Modeling Radiation Dose to Circulating Lymphocytes: Impact of Proton FLASH Radiotherapy during Brain Treatment

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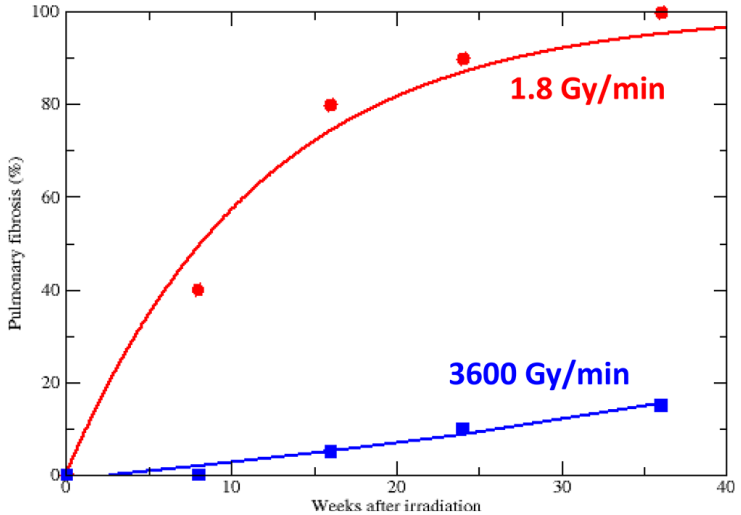
Background

- Ultra-high-dose rate radiotherapy (FLASH-RT) is characterized by dose rate >40 Gy/s
- FLASH-RT has shown superior normal tissue sparing and effective tumor control



Durante M et al., Br J Radiol 2018; 91: 20170628

Favaudon V et al. *Sci Transl. Med.* 2014; **6**: 245ra93
Vozenin MC et al. Clin Cancer Res. 2019 1 1;25(1):35–42
Montay-Gruel P al. Radiother Oncol. 2017 9;124(3):365–369

FLASH-Effect?

- Oxygen depletion
- Chromatin remodelling mediated by poly
- Reduction of hematologic toxicity

Fernet M et al. *Int. J. Radiat Biol* 2000; 76: 1621–9
Jin J. et al. Radiother Oncol. 2020; 149: 55–62
Durante M et al. Phys Med Biol 1999; 44: 1289–98

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FLASH-Effect?

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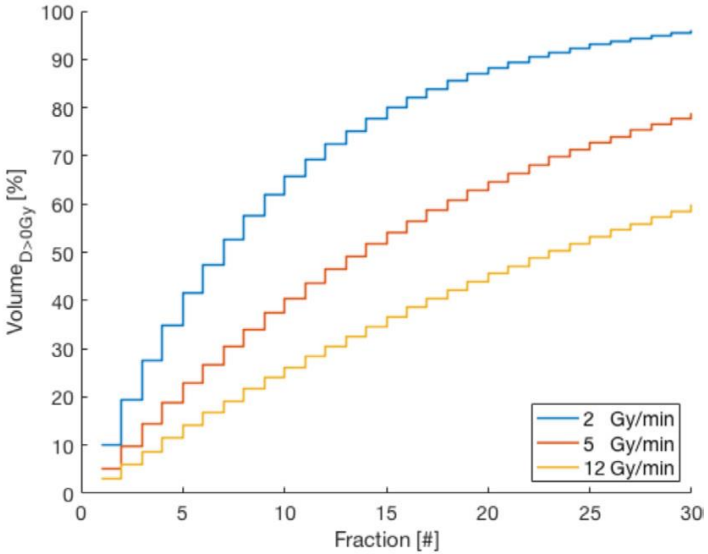
Effects of **dose-rate** on the **irradiated volume** of circulating blood



Hammi et al. Phys. Med. Biol. 2020; 65

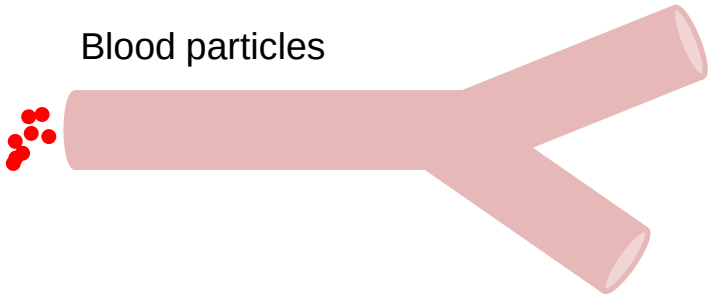
Is FLASH-RT beneficial for circulating lymphocytes ?

- Oxygen depletion
- Chromatin remodelling mediated by poly
- Reduction of hematologic toxicity

- Aims is to assess the **accumulated dose** to **circulating** lymphocytes when the dose rate matches the one of **Proton FLASH-RT** during **brain** treatment
- Comparison with **hypofractionated conventional** dose rate in Proton therapy

Dose to circulating lymphocyte

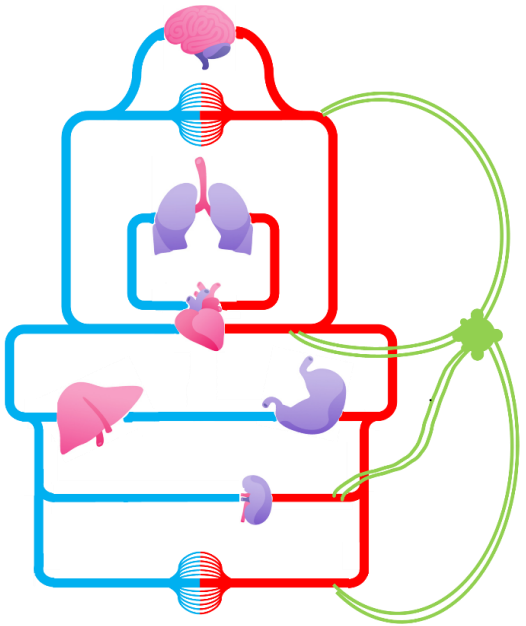
- **Spatio-temporal model of blood particles**
  - Blood vessels of the organ
  - Blood particles
  - Blood flow function



Dose to circulating lymphocyte

- Spatio-temporal model of blood particles
- **Circulatory System**
  - Cardiac output
  - Regional blood flow

