Mass General Brigham

Simulating dose to circulating immune cells How much does the integral dose matter?

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Disclosures

I have no relevant financial relationships to disclose
My presentation will not include off-label or unapproved products

- Grants / Research support from the National Cancer Institute
- ASTRO, PTCOG, ICRU committees
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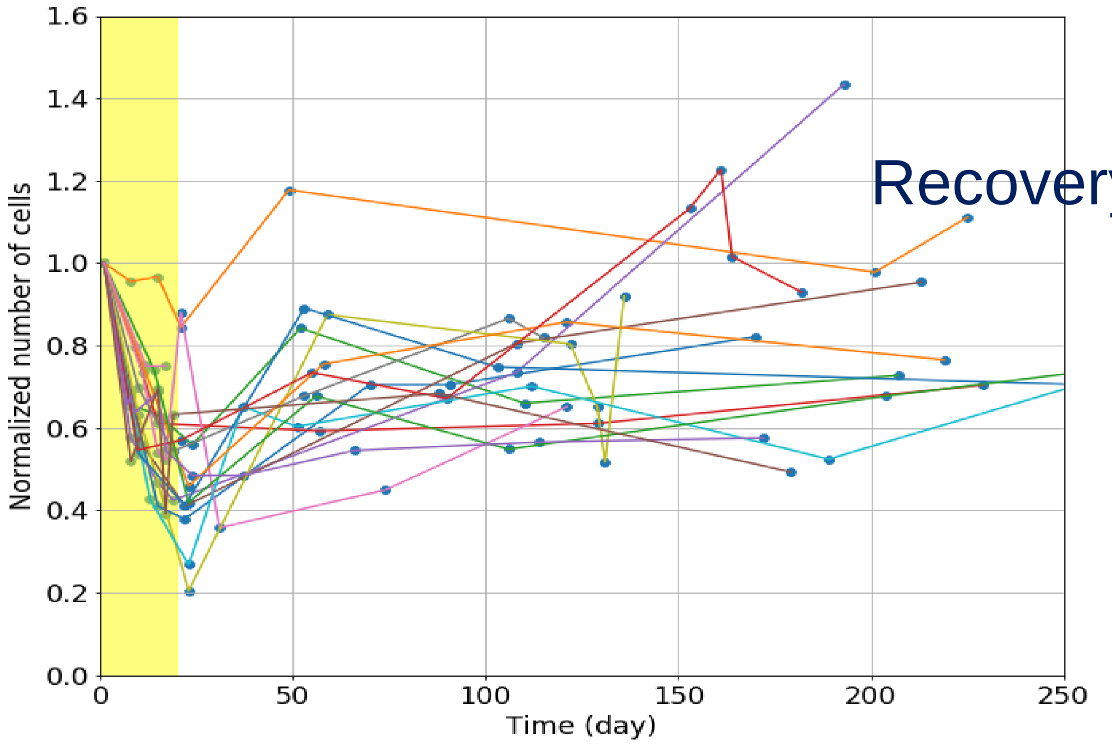
- Research collaborations with GE Global Research
- Book on “Proton Therapy Physics” with CRC Press / Taylor&Francis
- Executive Editorial Board: Phys. Med. Biol.

Radiation-induced lymphopenia

Lymphopenia: a lower-than-normal number of lymphocytes in the patient's blood

Radiation therapy causes the depletion of circulating lymphocytes

Absolute lymphocyte Couns (ALC) for liver (HCC) patients after proton therapy

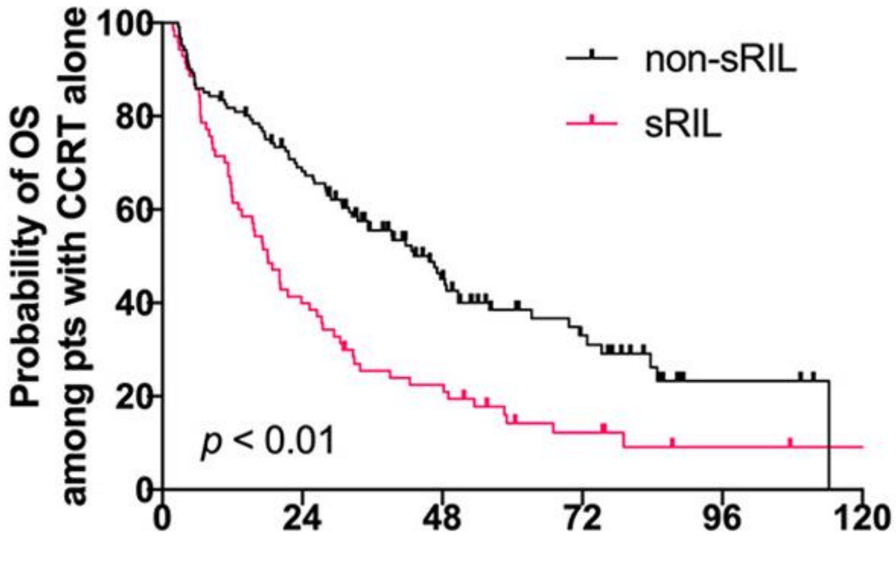


Recovery after treatment

Sung, … Paganetti: A Tumor-Immune Interaction Model for Hepatocellular Carcinoma based on measured Lymphocyte Counts in Patients undergoing Radiotherapy. Radiotherapy and Oncology 2020

Radiation-induced lymphopenia

Lymphopenia correlates with outcome



Time (months)

No. at risk					
non-sRIL	121	80	38	18	4
sRIL	71	29	16	7	3

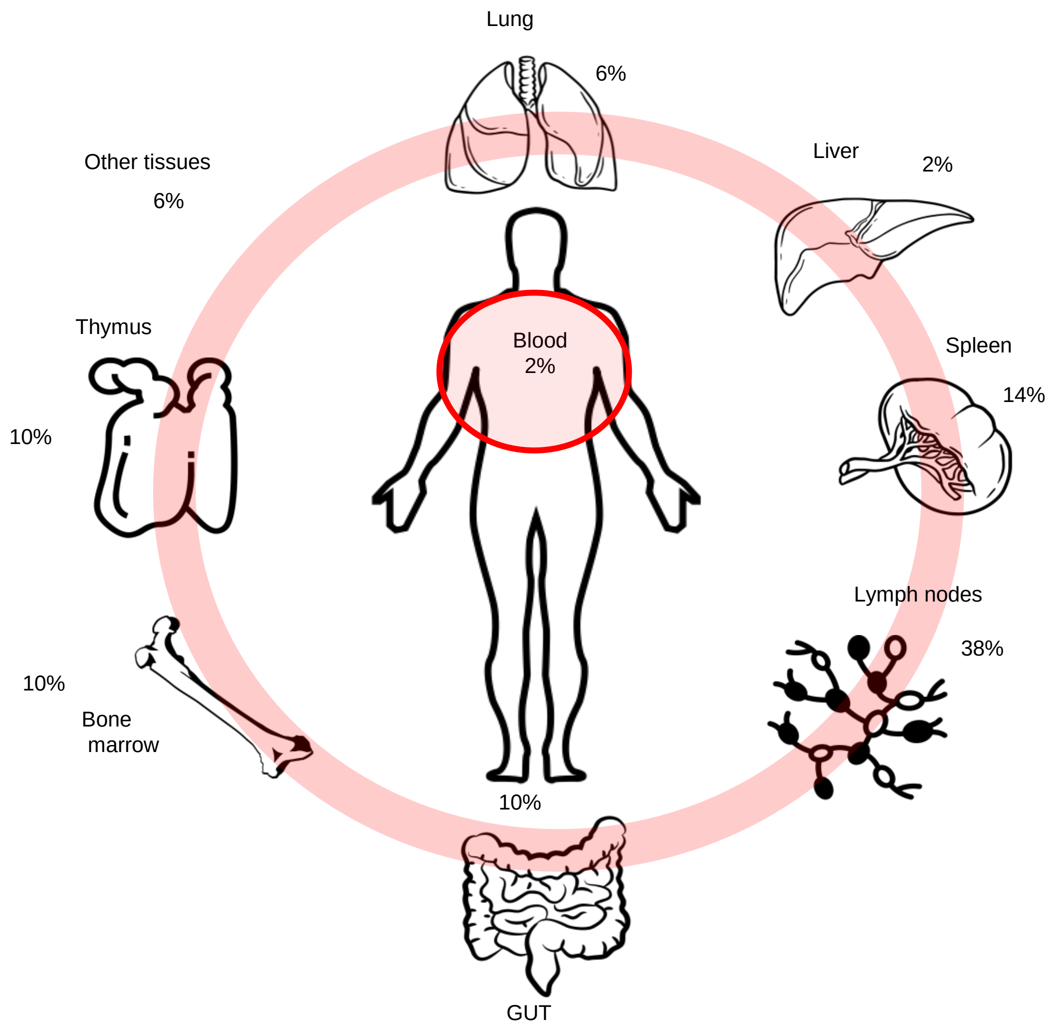
Patients treated with concurrent chemoradiation for locally advanced NSCLC

Severe radiation-induced lymphopenia (sRIL) = absolute lymphocyte count [ALC] < 0.23×10^9 cells/L

Jing et al. Severe Radiation-Induced Lymphopenia Attenuates the Benefit of Durvalumab After Concurrent Chemoradiotherapy for NSCLCJTO Clinical and Research Reports 2022

Radiation-induced lymphopenia

<u>Hypothesis:</u> Radiation-induced lymphopenia is caused by cell kill of circulating lymphocytes



Lymphopenia observed after irradiation of treatment sites that are

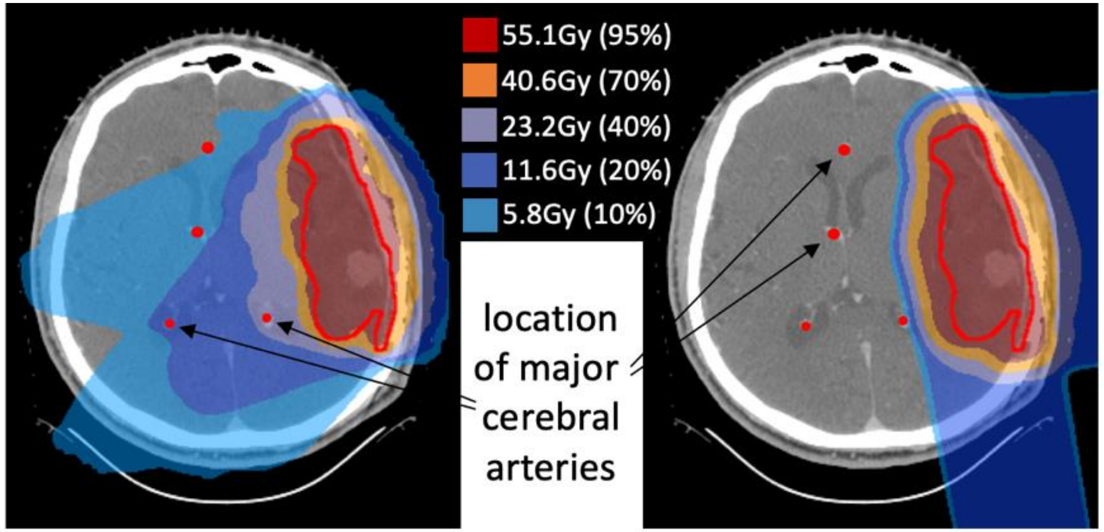
- Lymphatic-rich
  - Spleen
  - Lung
  - Pelvis
  - …
- Lymphatic-scarce
  - Brain
  - Extra-corporal blood irradiation
  - (some HCC)
  - …

We need to consider blood flow !

