the dosimetry with GafChromic EBT3 films, only the relative dose response was evaluated. For all the films irradiated the homogeneity index HI was always better than 3% and within 5% clinical tolerance level established at MedAustron. Regarding the measurement with ionization chamber (mainly Farmer type) it was observed that, in all experiments carried out in plastic phantoms, alanine pellets assess a systematic lower dose than the Farmer ionization chamber. The systematic deviation between the two dosimetric techniques was around $\approx 3\%$. Similar underestimation was found also from other authors [40,90,126] but not enough statistics was acquired in these papers in order to draw clear conclusions. More than 200 Alanine pellets irradiated in this study show a consistent underestimation of alanine in comparison to ionization chambers in plastic phantoms. Therefore, in order to remove one of the possible uncertainties due the dosimetry in plastic medium, we carried out a comparison of Alanine versus Farmer ionization chamber in water. No data on comparison in water between the Alanine/EPR method and the ionometric method are reported in literature. Similar deviations between the two dosimetric methods have been found also in water. Considering

the overall uncertainties of the two dosimetric techniques they agree within uncertainty of measurement techniques. The systematic deviation is at present not understood and, in the future, we want to investigate the different sources of possible uncertainty. They could be related to the uncertainty on the k_{Q,Q_0} for the ionization chambers and RE, stopping power ratio water to alanine, perturbation factors for Alanine pellets in proton beams or a combination of a number of these components. One source of uncertainty may be hidden on beam quality correction factors k_{Q,Q_0} tabulated in TRS-398 for Farmer chamber [127]. This is mainly an indication that perturbation factors in protons are not unity as assumed in TRS-398 and they could be easily add up to 1% corrections. Stopping powers for alanine and alanine pellet mixture have an uncertainty up to 2%. Measurements of stopping power for the alanine pellet mixture have been carried out in proton beam at MedAustron. As preliminary result we found a value for stopping power ratio water-to-alanine pellet material slightly higher ($\approx 1.5\%$) than the calculated one. This could be an indication that also the stopping ratio water-to-pure alanine could be slightly higher than the value 1.024 [90] used for our end-to-end tests. Further investigations based on Monte Carlo simulation need to be done. The Hansen-Olsen model [89] used to derive RE corrections in proton beams presents several uncertainties mainly related to the selected radial dose distribution in the track structure model. Most of the data in literature validate the model for heavier ions than proton [100, 104] (e.g. ^{12}C ions). The model may deviate substantially for proton beam as it is based on amorphous track structure models which may work better for the densely ionizing carbon ion track than for the more sparsely ionizing track of a proton. Further validation in proton beam is necessary. Perturbation factors of alanine in proton beams are not known and might be an additional source of uncertainty. An estimation of those factors can be assessed by Monte Carlo simulation and it is planned to be performed at MedAustron. Based on the excellent results in terms of consistency and reproducibility of the end-to-end testing performed with different dosimetric techniques (Alanine pellets, ionization chamber and EBT3 films), the new scanned proton beam technology has been properly implemented and integrated in clinical practice at MedAustron. This gave the green light to start with patient treatments by the end of 2016 at the HBL with proton beams. Similar end-to-end testing will be carried out for each of the beam line with protons and ^{12}C ions. For carbon more attention should be reserved to the detector “quenching” which is much larger (up to $\approx 30\%$ in the bragg peak region) due to the large amounts of fragments with $Z < 6$. Therefore, the implementation and validation of the RE correction factors in the TPS would be more challenging. Moreover, k_{Q,Q_0} for ionization chambers, stopping power data for Alanine and Alanine pellets, perturbation factors for Alanine

detectors and ionization chambers are challenging topics for future investigations in ^{12}C ion beams. Finally, our experience shows that alanine pellets are suitable detectors for dosimetry audits in proton beam therapy and the developed procedures can be used to support implementation of scanning beam delivery technology in clinical practice.

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LIST OF PUBLICATIONS

Publications on peer-reviewed journals during the PhD 2014-2017

1. **Antonio Carlino** et al., “Characterization of PinPoint ionization chambers in photon and proton beams”, *Phys Med Biol*, in submission.
2. **Antonio Carlino** et al., “End-to-end tests using alanine dosimetry in scanned proton beams.”, *Phys Med Biol*, in submission.
3. L. Grevillot, M. Stock, H. Palmans, J. Osorio, V. Letellier, R. Dreindl, A. Elia, H. Fuchs, **A. Carlino**, S. Vatnitsky, “Implementation of dosimetry equipment and phantoms in practice of light ion beam therapy facility: the MedAustron experience”, *Medical Physics*, submitted.
4. Maurizio Marrale, **Antonio Carlino** et al., “EPR/Alanine dosimetry for two therapeutic proton beams”, *Nuclear Instruments and Methods in Physics Research Section B: Beam Interactions with Materials and Atoms*, 2016.
5. Maurizio Marrale, Anna Longo, Giorgio Russo, Carlo Casarino, Giuliana Candi-
ano, Salvatore Gallo, **Antonio Carlino**, Maria Brai, “Dosimetry for electron Intra-
Operative RadioTherapy: comparison of output factors obtained through Alanine/EPR
pellets, ionization chamber and Monte Carlo-GEANT4 simulations for IORT mobile
dedicate accelerator”, *Nuclear Instruments and Methods in Physics Research Sec-
tion B: Beam Interactions with Materials and Atoms*, 2015.

6. Daria Boscolo, Emanuele Scifoni, **Antonio Carlino** et al. “TLD efficiency calculations for heavy ions: an analytical approach”, European Physical Journal D, 2015.

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