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Brachytherapy optimal planning with application to intravascular radiation therapy

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Abstract
We have been studying brachytherapy planning with the objective of minimizing the maximum deviation of the delivered dose from prescribed dose bounds for treatment volumes. A general framework for optimal treatment planning is presented and the minmax optimization is formulated as a linear program. Dose rate calculations are based on the dosimetry formulation of the American Association of Physicists in Medicine, Task Group 43. We apply the technique to optimal planning for intravascular brachytherapy of intimal hyperplasia using ultrasound data and ^{192}Ir seeds. The planning includes determination of an optimal dwell-time sequence for a train of seeds that deliver radiation while stepping through the vessel lesion. The results illustrate the advantage of this strategy over the common approach of delivering radiation by positioning a single train of seeds along the whole lesion.

Keywords: intravascular brachytherapy, linear program, optimization, radiotherapy, treatment planning

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1. INTRODUCTION

The inhibitive effect of radiation on proliferative cells is the basis for radiotherapy. Radiotherapy has long been recognized as a minimally invasive treatment for cancer (Mould, 1994). It has recently been proposed as an effective treatment for intimal hyperplasia, the proliferative component of restenosis or the renarrowing process of the vessel (Diamond and Vesely, 1998). The clinical relevance and importance of intravascular radiation therapy is revealed by the fact that intimal hyperplasia is usually stimulated by vascular injury, following, for example, coronary angioplasty (Teirstein *et al*., 1997). While radiotherapy of cancer is often not possible without subjecting healthy organs or structures at risk around the treatment site to some amount of radiation, the treatment is useful only if it sustains delivery of sufficiently large amounts of radioactive dose to the tumor. Treatment planning and optimization is therefore an integral part of cancer radiation therapy. A similar trade-off is revisited in radiotherapy of intimal hyperplasia; low doses of radiation stimulate neointimal proliferation, while high doses may cause vascular complications such as aneurysms and thrombosis (Diamond and Vesely, 1998).

Two main radiation treatment modalities include brachytherapy or treatment by radioactive seeds or implants, and external radiation therapy (Hendee and Ibbott, 1996). Brachytherapy is an interstitial or intracavitary radiation technique (brachy is the Greek word for near) where small sealed radioactive sources are applied to deliver

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radiation at a short distance from the treatment volume (Khan, 1994). Compared to external radiation therapy, this technique provides the advantage of delivering a large dose to a very localized treatment target, while sparing the surrounding normal tissue. In the past both radium and radon sources were used in brachytherapy, but today radionuclides such as ^{192}Ir, ^{125}I and ^{103}Pd are being used increasingly. Brachytherapy may be divided into high dose rate involving insertion of temporary radioactive material in close proximity of the target tissues, and low dose rate involving insertion of permanent radioactive implants (Hilaris *et al*., 1988). Even though the basic planning objectives, mathematical formulation and appropriate optimization techniques are similar for different treatment modalities, there are differences in dosimetry, the dose distribution forms and the associated gradient fields, and the physical quantities involved in the planning procedure. Different dose distribution forms and gradient fields affect suitable sampling strategies for point dose evaluations, and different physical quantities impose different constraints on the planning.

A typical treatment objective is delivery of a prescribed dose distribution to the treatment volume (Webb, 1993). The exact form of this problem, also known as inverse dosimetry, cannot be solved in general, i.e. in general it is not possible to determine the treatment variables so as to generate any desired dose distribution in a given volume (Webb, 1993). Alternatively, an optimization approach is followed where the treatment variables are determined so as to optimize a score or objective function associated with the dose distribution. The treatment variables (optimization variables) consist of the configuration of the sources (placement of seeds, orientation of beams, beam geometry etc.) and the weighting among them. Optimal weighting concerns optimal assignment of the radiation time of each source for high dose rate brachytherapy, the radioactive quantity of each source for low dose rate brachytherapy and the fraction of each beam contributing to the total delivered dose for external beam therapy. It holds for all treatment modalities that the delivered dose to each point is a linear function of the source weights. However the relationship between configuration variables such as placement and orientation and the dose values is nonlinear. In some cases, the treatment is fractionated which means treatment according to a schedule over a period of time. The formulation of fractionated treatment planning leads to an optimal control problem (Swan, 1981).

In this paper we focus on high dose rate brachytherapy. The ideal design objective is to confine the delivered dose to the target and surrounding tissues to prescribed bounds determined by an expert. We study situations where the prescribed bounds are not feasible. Even though the emphasis of the paper is directed towards high dose rate brachytherapy, the planning problem is stated in general terms. Therefore the presented formulation and techniques may be applicable to other treatment modalities. The design variables for high dose rate brachytherapy which are considered in this paper are optimal source weights or radiation times.

Earlier work

Niemierko and Goitein (1992) consider optimization of biological response to cancer radiation therapy. This requires a detailed modeling of the response as a function of the treatment variables (Niemierko and Goitein, 1993). Mohan *et al*. (1992) use simulated annealing to optimize the biological response to external beam therapy. The problem with such criteria is the unknown and often very complex response mechanism to radiation. There is an extensive literature on optimal treatment planning for external beam radiation therapy (Webb, 1993) where the goal is to deliver a dose distribution as close as possible to a prescribed distribution. This includes least-squares (Webb, 1991; Menguy *et al*., 1997) and dose bounding (Schweikard *et al*., 1994) formulations. The least-squares criterion has been solved by simulated annealing (Webb, 1991) and quadratic programming (Menguy *et al*., 1997). The quadratic programming solution to the least-squares criterion is more appropriate for computation of optimal beam weights since the least-squares objective function is quadratic in the weights. Linear programming has been applied to dose bounding (Schweikard *et al*., 1994). In connection with brachytherapy, Laarse and Prins (1994) summarize the commonly used optimization objectives and techniques. This includes dose bounding, least-squares and polynomial optimization. An interactive optimizer based on a genetic algorithm that uses expert opinion to rank competitive plans has also been suggested (Yu, 1997).

The formulation of planning objectives in this paper is in spirit close to the work of Schweikard *et al*. (1994). Contributions of this paper relative to the prior art may be summarized as follows. We present a general formulation for optimal treatment planning under infeasibility of the prescribed bounds on the delivered dose to the target and surrounding tissues. This formulation illustrates the connection between various planning objectives and considers uncertainty factors in the planning process. Minimizing the largest deviation of the delivered dose from the prescribed bounds (minmax optimization) is of special interest. Minmax optimization is used as a simple way to address problems arising in, for example, intravascular brachytherapy on the one hand, and generating feasible bounds to constraint optimization according to other objectives on the other. The most recent published works on high dose rate intravascular brachytherapy consider determination of the radiation time

for a single train of seeds or radioactive wire (see, for example, Chan *et al.*, 1998). In the approach considered here, we assume on the other hand, that a train of seeds is stepped throughout the vessel's length of interest. A common method of high dose rate radiation delivery uses an afterloader to step trains of seeds (Hendee and Ibbott, 1996). During the stepping process the train resides (dwells) at predetermined positions along the stepping path for specific durations of time. These positions and time durations are referred to as dwell positions and dwell times. Assuming that dwell times are much smaller than seed half-lives, the amount of dose delivered by the train at each dwell position is equal to the dwell time at that position multiplied by the dose delivery rate of the train. Moreover, the amount of delivered dose during the transience between two consequent dwell positions may be ignored due to high after loading velocity (typically 100–300 mm s^{-1} for transience between two consequent dwell positions). Hence for a fixed sequence of dwell positions, the sequence of dwell times wholly determine the dose distribution delivered by the train of seeds to the target and surrounding tissues. We consider optimization of the dwell-time sequence of such stepping train of seeds. The related optimization problem is formulated as a linear program which offers great computational advantage because of various existing numerical solutions (Bazaraa *et al.*, 1990). The technique can be readily generalized to high dose rate brachytherapy planning.

