Abstract. The aim of conformation in radiation therapy is to deliver the dose as high and as uniform as possible to diseased tissue sparing the organs at risk all around.

To achieve a conformational treatment needs to have a big precision in the acquisition and lecture of the data input. In fact, the list of tasks before the optimization process starts with an accurate determination of the three-
dimensional volumes of interest and ends up in realizing a threedimensional uniform and maximal as possible, the dose distribution. The use of therapeutic ions, especially carbon ions and protons is a new technique and a challenge in conformation of dose to targets due to energy deposition characteristics of hadron beams.

An appropriate treatment planning system is strictly necessary to take full advantage of this novel technique. We have developed, for this purpose, an analytical code in C++ language, running on Unix platform.

The package presented, is a code system dedicated to the treatment planning of radiotherapy with hadron beams. ANCOD++ is an analytical code using the voxel-scan technique as an active method for irradiating the patients.

The iterative algorithm used in ANCOD, allows to determine the best fluences of the individual beams to carry out the optimal dose distribution, delivering a maximum of dose on the target volume and a minimum of dose all around.

As input, the code use experimental data of energy-loss of a set of initial kinetic energies, and as a clinical data a complete set of CT images with contours of different volumes of interest. Inverse planning techniques are implemented in order to obtain the initial energies needed for each beam to have a uniform target dose distribution. The package can determine the fluences and energies of several thousand of pencil beams in few minutes. The performances of the program are tested with a full simulation.

I. Optimization and treatment planning

The management of the big flux of information acquired during the entire treatment steps is a big challenge. All information, from the hardware parameters of the beam to the patient positioning, must be studied and treated in such a way we can profit the maximum possible of all variable parameters (see figure 1). For this purpose many treatment planning packages were implemented and also commercialized specially for photon beams.

The last generation of these packages is adopting the newest numerical methods in the field of optimization with the objective of an optimal treatment setting. The best examples are software dedicated or adjusted to the Intensity Modulated Radiation Therapy (IMRT).
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Figure 1  Different stage of an optimized treatment planning.
The improvement offered by the most recent treatment planning computational tools arises from the use of fully three dimensional data to define anatomy, to design beams and finally to calculate doses and evaluate plans. These tools are becoming available as computational hardware becomes fast enough and as three-dimensional medical images becoming easier.

As illustrated before (figure 1), the planning in general could be done through six ordered steps. Starting with collecting information on patients using different medical imaging techniques (CT, MRI…). Then different anatomical volumes have to be well defined. Doctors have at this level and following the protocols prescribing the convenient dose and the fractions needed to deliver this dose.

The calculation part follows starting with a reading of data information of beams characteristics. According to the model adopted, forward planning, simulation or inverse planning the necessary parameters for the final treatment are calculated. The display part is necessary to have an overview on the quality of the treatment.

When it is intended to use a small number of rectangular fields with or without any accessory (wedges, blocking…), the treatment technique has to try a number of different beam weightings, compute the dose distribution, evaluate the plan and then repeat the task until the plan meets the prescribed requirements. This is known as forward treatment planning. What we can call a ‘subjective’ optimization and it is the traditional optimizing method, still of a widespread use.

In the conventional treatment planning process, beam parameters like gantry angles, beam weights, wedges…are adjusted manually to achieve the nearest dose distribution to our requirements. As the free parameters become numerous, the possibility to plan the wrong treatment becomes bigger and bigger, due to the fact that we do not try enough to find the best plausible beams set. For that purpose, it was necessary to think of a more objective method, starting with describing all the requirements, respecting the constraints, and looking for a ‘compromise’ for all the free parameters we have. This is what is called an inverse planning, which begins with a prescribed dose distribution and has the objective to derive a set of optimum beams intensities.
The inverse treatment planning can be classified in two studies. In the first one we look for improving our knowledge on the biological effects of radiation by incorporating various physical, biological and other factors into the objective function. The second category treats the different mathematical methods, and algorithms, to minimize or maximize this objective function, respecting our hardware constraints (computation time, memory management...).

Our software package is completely dedicated to hadrontherapy. It has been developed for proton, carbon ions and also other possible efficient hadron radiation therapies characterized by the Bragg peak dose deposition as a function of depth.

