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

Fatemeh Saberian[*], Archis Ghate[†], Minsun Kim[‡]

February 7, 2015

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.

Keywords: Nonconvex quadratically constrained quadratic programs; intensity modulated radiation therapy.

[*]Corresponding author: Fatemeh Saberian, Industrial and Systems Engineering, University of Washington, Box 352650, Seattle, WA 98195, USA; saberian@uw.edu

[†]Industrial and Systems Engineering, University of Washington, Seattle, USA

[‡]Radiation Oncology, University of Washington, Seattle, USA

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, 4, 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).

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

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

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

This formulation is based on the linear-quadratic (LQ) framework, which is currently the most widely used model of dose-response [6]. Here, α_0 and β_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 α_m and β_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 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 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 below 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

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

This is the largest possible dose that can be given in an equal-dosage schedule (that is, a schedule where $d_1 = d_2 = \ldots = d_N$) without violating inequality constraint (2) for OAR $m \in \mathcal{M}$. This dose is derived by solving the quadratic equation obtained by using $d_1 = d_2 = \ldots = d_N$ 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

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

Here, γ^* 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

$$\begin{aligned}
\text{(2VARLP)}\ \max_{x,y}\ & \alpha_0 x + \beta_0 y, \\
\text{subject to } & s_m x + s_m^2\rho_m y \le \mathrm{BED}_m,\ m \in \mathcal{M}, \\
& y \le \gamma^* x, && (5)\\
& c^* x \le y, && (6)\\
& x \ge 0,\ y \ge 0.
\end{aligned}$$

(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* $\sum_{t=1}^{N} d_t = x^*$, $\sum_{t=1}^{N} d_t^2 = y^*$, $d_t \geq 0$ *for* $t = 1, 2, \ldots, N$*; for example, the two-dose solution where* $d_3 = d_4 = \ldots = d_N = 0$*, and*

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

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

$$\begin{aligned}
\max_{\vec{d},x,y} \ & \alpha_0 x + \beta_0 y, \\
\text{subject to } & s_m x + s_m^2 \rho_m y \leq \text{BED}_m, \ m \in \mathcal{M}, \\
& x = \sum_{t=1}^{N} d_t, \ y = \sum_{t=1}^{N} d_t^2, \ \vec{d} \geq 0, \qquad (7) \\
& x \geq 0, \ y \geq 0.
\end{aligned}$$

Since $\vec{d} \geq 0$, 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 $\sqrt{y} \leq x \leq \sqrt{Ny}$ (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,

$$\begin{aligned}
\max_{\vec{d},x,y} \ & \alpha_0 x + \beta_0 y, && (8) \\
\text{subject to } & s_m x + s_m^2 \rho_m y \leq \text{BED}_m, \ m \in \mathcal{M}, && (9) \\
& x = \sum_{t=1}^{N} d_t, \ y = \sum_{t=1}^{N} d_t^2, \ \vec{d} \geq 0, && (10) \\
& \sqrt{y} \leq x \leq \sqrt{Ny}, && (11) \\
& x \geq 0, \ y \geq 0. && (12)
\end{aligned}$$

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

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

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

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

$$x \geq 0, \ y \geq 0. \tag{16}$$

That is, the variable $\vec{d}$ and constraints (10) can now be dropped from (8)-(12) to rewrite that problem as (13)-(16). To prove this intermediate claim, we let $\bar{x}$, $\bar{y}$ denote an optimal solution to (13)-(16). If $\sqrt{\bar{y}} = \bar{x}$, then the single-dosage solution $d_1 = \bar{x}$, $d_t = 0$ for $t = 2, 3, \ldots, N$, $\bar{x}$, $\bar{y}$ is optimal to (8)-(12). This follows from the property that the l_2 norm of a nonnegative vector equals its l_1 norm if and only if exactly one of the elements of the vector is positive and the others are zero. If $\sqrt{N\bar{y}} = \bar{x}$, then the equal-dosage solution $d_t = \bar{x}/N$ for $t = 1, 2, \ldots, N$, $\bar{x}$, $\bar{y}$ is optimal to (8)-(12). This again follows from the property that the l_2 norm of an N-dimensional nonnegative vector is $\sqrt{N}$ times its l_1 norm if and only if all elements of the vector are identical. Finally, if $\sqrt{\bar{y}} < \bar{x} < \sqrt{N\bar{y}}$, then any nonnegative $\vec{d}$ that satisfies the equations $\bar{x} = \sum_{t=1}^{N} d_t$ and $\bar{y} = \sum_{t=1}^{N} (d_t)^2$ is optimal to (8)-(12) and the set of such $\vec{d}$ is uncountable. Again, from a property of l_1 and l_2 norms, no single-dosage or equal-dosage solution can satisfy this system of equations. In this case, for example, setting $d_3 = d_4 = \ldots = d_N = 0$, $d_1 = \frac{\bar{x} + \sqrt{2\bar{y} - \bar{x}^2}}{2}$, $d_2 = \bar{x} - d_1$ works. These values of d_1 and d_2 were derived by solving the two equations $d_1 + d_2 = \bar{x}$ and $d_1^2 + d_2^2 = \bar{y}$ using the standard quadratic equation formula. Also note that these values of d_1 and d_2 are indeed nonnegative but in fact are both positive as required for an unequal multiple-dosage solution. This holds because, again, from the l_1, l_2 properties, we have, $\sqrt{\bar{y}} < \bar{x} \leq \sqrt{2\bar{y}}$, which implies that $\bar{y} < \bar{x}^2 \leq 2\bar{y}$. These last two inequalities imply that $0 \leq 2\bar{y} - \bar{x}^2 < \bar{x}^2$, which means that $\bar{x}/2 \leq d_1 < \bar{x}$ and $0 < d_2 \leq \bar{x}/2$.

