

Optimal modality selection in external beam radiotherapy

SEVNAZ NOUROLLAHI AND ARCHIS GHATE

Department of Industrial & Systems Engineering, University of Washington, Seattle, USA

AND

MINSUN KIM*

Department of Radiation Oncology, University of Washington, Seattle, USA

*Corresponding author: Email: mk688@uw.edu

[Received on 12 December 2017; revised on 7 August 2018; accepted on 13 August 2018]

The goal in external beam radiotherapy (EBRT) for cancer is to maximize damage to the tumour while limiting toxic effects on the organs-at-risk. EBRT can be delivered via different modalities such as photons, protons and neutrons. The choice of an optimal modality depends on the anatomy of the irradiated area and the relative physical and biological properties of the modalities under consideration. There is no single universally dominant modality. We present the first-ever mathematical formulation of the optimal modality selection problem. We show that this problem can be tackled by solving the Karush–Kuhn–Tucker conditions of optimality, which reduce to an analytically tractable quartic equation. We perform numerical experiments to gain insights into the effect of biological and physical properties on the choice of an optimal modality or combination of modalities.

Keywords: multi-modality radiotherapy; nonlinear optimization; fractionation.

1. Introduction

External beam radiotherapy (EBRT) uses high-energy, ionizing radiation generated outside the patients, e.g. by linear accelerators or cyclotrons, to kill cancerous tumour cells. Unfortunately, radiation also damages nearby organs-at-risk (OAR). Thus, the goal is to maximize the damage to the tumour while limiting below a tolerable level the toxic effects on the OAR. In an ongoing quest for attaining this goal, several modalities for delivering EBRT have been devised (Halperin, 2006; Schae & McBride, 2015; Baumann *et al.*, 2016). EBRT is most prevalent in the form of photon beam x-rays (Lawrence *et al.*, 2008; Halperin *et al.*, 2013). It is also administered using beams of charged particles such as protons (Schulz-Ertner *et al.*, 2006; Grutters *et al.*, 2010; Ramaekers *et al.*, 2011; Loeffler & Durante, 2013; Tommsino *et al.*, 2015). Heavier, carbon ions are emerging as yet another option for charged particle therapy (Ebner & Kamada, 2016; Schulz & Kagan, 2016). Among all patients receiving particle therapy by the end of 2013, 87.5% were treated with protons and 10.8% with carbon ions (Tommsino *et al.*, 2015). Other rarer delivery mechanisms such as neutrons, pions, boron-neutron capture therapy and charged-nuclei therapy have also been investigated (Halperin, 2006; Rong & Welsh, 2010).

Different modalities can be compared, at least in theory, based on three criteria: biological behaviour, physical (dosimetric) characteristics and cost (Halperin, 2006; Peeters *et al.*, 2010; Rong & Welsh, 2010; Mitin & Zietman, 2014). This paper focuses on the trade-offs introduced by biological and physical characteristics as described in the next two paragraphs. A cost-benefit analysis of different modalities would require entirely different techniques, and hence it is deferred to future research.

Differences in biological behaviour across modalities

Biological behaviour is comprised of two main items: relative biological effectiveness (RBE) and oxygen enhancement ratio (Halperin, 2006). RBE captures the fact that different modalities produce different levels of cell-damage for the same amount of physical radiation dose (measured in J/kg or Gy). Oxygen enhancement ratio is the ratio of radiation doses needed to produce the same level of tumour cell kill in poorly oxygenated conditions as in well-oxygenated conditions. This accounts for the observation that oxygen increases radiosensitivity of tumour cells. For example, neutrons have a higher RBE and a lower oxygen enhancement ratio than photons (Halperin, 2006; Rong & Welsh, 2010).

Differences in physical (dosimetric) characteristics across modalities

The main physical characteristic of a modality is its dose depth deposition profile (Halperin, 2006; Rong & Welsh, 2010; Mitin & Zietman, 2014). This profile describes the radiation dose deposited as a function of the distance travelled inside a medium. Photon x-rays deposit a high dose near the entry point and the dose then decreases with distance (Halperin *et al.*, 2013). Protons exhibit a different profile. The deposited dose is roughly constant with distance from the entrance point; abruptly reaches a peak (called the Bragg peak) deeper inside the medium; and then falls sharply after the peak (Halperin, 2006; Rong & Welsh, 2010; Ebner & Kamada, 2016). Thus, by positioning the Bragg peak precisely in the cancerous region, a large dose differential between the tumour and the OAR can be attained. This in turn means that a large dose can be delivered to the tumour while still keeping the OAR dose within tolerable limits (Grutters *et al.*, 2010). Carbon ions also exhibit a similar profile but with a slower post-peak drop in dose and have a higher RBE (Schulz-Ertner & Tsujii, 2007; Ebner & Kamada, 2016).

No universally superior modality

Each modality offers certain advantages and disadvantages with respect to the above two criteria (Rong & Welsh, 2010). For instance, neutrons are not superior to photons or to protons in terms of their dose deposition profiles, but have a much higher RBE. This high RBE does, however, imply that neutrons are highly toxic to both the tumours and the OAR (Halperin, 2006). The RBE of protons is only about 10% higher than photons (Paganetti *et al.*, 2002; Paganetti & van Luijk, 2013; Paganetti, 2014), but protons have a much favourable dose deposition profile as explained above. One important disadvantage with protons is that it is difficult to precisely position the Bragg peak in the cancerous region owing to various uncertainties; thus the risk of a high OAR toxicity has to be carefully managed (Paganetti, 2012; Baumann *et al.*, 2016). Treatment with protons and other charged particles is also currently much more expensive than photon therapy (Loeffler & Durante, 2013; Ramaekers *et al.*, 2013). In addition, due to the longest history of using photons in cancer treatments, the most sophisticated ancillary systems are currently available for photon EBRT to aid precise localization of the tumours, e.g. image-guided radiotherapy.

No clear winner that dominates all other modalities in all three criteria has emerged thus far. This was summarized by Halperin (2006) a decade ago: 'Neutrons, photons, pions, alpha particles, stripped nuclei, protons, and electrons vary in their biological, physical, and cost characteristics. None has yet met the test of being the generic ideal particle. Instead, each of these particles will probably offer advantages for particular histological types of cancer, at specific stages, in certain clinical conditions. An understanding of the biology of tumours should help to clarify the ideal particle for a clinical situation. Much of the history of the search for the ideal particle has yet to be created.' A similar sentiment was reiterated by McDermott and by Schulz & Kagan in 2016, and by Baumann *et al.* in 2016. Missing

a universally superior EBRT modality, some studies have considered combinations of two modalities (typically photons and protons) to leverage their physical and biological advantages (Yonemoto *et al.*, 1997; Bertuzzi *et al.*, 2001; Feuvret *et al.*, 2007; Torres *et al.*, 2009; DeLaney, 2009, 2011; DeLaney *et al.*, 2014; Maio *et al.*, 2015; Chen *et al.*, 2016).

Lack of randomized clinical trials

One hurdle in deciding an ideal modality or a combination of two modalities is that no randomized clinical trial results comparing outcomes of different modalities are currently available. For instance, the prevalent EBRT modality for prostate cancer is still photons, but it is also where proton therapy has been used most widely (Mitin & Zietman, 2014 reported that 70% of patients who received proton therapy by 2014 had prostate cancer). Nevertheless, in January 2016, Schiller *et al.* (2016) stated, 'There are still no completed randomized trials comparing proton-beam therapy with photon-beam therapy in men with clinically localized prostate cancer.' A year later, this has not changed. Indeed, in February 2017, Tyson *et al.* (2017) commented, 'Although there is some evidence that novel radiation therapies may improve the dose distribution with higher doses delivered locally to the tumor thereby preserving surrounding healthy tissues, these assertions remain unproven in studies to date there are no randomized clinical trials comparing proton therapy to conventional radiation therapy.' This lack of randomized clinical trials extends to other cancers where the use of proton beams is rarer than prostate. For example, after a retrospective comparison between photons and protons for 243,822 non-small cell lung cancer patients in the National Cancer Database (photons: 243,474; protons: 348), Higgins *et al.* (2017) stated in January 2017 that 'further validation in the randomized setting is needed.' Similarly, Ramaekers *et al.* (2011) performed a meta-analysis of 86 observational studies (74 photon, 5 carbon ion and 7 proton) on head-and-neck cancers and concluded in 2010: 'several reviews indicated that based on clinical evidence it remains unclear, mainly because of the absence of randomized trials, whether particle therapy is superior over radiotherapy with photons' A similar observation was repeated four years later by Ahn *et al.* (2014). This situation might not significantly change in the near future, given the ethical, financial and logistical difficulties involved in the design of randomized clinical trials (Goitein & Cox, 2008; Morgan, 2008; van Loon *et al.*, 2012; Dekker *et al.*, 2014; Lambin *et al.*, 2017).

Further challenges posed by fractionation

The selection of an appropriate modality is further complicated because radiotherapy is typically administered in multiple treatment sessions over several weeks. This is called fractionation. Healthy tissues possess better damage-repair capabilities than tumours (Withers, 1985; Hall & Giaccia, 2005). Fractionation thus gives healthy tissue time to recover between treatment sessions. For any single radiation modality, the optimal number of fractions and the corresponding dose in each fraction depend on (i) the relative difference between the tumour's and the healthy tissue's biological response to that modality, (ii) the dose deposition profile of that modality with respect to the anatomy of the irradiated area and (iii) the tumour proliferation rate. The trade-offs in determining an optimal number of fractions and doses have been studied over the past several decades mainly for photon therapy (Rockwell, 1988; Fowler, 1990, 2001, 2007, 2008; Fowler & Ritter, 1995; Jones *et al.*, 1995; Horiot *et al.*, 1997, 1992; Fu *et al.*, 2000; Garden, 2001; Armpilia *et al.*, 2004; Ahamad *et al.*, 2005; Trotti *et al.*, 2005; Yang & Xing, 2005; Ho *et al.*, 2009; Marzi *et al.*, 2009; Arcangeli *et al.*, 2010; Kader *et al.*, 2011; Keller *et al.*, 2012; Mizuta *et al.*, 2012; Bertuzzi *et al.*, 2013; Unkelbach *et al.*, 2013a, b; Bortfeld *et al.*, 2015; Saberian *et al.*, 2015, 2016, 2017; Badri *et al.*, 2016).