The present algorithms are implemented for an active scanning technique. This technique allows the individual irradiation of a large number of elementary volumes with a mono-energetic pencil beam.

A few mathematical tools have been tried and the final implemented solution gives the best parameterization set in the limit of the time constraint. Indeed, for avoiding undertaking the long way of Monte Carlo simulation, which is very time consuming, we used an analytical method, inverse planning based. This method is as well efficient as the Monte Carlo simulation since the results of the two methods are in good agreement but the analytical method is at least

II. Physical and biological properties of hadrontherapy.

Even if conventional radiation therapy with X-rays and electrons has undergone a great development in the last years with the advanced techniques of conformational and intensity modulation radiation therapy (IMRT), it has still unsatisfying results in case of deep-seated tumours and complex anatomical structures. In fact, for this kind of tumours, to spare some sensitive organs, which are sometimes vital, it is pointless insisting on the use of conventional radiation. More efficient radiation therapies with particles allowing better selectivity and high accuracy have been introduced. Therapeutic ion beams with their unique physical and radiobiological properties offer several advantages over photon radiation (see figure 2).

Protons and heavy ions permit a truly conformal radiotherapy of the target volume with millimetric precision.
 Principally, the radiobiological as well as physical factors determine local tumour control in radiation oncology. Both factors enter into the differential between tumour and normal tissue responses. While radiobiological factors generally aim for relatively greater damage in tumours with equal radiation dose, physical factors make it possible to give higher doses to the tumour than to the surrounding healthy tissues (high precision radiotherapy with superior dose distribution and good selectivity). Heavy ions making much more damages in the DNA structure decrease the probability of cell survival (see figure 3).

Figure 2 comparison of the relative dose distribution of the conventional radiations and hadrons (protons and carbon ions).
Figure 3  *Illustration of tracks of sparsely and densely ionizing radiations.*

Heavy ions are high LET radiations and they are more suited to treat radiosensitive tumours, which present 10% of all tumours.

**III. Description of the analytical code for hadrons ANCOD++.**

The code called ANCOD (ANalytical CODE) is based on two assumptions:
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- The dose delivery is done in elementary steps. At each step one voxel of the target is irradiated. It is, as described above, the active method of dose delivering called spot scanning technique.
- 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.

Two right-handed reference systems have been 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 z-axis along the beam direction and the y-axis pointing upwards.

The C++ language defines a class as the set of operations and function related to a separate task or a separate idea. The whole program can then be constituted of different classes, each of them making a part of the total job. The task of finding the optimal plan is shared between one base class and main six classes. There is one more class, \textit{Dose}, which is used to output the results.

The two first classes, \textit{CT} and \textit{Target}, depend on the patient data and make the necessary steps to provide all necessary information about.

The class \textit{Field} uses the CT scan information and according to the field direction, it computes the length water equivalent (lwe) of each beam in each voxel.

The class \textit{Energy} loads the energy loss tables for several energies, and computes the energies needed for the beams and the energies deposited by each beam in each voxel.

The following class \textit{Optimize} is based on an iterative algorithm to optimize an objective function to find the best fluences for each of the beams. This allows building the optimal plan, sparing as possible the organs at risk and delivering uniform and high dose as possible to the PTV. It is structured in such a way that makes possible any other future optimizations. Particularly, it will be necessary to add the biological effects to the optimization. Furthermore, 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.
This work discusses only the optimization of the physical dose (physical optimization), and the biological optimization is let to a later development. We remark that in the case of proton therapy the physical optimization is sufficiently accurate because the role that plays the biological effect of protons was considered till now, less important. Another class is the one called *Accelerator*: it presents all the constraints and limitations of the hardware, like the allowed energies and spot scanning positions. Obviously, the constraints of the accelerator system have to be considered during the optimization process.

The input data are the CT data files where Hounsfield numbers are stored and later are converted to electronic densities for each voxel in the *CT* class. The CT files contain also the information on the global volume treated, its dimensions and the voxel dimensions. Since the outputs of different CT machines have different formats, we need also to translate the actual output to the program input format.

The input file defining all the volumes of interest specifies only the contours of those sub-volumes and therefore needs some preliminary operation to establish the volumes delimited by those contours which each achieved by the *Target* class.

