MATHEMATICAL ASPECTS OF RADIATION THERAPY TREATMENT PLANNING: CONTINUOUS INVERSION VERSUS FULL DISCRETIZATION AND OPTIMIZATION VERSUS FEASIBILITY

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Abstract. A mathematical formulation of the radiation therapy problem consists of a pair of forward and inverse problems. The inverse problem is to determine external radiation beams, along with their locations, profiles, and intensities, that will provide a given dose distribution within the irradiated object. We discuss the inverse problem in its fully discretized formulation.

1. Introduction. This paper deals with radiation *teletherapy* where beams of penetrating radiation are directed at the lesion (tumor) from an external source. The other radiation delivery mode which involves direct implantation of radioactive sources inside the lesion, called *brachytherapy*, is not included in our discussion. Chapter 11 of the book by Censor and Zenios [9] and Brahme's special issue [6] and references therein, as well as the tutorial review of Altschuler, Censor, and Powlis [2], can be used as introductory material to this area.

Based on understanding of the physics and biology of the situation, there are two principal aspects of radiation teletherapy that call for mathematical modelling. The first is the calculation of the *radiation dose* which is a measure of the actual energy absorbed per unit mass everywhere in the irradiated tissue. In dose calculation, termed *dosimetry*, the relevant physical and biological characteristics of the irradiated object and the relevant information about the radiation source (geometry, physical nature, intensity, etc.) serve as input data. The result (output) of the calculation is a *dose function* whose values are the dose absorbed as a function of location inside the irradiated body.

The second aspect is the *mathematical inverse problem* of the first. In addition to all physical and biological parameters of the irradiated object we assume here that the relevant information about the capabilities and specifications of the available *treatment machine* (i.e., radiation source) is given. Based on medical diagnosis, knowledge, and experience, the physician prescribes a *desired dose function* to the case. The output of this problem should be a *radiation intensity function* whose values are the radiation intensity at the source as a function of source location, that would result in a dose function which is identical to the desired one. To be of practical value, this resulting radiation intensity function must be implementable, in a clinically acceptable form, on the available treatment machine.

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In what follows we discuss, from a mathematician's point of view, two main modelling dilemmas: (i) continuous inversion versus full discretization, and (ii) optimization versus feasibility.

Much of current *radiation therapy treatment planning* (RTTP) is still done in two dimensions where only a single plane through the center of the target is considered. RTTP is also still done mostly in a trial-and-error fashion by picking a machine setup that gives rise to a certain external radiation intensity field (function) and then using a forward-problem-solver software package to determine the resulting dose function, see Figure 1. If the discrepancy between this dose function and the prescribed dose function is unacceptable then some changes are made to the machine setup and the process is repeated until the physician and dosimetrist are satisfied with the resulting dose function. Only then actual patient treatment is performed.

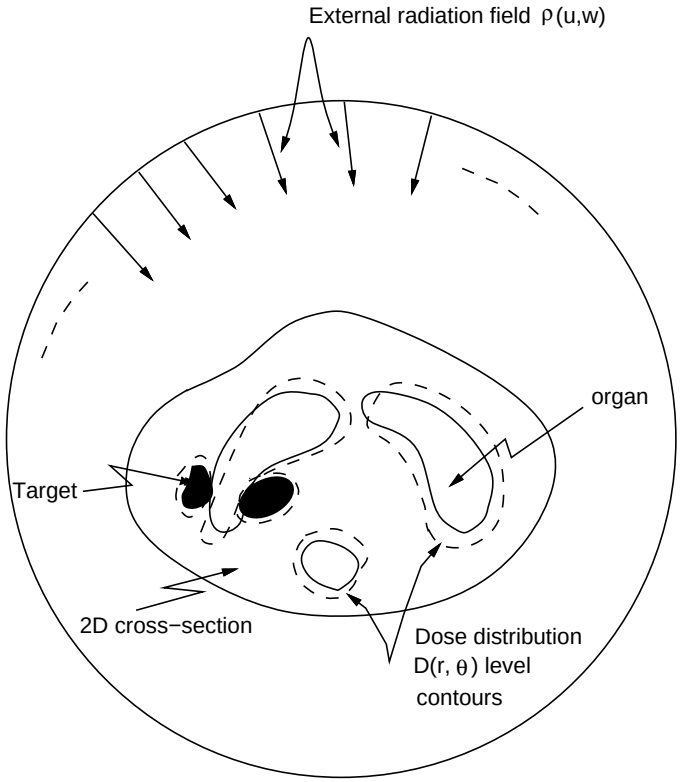

FIG. 1. *2D–RTTP, an external radiation field $\rho(u, w)$ results in a dose distribution $D(r, \theta)$.*

Such 2D–RTTP has achieved success due to accumulated experience and also because of the ever increasing quality and speed of forward-problem-solvers.

