4D Treatment Workshop on Particle Therapy 2021 (Delft)

How to get FLASH moving?

Beth Rothwell | Matthew Lowe

13th November 2021

The Christie NHS Foundation Trust

MANCHESTER 1824 The University of Manchester

The Precise Group

Overview

- Introduction to FLASH
  - Potential mechanisms

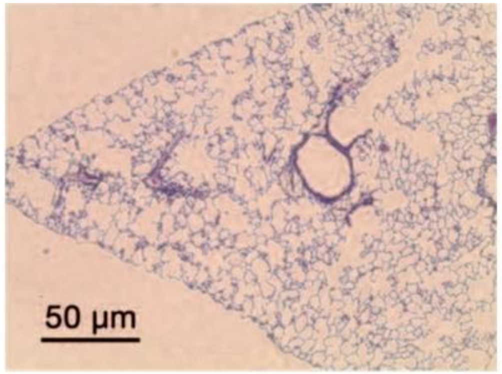
- Modelling oxygen depletion
  - The importance of timescales
  - Determining the FLASH parameter space

- Application to proton spot scanning
  - Mechanism focus: modelling oxygen depletion in PBS
  - Dose rate focus: defining dose rate and achieving FLASH dose rates.

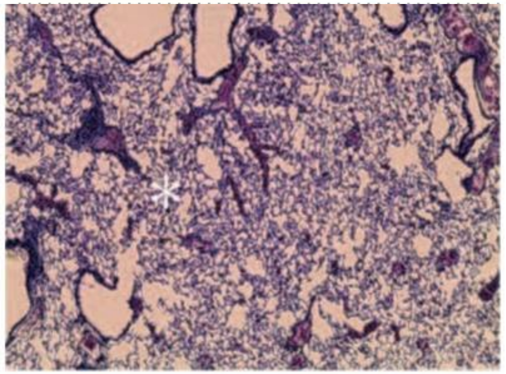
FLASH Radiotherapy: Introduction

- Ultra-high dose rate irradiation
  FLASH: > 40 Gy/s
  CONV: ~0.03 Gy/s

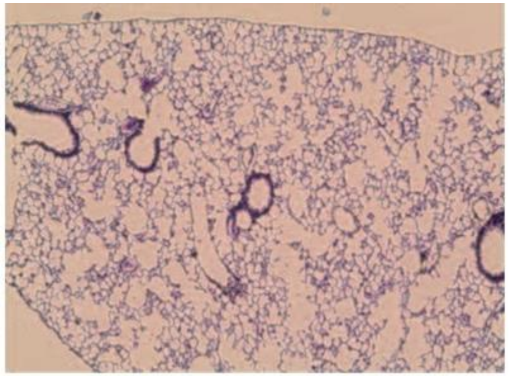
- Shown to have normal-tissue sparing capabilities



Control
(0 Gy)



CONV
(17 Gy, 0.03 Gy/s)



FLASH
(17 Gy, 60 Gy/s)

Favaudon et al. 2014. Sci. Transl. Med.

FLASH Radiotherapy: Introduction

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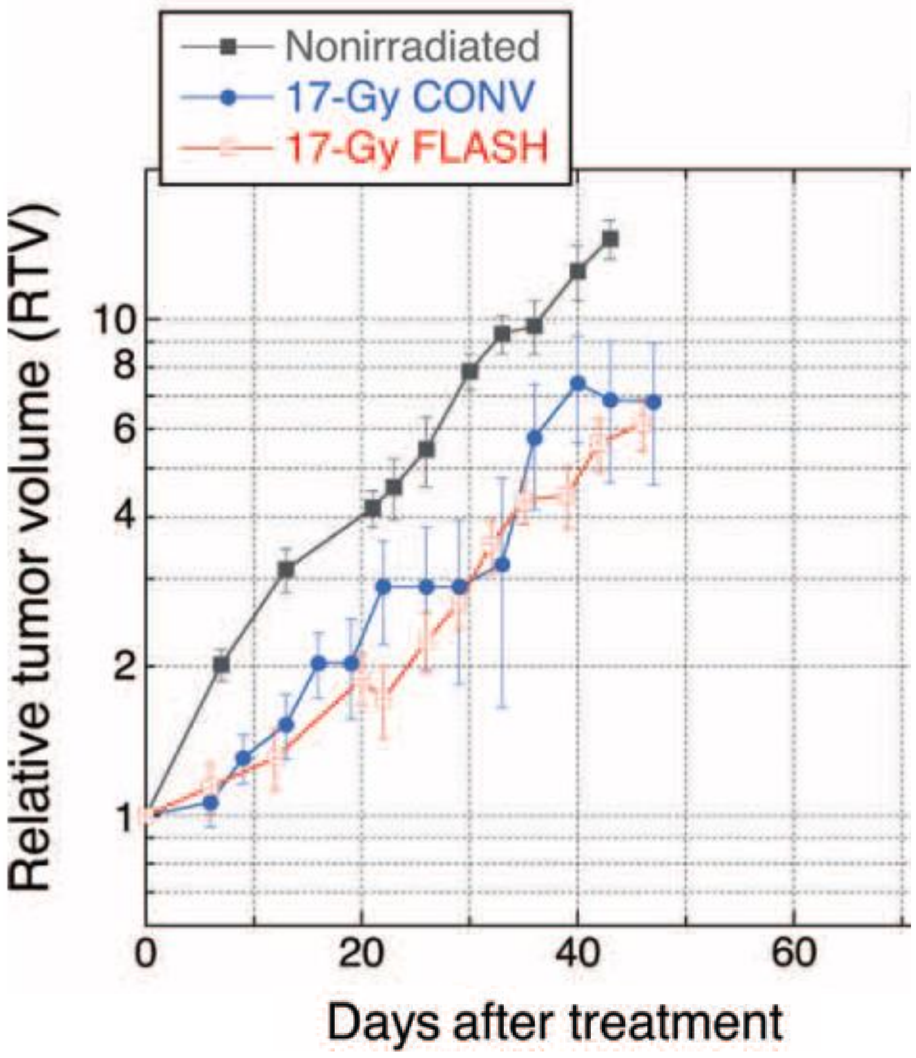
  FLASH: > 40 Gy/s
  CONV: ~0.03 Gy/s

- Shown to have normal-tissue sparing capabilities

- No compromise on tumour control



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FLASH Radiotherapy: Introduction

Potential Benefits:

- Normal tissue sparing capability
  - Studies suggest dose modifying factor of 1.2-1.5
- No compromise on tumour control
  - Dose modifying factor of 1
- Full treatments/fractions in < 0.1s
- Minimises motion during treatment

FLASH Radiotherapy: Introduction

Potential Benefits:

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- No compromise on tumour control
  - Dose modifying factor of 1
- Full treatments/fractions in < 0.1s
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Current Challenges:

- Technology/accurate dosimetry
- Clinical translation
  - Protons?
  - Multiple beams? Fractions?
  - Scanning/scattering to cover full target?
  - …
- What causes FLASH?

FLASH Radiotherapy: Introduction

Radiotherapy and Oncology 139 (2019) 18–22

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

First in Human

Treatment of a first patient with FLASH-radiotherapy

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A R T I C L E I N F O

Article history:
Received 1 April 2019
Received in revised form 12 June 2019
Accepted 14 June 2019
Available online 11 July 2019

Keywords:
FLASH-RT
Normal tissue protection
Differential effect
Clinical translation

A B S T R A C T

Background: When compared to conventional radiotherapy (RT) in pre-clinical studies, FLASH-RT was shown to reproducibly spare normal tissues, while preserving the anti-tumor activity. This marked increase of the differential effect between normal tissues and tumors prompted its clinical translation. In this context, we present here the treatment of a first patient with FLASH-RT.

Material & methods: A 75-year-old patient presented with a multiresistant CD30+ T-cell cutaneous lymphoma disseminated throughout the whole skin surface. Localized skin RT has been previously used over 110 times for various ulcerative and/or painful cutaneous lesions progressing despite systemic treatments. However, the tolerance of these RT was generally poor, and it was hypothesized that FLASH-RT could offer an equivalent tumor control probability, while being less toxic for the skin. This treatment was given to a 3.5-cm diameter skin tumor with a 5.6-MeV linac specifically designed for FLASH-RT. The prescribed dose to the PTV was 15 Gy, in 90 ms. Redundant dosimetric measurements were performed with GafChromic films and alanine, to check the consistency between the prescribed and the delivered doses.

Results: At 3 weeks, i.e. at the peak of the reactions, a grade 1 epithelitis (CTCAE v 5.0) along with a transient grade 1 oedema (CTCAE v5.0) in soft tissues surrounding the tumor were observed. Clinical examination was consistent with the optical coherence tomography showing no decrease of the thickness of the epidermis and no disruption at the basal membrane with limited increase of the vascularization. In parallel, the tumor response was rapid, complete, and durable with a short follow-up of 5 months. These observations, both on normal skin and on the tumor, were promising and prompt to further clinical evaluation of FLASH-RT.

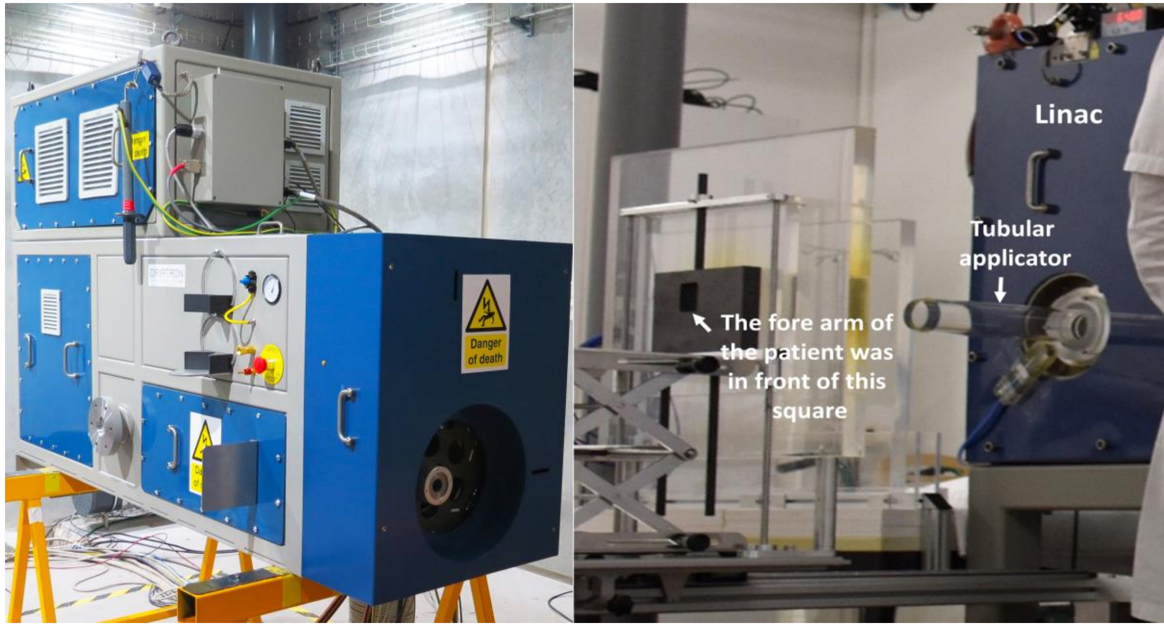
Conclusion: This first FLASH-RT treatment was feasible and safe with a favorable outcome both on normal skin and the tumor.

FLASH Radiotherapy: Introduction

Day 0
Before radiotherapy

3 weeks

5 months



FLASH Radiotherapy: Introduction

- FAST-01 Trial
- Feasibility study of FLASH for treatment of bone metastases
- Protons
- Cincinnati Children's/UC Health Proton Therapy Center

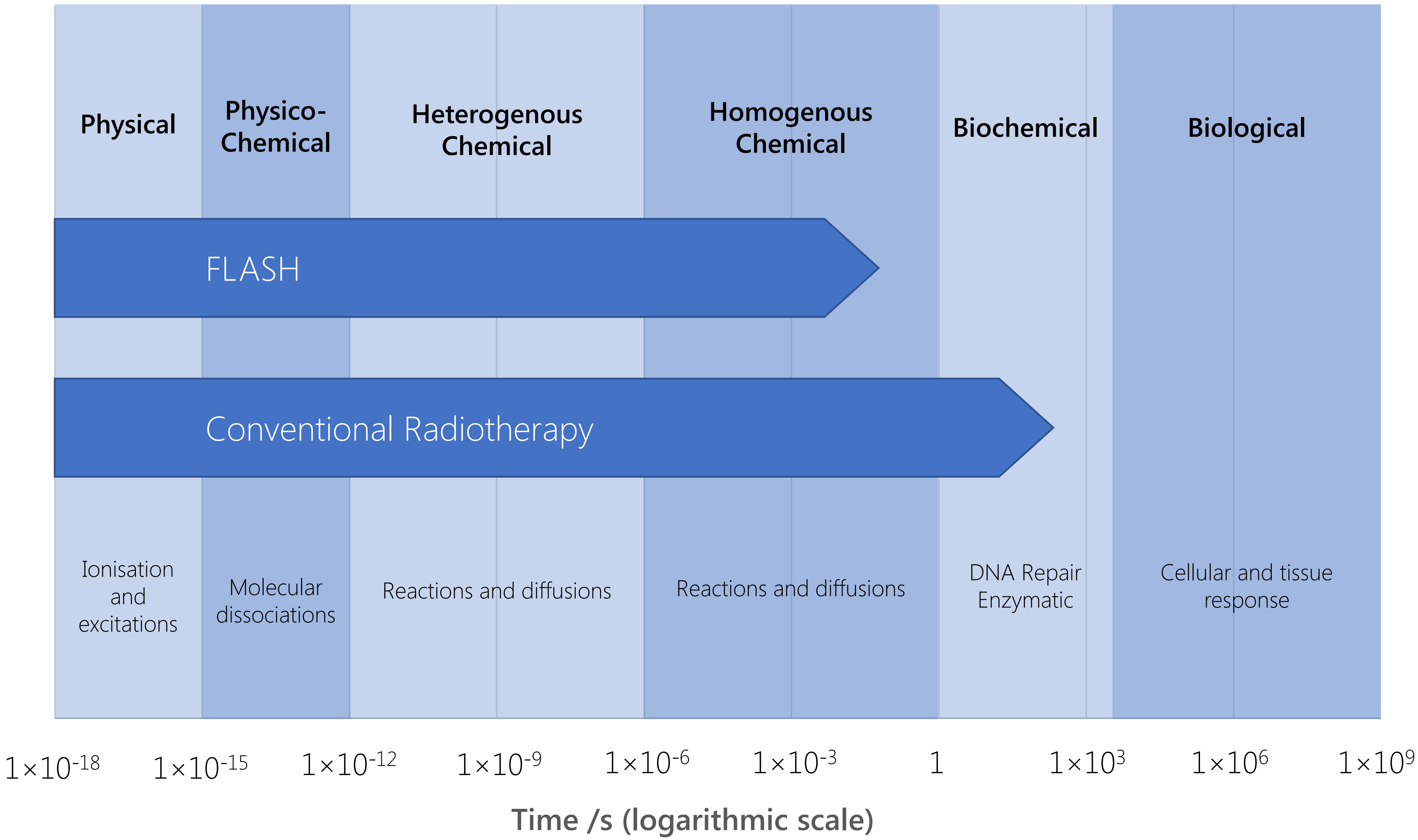
varian

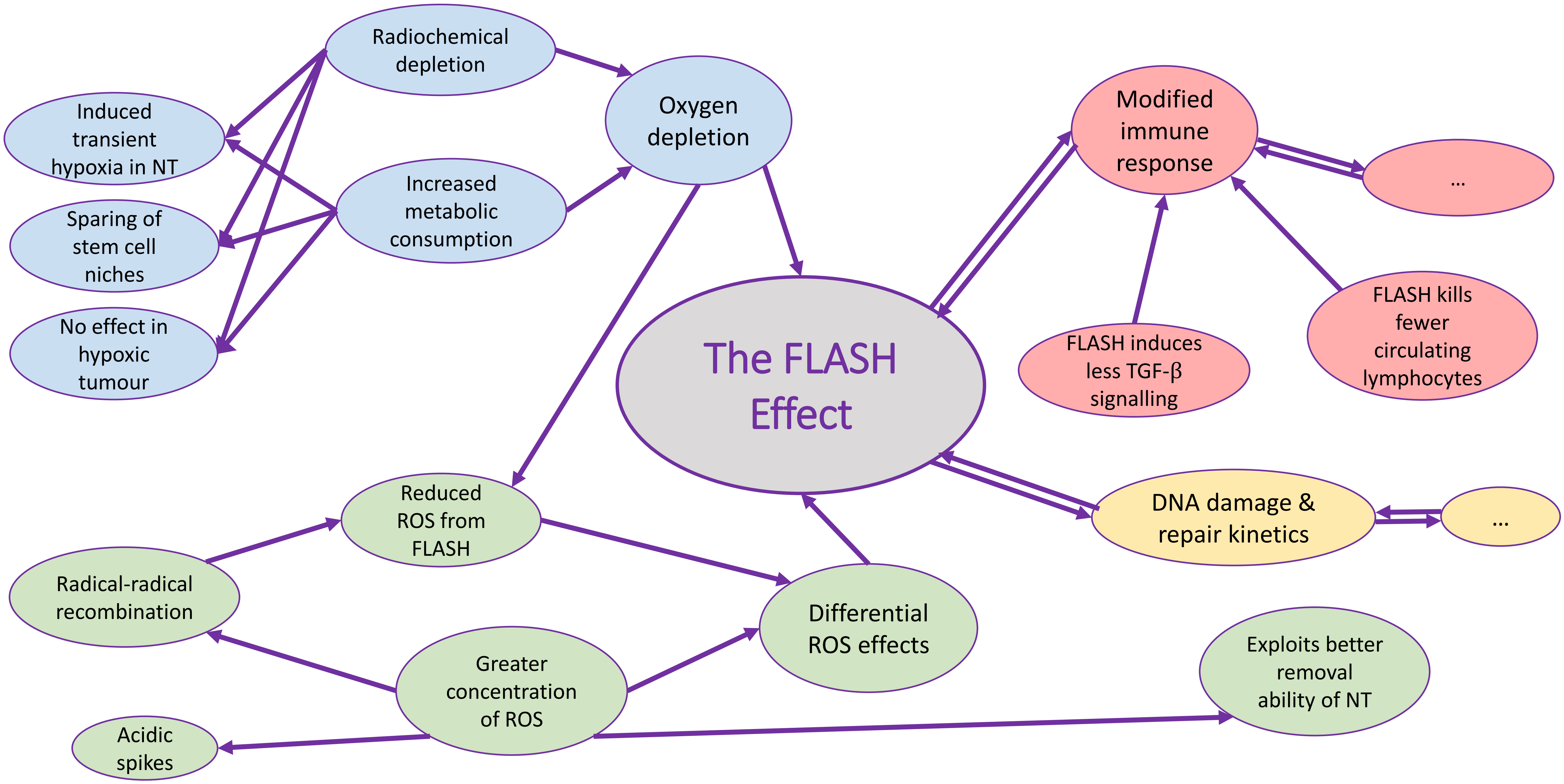
FLASH Radiotherapy: Introduction

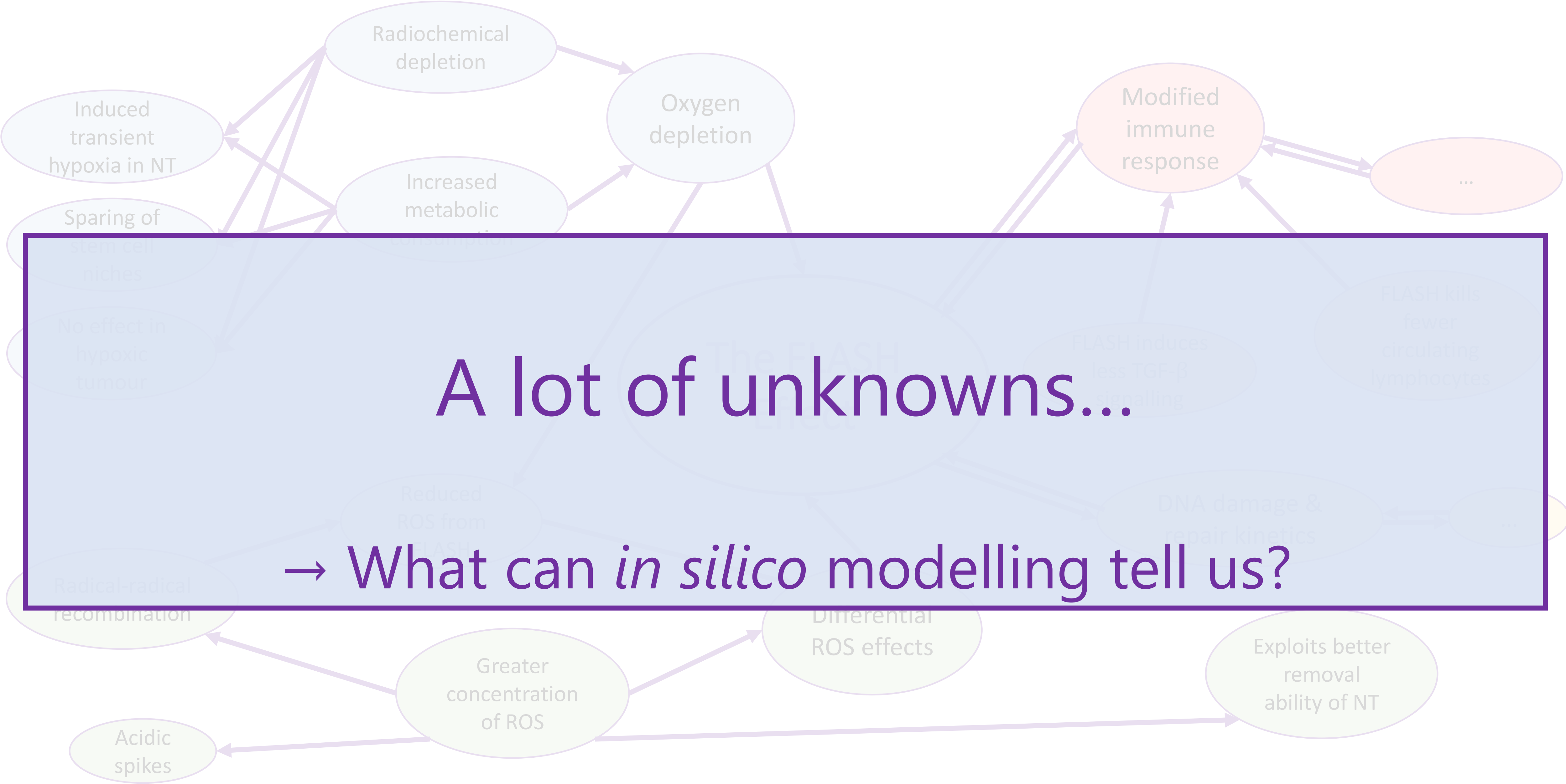
- Impulse Trial
- Dose-escalation FLASH study for skin metastases from melanoma
- Electrons
- Lausanne University Hospital (CHUV, Switzerland)

IntraOp®

What mechanisms are on offer?

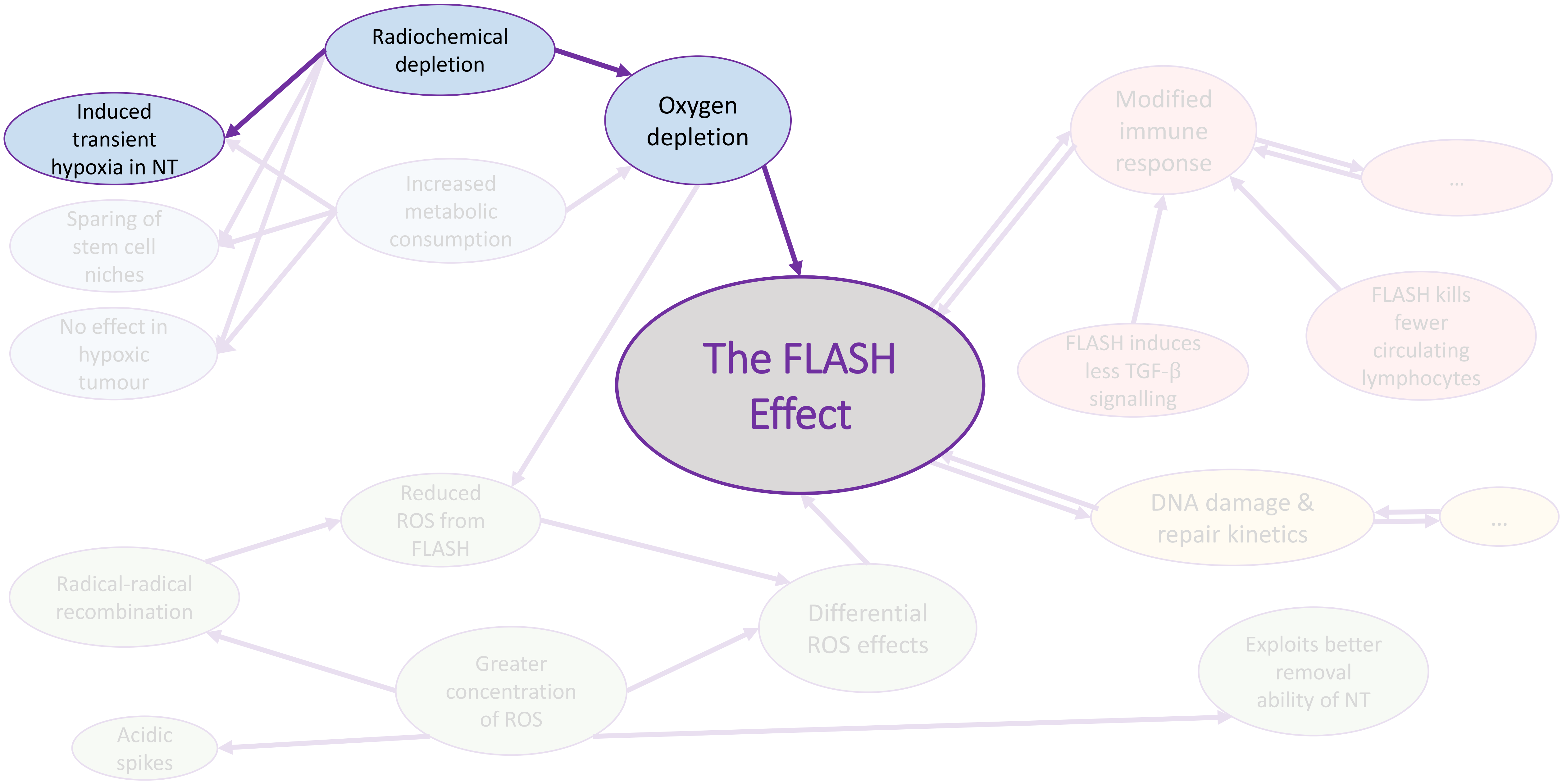

Physical
Physico-Chemical
Heterogenous Chemical
Homogenous Chemical
Biochemical
Biological
FLASH
Conventional Radiotherapy
Ionisation and excitations
Molecular dissociations
Reactions and diffusions
Reactions and diffusions
DNA Repair Enzymatic
Cellular and tissue response
1×10-18
1×10-15
1×10-12
1×10-9
1×10-6
1×10-3
1
1×103
1×106
1×109
Time /s (logarithmic scale)


Radiochemical depletion
Oxygen depletion
Induced transient hypoxia in NT
Increased metabolic consumption
Sparing of stem cell niches
No effect in hypoxic tumour
Modified immune response
...
The FLASH Effect
FLASH induces less TGF-β signalling
FLASH kills fewer circulating lymphocytes
Reduced ROS from FLASH
DNA damage & repair kinetics
...
Radical-radical recombination
Differential ROS effects
Greater concentration of ROS
Exploits better removal ability of NT
Acidic spikes



A lot of unknowns…

→ What can *in silico* modelling tell us?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Radical-radical recombination
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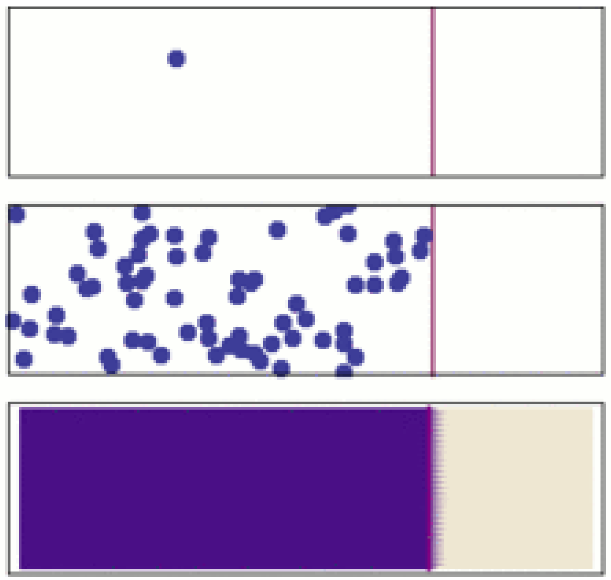
Exploits better removal ability of NT
Acidic spikes

Model: Reaction and Diffusion of O_2

1. **Diffusion of oxygen from a capillary**
   - Oxygen diffuses from nodes with high concentration to nodes with low concentration
   - Rate of diffusion depends on concentration gradient and diffusivity



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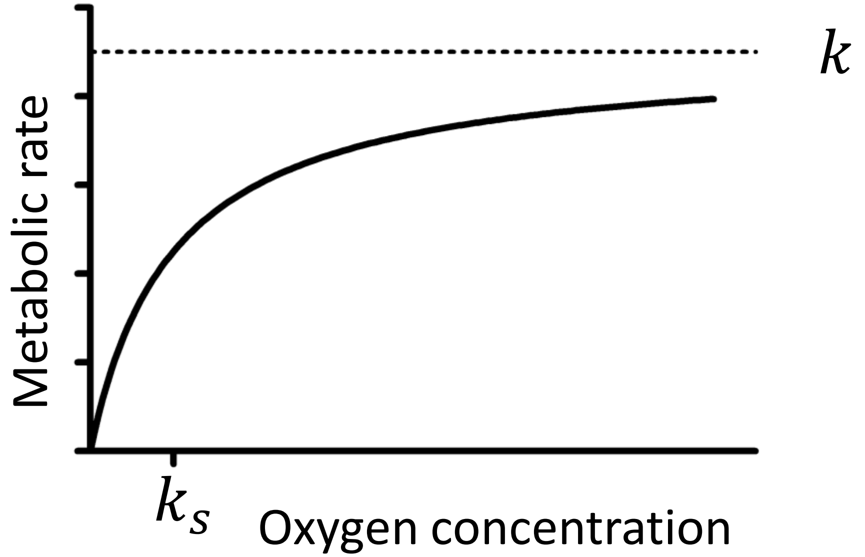
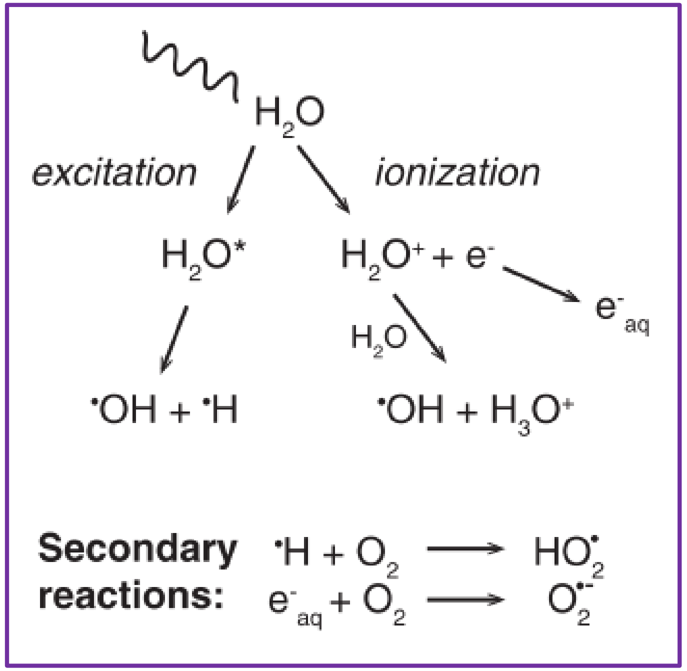


2.1 Metabolic consumption of oxygen

- Reaction happening **all the time** within each node
- At high O_2, consumption is constant
- At low O_2, consumption ∝ amount available

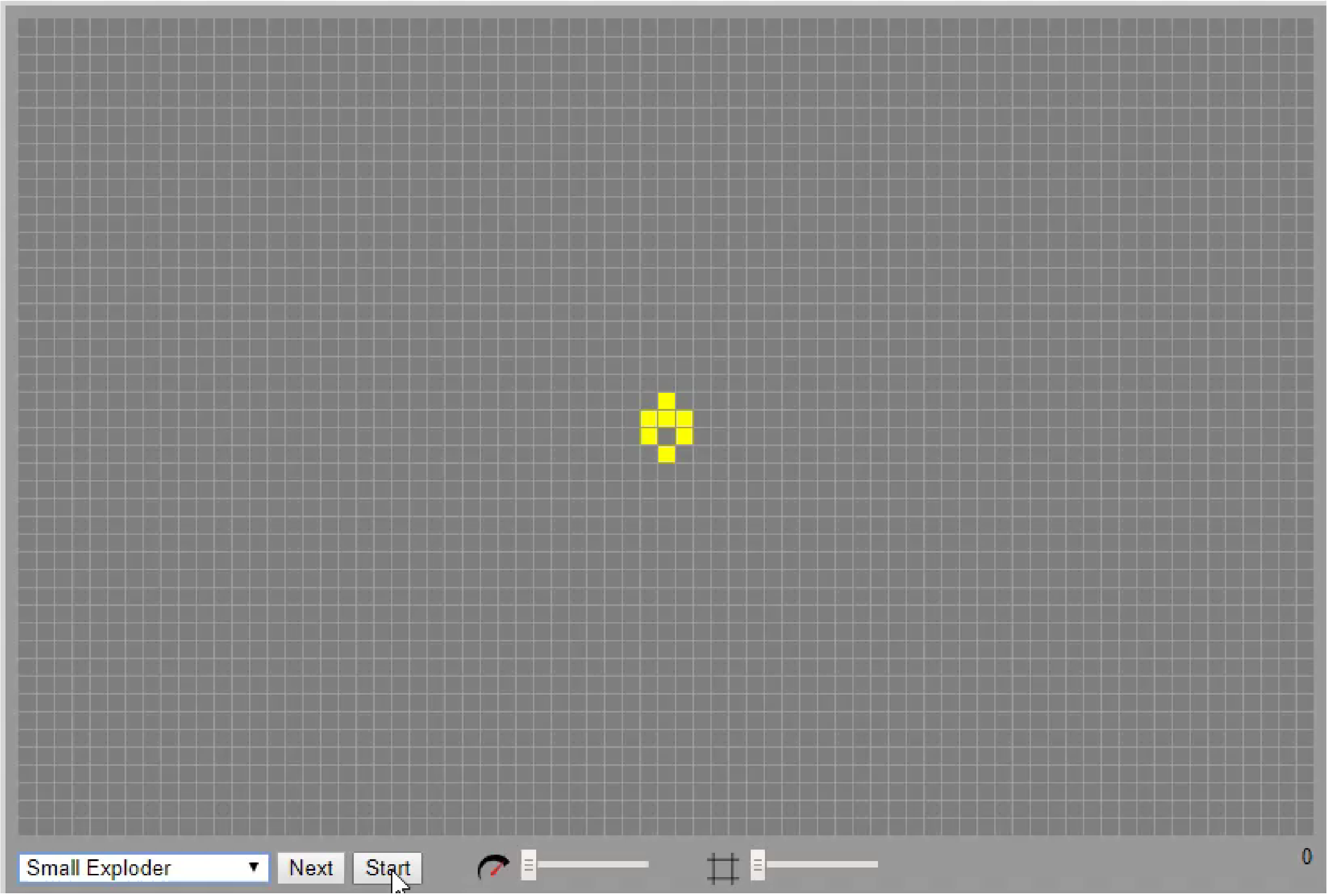
2.2 Radiation-induced consumption of oxygen

- Reaction happening **when radiation is 'on'**
- Radiolytic species are produced ∝ dose
- Species react with O_2 ∝ availability of each



Solution: Cellular Automaton

Conway's Game of Life



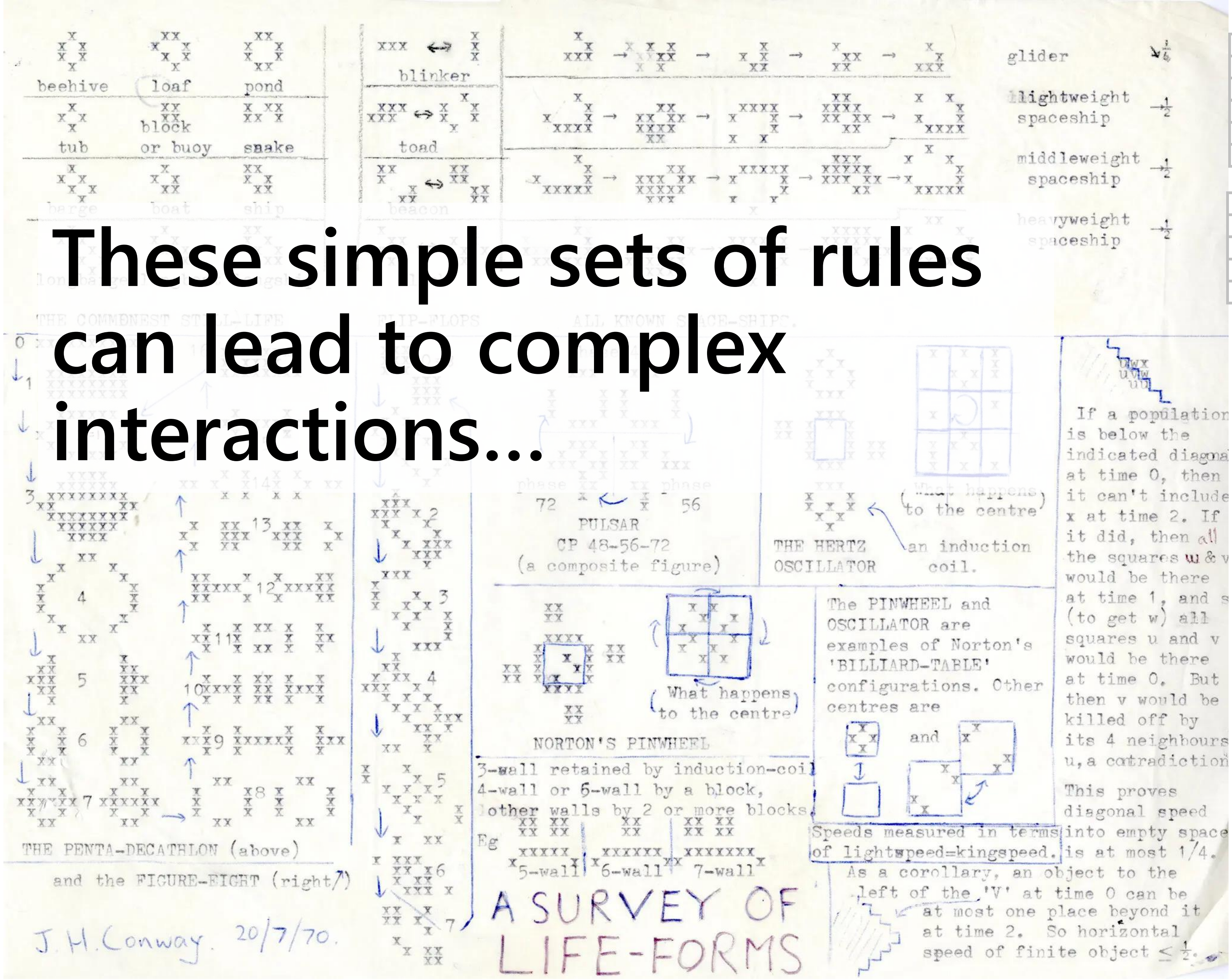
For a space that is 'populated':

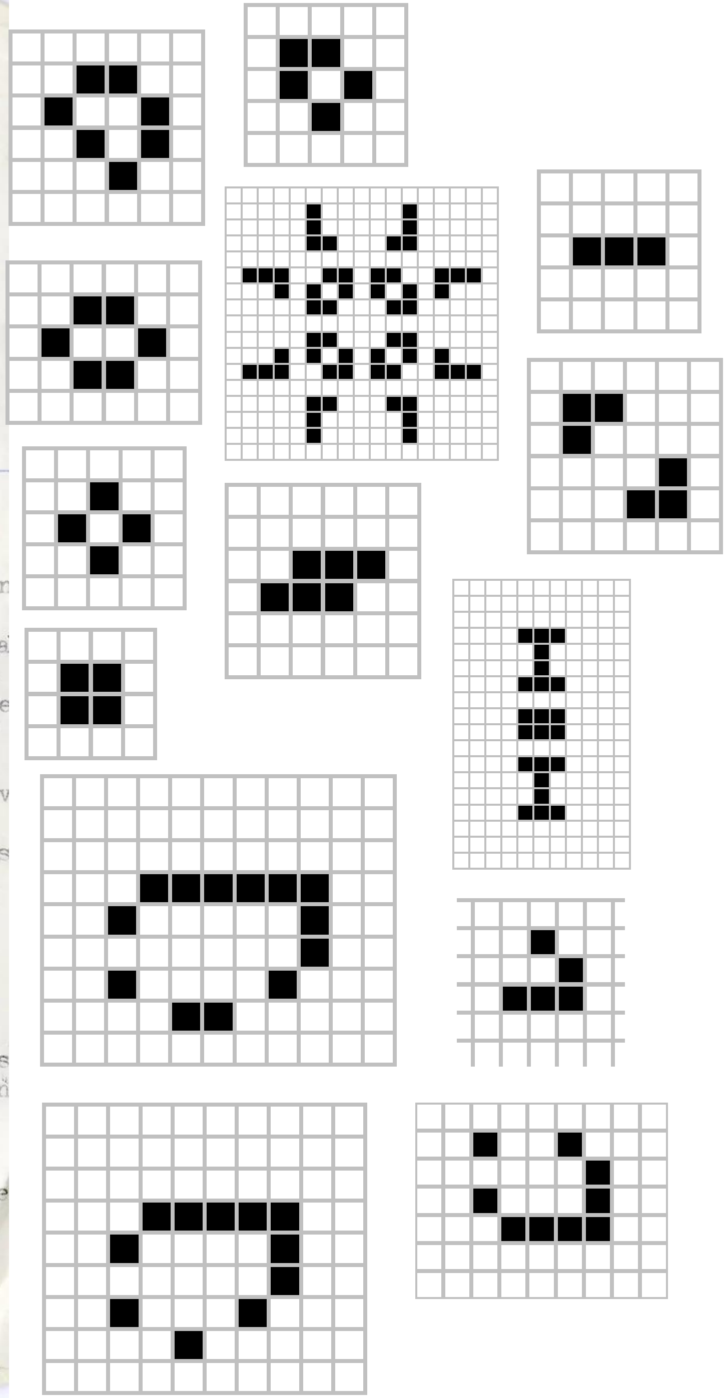
- Each cell with 1 or 0 neighbours dies, as if by solitude.
- Each cell with 4 or more neighbours dies, as if by overpopulation.
- Each cell with 2 or 3 neighbours survives.

For a space that is 'unpopulated'

- Each cell with 3 neighbours becomes populated.

These simple sets of rules can lead to complex interactions...





Solution: Cellular automaton

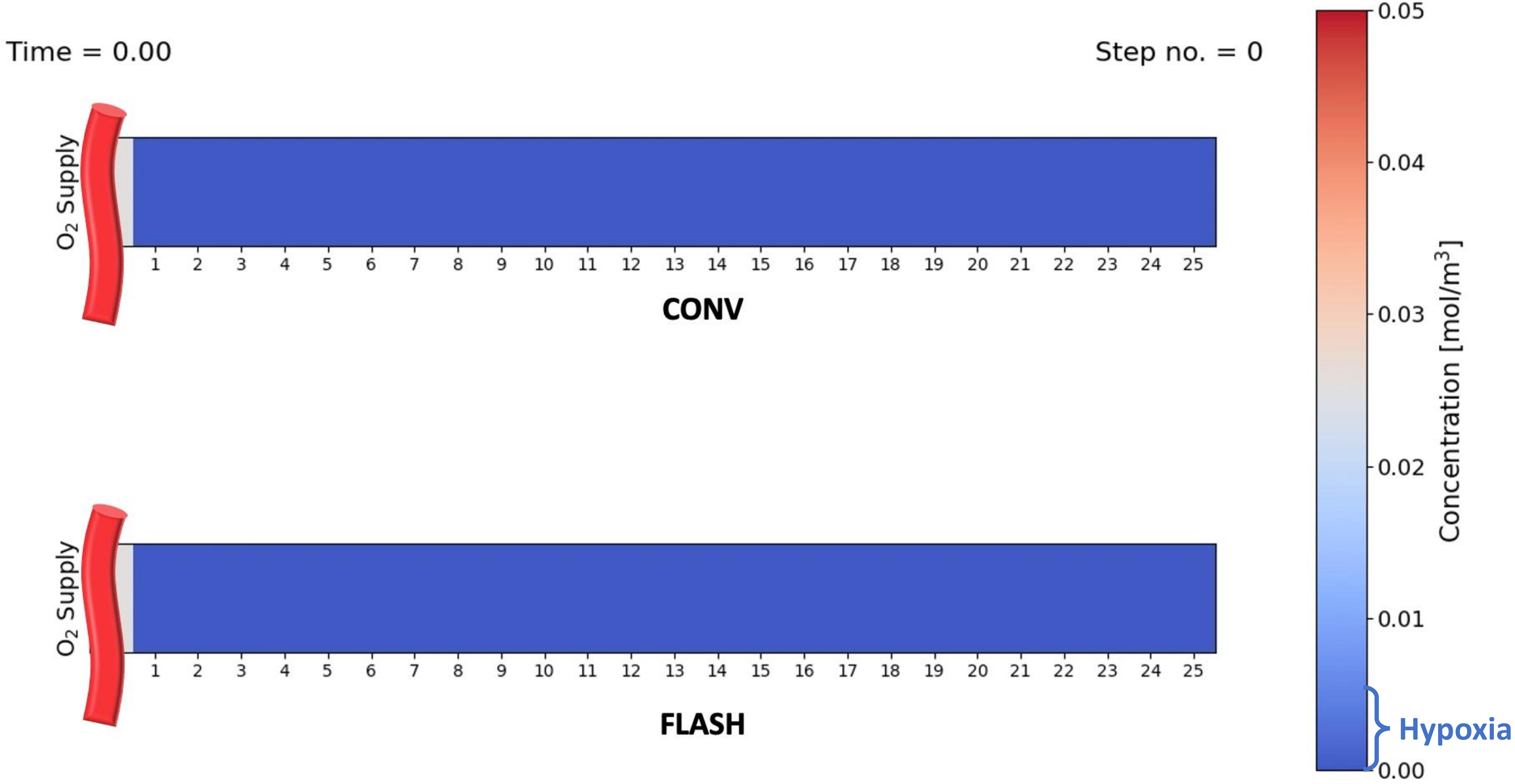
Game of Life

- 2D grid of cells
- State of cell changes at every timestep
- State of each cell:
  - Characterised by ‘dead’ or ‘alive’
- Rules:
  - Any live cell with 1 or 0 neighbours dies
  - Any live cell with 4 or more neighbours dies
  - Any live cell with 2 or 3 neighbours survives
  - Any dead cell with 3 neighbours becomes live

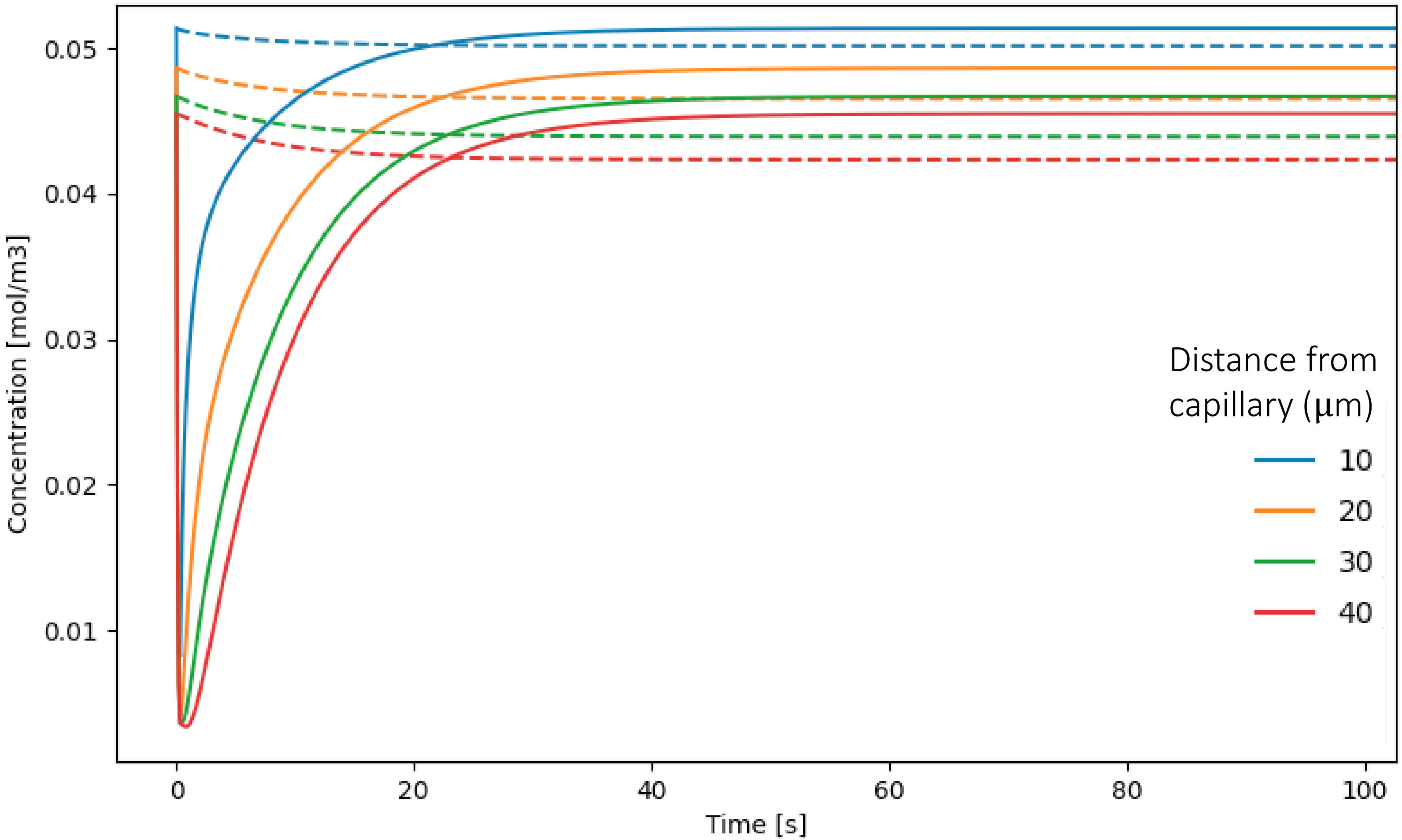
Our model

- 1D grid of cells (‘nodes’)
- State of cell changes at every timestep
- State of each cell:
  - Characterised concentration of oxygen, $[O_2]$
- Rules:
  - Any cell with $[O_2]$ greater than its neighbour exchanges O_2 (diffusion)
  - Every cell consumes O_2 via metabolic equation.
  - If radiation is ‘on’, radiolytic species are produced. If O_2 is available, species react with O_2.

Oxygen depletion



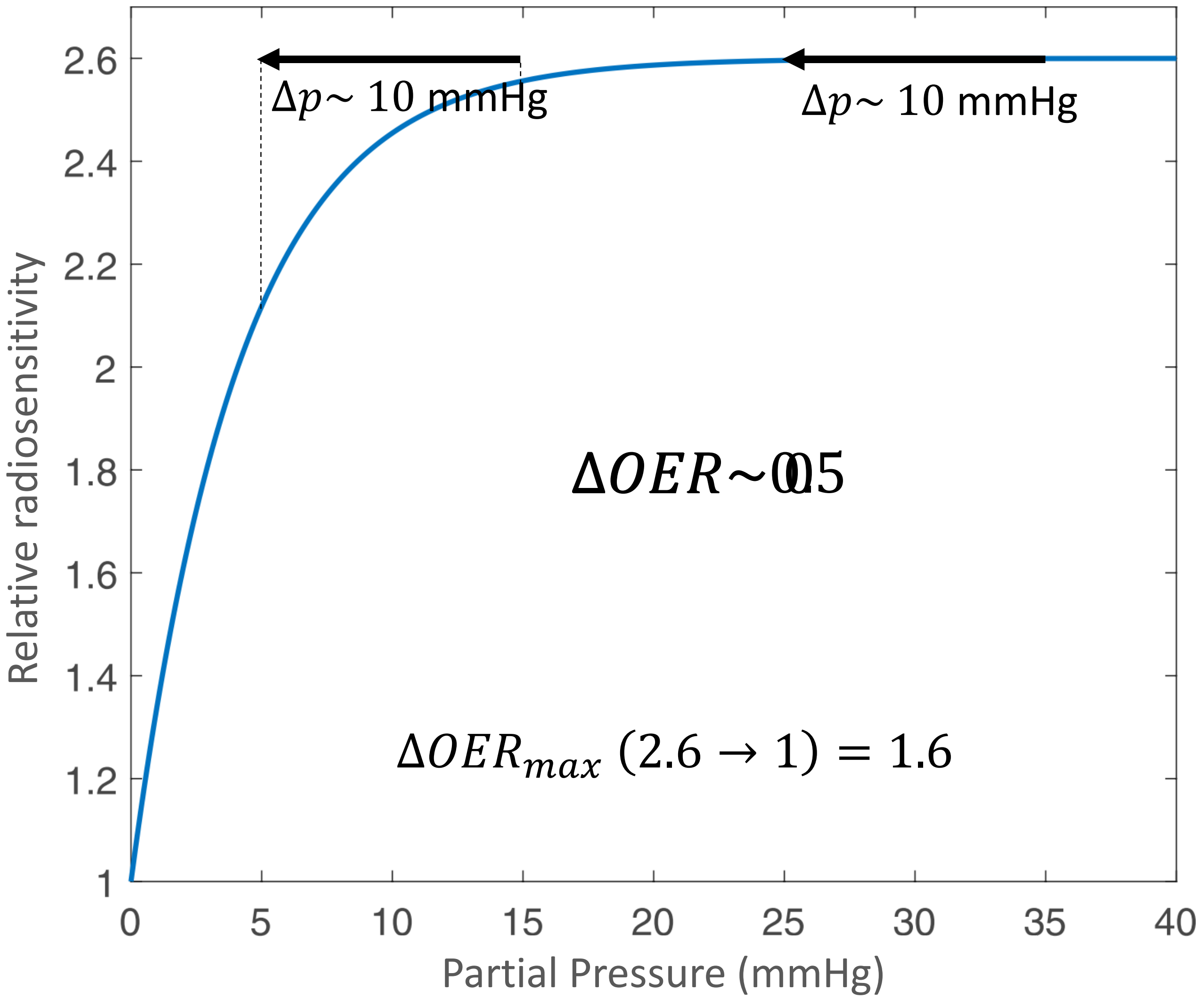
Oxygen depletion



--- Conventional radiotherapy (0.03 Gy/s)

— FLASH (40 Gy/s)

Oxygen depletion: change in radiosensitivity



$$OER = \frac{Cell\ kill\ in\ oxic\ conditions}{Cell\ kill\ under\ anoxia}$$

Grimes et al. Br J Radiol. 2017; 90:20160939

Oxygen depletion: parameters involved

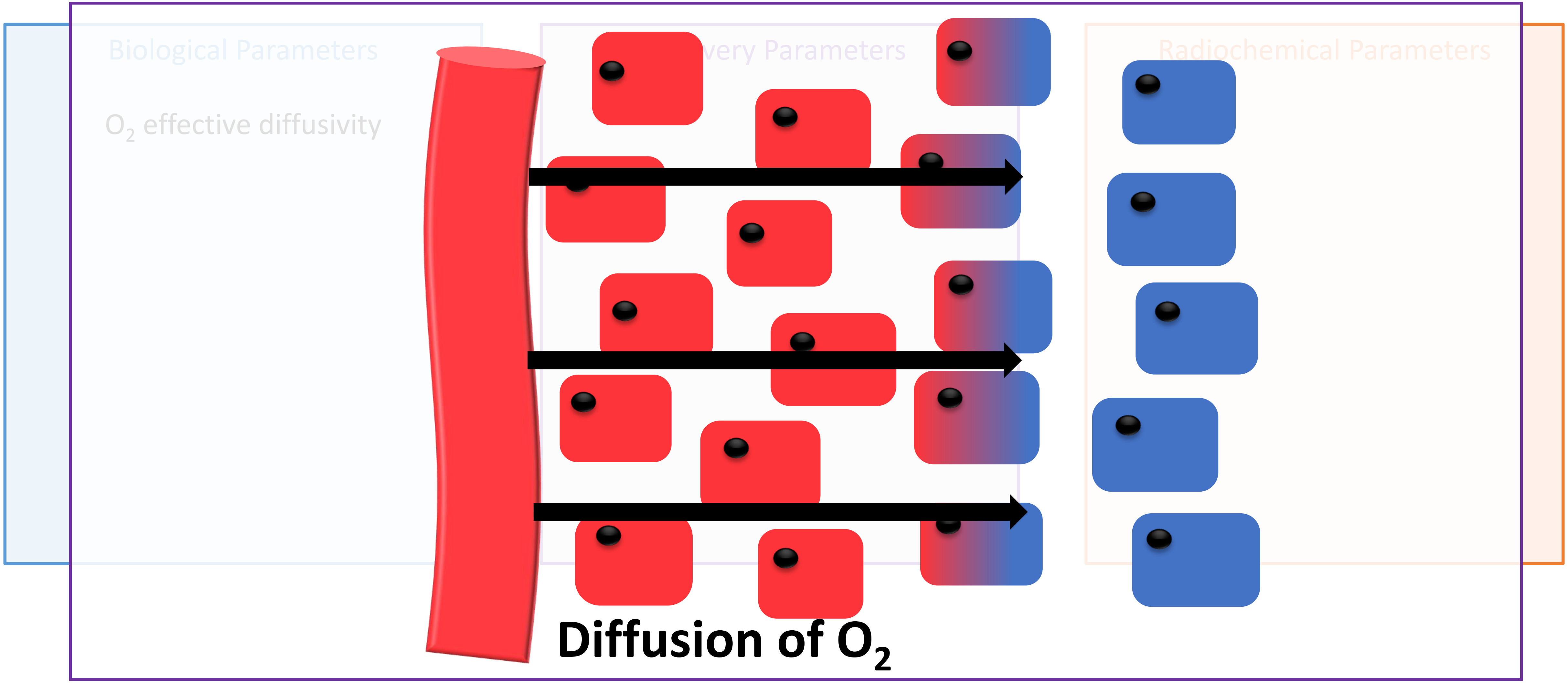
Biological Parameters

O_2 effective diffusivity

Delivery Parameters

Radiochemical Parameters

Oxygen depletion: parameters involved



Oxygen depletion: parameters involved

Biological Parameters

...very Parameters

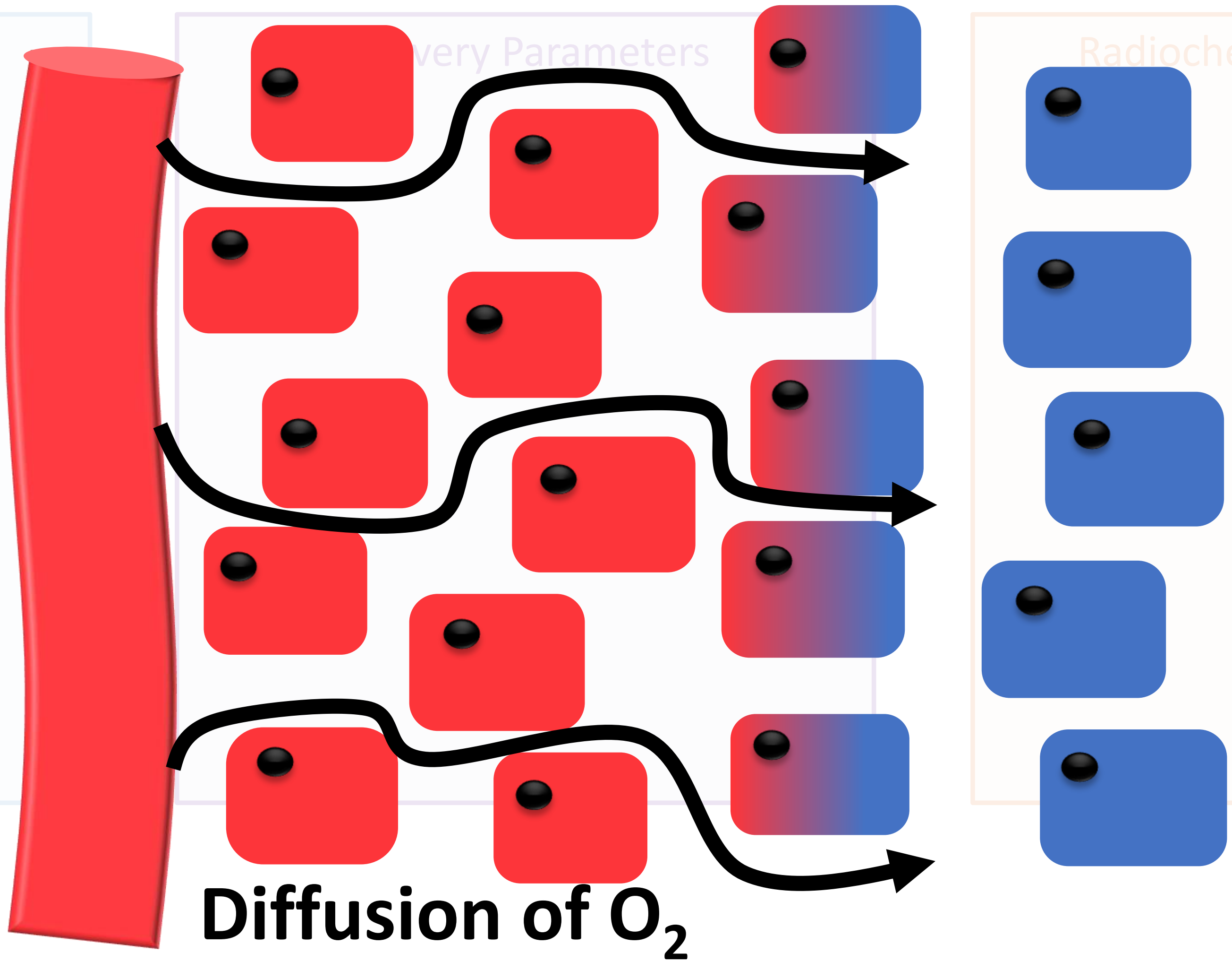
Radiochemical Parameters

O_2 effective diffusivity

$$D_{eff} = \frac{D_{mol}\,\varepsilon}{\tau}$$

ε = voidage

τ = tortuosity



Oxygen depletion: parameters involved

Biological Parameters

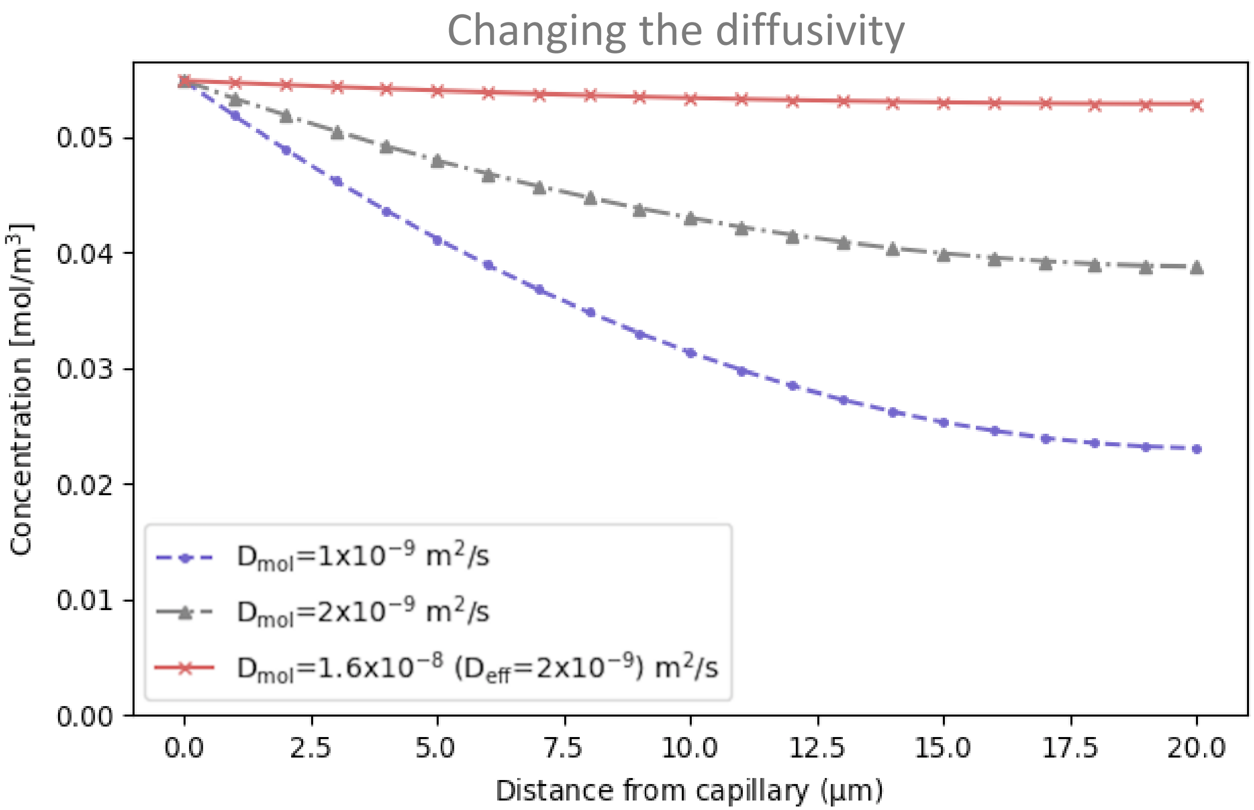
O_2 effective diffusivity
Capillary O_2 tension
Metabolic O_2 consumption rate

$$r_{metabolic} = \frac{kC}{k_s + C}$$

Delivery Parameters

Radiochemical Parameters

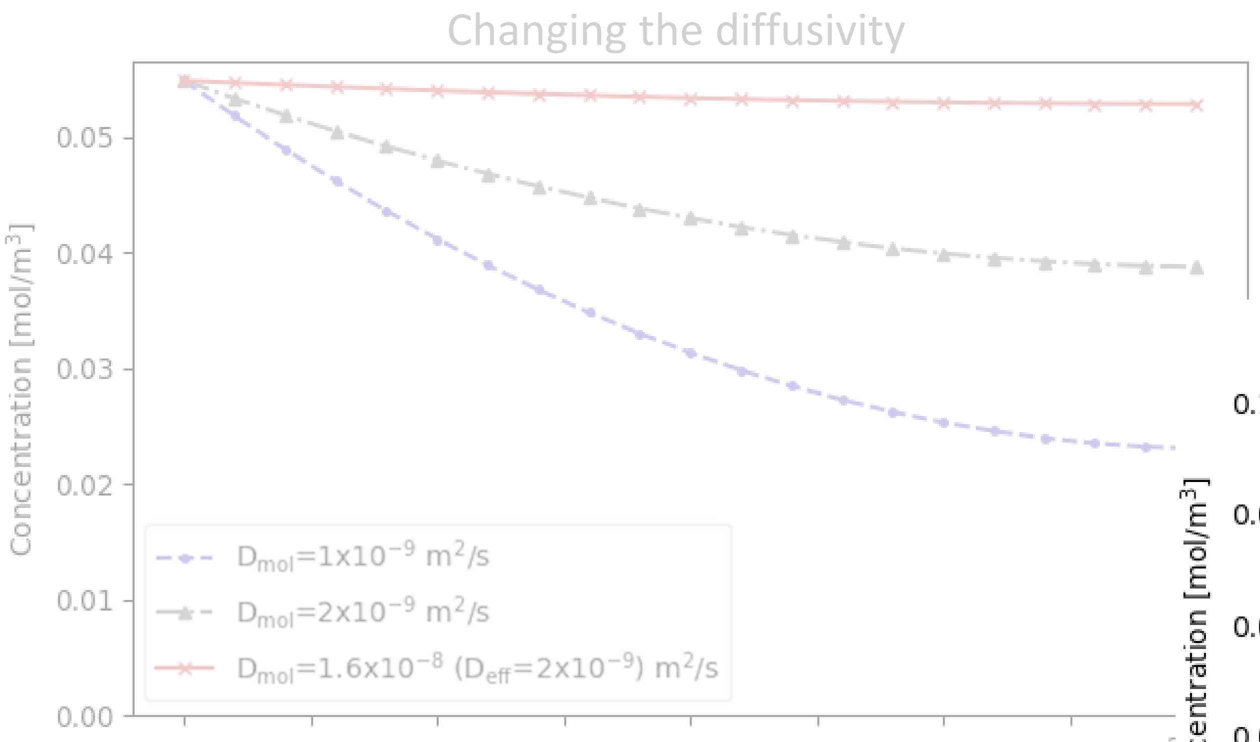
Oxygen depletion: biological parameters



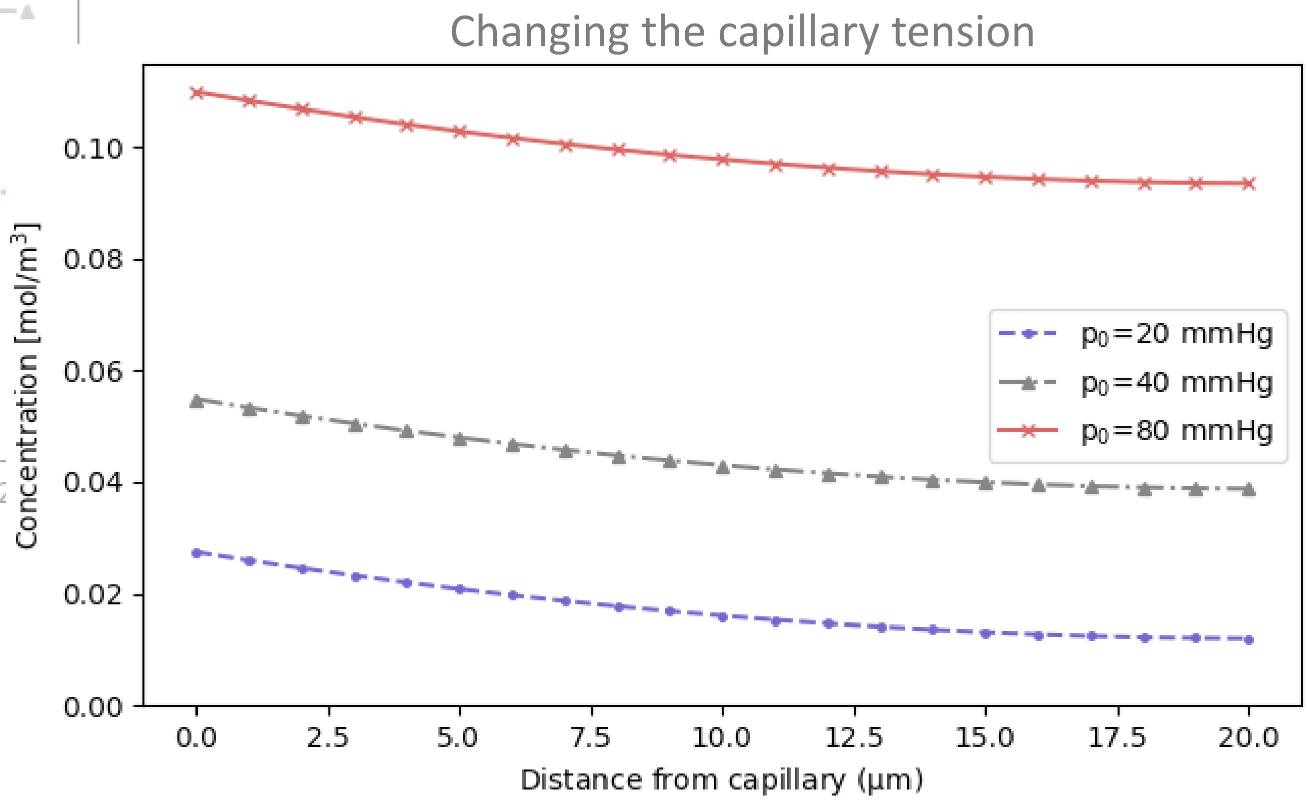
D_{mol}	$1, 2, 16 \times 10^{-9}$ m^2 s^{-1}	Gerlee and Anderson (2010) Pratx and Kapp (2019a) Curcio *et al* (2007) Kirkpatrick *et al* (2003)

Rothwell et al. 2021. Phys. Med. Biol.

Oxygen depletion: biological parameters



p_0	20, 40, 80 mmHg	Pratx and Kapp (2019a) McKeown (2014) Skeldon *et al* (2012) Curcio *et al* (2007) Goldman and Popel (2000) Kirkpatrick *et al* (2003)



Rothwell et al. 2021. Phys. Med. Biol.

Oxygen depletion: parameters involved

Biological Parameters

O_2 effective diffusivity
Capillary O_2 tension
Metabolic O_2 consumption rate

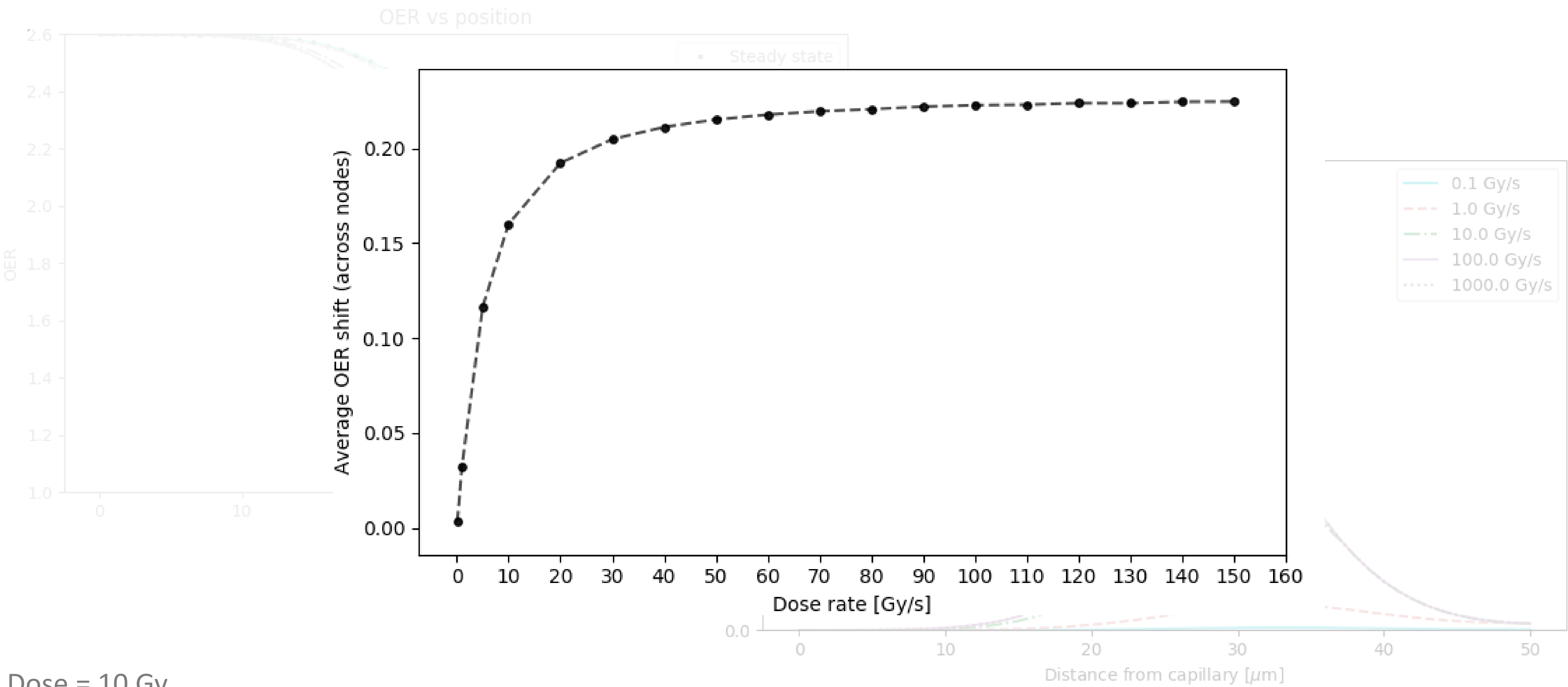
$$r_{metabolic} = \frac{kC}{k_s + C}$$

Delivery Parameters

Dose
Dose rate

Radiochemical Parameters

Oxygen depletion: dose rate



Dose = 10 Gy

Rothwell et al. 2021. Phys. Med. Biol.

Oxygen depletion: parameters involved

Biological Parameters

O_2 effective diffusivity
Capillary O_2 tension
Metabolic O_2 consumption rate (k and k_s)

$$r_{metabolic} = \frac{kC}{k_s + C}$$

Delivery Parameters

Dose
Dose rate

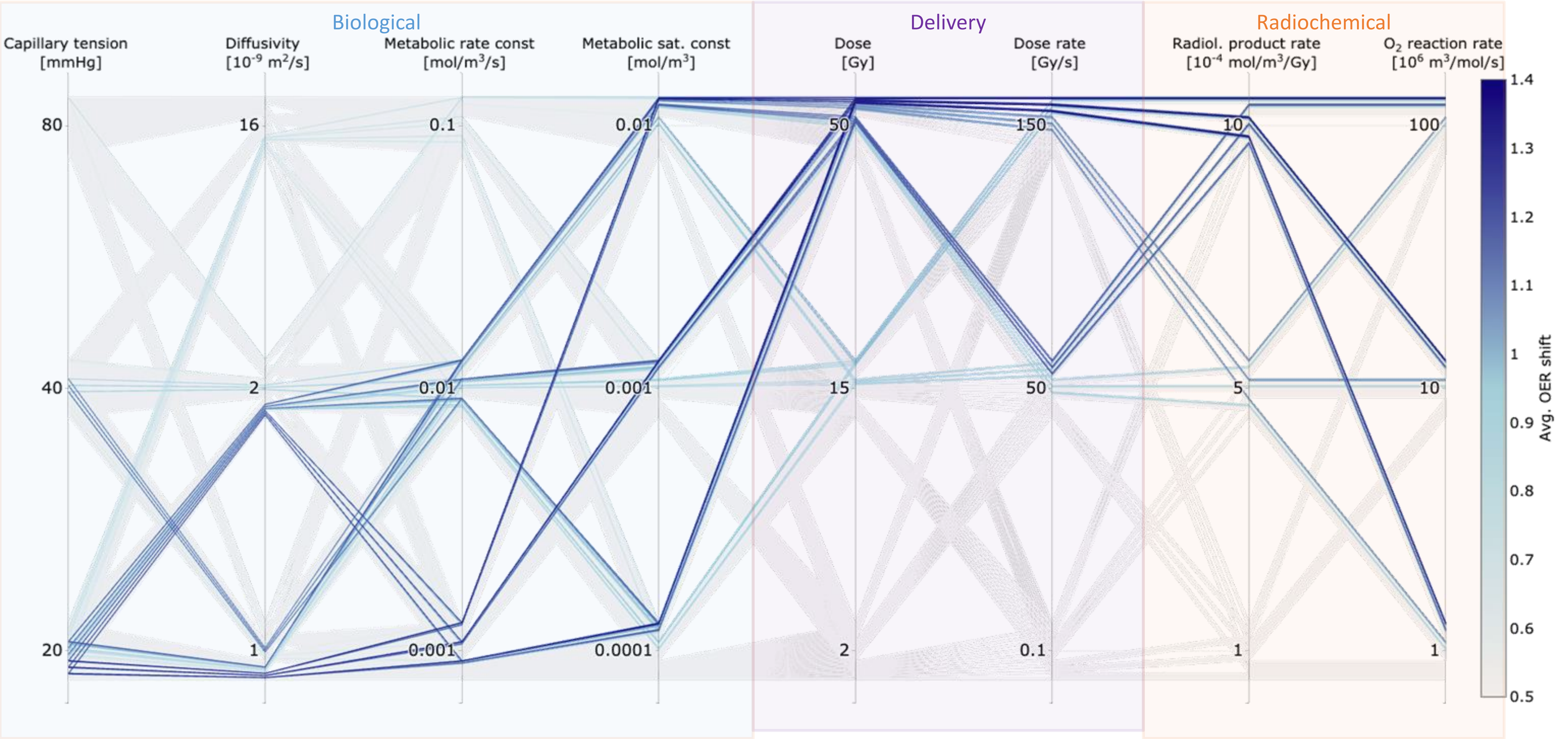
Radiochemical Parameters

Radiolytic depletion rate (k_1 *and* k_2)

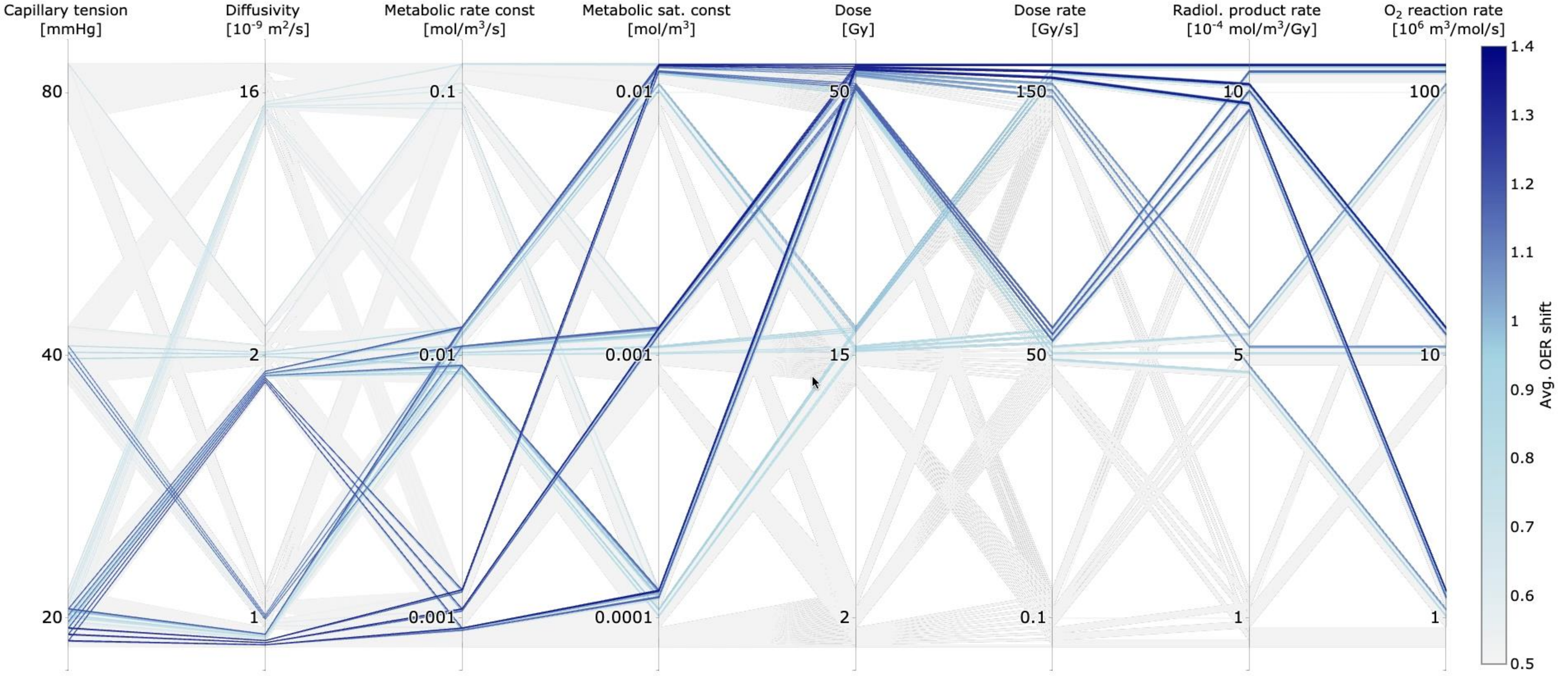
$$r_A = k_1\dot{D} - k_2[A]C$$

$$r_{O_2} = -k_2[A]C$$

Oxygen depletion: generating a parameter space



Oxygen depletion: generating a parameter space



IOP Publishing Phys. Med. Biol. 66 (2021) 055020 https://doi.org/10.1088/1361-6560/abe2ea

Physics in Medicine & Biology

IPEM Institute of Physics and Engineering in Medicine

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OPEN ACCESS

RECEIVED
12 November 2020

REVISED
15 January 2021

ACCEPTED FOR PUBLICATION
3 February 2021

PUBLISHED
25 February 2021

PAPER

Determining the parameter space for effective oxygen depletion for FLASH radiation therapy

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Keywords: FLASH radiotherapy, dose rate, oxygen depletion

Supplementary material for this article is available online

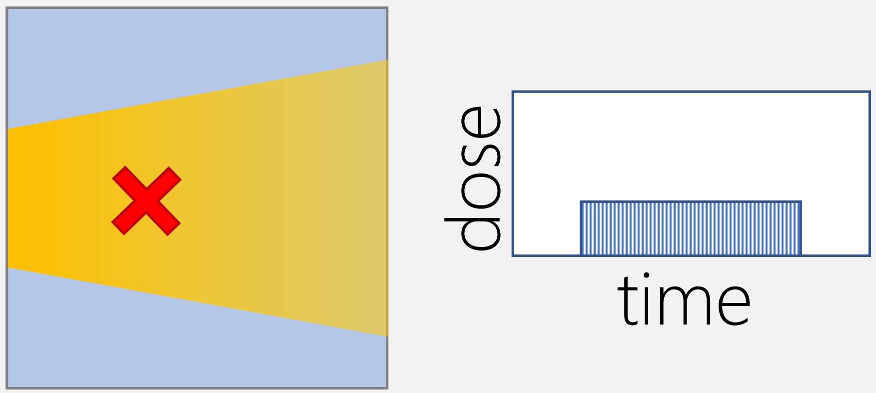
Abstract

There has been a recent revival of interest in the FLASH effect, after experiments have shown normal tissue sparing capabilities of ultra-high-dose-rate radiation with no compromise on tumour growth restraint. A model has been developed to investigate the relative importance of a number of fundamental parameters considered to be involved in the oxygen depletion paradigm of induced radioresistance. An example eight-dimensional parameter space demonstrates the conditions under which radiation may induce sufficient depletion of oxygen for a diffusion-limited hypoxic cellular response. Initial results support experimental evidence that FLASH sparing is only achieved for dose rates on the order of tens of Gy s^{-1} or higher, for a sufficiently high dose, and only for tissue that is slightly hypoxic at the time of radiation. We show that the FLASH effect is the result of a number of biological, radiochemical and delivery parameters. Also, the threshold dose for a FLASH effect occurring would be more prominent when the parameterisation was optimised to produce the

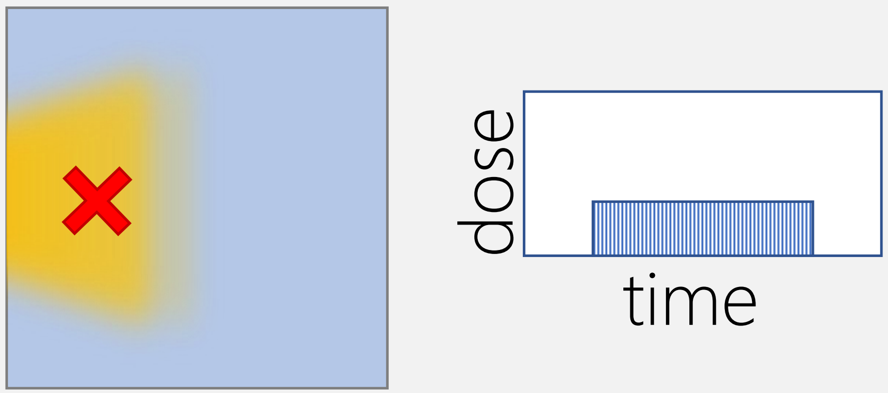
Application to proton pencil beam scanning

Proton PBS: comparing delivery patterns

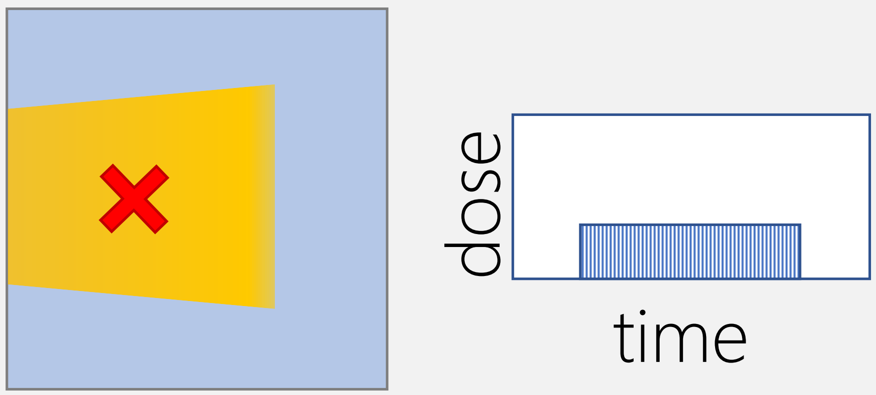
Photons



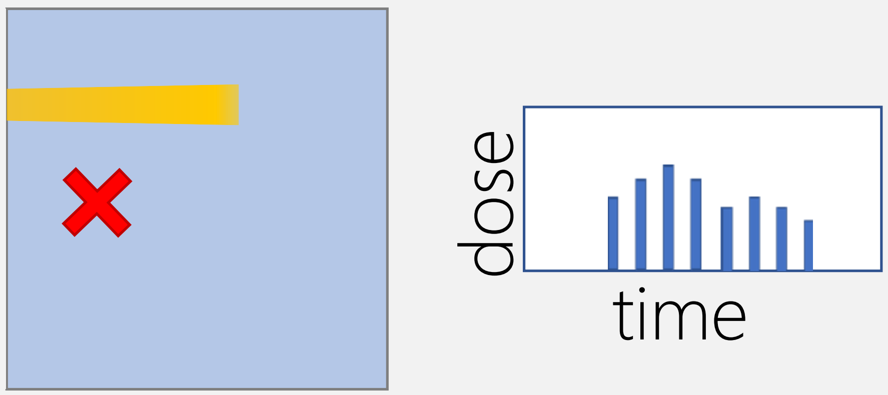
Electrons



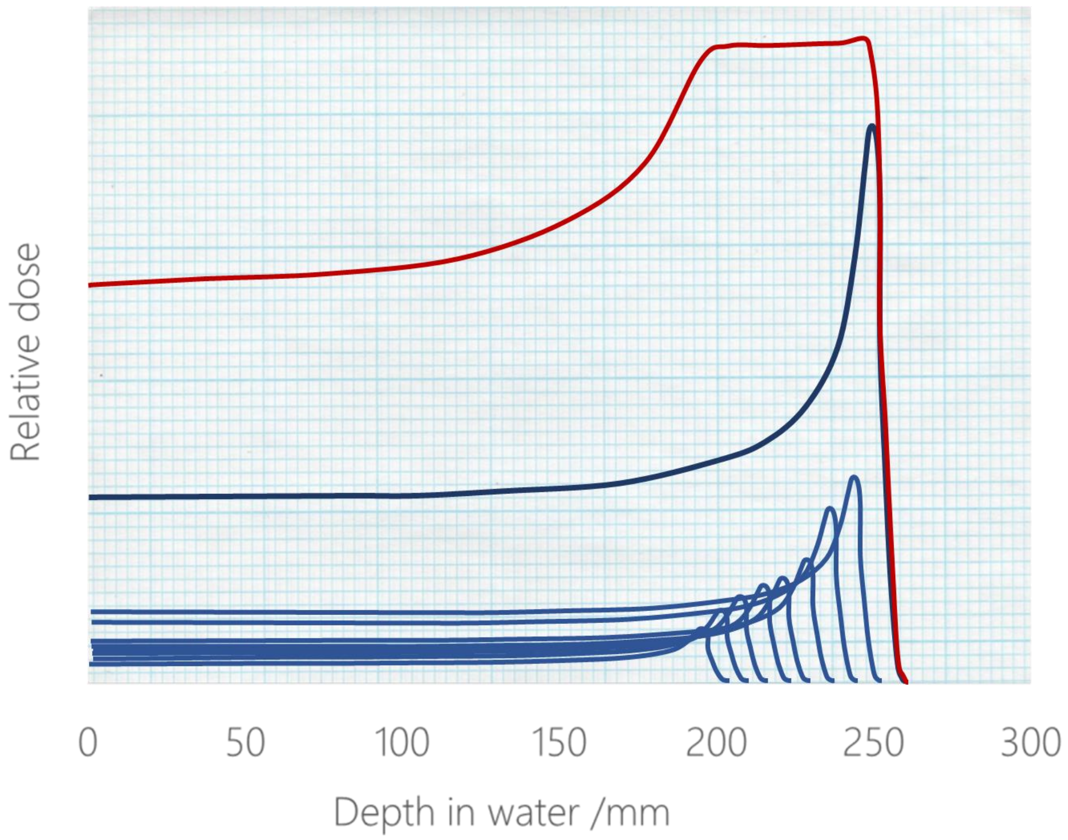
Passively scattered protons

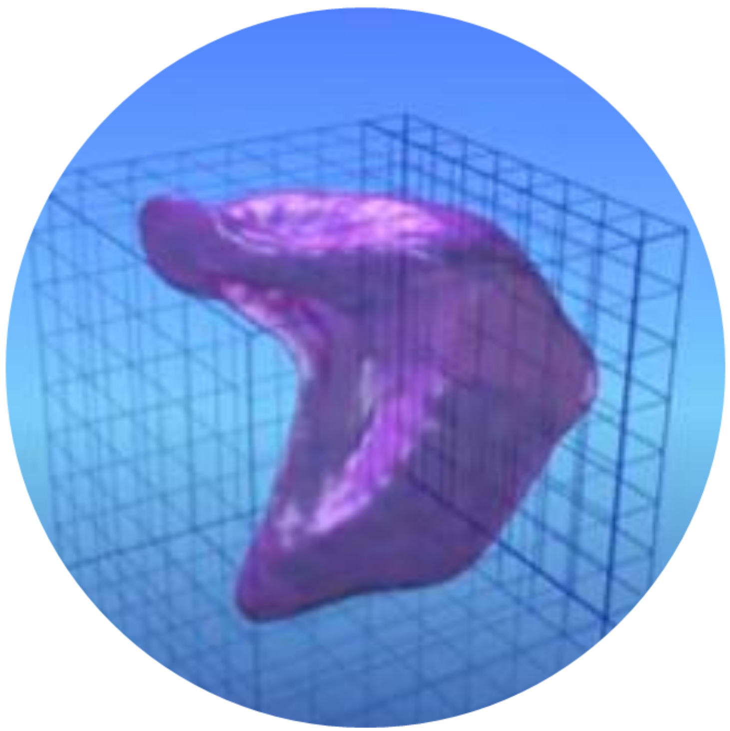


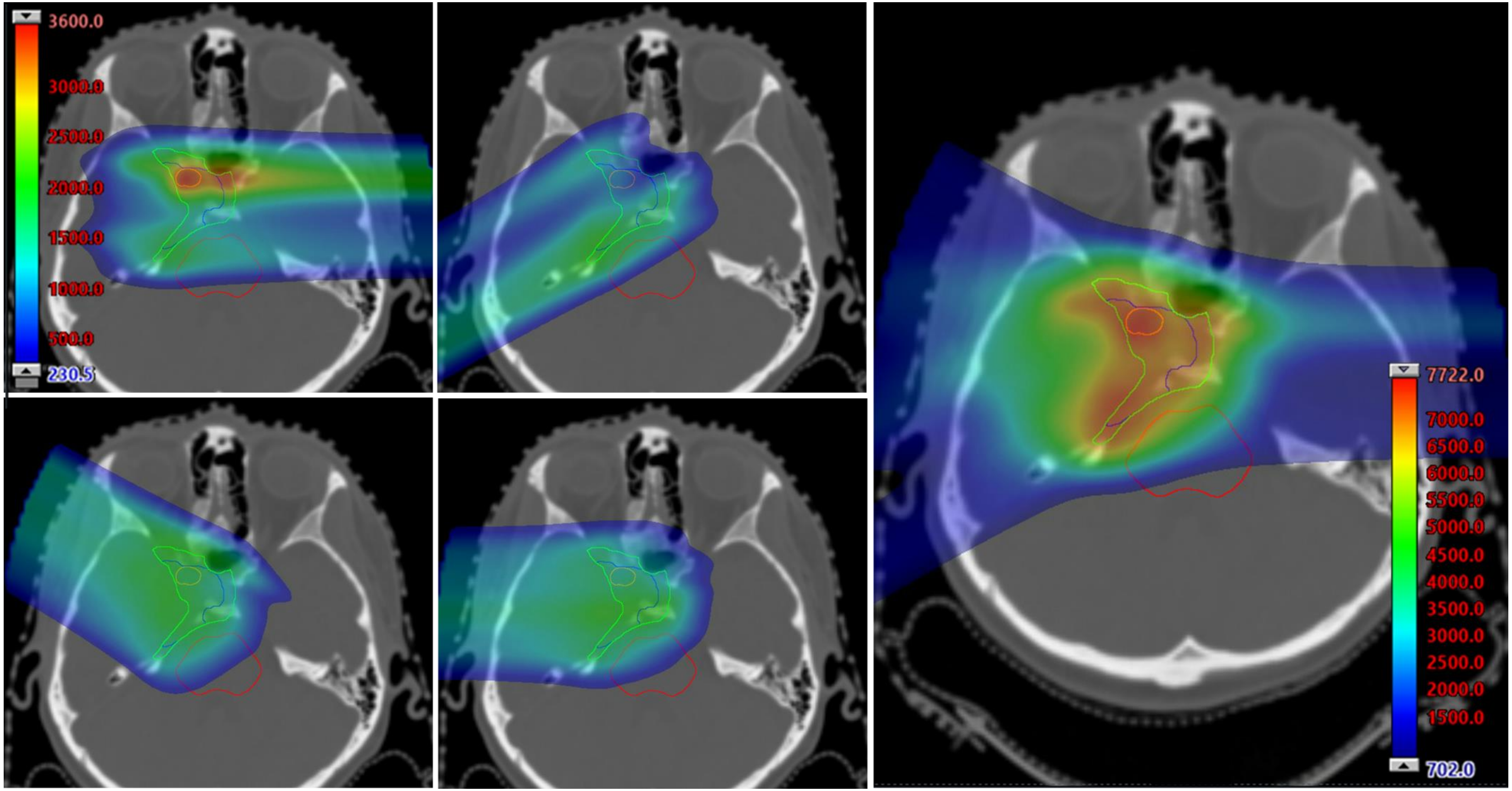
Pencil beam scanning protons



Proton PBS: treatment planning for FLASH






3600.0
3000.0
2500.0
2000.0
1500.0
1000.0
500.0
230.5
7722.0
7000.0
6500.0
6000.0
5500.0
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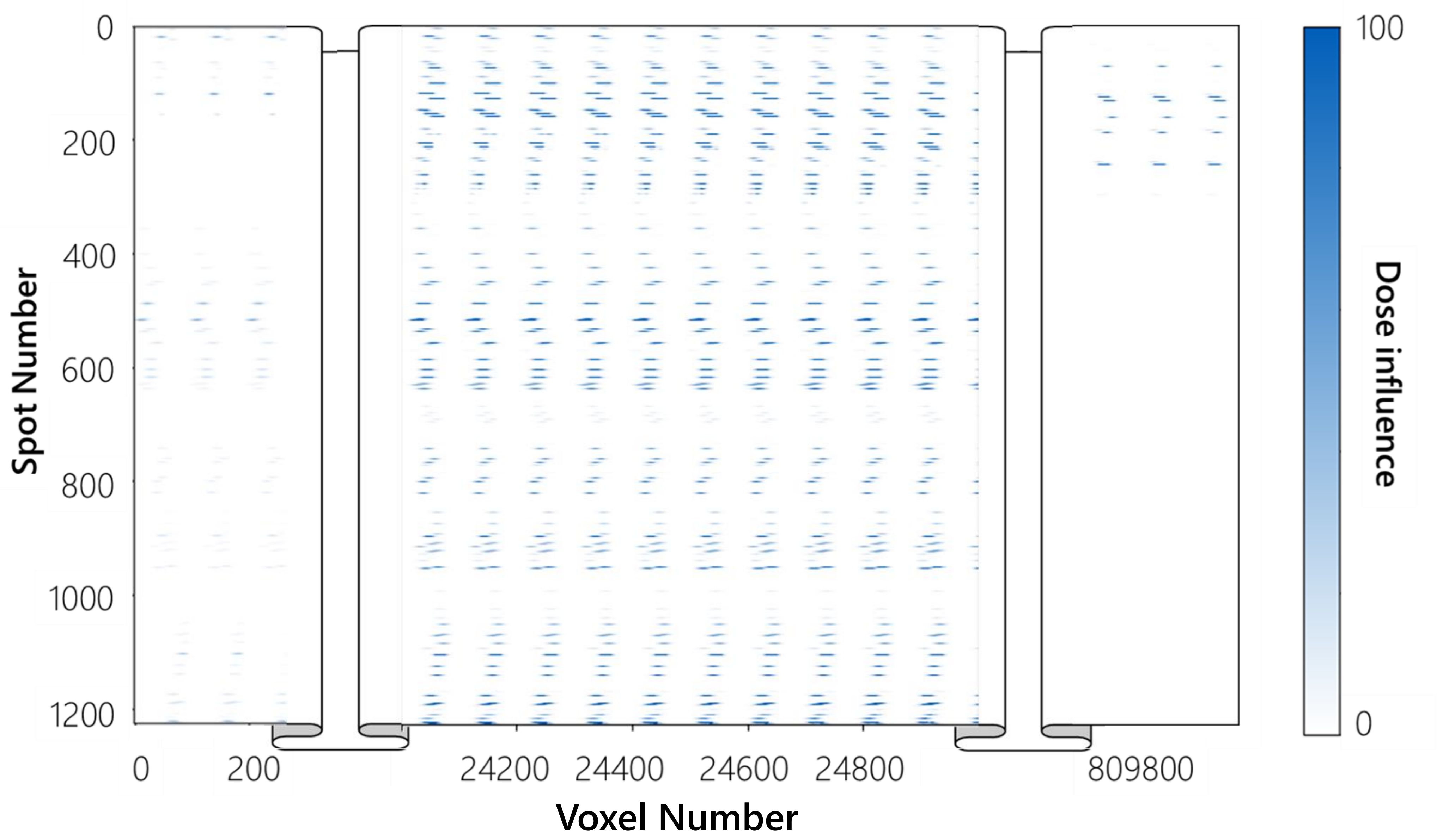
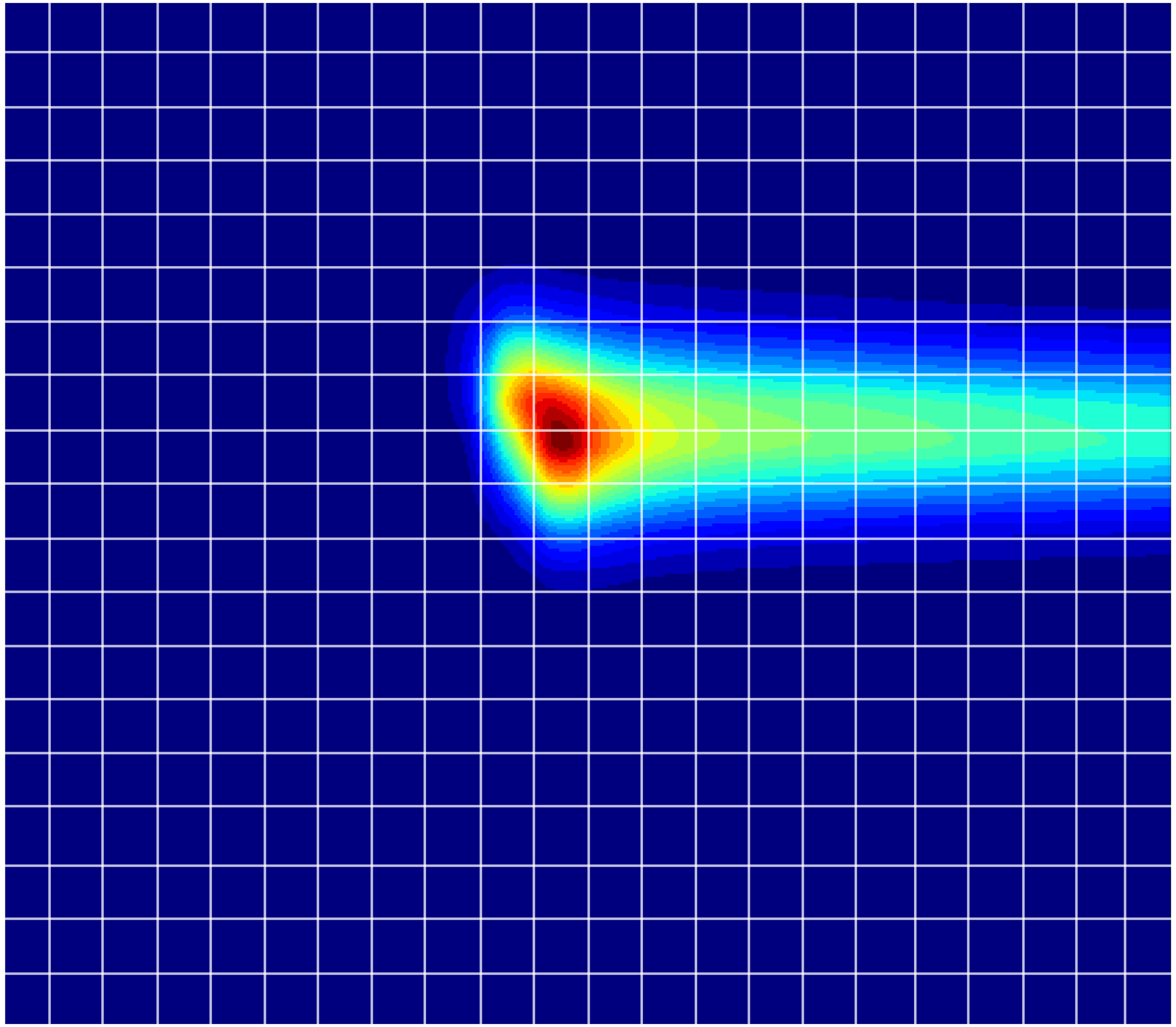
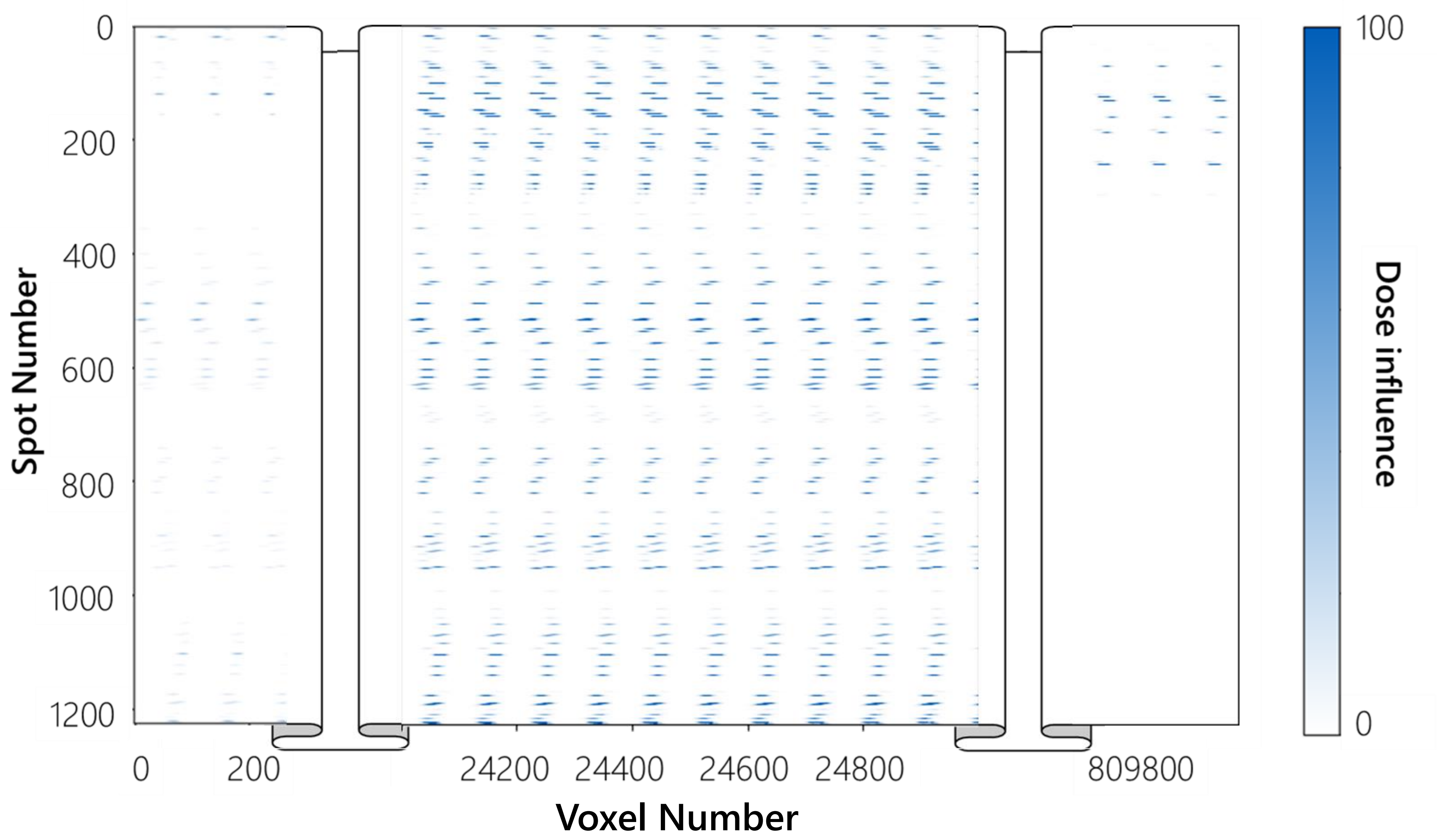
2000.0
1500.0
702.0



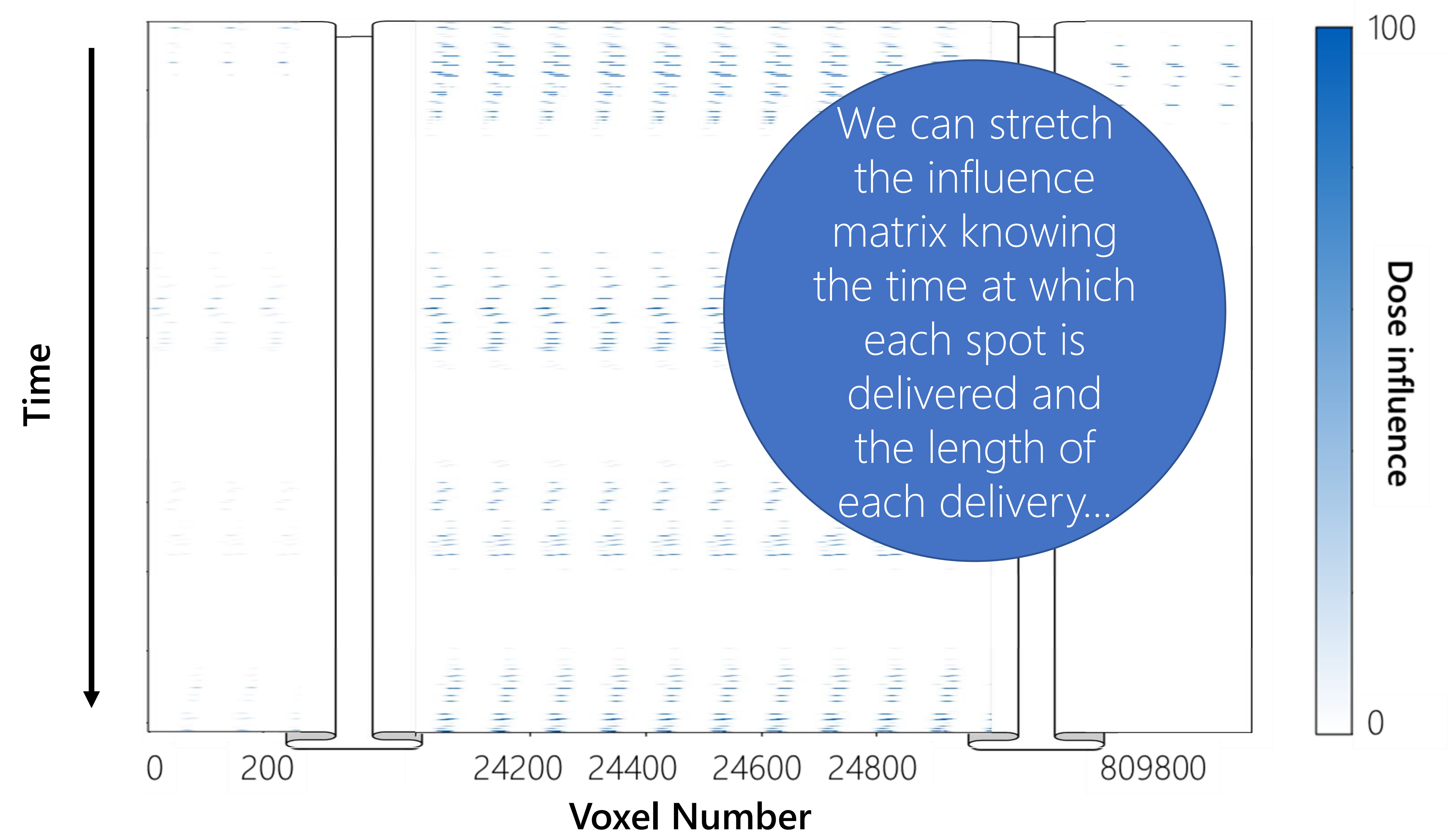
0
200
400
600
800
1000
1200
Spot Number
0
200
24200
24400
24600
24800
809800
Voxel Number
100
0
Dose influence

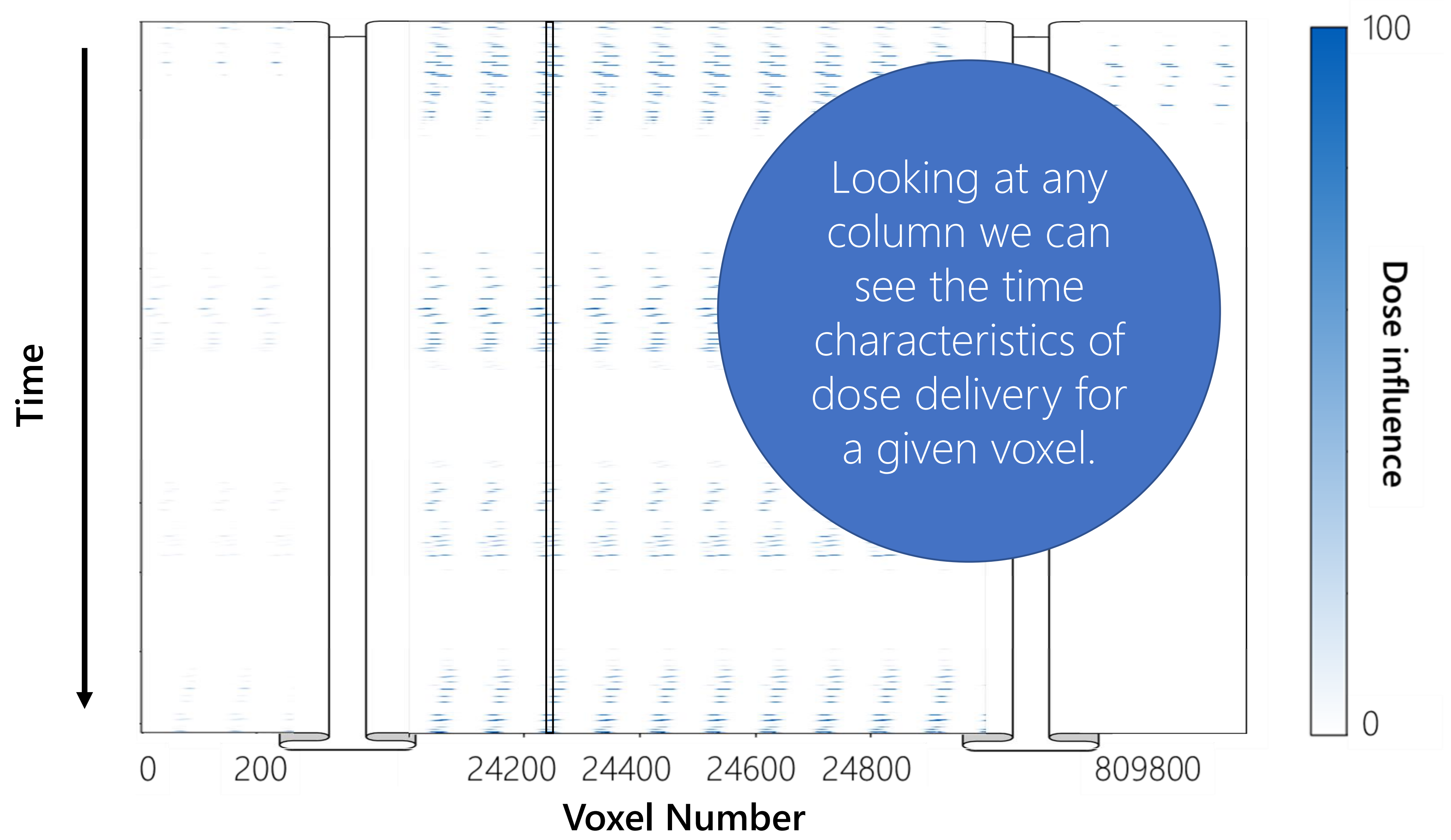


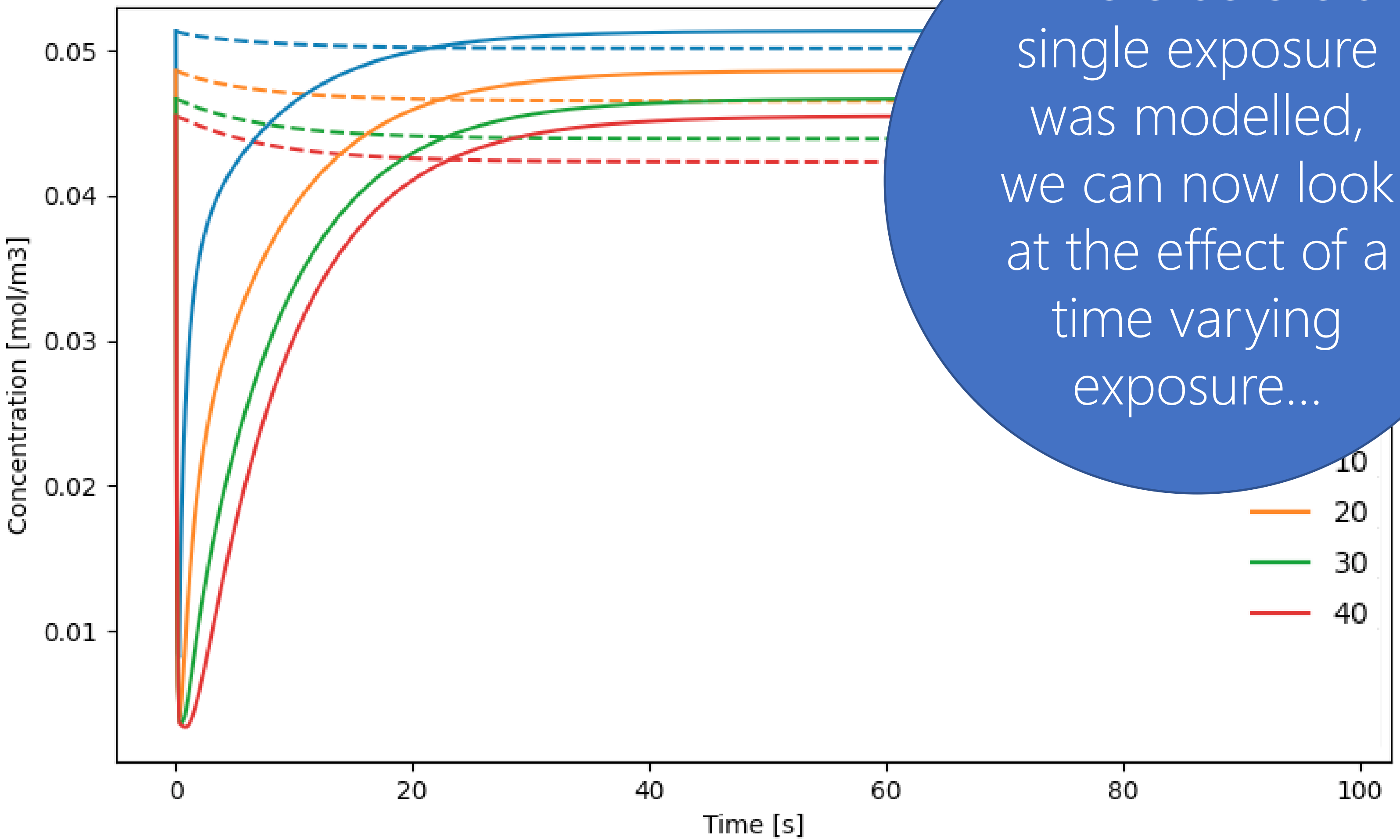
*actual voxels are ~5 times smaller than this...



0
200
400
600
800
1000
1200
Spot Number
0
200
24200
24400
24600
24800
809800
Voxel Number
100
0
Dose influence

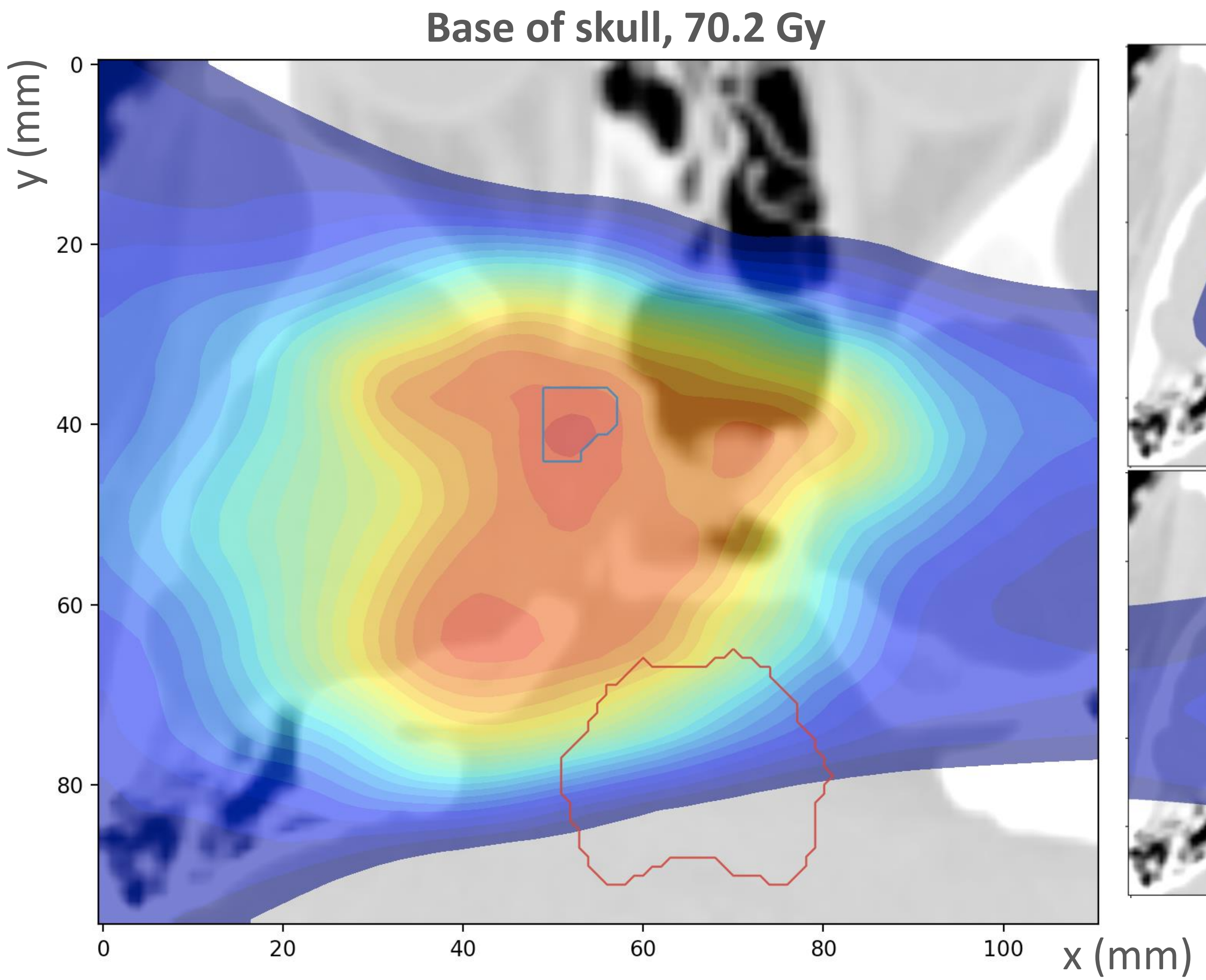

Time
0
200
24200
24400
24600
24800
809800
Voxel Number
100
0
Dose influence
We can stretch the influence matrix knowing the time at which each spot is delivered and the length of each delivery...

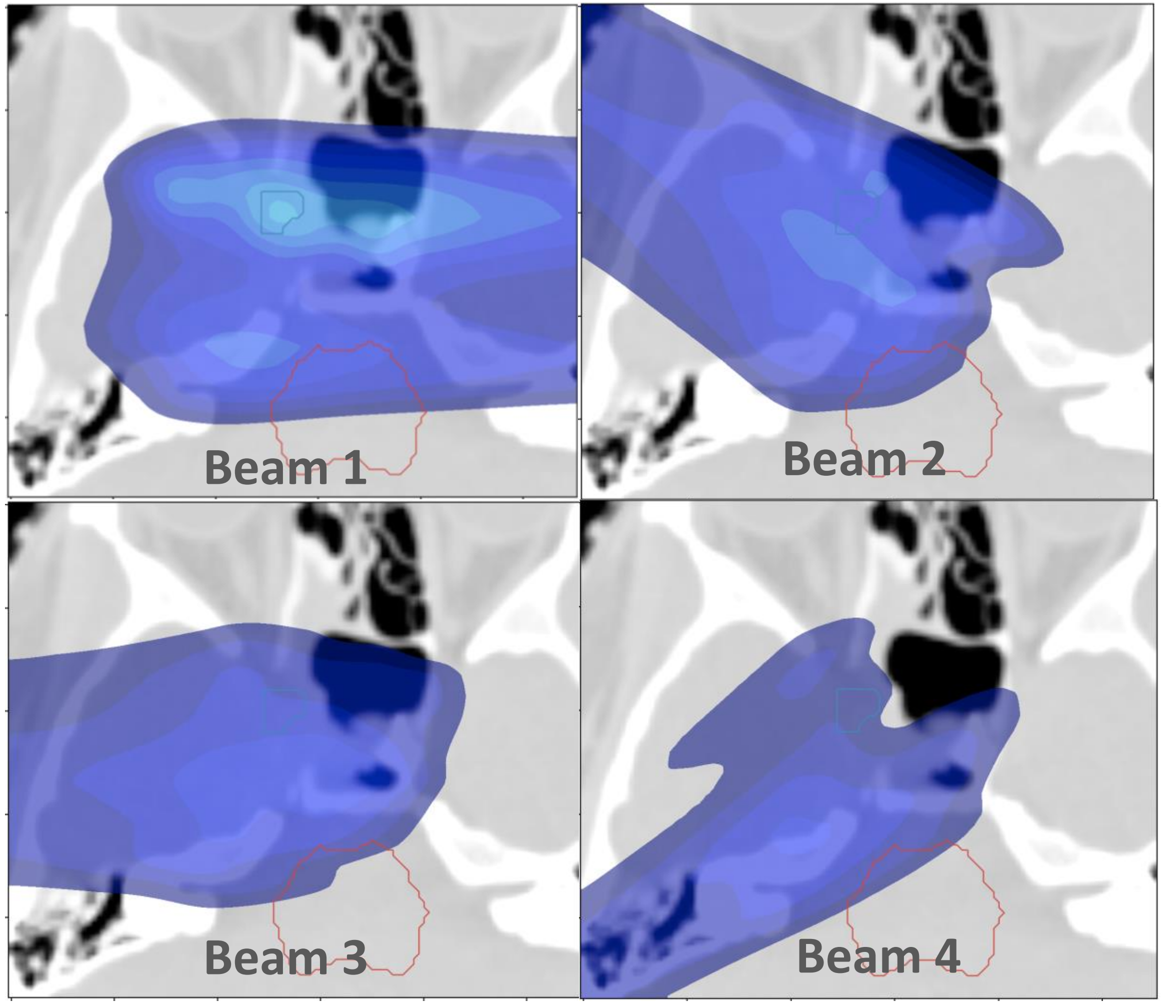

Looking at any column we can see the time characteristics of dose delivery for a given voxel.
Time
Voxel Number
0
200
24200
24400
24600
24800
809800
100
0
Dose influence



Where before a single exposure was modelled, we can now look at the effect of a time varying exposure…

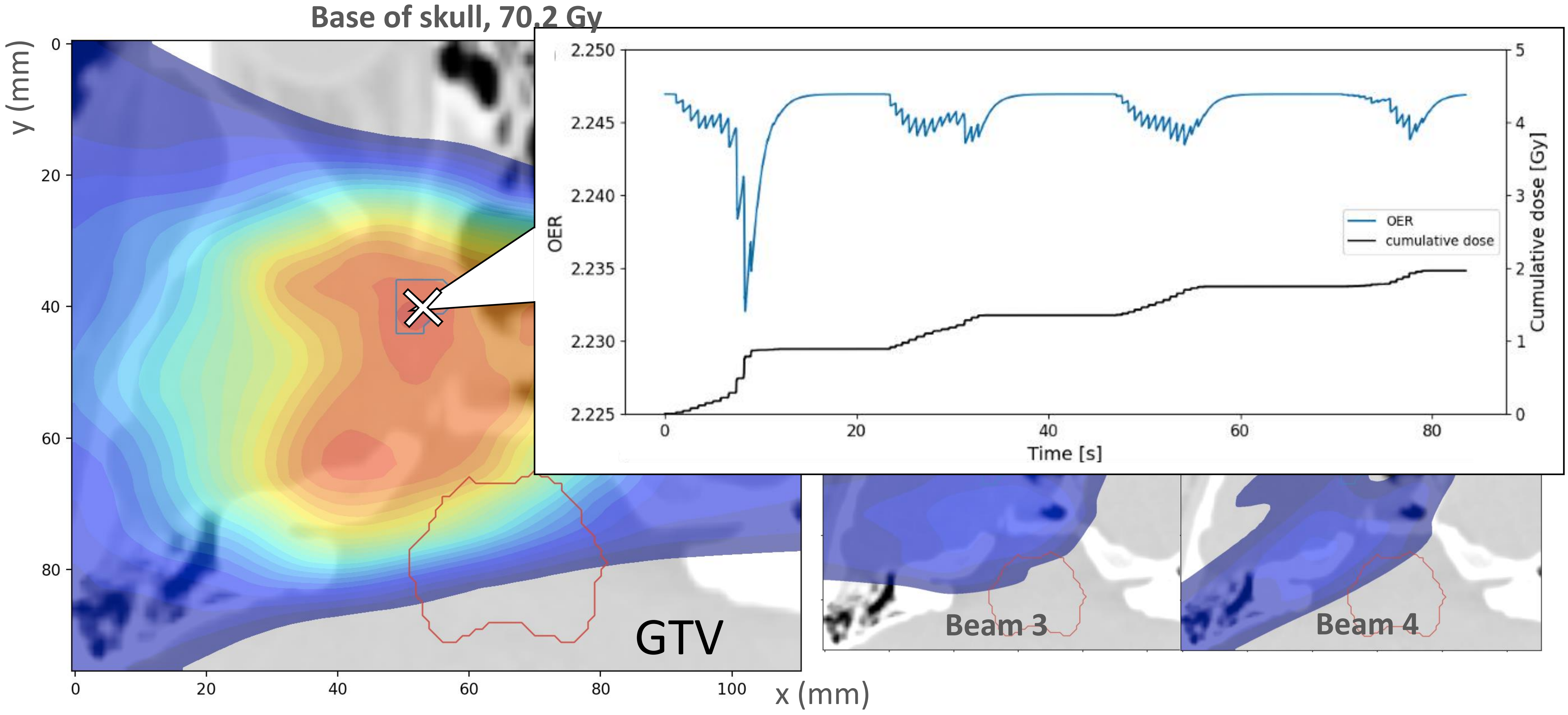
Proton PBS: modelling oxygen depletion





Rothwell et al. 2021, Radiation

Proton PBS: modelling oxygen depletion



Rothwell et al. 2021, Radiation

Transmission vs Bragg Peak dose delivery

Comparison against baseline oxygen depletion

Evaluating definitions of dose rate

Optimisation based on oxygen depletion

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Proton PBS: Dose rate

A framework for defining FLASH dose rate for pencil beam scanning

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Simon Busold
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Jessica Rika Perez
Varian Medical Systems International AG, Steinhausen 6312, Switzerland

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Varian Medical Systems, Inc, Palo Alto, CA 94304, USA

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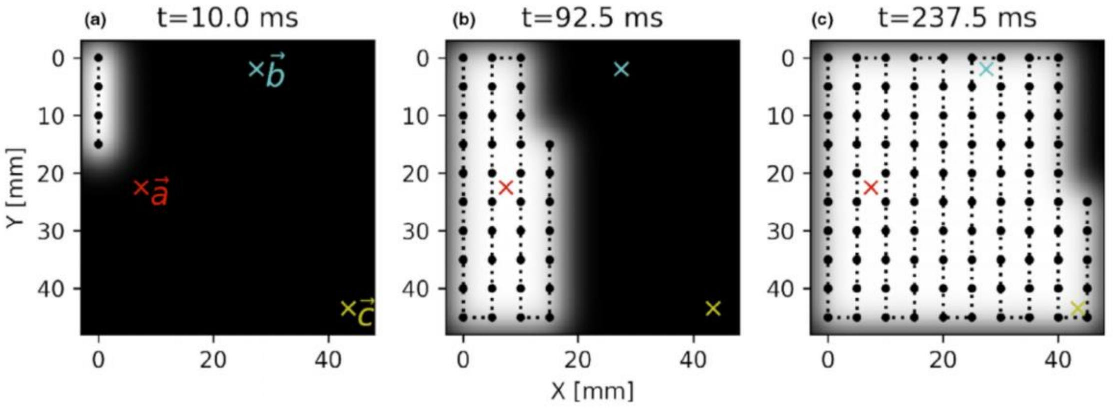
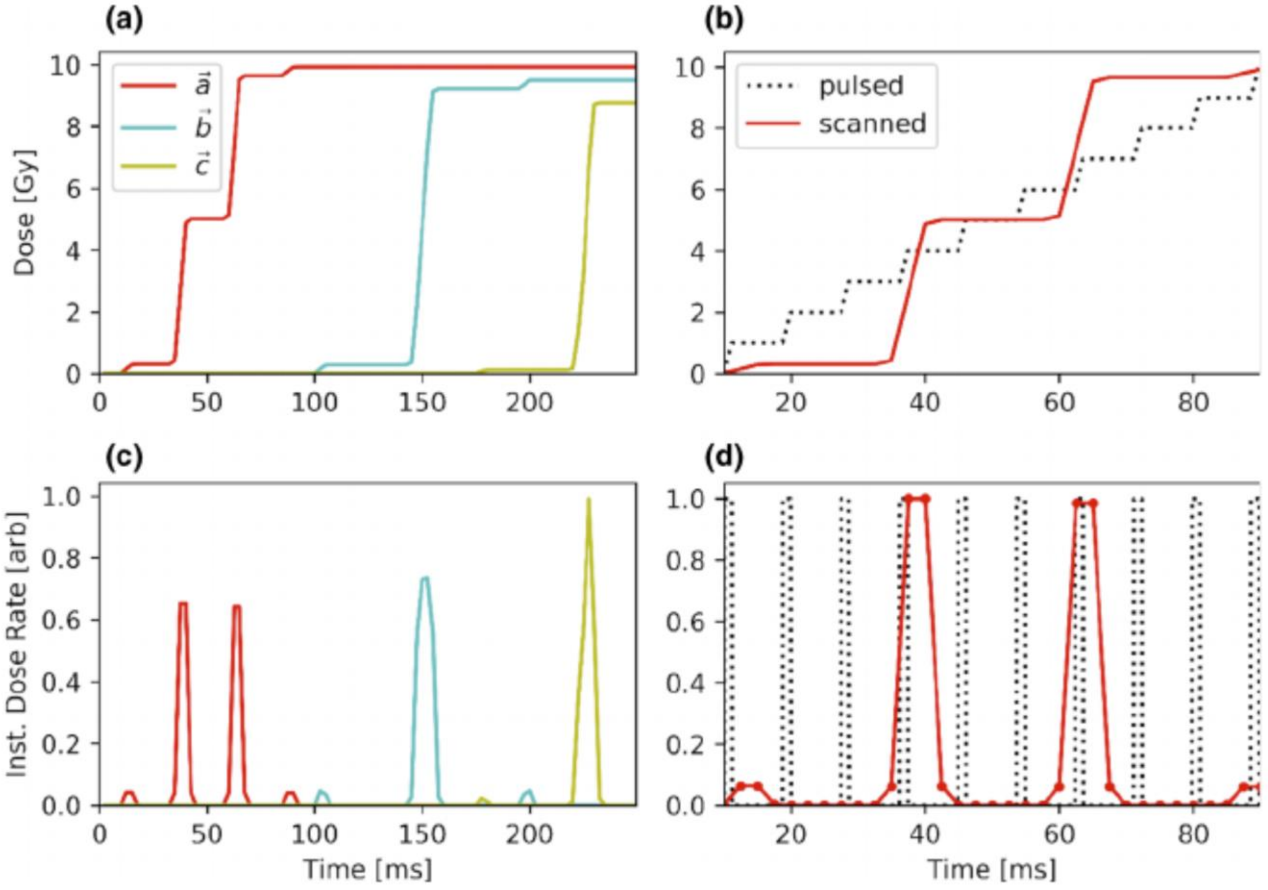
(Received 7 May 2020; revised 7 August 2020; accepted for publication 8 August 2020; published 15 November 2020)

Purpose: To develop a method of (a) calculating the dose rate of voxels within a proton field delivered using pencil beam scanning (PBS), and (b) reporting a representative dose rate for the PBS treatment field that enables correspondence between multiple treatment modalities. This method takes into account the unique spatiotemporal delivery patterns of PBS FLASH radiotherapy.
Methods: The dose rate at each voxel of a PBS radiation field is approximately the quotient of the voxel's dose and "effective" irradiation time. Each voxel's "effective" irradiation time starts when the cumulative dose rises above a chosen threshold value, and stops when its cumulative dose reaches its total dose minus the same threshold value. The above calculation yields a distribution of dose rates for the voxels within a PBS treatment field. To report a representative dose rate for the PBS field, we propose a user-selectable parameter of pth percentile of the dose rate distribution, such that

Proton PBS: Dose rate





Folkerts et al.: A framework for defining FLASH dose rate for PBS

Proton PBS: Dose rate

cancers MDPI

Article

Quantitative Assessment of 3D Dose Rate for Proton Pencil Beam Scanning FLASH Radiotherapy and Its Application for Lung Hypofractionation Treatment Planning

Minglei Kang *, Shouyi Wei , J. Isabelle Choi, Charles B. Simone II and Haibo Lin

New York Proton Center, New York, NY 10035, USA; awei@nyproton.com (S.W.); ichoi@nyproton.com (J.I.C.); csimone@nyproton.com (C.B.S.II); hlin@nyproton.com (H.L.)
* Correspondence: mkang@nyproton.com

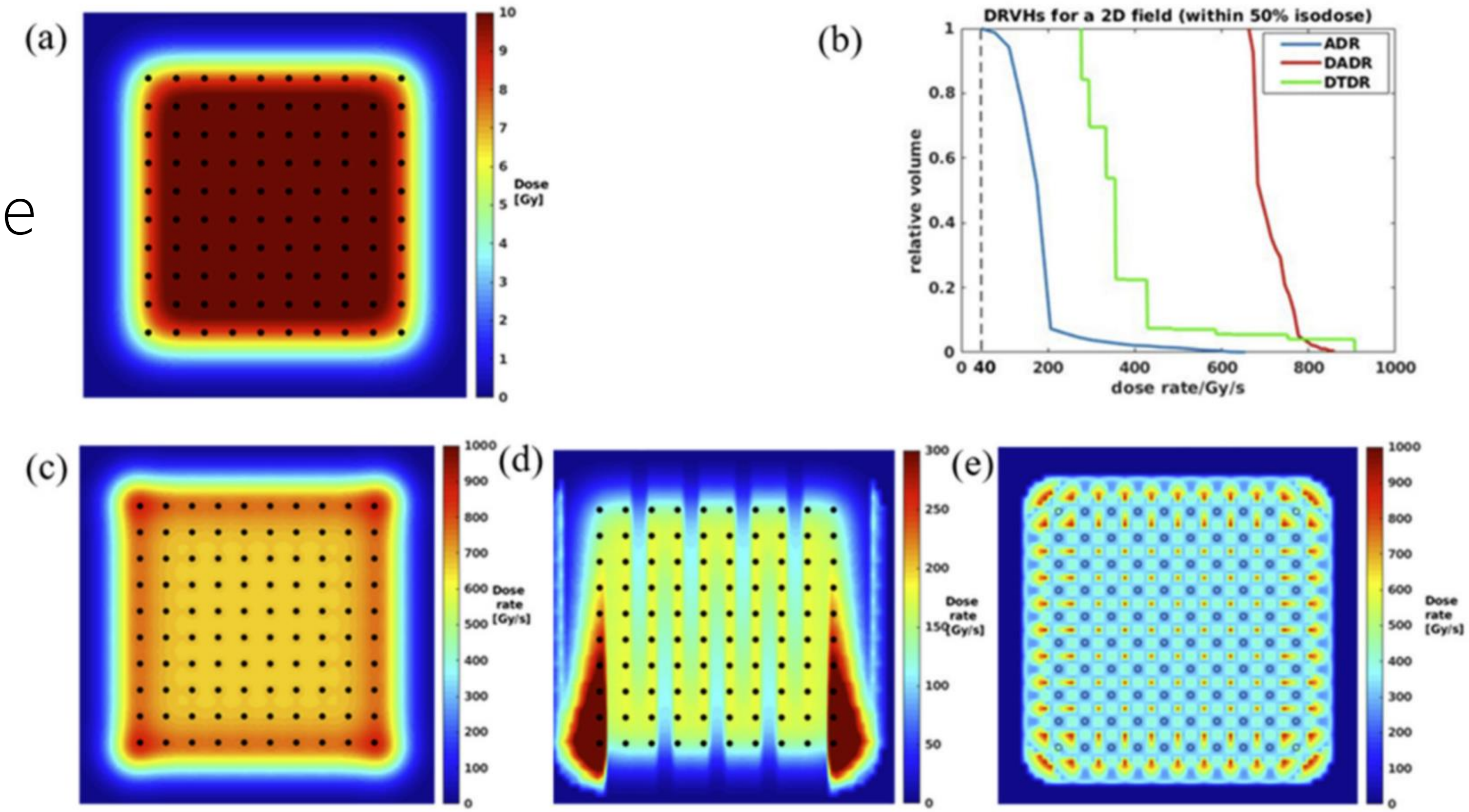
Simple Summary: As pencil beam scanning (PBS) proton therapy delivers doses via spot-scanning, the dose rate quantification is very different from the electron and scattering proton techniques in FLASH radiotherapy. Currently, there is no consensus on the definition of the PBS proton therapy dose rate calculation for normal tissues and targets. This study focuses on the dose rate quantification of organs-at-risk and target based on three proposed dose rate metrics using proton transmission beams. The differences in dose rate metrics have led a large variation for organs-at-risk dose rate assessment and may result in a different correlation expectation between dose rate and biological effects for pre-clinical experiments. An awareness of the differences in proton PBS dose rate calculation is important to design experiments and clinical trials to uncover FLASH-RT's biological and physiological mechanisms.

check for updates

Citation: Kang, M.; Wei, S.; Choi, J.I.;

Proton PBS: Dose rate

Dose



Dose average rate

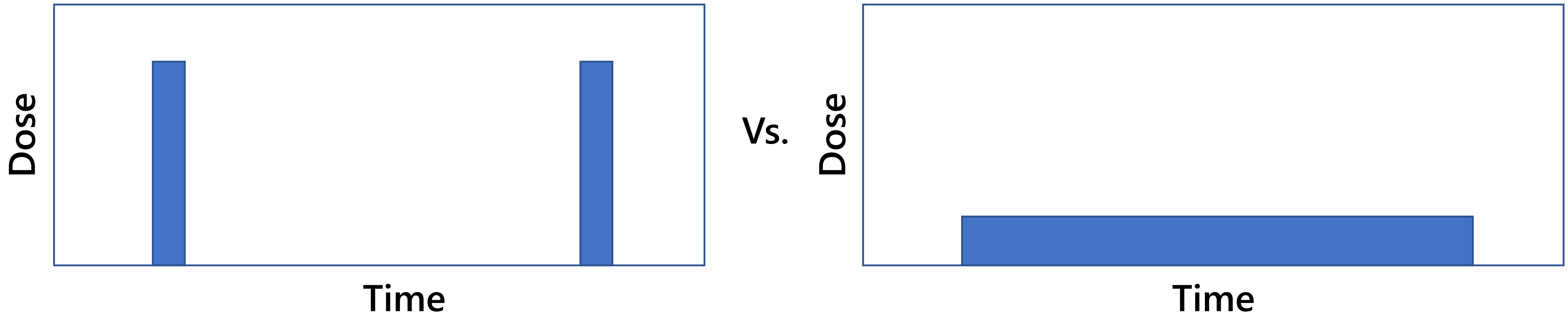
Time average dose rate

Dose threshold dose rate

Kang et al. Quantitative Assessment of 3D Dose Rate for Proton Pencil Beam Scanning FLASH Radiotherapy and Its Application for Lung Hypofractionation Treatment Planning

Proton PBS: Dose rate

- In this model we haven't abstracted to dose rate – knowing what dose rate is important will depend on mechanism. E.g. what is the time for recovery from conditions necessary to observe the FLASH effect
- Can also consider the effect of different energy layers – and can understand what we are comparing against clinically.



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Evaluating spot reduction strategies

Proton PBS: treatment planning for FLASH

Physics Contribution

Bringing FLASH to the Clinic: Treatment Planning Considerations for Ultrahigh Dose-Rate Proton Beams

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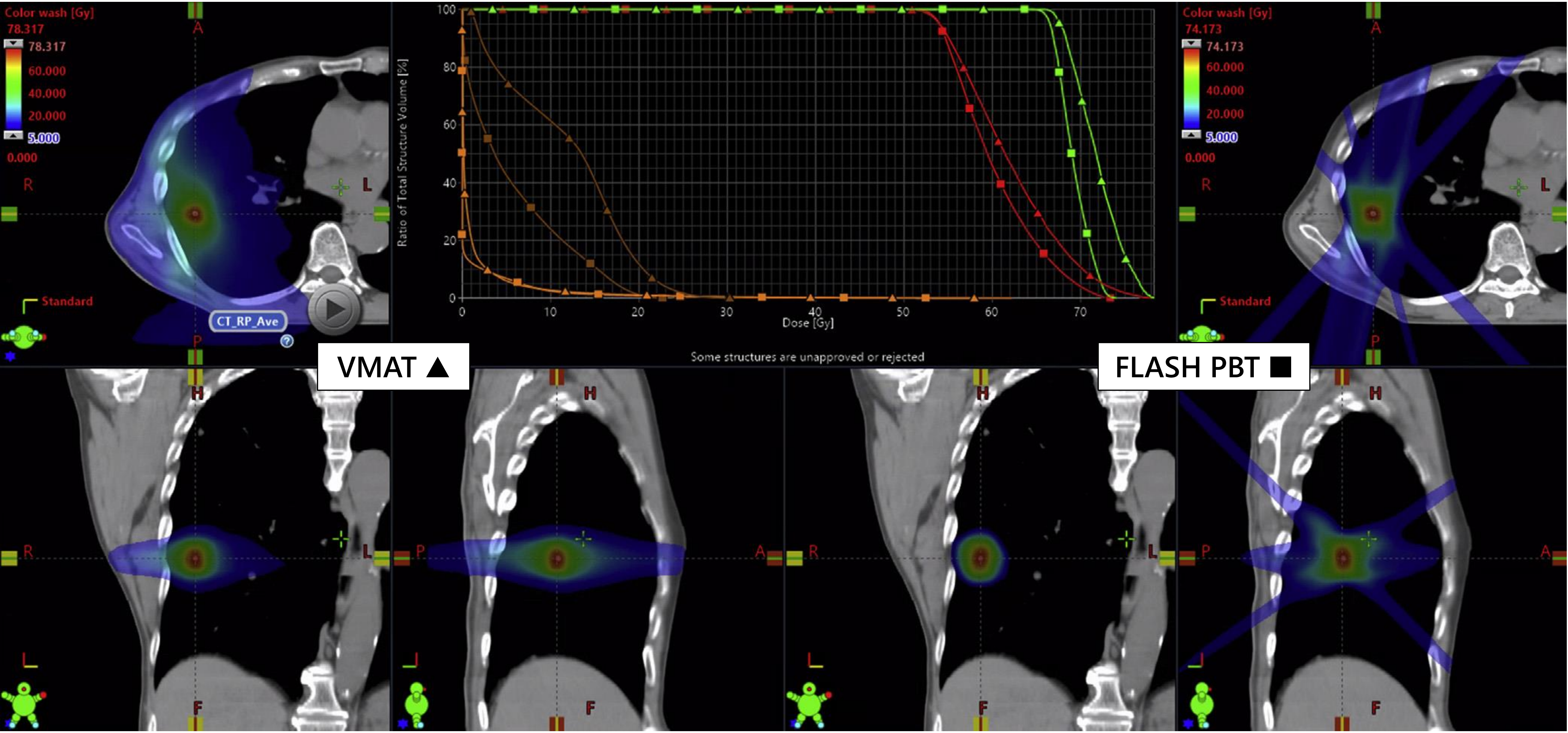
**Department of Radiation Oncology, Amsterdam UMC, Vrije Universiteit Amsterdam, Cancer Center Amsterdam, Amsterdam, the Netherlands and †Varian Medical Systems, 3120 Hansen Way, Palo Alto, California*

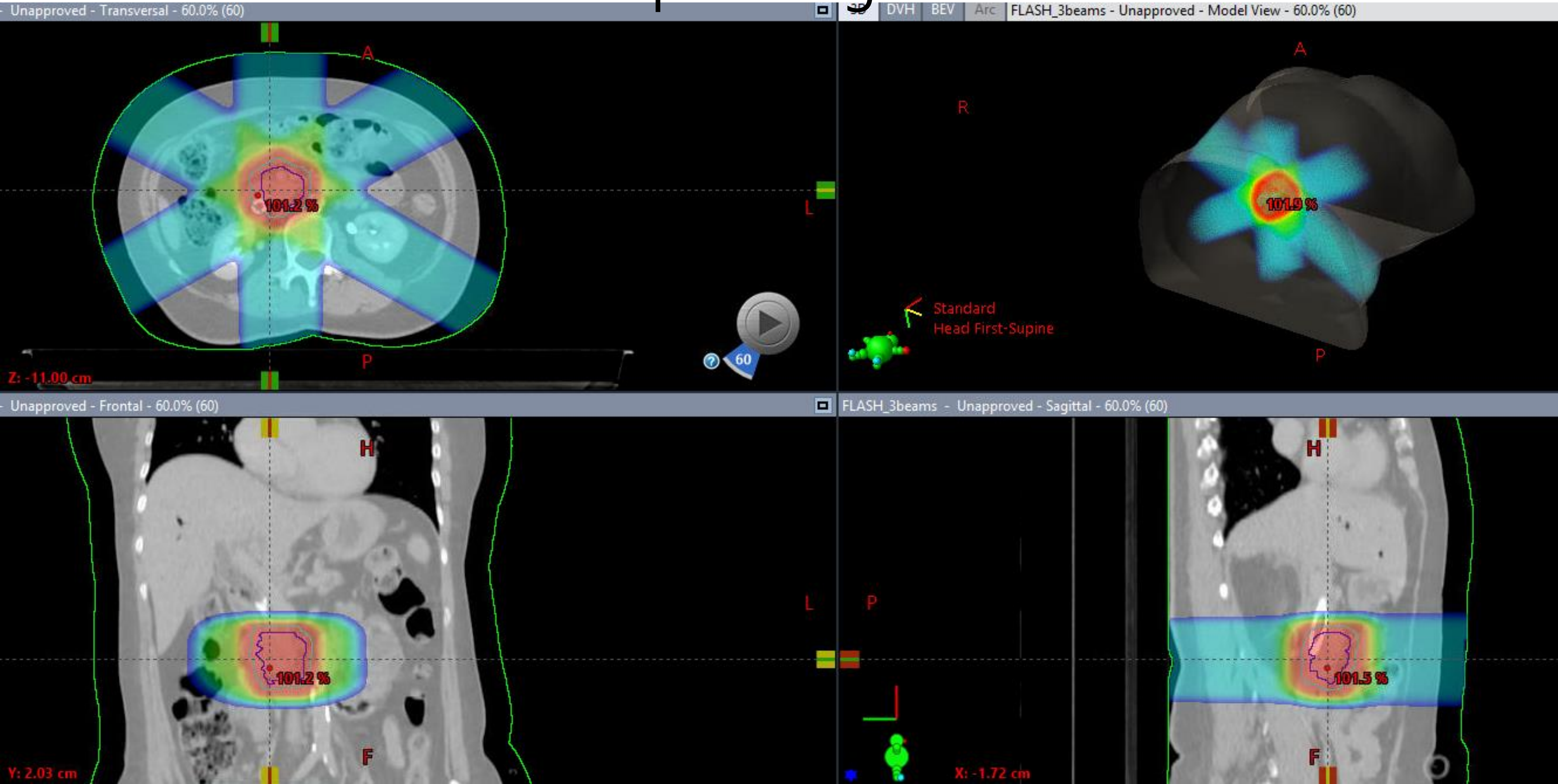
Received Jul 22, 2019, and in revised form Oct 14, 2019. Accepted for publication Nov 13, 2019.

Purpose: Preclinical research into ultrahigh dose rate (eg, ≥40 Gy/s) "FLASH"-radiation therapy suggests a decrease in side effects compared with conventional irradiation while maintaining tumor control. When FLASH is delivered using a scanning proton beam, tissue becomes subject to a spatially dependent range of dose rates. This study systematically investigates dose rate distributions and delivery times for proton FLASH plans using stereotactic lung irradiation as the paradigm.
Methods and Materials: Stereotactic lung radiation therapy FLASH-plans, using 244 MeV scanning proton transmission beams, with the Bragg peak behind the body, were made for 7 patients. Evaluated parameters were dose rate distribution within a beam, overall irradiation time, number of times tissue is irradiated, and quality of the FLASH-plans compared with the clinical volumetric-modulated arc therapy (VMAT) plans.
Results: Sparing of lungs, thoracic wall, and heart in the FLASH-plans was equal to or better than that in the VMAT-plans. For a spot peak dose rate (SPDR, the dose rate in the middle of the spot) of 100 Gy/s, ~40% of dose is delivered at FLASH dose rates, and for SPDR = 360 Gy/s this increased to ~75%. One-hundred percent FLASH dose rate cannot be achieved owing to small contributions from distant spots with lower dose rates. The total irradiation time varied between 300 to 730 ms, and around 85% of the dose-receiving body volume was irradiated by either 1 or 2 beams.
Conclusions: Clinical implementation of FLASH using scanning proton beams requires multiple treatment planning considerations: dosimetric, temporal, and spatial parameters all seem important. The FLASH efficiency of a scanning proton beam increases with SPDR. The methodology proposed in this proof-of-principle study provides a framework for evaluating the FLASH characteristics of scanning proton beam plans and can be adapted as FLASH parameters are better defined. It currently seems logical to optimize plans for the shortest delivery time, maximum amount of high dose rate coverage, and maximum amount of single beam and continuous irradiation.

Proton PBS: treatment planning for FLASH



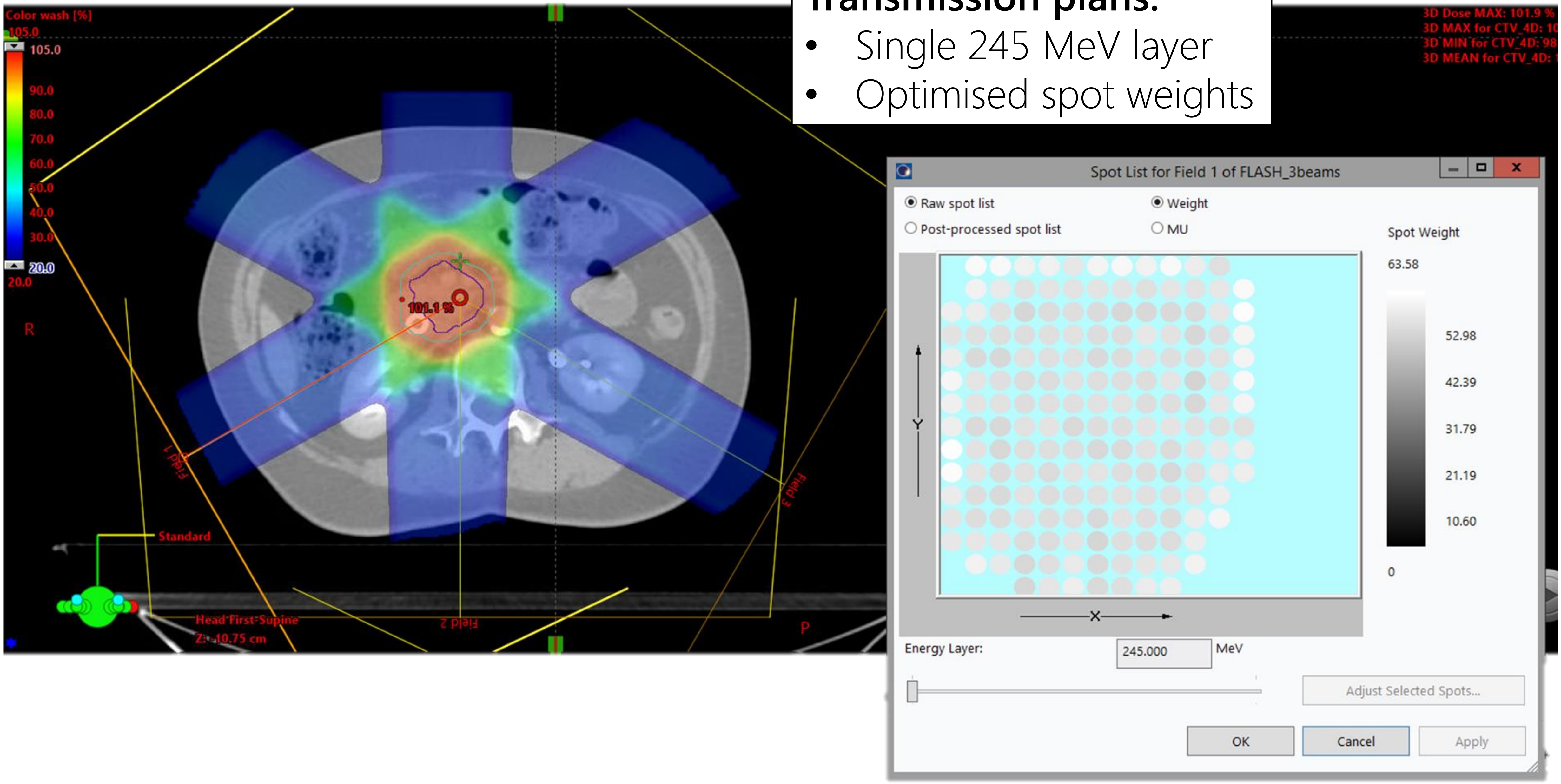
Proton PBS: treatment planning for FLASH



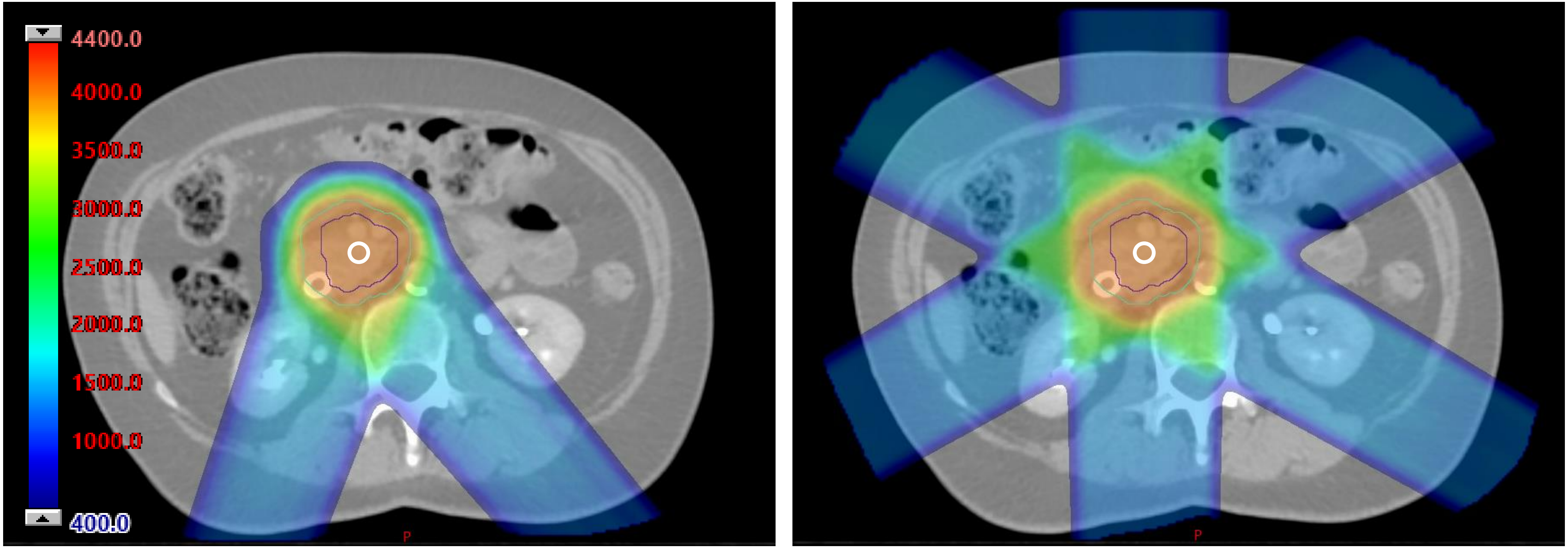
Proton PBS: treatment planning for FLASH

Transmission plans:

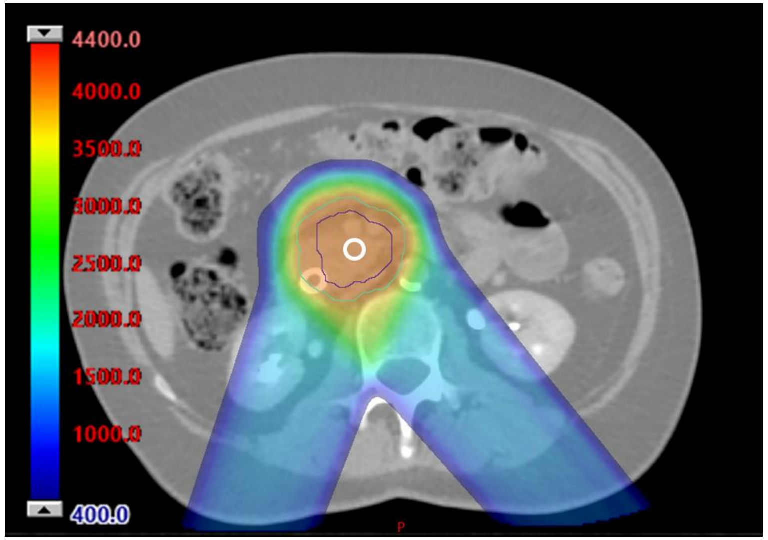
- Single 245 MeV layer
- Optimised spot weights

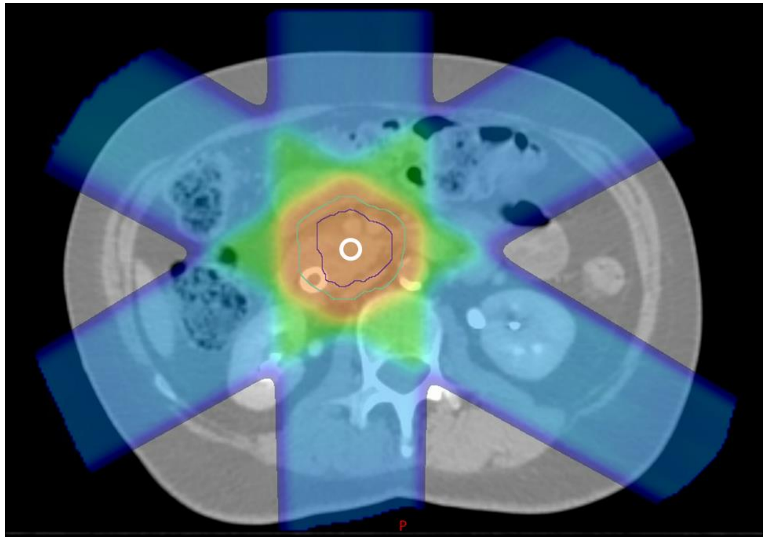


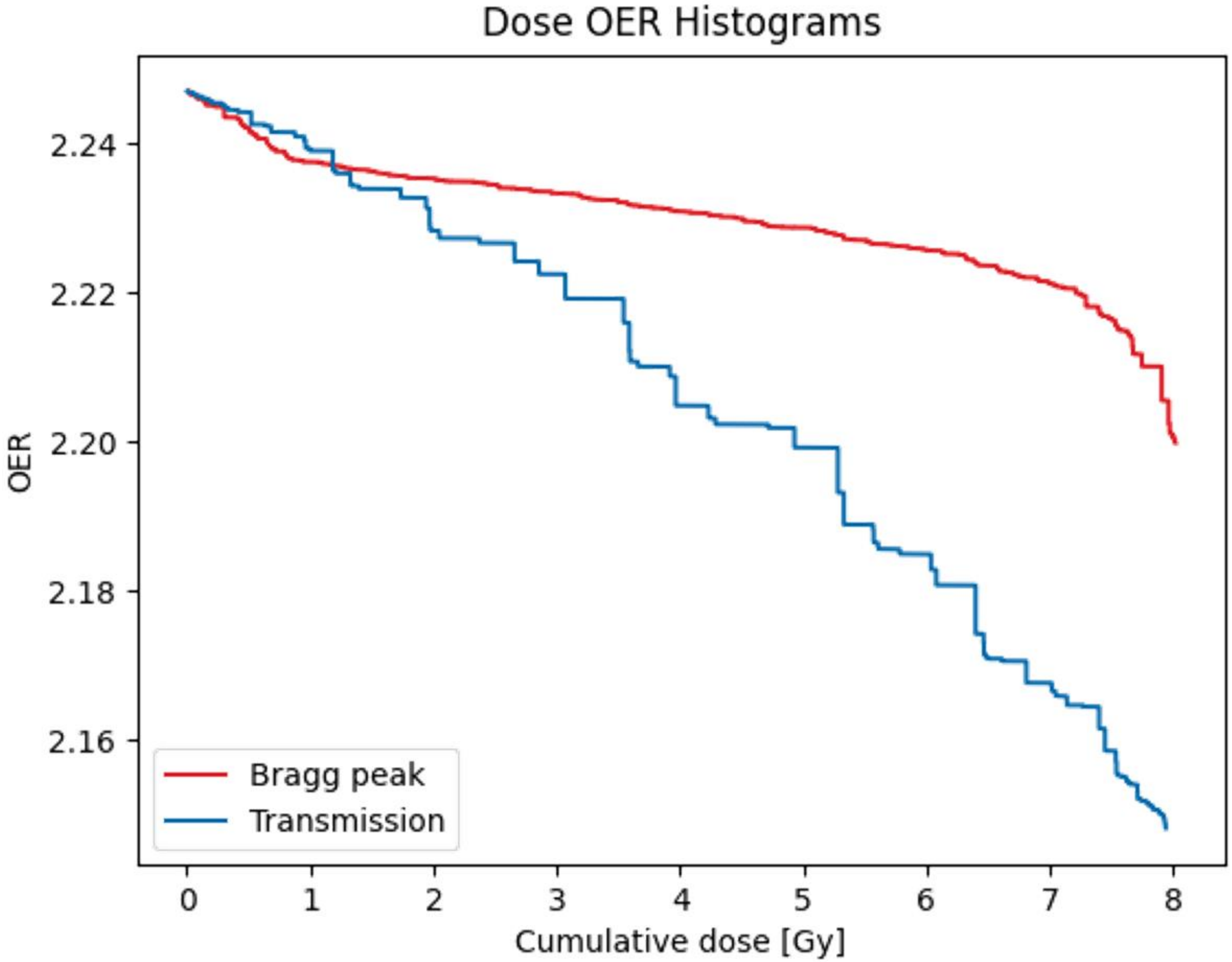
Proton PBS: treatment planning for FLASH



Proton PBS: treatment planning for FLASH







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Proton PBS: spot reduction

ACTA ONCOLOGICA
2019, VOL. 58, NO. 10, 1463-1469
https://doi.org/10.1080/0284186X.2019.1627416

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Towards FLASH proton therapy: the impact of treatment planning and machine characteristics on achievable dose rates

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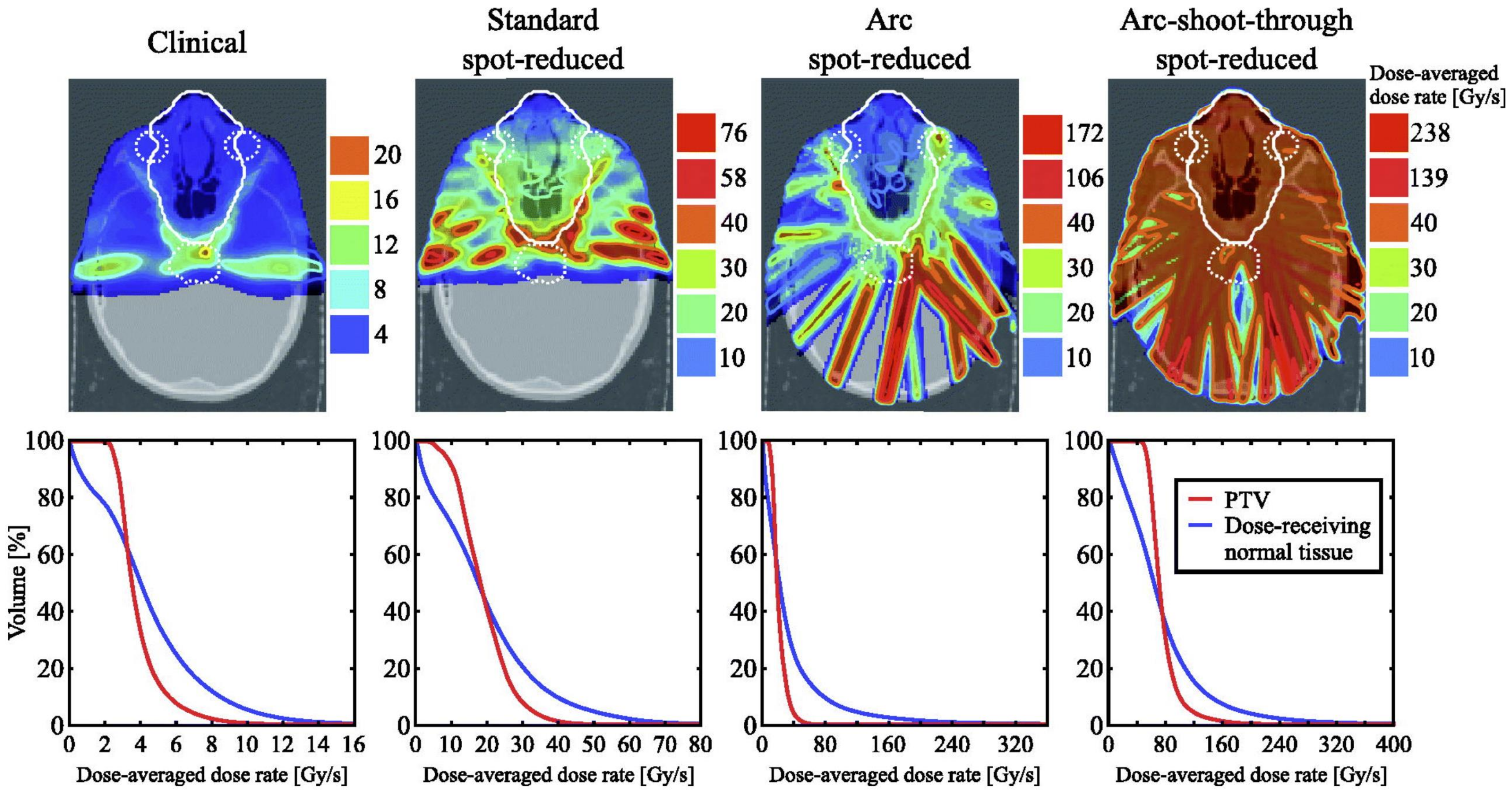
[a] Center for Proton Therapy, Paul Scherrer Institute, Villigen, Switzerland; [b] Department of Radiation Therapy, Rijksuniversiteit Groningen, Groningen, the Netherlands; [c] Department of Radiation Oncology, University Hospital of Bern, Bern, Switzerland; [d] Department of Radiation Oncology, University Hospital of Zürich, Zürich, Switzerland; [e] Department of Physics, ETH Zürich, Zürich, Switzerland

ABSTRACT

Background: This study aimed at evaluating spatially varying instantaneous dose rates for different intensity-modulated proton therapy (IMPT) planning strategies and delivery scenarios, and comparing these with FLASH dose rates (>40 Gy/s).

Material and methods: In order to quantify dose rates in three-dimensions, we proposed the 'dose-averaged dose rate' (DADR) metric, defined for each voxel as the dose-weighted mean of the instantaneous dose rates of all spots (i.e., pencil beams). This concept was applied to four head-and-neck cases, each planned with clinical (4 fields) and various spot-reduced IMPT techniques: 'standard' (4 fields), 'arc' (120 fields) and 'arc-shoot-through' (120 fields; 229 MeV only). For all plans, different delivery scenarios were simulated: constant beam intensity, variable beam intensity for a clinical Varian ProBeam system, varied per energy layer or per spot, and theoretical spot-wise variable beam intensity (i.e., no monitor/safety limitations). DADR distributions were calculated assuming 2-Gy or 6-Gy fractions

Proton PBS: spot reduction



Van de Water et al. Towards FLASH proton therapy: the impact of treatment planning and machine characteristics on achievable dose rates

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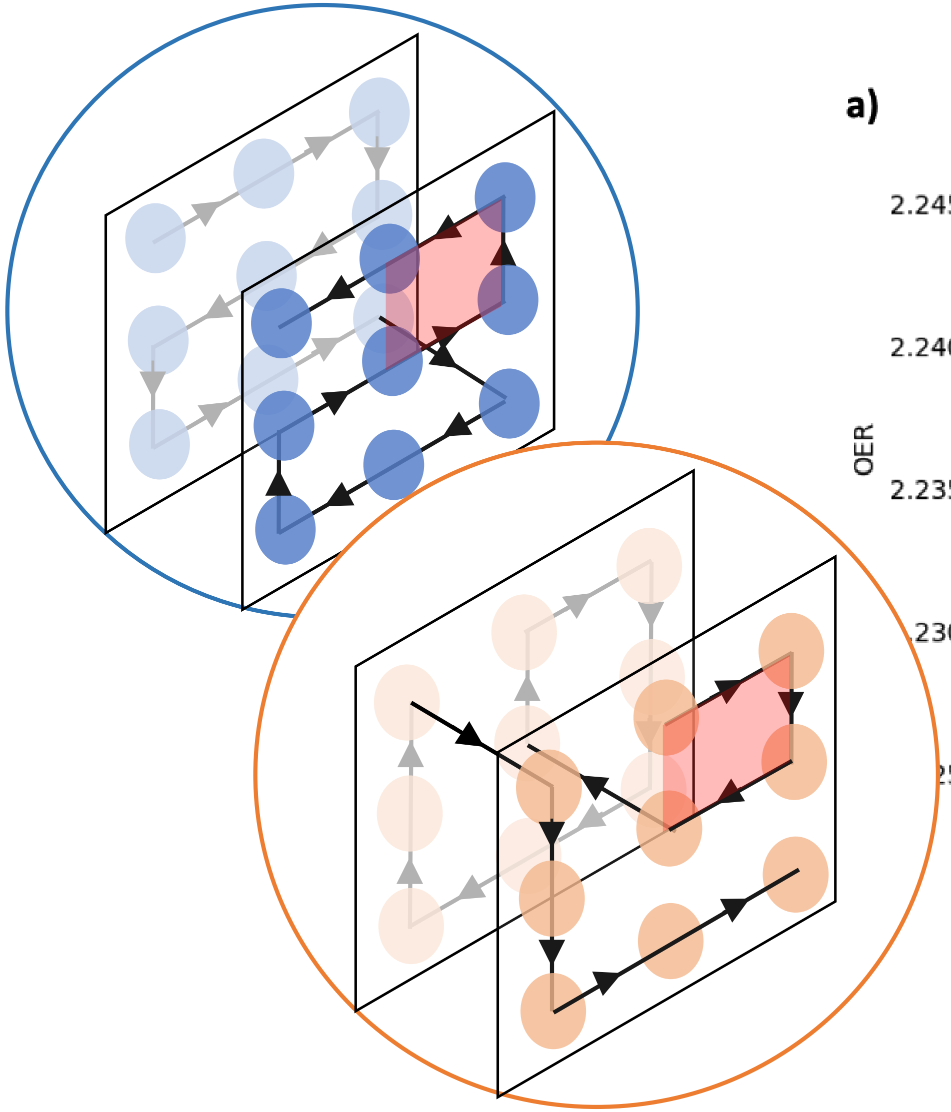
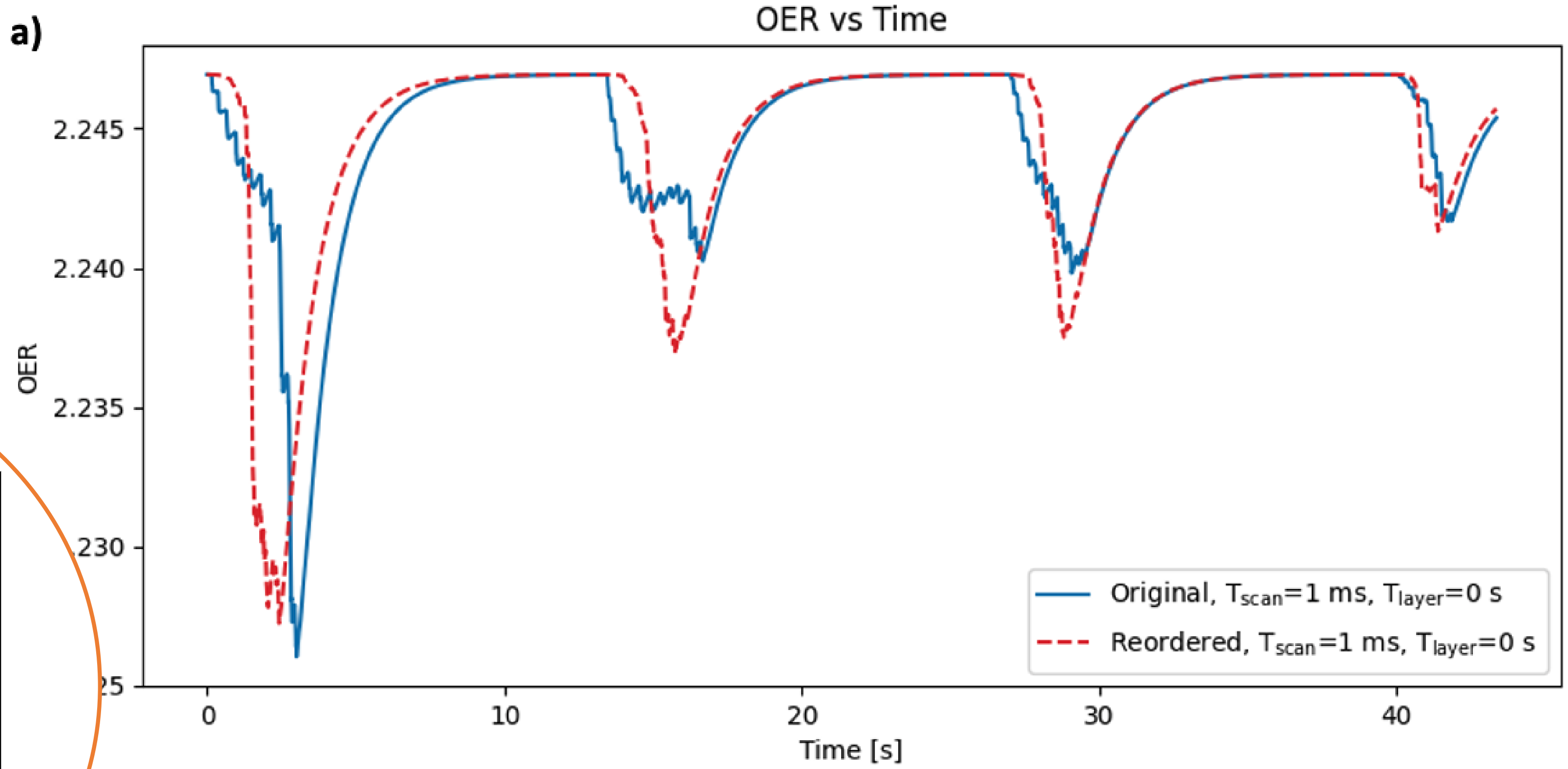
Proton PBS: modelling oxygen depletion



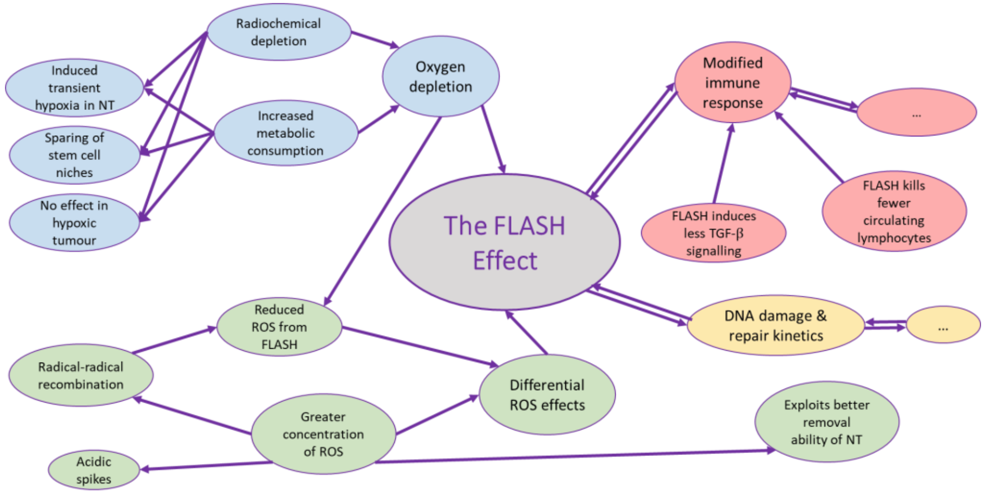


Rothwell et al. 2021, Radiation

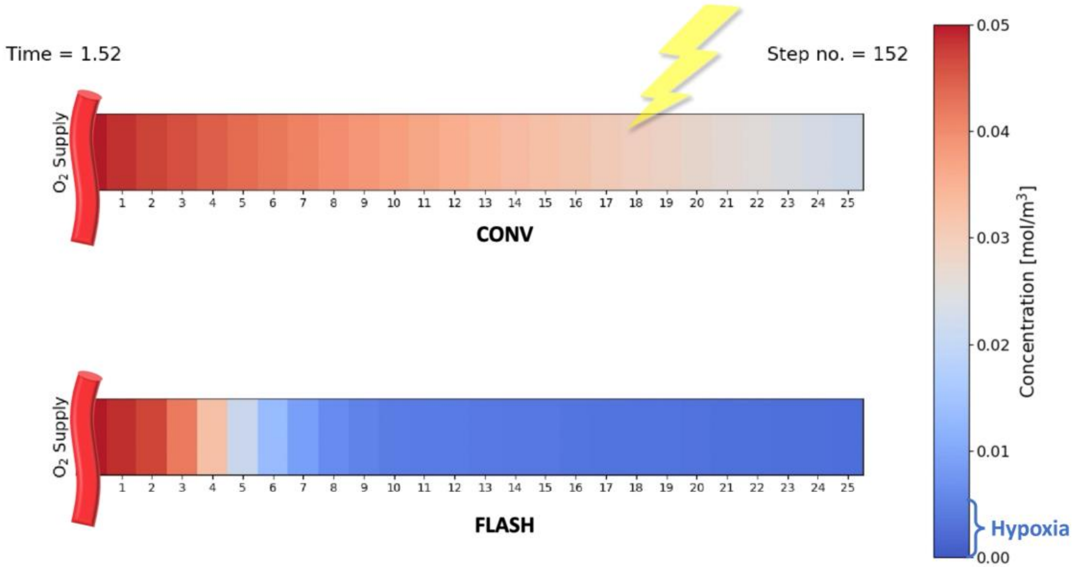
Proton PBS: modelling oxygen depletion

- Could also look to apply model to investigate:
  - Tumour vs normal tissue (incorporate tissue-specific parameters)
  - FLASH treatment plans
  - Other modalities with variable spatial/timing characteristics, e.g. minibeams

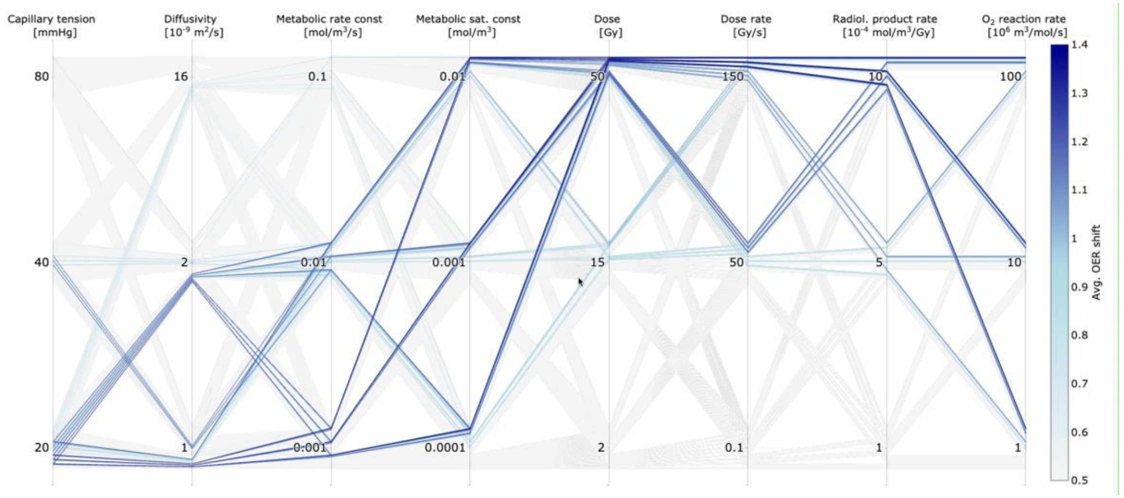
Summary



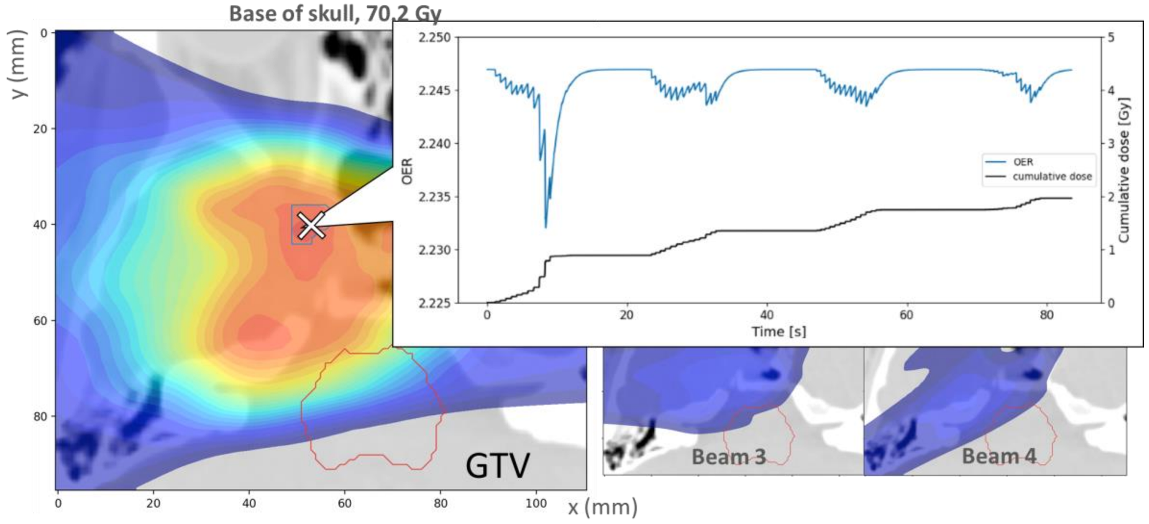
Radiochemical depletion
Oxygen depletion
Induced transient hypoxia in NT
Increased metabolic consumption
Sparing of stem cell niches
No effect in hypoxic tumour
The FLASH Effect
Modified immune response
...
FLASH induces less TGF-β signalling
FLASH kills fewer circulating lymphocytes
DNA damage & repair kinetics
...
Reduced ROS from FLASH
Radical-radical recombination
Differential ROS effects
Greater concentration of ROS
Exploits better removal ability of NT
Acidic spikes



Time = 1.52
Step no. = 152
O2 Supply
CONV
FLASH
Concentration [mol/m3]
Hypoxia



Capillary tension [mmHg]
Diffusivity [10-9 m2/s]
Metabolic rate const [mol/m3/s]
Metabolic sat. const [mol/m3]
Dose [Gy]
Dose rate [Gy/s]
Radiol. product rate [10-4 mol/m3/Gy]
O2 reaction rate [106 m3/mol/s]
Avg. OER shift



Base of skull, 70.2 Gy
y (mm)
x (mm)
GTV
Beam 3
Beam 4
OER
Cumulative dose [Gy]
Time [s]
cumulative dose

New horizon in
therapy & treatment
FRPT
FLASH
RADIOTHERAPY
& PARTICLE
THERAPY
2021
VIENNA & ONLINE
1-3 DECEMBER 2021
SAVE THE DATE
Willkommen
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CHUV
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InspireProject
Horizon 2020
institutCurie
MedAustron
PTB
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ESTRO
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THANK YOU FOR LISTENING

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