Technical Note: Optimization of spot and trimmer position during dynamically collimated proton therapy

Blake R. Smith^{a)}

Department of Medical Physics, School of Medicine and Public Health, University of Wisconsin-Madison, Madison, WI 53705, USA

Daniel E. Hyer and Ryan T. Flynn

Department of Radiation Oncology, University of Iowa, Iowa City, IA 52242, USA

Wesley S. Culberson

Department of Medical Physics, School of Medicine and Public Health, University of Wisconsin-Madison, Madison, WI 53705, USA

(Received 28 August 2018; revised 1 February 2019; accepted for publication 2 February 2019; published 5 March 2019)

Purpose: To demonstrate a novel theoretical optimization design which considers beam spot and trimmer positioning in addition to beamlet weighting for dynamically collimated proton therapy (DCPT) treatments. Prior to this, the previous methods of plan optimization used to study this emerging technology relied upon an intuitive selection criterion to fix the trimmers blades for a uniform grid of beam spots before determining the individual beamlet weights. To evaluate the potential benefit from this new optimization design, a treatment planning optimization study was performed in order to compare the algorithm's functionality against the existing methods of plan optimization.

Materials and methods: A direct parameter optimization (DPO) method was developed to determine beam spot and trimmer positions cohesively with beamlet weighting for DCPT treatment plans. Gradients were numerically determined from applying small adjustments to the aforementioned parameters and quantifying the resulting impact on an objective function. This technique was compared to the conventional trimmer selection algorithm (TSA) which does not optimize spot position concurrently with trimmer position. Both planning methods were used to optimize a set of brain treatment plans, and the resulting dose distributions were compared with dose-volume histogram quantities in addition to target coverage, homogeneity, and conformity metrics.

Results: An overall improvement to the target conformity and healthy tissue sparing was achieved with DPO over TSA while maintaining an equivalent planning target volume (PTV) coverage index for the three brain patients evaluated in this study. On average, the conformity index improved by 5.5% when utilizing DPO. A similar improvement in reducing the dose to several organs at risk was also noted.

Conclusion: Both the TSA and DPO planning methods can achieve highly conformal treatments with the dynamic collimation system (DCS) technology. However, an improvement in the target conformity and healthy tissue sparing was achieved by simultaneously optimizing beam spot position, trimmer location, and beamlet weights using DPO in comparison to the TSA technique. © 2019 American Association of Physicists in Medicine [<https://doi.org/10.1002/mp.13441>]

Key words: optimization, dynamic collimation, proton therapy

1. INTRODUCTION

Pencil beam scanning (PBS) proton therapy offers several distinct advantages over passive scattering, including a reduction in secondary neutron production¹ and the ability to deliver a composite dose distribution in discrete beamlet contributions.^{2–4} The discretization of spots, in combination with a multifield delivery approach, provides the necessary degrees of freedom during optimization to achieve a superior target conformity and healthy tissue sparing,^{5,6} even when compared to intensity modulated x-ray therapy (IMXT) for some clinical sites.^{5,7–13} For low-energy proton therapy treatments, such as those used for brain or head and neck sites, the large nominal spot size for some delivery systems can compromise the quality of a treatment due to the multiple Coulomb scattering in the nozzle and in the patient which

leads to a larger lateral penumbra at the depth of the target as compared to IMXT.^{14–16} The use of collimation, such as an aperture, is warranted in these special cases to provide an effectively smaller lateral penumbra than achievable from an uncollimated proton beam. Dynamically collimated proton therapy (DCPT) is an advanced form of collimated PBS that supplies an energy-specific aperture for each beam energy delivered. The dynamic collimation system (DCS) is an emerging technology which is designed to perform DCPT.¹⁷ The DCS is comprised of a range shifter followed by two pairs of orthogonal nickel trimmer blades oriented perpendicularly to the scanning proton beam. DCPT with a DCS operates conceptually in a “step-and-shoot” fashion: the trimmers move to a predefined location, beam spots are delivered, the beam is turned off, the trimmers move to their next locations, and the process is repeated for the delivery of the entire

energy layer. This technique effectively simulates an energy-layer specific aperture through the sequenced motion of the trimmer blades.

