The emergence of nonuniform spatiotemporal fractionation schemes within the standard BED model

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Purpose: Nonuniform spatiotemporal radiotherapy fractionation schemes, i.e., delivering distinct dose distributions in different fractions can potentially improve the therapeutic ratio. This is possible if the dose distributions are designed such that similar doses are delivered to normal tissues (exploit the fractionation effect) while hypofractionating subregions of the tumor. In this paper, the authors develop methodology for treatment planning with nonuniform fractions and demonstrate this concept in the context of intensity-modulated proton therapy (IMPT).
Methods: Treatment planning is performed by simultaneously optimizing (possibly distinct) IMPT dose distributions for multiple fractions. This is achieved using objective and constraint functions evaluated for the cumulative biologically equivalent dose (BED) delivered at the end of treatment. BED based treatment planning formulations lead to nonconvex optimization problems, such that local gradient based algorithms require adequate starting positions to find good local optima. To that end, the authors develop a combinatorial algorithm to initialize the pencil beam intensities.
Results: The concept of nonuniform spatiotemporal fractionation schemes is demonstrated for a spinal metastasis patient treated in two fractions using stereotactic body radiation therapy. The patient is treated with posterior oblique beams with the kidneys being located in the entrance region of the beam. It is shown that a nonuniform fractionation scheme that hypofractionates the central part of the tumor allows for a skin and kidney BED reduction of approximately 10%–20%.
Conclusions: Nonuniform spatiotemporal fractionation schemes represent a novel approach to exploit fractionation effects that deserves further exploration for selected disease sites. © *2015 American Association of Physicists in Medicine.* [http://dx.doi.org/10.1118/1.4916684]

Key words: intensity-modulated proton therapy (IMPT), nonuniform fractionation, biologically equivalent dose (BED)

1. INTRODUCTION

In current clinical practice, most radiotherapy treatments are fractionated. This is motivated by the observation that most healthy tissues can tolerate a much higher total dose if the radiation is split into small fractions. On the other hand, fractionation typically requires that a higher total dose is delivered to the tumor in order to achieve the same level of response. Fractionation decisions therefore face the tradeoff between increasing the number of fractions to spare normal tissues and increasing the total dose to maintain the same level of tumor control.

In that regard, the ideal treatment would fractionate in normal tissues and at the same time hypofractionate in the tumor. This appears to be impossible at the first glance because the dose to normal tissues is an unavoidable consequence of delivering dose to the tumor. Generally, increasing the dose to the tumor in a given fraction will increase the dose to healthy tissues in that fraction. However, interestingly it is possible to achieve some degree of hypofractionation in parts of the tumor while exploiting the fractionation effect in normal tissues. The latter can be achieved by delivering distinct dose distributions in different fractions. The fractions have to be designed such that their dose distributions are similar in normal tissues, but different fractions deliver high single fraction doses to different regions of the tumor. Proton therapy provides one mechanism to realize such dose distributions. The dose in the entrance region of a proton beam is almost independent of its range. This provides some freedom to modify the dose in the tumor without affecting the dose in the entrance region substantially.

The most widely used model to compare different fractionation regimens is the biologically equivalent dose (BED) model,[1] which assumes that the biologically equivalent dose b is given by the total physical dose multiplied by a correction factor that increases linearly with the dose per fraction,

$$b = nd\left(1 + \frac{d}{(\alpha/\beta)}\right). \tag{1}$$

Here, n is the number of fractions, d is the dose per fraction, and α/β is an endpoint specific constant. Equation (1) can be used to compare the expected effectiveness of altered fractionation schemes, and it has also been the basis for mathematical approaches to optimizing fractionation schemes. Optimal fractionation based on the basic BED model has been studied in Ref. 2. In addition, the implications of different extensions of Eq. (1) on fractionation decisions have been studied. The publications[3–5] consider the dependence of fractionation schemes on the spatial dose distribution in the

normal tissue. Other authors have considered extensions to incorporate effects from repopulation, the overall treatment time, and incomplete repair.[6–8]

The projected benefit of delivering different dose distributions in different fractions has been studied for a stylized proof-of-concept model in Ref. 9, and the idea was conceptually introduced in Refs. 10 and 11. It is known that small α/β-ratios in the tumor suggest hypofractionation while large α/β-ratios in the tumor suggest hyperfractionation. In Ref. 9, it was shown that (under idealized assumptions on the proton beam characteristics) a nonuniform fractionation scheme emerges for intermediate α/β-values, in which it is optimal to deliver distinct dose distributions in different fractions. The present paper extends this work. Its main contributions over previous works are the following:

- The possible benefit of nonuniform spatiotemporal fractionation schemes is demonstrated for realistic patient geometries and realistic proton beams. To our knowledge this is the first rigorous demonstration of the concept in this setting.
- Treatment plan optimization methodology is developed to address the inherent nonconvexity of BED based intensity-modulated proton therapy (IMPT) optimization problems.

The remainder of this paper is organized as follows: In Sec. 2, we develop treatment planning methods. In Sec. 2.A, we formulate the IMPT optimization problem for nonuniform fractions based on the BED model; in Sec. 2.C.2, a method to generate initial pencil beam intensities is developed, which is needed to obtain high quality treatment plans through local gradient based optimization. In Sec. 3, we show results for a spinal metastasis case treated with stereotactic body radiation therapy (SBRT) to demonstrate the benefit of nonuniform spatiotemporal fractionation schemes.

