“Integration of Monte Carlo simulation in radiotherapeutic treatment planning with proton beam”

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Summary

Introduction..................................................................................................................5

1 Optimization methods in proton therapy.........................................................7

1.1. Proton beam therapy.......................................................................................8

1.1.1. Proton physics interaction.........................................................................11

1.1.1.1. Electronic (collisional) stopping power...........................................12

1.1.1.2. Energy-range straggling: the Landau-Vavilov theory......................14

1.1.1.3. Multiple Coulomb Scattering..............................................................16

1.1.2. Heterogeneities in planning proton beam therapy....................................17

1.1.3. Proton biological effectiveness: the RBE-weighted absorbed dose........25

1.1.4. Beam delivery techniques and proton dose distribution.......................27

1.2. Dose calculation algorithm.........................................................................31

1.2.1. Ray tracing or broad beam algorithm...................................................33

1.2.2. Pencil beam algorithm............................................................................34

1.2.3. Monte Carlo calculations.........................................................................35

1.2.4. Chosen approach to in-house TPS. Long term research. Program.............37

1.3. Proton therapy plan optimization.................................................................39

1.3.1. Single field uniform dose (SFUD).........................................................41

1.3.2. Field patching.........................................................................................43

1.3.3. Intensity-modulated proton therapy (IMPT)..........................................43

1.4. Objective Function minimization.................................................................47

1.4.1. Deterministic approaches: steepest descendent methods, variable metric (Quasi-Newton) methods and conjugate gradient methods.49

1.4.2. Stochastic approaches: simulated annealing methods .........................50

1.5. Dose distribution comparison......................................................................51

1.5.1. Dose difference, distance to agreement (DTA) and gamma function.........................52
2. Monte Carlo simulations and results................................................. 55
   2.1. The Fluka Monte Carlo code and the ENEA GRID................................. 58
      2.1.1. FLUKA parallelization............................................................ 58
      2.1.2. FLUKA code, check about Landau-Vavilov distribution............... 60
   2.2. Simulation geometry and deposited energy distribution..................... 69
   2.3. Finding a formula for the Bragg curve using MC simulation as benchmark................................................................. 67
      2.3.1. Checking the Bragg peak dependence by the beam and the media characteristics.......................................................... 69
      2.3.2. Reproducing the Bragg curve.................................................... 73
         2.3.2.1. Mean residual proton energy................................................. 76
         2.3.2.2. Fit of the interpolated integrated deposited energy in lung and in bone versus the interpolated integrated deposited energy in water................................................................. 83
         2.3.2.3. Fit of the interpolated depth in lung and in bone versus the interpolated depth in water.................................................. 98
         2.3.2.4. Results.................................................................................. 103
   2.4. Multiple Coulomb scattering.......................................................... 125
      2.4.1. Fitting the transversal deposited energy distribution...................... 117
      2.4.2. The sigma parameter.................................................................... 127
   2.5. Oblique incidence............................................................................. 133
   2.6. Dose distribution optimization......................................................... 139
3. Beam composition................................................................................. 139
   Conclusions............................................................................................ 145
   BIBLIOGRAPHY...................................................................................... 147
Introduction

The TOP project (TOP is acronym of Terapia Oncologica con Protoni (Oncological Therapy with Protons)), whose aim has been perspective studies, designs and tests for realizing an innovative proton therapy facility in Rome, has been carried out on many years, and now seems to have a new impulse from new funding in the TOP-IMPLART project (TOP-IMPLART is the acronym of Terapia Oncologica con Protoni and Intensity Modulated Proton Linear Accelerator for Therapy). The program, which will be developed in collaboration with ENEA (Agenzia Nazionale per le nuove tecnologie, l’energia e lo sviluppo economico sostenibile), ISS (Istituto Superiore di Sanità) and IFO (Istituti Fisioterapici Ospedalieri), is in a preliminary phase, and the facility foresee reaching 250 MeV beam energies in order to treat also deep sited tumors.

In this viewpoint, great efforts have been done and will be done in order to develop modular linear accelerators, shielding systems, patient immobilization devices, detectors and sophisticated hardware for delivering and monitoring the released dose to the patient with the maximum accuracy and precision. Together with this issues it is of great importance to develop the knowhow about Treatment Plan Systems (TPS). Although commercial TPS are available, an accurate dose calculation requests the knowledge of the specific beam delivery modalities of the accelerator which will be used. Then it is needed to develop a totally known instrument, ideated for the specific realizing facility, by means of which checking the results of the commercial TPS.

The development of a TPS requests a multi-year research program, which should be carried out in integration with a medical physicist group, which has a tested experience in the TPS use even if only in radiotherapy with beams other than protons.
The work here done represents the initial phase of this program. In the first chapter the whole process which should be adjusted is outlined, while in the second and in the third chapters the original work up to here done is presented.
Chapter 1

OPTIMIZATION METHODS IN PROTON THERAPY

Since the beginnings of radiotherapy several techniques have been developed in order to deliver the prescribed dose to the tumour keeping the dose in the surrounding healthy tissue as low as possible. The most used radiotherapy techniques employ photon and electron beams to deliver the dose into the tumour volume. In the clinical practice, in order to irradiate selectively deep-seated tumors, radiotherapists use multiple beams directed towards the geometrical centre of the target and they conform the dose distribution to the target volume by Multi-Leaf Collimator (MLC) usage. Moreover a special technique, the Intensity Modulated Radiation Therapy (IMRT), allows conforming dose to the tumour by using a large numbers of variable-intensity beam-lets, delivered from multiple directions. Nowadays new techniques using proton and heavy ion beams have been developed in many radiotherapeutic centres worldwide. These new radiotherapeutic techniques allow high degree of precise conformation to the tumour with high dose gradient between target volume and healthy tissues. In order to meet the precision needed for highly conformal treatment, dose distribution within the patient has to be predicted with maximum accuracy, so the development of more and more accurate therapeutic treatment optimization is needed.

There are several methods of evaluating dose distribution in patient. Monte Carlo (MC) is, in principle, the only method capable of computing the dose distribution accurately for all situations encountered in radiation therapy. This includes also the accurate prediction of the dose near interfaces of materials with very dissimilar atomic number, such as near metal prostheses, or different densities, but it needs very long computing time. So, the development of optimized
treatment plan completely based on Monte Carlo is out of any realistic prospective for many years to come. Calculation algorithms, like broad beam algorithms and pencil beam algorithms, are faster, although they are less accurate. Nevertheless it is possible to match the precision of Monte Carlo simulations and the rapidity of analytical calculation in order to estimate dose distributions. This problem can be subdivided into two steps: the first is the research of an analytical optimized model constructed on Monte Carlo simulation for calculating dose distribution; the second is the optimization of pencil beams parameters such as directions, energies and intensities. Plan optimization is in principle an inverse problem which requires first the individuation and then the minimization of an objective function. Finally, a technique for dose comparison is needed in order to validate the results and to evaluate the agreement between planned dose and evaluated dose into a quality assurance program.

1.1. Proton beam therapy

Proton therapy offers an enhanced possibility of effective tumor control while minimizing treatment related side effects. The efficacy of proton therapy has been verified for several tumour categories; this is evident in terms of local control reached for chondrosarcoma of the skull base [1], uveal melanoma [2] [3] [4], hepatocellular carcinoma [5] [6], stage T1 non-small-cell lung cancer [7] [8], paranasal sinus carcinoma [9], sarcomas of the axial spine [10] and solid tumors in pediatric patients [11]. Proton therapy is a valid alternative to conventional therapies, mainly for tumours sited in the proximity of vitality organs or deep seated tumours close to radiosensitive organs.

In order to perform a radiotherapeutic treatment, the best way for delivering dose to tumor sparing normal tissues has to be determined and this is accomplished
by the use of the Treatment Plan System (TPS). The calculation algorithms implemented in the TPS should be able to evaluate the dose distributions for all the available beam delivery techniques in the facility. In fact calculation algorithms, and then dose distributions, are strictly related to the employed delivery technique. Furthermore the dose calculation requests a precise simulation of the patient anatomy, and this is obtained by accurate mapping of tissue density, by means of a planning Computed Tomography (CT), that is a series of the CT scans taken with the patient in the same immobilization device and possibly position to be employed during the treatment, preferably without contrast medium. On the basis of this patient representation, dose distributions have to be calculated and optimized, determining beam directions, intensities and energies.

The plan calculation is dissimilar in proton beam therapy with respect to photon beam therapy, and this is due to proton interaction properties, quite different from that of electron and photon. Proton has a high ionization density at the end of the range and it is subjected to a weak angular scattering. The entrance dose is relatively low (plateau) and most of the energy is released at the end of the path (Bragg Peak) with a rapid distal dose fall-off. The finite penetration depth of proton beam, which is greatly affected by the beam energy and by the nature (in particular by the density) of tissues traversed, allows ‘distal blocking’. Then the beam penetration depth can be modified by varying the beam energy or by putting materials with different density or different thickness on the beam path. Therefore a flat dose distribution region, the so called Spread-Out Bragg Peak (SOBP), can be obtained by the superposition of longitudinal (energy) modulated beams. Moreover the width of proton beam lateral penumbra\(^1\) varies with depth, being affected by scattering.

\[^1\] The lateral penumbra is the lateral distance from the 80% dose to the 20% dose level.
Also the plan optimization is dissimilar in proton beam therapy with respect to photon beam therapy: the proton penetration depth is finite, so with protons one needs to be concerned only about entrance tissues in choosing a beam direction (except when a critical sensitive structure is just behind the target volume), while with photons one needs to be concerned about both entrance and exit tissues. This implies that in proton therapy a wider range of desirable beam directions than in photon therapy is available to the planner. However superficial or shallow sensitive structures should be avoided. Then, in the beam direction choice, the beam has to be angled so as to achieve the maximum spatial separation between the Planning Target Volume (PTV) and distal critical Organs At Risk (OAR). Beam directions that lie tangent to a tissue-air interface or that intercept sharp heterogeneities must also be avoided. Furthermore, whereas with photons near-opposed beams or a pair of wedged fields some 90° apart are needed in order to compensate for the exponential dose fall-off, with protons only sufficient angular separation is requested to avoid an appreciable overlap of the beams on the skin, then the use of widely separated proton beams is not necessary [12]. Moreover a satisfactory treatment plan can be obtained with fewer proton beams than photon beams [13].

Better conformity causes the proton dose distribution to be more affected by uncertainties in beam delivery, patient setup/immobilization, tissue heterogeneities, organ motion and dose calculation with respect to photon dose distribution. The late in the clinical use of protons respect to photons is then related to the proton bigger need of precision in planning and assessing dose, apart from to the higher uncertainties.

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2 The PTV is a geometrical concept, introduced in order to select the appropriate beam sizes and beam arrangements to ensure that the prescribed dose is actually delivered to all parts of the clinical target volume (CTV). It surrounds the CTV with an additional margin to compensate for the different types of variations and uncertainties in the location of the beam relative to the CTV. With protons, different margins are generally required in the depth dimension than in the lateral directions.

3 The OAR (“critical normal structures”) are normal tissues whose radiation sensitivity may significantly influence treatment planning and/or prescribed dose.
proton beam facility cost. The improvement in beam delivery modalities, the advances in image science, with the development of more and more complex imaging techniques that allows better accounting for heterogeneities in the dose distribution calculation, the advances in studies of physical, biological, technical, and clinical aspects of proton therapy allowed the increasing use of protons in radiotherapy.

1.1.1. Proton physics interactions

In determining the distribution of absorbed dose in the patient, the processes by which protons slow down and deposit energy along their tracks have to be considered. Protons and heavy charged particles travels an almost straight path trough matter, losing energy almost continuously, primarily through the ionization and the excitation of atoms: a proton can transfer only a small fraction of his energy in a single electronic collision\(^4\), and its deflection in the collision is negligible; the ionization results in the production of secondary electrons, the so called δ ray. The proton can also suffer elastic or inelastic scattering from an atomic nucleus. The proton energy lost in radiative processes is instead negligible in the range of energies that are employed in therapy.

\(^4\) The proton to electron mass ratio is \(M/m_e=1836.15\), so the maximum energy that a proton having initial kinetic energy \(E_0\) can lose in colliding with an atomic electron is \(T_{\text{max}}=0.0022E_0\). In fact the maximum energy that a charged particle can lose is \(T_{\text{max}} = \frac{4m_e ME_0}{(M + m_e)^2}\). This formula is derived classically by hypothesizing elastic collision and by applying the momentum and energy conservation laws: it’s assumed that the charged particle moves rapidly compared with the atomic electron and that the energy transferred is large compared with the binding energy of the electron in the atom, that is the electron is considered to be initially free and at rest [14]. The relativistic expression of this formula is \(T_{\text{max}} = \frac{2m_e c^2 \beta^2 \gamma^2}{1 + 2\gamma \frac{m_e}{M} + \left(\frac{m_e}{M}\right)^2}\). In the low energy approximation, that is for \(2\gamma m_e/M<<1\), \(T_{\text{max}} = 2m_e c^2 \beta^2 \gamma^2\) [15].
In the next paragraphs will be summarized the principal physical effects which undergoes a proton beam during penetration in matter.

1.1.1.1. **Electronic (collisional) stopping power**

The slowing down of charged particles depends on the charge $z e$ and energy $E_0$ of the particle and on the characteristics of the material (density $\rho$, atomic number $Z$, atomic mass number $A$, and mean excitation energy $I$). Classical and quantum-mechanical theories have been developed in order to describe the energy loss of charged particles in matter; the phenomenon is well described defining the so called *stopping power* $S=-dE/dx$ of the medium for the particle, that is the average linear rate of energy loss of a heavy charged particle in the medium. $dE$ is the mean energy lost by the charged particle in electronic collisions while traversing the distance $dx$ in the medium. The stopping power is well expressed by the Bethe-Bloch equation [56] [17]:

$$S = -\frac{dE}{dx} = 0.1535 \frac{\rho Z^2 Z}{A} \frac{1}{\beta^2} \left[ \ln \frac{2m_e c^2 \beta^2 \gamma^2 T_{\text{max}}}{I^2} - 2\beta^2 - \delta(\beta \gamma) \right] [\text{MeV cm}^{-1}]^5,$$

where $T_{\text{max}}$ is the maximum kinetic energy which can be imparted to a free electron in a single collision (see note 4), $I$ is the mean excitation energy (in eV),

$$\gamma = 1 + \frac{E_0}{M}, \quad \beta = \sqrt{1 - \frac{1}{\gamma^2}}$$

is the relativistic velocity, $m_e c^2=0.510998918(44)$ MeV

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5 In the square brackets of Bethe-Bloch formula various correction terms have to be included at low energies, that is when the proton velocity is not large compared to the velocities of the atomic electrons. These terms are the shell corrections $C/Z$, which accounts for atomic binding, the Bloch corrections $z^2L_z(\beta)$, which take into account departures from the first-order Born approximation and the Barkas corrections $zL_t(\beta)$, which accounts for small differences in stopping power of particle with same mass and velocity and with opposite charge.
is the rest electron mass and $\delta(\beta\gamma)$ is the density effect correction to ionization energy loss\textsuperscript{6}.

Then the stopping power has a strong nonlinear dependence on the proton energy, and it depends linearly on the density and on the ratio $Z/A$. The value of this ratio is the same for the majority of interest materials ($Z/A = 0.5$), with the exception of highly hydrogenous materials ($Z/A > 0.5$) and elements of very high $Z$ ($Z/A < 0.5$). Thus, for many media, in order to eliminate the stopping power dependence from material, the so called proton mass stopping power $S/\rho$ is often used. However a little dependence on material is still given by the terms into the square brackets in the stopping power formula, which involve the mean excitation energy and the density effect correction.

The almost continuous energy loss of protons traversing a material causes the proton stopping range to be finite. In the Continuous-Slowing-Down Approximation (CSDA, that is a gradual and continue energy loss is assumed), the range of a particle is related to the stopping power $S$ by the

\begin{equation}
\delta(\beta\gamma) = \begin{cases} 
2(\ln 10)x - \bar{C} & \text{if } x \geq x_1; \\
2(\ln 10)x - \bar{C} + a(x_1 - x)^k & \text{if } x_0 \leq x < x_1; \\
0 & \text{if } x < x_0 \text{(nonconductors)}; \\
\delta_0 10^{2(x-x_0)} & \text{if } x < x_0 \text{(conductors)}
\end{cases}
\end{equation}

where $x = \log_{10} \eta = \log_{10} p/Mc$ and $\bar{C}$ is the negative of the quantity $C$ defined by Sternheimer and obtained by comparing the high energy value of the cited $\delta(\beta\gamma)$ parameterization with the limit value of $\delta(\beta\gamma)$, that is $\frac{\delta}{2} \to \ln \frac{\hbar \omega_p}{I} + \ln \beta\gamma - \frac{1}{2}$, ($\hbar \omega_p$ is the plasma energy

\[ \hbar \omega_p = \sqrt{4\pi N_e r_e^3 \frac{m_e c^2}{\alpha}} = 28.816 \sqrt{\rho \frac{Z}{A}} \text{ [eV]}. \]

\textsuperscript{6} The density effect, which is noticeable only for protons with energies above several hundred MeV, accounts for the reduction in the ionization loss due to medium polarization as the particle pass through it. The density effect correction is usually calculated using the Sternheimer's parameterization:

The almost continuous energy loss of protons traversing a material causes the proton stopping range to be finite. In the Continuous-Slowing-Down Approximation (CSDA, that is a gradual and continue energy loss is assumed), the range of a particle is related to the stopping power $S$ by the
expression: \( R = \int \frac{1}{S(E)} dE \). Thus, so like S, the penetration of protons is strongly affected by the density of the tissues through which they pass. As the range is inversely related to the stopping power, the penetration of a proton beam of a given energy, expressed in terms of mass thickness (that is \( \rho \, dx \), the product of material density \( \rho \) by thickness \( dx \)) is nearly independent of the material traversed.\(^7\)

1.1.1.2. Energy-range straggling: the Landau-Vavilov theory

Each particle experiences a different set of interactions due to the stochastic nature of the energy loss. So, when a group of particles which have the same initial energy traverse a thickness of absorber, two phenomena happen: energy straggling and range straggling, which consist in a distribution around a mean value respectively of the proton energy and of the stopping depth. These distributions can be calculated and they have a width that depends on the material and thickness of the absorber and on the particle energy. The probability distribution \( f(\Delta, t) \)\(^8\) of the energy loss \( \Delta \) by a particle in traversing a material of thickness \( t \) has been studied by Landau [18] and Vavilov [19]. In the Vavilov theory, which is a generalization of the Landau theory, the energy loss probability distribution depends on the particle velocity and on a parameter \( x \), indicative of the ratio of the mean energy loss \( \bar{\Delta} \) over the considered path length to the largest energy-transfer \( T_{\text{max}} \) possible in a single collision with an atomic electron (for the \( T_{\text{max}} \) formula, see note 4). The mean energy loss \( \bar{\Delta} \) over a short path length \( t \) (expressed in gr cm\(^{-2}\)) is given by the formula [20]:

\[
\bar{\Delta} = 0.30058 \frac{m_e c^2}{\beta^2} \frac{Z}{A} t \left[ \ln \frac{2m_e c^2 \beta^2 \gamma^2 T_{\text{max}}}{I^2} - 2\beta^2 - 2 \frac{C}{Z} - \delta(\beta \gamma) \right];
\]

\(^7\) An interesting property of the mass thickness is that the mass thickness of a composited medium is the sum of the mass thicknesses of the individual constituent materials.