The rest of the paper is organized as follows. Section 2 concerns optimal planning and dosimetry. This includes a general framework for optimal treatment planning, formulation of the planning objective for high dose rate brachytherapy as a linear program, and the physical background in dosimetry of radioactive implants. The planning framework of Section 2 is directed towards an audience with general interest in treatment planning problems and may be studied independently of any particular application. Section 3 discusses the application of the developed techniques to a treatment planning problem from the area of intravascular brachytherapy. Finally, Section 4 offers concluding remarks.

2. OPTIMAL TREATMENT PLANNING AND DOSIMETRY

Optimal treatment planning addresses the question of determining the treatment variables so as to achieve a desired distribution of delivered dose to the target and surrounding tissues. The prescribed dose distributions are in many cases stated as upper and/or lower dose bounds for target and surrounding tissues. For instance, radiotherapy of local disease involves delivering high amounts of dose to malformations such as tumors while keeping the dose to organs or structures at risk below a tolerance level. The numerical study of the paper concerns an important application from the area of intravascular brachytherapy where it is desired to deliver minimum and maximum amounts of radioactive dose to a target volume defined within the vessel. In this section, we first consider a general formulation of the planning problem (Subsection 2.1) independently of any particular application. Subsection 2.2 focuses on optimal planning of dwell-time sequences for high dose rate brachytherapy where the planning problem is formulated as a linear program. Finally in Subsection 2.3, we consider dosimetry or calculation of dose delivery rates which determine the coefficients of the linear program formulated in Subsection 2.2.

2.1. Optimal treatment planning

Given a set of bounds for the delivered dose to the target and surrounding tissues, which are referred to generically as target volumes in this paper, the ideal planning objective is to constrain the delivered dose values within the prescribed bounds. This task might however be impossible due to the infeasibility of the prescribed bounds. Infeasibility analysis of the bounds is therefore essential to the design of optimal treatment plans. We propose a minmax optimization as a way of dealing with infeasibilities and discuss ways of incorporating the obtained solution in problems where other planning objectives such as dose homogeneity are of primary interest.

Let us first state a general formulation of the treatment planning problem. Within this framework, we take into account the fact that the delivered dose to a voxel for any treatment parameter may be affected by a variable whose value is unknown (an uncertainty variable). This variable may consist of factors such as uncertain positioning of the seeds and uncertain dose calculation models. Furthermore, the prescribed upper and lower bounds for a voxel are assumed to be uncertain due to uncertainty in, for example, segmentation of the target volumes. Let $d(\theta; v, \delta)$, $\overline{d}(v, \delta)$ and $\underline{d}(v, \delta)$ denote, respectively, the delivered dose, dose upper bound and dose lower bound for voxel v and treatment parameter θ where all uncertainty factors are collected in the variable δ. The ideal dose bounding may be formulated as the problem of finding a $\theta \in \Theta$ such that

$$\underline{d}(v, \delta) \leq d(\theta; v, \delta) \leq \overline{d}(v, \delta) \tag{1}$$

for all $v \in \mathcal{V}$ and $\delta \in \Delta$ where Θ, $\mathcal{V}$ and Δ denote the set of physical or other feasible constraints on θ, all voxels of interest and all possible uncertainty values respectively. The prescribed bounds may be infeasible. Consider a sequence of non-negative variables $\{\alpha(v, \delta) | v \in \mathcal{V}, \delta \in \Delta\}$ for which the

inequalities

$$\begin{aligned} &\underline{d}(v,\delta) - \alpha(v,\delta) \le d(\theta; v, \delta) \le \overline{d}(v,\delta) + \alpha(v,\delta) \\ &\forall v \in \mathcal{V} \quad \forall \delta \in \Delta \end{aligned} \tag{2}$$

can be satisfied simultaneously for some $\theta \in \Theta$. There are infinitely many such sequences since α should merely be selected large enough for Equation (2) to hold. If $\{\alpha(v,\delta) = 0\}$ is one such sequence, the prescribed dose bounds are feasible. Under infeasibility conditions, however, we seek a sequence with smallest norm where the l_p norm of a sequence $\{f(z)|z \in \mathcal{Z}\}$ is defined by $(\sum_{\mathcal{Z}} |f(z)|^p)^{1/p}$. Hence, the general l_p optimization is defined as

$$\begin{aligned} &\min_{\theta\in\Theta, \alpha(v,\delta)\ge 0} \sum_{v,\delta} \alpha(v,\delta)^p \\ &\forall v \in \mathcal{V} \quad \forall \delta \in \Delta : \\ &\underline{d}(v,\delta) - \alpha(v,\delta) \le d(\theta; v, \delta) \le \overline{d}(v,\delta) + \alpha(v,\delta). \end{aligned} \tag{3}$$

Remark 1 Noting that for each given θ, the smallest value of $\alpha(v,\delta)$ satisfying

$$\underline{d}(v,\delta) - \alpha(v,\delta) \le d(\theta; v, \delta) \le \overline{d}(v,\delta) + \alpha(v,\delta)$$

is equal to

$$\max\left\{\overline{\alpha}_{\min}(\theta; v, \delta), \underline{\alpha}_{\min}(\theta; v, \delta)\right\}$$

where

$$\begin{aligned} \overline{\alpha}_{\min}(\theta; v, \delta) &= \max\{0, d(\theta; v, \delta) - \overline{d}(v,\delta)\} \\ \underline{\alpha}_{\min}(\theta; v, \delta) &= \max\{0, \underline{d}(v,\delta) - d(\theta; v, \delta)\} \end{aligned}$$

the general l_p optimization Equation (3) is equivalent to

$$\min_{\theta\in\Theta} \sum_{v,\delta} \left(\max\left\{\overline{\alpha}_{\min}(\theta; v, \delta), \underline{\alpha}_{\min}(\theta; v, \delta)\right\}\right)^p.$$

In the special case where the upper and lower bounds at a point are equal to a target dose at that point, i.e.

$$\overline{d}(v,\delta) = \underline{d}(v,\delta) = d_T(v,\delta)$$

the optimization may be formulated in the following simpler form:

$$\min_{\theta\in\Theta} \sum_{v,\delta} |d(\theta; v, \delta) - d_T(v,\delta)|^p.$$

The selected norm is dependent upon planning objectives. We identify several special cases of interest:

- as $p \to 0^+$, $\alpha(v,\delta)^p$ approaches an indicator function which is zero if $\alpha(v,\delta) = 0$ and 1 if $\alpha(v,\delta) > 0$, i.e. minimizing l_0 is equivalent to maximizing the number of elements of $\mathcal{V} \times \Delta$ that receive dose values within the prescribed bounds;
- $p = 1$ and 2 cases correspond to minimization of the mean and mean square of the sequence $\{\alpha(v,\delta)\}$ respectively;
- as $p \to +\infty$, the l_p optimization tends to minimization of $\max_{v,\delta} \alpha(v,\delta)$.

The case $p \to 0^+$ has a direct connection to the histogram over delivered dose values which from a clinical standpoint is one of the most important figures of merit for a treatment plan (Hendee and Ibbott, 1996). Unfortunately, optimization of the l_0 norm is a formidable task since for $p < 1$, the l_p norm is non-convex in α and as $p \to 0^+$ the problem becomes one of combinatorial nature.

The l_1 and l_2 problems are appealing since they both are convex in α and minimize the deviations in an average sense, hence resulting in homogeneous dose distributions. The l_2 norm for the case where the upper and lower dose bounds at a point are set equal to a target dose value at that point (see Remark 1) has received particular attention in the literature and is mostly referred to as least-squares optimization (C. Davatzikos *et al.*, personal communication). In forming the l_1 or l_2 norms, a weighted sum might be preferable where the weight at (v,δ), denoted by $w(v,\delta)$, may be defined as the loss associated with a unit dose deviation from the upper or lower bound at v multiplied by the probability of δ.

The case $p \to +\infty$ or the minmax problem is of particular interest in this paper. Firstly, the minmax formulation arises naturally in applications such as intravascular brachytherapy planning which is discussed in the numerical study of the paper. Secondly, the minmax analysis finds a lowest feasible upper bound on the sequence $\{\alpha(v,\delta)|v \in \mathcal{V}, \delta \in \Delta\}$. This bound may be used to constrain the solution to optimization problems where other criteria such as dose homogeneity are of primary concern. Finally, the l_∞ problem is computationally appealing.

Denote $\beta = \max_{v,\delta} \alpha(v,\delta)$. The minmax problem may simply be formulated as

$$\begin{aligned} &\min_{\theta\in\Theta, \beta\ge 0} \beta \\ &\forall v \in \mathcal{V} \quad \forall \delta \in \Delta : \\ &\underline{d}(v,\delta) - \beta \le d(\theta; v, \delta) \le \overline{d}(v,\delta) + \beta. \end{aligned} \tag{4}$$

Denoting the optimal value of β in Equation (4) by β^*_∞, the constraints

$$\begin{aligned} &\underline{d}(v,\delta) - \beta_0 \le d(\theta; v, \delta) \le \overline{d}(v,\delta) + \beta_0 \\ &\forall v \in \mathcal{V} \quad \forall \delta \in \Delta \end{aligned} \tag{5}$$

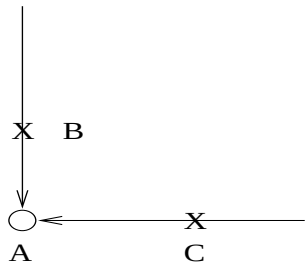


Figure 1. The beams of radiation are shown by directed lines that aim at A. Possible critical structures are marked by X.

are feasible iff $\beta_0 \geq \beta_\infty^*$. The above inequalities for $\beta_0 \geq \beta_\infty^*$ may be added to the constraint sets of any l_p optimization. Through constraining, for example, the l_1 or l_2 optimization by the inequalities of Equation (5), the average deviation is sought minimized while the worst deviation is ensured to be bounded by a selected value of β_0.

Finally, if the dose at (v, δ) should be bounded from one side only, the two-sided inequalities on $d(\theta; v, \delta)$ should obviously be modified to one sided throughout by keeping only the relevant side of the inequalities.

We illustrate the discussed planning concepts by means of a simple example.

Example 2.1 Consider two beams of radiation aiming at point A in Figure 1 and assume that the radiation dose is equal along the path of beam travel.

Point C is outlined as a critical structure, while point B might be a critical structure with some positive probability. Let the random variable $\delta = 0, 1$ be defined such that $\delta = 1$ if B is a critical structure and $\delta = 0$ otherwise, and let p_0 and p_1 denote the probabilities of $\delta = 0$ and 1 respectively. Suppose that the prescribed dose bounds (according to some unit for radiation) are given by

$$\begin{aligned} \underline{d}_{\mathrm{A}} &= \underline{d}(\mathrm{A}, \delta = 0, 1) = 2 \\ \overline{d}_{\mathrm{B0}} &= \overline{d}(\mathrm{B}, \delta = 0) = 1.5 \\ \overline{d}_{\mathrm{B1}} &= \overline{d}(\mathrm{B}, \delta = 1) = 0.5 \\ \overline{d}_{\mathrm{C}} &= \overline{d}(\mathrm{C}, \delta = 0, 1) = 0.5. \end{aligned}$$

Letting θ_1 and θ_2 denote the beam weights (variables that determine beam intensities and affect dose linearly) of the vertical and horizontal beams respectively, the delivered dose values are given by

$$\begin{aligned} d(\theta_1, \theta_2; \mathrm{A}, \delta = 0, 1) &= \theta_1 + \theta_2 \\ d(\theta_1, \theta_2; \mathrm{B}, \delta = 0, 1) &= \theta_1 \\ d(\theta_1, \theta_2; \mathrm{C}, \delta = 0, 1) &= \theta_2. \end{aligned}$$

The defined bounds are obviously infeasible and the minmax solution is $\beta_\infty^* = 0.33$ with 0.83 as the corresponding optimal value for θ_1 and θ_2. Now consider the non-negative variables α_{A}, α_{B0}, α_{B1} and α_{C} and constraints

$$\begin{aligned} \alpha_{\mathrm{A}} &\geq \underline{d}_{\mathrm{A}} - d(\theta_1, \theta_2; \mathrm{A}, \delta = 0, 1) \\ \alpha_{\mathrm{B0}} &\geq d(\theta_1, \theta_2; \mathrm{B}, \delta = 0) - \overline{d}_{\mathrm{B0}} \\ \alpha_{\mathrm{B1}} &\geq d(\theta_1, \theta_2; \mathrm{B}, \delta = 1) - \overline{d}_{\mathrm{B1}} \\ \alpha_{\mathrm{C}} &\geq d(\theta_1, \theta_2; \mathrm{C}, \delta = 0, 1) - \overline{d}_{\mathrm{C}}. \end{aligned} \tag{6}$$

The weighted l_2 problem may be stated as determining non-negative θ_1, θ_2, α_{A}, α_{B0}, α_{B1}, α_{C} so as to minimize

$$\alpha_{\mathrm{A}}^2 + p_0\alpha_{\mathrm{B0}}^2 + p_1\alpha_{\mathrm{B1}}^2 + \alpha_{\mathrm{C}}^2$$

subject to the linear constraints of Equation (6), and the constraints

$$\begin{aligned} \theta_1 + \theta_2 &\geq 2 - \beta_0 \\ \theta_1 &\leq 0.5 + \beta_0 \\ \theta_2 &\leq 0.5 + \beta_0 \end{aligned} \tag{7}$$

for some $\beta_0 > 0.33$ where this last set of inequalities ensures that the largest deviation always remains within predetermined bounds. Assuming that $p_0 = 0.8$ and $p_1 = 0.2$, the l_2 optimization without enforcing Equation (7) yields 1.21 and 0.64 as the optimal values of θ_1 and θ_2 respectively, i.e. 1.21 units of radiation at point B. Selecting $\beta_0 = 0.5$ and enforcing Equation (7) yields 1.00 and 0.75 as the optimal solution for θ_1 and θ_2. The reduction of the delivered dose to B by $\approx$0.2 units is done by $\approx$0.1 unit increase in the dose delivered to C and $\approx$0.1 unit decrease in the delivered dose to A. Through constraining the optimization by Equation (7), B is spared for excessive exposure to radiation in the event that it is a critical structure (even though such event is less likely). Notice further that the optimal dose at C according to the constrained l_2 solution is $\approx$0.1 units less than the corresponding dose provided by minmax optimization.

Remark 2 Kelley's cutting plane algorithm (Kelley, 1960; Zangwill, 1969; Luenberger, 1984) provides a simple method for optimization problems such as Equation (4). In general consider the problem:

$$\min_{x \in \mathcal{X}} f(x) \qquad g(x; y) \leq 0 \quad \forall y \in \mathcal{Y}$$

where $f(x)$ is convex in x, $\mathcal{X}$ is described by a set of linear inequalities, and $g(x; y)$ is convex and differentiable in x for all $y \in \mathcal{Y}$ ($\mathcal{Y}$ may in general be infinite). Starting with the solution to $\min_{x \in \mathcal{X}} f(x)$, the algorithm consists of the following steps which are performed iteratively. First x is fixed to its current solution and a value for y that maximizes

$g(x; y)$ is computed. Then y is fixed to this computed value and $g(x; y)$ is linearized in x around the current solution. The linearization step yields a linear constraint (in x) which is added to the set of constraints on x. A new value for x as the minimizing argument of $f(x)$ subject to the updated set of constraints is computed. The whole procedure is repeated until at some current solution, $g(x; y)$ is smaller than a selected small positive number for all $y \in \mathcal{Y}$. Now if Θ is described by a set of linear constraints, application of the algorithm to, for example, Equation (4) obviously requires sequential linear programming. Moreover, if $d(\theta; v, \delta)$ is linear in θ, the linearization step of the above procedure will no longer be necessary.

2.2. Optimal high dose rate brachytherapy

As mentioned in the introduction, high dose rate brachytherapy concerns delivery of radiation dose to target tissues by temporary insertion of radioactive material in close proximity of the target. A common method of high dose rate radiation delivery uses an afterloader to step trains of seeds along one or more paths (Hendee and Ibbott, 1996). With the assumption that the total irradiation times are much smaller than seed half-lives, the dose delivery rates may be assumed constant within the time intervals of radiation. So for a train of seeds dwelling at a certain position along its path, the amount of delivered dose to a point is equal to the dwell time of the train multiplied by the dose delivery rate to the point of interest for that dwell position. The total delivered dose to a point is equal to the superposition of delivered doses from each dwell position. The seed paths, relative positioning of the seeds within a train, initial and final positions of the trains on the paths, and the stepping lengths constitute the configuration of dose delivery. The goal of treatment planning is determination of the optimal configuration and the corresponding dwell-time sequence to deliver a desired dose distribution to the target and surrounding tissues. We address optimization of the dwell-time sequence for a given delivery configuration. Developing fast algorithms for dwell-time optimization enables the user to select an optimal plan by comparing dwell-time optimization results for various configurations. Such comparisons may alternatively be done by appropriate search algorithms.

Suppose that M target volumes, $V_1, \ldots, V_M$, are given where each target volume is specified by a set of sampled points (voxels) within the volume. We neglect the uncertainty variable and let $\overline{d}_i$ and $\underline{d}_i$ respectively denote $\overline{d}(v)$ and $\underline{d}(v)$ for $v \in V_i$. The more general situation can be handled using the techniques described in the earlier subsection. The linearity of dose in dwell times yields,

$$d(T_1, \ldots, T_n; v) = \phi_1(v)\, T_1 + \phi_2(v)\, T_2 + \cdots + \phi_n(v)\, T_n$$

where T_j is the dwell time of the train of seeds for positioning j, n is the total number of dwell positions, v denotes voxel and $\phi_j(v)$ denotes dose delivery rate at v for positioning j. We consider calculation of the delivery dose rates in the next subsection. The minmax problem in Equation (4) transforms into the linear program,

$$\begin{aligned} &\min \beta \\ &\underline{d}_i - \beta \le \sum_{j=1}^{n} \phi_j(v) T_j \le \overline{d}_i + \beta \qquad \forall i \forall v \in V_i \\ &T_1, \ldots, T_n \quad \beta \ge 0 \end{aligned} \tag{8}$$

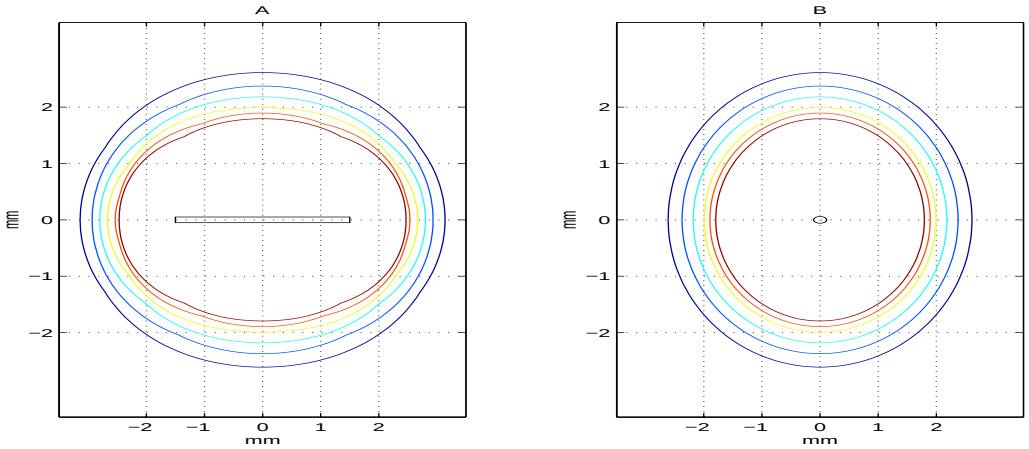
where the minimization is with respect to $T_1, \ldots, T_n, \beta$.