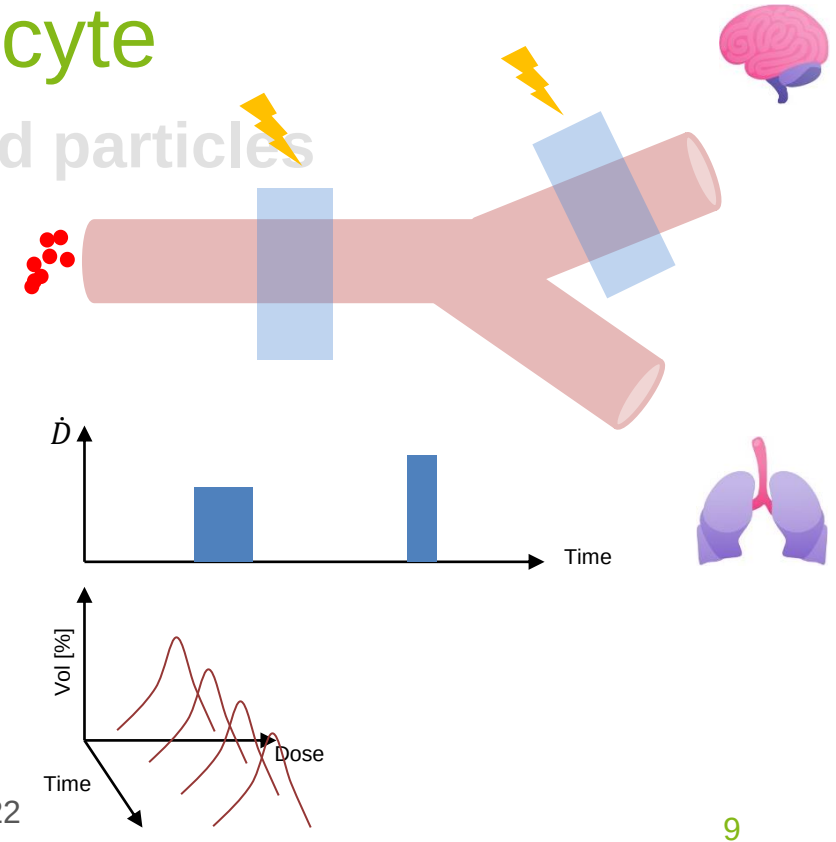
$$P\{O(t+\Delta t)=k \mid O(t)=j\}$$



Dose to circulating lymphocyte

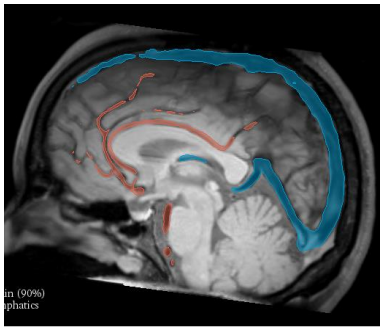
- Spatio-temporal model of blood particles
- Circulatory System
- **Dynamic Beam Delivery**
  - $\dot{D}(\mathrm{r},\mathrm{t})$
  - Dose scoring

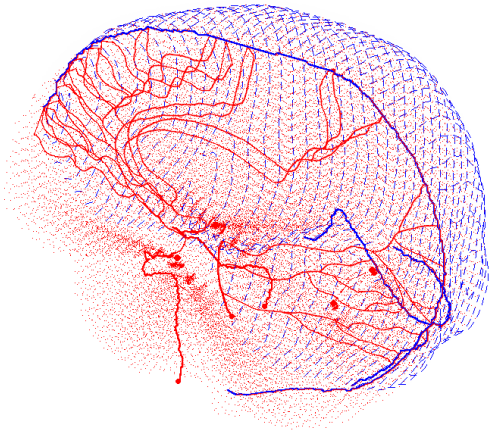
$$Dose_{BP} = \sum^{time} \sum^{path} \frac{\dot{d}(\vec{x},t)}{\bar{v}(\vec{x})} \Delta x$$

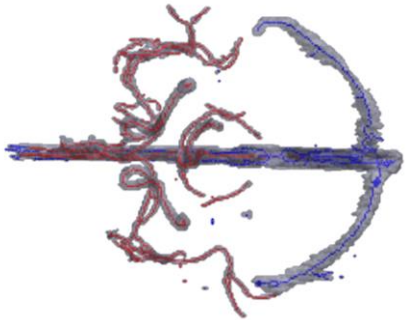


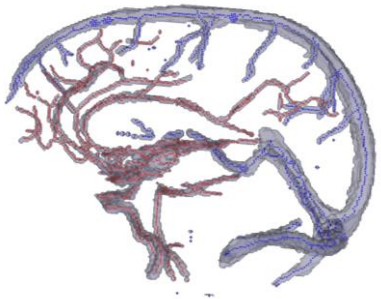
Intracranial blood flow model (Version 1)

- Anatomy-based vasculature model
- Generic vessel model (more than 1000 pathways)
  - Homogeneous coverage of entire brain (1 vessel / 4mm^2)





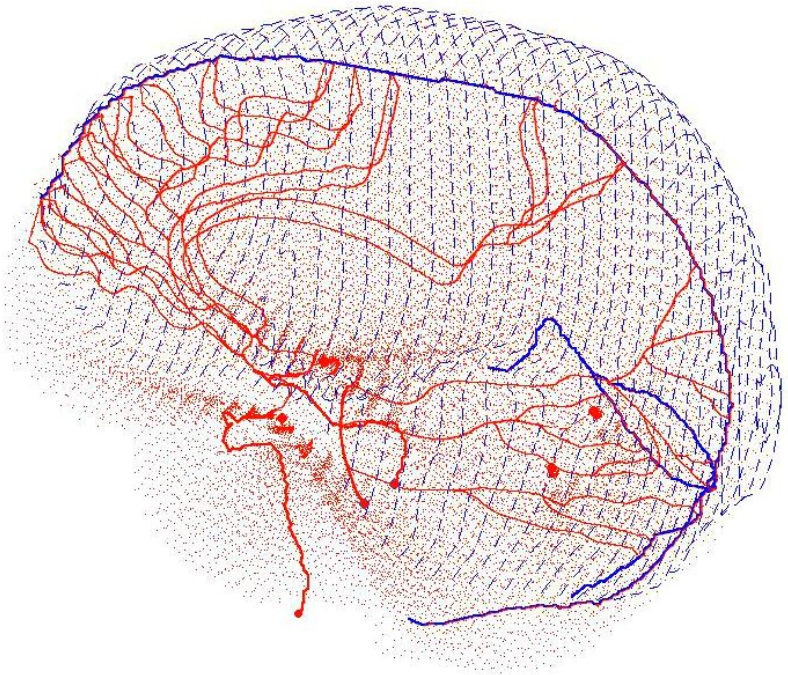




Hammi et al. Phys. Med. Biol. 2020; 65

Intracranial Blood Flow Model (Version 1)