\(^8\) \( f(\Delta, t)d\Delta \) represents the probability that a proton, in traversing a path thickness \( t \) in the target, due to several collisions with atomic electrons, undergoes a energy loss in the range from \( \Delta \) and \( \Delta + d\Delta \).
factor in the square brackets is independent from \( t \) and is a very slowly varying function of the particle energy, so it has been disregarded by Vavilov in defining his parameter \( x = \frac{\xi}{T_{\text{max}}} = \left( 0,30058 \frac{m_e c^2 Z}{\beta^2 A} \left\{ \frac{1}{T_{\text{max}}} \right. \right) \).

The value of this parameter determines the shape of the distribution:

- if \( x >> 1 \), that is if each energy transfer to electron is small \((\xi >> T_{\text{max}})\), the energy loss distribution \( f(\Delta, t) \) has a Gaussian shape;

- if \( x << 1 \), that is each energy transfer contributes significantly to the energy loss \( \Delta \) \((\Delta << T_{\text{max}})\), the Vavilov energy-loss distribution \( f(\Delta, t) \) assumes the Landau distribution shape: it is asymmetric with a tail at larger \( \Delta \) values; this asymmetry increases with decreasing of the material thickness \( t \). In the Landau theory the energy loss probability distribution has been obtained without any restriction to the allowed single energy transfer, and it is related to a parameter \( \lambda \).

- in intermediate case the distribution \( f(\Delta, t) \) is well described by the Vavilov theory: \( f(\Delta, t) d\Delta = \frac{1}{\xi} \varphi_v(\lambda_v, x, \beta^2) d\lambda_v \), where \( \varphi_v(\lambda_v, x, \beta^2) \) is function, other than \( x \) and \( \beta^2 \), also of the parameter \( \lambda_v \), which is related to the energy loss by the expression: \( \lambda_v = \frac{\Delta - \overline{\Delta}}{T_{\text{max}}} - x(1 + \beta^2 - \gamma_{\text{Eulero}}) \).

\[ \lambda = \frac{\lambda_v}{x} - \log x = \frac{\Delta - \overline{\Delta}}{\xi} - 1 - \beta^2 + \gamma_{\text{Eulero}} - \log x, \] where the value of the Eulero constant is \( \gamma_{\text{Eulero}} = 0,577216. \)
1.1.1.3. Multiple Coulomb Scattering

Protons that have travelled a thickness $dt$ in a material show a transverse distribution around the central beam axis with a width which can be calculated from multiple scattering theory and which also depends with a more complicated dependence on both the thickness of material traversed and the proton incident energy. Several theories have been developed in order to describe the multiple scattering effect, arising from many elastic collisions in the Coulomb field of the nuclei as the charged particle pass through the medium; Bethe [21] obtained a simpler derivation of the equations found by Molière in his theory of multiple scattering. This theory allows determining analytically the angular distribution of charged particles passing through a thin foil. The advantage of this theory is the dependence of the angular distribution by a single parameter $b$, which can be expressed in terms of the ratio between the unit probability angle $\chi_c$ and the screening angle $\chi'_a$. The former is defined in such a way that the total probability of single scattering through an angle greater than $\chi_c$ is one; $\chi_c$ depends, among others quantity, also from material thickness $t$ (which is expressed in gr/cm$^2$):

$$\chi_c^2 = 4\pi N t e^4 Z(Z + 1)z^2 / (pv)^2.$$  

In this formula $z$, $p$ and $v$ are respectively the charge, the momentum and the velocity of the particle and $N$ is the number of scattering atoms per cm$^3$. The characteristic screening angle $\chi_a$ describes the scattering atom and its evaluation has been obtained by Molière in the case of single scattering by a Thomas-Fermi potential$^{10}$:

$$\chi_a^2 = \chi_0^2 (1.13 + 3.76\alpha^2),$$

$$\chi_a^2 = 1.167\chi_a^2$$

with $\alpha = zZe^2 / (\hbar v)$ and $\chi_0 = \hbar / a = \hbar / (0.885a_0Z^{-\frac{1}{3}})$, where $\hbar$ is the De Broglie wavelength, $a_0$ the Bohr radius and $a$ the Fermi radius of the atom.

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$^{10}$ The Thomas-Fermi potential is not suitable to calculate the value of $\chi_a$ for materials with low atomic number.
The angle $\chi_0$ is such that the cross section $\sigma$, which decreases rapidly for large angles $\chi$ as $\chi^4$, begin complicated only for angle of the order of $\chi_0$. Then the parameter $b$ can be obtained by the relation $e^b = \frac{\chi c}{\chi a^2} = \frac{6680r (Z + 1)Z^2}{A(1 + 3.34\alpha^2)}$. The second factor in this formula represents the effective collision number per gr/cm$^2$ and it is often about unity. This parameter is related to the scattering angle $\theta$ by the relations: $b = B - \ln B$, and $\vartheta = \lambda B^{-\frac{1}{2}} = \theta l(\chi cB^{-\frac{1}{2}})$.

The Molière probability distribution of scattering angle can be expressed as the sum of three terms. The first term, $f^{(0)} = 2e^{-\vartheta^2}$, has a Gaussian shape and is dominant at small angles, that is when $\vartheta < 2$. In this angle region the width of the Gaussian is somewhat smaller than the expected: it is $\theta_w = \chi c(B - 1.2)^{\frac{1}{2}}$ and not $\theta_w = \chi c B^{\frac{1}{2}}$. At large angles, that is when $\vartheta > 2$, $f^{(0)}$ decreases exponentially, while the second term, $f^{(1)}$, goes over the single scattering Rutherford formula ($f^{(1)} = 2\vartheta^{-6}$). The third term is a correction which has to be included if an accuracy of 1 percent is required and if B is of order 10. Then the angular distribution can be approximated with $f^{(0)} = f^{(1)} + B^{-1}f^{(1)}$ at any angle.

1.1.2. Heterogeneity in planning proton beam therapy

Differences in the physics of photons and protons cause variations in planning with photon beams and with proton beams. Photon attenuation has a different dependence on the chemical composition of the medium than do proton-stopping power: photon intensity is exponentially related to photon attenuation

\[ \frac{dl}{l} = -\mu_{\text{material}} dx \]
coefficients $\mu^{\text{material}}$, which are functions of material electron density and atomic number $Z$. This implies that heterogeneities affect differently proton and photon beams: the medium density variation causes to photon beam an intensity change, while to proton beam a penetration depth change and no appreciable intensity alteration up to the end of the range. In order to account for proton penetration depth change caused by heterogeneities, the water equivalent thickness (WET) of a material has to be considered: for proton beam with an initial energy $E_i$ and residual range $R$ in water, and for a slab of material of thickness $\Delta t_{\text{mat}}$ and mass density $\rho_m$, the WET $\Delta t_{\text{water}}$ is defined as the thickness of a block of water that results in the same residual range $R$:  
\[ \Delta t_{\text{water}} = \Delta t_{\text{mat}} \frac{\rho_m}{\rho_{\text{water}}} \frac{S_m}{\bar{S}_{\text{water}}} = \Delta t_{\text{mat}} \frac{S_m}{\bar{S}_{\text{water}}} \]  
where $S_m = \bar{S}_m / \rho_m$ and $S_{\text{water}} = \bar{S}_{\text{water}} / \rho_{\text{water}}$ are the mean proton stopping power values of material and water respectively and $\rho_{\text{water}}$ is the mass density of water. In the first two figure of Fig. 1.1 is illustrated the WET mean: the depth of penetration in the water equivalent thickness (central figure) is the same as the material thickness (in the upper figure).

expression can be integrated over the material thickness $x$, leading to the following formula for the calculation of beam intensity after traversing the material:  
\[ I = I_0 e^{-\mu^{\text{material}} x} . \]

12 The mean mass proton stopping power is defined as $\bar{s} = \frac{\int s dE}{\int dE}$. Indeed, defining the path length averaged mass stopping power as $\bar{s}_t = \frac{\int \bar{s} dE}{\int dE}$, if the integral limit is the water thickness $t_w$, one can calculate the energy loss $\Delta E$ in the slab: $\Delta E(\rho t) = \bar{s}_t \rho t$. 

18
Fig. 1.1 Illustration of water equivalent thickness and water equivalent density. To be noted that in the lower figure is represented a fictitious material, indicated as “heavy water”, having the same composition of water and the density of the material considered in the upper figure.[77]

Another equivalent way to account for depth variations due to heterogeneity presence is by means of the water equivalent density $\rho_{eq}$ of a material. If $\Delta E = \bar{S}_m \Delta t_{mat}^m$ is the energy loss of a proton beam passing through a material thickness $\Delta t_{mat}^m$, the water equivalent density $\rho_{eq}$ is defined as the density of a block of (fictional) material of the same elemental composition as water and of the same thickness $\Delta t_{water} = \Delta t_{mat}^m$ that produces the same energy loss $\Delta E = \frac{\bar{S}_{water}}{\rho_{water}} \rho_{eq} \Delta t_{water}^m$, of the protons passing through it (this fictional material is represented in the lower figure in Fig. 1.1, as is shown, it produces a variation $\Delta R$ in range). The water equivalent density $\rho_{eq}$ can then be estimated in two ways:
from range-energy tables, by comparing the mass stopping powers in the media and in water. In fact, by imposing the equality in energy loss by a proton beam passing in the media and another one passing in water and accounting for equality in thickness ($\Delta t^\text{water}_m = \Delta t^\text{mat}_m$, so $\Delta E = S_{\text{m}} \Delta t^\text{mat}_m = \frac{S_{\text{water}}}{\rho_{\text{water}}} \rho_{\text{eq}} \Delta t^\text{mat}_m$), the water equivalent density can be obtained by the relation: $\rho_{\text{eq}} = \frac{S_{\text{m}}}{S_{\text{water}}} \rho_{\text{water}}$ \(^{13}\)

- by measuring the variation in range $\Delta R$ of protons passing through a water tank with and without a physical thickness $\Delta t^\text{mat}_m$ of the material in question inserted into the water tank in the path of the protons. In fact the relation between equivalent density and range variation can be obtained by considering the thickness so small that the range can be evaluated as $\Delta E/S$, so, the range variation is: $\Delta R = \frac{S_{\text{mat}}}{S_{\text{m}}} \rho_{\text{eq}} \Delta t^\text{mat}_m = \Delta t^\text{mat}_m \left(1 - \frac{\rho_{\text{eq}}}{\rho_{\text{water}}} \right)$ \(^{14}\)

$\Delta t^\text{mat}_m$ and $\rho_{\text{eq}}$ are the physical thickness (in cm) and the water-equivalent density.

\(^{13}\) The water equivalent thickness $\Delta t^\text{water}_m$ and the water equivalent density $\rho_{\text{eq}}$ are related by the equation obtained by equality of energy loss: $\Delta E = \frac{S_{\text{water}}}{\rho_{\text{water}}} \rho_{\text{water}} \Delta t^\text{water}_m = \frac{S_{\text{water}}}{\rho_{\text{water}}} \rho_{\text{eq}} \Delta t^\text{water}_m$

$$\Delta t^\text{water}_m \rho_{\text{water}} = \Delta t^\text{water}_m \rho_{\text{eq}} = \frac{S_{\text{m}}}{S_{\text{water}}} \rho_{\text{water}} \Rightarrow \Delta t^\text{water}_m \rho_{\text{water}} = \Delta t^\text{water}_m \rho_{\text{eq}} = \frac{S_{\text{m}}}{S_{\text{water}}} \rho_{\text{eq}}$$

\(^{14}\) This formula can be generalized in the case of a proton beam traversing a slab of material of composition other than that of the surrounding medium interposed in the beam path: $\Delta R = \frac{s(\rho^\text{medium}_{\text{eq}} - \rho^\text{slab}_{\text{eq}})}{\rho_{\text{water}}} \text{ (cm)}$, where $\rho^\text{medium}_{\text{eq}}$ is the water-equivalent density of the surrounding medium and $\rho^\text{slab}_{\text{eq}}$ is the water-equivalent density of the slab.

20
density of the interposed slab respectively. The mass density of water $\rho_{\text{water}}$, is taken to be unity when densities are expressed in units of gr cm$^{-3}$.

In proton therapy, in order to calculate the beam penetration depth accounting for its dependence from density, the Hounsfield numbers (H)$^{15}$ of the CT scan (used in photon and electron therapy and related to the tissue electron density) have to be converted into water equivalent density. This conversion must be established for each particular scanner and radiographic technique because the Hs are also, at typical diagnostic x-ray energies, fairly strong functions of the x-ray energy or energy spectrum. The quoted conversion is accomplished by measured look-up table, relating Hounsfield numbers to water-equivalent density. Look-up table can be obtained by two methods:

- the direct fit method, in which the H measured in a CT scanner and the water equivalent density measured in a proton beam are plotted against one another and then fitted $^{22}$ $^{23}$, as represented in Fig. 1.2(a), where is plotted the water equivalent length per pixel versus the CT number$^{16}$.

- the stoichiometric method $^{24}$ $^{25}$, in which the stopping power, and hence the water equivalent is calculated by the Bethe–Bloch formula and the Hounsfield number is obtained by an equation with three terms which refer to photoelectric effect, coherent scattering, and Compton scattering. These terms depend differently by Z and include multiplicative scanner dependent constants, which have to be deduced by fitting the equation to the measurements of the

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$^{15}$ Hounsfield numbers Hs vary from -1000 for air to 0 for water and assumes positive values for materials with greater attenuation than water. The quantity H measures a quantity related to the ratio of linear x-ray attenuation coefficients in the medium $\mu_{\text{tissue}}$, and in water $\mu_{\text{water}}$:

$$H = 1000 \left( \frac{\mu_{\text{tissue}}}{\mu_{\text{water}}} - 1 \right).$$

$^{16}$ The CT number is half of H, so the unit in abscissa of Fig. 1.2(a) is 10H=5CT number, and the axis range in the graph is [-250H; 250H]
CT scanner Hounsfield numbers for several tissue-equivalent materials of known chemical composition. In practice the tissue-equivalent materials are scanned, the resulting Hs are plotted versus effective Z-number of the tissue-equivalent material and then fitted with the equation in order to find the best fit determination of the CT scanner constant. With these constants, the H and the stopping powers can be calculated for any other tissue, whose composition is known by literature. The resulting plot of relative stopping power versus scaled H\textsuperscript{17}, as shown in Fig. 1.2 (b), is then fitted by several straight lines, which are used for the definition of the calibration curve. While a unique straight line is sufficient for bone compositions, the splitting of soft tissue data into several categories is needed in order to account for anatomical criteria and for difference in the elemental composition (in the enlarged box of Fig. 1.2 (b) are represented the data relative to organs and muscle, adipose tissue, breast, bone marrow and cartilage; the linear fits are plotted with dotted lines, and the resulting calibration curve with a solid line).

\[ H_{SC} = 1000 \frac{H_{tissue}}{H_{water}} = H + 1000 \]  

\textsuperscript{17} Scaled H are the Hounsfield number scaled by 1000: \( H_{SC} = 1000 \frac{H_{tissue}}{H_{water}} = H + 1000 \) so in Fig. 1.2 (b) the graph range of abscissa is [-1000H; 1500H] and the range of the enlarge box abscissa is [-200H; 150H].
Heterogeneities, apart from alterations in range, also cause modifications in the extent of lateral scattering of protons as they penetrate the medium. In fact, like the proton stopping power and range, also the degree of lateral scattering depends on medium density, and to a lesser extent, on atomic number.

When a proton beam penetrates the body, the heterogeneities (bone, air cavities, lung etc.) modify the dose distribution significantly compared to a homogeneous medium such as water [26] [27] [28]. Then, in order to account and compensate for heterogeneities, the calibration of the CT unit is of greater importance in proton beam therapy than in photon beam therapy. Two types of heterogeneities can be identified:
• *simple heterogeneity*, which can be modelled by taking into account its global density using a radiological depth equivalent to water, with a simple modification of the beam range, and no deformation of the distal edge, or the flat modulated; the compensation in penetration depth can be accomplished by beam modifiers, such as real or virtual compensator or bolus. The compensation of heterogeneities must include the effect of uncertainties in the evaluation of the planned dose distribution.

• *complex heterogeneity*, which has such a form, size or composition that implies large variations in depth in contiguous rays: the amount of multiple scattering is affected and, in consequence, so is the depth–dose curve. In clinical practice beam direction intercepting sharp heterogeneities are avoided. Moreover, when a proton beam partially intersects a heterogeneity, over- and under-dosage arise: a dose enhancement (hot spot) occurs on the low-density side, and a dose reduction (cold spot) occurs on the high-density side [28] [29]. This is due to the difference in the strengths of multiple scattering in the two adjacent materials, as illustrated in the Fig. 1.3 where the proton group I travels in a low-density material, like air, and the proton group II intersects an higher density heterogeneity, like tissue. Far from the interface between the two media, for example in the points Q’ and P’, the protons which undergo scattering processes are removed by the beam, but are substituted by scattered protons coming from next points, so the proton fluence is unchanged. Near the interface instead the proton fluence is affected by the scattering effect, resulting in an increase of the fluence in the low-density region, for example in point P, and a decrease of the fluence in the high-density region, for example in point Q. This is due to the lack of compensation near the interface region between protons scattered in the two media: proton group II is subject to major scattering effect and the number of protons
scattered in low density region are less than those scattered in the high density region.