There are several studies which have investigated the potential benefit of the DCS in PBS brain and head and neck treatments relative to uncollimated or single aperture-based collimated proton therapy treatments. The works of Moignier et al. showed that significant healthy tissue sparing is achievable with the DCS when integrated with both the IBA Universal and Dedicated Nozzle systems for brain and head and neck treatments.^{18–20} The work of Smith et al. directly compared DCPT with a DCS against aperture-based treatments and found that the healthy tissue sparing was nearly doubled when using the DCS.²¹ It is clear from these studies that the DCS technology can increase the healthy tissue sparing and target conformity. The previous methods of plan optimization placed beam spots in a fixed grid with a predetermined lateral spot and energy spacing. Trimmer positions were then selected on the assumption that providing the maximum amount of healthy tissue sparing at the depth of the Bragg peak would lead to a highly conformal treatment following beamlet weight optimization using dose–volume histogram metrics. While this was shown as an effective strategy, the previous methods of plan optimization used for these studies were relatively simple. Thus, further improvement in the target conformity, coverage, and overall organ at risk (OAR) sparing may be achievable.

There has been work previously published on algorithms developed for beamlet weighting,¹⁰ scanning patterns,²² and compensation filters and collimation²³ which make use of a multitude of optimization techniques. However, there is a lack of published work relating to the design of optimizers integrating spot placement, collimation, and individual beamlet weights regarding potential benefits compared to contemporary treatment planning methods used for DCPT. Therefore, it was the purpose of this work to demonstrate a novel theoretical optimization design which considers beam spot and trimmer positioning in addition to beamlet weighting. The treatment of beam spot position as a variable to optimize is novel, as most treatment planning systems rely upon the contour of the planning target volume (PTV) and pre-defined spacing limits to dictate the placement of beam spot positions. The arrangement of collimation about the target is then generally inferred based on the dosimetrist's experience. Special consideration is not normally given with respect to how the changes in one parameter could affect another. However, this concept is important to consider for the treatment planning cases of dynamic collimation since these three variables are interconnected. For example, a change in spot position has a similar relative effect on the resulting beamlet distribution as a change in trimmer position. Additionally, any change in the relative collimation of a proton beamlet will impact the fluence contribution towards the entire treatment plan's dose distribution. The sensitivity of how these factors influence a dose distribution is a unique characteristic of dynamic collimation that has an impact on the achievable target conformity with this new technology.

2. METHODS

2.A. Previous methods of trimmer positioning

The previous studies of the DCS and its implementation into PBS have relied upon a mathematically intuitive strategy to position trimmers based on the relative target coverage at the Bragg peak of the proton beamlet. For clarity within this work, this method is hereafter referred to as the trimmer selection algorithm (TSA). With the TSA method, beam spots are placed at a predefined lateral and depth resolution on a three-dimensional grid that contains the PTV. For each beam spot, the spot conformity function, $\mathcal{C}$, is calculated exhaustively for combinations of the X_1 , X_2 , Y_1 , and Y_2 trimmer positions between 0 and 2 cm from the beam spot's central axis, in 0.05 cm increments, as:

$$\mathcal{C}(X_1, X_2, Y_1, Y_2) = \frac{D_{\text{In target}}(X_1, X_2, Y_1, Y_2)}{D_{\text{Outside target}}(X_1, X_2, Y_1, Y_2)}, \quad (1)$$

where D_{Intarget} and $D_{\text{Outsidetarget}}$ are the integral dose values for a beam spot with trimmer positions (X_1, X_2, Y_1, Y_2) evaluated at the radiological depth equivalent to the beamlet's Bragg peak depth for all voxels within the PTV or outside the PTV, respectively. To avoid inducing hot spots due to over-collimation, the (X_1, X_2, Y_1, Y_2) trimmer position combinations that would result in the beam spot centroid shifting further than 2 mm inside of the PTV, denoted as the PTV retracted region in Fig. 1, are excluded. The trimmer positions for a given spot are then determined by numerically finding the (X_1, X_2, Y_1, Y_2) combination that maximizes $\mathcal{C}$. An example case is shown in Fig. 1.

FIG. 1. Illustration of geometric optimization problem using the TSA technique. The area, A, depicting the potential beamlet's centroid displacements (magenta) partially overlaps within the 2 mm retracted PTV region (green). The trimmer positions resulting in the centroid displacements within region of overlap, B (yellow), are removed from the potential solution space. [Color figure can be viewed at wileyonlinelibrary.com]

2.B. Direct parameter optimization method

A novel optimization algorithm was designed and implemented using an in-house treatment planning system.^{18–21} The treatment planning system was executed in MATLAB® (version R2017b and R2018a) using parallelized CPU calculations within MATLAB's parallel computing toolbox. The algorithm optimizes spot position and collimation by evaluating how small changes in each parameter influenced the overall dose distribution. This process is referred to as direct parameter optimization (DPO) and uses several optimization techniques in a parallel. Figure 2 illustrates the design of the DPO treatment planning method.

