Basics for vector implantation schemes in HDR brachytherapy using a new linear programming model

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Abstract

High Dose Rate (HDR) brachytherapy is a treatment technique which consists in moving a single radioactive source step-by-step along vectors (catheters) in order to submit a curative radiation dose to a cancerous tumour. The source may be stopped at several locations (dwell positions) within each catheter during specified times called dwell times. We consider the problem of designing a previsional dosimetry system for HDR brachytherapy, employing specification rules of the well-established implant system for Low Dose Rate brachytherapy known as the Paris System, but taking into account the possibility of optimizing dwell times and spacing between catheters. In this paper we describe the treatment process and the two interdependant optimization problems : dwell times optimization and catheter positioning, then we present how these problems are dealt with in the literature. We propose a new linear programming model for optimizing the dose in HDR brachytherapy. We incorporated this model in a freely available software program, allowing to modelize an implantation of catheters on a phantom target volume and perform the optimization of the dwell times. The main functionalities of this software program are described and the effectiveness of our approach is demonstrated by comparing the dose distribution obtained using the Paris System implantation schemes and those obtained through optimization.

1 Introduction

Radiation therapy is a set of modern techniques, based on the use of ionizing radiations (beta, gamma, or X-rays), for treating cancerous tumours. Their goal is to apply a prescribed radiation dose to a Primary Target Volume (PTV), while trying to avoid irradiating Organs At Risk (OAR) as most as possible. Two major techniques of radiation therapy exist, differing in the way the radiation is applied to the tumour. External radiotherapy consists in applying ionizing rays from outside the patient's body whereas brachytherapy uses radioactive sources which are placed within the body.

Intensity-modulated Radiation Therapy (IMRT) is an advanced mode of external radiotherapy that utilizes computer-controlled X-ray accelerators to deliver precise radiation doses to a malignant tumor or specific areas within the tumor. The radiation dose is designed to conform to the three-dimensional (3-D) shape of the tumor by modulating or controlling the intensity of the radiation beam to focus a higher radiation dose to the tumor while minimizing radiation exposure to the surrounding normal tissue.

Low Dose Rate brachytherapy (LDR) is a technique which is widely used for treating prostate cancer. In that specific case, it is made use of several iodine 125 radioactive sources which are being inserted in a final way within the patient's body. The sources activities are initially low, and decrease fast. Thus, the complete treatment is done when the activity of the sources has decreased to zero, making the removal of the sources useless. An other LDR brachytherapy techniques make use of wire-shaped iridium 192 sources, like those used in the Paris System, which is described by Dutreix *et al.* (Dutreix, Marinello & Wambersie 1982). They are inserted within the tumour through catheters also called "vectors", then removed once the prescribed dose has totally been delivered to the tumour.

High Dose Rate brachytherapy (HDR) makes use of a device called remote afterloader which is able to direct a single punctual iridium 192 source into catheters/vectors. The source may be stopped at several regularly spaced locations (dwell positions) within a catheter during determined times called dwell times. The total dose distribution is determined by the dwell positions the source stops at and the amount of time it dwells at each different position.

This paper focuses on HDR brachytherapy. Current optimization tools for HDR brachytherapy are efficient for the determination of the values of the dwell times. Their input data are the 3D representation of the PTV and the already implanted catheters. However, the rules for the implantation of the catheters are not clearly defined. Generally, radiation oncologists place the catheters using empirical methods based on experience. Other methods are inspired from the rules defined in LDR implantation systems such as the Paris System.

These latter methods seem to offer more warranties concerning the quality of the resulting treatment, since they use strict rules providing satisfying dose distribution and target volume coverage.

The goal of this study is to establish the basics of a new methodology based on optimization, which provides implantation schemes adapted to the modern treatment technologies. This methodology must take into account the constraints which are included in the existing LDR implantation methods, in order to ensure the reliability of any treatment obtained from an implantation scheme.

We developed optimization and visualization software which displays the result of the dwell times optimization on an arbitrary specified volume, and in addition enables to test a specified implantation of the catheters in a very straightforward way. This software is released under an open-source license, which allows anybody to use it freely (Galea n.d.).

1.1 Dwell times optimization

In most of optimization models for brachytherapy HDR, decision variables are reduced to source dwell times. The dwell positions are supposed to be known (uniformly distributed every 2,5 or 5 mm steps along the catheter), they correspond to the possible stops of the source along the catheter. For the moment the catheters positioning is not automated in the commercialy treatment planning systems but follows some conventional rules inspired from classical dosimetry systems.

With modern imaging modalities and fast computers now available, optimization approaches for dwell times computation based on anatomy are more often used. In this case the anatomical structures (PTV and OARs) are supposed to be identified and the desired dose for each volume of interest is specified by clinical criteria. Studies in dwell time optimization for HDR brachytherapy mainly use one type of objective. It consists in minimizing penalties associated to dose values above or below some dose value limits for each volume of interest. This concept known as anatomy based inverse planning/optimization is similar to that of inverse planning of intensity-modulated radiotherapy.

In a first approach the problem is transformed into a single objective problem using arbitrary importance factors for each conflicting goals.

For instance, Lessard *et al.* (Lessard & Pouliot 2001) try to minimize a weighted sum of penalties, each penalty being associated to the respect of a dose interval for one clinical criterion. Their optimization algorithm based on simulated annealing called IPSA (Inverse Planning Simulated Annealing) tries to find a combination of dwell times with minimum penalty. They explain that this optimization technique allows to escape from local minimum and to obtain rapidly a treatment plans for clinical applications. As the dose variations are linearly penalized in their approach, a formulation as a linear programming model would be more appropriate. In fact, tools based on the simplex method for linear programming provide the optimal solution, whereas simulated annealing offers a good solution without optimality guarantee. Recent studies in external radiation therapy treatment show that linear programming is very efficient to model and solve large instances encountered in practice. Romeijn *et al.* (Romeijn, Ahuja, Dempsey & Kumar 2006) propose a new linear programming approach to design optimal treatment plan for IMRT. They report on results obtained with clinical cases involving up approximately 80000 decision variables and 50000 constraints. Optimal solutions are found in less than 2 minutes using CPLEX 8 on a 2.8 GHz Pentium 4 computer with 1GB of RAM.

Milickovic *et al.* (Milickovic, Lahanas, Pagagiannopoulou, Zamboglou & Baltas 2002) propose a quadratic model using as objectives the variance of the dose distribution on the PTV surface and within the PTV and in OARs. Their formulation ensures that excessively high dose values are more likely to be avoided, and it allows to obtain more uniformly distributed moderate dose values. If OARs can be ignored then the objective functions are convex and gradient-based deterministic algorithm are very efficient. But in the presence of OARs such algorithms are trapped in local minima.

The other approach is multicriteria optimization. Evolutionary algorithms, and in particular genetic algorithms are dedicated to multicriteria optimization in HDR brachytherapy. The algorithm developed by Lahanas *et al.* (Lahanas, Baltas & Zamboglou 2003) called NSASGA for Non-dominated Sorting Archived and Supported Genetic Algorithm allows to obtain representations of the trade-off surfaces with 1000-2000 solutions in 2-5 minutes using a 933 MHz Intel III for a prostate implant with 125 dwell positions. If the optimization time is relatively short compared to other techniques, the decision making process performed after optimization represents a crucial and complex part for the planner. In fact, the treatment planner could have difficulty to understand the different possibilities offered from the large number of solu-

tions when the number of objectives increases. Some additional tools are therefore necessary to facilitate the analysis of the set of potential solutions.

1.2 Catheters positioning

As HDR brachytherapy is a very recent technique, most of studies focusing on catheter positioning do not include optimization. In most cases, the catheters geometry is based on the rules of well-established implant systems developed for LDR brachytherapy such as the Manchester system, the Quimby system and the Paris System (Gerbaulet, Pötter, Mazeron, Meertens & Limbergen 2002). These systems give guidelines which describe how the radiation source should be distributed in the body according to target volume dimensions. They also define methods for prescribing the dose and for calculating the resulting dose.