Depending on the sampling resolution, the number of constraints in the above linear program may be large, since each voxel introduces two inequalities (one inequality if the voxel belongs to a volume where the dose should be bounded from one side only). Linear programming is a well explored area in optimization for which numerous efficient algorithms and approaches exist (Dantzig, 1963; Murty, 1986; Bazaraa *et al.*, 1990; Saigal, 1994) even for high-dimensional cases. A simple way of dealing with the large number of inequalities of the above problem is a cutting plane method which is described in Remark 2 of the previous subsection.

2.3. Dosimetry

Let us now consider calculation of the dose rate values, i.e. the coefficients of the linear system of Equation (8). Each coefficient, $\phi_j(v)$, is calculated by summing over contributions from each seed to the dose rate at v when the train of seeds assumes positioning j.

The dose rate is not only a function of the configuration of the train of seeds but the physical characteristics of the radionuclide within the seed (gamma or beta source, energy spectrum and half-life). In cancer treatment, the radionuclides used for interstitial brachytherapy in the United States are gamma sources, most commonly ^{192}Ir and ^{125}I. Also, ^{103}Pd seeds have become available recently as alternative sources. In terms of vascular brachytherapy, the dose must be delivered to lesions in the range of 1–3 mm. Photons above an energy of 20 keV and electrons above an energy of 1.0 MeV are found to be adequately penetrating at this depth range (Nath and Liu, 1997). Dose rates >5 Gy min^{-1} are desired to deliver the prescribed dose at reasonable treatment times since longer times mean increased patient risk of complication due to reduced arterial blood flow. ^{192}Ir has been used in several animal and clinical trials (Crocker and Waksman, 1997) because it is considered a high-energy gamma emitter which provides an acceptable dose distribution within 5 mm from the source axis, and the prescribed dose can be delivered within a reasonable



(a) (b)

Figure 2. Isodose curves of a 3 mm long ^{192}Ir seed. The curves are plotted for dose rate values varying from 1 to 2 Gy min^{-1} with intervals of 0.2 Gy min^{-1}.

irradiation time. Other low-energy gamma sources (^{125}I, ^{103}Pd) as well as beta emitters (^{32}P, ^{90}Y) are under current investigation by several research groups (**?**).

In the numerical study of the paper (Section 3), we present the optimization results for the ^{192}Ir seed used for vascular brachytherapy. ^{192}Ir is a gamma emitter with a 73.8 day half-life and an average photon energy of 370 keV. The modeled ^{192}Ir seed is available commercially (Best Industries, Springfield, VA). This seed is in the form of a cylinder (3 mm long with a 0.5 mm diameter), and has a 0.1 mm diameter core of 30% Ir–70% Pt encapsulated by a 0.2 mm thick stainless steel cladding.

For calculation of dose rate from a seed to a point, we assume that seeds are line sources and follow the American Association of Physicists in Medicine (AAPM) task group 43 (TG43) formalism (Nath *et al*., 1995) as recommended by the AAPM-TG60 (R. Nath *et al.*, unpublished) for photon-emitting sources. For small distances between the point and the source center (range of several millimeters), which are typical for intravascular brachytherapy, the line-source assumption yields more accurate results than the more common point-source approximation, mainly due to suppression of the inverse squared dependency of the dose rate upon small distances in line-source dose calculations (Nath *et al*., 1995). The dose rate value calculated on the basis of line-source approximation also depends on the seed direction which is equivalent to the tangent to the seed path at the location of the seed. The information required for calculation of dose rate values on the basis of the TG43 formalism is relative positioning of the target volumes with respect to the seeds. The data needed for dosimetry and treatment planning are typically image based. Common image modalities are computed tomography (CT), magnetic resonance (MR) and ultrasound. In the numerical study of the paper, tomographic sections of intravascular ultrasonography (IVUS) are employed for calculation of dose delivery rates to the target volume.

Figure 2 illustrates isodose curves of a 3 mm long ^{192}Ir line source with an air kerma strength of 400 U; kerma stands for kinetic energy released per unit mass and is a measure of the energy released in a volume of air at some distance from a radioactive source (see Nath *et al*., 1995). The curves are computed on the basis of TG43 formalism. Figure 2a shows isodose curves on a plane containing the source, while Figure 2b plots the curves on a plane perpendicular to the source where the origin coincides with the seed center. Notice that in contrast to Figure 2b, the isodose curves of Figure 2a are anisotropic which is a result of the line-source assumption.

3. NUMERICAL EXAMPLE: ULTRASOUND-GUIDED INTRAVASCULAR DOSIMETRY

Coronary angioplasty is a minimally invasive technique for treatment of atherosclerosis, the principal process of heart disease. Despite its wide acceptance, coronary angioplasty is limited by rates of restenosis of 30–60% (Teirstein *et al*., 1997). A major component of the restenosis process is intimal hyperplasia which refers to the proliferative response to vascular injury. While coronary stents virtually remove recoil and remodeling (other components of the restenosis

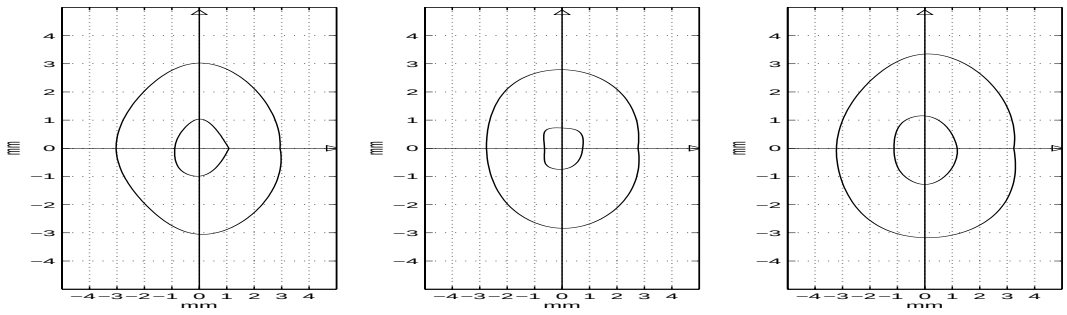


Figure 3. Media boundaries outlined on a series of tomographic sections.

process) they do not decrease the proliferative response caused by angioplasty. Recent studies show that ionizing radiation, administered during or after angioplasty, can inhibit the proliferative component of restenosis (Waksman, 1996). Possible radiation techniques are temporary or high dose rate catheter-based brachytherapy using radioactive seeds, wire or liquid-filled balloons, permanent or low dose rate brachytherapy using radioactive stents and external beam radiation. Treatment planning is essential since low doses of radiation stimulate neointimal proliferation and high doses may cause vascular complications such as aneurysms and thrombosis (Diamond and Vesely, 1998).