The initial parameters required prior to optimization include the DVH optimization goals, a list of OARs and their voxel positions that will be used in the DVH metrics, planned energy layers, and an initial grid of beam spot positions. Initially, all beam spots are treated as uncollimated. During the preoptimization stage, several iterations of subsequent-substitution beamlet weighting optimization are performed to minimize the following objective function adopted from the work of Flynn,²⁴

$$F = \sum_{k=1}^K \left(\frac{1}{T_k} \sum_{i \in \tau_k} [\beta_k^+ c_{(0,\infty)}^2(d_i - d_{i,k}^+) + \beta_k^- c_{(-\infty,0)}^2(d_i - d_{i,k}^-) + \beta_k^{V^+} c_{(0,\Delta D_k^+)}^2(d_i - d_{i,k}^{V^+}) + \beta_k^{V^-} c_{(\Delta D_k^-,0)}^2(d_i - d_{i,k}^{V^-})] \right), \quad (2)$$

where,

$$c_{(a,b)}(x) = \begin{cases} x & \text{if } a \leq x \leq b \\ 0 & \text{else} \end{cases}. \quad (3)$$

As summarized in Table I, the objective function, F , includes dose–volume histogram penalties weighted by β from a comparison of the current dose values, d_i , against the desired dose values, $d_{i,k}$, for an OAR, k , and specified target,

TABLE I. Definitions of variables used in Eqs. (2) and (5).

Variable	Description
τ_k, T_k	Subset voxel indices and number of voxels, respectively, that are inside tissue k with $k \equiv \xi$ denoting the target
$d_{i,k}^{\pm}, \beta_k^{\pm}$	Dose threshold for voxel i and penalty weight, respectively, for overdose(+) and underdose(–) penalties for tissue k
$d_{i,k}^{V^{\pm}}, V_k^{\pm}, \beta_k^{V^{\pm}}$	Dose threshold and penalty weight, respectively, for dose–volume overdose(+) and underdose(–) penalties for tissue k
$\Delta D_k^{V^{\pm}}$	Difference between the dose planned and desired to $V_k^{\pm}$ in the cumulative dose–volume histogram for tissue k

ξ . Upon completion of an initial preoptimization stage, the nominal beam weights and a baseline objective function value from Eq. (2) are acquired and used for further stages within the algorithm.

Following the first stage, an initial set of trimmer blade and beam spot positions for each collimated beam spot are determined from a single iteration of gradient descent optimization (GDO). The intention of the second stage is to maximize the target conformity and healthy tissue sparing. During this process, the spot and trimmer positions for each collimated beamlet are chosen so the value in Eq. (5) is minimized. This is accomplished by evaluating the first derivative of Eq. (5) with respect to the spot and trimmer position parameters, denoted as a single vector $\vec{v}$, separately.

$$\epsilon = \sum_{k=1}^K \frac{D_k}{D_{\xi}} \cdot \frac{T_{\xi}}{T_k} \beta_k, \quad \text{where, } D = \sum_{i \in \tau_k} d_i \quad (4)$$

The GDO technique uses a numerical approximation to determine the gradient, $\vec{g} \equiv \partial \epsilon / \partial \vec{v}$, at each point in parameter space to define a step direction, $\vec{\Delta}_v$. Each parameter in $\vec{v}$ is adjusted by a step size, $\vec{\lambda}$, in the direction, $\vec{\Delta}_v$, for each iteration. A user-defined limit to the step size, $\vec{\lambda} \cdot \vec{\Delta}_v \leq \vec{\lambda}_{\max}$, is preferred to avoid overshooting the solution since the

FIG. 2. A simplified flowchart of the DPO algorithm which includes least-squares gradient descent (LSq-GD) and Levenberg–Marquardt (L–M) optimization techniques. Start and end points are shown in green rounded rectangles, information passage is defined by aqua parallelograms, processes are shown in blue rectangles, logic tasks are defined with red diamonds, and a modification process or preparation task is shown in yellow octagons. [Color figure can be viewed at wileyonlinelibrary.com]

evaluated gradients in Eq. (5) can be quite large. Mathematically, each parameter is adjusted per iteration, i , by,

$$\vec{v}_{i+1} = \vec{v}_i + \vec{\lambda}_i \cdot \vec{\Delta}_{v,i}, \quad (5)$$

where

$$\vec{\Delta}_v = -\vec{g}. \quad (6)$$

There are six derivatives which must be considered for each iteration of GDO accounting for changes in the four collimation trimmer positions and the two lateral beam spot positions. During this process, the nominal spot positions of the collimated beamlets are initially prohibited to enter any closer than 2 mm to the PTV perimeter as the minimization of Eq. (5) inherently induces beam spots and collimation trimmer positions to be directed toward the PTV perimeter to avoid multiple beam spots that are close together from having a large weighting in a localized region of the plan. Following this first iteration, a set of subsequent-substitution iterations occur reoptimizing the individual beamlet weights over the objective function of the DVH constraints shown in Eq. (2). Since the initial iteration only considers maximizing the healthy tissue sparing, a set of subsequent iterations are performed utilizing Levenberg–Marquardt optimization (LMO) methods which considers both the target coverage and healthy tissue sparing goals. These methods are used to minimize the gradient and curvature of Eq. (2) accounting for the covariance between changes in spot position and trimmer position. The gradients associated with a vector of parameters, $\vec{v}$, are numerically evaluated in the Taylor series expansion of Eq. (5) ignoring higher-order terms,

$$\frac{\partial F}{\partial(\delta\vec{v}_k)} = \frac{\partial F_0}{\partial\vec{v}_k} + \sum_{j=1}^{|\vec{v}|} \left(\frac{\partial^2 F_0}{\partial\vec{v}_j \partial\vec{v}_k} \delta\vec{v}_j \right) = 0, \quad (7)$$

which can be solved using matrix algebra,

$$\rho = (\delta\vec{v})\alpha \rightarrow \delta\vec{v} = \rho\alpha^{-1}, \quad (8)$$

where ρ and α are row and square matrices, respectively, with:

$$\rho_k = \frac{1}{2} \frac{\partial F}{\partial v_k} \text{ and } \alpha_{j,k} = \frac{1}{2} \frac{\partial^2 F}{\partial v_j \partial v_k}. \quad (9)$$

Simply per i^{th} iteration,

$$\vec{v}_{i+1} = \vec{v}_i + \delta\vec{v}. \quad (10)$$

This calculation is simplified in that not all of the trimmer blades must actually be considered. In most scenarios, only two of the four trimmer blades need to be used to collimate a beam spot, thus reducing the number of variables which must

be computed in this process from six to four. Beam spot weighting is not incorporated within the LMO process since the asymmetric beamlet model used to numerically evaluate the trimmer and spot position gradients only calculates a relative distribution. Therefore, the change in fluence could not be directly accounted for in the LMO process. Instead, several subiterations of beam spot weighting using a subsequent-substitution optimization is performed when numerically evaluating the gradients to project the cost function value in Eq. (2) to its expected value at convergence. The gradients calculated at a single iteration are graphically shown in Fig. 3 for a single collimated beamlet.

Figure 4 illustrates the progression of the optimization process at the radiological projection of the PTV equivalent to the Bragg peak depth of the proton energy layer from a single field. The first column of Fig. 4 illustrates the original starting positions of the beam spots. The second column shows the resulting distribution of spot positions and relative dose distribution at the energy layer following the sequential optimization processes of the gradient descent and LMO iterations to achieve the necessary coverage while still maintaining a high degree of target conformity. By design, no limit was placed upon the relative positions of collimated beam spots during the optimization process. As a result, some spot positions may reside in close proximity to one another. A final step is then taken to group any beam spots that are within the initial, predefined lateral spacing producing a more practically deliverable spot distribution for each energy layer. The average lateral spacing coordinates and relative collimation trimmer positions from all of the grouped beam spots are chosen when replacing the beam spot group with a single beam spot. The third column shows the result after this grouping procedure. Following this step, it is still possible for a beamlet residing inside the target and a collimated beamlet outside the target to be as close as 2 mm from one another. This is a consequence of defining uncollimated beamlets from an initialized uniform grid of beam spots and allowing the optimizer to freely move trimmed beamlets throughout the optimization process while maintaining the hard constraint of spot proximity toward the target periphery as previously discussed.

2.C. A treatment planning study

Three intracranial treatment plans, which were used during the investigations of Moignier et al.^{18–20} and Smith et al.²¹, were replanned with an in-house TPS, RDX, using the asymmetric beamlet model for the IBA Universal Nozzle system.²⁵ In each of these cases, the CT planning dataset was converted from CT HU values to relative proton stopping powers for air, adipose, muscle, and cortical bone following the treatment planning calibration curves taken from the work of Schneider et al.²⁶ A summary of these treatment planning metrics are listed in Table II. An initial lateral and distal spot spacing of 4 and 5 mm, respectively, were used to place beam spots within a fixed grid about an expanded PTV. Each of the three treatment plans was optimized using the original

FIG. 3. Example two-variable gradient maps calculated from Eq. 2 for a collimated beam spot. To find the minimum, a small step (blue arrow) is taken in the direction opposite of the gradient (black arrows). For this example, the LMO iteration is suggesting the beam spot position be moved in the positive x direction while the two X_2 and Y_2 trimmer blades brought closer to the beamlet's central axis. [Color figure can be viewed at wileyonlinelibrary.com]

FIG. 4. Beam spot positions and relative dose distribution for a single 142 MeV energy layer during DPO. Each column illustrates a major portion of the DPO algorithm illustrated in the flowchart in Figure 2 including the initialized uniform grid of beam spots (left), the resulting beamlet positions immediately following the LMO process in the DPO algorithm (middle), and the final distribution of beam spot positions after grouping abutting sets of collimated beamlets (right). A relative dose distribution is shown for each frame. [Color figure can be viewed at wileyonlinelibrary.com]

TSA technique and the new DPO algorithm. The resulting treatment plans were qualitatively compared visually and quantitatively evaluated based on the plan's conformity index, defined as the ratio of the prescription 90% or 50% isodose volumes to the PTV volume, the coverage index, defined as the ratio of the PTV volume receiving at least 90% of the prescription dose to the entire PTV volume, the homogeneity index, defined as the difference between the PTV $D_{95\%}$

and $D_{5\%}$ to the mean PTV dose, and several OAR $D_{50\%}$ values.

2.D. Evaluating solution stability

The apex field of the chordoma treatment plan was used as a test plan to evaluate the impact of local minima and solution stability between the DPO method and TSA

TABLE II. List of treatment plans investigated including each plan's PTV, radiological depth of each beam, prescribed dose, and beam orientations used during treatment planning.

Plan	Diagnosis	Planning target volume (cm ³)	Radiological prescribed beam		
			Depth (cm)	Dose (Gy)	Orientations
P1	Chordoma	42	13.5–21.6 8.7–16.9	50	Apex Right lateral
P2	Ependymoma	150	7.4–17.1 7.4–17.1	54	Apex Left superior oblique
P3	Low-grade glioma	92	7.4–16.9 16.4–20.7	54	Left lateral Left superior oblique

algorithm. The initial optimization of this field was repeated for several scenarios. In the first case, the initial starting positions of the trimmers for the DPO treatment plan were randomly set between 0 and 2.5 cm from the beamlets central axis. In the second case, 2 mm shifts in the initialized spot grid were applied along the X axis, the Y axis, or both axis simultaneously, after which TSA and DPO methods were used. A final set of calculations were done by randomly displacing the final trimmed beam spot positions as would be done via a simulated annealing step to see if a better solution could be found from the current solution of the DPO treatment plan. These random changes to a spot's

position and trimmer positions were made simultaneously assuming a uniform distribution of ± 1 mm.

3. RESULTS

The resulting dose–volume histograms are shown in Fig. 5 for the TSA technique and DPO algorithm. A representative coronal distribution from each of the treatment planning cases is shown above the respective DVHs. Table III summarizes the coverage indices, conformity indices, homogeneity indices, and $D_{50\%}$ values from the normal tissue DVHs. For all three treatment plans investigated, DPO afforded a greater healthy tissue sparing than the TSA technique alone while maintaining an equivalent PTV coverage and comparable target uniformity. A 3.98%, 4.87%, and 7.19% reduction, with respect to the prescribed dose to the PTV, in the median dose to the 10 mm ring of healthy tissue surrounding the PTV was achieved using DPO over the TSA in the chordoma, ependymoma, and glioma treatment plans, respectively. The conformity index evaluated at the 50% isodose line was improved with DPO method in comparison to the TSA. The conformity index at the 90% isodose level was noticeable improved using DPO for the smaller PTVs, such as the chordoma and glioma plans, but only slight improvements were observed for the ependymoma brain treatment.

With respect to changes in the placement of beam spots, DPO clearly offers a less sensitive plan than the TSA technique. The results, presented using DVHs, are shown below

FIG. 5. Coronal views of the dose distribution determined using the custom research DPO algorithm (top row). The resulting dose–volume histograms for the treatment plan coverage of the target and surrounding OARs for both the (TSA) and (DPO) method. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE III. Target coverage and conformity for the treatment plans optimized with TSA and DPO. The DVH median dose for the 10 mm ring of healthy tissue is taken from the $D_{50\%}$ value.

