Reoptimization of IMPT plans based on linear energy transfer

Supplementary material
for the paper

Reoptimization of intensity-modulated proton therapy plans based on linear energy transfer

A Parameterization of RBE effects

Figure 6 illustrates the simplified RBE model (equation 3) used in this work. Figure 6a shows the physical dose $d_i$ for $10^9$ protons for a single pencil beam, delivering approximately 4.5 Gy at the Bragg peak, which is located at the distal edge of the target volume. Figure 6b shows the additional biological dose $cL_id_i$ in Gy for $c = 0.04 \, \mu m/keV$. The sum of $cL_id_i$ and $d_i$ yields the RBE-weighted dose in Figure 6c. The RBE (Figure 6d) is the ratio of RBE-weighted dose and physical dose, which becomes ill-defined where the dose goes to zero. For our model, RBE essentially represents dose-averaged LET. For $c = 0.04 \, \mu m/keV$, $cL_id_i$ adds another 1.5 Gy to the physical dose near the Bragg peak, resulting in an RBE of approximately 1.3. In the falloff region distal to the Bragg peak the RBE increases to values around 1.5 to 1.6.

The simplified RBE model used in this paper is sufficient in order to model the basic observation that the RBE increases towards the end of range. It provides the motivation for using LETxD to guide treatment planning, and should not be understood as an attempt to accurately model RBE. It is a simplification of previous RBE models [11-14], which are based on the linear-quadratic cell survival model. The quadratic term is needed to describe fractionation effects and a dependence of the RBE on the dose per fraction. By neglecting the quadratic term, our simplified model does not explicitly describe these effects. However, in the situations that our method is intended for, this is not necessary. For example, for the intracranial cases presented in this work, the fractionation scheme is predetermined at the time of treatment planning. In addition, we are interested primarily in the high dose region, i.e. in normal tissues that receive doses close to the prescription dose. Hence, we are interested in the RBE at a fixed dose level (in this case 1.7 Gy per fraction, 50 Gy in 30 fractions). Therefore, explicitly modeling of fractionation effects during treatment plan optimization is not needed.

The LETxD distribution used to guide plan optimization and evaluation in our work is a physical quantity that, unlike RBE models, does not depend on uncertain additional parameters. At the same time, it can be interpreted, up to a scaling factor $c$, as the biological extra dose resulting from elevated LET. Depending on personal opinions and preferences, this combination of simplicity and interpretability of LETxD can be seen as an advantage over the use of RBE models.
Figure 6: Illustration of the RBE model used to guide IMPT planning.
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B  GPU based Monte-Carlo calculation of dose and LET

Although analytical approaches have been reported to calculate dose-averaged LET [20, 21, 19], Monte-Carlo simulations are considered the gold standard. For this study, a GPU based Monte-Carlo code, gPMC, was extended to score dose-averaged LET in addition to physical dose. The implementation was benchmarked against TOPAS for dose [16,17] and LET calculation. In turn, TOPAS has been extensively benchmarked for dose, LET and other simulations. Specifically for LET, it has been experimentally validated using Fluorescence Nuclear Track detectors (FNTD).

To generate dose $D_{ij}$ and LET contributions $L_{ij}$ for IMPT planning, each pencil beam was individually simulated using $10^6$ protons, reaching an accuracy of <1% standard deviation. We use a beam model that represents a modern proton beam line with spot sizes ranging from 5.6 to 2.2 mm sigma and energy spreads from 0.56 to 0.82 MeV for nominal proton energies between 60 and 230 MeV. Pencil beams are placed at 1 sigma lateral distance within an energy layer. Energy layers are separated by 0.7 times the Bragg peak width at 80%. Bragg peaks are placed within the target volume plus a 1-2 cm margin surrounding the target. The large margin for spot placement was applied to provide sufficient degrees of freedom for the reoptimization step and not restrict the ability to redistribute LET by spot placement. On average, approximately 2000 pencil beams per field are used. The average calculation time per pencil beam was 3-4 s on a NVIDIA TESLA C2075, corresponding to 2 hours computation time per field.
C Treatment plan optimization

In this section we detail the treatment plan optimization methods.