![Diagram](image.png)

Fig. 1.3 Under- and over-dosage for a parallel proton beam impinging on a low density - high density interface [28]

1.1.3. Proton biological effectiveness: the RBE-weighted absorbed dose

The energy locally deposited by radiation cause cell damage; different radiations, diversely interacting, could origin diverse biological effects. The dose delivered by a charged particle and the biological effectiveness of the radiation are related to the stopping power $S$, which is also referred to as the *unrestricted linear energy transfer* (unrestricted LET $^{18}$) $L_{\infty}$ of the particle in water. At the energies employed in therapy, protons can be regarded as low-LET radiation; however, a

$^{18}$ The *restricted linear energy transfer* (LET) or *restricted linear collision stopping power* $L_\Delta$ of a material, for charged particles, is defined as the quotient of $dE_\Delta$ by $dx$, where $dE_\Delta$ is the energy lost by a charged particle due to electronic collision in traversing a distance $dx$, minus the sum of the kinetic energies of all the electrons released with kinetic energies in excess of $\Delta$: $L_\Delta = \frac{dE_\Delta}{dx}$ (Jm$^{-1}$). In other words, the restricted LET expresses the energy *locally transferred*, that is the difference between the energy lost by the primary charged particle in collisions with electrons along a track segment $dx$, and the energy carried away by secondary electrons having kinetic energies greater than $\Delta$. If $\Delta=\infty$, then the LET is referred as *unrestricted linear energy transfer* $L_{\infty}$.
small portion of the energy loss of protons is through nuclear interactions, leading to a small probability of large local depositions of energy. For protons, the LET increases slowly along the particle path and then quite rapidly at the end of the particle range, resulting in the formation of the Bragg peak.

In the calculation of the dose assessed by a proton beam to the tumour and to the healthy surrounding tissues, a factor has to be considered in order to account for the proton biological effectiveness. This factor is the so called relative biological effectiveness (RBE), which, for proton beams, is the ratio of the photon dose to the proton dose required to give the same biological effect of photon beam under identical irradiation conditions. So in the treatment planning, instead of the absorbed dose\textsuperscript{19} $D$, it should be used the $RBE$-weighted absorbed dose $D_{RBE}$, which is obtained as the product of absorbed dose by the RBE value:

$$D_{RBE} = D(\text{Gy}) \times \text{RBE} \quad [\text{Gy(RBE)}]$$

Determinations in vivo and in vitro revealed that the RBE is constant across the plateau and the SOBP, except for the terminal 5 mm to 10 mm of the SOBP, where the LET values are well in excess of 10 keV \(\mu\text{m}^{-1}\), and the RBE values are some 8 percent to 10 percent higher. Moreover the RBE varies depending on the energy of the proton, the dose per fraction, the number of fractions, the tissue types, the level of oxygenation, and the studied biological endpoint. Despite this variability, the ICRU recommends a generic RBE value of 1.1 for the therapeutic use of protons, independently of total dose, dose per fraction, fraction number and tissue type because, although these assumptions are not strictly correct, they are of modest clinical significance and the specification of a generic clinical RBE is an important aspect to ensure uniform standards of proton dose prescription. Such standards are

\textsuperscript{19} The primary dosimetric quantity of interest in radiotherapy is the absorbed dose $D$, which is defined as the mean energy imparted per unit mass of material: it's the quotient of the mean energy $d\bar{E}$ imparted to material of mass $dm$ by $dm$, $D = \frac{d\bar{E}}{dm}$ (Gy = J Kg\(^{-1}\))

26
essential for the design of clinical trials, for the evaluation of clinical data from the various proton therapy facilities, and for assessing the efficacy of proton radiation therapy relative to photon or other radiation treatments.

Then for practical use in proton therapy the RBE-weighted absorbed dose has to be determined as:

\[ D_{\text{RBE}} [\text{Gy (RBE)}] = 1.1 \times D_{\text{Gy}} \]

1.1.4. Beam delivery techniques and proton dose distribution

Proton dose distribution calculations are peculiar to techniques adopted for delivering dose to the target volume. Depending on the proton accelerator characteristics, passive or active techniques are available in order to longitudinally modulate and to transversally move the beam position.

The longitudinal modulation, resulting in the SOBP, can be performed in passive mode by range shifter or in active mode by modifying the beam energy. The transversal sizes of the radiation field can be modified passively trough diffusers and collimators, or actively by two orthogonal bending magnets:

- **Scattered beams**, obtained by passive techniques, are generally designed to produce a near-uniform dose distribution within the target volume for each beam. In order to conform high dose to the distal surface of the target over the entire field, the scattered beams require the interposition in the beam path of a *compensator* that is a low-Z material, whose thickness varies across the field.

In Fig. 1.4 is illustrated a schematic representation of the scattering technique: the scattering foils broaden the beam longitudinally and laterally; the collimator and the compensator allows to conform the dose to the lateral edge and to the distal surface of the target volume, while the dose release into the PTV volume is accomplished by a range shifter wheel.
Scanned beams can either produce a near-uniform dose distribution or, more usually, a highly non-uniform dose distribution within the target volume for each beam. The scanning can be performed in a continue mode by *raster scanning*, with a horizontal displacement faster than the vertical, or in a discrete mode by *spot scanning*.

In fig. Fig. 1.5 the scanning technique is illustrated: the magnetic scanners move the spot transversally, while the energy variation, accomplished by a change in accelerator energy or by interposing a range shifter plate on the beam path, move the spot longitudinally. At the same time the beam is modulated in intensity, so to obtain, from the superposition of longitudinally displaced spot, the SOBP, showed in the upper right side of the figure.
- Wobbled beams generally produce a near-uniform dose within the target volume for each beam. Wobbling is an intermediate mode between scattering and scanning: the dose in a defined closed area can be delivered by the use of wobbler magnets and scatterers. The magnets smear out on rings the beam particles for each pulse and the scatterers allows a better dose uniformity. Wobbling can be performed with a sequence of static pencil beam, or with continuous scanning mode, and several scan pattern are allowed \([30]\) (as illustrated in Fig. 1.6, where in the left side of each mode the beam pattern is shown, while in the right side the magnetic field waveforms are shown):
  
  o spiraling wobbling, Fig. 1.6(a): modulated sinusoidal current variation in wobbler magnets cause the beams to scan a field circularly, with a radius proportional to the square root of time. The irradiation area in unit time should be constant;
  
  o zigzag wobbling, Fig. 1.6(b): the wobbler currents are not modulated in amplitude causing the beam to scan a field uniformly in a zigzag pattern. With this mode the power supply does not have the rapid change of the wobbler current which is a feature of the spiral method and which could cause wobbler magnet instability;
  
  o regulated wobbling, Fig. 1.6(c): the amplitude of the magnetic field waveforms is varied by multiplying it by a factor \(\alpha\), called degree of regulation. In this way the regulated wobbling method produce a larger uniform irradiation field compared with the normal spiral and zigzag wobbling methods;
  
  o single-ring wobbling, Fig. 1.6(d): constant sinusoidal current variation of two orthogonal magnets with the same frequency and with a 90° phase shift causes the beam to scan a field circularly. The beam is spread out by a scatterer so to paint an annulus.
3D dynamic beam scanning is a fully (longitudinal, and transversal) active scanning technique that allows to obtain the best conformal dose within the tumour. Longitudinally and transversally active scanned beam does not need a compensator, because the variation in proton-beam penetration is achieved by upstream changes in the pencil-beam energies (virtual compensator). The active longitudinal scanning, combined with transverse positional scanning and a high pulse frequency, facilitate the so called dose repainting: in order to keep the organ motion into account, the same beam is applied multiple times over many respiration cycles while reducing the dose per application proportionately. Moreover dose repainting, in association with a online dose monitoring system, allows to compensate for possible under- or over-dosage in previous dose painting. Then repainting capability allows a better dose homogeneity on the PTV.

Active scanning has a number of advantages over the more traditional passive scattering approach. First, it can be fully automated and computer controlled and it is not necessary to use collimators and compensators to achieve dose conformation.
Second, it is more efficient than passive scattering in that fewer protons need to be delivered in order to achieve a given total dose to the tumor and therefore fewer doses is delivered to the normal tissues. Last, active scanning is an inherently more flexible technique than passive scattering.

On the other hand scanning beams have a higher sensitivity to treatment uncertainties caused by range errors or set-up and target motions than is present in passive scattering techniques. Currently there are two primary ways to reduce motion errors: beam *gating* (the beam is turned off when the target has moved out of the target position for which the treatment plan was calculated); or *repainting* spots, layers, or the entire treatment volume. Errors in target motion can be reduced in proportion to the number of repainting.

Scanned beams, either with the spot scanning or the raster scanning approach, are suitable for use in the Intensity Modulated Proton Therapy (IMPT). If the accelerator used allows intensity beam modulation (possibility to vary the beam current from pulse to pulse), the system allows a 4D dynamic scanning that is intrinsically an IMPT. If the accelerator does not allow to vary the beam current in a suitable way, the same IMPT can be achieved varying the horizontal displacement velocity of a raster scanning, or remaining more time on a position in a spot scanning (i.e. repainting).

### 1.2. Dose calculation algorithm

In calculating dose distributions, one of the simplest approaches of beam calculation algorithms is to decompose the radiation beam into primary and secondary or scatter components, and to handle each component independently. As a first approximation, for calculating the primary component, it could be sufficient accounting for the *depth* of the calculation point that is the tissue thickness along the line joining the source to the calculation point. This depth can be expressed as a
geometrical distance (as the patient were made of water) or be corrected for tissue heterogeneities, by considering the *equivalent path length* (called also *radiological* or *water equivalent thickness*), that is the integral along a straight line with respect to the path length of any material of water-equivalent density\(^ {20} \) between the source and the calculation point. In photon beam dose calculation, in order to account for scattered photons and secondary electrons, is applied the *O’Connor theorem* [31], which allows to extend the equivalent path length method to the lateral dimension: when considering two media of different densities but the same atomic composition exposed to the same beam, the dose at corresponding points in the two media will be the same provided that all geometric distances in the two media, including field sizes, are scaled inversely with density. However the calculation problem is a 3D problem and the algorithms should be able to account not only for what happens along the line joining the source to the calculation point but also for the contributions to the dose at that point from the scattered radiation arising in the rest of the medium.

In proton beam therapy, algorithm approaches are similar to those in photon and electron beam therapy, but in proton beam therapy dose calculation requires a detailed knowledge of the beam delivery techniques, which strongly affect the dose distribution. The three primary models for the calculation of dose delivered by a proton beam, which will be detailed in the next paragraph, are:

- *broad beam algorithms* (which can only be used for scattered and wobbled beams), also called *ray tracing* or *uniform-intensity beam algorithms*, which calculate the dose at a specified point by determining the radiological depth in the body [32] [33] [34] [35]. These algorithms take into consideration heterogeneities effects in variation of depth penetration, but not under- and over-dosage occurring in the target volume due to multiple scattering.

\(^ {20} \) The water-equivalent density has been defined yet in section 1.1.2
effects. Corrective factors for the inverse of the square distance and for the penumbra are also used.

- **pencil-beam algorithms** (which can be used for any type of beam), which account for multiple scattering by modelling narrow beams with Gaussian profiles [36] [37] [38] [32] [35] [39] [40] [41] [42] [43] [44]. The dose distribution generated by beams of greater cross-sectional area and irregular shape is given by superposition (or convolution) of these elementary beams.

- **Monte Carlo calculations** (which can be used for any type of beam), which allow accurate computations of dose distributions in presence of heterogeneities [37] [45] [46], by modelling the elementary interactions and then combining the “histories” of a large number of particles.

### 1.2.1. Ray tracing or broad beam algorithm

A **broad beam** is a non divergent beam which is large enough so that the relative depth dose curve on the central axis does not depend on the field amplitude. Ray tracing method calculates the dose in each point into the body by estimating the dose from Bragg curves referred to water equivalent path length. The input data to the dose calculation, that is the relative depth dose and the lateral dose profiles at representative depths of a broad beam impinging at several energies on a flat surfaced water-equivalent phantom, are either experimentally measured data or numerical fits to experimentally measured data.

The calculation of lateral penumbra can be performed with models similar to those used for photon and electron beams [49] [50] [51]. The penumbra broadening is determined by the depth, the distance from the final collimator, the presence of beam modifiers such as compensators [26], the air gap between the compensator and the patient surface [52], the characteristics and the position of beam-shaping devices and the original beam divergence. The lateral fall-off due to collimation is
usually fit by an error function in which the 50 percent level aligns with the projected edge of the collimator [36].

The ray tracing algorithm method is not accurate, since it does not account for multiple scattering effects.

1.2.2. Pencil beam algorithm

A pencil beam is a beam with infinitesimal cross section area. Typically, in a pencil beam algorithm, an incident beam of greater cross-sectional area or irregular shape is modeled using a number of closely spaced finite pencil beams; at each pencil beam is assigned a weight that is directly proportional to the particle fluence of the beam for the pencil position. The resultant dose at any point is then computed by summing the contributions from each of the pencil beams, with each calculated point taken to be at its actual water-equivalent depth: the pencil beam algorithm is then based on superposition/convolution method, which calculates the dose distribution starting from an energy deposition kernel. The kernel describes, as accurate as possible, the energy deposition by a narrow elementary radiation beam or pencil beam. The kernel should account for all possible radiation effects arising from the interaction of the beam, such as scattering and absorption of secondary electron production. In fact the single pencil beam, in penetrating in tissues, broadens due to multiple Coulomb scattering within the patient. The lateral shape and the depth dose distribution of the pencil beam have to be modeled, and this can be accomplished by measuring, calculating or simulating energy deposition kernel in water. Several analytical pencil beam algorithms are based on a model which considers a central axis term and a Gaussian off axis term in which $\sigma$ is a function of the calculation depth and is given by the root mean square (rms) of the multiple scattering distance at the calculation water equivalent depth. These algorithms can differ for instance in the way by which they calculate $\sigma$. 

34
Calculations by pencil beam algorithms can have appreciable errors when there are complex heterogeneities in the beam path or when metallic implants are present adjacent to or in the target volume.

1.2.3. Monte Carlo calculations

The most accurate dose-estimation methods are Monte Carlo (MC) simulations [47] [48]: MC calculations have the potential to increase the accuracy of dose calculations in those instances where pencil beam algorithms have difficulty. MC takes into account the physics of particle interactions on a particle-by-particle basis using theoretical models or experimental cross-section data for electromagnetic and nuclear interactions. Protons and secondary particles produced are tracked, in a statistical sense, as they interact with the material through which they pass. In detail, if the physical processes are well represented in the MC simulation code, the MC code is capable of estimating, with good probabilities:

- Coulomb interactions, which lead to energy loss and scattering of protons
- nuclear interactions, which are responsible for the following effects:
  - loss of primary protons along the beam path;
  - production of secondary protons, which produce a dose halo around the beam path;
  - production of neutrons, which largely escape from the patient, but may have some importance as regards somatic effects;
  - production of heavy secondary nuclei (e.g., alpha particles, deuterons, and other nuclear fragments), which deposit dose locally near the site of the nuclear interaction. The production of heavy secondary ionizing particles is responsible in part for the elevated RBE observed throughout the SOBP and within the plateau region.

The application of MC code to radiation therapy is allowed by Central Limit Theorem application to the radiation transport problem. The radiation field
macroscopic features (e.g. the average track-length per incident particle in a given volume of space) are computed as an average over many individual particle simulations or histories, which are based on physical law knowledge. Hypothesizing that the true average \( \bar{x} \) exists and the distribution in x has a true finite variance, \( \sigma_x^2 \), the Monte Carlo estimator \( <x> \) for \( \bar{x} \), can be made arbitrarily close to \( \bar{x} \) by increasing the number N of particle histories simulated thanks to the Central Limit Theorem [53] [54]. Furthermore, \( <x> \) has a Gaussian distribution, characterized by a variance \( \sigma_{<x>}^2 \) that may be simply estimated in the simulation. The Central Limit Theorem also predicts that, in the limit \( N \to \infty \), \( \sigma_{<x>}^2 \to 0 \), and this is also proven by the Strong Law of Large Numbers [54].

Charged particles are subjected, in traversing material, to a high number of interactions (of the order of \( 10^5 \)); simulating each interaction requests a lot of time and resources. In order to overcome this problem, Berger (1963) has developed a technique, the Condensed History Electron Transport, based on the realization that, whereas electrons undergo many interactions, relatively few of these interactions cause a great deal of energy loss or directional change. Therefore, it is possible to combine the effect of numerous small-effect interactions, which involve little energy loss or small angular deflections, into single virtual large effect interactions. These large-effect interactions can be theoretically predicted through cumulative-event theories:

- in the CSDA method the energy losses are evaluated by the stopping power [17] [55] [56] [57] or by distributions that are a function of the length of the electron path [18] [19].
- several small-angle theories [58] [59] [60] [21] predict the effect of cumulative elastic scattering events; the any-angle theory of Goudsmit and Saunderson [61] [62] has overtaken these theories.
Mathematic topics basic for the development of a Monte Carlo code are random number generation, sampling theory, displacements and rotations, estimating means and variances, geometry.

To obtain sufficient statistical accuracy for useful dose distributions tens of millions of histories usually must be traced for each single beam position. Such calculations can take hours or even days to process, and then they cannot be used in the clinical routine. In order to reduce the calculation time by one to two orders of magnitude, some Monte Carlo codes intended for proton-beam therapy simulation just follow analytically the primary protons and model contributions from secondary particles [48]. Another way to reduce the long computational time is to use a faster algorithm in developing and optimizing the treatment plan, and then to use a Monte Carlo algorithm in recomputing, and perhaps fine-tuning, the final plan.

1.2.4. Chosen approach to in-house TPS. Long term research program

In order to clarify the thesis work, it is needed considering methods to be developed over some years of research program. The aim of the work is to found an analytical way of describing the dose distribution in a heterogeneous material, starting from Monte Carlo simulation of a proton beam impinging in water and in other materials. Data in water can be used as benchmark in order to reproduce, using the water equivalent density approach, dose distributions in other materials. In order to find the analytical function for dose description, several steps have to be done:

1) the deposited dose along the beam axis (Bragg curve) in several materials has to be represented in terms of analytical Bragg curve, using also the water equivalent density approach. A suitable analytical way of reproducing the deposited energy integrated over the transverse plane in terms of that in water is presented in paragraph 2.3 for several beam energies.
2) multiple scattering in water and in other materials has to be reproduced. This is accomplished by fitting the dose distribution in the plane orthogonal to the beam direction at several penetration depths for beams of various energies impinging in different materials. A suitable fit function, as described in paragraph 2.4, could be a sum of two Gaussian functions, whose significant parameter is the sigma. An analytical expression should be found for the sigma values relative to different target, as explained in paragraph 2.4.2. Moreover the sum of the two amplitudes of the Gaussian at each penetration depth can represent the corresponding deposited energy along the beam axis. The fit over the transverse plane can then give the solution to the problem of analytical formulation.

3) the effect of beam incidence angle not orthogonal to the entrance surface have to be accounted in order to have a complete description of the dose distribution. Several simulations of proton beam impinging at different angles respect to the surface normal for various energies has been accomplished and the results are described in paragraph 2.5. Then the results of these works have to be harmonized in an all-in analytical solution of the problem. Then, starting from the CT scan data, suitably converted in water-equivalent density, it should be possible to evaluate the dose distribution accounting for the heterogeneities, the multiple scattering and the beam incidence not orthogonally to surface. This evaluation has to be compared with experimental measure in order to validate the method.