Treatment	Optimization	CI	CoI (90%)	CoI (50%)	NT ring $D_{50\%}$ (Gy)	HI
Chordoma	TSA	0.99	1.73	3.47	37.93	0.13
Chordoma	DPO	0.99	1.62	3.31	35.94	0.13
Ependymoma	TSA	0.99	1.48	2.03	43.28	0.11
Ependymoma	DPO	0.99	1.42	1.97	40.65	0.13
Glioma	TSA	0.97	1.52	2.56	39.88	0.15
Glioma	DPO	0.97	1.44	2.39	36.00	0.17

in Fig. 6. The amount of benefit in reduced sensitivity to plot alignment using DPO is clear for the DVHs of the 10 mm ring of surrounding healthy tissue, which is the primary region of interest with the DCS technology. Any randomization of the initial starting trimmer positions converges upon the same DVH curves indicating that the effects of local minima appear to be minimal.

4. DISCUSSION

The critical structure avoidance and normal tissue sparing achieved in the works of Moignier^{18–20} and Smith²¹ were accomplished through the TSA method which optimized the energy-layer specific collimation for an entire treatment plan. Specifically, the original TSA approach used a simple selection criteria which maximized the dose contribution of an

individual beam spot to the target while minimizing the degree of healthy tissue irradiated by the same beamlet at the Bragg peak radiological depth. While shown as an effective strategy, DPO improves upon the existing TSA technique by optimizing both collimation trimmer and beam spot positions cohesively.

While the DPO method solely uses GDO methods, the consequences of local minima upon the final solution appear to be small. Both objective functions used in this work are quadratic in nature, and no further improvement was found from sampling other spot positions or trimmer positions from the accepted solution point. Furthermore, the variables of trimmer and beam spot position are correlated in a relative sense. A movement of a beam spot toward a trimmer or a trimmer toward a beamlet's central axis will produce the same relative distribution. However, the exact position of the beam spot in space may not be the same. The asymmetric beamlet algorithm used in these calculations refers to all coordinates relative to the beamlet's central axis and cannot have a negative trimmer position. Because of this, the optimization is unavoidably and inherently biased prohibiting results where the beam spot position and trimmer position oppose each other. However, given the physical context of the problem, this is not expected to substantially influence the final result in a negative manner.

In addition to improving target conformity while maintaining comparable target coverage, the DPO method also improved the plan's sensitivity toward the initialization of spot placement as compared to the TSA technique. While GDO may have a tendency to be trapped within a local

FIG. 6. Plan sensitivity test results between the TSA technique (right) and DPO method (left) for the apex field of the chordoma treatment plan with respect to changes in the initial spot positions, shown in dashed lines. Additional sensitivity tests were performed on the treatment plan using DPO by altering the initial starting trimmer positions and adding a sequential simulated annealing (S-A) step. [Color figure can be viewed at wileyonlinelibrary.com]

minima during optimization, it appears from the results shown in Fig. 6 from the sensitivity study, which randomized and re-optimized beamlet positions, trimmer positions, and beamlet weights in a simulated annealing step from the optimized plan, that the final solution did not substantially change. The only instance that a noticeable change occurred was for the right optic nerve during a shift in the initialized spot placement. However, this was the greatest source of variance in its respective DVH coverage for both the DPO and TSA techniques. Despite that, the DPO plan was still less sensitive to these changes than the TSA plan, and the plans optimized with the new spot spacing arrangement do not improve upon the existing dose distributions.

In some cases, the amount of benefit was small. Large spheroidal targets, such as in the ependymoma treatment plan, experienced little change in the target conformity. For other cases involving complex-shaped, small- and medium-sized targets, such as the chordoma and glioma treatment plans, large improvements in the target conformity at both the 90% and 50% isodose level could be achieved. This result does not necessarily indicate any dependence on the target shape between the effectiveness of DPO over the TSA technique, but highlights a confounding factor among the collimated treatments. Since all treatment plans in this study utilized the same spot spacing, the majority of the PTV coverage for larger targets originate from the beamlets placed within the PTV whereas smaller targets rely upon a larger portion of beamlets delivered around the perimeter of the target to achieve the necessary target coverage. Therefore, for larger PTVs, changes to the collimation of beamlets around the perimeter of the target will have less influence on the overall plan coverage, homogeneity, and high-isodose conformity.

