SPATIALLY RESOLVED SIMULATION OF GLUCOSE METABOLISM IN THE HUMAN LIVER

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5th European Conference on Computational Mechanics (ECCM V)
Barcelona, 2014-07-21

virtual liver network

Fraunhofer MEVIS

Outline

1. Motivation

2. Three-Scale Model
   - Model
   - Results

3. Four-Scale Model
   - Model
   - Results

4. Outlook

1. Motivation

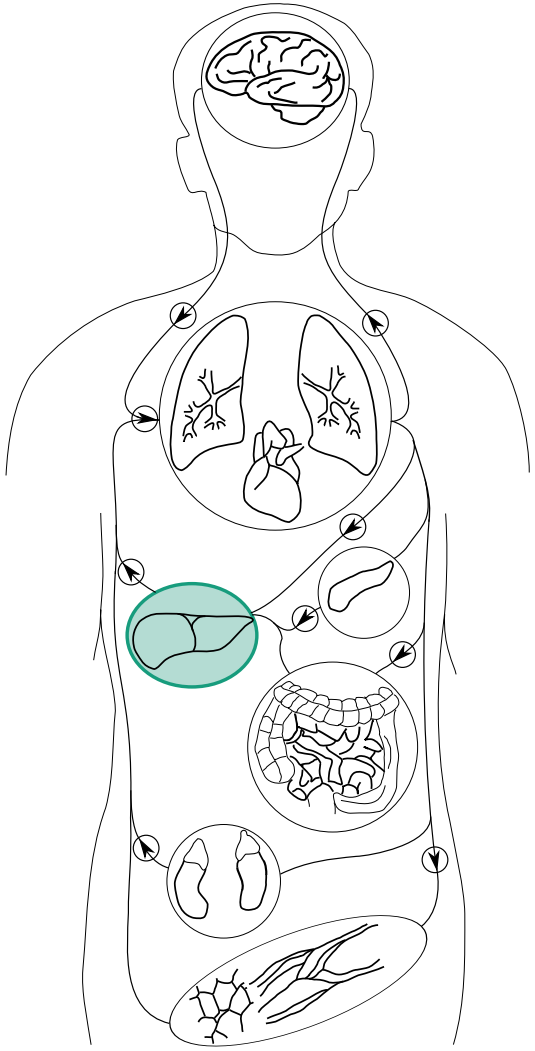
Contents

1. Motivation

Introduction: The Liver

Tasks (among others)

- metabolism
- detoxification
- homeostasis (regulation of blood glucose levels)



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http://upload.wikimedia.org/wikipedia/en/2/22/WholeBody_wiki.svg

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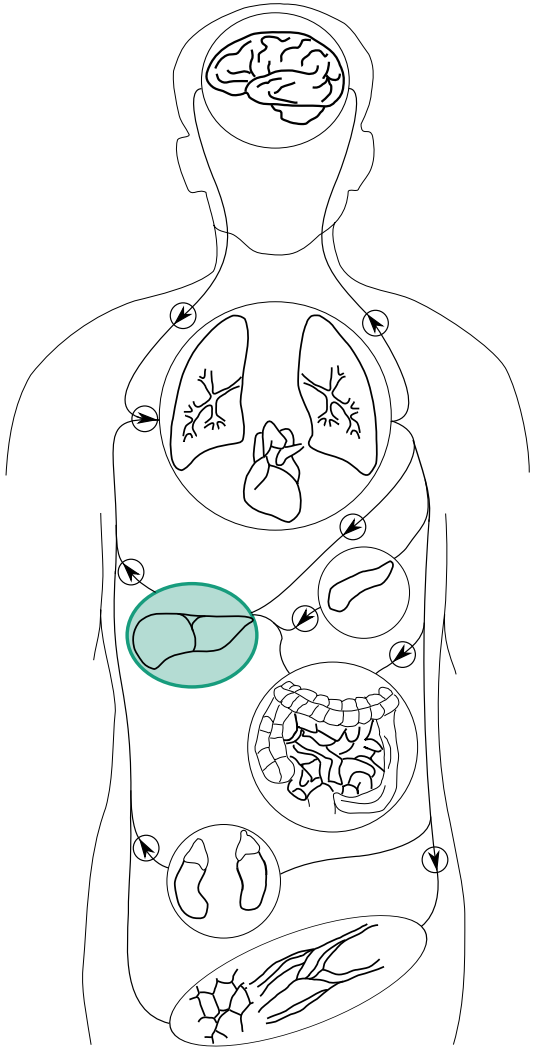
- vascular systems for
  - blood supply
  - drainage



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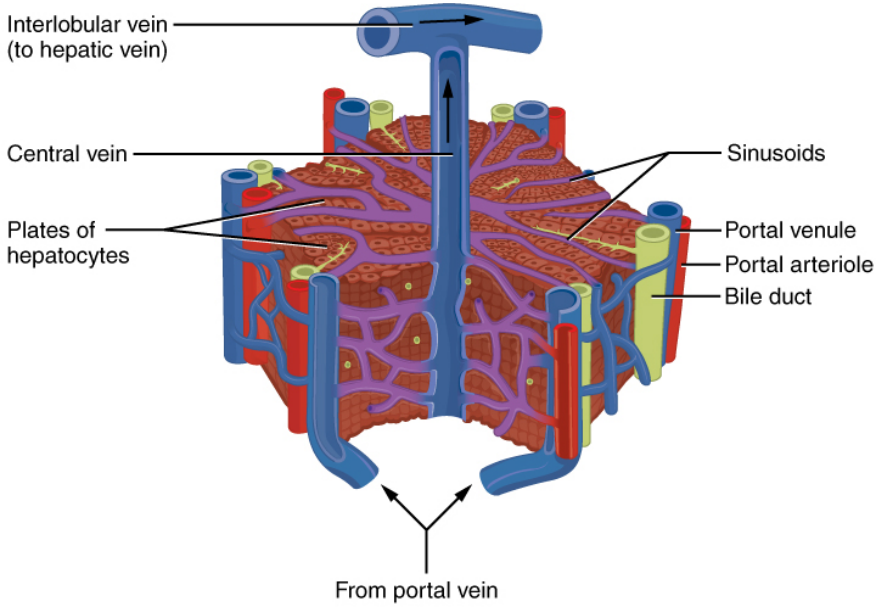

adapted from OpenStax College: Anatomy & Physiology
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1. Motivation

Introduction: The Liver

Tasks (among others)

- metabolism
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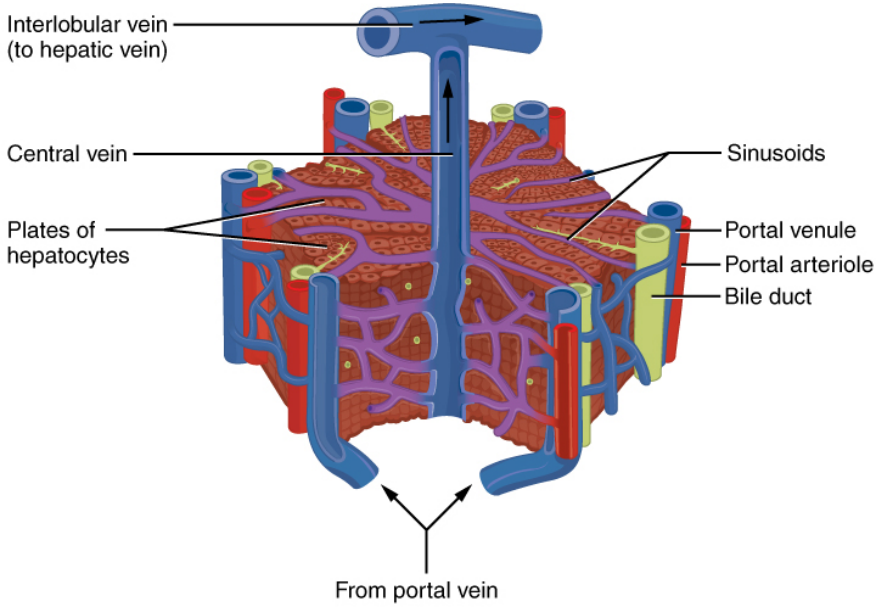
Structure

- vascular systems for
  - blood supply
  - drainage
- lobuli as functional units hepatocytes organized along sinusoids
- not necessarily homogeneous



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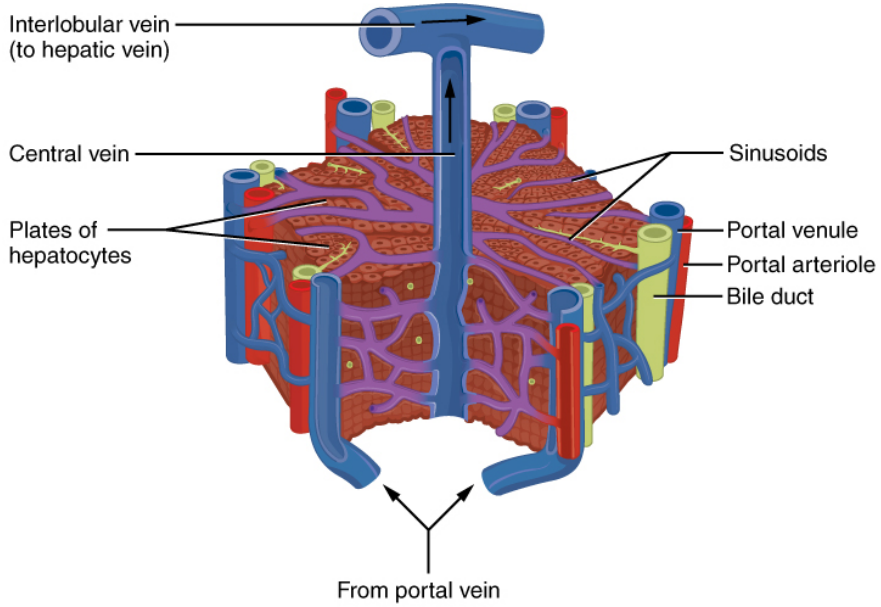
1. Motivation

Inhomogeneity

Mechanisms

- concentration gradients
- cell variability
- pathologies



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1. Motivation

Inhomogeneity

Mechanisms

- concentration gradients
- cell variability
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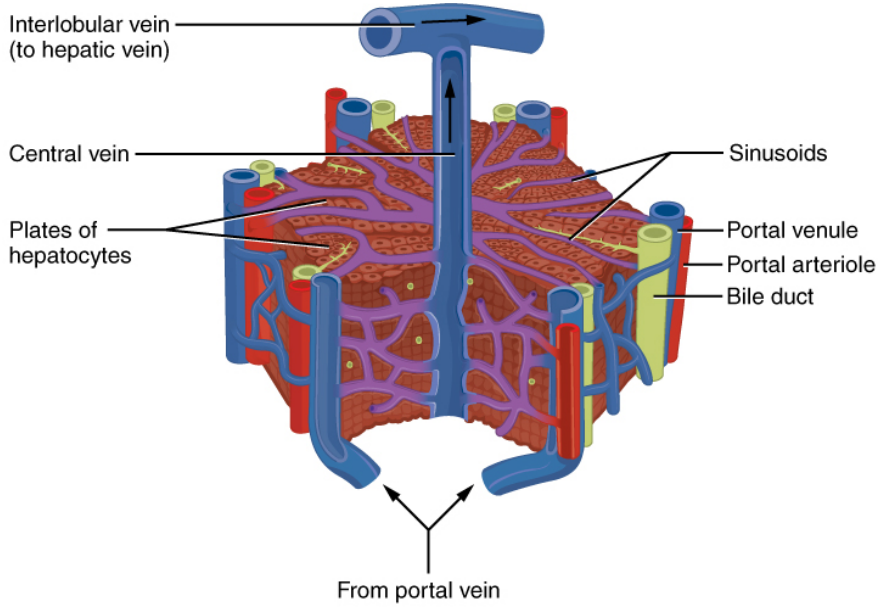
Scales

- zonation within lobuli (along sinusoids)
- inhomogeneity across organ



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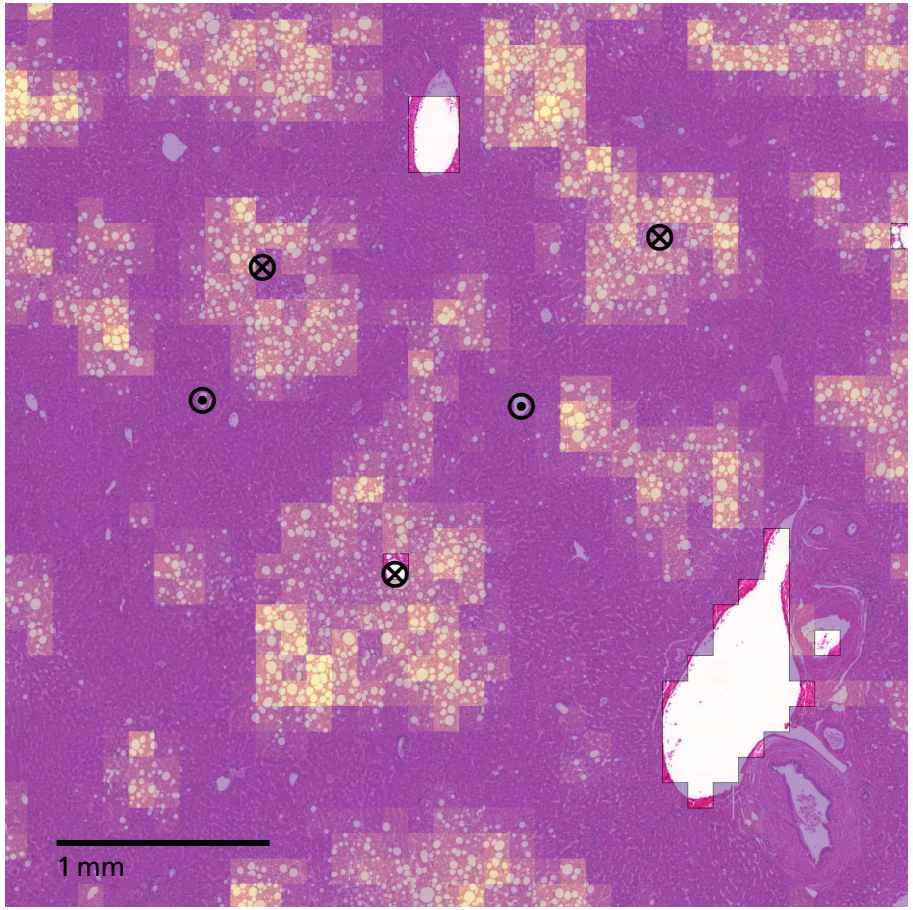
1. Motivation

