1
Introduction

The goal in external beam radiotherapy (see Figure 1.1) for cancer is to kill the tumor while limiting toxic effects of radiation on nearby organ(s)-at-risk (OAR). At least three avenues can be pursued to attain this goal: spatial localization of radiation dose (energy per unit mass); temporal dispersion of radiation dose; and selection of an appropriate radiation modality to administer the dose.

In spatial localization, a high dose is prescribed to the tumor, while upper limits are recommended on doses to the OAR. The fluence-map optimization problem then seeks a radiation intensity profile that meets this protocol as closely as possible. Modern technology such as intensity-modulated radiation therapy (IMRT) can be employed to deliver the resulting optimal intensity profile. See Figure 1.2.

Healthy cells are better at recovering from radiation damage than tumor cells. Thus, the planned total dose is administered over multiple treatment sessions. This is called fractionation, and it gives healthy cells some time to recover between sessions, thereby reducing the overall toxic effect. This might suggest that the larger the number of sessions, the better. However, the tumor can grow over the treatment course, and thus it is crucial to eliminate viable tumor cells with a short course. Moreover, in some cases, a short course could be more effective, even without tumor proliferation, because the tumor's response to radiation is similar to that of a nearby OAR. Treatment planners are thus interested in finding an optimal number of treatment sessions and also the dose in each session. This is called the optimal fractionation problem. The differences between the radiobiological response of the tumor and various OAR are at the heart of this temporal problem. See Figure 1.3.

Radiotherapy can be administered via different modalities such as photons and protons. The choice of a modality may depend on the cancer anatomy;

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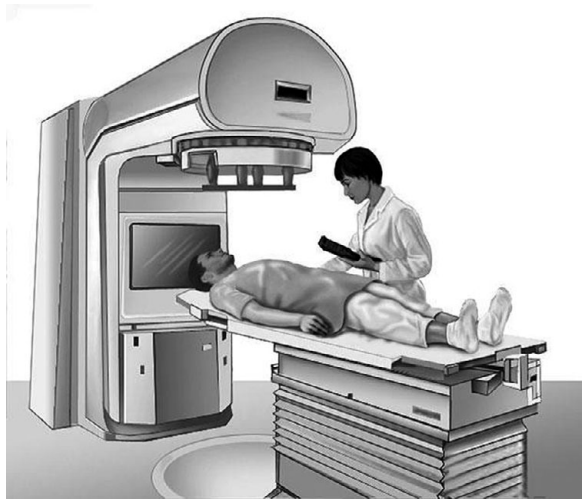

Figure 1.1 A linear accelerator machine for external beam radiotherapy. Radiation beams emerge from the top of the machine and pass through the patient's body. Source: National Cancer Institute, www.cancer.gov/about-cancer/treatment/types/radiation-therapy/external-beam and https://visualsonline.cancer.gov/details.cfm?imageid=9413. Reused per policy available at www.cancer.gov/policies/copyright-reuse.

physical properties, such as the so-called dose-deposition profile, of the modalities (see Figure 1.4); biological properties, such as the relative dose sensitivities of the tumor and OAR to these modalities; and the capital investment or operating cost of administering treatment with these modalities. A modality that is superior from one perspective under certain disease conditions may be inferior under different disease conditions or from a different perspective. As such, there is no universally dominant modality. These trade-offs between modalities are further complicated when a treatment planner attempts to determine the number of treatment sessions and the doses that should be administered via each available modality. This can be viewed as optimal fractionation with multiple modalities.

This monograph describes mathematical optimization models and solution methods for the fractionation problem with one and two modalities. All optimization models in this monograph are based on the linear-quadratic (LQ) framework of dose response. According to this framework, the damage caused by radiation to the tumor or an OAR is modeled using two components. The first component is linear in dose whereas the second is quadratic in dose. Tumor proliferation is modeled using a separate, third component that