The ultimate step is the use of the analytical function derived from MC simulation to derive dose distributions which can be used as kernel in an optimization model implemented in a TPS.
1.3. Proton therapy plan optimization

In order to conform the desired dose to the target volume avoiding the OARs, several planning methods have been developed, related also to the beam delivery technique. These methods, presented here with reference to photon methods, will be better explained in the next paragraphs. The spot scanning equivalent of treating with ‘open’ fields is the SFUD (Single Field Uniform Dose), that is the combination of individually optimized fields, each of which deliver a more or less homogenous dose across the target volume. The passive scattering proton therapy equivalent of IMRT are field patching and field matching, while the spot scanning equivalent of IMRT is IMPT, that is the simultaneous optimization of all Bragg peaks from all fields (with or without additional dose constraints to neighboring critical structures), such that, when all fields are delivered to the patient, their combination results in a dose distribution in the target volume and OARs and healthy tissues that approach as much as possible the desired dose distribution. In contrast with IMRT (where equally-spaced angles are used), the delivery angles have to be selected more judiciously for protons than for photons, and this is due to the proton lack of skin sparing. IMPT is computationally more demanding than IMRT, as one has to consider a whole additional dimension of range variability, that is beam energy variations.

Proton therapy, like IMRT, would require an inverse optimization approach\(^{21}\), researching the best combination of incident beam configuration, shape and intensity map for controlling the tumor growth, with the minimum of damage to

\(^{21}\) Instead classical radiation therapy planning in the clinical practice is essentially a forward process, as it tries to obtain the best absorbed dose distribution in the target volume and surrounding normal tissues for a given target volume, associated patient geometry and suggested configuration of the incident beams. Classical-radiation-therapy optimization is therefore generally a trial and error process, where gradually improved dose plans can be found by trying an increasing number of configurations of the incident beams.
normal tissues, by specifying dose constrains to the tumor and OARs. The inverse planning determines the beam-input intensity (that is monitor units for a scattered beam and pencil beam fluences for a scanned beam) by which best reproducing the three-dimensional map of the desired dose throughout the patient volume.

The treatment plan can be designed by computer in a totally automatic mode, but this requests the reduction of several possible optimization parameters only to one number, the so called score of the plan, representing the goodness of the treatment. In fact a set of variable treatment-delivery parameters determines the three dimensional dose distributions, which can be reduced to a single number, the score, by the use of an objective function. So the development of scoring schemes and satisfactory algorithms able to find the best plan score value are requested: the plan optimization, that is the process of finding the values of treatment-delivery variables that would result in an extreme of the score function, demands the minimization or the maximization of the objective function. The definition of this objective function can be based on:

- physical parameters, like dose and volume: the objective function can be optimized by minimizing the difference between target dose and prescribed dose, or by requiring the dose in OAR within a tolerance value, or by imposing Dose Volume Histogram (DVH) constraints, or by requesting conformal dose distribution.
- biological models, like Tumor Control Probability (TCP) and Normal Tissue Complicance Palbsobility (NTCP) or Equivalent Uniform Dose (EUD), which require the knowledge of further parameters, such as the tissue radiosensibility: the objective function can be optimized by maximize TCP for given NTCP.
- a combination of both.

Then the requirements for computer assisted plan optimization are:
- a unique goal and a set of constraints, that is the clinician’s instructions for the planning process;
- a method of giving a score to a plan;
- the definition of which pencil beam variables to adjust;
- an initial guess at a plan: a good optimization algorithm should be insensitive to the starting values used for the variables being adjusted, but it is not the case for all the algorithms;
- a method of searching for that set of plan variables that maximizes or minimizes the score.

The IMPT optimization process looks for the best value for each of the numerous variables of the problem, so, in order to reduce the problem complexity and hence the computational time needed for the calculation, it is common to perform a semi-automatic process, choosing manually a number of variables. These often include the choice of the number of beams, the modality of each beam, and the placement and direction of each beam. In uniform-intensity-beam radiation therapy, a trial-and-error process similar to that of classical radiation therapy planning is usually undertaken. However, it may also be done automatically or semi-automatically, employing optimization techniques similar to that used in IMRT.

Several planning methods utilized in TPS will be described in the next paragraphs.

1.3.1. Single field uniform dose (SFUD)

Initially called single optimized uniform field, the single field uniform dose (SFUD) treatment plan, consists of one or more individually optimized fields, generally cross firing on the target volume, and each delivering a close-to-uniform dose to the target volume. These single optimized fields are created:
- in the passive scattering technique by the superposition of a fixed set of broad beam Bragg peaks, each modulated in range and intensity [63]

22 Instead in photon therapy there is an unavoidable gradient of dose with depth.
in the spot scanning technique by optimizing spot patterns for single treatment fields to achieve a desired, usually uniform, dose distribution in the target volume [64] [65].

In order to create a uniform optimized field the spots have to be defined and selected. The so obtained initial dose distribution then has to be uniformed by optimizing the spot weights, as illustrated in Fig. 1.7., where are also displayed the initial dose distribution calculated considering the selected spots and the optimized dose distribution evaluated starting from the weighted spots.

**Fig. 1.7 Steps needed in order to optimize spot patterns for single treatment fields of a SFUD plan: spot definition, spot selection and spot weight optimization [66]**

The SFUD plan dose is obtained by the superposition of two or more optimized uniform field doses. The direction of incidence of each field is often chosen to avoid, to the extent possible, adjacent critical normal tissues and metallic objects which might have been implanted into the patient. So far as beam intensities are concerned, in uniform-intensity-beam radiation therapy, one has only to adjust the weights of the individual fields.
1.3.2. Field patching and matching

*Field patching* can be considered to be a “manual” IMPT approach: since a proton beam has a defined range of penetration, it is possible to “patch” two fields together by joining the distal penumbra 50% dose value of one field (patch beam) to the lateral penumbra 50% dose value of another (thru beam), avoiding a critical structure with the lateral penumbras: the two fields are positioned so the end of one abuts the side of the other, creating an “L” shaped dose distribution, as illustrated in Fig. 1.8. This technique is distinct from “matching” method, where two fields are joined edge to edge.

![Field patching: axial CT image with color-wash dose display](image)

Patch junctions are always selected to be within the target volume, because it’s difficult to obtain a uniform dose along the patch junction due to tissue heterogeneity.

1.3.3. Intensity-modulated proton therapy (IMPT)

IMPT allows the realization of highly localized and conformed dose distributions, by simultaneously optimizing all the Bragg peaks from all fields. For IMPT the energy of every individual beam spot must be taken into account during
the optimization process in addition to the fluence patterns. IMPT delivers intentionally non-uniform dose distributions from each treatment field at a given direction. When all fields are delivered to the patient, their combination results in a desired uniform or non-uniform dose distribution in the target volume and OARs. The desired dose distribution in the target volume is non-uniform when dose escalation is required: IMPT allows delivering simultaneous boost dose. Even when the treatment goal is to deliver a uniform dose distribution, there are usually low-level hot and/or cold spots in the dose distribution.

Moreover in IMPT, the dose distribution is sensitive to the uncertainties in each individual Bragg peak position, which can result in unacceptable hot and cold regions in the target volume. A approach to improving IMPT treatment planning is to include errors in the optimization calculations in such a way as to ensure that the treatment plan predicts actual dose distributions more reliably.

There are several methods for delivering dose to the target volume with IMPT technique; those identified by Lomax in an intercomparison study are [68]:

- **2D**, shown in Fig. 1.9 (A): the field consists of fixed extent SOBPs [63], which intensities are modulated in both the transversal dimensions of the target volume; the distal edge of the SOBPs is matched to the distal edge of the target by a fixed and specified compensator [69]

- **Distal Edge Tracking (DET)**, devised by Deasy et al. [70] and shown in Fig. 1.9 (B), replaces the fixed range SOBPs of the 2D modulation with single monoenergetic beams, whose Bragg peaks match only the distal edge of the target volume and thereby creates a highly non-uniform dose per treatment field. The beam intensities are modulated in both the transversal dimensions, by maximizing

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23 Instead for IMXT, only the 2-dimensional fluence matrices for a preselected number of beams have to be directly derived from the desired 3D dose distribution by an inverse treatment planning system.
the ratio between the target dose and the dose to the proximal normal structures, considering at the same time that the desired uniform dose is obtained by superimposing multiple fields from different directions.

- **2.5D**, shown in Fig. 1.9 (C), uses variable extent SOBP pencil beams, which are individually adapted to the proximal and distal edge of the target volume, such that the dose is constant along the depth of the target volume. The weights (i.e., intensities) of the SOBP pencil beams are modulated in both the transversal dimensions of the target volume

- **3D**, shown in Fig. 1.9 (D), delivers individually intensity modulated Bragg Peaks of narrow beams over all the target volume: then intensity three dimensional modulation of three dimensional distributed Bragg peaks must be accomplished.

![Fig. 1.9 IMPT methods: (A) 2D modulation; (B) DET; (C) 2.5D modulation; (D) 3D modulation](image)

[68]

The Lomax study shows that with all techniques, using large numbers of fields, both good target homogeneity and sparing of neighbouring critical structures are
achieved, but, as the number of fields is decreased, only a full 3D modulation of individual Bragg peaks can preserve both target coverage and sparing of normal tissues. Furthermore, the LET depends from the adopted beam IMPT delivery technique; the distal edge of the Bragg peak with its high LET and hence RBE may produce some biological effects. Wilkens and Oelfke [71] showed that for DET considerable RBE variations are observable within the PTV, while for 3D modulation the RBE distribution is more or less homogeneous in the PTV. In order to compensate these unfavorable effects Wilkens and Oelfke had proposed a new method which allows the simultaneous multifield optimization of the biological effect by the introduction of a biological objective function. This objective function led to a more homogeneous distribution of the RBE weighted dose in the PTV [72].

Several studies have been carried out in order to compare IMRT, proton plan and IMPT, highlighting that IMRT can produce dose distributions comparable with, and in some cases better of proton distributions in terms of target conformality and dose gradients in the high-dose region. IMPT results to be better than proton therapy and comparable with IMRT. Although proton plans show no significant improvement in terms of target volume dose, with protons there is a reduction in the released integral dose and an improvement in terms of organs at risk. Better dose conformality to the target with dose reduction to organs is achieved by IMPT respect to other techniques employing photons when a distal critical organ is near the PTV. IMPT treatments can allow to obtain at most two of these benefit, but not all of them [74]:

- an improved dose conformality and steeper dose gradients,
- a further reduction of integral dose,
- a less sensitivity to range uncertainties and other sources of uncertainty
1.4. Objective Function minimization

Plan optimization problem can be subdivided into three steps: the individuation of the set $x$ of the variable treatment parameters that can be used in the optimization procedure, the definition of the objective function $OF(x)$, and the method to extremize this objective function. The objective function can be represented as a multi-dimensional surface in the space of the variable treatment parameters $x$. The objective function may have several local extremes, so the optimization technique should be able to locate, among the objective function local extremes, the global extreme and this is a very difficult problem. Often the extreme search algorithms are heuristic optimization strategies, that is they have a high probability of finding an acceptable solution, but the best solution cannot be obtained. In order to prevent local deterministic algorithms to be trapped into local extremes, objective functions like convex functions (as the quadratic objective function), which have only one minimum are used. Otherwise global optimization algorithms, like simulated annealing, can be applied. The simulated annealing method is suitable for optimization problems of large scale, especially ones where a desired global extreme is hidden among many poorer local extremes. So the choice of the optimization method is determined by the characteristics of the objective function used. In order to reduce the computation time, efficiently computable gradient and good directional conjugacy are two desirable properties for an objective function. In fact the knowledge of the gradient gives information about the direction in which the extreme has to be searched; for a directionally conjugate objective function with several local extremes the algorithm has not to repeat the optimization along previously optimized directions, differently if the function is not directionally conjugate, re-optimization is needed. The methods able to find function extreme can be classified in:
- *geometric algorithms* like the downhill simplex algorithm, which work on the objective function only;
- *gradient-based algorithms* like the conjugate gradient methods and the variable metric (quasi-Newton) methods, which need, apart from the objective function, also the calculation of its gradient;
- *probabilistic algorithms*, like the simulated annealing methods and genetic algorithm methods, which operate with random step in order to avoid local extremes.

Optimization is an iterative process, which ends when a termination criterion is fulfilled. In every iteration the algorithm chooses a search direction and a step size in the space of variable treatment parameters. Optimization problems can take many iterations to converge and they can benefit from good starting guesses, improving the execution efficiency and allowing locating the global minimum instead of a local minimum. Often an evolutionary approach can help to better solve advanced problems, answering first to the requests of sub-problems with a smaller number of independent variables: solutions from lower order problems can be used as starting points for higher order problems by using an appropriate mapping. The use of simpler cost functions and less stringent termination criteria in the early stages of an optimization problem can also reduce computation time. Such an approach often produces superior results by avoiding local minima. Because the intensity maps are dependent from beam direction, in IMRT, a hybrid technique is often used, adopting in an outer loop the simulated annealing method in order to optimize the beam direction, and in an inner loop, for every beam settings, a fast gradient descendent method in order to optimize the intensity maps.
1.4.1. Deterministic approaches: steepest descendent methods, variable metric (Quasi-Newton) methods and conjugate gradient methods

The gradient of the objective function and the matrix of the second derivatives (Hessian) of the objective function can help to better solve the optimization problem. The gradient $\nabla OF(x)$ shows the steepest direction along the objective function surface, so, in the gradient-based algorithms, the change in the parameters $x$ from iteration $i$ to iteration $i+1$ generally happens by the rule:

$$x(i + 1) = x(i) - \alpha \cdot \nabla OF(x(i)),$$

where $\alpha$ is a constant, the damping factor, which changes the step size of the iterative process, determining the speed and success of the optimization. In the steepest descendent method the steps are conducted along the steepest direction adopting a fixed damping factor $\alpha$, independently from the position, so with this algorithm many small step are performed also when few greater step are sufficient. The Newton methods utilizes instead the inverse Hessian $H^{-1}$ of the second derivatives of the objective function in the definition of the damping factor, so the change in the parameters $x$ from iteration $i$ to iteration $i+1$ generally happens by the rule:

$$x(i + 1) = x(i) - H^{-1}(x(i))\nabla OF(x(i)) = x(i) - \alpha_{Newton} \nabla OF(x(i))$$

At each iteration the complete inverse Hessian should be calculated, and this is time expensive, so, the quasi-Newton methods utilize an approximation of the inverse Hessian. In the steepest descendent and in the Newton methods the search direction in each iteration is independent from the previous search direction, causing slowing of the optimization process. In order to overcome this problem, the conjugate gradient method chooses the search direction accounting for the previous directions. The use of both the gradient at the previous position and that at the actual position allows to search along directions which are conjugate to each other.
An improved optimization algorithm based on the limited-memory Broyden-Fletcher-Goldfarb-Shanno (L-BFGS) routine, which is a quasi-Newton method, has been implemented in the in-house inverse planning tool KonRad at the German Cancer Research Center (DKFZ); Pflugfelder et al. [75] [76] showed that the improved algorithm has a higher speed and converges to a lower objective function value than the previously used standard quasi-Newton algorithm. The results obtained with the conjugate gradient method are intermediate between the results of the other two cited quasi-Newton algorithm.

1.4.2. Stochastic approaches: simulated annealing methods and genetic algorithms

The stochastic optimization algorithms are able to determine the extreme of an objective function with several local extremes, but they are time expensive. In the simulated annealing method, in order to escape from the traps of local minima, climbing uphill and tunneling strategies are employed. In both strategies the search for a global extreme is continued also when a local extreme is found: the search starts from the local minimum in a uphill direction for the climbing uphill strategy, from another point of the space for the tunneling strategy. The step size is randomly chosen from a displacement distribution, whose width decrease as the optimal solution is approached. The displacement, and hence the new set of variable treatment parameters are accepted not only if there is an improvement in the objective function value, but also when the objective function value is worse. In the latter case the displacement is accepted with a probability which depends from a parameter T(i), the “temperature”\(^24\): the greater is the temperature value and the

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\(^{24}\) The simulated annealing method and its parameter temperature owe their names to the solid physics area, where the annealing process is a thermal treatment which consists in heating and controlled cooling a material; this treatment is carried out in order to minimize the internal energy of the solid, so that a structure corresponding to a lower internal energy than the initial one can be obtained.
greater is the probability of accepting the displacement, so, during the optimization, the temperature value decreases with the increase of the number of iterations. When the search space is complex and other algorithms like simulated annealing encounter difficulties, genetic algorithms can be used. The processes composing these algorithms can be called, using biology nomenclatures, encoding, crossover, mutation and decoding: a way of representing a starting set of variables by a unique code have to be found (encoding), and several initial codes are matched together (crossover), but are also subject to changes (mutation); these process continue until an optimal solution is reached. Then the optimized code is transformed in the optimal set of variables (decoding).

1.5. Dose distribution comparison

Plan optimization requests the definition of an objective function, which sometimes have been described using dose distribution comparison methods, in order to minimize the difference between analytically calculated dose and desired dose. Dose comparison methods can be also used inside the quality assurance (QA) program. Because a reproducible, accurate, and safe fulfilment of the treatment prescription should be ensured, in order to check the correspondence between planned and administered doses, treatment-planning systems should be validated by comparing calculated with measured doses.

In order to compare two three-dimensional dose distributions, either measured or calculated, several techniques have been developed, the most used of which is the gamma function. The two distributions to be compared are referred as reference and evaluated distribution; the labels are necessary because some of the methods aren’t symmetric with respect to which distribution is selected for each role. The reference distribution is typically a measurement benchmark to which a calculated, evaluated distribution has to be compared.
1.5.1. Dose difference, distance to agreement (DTA) and gamma function

The simplest method to compare two dose distributions is dose difference test; it computes numerical dose difference between the two distributions, point by point, using local spatial interpolation if necessary to co-locate the evaluated dose distribution and the reference dose distribution. Nevertheless the dose difference test has a limitation: it becomes overly sensitive in steep dose gradient region, where the dose differences are typically marked by numerically large values. Moreover, the dose difference test is anti-symmetric with respect to which distribution is selected as the reference distribution.

The dose differences may be represented with histograms; they can be differential or cumulative histograms: in both the values of the dose difference are shown on the horizontal axis, but in the former the counts of the number of pixel that are within the width of a specified dose difference are shown on the vertical axis, while in the last the cumulative number of pixels which has that specified dose difference or more are shown on the vertical axis.