As expected, due to the improved conformity, most of the OARs among the three studied treatment plans resulted in lower average doses with DPO over TSA. In particular, the mean dose was reduced by 1.2 Gy, 1.4 Gy, and 2.4 Gy to the 10 mm of healthy tissue surrounding the target for the chordoma, ependymoma, and glioma treatment plans, respectively. Several smaller OARs, such as the brainstem and optic chiasm, also experienced a sparing effect with the chordoma and glioma treatment plans optimized using DPO. Specifically, the mean dose to the brainstem in the chordoma treatment was reduced by 0.6 Gy and the Optic Chiasm in the glioma treatment was reduced by 1.48 Gy. There were two exceptions in which the mean dose was found to increase while using DPO. The mean dose to the pituitary and left cochlea (not shown in the DVHs) in the glioma treatment increased by 1.0 and 1.7 Gy, respectively. The pituitary was located near the 5% isodose lines between the DPO and TSA treatment plans. While the medium-to-high isodose lines conform closer to the target with DPO, the low isodose lines are neither more nor less conformal to the PTV on average but interchange radially around the PTV. The left cochlea, on the other hand, was a very small OAR occupying only a few voxels and situated adjacent to the PTV.

Direct parameter optimization is more computationally expensive than the TSA technique. TSA requires a single

calculation instance from which the trimmers are fixed for the remainder of the beamlet's weight optimization. The entire optimization process can be performed in a matter of tens of minutes using a single core, and the entire process requires less memory than DPO. DPO requires more memory as higher order gradients in a two-variable system are calculated from the DVH objective function. Additionally, during each iteration the beamlet weights must be continually updated to compare the projected, achievable cost function value from a baseline value. Therefore, each iteration can take several minutes to calculate using multiple CPUs. However, it is hypothesized that further work into parallel computing and GPU techniques could assist in reducing the calculation time.

While this work demonstrates the potential benefit from DPO for DCPT treatment plans using a DCS, further work will need to be accomplished prior to clinical implementation. This includes refining the optimization parameters which delegate step size throughout the optimization process and incorporation of these mathematical optimization methods into a clinical treatment planning system. While shown as a successful optimization technique on its own, the DPO method developed in this work could be further extended to incorporate a population-based optimization approach such as with genetic optimization. This may be a favorable technique that could further improve the achievable dose distributions by sampling multiple histories and using evolution-based metrics to progress a system of solutions towards a final answer. The use of multiple starting points may assist in avoiding convergence in a local minima during optimization since DPO is a deterministic method for which the final solution is dependent upon the initial starting parameters. An additional component is also necessary to consider the treatment time in addition to the evaluated plan quality since the movement of trimmers within the DCS are expected to move slower than the scanning speed of the proton beam. Thus, the implications and management of treatment time must be considered and implemented within the treatment planning optimizer.

5. CONCLUSION

This work was motivated by the desire to improve upon the achievable healthy tissue sparing and target conformity afforded by the DCS technology. To accomplish this, a new DPO treatment planning algorithm was developed uniquely for DCPT treatments using the DCS and was compared to the existing TSA technique. Both methods of plan optimization can be used to create highly conformal treatment plans which provide superior healthy tissue sparing relative to uncollimated PBS proton therapy. DPO can achieve an additional amount of healthy tissue sparing as compared to the TSA technique but presently with the cost of increased computation time. The benefit afforded by the DPO method, however, would seem to outweigh this associated cost. This is especially the case when the achievable plan conformity may be compromised in order to account for the sensitivity of the target coverage or minimize the additional treatment time

resulting from the sequenced motion of the trimmer blades during treatment.

ACKNOWLEDGMENTS

The authors thank the University of Wisconsin Radiation Calibration Laboratory (UWRCL) and the University of Wisconsin Accredited Dosimetry Calibration Laboratory (UWADCL) customers, whose calibrations help support ongoing research at the University of Wisconsin Medical Radiation Research Center (UWMRRC).

CONFLICTS OF INTEREST

Mr. Blake Smith and Dr. Wesley Culberson have nothing to disclose. Dr. Daniel Hyer and Dr. Ryan Flynn are co-inventors on a patent that has been licensed to IBA.

^{a)} Author to whom correspondence should be addressed. Electronic mail: bsmith34@wisc.edu.