2. BED BASED SPATIOTEMPORAL TREATMENT PLANNING

2.A. Problem formulation

We consider treatment planning for intensity-modulated proton therapy (IMPT). Usually, IMPT planning is based on the physical dose distribution within the patient. The dose distribution d is a linear function of pencil beam intensities x and is given by $d_i = \sum_j D_{ij} x_j$. Here, d_i is the physical dose in voxel i, x_j is the intensity of pencil beam j, and D_{ij} is the dose-influence matrix. The latter stores the dose contribution of pencil beam j to voxel i for unit intensity. The spot intensities x_j are determined by solving an optimization problem where an objective function $f(d)$ is minimized, subject to constraints $c_k(d) \le u_k$. In this case, objective and constraint functions are functions of the dose distribution. Furthermore, the pencil beam intensities x_j are identical in all fractions.

We now aim at simultaneously optimizing n possibly distinct fluence maps x_t, where n is the number of fractions. This will be performed using the concept of BED. To that end, we generalize the BED equation in (1) to the situation in which different doses are delivered in different fractions. The cumulative BED in voxel i over the entire treatment is then given by

$$b_i = \sum_{t=1}^{n} \left[d_{ti} + \frac{1}{(\alpha/\beta)_i} d_{ti}^2 \right], \tag{2}$$

where d_{ti} is the physical dose delivered to voxel i in fraction t and $(\alpha/\beta)_i$ is the α/β ratio of the tissue that voxel i belongs to. In principle, we can apply the same objective and constraint functions for treatment planning as before, except that we evaluate these functions for the cumulative BED instead of the physical dose. We can thus formulate the simultaneous optimization of multiple fractions as the following problem:

$$\underset{x}{\text{minimize}} \quad f(b) \tag{3}$$

subject to

$$c_k(b) \le u_k \qquad \forall k, \tag{4}$$

$$b_i = \sum_{t=1}^{n} b_{ti} \qquad \forall i, \tag{5}$$

$$b_{ti} = d_{ti} + \frac{1}{(\alpha/\beta)_i} d_{ti}^2 \qquad \forall i, \forall t, \tag{6}$$

$$d_{ti} = \sum_j D_{ij} x_{tj} \qquad \forall i, \forall t, \tag{7}$$

$$x_{tj} \ge 0 \qquad \forall j, \forall t. \tag{8}$$

2.B. Example case: Spinal metastasis SBRT treatment

To demonstrate the concept of nonuniform spatiotemporal fractionation schemes, we consider the spinal metastasis case shown in Fig. 1. For this case, the tumor is located anterior to the spinal cord. The patient is treated with posterior oblique fields, so that the kidneys are partially located in the entrance region of the beam.

We attempt to solve the treatment plan optimization problem (3)–(8) for the following choice of the objective function:

$$f(b) = \frac{10}{N_T} \sum_{i \in T} (b^{\text{pres}} - b_i)_+^2 \quad \text{(underdose)} \tag{9}$$

$$+ \frac{1}{N_T} \sum_{i \in T} (b_i - b^{\text{pres}})_+^2 \quad \text{(overdose)} \tag{10}$$

$$+ \frac{1}{N_K} \sum_{i \in K} b_i \quad \text{(mean kidney dose)} \tag{11}$$

$$+ \frac{1}{N_S} \sum_{i \in S} b_i \quad \text{(mean spinal cord dose)} \tag{12}$$

$$+ \frac{1}{N_H} \sum_{i \in H} b_i \quad \text{(mean health tissue dose)}, \tag{13}$$

where b^{pres} is the prescribed tumor BED, and T, S, K, and H denote the sets of voxels in the target, spinal cord, kidneys, and the remaining healthy tissue. In words, we minimize a weighted sum of a piecewise quadratic objective function for the target and the mean doses in healthy tissues. The most critical normal tissue is the spinal cord, which represents

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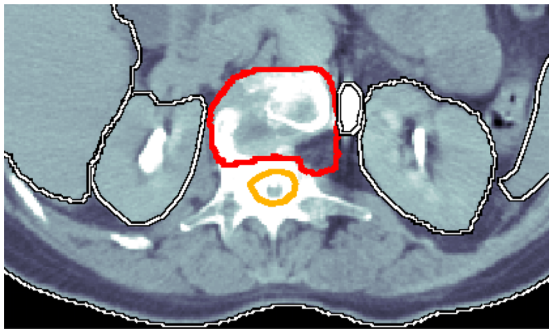

FIG. 1. Geometry of a spinal metastasis treatment. The target volume (solid contour) is located anterior to the spinal cord. Additional organs to spare are the kidneys.

a serial structure. We therefore impose a constraint on the maximum spinal cord BED,

$$b_i \le b_S^{\max} \quad \forall i \in S. \tag{14}$$

Additional parameters are chosen as follows:

1. We consider a two-fraction treatment ($t \in \{1,2\}$).
2. The α/β-ratios are chosen as $(\alpha/\beta)_T = 10$ for the tumor, $(\alpha/\beta)_S = 2$ in the spinal cord, and $(\alpha/\beta)_K = (\alpha/\beta)_H = 4$ in the kidneys and the remaining healthy tissues.
3. The prescribed BED b^{pres} is set to 72 Gy, corresponding to 60 Gy physical dose in 2 Gy fractions. This corresponds to a physical dose of 14.6 Gy per fraction in a uniform two-fraction treatment and a single fraction dose of 22.3 Gy.
4. The maximum BED to the spinal cord $b_S^{\max}$ is set to 60 Gy. For $(\alpha/\beta)_S = 2$, this corresponds to a single fraction dose of 10 Gy, which represents a recommended tolerance dose[12] for spine SBRT treatments. The corresponding maximum dose in a uniform two-fraction treatment is 13.6 Gy.
5. Two posterior oblique beam directions at 135° and 225° are used.
6. For IMPT planning, we use Gaussian pencil beams with a 5 mm sigma at the patient surface, spaced on a 5 mm grid.