The prescribed doses in each voxel and in each of the defined volumes of interest are an important input, and it affects directly the accuracy of the optimization. In fact, it is necessary to start the optimization with the right energy loss data input.

Another set of input data is constituted by the parameters necessary to reconstruct the beam energy loss as a function of the depth in matter. Our choice for carbon ion beams is based on tables containing the loss values as a function of energy and depth. In a file are stored a list of 46 energies ranged between 50 Mev/u and 500 Mev/u corresponding to a range in tissue between 7.4mm and 392.6mm respectively. The corresponding energy losses have been estimated in steps of 0.2mm for each specific energy. For several energies the used input data have been checked to be compatible with the experimental data [1].
The use of other kinds of heavy ions or proton requires changing the input data file. The algorithm I will describe in the following paragraphs is available for planning the treatment with carbon ion beams as well planning any other therapeutic beams characterized by the Bragg peak energy deposition.

The optimization part is the most important in the whole code. In fact, once we have all the values of the linear energies deposited by each beam in each voxel, and according to the physician’s prescription and requirements, we define a linear system (see eq. (1)), where the unknowns are the fluence values.

Our goal is summarized in two main points:

a. Maximal and uniform dose on the target.

b. Minimal dose all around.

Explicitly the above conditions are expressed by a linear system, which is defined as follows:

\[ D_{\text{required}}(i) = \sum_{\text{beam}}^{\text{max spots}} w(j)E_d(j,i) \quad (1) \]

where \( D_{\text{required}}(i) \) is the required dose in the i-th voxel, \( E_d(j,i) \) is the deposited energy in the i-th voxel by the j-th beam, and finally \( w(j) \) is the unknown weight (fluence) of the j-th beam.

We notice that \( D_{\text{required}}(i) \) is the sum of the doses released by all the beams, though for a large number of the beams the contribution is negligible, being the beam width typically quite narrow. Thus, only for the beams crossing the i-th voxel \( E_d(j,i) \) is different from zero. The number of equations is equal to the number of voxels, max spots, inside the target to be treated, and symmetrically the number of beams equals the number of voxels. As already stated this condition is not strictly necessary. Almost certainly it will have to be removed, due to the fact that the accelerator system can hardly follow such a treatment planning aiming to every single voxel. The solution depends somewhat on the accelerator performances and has to be implemented accordingly.
The optimization algorithm is based on a solution of the linear system by iteration. The dose required in a specific voxel is corrected after each iteration by a small amount with respect to the previous one. We start by computing the weight of the beam aiming to an arbitrary voxel (voxel = 1 in the following example). In other words, the calculation starts by considering only the beam giving the Bragg peak right in the center of the arbitrary voxel. The weight of the beam aiming to the next voxel (next is again chosen arbitrarily) is calculated taking into account the contribution of the previous beam. As one proceeds along the first step of the iteration, the weights are computed after the contributions due to the previous beams have been subtracted. The steps are explicitly reported:

\[
\begin{align*}
  w^0(1) &= \frac{D^0_{\text{required}}(1)}{E_d(1,1)} \\
  w^0(2) &= \frac{D^0_{\text{required}}(2) - w^0(1)E_d(1,2)}{E_d(2,2)} \\
  &\quad \vdots \\
  w^0(j) &= \frac{D^0_{\text{required}}(j) - \sum_{b \neq j} w^0(b)E_d(b, j)}{E_d(j, j)}
\end{align*}
\]

(2)

Once the first iteration has been completed with the calculation of a set of weights, \( w^0(j) \), the algorithm requires to use them to evaluate the next-iteration values, \( w^1(j) \). On the other hand, the weights \( w^0(j) \) inferred into the relations (IV-7) give a set of values for the dose, \( D^0(j) \), in each voxel. Analogously the set \( w^1(j) \) will give a new set of calculated doses \( D^1(j) \).
The \(i\)-th iteration can be explicitly written as:

\[
W^i(j) = \frac{\left[D_{\text{required}}^0(j) - \sum_{b \neq j} w^i(b) E_d(b,j)\right]}{E_d(j,j)}
\] (3)

Again, with these results a new set of doses, \(D^i(j)\), is computed.