Automated solution of the inverse problem of RTTP should be useful in handling difficult planning cases, particularly in 3D–RTTP, see Figure 2. There, it would be much more difficult to reach an acceptable plan by trial-and-error because of the multitude of potential directions from which the 3D object can be irradiated. Nonetheless, even a 2D discussion, as given here, is enough to expose the nature of the dilemmas that we consider.

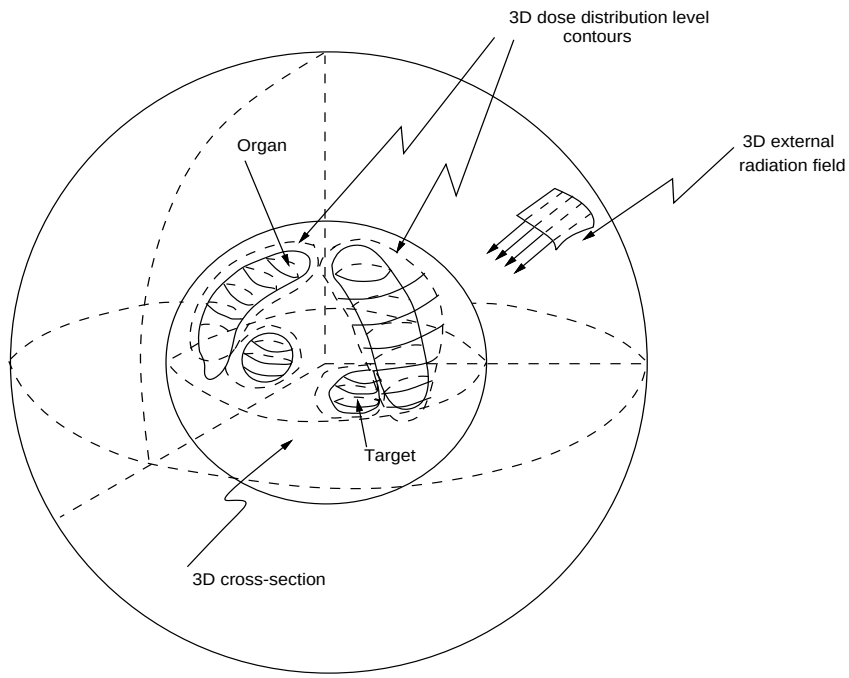

FIG. 2. *3D–RTTP, fully 3D cross section, external radiation field and dose distribution.*

In addition to the references given in the sequel we recommend also Mackie et al. [16], Raphael [18], Webb [19], and Xing and Chen [20].

2. Problem definition and the continuous model. Let $D(r, \theta)$ be a real-valued nonnegative function, of the polar coordinates r and θ, whose value is the dose absorbed at a point in the patient's planar cross-section coincident with the plane of the machine's gantry motion. This is the *dose function*, or dose distribution. A *ray* is a directed line along which radiated energy travels away from the *source*, i.e., the *teletherapy source*. Rays are parametrized by variables u and w in some well-defined way and the real-valued nonnegative function $\rho(u, w)$ represents the *radiation intensity* along the ray (u, w) due to a point source on the gantry circle. The continuous forward problem of RTTP is the following. Assume that the cross section Ω of the patient and its radiation absorption characteristics are known. Given

a radiation intensity function $\rho(u,w)$ for $0 \le u < 2\pi$ and $-W \le w \le W$, find the dose function $D(r,\theta)$ for all $(r,\theta) \in \Omega$ from the formula

$$D(r,\theta) = \Delta[\rho(u,w)](r,\theta), \tag{2.1}$$

where Δ is the *dose operator*. This operator relates the dose function to the radiation intensity function. See, e.g., [8] or [9, Chapter 11], for a description of the specific coordinate system.

