**LET-guided biological optimization in IMPT**

It is well known that the relative biological effectiveness (RBE) for proton therapy depends on dose\(^1\), endpoint\(^2\), LET\(^3\) and other factors. As it has been previously demonstrated in the literature\(^4\), different pencil beam placement techniques in intensity modulated proton therapy (IMPT) lead to distinctly different linear energy transfer (LET) distributions. Thus by combining different beam placement distributions we can potentially shape the LET distribution, and subsequently RBE, towards a biologically-optimized treatment planning, while keeping clinically equivalent physical dose distribution. In our study we investigate the feasibility of using the LET distribution as an additional decision tool, while navigating on a Pareto-surface in a multi-objective optimization (MCO) platform within our proton beam scanning planning system ASTROID.

Towards this purpose, we first demonstrate the variation of LET distribution for different Pareto-optimal base plans, used for the navigation. Then we show the accuracy of our LET calculation method as a dose-weighted average (eq. 1) of pre-calculated LET distributions corresponding to the Pareto-optimal base plans.

\[
LET_d = \frac{\sum D_i \cdot LET_{d,i}}{\sum D_i}
\]  
*(Eq. 1)*

A pediatric chordoma case was selected as a patient case to test the feasibility of LET-guided IMPT optimization. This case resembles a relatively complicated patient geometry (irregular tumor shape, very close to organs at risk – fig 1). The variability of LET distributions and volume histograms (LVHs) for different base plans is shown in figures 2 and 3. There are clear differences in LET distributions, in particular for organs at risk. In addition, a trade off between low dose and low LET values was observed especially for the OARs (figure 5). While the clinical significance in terms of biological effect might be uncertain due to RBE uncertainties as a function of endpoint, it nevertheless adds an additional degree of freedom to MCO based treatment planning in IMPT.

For validation, figure 4 shows the comparison between LET distributions calculated directly in the MC and those obtained by weighted base plans: no significant differences are noticeable (< 0.3 keV/µm for most structures) indicating non-significant differences between the two methods of calculation.

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**Figure 1:** LET distributions for the four base plans, contributing to the clinically acceptable plan. Significant differences among the various plans are obvious.

**Figure 2:** Axial section of a pediatric chordoma case showing the CT, segmentation and the IMPT plan, as produced by Astroid MCO module.
References: