A SPATIO-TEMPORALLY RESOLVED HEPATIC PHARMACOKINETICS MODEL

Lars Ole Schwen[1], Markus Krauss[2], Felix Gremse[3], Fabian Kiessling[3], Tobias Preusser[1], Lars Küpfer[2]

[1] Fraunhofer MEVIS, Bremen
[2] Bayer Technology Services, Leverkusen
[3] University Hospital Aachen

VLN Retreat

Hünfeld, 2012-11-28

virtual liver network

Fraunhofer MEVIS

Outline

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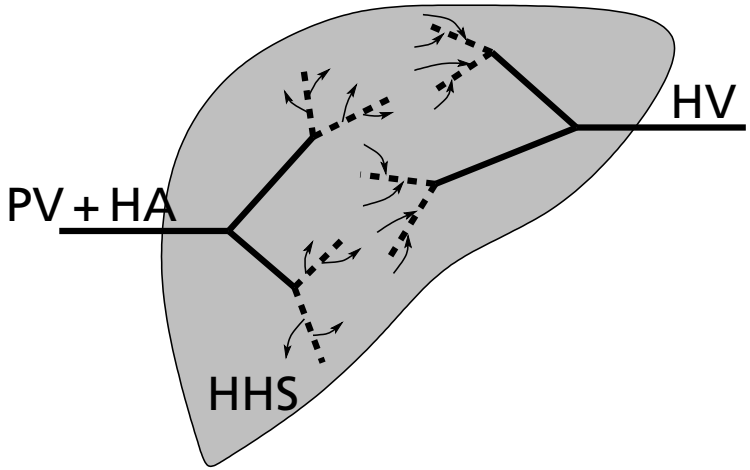
3. Outlook

1. Perfusion Model

Contents

1. Perfusion Model

Model Overview



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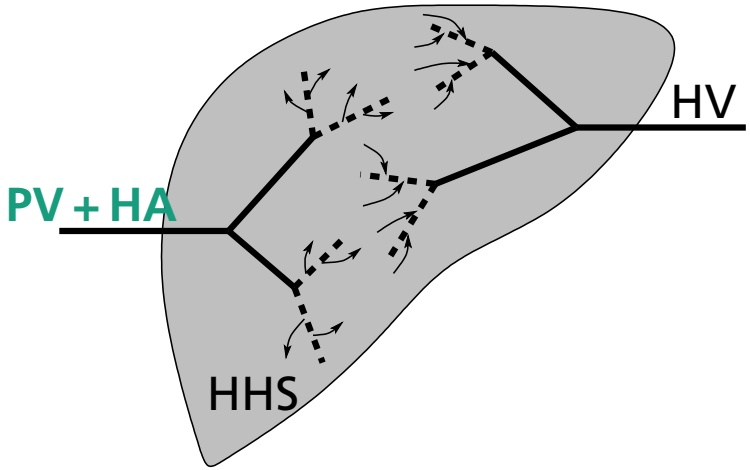

- supplying vascular system PV + HA

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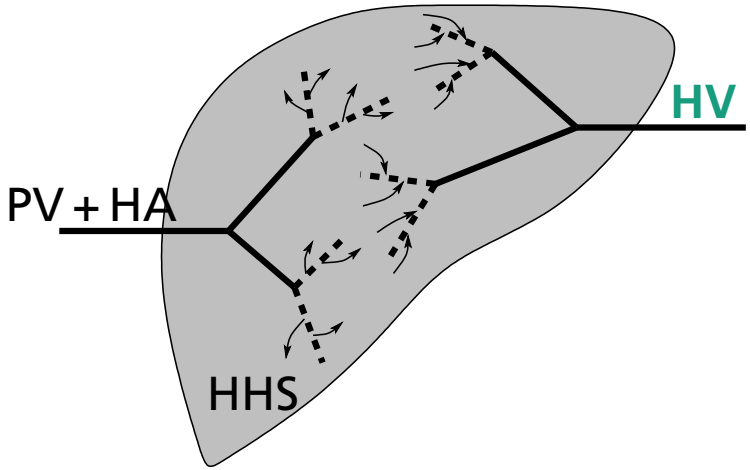

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- draining vascular system HV

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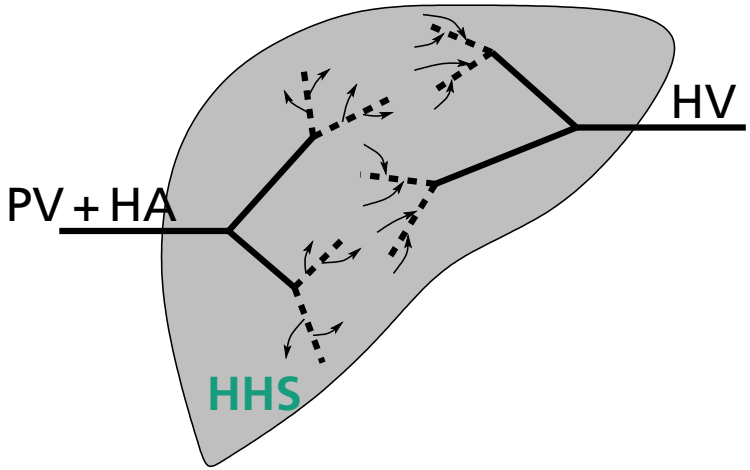
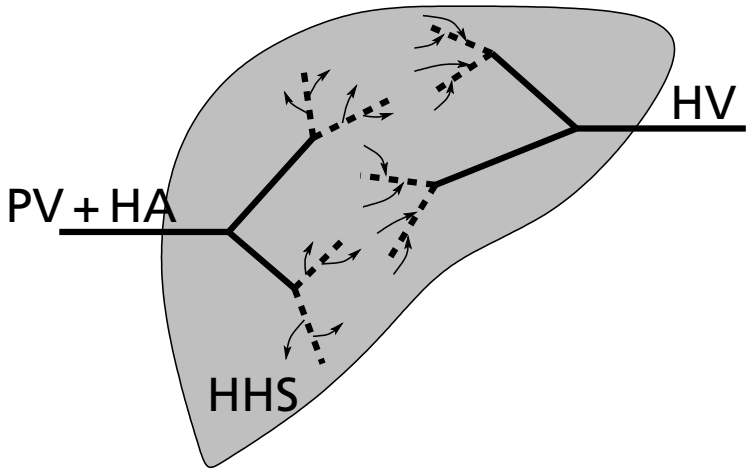


- supplying vascular system PV + HA
- draining vascular system HV
- homogenized hepatic space HHS = $HHS_{sin} + HHS_{cell} + HHS_{rest}$
  - sinusoidal volume fraction (blood flow)
  - cellular volume fraction (metabolization)
  - remaining volume