Radiation-induced lymphopenia

The “low dose bath” impacts dose to lymphocytes

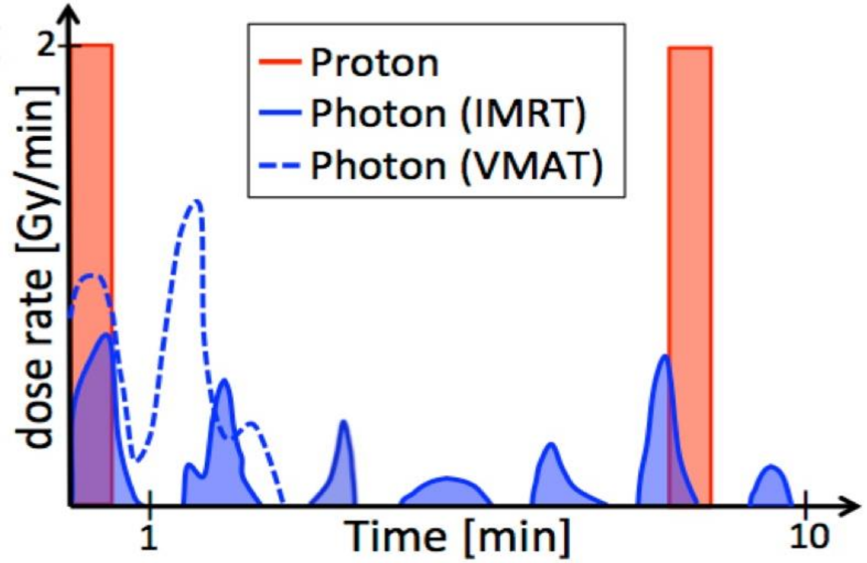
Difference in dose bath



IMRT

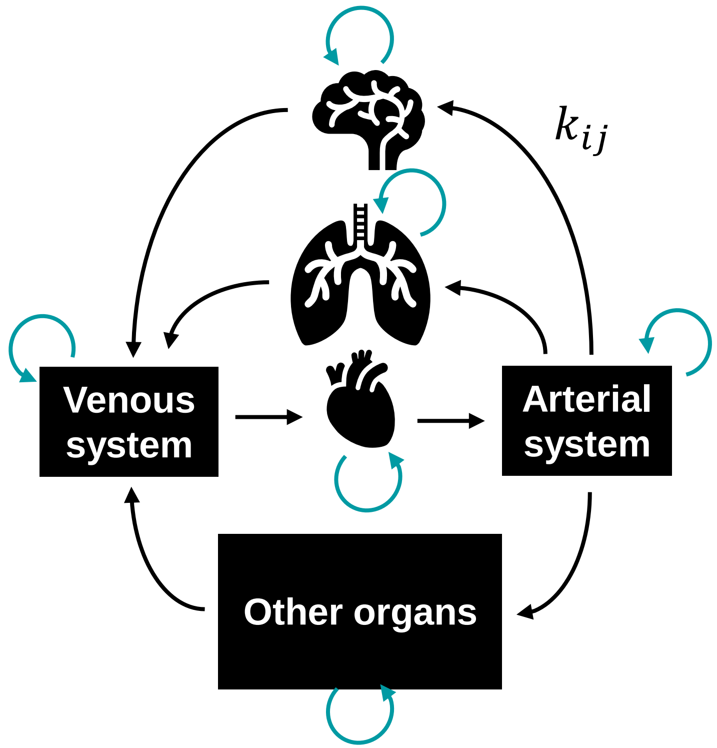
Proton Therapy

Difference in delivery time distribution



Modeling dose to the blood

Stochastic compartment model of blood flow



→ Simulate blood flow by blood particles moving between compartments

- Jump probabilities between compartments I and j:

$$p(c_i \rightarrow c_j) = p_{ij} = k_{ij}\Delta t$$

- Probability to stay in current compartment:

$$p_{ii} = 1 - \sum_{i \neq j} p_{ij}$$

L: Conditional probability that a particle leaves during time interval Δt, given it has not left until now

$$L = \frac{f(\tau) \cdot \Delta t}{S(\tau)} = h(\tau) \cdot \Delta t = \frac{\Delta t}{MTT}$$

Survival function

Hazard function (probabilistic rate at which particles leave)

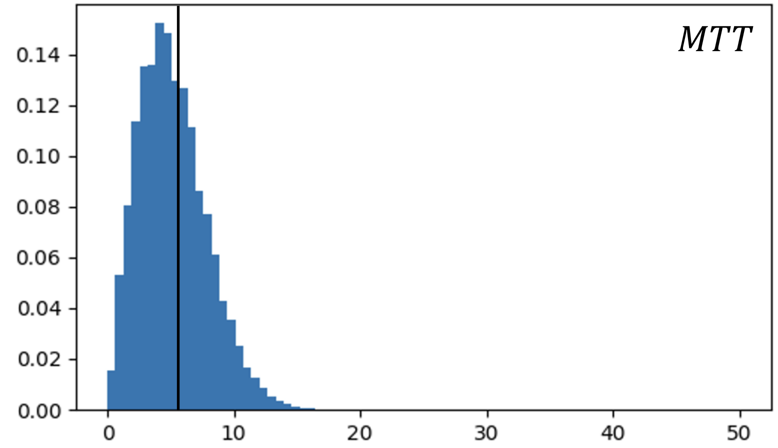
Beekman C … Paganetti H: A stochastic model of blood flow to calculate blood dose during radiotherapy. Physics in Medicine and Biology

Modeling dose to the blood

Blood flow as a Markov Process

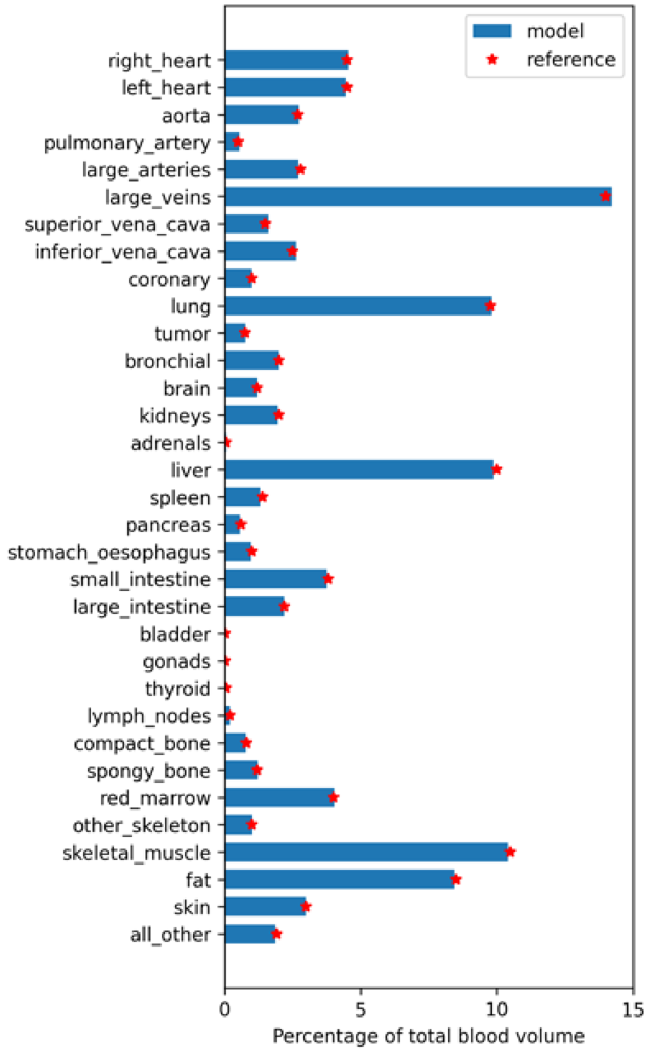
'Mean Transit Time' (MTT) in every compartment:

$$MTT_i = \frac{blood\ volume\ of\ compartment}{total\ blood\ flow\ out\ of\ compartment} = BV_i / \sum_{j \in \{i\}} Q_{ij}$$



$f(\tau)$: Weibull distribution of transit times

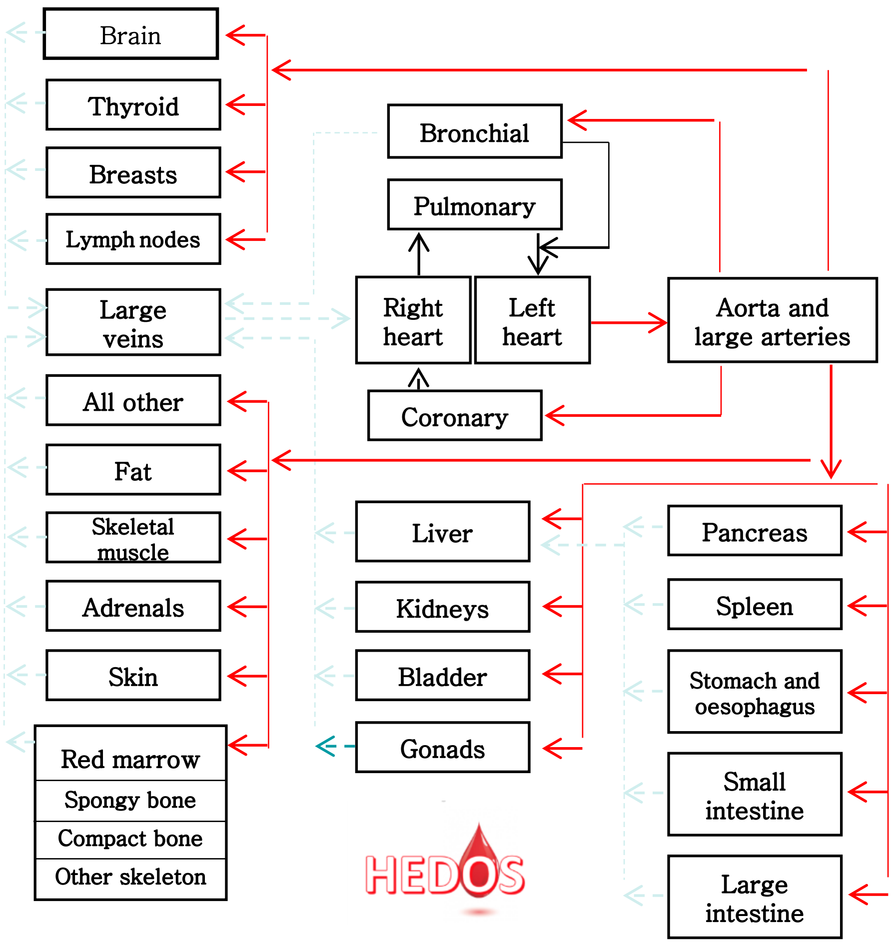
Mean transit times
(ICRP 89 as reference)
have to be calibrated with blood flow



