A treatment planning code for inverse planning and 3D optimization in hadrontherapy

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Abstract

The therapeutic use of protons and ions, especially carbon ions, is a new technique and a challenge to conform the dose to the target due to the energy deposition characteristics of hadron beams. An appropriate treatment planning system (TPS) is strictly necessary to take full advantage.

We developed a TPS software, ANCOD++, for the evaluation of the optimal conformal dose. ANCOD++ is an analytical code using the voxel-scan technique as an active method to deliver the dose to the patient, and provides treatment plans with both proton and carbon ion beams. The iterative algorithm, coded in C++ and running on Unix/Linux platform, allows the determination of the best fluences of the individual beams to obtain an optimal physical dose distribution, delivering a maximum dose to the target volume and a minimum dose to critical structures.

The TPS is supported by Monte Carlo simulations with the package GEANT3 to provide the necessary physical lookup tables and verify the optimized treatment plans. Dose verifications done by means of full Monte Carlo simulations show an overall good agreement with the treatment planning calculations. We stress the fact that the purpose of this work is the verification of the physical dose and a next work will be dedicated to the radiobiological evaluation of the equivalent biological dose.

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1. Introduction

Charged particle beams have stimulated a great deal of interest in tumor therapy primarily due to the superior dose distributions compared to those produced by photon or neutron therapy techniques [1]. In contrast to the exponential deposition of photons and neutrons, protons and carbon ions have a rapid energy loss in the last few millimeters of penetration (Bragg peak) followed by sharp dose fall-off. This physical selectivity allows a higher degree of dose conformation to the tumor volume.

In order to better exploit the advantages of these particle beams, various scanning techniques have been implemented [2–4]. They use magnetic deflection of narrow pencil-like beams to cover the target volume. The beam energy is modulated to cover different slices at different depths. An appropriate treatment planning system (TPS) is hence mandatory to take full advantage of the techniques.
In this article we describe the principles of the planning methods implemented in a TPS based on an analytical code written in C++ language (from this the acronym ANCOD++) to evaluate the best energies and fluences for proton and carbon ion beams to obtain a conformal dose distribution as high and as uniform as possible, minimizing the dose delivered to healthy tissues.

Carbon ions offer further advantages over protons or lighter charged hadrons. For example they exhibit dose distribution gradients up to three times steeper than protons, mainly due to the smaller lateral scattering of the beam, thus allowing a sharper lateral penumbra. But the main potential advantage for using these particles for therapy is their enhanced relative biological effectiveness (RBE) [6]. In particular the increased effectiveness is more pronounced in the stopping region at the Bragg peak, leading to a further therapeutic advantage and allowing a better ratio of biologically effective doses in the tumor and normal tissue [7–9]. The radiobiological aspects of the TPS will be addressed in a separate paper.

The article is structured in two main parts. Part one describes the details of the implementation of ANCOD++ TPS, the beam model and the strategy used to achieve a fast dose calculation and optimization. In the second part, we analyze the treatment plans obtained for two clinical cases and compare them with full Monte Carlo (MC) simulations.

2. Methods and materials

2.1. General description

ANCOD++ assumes the method of voxel scanning as the irradiation technique and it is based on the following assumptions:

- the dose delivery is done in elementary steps. At each step, one voxel of the target is irradiated;
- the beams, composing each field, are described as a mono-energetic pencil beam aiming at the voxel center and the energy is computed so as to have the Bragg peak right in the center of the voxel.

The number of beams for a given treatment is hence assumed to be equal to the number of voxels in the target volume [10,11]. In the following we will address voxels with symbol \( \lambda \) and beams with symbol \( \eta \). The set of voxels, \( \{ \lambda \} \), and the set of beams, \( \{ \eta \} \), if not otherwise stated, are arbitrarily sorted, provided that \( \eta = \lambda \) when addressing beams which have the Bragg peak in the center of the voxel.