In the short-term study of patients with previous coronary restenosis that was conducted at the Scripps clinic and research foundation, it was demonstrated that coronary stenting followed by catheter-based intracoronary radiotherapy substantially reduced the rate of subsequent restenosis (Teirstein *et al*., 1997). The target volume was defined to be the media which is a smooth muscle cell layer of the vessel filling the area between the innermost intima and the outermost adventitia. The volume boundaries were outlined on a series of tomographic sections obtained by ultrasonography and dosimetry included calculation of the radiation time for a single train of seeds with the goal of delivering a minimum of 8 Gy and a maximum of 30 Gy to the target volume. In computing the optimal radiation time, it was assumed that the path traveled by the pull-back ultrasound imaging device was a straight line and equivalent to the path of the train of seeds. This assumption holds throughout the rest of this section unless otherwise stated. Figure 3 illustrates typical delineation of media boundaries on three tomographic sections where the origin of each section coincides with the position of the imaging device during its passage through that section. Let $\underline{P}$ and $\overline{P}$ be the closest and furthest media points from the path of the sonographic device (equivalent to the path of the train of seeds) respectively. These two points may be determined by simple examination of boundary point positions relative to the origins on the tomographic sections. Under the above assumptions and noting that dose rate falls monotonically with distance from the radioactive source, the dosimetry planning of the Scripps trial may be stated as a determination of the radiation time of a single train of seeds with the goal of a minimum of 8 Gy delivery to $\overline{P}$ and a maximum of 30 Gy delivery to $\underline{P}$.

We extend the dosimetry planning of the Scripps trial to treatment planning on a 36 mm long coronary lesion where the treatment variable is the dwell-time sequence of a stepping train of seeds rather than the radiation time of a single train. Ultrasound tomographic sections of the lesion which are 1 mm apart are obtained with the use of a pull-back apparatus. The media boundaries are outlined manually on the sections of the lesion. Inner and outer boundary points at longitudinal and angular resolutions of 0.25 mm and 10° are computed by interpolation. On each slice i (of the 0.25 mm apart slices), we determine two points, $\underline{P}_i$ and $\overline{P}_i$, that are closest to and furthest from the origin of that slice. Recalling that dose rate falls monotonically with distance from the source, the ideal dose bounds of the Scripps trial may be stated as

$$\begin{aligned} d(T_1, \ldots, T_n; v) &\leq 30\ \text{Gy} \qquad \forall v \in V_1 \\ d(T_1, \ldots, T_n; v) &\geq 8\ \text{Gy} \qquad \forall v \in V_2 \end{aligned} \tag{9}$$

where V_1 and V_2 represent the sets of points $\{\underline{P}_i\}$ and $\{\overline{P}_i\}$ respectively and $T_1,\ldots,T_n$, as earlier, denote the sequence of dwell times.

Remark 3 Even though we have assumed equivalence of the paths of the train of seeds and the imaging device, the extension to cases where this equivalence does not hold is straightforward under a straight midline assumption. At each slice i, the points $\underline{P}_i$ and $\overline{P}_i$ should merely be determined as points closest to and furthest from a possible positioning of the source relative to the center of the slice. As a result of monotonic dose rate decrease with distance, the inequalities

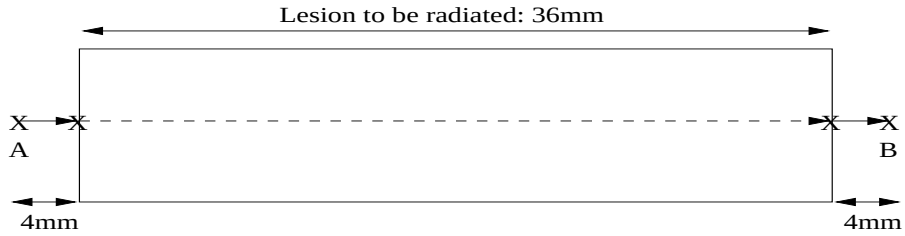


Figure 4. Side projection of the vessel to be radiated. The centers of the seeds are marked by X and the travel path of the seeds is illustrated by the directed lines connecting points A and B.

of Equation (9) will in this case imply that the dose is bounded at all media points for all possible non-centering uncertainties.

The bounds in Equation (9) may be infeasible in which case an optimization approach should be followed. We select the minmax approach as a natural extension of the dosimetry planning of the Scripps trial. The reason is that for $n = 1$ we obviously have

$$d(T_1; \underline{P}) = \max_{v \in V_1} d(T_1; v)$$
$$d(T_1; \overline{P}) = \min_{v \in V_2} d(T_1; v).$$

Hence dosimetry planning with the objective of bounding $\max_{v \in V_1} d(T_1, \ldots, T_n; v)$ and $\min_{v \in V_2} d(T_1, \ldots, T_n; v)$ covers the dosimetry planning of the Scripps trial as a special case for $n = 1$. For $n > 1$, more desirable dose distributions may be achieved through adjustment of the dwell times to variations in the vessel diameter. These variations may be represented by slicewise variations in the diameters of inner and outer circles around the IVUS catheter (imaging device) where the radii of the circles are respectively equal to the smallest and largest distances of the media from the IVUS catheter. Notice that all points on each one of the inner and outer circles receive the same radioactive dose. The surfaces described by the inner and outer circles are referred to as inner and outer surfaces. Under the straight midline assumption for the lesion, the inner and outer surfaces may be obtained by simple stacking of the circles. In general, obtaining the surfaces requires establishing coordinates of the points with respect to a fixed coordinate system. Even though IVUS tomographic sections provide excellent structural information, they do not provide direct information about the coordinates of points with respect to a fixed coordinate system and a reconstruction step is therefore necessary. Transcutaneous ultrasonography (McPherson, 1996), MR or CT scans, on the other hand, directly establish global coordinates but are not commonly used. Three-dimensional reconstruction of the surfaces which are spanned by the outlined circles requires extra information about the curvature and twist of the midline of the vessel obtainable by, for example, magnetic tracking of the IVUS catheter (McPherson, 1996) or data fusion with biplane angiograms (Prause *et al*., 1996).