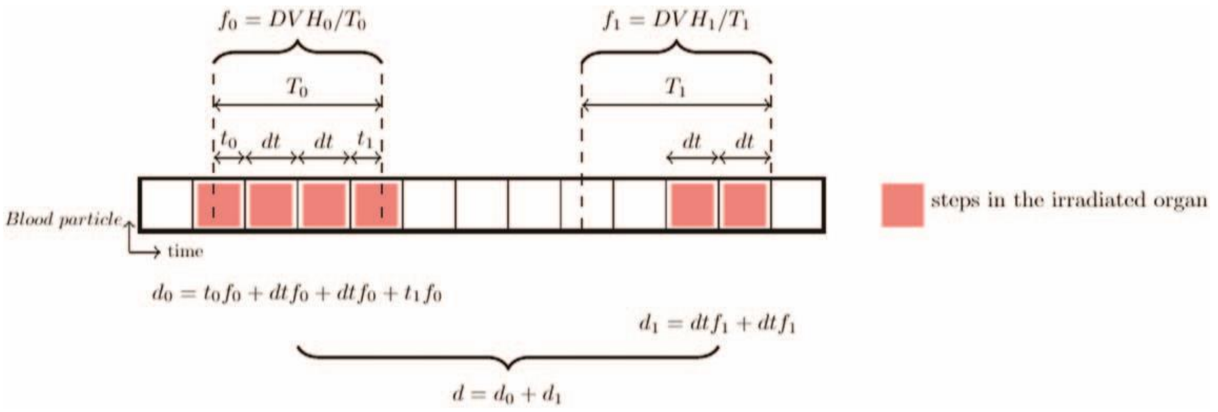
Beekman C … Paganetti H: A stochastic model of blood flow to calculate blood dose during radiotherapy. Physics in Medicine and Biology

Modeling dose to the blood

Blood flow model ("HEDOS") based on ICRP organs and hemodynamic data (gender, age…)



Blood particles receive dose based on organ DVHs and proportional to the time spent in the irradiated organ



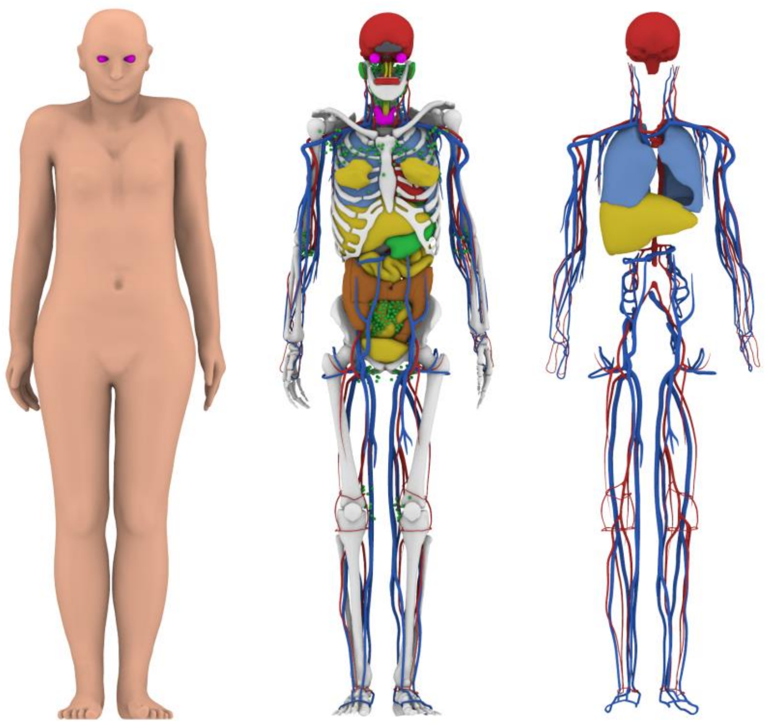
Model input: Delivery time structure and organ DVH (https://github.com/mghro/hedos)

Shin …, Paganetti, Grassberger: HEDOS - a computational tool to assess radiation dose to circulating blood cells during external beam radiotherapy based on whole-body blood flow simulations. Phys Med Biol 2021

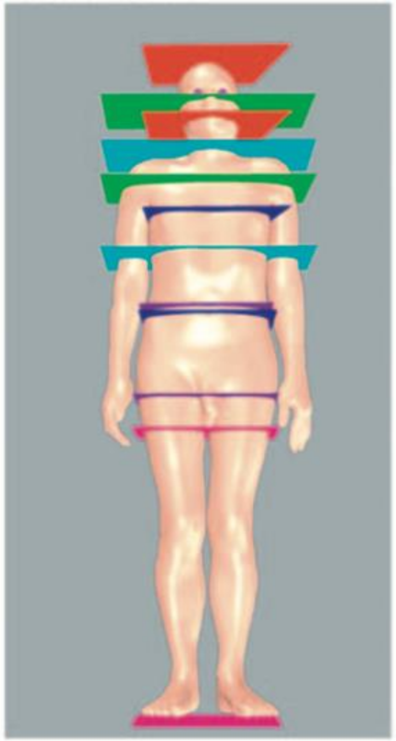
Beekman C … Paganetti H: A stochastic model of blood flow to calculate blood dose during radiotherapy. Physics in Medicine and Biology

Modeling dose to the blood

Considering dose to un-contoured areas



Whole-Body Adult/Female ICRP 145 | Skin and Muscle Removed | Large Vessels and Brain | Lungs | Liver

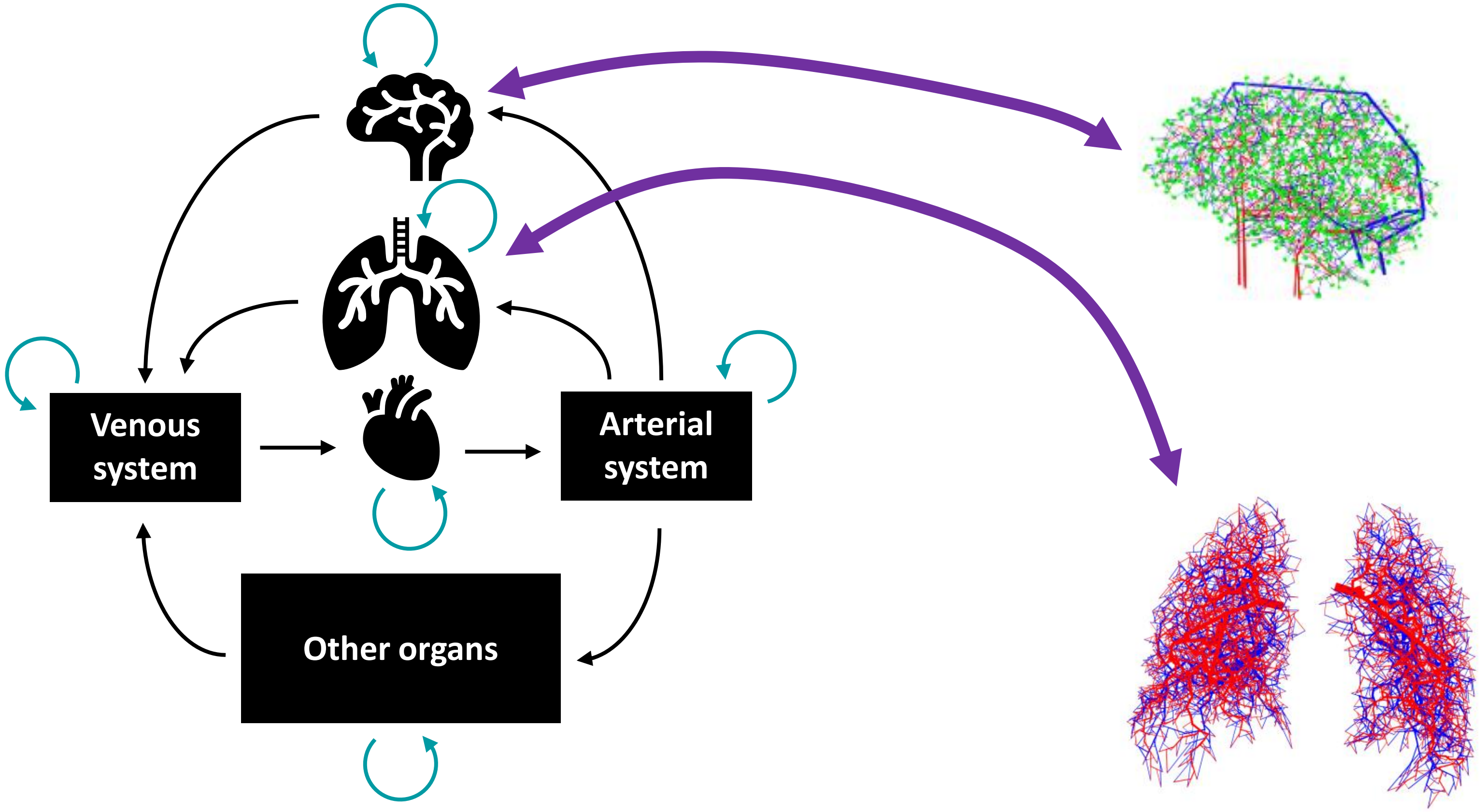


B. Relative Volume (%) of Tissue per Body Region compared to entire Body

Tissue	Brain	Neck	Chest	Abdomen	Pelvis	Lower Extremity
Blood in Large Arteries	0.03	9.46	27.72	23.38	16.98	25.23
Blood in Large Veins	0.03	5.55	18.46	8.49	19.03	30.40
Muscle	2.01	11.52	21.47	11.90	22.80	30.20
Residual Soft Tissue (FAT)	4.02	11.66	27.24	29.93	21.89	23.03
Skin (100um)	5.77	9.14	19.89	12.61	13.76	31.51
Bone	10.68	14.29	24.99	13.99	21.64	31.49