Inhomogeneity Example



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⊗ central veins
⊙ portal fields (selection)

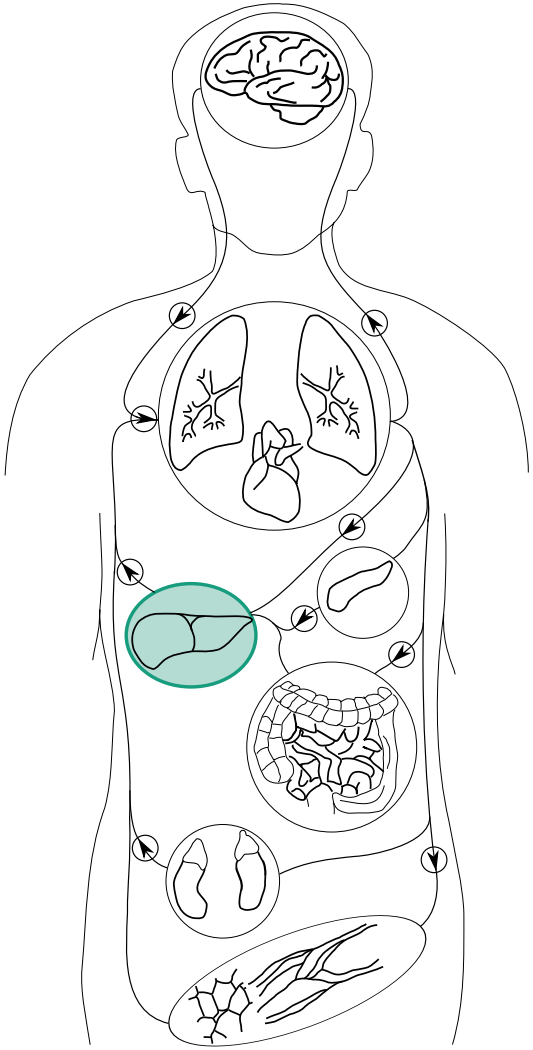
pericentral zonation of steatosis in a human liver

1. Motivation

Two-Scale Pharmacokinetics Models

Compartment models

- few “well stirred” compartments per organ
  - no spatial resolution
  - single ODE per organ
- mass flow between organs
- cannot reflect spatial inhomogeneity



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2. Three-Scale Model

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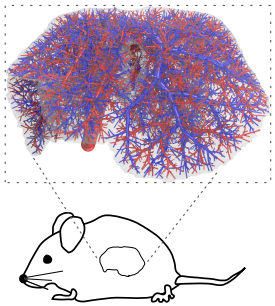
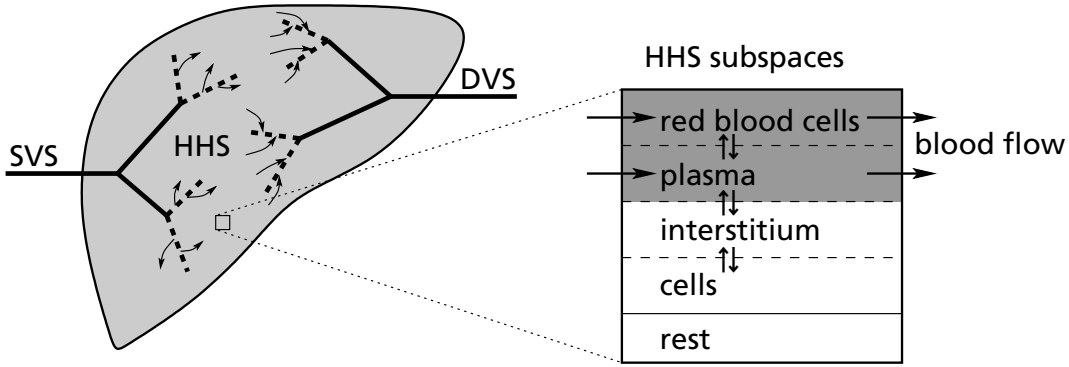
Model Structure

Three Scales

- organism
- organ
- cell





[Schwen et al., PLoS Comp. Biol. 10(3), 2014]

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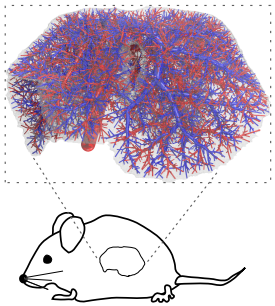

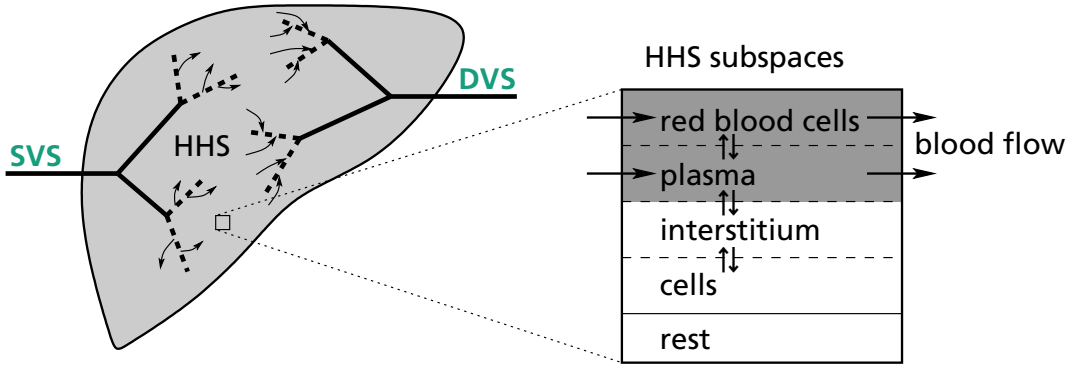

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Processes

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  - blood flow (1D advection)

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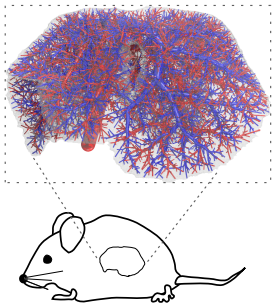

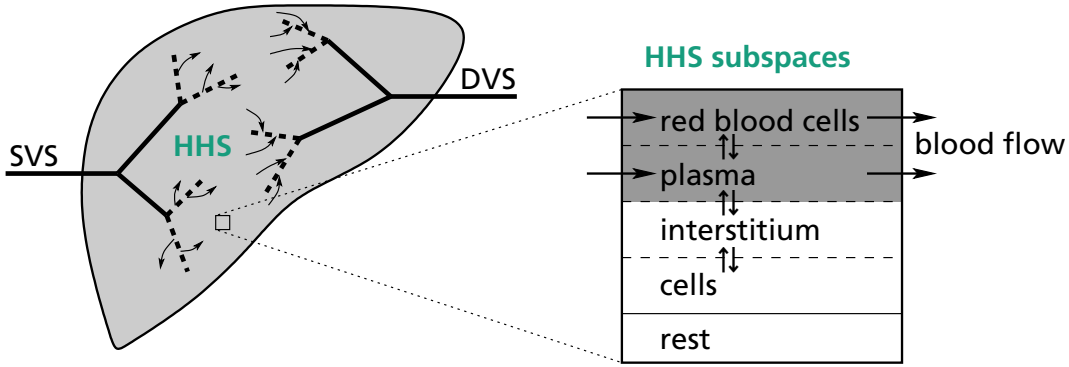

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Processes

- flow through supplying/draining vascular system
  - blood flow (1D advection)
- homogenized hepatic space HHS
  (multi-phase, porous medium representation of “in-between”)
  - blood flow (3D advection)
  - exchange and metabolism (pointwise reaction/ODE)

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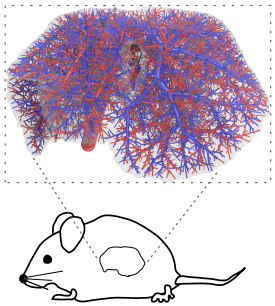

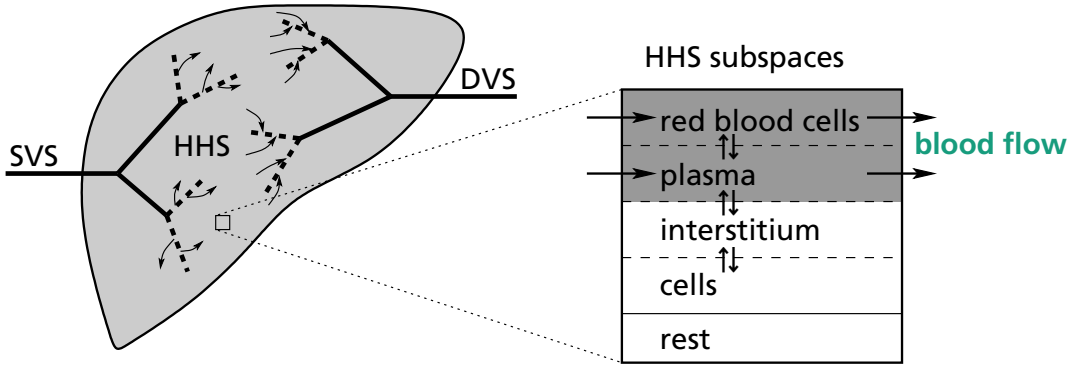

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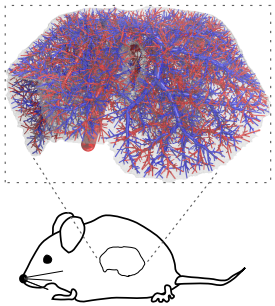

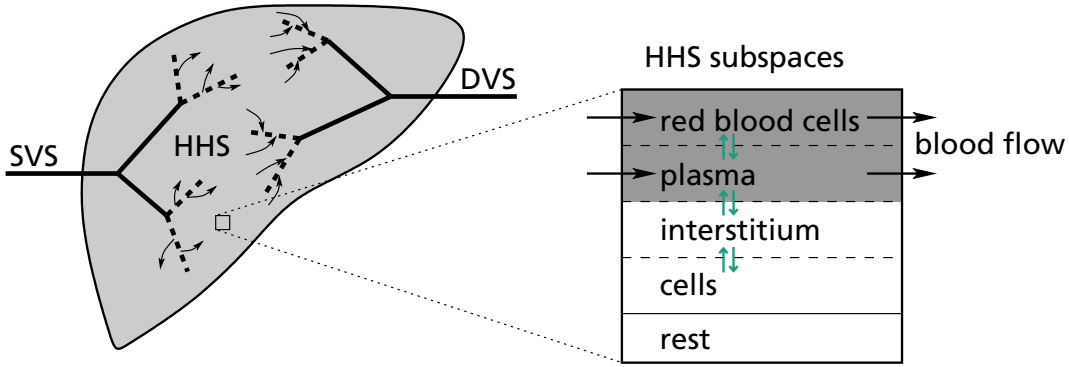

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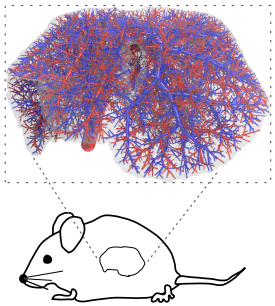

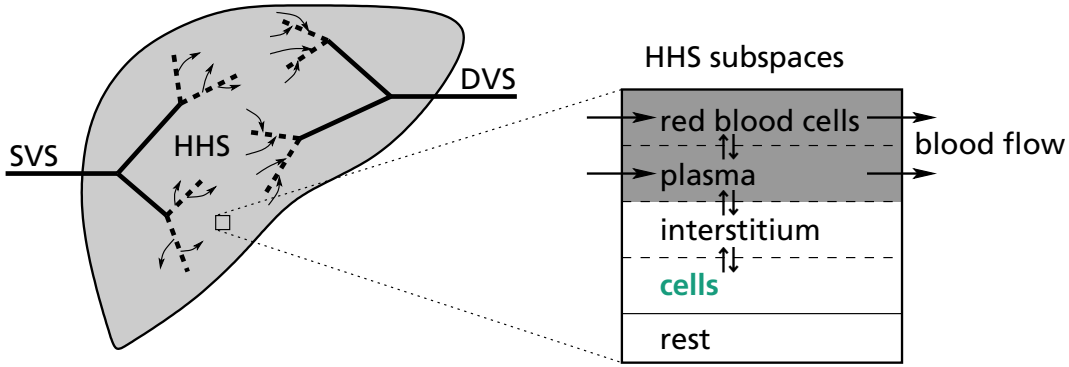

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2. Three-Scale Model

Distribution of a Tracer

CFDA SE (Carboxyfluorescein diacetate succinimidyl ester)