The distance to agreement (DTA) technique was developed in order to overcome the dose difference sensitivity to steep dose gradient. For a specific reference point, the minimum distance between the reference point and the nearest point of the evaluated dose distribution with the same dose value is measured; it is equivalent to locate the closest approach of the isodose line or surface in the evaluated distribution corresponding to the same dose as the reference point. Spatial interpolation is generally required to determine the minimum distance. The DTA technique is not overly sensitive in steep-dose gradient regions; however, in shallow dose gradient regions, a large DTA value may be computed even for relatively small dose differences. DTA method is not anti-symmetric with respect to which distribution is selected as the reference distribution.
In principle, regions where one test is overly sensitive will be the same region that the complementary test is appropriately sensitive, so failure in both criteria indicates that the two distributions significantly disagree. Then Low et al. [87] developed a composite method, the gamma function, that quantitatively compares dose distributions, either measured or calculated, degenerating to the dose difference and distance to agreement tests in shallow and very steep dose gradient regions, respectively. The gamma function combines the two methods using a predetermined tolerance, typically $\Delta d=3$ mm for the spatial tolerance and $\Delta D=3\%$ of the maximum dose for the dose difference, independently from dose gradient, dose level or spatial location. The generalized gamma function, computed for all evaluated position $\vec{r}_e$ and reference position $\vec{r}_r$ is defined as

$$\Gamma(\vec{r}_e, \vec{r}_r) = \sqrt{\frac{r^2(\vec{r}_e, \vec{r}_r)}{\Delta d^2} + \frac{\delta^2(\vec{r}_e, \vec{r}_r)}{\Delta D^2}},$$

where $r(\vec{r}_e, \vec{r}_r) = |\vec{r}_e - \vec{r}_r|$ is the spatial distance between the evaluated and the reference dose points, and $\delta(\vec{r}_e, \vec{r}_r) = |D_e(\vec{r}_e) - D_r(\vec{r}_r)|$ is the difference between evaluated dose $D_e(\vec{r}_e)$ at position $\vec{r}_e$ and reference dose $D_r(\vec{r}_r)$ at position $\vec{r}_r$.

The gamma function is defined as the minimum generalized gamma function in the set of evaluated points:

$$\gamma(\vec{r}_r) = \min \{ \Gamma(\vec{r}_e, \vec{r}_r) \} \forall \{ \vec{r}_e \}$$

The pixel spacing of the evaluated distribution needed to be sufficiently small to provide accurate calculations of the gamma function in steep dose gradient regions; as a general rule, the pixel spacing should be less than or equal to 1/3 of the distance to agreement criterion $\Delta d$. 

53
Chapter 2
MONTE CARLO SIMULATIONS AND RESULTS

The research of an analytical optimized model for calculating proton beam dose distribution has been based on Monte Carlo simulations of deposited energy in water and in different tissues and at various energies. In particular some physical proton beam characteristics, like the dependence of penetration depth on proton energy and on target material density, have been verified. The residual proton energy and the spatial beam spread at several depths has been studied from MC simulations, assuming the beam incidence angle orthogonal to the material surface; moreover the beam energy has been varied from 100 to 230 MeV, typical beam energy of active scanning proton beam, and the dose distribution has been assessed in different materials (water, bone, ...). In order to delineate the analytical model, the beam has been modelled with a sum of two Gaussian distributions in a plane orthogonal to the beam axis. The fit parameters have been optimized to reproduce the dose distribution carried-out from MC simulation at several depths. In order to evaluate dosimetric accuracy of the analytical model, the dose distribution obtained from MC simulation has been compared with that calculated by the analytical model. Moreover simulations of a beam impinging on different materials (water, bone, ...) with several incidence angles (2°, 5°, 10°, 15°) and energies (100 MeV, 150 MeV, 200 MeV, 230 MeV) have been performed.

2.1. The FLUKA Monte Carlo code and the ENEA GRID.

FLUKA [88] [89] is a multipurpose and multi-particle transport Monte Carlo code able to simulate interaction and transport of hadrons, heavy ions and electromagnetic particles from few keV (or thermal neutron) to cosmic ray energies.
in whichever material. The code characteristics at intermediate energies make it particularly reliable in treating problems in the fields of radiotherapy.

FLUKA is used to predict the expectation value of one or more quantities, as determined by the radiation field and by the material geometry described by the user: for such a task several different estimators are available. The corresponding detectors can be requested in any number, and they can be written as unformatted or text files identified by user specified logical unit. Between the available estimators, we have in particular used USRBIN and USRBDX. The latter is the command required to define a detector for the boundary-crossing estimator. It calculates fluence or current, mono- or bi-directional, differential in energy and angle on any boundary between two selected regions. Instead option USRBIN provides detailed space distributions of energy deposition, star density or integrated fluence.

FLUKA code is developed for serial running, but the following two assumptions taken by this code allow “parallelizing” the run:

- particles from a radiation source interact with matter but not with each other;
- radiation histories do not perturb each other.

Thus, in order to reduce the running time it is possible adopting the *embarrassingly parallel* approach: the user can use multiple processors concurrently to solve the problem, executing different batches of histories independently. This approach provides multiple output files which can be combined together, obtaining results identical to that of a serial computation of all histories, one after another, on a single processor: instead of running a long simulation treating all histories on a single processor, the user can run many short simulations treating a reduced number of histories in parallel on many processors.

For this purpose is used a grid, that is a collection of machines typically spread
across multiple administrative domains, and with different heterogeneous architecture and infrastructure.

An agreement between the ISS (Istituto Superiore di Sanità) and the ENEA (Agenzia Nazionale per le nuove tecnologie, l’energia e lo sviluppo economico sostenibile) has been allowed running MC simulations on the Cresco system of the ENEA GRID, for obtaining simulation data with a better statistic in less time. The Cresco system is a project developed in Portici. The user accessing to computational resources is allowed by AFS, Citrix or SSH connection. AFS (Andrew File System) [93] is a distributed file system which joins together the file systems of multiple file server machines, making it as easy to access files stored on a remote file server machine as files stored on the local disk: by authenticated access, the AFS shares data between all machines of a qualified workstation pool, independently by the effective system access point. AFS hides its distributed nature, so working with AFS files looks and feels like working with files stored on the user’s local machine, except that the user can access many more files. Moreover LSF (Load Share Facility) [94] [95] is the software utilized by the Cresco system for scheduling batch and interactive workload in cluster and grid environments. Several LSF queues are available for running jobs on the Cresco system; a queue is a cluster wide container for jobs; when a job is submitted to a queue, LSF schedules and dispatches it to the best available execution host in the cluster to run that job. The factors affecting which queue to choose are user access restrictions, size of job, resource limit of the queue, scheduling priority of the queue, active time windows of the queue, hosts used by the queue, and scheduling load conditions. LSF commands allow the user to choose between queues and to submit and to monitor a job. When a parallel job is submitted to a queue, the system assigns to the job a unique identifier number, the job ID; moreover it assigns to every parallel job an identifier number, the job INDEX. The job ID and
the job INDEX have been used to avoid that the returning output files overwriting each other.

Thus, in order to “parallelize” the FLUKA run we have:

- modified the input file introducing a variable that allows initializing different and independent random number sequences;
- written the `lancia_parallelo.sh` bash script, which, running on Linux systems, allows us to submit a parallel job on Cresco;
- written the `sumUSRBINBDX.sh` bash script, that, running on Linux systems, allow us to combine the output files from different GRID processors, calling some FLUKA post-processing routines.

These steps are better explained in the next paragraph.

### 2.1.1. FLUKA parallelization

The FLUKA results are normalized per primary particle, however in the FLUKA input file the user is able to select the number of histories per run by the START card in the input file; moreover it is possible to perform several statistical independent serial runs in a cycle by the `rfluka` script present in the FLUKA package. In this way several output files for the same problem can be combined together in order to have a final file with a content statistically equivalent to that of the sum of the files used to obtain it. Moreover, with statistical independent runs, information about statistical errors can be obtained; for this purpose, in the FLUKA package some programs for summarizing output files are available. The `usbsuw.f` program sums the binary output files requested through USRBIN card generating a binary file which can be passed to `usbrea.f` program for obtaining an ascii file; the `usxsuw.f` program sums the output files requested by USRBIDX card, generating two ascii files and a binary file.

RANDOMIZE card in the FLUKA input file starts a new independent random number sequence and it can be used for running several identical jobs in
parallel for the same problem. In particular, a variable, called __DACAM__, has been putted in the card RANDOMIZE, and has been randomly varied by a bash script, `lancia_parallelo.sh`, that, called by the submission command, allows us to submit parallel jobs on Cresco system of the ENEA GRID infrastructure; the chosen queue, the number of parallel jobs and the FLUKA input file to be run are also set in the submission command (appointed in the `sottometti.sh` script). Thus the `lancia_parallelo.sh` script:

- sets the environmental variable;
- makes a folder identified by the job ID;
- makes, in the folder identified by the job ID, as many subfolders as many parallel jobs are required by the submission command; these folders are identified by the job INDEX;
- in every subfolder identified by the job INDEX the script substitutes in the FLUKA input file the __DACAM__ variable with a random number and it launch the FLUKA input file run, specifying the number of cycles to be run (the user have to pay attention that the total run time is not greater than the maximum run time allowed by the chosen queue).

The output files sited in the subfolders are then combined using the `sumUSRBINBDX.sh` script, which:

- sets the environmental variable;
- for every output file format (the format is related to the FLUKA estimator), it makes a file, `nomi_file.txt`, which lists the path and names of the specified format files that are present in the folder identified by the job ID; in this file the output file name are also written;
- calls the `usbsuw.f`, the `usbrea.f` and the `usxsuw.f` program, in order to sum the USRBIN and the USRBDX output files, passing the `nomi_file.txt` file as input for these programs;
- for the USRBIN output obtained with *usbrea.f*, deletes the header and separates data from percentage errors, generating two distinct ascii files.

Then the ascii files have been analyzed by means of the MATLAB language for technical computing, version 7.4.0.287(R2007a).

In the following diagram blocks (Fig. 2.1) the steps followed from writing FLUKA input file to analyzing the output files are summarized:

![Diagram](image)

**Fig. 2.1 Schematic representation of work steps from writing FLUKA input file to analyzing the results.**

### 2.1.2. FLUKA code, check about Landau-Vavilov distribution

FLUKA adopts a “condensed history” approach. “Continuous” processes (such as energy loss and angular deflections due to Coulomb interactions) and “discrete”, or “explicit”, processes (delta-ray production, nuclear interactions, decays, bremsstrahlung and photon interaction) are treated separately. Energy loss by charged particles is described on the basis of the Bethe theory, supplemented with average ionization potentials, density and shell corrections according to ICRU
publications n. 37 and 49 [57]. The description of multiple Coulomb scattering relies on Moliere’s theory. The production of delta-rays is described explicitly (from a sophisticated statistical approach which includes “close” collisions, plus a two-oscillators model for “distant” collisions) above a user-defined threshold (set at 10 keV by DELTARAY card in our INPUT files), below which a continuous energy loss with statistical fluctuations is assumed.

Statistical fluctuation in energy loss, that is the unequal energy loss along tracks of particles that travel under identical conditions, is called energy straggling. The most popular solutions to the problem about fluctuations associated with charged particle energy losses are provided by the Landau-Vavilov theory (see paragraph 1.1.1.2). These solutions of the problem about fluctuations associated with charged particle energy losses are of difficult application in Monte Carlo approaches, so the FLUKA developers have been devised an alternative approach to fluctuation in energy losses, using very general statistical properties [91]. This approach exploits the properties of the cumulants [92] of distributions, and in particular of the cumulants of the distribution of Poisson distributed variables. Once for a given particle, energy, step length and threshold combination, the cumulants of the energy loss distribution are known, the sampling from a distribution of given cumulants/moments is accomplished in FLUKA making use of a set of expansions for transforming a Gaussian random variate into a variate of given cumulants. The FLUKA model has been checked by developers for 2GeV/c protons traversing 100 μm of Si, as is shown in the next figure.
In order to check the correspondence of the FLUKA model to the Landau-Vavilov theory also for a proton beam impinging with energy between 50 and 200 MeV on a water phantom, we have performed several simulations, evaluating the distribution of the deposited energy by a single proton in the first millimetre, with a statistic of 90000 particles.

The proton beam is directed along the z axis of a Cartesian reference system. The coordinates of the point from which transport starts are x=0, y=0, z=-0,1 cm. The target is a circular cylinder of height of 30 cm parallel to the z axis and of 15 cm radius, with base centered at point x=0, y=0, z=0; it is inside a “vacuum” box of side l=200 cm, contained within an external “blackhole” region\(^{25}\).

\(^{25}\) In FLUKA the “blackhole” is a mandatory region surrounding the whole geometry. This region is made of a fictitious material used to terminate particle trajectories. Any particle is discarded when reaching a “blackhole” boundary, so the “blackhole” region must be limited by a closed body (we have used a box whose dimensions are much larger than the geometry dimension). Moreover, it is suggested to chose the beam starting point in a buffer “vacuum” region contained within the external “blackhole” region and containing the whole geometry.
The energy density (in GeV per cm$^3$ per unit primary weight) is requested by the USRBIN card in a regular spatial structure (binning) having shape of rectangular parallelepiped contained in the cylindrical target and with the base centered at point $x=0$, $y=0$, $z=0$. Mesh is:

- 1 bin between $x = -4.1$ cm and $x = 4.1$ cm,
- 1 bin between $y = -4.1$ cm and $y = 4.1$ cm,
- 1 bin between $z = 0$ cm and $z = 0.1$ cm

![Simulation geometry](image)

**Fig. 2.3** Simulation geometry: the region between the external and the internal box is the mandatory “blackhole” region; the region between the internal box and the cylinder is the “vacuum” region; the beam, in red, starts in this region; the cylindrical region is the target made of water; the parallelepiped inside the cylindrical target is the detector volume.

For each energy (50, 100, 150, 200 MeV) we have submitted a job composed by 1.000 parallel cycles of 90 runs of 1 primary particle, so to work with a statistic of 90.000 protons. We was interested in the deposited energy by a single proton in the first millimeter in water, so with several for cycles in the Matlab script *Ipart<energy>*.m (which has been run on the grid) we have read all the Fluka output files presents in all the folders identified by the job INDEX, and we have stored all these information about the energy (integrated over the
transverse plane) deposited in the first millimetre in an array $E_z$ (this energy has been expressed in MeV per primary particle). Then for each energy we have calculated the values of $\beta^2$ and of the Vavilov parameter $x=\bar{\xi}/T_{\text{max}}$ (see paragraph 1.1.1.2) in order to identify the correct tabulation of Vavilov distribution among that included in “Studies in penetration of charged particles in matter” [20]. These tabulation gives, for determined $\beta^2$ and $x$ values, the Vavilov distribution values corresponding to the scaled energy-loss variables $\lambda$ from which energy loss probability distribution $f(\Delta,t)$ depends. Using the script $istogramma<energy>.m$, by inverting the formula $\lambda = \frac{\Delta - \Delta_{mp}}{\xi}$, where

$$\Delta_{mp} = \bar{\xi} \left[ \ln \frac{2mc^2\beta^2\gamma^2}{I} + \ln \frac{\bar{\xi}}{I} - \beta^2 + 1 - \gamma_{\text{Eulero}} \right]$$

is the most probable energy loss, we have obtained the energy values $\Delta$, against which the Vavilov distribution can be plotted. Then we have normalized the Vavilov distribution respect to the area so to compare it with the $E_z$ value distribution. As illustrated in Fig. 2.4 the comparisons between the renormalization of the Vavilov distribution obtained from tabulations and the distributions of energy (integrated in the transverse plane) deposited in 1 mm thickness of water by a single proton impinging with an energy of 200 MeV (in Fig. 2.4(a)), 150 MeV (in Fig. 2.4(b)) and 50 MeV (in Fig. 2.4(d)) show a good accordance, while the comparison for the 100 MeV (in Fig. 2.4(c)) energy has a worse accordance, probably due to a greater disagreement between the calculated $x$ value ($x=0.20307$) and the available $x$ value in the tabulation of the Vavilov distribution ($x=0.1$) which better approaches the calculated value. In Fig. 2.4 the Vavilov tabulations is represented by the red line, while the Fluka data are the blue points; the smoothing of the Fluka data is represented by the black line.
Comparison between the distribution of values of energy deposited (integrated over the transverse plan) per primary particle along beam axis in the first millimeter by one proton of 200 MeV energy in water (88477 bin da 150 eV, 900000 protons) and the normalized Vavilov distribution, obtained from tabulations of "Studies in penetration of charged particle" (a=0.04, beta^2=0.3)

\[ E = 200 \text{ MeV} \]
\[ \text{Calculated values:} \]
\[ a=0.055289 \]
\[ \text{beta}^2=0.32054 \]

Comparison between the distribution of values of energy deposited (integrated over the transverse plan) per primary particle along beam axis in the first millimeter by one proton of 150 MeV energy in water (95583 bin da 150 eV, 900000 protons) and the normalized Vavilov distribution, obtained from tabulations of "Studies in penetration of charged particle" (a=0.1 beta^2=0.3)

\[ E = 150 \text{ MeV} \]
\[ \text{Calculated values:} \]
\[ a=0.084329 \]
\[ \text{beta}^2=0.25867 \]
Fig. 2.4 Comparison between the normalized Vavilov distribution obtained from tabulations and the distribution of values of energy deposited (integrated over the transverse plane) per primary particle along beam axis in the first millimeter by one proton of 100 MeV energy in water and 150 eV, 90eV0 protoons) and the normalized Vavilov distribution, obtained from tabulations of "Studies in penetration of charged particle" \(x=0.1, \beta^2=0.2\) (c) and \(E=50\text{ MeV} \quad x=0.7, \beta^2=0.1\) (d).
particle along the beam axis in the first millimeter in water by one proton of (a) 200 MeV; (b) 150 MeV; (c) 100 MeV; (d) 50 MeV. The Vavilov tabulations is represented by the red line, while the Fluka data are the blue points. The black line is the smoothing of the Fluka data.

2.2. Simulation geometry

Simulations, with a proton beam having a Gaussian spatial profile impinging on a homogeneous target, have been performed varying the beam energy and the target material. The simulated beam energies are 230 MeV, 200 MeV, 150 MeV and 100 MeV. The target materials are water, compact bone (ICRU), and a fictitious material having lung composition and density of 0,3 gr/cm³; moreover, simulations with the proton beam impinging on a composited target, containing all the three previous materials have been performed. In this work, the composited target will be called WLB (because made of water, lung and bone).