Shin …, Paganetti, Grassberger: HEDOS - a computational tool to assess radiation dose to circulating blood cells during external beam radiotherapy based on whole-body blood flow simulations. Phys Med Biol 2021

Modeling dose to the blood

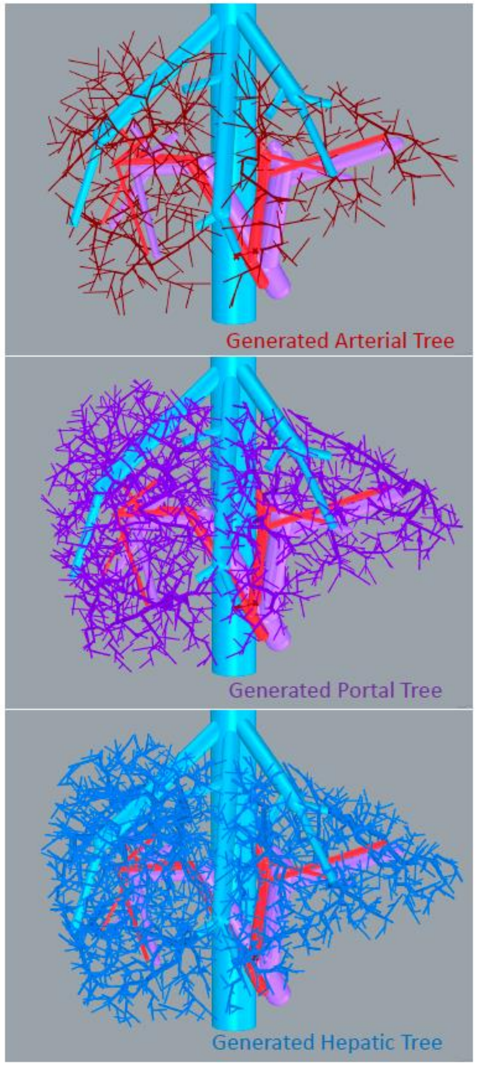


Blood flow as a compartmental model

Blood flow modeled explicitly

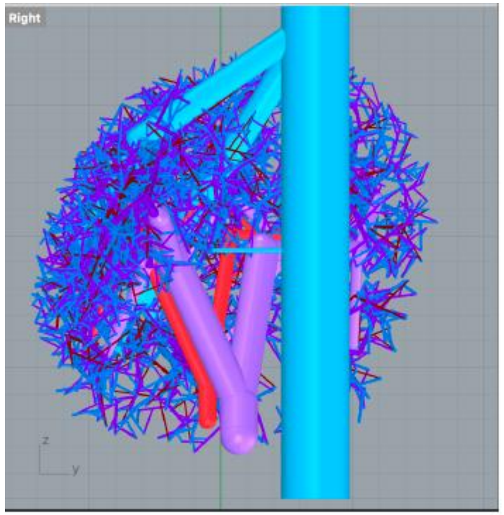
Modeling dose to the blood

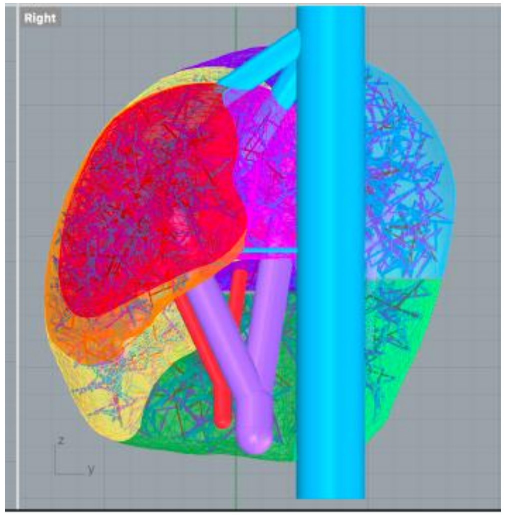
Arterial Portal Venous



Physical Principles:

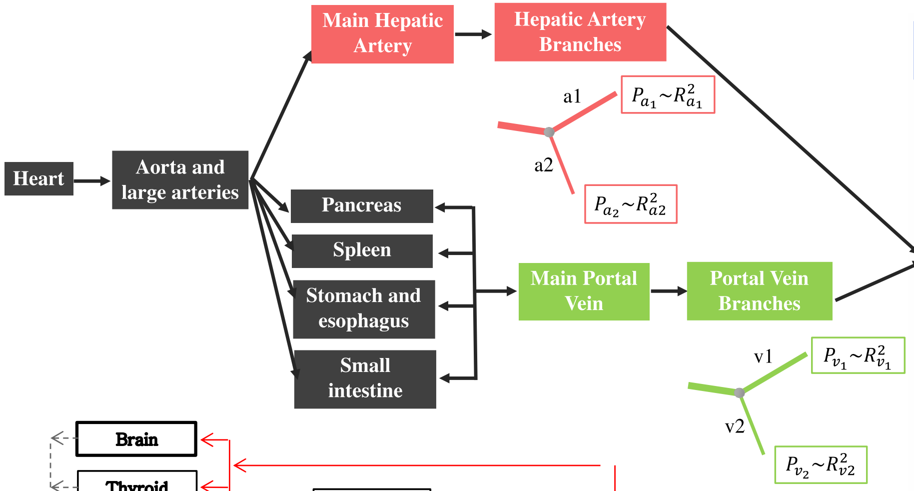
- Conservation of Blood Flow at each bifurcation
- Murray's Law used to relate each parent vessel with its successors
- Gradient pressure computed at each step using Poiseuille's law

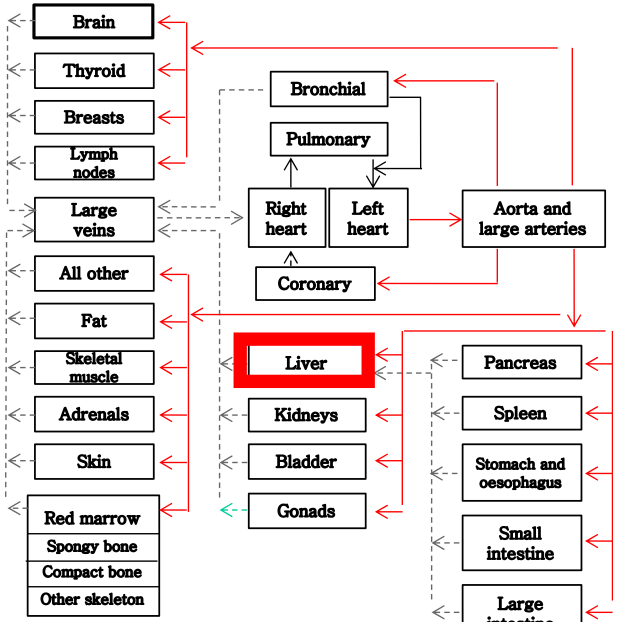


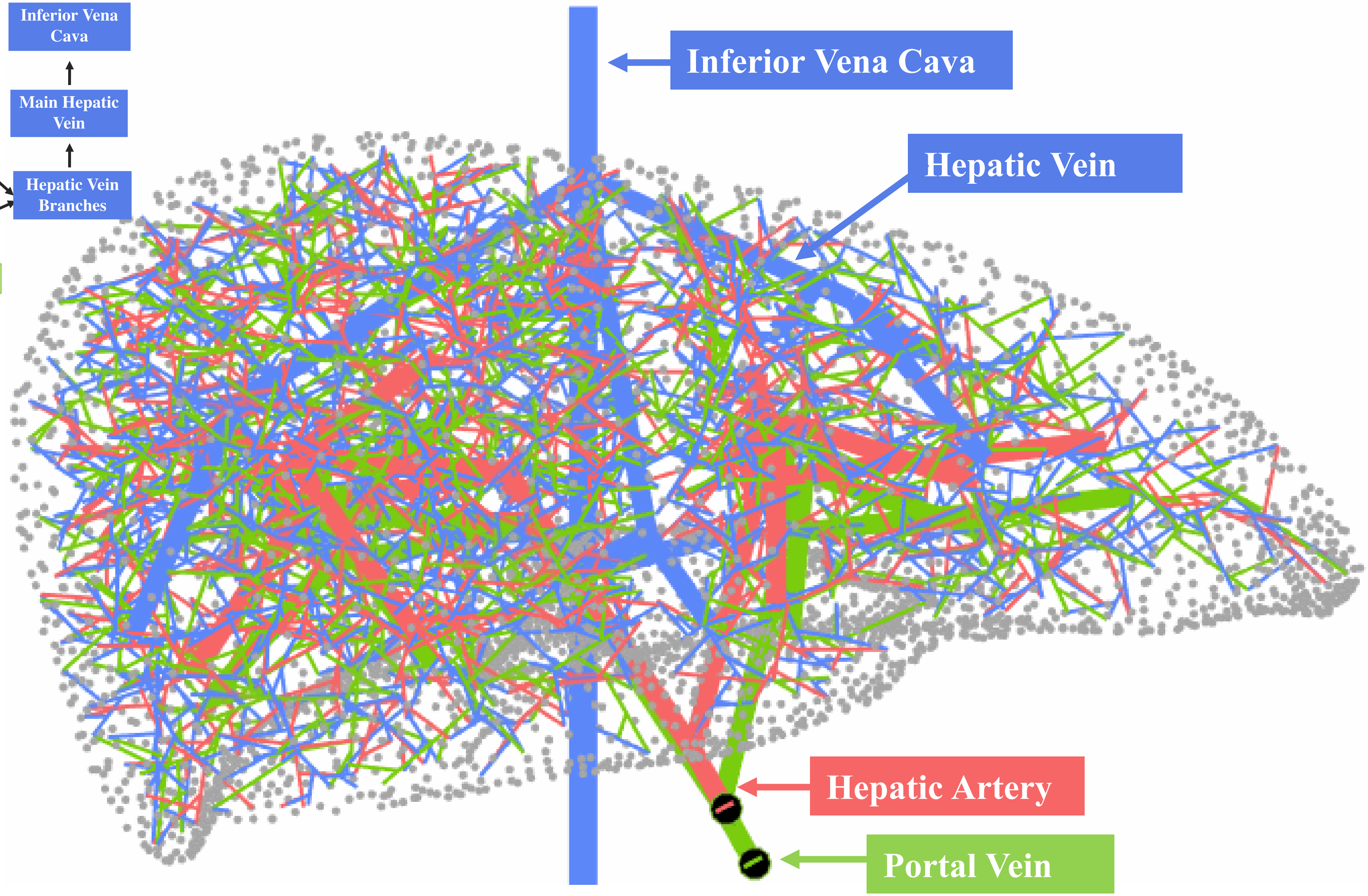


Correa-Alfonso C; Withrow JD; Domal SJ; Xing S; Shin J; Grassberger C; Paganetti H and Bolch WE: A mesh-based model of liver vasculature: Implications for improved radiation dosimetry to liver parenchyma for radiopharmaceuticals. EJNMMI-Physics 2022 9; 28