Literature on mathematical optimization models for single-modality fractionation

Given the aforementioned difficulties in designing randomized clinical trials, many of the above studies formulate and solve theoretical optimization models of the single modality fractionation problem to guide decisions. These formulations are rooted in the following linear-quadratic (LQ) model of tumour's response to radiation dose (Hall & Giaccia, 2005; O'Rourke *et al.*, 2009):

$$f = e^{-N(\alpha^\tau d + \beta^\tau d^2) + \pi(N)}. \quad (1)$$

Here, f is the fraction of tumour cells that survive; N is the number of treatment sessions; d is the dose per session; $\pi(N)$ models tumour proliferation as a function of N ; and α^τ, β^τ are tumour-specific parameters. The goal is to minimize the fraction of surviving tumour cells subject to upper limit constraints on the biological effect (BE) (Hall & Giaccia, 2005) on OAR. In the LQ framework, BE is defined by the expression

$$N \left(\alpha^\phi (sd) + \beta^\phi (sd)^2 \right). \quad (2)$$

Here, α^ϕ, β^ϕ are OAR-specific parameters, and s is the so-called sparing factor, which equals the ratio of doses delivered to the OAR and tumour. This results in a non-convex quadratically constrained quadratic programming problem. Such problems in general belong to the class NP-hard (Luo *et al.*, 2010). Existing work on solving this theoretical single modality fractionation model thus includes various heuristic and exact solution methods that exploit the structure of its formulation. For example, a closed-form solution is derived in Bortfeld *et al.* (2015), Fowler (2008), Fowler & Ritter (1995), Jones *et al.* (1995), Mizuta *et al.* (2012), Saberian *et al.* (2016) and Unkelbach *et al.* (2013a) for the case of a single OAR; a simulated annealing heuristic is used in Yang & Xing (2005) and Karush–Kuhn–Tucker (KKT) conditions are employed in Bertuzzi *et al.* (2013) for an extension with two OAR; we showed in Saberian *et al.* (2016) that an exact solution can be derived for the case of multiple OAR using KKT conditions when problem parameters are ordered a certain way; it is shown in Badri *et al.* (2016) and Saberian *et al.* (2015) that the problem with multiple OAR can be solved to optimality by reformulating it as a two-variable linear program.

There is a different stream of literature, where single-modality dosing decisions are made by combining the LQ model with differential equations that describe tumour growth. Analytical solution of those formulations is typically not possible, and numerical simulations are often performed to compare select few dosing strategies (Enderling *et al.*, 2006, 2007, 2010; Corwin *et al.*, 2013; Poleszczuk *et al.*, 2013; Powathil *et al.*, 2013, 2007; Lewin *et al.*, 2018).

When two modalities are available, additional trade-offs arising from their RBE and dose deposition profiles need to be considered. To the best of our knowledge, no existing mathematical work has modelled this fractionation problem with two modalities.

Contributions of this paper

The objective of this paper is to propose a novel, mathematical framework to systematically investigate the selection of optimal modalities in radiotherapy, balancing the trade-off in the biological and physical (dosimetrical) characteristics unique to each radiation modality currently available in practice. The rest of this paper is organized as follows. In Section 2 of this paper, we provide a mathematical formulation of the fractionation problem with two modalities, where the goal is to find an optimal number of treatment sessions and the corresponding dose per session for each modality. We show that KKT

conditions for this formulation can be tackled by solving an analytically tractable quartic equation. In Section 3, we perform sensitivity analyses to gain insight into the effect of problem parameters on the choice of optimal modalities. These parameters characterize biological and physical behaviours of the two modalities under consideration. In one set of sensitivity analyses (Section 3.1), we consider two modalities that have comparable physical characteristics but distinct biological characteristics. One example of this could be photons and neutrons. In the second set of sensitivity analyses (Section 3.2), we consider two modalities that have comparable biological characteristics but distinct physical characteristics. One example of this could be photons and protons. This ‘one-at-a-time’ manner of performing sensitivity analyses facilitates the interpretation of results, although it is not a requirement of our mathematical model itself. Finally, although our initial formulation focuses on the single OAR case for ease of exposition, we briefly describe how our KKT approach can be extended to multiple OAR in Section 4. We conclude in that section by outlining opportunities for future work.

2. Problem formulation and solution

In this section, we provide a formulation of the fractionation problem with two modalities using the LQ dose-response model. We use notation that is standard in the single modality fractionation literature, except that, in our case, modalities are indexed by $i = 1, 2$. Modality 1 is assumed to be the ‘conventional’ modality such as photon EBRT. Let N_i denote the number of treatment sessions administered (once daily) with modality i . Similarly, let d_i denote the tumour-dose in each one of the N_i sessions for modality i . Moreover, $\alpha_i^\tau, \beta_i^\tau$ denote the parameters of the tumour’s LQ dose-response model for modality i . Notation $\pi(N_1 + N_2)$ represents tumour proliferation over a treatment course that includes $N_1 + N_2$ sessions. We employ a particular form for the proliferation function $\pi(\cdot)$ in our numerical results later; in this section, we simply emphasize that it depends on the length of the treatment course as is standard in the literature. Let s_i denote the OAR’s sparing factor for modality i . That is, the dose to OAR i equals $s_i d_i$. A procedure for calculating sparing factors is described in [Saberian *et al.* \(2016\)](#). Let $\alpha_i^\phi, \beta_i^\phi$ denote the OAR’s LQ dose-response parameters for modality i . Suppose that the OAR is known to tolerate a dose of d_{conv} per session when administered using the conventional modality 1 in N_{conv} sessions. Then, the BE of this conventional treatment plan equals $B = N_{\text{conv}} \alpha_1^\phi d_{\text{conv}} + N_{\text{conv}} \beta_1^\phi (d_{\text{conv}})^2$. As in [Saberian *et al.* \(2017\)](#), N_{max} is a constant, which is interpreted as a loose upper bound on the total number of sessions that is logistically viable in practice irrespective of the selected modality. Using a large value for this constant (say 100 or 200 sessions) ensures that all relevant combinations of N_1 and N_2 will be evaluated by our solution method. The thought process in our stylized formulation is that s_1, s_2 characterize the physical properties of the two modalities, whereas α, β and τ correspond to the biological ones.

We pursue the standard approach of minimizing the fraction of surviving tumour cells subject to the constraint that the BE of the treatment plan is no more than the conventional BE that the OAR is known to tolerate. This yields the formulation

$$(P) \quad \min_{N_1, d_1, N_2, d_2} e^{-N_1 \alpha_1^\tau d_1 - N_1 \beta_1^\tau (d_1)^2 - N_2 \alpha_2^\tau d_2 - N_2 \beta_2^\tau (d_2)^2} + \pi(N_1 + N_2) \quad (3)$$

$$N_1 \left[\alpha_1^\phi (s_1 d_1) + \beta_1^\phi (s_1 d_1)^2 \right] + N_2 \left[\alpha_2^\phi (s_2 d_2) + \beta_2^\phi (s_2 d_2)^2 \right] \leq B, \quad (4)$$

$$d_1 \geq 0, \quad (5)$$

$$d_2 \geq 0, \quad (6)$$

$$N_1 + N_2 \leq N_{\max}, \quad (7)$$

$$0 \leq N_1 \text{ integer}, \quad (8)$$

$$0 \leq N_2 \text{ integer}. \quad (9)$$

Note that the above formulation explicitly allows $N_1 = 0$ or $N_2 = 0$, which corresponds to the single modality case. It also allows other combinations where both $N_1 > 0$ and $N_2 > 0$, which corresponds to administering a combination of modalities as has been attempted in some clinical studies cited in Section 1 (Yonemoto *et al.*, 1997; Bertuzzi *et al.*, 2001; Feuvret *et al.*, 2007; Torres *et al.*, 2009; DeLaney, 2009, 2011; DeLaney *et al.*, 2014; Maio *et al.*, 2015; Chen *et al.*, 2016). A benefit of this approach is that it exhaustively compares all such possibilities in one shot.

We now make a few observations about problem (P). It can be tackled by first solving the indexed group of problems

$$(P(N_1, N_2)) \min_{d_1, d_2} e^{-N_1 \alpha_1^\tau d_1 - N_1 \beta_1^\tau (d_1)^2 - N_2 \alpha_2^\tau d_2 - N_2 \beta_2^\tau (d_2)^2} + \pi(N_1 + N_2) \quad (10)$$

$$N_1 \left[\alpha_1^\phi (s_1 d_1) + \beta_1^\phi (s_1 d_1)^2 \right] + N_2 \left[\alpha_2^\phi (s_2 d_2) + \beta_2^\phi (s_2 d_2)^2 \right] \leq B, \quad (11)$$

$$d_1 \geq 0, \quad (12)$$

$$d_2 \geq 0, \quad (13)$$

for all non-negative integer pairs (N_1, N_2) such that $0 \leq N_1 + N_2 \leq N_{\max}$. In particular, let $d_1^*(N_1, N_2)$ and $d_2^*(N_1, N_2)$ denote optimal doses for modalities 1, 2 in problem $(P(N_1, N_2))$, respectively. Let $F^*(N_1, N_2)$ denote the optimal objective value of problem $(P(N_1, N_2))$. Then problem (P) can be solved by minimizing $F^*(N_1, N_2)$ over all integer pairs (N_1, N_2) such that $0 \leq N_1 + N_2 \leq N_{\max}$. If the pair N_1^*, N_2^* is optimal for this problem, then the quadruple $N_1^*, d_1^*(N_1^*, N_2^*), N_2^*, d_2^*(N_1^*, N_2^*)$ is optimal for problem (P). Since the exponential function is monotonic in its argument, minimizing the objective function in $(P(N_1, N_2))$ is equivalent to minimizing $-N_1 \alpha_1^\tau d_1 - N_1 \beta_1^\tau (d_1)^2 - N_2 \alpha_2^\tau d_2 - N_2 \beta_2^\tau (d_2)^2 + \pi(N_1 + N_2)$. Further, since the pair N_1, N_2 is fixed in problem $(P(N_1, N_2))$, the proliferation term $\pi(N_1 + N_2)$ is a constant that can be ignored without loss of optimality. Finally, the objective function is decreasing in d_1 and d_2 and the left-hand side of constraint (11) is increasing in d_1 and d_2 . Thus, constraint (11) must be active at an optimal solution. In other words, solving $(P(N_1, N_2))$ is equivalent to solving

$$(Q(N_1, N_2)) \min_{d_1, d_2} - \left(N_1 \alpha_1^\tau d_1 + N_1 \beta_1^\tau (d_1)^2 + N_2 \alpha_2^\tau d_2 + N_2 \beta_2^\tau (d_2)^2 \right) \quad (14)$$

$$N_1 \left[\alpha_1^\phi (s_1 d_1) + \beta_1^\phi (s_1 d_1)^2 \right] + N_2 \left[\alpha_2^\phi (s_2 d_2) + \beta_2^\phi (s_2 d_2)^2 \right] = B, \quad (15)$$

$$d_1 \geq 0, \quad (16)$$

$$d_2 \geq 0. \quad (17)$$

TABLE 1 Legend of colours showing three different modality choices.