In the input file, which name recalls the simulation details (p<energy>_<_angle>_<_material>_<_date>.inp), the proton beam has the following characteristics:

- FWHM of a Gaussian momentum distribution:
  \[ \text{FWHM}_{\text{momentum}} = 2.355 \sigma_{\text{momentum}} = 0,72 \times 10^{-03} \text{ GeV/c} \]
- divergence (FWHM of a Gaussian angular distribution):
  \[ \text{FWHM}_{\text{divergence}} = 2.355 \sigma_{\text{divergence}} = 0.35325 \text{ mrad} \]
- profile (FWHM of a Gaussian profile in x- and y- directions):
  \[ \text{FWHM}_x = 2.355 \sigma_x = 0,471 \text{ cm}; \]
  \[ \text{FWHM}_y = 2.355 \sigma_y = 0,471 \text{ cm} \]

The simulation geometry of the p<energy>_<_angle>_<_material>_<_date>.inp files can be briefly summarized:

- the proton beam is directed along the z axis; the coordinates of the centre of the beam spot (i.e., the point from which transport starts) are \( x = 0, \ y = 0, \ z = - 5 \text{ cm} \);
• the target is a circular cylinder of height parallel to the z axis and of 15 cm radius, with base centered at point \( x = 0, y = 0, z = 0 \), and height set relatively to the beam energy and to the assigned material. The cylindrical region is inside a “vacuum” box of side \( l=200 \) cm, contained within the external (mandatory) “blackhole” region;

• the energy density (in GeV per cm\(^3\) per unit primary weight) is requested by the USRBIN detector in a regular spatial structure (binning), having shape of rectangular parallelepiped, subdivided in voxel of 1 mm\(^3\) and fully contained into the cylindrical target. Numbers of bin and parallelepiped dimensions depend on beam energy, target material and incidence angle;

![Diagram](image)

Fig. 2.5 Simulation geometry: the region between the external and the internal box is the mandatory “blackhole” region; the region between the internal box and the cylinder is the “vacuum” region; the beam, in red, starts in this region; the cylindrical region is the target; the parallelepiped inside the cylindrical target is the detector volume; (a) the cylindrical target is made of homogeneous material (water, bone or lung); (b) the compositd cylindrical target is made of the succession of three homogeneous material (water, lung and bone (WLB)).

• moreover, in order to evaluate the residual proton energy at several depths, some planes parallel to the cylinder base have been introduced; the
cylindrical region is so subdivided in numerous cylindrical regions, and several USRBDX detectors are requested at the region boundaries, estimating the double differential distributions of current in energy and solid angle. Then, integrating respect to the solid angle, the crossing current distribution in energy is obtained. For every simulation we have submitted a job composed by 100 parallel cycles of 10 runs of 100,000 primary particles, equivalent to a single run of 100,000,000 of primary particles.

2.3. Finding a formula for the Bragg curve using MC simulation as benchmark

2.3.1. Checking the Bragg peak dependence by the beam and the media characteristics

The Bragg curve, representing the deposited energy along the central beam axis has, at the end of the proton range, a peculiar peak, the so called Bragg peak. The depth, the height and the width of the Bragg peak and the peak to plateau ratio are dependent by the medium properties and by the initial proton energy:

- the position of the Bragg peak moves towards deeper positions with increasing beam energy or decreasing the target density;
- the decrease in peak height with increasing energy (see Fig. 2.6) is a consequence of the increasing probability of inelastic nuclear interaction at higher primary energies; the peak height decreases also with beam width due to multiple scattering effect;
- the increase in peak width with increasing energy is a consequence of the larger energy-range straggling; the Bragg peak width depends also on the energy spread of the beam;
- the decrease in peak to plateau ratio with increasing energy is a combined result of increased energy-range straggling and larger proton planar fluence loss in inelastic nuclear interaction.

![Deposited energy per volume unit and per primary particle along beam axis for several beam energies](image)

**Fig. 2.6** Deposited energy per volume unit and per primary particle along the beam axis for several beam energies in water

When integrating the deposited energy over the transverse xy plane, the Bragg peak is more evident because also the energies of the scattered protons contributes to the integral energy. The Bragg peak behavior as regards to beam energy changes and medium density variations is evident in the figure Fig. 2.7, where the deposited energy per length unit and per primary particle integrated over the transverse plane versus the beam penetration depth is represented for beams impinging perpendicularly to the surface of various materials (water, bone, lung) with different energies (100, 150, 200, 230 MeV):
Fig. 2.7 Deposited energy per length unit and per primary particle integrated over the transverse plane versus the beam penetration depth for beams impinging perpendicularly to the surface of various materials (water, bone, lung) with different energies (100, 150, 200, 230 MeV)

The greatest dependence of the deposited energy from the medium is on the density of the target material, due to the explicit linear dependence of the Bethe-Bloch formula for the stopping power (as seen in paragraph 1.1.1.1) on the material density. Then, it is possible grouping the Bragg curves of beams having the same energy and impinging on different targets (as illustrated in Fig. 2.8) simply by:

- dividing the beam energy per primary particle and per length unit deposited along the beam direction and integrated over the transverse plane (in MeV/cm) by the density (in gr/cm$^3$) so to obtain a “mass integrated deposited energy” (MIDE) expressed in MeV*cm$^2$/gr,
- multiplying the penetration depth (in cm) by the material density (in gr/cm$^3$), so to obtain a “mass depth” expressed in gr/cm$^2$. 

71
Fig. 2.8 Mass integrated deposited energy (MIDE, in GeV\textsuperscript{-}cm\textsuperscript{2}/gr) versus the mass depth (in gr/cm\textsuperscript{2}) for beams impinging perpendicularly to the surface of various materials (water, bone, lung) with different energies (100, 150, 200, 230 MeV)

The different heights of the Bragg peaks in Fig. 2.7 for beams impinging on a same material with different energies are imputable to the different residual mean energy with which the protons reaches the Bragg peak depth. To verify this assertion, starting from the mean residual energy value which a proton has at a depth corresponding with that of the Bragg peak, we have compared the MIDE value in correspondence of the Bragg peak depth with the stopping power from NIST data (see paragraph 2.3.2.1 for more information about the mean residual value and the NIST data). The ratio between these two quantities, as illustrated in Tab. 2.1, is about the same for several energies and materials and this is indicative of the correctness of the data.
<table>
<thead>
<tr>
<th>Material</th>
<th>Beam energy (MeV)</th>
<th>Mean residual energy (MeV)</th>
<th>MIDE value at Bragg peak (MeV*gr/cm²)</th>
<th>Stopping power from NIST (MeV*gr/cm²)</th>
<th>Ratio Stopping power/MIDE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>100</td>
<td>6.88</td>
<td>40.71</td>
<td>61.41</td>
<td>1.51</td>
</tr>
<tr>
<td>Water</td>
<td>150</td>
<td>12.73</td>
<td>28.84</td>
<td>37.43</td>
<td>1.30</td>
</tr>
<tr>
<td>Water</td>
<td>200</td>
<td>16.15</td>
<td>21.48</td>
<td>30.93</td>
<td>1.44</td>
</tr>
<tr>
<td>Water</td>
<td>230</td>
<td>18.69</td>
<td>18.11</td>
<td>27.53</td>
<td>1.52</td>
</tr>
<tr>
<td>Bone</td>
<td>100</td>
<td>8.82</td>
<td>34.94</td>
<td>46.03</td>
<td>1.32</td>
</tr>
<tr>
<td>Bone</td>
<td>150</td>
<td>9.55</td>
<td>25.98</td>
<td>43.34</td>
<td>1.67</td>
</tr>
<tr>
<td>Bone</td>
<td>200</td>
<td>14.34</td>
<td>19.38</td>
<td>31.34</td>
<td>1.62</td>
</tr>
<tr>
<td>Bone</td>
<td>230</td>
<td>19.30</td>
<td>24.66</td>
<td>16.55</td>
<td>1.49</td>
</tr>
</tbody>
</table>

Tab. 2.1. Comparison between the MIDE value in correspondence of the Bragg peak depth with the stopping power from NIST data

### 2.3.2. Reproducing the Bragg curve

Due to the dependence from medium characteristics of the terms into the square bracket of the stopping power formula (see paragraph 1.1.1.1) and to the differences in range-energy loss straggling, the use of density is not sufficient to achieve an accurate calculation of dose deposited by a proton beam in a material other than water. This is illustrated in the Fig. 2.9 (a-d), which enlarges the Fig. 2.8 and shows the MIDE curves relatively to proton beams impinging on water, bone and lung for energies of 100 MeV, 150 MeV, 200 MeV, and 230 MeV respectively:
Fig. 2.9 MIDE (in GeV*cm$^2$/gr) versus the mass depth (in gr/cm$^2$) for beams impinging perpendicularly to the surface of various materials (water, bone, lung) with energies of: (a) 100 MeV, (b) 150 MeV, (c) 200 MeV, (d) 230 MeV.
In order to obtain best results, we have reproduced the MIDE in bone and in lung starting from that in water at the same energy. The steps needed in order to obtain this result, listed here, will be explained in detail in the next paragraphs:

1) the evaluation of the **mean residual proton energy** from the double differential distributions of proton current in energy and solid angle obtained by the USRBDX estimator;

2) the fit of the interpolated MIDE in lung and in bone versus the MIDE in water, starting from the interpolation of the integrated deposited energy in lung and in bone versus the mean residual proton energy at the same depth;

3) the fit of the interpolated depth in lung and in bone versus the depth in water, starting from the interpolation of the depth in lung and in bone versus the mean residual proton energy;

4) the check of the results and the generalization to any energy

**2.3.2.1. Mean residual proton energy**

The USRBDX estimator allows obtaining information about the double differential distribution of proton “current”\(^ {26} \) in energy and in solid angle by setting the range and the bin number of energy and solid angle. By integrating over the solid angle, the differential distribution of “current” in energy can be obtained. The files *outsuw_<input_file_name>_<logic_unit>_tab.lis* created by the *usxsuw.f* routine called by the *sumUSRBINBDX.sh* script, have a simple 4-column structure for the differential “current” integrated over solid angle. In each row of the four columns are represented respectively the maximum and the minimum bin energy value \( E_{\text{min}} \) and \( E_{\text{max}} \), the bin differential “current” \( F_{\text{bin}} \) and the bin statistical error in percentage.

---

\(^ {26} \) In FLUKA the term “current” is indicated as representing the number of particle that cross a boundary surface per area unit, without any reference to the time. The “current” is different by the fluence, available also by means of the USRBDX estimator. The “fluence” also counts the total number of particle crossing the surface per area unit, weighting each particle with the secant of the angle between the particle trajectory and the normal to the boundary surface at the crossing point.
In a first time, for each beam energy (100, 150, 200, 230 MeV) and for each media (water, bone, lung), we have think to evaluate, at each depth in which the USRBDX estimator has been requested, the mean residual proton energy as the parameter of the Gaussian fit to the differential distribution of “current” representing the centre of the distribution, as illustrated for example in Fig. 2.10 (a) for the 200 MeV proton beam in water at a depth of 11 mm. This evaluation could be correct in the first part of the proton path, when the protons have lost part of their initial energy, but in the last part of the proton path, the energy straggling cause a deviation of the distribution from Gaussian shape (as shown for example in Fig. 2.10 (b) for the 200 MeV proton beam in water at a depth of 25,1 mm) so the central Gaussian distribution parameter is not too accurate in representing the mean residual energy.

![Proton current energy distribution per primary particle per surface unit integrated over solid angle at z= 11 mm](p200_water_0gr_2010.04_21)

\[
277.3415 \times \exp\left(-\left(x-0.14604\right)/0.0018019\right)^2
\]

energy fwhm = 0.0030005 GeV.

moment fwhm = 0.0059864 GeV/c.
Fig. 2.10 Evaluation of the correctness in estimating mean residual proton energy from a Gaussian fit of the differential distribution of "current" in energy for a 200 MeV proton beam impinging in a water target at a depth of (a) 11 mm and (b) 25.1 mm

Starting from the 4-column values of the files `outsuw_<input_file_name>_logic_unit_tab.lis`, a more correct approach has been the calculation, by means of the Matlab script `tab_lis_<media><date>.m`, of the mean residual proton energy

\[ \bar{E} = \frac{\sum_{bin} E_{bin} \cdot F_{bin}}{\sum_{bin} F_{bin}} \]

(where the mean bin energy is

\[ E_{bin} = E_{min_{bin}} + \frac{(E_{max_{bin}} - E_{min_{bin}})}{2} \]

in case of linear binning) at each depth corresponding to a location of the USRBDX estimator for each material (water, bone, lung) and for each beam energy (100, 150, 200, 230 MeV); in Fig. 2.11 is

\[ 51.9512 \exp(-((x-0.029557)/0.0076735)^2) \]

energy fwhm = 0.012778 GeV.

moment fwhm = 0.052404 GeV/c.
shown the location of the so calculated mean residual energy at the same conditions of Fig. 2.10 (b) that is at a depth of 25.1 mm for a 200 MeV proton beam impinging on a water target.

**Fig. 2.11 Mean residual proton energy calculated from the differential distribution of “current” in energy for a 200 MeV proton beam impinging in water at a depth of 25.1 mm**

We have so obtained the mean residual proton energy at several depths in water, in bone and in lung for proton beams of several energies, as illustrated in Fig. 2.12:
Fig. 2.12 Mean residual proton energy evaluated from the differential distribution of “current” in energy versus depth for beams impinging perpendicularly to the surface of various materials (water, bone, lung) with different energies (100, 150, 200, 230 MeV)

In order to check if the mean residual proton energy values found in this way are really correct, we have compared them with the values calculated from the energy-stopping power table of the NIST (National Institute of Standard). The PSTAR database on the NIST web site allows obtaining the mass electronic (collision) stopping power, the mass nuclear stopping power, the total mass stopping power (all in MeV*cm²/gr), the CSDA range, the projected range (in gr/cm²) and the detour factor (ratio of projected range to CSDA range) of a material included in a list of 74 materials 27 at 100 default energies or at user defined energies (in MeV).

---

27 The user available material information utilized by the PSTAR consists of the atomic number and fraction per weight of the constituent atoms, the density (at 20°C and 1 atm) and the mean excitation
The total stopping power is the sum of the collisional and nuclear stopping power contributions. The PSTAR database, for protons, at energies higher than 0.5 MeV, calculates collision stopping powers using Bethe stopping-power formula, while at lower energies, utilizes fitting-formulas which are based on experimental stopping power data. The used stopping power formula includes shell corrections, the Barkas and Bloch corrections, and the density-effect correction (see notes 5 an 6 in paragraph 1.1.1.1). Nuclear stopping powers are instead calculated using the relation between the deflection angles and the energy transfers to the recoiling atom in elastic collisions. Cross sections for the elastic scattering of charged particles by atoms are obtained by a classical-mechanics orbit calculation, using the method of Everhart, Stone and Carbone [98]. For protons the screened potential is assumed to be the Thomas-Fermi potential as parameterized by Molière [58].

So, we have runned the PSTAR with a list of energies in the range from 200 MeV to $10^{-3}$ MeV, obtaining the corresponding total stopping power values. Hypothesizing that in a millimeter the stopping power does not change appreciably, we have calculated with the Matlab script `enRes100_150_200def.m`, for each energy (100, 150 and 200 MeV) and for each medium (water and bone), at each millimeter:

- the energy lost, obtained as the product of the stopping power at the proton residual energy by the thickness (0.1 cm) and by the density
- the residual energy, obtained as the difference between the energy in the previous millimeter and the energy lost.

The comparison between the so calculated data and that previously evaluated is shown in the Fig. 2.13:

---

energy. The values of the mean excitation energies used in the stopping power formula are the same as those adopted in ICRU Report 37 (ICRU, 1984).
Fig. 2.13 Comparison between the mean residual proton energy values calculated starting from NIST energy-stopping power data and that evaluated from the differential distribution of “current” in energy for beams impinging perpendicularly to the surface of various materials water and bone with energies of 100, 150, 200 MeV.

Moreover we observed that it is possible grouping also the mean residual energy data relative to beam having the same energy and impinging in different media by expressing the lengths in terms of mass lengths, as shown in Fig. 2.14.
2.3.2.2. **Fit of the interpolated integrated deposited energy in lung and in bone versus the integrated deposited energy in water**

We have utilized the knowledge of the mean residual proton energy at several depths in order to find an analytical expression to evaluate MIDE in bone and in lung starting from the data of the MIDE in water.

First we have plotted, for all the materials and energies, the MIDE versus the residual proton energy at the same corresponding depth (as illustrated in Fig. 2.15)
and we have interpolated\textsuperscript{28} these data, as globally illustrated in Fig. 2.16, and individually for each beam energy and material medium in Fig. 2.17:

\textbf{Fig. 2.15} MIDE (in GeV*cm\textsuperscript{2}/gr) versus the residual mean energy (in GeV) for beams impinging perpendicularly to the surface of various materials (water, bone, lung) with energies of: 100 MeV, 150 MeV, 200 MeV, and 230 MeV.

\textsuperscript{28}The interpolation is needed in order to have the data in bone and in lung at the same residual proton energy values than water, so that it is then possible plotting data in bone and in lung versus data in water. The interpolation has been done with the Matlab \textit{interp} function, using the \textit{spline} method.
Fig. 2.16 Interpolation of MIDE (in GeV*cm$^2$/gr) versus the residual mean energy (in GeV) for beams impinging perpendicularly to the surface of various materials (bone, lung) with energies of: 100 MeV, 150 MeV, 200 MeV, and 230 MeV.
Interpolation of MIDE for a 100MeV proton beam impinging in bone

Interpolation of MIDE for a 100MeV proton beam impinging in lung
Interpolation of MIDE for a 150MeV proton beam impinging in bone

![Graph showing interpolated deposited energy per primary particle and per length unit (GeV cm$^2$/g) for bone and water.]

Interpolation of MIDE for a 150MeV proton beam impinging in lung

![Graph showing interpolated deposited energy per primary particle and per length unit (GeV cm$^2$/g) for lung and water.]