We study intravascular radiation therapy for ^{192}Ir seeds with air kerma strength of 400 U (see Section 2 for physical properties). We consider two different delivery configurations C1 and C2. Figure 4 illustrates the positions that the seed centers of both C1 and C2 may assume relative to the lesion. In both configurations the length of each seed is 3 mm and the centers of two neighboring seeds are 4 mm apart, i.e. a gap of 1 mm between two neighboring seeds. These dimensions are commonly used in intravascular brachytherapy (Jani *et al*., 1998). Configuration C1 corresponds to a single train of 12 seeds (i.e. a total length of 44 mm between the centers of the seeds at the two ends of the train), covering the 36 mm long lesion. The single-train configuration of C1 is consistent with the delivery setting of the Scripps trial or the work of Chan *et al*. (1998). There is only one dwell time (equal to the total radiation time) associated with C1. For configuration C2, a train of two seeds is stepped throughout the lesion dwelling at six distinct positions. The step length is uniformly selected to be 8 mm, i.e. a total length of $4\text{ mm} + 5 \times 8\text{ mm} = 44$ mm, which is equal to the total length covered by C1, is spanned between the furthest locations the seed centers may assume. We use the procedure of the previous section to compute the optimal dwell times, and compare the result for these two configurations. The minmax problem is formulated as

$$\begin{aligned} &\min \beta \\ &\sum_{j=1}^{n} \phi_j(v) T_j \le 30 + \beta \qquad \forall v \in V_1 \\ &\sum_{j=1}^{n} \phi_j(v) T_j \ge 8 - \beta \qquad \forall v \in V_2 \\ &T_1, \ldots, T_n \qquad \beta \ge 0. \end{aligned}$$

The total number of points that participate in the optimization, i.e. the total number of points in V_1 and V_2, is equal to $[36\text{ mm} \times (1/0.25\text{ mm}) + 1] \times 2 = 290$.

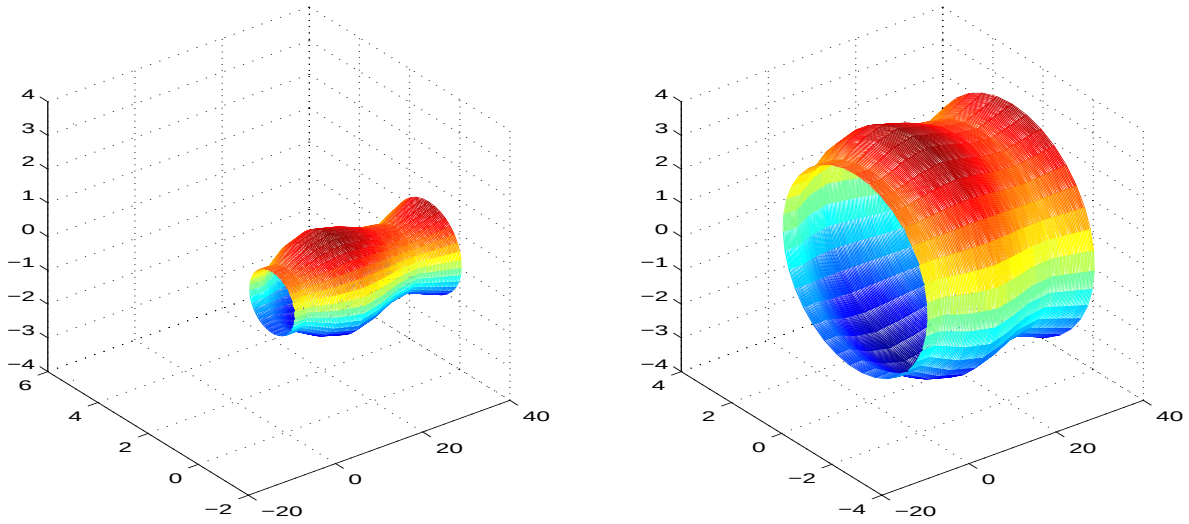


Figure 5. Inner (left figure) and outer (right figure) surfaces.

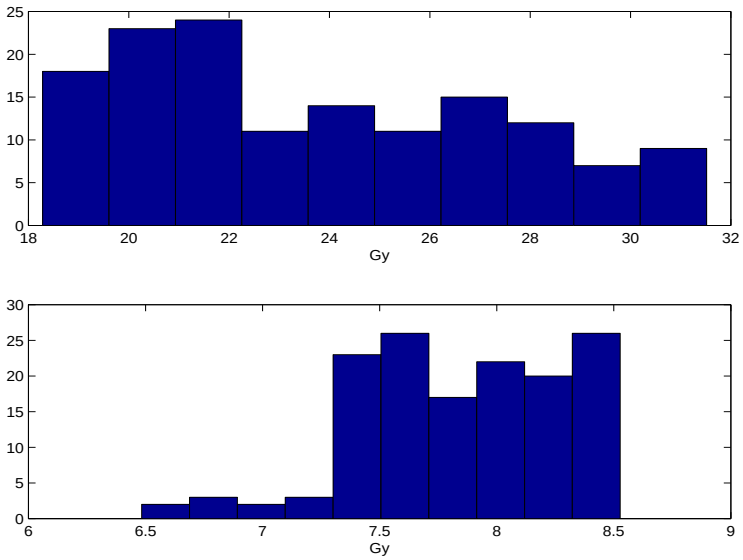


Figure 6. Dose distribution on V_1 (top figure) and V_2 (bottom figure) for C1. The area of each box represents the number of surface points receiving dose values within the horizontal range of the box.

We perform the computations on a SGI Octane workstation with MATLAB[a] software. The inner and outer surfaces are visualized in Figure 5 for which a longitudinal resolution of 1 mm and angular resolution of 10° are selected. The optimization results are summarized in Table 1 where the optimization time refers to the time needed to solve the linear program. Since the optimization of the original linear program is fast, no cutting plane method is applied. For the configuration C2, Figure 8 plots the optimal dwell-time sequence as a function of the distance from the initial position of the train where the train enters the lesion from coordinates $(0, 0, 0)$ in Figure 5. Comparing Figures 8 and 5 shows that the optimization responds to variations in the diameter by corresponding adjustments in the dwell times (i.e. smaller dwell times correspond to smaller radii and vice versa). Finally, the dose histograms for the two

[a]MATLAB is a registered trademark of the Mathworks Incorporation.

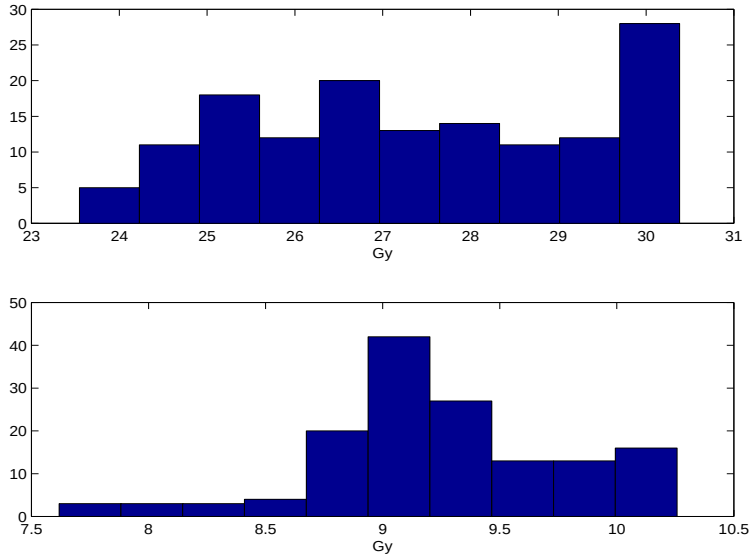


Figure 7. Dose distribution on V_1 (top figure) and V_2 (bottom figure) for C2. The area of each box represents the number of surface points receiving dose values within the horizontal range of the box.

