# Linear and Nonlinear Models and Algorithms in Intensity-Modulated Radiation Therapy (IMRT)

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IMRT, abbreviating Intensity-Modulated Radiation Therapy, refers to a method of introducing spatial variation in the intensity (analogous to flow) of radiation directed across a beam front based on desired objectives concerning the resulting dose distribution within the body. Dose, like temperature, is a quantity that can be attached to each point of an irradiated body. The distribution of dose over critical organs and tumor targets bears a relation, albeit imperfect, to end-goals such as rates of complication and cure. The principles underlying the new IMRT approach are that treatment parameters (such as machine settings) can be arranged to yield an intensity map for each incident beam, that an accurate dose distribution can be determined from knowledge of all the beam intensity maps, and that some dose distributions are preferred over others.

Linearity enters because the contributed dose is a linear combination of the intensities carried by the infinitesimally small elements of the beam; of course, the actual units into which the beam front is decomposed and to which intensities are to be assigned may only approximate the notion of infinitesimally small. Many real problems of interest to readers of this journal emerge from these concepts.

Three-Dimensional Conformal Radiation Therapy (3DCRT), the precursor of IMRT, used a few (generally about two to six) fields with uniform or uniformly-changing unmodulated intensity to irradiate a target in a patient's body. Each field defined a direction and aperture through which the beam was directed, with the aperture almost always conforming to the projection of the target onto the beam-front. IMRT is the result of convergence of two relatively simultaneous developments. One was the integration of computer algorithms with dose calculation software to manage more complex treatment plans comprising more treatment fields over which intensity could be varied. These algorithms worked in the backward direction relative to traditional techniques. That is, they started with a desired dose distribution and worked toward fields that aimed at producing that distribution. This was called "solving the inverse problem." The other development was the proliferation of mechanical techniques for delivering these complex treatment plans.

These techniques became widely-adopted with the introduction of the multileaf collimator (MLC) that transacted a field into smaller units whose exposure could be selectively changed by applying stepped or continuous mechanical movements to a paired stack of narrow blocks. An intensity map could be generated by composing a weighted sum of the apertures corresponding to the openings created by the gap between the block pairs. The weights were equivalent to the lengths of times that the beam was directed through each aperture. Alternatives either available or currently under consideration include binary collimators coupled to a couch carrying the body that is moved in a stepped or continuous fashion, fixed or moving radiation attenuators of varying caliber, superimposed sets of rotating beams, scanned spot beams, or narrow beams whose spatial movement is controlled. Thus, the idea of confining our search for useful treatment fields to the ones that conformed to the silhouette of the target (the 3DCRT approach) gave way to including a much larger number of fields, divided into discrete segments or even continuously deforming apertures that might irradiate only portion of the target volume at a time. This departure produced exciting results in terms of the achievable dose distributions. The dose distributions were dramatically different because they could reduce the dose delivered to defined regions of healthy tissues that were near the target tissues.

The *inverse problem* of IMRT is to produce a useful set of intensity maps given a statement of desired end-goals in the dose distribution. These end-goals need not to be given in terms of the dose assigned to each point in the body, but rather are usually phrased in terms of aggregate functions such as maximum dose in an organ, minimum dose, volume receiving above or below a threshold value, dose homogeneity, or potentially nonlinear functions of the distribution (e.g., a weighted geometric mean); the statements may be in the form of hard or soft constraints, a formal objective function, multiple objectives, and may be supplemented by requirements for robustness to uncertainty.

Another class of problems, that can be labeled *delivery*, is to construct an arrangement of treatment elements (such as the leaves of the multileaf collimator (MLC)) that will realize the intensity maps in a practical way. Many problems of this sort can be formed depending on how "practical" is defined (e.g., number of treatment elements, number of element changes, expenditures of radiation or real time, etc.) and on whether one seeks a delivery scheme based on an input of desired intensity values computed from the dose objectives or upon an input of desired dose objectives directly.

A third kind of problems could be called problems of *specification*. These concern the process by which physician preferences are translated into formal problem statements. They also involve the quality of the generated solution is presented to the physician; issues of feasibility, multiobjective handling, determinacy, degeneracy, choice ranking, admissibility (of constraint violations or objective shortfalls) enter into discussion. Yet another set of problems concerns *presentation*, encompassing questions of how trade-offs are to be determined and exhibited, the manner in which decision makers can explore trade-offs, and the ease by which the decision maker can recognize violations or shortfalls, and the options available in response.

The answers to these questions have immediate important practical ramifications. Radiation treatments, alone or in conjunction with surgery, are used in about one half of cancer patients (i.e., about 600,000 cases per year in the US alone), nearly always with the aim of eradicating disease within a geometrically-defined region of the body. The basic issue with using radiation generated from a machine placed outside the body is that the beam paths traverse normal tissue as they pass through the tumor. The goal of increasing the dose to regions that harbor tumor cells must be balanced against the need to maintain a dose that can be tolerated by the surrounding healthy structures. Changes in dose of about 10% in magnitude, or a few millimeters in position can precipitate unacceptable complications, while for tumors controlled about half the time, each 1% increment in dose improves the likelihood of sterilization by about 1.5%. Twenty five years have passed since IMRT was invented, and it seems that progress is made in IMRT at an ever increasing pace, see, e.g., Ahnesjö et al. [1], Bortfeld [3], Palta and Mackie [4] and Webb [5].

A new generation of problems is emerging with the advent of Image-Guided Radiotherapy (IGRT), that supplies information concerning changes in anatomy that occur over the treatment course or even over the treatment session, see, e.g., Bortfeld et al. [2]. In principle, it enables treatment design decisions to be made over time as well as space, a process that has come to be known as *4D-radiotherapy*.

The topics discussed in this volume lay the foundation for a rising network of problems that promise to be mathematically challenging, medically important, and intricate in nature. They connect with recognized subjects in network design, decomposition theory, analytic and algebraic inversions, and combinatorial geometry. They pose theoretic challenges for algorithm engineers, with results testable over wide populations. This increasingly leads to the involvement of applied mathematicians, optimization theory experts and operations research scientists in the efforts to advance the field. We hope that this special issue will stimulate interest in these topics drawn from radiation planning, form new ways of thinking about old problems, and open up alliances between the mathematics, physics, and medical communities.

This issue contains a collection of peer-reviewed research papers which constitutes a snapshot of some of the current research that is being conducted in this field. The versatility of the contributions testifies to the continued interest in the interface between mathematics and IMRT. In compiling this special issue we were privileged to receive excellent submissions and to have the assistance of expert referees. We are grateful to all those who helped us.

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