The Paris system designed by Dutreix *et al.* (Dutreix et al. 1982) is widely used in LDR brachytherapy, it is based upon main rules, namely : the radioactive lines must be parallel and equidistant, and arranged so that their centres are placed in a same plane called the central plane, which is perpendicular to the direction of the linear sources. According to the thickness of the tumour, the radioactive lines are arranged over one plane or multiple planes. The activity must be uniform and identical along the lines. Given a shape, dimensions, and the prescribed dose, the system determines a way to implant the wires, including the number of radioactive wires, the number of planes, the spacing between the wires and the way they are organized. In a first step some rules (geometry implantation and spacings) of the Paris System have been transposed to the HDR case, simply assuming all dwell times along the catheters are equal to a constant, which reproduces the effect of linear sources. This way of proceeding ensures that the HDR treatment will not be less efficient than the standard LDR treatment. Hennequin *et al.* (Hennequin, Mazeron & Chotin 2001) review the main rules of the Paris System one by one and explain why they are not always valid in the context of stepping sources. If the current practices show that the use of parallel catheters is still the easiest way to realize the implantation, the rule concerning the linearity and the uniformity of the radioactivity is abandoned for HDR brachytherapy. To the best of our knowledge, to date, one optimization model for the catheters positioning in HDR brachytherapy has been developed by Baltas and Lahanas (Lahanas, Karouzakis, Giannouli, Mould & Baltas 2004). They include explicitly the number of catheters in the set of objectives. The optimization algorithm then tries to determine the minimal number of catheters and their optimal position, additional to dwell times of the selected catheters. These discrete models correspond to the case where catheters are parallel to each other and where possible locations are evenly spaced.

1.3 Treatment planning systems

A large variety of dose optimization methods for dwell times computation are now incorporated in commercial treatment planning systems. Treatment planning systems are software developed to assist clinicians. Based on 3D imaging they enable a clinician to visualize the PTV, the critical organs and the positioning of the catheters. The clinician can act manually on the various parameters like dwell times, number and positions of dose reference points (see section 3.1) or select an optimization tool which automatically generates dwell times according to the specified dose constraints. For example, multiobjective optimization algorithms from Lahanas *et al.* have been developed, implemented and tested in a Windows based program called WinOpt-HDR, whose demonstration version is available on the web (WinOpt-HDR n.d.). Their methods are now integrated into the treatment planning system $SWIFT^{TM}$ of Nucletron (Nucletron URL).

Treatment planning systems also provide a quantity of numerical and graphical information like COIN index, dose-volume histograms which allow to evaluate the quality of the ap-

plied dose. $Eclipse^{TM}$ software produced by Varian medical systems (USA) (Varian n.d.), $HDRplus^{TM}$ developed by sonoTECH Medical Electronics (Germany) (SonoTECH n.d.), and $PLATO^{TM}$ provided by Nucletron (Netherlands) are famous treatment planning systems for HDR brachytherapy. $SWIFT^{TM}$ (Nucletron) is dedicated for HDR prostate treatment.

Current treatment planning systems are very useful for physicians to achieve a treatment plan once the catheter have been implanted. In our study we seek to provide an automated tool placed upstream in the treatment process, corresponding of the step 2 of the process (see section 2), that means before the implant procedure, to replace current previsional dosimetry systems and to help in this manner physicians to find an adequate implantation scheme.

1.4 Contributions and organization

The Paris System has demonstrated its reliability in many clinical situations treated with LDR brachytherapy and is well accepted in the brachytherapist community. Our work is motivated by the need to develop a new system employing well accepted specification rules like the Paris System but taking into account the actual concepts of HDR brachytherapy. This study has been suggested by Gilbert Boisserie, from the physics unit of the radiotherapy service of Pitié-Salpétrière hospital in Paris. To this end we studied the possibility of having a 3D previsional dosimetry system, in HDR brachytherapy, for phantoms of regular implant as in the Paris system. These phantoms are simple geometrical volumes surrounding the lesion. Specifically our contributions are as follows.

- We proposed a linear programming model to find an optimal dwell times distribution for optimizing the dose distribution in HDR brachytherapy
- We developed a freely available software called "Isodose 3D" with a graphical user interface and an optimization module. This module allows to compare easily the dose distribution obtained with the Paris System and with our own optimization routines, and enables to test different values of catheter spacing.

This paper is organized as follows. In section 2, we describe the treatment process applied in this unit for interstitial therapy and we emphasize on two interdependent optimization problems: dose optimization and catheter positioning. These two problems involve the computation of the dose distribution which is presented in §3. In §4 we detail the framework of our study and present a linear programming model for optimizing dose in HDR brachytherapy. This model incorporates constraints on the diameter of the hyperdose sleeves as recommended in Paris System. Section 5 is dedicated to the description of the "Isodose 3D" software. In §6 we discuss the results of our approach on a set of five phantoms in terms of dose distribution and dose volume histograms. The paper concludes with §7 in which we outline avenue for future research.

2 Treatment process

HDR brachytherapy involves placing a single radioactive source within a tumour or cavity of the body. This source moves within a set of catheters, and may be stopped at various intervals. This allows the radiation oncologist to conform the radiation to the tumour, to regulate the amount being emitted at each point, and to diminish any exposure to healthy tissue. The typical procedure of HDR brachytherapy is presented step by step.

- Step 1. **Locate the primary target volume** The physician contours the tumor and all the surrounding critical organs, in this task he uses medical imaging (computed tomography scan, magnetic resonance imaging scan), and if necessary a physical examination is performed.

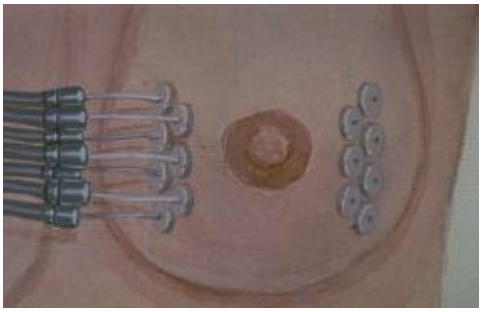


Figure 1: Breast cancer

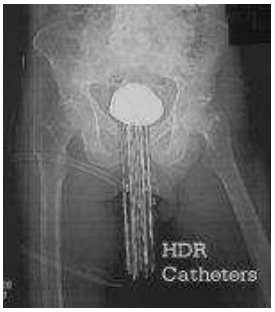


Figure 2: Prostate cancer

- Step 2. **Catheters placement** This step corresponds to the placement of the brachytherapy catheters within a body site. In the radiotherapy unit of Pitié-Salpétrière hospital in Paris, the physician follows the rules of a dosimetry system (Paris System) to arrange the catheters based on location, tumour extent and other factors. In current practice the catheters are inserted through a template or positioned by free-hand. The template is a kind of rectilinear grid with a regular distribution of holes. And each catheter is placed at a specific template hole. The rectilinear template based brachytherapy technique ensures parallel insertion of catheters.

- Step 3. **3D Imaging** After the implantation procedure, computed tomography and/or magnetic resonance imaging make it possible to radiation therapists to determine the exact location of the implant in the body and the relationship to adjacent organs. At this step, specific procedure using radiopaque markers, for instance, is used to detect the dwell position coordinates (Lachance, Beliveau-Nadeau, Lessard, Chretien, Hsu, Pouliot, Beaulieu & Vigneault 2002).

- Step 4. **Dosimetry** Once the patient anatomy and dwell positions are obtained, the dosimetrist then "fine tunes" the implant by increasing or decreasing the time the source spends in each dwell position to achieve the shape and doses that the physician wants to the tumour and the nearby structures. In general, this step is carried out automatically by HDR brachytherapy planning systems wich provide appropriate treament plans by optimizing the dwell time values. The average time determined by the treatment planning computer is merely a few minutes. Then, the planned radiation dose is delivered by remote afterloader HDR machine.

- Step 5. **Treatment** The patient is moved into the brachytherapy treatment room. The ends of the applicator or treatment catheters that protrude outside the body are connected to "transfer" tubes which are then connected to the afterloader (see figure 3). The programmed instructions tell the afterloader where to direct the source and how long the source will stay at each dwell position. The time the source spends in the implant is about 10 to 15 minutes. The entire treatment process takes about 30-60 minutes.

- Step 6. **Implant removal** After the treatment, all radiation sources are withdrawn into the remote afterloading HDR machine, the applicator is removed, and the patient is allowed to go home shortly thereafter.