In other words, the forward problem amounts to the calculation of the total dose absorbed at each point of a patient section when all parameters of each radiation beam are specified and the description of the patient section is known. The difficulties associated with the forward problem stem from the fact that there exists no closed-form analytic representation of the dose operator Δ that will enable us to use equation (2.1) for the calculation of $D(r,\theta)$. Although the interaction between radiation and tissue is measured and understood at the atomic level, the situation is so complex that, to solve the forward problem in practice, a good state-of-the-art computer program, which represents a *computational approximation* of the operator Δ and which enables reasonably good dose calculations, must be used.

Let us elaborate on what we mean by stating "there exists no close-form analytic representation of the dose operator Δ." We actually mean the following: If drastically simplifying assumptions are made about the physics of the model as well as the particulars of the desired dose distribution, then it is sometimes possible to express the dose operator in a closed-form analytic formula. This has been done first by Brahme, Roos and Lax [4] and extended by Cormack and co-workers, consult the review paper of Cormack and Quinto [12] for further references. See also Brahme's recent review [5] and Goitein's editorial [13].

In current practice of RTTP, when dose calculations are performed to verify the dose that will result from a proposed treatment plan, the goal is to obtain results that are as accurate as possible. To achieve this, various empirical data, which are often condensed in look-up tables, are incorporated into the forward calculation. Thus, the true forward calculation, or true dose operator, is not represented by a closed-form analytic relation between the radiation intensity function $\rho(u,w)$ and the dose function $D(r,\theta)$, but by a software package that calculates $D(r,\theta)$ from $\rho(u,w)$. Thus, what we really mean by saying that there is no closed-form analytic expression for Δ is that we choose to adhere to the software representation rather than compromise by allowing simplifying assumptions that might lead to a closed-form analytic mathematical formula.

The *inverse problem* of radiation therapy is the treatment planning problem:

Given a description of the patient section, the dose prescribed for the target, and the maximum permissible doses to the target, critical organs, and other tissues, calculate the external configuration and relative inten-

sities of radiation sources (i.e., the radiation field) that will deliver the specified radiation doses (or some acceptable approximation thereof).

Assuming that the cross section Ω of the patient and its radiation absorption characteristics are known, and given a prescribed dose function $D(r,\theta)$, the problem is to find a radiation intensity function $\rho(u,w)$ such that equation (2.1) holds, or $\rho(u,w) = \Delta^{-1}[D(r,\theta)]$ where Δ^{-1} is the inverse operator of Δ. This is the inversion problem that we want to solve, in a computationally tractable way, although no closed-form analytic mathematical representation is available for the dose operator Δ. The dose at (r,θ) is the sum of the dose contributions from the sources at all the different gantry angles. Thus

$$D(r,\theta) = \sum_{i=1}^{S} y_i D_i(r,\theta), \tag{2.2}$$

where, for each $i = 1,2,\ldots,S$, the value $D_i(r,\theta)$ is the dose deposited at point (r,θ) by a beam of unit intensity from the ith source, and y_i is the time the ith beam is kept on.

It will be assumed here that the dose $D_i(r,\theta)$ can be calculated accurately once the beam parameters and patient section information are specified. That is, we assume that we can solve the forward problem and calculate $D(r,\theta)$ accurately from (2.2). This assumption is confirmed by innumerable direct measurements in water and tissue-equivalent phantoms.

Whereas a dose distribution that solves the forward problem is always obtained for a specified radiation intensity field, the inverse problem may have no solution at all, since some prescribed dose functions may be unobtainable from any radiation field.

3. Discretization of the problem. In the approach presented here, we adhere to the computerized calculation of the dose operator Δ. Full discretization of the problem at the outset is used to circumvent the difficulties associated with the inversion of Δ. We also neglect the effect of scatter. The patient's cross section Ω is discretized into a grid of points represented by $\{(r_j,\theta_j) \mid j = 1,2,\ldots,J\}$. Define $\Delta_j[\rho]$ by

$$\Delta_j[\rho] = [\Delta\rho](r_j,\theta_j) \tag{3.1}$$

and call Δ_j a *dose functional*, for every $j = 1,2,\ldots,J$. Acting on a radiation intensity function $\rho(u,w)$, the functional Δ_j provides $\Delta_j[\rho]$, which is the dose absorbed at the jth grid point of the patient's cross section Ω due to the radiation intensity field ρ.