Modeling dose to the blood

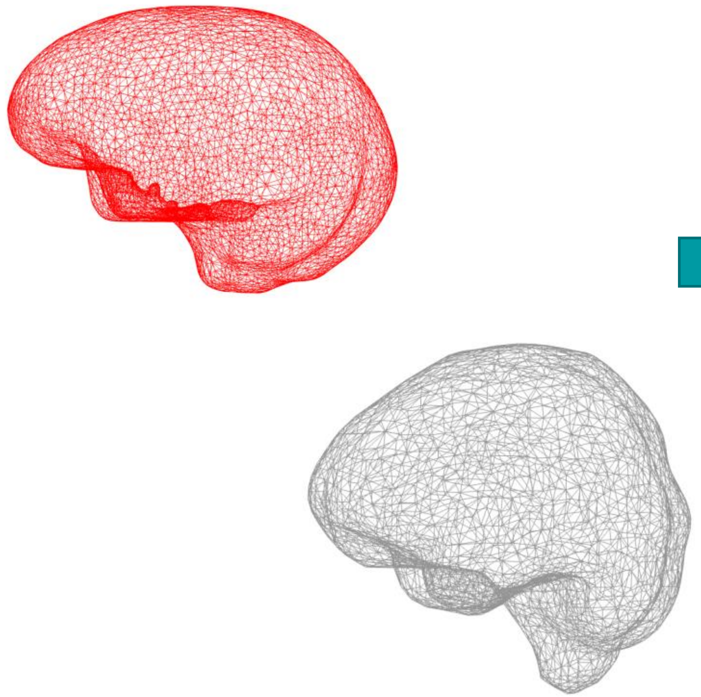




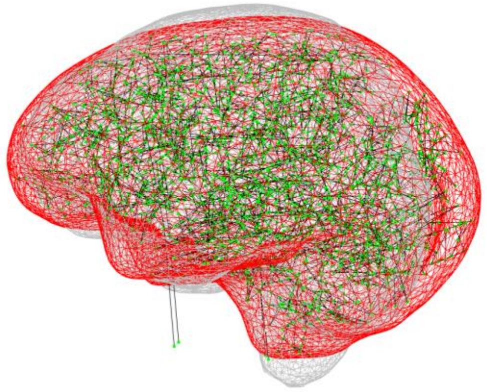


Xing, … Grassberger, Paganetti: A dynamic blood flow model to compute absorbed dose to circulating blood and lymphocytes in liver external beam radiotherapy. Phys Med Biol 2022

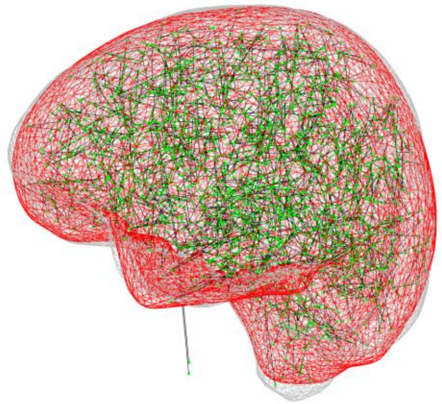
Modeling dose to the blood

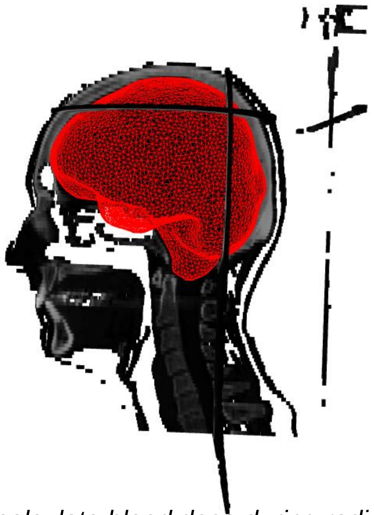


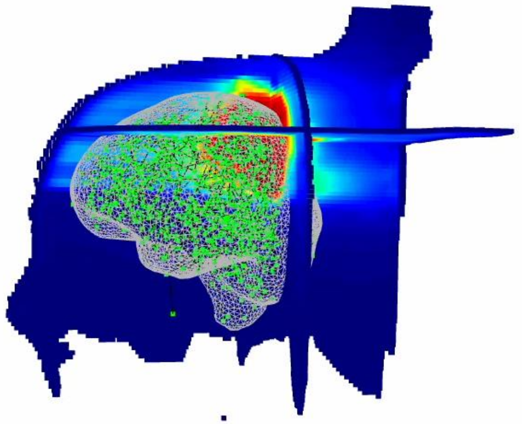
Rigid alignment



Deformable registration



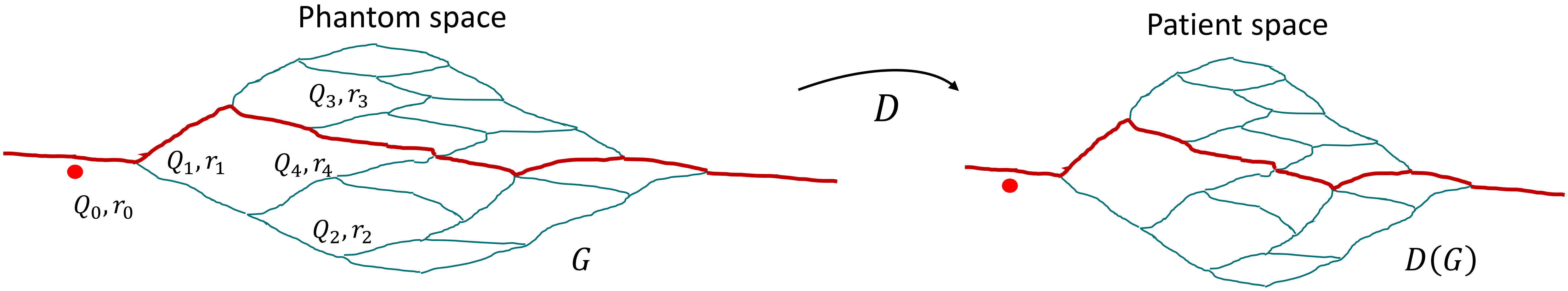




→ Simulate blood particles traversing through dose field patient, accumulating dose.

Beekman C … Paganetti H: A stochastic model of blood flow to calculate blood dose during radiotherapy. Physics in Medicine and Biology

Modeling dose to the blood



Phantom space

- Parametrize every possible trajectory through the vasculature and solve for $s(t)$ (parameterization of a path) using ODE

→ Computationally <u>expensive</u>

Patient space

- Re-use the solution to the ODEs for each path
- Distribution of paths for each blood particle
- Accumulate dose

→ Computationally <u>cheap</u>

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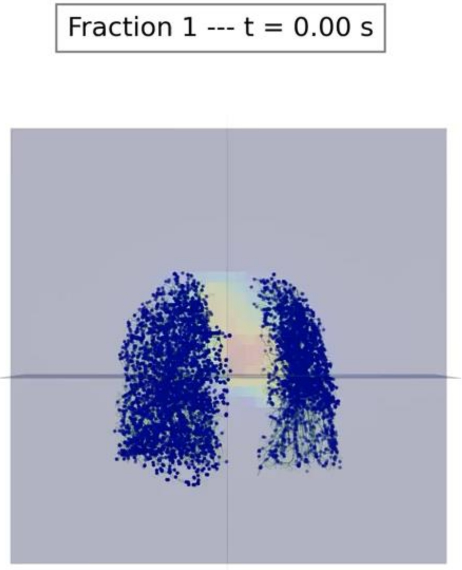
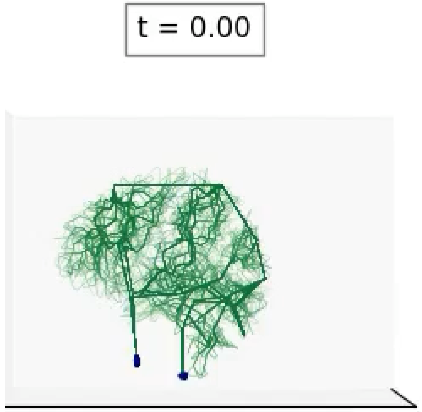
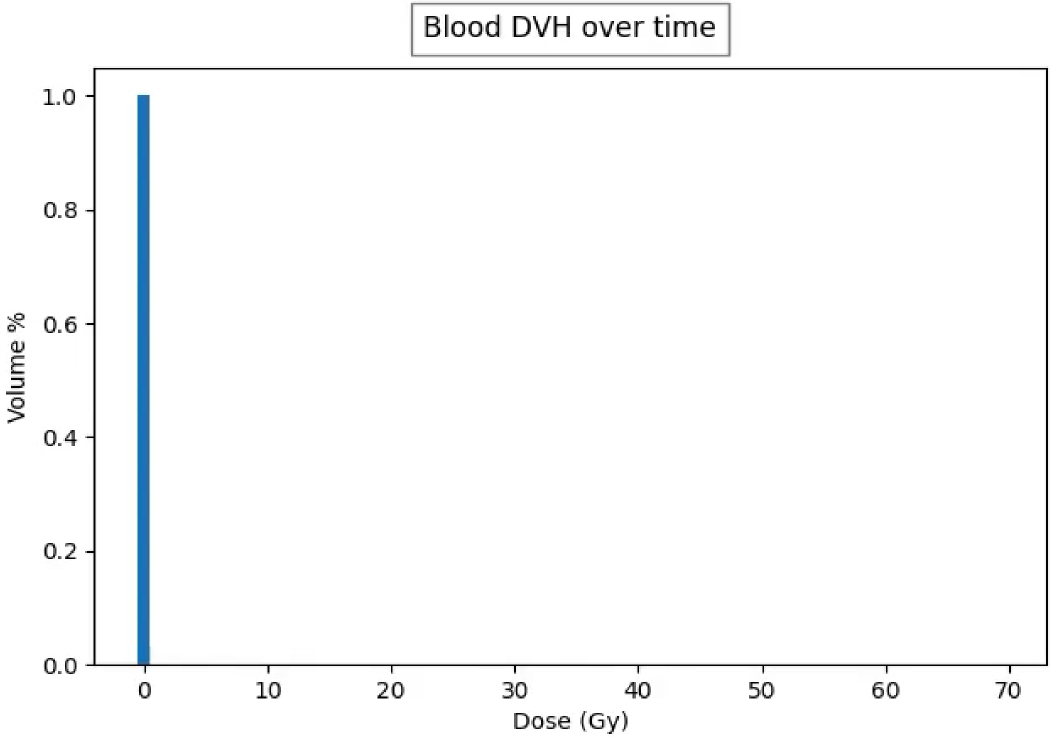
Modeling dose to the blood







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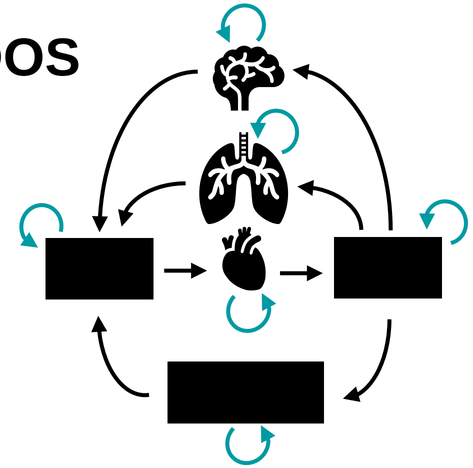
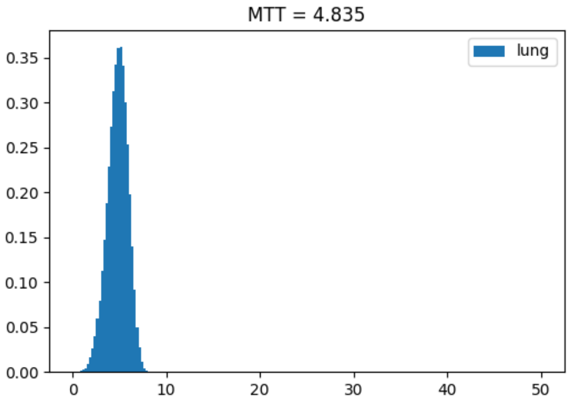
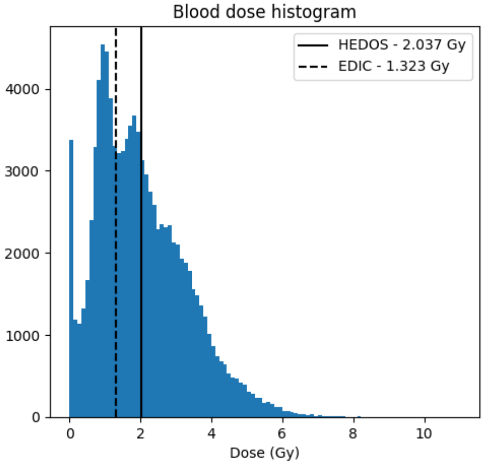
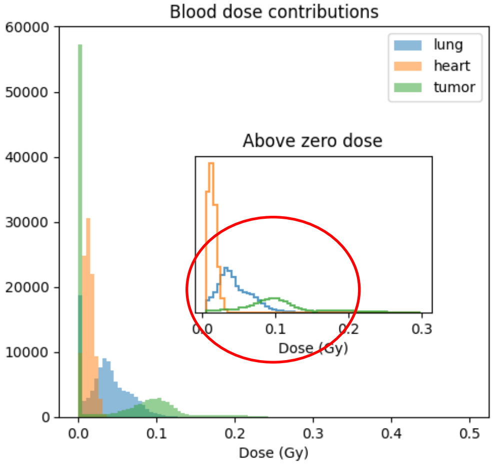
Modeling dose to the blood

HEDOS





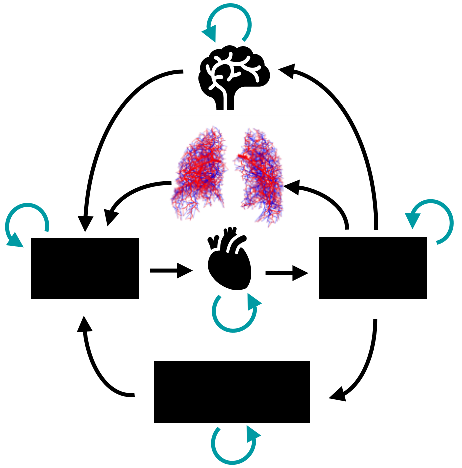


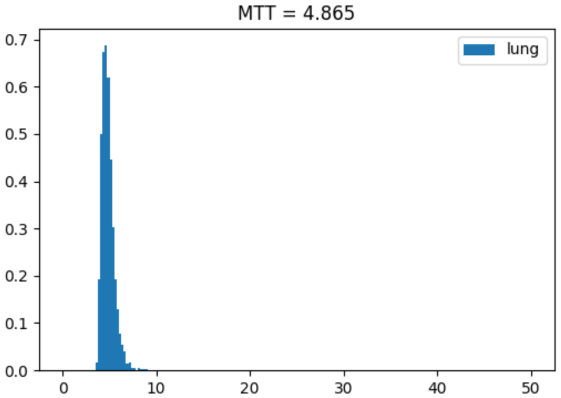


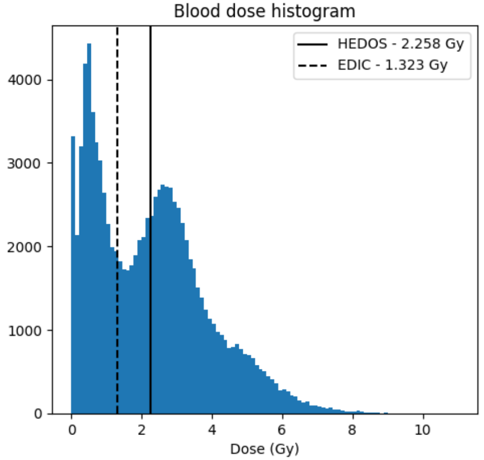
HEDOS & explicit lung

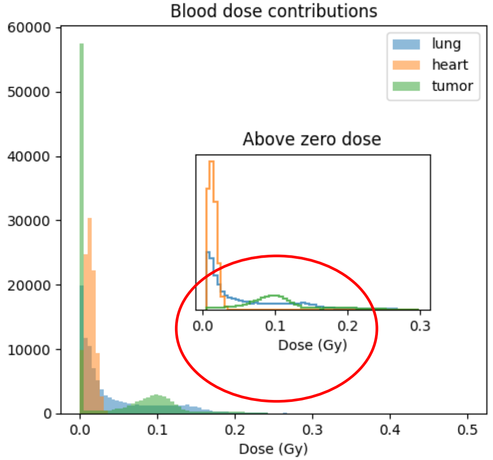
Transit time distribution similar…

… yet dose distribution different.









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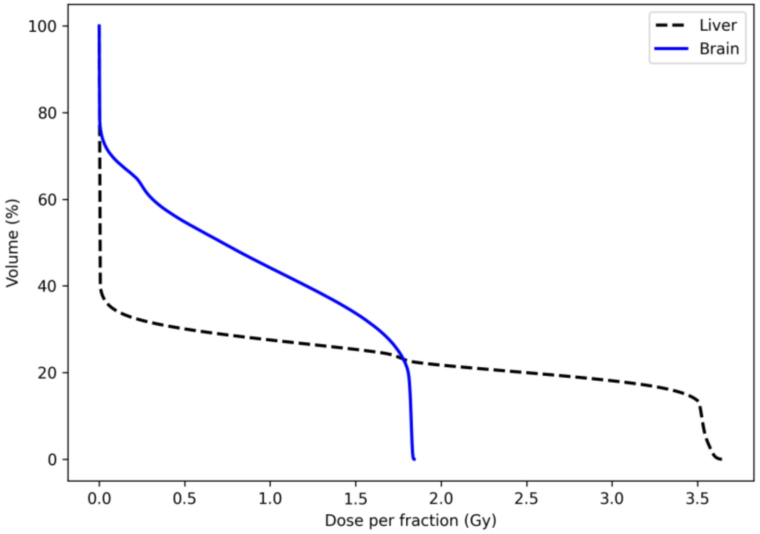
Modeling dose to the blood - Results

Brain and liver fields with similar volume but different blood volume and transition time

	Brain	Liver
Target volume (cc)	298.2 cc	353.8 cc
Organ volume (cc)	1329.6 cc	1627.6 cc
Target/Organ ratio	**0.22**	**0.22**
Prescription dose	59.4 GyRBE	52.5 GyRBE
Fractionation size	33	15
Blood volume (%)	**1 %**	**10 %**
Transition time (s)	**6.4 s**	**24 s**

Treatment dose



Blood dose

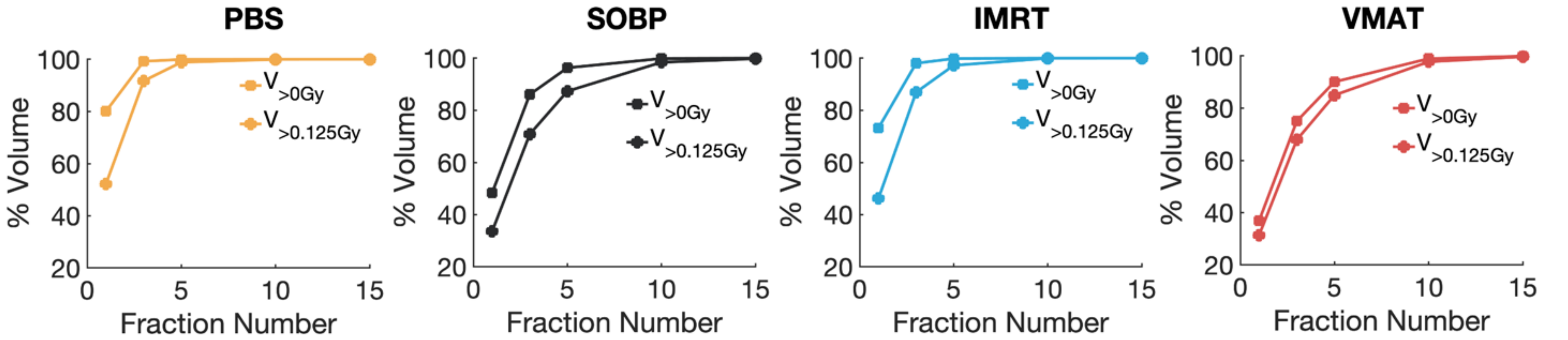
	Brain	Liver
Blood with dose > 0.0 Gy	6.0 %	9.2 %
Mean dose (Gy)	0.16 Gy	0.17 Gy
Max dose (Gy)	1.3 Gy	0.65 Gy