Building a TPS needs an ensemble of auxiliary codes which respond to its different requirements. ANCOD++ is structured in several modules (see Fig. 1) that can be grouped in three main parts. The first part of the code is an interface for reading and converting the medical images and data concerning the target volume. The second part allows the beam setting and calculation of the corresponding energies taking into account the hardware constraints. The optimization routine then provides the set of the best beam intensities to reach the most conformal dose distribution to the planning target volume (PTV). Finally, we calculate the final dose distribution optimized and the relevant graphs for the evaluation of the plan. These parts are described in the following sections.

2.2. Input data

The first step of the TPS concerns the acquisition and manipulation of computed tomography (CT) data scan and contours data relative to the PTV and the organs at risk (OARs), to generate a three-dimensional digital model of the irradiation region. For this purpose ANCOD++ allows the reading of Digital Imaging and Communications in Medicine (DICOM) data format [16].

Two right-handed reference systems are introduced:

- Target reference system (TRS), which is related to the CT volume, with \( x \)-axis parallel to the sagittal, \( y \)-axis parallel to the coronal, and the \( z \)-axis parallel to the axial tomography slice.
- Beam reference system (BRS), which is related to the beam and the field, with the \( x \)-axis along the beam direction and the \( z \)-axis pointing upwards.

A virtual, regularly spaced, voxel grid is created in the BRS. Then, the CT data in TRS is mapped on the voxel grid through an arbitrary rotation about three axis and a translation. The translation puts the PTV isocenter exactly on the coordinate origin of BRS. The mapping of CT data over the new voxel grid is obtained via a 3D interpolation based on non-linear weighting functions of the distance between voxel centers.

Once the target contours are read and the voxel geometry defined, a filling algorithm specifies all the voxels inside the target volume they belong to. This determines the direction
losses of tables, with the aim of having very fast calculation. The necessary code that uses pre-calculated data sets stored in look-up planning in clinical practice.

rules out the use of these simulation techniques for treatment major handicap in their large time consumption. This effectively for calculating the detailed transport of particle beams in tissues the transport of protons and carbon ions in tissue in a way

2.3. Calculation of beam energies and physical dose

The main requirement of TPS lies in its ability to describe the transport of protons and carbon ions in tissue in a way suitable for fast treatment planning. The most reliable method for calculating the detailed transport of particle beams in tissues is based on MC simulations. However, such methods have a major handicap in their large time consumption. This effectively for simulating low energy experiments like those we perform physics and now it has became a valid and efficient tool also
cross-section for X-rays, while the ion stopping power is due

While this is a good approximation for carbon ion beams, it

determined the ion stopping power and hence the

The simulations are implemented using the GEANT4 libraries developed at CERN [13]. GEANT4 is a simulation package which was first implemented to be used in high energy physics and now it has become a valid and efficient tool also for simulating low energy experiments like those we perform in hadrontherapy. In particular, these simulations take into account the specific features of energy loss for these particles: the multiple scattering and the straggling for protons, and the projectile fragmentation for carbon ion beams [14]. A second set of simulations for the verification of the TPS are implemented with a previous version of the same package, GEANT3, and it will be described in Section 3.

In order to take into account tissue inhomogeneities for dose computation, CT data are mandatory. CT data, taken without contrast drugs, can be related to the tissue electron density \( \rho_e \), which determines the ion stopping power and hence the dose deposition. We convert the Hounsfield numbers to the relative electronic densities with respect to water \( \rho_e/\rho_w \) with a calibration curve and we use re-mapped voxel coordinates in water-equivalent distances \( x_w = \int_0^x (\rho_e(\mathbf{x}')/\rho_w) \, d\mathbf{x}' \) to compute the range crossed by each beam in each elementary volume [12]. Notice, however, that the Hounsfield number reflects the cross-section for X-rays, while the ion stopping power is due mainly to energy loss processes that have different functional dependences on the atomic number \( Z \) and atomic mass \( A \) of the contributing atoms. Hence, there is no theoretical functional relation between CT data and penetration depth of particles and the calibration curve used for the conversion has to be referred to direct measurements, for example with the use of heavy-ion CT (HICT) technique [15], and it is specific to the scanner device used to obtain the CT data.