C.1 Optimization of reference plans

We first consider IMPT optimization for reference plans based on physical dose. We minimize the objective function

\[ f(d) = \frac{10}{N_T} \sum_{i \in T} (d_{\text{pres}}^T - d_i)^2 + \frac{5}{N_T} \sum_{i \in T} (d_i - d_{\text{max}}^T)^2 + \frac{10}{N_O} \sum_{i \in O} (d_i - d_{\text{max}}^O)^2 + \frac{1}{N_R} \sum_{i \in R} (d_i - d_{\text{max}}^R)^2 + \frac{1}{N_B} \sum_{i \in B} d_{\text{pres}}^i \] (target coverage)

\[ + \frac{1}{N_O} \sum_{i \in O} (d_i - d_{\text{max}}^O)^2 + \frac{1}{N_R} \sum_{i \in R} (d_i - d_{\text{max}}^R)^2 + \frac{1}{N_B} \sum_{i \in B} d_{\text{pres}}^i \] (OAR maximum dose)

\[ + \frac{1}{N_R} \sum_{i \in R} (d_i - d_{\text{max}}^R)^2 + \frac{1}{N_B} \sum_{i \in B} d_{\text{pres}}^i \] (conformity)

\[ + \left( \frac{1}{N_B} \sum_{i \in B} d_{\text{pres}}^i \right)^{1/p} \] (brainstem gEUD)

\[ + \frac{1}{N_H} \sum_{i \in H} d_i \] (mean brain dose)

under the following set of constraints:

\[ d_i \geq d_{\text{min}}^T \quad \forall i \in T \] (minimum target dose)

\[ d_i = \sum_{j} D_{ij} x_j \quad \forall i \] (physical dose in voxel i)

\[ x_j \geq 0 \quad \forall j \] (non-negative pencil beam fluence)

Here, \( x_j \) denotes the fluence of pencil beam \( j \), \( d_i \) is the physical dose in voxel \( i \), and \( D_{ij} \) denotes the physical dose contribution of beamlet \( j \) to voxel \( i \) for unit fluence. \( T \) denotes the set of voxels contained in the target volume, \( O \) contains all OAR voxels (optic structures, brainstem and pituitary gland), \( R \) the voxels in a 1 cm rim surrounding the target, \( B \) the voxels in the brainstem, and \( H \) is the set of all normal tissue voxels outside of the target. The target prescription is set to \( d_{\text{pres}}^T = 50 \) Gy, \( d_{\text{min}}^T = 45 \) and \( d_{\text{max}}^T = 52.5 \). The maximum OAR dose is set to \( d_{\text{max}}^O = 50 \), and the gEUD exponent in the brainstem is set to \( p = 5 \). The maximum dose \( d_{\text{max}}^i \) in the conformity objective (10) depends linearly on the euclidean distance \( z_i \) of a normal tissue voxel \( i \) from the target contour:

\[ d_{\text{max}}^i = d_{\text{pres}}^i - z_i (d_{\text{pres}}^T - d_R^T) \] (16)

where we set \( d_R^T = 20 \) Gy and measure \( z \) in cm. Hence, a falloff of the dose from 50 Gy at the edge of the target to 20 Gy at 1 cm distance is aimed for.

To find the minimum of the optimization problem, we use our own implementation of the L-BFGS quasi-Newton method [22], together with an augmented Lagrangian method for handling constraints [18].
C.2 Reoptimization of LETxD distributions

Treatment plan reoptimization for the LETxD distribution solves the following optimization problem:

\[
\begin{align*}
\text{minimize} & \quad \frac{1}{N_O} \sum_{i \in O} \left( \bar{L}_i d_i - L d_{\text{ref}} \right)^2 + \\
\text{subject to} & \quad f_{\text{ref}}^T \geq \frac{10}{N_T} \sum_{i \in T} \left( d_{\text{pres}}^T - d_i \right)_+^2 + \frac{5}{N_T} \sum_{i \in T} (d_i - d_{\text{max}}^T)_+^2 \quad \text{(target coverage)} \quad (18) \\
& \quad f_{\text{ref}}^O \geq \frac{10}{N_O} \sum_{i \in O} (d_i - d_{\text{max}}^O)_+^2 \quad \text{(OAR maximum dose)} \quad (19) \\
& \quad f_{\text{ref}}^R \geq \frac{1}{N_R} \sum_{i \in R} (d_i - d_{\text{max}}^i)_+^2 \quad \text{(conformity)} \quad (20) \\
& \quad \epsilon_{f_{\text{ref}}}^B \geq \left( \frac{1}{N_B} \sum_{i \in B} d_i^p \right)^{1/p} \quad \text{(brainstem gEUD)} \quad (21) \\
& \quad \epsilon_{f_{\text{ref}}}^H \geq \frac{1}{N_H} \sum_{i \in H} d_i \quad \text{(mean brain dose)} \quad (22) \\
& \quad d_i \geq d_{\text{min}}^\text{T} \quad \forall i \in T \quad \text{(minimum target dose)} \quad (23) \\
& \quad d_i = \sum_j D_{ij} x_j \quad \forall i \quad \text{(physical dose in voxel } i) \quad (24) \\
& \quad \bar{L}_i d_i = \sum_j L_{ij} D_{ij} x_j \quad \forall i \quad \text{(LETxD in voxel } i) \quad (25) \\
& \quad x_j \geq 0 \quad \forall j \quad \text{(non-negative pencil beam fluence)} \quad (26)
\end{align*}
\]

Here, $f_{\text{ref}}^T$ denotes the corresponding objective values in the reference plan, $\epsilon = 1.03$ is the slack factor, and $L_{ij}$ is the dose averaged LET of pencil beam $j$ in voxel $i$. 
D Results for additional patients

D.1 Base-of-skull chordoma (case 4)

Figure 7a shows a second chordoma case where the target volume wraps around the brainstem. The patient is treated with 6 coplanar beams. Treatment planning based on physical dose alone may lead to high LETxD values in the brainstem due to pencil beams that stop in front of the brainstem. LETxD values can be reduced by using pencil beams that avoid the brainstem laterally.

D.2 Ependymoma (case 5)

Figure 8a shows a second ependymoma case where the target volume overlays the brainstem. The patient is treated with 3 coplanar beams, a posterior-anterior beam plus two posterior oblique beams, which is common for this indication. The beam arrangement leads to high LETxD values in the brainstem distal to the target volume (Figure 8e). Figures 8d/f show the reoptimized plan, demonstrating the ability to avoid LETxD hotspots in the brainstem. Even though the physical dose distribution fulfills the constraint that brainstem gEUD and mean normal tissue dose increase by only 3% compared to the reference plan, it is visually apparent that LETxD reduction in the brainstem comes at the price of higher physical dose in normal brain. For this beam arrangement, high LETxD in the brainstem can only be avoided via pencil beams that overshoot into the brainstem and the normal brain anterior to the brainstem. Thereby, high LET is shifted away from the high dose region distal to the target and into the normal brain that receives lower doses.
Figure 7: Base-of-skull chordoma (Case 4): The target volume (red contour) wraps around the brainstem and spinal cord (green). The parotid glands (yellow) are located near the target. The GTV is shown by the brown contour.
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Figure 8: Ependymoma (Case 5): The target volume (red) contains parts of the brainstem (green). The GTV is shown by the brown contour.
E  Dose escalation

E.1 Treatment plan optimization

In order to assess the possible increase in tumor mean dose that can be achieved without worsening planning goals for the normal tissue, we solve the following treatment planning problem.