- Brain
  - > 250’000 individual “blood particles”
  - Time resolution 0.01s



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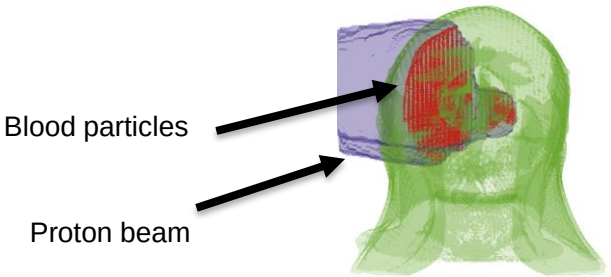
Accuracy of dose scoring

- Dose scoring

$$D_{ID} = \sum_{path}^{N} \frac{\dot{d}(\vec{x}, t)}{\bar{v}(\vec{x})} \Delta x$$



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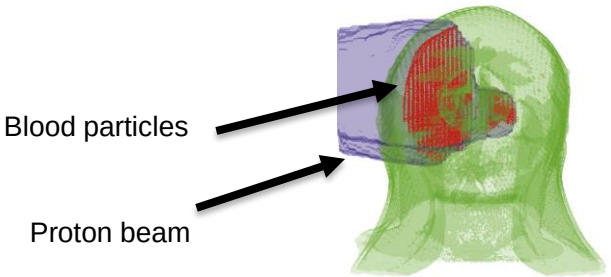
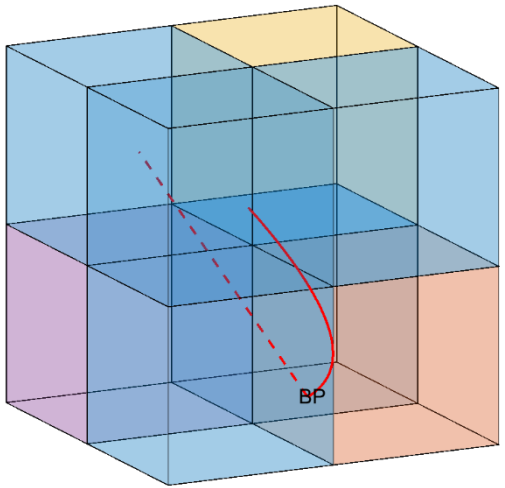
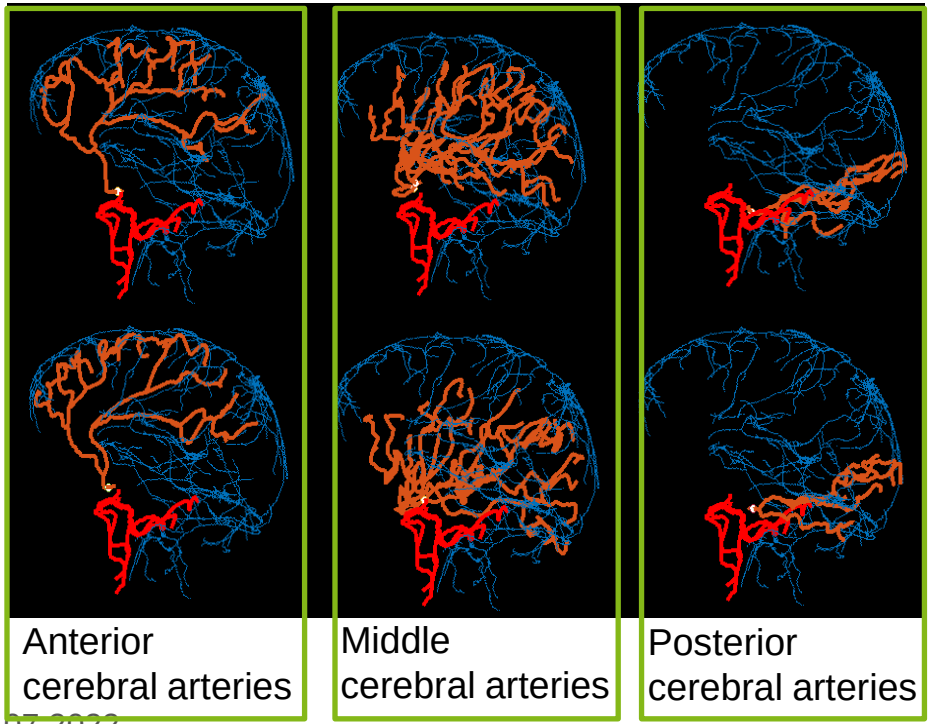


$\dot{d}(\vec{x},t)$



Propagation function of blood

- Realistic vascular architecture
  - Internal carotid arteries
  - Six major cerebral arterial trees
  - Venous system



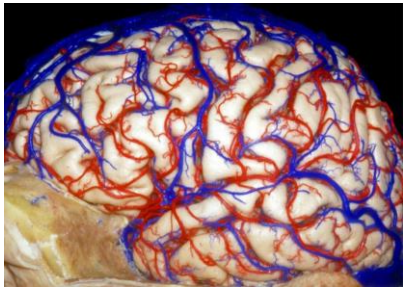
Mut, F. et al. *Int. J. Numer. Method Biomed Eng*. 2014;30

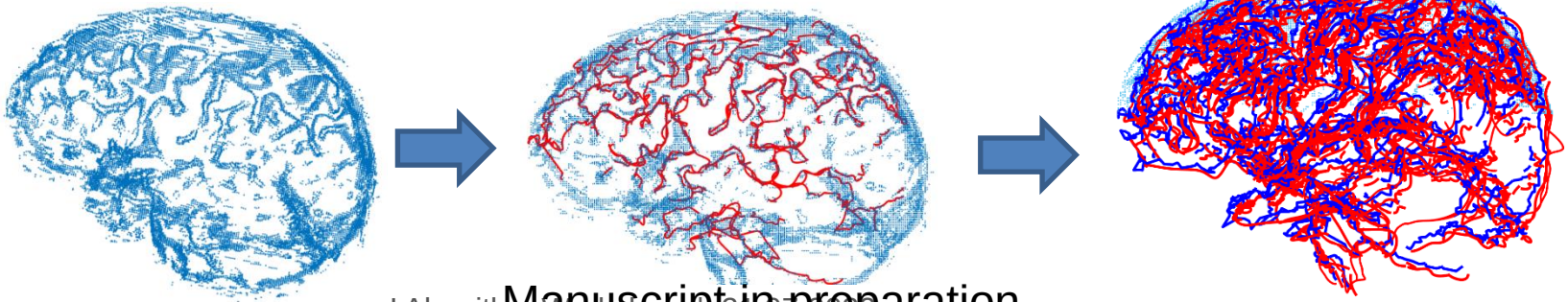
Topographic cortical vessel extraction

- Vessels occupy **convex folds** and **valleys** of the surface of the brain

$$\hat{d}_i = \left\| (c_i'' - c_i') \cdot v^{\,i} \right\| / \left\| (c_i'' - c_i') \right\|$$

$$(v_i, v_j) = \frac{1}{\sqrt{2\pi\sigma_i\sigma_j}} exp\left(\frac{(x_i - x_j)^2}{\sigma_i\sigma_j} \right), \qquad i \neq j$$

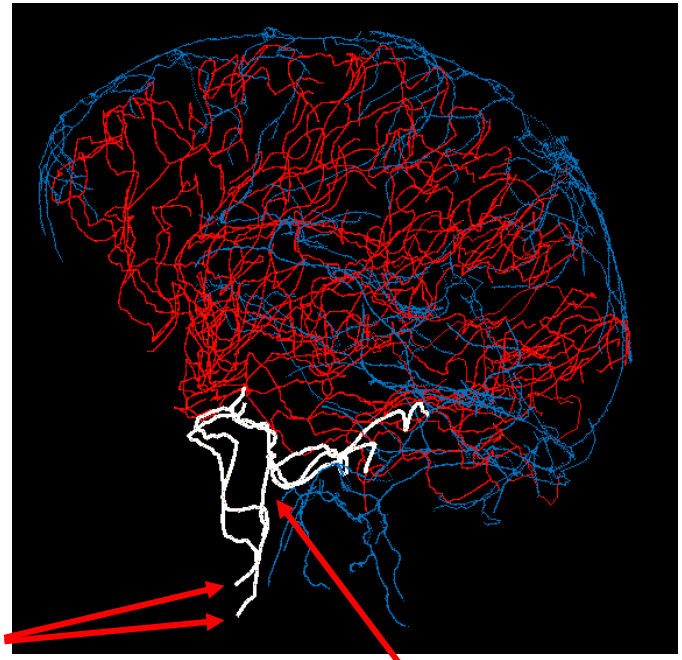




Manuscript in preparation

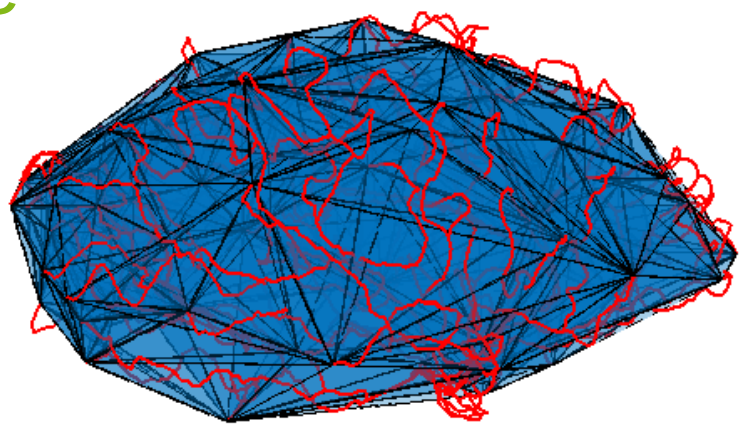
Realistic vascular architecture

- Blood supply through two sources
- More than 400 single blood vessels



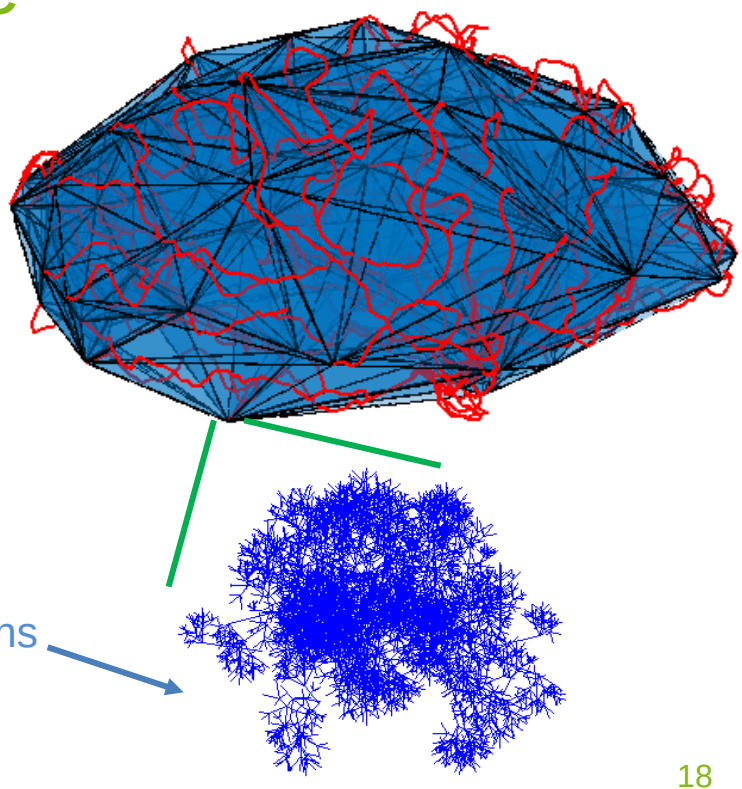
Hybrid vascular architecture

- Realistic vascular architecture
- Generic vascular architecture
  - 100 subregions (tetrahedrons)



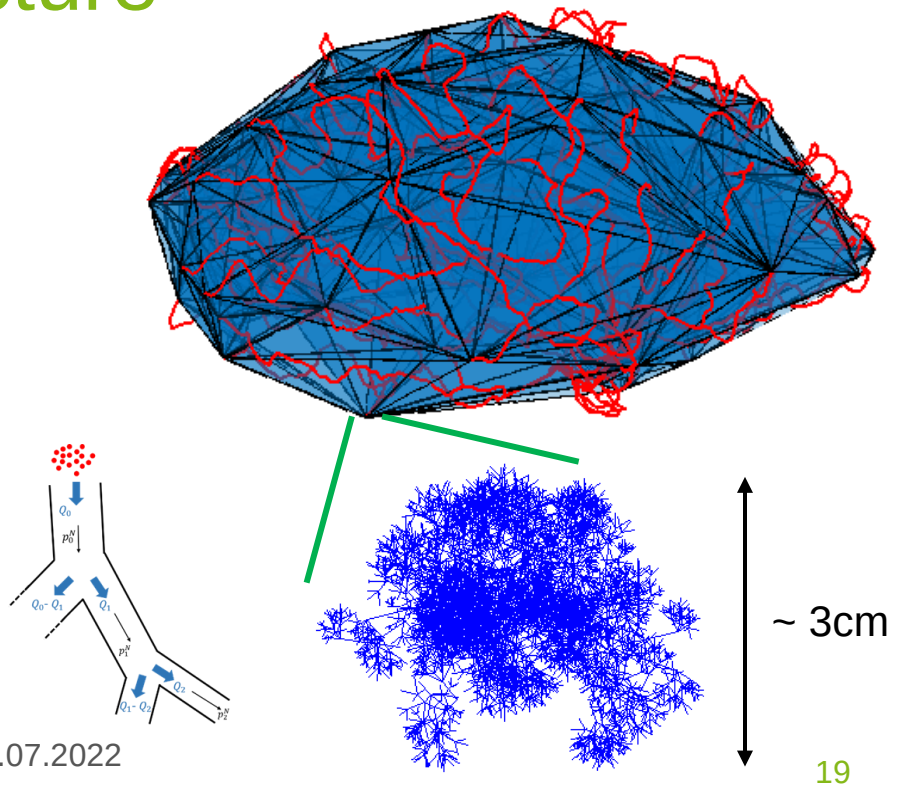
Hybrid vascular architecture

- Realistic vascular architecture
- Generic vascular architecture
  - 100 subregions (tetrahedrons)
  - Fractal vascular architecture



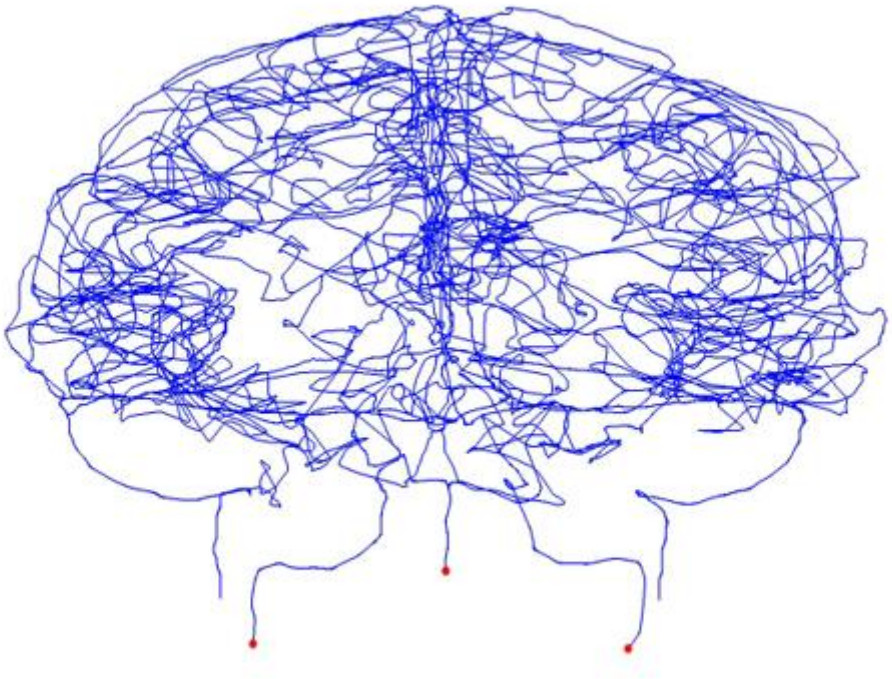
Hybrid vascular architecture

- Realistic vascular architecture
- Generic vascular architecture
  - 100 subregions (tetrahedrons)
  - Fractal vascular architecture
  - Fine scales for individual arteries and veins with vascular subregions



Dynamic Brain model

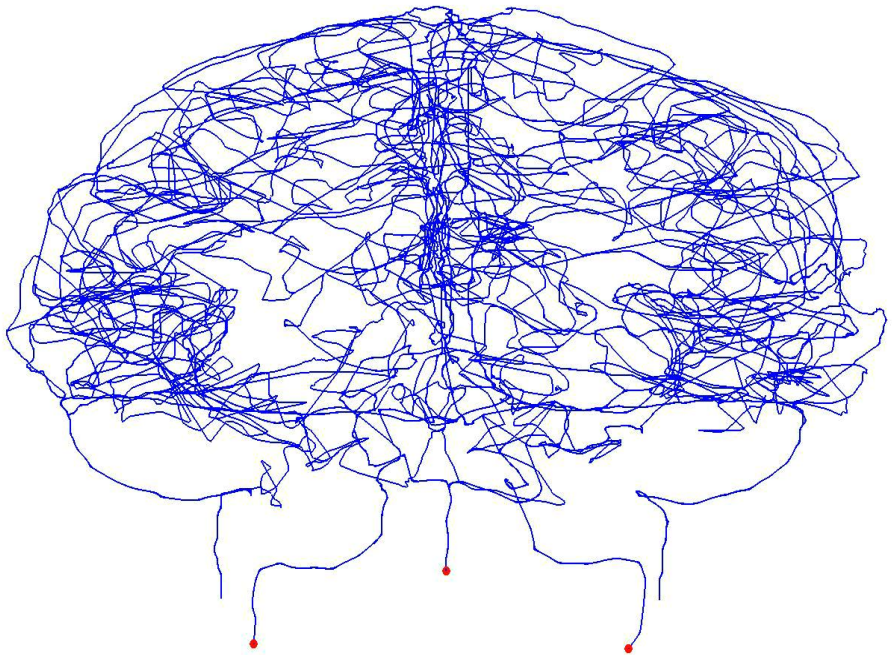
- More than 8000 vessels
- > 1.2*10^6 Blood particles



Dynamic Brain mo

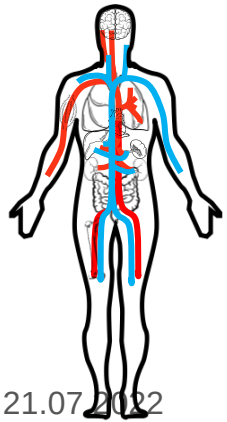
- More than 8000 vessels
- > 1.2*10^6 Blood particles
- Time resolution ΔT= 250 ns

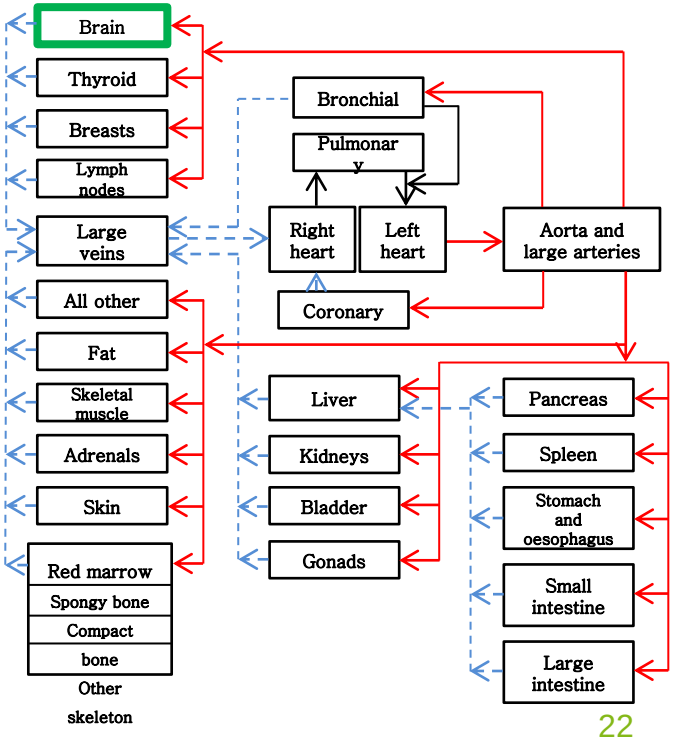
$$BP_i(\vec{r}, v(\vec{r}), t, d)$$



Blood flow model for the entire human body

- Based on ICRP data (24 organs)
- ICRP hemodynamic references (gender, age…)
- More than 50 Mio. Blood particles

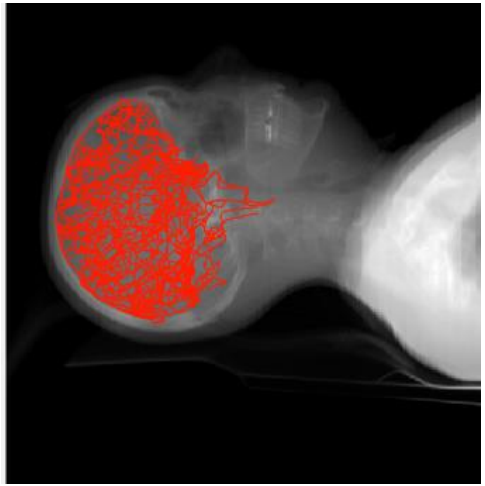


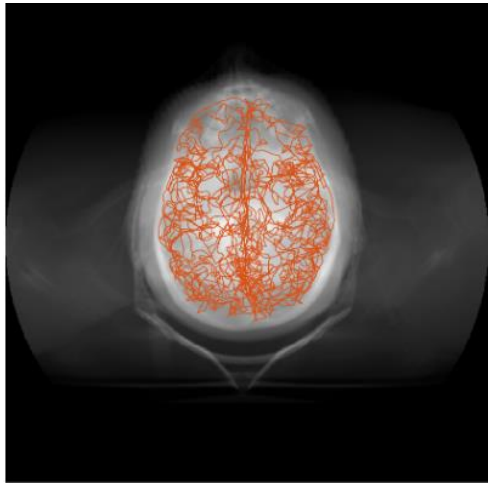


Hammi et al. Phys. Med. Biol. 2020; 65

Patient’s brain model

- Vessels are co-registered to the planning CT

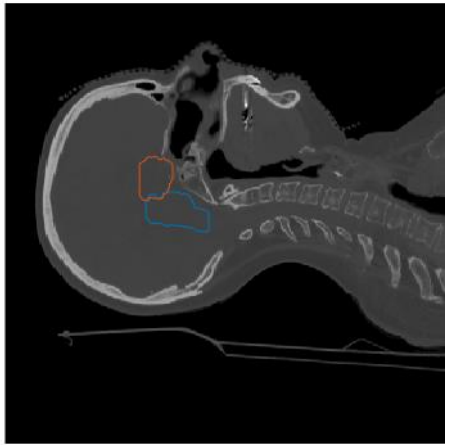


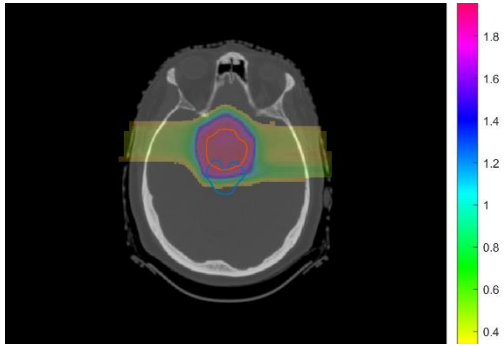


Clark et al. *Journal of Digital Imaging*. 2013 ;26(6)

Treatment regime

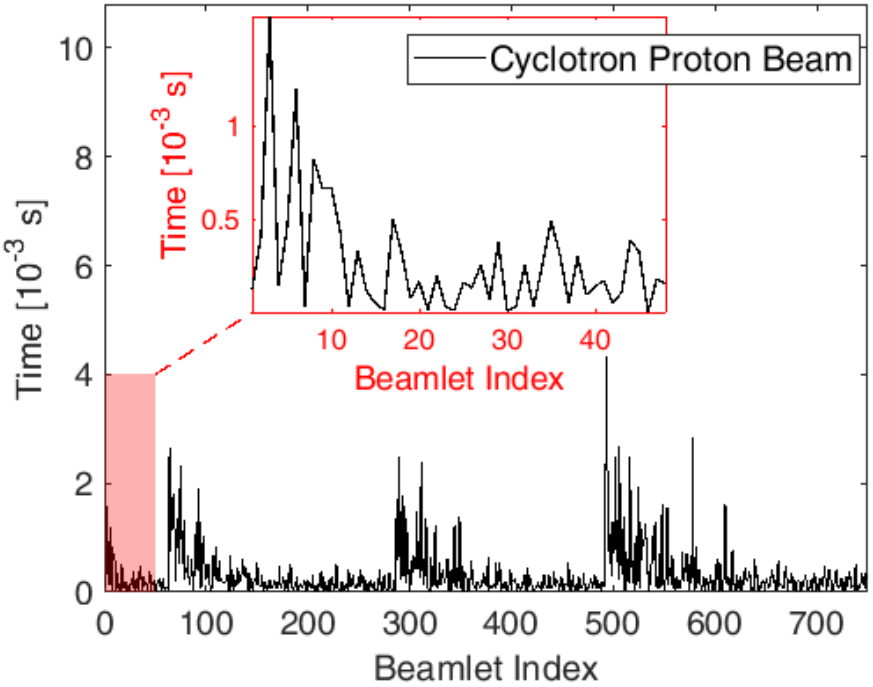
- Total Dose: 55Gy
- Target size 17.2cc
- 4x treatment fields
- Treatment regime:
  - FLASH mode Single fraction (1x Fx)
  - Hypofractionated mode 3, 5 and 10 fractions (x Fx)