The first step of the calculation is related to the interpolations made to compute the kinetic energy \( E_k(\eta) \) of each beam \( \eta = \lambda \) needed to deliver the Bragg peak exactly at the water-equivalent center of the \( \lambda \)-th voxel, \( x_w(\lambda) \):

\[
E_k(\eta = \lambda) = E_k^*(m) + (x_w(\lambda) - x_{peak}^*(m)) \\
x \left( \frac{E_k^*(m + 1) - E_k^*(m)}{x_{peak}(m + 1) - x_{peak}(m)} \right)
\]

where \( E_k^*(m) \) is the kinetic energy of the \( m \)-th tabulated beam and \( x_{peak}^*(m) \) is the position of its Bragg peak, so that \( x_{peak}^*(m) < x_w(\lambda) < x_{peak}^*(m + 1) \). The calculation of the energy deposited in each voxel becomes fast since we use a similar bi-linear interpolation method over the set \( \{E_k^*(m), x_{peak}^*(m)\} \) to obtain it as a function of kinetic energy of the beams and penetration depth \( E_d = E_d(E_k, x_w) \). A first interpolation is made to fix the depth where we want to know the deposited energy and a second one is made to find the energy deposited at this point. The deposited dose in the \( \lambda \)-th voxel due to the \( \eta \)-th beam with kinetic energy \( E_k = E_k(\eta) \) is hence evaluated through

\[
D(\eta, \lambda) = k \times \exp \left( -\frac{1}{2} \frac{r(\eta, \lambda)^2}{\sigma^2} \right) \\
\quad \times \frac{1}{L(\lambda)} \int_{L(\lambda)} E_d(E_k(\eta), x_w) \, dx_w
\]

where \( r(\eta, \lambda) \) is the distance of the \( \lambda \)-th voxel from the \( \eta \)-th beam axis, \( \sigma \) is the variance of the Gaussian profile of the beam, and \( k \) is a constant. The value of \( \sigma \) is kept constant. While this is a good approximation for carbon ion beams, it should be replaced with a variable one, \( \sigma = \sigma(x_w) \) in the case of proton beams in order to reproduce the effect of scattering. The integral is made along the direction of the beam and it is the average of deposited energy in the \( \lambda \)-th voxel with thickness \( L(\lambda) \). Notice that in this point of the evaluation we assume the beams to be nearly-parallel to the \( x \)-axis. The approximation is reasonable assuming the lateral dimension of PTV to be of the order of 10 cm and distance of its isocenter to the beam deflecting magnet of the order of 5 m, that is the geometry set-up we used in the applications described in the next section.

Following the described procedures, we are able to obtain for a set \( \{\eta\} \) of beams corresponding to a given irradiating field, the directions \( (\theta(\eta), \phi(\eta)) \) of the beams, their kinetic energies, \( E_k(\eta) \), and the corresponding energy loss, \( E_d(\eta, \lambda) \), at each crossed \( \lambda \)-th voxel. The fourth characteristic of the beams, the fluences \( w(\eta) \), are free parameters and will be calculated in the optimization part.
2.4. Optimization

Once we have all the values of the linear energies deposited by each beam in each voxel, the main task of the TPS is to build the optimal plan according to the physician’s dose prescriptions, sparing as much as possible the OARs and delivering a uniform and maximal dose as possible to the PTV.

The use of a water-equivalent distance permits to simplify the dose optimization since these computations can be done directly in the water-equivalent system in beam’s-eye view. On the other hand this allows to optimize only a single field (or beam port) at a time. Different fields can be added later in the final plan, but cannot be optimized as a whole.

For a given field, the goal of the optimization is summarized in two main points:

- maximal and uniform dose to the target;
- minimal dose outside the target.

We cast the above conditions in a linear system, which is defined as follows:

$$D_{\text{req}}(\lambda) = \sum_{\eta=1}^{N_{\text{beams}}} w(\eta) \times D(\eta, \lambda)$$

(4)

where $D_{\text{req}}(\lambda)$ is the required dose in the $\lambda$-th voxel. The number of equations is equal to the number of voxels inside the volume to be treated, $N_{\text{voxels}}$, and in the following we assume that the number of beams of the plan $N_{\text{beams}} = N_{\text{voxels}}$, even if this condition is not strictly necessary.