2.C. Optimization methods

In this work, we use the L-BFGS Quasi-Newton method[13] to find a local minimum to problem (3)–(8). Dose constraints are handled via an augmented lagrangian method.[14] The main difficulty consists in handling the nonconvexity of problem (3)–(8) for simultaneous optimization of multiple dose distributions. For the special choice of objective functions (9)–(13), it is apparent that the term that causes the nonconvexity is quadratic penalty function (9) for underdosing the tumor.

The mean BED objectives for healthy tissues correspond to convex quadratic functions of the pencil beam intensities that are minimized and hence do not introduce nonconvexity to the problem. Term (10) for penalizing overdose can equivalently be written as

$$\frac{1}{N_T}\sum_{i\in T} o_i^2, \tag{15}$$

a convex quadratic function of the overdose o_i in voxel i. The quadratic equation that defines the overdose can than be relaxed and replaced by convex inequality constraints,

$$o_i \ge \sum_{t=1}^{n}\left(d_{ti} + \left(\frac{\beta}{\alpha}\right)_i d_{ti}^2\right) - b^{\text{pres}}, \tag{16}$$

$$o_i \ge 0. \tag{17}$$

Likewise, maximum BED constraints and quadratic overdose penalties for OARs can be handled without introducing nonconvexity. However, the same does not hold for the target underdose objective, because the analog of inequality (16) is a concave (rather than convex) quadratic inequality.

2.C.1. Generating a uniform reference plan

We first consider the optimization of a reference plan that delivers the same dose distribution in both fractions. This corresponds to enforcing the constraint $x_{1j} = x_{2j}$, which is equivalent to optimizing pencil beam intensities x_{1j} for a single fraction using formulation (3)–(8) while replacing the cumulative BED constraint in Eq. (5) by $b_i = 2b_{1i}$. In general, quadratic underdose objective function (9) can be a nonconvex function even if evaluated for a single dose distribution. However, in Appendix A we show that, for the parameters chosen in this paper, the objective is convex within the domain of relevant dose values. Therefore, the optimization of the uniform reference plan can be formulated as a convex optimization problem. Consequently, the global optimum can be found with gradient based optimization such as the L-BFGS Quasi-Newton method used in this work.

2.C.2. Generating initial pencil beam intensities for nonuniform treatments

Unlike the uniform fractionation case, treatment plan optimization for nonuniform spatiotemporal fractionation schemes represents an inherently nonconvex problem.[15] Based on our experience, local optima of nonuniform two-fraction treatments that are obtained through L-BFGS and a generic choice of initial pencil beam intensities do not yield good treatment plans. By generic initial intensities we mean random starting positions, uniform initial intensities, and small random perturbations of uniform intensities. We therefore suggest a combinatorial optimization approach to generate initial pencil beam intensities that are used as starting point for a subsequent local optimization.

We start with the optimized pencil beam intensities of the reference plan which we denote by x_j^{ref}. The method then divides the pencil beams into two sets, which are assigned to either fraction one or fraction two using binary variables $z_j \in \{-1,1\}$. We let $z_j = 1$ denote the case that pencil beam j is assigned to the first fraction so that $x_{1j} = 2x_j^{\text{ref}}$ and $x_{2j} = 0$. The total intensity of each pencil beam, and therefore the physical dose, remains unchanged compared to the reference plan. The objectives in the assignment of pencil beams to one of the two fractions are to maximize the mean BED in the target and to minimize the mean BED in normal tissues. Since the total

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physical dose remains unchanged, this has to be achieved by maximizing the difference in physical dose between fractions in the target, while minimizing the difference in normal tissues. In this case, the optimal assignment of pencil beams can be formulated as a binary quadratic optimization problem. We consider the mean quadratic dose difference in the tumor, which can be written as a quadratic function of $z_j \in \{-1,1\}$,

$$\frac{1}{N_T}\sum_{i\in T}(d_{1i}-d_{2i})^2 = \frac{1}{N_T}\sum_{i\in T}\left(\sum_j 2D_{ij}x_j^{\text{ref}}z_j\right)^2$$
$$= \sum_{j,k} z_j z_k \underbrace{\left(\frac{4}{N_T}\sum_{i\in T} D_{ij}x_j^{\text{ref}}D_{ik}x_k^{\text{ref}}\right)}_{Q_{jk}^T} \quad (18)$$
$$= \sum_{j,k} Q_{jk}^T z_j z_k. \quad (19)$$

The mean quadratic dose difference in the normal tissue can be formulated accordingly using a matrix Q_{jk}^U where a summation is performed over all normal tissue voxels that receive a dose larger than 1 Gy in the reference plan. To find an initialization of pencil beam intensities, we maximize the weighted sum of dose differences in the target and the healthy tissues,

$$\underset{z}{\text{maximize}} \quad \sum_{j,k}\underbrace{(Q_{jk}^T - \lambda Q_{jk}^U)}_{Q_{jk}} z_j z_k, \quad (20)$$

where $\lambda \geq 0$ is a parameter that weights fractionation in normal tissues against hypofractionation in the target. An approximate solution to problem (20) can be obtained through semidefinite programming and randomized rounding as outlined in Appendix B.

3. RESULTS

3.A. Uniform two fraction reference plan

We first consider the optimal uniform reference plan that delivers the same dose distribution in two fractions, which is illustrated in Fig. 2. Figure 2(a) shows the dose distribution delivered per fraction, featuring a homogeneous dose of 14.6 Gy in the target volume. Figures 2(b) and 2(c) show the dose contributions of the two incident beam directions.

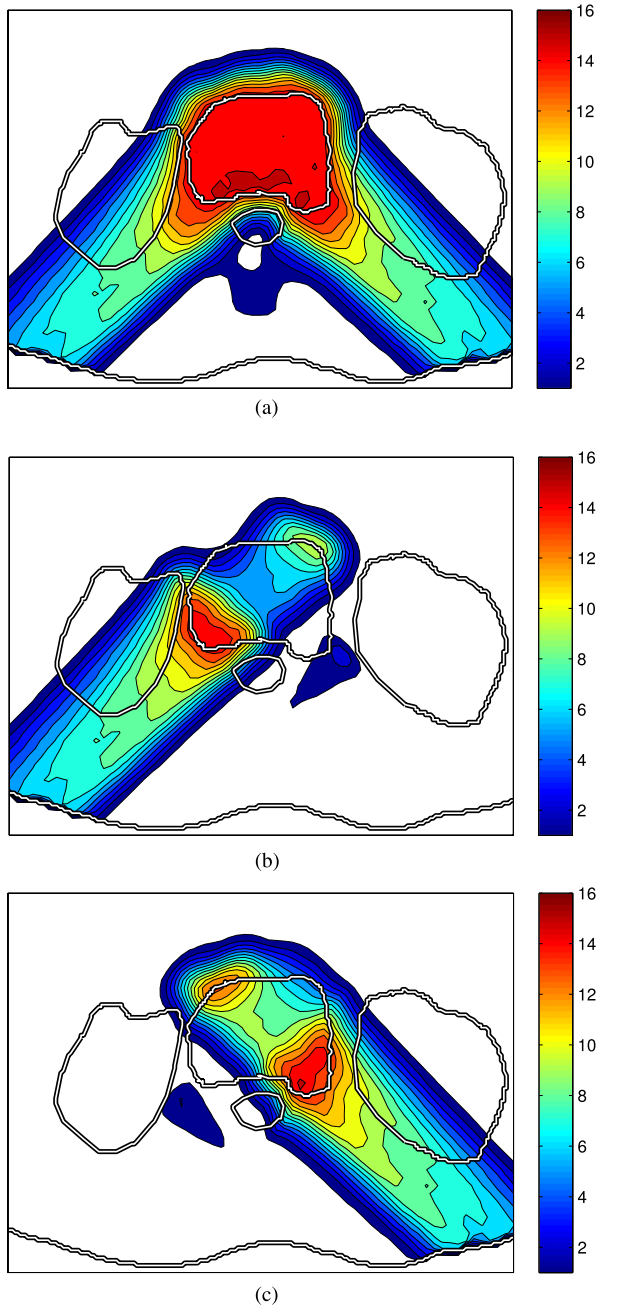

FIG. 2. Uniform reference treatment plan using two oblique beams. Both incident beams together deliver a uniform dose of 14.6 Gy per fraction to the target volume, corresponding to the prescribed BED of 72 Gy. (a) Physical dose per fraction, (b) contribution of beam 1, (c) contribution of beam 2.

3.B. Optimization of a nonuniform plan

Next, we optimize a nonuniform treatment plan based on the same objectives used to determine the reference plan. To that end, we employ a constrained formulation of the treatment planning problem. We minimize the mean BED delivered to the kidneys and the healthy tissue, subject to the constraints that the treatment goals for target and spinal cord do not worsen compared to the reference plan. The corresponding problem formulation is

$$\underset{x}{\text{minimize}} \quad \frac{1}{N_K}\sum_{i\in K} b_i + \frac{1}{N_H}\sum_{i\in H} b_i \quad (21)$$

subject to Eqs. (5)–(8) and

$$f_T^\star \geq \frac{10}{N_T}\sum_{i\in T}(b^{\text{pres}}-b_i)_+^2 \frac{1}{N_T}\sum_{i\in T}(b_i-b^{\text{pres}})_+^2, \quad (22)$$
$$f_S^\star \geq \frac{1}{N_S}\sum_{i\in S} b_i, \quad (23)$$
$$b_i \leq b_S^{\max} \quad \forall i \in S, \quad (24)$$

where $f_S^\star$ and $f_T^\star$ are the objective values for spinal cord and the target obtained for the uniform two fraction reference plan. A treatment plan is optimized based on a local optimization