- dye used to track proliferation in animal cells

2. Three-Scale Model

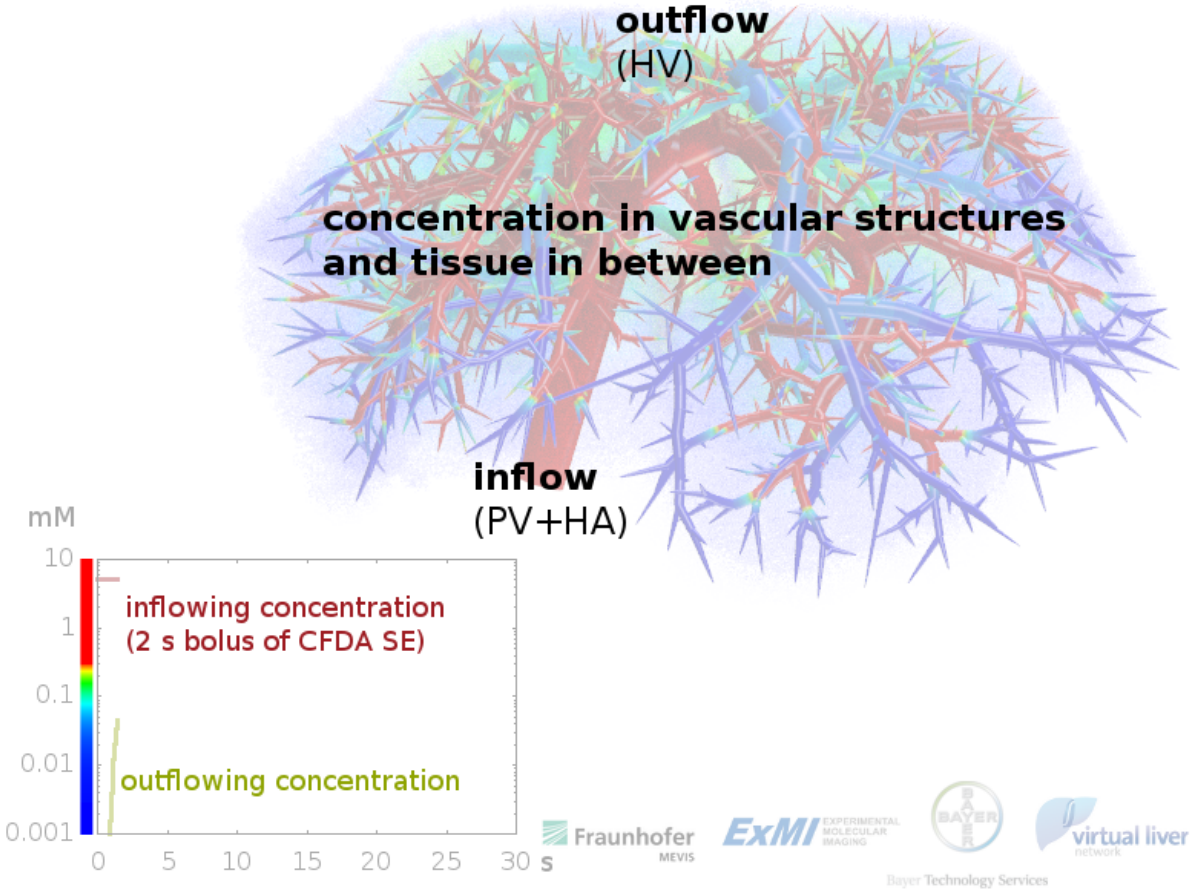
Distribution of a Tracer

CFDA SE (Carboxyfluorescein diacetate succinimidyl ester)

- dye used to track proliferation in animal cells
- exchange between subspaces only, no metabolism

2. Three-Scale Model

Distribution of a Tracer



spatio-temporal distribution (volume rendering) [→ Video]

2. Three-Scale Model

Extensions of this Approach

- well suited for first-pass effects
- well suited for organ-scale inhomogeneity

✘ computationally expensive (already for minutes of simulated time)
✘ representing cellular length scale not feasible

✔ consider lobule-scale model → next talk
✔ introduce sinusoid scale

3. Four-Scale Model

Contents

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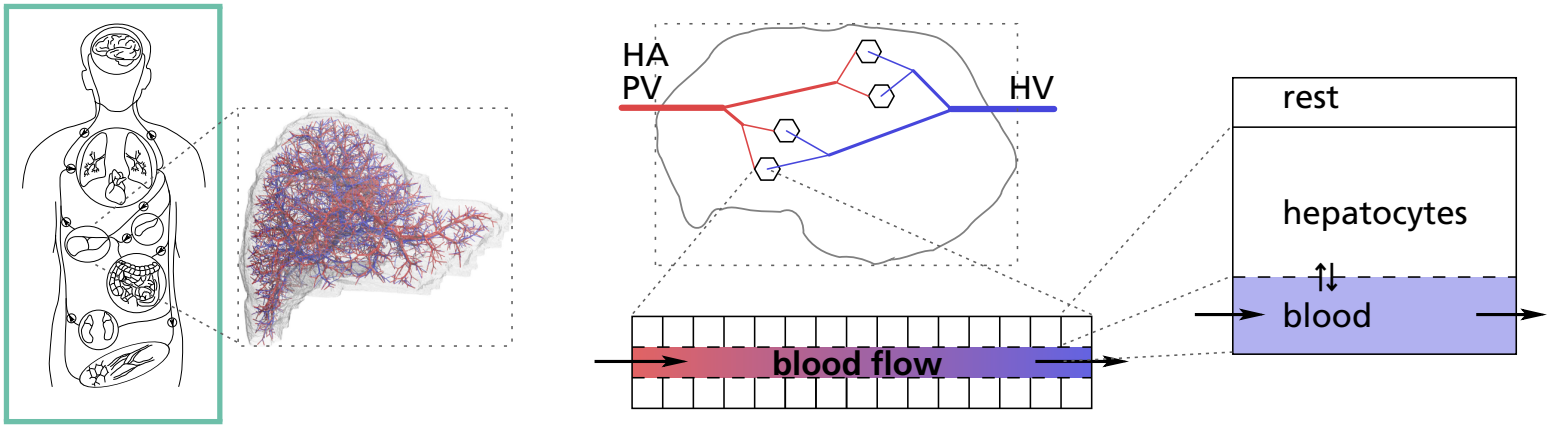
Liver Model Overview



Four Scales

- organism

3. Four-Scale Model

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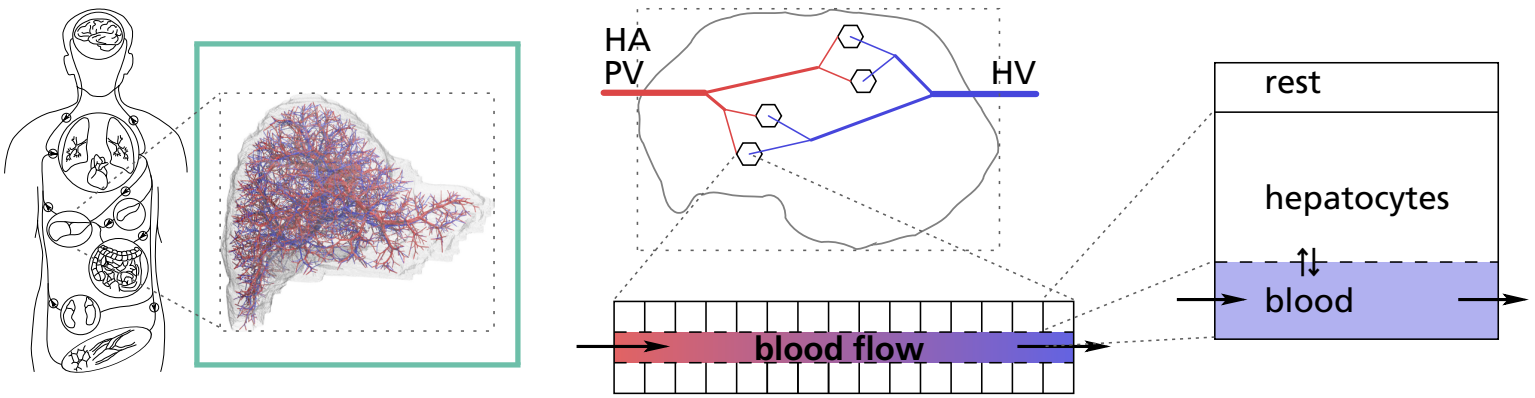

Four Scales

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- organ

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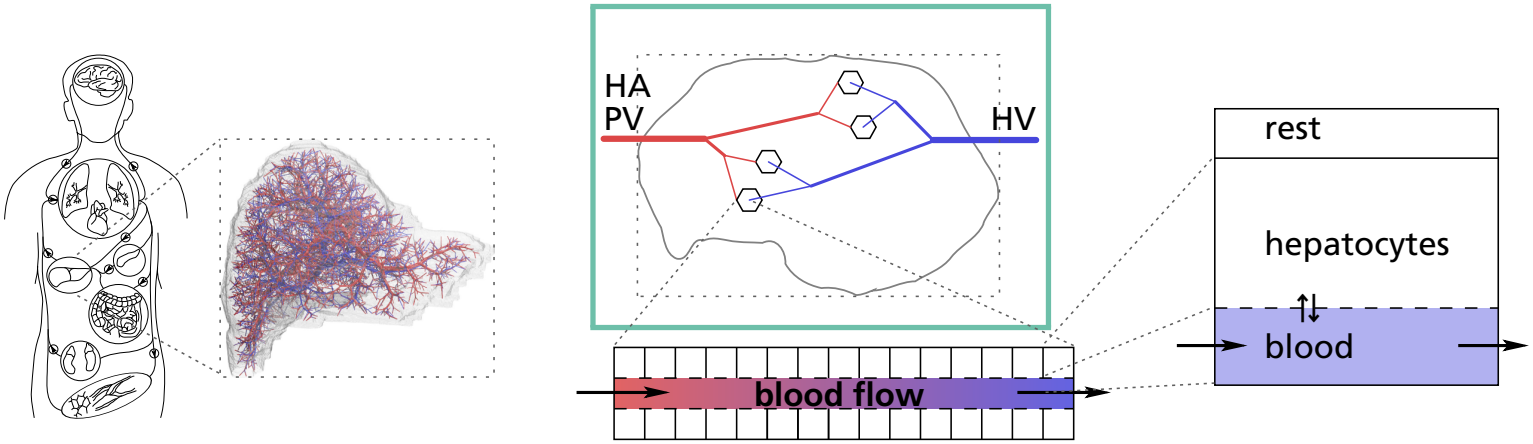

Four Scales

- organism
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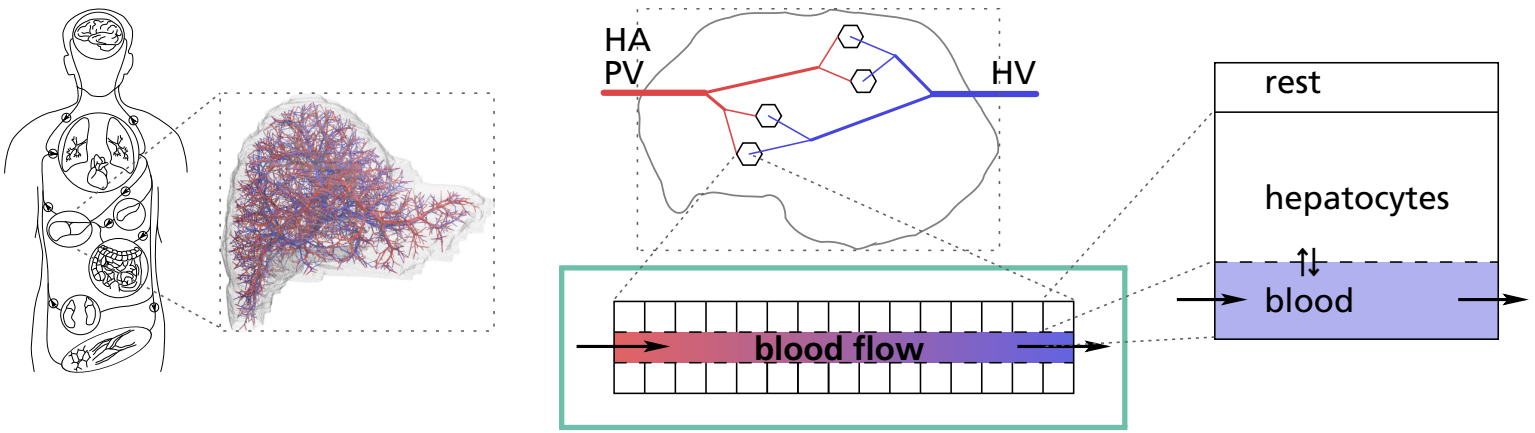