We can arrange the deposited doses $D(\eta, \lambda)$ in a square matrix, providing an arbitrary sorting of the voxels/beams. Since the beams are characterized by high physical selectivity, the main contribution to the dose $D_{\text{req}}(\lambda)$ is typically given by $D(\eta, \lambda)$, i.e. the matrix is quasi-diagonal (Fig. 2). This fact permits to achieve the solution of the linear system by a fast iterative algorithm in which the dose required in a specific voxel is corrected, after each iteration, by a small amount with respect to the previous one. Due to the sharp fall-off of the Bragg peaks, distal peaks are less perturbed by the presence of proximal peaks. Hence the optimization is faster if we start evaluating distal peaks, that will require minimal corrections at subsequent iterations, and then proceed evaluating proximal ones. Accordingly, we choose to sort the voxels/beams ranking them as a decreasing function of depth $x_w(\lambda)$, i.e. we have $x_w(\lambda + 1) \leq x_w(\lambda)$ for each $\lambda$.

We start by computing the fluence $w^0(1)$ of the beam aiming to voxel 1. In other words, the calculation starts by considering only the beam giving the Bragg peak right in the center of this voxel. The fluence of the beam aiming to the next voxel $w^0(2)$ is calculated taking into account the contribution of the previous beam. As one proceeds along the first step of the iteration, the fluences $w^0(\lambda)$ are computed after the contributions due to the previous beams have been subtracted. The steps are explicitly...
reported:

\[
w^0(1) = \frac{D_{\text{req}}(1)}{D(1, 1)}
\]

\[
w^0(2) = \frac{D_{\text{req}}(2) - w^0(1)D(1, 2)}{D(2, 2)}
\]

\[\vdots\]

\[
w^0(\lambda) = \frac{D_{\text{req}}(\lambda) - \sum_{\eta=1}^{\lambda-1} w^0(\eta)D(\eta, \lambda)}{D(\lambda, \lambda)}
\]

Once the first iteration has been completed with the calculation of a set of fluences \(\{w^0(\eta)\}\), the algorithm requires to use them to evaluate the next-iteration values, \(\{w^1(\eta)\}\). The \(n\)-th iteration can be explicitly written as

\[
w^0(\lambda) = \frac{D_{\text{req}}(\lambda) - \sum_{\eta=1}^{\lambda-1} w^0(\eta)D(\eta, \lambda)}{D(\lambda, \lambda)}
\]

where the expression \(\sum_{\eta=1}^{\lambda-1} w^0(\eta)D(\eta, \lambda)\) is the contribution to the dose for beams \(\eta > \lambda\) that are evaluated in the previous iteration \((n-1)\), and \(\sum_{\eta=1}^{\lambda-1} w^0(\eta)D(\eta, \lambda)\) is the contribution to the dose for beams \(\eta < \lambda\) that are already evaluated in the present iteration \((n)\).

Negative fluences are set to zero and it is also defined an upper limit for plausible fluence values. At each iteration, a new voxel, \(x(\lambda), y(\lambda), z(\lambda)\) within the irradiated volume as well as the absorbed dose level [17].

\[\vdots\]

3. Results

In view of the complexity of the dose calculation and optimization, a mean of overall verification of the planning procedure is indispensable. We present here a MC verification of the approximated method used in our TPS code. For this purpose, we optimized treatment plans for two real clinical cases, using both proton and carbon ion beams, then we performed full MC simulations of the treatment plans and compared the results with those obtained directly with the evaluation of ANCOD + + .

The MC simulations were implemented using the package GEANT3. While for the proton beam we used the explicit modules of GEANT3, for the nuclear interaction we used an external module describing the fragmentation of carbon ion beams based on the Sihver model for the fragmentation of heavy ions [18].

GEANT3 allows the descriptions of an experimental setup by a structure of geometrical volumes characterized by different tracking medium parameters. In our setup, the medium is built as an ensemble of voxels whose densities are deduced from the CT data.