Although problem (13)-(16) only includes two variables, it is nonconvex because of constraint (15). We surmount this difficulty by showing that constraints (15) can be replaced with constraints (5)-(6) without loss of optimality, which yields (2VARLP). A geometric proof is shown in Figure 1. The idea is that replacing the constraints this way does not exclude any optimal solution(s) of problem (13)-(16) and does not introduce any new optimal solutions. That is, (2VARLP) cannot have any optimal solutions in the newly added region (shown with vertical hatch lines) between the dotted line segment OA and the thick black curve $y = x^2$ also connecting O and A. Note in the figure that that the function $y = x^2$ is convex in x and hence line segment OA is above the curve $y = x^2$. Similarly, (13)-(16) does not have any optimal solutions in the chopped off feasible region (shown with horizontal hatch lines) between the dotted line segment OD and the thick black curve $y = x^2/N$ also connecting O and D. Note again that the function $y = x^2/N$ is convex in x and hence the line segment OD is above the curve $y = x^2/N$. These facts about the precise locations of optimal solutions (13)-(16) and (2VARLP) are rooted in the structure of problem (13)-(16) in that (i) all of its linear constraints as well as its objective function have negative slopes; (ii) the only location where an optimal solution to (13)-(16) can occur on the curve $y = x^2$ is at its corner point (point A in Figure 1) and this property also holds for the segment OA given by $y = \gamma^* x$ in (2VARLP); and (iii) the only location where an optimal solution to (13)-(16) can occur on the curve $y = x^2/N$ is at its corner point (point B in Figure 1) and this property also holds for the segment OD given by $y = c^* x$ in (2VARLP). In summary, (2VARLP) is equivalent to (OPTFRAC) and every optimal solution of one problem can be transformed into an optimal solution of the other.