\[
\begin{align*}
\text{maximize} & \quad \sum_{i \in G} d_i \\
\text{subject to} & \quad f_{\text{reopt}}^U \geq \frac{10}{N_T} \sum_{i \in T} \left( d_{\text{pres}}^T - d_i \right)^2_+ \quad \text{(target underdose)} \\
& \quad f_{\text{reopt}}^P \geq \frac{1}{N_T} \sum_{i \in P} \left( d_i - d_{\text{max}}^T \right)^2_+ \quad \text{(PTV overdose)} \\
& \quad f_{\text{ref}}^O \geq \frac{10}{N_O} \sum_{i \in O} \left( d_i - d_{\text{max}}^O \right)^2_+ \quad \text{(OAR maximum dose)} \\
& \quad f_{\text{ref}}^R \geq \frac{1}{N_R} \sum_{i \in R} \left( d_i - d_{\text{max}}^i \right)^2_+ \quad \text{(conformity)} \\
& \quad \epsilon f_{\text{ref}}^B \geq \left( \frac{1}{N_B} \sum_{i \in B} d_i^p \right)^{1/p} \quad \text{(brainstem gEUD)} \\
& \quad \epsilon f_{\text{ref}}^H \geq \frac{1}{N_H} \sum_{i \in H} d_i \quad \text{(mean brain dose)} \\
& \quad f_{\text{ref}}^L \geq \frac{1}{N_O} \sum_{i \in O} \left( \bar{L}_i d_i - L d_{\text{max}}^\text{LETxD} \right)^2_+ \\
\end{align*}
\]

\( d_i \geq d_{\text{min}}^T \quad \forall i \in T \) \quad \text{(minimum PTV dose)}

\( d_i = \sum_j D_{ij} x_j \quad \forall i \), \quad \text{(physical dose in voxel } i) \)

\( \bar{L}_i d_i = \sum_j L_{ij} D_{ij} x_j \quad \forall i \), \quad \text{(LETxD in voxel } i) \)

\( x_j \geq 0 \quad \forall j \), \quad \text{(non-negative pencil beam fluence)}

Here, \( G \) denotes the set of voxels in the GTV and \( P \) denotes the set of voxels in the PTV excluding the GTV. \( f_{\text{reopt}}^U \) is the value of the target underdose penalty function evaluated for the plan reoptimized for LETxD, i.e. after solving the treatment planning problem (17-26). Accordingly, \( f_{\text{reopt}}^P \) is the value of the PTV overdose penalty functions. Hence, treatment planning maximizes the mean dose in the GTV while limiting the target dose outside of the GTV to the value in the reoptimized plan. \( f_{\text{ref}}^L \) denotes the value of the LETxD objective for OARs in the reoptimized plan.
E.2 Results

Figure 9: LETxD distribution (scaled with $c = 0.04 \, \mu\text{m/keV}$) for the dose escalation plan in figure 5 in the main manuscript. Higher physical dose in the GTV leads to higher LETxD in the GTV as a secondary effect since LETxD increases linearly with the pencil beam fluence.
F Dose-Volume histograms

Figures 10-13 show DVH comparisons between reference plan (solid lines) and reoptimized plans (dashed lines) for patients 2-5. DVHs are evaluated for physical dose (a) and LETxD scaled with $c = 0.04 \mu m/keV$ (b). Black lines show the DVH for a 1 cm wide margin of normal tissue surrounding the target volume. For the calculation of the LETxD DVH for the brainstem, voxels that receive a dose smaller than 10 Gy in the reference plan have been removed to better visualize the high dose region.

The physical dose DVHs confirm that target coverage and conformity are almost identical in the reference and reoptimized plans. For the brainstem, the physical dose is similar in the high dose region due to the constraints imposed during reoptimization. However, the brainstem mean dose is increased in the reoptimized plan. The LETxD DVHs show the reduction of LETxD in the brainstem after reoptimization. LETxD within the target volume and the normal brain surrounding the target is similar between reference and reoptimized plan.

References


Figure 10: Ependymoma (Case 2): DVHs evaluated for physical dose (a) and c LETxD (b). The solid lines show the reference plan, dashed lines the re-optimized plan.
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Figure 11: Base-of-skull chordoma (Case 3): DVHs evaluated for physical dose (a) and c LETxD (b). The solid lines show the reference plan, dashed lines the re-optimized plan.
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Figure 12: Base-of-skull chordoma (Case 4): DVHs evaluated for physical dose (a) and c LETxD (b). The solid lines show the reference plan, dashed lines the re-optimized plan.
Figure 13: Ependymoma (Case 5): DVHs evaluated for physical dose (a) and c LETxD (b). The solid lines show the reference plan, dashed lines the re-optimized plan.