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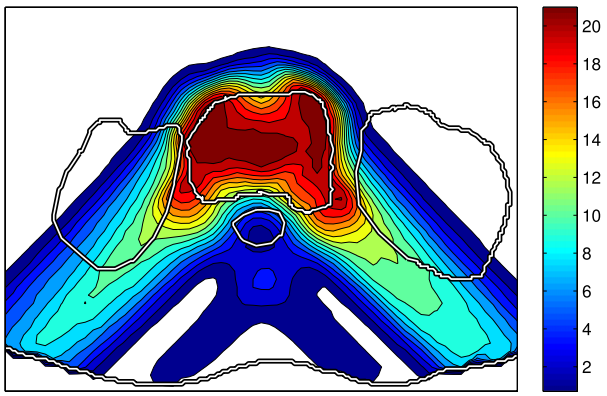
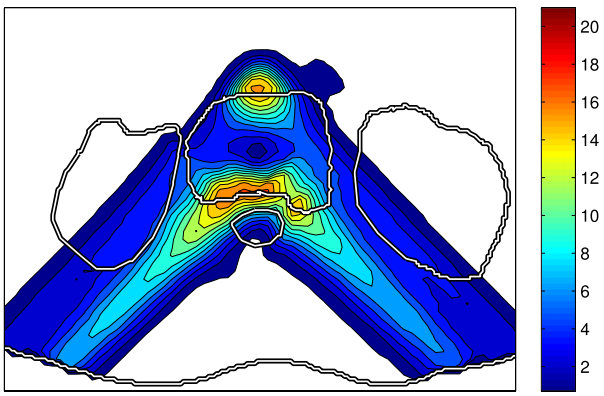
of this problem using the L-BFGS Quasi-Newton method and using initial beam intensities obtained by the method described in Sec. 2.C.2.

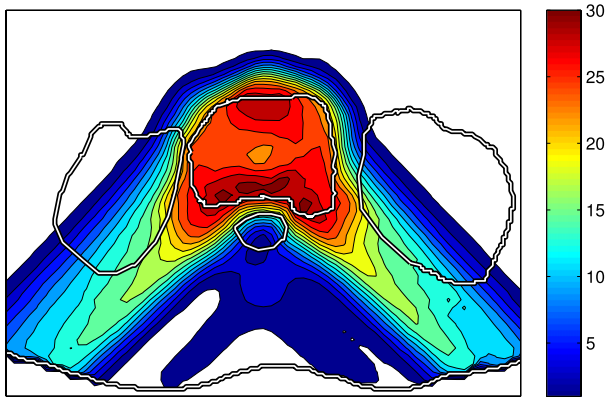
The resulting treatment plan is shown in Fig. 3. Figures 3(a) and 3(b) show the physical dose distributions delivered in fractions 1 and 2, respectively. Fraction 1 delivers a dose of approximately 21 Gy to the central part of the tumor, which yields most of the prescribed BED of 72 Gy. Fraction 2 delivers the missing dose to the proximal parts of the tumor. The spinal cord represents the most critical normal tissue and has a lower α/β-ratio than the tumor. In order to satisfy the spinal cord maximum BED constraint, the dose is fractionated in the posterior part of the tumor that abuts the spinal cord. The dose contribution to the normal tissue in the entrance region of the beam is similar in both fractions. The cumulative physical dose distribution is shown in Fig. 3(c). Although both fractions together deliver the prescribed homogeneous BED to the tumor, the cumulative physical dose distribution is inhomogeneous. This is because the central part of the tumor is hypofractionated and the prescribed BED is achieved with a lower physical dose (22.3 Gy instead of 29.2 Gy).



(a) Fraction 1



(b) Fraction 2

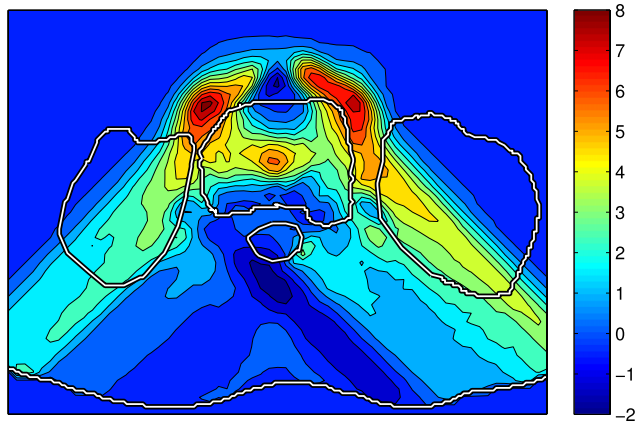


(c) Cumulative physical dose

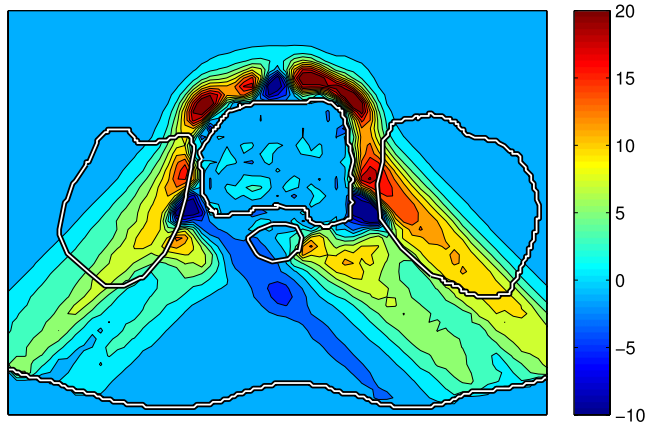
FIG. 3. Nonuniform treatment plan delivering different dose distributions in the first (a) and second fraction (b). The cumulative physical dose is shown in (c).