In continuing the discretization process of the problem it is assumed that a set of I *basis radiation intensity fields* is fixed and that their nonnegative linear combinations can give adequate approximations to any radiation intensity field we wish to specify. This is done by discretizing the

region $0 \le u < 2\pi$, $-W \le w \le W$ in the (u,w)-plane into a grid of points given by $\{(u_i, w_i) \mid i = 1, 2, \ldots, I\}$. A radiation intensity function

$$\sigma_i(u,w) = \begin{cases} 1, & \text{if } (u,w) = (u_i, w_i), \\ 0, & \text{otherwise,} \end{cases} \tag{3.2}$$

is a *unit intensity ray* and serves as a member of the set of basis intensity fields, $i = 1, 2, \ldots, I$. A desired radiation intensity function ρ that solves the inverse problem is approximated by

$$\widehat{\rho}(u,w) = \sum_{i=1}^{I} x_i \sigma_i(u,w), \tag{3.3}$$

where x_i is the intensity of the ith ray, and it is required that $x_i \ge 0$, for all $i = 1, 2, \ldots, I$. Once the grid points are fixed, any radiation intensity function $\widehat{\rho}$ that can be presented as a nonnegative linear combination of the rays is uniquely determined by the coefficients x_i, $1 \le i \le I$. The vector $x = (x_i)$, in the I-dimensional Euclidean space $\mathbb{R}^I$, is referred to as the *radiation vector* or *basic solution*.

Further, assume that the dose functionals Δ_j are linear and continuous. This assumption cannot be mathematically verified due to the absence of an analytic representation of Δ or Δ_j, but it is a reasonable assumption based on the empirical knowledge of Δ_j. Using linearity and continuity of all Δ_j's, we can write $\Delta_j[\rho] \simeq \Delta_j[\widehat{\rho}] = \sum_{i=1}^{I} x_i \Delta_j[\sigma_i]$. For $j = 1, 2, \ldots, J$, and $i = 1, 2, \ldots, I$, denote by

$$a_{ij} = \Delta_j[\sigma_i] \tag{3.4}$$

the dose deposited at the jth point (r_j, θ_j) in the patient's cross section Ω due to a unit intensity ray $\sigma_i(u,w)$. The *fully discretized inverse problem* of RTTP then becomes to find a radiation vector $x \in \mathbb{R}^I$ such that

$$A^T x = b\ , \quad x \ge 0\ , \tag{3.5}$$

where $A = (a_{ij})$ is the $I \times J$ matrix with elements as in (3.4) and $b = (b_j) \in \mathbb{R}^J$ is the discretized desired dose vector.

This fully discretized model calls for the quantities a_{ij} which can be precalculated with any state-of-the-art forward-problem-solver. If the latter is beam-driven the apportionment of beam dose per unit intensity among all rays, into which the beam has been discretized, is necessary, see Censor, Altshuler and Powlis [8], Powlis et al. [17]. Numerous iterative techniques are available for the solution of (3.5), both in the consistent case, see, e.g., the recent review of Bauschke and Borwein [3], and the inconsistent case, e.g., Combettes [11], Byrne and Censor [7].

The tendency to make the discretization finer results in very large values of I and J. As long as the available treatment machines cannot deliver such finely discretized radiation intensity fields, we need an additional computational step after a solution vector x^* (or approximation thereof) of the system (3.5) has been obtained. This is a "consolidation" step in which a clinically acceptable machine setup, usually at few (up to 5–6) beam positions, is derived from the fully discretized solution vector x^*, see [17]. To sum up, the fully discretized model is not difficulties-free, but it offers a route of circumventing the inversion problem of the computational dose operator Δ without compromising on any of the heuristics and empiricism involved in it.

4. Optimization versus feasibility.

4.1. Feasibility. The *feasibility formulation* relaxes the equality (2.1). Let $\overline{D} = \overline{D}(r,\theta)$ and $\underline{D} = \underline{D}(r,\theta)$ be two dose functions whose values represent upper and lower bounds, respectively, on the permitted and required dose inside the patient's cross section. A radiation therapist defines $\overline{D}$ and $\underline{D}$ for each given case and will accept as a solution to the RTTP problem any radiation intensity function $\rho(u,w)$ that satisfies

$$\underline{D}(r,\theta) \le \Delta[\rho(u,w)](r,\theta) \le \overline{D}(r,\theta), \quad \text{for all} \quad (r,\theta) \in \Omega. \tag{4.1}$$

In target regions (tumors) the lower bound $\underline{D}$ is usually the important factor because the dose there should exceed some given value. In critical organs and other healthy tissues $\underline{D}(r,\theta) = 0$, so that $\overline{D}(r,\theta)$ is the dose that cannot be exceeded. Any solution $\rho(u,w)$ that fulfills (4.1), for given $\overline{D}$ and $\underline{D}$, is a *feasible solution* to the RTTP problem. In order to discretize (4.1) we must specify the dose functions $\overline{D}$ and $\underline{D}$ at the grid points by giving, for all $j = 1,2,\ldots,J$,

$$\overline{D}(r_j,\theta_j) = \overline{D}_j, \qquad \underline{D}(r_j,\theta_j) = \underline{D}_j, \tag{4.2}$$

thus converting (4.1) into a finite system of *interval inequalities*

$$\underline{D}_j \le \Delta_j[\rho] \le \overline{D}_j, \qquad j = 1,2,\ldots,J. \tag{4.3}$$

Denoting hereafter by $\overline{D}$ ($\underline{D}$) the J-dimensional column vector whose jth element is $\overline{D}_j$ ($\underline{D}_j$), the inverse problem of RTTP is restated as follows:

Given vectors $\overline{D}$ and $\underline{D}$ of permitted and required doses at J grid points in the patient's cross section Ω, find a radiation intensity distribution $\rho = \rho(u,w)$ such that (4.3) holds. The *fully discretized feasibility inverse problem* of RTTP then becomes the linear interval feasibility problem of finding a vector $x \in \mathbb{R}^I$ such that

$$\begin{aligned} \underline{D}_j \le \sum_{i=1}^{I} x_i d_{ij} \le \overline{D}_j, &\quad j = 1,2,\ldots,J, \\ x_i \ge 0, &\quad i = 1,2,\ldots,I. \end{aligned} \tag{4.4}$$

Let the set of pixels in the discretized patient cross section be denoted by $N = \{1, 2, \ldots, J\}$. Organs within the patient section are then defined as subsets of N. The subsets $B_k \subset N$, where $k = 1, 2, \ldots, K$ denote K critical organs to be spared from excessive radiation. Let the values b_k denote the corresponding upper bounds on the dose permitted in each critical organ. The subsets $T_q \subset N$, where $q = 1, 2, \ldots, Q$, denote Q target regions. Let the values t_q denote the corresponding prescribed lower bounds for the absorbed dose in each. All the B_k and T_q are pairwise disjoint. The set of pixels inside the patient section that are not in any B_k or T_q are called the *complement*, denoted as the subset $C \subset N$, and c is the upper bound for the total permitted dose there. It is assumed that the definition of all subsets B_k, T_k, and C and the prescription of all b_k, t_q, and c are given by the radiotherapist as input data for the discretized treatment planning problem.

Problem (4.4) then becomes the following system of linear inequalities, which we call the *basic model*:

$$\sum_{i=1}^{I} d_{ij} x_i \leq b_k, \quad \text{for all} \quad j \in B_k,\ k = 1, 2, \ldots, K, \tag{4.5}$$

$$t_q \leq \sum_{i=1}^{I} a_{ij} x_i, \quad \text{for all} \quad j \in T_q,\ q = 1, 2, \ldots, Q, \tag{4.6}$$

$$\sum_{i=1}^{I} a_{ij} x_i \leq c, \quad \text{for all} \quad j \in C, \tag{4.7}$$

$$x_i \geq 0, \quad \text{for all} \quad i = 1, 2, \ldots, I. \tag{4.8}$$

With b_k, t_q, and c given and the a_{ij}'s calculated from (3.4), the mathematical question represented by the basic model (4.5)–(4.8) is to find a nonnegative solution vector $x^* = (x_i^*)$ for a system of linear inequalities. The remarks about clinical acceptability of x^* from the end of the last section apply also here.

We first proposed this fully discretized feasibility inverse problem in Altschuler and Censor [1], see also [9, Section 11.7] for a brief review of other approaches and references.

4.2. Optimization. When it comes to discussing an optimization approach to RTTP we must distinguish between two different kinds of optimization problems depending on the space in which they are formulated. One possibility is to define an objective function $f : \mathbb{R}^I \to \mathbb{R}$, i.e., over the space of radiation intensity vectors x and use either the system (3.5)

or the constraints (4.5)–(4.8) as the feasible set. For example, choosing $f(x) = \frac{1}{2}\|x\|^2$ ($\|\cdot\|$ stands for the Euclidean norm) and solving a minimization problem will lead to a minimum-norm solution vector x^*. I.e., a feasible vector closest to the origin so that the total radiation intensity is smallest possible in the Euclidean norm sense. A special-purpose iterative minimization method such as Hildreth's algorithm, see, e.g., [9], applies in this case.