The particle beams used in both MC simulation and ANCOD + + computation, are shaped with a Gaussian profile, and have a full width half maximum (FWHM) of 4.7 mm, according to the chosen scanning step. The angles that specify the directions of the beams \(\{\theta(\eta), \phi(\eta)\}\), the kinetic energies \(\{E_k(\eta)\}\) needed to cover with Bragg peaks the voxels of the target, and the optimal set of fluences \(\{w(\eta)\}\) are obtained directly from the plans generated by ANCOD + + .

3.1. Clinical cases

The first clinical case is a parietal-occipital glioblastoma (Fig. 4(a,b)) and the second one is an orbital meningioma (Fig. 4(c,d)). We used CT images from the top of the head to the foramen magnum with 80 slices (first case) and 67 slices (second case). The slice’s matrix is 512 × 512 pixels. We used a voxel-scan grid for the treatment planning reducing the subdivision of \(x, y\)-plane to 128 × 128 pixels and maintaining the
same number of slices along the z-axis. The dimension of the voxels of both cases is $1.96 \times 1.96 \times 3.0 \text{mm}$.

In the first case the isocenter of the PTV is at 6 cm depth from the parietal-occipital cranial bone. We delivered the dose to this target using only one beam port at 30° with respect the TRS. In the second case the isocenter of the PTV is 10 cm in depth and the target is located in the posterior aspect of the left orbit, displacing the optic nerve. We chose to irradiate this target using two different coplanar beam ports at 0° and 40°, respectively. The two beam ports are optimized independently.

The directions of the beams were chosen to respect the relative and absolute dose constraints of the OARs. The OARs considered for the first case are: brain, brain stem, chiasm, left cochlea, and pituitary gland. For the second case we considered more OARs due to their vicinity to the tumor: brain, brain stem, chiasm, pituitary gland, optic nerves (left and right), retinae (left and right), left lens, and lacrimal gland.

The particle kinetic energies used in the plans ranged from 65 to 125 MeV/n for protons and from 110 to 230 MeV/n for carbon ions. The number of beams used to treat the first case are $N_{\text{beam}} \sim 4000$ while in the second case the volume of the tumor is smaller and we used $N_{\text{beam}} \sim 2000$ per beam port. For the MC simulation of the proton treatment, we generated an average amount of about $10^5$ particles per beam. Since carbon ions have larger LET, we were able to deliver the same dose with less simulated events than protons. Hence, in order to limit
the amount of CPU time, the simulated number of ions was scaled down by a factor of 10. The total computing time for MC simulation is of the order of a few days. This is to be compared with the execution time of our code, for the optimization of the plan, that is of the order of a few seconds on an average PC equipped with an Intel P4 processor clocked at 2.0 GHz.

The isodoses of the spatial dose distribution for carbon ions evaluated with ANCOD++ and with MC simulations, for cases 1 and 2, are reported in Fig. 4. We remark that in both cases the dose distributions evaluated with ANCOD++ as well as with GEANT3 simulation are well conform to the contours of the target regions. The comparison shows also a general good agreement between the 3D dose distribution evaluated using the two different methods. Notice that in the isodoses of case 2 (Fig. 4 (c,d)) it is possible to appreciate the effect of dose perturbation due to the presence of air cavities near the target tumoral volume. The effect is reproduced by both evaluating methods.

The $\gamma$ value is used for dose distribution comparisons and it is defined as a distance of distributions in both dose and spatial coordinates [19]:

$$
\gamma(\lambda) = \min_{\lambda'} \left( \frac{\sqrt{r^2(\lambda, \lambda') + \delta^2(\lambda, \lambda')}}{\sigma_{\lambda'}} + 1 \right)
$$

(11)

where $r(\lambda, \lambda')$ is the distance between voxels $\lambda$ and $\lambda'$, and $\delta(\lambda, \lambda') = D(\lambda) - D(\lambda')$. The acceptance criteria ($\gamma < 1$) is defined by the tolerances $\sigma_{\lambda} = 3\, \text{mm}$ and $\sigma_{D} = 3\%$ with respect the average dose found in the flat region of the spread out Bragg peak (SOBP). The spatial dose distributions obtained by MC simulation are normalized to the TPS results by a minimization of the $\gamma$ values evaluated for each voxel in a box of $30 \times 30 \times 15$ voxels, centered on the isocenter of the PTV. The results of the $\gamma$-test are reported in Table 1 and in Fig. 5, where a full comparison of the profiles of SOBPs for a single beam port of protons and carbon ions, applied to case 2, is also shown. From the $\gamma$-test analysis we found that in both cases, some discrepancies arise in the distal region of the SOBP, in the sharp fall-off of the dose profiles.