REFERENCES

- Andujar A, Newhauser W, DeLuca P. Neutron production from beam-modifying devices in a modern double scattering proton therapy beam delivery system. *Phys Med Biol*. 2009;54:993–1008.
- Chu W, Curtis S, Llacer J, Renner T, Sorensen R. Wobbler facility for biomedical experiments at the Bevalac. *IEEE Trans Nucl Sci*. 1985;32:3321–3323.
- Pedroni E, Blattmann H, Bohringer T, et al. Voxel scanning for proton therapy. in *NIRS-M-81 1992*, Proceedings of the NIRS International Workshop on Heavy Charged Particle Therapy and Related Subjects (National Institute of Radiological Sciences, Chiba) 1991. 94–109.
- Chu W, Ludewigt B, Renner R. Instrumentation for treatment of cancer using proton and light-ion beams. *Rev Sci Instrum*. 1993;64:2055–2122.
- Paganetti H, Bortfeld T, Kooy H. Proton beam radiotherapy—The state of the art. *Med Phys*. 2005;32:2048.
- Pedroni E, Scheib S, Bohringer T, et al. Experimental characterization and physical modelling of the dose distribution of scanned proton pencil beams. *Phys Med Biol*. 2005;50:541–561.
- Glimelius B, Isacson U, Blomquist E, Grusell E, Jung B, Montelius A. Potential gains using high-energy protons for therapy of malignant tumors. *Acta Oncol*. 1999;38:137–145.
- Lomax A, Bortfeld T, Goitein G. A treatment planning inter-comparison of proton and intensity modulated photon radiotherapy. *Radiother Oncol*. 1999;51:257–271.
- Lomax A, Bohringer T, Bolsi A, et al. Treatment planning and verification of proton therapy using spot scanning: Initial experiences. *Med Phys*. 2004;31:3150–3157.
- Flynn R, Barbee D, Mackie T, Jeraj R. Comparison of intensity modulated x-ray therapy and intensity modulated proton therapy for selective subvolume boosting: a phantom study. *Phys Med Biol*. 2007;52:6073–6091.
- Flynn R, Bowen S, Bentzen S, Mackie T, Jeraj R. Intensity modulated x-ray (IMXT) vs. proton (IMPT) therapy for theragnostic hypoxia-based dose painting. *Phys Med Biol*. 2008;53:4153–4167.
- Merchant T, Hua C, Shukla H, Ying X, Nill S, Oelfke U. Proton versus photon radiotherapy for common pediatric brain tumors: comparison of models of dose characteristics and their relationship to cognitive function. *Pediatr Blood Cancer*. 2008;51:110–117.
- Bolsi A, Fogliata A, Cozzi L. Radiotherapy of small intracranial tumours with difference advanced techniques using photon and proton beams: a treatment planning study. *Radiother Oncol*. 2008;68:1–14.
- Engelsman M, Schwarz M, Dong L. Physics controversies in proton therapy. *Semin Radiat Oncol*. 2013;23:88–96.
- Schippers J, Lomax A. Emerging technologies in proton therapy. *Acta Oncol*. 2011;50:838–850.
- Widesott L, Lomax A, Schwarz M. Is there a single spot size and grid for intensity modulated proton therapy? Simulation of head and neck, prostate, and mesothelioma cases. *Med Phys*. 2012;39:1298–1308.
- Hyer D, Hill P, Wang D, Smith B, Flynn R. A dynamic collimation system for penumbra reduction in spot-scanning proton therapy: proof of concept. *Med Phys*. 2014;41:091701.
- Moignier A, Gelover E, Wang D, et al. Theoretical benefits of dynamic collimation in pencil beam scanning proton therapy for brain tumors: dosimetry and radiobiological metrics. *Int J Radiat Oncol*. 2015;95:171–180.
- Moignier A, Gelover E, Smith B, et al. Toward improved target conformity for two spot scanning proton therapy delivery systems using dynamic collimation. *Med Phys*. 2016;43:1421–1427.
- Moignier A, Gelover E, Wang D, et al. Improving head and neck cancer treatments using dynamic collimation in spot scanning proton therapy. *Int J Part Ther*. 2016;2:544–554.
- Smith B, Gelover E, Moignier A, et al. Technical note: a treatment plan comparison between dynamic collimation and a fixed aperture during spot scanning proton therapy for brain treatment. *Med Phys*. 2016;43:4693–4699.
- Meier G, Leiser D, Besson R, et al. Contour scanning in pencil beam scanned proton therapy for skull-base tumors. *Int J Part Ther*. 2015;2:256–257.
- Gustafsson A, Lind B, Svensson R, Brahme A. Simultaneous optimization of dynamic multileaf collimation and scanning patterns or compensation filters using a generalized pencil beam algorithm. *Med Phys*. 1994;22:1141–1156.
- Flynn R. *A comparison of intensity modulated x-ray therapy to intensity modulated proton therapy for the delivery of non-uniform dose distributions*. Ph.D. thesis, University of Wisconsin-Madison (2007).
- Gelover E, Wang D, Hill P, et al. A method for modeling laterally asymmetric proton beamlets resulting from collimation. *Med Phys*. 2015;42:1321–1334.
- Schneider U, Pedroni E, Lomax A. The calibration of CT Hounsfield units for radio-therapy treatment planning. *Phys Med Biol*. 1996;41:111–124.