1. Perfusion Model

Blood Flow



- transport through PV + HA

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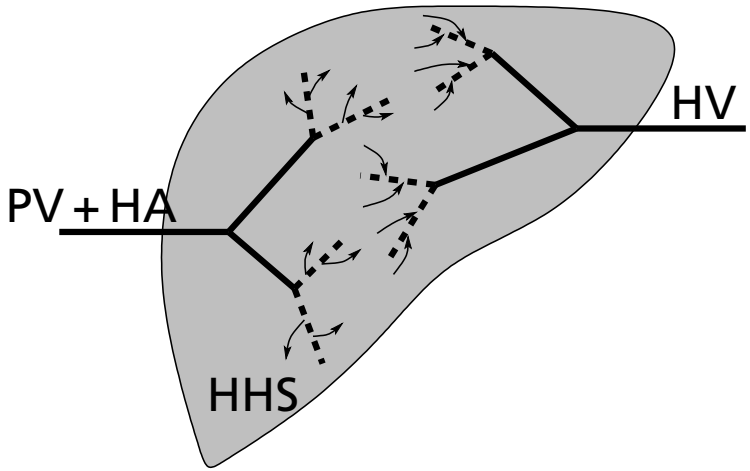

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- outflow from terminal edges PV + HA → HHS_{sin}

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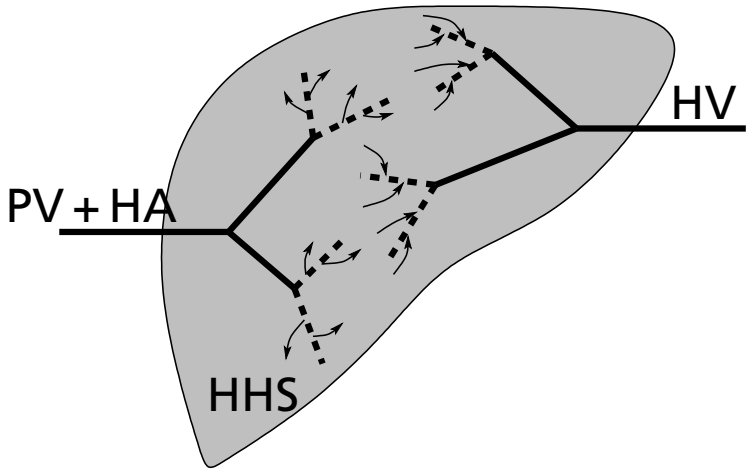
Blood Flow



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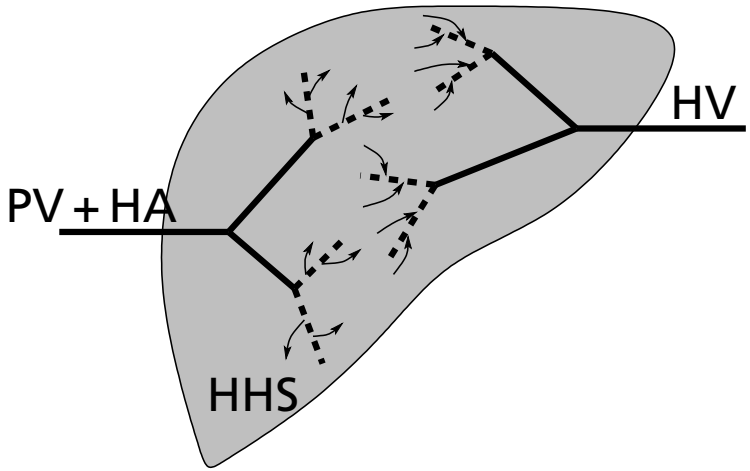

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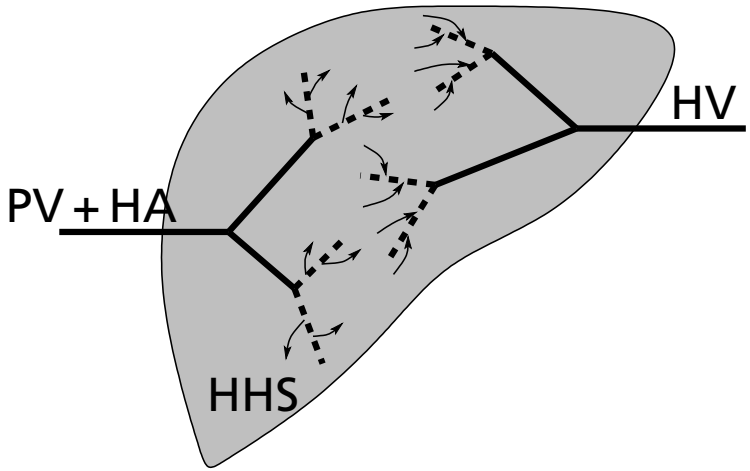

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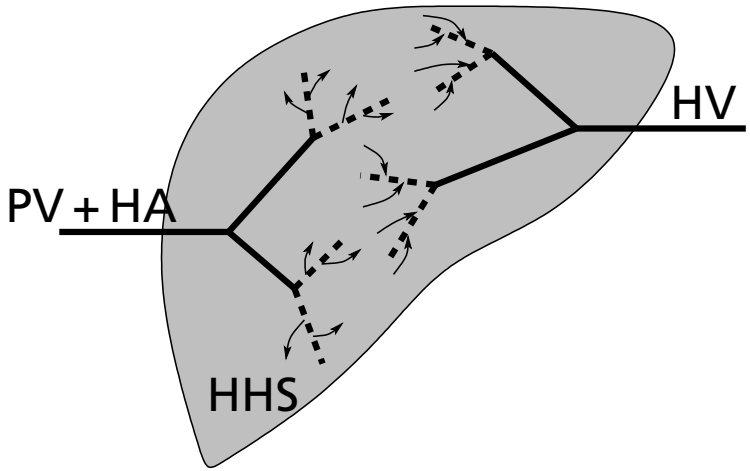

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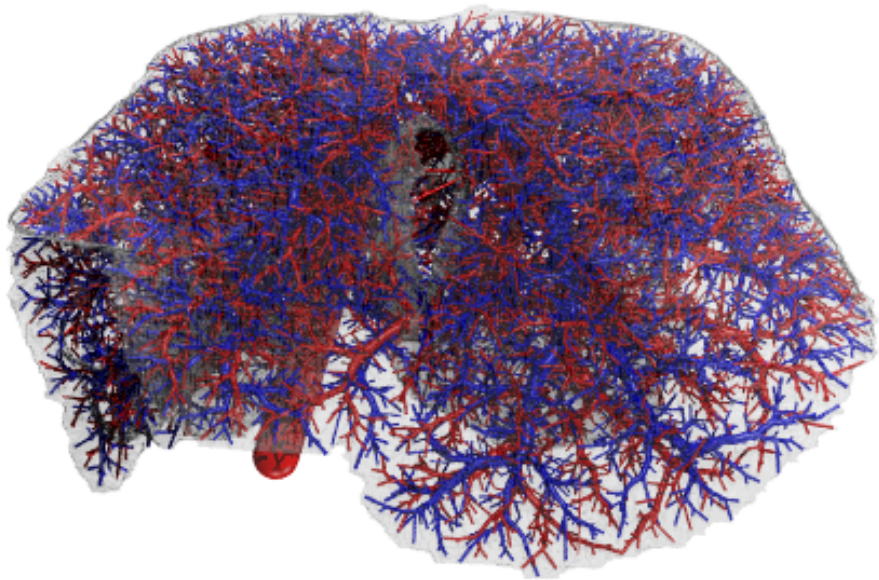
Transport described by velocities $v(x)$, constant in time.

1. Perfusion Model

Target Resolution

Mouse liver vascular systems down to lobular scale



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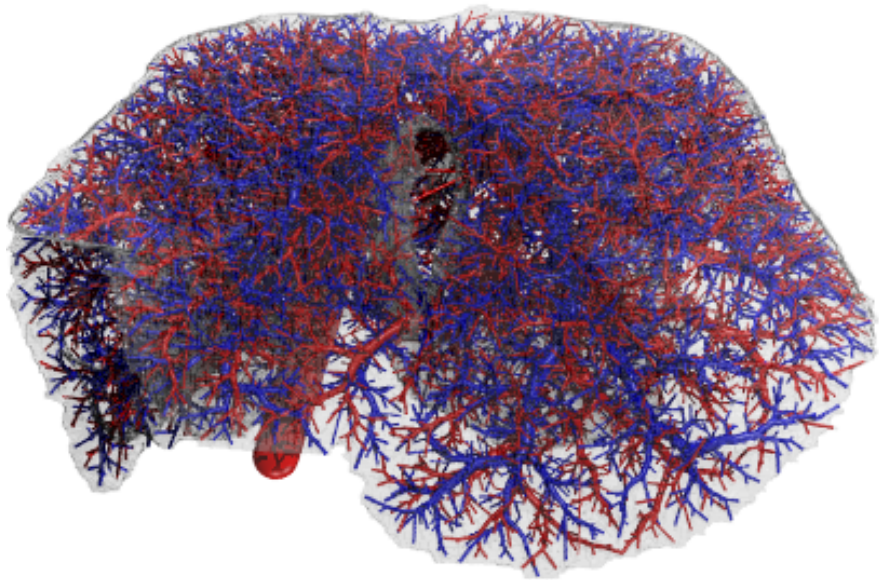

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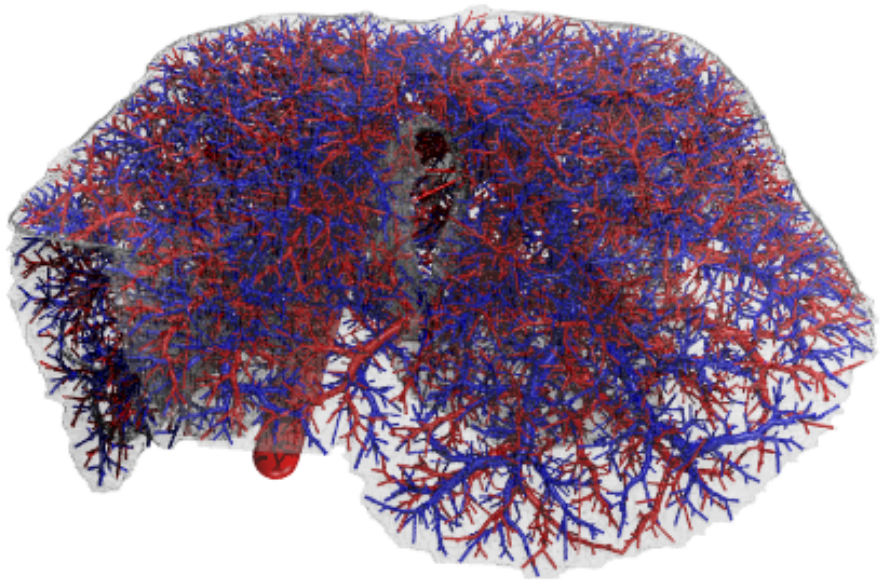
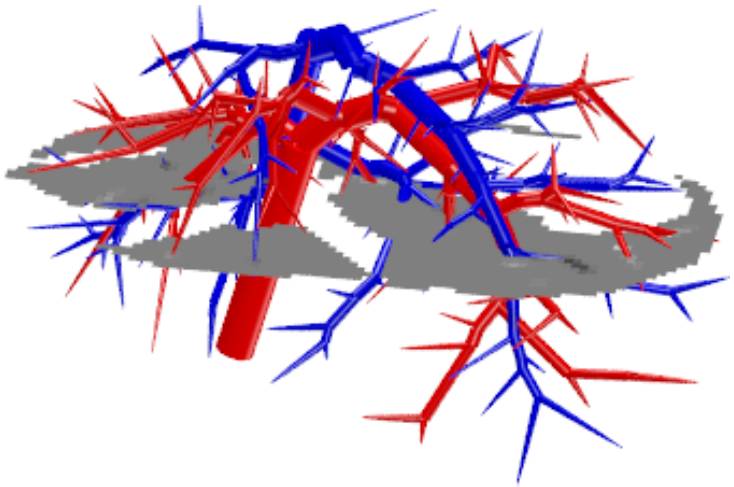
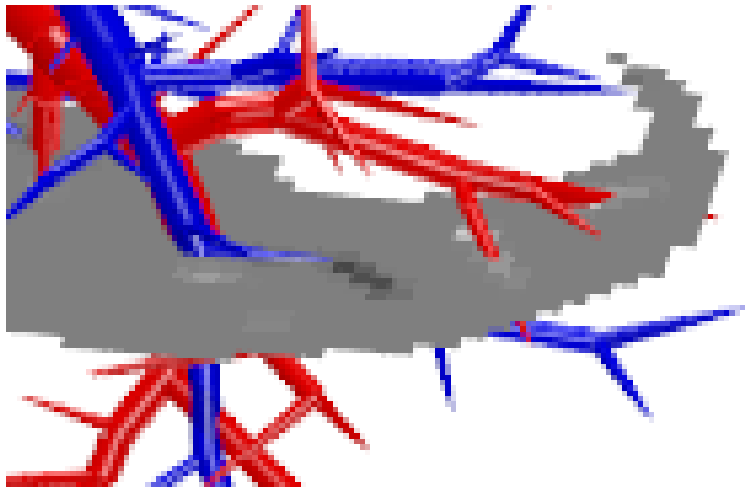


we can’t see anything here
…so let’s consider a coarser tree

1. Perfusion Model

Velocity Computation I – Flow Sources





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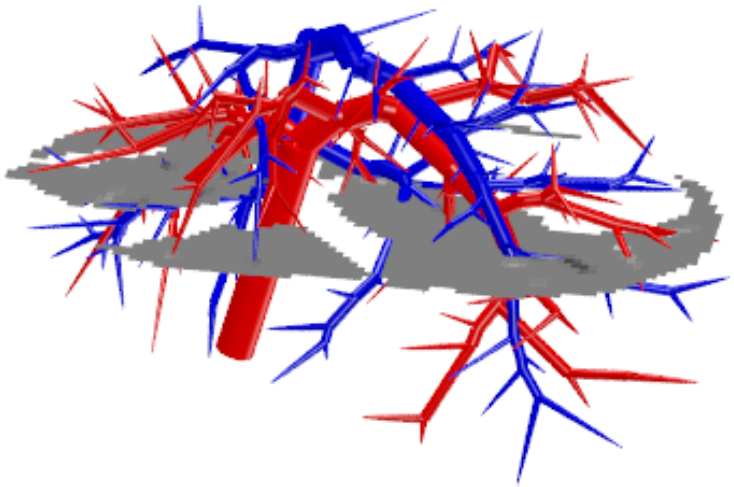

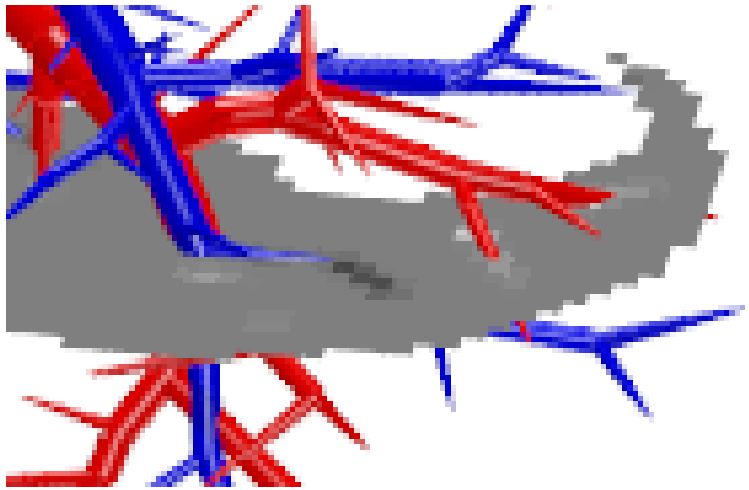

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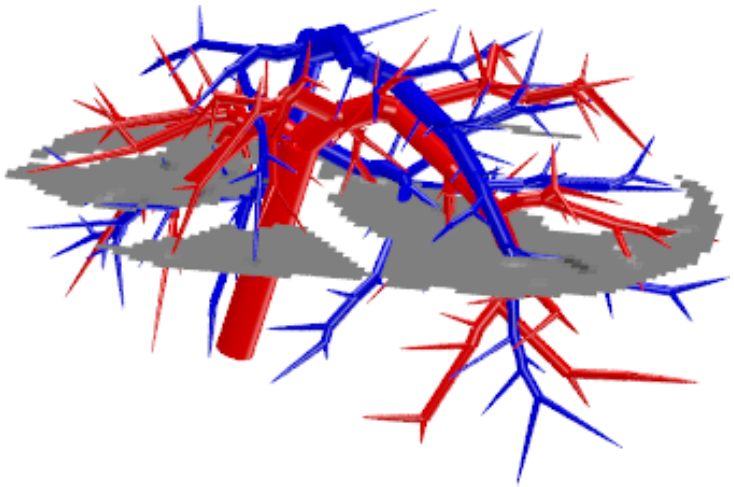

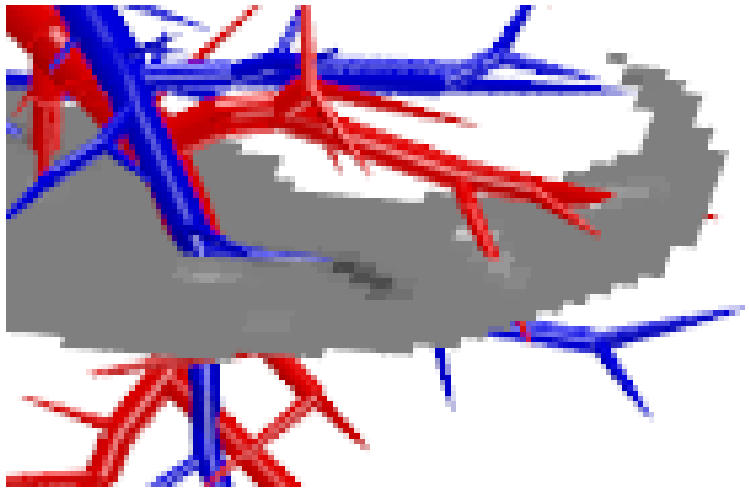

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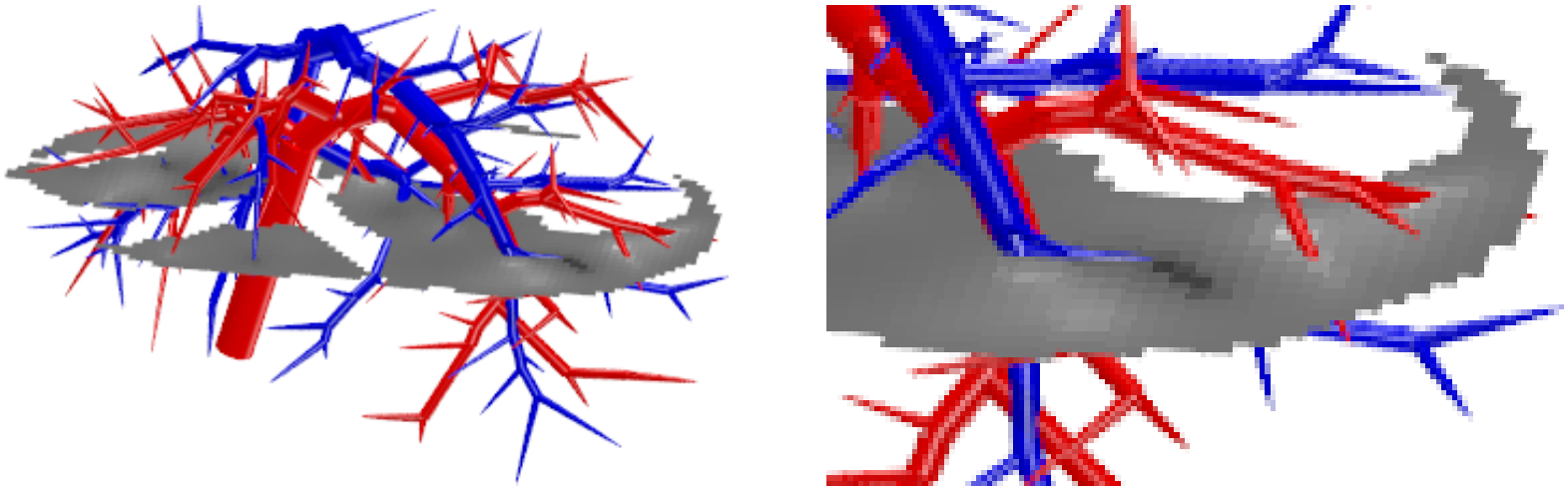
this translates to a PDE

$$-\mathrm{div}(\alpha(x)\nabla p(x)) = \text{1D flow sources at terminal edges}$$

