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# A two-variable linear program solves the standard linear–quadratic formulation of the fractionation problem in cancer radiotherapy

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ABSTRACT

The standard formulation of the fractionation problem with multiple organs-at-risk based on the linear–quadratic dose–response model requires the solution of a nonconvex quadratically constrained quadratic program. Existing literature therefore uses heuristic methods without any analyses about solution quality. There is no known method that is guaranteed to find an optimal solution. We prove that this formulation of the fractionation problem can in fact be solved to optimality by instead solving a two-variable linear program with a few constraints.



## 1. Background and motivation

The goal in cancer radiotherapy is to maximize damage to the tumor while limiting toxic effects of radiation on nearby organs-at-risk (OAR). The fractionation problem attempts to achieve this goal by finding a damage-maximizing sequence $\vec{d} = (d_1, d_2, \ldots, d_N)$ of radiation doses given to the tumor in $N$ treatment sessions while ensuring that the corresponding doses given to the nearby OAR are safely tolerable. This problem has been studied extensively for over a century [13].

A majority of mathematical research on the fractionation problem has considered a single OAR, and in this stylized case, an optimal solution is known in closed-form (see, for example, [3–5,7,12,15] and references therein). However, as essentially all tumors are surrounded by multiple OAR, the focus has recently shifted to this more realistic and difficult case where the problem has the following form (see [2,14,16,18], for instance).

$$\text{(OPTFRAC)} \quad \max_{\vec{d}} \ \alpha_0 \sum_{t=1}^{N} d_t + \beta_0 \sum_{t=1}^{N} d_t^2, \tag{1}$$

$$\text{subject to } s_m \sum_{t=1}^{N} d_t + \rho_m s_m^2 \sum_{t=1}^{N} (d_t)^2 \le \text{BED}_m, \quad m \in \mathcal{M}, \tag{2}$$

$$\vec{d} \ge 0. \tag{3}$$

This formulation is based on the linear–quadratic (LQ) framework, which is currently the most widely used model of dose–response [6]. Here, $\alpha_0$ and $\beta_0$ are the LQ dose–response parameters for the tumor. The objective function equals the biological effect of $\vec{d}$ on the tumor and it is a standard quantitative measure of tumor-damage [6]. The set $\mathcal{M} \triangleq \{1, 2, \ldots, M\}$ is the set of OAR under consideration. For OAR $m \in \mathcal{M}$, $\rho_m = \beta_m/\alpha_m$ is the ratio of its LQ dose–response parameters $\alpha_m$ and $\beta_m$. Parameter $s_m$ is the so-called effective sparing factor for OAR $m$ and it equals the proportion of tumor dose that is delivered to this OAR. The left hand side of the inequality constraint (2) for OAR $m \in \mathcal{M}$ is then the formula for the biologically effective dose (BED) delivered to OAR $m$ according to the LQ model [6]. The dose-tolerance parameters $\text{BED}_m$ are BED values that the various OAR are known to tolerate. These can be derived from standard treatment guidelines available in [11]. In summary, formulation (OPTFRAC) follows the standard approach of maximizing the biological effect on tumor subject to upper bound constraints on OAR BED.

The above formulation is general enough to include serial and parallel OAR with maximum dose, mean dose, and dose–volume type constraints. Formulas for effective sparing factors for OAR with maximum dose, mean dose, and dose–volume type constraints are available, for example, in [3,8,14,15]. In this paper, we do not consider the trivial case of $N = 1$, where (OPTFRAC) can be readily solved in closed-form. Typical values of $N$, and hence the number of variables in (OPTFRACT), are in the range 25–45 corresponding to a 5–9 week treatment course.

Formulation (1)–(3) is a *nonconvex* quadratically constrained quadratic program (QCQP)—although the constraints are convex

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in $\vec{d}$, the objective is to *maximize* a convex function (this latter being the source of nonconvexity). Such problems are typically computationally difficult to solve, and in general belong to the class NP-hard [10]. A recurrent theme in the fractionation literature therefore is to use heuristic methods or to obtain optimal solutions for certain special cases. For example, simulated annealing is used in [18] for the case of two OAR; a local search heuristic is contemplated but not implemented in [16]; Karush–Kuhn–Tucker (KKT) conditions are employed to characterize somewhat complicated optimal solutions for the case of two OAR in [2]; and an exact solution is derived in [14] using either a tedious algebraic proof or a tedious KKT approach when problem parameters are ordered a certain way. There is no known method that is guaranteed to find an optimal solution in general. As such, problem (OPTFRAC) has thus remained unsolved.

## 2. Results

We show in Theorem 1 the perhaps surprising result that an optimal solution to (OPTFRAC) can in fact be derived in closed-form from the solution of a two-variable linear program (LP) with nonnegative variables and $M$ constraints. We emphasize here that since the number of constraints $M$ is equal to the number of OAR, this number is small. For example, we could have four OAR in head-and-neck cancer—spinal cord, brain stem, and left/right parotids. Similarly, in prostate cancer, we could have four OAR—left/right femurs, bladder, and rectum. From our experience in radiotherapy, it seems unlikely that $M$ would be more than ten or twenty. In short, our two-variable LP is easily solvable.