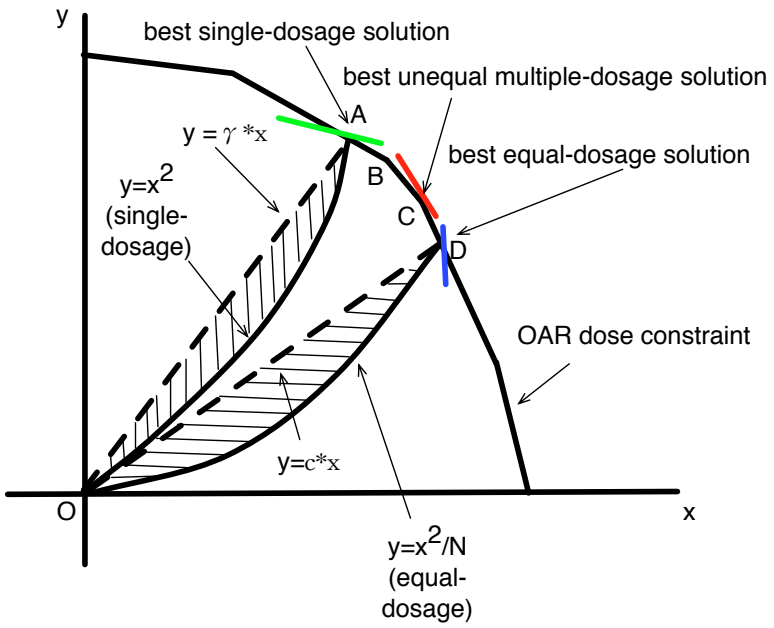

Figure 1: A geometric proof of the equivalence between problem (13)-(16) and problem (2VARLP). Based on properties of l_1 and l_2 norms discussed in the text, the curve $y = x^2$ corresponds to the set of single-dosage solutions whereas the curve $y = x^2/N$ corresponds to the set of equal-dosage solutions. Problem (2VARLP) is created by (i) adding the vertically hatched area to the feasible region of (13)-(16) and (ii) by removing the horizontally hatched area from the feasible region of (13)-(16). Nevertheless, optimal solutions to both problems occur at points such as A, B, C, or D depending on the slope of the objective function (see the green, blue, and red objective function lines for example).

The three possibilities stated in the theorem then follow from the properties of l_1 and l_2 norms discussed above and then deriving the best single-dosage, the best equal-dosage, and any feasible unequal-dosage solution that satisfies the system $x^* = \sum_{t=1}^{N} d_t$ and $y^* = \sum_{t=1}^{N} (d_t)^2$, respectively. The best single-dosage solution delivers dose γ^* is a single session; the best equal-dosage solution delivers dose c^* in each one of the N sessions; and finally, the stated two-dose solution is one optimal unequal multiple-dosage solution that satisfies $x^* = d_1 + d_2$ and $y^* = d_1^2 + d_2^2$ as explained above.

Necessity of the three conditions follows from the mapping between optimal solutions to (OPT-FRAC) and (2VARLP). □

Remark 1. *In the third situation in the above theorem where an uncountable number of unequal multiple-dosage solutions is optimal, we specifically provided an optimal solution that gives only two doses because this could be logistically the most convenient. Moreover, a two-dosage solution is uniquely recoverable given x^*, y^*. It is also possible to derive (although not uniquely) other unequal multiple-dosage optimal solutions that give $2 < k \leq N$ doses as follows. Select any $N - k$ sessions and set the doses in those session to zero. Of the remaining k sessions, select any $k - 2$ sessions and set the doses in those sessions to any arbitrarily chosen values from the interval $[0, x^*/k]$. For instance, one possibility is to sample these values uniformly at random from the interval $[0, x^*/k]$. Suppose these values are $d_1^*, d_2^*, \ldots, d_{k-2}^*$. Then define $\bar{x} = x^* - \sum_{t=1}^{k-2} d_t^*$, $\bar{y} = y^* - \sum_{t=1}^{k-2} (d_t^*)^2$ and let*

$$d_{k-1}^* = \frac{\bar{x} + \sqrt{2\bar{y} - \bar{x}^2}}{2}, \quad d_k^* = \bar{x} - d_1.$$

Then this k-dosage solution is optimal. Note however that in clinical practice, such an arbitrarily derived optimal solution may not be desirable; in this case, the clinical decision maker has the

option to choose, according to his/her judgement, any one of the uncountably many solutions that are deemed optimal according to our mathematical model.

Since single-dosage and equal-dosage solutions are easier to implement in practice, it would be helpful to know precisely when they are the only optimal solutions and also precisely when they are not optimal. The next corollary of Theorem 1 provides a complete answer to this issue.

Corollary 1. *We have:*

1. *There are no optimal solutions other than the N different single-dosage optimal solutions described in Theorem 1 if and only if there is a unique optimal solution (x^*, y^*) to (2VARLP) and it satisfies $x^* = \sqrt{y^*}$.*

2. *The equal-dosage solution described in Theorem 1 is the unique optimal solution if and only if there is a unique optimal solution (x^*, y^*) to (2VARLP) and it satisfies $x^* = \sqrt{Ny^*}$.*

3. *No single-dosage solution is optimal, no equal-dosage solution is optimal, and an uncountable number of unequal multiple-dosage solutions (including the two-dosage solution defined in Theorem 1) is optimal if and only if every pair (x^*, y^*) that is optimal to (2VARLP) satisfies $\sqrt{y^*} < x^* < \sqrt{Ny^*}$.*

Proof. Follows from the mapping between optimal solutions to (OPTFRAC) and to (2VARLP), and from the properties of l_1, l_2 norms discussed in the proof of Theorem 1. □

3 Discussion

We now provide intuition, in terms of the parameters of (OPTFRAC), behind the relationships between x^* and y^* that occurred throughout this paper.