1. Perfusion Model

Velocity Computation II – Relative Pressures



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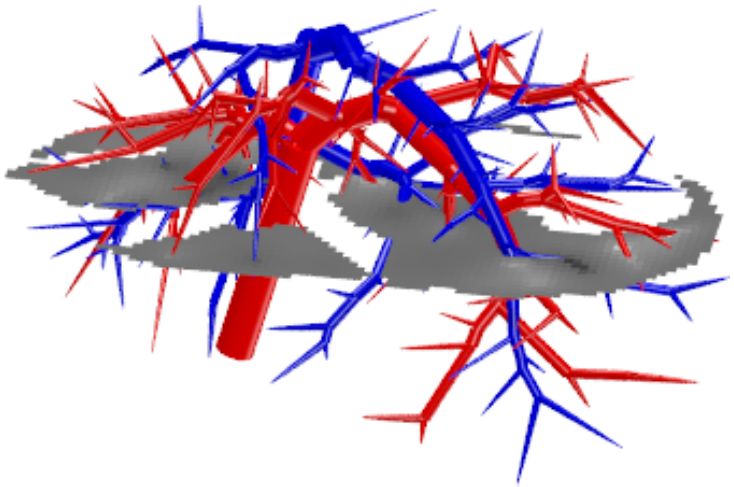

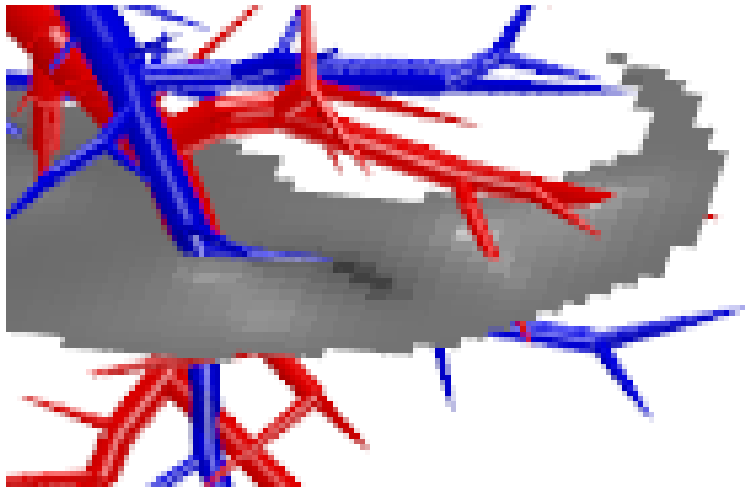

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- velocity along pressure gradient (Darcy)

$$v(x) = \frac{\alpha(x)}{n(x)} \nabla p(x)$$

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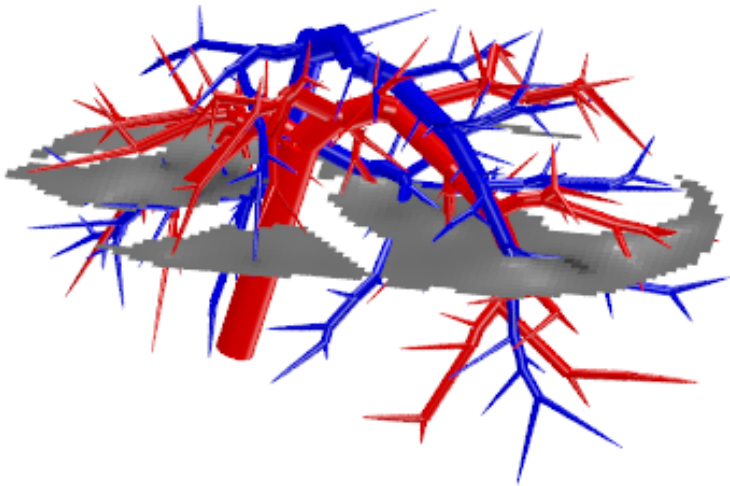

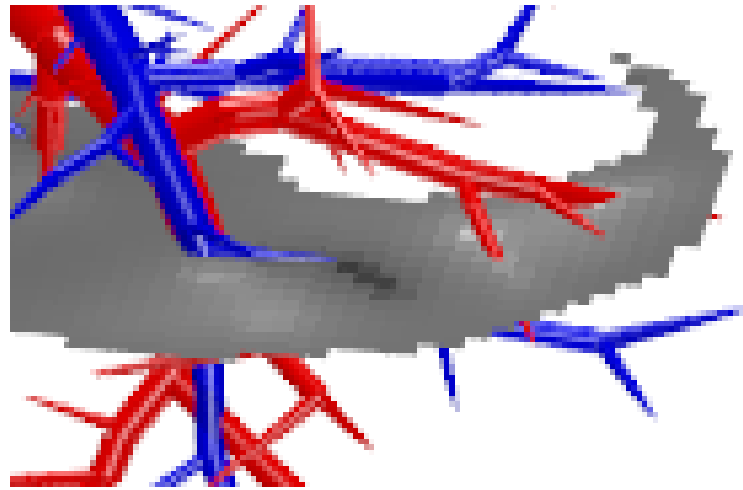

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- velocity is directed PV + HA outflows → HV inflows

2. Metabolization Model

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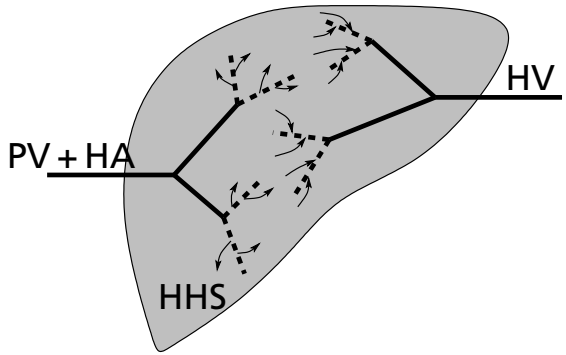

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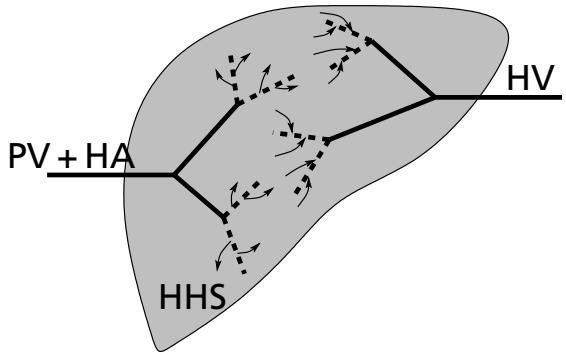

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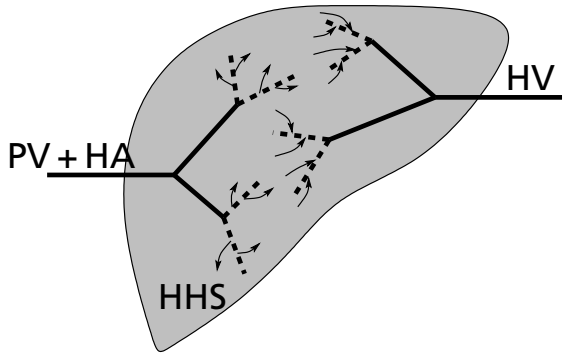

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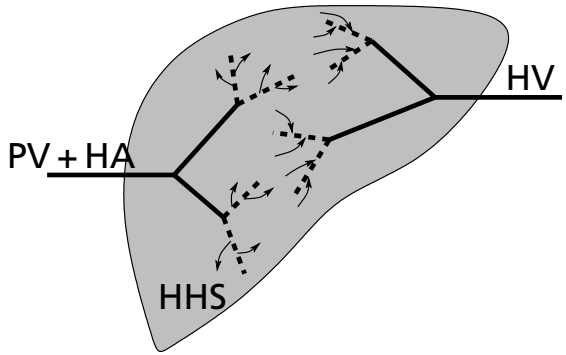

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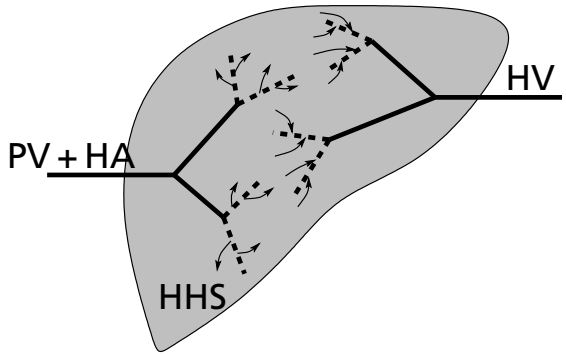

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- one ODE per discretization point in HHS

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Simplest Example: Macromolecular Contrast Agent (Bolus)

- only transported with blood flow
- no transport $HHS_{sin} \longleftrightarrow HHS_{cell}$

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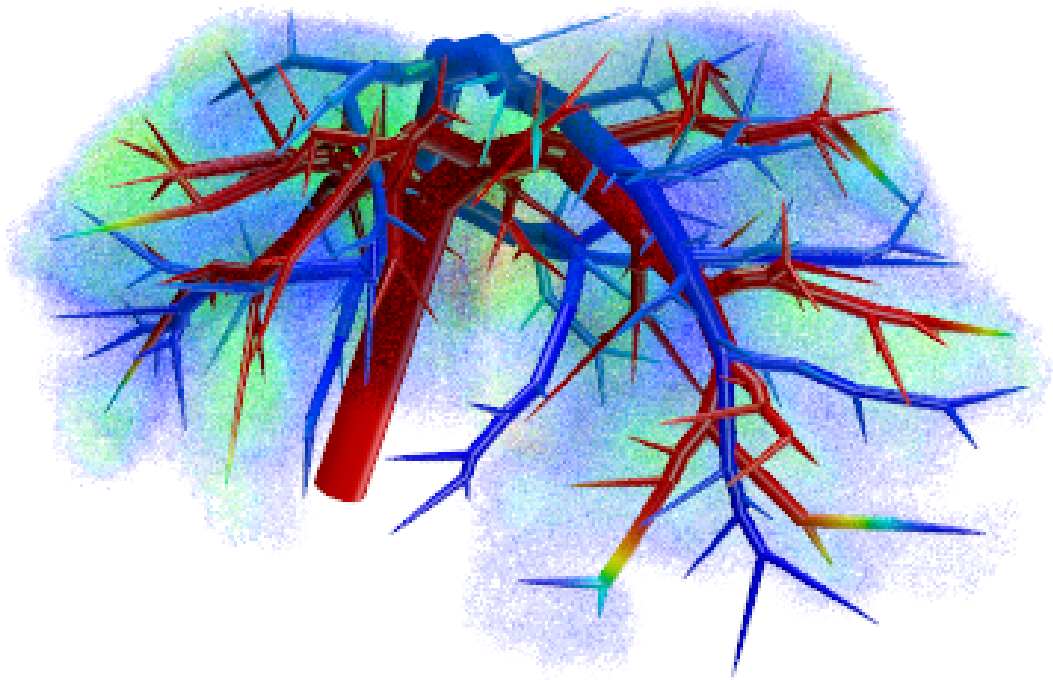
→ Video



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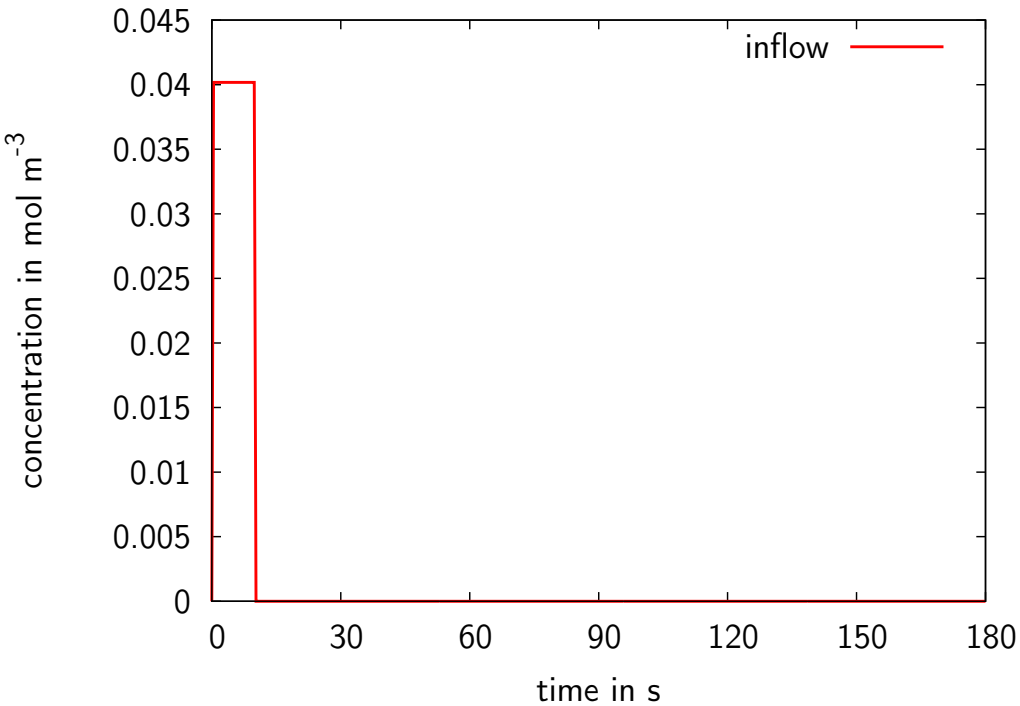