One can compare the values \(D^i(j)\) given by the \(i\)-th iteration to the required ones, \(D_{\text{required}}^0(j)\), to verify the overall deviation.

The algorithm described above allows a fast convergence due to three particularities:
1. Setting to zero negative fluence values.
2. Defining an upper limit of the plausible fluence values.
3. The matrix \(\text{dep(beam, voxel)}\) has the maximal values on the diagonal and is dense around.

At each iteration, as stated above, we computed the dose released in the voxels within the target and the sum of the doses.

The algorithm has been coded in such a way that it is possible to fix the maximum number of iteration, otherwise the iteration is stopped once the objective function \(F(w)\), defined in the equation (4), reaches the minimum.

\[
F(w) = \sqrt{\sum_{i}^{\text{voxels}} \left[ D_i - \sum_{j}^{\text{beams}} w(j) E_d(i,j) \right]^2}
\] (4)

In our case, the evolution of the objective function \(F(w)\) take a particular gait (see figure 4) due to the three condition described above.
Figure 4  Example of the evolution of the objective function.

The output part is treated in one class called \textit{Dose}. This class makes the output of the optimization ready to be consulted. There, we reconstruct the 3D structure and calculate the final dose in each voxel considering the fluence values from the optimal plan. We extract then the DVHs, which can give an overview on the quality of the optimization: in general, this is more difficult to be evaluated with the explicit three dimensional dose distributions for each slice of the treated volume.
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**Figure 5** Isodoses in a central slice of a cranial CT scan, the red color is fitting with the target contour.

**Figure 6** Dose volume histogram evolution from the first iteration to the finale optimization. A clear difference due to the iterative method is seen for the curve associated to the target volume, but also such difference even not so important in the volume crossed by the beams around the target.
We can see in figures (5,6) an example of treatment plan for a tumour in the cranial part, optimized with ANCOD++ in few minutes. The corresponding DVHs allow to have an overview on dose distribution in the entire volume. We can see also how much can change the dose distribution in few iterations and in brief time to reach the optimal values.

IV. Verification of ANCOD results with a Monte Carlo simulation.

The verification of our results with a real treatment is not yet possible. Therefore, a full Monte Carlo simulation with the package GEANT3 was a good solution to test the code and to see how much accurate are the analytical calculations. The structure of GEANT is extremely flexible to describe volumes of different characteristics and to follow the electromagnetic and hadronic interactions of the particles, parents and daughters, along the track path.

ANCOD calculation and GEANT simulation results are in agreement for what concerns the target volume while the lower dose levels differ for the two cases. We ascribe this effect to the low statistics of the simulation and the pencil beam assumption.

It is noticeable the low dose along the field outside the target where the percentage level stays below 20\% of the maximum dose. In figure (7a,c) we plot the isodose for the central slice and a line of voxels at constant x. Explicitly, referring to figure (7a,b), we cut the bi-dimensional plot at x=53 to have the profile shown in the figures (7b,d). The spread of the dose on the target is ±3\%. 
Figure 7 Comparison of isodoses resulting from ANCOD calculation and those resulting from a MC simulation with GEANT for an irradiation with four orthogonal fields. Profiles of dose distribution in a central slice respectively calculated with ANCOD++ and verified with the simulation GEANT3.
V. Conclusion and perspectives.

As a treatment planning software package, ANCOD++ has the possibility to make a physical optimization in a short time and the comparison with the Monte Carlo simulation shows a good agreement. Though the results are satisfactory, it does not prevent a future possibility of other optimizations.

In fact, the time constraint was limiting the possible attempts for improving the quality of the planning. Therefore, it was out of matter even thinking to introduce more parameters to be optimized.

One of the future steps in the development of ANCOD will be the optimization involving the biological properties characterizing the heavy ion therapy.

When the dose delivery is shared between two or more fields irradiating the same target, it is necessary to optimize the fields simultaneously. This will be a major step of ANCOD future development.

In the hadrontherapy case adopting the voxel scanning method the optimization of field orientation takes an aspect very different than and could be obtained with a larger number of possibilities. The criteria driving the optimization are different: the idea could be based on the target shape dependence and does not need the use of a configuration of a multi-field irradiation. One or two fields could be enough precise to have the required selectivity.

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