3.C. Plan comparison

In order to further analyze the benefit of nonuniform spatiotemporal fractionation, we consider the difference of the reference plan and the nonuniform plan. Figure 4(a) shows the difference in physical dose (positive values correspond to higher dose in the reference plan). It is apparent that the nonuniform plan generally delivers less physical dose (as expected). In particular, the dose in the central part of the target is reduced by 5–6 Gy, which leads to a dose reduction in normal tissues. The amount of dose reduction in the entrance



(a) Physical dose difference



(b) BED difference

FIG. 4. Physical dose (a) and BED (b) difference between the two plans. The dose of the nonuniform plan is subtracted from the reference plan, i.e., positive values indicate a higher dose in the reference plan.

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region of the beam is typically 2–3 Gy but depends on location and reaches values up to 6 Gy. Figure 4(b) shows the difference in BED. By construction, both plans deliver the prescribed BED to the tumor so that the BED difference in the tumor is close to zero. In addition, the spinal cord BED is constrained to the same value in both plans. The reduced physical dose in the entrance region leads to a net reduction of BED because both fractions of the nonuniform plan deliver dose. In this example, the BED in the entrance region and at the skin is reduced by approximately 5–10 Gy. The reduction in kidney mean BED is 25%. Table I summarizes the mean BED reductions of the normal tissues. Figure 5 compares the DVH (evaluated for BED) for the two treatment plans. While the DVHs for spinal cord and tumor are nearly indistinguishable, the DVHs for the remaining healthy tissues are consistently better for the nonuniform plan.

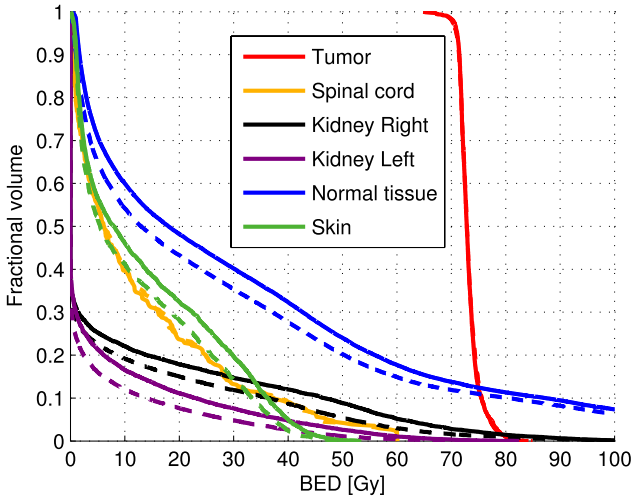

FIG. 5. DVH comparison between the reference plan (solid line) and the nonuniform plan (dashed line). The DVHs for the tumor and the spinal cord are nearly indistinguishable. For the spinal cord, the normal tissue, and the skin, the DVHs refer to the irradiated part of the tissue, i.e., the volume that receives zero dose in both plans is removed. The skin is defined as a 5 mm thick layer of tissue at the patient surface.

4. DISCUSSION

Fractionation increases the tolerance of normal tissues to radiation but typically requires a higher total dose to achieve the same level of tumor control. Ideally, the dose in normal tissues would be fractionated, while the tumor is hypofractionated. Clearly, this is not generally possible since the dose in healthy tissues is linked to the dose delivered to the tumor. This paper demonstrates that, by delivering distinct dose distributions in different fractions, it is indeed possible to achieve some degree of hypofractionation within the tumor while staying close to uniform fractionation in normal tissues.

The benefit of nonuniform fractions depends on the ability to modify the dose distribution within the target volume between fractions, while delivering similar doses to normal tissues. In general, this depends on the patient geometry and the beam arrangement. While not all treatment sites are suited in that regard, this paper demonstrates that situations exist in which a sizeable benefit of nonuniform fractions is predicted. In the spinal metastasis case presented here, the incident beam directions are limited to posterior beams (partly due to range and motion uncertainties associated with anterior beams entering through the abdomen). In addition, the spinal cord is to be avoided. This leads to the incident beam profiles shown in Fig. 2, indicating that both beams need to utilize both distal and proximal Bragg peaks to cover the target volume with the prescription dose. Thereby, Fig. 2 intuitively explains the observed benefit of nonuniform fractions. By delivering the distal Bragg peaks in fraction one, and the proximal Bragg peaks in fraction two, the distal part of the target volume can be hypofractionated, while the entrance dose in the normal tissue is largely unaffected.[16] For the case shown here, this leads to a BED reduction of 10%–20% in the entrance region of the proton beams.

Typically, the presence of a serial organ with low α/β-ratio adjacent to the tumor tends to work against the benefit of nonuniform fractionation schemes. In this case, the maximum physical dose to the organ in any fraction is approximately equal to the dose received by the adjacent part of the target volume. Thus, if the α/β ratio of the organ is low compared to the tumor, nonuniform fractionation may be harmful. However, the example presented in this paper illustrates that serial structures adjacent to the tumor do not necessarily eliminate the benefit of spatiotemporal fractionation schemes. In the example, the central and distal parts of the target volume are hypofractionated, which are not adjacent to the spinal cord. It is inherent to the approach that not all of the target volume can be hypofractionated if some degree of fractionation is to be achieved in the normal tissue. In our spinal metastasis example, the spinal cord is adjacent to the posterior part of the target volume, which is fractionated.