Four Scales

- organism
- organ
- sinusoid

3. Four-Scale Model

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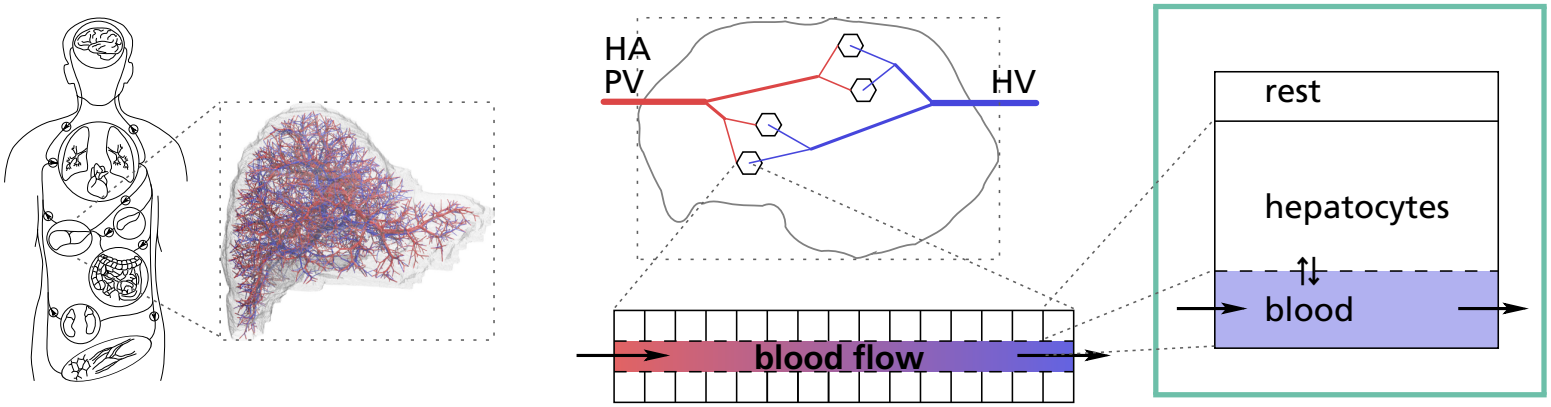
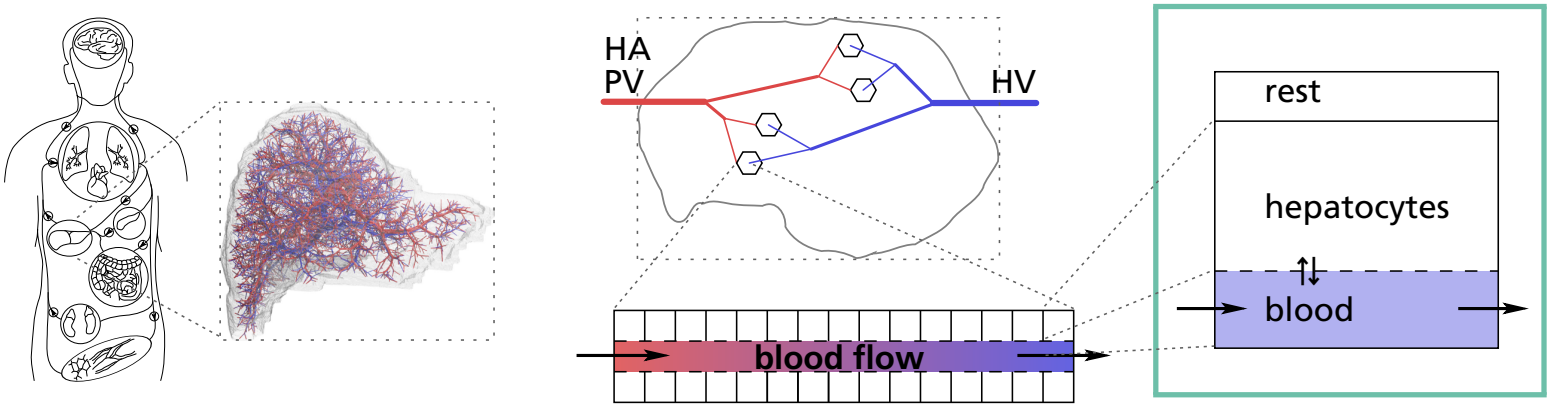


Four Scales

- organism
- organ
- sinusoid
- cell

3. Four-Scale Model

Cellular Scale



- reflects organ compartments from PBPK model
- reaction term describes
  glucose in blood ⟷ glygogen in cells

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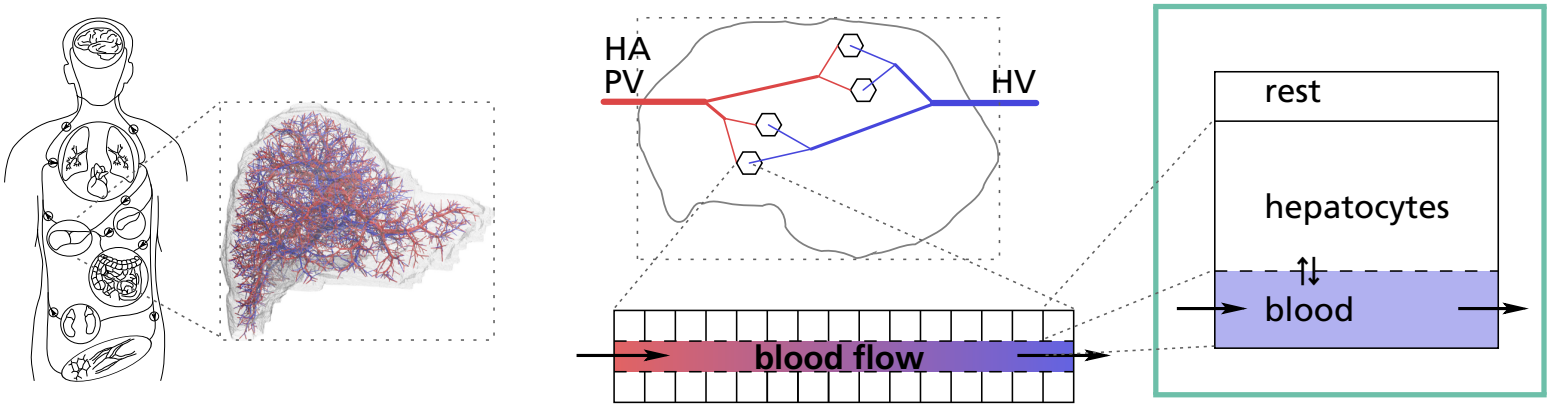
Cellular Scale

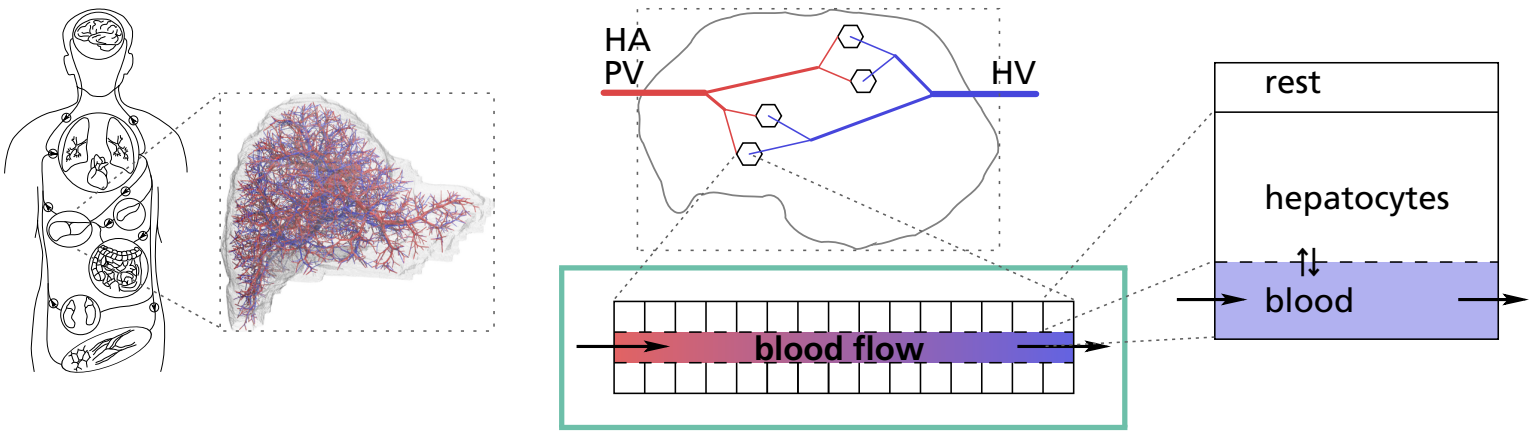


- reflects organ compartments from PBPK model
- reaction term describes
  glucose in blood ⟷ glygogen in cells
- polynomial ODE (reduction of detailed kinetic model)
  - glycogen in cells
  - glucose in blood

[König et al., PLoS Comp. Biol. 8(6), 2012]

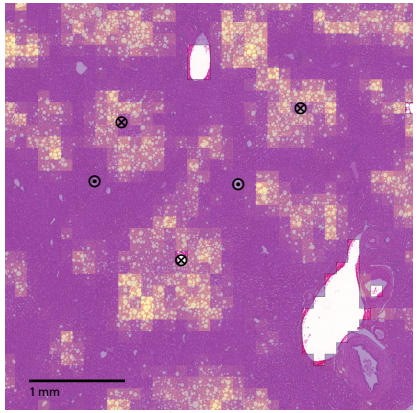
3. Four-Scale Model

Sinusoid and Organ Scale



Representative sinusoids

- zonation
  - ⇒ parameters depend on position along rep. sin.



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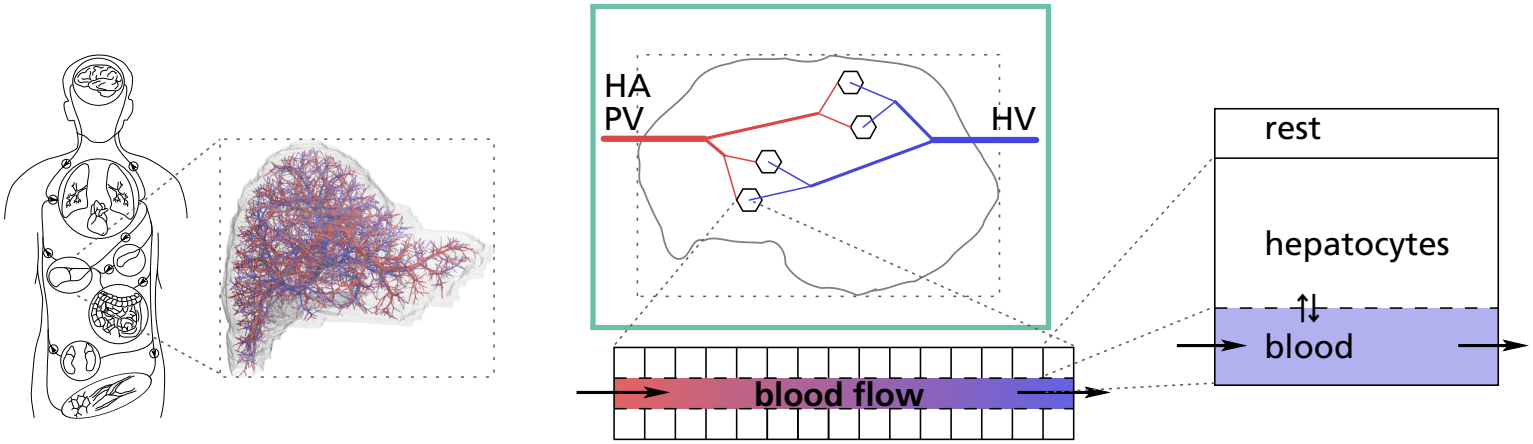
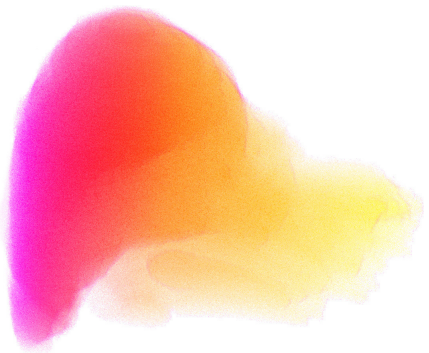