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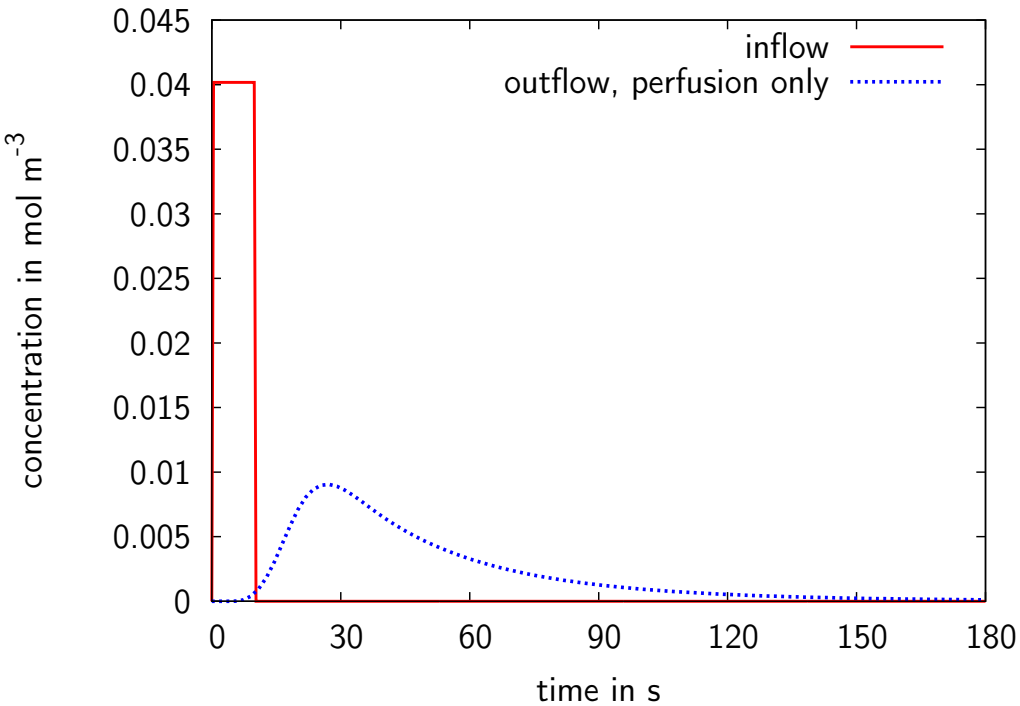

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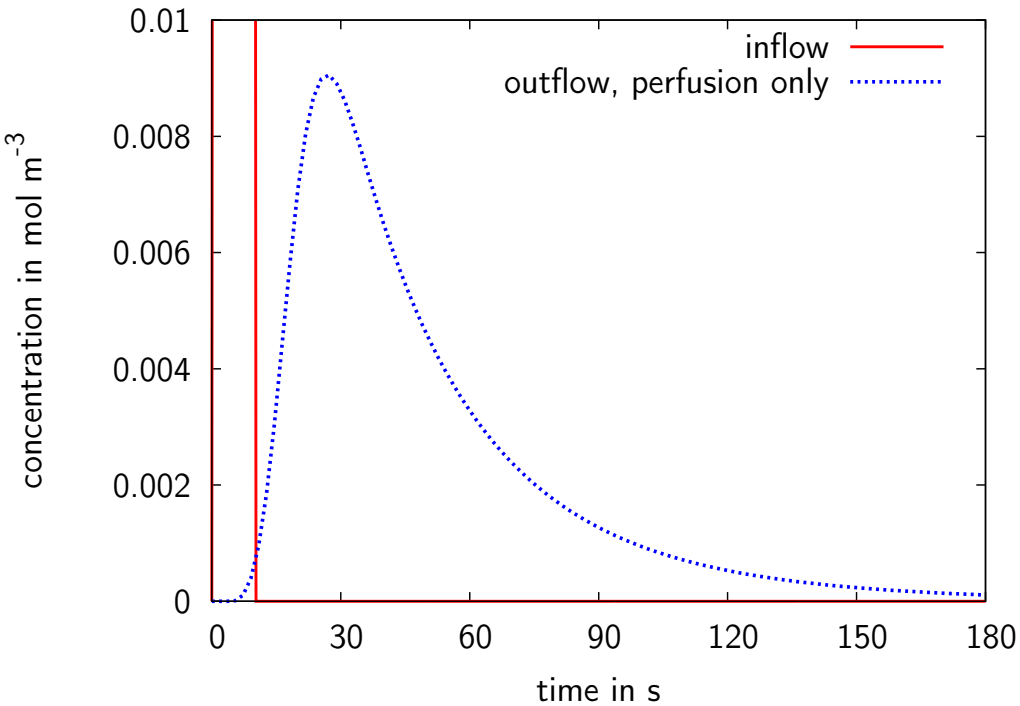

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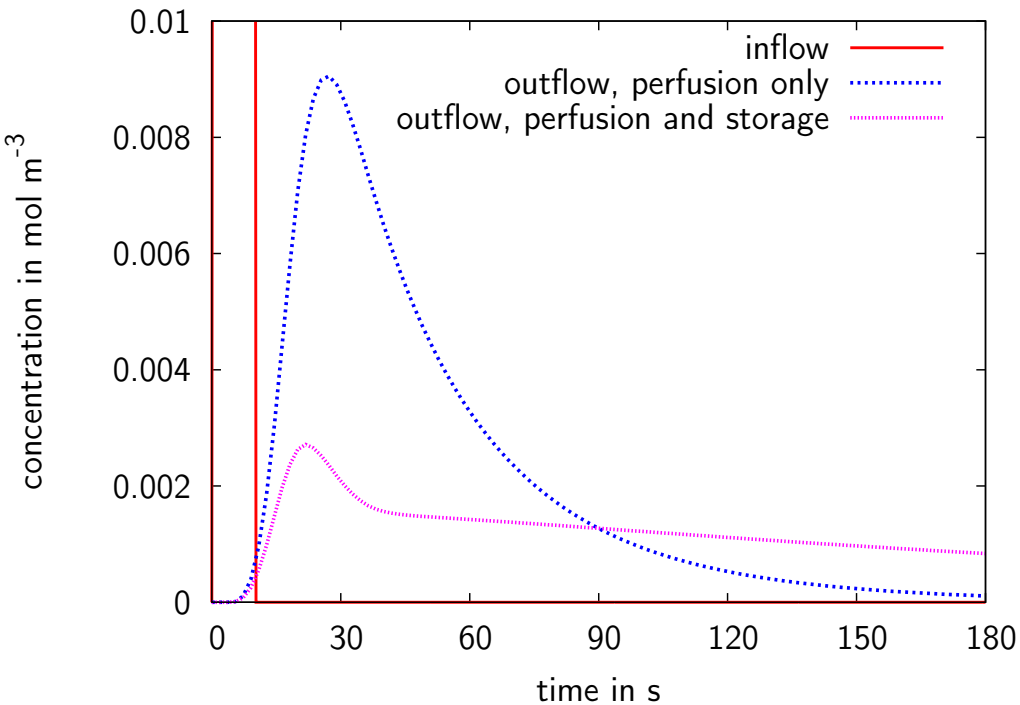