The quality of the plans themselves can be checked and quantified by means of dose volume histograms (DVHs). The DVHs were computed for each case and particle beam type. The analyzed volumes are the PTV and the OARs specified by the radiation oncologist. The results for case 2 and for carbon ion beams are reported in Fig. 6 and in Table 2. Case 2, compared with case 1, presents the major criticality for the OARs, in particular for the proximity of the PTV to the left optic nerve, which, for a small fraction of volume, receives dose up to 80%. In any case the dose distribution respects the given prescription,

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Percentage of voxels in which $\gamma &lt; 1$ for proton and carbon ions, cases 1 and 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>% ($\gamma &lt; 1$)</td>
<td>Case 1</td>
</tr>
<tr>
<td>Protons</td>
<td>94</td>
</tr>
<tr>
<td>Carbon ions</td>
<td>97</td>
</tr>
</tbody>
</table>

The evaluation is performed in a $30 \times 30 \times 15$ box centered on the PTV.
Fig. 6. DVHs for case 2 evaluated from ANCOD ++ (a) and from MC GEANT3 (b) dose distribution evaluations. The histograms are evaluated for the PTV and for several OAR.

Table 2
Comparison between DVH values of PTV and left optic nerve (LON) obtained from ANCOD ++ and GEANT3 simulations

<table>
<thead>
<tr>
<th></th>
<th>%D90</th>
<th>D90</th>
<th>%D50</th>
<th>D50</th>
<th>%V80</th>
<th>V80</th>
<th>%V50</th>
<th>V50</th>
<th>%V20</th>
<th>V20</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTV (ANCOD ++ )</td>
<td>81.9</td>
<td>100</td>
<td>100</td>
<td>91.4</td>
<td>98.7</td>
<td>100</td>
<td>98.7</td>
<td>100</td>
<td>98.7</td>
<td>100</td>
</tr>
<tr>
<td>PTV (GEANT3)</td>
<td>76.2</td>
<td>96.6</td>
<td>99.8</td>
<td>87.0</td>
<td>98.7</td>
<td>100</td>
<td>98.7</td>
<td>100</td>
<td>98.7</td>
<td>100</td>
</tr>
<tr>
<td>LON (ANCOD ++ )</td>
<td>12.4</td>
<td>20.5</td>
<td>47.3</td>
<td>3.4</td>
<td>17.1</td>
<td>52.8</td>
<td>17.1</td>
<td>55.4</td>
<td>17.1</td>
<td>55.4</td>
</tr>
<tr>
<td>LON (GEANT3)</td>
<td>10.4</td>
<td>20.1</td>
<td>46.1</td>
<td>2.2</td>
<td>17.1</td>
<td>55.4</td>
<td>17.1</td>
<td>55.4</td>
<td>17.1</td>
<td>55.4</td>
</tr>
</tbody>
</table>

In the tables, %Dv is the relative dose received by at least %v of the organ volume, and %Vd is the relative volume of the organ that receive at least %d of dose.

We have compared treatment planning for two clinical cases with full MC simulations. The comparison of spatial dose deposition evaluated with ANCOD ++ and MC simulations shows quantitative good agreement.

ANCOD ++ is presently in further development. For example, a better treatment planning will be implemented by a simultaneous optimization of several overlapping fields from fixed directions. An even further optimization will have to find the best choice of the field directions.

One of the steps we are presently taking is the implementation of the optimization involving the evaluation of the biological effects characterizing the carbon ion therapy. The analytical method used in ANCOD ++ for the fast evaluation of physical dose provides a good scheme for the inclusions of the radiobiological effects into a treatment plan. The details of the fast radiobiological evaluation and their inclusion in the TPS will be the subject of a separate forthcoming paper.

Conflict of interest statement

None declared.

References


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