87
Interpolation of MIDE for a 200MeV proton beam impinging in bone

Interpolation of MIDE for a 200MeV proton beam impinging in lung
Interpolation of MIDE for a 230MeV proton beam impinging in bone

Interpolation of MIDE for a 230MeV proton beam impinging in lung

Fig. 2.17 Interpolation of the MIDE (in GeV·cm²/gr) versus the residual mean energy (in GeV) for beams impinging perpendicularly to the surface of (a) bone with energy of 100 MeV, (b) lung with energy of 100 MeV, (c) bone with energy of 150 MeV, (d) lung with energy of 150 MeV, (e) bone with energy of 200 MeV, (f) lung with energy of 200 MeV, (g) bone with energy of 230 MeV, (h) lung with energy of 230 MeV.
The interpolation has permitted us to plot the MIDE in bone and in lung versus that in water. We have then fitted these data with a linear curve for the pre-Bragg-peak data and with a quadratic curve for the post-Bragg peak data for 150, 200 and 230 MeV energies, but not for the 200 MeV energy because few pre-Bragg-peak data was available. These fits are shown in Fig. 2.18 for each proton energy and for each medium. The relations between the MIDE in bone (IED\_bone) and in lung (IED\_lung) respect to that in water (IED\_water) are then:

\[
\begin{align*}
\text{MIDE\_bone} &= \begin{cases} 
b1 \times \text{MIDE\_water} + b2 & \text{pre – Bragg\_peak} 
b3 \times \text{MIDE\_water}^2 + b4 \times \text{MIDE\_water} + b5 & \text{post – Bragg\_peak}
\end{cases} \\
\text{MIDE\_lung} &= \begin{cases} 
l1 \times \text{MIDE\_water} + l2 & \text{pre – Bragg\_peak} 
l3 \times \text{MIDE\_water}^2 + l4 \times \text{MIDE\_water} + l5 & \text{post – Bragg\_peak}
\end{cases}
\end{align*}
\]

where b1, b2, b3, b4, b5 and l1, l2, l3, l4, l5 are the fit coefficients relatively to bone and lung respectively.
Fit of the MIDE versus the MIDE in water

(a) 100 MeV bone 0°

(b) 100 MeV lung 0°
Deposited Energy per primary particle and per length unit in water [Gev cm$^2$/gr]

**Fit of the MIDE versus the MIDE in water**

(c) 150 MeV bone 0°

(d) 150 MeV lung 0°
Deposited Energy per primary particle and per length unit in water [Gev*cm$^2$/gr]

Fit of the MIDE versus the MIDE in water

200 MeV bone 0°

Fit of the MIDE versus the MIDE in water

200 MeV lung 0°
Fig. 2.18 Fit of the MIDE (in GeV*cm²/gr) for beams impinging perpendicularly to the surface of:
(a) bone with energy of 100 MeV, (b) lung with energy of 100 MeV, (c) bone with energy of 150 MeV, (d) lung with energy of 150 MeV, (e) bone with energy of 200 MeV, (f) lung with energy of 200 MeV, (g) bone with energy of 230 MeV, (h) lung with energy of 230 MeV, versus the MIDE (in GeV*cm²/gr) in water.
To check the fit correctness we have compared the so fitted MIDE in bone and in lung versus the residual mean proton energy in water with the original data, as is shown globally in Fig. 2.19:

![Graph showing fitted data versus residual mean energy in water](image)

**Fig. 2.19** Fit of the MIDE (in GeV*cm²/gr) versus the residual mean energy (in GeV) for beams impinging perpendicularly to the surface of various materials (bone, lung) with energies of: 100 MeV, 150 MeV, 200 MeV, and 230 MeV.

These fits are not sufficient in order to reproduce the integrated deposited energy in lung and in bone versus mass depth starting from the data in water because a correction over the mass depth is also necessary, especially for bone, as demonstrated by the Fig. 2.20, where the fitted data, in black, with the MC data for comparison, are plotted versus the mass depth:
Fig. 2.20 Fit of the MIDE (in GeV*cm²/gr) versus the non fitted mass depth (in gr/cm²) for beams impinging perpendicularly to the surface of various materials (bone, lung) with energies of: (a) 230 MeV; (b) 200 MeV; (c) 150 MeV; (d) 100 MeV.
2.3.2.3. **Fit of the interpolated mass depth in lung and in bone versus the mass depth in water**

In order to obtain a best result, we have interpolated\(^{29}\), for all the materials and energies, the mass depth versus the residual proton energy, in a similar way than in the 2.3.2.2 paragraph.

The interpolation has permitted us to plot the mass depth in bone and in lung versus that in water. We have then fitted these data with a straight line for each proton energy and for each medium, as shown in Fig. 2.21 The relations between the mass depth in bone (\(z_{\text{bone}}\)) and in lung (\(z_{\text{lung}}\)) respect to that in water (\(z_{\text{water}}\)) are:

\[
\begin{align*}
\text{z}_\text{bone} &= b_z1 \ast \text{z}_\text{water} + b_z2 \\
\text{z}_\text{lung} &= l_z1 \ast \text{z}_\text{water} + l_z2 
\end{align*}
\]

where \(b_z1\), \(b_z2\), and \(l_z1\), \(l_z2\) are the fit coefficients relatively to bone and lung respectively.

\(^{29}\)The interpolation is needed in order to have the data in bone and in lung at the same residual proton energy values than water, so that it is then possible plotting data in bone and in lung versus data in water.
Fig. 2.21 Fit of the mass depth (in gr/cm$^2$) versus the residual mean energy (in GeV) for beams impinging perpendicularly to the phantom surface with energies of: (a) 100 MeV in bone; (b) 100 MeV in lung; (c) 150 MeV in bone; (d) 150 MeV in lung; (e) 200 MeV in bone; (f) 200 MeV in lung; (g) 230 MeV in bone; (h) 230 MeV in lung.
2.3.2.4. Results

Utilizing the formulas found in the previous paragraphs, we have reproduced the Bragg curves in bone and in lung starting from that in water, as illustrated in Fig. 2.22. For the 100 MeV energy beams in lung and in bone.
Fig. 2.22 Fit of the MIDE (in GeV*cm$^2$/gr) versus the mass depth (in gr/cm$^2$) for beams impinging perpendicularly to the surface of: (a) bone with energy of 100 MeV, (b) lung with energy of 100 MeV, (c) bone with energy of 150 MeV, (d) lung with energy of 150 MeV, (e) bone with energy of 200 MeV, (f) lung with energy of 200 MeV, (g) bone with energy of 230 MeV, (h) lung with energy of 230 MeV.

In order to obtain a generalization of the previous fits at all the energies available in the radiotherapeutic range, we have plotted the fit coefficients versus energy and then we have fitted these data with straight lines. The plot of the fits of the two coefficients $b_1$, $b_2$, $l_1$ and $l_2$ relative to the mass depth fits are represented in the Fig. 2.23:
Fig. 2.23 Fit of the zeta fit coefficients (a) $b_{z1}$ and $l_{z1}$; (b) $b_{z2}$ and $l_{z2}$.
The Fig. 2.24 shows instead the fits of the coefficients relative to the deposited energy $b_1$, $b_2$, $b_3$, $b_4$, $b_5$ and $l_1$, $l_2$, $l_3$, $l_4$, $l_5$: 

![Diagram showing fits of MIDE coefficients $b_1$ and $l_1$ vs. beam energy (MeV).](image_url)
Fig. 2.24 Fit of the MIDE fit coefficients: (a) $b_1$ and $l_1$; (b) $b_2$ and $l_2$; (c) $b_3$ and $l_3$; (d) $b_4$ and $l_4$; (e) $b_5$ and $l_5$. 

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111
Then, indicating with coeff<i>_zeta_<material>_1, coeff<i>_zeta_<material>_2, coeff<j>_MIDE_<material>_1 and coeff<j>_MIDE_<material>_2 the coefficients of the linear fits of Fig. 2.23 and Fig. 2.24, the equations that allows to find the parameters bz<i>, lz<i>, b<j> and l<j> at a specified energy E are:

bz<i> = coeff<i>_zeta_bone_1*E + coeff<i>_zeta_bone_2;

lz<i> = coeff<i>_zeta_lung_1*E + coeff<i>_zeta_lung_2;

b<j> = coeff <j>_MIDE_bone_1*E + coeff <j>_MIDE_bone_2;

l<j> = coeff<j>_MIDE_lung(1)*E + coeff<j>_MIDE_lung(2);

The plot of the MIDE fit in bone and in lung at several depth using this derived coefficients instead of that previously calculated, shows a good accordance with the FLUKA data, as illustrated in Fig. 2.27:
(b) Fit of the MIDE

(c) Fit of the MIDE
Then, using the fit values calculated in this paragraph instead of the values previously derived in paragraphs 2.3.2.2) and 2.3.2.3), the MIDE in a material can be calculated starting from the MIDE data in water at the same energy.

As pointed out in paragraph 1.1.2, a way developed in order to account for material dependence of energy loss mechanisms, is by means of the water equivalent thickness concept. A further step in exploring the deposited energy behavior is evaluating if considering the stopping power ratio in a water equivalent approach is the same as utilizing the fit coefficients found here.

Fig. 2.25 Fit of the MIDE (a) bone 230 MeV; (b) lung 230 MeV (c) bone 200 MeV (d) lung 200 MeV; (e) bone 150 MeV; (f) lung 100 MeV; (g) bone 100 MeV
2.4. Multiple Coulomb scattering effect

2.4.1. Fitting the transversal deposited energy distribution

Due to the symmetry of the geometry, the energy distribution is symmetric along the x and y directions orthogonal to the beam axis (z). For example, in Fig. 2.26 the energy distribution at a depth of 25.7 cm for a 200 MeV proton beam impinging in water\(^{30}\) is represented; the height of the distribution is proportional to the energy value, represented also by a colorwash; the bidimensional representation of the deposited energy in the small box of Fig. 2.26 outlines the energy distribution symmetry.

![Energy distribution diagram](image)

**Fig. 2.26** Three dimensional representation of the energy distribution per unit area and per primary particle in the xy plane at a depth of 25.7 cm for a 200 MeV proton beam impinging in water; in the small box a bidimensional representation is showed.

\(^{30}\) The depth of 25.7 cm corresponds to the Bragg peak position for a 200 MeV proton beam impinging in water.
The deposited energy per primary particle and per unit volume along the x direction perpendicular to the beam axis (z) is represented in Fig. 2.27 at several depths. The integral over y of the deposited energy along x, at each depth, could be approximated with a Gaussian distribution, but this approximation fails at several depths, where there is a little disagreement in the tails, as shown in Fig. 2.28.

**Fig. 2.27** Energy distribution per unit volume and per primary particle in the xy plane at several depths for a 200 MeV proton beam impinging in water
Fig. 2.28 Disagreement in the tail between the Gaussian fit of the energy distribution per unit volume and per primary particle along x integrated over y for a 200 MeV proton beam impinging in water.

The deposited energy per primary particle and per volume unit integrated over the yz slice is represented, for example for the 0° 200 MeV proton beam, in Fig. 2.29.
In order to obtain an analytical expression for the deposited energy, we have fitted, at each depth, for each medium (water, bone, lung) and for each energy (100, 150, 200, 230 MeV) the deposited energy per primary particle and per unit volume in the xy plane orthogonal to the beam direction.

The fit problem has been decomposed into small step.

1) - Definition of the fit function - The distribution function with which we have tried to fit the energy distribution at each depth are:
   - a Gaussian distribution,
   - a sum of two Gaussian functions
   - the previous distributions with a offset and centered in the point of the xy plane corresponding to the beam center point in the xy plane.

Fig. 2.29 *Energy distribution per unit length and per primary particle along x integrated over the yz plane for a 200 MeV proton beam impinging in water*
the previous distributions with and without the offset and centered at the point of the xy plane corresponding to the beam center point in the xy plane.

2) - Fit of the deposited energy values -

*FitBidimDef.m* reads the `sumUSRBDX<data><material>.sh` output file, creates the energy distribution matrix, and calls `myGaussianFit.m` in order to individuate the guess parameters and to fit the data for each penetration depth:

- the guess parameters of a unidimensional Gaussian distribution are calculated with the Matlab script `centerofmass.m`;

- `myGaussianFit.m` script utilizes these parameters for minimizing the square root difference between the sum of the unidimensional fit function, annotated in the `myfitgaussian1D.m` file, and the unidimensional energy distributions along the x central section and along the y central section of the beam. Due to the distribution symmetry, the parameter values relatively to the distribution along the x axis should be the same that those along the y axis. For example, in Fig. 2.30 is represented the fit with a Gaussian of the energy distribution per unit length and per primary particle along the x axis at a depth of z=43 mm for a 200 MeV proton beam impinging in water.
- The mean of the fit parameters values relatively to the unidimensional energy distributions along the x central section and along the y central section, are used as guess values by `myGaussianFit.m` file for minimizing the difference between the bidimensional fit function, annotated in `myfitgaussian2D.m`, and the deposited energy data. In this way for the chosen function the optimal parameter set are obtained.

3) - Check of the fit -

In order to check for the fit correctness, we have ideated several qualitative test.

- We have plotted, for each depth, the fit function and the data relatively to the energy deposited along the central x and y axis checking for the accordance between fit and data, as shown in Fig.
2.31 for a 200 MeV proton beam in water at a penetration depth of 20 mm. In Fig. 2.31 the superposition of the two distributions along the x and y axis, due to their symmetry, is evident.

![Diagram of energy deposition in water](image)

**Fig. 2.31** One dimensional (superimposed) views along the x axis and y axis of the fit with a bidimensional Gaussian of the energy distribution per unit length and per primary particle at z=43 mm for a 200 MeV proton beam impinging in water

- Another visual check is done by placing side by side the 3D plot of the deposited energy in the xy plane and the 3D plot of the corresponding fit. Moreover the difference between data and fit is also plotted. An example of such plots, for a 200 MeV proton beam in water at a depth of 22 mm, is displayed in Fig. 2.32, where (in the lower right side) the position, along the integrated Bragg curve, to which the other plots refer is also visualized.
Fig. 2.32 Upper left side: 3D view of the deposited energy data in xy plane at a depth of 22 mm in water for a 200 MeV proton beam - Upper right side: The corresponding fit with a Gaussian function - Lower left side: The corresponding difference between data and fit - Lower right side: deposited energy integrated over the transverse plane: the red line identify the penetration depth to which the data refer.

- The last check is done by visualizing the bidimensional plot of the deposited energy (in the xy plane at a specified depth) near the plot of the percentage difference, point by point, between the data and the fit value. The values of percentage difference integrated over cylindrical sections of $\sqrt{2}$ mm thickness is also plotted versus beam radius, and, for understanding in which point the data do not match, the one dimensional deposited energy distribution is also shown, as illustrated in Fig. 2.33 for a 200 MeV proton beam at a depth of 233 mm in water.
Fig. 2.33 Lower left side: Bidimensional view of the deposited energy data in xy plane at a depth of 233 mm in water for a 200 MeV proton beam - Upper left side: The percentage difference between the deposited energy data and the corresponding fit with a Gaussian function – Upper right side: Percentage difference between the deposited energy data and the corresponding fit, both integrated over cylindrical sections of thickness of $\sqrt{2}$. Lower right side: deposited energy distribution along the beam radius

4) - Fit comparison and chose of the best fit -

The fit goodness are evaluated by visually comparing the plots of the percentage difference between data and fit integrated over the whole binning surface versus penetration depth. For example in Fig. 2.34(a) the percentage difference relatively to the fit with a sum of two Gaussian distribution is represented for the 100 MeV proton beam in lung. Great values in percentage difference are observed few millimeter behind the Bragg peak, just behind the
fall-off, where the deposited energy is near zero (for understanding in which point the data does not match, in Fig. 2.34(a) the integrated Bragg curve is shown). However the fit procedure used may be further improved, to obtain a best agreement with experimental data, avoiding sharp variations in parameters behavior with depth.

![Graph 1](image1.png)

**Fig. 2.34 (a)** Percentage difference between data and fit integrated over the whole binning surface versus penetration depth; **(b)** MIDE
2.4.2. The sigma parameter

The fit of the deposited energy on the transverse xy plane at each depth gives the values of the fit parameters for the chosen fit function. The evaluation of the fit results has conducted us to think that the best fit is achieved with the sum of two Gaussian function. Then by summing the two amplitude parameters at each depth the non integrated Bragg curve can be reconstructed, as shown in Fig. 2.35

![Graph showing comparison between the sum of the two amplitude parameters of the fit and the MIDE](image)

**Fig. 2.35** Comparison between the sum of the two amplitude parameters of the fit and the MIDE

The widths of the two Gaussian function, indicated by the sigma parameters, vary with beam energy and with the target medium, as shown in Fig. 2.36
The sigma values of the Gaussian with higher amplitude (called in this work first Gaussian) are indicative of the displacement due to multiple Coulomb scattering suffered by protons in passing through the medium.

The conversion from angular $d\varphi$ to radial displacement $dy$ is given, at a depth $t$ starting from depth $x$ in the material, by $d\varphi \approx d(tg\varphi) = \frac{dy}{t-x}$.

Fig. 2.36 Values of the sigma1 parameters for beams of several energies (230, 200, 150 and 100MeV) impinging on various material (water, bone, lung)
Several efforts have been done in this years in order to find an analytic form for the multiple scattering angle. Almost all theories approximate the angular distribution of the beam particle passing through a thickness with a Gaussian. Here we will refer to the projected positions and angles $y$ and $\theta$, which are related to the corresponding not projected quantities (for example $\theta = \theta_{RMS}^{plane} = (1/\sqrt{2})\theta_{RMS}^{space}$), so that other quantities like angular variance $\theta^2$, covariance $y\theta$, spatial variance $y^2$, scattering power $T$ and constant energy $E_S^2$ are $1/2$ of the corresponding non projected quantities. Then in the Molière angular theory whose distribution, as pointed out in the paragraph 1.1.1.3, has Gaussian behavior at small angles and goes as $1/\theta^4$ at large angles, the projected rms angle is $\theta_{RMS}^M = \frac{\chi_c}{\sqrt{2}} B^{\frac{1}{2}}$, and the form corrected by Hanson in order to account for the narrower width due to non Gaussian term is $\theta_{RMS}^{MH} = \frac{\chi_c}{\sqrt{2}} (B - 1.2)^{\frac{1}{2}}$.