Before the implantation of the catheters in step 2, the real shape of the tumour is not exactly known, and the physisican has to choose an implantation scheme according the general

Figure 3: Nucletron remote afterloader

measurements of the target volume. That is why the system we propose is based on the use of "phantoms" of regular shape to define vector implantation schemes, as with the Paris System.

3 Dose calculation

The calculation of the dose distribution is essential either for dwell times optimization or, after optimization, to produce statistical parameters.

3.1 Dose reference points

As it is impossible to calculate the dose in every point of the space, the dose calculation is carried out by selecting a set of reference points. These points are chosen by different ways. Every case study in brachytherapy insists on the fact that the quality of the resulting dose distribution depends on the way these points have been chosen, and on their number. The choices that are made for finding "representative" points differ from one study to another. They can be chosen on a grid of regular spaced points, randomly chosen on the plane (uniform distribution), or selected to fit certain distribution rules.
For instance, Lessard *et al.* (Lessard & Pouliot 2001) uniformly select their dose calculation points on the contours, extremities, and inside the target volume and organs at risk. They also generate uniformly dose reference points outside the PTV to impose a limited dose to the normal tissue.
Lahanas *et al.* (Lahanas et al. 2003) generate randomly-distributed points inside the PTV, OARs, and the surrounding normal tissue. They also generate points uniformly distributed on the triangulated PTV surface.
The accurate determination of statistical parameters which allow to evaluate the dose distribution, and which consequently are incorporated into dose optimization models, requires a very high density of dose reference points (up to 10^6 uniform distributed dose reference points for large implants). The optimization time and the solution quality is therefore very linked to the choice and the number of dose reference points (Lahanas, Baltas, Giannouli, Milickovic & Zamboglou 2000). When statistical parameters are only used to compare the quality of different treatment plans, it is possible to use a greater number of dose reference points than during the

optimization process.

3.2 Dose contribution function

The total dose received by a dose reference point i from a punctual unitary source which stops at many dwell position j (J is the set of possible dwell positions) is determined by the following conventional formula (see chapter Radiophysics of (Gerbaulet et al. 2002)) :

$$d_i = \sum_{j \in J} \dot{K}_R D(dist(i,j)) t_j. \tag{1}$$

The expression "$dist(i,j)$" is the distance between the dwell position j and the point i, $\dot{K}_R$ is the air kerma strength of the source and t_j the dwell time of the source at position j.
$D(.)$ is the dosimetric kernel describing the dose rate per unit source strength at point i from a source at dwell position j so that

$$D(dist(i,j)) = \frac{1}{dist(i,j)^2}.\phi(dist(i,j)).(\mu_{en}/\rho)^{\text{tissue}}_{\text{air}}, \tag{2}$$

where :

- $\frac{1}{dist(i,j)^2}$ is the geometrical factor (m^{-2}) taking into account the dispersion of the photons in the body from the punctual source,
- $(\mu_{en}/\rho)^{\text{tissue}}_{\text{air}}$ is the ratio of the mean mass energy transfer coefficents in tissue and in air,
- $\phi(dist)$ is the effective transmission function through tissue at distance $dist$; this function can be approximated by a degree 3 polynom for a distance that is lower than 10 centimeters. In (Chotin 2000) a generic approximation formula of the the function $\phi(dist)$is given:

  $$\phi(dist) = \gamma \frac{1 + \gamma_1 dist^2}{1 + \gamma_2 dist^2}, \tag{3}$$

  where γ, γ_1 and γ_2 are provided according to the source used.

This function decreases similarly to $\frac{1}{dist^2}$. One can observe that the dose received by a point which is very close to the source is very high, whereas beyond a certain distance the value of $D(dist)$ is close to zero.

In the following parts, we simplify the notations by considering that the dose d_i in reference point i is given by :

$$d_i = \sum_J m_{ij} t_j, \tag{4}$$

where m_{ij} is a constant value which denotes the dose rate contribution of dwell source j at point i, ($m_{ij} = \dot{K}_R D(dist(i,j))$).

3.3 Evaluation of dose distribution

In our model, we assume that the PTV is specified and the dwell source positions are known. We also assume that the dose reference points have been defined geometrically and they are supposed to represent some anatomical structures like PTV and critical structures. Then, the problem is to quantify the quality of a dose distribution. A good implant could be judged following:

- the coverage of the PTV,
- a high dose uniformity inside the target volume,
- a dose fall-off outside the target volume.

There are no commonly accepted criteria for the evaluation of dose distributions. Several dosimetric parameters have been proposed to numerically quantify the quality of a dose distribution for each implant. In our study dose-volume histograms DVHs and the conformal index $COIN$ are used for quantitative evaluation of dose plans. The dose-volume histogram DVH plots the exact radiation dose level received by the target volume and adjacent tissue in graphic form, and is the major quantitative method used to assess the implant adequacy. The conformal index ($COIN$) takes into account both the coverage of the target and the unwanted irradiation outside the target (Baltas, Kolotas, Geramani, Mould, Ioannidis, Kekchidi & Zamboglou 1998). $COIN$ is defined as $c_1.c_2$, where $c_1 = PTV_{ref}/PTV$ and $c_2 = PTV_{ref}/V_{ref}$. PTV is the volume of the target, PTV_{ref} is the part of the target volume covered by prescribed dose, and V_{ref} is the total volume covered by prescribed dose. This index is evaluated to describe the conformality of the dose distribution. As the two coefficents c_1 and c_2 have two different meanings, it may also be possible to use them separately.

4 Model formulation

4.1 Framework

Here we are interested in phantoms of regular implant as in the Paris system. These phantoms are simple geometrical volumes as small as possible including the tumor. The use of phantoms is especially useful for simple dosimetric studies, such as comparisons between the dose distribution obtained with the Paris System and the dose distribution obtained by optimization. The phantom is defined as a simple volume in an oriented three-dimensional Euclidean Space $(0, x, y, z)$. Catheters are parallel to the axis (O, y) and are arranged in squares or in triangles according to the volume considered. Because of symmetries, it is enough to calculate the dwell times on only one part of space (see figures 5(a), 5(b), 5(c)). Catheters are evenly spaced and the spacing between catheters is either fixed according to the Paris System rules, or a variable parameter δ to optimize.

The choice of the number of dose reference points can differ depending on the operation which we intend to perform.

For the resolution of the dwell times problem, each dose reference point corresponds to a constraint in the linear programming model. Hence, the points must be numerous enough to provide a suitable accuracy of the resolution, while allowing acceptable calculation times for a real-life treatment process. A smart way for the choice of these points is to privilege the accuracy of the coverage of the PTV surface: if the PTV surface is suitably covered, the dose inside the PTV will inevitably be higher. We still have a strong warranty for the uniformity of the dose distribution inside the PTV, thanks to the hyperdose constraints that we describe in paragraph 4.3.

When computing the dose distribution indices after the optimization, the number of dose reference points can be higher. Indeed, the dose is only calculated once for each point, unlike in an optimization process, where the dose gets calculated a high number of times for each point. In that case, the points must be uniformly distributed in the optimization space, which allows to consider that volume ratios like PTV_{ref}/PTV and those necessary for DVH calculation (see paragraph 3.3) correspond the ratios of the corresponding number of points inside the different volumes.