Representative sinusoids

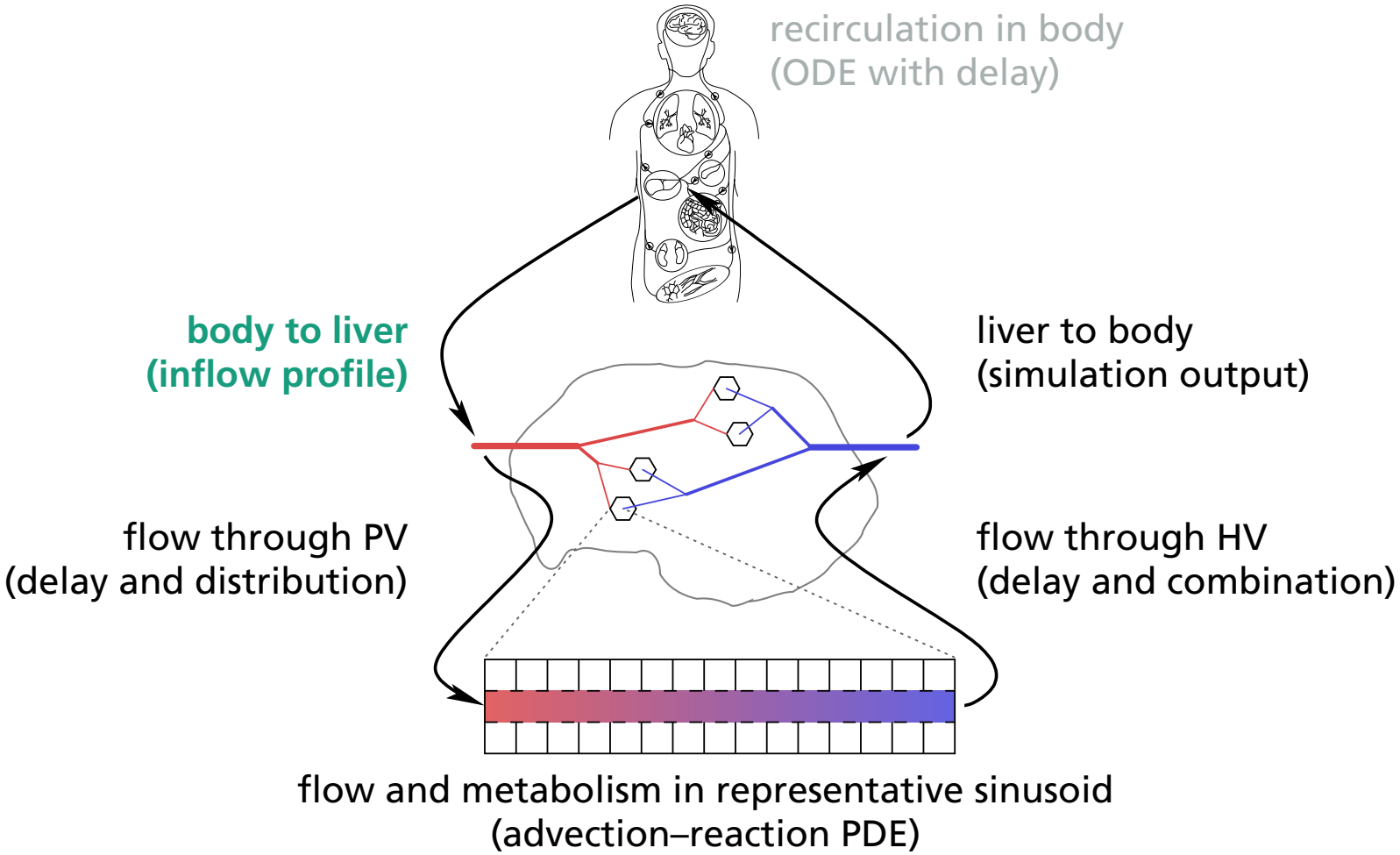
- zonation
  - ⇒ parameters depend on position along rep. sin.
- organ-scale inhomogeneity
  - ⇒ one rep. sin. per 'region'



(synthetic steatosis data)

3. Four-Scale Model

Integration to Body Scale



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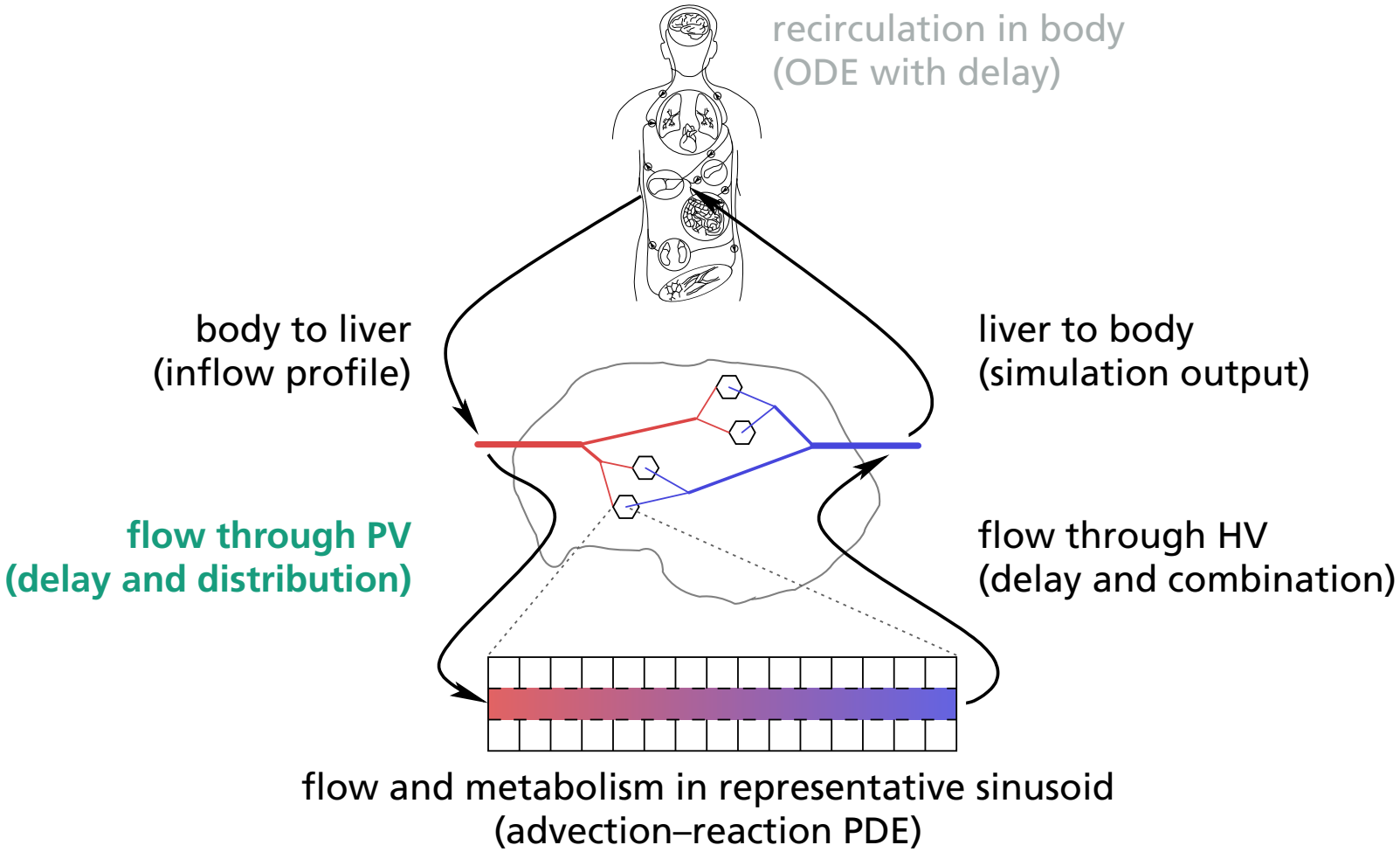

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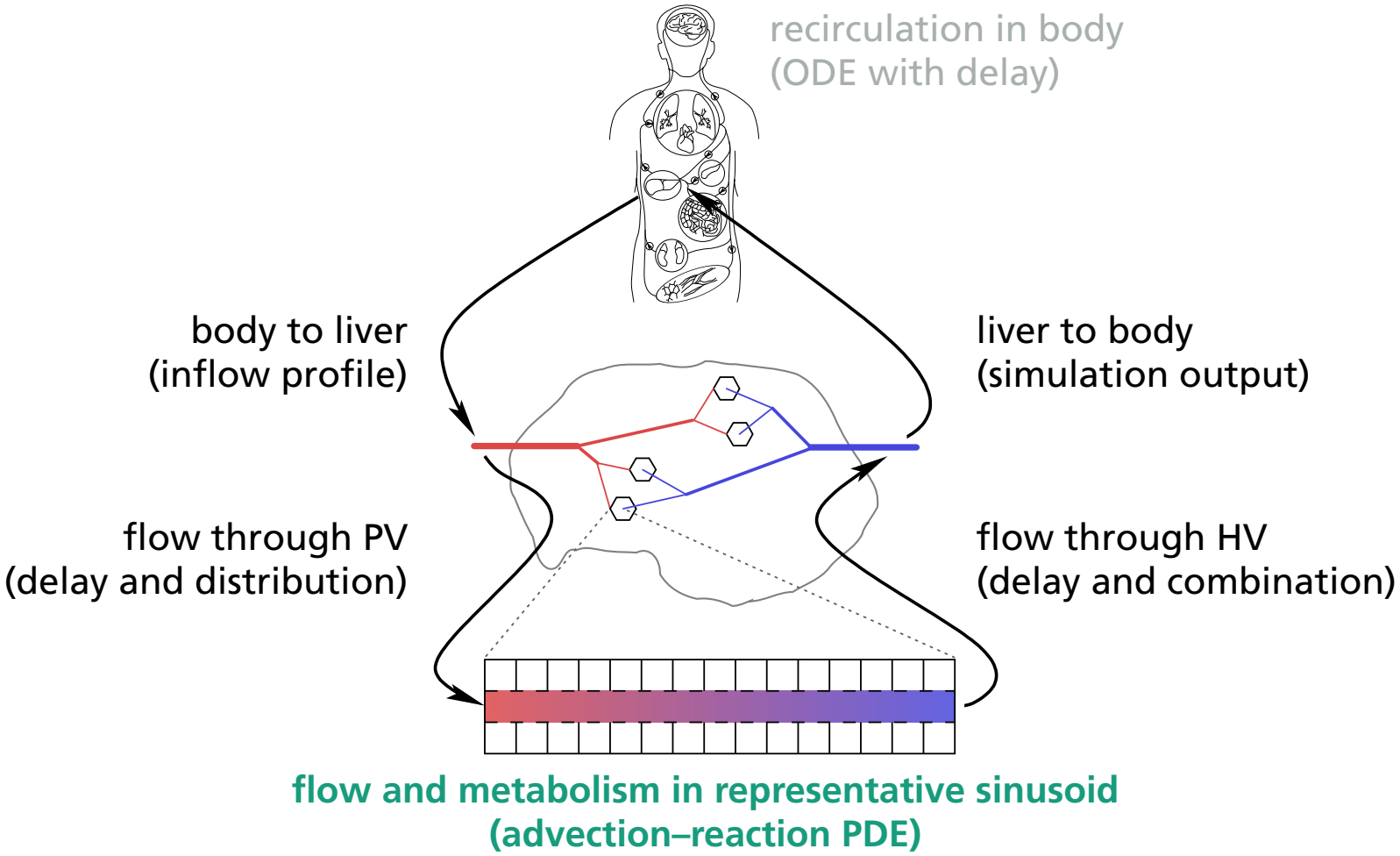

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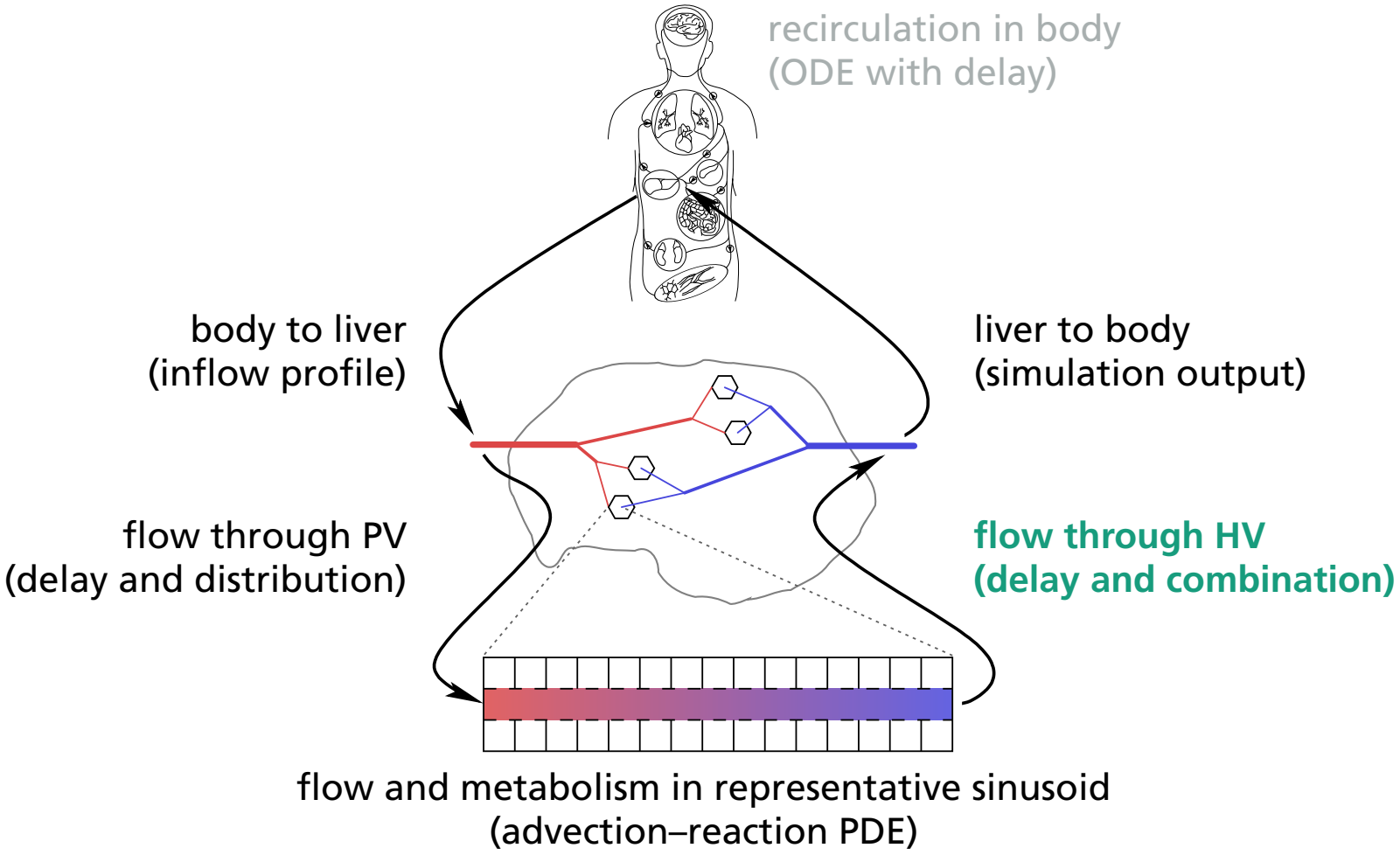