Table 1. Summary of optimization results for configurations C1 and C2.

	Configuration	
	C1	C2
Radiation time (min)	4.4	31.4
Max. deviation (Gy)	1.52	0.38
Dose histograms	Figure 6	Figure 7
Optimization time (s)	<1	<1

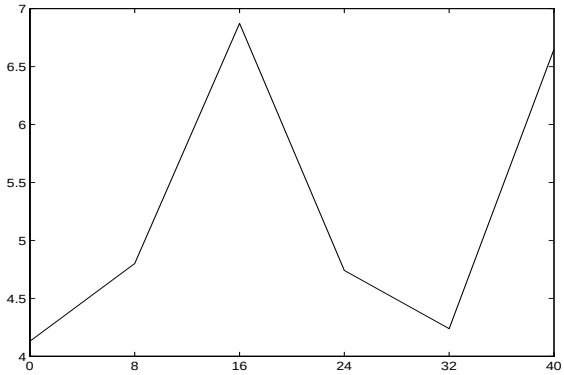


Figure 8. Dwell time of the train of seeds (configuration C2) as passing through the lesion.

configurations are plotted in Figures 6 and 7. Comparison of these histograms shows improved results for the stepping train of seeds strategy. There is a maximum deviation of 1.52 Gy from the prescribed bounds for the single train of seeds configuration versus 0.38 Gy for the stepping train of seeds where the underdose and overdose deviations are equal to the optimum for both configurations. The price to pay is larger total radiation time (31.4 min for C2 obtained by summing over the optimized dwell times versus 4.4 min for C1). However, a delivery system that irradiates the whole lesion for 4.0 min (minimum dwell time of C2) using a single train of seeds, and afterwards steps the train of two seeds, dwelling 4 min less than the designed dwell time of C2 at each dwell position, will save $4 \times 6 - 4 = 20$ min in total radiation time. Such a delivery system will reduce the total radiation time of C2 to about 10 min.

Further analysis of the minmax solution

As a direct generalization of the Scripps trial dosimetry planning, we have proposed multiple dwell-time minimization of maximum dose deviation from the prescribed bounds. In reality, however, other generally accepted factors such as dose uniformity and the fraction of volume receiving desirable dose values should not be neglected. Assessing the minmax solution with respect to these factors is in particular relevant since the minmax criterion is in general known to compromise dose uniformity for minimized worst deviation. We investigate this point for intravascular radiotherapy

Table 2. Comparison of l_∞ and l_1 optimization results for vessel models TM1 and TM2. MD, SD and PSC abbreviate maximum deviation, sum of deviations and percentage of satisfied constraints respectively.

	TM1		TM2	
	l_∞	l_1	l_∞	l_1
MD	0.3821	0.4779	0.6424	1.6903
SD	0.2701	0.1693	0.3957	0.3663
PSC	92%	97%	60%	62%

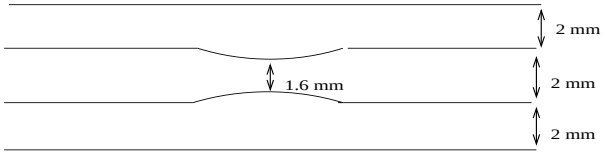


Figure 9. Longitudinal cross-section for TM2.

planning with multiple dwell times. We assume two tubular models TM1 and TM2 for the vessel. For both TM1 and TM2, we assume the same vessel length as before and the delivery configuration C2. For TM1 we assume cross-sectional inner and outer radial variations identical to those of Figure 5, and for TM2 we assume the longitudinal cross-section illustrated in Figure 9. The reason for this selection is that TM2 exhibits a single narrowing around the middle of the vessel in contrast to TM1 where variations occur throughout the vessel. We compute the optimal sequence of dwell times according to both the minmax (l_∞) and sum of absolute deviations from the bounds (l_1) criteria. The latter is representative of criteria that possess optimality properties in an average sense, therefore resulting in more uniform dose distributions. The results are summarized in Table 2. The table entry PSC (percentage of satisfied constraints) refers to the number of points receiving dose values within prescribed bounds divided by the total number of points. The results indicate that for a delivery configuration that allows adjustment of dwell times in accordance with variations along the vessel (multiple dwell times), the dose uniformity is relatively preserved at the minmax optimum. In general cases where the uniformity is compromised, the relaxation method of Section 2 may be followed, i.e. constraining the l_1 or l_2 optimization by the inequalities of Equation (5).

4. DISCUSSION AND CONCLUDING REMARKS

We have studied optimal planning for brachytherapy with application to intravascular radiotherapy of intimal hyperplasia. We presented a general formulation for optimal treatment planning and focused on the important planning criterion of minimizing the largest deviation from prescribed dose bounds for the delivered dose to volumes around the treatment site. In reality, however, a plan should be evaluated and selected according to multiple criteria (mostly calculable from dose–volume or dose–surface histograms such as the sum of absolute or squared deviations and the fraction of points receiving desirable dose values). Hence either various criteria should be combined in one optimization (quite similar to the relaxation method of Section 2) or a post-optimization analysis should be performed to assess the appropriateness of a plan that is optimal with respect to one selected criterion. The general formulation of the paper allows uncertainties to be taken into account and optimization with respect to non-linear factors. The functional dependency of dose upon the treatment parameter and the defined planning objectives affect the appropriate optimization tool to be employed. Factors such as non-convexity of the objective function, non-linearity and non-convexity of the dose-treatment parameter dependency, and the discreteness of the decision space for treatment parameters may significantly raise the complexity level of the planning problem. The minmax optimization of the dwell-time sequence of a stepping train of seeds is formulated as a linear program which offers great numerical convenience.

The technique is applied to planning for intravascular brachytherapy. Unlike methods that are based on optimizing the radiation time for a single train of seeds, our approach allows for adjustment of dwell times in accordance with variations in the vessel diameter, hence delivering more desirable dose distributions. Numerical experience with ultrasound-based treatment planning on a 36 mm long coronary lesion indicates significant improvement of the worst deviation from the prescribed dose bounds relative to the single train of seed strategy followed in, for example, the Scripps trial. The drawback of a stepping train strategy is longer radiation times. Nevertheless, increasing the air kerma strength, improving the geometry of the commercially available seeds and designing novel delivery systems (which are active areas of academic and industrial research) will reduce the total radiation times of the optimal strategy to the range of clinically desirable radiation times (<10 min). Post-optimization analysis indicates that the minmax optimum in the multiple dwell-time case is desirable from a dose uniformity standpoint.

The clinical importance of these improved results is unknown and requires further investigation by the medical community. Similar to dosimetry planning of the Scripps trial, the lesion path is assumed to follow a straight line. This might not be true and a combination of treatment planning with reconstruction techniques to obtain the correct 3-D shape of the vessel poses an interesting direction for future studies.

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