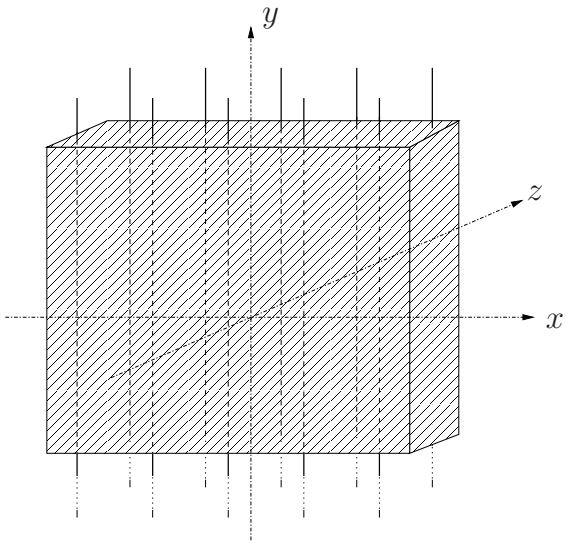
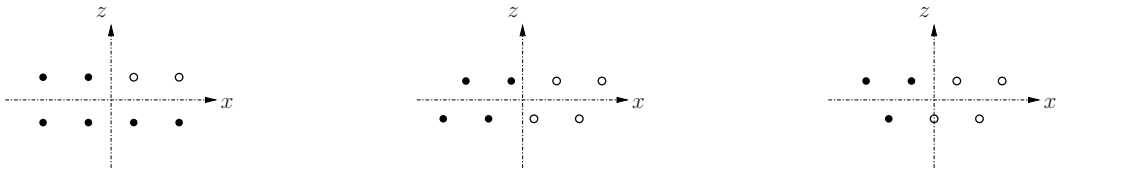


Figure 4: Phantom with a square organization of catheters



(a) Squares organization

(b) Triangles organization with an even number of catheters

(c) Triangles organization with an odd number of catheters

Figure 5: Different catheters organizations. Dwell times on white catheters are optimized and values are obtained by symmetries on black catheters

4.2 A linear programming formulation

The optimization problem is to compute dwell times over all dwell positions in the implant to deliver a dose distribution that conforms a high dose radiation to a defined target, while restricting dose to the surrounding sensitive structures. For this task, after contouring volumes of interest, the physician must define specific dose volume constraints for the target as well as for OARs and normal tissue. Inverse planning consists in minimizing a weighted sum of the differences between prescribed doses and obtained doses in all reference points. This problem can be formulated as a linear program. We let E denote the set of dose reference points and N_S the total number of reference points in volume S. We will denote the decision variable t_j representing the dwell time of the source at position j and j belongs to the set J of possible dwell positions. For each volume of interest $S \in$ VOI, $\underline{D_S}$ and $\overline{D_S}$ represent the lower and the upper range of acceptable doses. If the dose at a reference point i of this volume S goes below or above this range, the variable u_i^S, respectively v_i^S measures the variation. The objective function is then a weighted sum of the variations, where α_S and β_S denote the penalty weight

associated to each violation of the dose interval. The resulting linear program follows :

$$\min_{\mathbf{t},\mathbf{u},\mathbf{v}} \quad \sum_{S\in \mathrm{VOI}} \frac{\alpha_S}{N_S}\sum_{i\in S} u_i^S + \frac{\beta_S}{N_S}\sum_{i\in S} v_i^S, \tag{5}$$

subject to

$$\sum_J m_{ij}t_j + u_i^S \geq \underline{D_S} \qquad \forall i \in S, \forall S \in \mathrm{VOI}, \tag{6}$$

$$\sum_J m_{ij}t_j - v_i^S \leq \overline{D_S} \qquad \forall i \in S, \forall S \in \mathrm{VOI}, \tag{7}$$

$$u_i \geq 0, v_i \geq 0 \qquad \forall i \in E, \tag{8}$$

$$t_j \geq 0 \qquad \forall j \in J. \tag{9}$$

Note that in practice $\underline{D_S}$ and $\overline{D_S}$ are often expressed as a percentage of the prescribed dose, which does not enter explicitly in the formulation. In fact, calculations are performed with a fictitious dose equal to 1, and at the end, dwell times are mutliplied by a constant to reach the prescribed dose. For instance, $\underline{D_{\mathrm{target}}} = 1$ and $\overline{D_{\mathrm{target}}} = +\infty$ mean that all reference points within the target volume should receive at least 100% of the prescribed dose. On the other hand, if the reference point belongs to an OAR, the value $\underline{D_{\mathrm{OAR}}}$ is equal to 0, and $\overline{D_{\mathrm{OAR}}}$ is set according clinical criteria. $\overline{D_{\mathrm{OAR}}} = 1/2$ means that all reference points within the OAR volume should receive less than 50% of the prescribed dose. For normal tissue there are no explicitly dose limits, $\underline{D_{\mathrm{NT}}}$ and $\overline{D_{\mathrm{NT}}}$ could be set respectivly at 0 and $+\infty$. It is also possible to set the upper dose limit at a relatively small percentage and to associate a very weak weight β_{NT}. The α_S and β_S parameters are used for weighting the importance for dose interval violation in the volume of interest S. Basically, α_S and β_S will depend on the kind of volume of interest S, and will be set such that they best fit the clinical needs. In some cases, it will never be possible to cover the PTV with the total prescription dose, while avoiding to irradiate some OARs. The α_S and β_S points are a way to choose which clinical criterion to privilege against another.

4.3 Hyperdose constraints

As our study investigates the impact of dwell times optimization on the treatment planning compared to the use of classical dosimetry Paris System, we have to incorporate specific constraints related to Paris System in our general model.

The Paris System defines the volumes called *hyperdose sleeves*. These volumes can be considered as the set of points in the calculation space for which the received dose is at least 200% of the prescribed dose. In an application consisting of wire-shaped radioactive lines, they are cigar-shaped volumes surrounding the wires.

One rule of the Paris System indicates that the diameter of the hyperdose sleeves should not exceed one centimeter. This is a warranty for dose uniformity inside the volume of the PTV, which also eliminates some of the risks of medical complications linked to high doses inside the PTV.

To model this kind of constraints we consider a set H of specific points. These points are selected so that an overdose on one of these points automatically implies the detection of a diameter of sleeve higher than one centimeter.

Figures 6 and 7 show how these points are chosen according to the arrangement of catheters. For all cases, the points are located on the intersection between each plane of dwell positions

and the plane of catheters. On each plane of dwell positions, for a given vector spacing δ, two cases may occur. If δ is lower or equal than one centimeter, one point is disposed on the middle of the segments connecting each pair of neighbour dwell positions. Otherwise, two points are placed between each pair of vectors, at distances of 0.5 cm of the vectors.

The hyperdose constraint is written as follows and may be added to the previous linear program:

$$\sum_J m_{ij} t_j \leq 2 \quad \forall i \in H. \tag{10}$$

(a) $\delta \geq 1$ cm (b) $\delta \leq 1$ cm

Figure 6: Hyperdose points with a square organization (hyperdose points are represented by a cross, and catheters by a dot)

(a) $\delta \geq 1$ cm (b) $\delta \leq 1$ cm

Figure 7: Hyperdose points with a triangle organization

5 An open source software program : "Isodose 3D"

Isodose 3D has been developed in order to obtain a visualization of the searched results. This provides the two following advantages: first, for an optimization researcher to get a comprehensive visualization of physical and physiological phenomena for which he doesn't master all the aspects; and second, to show in a straightforward way the obtained results to physicists and radiation oncologists.

Globally, the idea behind this software is to provide all the visual and computation tools, allowing to obtain isodose surfaces for implantations defined under the terms of the Paris System. The software optimizes, for a standard ^{192}Ir source type, the dwell times in such a way that the prescribed dose on the target volume equals to 1 Gy. As explained in paragraph 4.2, isodoses are the same whatever the prescribed dose, because the dose calculation function is linear.

The application is constituted by a graphical interface for the input of the parameters of the implantation problem, associated to a 3D visualization module. It has been developed in C language on a GNU/Linux PC. The graphical interface API is GTK+, and the 3D rendering is being done through the use of OpenGL.

5.1 Functionalities

Isodose 3D allows the definition of a phantom (named target volume in the software) of the kind of those defined in the Paris System: right-angled parallelepiped or prism with isosceles

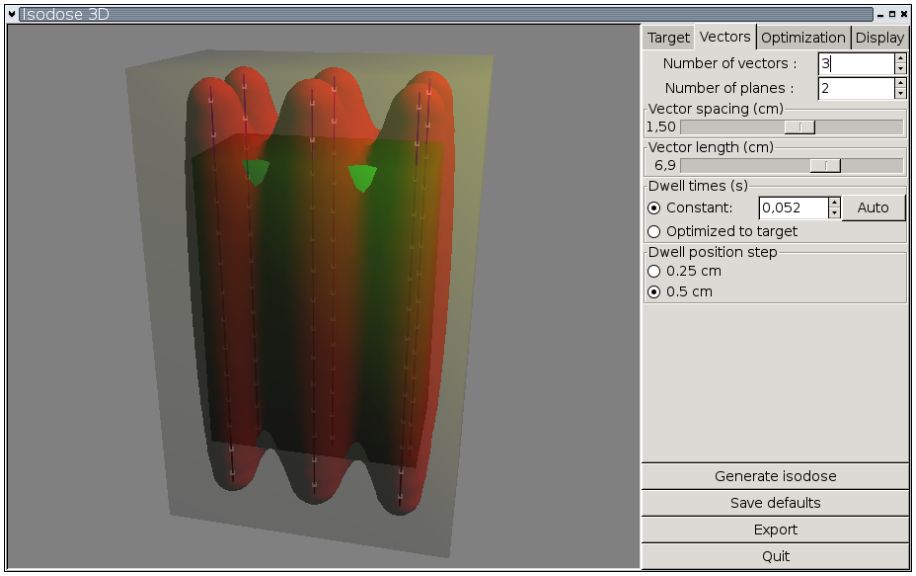


Figure 8: General view of the *Isodose 3D* interface

trapezoidal base. The user freely chooses the dimensions of target volume, in the three space directions. The target volume is directly visible on the screen.

The user chooses a positioning for the vectors (squares or triangles organization, a number of planes, vectors per plane, length and spacing of the vectors), and can directly observe their placement in superposition with the target volume. From this positioning, it is possible to generate the reference isodose surface (surface of points receiving a dose equal to the prescribed dose), according to various possibilities:

- by manually specifying a constant dwell time value;
- by calculating the basic dose rate as defined by the Paris System (Dutreix et al. 1982), and by deducing a constant dwell time value allowing to obtain a reference dose of 1 Gy on the isodose of 85 % of the basic dose rate;
- by optimizing the dwell times with the linear programming formulation defined in paragraph 4.2.

With each isodose generation a DVH is generated, and the values of c_1, c_2, and the $COIN$ are calculated (see section 3.3). This provides, in addition to the visual appreciation of reference isodose obtained, analysis tools the radiation oncologists are accustomed to handling.

Figure 8 presents a general view of the application interface. The left part of the screen displays a 3D representation of the problem. We can simultaneously see the target volume, the generated reference isodose (3D surface), and the vectors of the application, represented by the black segments. The white points distributed on the vectors are the possible dwell positions of the source. All these objects are visible simultaneously on the 3D representation, thanks to the use of object transparency. That makes possible to easily observe and appreciate the covering of the target volume by the reference isodose.

The generated isodose surface is an approximation made of small triangles. The approximation method is a well-known technique in 3D modeling, called the *Marching Cubes* algorithm (Lorensen & Cline 1987). The smooth shading lighting technique is a visual effect to give the user the impression the surface is actually smooth.

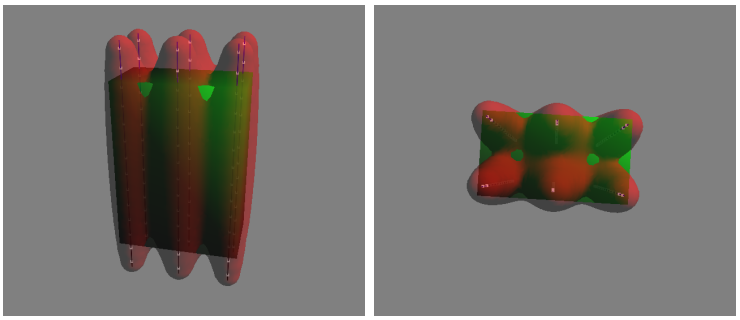
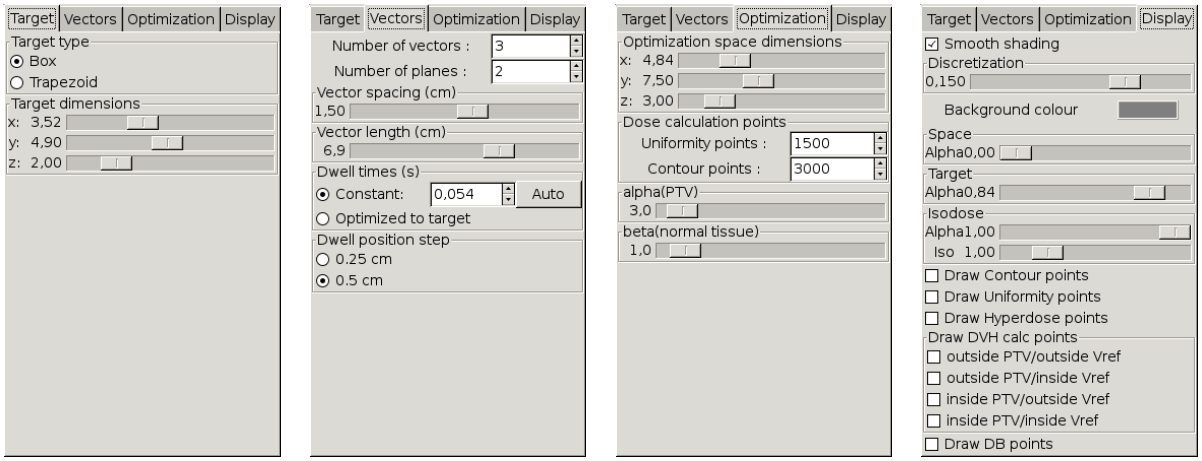


Figure 9: The same 3D scene, viewed under two different angles



(a) Target volume (b) Vectors (c) Optimization parameters (d) Display

Figure 10: *Isodose 3D*'s different control tabs

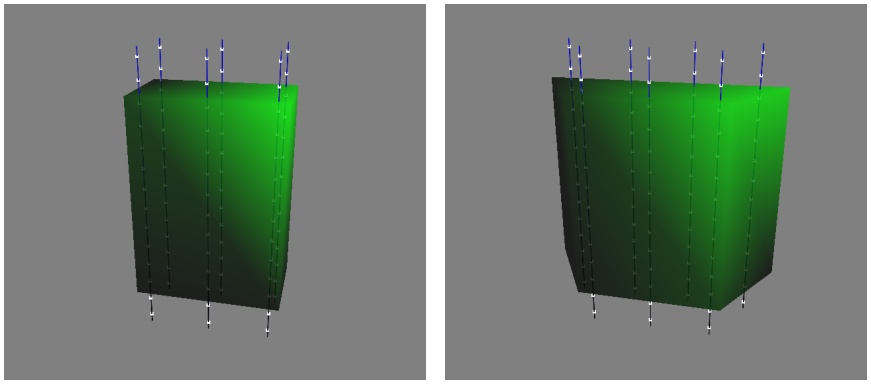
It is possible to observe the problem from various angles, which has the advantage of potentially not missing any aspect of the problem. Moreover, certain view angles make it possible to better illustrate one aspect of the problem or another. For example, figure 9 shows the same 3D scene under two different angles. That makes visible various parts of the target volume not covered by the reference isodose, according to the selected angle.

The right-hand side of the screen features a set of controls split inside a tabbed notebook (Figure 10). Each tab groups the following functionalities:

- target specification
- vector positioning specification
- optimization parameters settings
- display settings

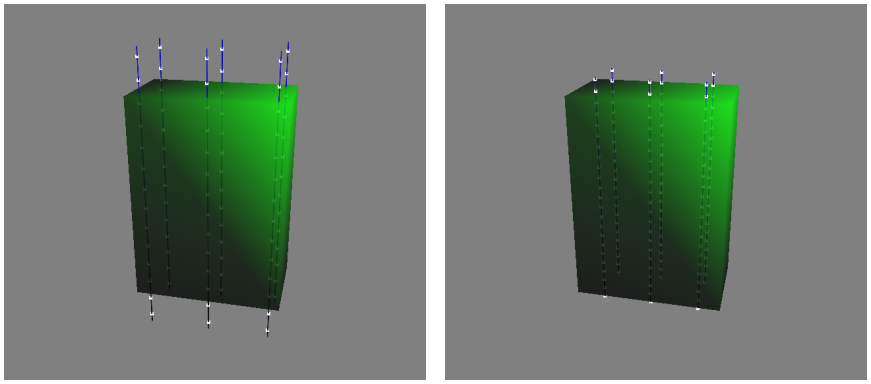
5.2 Target Volume specification

In this tab (Figure 10(a)), the user chooses the type of target volume. The two possible volume types are right-angled parallelepiped or prism with isosceles trapezoidal base. The dimensions of the target volume can be freely chosen, and any modification is directly visible on the 3D



(a) Square disposition (b) Triangle disposition

Figure 11: The possible volume types, and the corresponding vector dispositions



(a) Spacing = 1.50 cm, length= 6.9 cm, dwell position spacing = 0.5 cm (b) Spacing = 1.20 cm, length= 5.6 cm, dwell position spacing = 0.25 cm

Figure 12: Two different vector dispositions for a parallelepipedic target volume, of width: 3.52 cm, height: 4.90 cm, and depth: 2 cm.

representation. Figure 11 illustrates the available target volume types.

5.3 Definition of the Vectors

In this tab (Figure 10(b)), it is possible to specify the positioning of the vectors. The possible settings are the number of planes, the number of vectors per plane, the constant spacing between vectors, and the length of the vectors.

The type of vector disposition (square or triangle) depends on the specified target volume type. Concerning the number of vectors per plane in the case of a vector triangle disposition, the "number of vectors per plane" parameter concerns the first plane of the application. Whenever a second plane is added, it will feature one more vector, and so on for every additional plane.

The user can also choose the spacing of dwell positions inside the vectors. The two possible choices (0.5 cm and 0.25 cm) correspond to the most common real-case values, depending on the afterloader in use.

As well as in the first tab, any modification is directly visible on the 3D display. Figure 12 shows two different vector dispositions for the same target volume.

5.4 Optimization Settings

In this tab (Figure 10(c)), the user can first specify the optimization space dimensions, the number of *uniformity* and *contour points*.

For the studied cases (see section 6), the expression of dose constraints in the linear program is limited to a lower dose bound for points inside the PTV, and an upper dose bound for points inside the surrounding space. Thus there are only two weighting coefficients of the objective function, one applied to the lower dose bound variations in the PTV (noted α_{PTV}), and the other to the upper dose bound variations, noted β_{NT}. The values for these parameters can also be input from this settings tab.

The optimization space is represented by an imaginary box created around the target volume and the normal tissue (see figure 8). The *uniformity points* are dose reference points generated uniformly in the calculation box. The *contour points* are generated at the surface of the target volume. The volume of this box, defined by the user, must be large enough to represent a significant amount of normal tissue around the target volume. The volume should as well be small enough, in order to allow a maximal density of dose reference points, while limiting their number. In general, once this volume has been specified, the user chooses to hide it, in order not to overload the display.

5.5 Display settings

The available controls in this tab (Figure 10(d)) enable to setup the display.

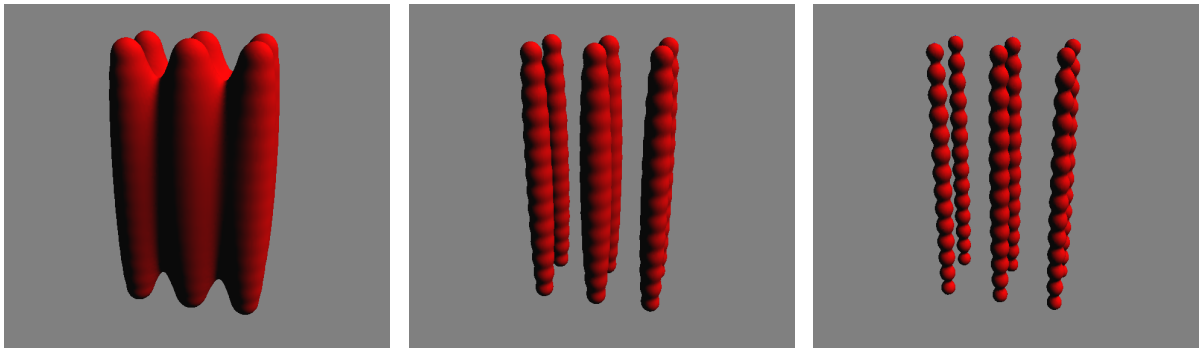
Two different 3D object lighting methods are proposed: smooth shading and flat shading. Object lighting is used to emphasize the 3D volume shape, which gives the user good visual information about the volume shape. If no lighting is used, only the contour of single-color shapes would be visible. Smooth shading simulates natural reflection of a light source on a smooth object, even though the represented object is made of polygons. In the opposite, flat shading emphasizes the polygons by setting a single color to each polygon, depending on its orientation relatively to the light source and the point of view.

The space discretization which is used by the *Marching Cubes* algorithm for the generation of the isodose surface can be modified by the user. A smaller discretization provides a more accurate representation of the surface, because the approximation is done with smaller triangles. Though, as the number of triangles increases quickly when the discretization is reduced, the amount of necessary memory and computation power increases in the same way.

For the different generated 3D objects, it is possible to set an opacity parameter. The opacity determines the transparency of objects, and setting different opacity values for the different objects allows to view different objects at the same time, even when some are partially or totally covering others. The opacity value for an object varies from zero, where the object is invisible, to one, where the object is fully opaque and no other object can be seen through it.

Another display setting is the isodose level. For example, choosing an isodose level of 2 will diplay the isodose volume which contains 200% of the prescribed dose, which corresponds to the hyperdose sleeves defined in the Paris System. Figure 13 shows generated 100%, 150% and 200% isodoses for the same application.

Various points of interest can also be displayed: the dose reference points used in the optimization (*uniformity* and *contour points*), the hyperdose points, and the calculation points used for the DVH generation. Each sort of points is displayed in different colors, which can for example provide good visual information complementarily to the calculated dose conformality indices.



(a) Isodose 100 % (b) Isodose 150 % (c) Isodose 200 %

Figure 13: Isodose 100 %, 150 % and 200 % of the prescribed dose for the same application of the Paris System

6 Results

In this investigation we consider five phantoms of regular implant consisting of catheters arranged in squared and triangular pattern recommended by the Paris dosimetry system. All theses phantoms are described in figure 14.

The first implant (phan1) corresponds to three catheters arranged in the same plane with a spacing of 18 mm. The second implant (phan2) is a double-plane implant were catheters are parallel and evenly spaced of 18 mm. The third implant (phan3) is based on six catheters arranged in a squared pattern and 15 mm spacing. The fourth (phan4) and the fifth implant (phan5) are double-plane implants consisting of catheters arranged in a triangular pattern with respectively 15 and 17 mm spacing. For each case, the spacing between the sources is fixed to 5 mm, as frequently used in practice. The active length and the treated length of the implants are measured as described in the Paris System and given for each implant. Inside the PTV (here the volume supposed to include the tumor) the dose has to be equal or greater than an arbitrary value of 1 Gy and a maximal dose of 0.5 Gy is fixed for the points of the surrounding normal tissue. For each case, we calculated the constant dwell time for the different positions of the source to mimick the effect of linear sources as defined in the Paris System. This makes comparisons possible between implantations with optimized dwell times and implantations obtained by using Paris System linear sources.

The software calculates the dose inside an imaginary box created around the phantom and the normal tissue. Analyses are done with dose reference points uniformly generated in this box, and with dose reference points uniformly distributed at the surface of the PTV. For each case, we use 1500 points (*uniformity points*) uniformly distributed in the calculation box, that means inside and outside the PTV and 3000 points (*contour points*) at the surface of the PTV. This number may be sufficient for the optimization process but is increased to 50 000 points for determining statistical parameters to improve the accuracy of the results.

The results were obtained on a 1,5 GHz PC with a Celeron M 370 processor and 512 GB of RAM, using the different linear programming solvers: GLPK 4.10, LP_solve 5.5.0.6, CLP 1.03.01 and CPLEX 9.1.0. The first three are free and open source software, which allows whoever to freely use them and to modify them if needed, thanks to the availability of the source code, whereas CPLEX is commercial software.