We exercised care to ensure that the improvement of the nonuniform treatment scheme is truly attributed to allowing distinct dose distributions in different fractions. To that end, the nonuniform plan was optimized for exactly the same treatment objectives as the uniform reference plan. In addition, the uniform reference plan was generated through a convex optimization problem, and the optimality of the solution was verified using different optimization solvers. Thus, the

TABLE I. Mean BED reductions in normal tissues. The skin is defined as a 5 mm thick layer of tissue at the patient surface. For the normal tissue and the skin, the values refer to the mean BED in the irradiated volume, i.e., the tissue that receives zero dose in both plans is removed. For the kidneys, the mean BED refers to the entire organ. Note that the mean quadratic deviation from the prescribed tumor BED of 72 Gy is the same for both plans, as enforced by constraint (22). Likewise, the spinal cord maximum BED (60 Gy) and the spinal cord mean BED are identical for both plans.

	Reference (Gy)	Nonuniform (Gy)	Reduction (%)
Kidneys (combined)	7.91	5.95	25
Kidney (right)	10.08	7.97	21
Kidney (left)	5.81	3.99	31
Normal tissue	31.8	28.2	11
Skin	14.2	12.3	13

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observed benefit of the nonuniform plan is not an artifact related to a suboptimal reference plan. We further point out that, for the α/β-ratios and objective functions chosen here, a uniform two fraction plan is superior to a single fraction plan.[17] Therefore, the nonuniform plan does not only improve over the two fraction reference plan but also the optimal single fraction plan to a greater extend.

Previous work[9] discusses criteria that a treatment site should fulfill in order to benefit from nonuniform fractions. Potential candidates are lesions treated using stereotactic radiosurgery (SRS) or SBRT, i.e., lesions that are treated to high doses per fraction with accurate patient positioning. Here, the concept of delivering nonuniform fractions is demonstrated for a spinal metastasis case treated in two fractions. Clinically, a variety of hypofractionated schedules are applied including single fraction SBRT treatments. Thus, the proposed schedule is within the range of commonly used doses per fractions (see, e.g., Ref. 12 for a review on SBRT for spinal neoplasms). Further work is needed to quantify the benefit of nonuniform fractionation for different geometries and identify treatment sites that may clinically benefit from the approach.

In order to relate this paper to previous work on optimal fractionation in the context of the BED model, we point out the following. It has been shown that extensions of the BED model such as accelerated repopulation and incomplete repair suggest nonstationary fractionation schemes, i.e., varying doses per fraction over the course of fractionated radiotherapy.[6,8,18] However, the standard BED model in Eq. (1) usually suggests a stationary fractionation scheme,[2] i.e., delivering the same dose in all fractions. In this work it is demonstrated that, if fractionation effects and the optimization of the spatial dose distribution are considered jointly, nonstationary treatment schemes arise—even in the absence of time dependencies in radiation response of tumor and normal tissues.

5. CONCLUSIONS

Delivering distinct dose distributions in different fractions can potentially improve the therapeutic ratio even in the absence of time dependencies in radiation response of tumor and normal tissues. This is the case if the dose distributions can be designed as to hypofractionate subregions of the tumor while delivering similar doses to normal tissues. To some degree this is possible in proton therapy due to the week dependence of the entrance dose on the proton range. The paper demonstrates this concept for a spinal metastasis SBRT treatment. It is shown that for suitable geometries and hypofractionated regimens, a sizeable biological dose reduction of 10%–20% can be achieved in the entrance region of the beams. Future work is needed to identify treatment sites that may clinically benefit from the approach.

APPENDIX A: CONVEXITY OF THE UNIFORM PLAN OPTIMIZATION PROBLEM

In this section, we discuss the convexity properties of objective functions (9)–(13). We show that, within the relevant domain, the optimization problem for the uniform reference plan is convex. Hence, the globally optimal plan can be found using gradient descent based optimization techniques. This suggests that the observed improvements of the nonuniform treatment plan can truly be attributed to allowing distinct dose distributions in the two fractions (i.e., cannot be explained by comparing to a suboptimal reference plan).

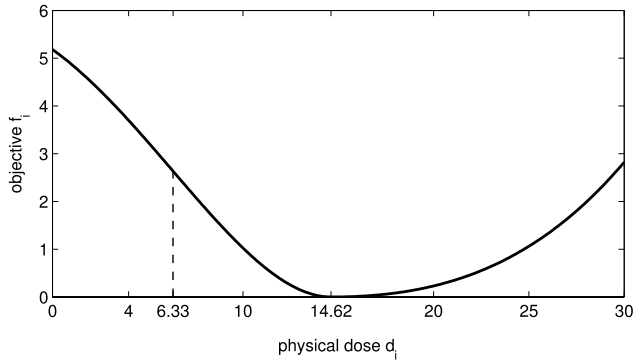

FIG. 6. Visualization of the piecewise quadratic BED objective for a single target voxel as a function of physical dose.