Regardless of the specific choice of f, in this approach the interval-constrained optimization problem

$$\begin{aligned} &\min f(x) \\ &\text{s.t.} \quad \alpha \leq A^T x \leq \beta, \\ &\qquad\quad x \geq 0, \end{aligned} \tag{4.9}$$

is still aiming at solution of the fully discretized formulation of the inverse problem. A solution vector x^* will represent a radiation field that will deliver a dose which is both feasible (i.e., adheres to the upper and lower doses imposed by the physician) and is optimal in the sense of the objective function f. This approach of optimization in the space of radiation intensity vectors will be called henceforth *radiation intensity optimization*.

The second possibility for introducing an optimization problem in RTTP is to use (3.5) or (4.5)–(4.8) as constraints but choose an objective function $g : \mathbb{R}^J \to \mathbb{R}$ defined over the space of dose vectors. Such objective functions may be either *biological*, or *physical*. Biological objective functions represent knowledge (statistical or other) about various biological mechanisms that affect our ability to control the disease. An example is the conditional probability of having tumor control without severe injury, denoted in RTTP literature by P_+. Physical objective functions aggregate physical features which are important for tumor control and prevention of normal tissue complications, such as dose variance over target volume or peak dose to organs at risk. A thorough discussion of biological and physical objective functions can be found in Brahme [5]. Let us call this kind of optimization, over the space of dose vectors, *dose optimization*.

5. Discussion. The trade-off between the continuous model and full discretization has already been explained in Section 3. Brahme reaches also a conclusion in favor of full discretization and says [5, p. 216]: "... In either case it is very useful to transform the relevant integral equation into an algebraic form by discretizing the transport quantities along the coordinates of the free variables."

The question of feasibility versus optimization is not crucial if only radiation intensity optimization (as defined above) is considered. This is so because both the feasibility formulation and the optimization formulation (regardless of the particular choice of the objective function $f(x)$) occur in the same space (of radiation intensity vectors) and, thus, aim at a solution

of the discretized inverse problem. Therefore, the difference between these two formulations is, from the mathematical point of view, only technical. Recently, Cho et al. [10] reported on the advantage of the feasibility approach over a global optimization model solved by simulated annealing. In contrast, the dose optimization (as defined above) approach leads to a problem of the form

$$\begin{aligned} &\min g(A^T x) \\ &\text{s.t.} \quad \alpha \leq A^T x \leq \beta, \\ &\qquad\qquad x \geq 0. \end{aligned} \tag{5.1}$$

If a set of dose vectors $b^\ell \in \mathbb{R}^J$, for $\ell = 1, 2, \ldots, L$, each of which represents a deliverable treatment plan, are given, then the values of a biological or physical dose objective function $g(b^\ell)$ can be calculated for each and compared. Choosing the plan with lowest $g(b^\ell)$ in such circumstances means that we are merely doing a comparison (among rival plans) which are given (i.e., constructed in some way prior to the comparison).

In case when the composite function $g(A^T x)$ is simple enough (the approach of (5.1) can still be efficiently used for solving directly the (discretized) inverse problem in its full generality. Otherwise, the inversion problem has to be abandoned and the optimization can be performed with respect to only few parameters of the external radiation field. See, for example, Gustafsson [14] and Gustafsson, Lind and Brahme [15]. This is done while other important parameters are left out of the optimization problem and must be given as input to the process, see also the discussion in [9, Section 11.7].

The question whether to adhere to the mathematical inverse problem (and possibly confront a difficulty when translating a radiation intensity solution vector x^* into an implementable and clinically acceptable treatment plan) or to use biological or physical objective functions in the space of dose vectors (and thereby possibly compromise on the full generality of the inverse problem)—remains unsettled.

Acknowledgements. The author gratefully acknowledges useful discussions with Martin Altschuler, Gabor Herman, William Powlis, and the comments of Christopher Borgers on an earlier version of the paper. Part of the material presented here appears in [9, Chapter 11]. This work was partially supported by NIH grant HL–28438 at the Medical Image Processing Group (MIPG), Department of Radiology, University of Pennsylvania, Philadelphia, PA, USA, and by the Israeli Science Foundation founded by The Israel Academy of Sciences and Humanities. The work of Ms. Patricia Brick and her team at IMA in preparing this manuscript in Tex is greatly appreciated.

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