Table 1 shows the dimensions and the times of the optimization process obtained with LP_solve 5.5.0.6 for the 5 cases. It highlights that taking the symmetries into account clearly

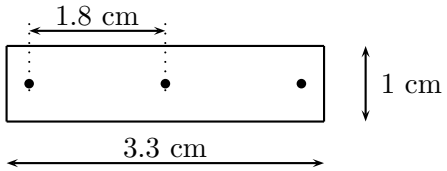
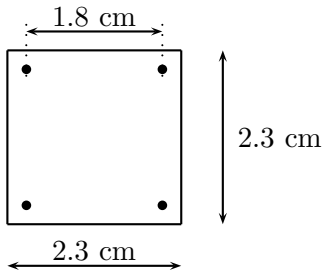
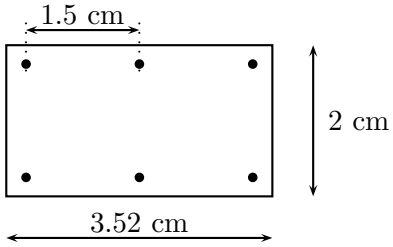
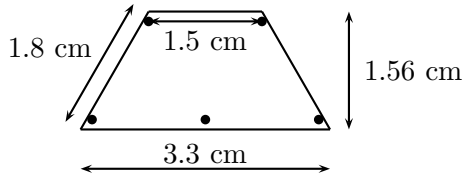
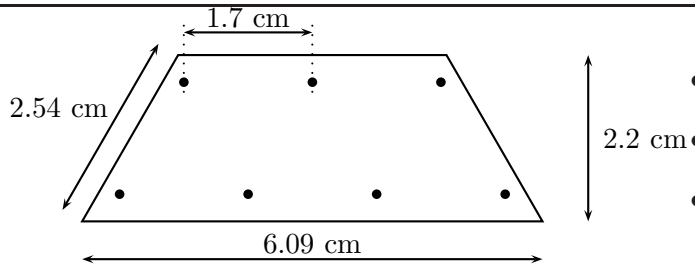
Instance	Layout	
phan1		• treated length: 4.2 cm • active length: 6 cm • constant dwell time: 0.091 s
phan2		• treated length: 4.9 cm • active length: 7 cm • constant dwell time: 0.076 s
phan3		• treated length: 4.9 cm • active length: 7 cm • constant dwell time: 0.052 s
phan4		• treated length: 4 cm • active length: 5.7 cm • constant dwell time: 0.053 s
phan5		• treated length: 7.1 cm • active length: 10 cm • constant dwell time: 0.049 s

Figure 14: The phantoms used in the experimentations

Instance	Calculation time (seconds)		
	without symmetries	with symmetries	acceleration
phan1	5,5	2,9	1,9
phan2	8,4	2,0	4,2
phan3	15,9	3,3	4,8
phan4	10,7	3,8	2,8
phan5	24,7	6,2	4,0

Table 1: Execution time for dwell times optimization with and without symmetries

	c_1	c_2	$COIN$
phan1	0,980	0,565	0,553
phan2	0,998	0,509	0,508
phan3	0,996	0,627	0,625
phan4	0,998	0,463	0,462
phan5	0,975	0,668	0,661

Table 2: $COIN$ values with the Paris System

accelerates the computing times, since the number of dwell positions is reduced.

To validate our linear optimization model, and to compare solutions with the non-optimized Paris System we have adopted criteria largely employed in the radiotherapy community, namely the parameters c_1, c_2 and their product $COIN$ previously defined in 3.3. Their calculations require the calculation of the cumulative dose volume histograms for the PTV and for normal tissue. Physicians of the radiotherapy unit of Pitié-Salpétrière consider that the treatment is effective provided if the target volume is well covered by the prescribed dose, which means that the indice c_1 must be close enough to 1. Values of c_2 and $COIN$ do not have importance if this first condition is not observed. Table 2 presents the values of the different parameters obtained using Paris System sources.

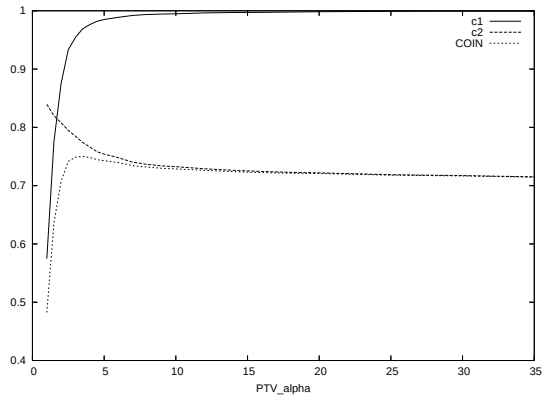
For our linear programming model, we analyzed the influence of the different α_S and β_S weights. As explained in section 4.2 and for the five cases considered, we set the values of $\underline{D_{PTV}}$ and $\overline{D_{PTV}}$ to 1 and $+\infty$ respectively, and those of $\underline{D_{NT}}$ and $\overline{D_{NT}}$ to 0 and 0.5. This implicates that only a lower bound for the dose is set to the calculation points of the PTV, and only an upper bound is set to the points of the surrounding normal tissue. The objective function (6) becomes:

$$\frac{\alpha_{PTV}}{N_{PTV}} \sum_{i \in PTV} u_i^{PTV} + \frac{\beta_{NT}}{N_{NT}} \sum_{i \in NT} v_i^{NT}. \tag{11}$$

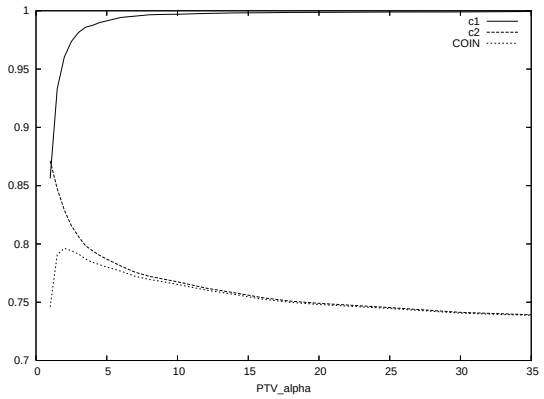
To simply the notations in the following, the corresponding weights for dose bound violations are denoted α_{PTV} for $\frac{\alpha_{PTV}}{N_{PTV}}$ and β_{NT} for $\frac{\beta_{NT}}{N_{NT}}$.

Having only two tuning parameters to deal with allows us to fix the value of one of them while examining the effects of changing values to the other. Indeed, the generated treament plans only differ from the value of the ratio of the two parameters. Hence, we analyzed the effects of variations of the α_{PTV} parameter while fixing β_{NT} to 1.

Figure 15 presents the evolution of the indices c_1, c_2 and $COIN$ for the $phan3$ and $phan5$ cases when α_{PTV} increases. We firstly observed, that in all cases, when the parameter α_{PTV} increases, the tumor coverage index c_1 also increases. When α_{PTV} reaches a value of 20, c_1 gets very close to 1. Indeed, the more the coverage of the PTV is privileged, the more the reference isodose encompasses a great number of points of the PTV. On the contrary, the coefficient



(a) phan3



(b) phan5

Figure 15: Evolution of c_1, c_2, and $COIN$ according to the increase of α_{PTV}.

	δ_{Paris}	c_1	c_2	$COIN$
phan1	1,8	0,998	0,641	0,639
phan2	1,8	0,997	0,629	0,627
phan3	1,5	0,998	0,722	0,721
phan4	1,5	0,998	0,581	0,579
phan5	1,7	0,999	0,758	0,758

Table 3: $COIN$ values after dwell times optimization with Paris System initial vector spacing

c_2, which measures the conformality of the reference isodose with the shape of the tumour, decreases as α_{PTV} increases. That is due to the fact that the increase of α_{PTV} involves the increase of the volume of the reference isodose, and consequently a more significant number of points of normal tissue is covered by this isodose. Nevertheless the observed values on the curve of c_2 remain above the values obtained Paris System linear sources. It results from this increase of c_1 and this reduction of c_2 that the value of $COIN$ increases until α_{PTV} reaches a value in the interval ranging between 1.5 and 3. Then, $COIN$ decreases then when α_{PTV} increases. From this analysis, we can conclude that the $COIN$ value is not sufficient to evaluate the quality of a treatment plan as it artificially combines two different measurements.