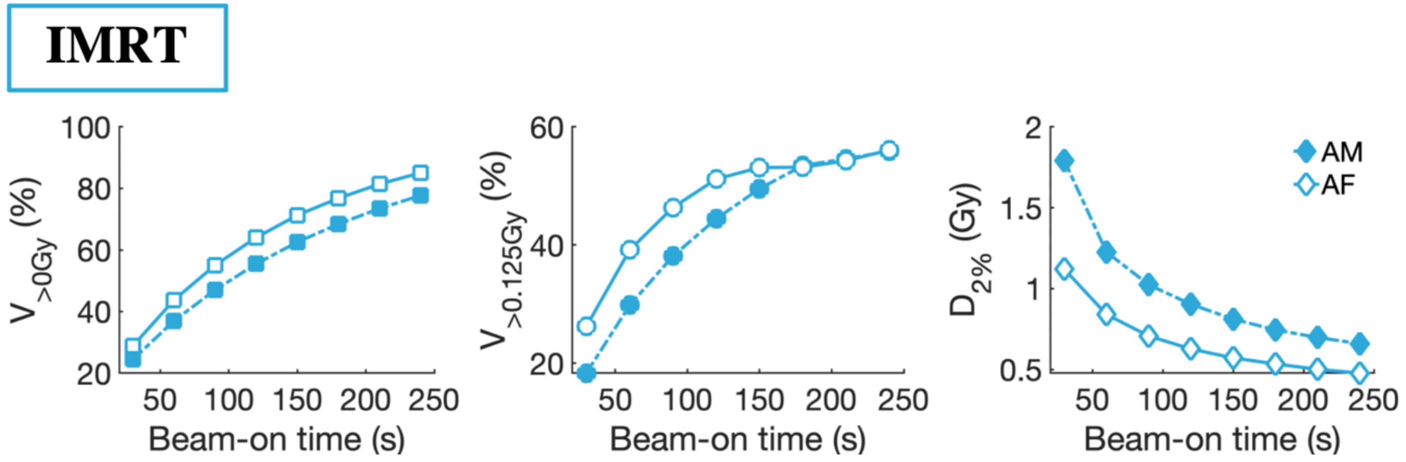
In 10 mins,
76% and 97% of BPs pass at least once through brain and liver
43% and 85% of BPs pass multiple times through brain and liver

Shin …, Paganetti, Grassberger: HEDOS - a computational tool to assess radiation dose to circulating blood cells during external beam radiotherapy based on whole-body blood flow simulations. Phys Med Biol 2021

Modeling dose to the blood - Results

Build-up of blood dose (6 patients)

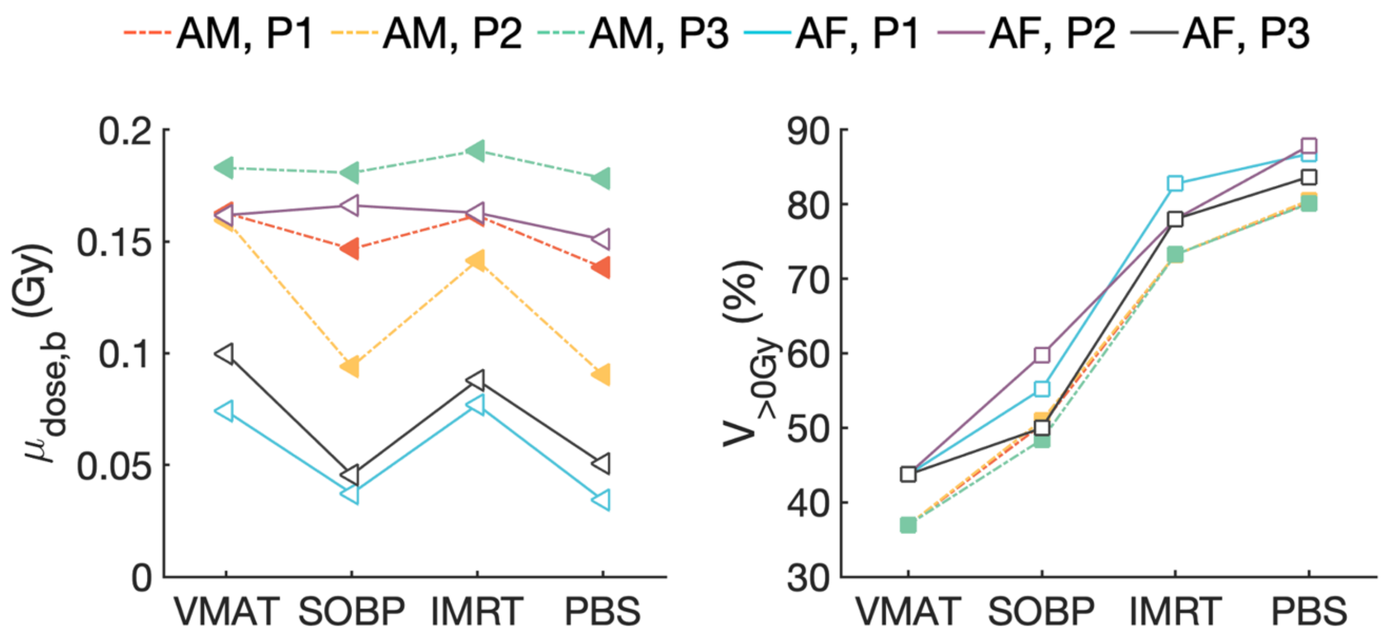




Xing, … Grassberger, Paganetti: A dynamic blood flow model to compute absorbed dose to circulating blood and lymphocytes in liver external beam radiotherapy. Phys Med Biol 2022

Modeling dose to the blood - Results

Actual delivery parameters
(6 patients)



Mean Blood Dose

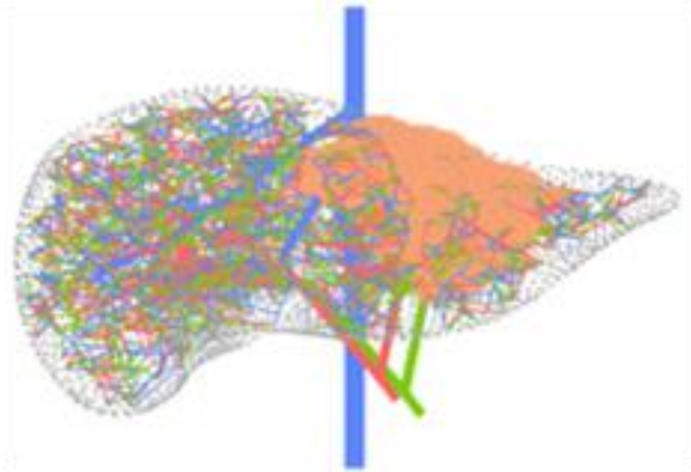
% Blood exposure

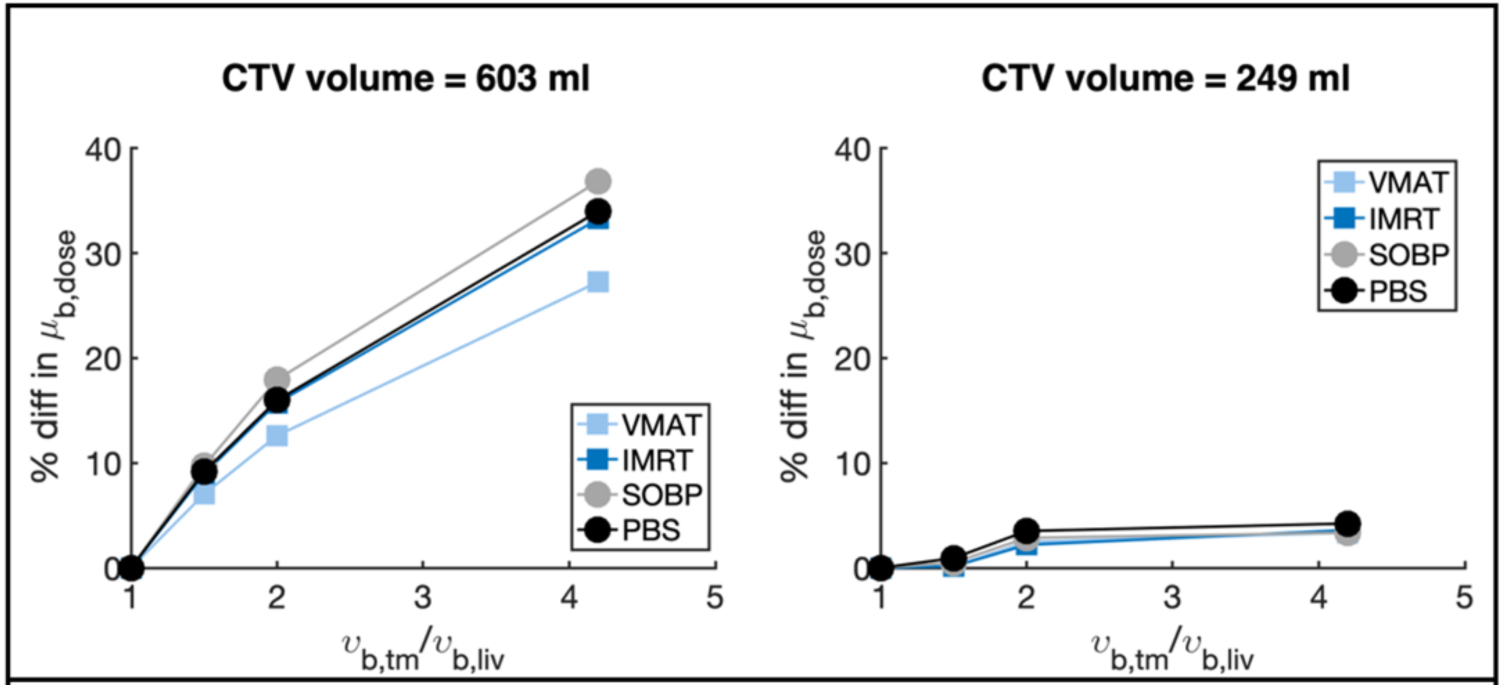
- Treatment time dependent tradeoff between low-dose to a large fraction of blood and high-dose to a small fraction of blood
- Delivery time is more important for understanding the dose to circulating blood than dose conformality (integral dose)

Xing, … Grassberger, Paganetti: A dynamic blood flow model to compute absorbed dose to circulating blood and lymphocytes in liver external beam radiotherapy. Phys Med Biol 2022

Modeling dose to the blood - Results

Tumor volume (increasing blood speed in the tumor)