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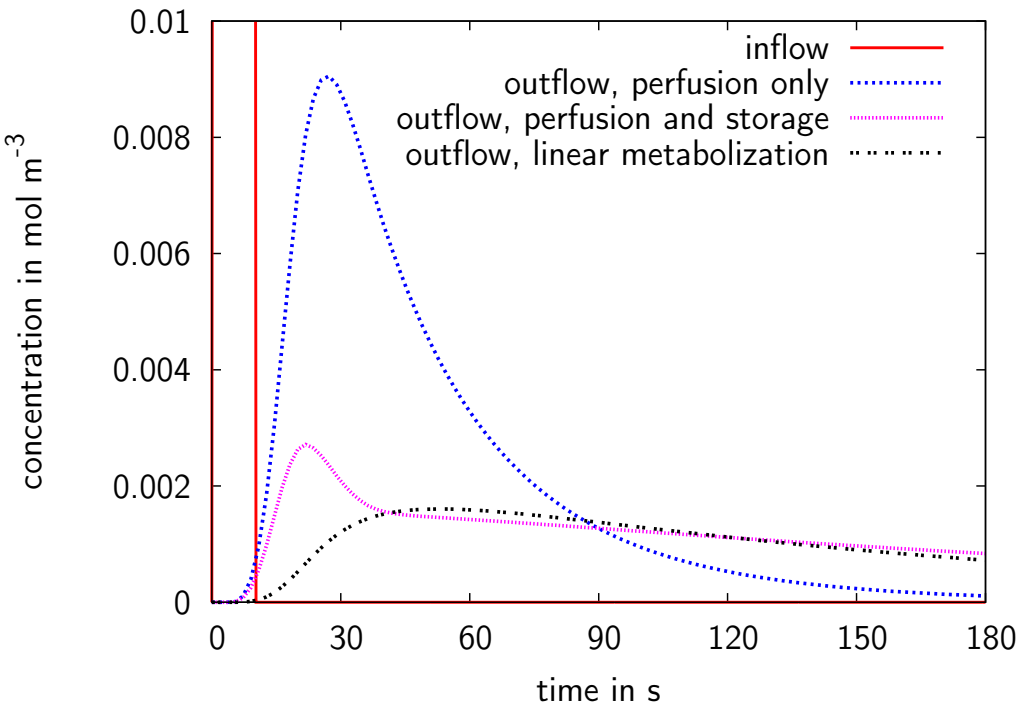

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Complicated Example: “Glycolysis” Model

[BioModels Database # 42]

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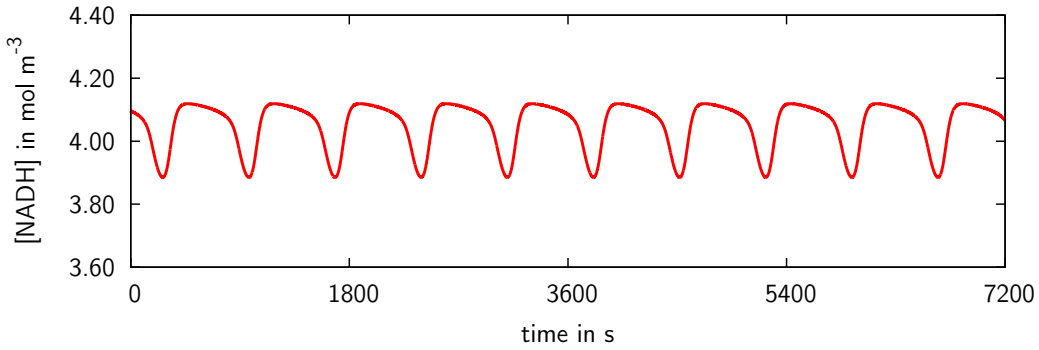
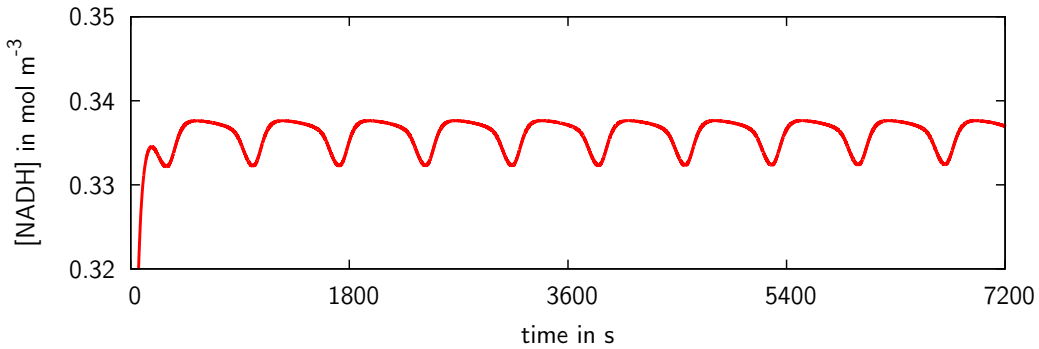


outflow from bioreactor model



PV outflow our model

3. Outlook

Contents

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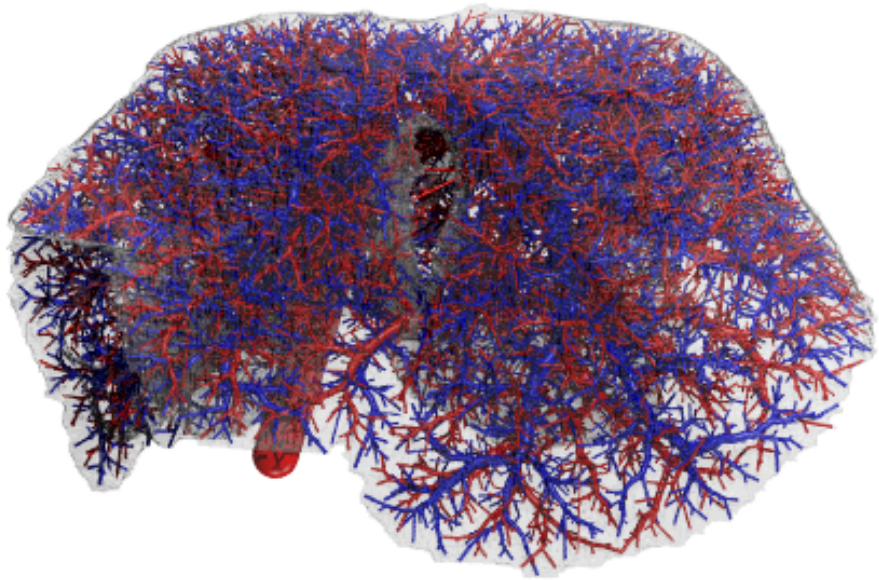
Required Input

- vascular geometry



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- vascular geometry
- total perfusion
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- inflow concentrations of considered substances
- ODE (form and parameters) describing metabolization

3. Outlook

Challenges

- proper implementation

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- experimental input data

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- efficient implementation

  ODE needs to be solved for 100 000s of points
- experimental input data

  but that is your (the experimentalist's) job ☺

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After we've finished a first implementation and publication …

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- better geometric model of vascular structures

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- other metabolization reactions

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- other metabolization reactions
- validation

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References

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