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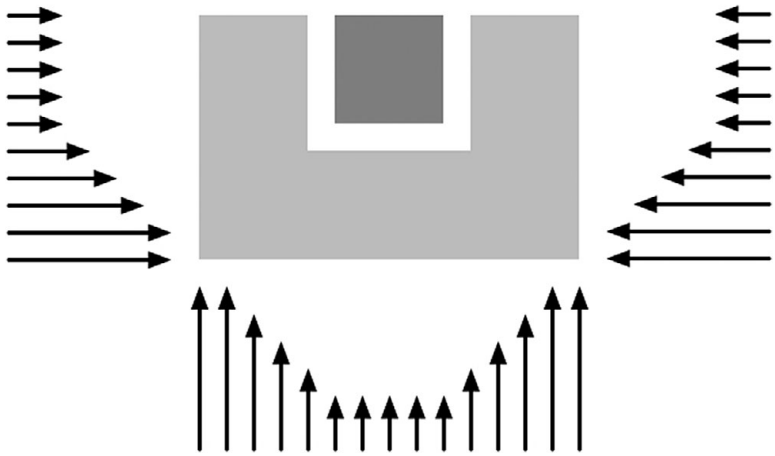

Figure 1.2 The fluence-map problem seeks a radiation intensity profile (black arrows) that administers a high dose to the tumor (light gray U shape) and a low dose to the OAR (dark gray square). The lengths of the arrows represent radiation intensity. Radiation beams from multiple directions (three here) are employed to ensure that all parts of the tumor receive sufficient dose.

depends on the length of the treatment course. According to this framework, the surviving fraction of tumor cells is modeled as

$$\exp\left(-\alpha_0 \sum_{t=1}^{N} d_t - \beta_0 \sum_{t=1}^{N} (d_t)^2 + \tau(N)\right). \tag{1.1}$$

Here, d_t is the dose administered to the tumor in session t; N is the number of sessions; $\alpha_0 > 0$ and $\beta_0 > 0$ are parameters; and $\tau(N)$ is the proliferation term that depends on the number of sessions N. This LQ dose-response model is simple and has been validated with data. It is commonly employed for calculating and comparing effects of competing dosing plans. This monograph relies on the simplicity of this framework to derive insights into solutions of various optimization models via an interplay between algebra, geometry, and calculus.

Chapters 2–5 assume that a radiation intensity profile is determined a priori; the decision-maker only needs to decide how to disperse the resulting total dose across treatment sessions. This can be viewed as spatiotemporally separated fractionation, and the corresponding optimization problems can be solved exactly. This could be suboptimal as compared to simultaneously determining both the intensity profile and the dose dispersion plan. This

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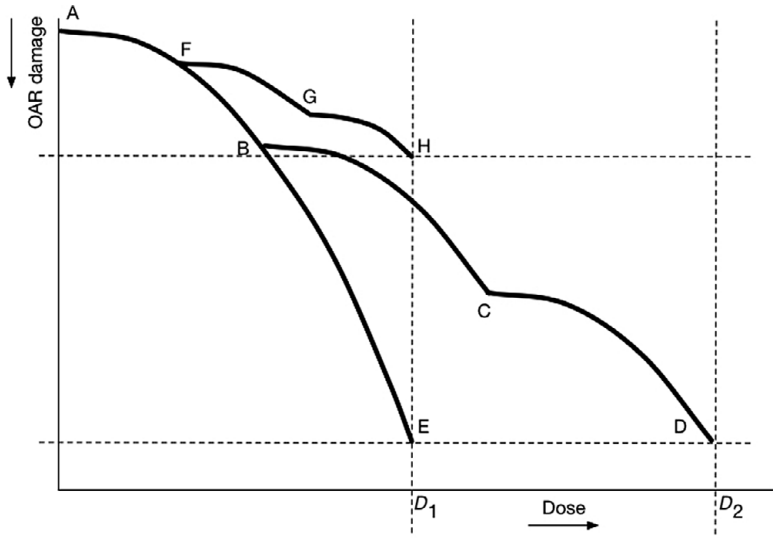

Figure 1.3 The damage to the OAR depends on how the total radiation dose is dispersed across multiple treatment sessions. A total dose of D_1 in a single session (curve AE) causes the same damage as a larger total dose of D_2 if it is broken into three sessions (curves AB–BC–CD). Similarly, if the total dose of D_1 is broken into three sessions (curves AF–FG–GH), the damage to the OAR is less than administering D_1 in a single session. Similar curves can also be sketched for the tumor, and the differences between the OAR curves and the tumor curves introduce trade-offs into the optimal fractionation problem. Adapted with permission from [59, Figure 3].

latter, computationally more demanding, approach is termed spatiotemporally integrated fractionation. Chapters 6 and 7 describe mathematical models and approximate solution methods to compute the number of sessions and the intensity profiles in each session for spatiotemporally integrated fractionation. Chapters 8 and 9 describe spatiotemporally separated mathematical models and exact solution methods for optimal fractionation with two modalities. The monograph concludes by outlining directions for future research in Chapter 10.

A comment on terminology: we use increasing to mean nondecreasing and use decreasing to mean nonincreasing throughout. The terms strictly increasing and strictly decreasing are used rarely, only when absolutely necessary. Notation such as $t = 1 : N$ is short for the more familiar form $t = 1, 2, \ldots, N$.

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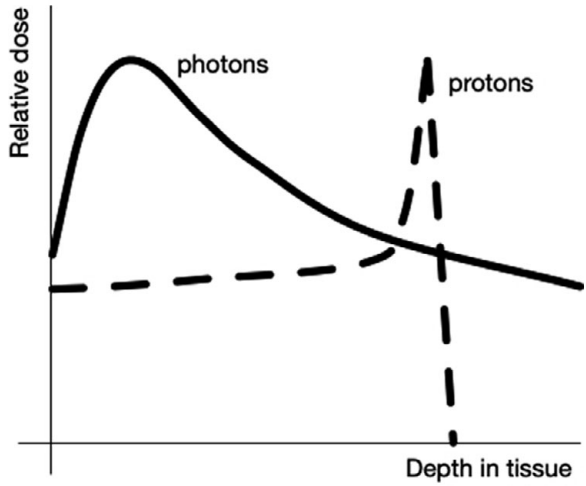

Figure 1.4 A rough schematic of the relative radiation dose deposited as a function of the distance traveled inside a tissue. This is called a dose-deposition profile. The sharp spike in the proton profile is called the Bragg peak. Reused with permission from [61, figure 4].

Bibliographic Notes

Information about IMRT is available in [89, 128]. IMRT is considered by some to be one of the most successful developments in radiation oncology [33]. Others have expressed concerns about its merits. A discussion about the benefits offered and challenges posed by IMRT is included in section 1A of [128], in a point-counterpoint format. Sophisticated models and solution algorithms for fluence-map optimization have been developed over the last three decades [9, 28, 34, 41, 42, 62, 98, 99, 110, 118, 128, 136]. The optimal fractionation problem has a hundred-year history in the clinical literature [3, 10, 16, 20, 54, 58, 68, 69, 70, 85, 97, 100, 120, 134]. Mathematical models of this problem almost exclusively utilize the LQ framework of dose response. A textbook description of the LQ framework and illustrations similar to Figure 1.3 are available, for example, in [65]. The LQ framework was proposed at least as early as the 1940s [83] and has been reviewed repeatedly over the last several decades [24, 35, 46, 52, 73, 94, 106, 111, 119, 124, 130]. Several favorable properties of the LQ framework are listed in [24], stating that "it is reasonably well validated, experimentally and theoretically ...." Estimated values of the

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parameters in the LQ framework have also been reported [57, 121, 124, 132]. Nevertheless, questions have been raised about its appropriateness for clinical decision-making [26, 80, 137]. An illuminating account of the history; clinical applicability; usage; mechanistic, empirical, and mathematical underpinnings; and concerns about the validity of the LQ framework is available in [86]. This monograph does not take any position on the appropriateness of the LQ framework. It simply provides various mathematical formulations and corresponding solutions of the fractionation problem to guide decision-makers who may wish to utilize the LQ framework. Discussions of the pros and cons of various competing modalities for external beam radiotherapy are included in [38, 40, 64, 66, 67, 125]. Scientifically accurate versions, drawn to scale based on real data/analytical calculations/simulations, of the rough schematic in Figure 1.4 are available, for example, in [27, 66, 81]. These publications also include a technical description of the Bragg peak.