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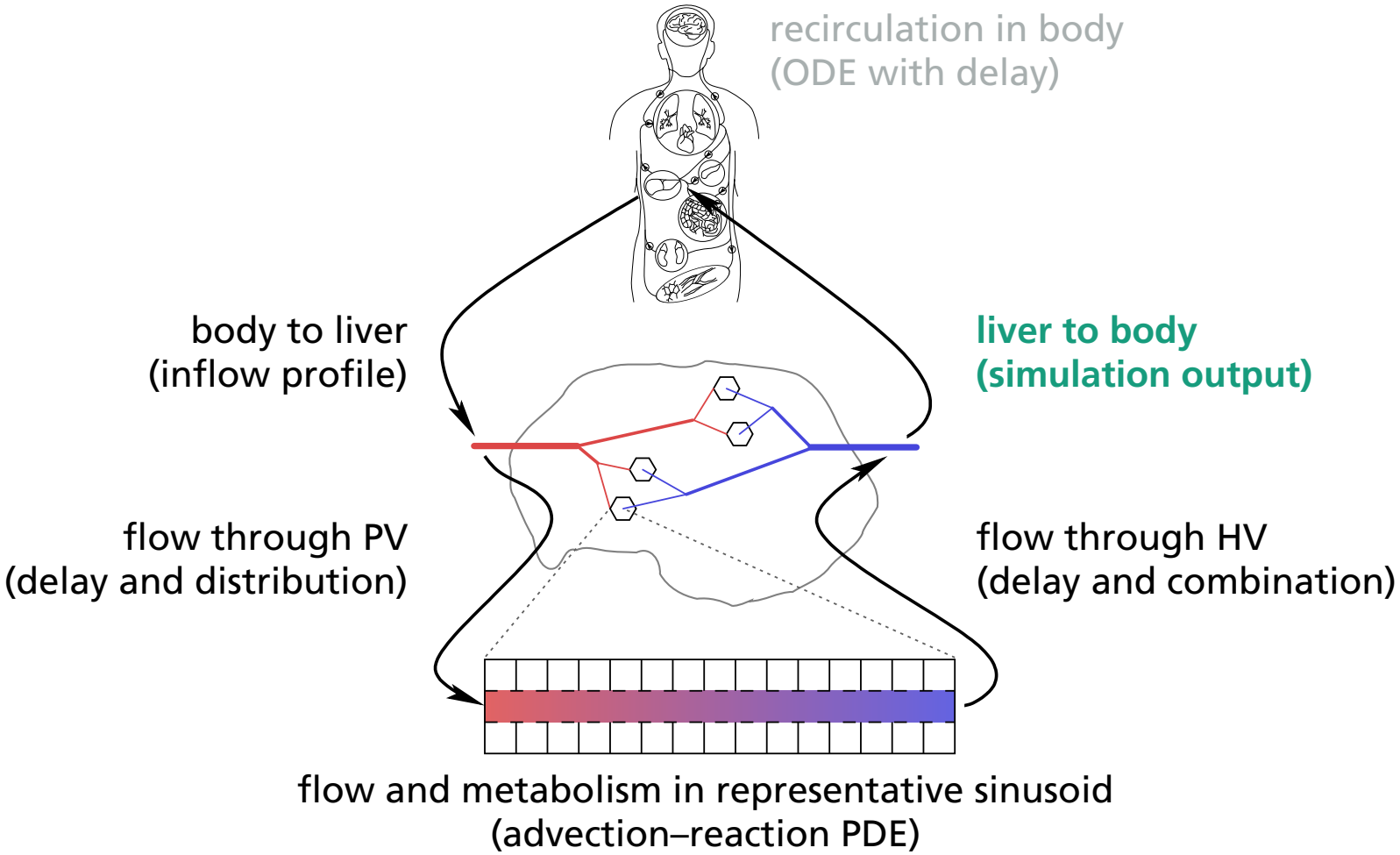

3. Four-Scale Model

Glucose Metabolism

- glucose (liver) inflow profile: three meals per day
- simulate glycogen storage and glucose (liver) outflow
- currently no recirculation

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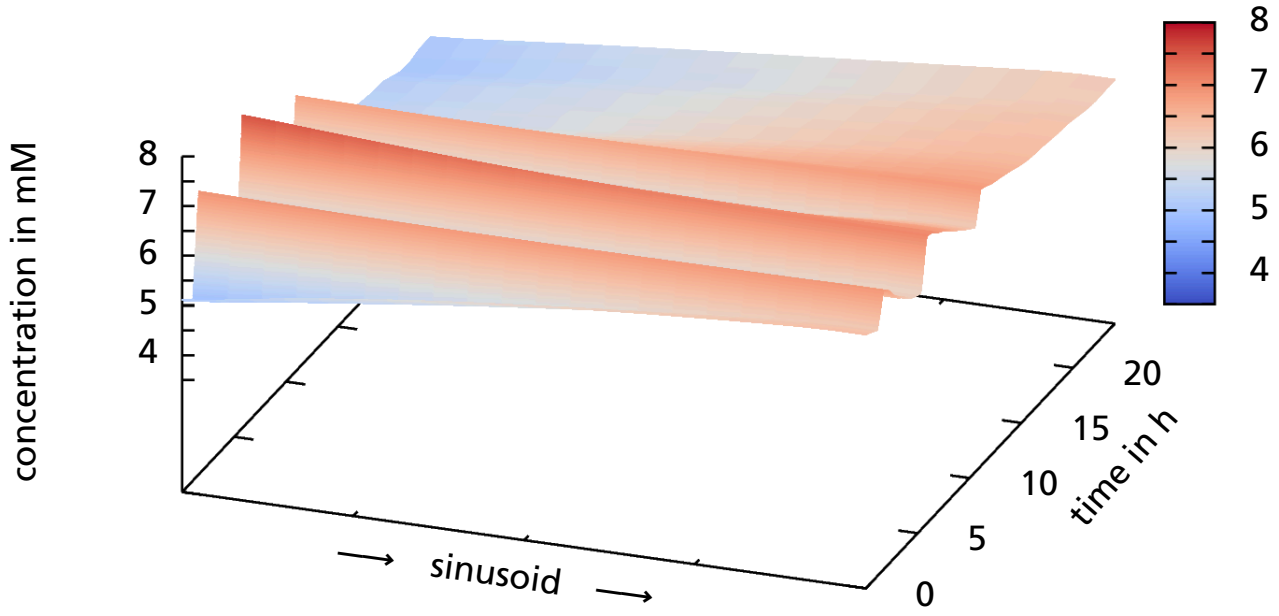
Steatosis

- reduction of cellular volume
- any other effects currently ignored

3. Four-Scale Model

Single Representative Sinusoid

Glucose concentration (in blood)



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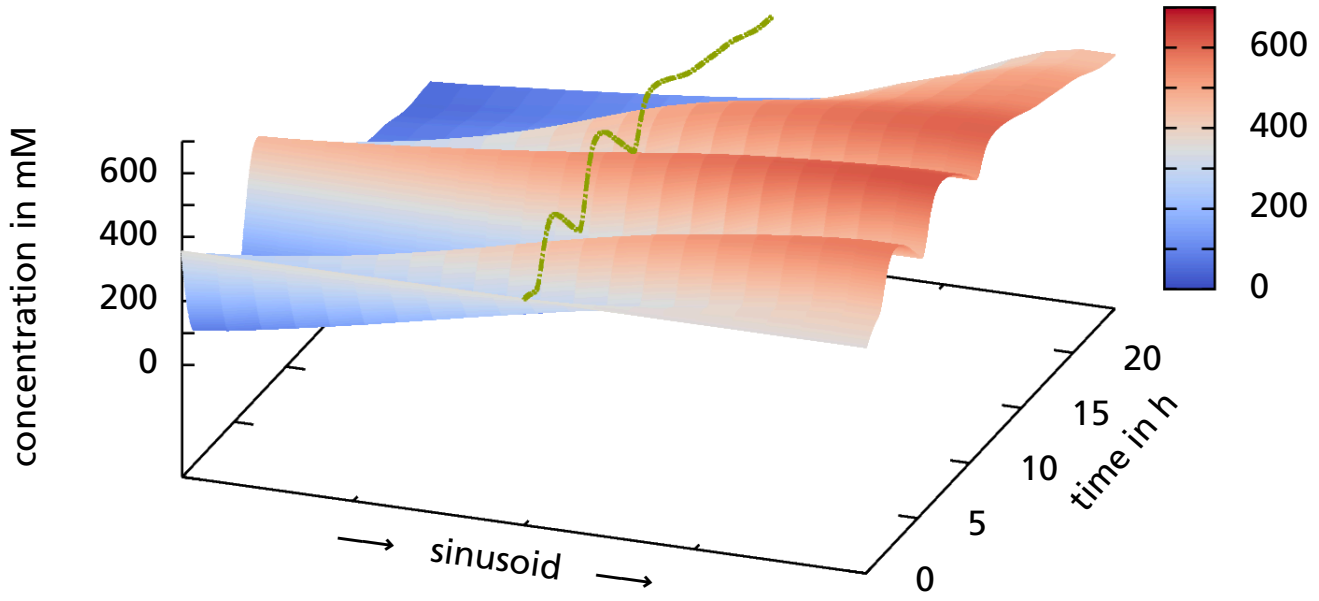
Single Representative Sinusoid

Glycogen concentration (in cells)



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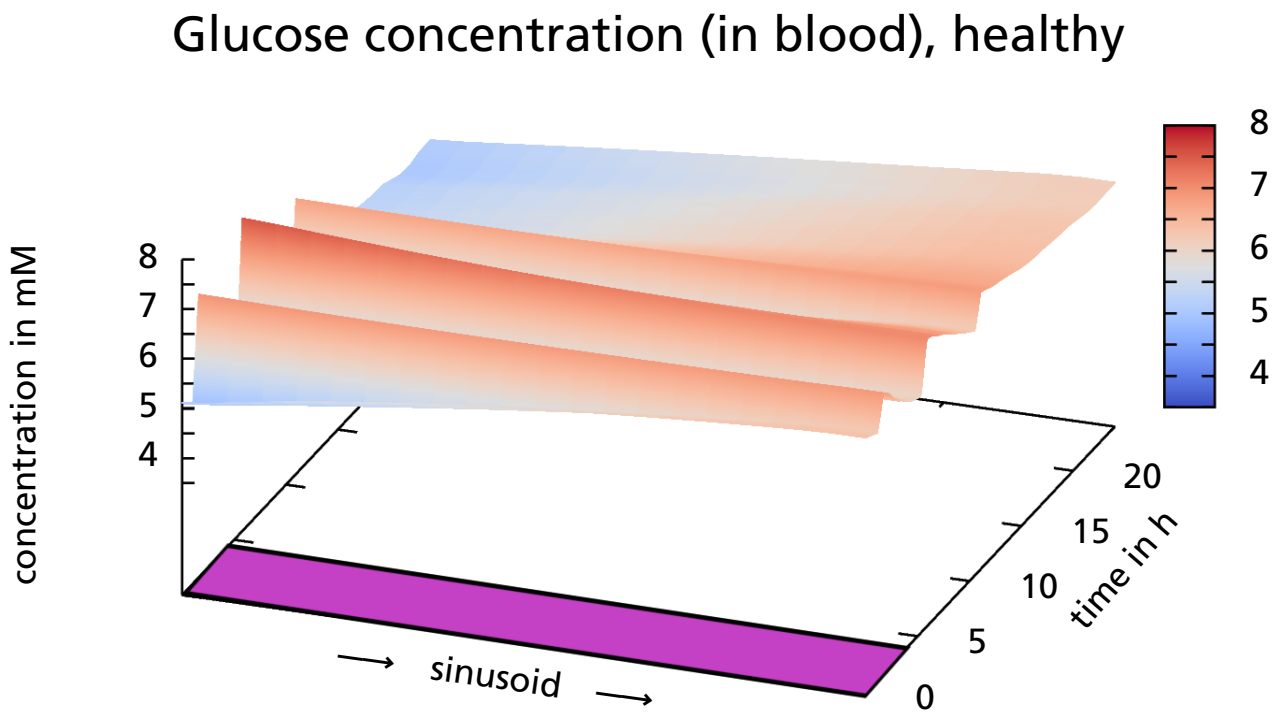
Influence of Steatosis (Single Representative Sinusoid)



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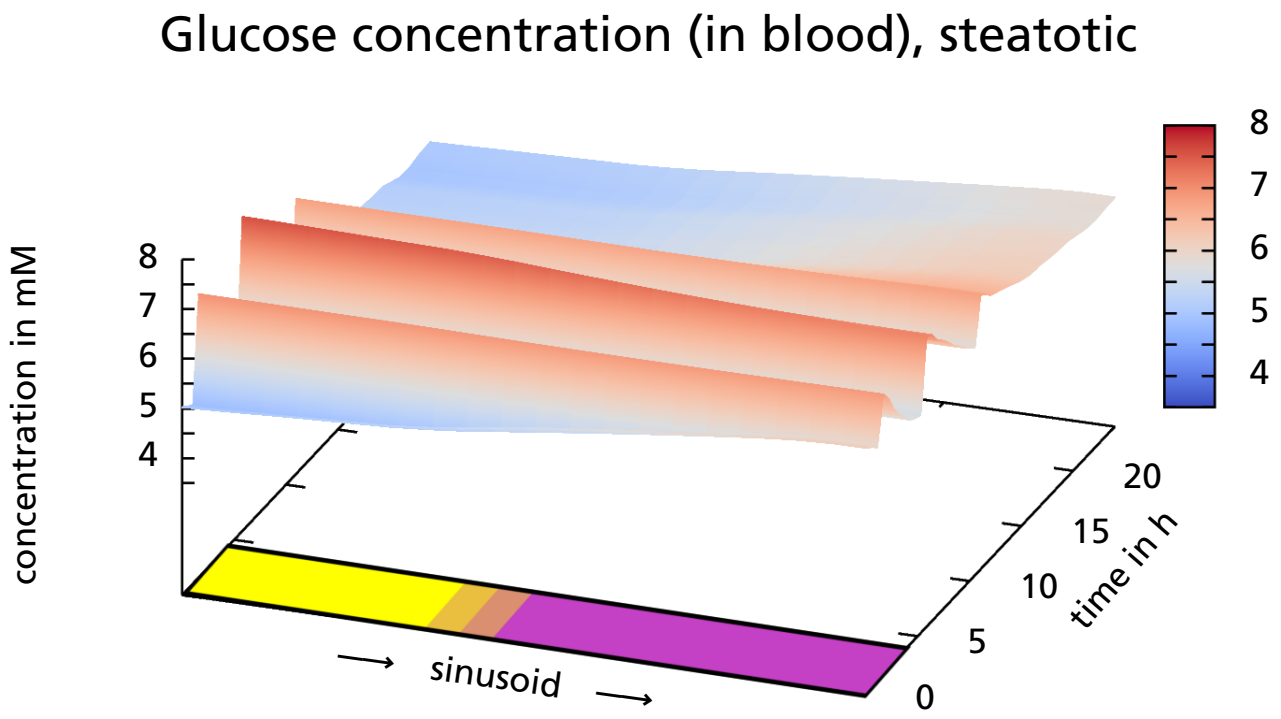

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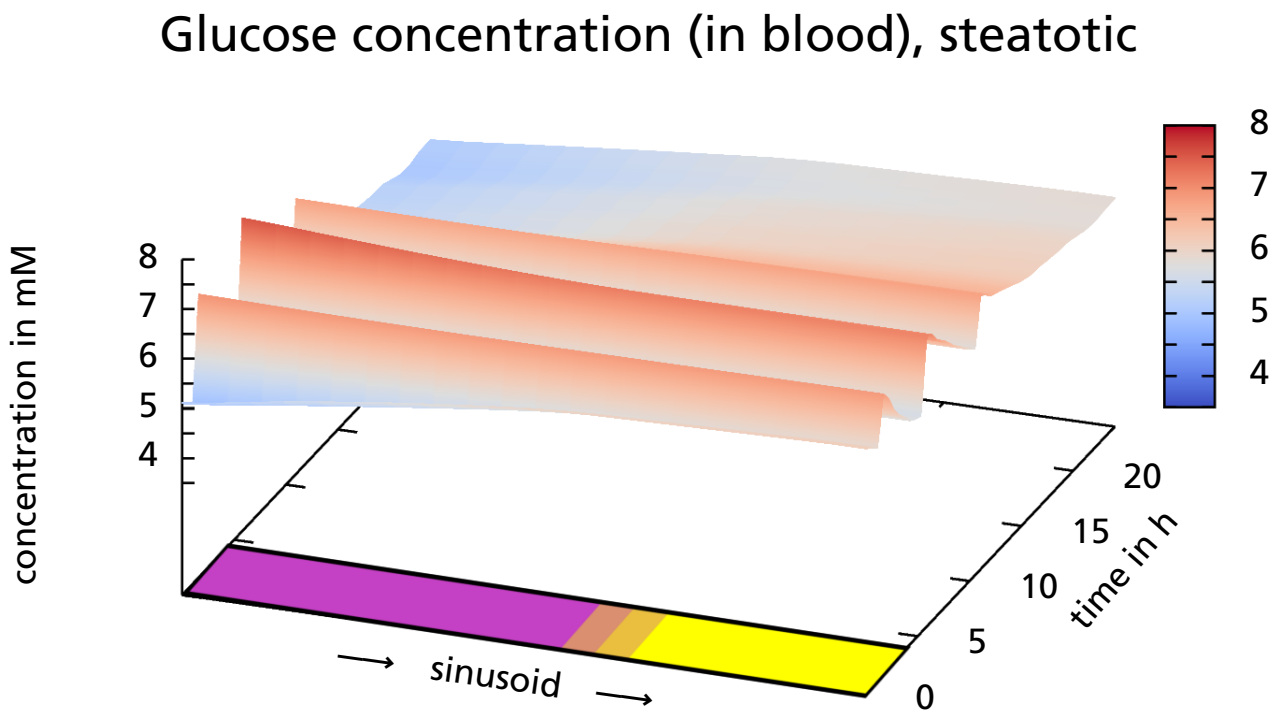

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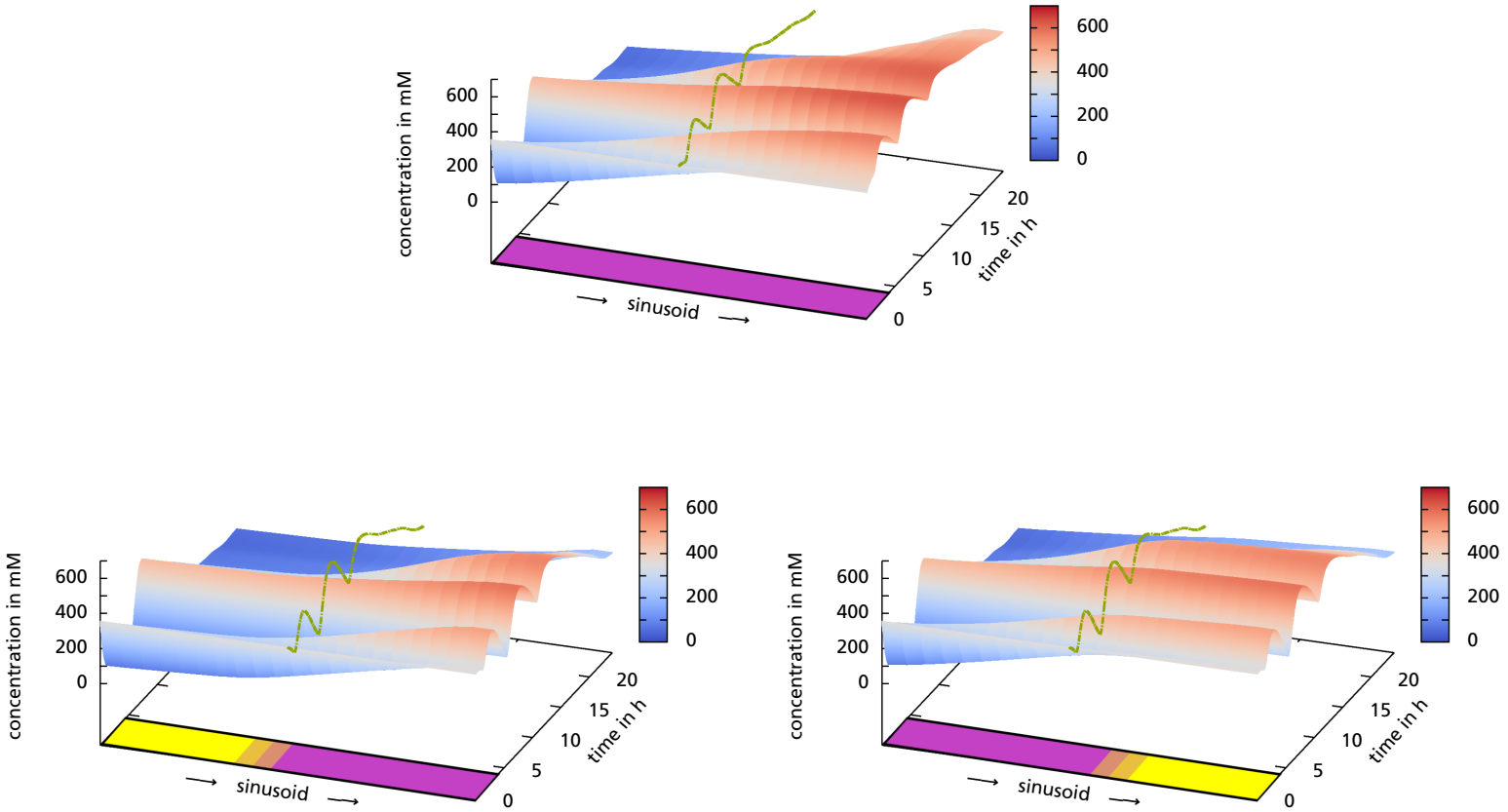
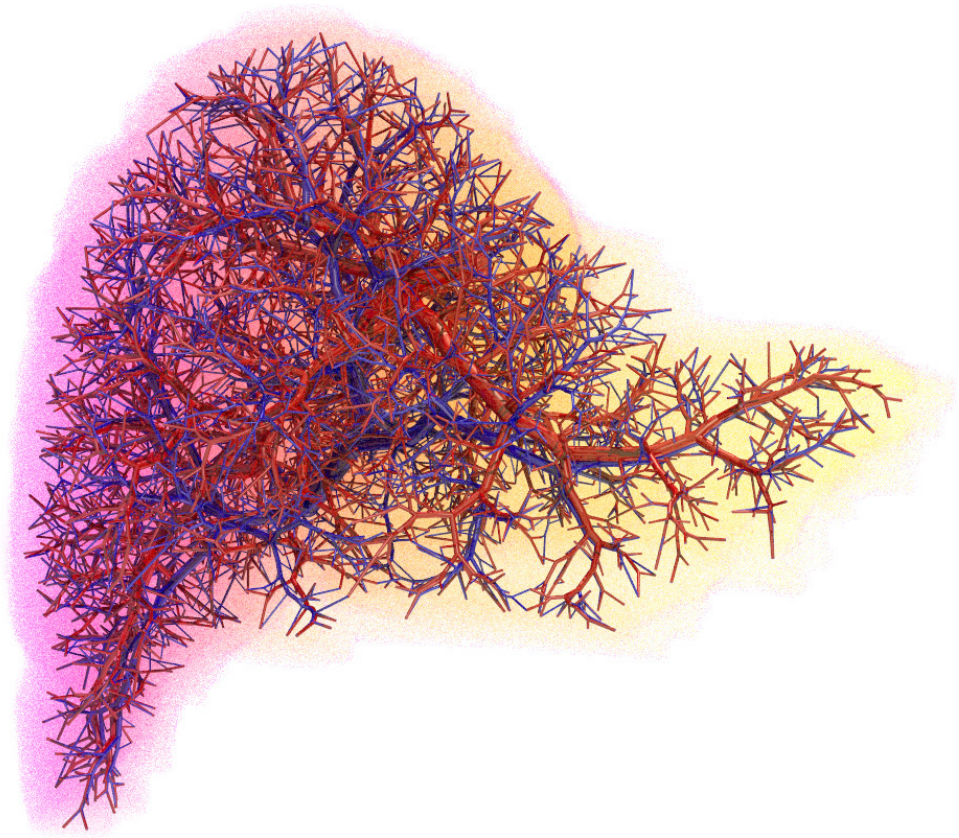


3. Four-Scale Model

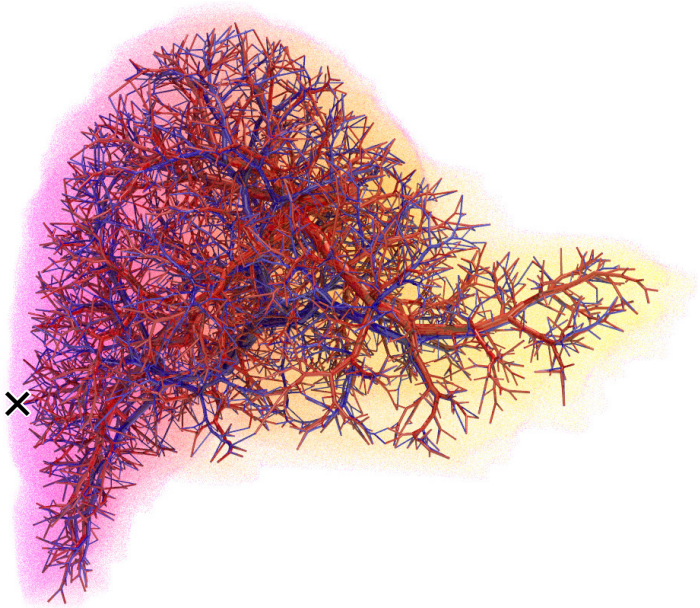
Organ-Scale Representative Sinusoid Simulation I