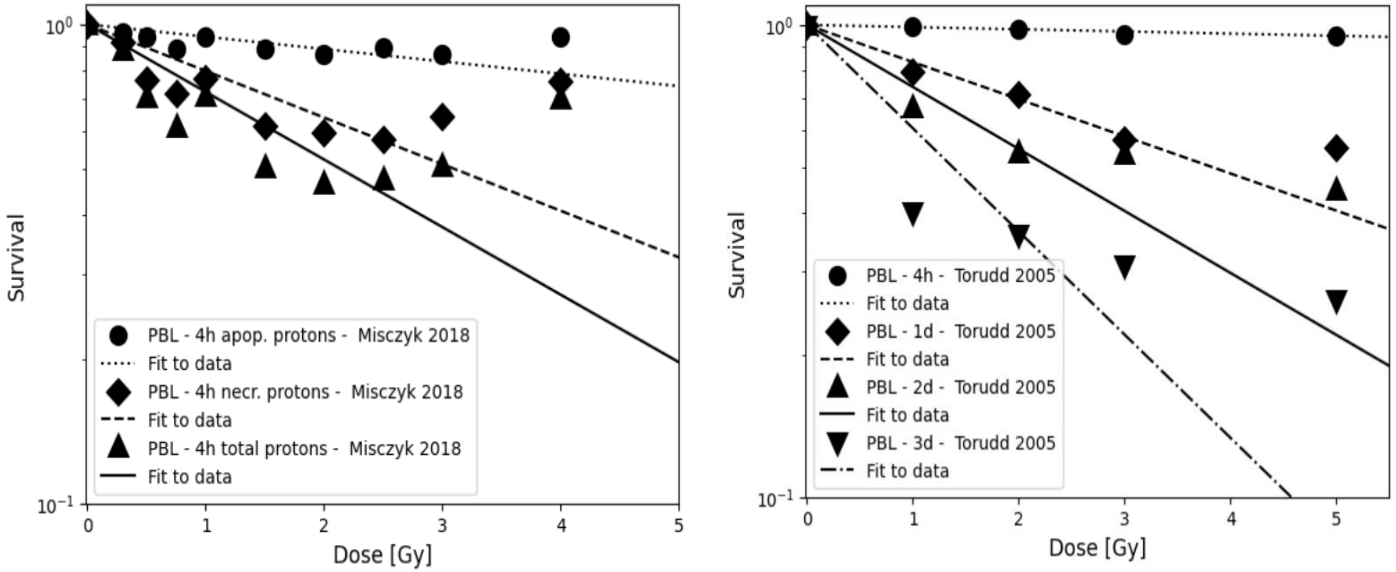
Increasing blood velocity ratio

Take-home messages

- Lymphopenia correlates with outcome
- Blood might have to be included as organ at risk in treatment planning decisions
- Dose to the blood (i.e. circulating lymphocytes) can not be estimated by solely considering integral dose
- Good estimates can be achieved using HEDOS (open source)
- For highly inhomogeneous dose distributions or organs, explicit vasculature models deformed to patient anatomy are required
- Is lymphopenia really caused by dose to the circulating lymphocytes?

- The radiosensitivity of lymphocyte sub-populations in lymphatic organs as well as the blood and tumor is unclear
- The difference between blood transit times and lymphocyte transit needs to be better understood

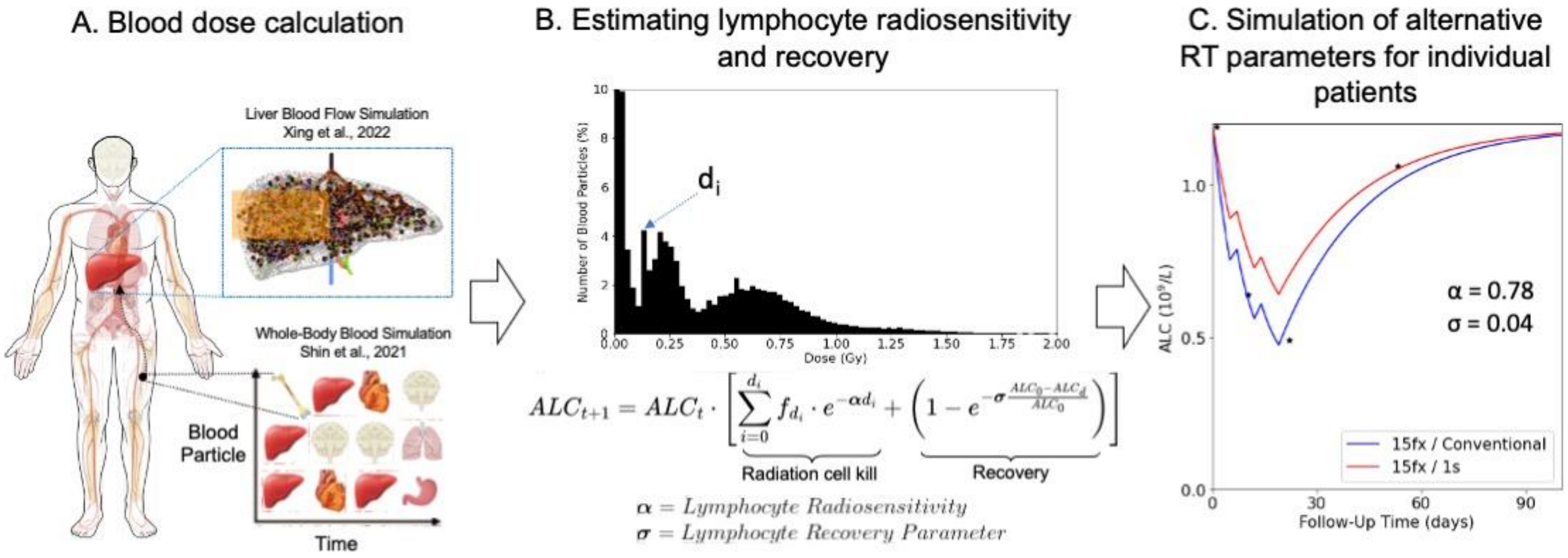
Modeling dose to lymphocytes



- radiosensitivity of lymphocytes is in the same order of magnitude as normal fibroblasts
- B cells appear to be more radiosensitive than T cells, and NK cells appear to be the most resistant.

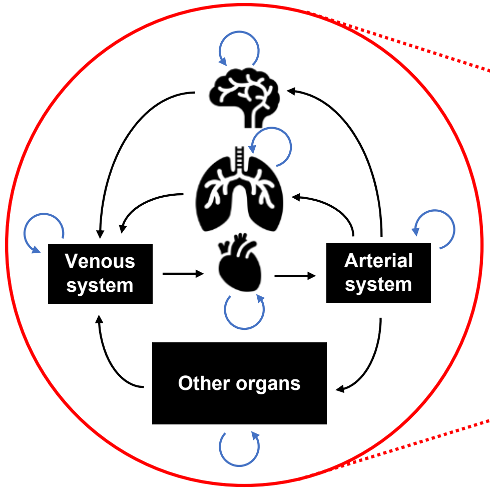
Paganetti H: A review on lymphocyte radiosensitivity and its impact on radiotherapy. Frontiers in Oncology 2023

Modeling dose to lymphocytes

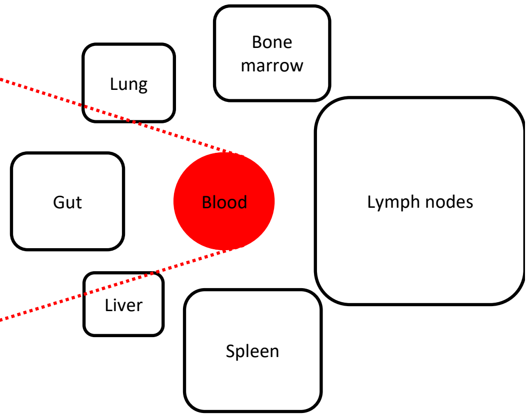


McCullum L;…; Bolch WE; Paganetti H and Grassberger C. Int J Radiat Oncol Biol Phys. 2023

Modeling dose to lymphocytes



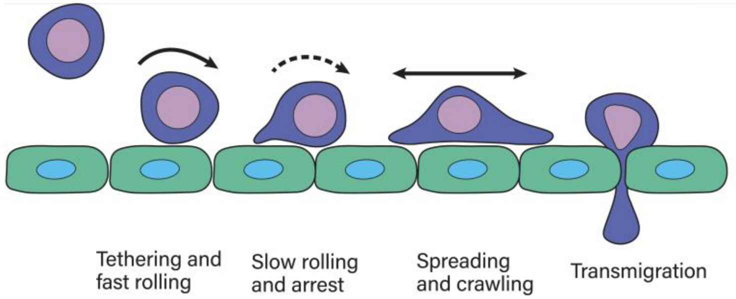
A. Blood flow model



B. Lymphocyte recirculation model

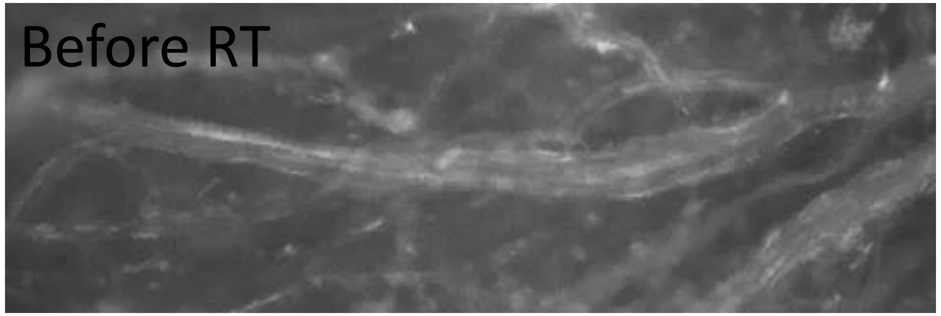
Lymphocytes traverse capillary <u>much</u> slower than blood due to

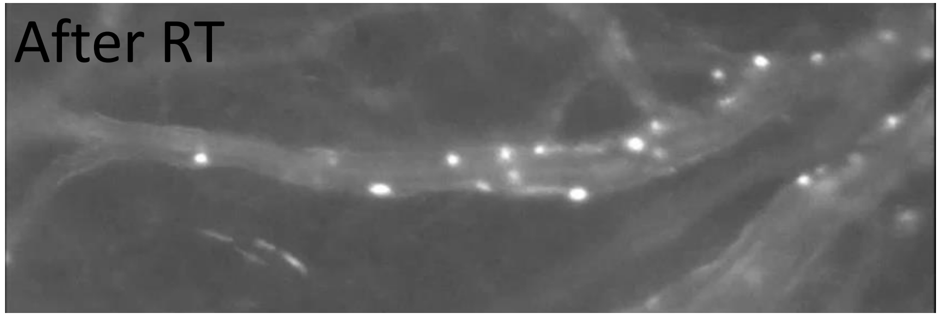
1. Time required to deform to squeeze through
2. Process of adhesion to endothelial cells



Guenther, C., 2022. *Frontiers in Immunology*.

RT increases adherence of lymphocytes to endothelial cells





Weijerathne, H. et al. 2021. *Radiother Oncol*.

Team Paganetti Within Physics Research









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Nadya Shusharina

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Hoyeon Lee
Isaac Meyer
Nils Peters
Carlos Huesa
Wook-Geun Shin
Qianyi Huang
Victor Valladolid (starting Nov 15)
Jesus Bosque (starting Dec 1)
Nicolo Cogno (starting Jan 1)

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