We first introduce additional notation. We define, as in the existing literature, the dose

$$b_m(N) \triangleq \frac{-1+\sqrt{1+4\rho_m \mathrm{BED}_m/N}}{2s_m\rho_m}, \quad m \in \mathcal{M}. \tag{4}$$

This is the largest possible dose that can be given in an equal-dosage schedule (that is, a schedule where $d_1 = d_2 = \cdots = d_N$) without violating inequality constraint (2) for OAR $m \in \mathcal{M}$. This dose is derived by solving the quadratic equation obtained by using $d_1 = d_2 = \cdots = d_N$ and then setting the left hand side in (2) equal to the right hand side for OAR $m \in \mathcal{M}$. We use $b_m(1)$ to denote the dose obtained by substituting $N = 1$ into formula (4); in other words, $b_m(1)$ is the largest possible dose that can be given in a single-dosage schedule (that is, a schedule where all doses except one are zero) without violating inequality constraint (2) for OAR $m \in \mathcal{M}$. Moreover, we define

$$\gamma^* = \min_{m\in\mathcal{M}} b_m(1), \quad \text{and} \quad c^* = \min_{m\in\mathcal{M}} b_m(N).$$

Here, $\gamma^*$ is the largest possible (hence optimal) dose in a single-dosage solution, whereas $c^*$ is the largest possible (hence optimal) dose per session in an equal-dosage solution. Note here that these optimal doses are obtained by finding the minimum over all OAR because an OAR that attains the minimum is a "dose-limiting" OAR and any higher dose will be infeasible.

We show below that an optimal solution to OPTFRAC can be derived in closed-form from an optimal solution of the two-variable LP

$$\text{(2VARLP)} \quad \max_{x,y} \ \alpha_0 x + \beta_0 y,$$

$$\text{subject to } s_m x + s_m^2 \rho_m y \le \mathrm{BED}_m, \quad m \in \mathcal{M},$$

$$y \le \gamma^* x, \tag{5}$$

$$c^* x \le y, \tag{6}$$

$$x \ge 0, \qquad y \ge 0.$$

(2VARLP) does indeed have an optimal solution because its feasible region is bounded. In the sequel, we use the phrase "unequal multiple-dosage" to mean any dosing schedule that is neither single-dosage nor equal-dosage. We then have,

**Theorem 1.** *Let $x^*, y^*$ be an optimal solution to* (2VARLP)*. Then exactly one of the following three situations must hold.*

1. *$x^* = \sqrt{y^*}$: it is optimal to set $d_t = \gamma^*$ in exactly one session $t$ and set the other $N-1$ doses $d_s$, for $s \neq t$, to zero; that is, a single-dosage solution is optimal.*
2. *$x^* = \sqrt{Ny^*}$: it is optimal to set $d_t = c^*$, for $t = 1, 2, \ldots, N$; that is, an equal-dosage solution is optimal.*
3. *$\sqrt{y^*} < x^* < \sqrt{Ny^*}$: we have an uncountable number of unequal multiple-dosage optimal solutions that satisfy $\sum_{t=1}^N d_t = x^*$, $\sum_{t=1}^N d_t^2 = y^*$, $d_t \ge 0$ for $t = 1, 2, \ldots, N$; for example, the two-dose solution where $d_3 = d_4 = \cdots = d_N = 0$, and*

$$d_1 = \frac{x^* + \sqrt{2y^* - (x^*)^2}}{2}, \qquad d_2 = x^* - d_1,$$

*is optimal.*

*Moreover, the above three conditions are necessary. That is,*

1. *Suppose a single-dosage solution is optimal. Then there exists a pair $(x^*, y^*)$ that is optimal to* (2VARLP) *such that $x^* = \sqrt{y^*}$.*
2. *Suppose an equal-dosage solution is optimal. Then there exists a pair $(x^*, y^*)$ that is optimal to* (2VARLP) *such that $x^* = \sqrt{Ny^*}$.*
3. *Suppose an unequal multiple-dosage solution is optimal. Then there exists a pair $(x^*, y^*)$ that is optimal to* (2VARLP) *such that $\sqrt{y^*} < x^* < \sqrt{Ny^*}$.*

**Proof.** We use the transformations $x = \sum_{t=1}^N d_t$ and $y = \sum_{t=1}^N d_t^2$ to reformulate (OPTFRAC) as

$$\max_{\vec{d},x,y} \ \alpha_0 x + \beta_0 y,$$

$$\text{subject to } s_m x + s_m^2 \rho_m y \le \mathrm{BED}_m, \ m \in \mathcal{M},$$

$$x = \sum_{t=1}^N d_t, \ y = \sum_{t=1}^N d_t^2, \ \vec{d} \ge 0, \tag{7}$$

$$x \ge 0, \ y \ge 0.$$

Since $\vec{d} \ge 0, x$ and $\sqrt{y}$ can be seen as the $l_1$ and $l_2$ norms of $\vec{d}$, respectively. Consequently, every $x, y, \vec{d}$ combination that is feasible to constraints (7) also satisfies the two inequalities $\sqrt{y} \le x \le \sqrt{Ny}$ (this is a well-known relationship between $l_1$ and $l_2$ norms). Thus, we first add these two inequalities to the above problem without altering its feasible region. This yields,

$$\max_{\vec{d},x,y} \ \alpha_0 x + \beta_0 y, \tag{8}$$

$$\text{subject to } s_m x + s_m^2 \rho_m y \le \mathrm{BED}_m, \ m \in \mathcal{M}, \tag{9}$$

$$x = \sum_{t=1}^N d_t, \ y = \sum_{t=1}^N d_t^2, \quad \vec{d} \ge 0, \tag{10}$$

$$\sqrt{y} \le x \le \sqrt{Ny}, \tag{11}$$

$$x \ge 0, \qquad y \ge 0. \tag{12}$$

We now claim that an optimal sequence of doses for (8)–(12) can be recovered from any optimal solution of

$$\max_{x,y} \ \alpha_0 x + \beta_0 y, \tag{13}$$

$$\text{subject to } s_m x + s_m^2 \rho_m y \le \mathrm{BED}_m, \quad m \in \mathcal{M} \tag{14}$$

$$\sqrt{y} \le x \le \sqrt{Ny}, \tag{15}$$

$$x \ge 0, \qquad y \ge 0. \tag{16}$$