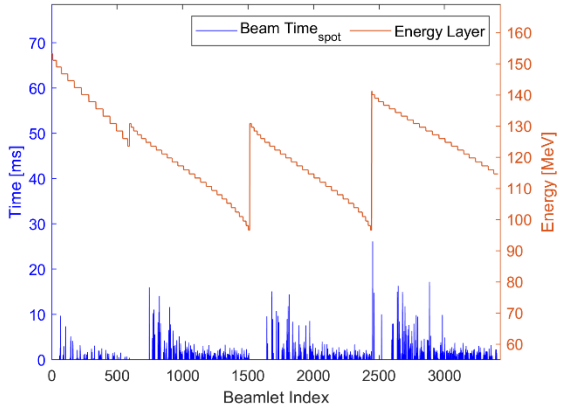


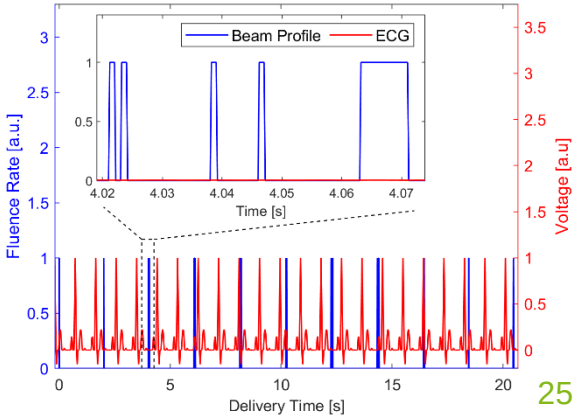


Wieser, Hans-Peter, et al. Medical Physics, 2017, 44.6

Dynamic beam delivery

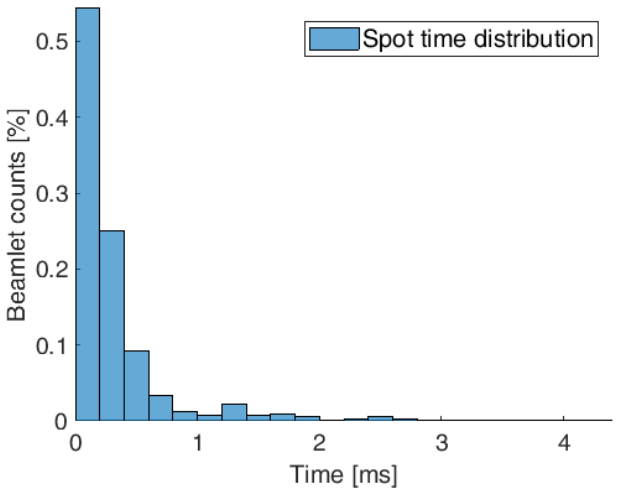




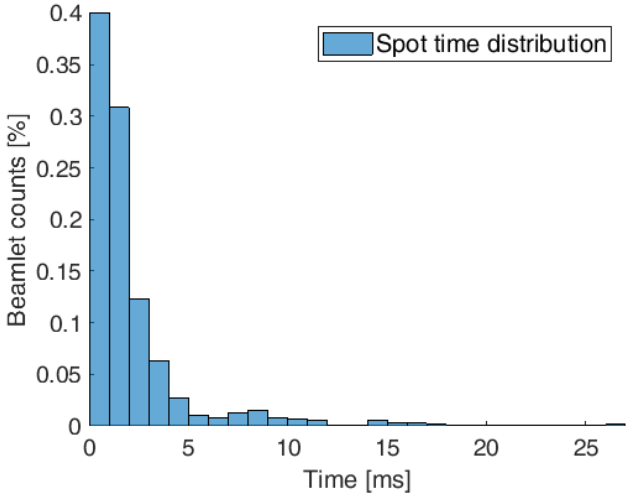


Dose rate delivery

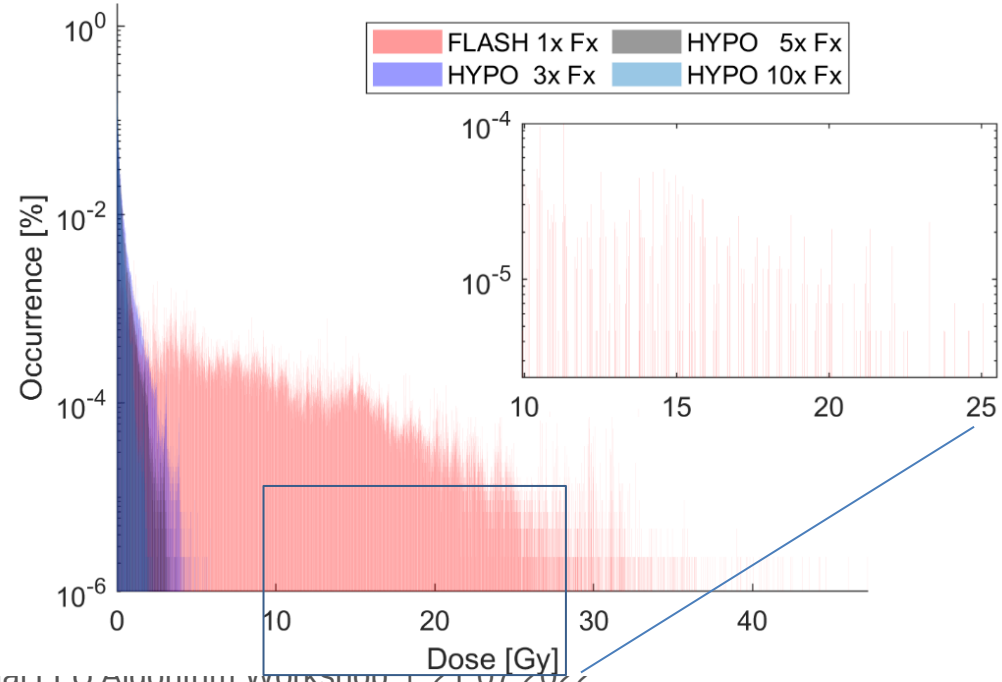
- FLASH
  - I_{max}= 300nA



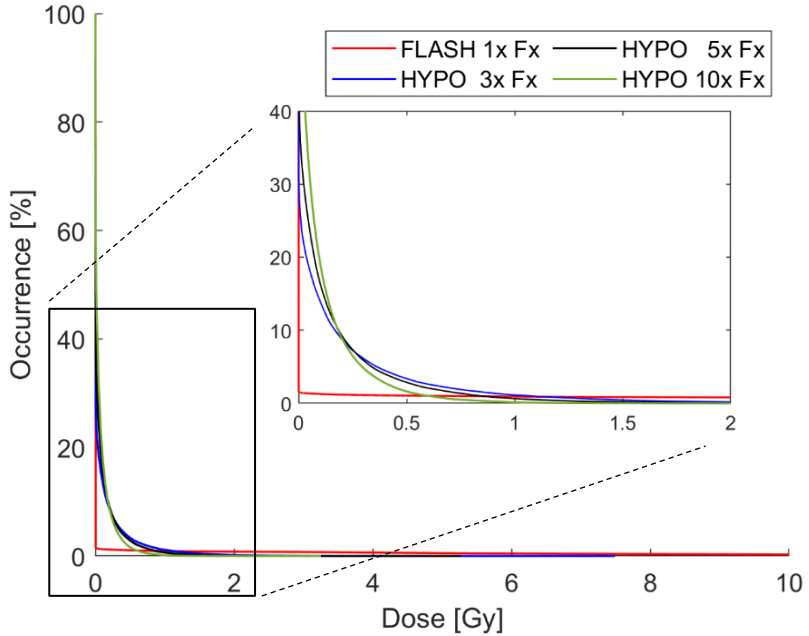
- Conv. PBS
  - I_{max}= 2nA



Histogram of the dose hits

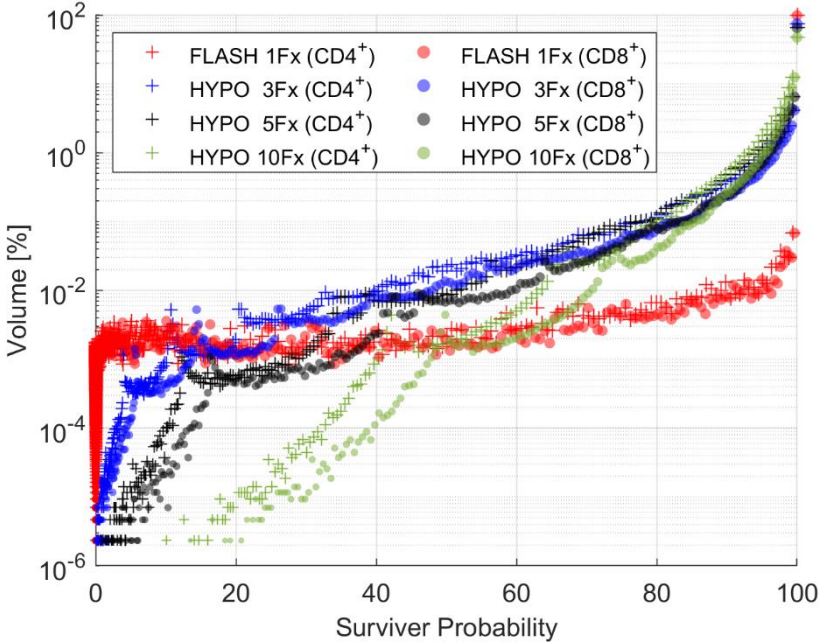


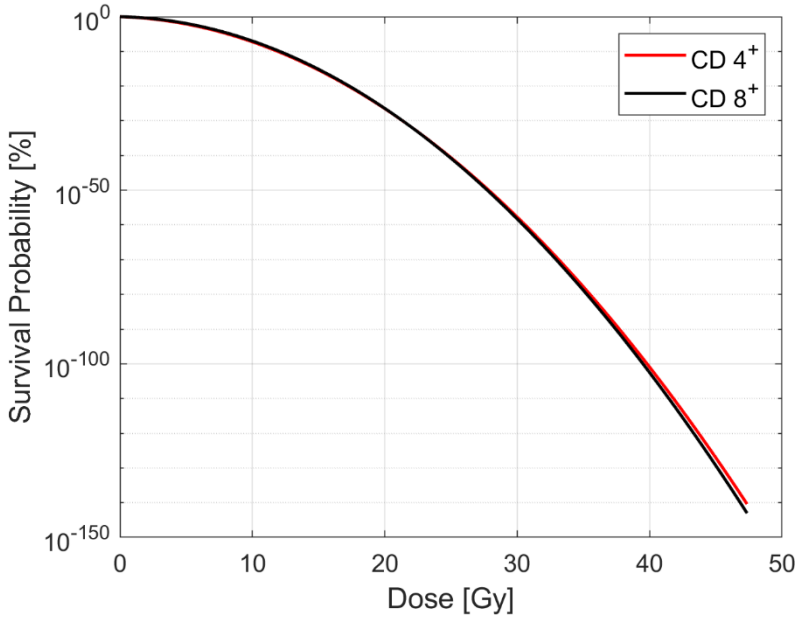
DVH of the treatment regime



	FLASH	Hypo 3Fx	Hypo 5Fx	Hypo 10Fx
$V_{D>0Gy}[\%]$	1.52	30.97	44.58	68.07
$V_{D>0.07Gy}[\%]$	1.32	16.35	20.45	25.44
$V_{D>1Gy}[\%]$	0.93	1.14	0.64	0.13
$D_{V=2\%}[\mathrm{Gy}]$	46.31	7.24	5.06	3.09
$D_{V=5\%}[\mathrm{Gy}]$	44.89	7.02	4.91	2.99

Radiobiological effect





Nakamura et al. 1990

Conclusion

- We modeled a FLASH dose rate effect on depleting the circulating immune cells by modeling the dose to the circulating blood in the brain.
- Hybrid brain vascular Model was developed based on realistic vasculature network of the human brain.
- FLASH-RT was found to spare circulating immune cells in comparison to hypofractionated treatment using conventional dose rate.

Thank you for your attention!

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