M1
(M1,M2)
M2

TABLE 2 Parameters for the conventional modality M_1 .

$\alpha_1^\tau = 0.35 \text{ Gy}^{-1}$	$\beta_1^\tau = 0.035 \text{ Gy}^{-2}$
$\alpha_1^\phi = 0.35 \text{ Gy}^{-1}$	$\beta_1^\phi = 0.175 \text{ Gy}^{-2}$

An exact solution method based on KKT conditions for $(Q(N_1, N_2))$ is developed in Appendix A. This method is applied to perform numerical sensitivity analyses in the next section.

3. Numerical results

Let M_1 denote a conventional modality such as photon EBRT, and let M_2 denote an alternative modality. Table 1 illustrates a legend for three colours that will be employed throughout this section to indicate the use of modalities M_1 , (M_1, M_2) mixture and M_2 , respectively.

Our numerical results are categorized into two parts that are presented in Sections 3.1 and 3.2, respectively. Section 3.1 investigates the trade-offs between M_1 and a biologically superior M_2 . Section 3.2 studies the trade-offs between M_1 and a physically superior M_2 . Recall that biological and physical are the two main characteristics of a modality as described in Section 1. As stated in Section 1, we pursue this one-at-a-time method of performing sensitivity analyses because it facilitates interpretation of our results. In both Sections 3.1 and 3.2, these trade-offs are explored for different values of a biological parameter $r = \alpha_2^\phi / \alpha_2^\tau$ that we introduce in this paper. The thought process behind this parameter is as follows. A biologically superior modality will inflict a higher damage on both the tumour and the OAR. The ratio r attempts to capture the differential in the damage to the tumour and the OAR. As r increases, the damage to the OAR relative to the damage to the tumour using M_2 increases, when all other things are equal. Thus, M_2 becomes less desirable as r increases. For the conventional modality M_1 , we used $s_1 = 1$ as the base value of physical characteristics throughout this paper. Also, for M_1 , we used $\alpha_1^\tau / \beta_1^\tau = 10 \text{ Gy}$, $\alpha_1^\phi / \beta_1^\phi = 2 \text{ Gy}$ and the OAR tolerance was assumed to be $N_{\text{conv}} d_{\text{conv}} = 50 \text{ Gy}$ delivered in $N_{\text{conv}} = 25$ fractions (Hall & Giaccia, 2005; Marks *et al.*, 2010). Table 2 shows other specific parameter values for M_1 . Similarly, β_2^ϕ was fixed at 0.175 Gy^{-2} and β_2^τ was fixed at 0.035 Gy^{-2} throughout this paper. These values are standard in the clinical literature (Hall & Giaccia, 2005; Fowler, 2007, 2008; Marks *et al.*, 2010), and yield $B = 35$ as the right-hand side of constraint (4).

For the tumour repopulation term $\pi(N_1 + N_2)$ in the expression for BE in the objective function of problem (P), we used

$$\pi(N_1 + N_2) = \frac{\left[(N_1 + N_2) - 1 - T_{\text{lag}} \right]^+ \ln 2}{T_d}, \quad (18)$$

where T_d and T_{lag} are tumour doubling time and lag time, respectively; and $[\cdot]^+ = \max(\cdot, 0)$. This functional form for tumour repopulation is common in the literature (Hall & Giaccia, 2005; Fowler, 2007), and it assumes that tumour repopulation does not start until T_{lag} days after treatment begins.

In this study, we present results with $T_d = 3$ days and $T_{lag} = 0$ day as representative values since qualitative trends in our results were invariant with respect to these numbers. We fixed N_{max} at 200 days throughout.

Our evaluation criterion equals the ratio of surviving cells attained by an optimal modality relative to that attained by the conventional modality. We assume that ‘standard practice’ delivers radiotherapy using conventional modality (M_1) only for 25 fractions, i.e. $N_{conv} = 25$. We compute the ratio of surviving cells in three ways. First, we fix the number of treatment sessions to $N_{conv} = 25$, and compute the ratio of surviving cells attained by an optimal modality relative to that attained by the conventional modality. This amounts to comparing the effect of optimizing the choice of modality (without optimizing the number of sessions) against standard practice. Second, we re-compute this ratio, but this time by also optimizing the number of sessions in the numerator. This amounts to comparing the effect of solving problem (P) against standard practice. Finally, we calculate this ratio again, but this time by also optimizing the number of sessions in the denominator.

3.1 Biologically superior modality M_2 combined with conventional modality M_1

In this section, we investigate the case where M_2 is biologically superior to M_1 (when $r = 1$) as characterized by higher values of α_2^r in the range 0.35–0.8 Gy⁻¹. The physical characteristics of M_2 are assumed to be similar to M_1 and hence s_2 is fixed at 1 in this section. For example, this section therefore studies trade-offs between conventional photon EBRT and neutrons. Results are summarized in Tables 3–6.

Table 3 shows the ratio of surviving cells when an optimal modality (or combination) is used with the total number of fractions fixed at $N_{conv} = 25$, relative to the standard practice of using M_1 with $N_{conv} = 25$ fractions. The table shows that for a fixed α_2^r , the optimal modality switches from M_2 to M_1 as r increases since the relative damage to the OAR from M_2 becomes larger, making M_2 less desirable. For a fixed r , the optimal modality switches from M_1 to M_2 as α_2^r increases since the biological power of M_2 becomes larger. Therefore, for sufficiently low fixed values of r , i.e. when the damage to the OAR from M_2 is relatively lower than the damage to the tumour, M_2 dominates M_1 for all values of

TABLE 3 Ratio of surviving cells attained by using an optimal modality (or combination) with $N_{conv} = 25$ fractions, relative to using M_1 with $N_{conv} = 25$ fractions.

		Tumor alpha2									
		0.35	0.40	0.45	0.50	0.55	0.60	0.65	0.70	0.75	0.80
r	0.2	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	0.4	0.003	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	0.6	0.026	0.004	0.001	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	0.8	0.178	0.037	0.009	0.002	0.001	0.000	0.000	0.000	0.000	0.000
	1.0	1.000	0.283	0.092	0.033	0.013	0.006	0.003	0.002	0.001	0.000
	1.2	1.000	1.000	0.701	0.322	0.162	0.089	0.052	0.033	0.022	0.015
	1.4	1.000	1.000	1.000	1.000	0.987	0.787	0.572	0.417	0.313	0.242
	1.6	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	0.998	0.960
	1.8	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000

α_2^T because of M_2 's superior biological power ($\alpha_2^T > \alpha_1^T$). Similarly, M_1 dominates M_2 for all values of α_2^T for sufficiently high values of r due to the high toxicity to the OAR from M_2 . The switch from M_1 to M_2 occurs at higher values of α_2^T as r increases. This is because, the biological power of M_2 , i.e. α_2^T has to be sufficiently high for that modality to become desirable despite its higher damage to the OAR (large r). Similarly, the switch from M_2 to M_1 occurs at higher values of r as α_2^T increases. For each fixed value of α_2^T , the surviving cell ratio is nondecreasing as r increases because M_2 becomes less desirable. Similarly, for each fixed value of r , the surviving cell ratio is nonincreasing as α_2^T increases because M_2 becomes more desirable.

Table 4 shows optimal modalities and the optimal number of fractions obtained by solving problem (P) (in contrast with Table 3 wherein the number of fractions is not optimized). The qualitative trends in the choice of optimal modality are identical to that in Table 3 as expected. Moreover, for each fixed α_2^T , the optimal number of fractions is nonincreasing as r increases when M_2 is the optimal modality. This may be because as M_2 damages the OAR more and more relative to the tumour, prolonged fractionation is less desirable. For each fixed r , the optimal number of fractions follows a more complicated trend as α_2^T increases when M_2 is the optimal modality. For some values of r , it first increases and then decreases, whereas for other values of r it decreases. The optimal number of fractions is independent of α_2^T and r as expected, when M_1 is the optimal modality.