Referring back to Figure 1, we note that the only point in the feasible region of (2VARLP) where the pair x^*, y^* satisfies $x^* = \sqrt{y^*}$ is at corner point A. An optimal solution to (2VARLP) occurs at corner point A if the magnitude of the slope of the objective function line (see the green line for example) is less than or equal to the magnitudes of the slope of all OAR constraint lines. That is, if

$$\frac{\alpha_0}{\beta_0} \leq \min_{m \in \mathcal{M}} \left\{ \frac{\alpha_m/\beta_m}{s_m} \right\}. \tag{17}$$

Thus, (17), which states that the tumor α/β ratio is no bigger than the effective α/β ratio of all OAR, is a sufficient condition for the optimality of the single-dosage solution that delivers dose γ^* in one fraction.

Similarly, referring back to Figure 1 again, we note that the only point in the feasible region of (2VARLP) where the pair x^*, y^* satisfies $x^* = \sqrt{Ny^*}$ is at corner point D. An optimal solution to (2VARLP) occurs at corner point D if the magnitude of the slope of the objective function line (see the blue line for example) is at least as big as the magnitude of the slope of all OAR constraint lines. That is, if

$$\frac{\alpha_0}{\beta_0} \geq \max_{m \in \mathcal{M}} \left\{ \frac{\alpha_m/\beta_m}{s_m} \right\}. \tag{18}$$

Thus, (18), which states that the tumor α/β ratio is no smaller than the effective α/β ratio of all OAR, is a sufficient condition for the optimality of the equal-dosage solution that delivers dose c^* in each one of the N fractions.

A remaining question is what happens when neither (17) nor (18) holds; that is, when

$$\min_{m\in\mathcal{M}}\left\{\frac{\alpha_m/\beta_m}{s_m}\right\} < \frac{\alpha_0}{\beta_0} < \max_{m\in\mathcal{M}}\left\{\frac{\alpha_m/\beta_m}{s_m}\right\}. \tag{19}$$

Can we claim in this case that no single-dosage solution is optimal and no equal-dosage solution is optimal and therefore we *must* use an unequal multiple-dosage solution if we demand optimality with respect to formulation (OPTFRAC)? It turns out that this claim does *not* hold. This is because it is possible to construct numerical examples where (19) holds but all three types of solutions are optimal because of ties. This uniqueness issue is in fact addressed in Corollary 1 above (especially the third item in that corollary).

Our results hold without change if a tumor proliferation term is included in calculating the biological effect on tumor. One common way to model proliferation involves changing the objective in (OPTFRAC) to

$$\alpha_0\sum_{t=1}^{N} d_t + \beta_0\sum_{t=1}^{N} d_t^2 - \frac{[(N-1)-T_{\text{lag}}]^+\ln 2}{T_{\text{double}}}.$$

See, for example, [1, 4, 5, 7]. Here, T_{double} represents the doubling time for the tumor and T_{lag} denotes the time-lag after which tumor proliferation actually starts. Specifically, since, in this model, the proliferation term does not depend on dose, all of our mathematical analysis about optimal dosing goes through without change. Moreover, by including tumor proliferation this way, one can also optimize the number of treatment sessions N. This can be done by plotting the optimal biological effect versus N after solving (2VARLP) for different values of N within a clinically viable range and then choosing an N that maximizes this optimal biological effect as in [3, 14] and references therein.

Although our results resolve a particular form of the optimal fractionation problem based on the LQ model that has recently received attention in the radiotherapy literature, their proofs appear fragile in that they are highly dependent on the structure of (OPTFRAC). Consequently, similar results would not hold for more difficult variants of optimal fractionation where the fluence-map itself is directly optimized instead of optimizing a sequence of tumor doses. Unlike the extended LQ model in [18], (OPTFRAC) does not incorporate repair, redistribution and reoxygenation. As in [18], such a variation of (OPTFRAC) would call for a heuristic solution method like simulated annealing, and then analytical results similar to ours would not be possible. Unlike our work in [9], (OPTFRAC) ignores the uncertainty in radiobiological parameters of the LQ model. It also does not incorporate tumor-volume dependent radiobiological parameters, redistribution of cells in different phases of the cell cycle, and reoxygenation (see [17]). Incorporating these types of uncertain and dynamic biological features usually calls for control theoretic formulations of fractionation problems, where analytical results similar to ours are essentially impossible to derive.

We conclude by mentioning that our results here may be of interest to the wider scientific community. Problem (OPTFRAC) can be seen as the N-dimensional problem of finding the longest distance to any point within the intersection of M collinear hyperspheres from a point that lies on the line connecting the centers of these hyperspheres. Such geometric problems of finding the longest distance between a given point and the intersection of convex sets are in general computationally difficult. Our results here show that a special case of these problems is in fact easy to solve. This is because, in our special case, (i) the convex sets are hyperspheres, (ii) the centers of the hyperspheres lie on a single line, and (iii) the given point also lies on this same line.

4 Acknowledgments

Funded in part by the National Science Foundation through grant #CMMI 1054026.

References

[1] C I Armpilia, R G Dale, and B Jones. Determination of the optimum dose per fraction in fractionated radiotherapy when there is delayed onset of tumour repopulation during treatment. *The British Journal of Radiology*, 77(921):765–767, 2004.

[2] A Bertuzzi, C Bruni F Papa, and C Sinisgalli. Optimal solution for a cancer radiotherapy problem. *Journal of Mathematical Biology*, 66(1-2):311–349, 2013.

[3] T Bortfeld, J Ramakrishnan, J N Tsitsiklis, and J Unkelbach. Optimization of radiotherapy fractionation schedules in the presence of tumor repopluation. `http://pages.discovery.wisc.edu/~jramakrishnan/BRT2013_repop.pdf`, December 2013.

[4] J F Fowler. Optimum overall times II: Extended modelling for head and neck radiotherapy. *Clinical Oncology*, 20(2):113–126, 2008.

[5] J F Fowler and M A Ritter. A rationale for fractionation for slowly proliferating tumors such as prostatic adenocarcinoma. *International Journal of Radiation Oncology Biology Physics*, 32(2):521–529, 1995.

[6] E J Hall and A J Giaccia. *Radiobiology for the Radiologist*. Lippincott Williams & Wilkins, Philadelphia, Pennsylvania, USA, 2005.

[7] B Jones, L T Tan, and R G Dale. Derivation of the optimum dose per fraction from the linear quadratic model. *The British Journal of Radiology*, 68(812):894–902, 1995.

[8] H Keller, G Meier, A Hope, and M Davison. Fractionation schedule optimization for lung cancer treatments using radiobiological and dose distribution characteristics. *Medical Physics*, 39(6):3811–3811, 2012.

[9] M Kim, A Ghate, and M H Phillips. A stochastic control formalism for dynamic biologically conformal radiation therapy. *European Journal of Operational Research*, 219(3):541 – 556, 2012.

[10] Z-Q Luo, W-K Ma, A M C So, and Y Ye. Semidefinite relaxation of quadratic optimization problems. *IEEE Signal Processing Magazine*, 27(3):20–34, 2010.

[11] L B Marks, E D Yorke, A Jackson, R K Ten Haken, L S Constine, A Eisbruch, S M Bentzen, J Nam, and J O Deasy. Use of normal tissue complication probability models in the clinic. *International Journal of Radiation Oncology Biology Physics*, 76(3):S10–S19, 2010.

[12] M Mizuta, S Takao, H Date, N Kishimoto, K L Sutherland, R Onimaru, and H Shirato. A mathematical study to select fractionation regimen based on physical dose distribution and the linear-quadratic model. *International Journal of Radiation Oncology Biology Physics*, 84(3):829 – 833, 2012.

[13] S Rockwell. Experimental radiotherapy: a brief history. *Radiation Research*, 150(Supplement):S157–S169, November 1998.

[14] F Saberian, A Ghate, and M Kim. Optimal fractionation in radiotherapy with multiple normal tissues. accepted for publication subject to minor revision, available online at `http://papers.ssrn.com/sol3/papers.cfm?abstract_id=2478481`, November 2014.

[15] J Unkelbach, D Craft, E Saleri, J Ramakrishnan, and T Bortfeld. The dependence of optimal fractionation schemes on the spatial dose distribution. *Physics in Medicine and Biology*, 58(1):159–167, 2013.

[16] J Unkelbach, C Zeng, and M Engelsman. Simultaneous optimization of dose distributions and fractionation schemes in particle radiotherapy. *Medical Physics*, 40(9):091702, 2013.

[17] L M Wein, J E Cohen, and J T Wu. Dynamic optimization of a linear-quadratic model with incomplete repair and volume-dependent sensitivity and repopulation. *International Journal of Radiation Oncology Biology Physics*, 47(4):1073–1083, 2000.

[18] Y Yang and L Xing. Optimization of radiotherapy dose-time fractionation with consideration of tumor specific biology. *Medical Physics*, 32(12):3666–3677, 2005.