Time-dependent dose calculation for FLASH treatment planning

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INTRODUCTION

ABSTRACT

A model is presented that calculates the time-dependence of dose delivery to each voxel of an IMPT treatment. This model is intended to be used as a tool in the development of delivery techniques that take advantage of the FLASH effect while maintaining IMPT conformality. The ordering of spots within the volume is shown to have a large effect on the amount of the volume that receives dose at FLASH dose rates. It is also demonstrated that adjacent volumes can be delivered separately, each at a FLASH dose rate, with a minimal portion of the total volume receiving its dose below the FLASH threshold. This supports the possibility of 'stitching together' smaller, FLASH-treated volumes in order to treat an arbitrarily large volume with intensity-modulated spots.

KEY POINTS:

- FLASH therapy research suggests that radiation treatments delivered at **high dose rates** (above 40 Gy/s) show **less normal tissue toxicity**, while maintaining tumor control. [1]
- Alternatively, the **FLASH effect can be thought of as a timescale effect**,[2] with healthy tissue sparing occurring so long as dose is delivered in less than a certain timescale. Here we use 500 ms as an example "FLASH threshold."
- We use Monte Carlo modeling to demonstrate that over the course of a treatment, it is possible **constrain local delivery times to within FLASH timescales** for all or most of the volume.
- **Small volumes can be combined** to make larger volumes with only small areas violating FLASH time thresholds.
- **Collimation helps to decouple dose vs. time for neighboring volumes,** making it easier to achieve shorter local delivery times, particularly when combining volumes.

MODELING and ANALYSIS

SIMULATION:

- **Software**: The Toolkit for PArticle Simulation (TOPAS), a wrapper for the Geant4 Monte Carlo simulation package
- **Machine modeled:** Mevion S250i
- **Target:** 3cm cubes delivered to a simulated water tank.

DELIVERY:

Simulated pulses were rearranged in post-processing to achieve different time structures for delivery. Compare rows A and B for the effect of different spot orderings. Each cube was collimated, the Mevion adaptive aperture aligned to form the edges of a 3cm square.

ANALYSIS:

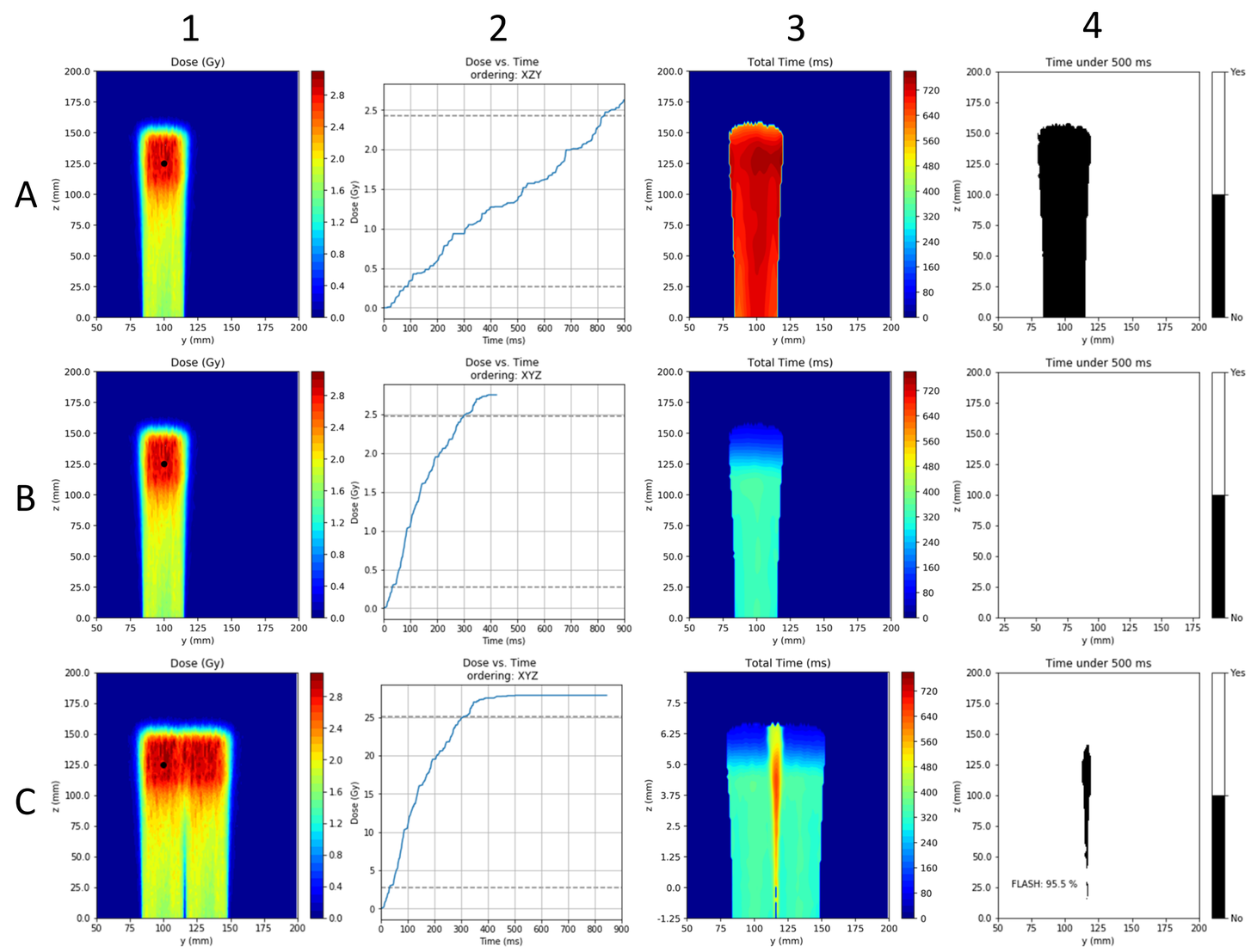
Time histories (column 2): Time histories for individual points can be plotted to give an idea of the time-scales involved.

Analog FLASH metric (column 3): Delivery time for an individual voxel from 10% to 90% final dose.

Binary FLASH metric (column 4): The FLASH cutoff is taken to be 500 ms. Applying this binary condition across the target region allows us to see where a particular ordering is underperforming in a FLASH delivery.

REFERENCES:

1. Favaudon V, Caplier L, Monceau V, et al. Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice [published correction appears in Sci Transl Med. 2019 Dec 18;11(523):]. *Sci Transl Med*. 2014;6(245):245ra93.
2. Patriarca A, Fouillade C, Auger M, et al. Experimental Set-up for FLASH Proton Irradiation of Small Animals Using a Clinical System. *Int J Radiat Oncol Biol Phys*. 2018;102(3):619-626. doi:10.1016/j.ijrobp.2018.06.403
3. Plotting and analysis performed in Python using the NumPy, Scikit, and Matplotlib packages



Cols. 1-4 show the dose distribution delivered, the dose vs. time history of the marked voxel, the total time for delivery (10% to 90% total dose for each voxel), and a binary map showing voxels above and below the FLASH time threshold. Cols 3-4 only include voxels with total dose over .5 Gy. **Row A**: One 3 cm cube in which spots are delivered along a serpentine path in the x-z plane before y position is iterated. **Row B**: Beam energy is held constant while spots are visited along a serpentine path before shifting to the next depth layer. **Row C**: Two 3 cm cubes, each delivered as in case A. For all cases, each individual cube was collimated, the Mevion adaptive aperture arranged in the simulation to conform to the edges of a 3 cm square.

RESULTS

TIMING MODEL:

We use a simplified model of the Mevion S250i machine timing that takes into account the time between beam pulses (1.3 ms) and the layer switching time (10 ms). The 10% and 90% dose marks are labeled on the plot and are used as the effective start and end times for treatment in a given voxel.

SPOT ORDERING:

Different orderings were attempted: **Order A** illustrates serpentine spot delivery in the X, Z and then Y directions. **Order B** shows the timing for serpentine delivery in X, Y, and then Z.
Plots of the total time for delivery (time to 90% - time to 10%) illustrate the corresponding effect for different spot orderings. A large benefit is observed for minimizing layer switching time, which is generally longer than the normal spot time. The fastest ordering was used for the ensuing tests of combined volumes.

COMBINING FLASH VOLUMES:

If two FLASH volumes are combined, the resulting treated volume still receives FLASH dose rates to all but a small fraction of the overall area. Approximately 95% of the treated voxels remain within the 500 ms treatment window. The collimation of the edges of each of the cubes allows for this isolation of the two cubes. Collimation makes the dose vs. time histories for the two cubes almost independent of each other, as can be observed in column two of example C. There is very little observable increase in the dose delivered to the marked voxel once the first cube has been completed.

CONCLUSIONS + FUTURE WORK

Spot ordering is important in determining local effective dose rate and could be structured to prioritize fast delivery to areas of healthy tissue. Delivery plans layered in depth are best at isolating spots of dose delivery from each other and shortening the effective delivery time. With collimation, scanning systems can potentially achieve FLASH delivery to upwards of 90% of an arbitrarily large volume by stitching together smaller volumes. Because each smaller volume contains intensity-modulated spots, and volumes can be weighted relative to each other, this result points to the possibility of large-scale FLASH treatments delivered with the conformality of IMPT. Future research will include the automation of spot ordering as an element of FLASH treatment planning.