Table 5 shows the ratio of surviving cells when an optimal modality is used with an optimal number of fractions, relative to the standard practice of using M_1 with $N_{\text{conv}} = 25$ fractions (in contrast to

TABLE 4 *Optimal number of fractions and optimal modality.*

		Tumor alpha2									
		0.35	0.40	0.45	0.50	0.55	0.60	0.65	0.70	0.75	0.80
r	0.2	66	77	87	95	102	108	113	116	119	121
	0.4	44	49	53	55	57	59	59	60	60	60
	0.6	32	35	36	37	38	38	38	38	37	37
	0.8	25	26	27	27	27	27	27	26	26	25
	1.0	20	20	21	21	21	20	20	20	19	19
	1.2	20	20	16	16	16	16	16	15	15	15
	1.4	20	20	20	20	13	13	13	12	12	12
	1.6	20	20	20	20	20	20	20	10	10	9
	1.8	20	20	20	20	20	20	20	20	20	20

TABLE 5 *Ratio of surviving cells attained by using an optimal modality with an optimal number of fractions, relative to using M_1 with $N_{\text{conv}} = 25$ fractions.*

		Tumor alpha2									
		0.35	0.40	0.45	0.50	0.55	0.60	0.65	0.70	0.75	0.80
r	0.2	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	0.4	0.001	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	0.6	0.022	0.003	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	0.8	0.178	0.037	0.009	0.002	0.001	0.000	0.000	0.000	0.000	0.000
	1.0	0.880	0.256	0.084	0.031	0.012	0.005	0.003	0.001	0.001	0.000
	1.2	0.880	0.880	0.475	0.213	0.104	0.054	0.030	0.018	0.011	0.007
	1.4	0.880	0.880	0.880	0.880	0.550	0.327	0.205	0.134	0.091	0.065
	1.6	0.880	0.880	0.880	0.880	0.880	0.880	0.880	0.664	0.487	0.367
	1.8	0.880	0.880	0.880	0.880	0.880	0.880	0.880	0.880	0.880	0.880

TABLE 6 Ratio of surviving cells attained by using an optimal modality with an optimal number of fractions, relative to using M_1 only with a number of fractions that is optimal for M_1 .

		Tumor alpha2									
		0.35	0.40	0.45	0.50	0.55	0.60	0.65	0.70	0.75	0.80
r	0.2	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	0.4	0.001	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	0.6	0.025	0.003	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	0.8	0.203	0.042	0.010	0.003	0.001	0.000	0.000	0.000	0.000	0.000
	1.0	1.000	0.291	0.095	0.035	0.014	0.006	0.003	0.001	0.001	0.000
	1.2	1.000	1.000	0.540	0.242	0.118	0.062	0.034	0.020	0.013	0.008
	1.4	1.000	1.000	1.000	1.000	0.625	0.372	0.233	0.152	0.104	0.073
	1.6	1.000	1.000	1.000	1.000	1.000	1.000	1.000	0.755	0.554	0.417
	1.8	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000

TABLE 7 Ratio of surviving cells attained by using an optimal modality (or combination) with $N_{conv} = 25$ fractions, relative to using M_1 with $N_{conv} = 25$ fractions.

		s2					
		1.00	0.95	0.90	0.85	0.80	0.75
r	0.2	0.000	0.000	0.000	0.000	0.000	0.000
	0.4	0.003	0.001	0.000	0.000	0.000	0.000
	0.6	0.026	0.006	0.001	0.000	0.000	0.000
	0.8	0.178	0.043	0.009	0.001	0.000	0.000
	1.0	1.000	0.273	0.063	0.012	0.002	0.000
	1.2	1.000	1.000	0.371	0.080	0.014	0.002
	1.4	1.000	1.000	1.000	0.445	0.089	0.014
	1.6	1.000	1.000	1.000	1.000	0.466	0.084
	1.8	1.000	1.000	1.000	1.000	1.000	0.417

Table 3 wherein the number of fractions is not optimized). As expected, the surviving cell ratios are lower in Table 5 than in Table 3. This is because (for the optimal modality) the number of fractions is optimized in Table 5 whereas it is fixed at $N_{conv} = 25$ in Table 3. All other qualitative trends regarding the choice of optimal modalities in Table 5 are identical to those in Table 3.

Finally, Table 6 shows the ratio of surviving cells when an optimal modality is used with an optimal number of fractions, relative to using M_1 with a number of fractions that is optimal for M_1 (contrast this with Tables 5 and 3). As expected, the surviving cell ratios are higher in Table 6 than in Table 5. This is because the number of fractions with M_1 is optimized in Table 6 but not in Table 5. All other qualitative trends regarding the choice of optimal modalities in Table 6 are identical to those in Table 5.

3.2 Physically superior modality M_2 combined with conventional modality M_1

In this section, we investigate the case where M_2 is physically superior to M_1 as characterized by $s_2 < s_1 = 1$ (recall that we fix $s_1 = 1$ in all numerical experiments). The biological characteristics of M_2 are assumed to be similar to M_1 when $r = 1$. For example, this section therefore studies trade-offs between conventional photon EBRT and protons. Results are summarized in Tables 7–10 over the ranges of 0.2–1.8 for r , and 1.0–0.75 for s_2 .

Table 7 shows the ratio of surviving cells when an optimal modality (or combination) is used with the total number of fractions fixed at $N_{conv} = 25$, relative to the standard practice of using M_1

with $N_{\text{conv}} = 25$ fractions. The table shows that for a fixed s_2 , the optimal modality switches from M_2 to M_1 as r increases because the relative damage to the OAR from M_2 becomes larger, making M_2 less desirable. For a fixed r , the optimal modality switches from M_1 to M_2 because M_2 delivers less dose to the OAR (superior physical characteristics). Therefore, for sufficiently low fixed values of r , M_2 dominates M_1 for all values of s_2 because M_2 inflicts only a small damage to the OAR compared to the tumour. Similarly, for sufficiently high values of r , M_1 or (M_1, M_2) dominates M_2 for all values of s_2 . The switch from M_1 to M_2 occurs at lower values of s_2 as r increases. Similarly, the switch from M_2 to M_1 occurs at higher values of r as s_2 decreases. For each fixed value of s_2 , the surviving cell ratio is nondecreasing as r increases because M_2 becomes less desirable. Similarly, for each fixed value of r , the surviving cell ratio is nonincreasing as s_2 decreases because M_2 becomes more desirable. The logic behind all these trends is qualitatively similar to that in Table 3.

Table 8 shows optimal modalities and the optimal number of fractions obtained by solving problem (P) (in contrast with Table 7 wherein the number of fractions is not optimized). The qualitative trends

TABLE 8 *Optimal number of fractions and optimal modality.*

		s_2					
		1.00	0.95	0.90	0.85	0.80	0.75
r	0.2	66	71	78	84	92	102
	0.4	44	47	51	54	59	63
	0.6	32	34	36	39	41	44
	0.8	25	26	27	29	31	32
	1.0	20	20	21	22	24	25
	1.2	20	20	17	18	19	19
	1.4	20	20	20	14	15	15
	1.6	20	20	20	12	12	12
	1.8	20	20	20	20	10	10

TABLE 9 *Ratio of surviving cells attained by using an optimal modality with an optimal number of fractions, relative to using M_1 with $N_{\text{conv}} = 25$ fractions.*

		s_2					
		1.00	0.95	0.90	0.85	0.80	0.75
r	0.2	0.000	0.000	0.000	0.000	0.000	0.000
	0.4	0.001	0.000	0.000	0.000	0.000	0.000
	0.6	0.022	0.004	0.001	0.000	0.000	0.000
	0.8	0.178	0.043	0.009	0.001	0.000	0.000
	1.0	0.880	0.250	0.060	0.012	0.002	0.000
	1.2	0.880	0.880	0.275	0.063	0.011	0.002
	1.4	0.880	0.880	0.880	0.247	0.052	0.008
	1.6	0.880	0.880	0.880	0.762	0.180	0.034
	1.8	0.880	0.880	0.880	0.880	0.511	0.106

TABLE 10 Ratio of surviving cells attained by using an optimal modality with an optimal number of fractions, relative to using M_1 only with a number of fractions that is optimal for M_1 .

		s_2					
		1.00	0.95	0.90	0.85	0.80	0.75
r	0.2	0.000	0.000	0.000	0.000	0.000	0.000
	0.4	0.001	0.000	0.000	0.000	0.000	0.000
	0.6	0.025	0.005	0.001	0.000	0.000	0.000
	0.8	0.203	0.049	0.010	0.002	0.000	0.000
	1.0	1.000	0.284	0.068	0.013	0.002	0.000
	1.2	1.000	1.000	0.313	0.071	0.013	0.002
	1.4	1.000	1.000	1.000	0.281	0.059	0.010
	1.6	1.000	1.000	1.000	0.866	0.205	0.038
1.8	1.000	1.000	1.000	1.000	0.580	0.121	

in the choice of optimal modality are identical to that in Table 7 as expected. Moreover, for each fixed s_2 , the optimal number of fractions is nonincreasing as r increases when M_2 is the optimal modality. Again, this may be because as M_2 damages the OAR more and more relative to the tumour, prolonged fractionation is less desirable. For each fixed r , the optimal number of fractions seems to be nondecreasing as s_2 decreases when M_2 is the optimal modality. This may be because the damage to the OAR decreases as s_2 decreases and hence prolonged fractionation could be beneficial. The optimal number of fractions is independent of s_2 and r as expected, when M_1 is the optimal modality.

Table 9 shows the ratio of surviving cells when an optimal modality is used with an optimal number of fractions, relative to using M_1 with $N_{\text{conv}} = 25$ fractions (in contrast to Table 7 wherein the number of fractions is not optimized). As expected, the surviving cell ratios are lower in Table 9 than in Table 7. This is because (for the optimal modality) the number of fractions is optimized in Table 9 whereas it is fixed at $N_{\text{conv}} = 25$ in Table 7. All other qualitative trends regarding the choice of optimal modalities in Table 9 are identical to those in Table 7.

Finally, Table 10 shows the ratio of surviving cells when an optimal modality is used with an optimal number of fractions, relative to using M_1 with a number of fractions that is optimal with M_1 (contrast this with Tables 9 and 7). As expected, the surviving cell ratios are higher in Table 10 than in Table 9. This is because the number of fractions with M_1 is optimized in Table 10 but not in Table 9. All other qualitative trends regarding the choice of optimal modalities in Table 10 are identical to those in Table 9.

4. Conclusions

We presented the first-ever mathematical formulation of the optimal fractionation problem with two modalities under the LQ dose-response model. We showed that KKT conditions for this formulation can be tackled by solving a quartic equation. Our numerical experiments explored the effect of varying, in a one-at-a-time manner, parameters that characterize physical and biological properties of the two modalities. The results of these experiments were consistent with clinical intuition. This at least partially validates our formulation and solution methodology, and therefore, the proposed framework may provide optimal solutions for more complex scenarios where clinical intuition is less obvious.