The critical term in the objective function is the quadratic underdose penalty for target voxels. In general, this function is nonconvex, which is illustrated in Fig. 6. We consider a single voxel i and its objective

$$f_i(d_i) = 10(b^{\text{pres}} - b_i)_+^2 + (b_i - b^{\text{pres}})_+^2$$

as a function of physical dose d_i. For the parameters chosen in this paper ($\alpha/\beta = 10$, $b^{\text{pres}} = 72$, $n = 2$), the function is convex for large dose values and only becomes nonconvex for small doses. More specifically, the second derivative of the function $f_i(d_i)$ is positive if

$$d_i > -\frac{1}{2}\frac{\alpha}{\beta} + \sqrt{\left(\frac{1}{2}\frac{\alpha}{\beta}\right)^2 - \frac{1}{6}\left[\left(\frac{\alpha}{\beta}\right)^2 - 2\frac{b^{\text{pres}}}{n}\frac{\alpha}{\beta}\right]}$$

which evaluates to $d_i > 6.328$ Gy. Thus, if we introduce additional linear constraints $d_i > 6.328$, the optimization problem becomes convex. Since the prescribed dose per fraction is 14.62 Gy, these constraints are not binding and have no impact on the global optimum of the original problem. The solution for the reference plan has also been verified with the publicly available interior point solver IPOPT.[19]

APPENDIX B: FINDING NEAR-OPTIMAL SOLUTIONS TO THE PENCIL BEAM INITIALIZATION PROBLEM

In this section, we outline a method to find a near-optimal solution to optimization problem (20), following an approach described in Ref. 20, Sec. 4.3.3. The function we are maximizing is a quadratic function in each z_j with no linear terms and can be written as

$$\max_{z\in\{-1,1\}^m} z^{\text{T}}Qz = \max_{z\in\{-1,1\}^m} \text{tr}(Qzz^{\text{T}}), \tag{B1}$$

where $\text{tr}(\cdot)$ denotes the trace of a matrix and m is the number of pencil beams. If we think of zz^{T} as a $m \times m$-matrix

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with elements $z_j z_k$, the objective is linear in these matrix elements. Furthermore, zz^{T} represents a symmetric positive semidefinite matrix for which all diagonal elements are equal to one. This gives rise to a convex relaxation of the integer program in the form of a semidefinite optimization problem. To that end, we introduce a $m \times m$-matrix Z with elements Z_{jk} as new continuous variables and consider the optimization problem

$$\underset{Z}{\text{maximize}} \qquad \mathrm{tr}(QZ) \tag{B2}$$

subject to

$$Z^{\mathrm{T}} = Z \quad (Z \text{ symmetric}), \tag{B3}$$

$$Z \succcurlyeq 0 \quad (Z \text{ positive semidefinite}), \tag{B4}$$

$$Z_{jj} = 1 \quad \forall\, j. \tag{B5}$$

Semidefinite optimization problems can be solved efficiently with specialized optimization algorithms that are generalizations of classical algorithms developed for linear optimization. In our computations we used the SeDuMi 1.32 solver.[21]

After obtaining an optimal solution Z^* of the convex relaxation, Z^* has to be converted into a vector $z^* \in \{-1,1\}^m$ to obtain a feasible solution of our original optimization problem. If the rank of Z^* is equal to one, Z^* can be decomposed as $z^* z^{*\mathrm{T}}$ and z^* is the optimal solution to (B1). However, in general we only have $Z = VV^{\mathrm{T}}$ for some $m \times m$-matrix V. In this work, we determine V through Cholesky decomposition. The decomposition $Z^* = VV^{\mathrm{T}}$ gives rise to an interpretation of the relaxation: each variable $z_j \in \{-1,1\}$ is effectively replaced by an m-dimensional vector v_j satisfying $\|v_j\| = 1$. A rounding procedure to round the vectors v_j to binary variables z_j^* can now be defined as follows: select a hyperplane through the origin, and round all v_j's on one side of it to $+1$ and the remaining ones to -1. The procedure can also be randomized by selecting several hyperplanes uniformly randomly (by selecting its normal vector uniformly randomly on the unit sphere). Finally, the best z^* obtained in this way is used. The randomized rounding procedure is a computationally inexpensive step. In our implementation we therefore use a generous number of 100 000 repetitions, which is performed within seconds.

We shall mention that, depending on the parameter λ that controls the relative importance of tumor versus normal tissue, the coefficient matrix Q may be positive definite, negative definite, or indefinite. For small λ, i.e., hypofractionation in the target is prioritized, Q becomes positive definite. In this case, the method was found to reproduce the intuitive result in which all pencil beams are assigned to one of the two fractions, and zero dose is delivered in the other fraction. For large λ, i.e., fractionation in the normal tissue is prioritized, Q becomes negative definite. In this case, $z^{\mathrm{T}} Q z$ is a concave function of continuous variables $-1 \le z_j \le 1$. The function is maximized for $z_j = 0$, suggesting that uniform fractionation is optimal.[22] Intermediate values of λ are most relevant for this work, in which case Q is indefinite and a nonuniform fractionation scheme is beneficial.

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[16]In fact, for this patient, the combinatorial optimization described in Sec. 2.C.2 reproduces this type of reassignment of pencil beams which is intuitively expected.
[17]The physical dose distribution for a plan optimized based on BED for a single fraction is almost identical to the physical dose distribution of the two fraction reference plan (except for a scaling factor of 22.3/29.2). Furthermore, the BED of the two fraction plan is lower in all kidney and healthy tissue voxels for which the dose is higher than 40% of the prescription dose (Refs. 2 and 4), making the two fraction plan superior overall.
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