Fermi and Eyges [59] also developed a theory for Gaussian beam transport in matter, where number density $\Phi$ at transverse position $y$ and angle $\theta$ for a $N$-particle system is described as

$$\Phi(y, \theta) = \frac{N}{2\pi} \frac{1}{\sqrt{\bar{y}^2 \bar{\theta}^2 - \bar{y} \bar{\theta}^2}} \exp \left( -\frac{1}{2} \frac{\bar{\theta}^2 y^2 - 2 \bar{y} \bar{\theta} \theta + \bar{\theta}^2 \theta^2}{\bar{y}^2 \bar{\theta}^2 - \bar{y} \bar{\theta}^2} \right),$$

and is characterized by angular variance $\bar{\theta}^2 = \sum_{i=1}^{N} \theta_i^2 / N$, spatial variance $\bar{y}^2 = \sum_{i=1}^{N} y_i^2 / N$ and covariance $\bar{y} \bar{\theta} = \sum_{i=1}^{N} y_i \theta_i / N$. Due to energy loss and multiple scattering, these quantities are modified during the penetration of the particle in this way:

$$\bar{\theta}^2(x) = \int_0^x T(x') dx', \quad \bar{y} \bar{\theta} (x) = \int_0^x (x - x') T(x') dx', \quad \text{and} \quad \bar{y}^2 (x) = \int_0^x (x - x')^2 T(x') dx',$$

where $\overline{T} = [\bar{\theta}^2 (x + \Delta x) - \bar{\theta}^2 (x)] \Delta x$ is the scattering power, which gives the beam behavior along longitudinal position $x$, for small step $\Delta x$. An analytical way to...
obtain this quantity has been formulated by Fermi and Rossi [101] by the formula

\[
T_{FR} = \frac{d\theta_{FR}^2}{dx} = \frac{E_s^2}{X_0} \left( \frac{z}{pv} \right)^2,
\]

where \( E_s = m_e c^2 \sqrt{2\pi / \alpha} \approx 15.0 \text{MeV} \), and \( X_0 \) is the radiation length, given in gr/cm\(^2\). This quantity has been introduced because the mean square scattering angle depends from the density in a similar way than the stopping power, so the dependence of the scattering angle from medium can be removed by means of the radiation length. The radiation length is the characteristic amount of matter traversed for electrons to produce bremsstrahlung and for photons to produce e+e- pair. It is both (a) the mean distance over which a high-energy electron loses all but 1/e of its energy by bremsstrahlung, and (b) 7/9 of the mean free path for pair production by a high-energy photon. The radiation length has been calculated by Tsai [102] [103]:

\[
\frac{1}{X_0} = 4\alpha c^2 \left( \frac{N_A}{A} \right) \{ Z^2 \left[ L_\text{rad} - f(Z) \right] + Z L'_\text{rad} \},
\]

with \( L_\text{rad} \) and \( L'_\text{rad} \) given in table 2.2, and \( f(Z) = (\alpha Z)^2 \left[ (1+(\alpha Z)^2)^{-1} + 0.20206 - 0.0369(\alpha Z)^2 + 0.0083(\alpha Z)^4 - 0.002(\alpha Z)^6 \right] \)

<table>
<thead>
<tr>
<th>Element</th>
<th>Z</th>
<th>( L_\text{rad} )</th>
<th>( L'_\text{rad} )</th>
</tr>
</thead>
<tbody>
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<td>H</td>
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<td>5.31</td>
<td>6.144</td>
</tr>
<tr>
<td>He</td>
<td>2</td>
<td>4.79</td>
<td>5.621</td>
</tr>
<tr>
<td>Li</td>
<td>3</td>
<td>4.74</td>
<td>5.805</td>
</tr>
<tr>
<td>Be</td>
<td>4</td>
<td>4.71</td>
<td>5.924</td>
</tr>
<tr>
<td>Others</td>
<td>&gt; 4</td>
<td>( \ln(184.15 Z^{-1/3}) )</td>
<td>( \ln(1194 Z^{-2/3}) )</td>
</tr>
</tbody>
</table>

Tab. 2.2. \( L_\text{rad} \) and \( L'_\text{rad} \) values

Despite this formulation does not account for the tail at large angle, the Fermi-Eyges theory has used an equivalent form: \( T \propto \left( \frac{z}{pv} \right)^2 \).

Higland has introduced a correction term to the integral formula of the Fermi-Rossi theory with an optimized energy constant. Generalizing this formalism, the formula for thick targets have been derived by Gottschalk et al [104]:

130
\[ \theta_{th}(x) = \left( 1 + \frac{1}{9} \log \frac{x}{X_0} \right) \sqrt{\int_0^x \left( \frac{14.1(MeV)z}{p_v(x')} \right) \frac{dx'}{X_0(x')}}, \quad \text{where } x \text{ is the traversed homogeneous material thickness; for heterogeneous materials Kanematsu [105] has found a further generalization for the rms angle } \theta_{th} \text{ growing with } x:\]

\[ \theta_{th}(x) = \left( 1 + \frac{1}{9} \log \ell(x) \right) \sqrt{\int_0^x \left( \frac{14.1(MeV)z}{p_v(x')} \right) \frac{dx'}{X_0(x')}}, \quad \text{where } x \text{ is the longitudinal position in the target and } \ell(x) \text{ is the radiative path length, defined as }\]

\[ \ell(x) = \int_0^x \frac{dx'}{X_0(x')} .\]

Overas [106] derived a relation between \( p_v \) and the residual range \( R \) in water,

\[ \left( \frac{p_v}{p_0 v_0} \right)^2 = \left( \frac{R}{R_0} \right)^k \] (k=1.08 is a constant and \( p_0, v_0 \) and \( R_0 \) are the initial values of the incidence) and Schneider [107] corrected the Fermi-Rossi formula with the Overas relation

\[ \theta_{OS}(R) = \frac{E_S z}{p_0 v_0} \sqrt{\frac{R_0 / \rho_S}{(k-1) X_0} \left[ \left( \frac{R_0}{R} \right)^{k-1} - 1 \right]} \sqrt{c_0 + c_1 \left( \frac{1}{2} - \frac{R}{R_0} \right)^4}, \] with

\[ c_0 = 0.888 - \frac{0.00406 \rho X_0}{g/cm^2}, \quad c_0 = \frac{0.0380 \rho X_0}{g/cm^2} - 4.86; \] in this formulation, the scattering power is analytically given by

\[ T_{OS}(R) = \frac{E_S z}{X_0 (p_0 v_0)} \left( \frac{R_0}{R} \right)^{k} \left[ c_0 + c_1 \left( \frac{1}{2} - \frac{R}{R_0} \right)^4 + \frac{4 c_1}{k-1} \left( \frac{1}{2} - \frac{R}{R_0} \right)^k \frac{R}{R_0} \left[ 1 - \left( \frac{R_0}{R} \right)^{k-1} \right] \right]. \]

Kanematsu [100] pointed out that a better approximation can be achieved by introducing in the Highland scattering power the Overas corrective factor:

\[ T_{ah} = \frac{d \Theta_{ah}^2}{dx} = f_{ah}(\ell) \frac{E_S z}{X_0} \left( \frac{z}{p_v} \right)^2, \] where
\[ f_{dt}(\ell) = \left( \frac{14.1(\text{MeV})}{E_s} \right)^2 \frac{d}{d\ell} \left[ \left( 1 + \frac{1}{9} \log \ell \right)^2 \right] \approx 0.970 \left( 1 + \frac{\ln \ell}{20.7} \right) \left( 1 + \frac{\ln \ell}{22.7} \right). \]

Kanematsu, in order to calculate the deviations in heterogeneous media, has developed a stepwise approach, translating the integrals in the scattering power definition into increments and eliminating the dependence by medium through the introduction of the stopping power ratio \( \rho_s \) with respect to water. By means of this approach he obtained the last increment

\[ \Delta y^2 = \int_0^\infty \left( \frac{R'}{\rho_s} \right)^2 T(R') \frac{dR'}{\rho_s} = f_{dt} \frac{E_s z}{X_0 \text{MeV}} m \left( \frac{R}{\rho_s} \right)^3 \frac{1}{3-k} \left( \frac{m_p z^2 R}{m \lambda \text{cm}} \right)^{-k}, \]

using conversion \( x' \rightarrow R' = R_0 - \rho_s x' \). In homogeneous media the analytical end point displacement is

\[ \sigma_{y_0}(R_0) = \frac{E_s}{\text{MeV}} \sqrt{\int f_{y_0}(R_0) \left( \frac{R}{\rho_s} \right)^3 \left( \frac{R_0}{\lambda \text{cm}} \right)^{3-k} \left( \frac{m}{m_p} \right)^{z-1-k} dR}, \]

with

\[ f_{y_0}(R_0) = \frac{3}{R_0^3} \int_0^{R_0} f_{dt} R^2 dR \approx 0.816 \left( 1 + \frac{1}{9.95} \log \frac{R_0}{\rho_s X_0} \right). \]

It should be outlined that all these theories accounts for the material dependence of the particle scattering by a factor, the radiation length \( X_0 \), which could be used in similar way in which the density has been used for correlating the deposited energy in a material to that in water.

In the FLUKA code a special transport algorithm [99], based on Molière theory of multiple Coulomb scattering as improved by Bethe [21] [58] [60], has been implemented. It accounts for several correlations:

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

A line of research in order to find an analytical solution to reproduce the Gaussian distribution could be trying to reproduce the lateral beam spread behaviour using
the Molière theory of multiple scattering or the Kanematsu approach, making the beam independent from the medium by introducing a factor accounting for the radiation length or a more suitable material dependent parameter.

Here we can only point out that in a preliminary approach, we have fitted with a gaussian the unidimensional energy distribution per primary particle and per volume unit along the x axis for several beam energies at each bin depth (a bin is 1 mm wide); we have then plotted the square of the parameter sigma so to make the maximums position of the $\sigma^2$ be coincident with the position of the 200 MeV proton beam, and reporting for each depth the traslated $\sigma^2$ versus energy, we have determined a polynomial (cubic) dependence of the $\sigma^2$ parameter by the beam energy at each depth and the fit parameters at several depth are of the same order, so it is possible, by fitting the $\sigma^2$ at each depth, finding the mean of the fitting parameter in order to make the beam broadening for a beams of several energies dependents from a known spreading at a selected energy. This method can be further improved using, instead of the unidimensional Gaussian fit, the previously described fit with a sum of two bidimensional Gaussians.

### 2.5. Oblique incidence

A great number of simulations has been performed in order to evaluate the effect of beam entrance not orthogonal to surface. Beams impinging on different materials (water, bone, lung, WLB) with several incidence angles respect to the surface normal ($2^\circ$, $5^\circ$, $10^\circ$, $15^\circ$) and various energies (100 MeV, 150 MeV, 200 MeV, 230 MeV) have been simulated.

In the following we will consider a Cartesian reference system in agreement with the binning system, that is with the z axis orthogonal to the entrance surface of the phantom. The beam rotation has been performed so to preserve the central
beam entrance position of the normally incident beam, which is located in the point (x=41 mm, y=41 mm).

In Fig. 2.37 the energy distribution in the yz section at the beam central axis (y=41 mm) and that in the xy section at a depth of 248 mm are represented for a 200 MeV proton beam impinging at 15° respect to the normal of the water phantom surface. The depth of 248 mm corresponds to the new Bragg peak position $z_{BP}$, which can be geometrically evaluated respect to the normal incidence beam Bragg peak position $z_{BP}^{0°}$ =257 mm by means of the formula: $z_{BP} = z_{BP}^{0°} \cos \vartheta$, where $\vartheta$ is the incidence angle with respect to the surface normal.

![Deposited energy per primary particle and per volume unit](image)

**Fig. 2.37** Deposited energy per primary particle and per volume unit (a) in xz plane along the beam central axis (y=41 mm); (b) in xy plane at a depth of 248 mm

In Fig. 2.38(a) we have represented, at several x positions, the deposited energy, for the same 15° 200 MeV beam of the Fig. 2.37, along the y=41 mm axis, which corresponds to the central axis of the perpendicularly incident beam. The deposited energy distribution shape varies with the x value considered; however a simple geometrical consideration can be done about the non zero deposited distribution along the x=41 mm. The $z_{lim}$ value for which energy deposition should
not be appreciable is given by \( z_{\lim} = \frac{1}{2} 2.35 \sigma_0 \cos \theta \). The \( z_{\lim} \) value for the 15° 200 MeV beam of Fig. 2.38(b), is, for example, \( z_{\lim} = \frac{1}{2} 47.1 \cos \theta = 23 \text{mm} \).

![Depicted energy per primary particle per volume unit along z beam axis at y=41 mm, p200 water, 15°](image)

**Fig. 2.38** Deposited energy per primary particle and per volume unit along z axis at y=41 mm in water for a 200 MeV proton beam (a) at several x values; (b) at x=41 mm.
Naturally, when the deposited energy is integrated over the xy transverse plane the Bragg peak curve appears, but, respect to the normally incident beam, is shorten, and the peak, as seen previously, has the position: \( z^\text{BP}_\theta = z^\text{BP}_0 \cos \theta \)

![Deposited energy per primary particle and per length unit](image)

**Fig. 2.39** Deposited energy per primary particle and per length unit

The energy deposition profile in the x direction for a non-orthogonal beam incidence is skewed respect to that of a normally incident beam. This evidence is shown in Fig. 2.40(b) for the 15° 200 MeV beam at the Bragg peak depth \( z^\text{BP}_{15°} = 248 \); the distribution are centred at the position \( z^\text{BP}_\theta \), which is related to the \( z^\text{BP}_0 \) Bragg peak depth of the orthogonal incidence beam by the geometrical relation \( x^\text{BP}_\theta = z^\text{BP}_0 \sin \theta \).
Fig. 2.40 Deposited energy per primary particle and per volume unit (a) at several depths; (b) at $z=248\text{mm}$, with a gaussian fit which highlights the distribution skewness.
In Fig. 2.41 is represented the integral over the yz plane of the energy deposited per primary particle and per volume unit. The distribution is the sum of all contribution of the type described in Fig. 2.40 and extends more or less from the distribution position of the normally incident beam, which was centered at x=41 mm, to the position of the distribution correspondent to the Bragg peak position, given by $x^{BP}_g = z^{BP}_0 \sin \mathcal{G}$.

![Deposited energy integrated over the yz plane per primary particle and per volume length](image)

**Fig. 2.41** Deposited energy integrated over the yz plane per primary particle and per volume length

The cited two relations naturally are true also for a generic depth $z_g$:

$$z_g = z_0 \cos \mathcal{G} \quad \text{and} \quad x_g = z_0 \sin \mathcal{G}$$

Using these relations it should be possible finding a way to express the energy distributions of the not orthogonal beam respect to the correspondent normally incident beam distribution.
Chapter 3

DOSE DISTRIBUTION OPTIMIZATION

In order to treat with proton beam spot scanning technique a tumour having a great size volume, several tenths of thousand of pencil beams with appropriate directions, energies and intensities must be sent through the human body. The choice of these parameters must be optimized in order to deliver the uniform prescribed dose (within a few percent) to the target volume while maximizing contrast between cancerous cells and surrounding healthy tissues also with an appropriate choice of beam entrance ports.

The first step in achieve this objective is the reproduction of an uniform dose distribution in a limited spatial homogeneous region by composing beams with a fixed entrance direction. Transversal modulation can be achieved optimizing the step size of the lateral beam translation and the beam intensity for a beam of fixed energy. Longitudinal uniformity (SOBP) can be instead achieved researching the optimal set of beam energies and intensities.

Here it is discussed only the composition of non modulated beam so to achieve an uniform transversal dose distribution at a specified dept.

3.1. Beam composition

The deposited energy distribution can be modulated and composed so to obtain an homogeneous dose distribution at a specified depth in a limited spatial region. We have composed, as done in a previous work by D’Ambrosio [108], the beam transversally in x and in y translating it at step of 2 mm and we have seen the change in energy deposited at the center of the dose distribution as the number of traslation is increased; naturally the minimum number \( n_{\min} \) of traslation for which the intensity does not change depends from the step size and the beam width. The beam width varies with the depth, so \( n_{\min} \) varies also with depth, as illustrated in Fig. 3.1 where the energy deposited in the distribution centre is plotted versus step
number at several depth (1, 100, 220, 257) for the 0° 200 MeV proton beam in water

![Deposited energy in the center of dose distribution per primary particle and per volume unit versus translation step numbers for the 200 MeV proton beam in water](image)

**Fig. 3.1** Deposited energy in the center of dose distribution per primary particle and per volume unit versus translation step numbers for the 200 MeV proton beam in water

The energy deposition at the depth of the Bragg peak is showed in the xz section for 30 traslations of 2 mm in Fig. 3.2 and in a three dimensional view of the xy section in Fig. 3.3 for the 200 MeV proton beam.
Fig. 3.2 Deposited energy in the yz plane per primary particle and per volume unit

Fig. 3.3 Deposited energy in the xy plane per primary particle and per volume unit
In order to check if the fit with a sum of two Gaussian can also reproduce the same dose, we have composed it at the same way of the data of FLUKA and, as shown in Fig. 3.4, we have found a good agreement between data (in red) and fit distribution (in colorwash).

The percentage difference between FLUKA data composition and fit data composition are illustrated in Fig. 3.5, showing a good agreement in the central part of the distribution (the inner line in Fig. 3.5(a) represents the percentage difference of 1%). These data should better be compared with a gamma function (see paragraph 1.5), because the greatest disagreement is in the region with high energy gradient.

**Fig. 3.4** Deposited energy in the xy plane per primary particle and per area unit: in red the simulation data composition, in colorwash the fit composition data with 29 traslation of 2mm at depth of 25.7 cm for the 200 MeV proton beam in water.
Fig. 3.5 Percentage difference in deposited energy in the xy plane per primary particle and per area unit between simulation data composition and the fit composition with 29 translation of 2mm at depth.
of 25.7 cm for the 200 MeV proton beam in water (a) contour plot, with the inner line representing percentage difference of 1% (b) three dimensional view

This is only the first step in obtaining an uniform dose at a fixed depth, which can be reached by optimizing beam intensities and positions of the fit function which, having an analytical expression, can be easier handled than the FLUKA data matrix. A mathematical model of a uniform dose distribution is easily achieved, so the optimization can be done by the minimization of the difference between the desired uniform dose distribution and a function, which results in the sum of the fit functions, whose intensity and position represent the parameters to be optimized.
CONCLUSIONS
This work is an initial phase of a long term program which will enable to acquire a valid instrument for the treatment plan optimization of a fully active (longitudinal modulation (energy), transverse modulation and beam current intensity) proton therapy facility. We have performed a great number of Monte Carlo simulations of several energy proton beam impinging on different materials with various incidence angle respect to the surface normal, evaluating the deposited energies. In this preliminar study we have used only homogeneous target, composed by water, bone, a fictious “lung”, or by a composition of these three materials. This work is a first approach to evaluate dose distribution even when heterogeneities are present, researching the methodic to make the deposited energy independent from materials other than water. The program foresee the development of several points, delineated and faced in this work and on which more study has to be done in the next years:

- The first point is the research of a way of referring the deposited energy of several materials to that of water. In this viewpoint is of outermost importance the analytical formulation of the dependence of the deposited energy from depth, energy and medium. In particular we have developed a methodic in order to make independent the deposited energy in several medium by material characteristics, referring it to the deposited energy in water.

- A second point in the research program is the analysis of the dependence of the beam broadening by the beam energy and by the medium material. We have found a way to make the beam broadening independent from beam energy and we have traced the lines to found the independence also from medium material, by expressing the broadening in a material in terms of that in water.

- The third point in the research program is the analysis of the beam incidence at angles others than 90° respect to the phantom surface, in order to find an
algorithm which, starting from the data of the perpendicularly incident beam, can reconstruct the propagation behavior of not perpendicularly incident beams. We have then performed several simulations at different beam incidence angles and energies, delineating the problem and finding the fundamental geometrical transformation to obtain the not incident beam distribution from that of the incident beam distribution.

- The last point in the program is the beam spatial composition so to conform the dose to a desired distribution. For example by imposing a flat distribution and a rapid dose fall off the optimal set of beam amplitudes and positions can be found. By means of optimization algorithms, it should be found the optimal beam delivery modality (beam directions, intensities, positions, energies).
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