Although we focused on the case of a single OAR for simplicity, our methodology can be easily extended to multiple OAR. To see this, consider a problem with M OAR. Its formulation would include

M constraints similar to (4). At least one of these constraints must be active at an optimal solution. So, if there is exactly one constraint active at an optimal solution, we need to consider M different possibilities. Furthermore, at most two active constraints are needed to uniquely determine a (d_1, d_2) combination. There are $\binom{M}{2}$ ways in which we can have two active constraints. These observations suggest that a problem with M OAR can be solved by (i) solving M problems with one OAR each via the method presented in this paper, (ii) solving $\binom{M}{2}$ quartic equations to uniquely identify additional candidate (d_1, d_2) pairs and (iii) identifying and comparing all feasible (d_1, d_2) pairs derived from steps (i) and (ii).

The framework proposed in this paper can be further extended to clinically relevant scenarios. For example, uncertainty in various problem parameters was not explicitly incorporated into our formulation, although it is of special interest in some modalities such as protons. Effects of uncertainty were only indirectly studied via sensitivity analyses. Formulations that explicitly include uncertainty in parameters may provide an interesting direction for future research.

Acknowledgements

This research was funded in part by the National Science Foundation through grant 1560476.

REFERENCES

- AHAMAD, A., ROSENTHAL, D. I. & ANG, K. K. (2005) *Squamous Cell Head and Neck Cancer: Recent Clinical Progress and Prospects for the Future*. Current Clinical Oncology. Totowa, NJ, USA: Humana Press.
- AHN, P. H., LUKENS, J. N., TEO, B-K. K., KIRK, M. & LIN, A. (2014) The use of proton therapy in the treatment of head and neck cancers. *Cancer J.*, **20**, 421–426.
- ARCANGELI, G., SARACINO, B., GOMELLINI, S., PETRONGARI, M. G., ARCANGELI, S., SENTINELLI, S., MARZI, S., LANDONI, V., FOWLER, J. & STRIGARI, L. (2010) A prospective phase iii randomized trial of hypofractionation versus conventional fractionation in patients with high-risk prostate cancer. *Int. J. Radiat. Oncol. Biol. Phys.*, **78**, 11–18.
- ARMPILIA, C. I., DALE, R. G. & JONES, B. (2004) Determination of the optimum dose per fraction in fractionated radiotherapy when there is delayed onset of tumour repopulation during treatment. *Br. J. Radiol.*, **77**, 765–767.
- BADRI, H., WATANABE, Y. & LEDER, K. (2016) Optimal radiotherapy dose schedules under parametric uncertainty. *Phys. Med. Biol.*, **61**, 338.
- BAUMANN, M., KRAUSE, M., OVERGAARD, J., DEBUS, J., BENTZEN, S. M., DAARTZ, J., RICHTER, C., ZIPS, D. & BORTFELD, T. (2016) Radiation oncology in the era of precision medicine. *Nat. Rev. Cancer*, **16**, 234–249.
- BERTUZZI, A., BRUNI, C., PAPA, F. & SINISGALLI, C. (2013) Optimal solution for a cancer radiotherapy problem. *J. Math. Biol.*, **66**, 311–349.
- BONNET, R. B., BUSH, D., CHEEK, G. A., SLATER, J. D., PANOSSIAN, D., FRANKE, C. & SLATER, J. M. (2001) Effects of proton and combined proton/photon beam radiation on pulmonary function in patients with resectable but medically inoperable non-small cell lung cancer. *Chest*, **120**, 1803–1810.
- BORTFELD, T., RAMAKRISHNAN, J., TSITSIKLIS, J. N. & UNKELBACH, J. (2015) Optimization of radiotherapy fractionation schedules in the presence of tumor repopulation. *INFORMS J. Comput.*, **27**, 788–803.
- BOYD, S. & VANDENBERGHE, L. (2004) *Convex Optimization*. Cambridge, UK: Cambridge University Press.
- CHEN, Z., WANG, J. & HU, W. (2016) SU-F-T-199: A new strategy for integrating photon with proton and carbon ion in the treatment planning. *Med. Phys.*, **43**, 3507–3508.
- CORWIN, D., HOLDSWORTH, C., ROCKNE, R. C., TRISTER, A. D., MRUGALA, M. M., ROCKHILL, J. K., STEWART, R. D., PHILLIPS, M. & SWANSON, K. R. (2013) Toward patient-specific, biologically optimized radiation therapy plans for the treatment of glioblastoma. *PLOS One*, **8**, e79115.
- DEKKER, A. L. A. J., GULLIFORD, S. L., EBERT, M. A. & ORTON, C. G. (2014) Point/counterpoint: future radiotherapy practice will be based on evidence from retrospective interrogation of linked clinical data sources rather than prospective randomized controlled clinical trials. *Med. Phys.*, **41**, 1–3.

- DELANEY, T. F. (2009) Phase II study of high-dose photon/proton radiotherapy in the management of spine sarcomas. *Int. J. Radiat. Oncol. Biol. Phys.*, **74**, 732–739.
- DELANEY, T. F. (2011) Proton therapy in the clinic. *Front. Radiat. Ther. Oncol.*, **43**, 465–485.
- DELANEY, T. F., LIEBSCH, N. J., PEDLOW, F. X., ADAMS, J., WEYMAN, E. A., YEAP, B. Y., DEPAUW, N., NIELSEN, G. P., HARMON, D. C., YOON, S. S., CHEN, Y. L., SCHWAB, J. H. & HORNICEK, F. J. (2014) Long-term results of phase ii study of high dose photon/proton radiotherapy in the management of spine chordomas, chondrosarcomas, and other sarcomas. *J. Surg. Oncol.*, **110**, 115–122.
- EBNER, D. K. & KAMADA, T. (2016) The emerging role of carbon-ion radiotherapy. *Front. Oncol.*, **6**, 1–6.
- ENDERLING, H., ANDERSON, A. R. A., CHAPLAIN, M. A. J., MUNRO, A. J. & VAIDYA, J. S. (2006) Mathematical modelling of radiotherapy strategies for early breast cancer. *J. Theor. Biol.*, **241**, 158–171.
- ENDERLING, H., CHAPLAIN, M. A. J., ANDERSON, A. R. A. & VAIDYA, J. S. (2007) A mathematical model of breast cancer development, local treatment and recurrence. *J. Theor. Biol.*, **246**, 245–259.
- ENDERLING, H., CHAPLAIN, M. A. J. & HAHNFELDT, P. (2010) Quantitative modeling of tumor dynamics and radiotherapy. *Acta Biotheor.*, **58**, 341–353.
- FEUVRET, L., NOEL, G., WEBER, D. C., POMMIER, P., FERRAND, R., DE MARZI, L., DHERMAIN, F. & ALAPETITE, C. (2007) A treatment planning comparison of combined photon–proton beams versus proton beams—only for the treatment of skull base tumors. *Int. J. Radiat. Oncol. Biol. Phys.*, **69**, 944–954.
- FOWLER, J. F. (1990) How worthwhile are short schedules in radiotherapy? A series of exploratory calculations. *Radiother. Oncol.*, **18**, 165–181.
- FOWLER, J. F. (2001) Biological factors influencing optimum fractionation in radiation therapy. *Acta Oncol.*, **40**, 712–717.
- FOWLER, J. F. (2007) Is there an optimal overall time for head and neck radiotherapy? A review with new modeling. *Clin. Oncol.*, **19**, 8–27.
- FOWLER, J. F. (2008) Optimum overall times ii: extended modelling for head and neck radiotherapy. *Clin. Oncol.*, **20**, 113–126.
- FOWLER, J. F. & RITTER, M. A. (1995) A rationale for fractionation for slowly proliferating tumors such as prostatic adenocarcinoma. *Int. J. Radiat. Oncol. Biol. Phys.*, **32**, 521–529.
- FU, K. K., PAJAK, T. F., TROTTI, A., JONES, C. U., SPENCER, S. A., PHILLIPS, T. L., GARDEN, A. S., RIDGE, J. A., COOPER, J. S. & ANG, K. K. (2000) A radiation therapy oncology group (RTOG) phase iii randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: first report of RTOG 9003. *Int. J. Radiat. Oncol. Biol. Phys.*, **48**, 7–16.
- GARDEN, A. S. (2001) Altered fractionation for head and neck cancer. *Oncology*, **15**, 1326–1332.
- GOITEIN, M. & COX, J. D. (2008) Should randomized clinical trials be required for proton radiotherapy. *J. Clin. Oncol.*, **26**, 175–176.
- GRUTERS, J. P., KESSELS, A. G. H., PIJLS-JOHANNESMA, M., DE RUYSSCHER, D., JOORE, M. A. & LAMBIN, P. (2010) Comparison of the effectiveness of radiotherapy with photons, protons and carbon-ions for non-small cell lung cancer: a meta-analysis. *Radiother. Oncol.*, **95**, 32–40.
- HALL, E. J. & GIACCIA, A. J. (2005) *Radiobiology for the Radiologist*. Philadelphia, PA, USA: Lippincott Williams & Wilkins.
- HALPERIN, E. C. (2006) Particle therapy and treatment of cancer. *Lancet Oncol.*, **7**, 676–685.
- HALPERIN, E. C., BRADY, L. W. & PEREZ, C. A. (2013) *Perez and Brady's Principles and Practice of Radiation Oncology*. Philadelphia, PA, USA: Lippincott Williams and Wilkins (Wolters Kluwer Health).
- HIGGINS, K. A., O'CONNELL, K., LIU, Y., GILLESPIE, T. W., MCDONALD, M. W., PILLAI, R. N., PATEL, K. R., PATEL, P. R., ROBINSON, C. G., SIMONE, C. B., OWONIKOKO, T. K., BELANI, C. P., KHURI, F. R., CURRAN, W. J., RAMALINGAM, S. S. & BEHERA, M. (2017) National cancer database analysis of proton versus photon radiation therapy in non-small cell lung cancer. *Int. J. Radiat. Oncol. Biol. Phys.*, **97**, 128–137.
- HO, K. F., FOWLER, J. F., SYKES, A. J., YAP, B. K., LEE, L. W. & SLEVIN, N. J. (2009) Imrt dose fractionation for head and neck cancer: variation in current approaches will make standardisation difficult. *Acta Oncol.*, **48**, 431–439.

- HORIOU, J. C., BONTEMPS, P., VAN DEN BOGAERT, W., FUR, R. L., VAN DEN WEIINGAERT, D., BOLLA, M., BERNIER, J., LUSINCHI, A., STUSCHKE, M., LOPEZ-TORRECILLA, J., BEGG, A. C., PIERART, M. & COLLETTE, L. (1997) Accelerated fractionation (AF) compared to conventional fractionation (CF) improves loco-regional control in the radiotherapy of advanced head and neck cancers: results of the eortc 22851 randomized trial. *Radiother. Oncol.*, **44**, 111–121.
- HORIOU, J. C., LE FUR, R., N'GUYEN, R., CHENAL, C., SCHRAUB, S., ALFONSI, S., GARDANI, G., VAN DEN BOGAERT, W., DANCZAK, S. & BOLLA, M. (1992) Hyperfractionation versus conventional fractionation in oropharyngeal carcinoma: final analysis of a randomized trial of the eortc cooperative group of radiotherapy. *Radiother. Oncol.*, **25**, 231–241.
- JONES, B., TAN, L. T. & DALE, R. G. (1995) Derivation of the optimum dose per fraction from the linear quadratic model. *Br. J. Radiol.*, **68**, 894–902.
- KADER, H. A., MYDIN, A. R., WILSON, M., ALEXANDER, C., SHAHI, J., PATHAK, I., WU, J. S. & TRUONG, P. T. (2011) Treatment outcomes of locally advanced oropharyngeal cancer: A comparison between combined modality radio-chemotherapy and two variants of single modality altered fractionation radiotherapy. *Int. J. Radiat. Oncol. Biol. Phys.*, **80**, 1030–1036.
- KELLER, H., MEIER, G., HOPE, A. & DAVISON, M. (2012) Fractionation schedule optimization for lung cancer treatments using radiobiological and dose distribution characteristics. *Med. Phys.*, **39**, 3811.
- LAMBIN, P., ZINDLER, J., VANNESTE, B. G. L., DE VOORDE, L. V., EEKERS, D., COMPTE, I., PANTH, K. M., PEERLINGS, J., LARUE, R. T. H. M., DEIST, T. M., JOCHEMS, A., LUSTBERG, T., VAN SOEST, J., DE JONG, E. E. C., EVEN, A. J. G., REYEMEN, B., REKERS, N., VAN GISBERGEN, M., ROELOFS, E., CARVALHO, S., LEIJENAAR, R. T. H., ZEGERS, C. M. L., JACOBS, M., VAN TIMMEREN, J., BROUWERS, P., LAL, J. A., DUBOIS, L., YAROMINA, A., VAN LIMBERGEN, E. J., BERBEE, M., VAN ELMPT, W., OBERIJE, C., RAMAEKERS, B., DEKKER, A. L. A. J., BOERSMA, L. J., HOEBERS, F., SMITS, K. M., BERLANGA, A. J. & WALSH, S. (2017) Decision support systems for personalized and participative radiation oncology. *Adv. Drug Deliv. Rev.*, **109**, 131–153.
- LAWRENCE, T. S., TEN HAKKEN, R. K. & GIACCIA, A. (2008) *Principles of Radiation Oncology*. Philadelphia, PA, USA: Lippincott Williams and Wilkins.
- LEWIN, T. D., MAINI, P. K., MOROS, E. G., ENDERLING, H. E. & BYRNE, H. M. (2018) The evolution of tumour composition during fractionated radiotherapy: implications for outcome. *Bull. Math. Biol.*, **80**, 1207–1235.
- LOEFFLER, J. S. & DURANTE, M. (2013) Charged particle therapy-optimization, challenges and future directions. *Nat. Rev. Clin. Oncol.*, **10**, 411–424.
- VAN LOON, J., GRUTTERS, J. P. & MACBETH, F. (2012) Evaluation of novel radiotherapy technologies: what evidence is needed to assess their clinical and cost effectiveness, and how should we get it? *Lancet Oncol.*, **13**, e169–e177.
- LUO, Z.-Q., MA, W.-K., SO, A. M. C. & YE, Y. (2010) Semidefinite relaxation of quadratic optimization problems. *IEEE Signal Process. Mag.*, **27**, 20–34.
- MAIO, S. DI, YIP, S., AL ZHRANI, G. A., ALOTAIBI, F. E., AL TURKI, A., KONG, E. & ROSTOMILY, R. C. (2015) Novel targeted therapies in chordoma: an update. *Ther. Clin. Risk Manag.*, **11**, 873–883.
- MARKS, L. B., YORKE, E. D., JACKSON, A., TEN HAKEN, R. K., CONSTINE, L. S., EISBRUCH, A., BENTZEN, S. M., NAM, J. & DEASY, J. O. (2010) Use of normal tissue complication probability models in the clinic. *Int. J. Radiat. Oncol. Biol. Phys.*, **76**, S10–S19.
- MARZI, S., SARACINO, B., PETRONGARI, M., ARCANGELI, S., GOMELLINI, S., ARCANGELI, G., BENASSI, M. & LANDONI, V. (2009) Modeling of alpha/beta for late rectal toxicity from a randomized phase ii study: conventional versus hypofractionated scheme for localized prostate cancer. *J. Exp. Clin. Cancer Res.*, **28**, 117–124.
- MCDERMOTT, P. N. (2016) *Tutorials in Radiotherapy Physics: Advanced Topics with Problems and Solutions*. Boca Raton, Florida, USA: CRC Press.
- MITIN, T. & ZIETMAN, A. L. (2014) Promise and pitfalls of heavy-particle therapy. *J. Clin. Oncol.*, **32**, 2855–2863.
- MIZUTA, M., TAKAO, S., DATE, H., KISHIMOTO, N., SUTHERLAND, K. L., ONIMARU, R. & SHIRATO, H. (2012) A mathematical study to select fractionation regimen based on physical dose distribution and the linear-quadratic model. *Int. J. Radiat. Oncol. Biol. Phys.*, **84**, 829–833.

- MORGAN, J. P. (2008) A patient's perspective on randomized clinical trials for proton radiotherapy. *J. Clin. Oncol.*, **26**, 2592.
- O'ROURKE, S. F. C., MCANENEY, H. & HILLEN, T. (2009) Linear quadratic and tumour control probability modelling in external beam radiotherapy. *J. Math. Biol.*, **58**, 799–817.
- PAGANETTI, H. (2012) Range uncertainties in proton therapy and the role of Monte Carlo simulations. *Phys. Med. Biol.*, **57**, R99–R117.
- PAGANETTI, H. (2014) Relative biological effectiveness (RBE) values for proton beam therapy. Variations as a function of biological endpoint, dose, and linear energy transfer. *Phys. Med. Biol.*, **59**, R419–R472.
- PAGANETTI, H., NIEMERKO, A., ANCUKIEWICZ, M., GERWECK, L. E., GOITEIN, M., LOEFFLER, J. S. & SUIT, H. D. (2002) Relative biological effectiveness (RBE) values for proton beam therapy. *Int. J. Radiat. Oncol. Biol. Phys.*, **53**, 407–421.
- PAGANETTI, H. & VAN LUIJK, P. (2013) Biological considerations when comparing proton therapy with photon therapy. *Semin. Radiat. Oncol.*, **23**, 77–87.
- PEETERS, A., GRUTTERS, J., PIJLS-JOHANNESMA, M., REIMOSER, S., DE RUYSSCHER, D., SEVERENS, J. L., JOORE, M. A. & LAMBIN, P. (2010) How costly is particle therapy? Cost analysis of external beam radiotherapy with carbon-ions, protons and photons. *Radiat. Res.*, **95**, 45–53.
- POLESZCZUK, J., WALKER, R., MOROS, E., LATIFI, K., CAUDELL, J. & ENDERLING, H. (2018) Predicting patient-specific radiotherapy protocols based on mathematical model choice for proliferation saturation index. *Bull. Math. Biol.*, **80**, 1195–1206.
- POWATHIL, G. G., ADAMSON, D. J. A. & CHAPLAIN, M. A. J. (2013) Towards predicting the response of a solid tumour to chemotherapy and radiotherapy treatments: Clinical insights from a computational model. *PLOS Comput. Biol.*, **9**, e1003120.
- POWATHIL, G. G., KOHANDEL, M., SIVALOGANATHAN, S., OZA, A. & MILOSEVIC, M. (2007) Mathematical modeling of brain tumors: effects of radiotherapy and chemotherapy. *Phys. Med. Biol.*, **52**, 3291–3306.
- RAMAEKERS, B. L., GRUTTERS, J. P., PIJLS-JOHANNESMA, M., LAMBIN, P., JOORE, M. A. & LANGENDIJK, J. A. (2013) Protons in head-and-neck cancer: bridging the gap of evidence. *Int. J. Radiat. Oncol. Biol. Phys.*, **85**, 1282–1288.
- RAMAEKERS, B. L., PIJLS-JOHANNESMA, M., JOORE, M. A., VAN DEN ENDE, P., LANGENDIJK, J. A., LAMBIN, P., KESSELS, A. G. H. & GRUTTERS, J. P. (2011) Systematic review and meta-analysis of radiotherapy in various head and neck cancers: comparing photons, carbon-ions and protons. *Cancer Treat. Rev.*, **37**, 185–201.
- ROCKWELL, S. (1998) Experimental radiotherapy: a brief history. *Radiat. Res.*, **150**(Supplement), S157–S169.
- RONG, Y. & WELSH, J. (2010) Basics of particle therapy II biologic and dosimetric aspects of clinical hadron therapy. *Am. J. Clin. Oncol.*, **33**, 646–649.
- SABERIAN, F., GHATE, A. & KIM, M. (2015) A two-variable linear program solves the standard linear-quadratic formulation of the fractionation problem in cancer radiotherapy. *Oper. Res. Lett.*, **43**, 254–258.
- SABERIAN, F., GHATE, A. & KIM, M. (2016) Optimal fractionation in radiotherapy with multiple normal tissues. *Math. Med. Biol.*, **33**, 211–252.
- SABERIAN, F., GHATE, A. & KIM, M. (2017) Spatiotemporally optimal fractionation in radiotherapy. *INFORMS J. Comput.*, **29**, 422–437.
- SCHAU, D. & MCBRIDE, W. H. (2015) Opportunities and challenges of radiotherapy for treating cancer. *Nat. Rev. Clin. Oncol.*, **12**, 527–540.
- SCHILLER, K. C., HABL, G. & COMBS, S. E. (2016) Protons, photons, and the prostate—is there emerging evidence in the ongoing discussion on particle therapy for the treatment of prostate cancer? *Front. Oncol.*, **6**, 1–7.
- SCHULZ, R. J. & KAGAN, A. R. (2016) Carbon-ion therapy: one more step in the endless quest for the ideal dose distribution. *Int. J. Radiat. Oncol. Biol. Phys.*, **95**, 561.
- SCHULZ-ERTNER, D., JAKEL O. & SCHLEGEL, W. (2006) Radiation therapy with charged particles. *Semin. Radiat. Oncol.*, **16**, 249–259.
- SCHULZ-ERTNER, D. & TSUJII, H. (2007) Particle radiation therapy using proton and heavier ion beams. *J. Clin. Oncol.*, **25**, 953–964.
- TOMMSINO, F., SCIFONI, E. & DURANTE, M. (2015) New ions for therapy. *Int. J. Part. Ther.*, **2**, 428–438.