The analysis of the previous figures shows that a relatively good coverage of the PTV (c_1 near to 1) is achieved when α_{PTV} is set to 15 and $\beta_{NT} = 1$. Table 3 presents the values of c_1, c_2 and $COIN$ obtained with our optimization method when $\alpha_{PTV} = 15$ and $\beta_{NT} = 1$, using the original vector spacing δ_{Paris}.

As mentioned in section 4.1, our software can provide the value of the $COIN$ index according to the spacing of the catheters and allows in this manner to choose the best possible spacing for a clinical implant. The best value can be selected by the physician through simple graphic reading. Figure 16 shows such a graphic representation of the influence of vector spacing on the c_1, c_2 and $COIN$ dosimetric indices. Also let us note that spacings varying from more or less 1 mm in the neighbourhood of the optimal value of the $COIN$ produce values of conformality indices very close to the optimum. Thus we have the guarantee that unavoidable imprecision in the process of manual insertion of the vectors by the oncologist is not dramatic and only degrades in a very low extent the quality of the final treatment. Table 4 presents the values of c_1, c_2 and $COIN$ with the optimal spacing δ_{opt} obtained by graphical reading for each implant and shows the improvement factor.

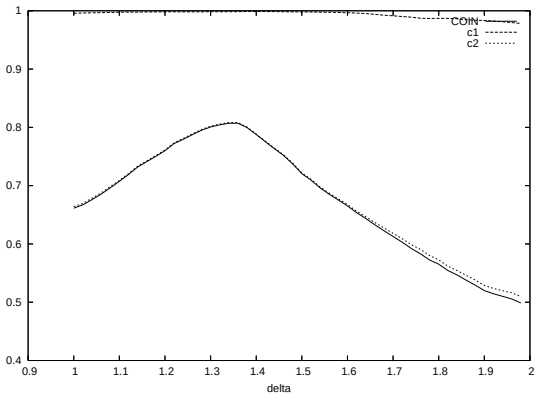


Figure 16: Evolution of c_1, c_2, and $COIN$ according to vector spacing (instance: phan3)

	δ_{opt}	c_1	c_2	$COIN$	improvement
phan1	1,6	0,998	0,685	0,684	+7%
phan2	1,52	0,999	0,766	0,765	+22%
phan3	1,35	0,999	0,808	0,807	+12%
phan4	1,23	0,999	0,710	0,710	+23%
phan5	1,7	0,999	0,758	0,758	+0%

Table 4: $COIN$ values after dwell times optimization with an optimal spacing between catheters

7 Conclusion

In this paper, we have presented a linear programming formulation of the dwell times optimization problem. Using this modelization, we managed to obtain very good results in terms of the most commonly used dose conformality indices (c_1, c_2, $COIN$) on phantom volumes defined in a LDR dosimetry system: the Paris System.

Our modelization differs from other models proposed in literature, which make use of metaheuristics and integer programming.

We have shown that HDR brachytherapy applications implanted according to the Paris System rules can be improved, which was the main objective of this study.

We developed simulation and 3D visualization software allowing the clinicians to:

- define implantations according to the principles of the Paris System: geometry of the PTV and vectors, calculation of the constant time which simulates iridium 192 wire-shaped sources;
- apply dwell times optimization on the designed implantations;
- to generate 3D isodoses, establish dose-volume histograms, and to deduce the values of the dose conformality indices.

This kind of analysis tool may certainly contribute, on one hand to lower the difficulty the optimization researchers to deal with the problems posed in medicine, and on the other hand to facilitate the comprehension for the medical community of the modelizations and techniques provided by the computer scientists' expertise.

We have studied the influence of the linear program objective function coefficients, and shown that generic values could be found, providing acceptable results, in terms of tumor cov-

erage (c_1 index) and dose conformality (c_2 index).

The experimentations we performed have proved their efficiency on "phantom" target volumes. The interest of working on such phantom volumes is that we will be able to treat any volume, provided we are able to surround it with such a generic target volume type. Obviously, the final dose optimization should take the real shape of the tumour into account. But as we shown in section 2, at the time we have to choose a positioning for the vectors, we still don't have a precise visualization of the target volume, but only general measurements including width, heigth and thickness. Precise vizualization is only possible when the vectors are already inserted, allowing accurate dose distribution optimization.

Acknowledgments

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References

Baltas, D., Kolotas, C., Geramani, K., Mould, R., Ioannidis, G., Kekchidi, M. & Zamboglou, N. (1998). A conformal index (coin) to evaluate implant quality and dose specification in brachytherapy, *Radiotherapy and Oncology* **40**: 515–524.

Chotin, G. (2000). Calcul des doses par ordinateur, *Enseignement Post-Universitaire : Evolution des techniques de curiethérapie*, Université Paris XII, Département de Cancérologie du CHU Henri Mondor, Créteil, pp. 93–107.

Dutreix, A., Marinello, G. & Wambersie, A. (1982). *Dosimétrie en curiethérapie*, Masson, Paris.

Galea, F. (2006). *Problèmes d'optimisation en curiethérapie*, PhD thesis, Université de Versailles, 45 avenue des Etats-Unis, F-78035 Cedex, France.

Galea, F. (n.d.). Isodose 3D, website. `http://www.prism.uvsq.fr/~fgalea/isodose_3d.html`.

Gerbaulet, T., Pötter, R., Mazeron, J., Meertens, H. & Limbergen, E. V. (2002). *The GEC-ESTRO Handbook of Brachytherapy*, ESTRO, Brussels, Belgium.

Hennequin, C., Mazeron, J. & Chotin, G. (2001). How to use the Paris System in the year 2001?, *Radiotherapy and Oncology* **58**: 5–6.

Lachance, B., Beliveau-Nadeau, D., Lessard, E., Chretien, M., Hsu, I., Pouliot, J., Beaulieu, L. & Vigneault, E. (2002). Early clinical experience with anatomy-based inverse planning dose optimization for high-dose rate boost of the prostate, *International Journal of Radiation Oncology-Biology-Physics* **54**: 86–100.

Lahanas, M., Baltas, D., Giannouli, S., Milickovic, N. & Zamboglou, N. (2000). Generation of uniformly distributed dose points for anatomy-based three dimensional dose optimization methods in brachytherapy, *Medical Physics* **27**: 1034–1046.

Lahanas, M., Baltas, D. & Zamboglou, N. (2003). A hybrid evolutionary algorithm for multiobjective anatomy based dose optimization in hdr brachytherapy, *Phys. Med. Biol.* **48**: 399–415.

Lahanas, M., Karouzakis, K., Giannouli, S., Mould, R. & Baltas, D. (2004). Inverse planning in brachytherapy: Radium to high dose rate 192 iridium afterloading, *Technical report*, Dept. of Medical and Physics Engineering, Klinikum Offenbach (Germany).

Lessard, E. & Pouliot, J. (2001). Inverse planning anatomy-based dose optimisation for hdr-brachytherapy of the prostate using fast simulated annealing and dedicated objective function, *Medical Physics* **28**: 773–779.

Lorensen, W. E. & Cline, H. E. (1987). Marching cubes: A high resolution 3d surface construction algorithm, *Computer Graphics (Proceedings of SIGGRAPH '87)* **21**(4): 163–169.

Milickovic, M., Lahanas, M., Pagagiannopoulou, M., Zamboglou, N. & Baltas, D. (2002). Multiobjective anatomy-based optimization for hdr-brachytherapy with constrained free deterministic algorithms, *Phys. Med. Biol.* **47**: 2263–2280.

Nucletron (URL). Medical systems for brachytherapy. `http://www.nucletron.com`.

Romeijn, H., Ahuja, R., Dempsey, J. & Kumar, A. (2006). A new linear programming approach to radiation therapy treatment planning problems, *Operations Research* **54**(2): 2449–2457.

SonoTECH (n.d.). Medical systems for brachytherapy, website. http://www.sonotech.de.

Varian (n.d.). Medical systems for brachytherapy, website. http://www.varian.com.

WinOpt-HDR (n.d.). Toolkit for multiobjective anatomy based dose optimization in HDR-brachytherapy, website. http://www.mlahanas.de/WinOpt/WinOpt_HDR.htm.