- TORRES, M. A., CHANG, E. L., MAHAJAN, A., LEGE, D. G., RILEY, B. A., ZHANG X., LI, M., KORNGUTH, D. G., PELLOSKI, C. E. & WOO, S. Y. (2009) Optimal treatment planning for skull base chordoma: photons, protons, or a combination of both? *Int. J. Radiat. Oncol. Biol. Phys.*, **74**, 1033–1039.
- TROTTI, A., FU, K. K., PAJAK, T. F., JONES, C. U., SPENCER, S. A., PHILLIPS, T. L., GARDEN, A. S., RIDGE, J. A., COOPER, J. S. & ANG, K. K. (2005) Long term outcomes of RTOG 90–03: a comparison of hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinoma. *Int. J. Radiat. Oncol. Biol. Phys.*, **63**(Supplement 1), S70–S71.
- TYSON, M. D., PENSON, D. F. & RESNICK, M. J. (2017) The comparative oncologic effectiveness of available management strategies for clinically localized prostate cancer. *Urol. Oncol.*, **35**, 51–58.
- UNKELBACH, J., CRAFT, D., SALERI, E., RAMAKRISHNAN, J. & BORTFELD, T. (2013a) The dependence of optimal fractionation schemes on the spatial dose distribution. *Phys. Med. Biol.*, **58**, 159–167.
- UNKELBACH, J., ZENG, C. & ENGELSMAN, M. (2013b) Simultaneous optimization of dose distributions and fractionation schemes in particle radiotherapy. *Med. Phys.*, **40**, 091702.
- WITHERS, H. R. (1985) Biologic basis for altered fractionation schemes. *Cancer*, **55**, 2086–2095.
- YANG, Y. & XING, L. (2005) Optimization of radiotherapy dose-time fractionation with consideration of tumor specific biology. *Med. Phys.*, **32**, 3666–3677.
- YONEMOTO, L. T., SLATER, J. D., ROSSI JR, C. J., ANTOINE, J. E., LOREDO, L., ARCHAMBEAU, J. O., SCHULTE, R. W., MILLER, D. W., TEICHMAN, S. L. & SLATER, J. M. (1997) Combined proton and photon conformal radiation therapy for locally advanced carcinoma of the prostate: preliminary results of a phase I/II study. *Int. J. Radiat. Oncol. Biol. Phys.*, **37**, 21–29.

Appendix A. Technical details about solution method for $Q(N_1, N_2)$

There are three possibilities: $d_1 > 0, d_2 = 0$; $d_1 = 0, d_2 > 0$; and $d_1 > 0, d_2 > 0$. In the first two cases, the problem reduces to a single modality problem, which can be solved simply by solving a quadratic equation derived from constraint (15). Specifically, in the first case, a candidate d_1 is given by

$$d_1 = \frac{-N_1 s_1 \alpha_1^\phi + \sqrt{N_1^2 s_1^2 (\alpha_1^\phi)^2 + 4N_1 \beta_1^\phi s_1^2 B}}{2N_1 \beta_1^\phi (s_1)^2}. \quad (\text{A.1})$$

In the second case, a candidate d_2 is given by

$$d_2 = \frac{-N_2 s_2 \alpha_2^\phi + \sqrt{N_2^2 s_2^2 (\alpha_2^\phi)^2 + 4N_2 \beta_2^\phi s_2^2 B}}{2N_2 \beta_2^\phi (s_2)^2}. \quad (\text{A.2})$$

In order to explore the third case, we attach Lagrange multipliers λ , μ_1 and μ_2 with the three constraints (11)–(13), respectively. Then KKT conditions (see Equations (5.49) on page 243 of [Boyd & Vandenberghe, 2004](#)) for this problem can be written as $\mu_1 \geq 0$, $\mu_2 \geq 0$, $\mu_1 d_1 = 0$, $\mu_2 d_2 = 0$, $d_1 \geq 0$, $d_2 \geq 0$ and

$$N_1 s_1 \alpha_1^\phi d_1 + N_1 \beta_1^\phi (s_1 d_1)^2 + N_2 s_2 \alpha_2^\phi d_2 + N_2 \beta_2^\phi (s_2 d_2)^2 = B, \quad (\text{A.3})$$

$$\begin{bmatrix} -\mu_1 \\ -\mu_2 \end{bmatrix} + \lambda \begin{bmatrix} N_1 s_1 \alpha_1^\phi + 2N_1 \beta_1^\phi s_1^2 d_1 \\ N_2 s_2 \alpha_2^\phi + 2N_2 \beta_2^\phi s_2^2 d_2 \end{bmatrix} = \begin{bmatrix} N_1 \alpha_1^\tau + 2N_1 \beta_1^\tau d_1 \\ N_2 \alpha_2^\tau + 2N_2 \beta_2^\tau d_2 \end{bmatrix}. \quad (\text{A.4})$$

Since $d_1 > 0$ and $d_2 > 0$, we know that $\mu_1 = \mu_2 = 0$. Substituting this into the system (A.4) of equations yields

$$d_1 = \frac{\lambda s_1 \alpha_1^\phi - \alpha_1^\tau}{2(\beta_1^\tau - \lambda \beta_1^\phi s_1^2)}, \quad (\text{A.5})$$

$$d_2 = \frac{\lambda s_2 \alpha_2^\phi - \alpha_2^\tau}{2(\beta_2^\tau - \lambda \beta_2^\phi s_2^2)}. \quad (\text{A.6})$$

Substituting this back into (A.3) yields the following quartic equation:

$$\begin{aligned} & \lambda^4 \left(-16B(\beta_1^\phi)^2 (\beta_2^\phi)^2 s_1^4 s_2^4 - 4(\alpha_1^\phi)^2 \beta_1^\phi (\beta_2^\phi)^2 N_1 s_1^4 s_2^4 - 4(\alpha_2^\phi)^2 \beta_2^\phi (\beta_1^\phi)^2 N_2 s_2^4 s_1^4 \right) \\ & + \lambda^3 \left(32B(\beta_1^\phi)^2 \beta_2^\phi \beta_2^\tau s_1^4 s_2^2 + 16(\alpha_1^\phi)^2 \beta_1^\phi (\beta_2^\phi)^2 N_1 s_1^4 s_2^2 - 8(\alpha_1^\phi)^2 \beta_1^\phi \beta_2^\phi \beta_2^\tau N_1 s_1^4 s_2^2 \right. \\ & + 8(\alpha_2^\phi)^2 (\beta_1^\phi)^2 \beta_2^\tau N_2 s_1^4 s_2^2 + 32B\beta_1^\phi \beta_1^\tau (\beta_2^\phi)^2 s_1^2 s_2^4 + 8(\alpha_1^\phi)^2 \beta_1^\tau (\beta_2^\phi)^2 N_1 s_1^2 s_2^4 \\ & \left. 16(\alpha_2^\phi)^2 (\beta_1^\phi)^2 \beta_2^\phi N_2 s_1^2 s_2^4 - 8(\alpha_2^\phi)^2 \beta_1^\phi \beta_1^\tau \beta_2^\phi N_2 s_1^2 s_2^4 \right) \\ & + \lambda^2 \left(-16B(\beta_1^\phi)^2 (\beta_2^\tau)^2 s_1^4 - 8(\alpha_1^\phi)^2 \beta_1^\phi (\beta_2^\phi)^2 N_1 s_1^4 + 4(\alpha_1^\phi)^2 \beta_1^\phi (\beta_2^\tau)^2 N_1 s_1^4 \right. \\ & - 8\alpha_2^\phi \alpha_2^\tau (\beta_1^\phi)^2 \beta_2^\tau N_2 s_1^4 s_2 - 64B\beta_1^\phi \beta_1^\tau \beta_2^\phi \beta_2^\tau s_1^2 s_2^2 - 16(\alpha_1^\phi)^2 \beta_1^\tau (\beta_2^\phi)^2 N_1 s_1^2 s_2^2 \\ & - 16(\alpha_2^\phi)^2 (\beta_1^\phi)^2 \beta_2^\tau N_2 s_1^2 s_2^2 - 16\alpha_1^\phi \alpha_1^\tau \beta_1^\phi (\beta_2^\phi)^2 N_1 s_1^3 s_2^2 + 16\alpha_1^\phi \alpha_1^\tau \beta_1^\phi \beta_2^\phi \beta_2^\tau N_1 s_1^3 s_2^2 \\ & + 4(\alpha_2^\tau)^2 (\beta_1^\phi)^2 \beta_2^\phi N_2 s_1^4 s_2^2 - 16\alpha_2^\phi \alpha_2^\tau (\beta_1^\phi)^2 \beta_2^\phi N_2 s_1^2 s_2^3 + 16\alpha_2^\phi \alpha_2^\tau \beta_1^\phi \beta_1^\tau \beta_2^\phi N_2 s_1^2 s_2^3 \\ & - 16B(\beta_1^\tau)^2 (\beta_2^\phi)^2 s_2^4 - 8(\alpha_2^\phi)^2 (\beta_1^\phi)^2 \beta_2^\phi N_2 s_2^4 + 4(\alpha_2^\phi)^2 (\beta_1^\tau)^2 \beta_2^\phi N_2 s_2^4 \\ & - 8\alpha_1^\phi \alpha_1^\tau \beta_1^\tau (\beta_2^\phi)^2 N_1 s_1 s_2^4 + 4(\alpha_1^\tau)^2 \beta_1^\phi (\beta_2^\phi)^2 N_1 s_1^2 s_2^4 \left. \right) \\ & + \lambda \left(32B\beta_1^\phi \beta_1^\tau (\beta_2^\tau)^2 s_1^2 + 8(\alpha_1^\phi)^2 \beta_1^\tau (\beta_2^\phi)^2 N_1 s_1^2 + 8\alpha_1^\phi \alpha_1^\tau \beta_1^\phi (\beta_2^\phi)^2 N_1 s_1^3 \right. \\ & - 8\alpha_1^\phi \alpha_1^\tau \beta_1^\phi (\beta_2^\tau)^2 N_1 s_1^3 + 16\alpha_2^\phi \alpha_2^\tau (\beta_1^\phi)^2 \beta_2^\tau N_2 s_1^2 s_2 + 32B(\beta_1^\tau)^2 \beta_2^\phi \beta_2^\tau s_2^2 \\ & + 8(\alpha_2^\phi)^2 (\beta_1^\phi)^2 \beta_2^\tau N_2 s_2^2 + 16\alpha_1^\phi \alpha_1^\tau \beta_1^\tau (\beta_2^\phi)^2 N_1 s_1 s_2^2 - 8(\alpha_1^\tau)^2 \beta_1^\phi \beta_2^\phi \beta_2^\tau N_1 s_1^2 s_2^2 \\ & - 8(\alpha_2^\tau)^2 \beta_1^\phi \beta_1^\tau \beta_2^\phi N_2 s_1^2 s_2^2 + 8\alpha_2^\phi \alpha_2^\tau (\beta_1^\phi)^2 \beta_2^\phi N_2 s_2^3 - 8\alpha_2^\phi \alpha_2^\tau (\beta_1^\tau)^2 \beta_2^\phi N_2 s_2^3 \left. \right) \\ & + \left(-16B(\beta_1^\tau)^2 (\beta_2^\tau)^2 - 8\alpha_1^\phi \alpha_1^\tau \beta_1^\tau (\beta_2^\phi)^2 N_1 s_1 + 4(\alpha_1^\tau)^2 \beta_1^\phi (\beta_2^\tau)^2 N_1 s_1^2 \right. \\ & \left. - 8\alpha_2^\phi \alpha_2^\tau (\beta_1^\phi)^2 \beta_2^\tau N_2 s_2 + 4(\alpha_2^\tau)^2 (\beta_1^\tau)^2 \beta_2^\phi N_2 s_2^2 \right) = 0. \end{aligned}$$

This quartic equation can be easily solved analytically or numerically. Its real roots can then be substituted back into (A.5) and (A.6) to obtain candidate solutions. After solving the quartic equation, there are four possible cases for each real root that need to be considered separately based on the form of (A.5) and (A.6). In particular, the cases evaluate whether or not the numerator and/or denominator in (A.5) and (A.6) are zero.

1. Denominator and numerator of (A.5) are zero: $\lambda = \beta_1^\tau / (\beta_1^\phi s_1^2) = \alpha_1^\tau / (s_1 \alpha_1^\phi)$.

(a) Denominator of (A.6) is zero: $\lambda = \beta_2^\tau / (\beta_2^\phi s_2^2)$.

i. Numerator of (A.6) is zero: $\lambda = \alpha_2^\tau / (\alpha_2^\phi s_2)$.

The only way this can happen is if the two modalities behave identically, in the sense that $\frac{\alpha_1^\tau}{(\alpha_1^\phi s_1)} = \frac{\alpha_2^\tau}{(\alpha_2^\phi s_2)} = \frac{\beta_1^\tau}{(\beta_1^\phi s_1^2)} = \frac{\beta_2^\tau}{(\beta_2^\phi s_2^2)} = c$, for some constant c . In fact, in this case, we do not even need the KKT conditions, since problem $(P(N_1, N_2))$ can be rewritten by replacing α_1^τ and β_1^τ with $\alpha_1^\phi s_1 c$ and $\beta_1^\phi s_1^2 c$, respectively. This yields

$$\begin{aligned} \min \quad & -cB \\ & N_1 s_1 \alpha_1^\phi d_1 + N_1 \beta_1^\phi (s_1 d_1)^2 + N_2 s_2 \alpha_2^\phi d_2 + N_2 \beta_2^\phi (s_2 d_2)^2 = B, \\ & d_1, d_2 \geq 0. \end{aligned}$$

Thus, all feasible solutions are optimal as they all have the same objective function value of $-cB$ (note that the problem does have feasible solutions, e.g. $d_2 = 0$ and d_1 obtained by solving a quadratic equation).

ii. Numerator of (A.6) is not zero: $\lambda \neq \alpha_2^\tau / (\alpha_2^\phi s_2)$.

This situation does not yield a feasible d_2 , because the denominator in (A.6) is zero but the numerator is not. Thus, this case does not yield any candidate solutions.

(b) Denominator of (A.6) is not zero: $\lambda \neq \beta_2^\tau / (\beta_2^\phi s_2^2)$.

i. Numerator of (A.6) is zero: $\lambda = \alpha_2^\tau / (\alpha_2^\phi s_2)$.

This implies from (A.6) that $d_2 = 0$. This is contrary to the assumed scenario that $d_1 > 0$ and $d_2 > 0$. Thus, this case does not yield any candidate solutions.

ii. Numerator of (A.6) is not zero: $\lambda \neq \alpha_2^\tau / (\alpha_2^\phi s_2)$.

In this case, we can obtain d_2 from (A.6), substitute its value into (A.3) and solve a quadratic equation to get d_1 . That is,

$$d_1 = \frac{-N_1 s_1 \alpha_2^\phi + \sqrt{N_1^2 s_1^2 (\alpha_1^\phi)^2 + 4N_1 \beta_1^\phi s_1^2 (B - N_2 s_2 \alpha_2^\phi d_2 - N_2 \beta_2^\phi s_2^2 d_2^2)}}{2N_1 \beta_1^\phi s_1^2}. \quad (\text{A.7})$$

2. Denominator of (A.5) is zero but numerator is not: $\lambda = \beta_1^\tau / (\beta_1^\phi s_1^2)$ and $\lambda \neq \alpha_1^\tau / (\alpha_1^\phi s_1)$.

This situation does not yield a feasible d_1 because the denominator in (A.5) is zero but the numerator is not. Thus, this case does not yield any candidate solutions.

3. Denominator of (A.5) is not zero but numerator is: $\lambda \neq \beta_1^\tau / (\beta_1^\phi s_1^2)$ and $\lambda = \alpha_1^\tau / (\alpha_1^\phi s_1)$.

This implies from (A.5) that $d_1 = 0$. This is contrary to the assumed scenario that $d_1 > 0$ and $d_2 > 0$. Thus, this case does not yield any candidate solutions.

4. Neither the denominator nor the numerator of (A.5) is zero: $\lambda \neq \beta_1^\tau / (\beta_1^\phi s_1^2)$ and $\lambda \neq \alpha_1^\tau / (\alpha_1^\phi s_1)$.

(a) Denominator of (A.6) is zero: $\lambda = \beta_2^\tau / (\beta_2^\phi s_2^2)$.

i. Numerator of (A.6) is zero: $\lambda = \alpha_2^\tau / (\alpha_2^\phi s_2)$.

Here d_1 can be obtained from (A.5). We can substitute its value into (A.3) and solve a quadratic equation to calculate d_2 . That is,

$$d_2 = \frac{-N_2 s_2 \alpha_1^\phi + \sqrt{N_2^2 s_2^2 (\alpha_2^\phi)^2 + 4N_2 \beta_2^\phi (s_2)^2 (B - N_1 s_1 \alpha_1^\phi d_1 - N_1 \beta_1^\phi s_1^2 d_1^2)}}{2N_2 \beta_2 (s_2)^2}. \quad (\text{A.8})$$

ii. Numerator of (A.6) is not zero: $\lambda \neq \alpha_2^\tau / (\alpha_2^\phi s_2)$.

Here we cannot obtain any feasible d_2 because the denominator in (A.6) is zero but the numerator is not. Thus, this case does not yield any candidate solutions.

(b) Denominator of (A.6) is not zero: $\lambda \neq \beta_2^\tau / (\beta_2^\phi s_2^2)$.

i. Numerator of (A.6) is zero: $\lambda = \alpha_2^\tau / (\alpha_2^\phi s_2)$.

Here (A.6) yields $d_2 = 0$. This is contrary to the assumed scenario that $d_1 > 0$ and $d_2 > 0$. Thus, this case does not yield any candidate solutions.

ii. Numerator of (A.6) is not zero: $\lambda \neq \alpha_2^\tau / (\alpha_2^\phi s_2)$.

In this case, d_1 and d_2 can be obtained from (A.5) and (A.6).

The objective values of all candidate solutions can then be compared to find an optimal solution.