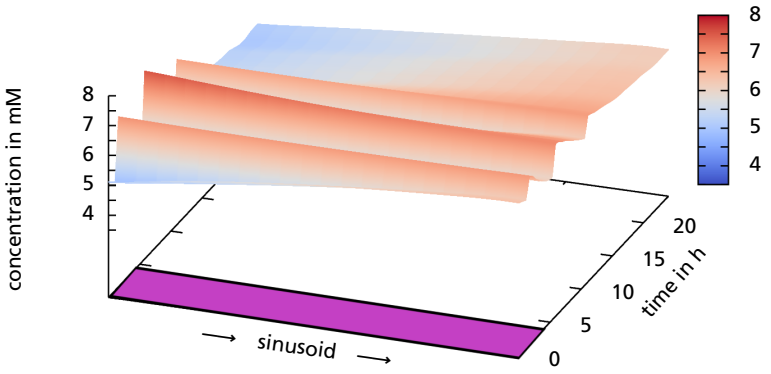
- realistic geometric model with 3200 representative sinusoids
- macroscopically and microscopically inhomogeneous (synthetic) steatosis

3. Four-Scale Model

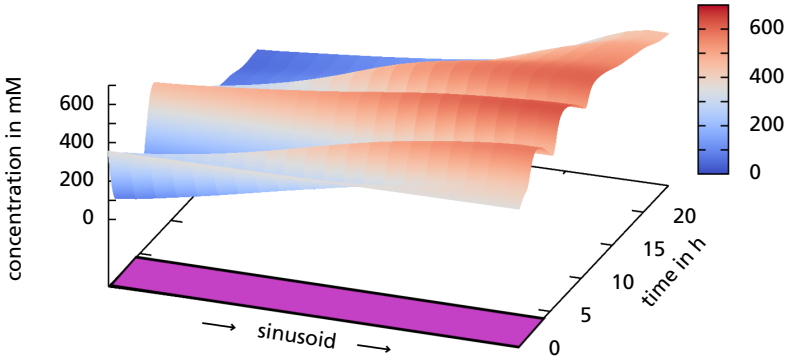
Organ-Scale Representative Sinusoid Simulation II



Glucose concentration (blood)



Glycogen concentration (in cells)



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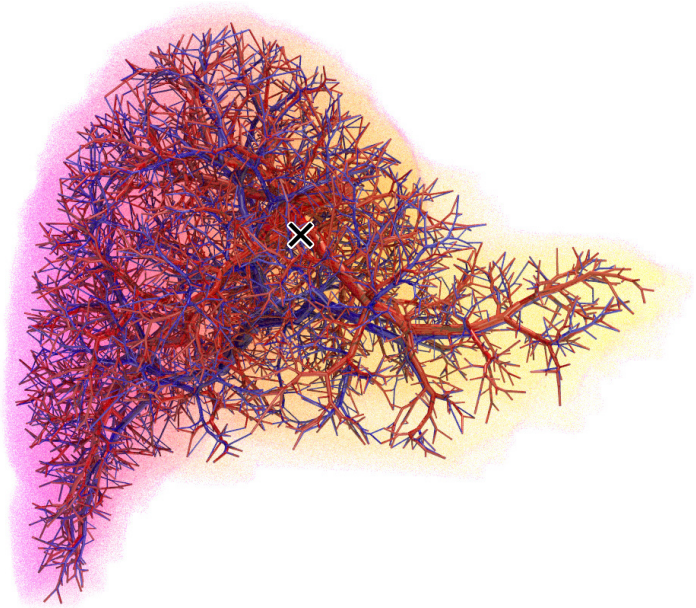
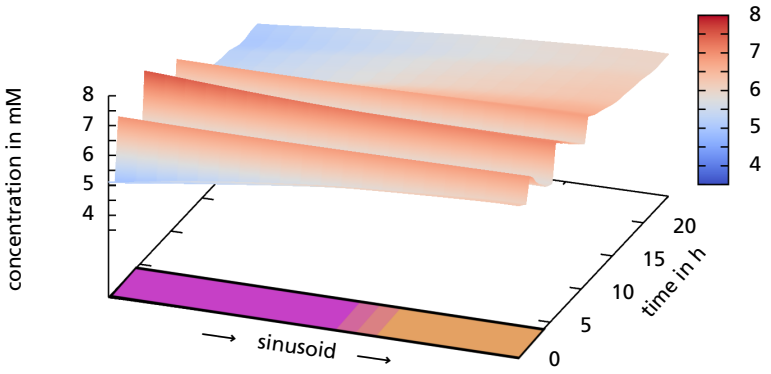
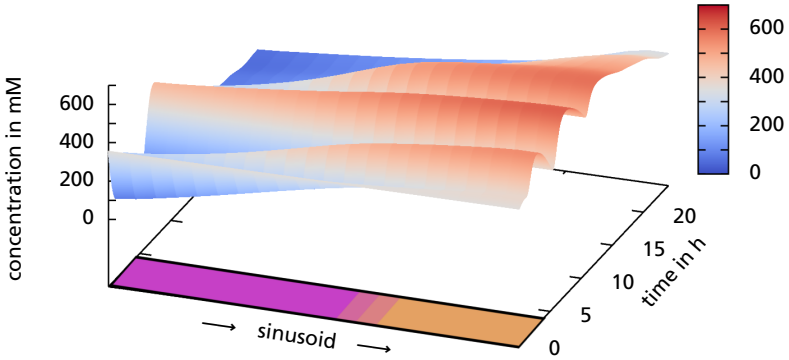
Organ-Scale Representative Sinusoid Simulation II



Glucose concentration (blood)



Glycogen concentration (in cells)



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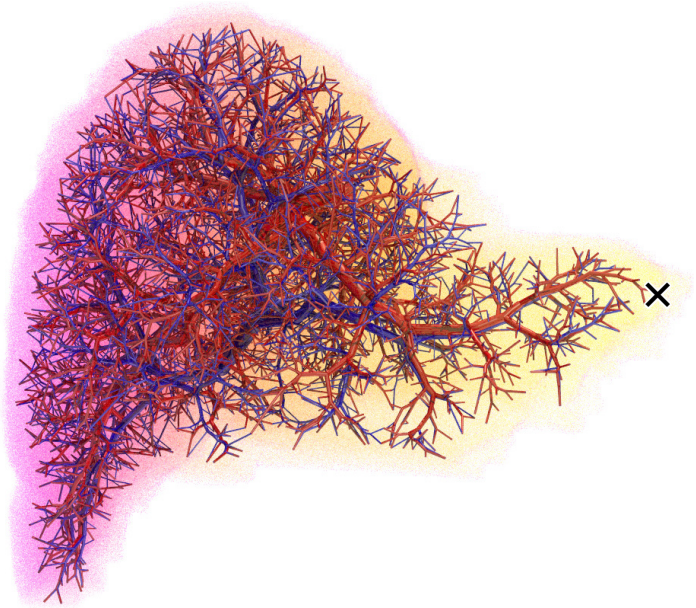
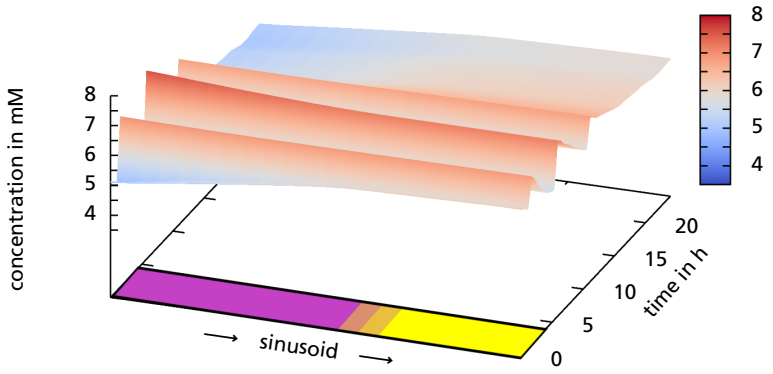
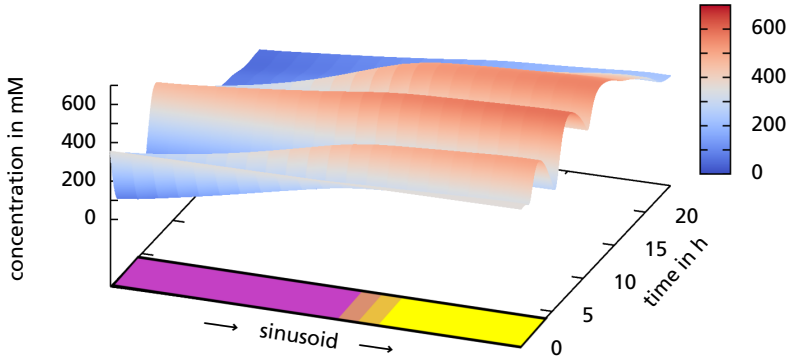
Organ-Scale Representative Sinusoid Simulation II



Glucose concentration (blood)

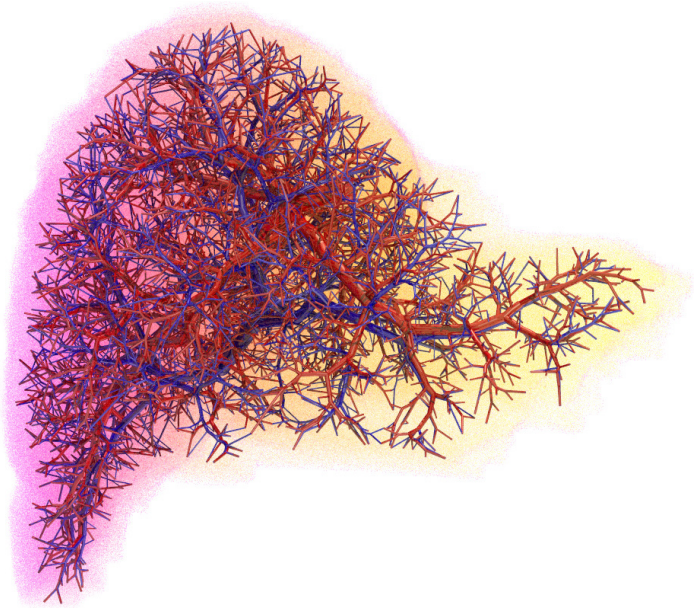


Glycogen concentration (in cells)



3. Four-Scale Model

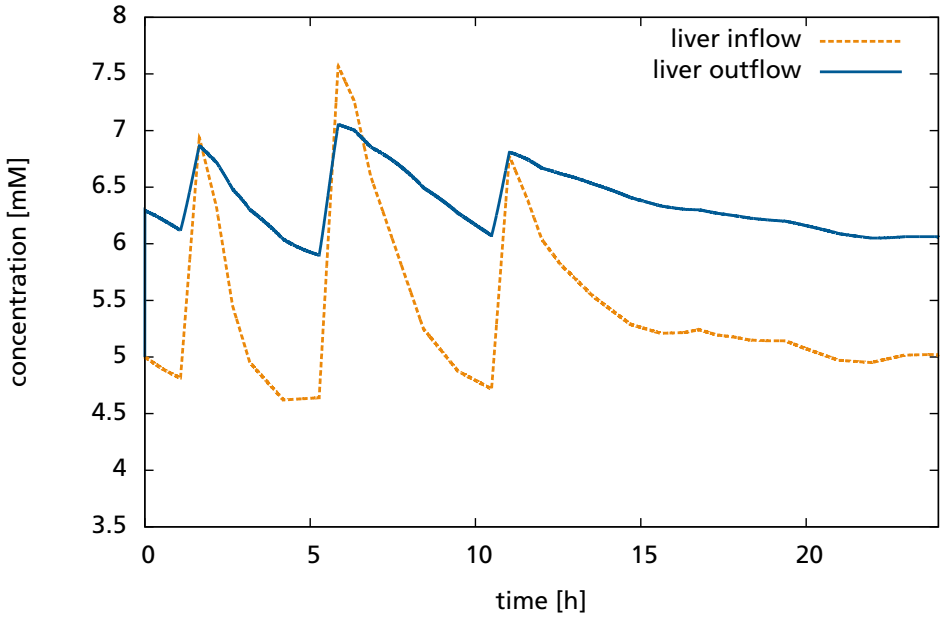
Organ-Scale Representative Sinusoid Simulation III



all 3200 representative sinusoids

⇓

Glucose concentrations (in blood)



4. Outlook

Contents

4. Outlook

- refine glucose model
  - zonated hepatic glucose metabolism
  - glucose metabolism outside liver
  - more compounds in model

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- more refined steatosis model
- other pathological conditions

4. Outlook

- refine glucose model
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- experimental validation

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- André Homeyer
- Michael Schwier

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- Felix Gremse

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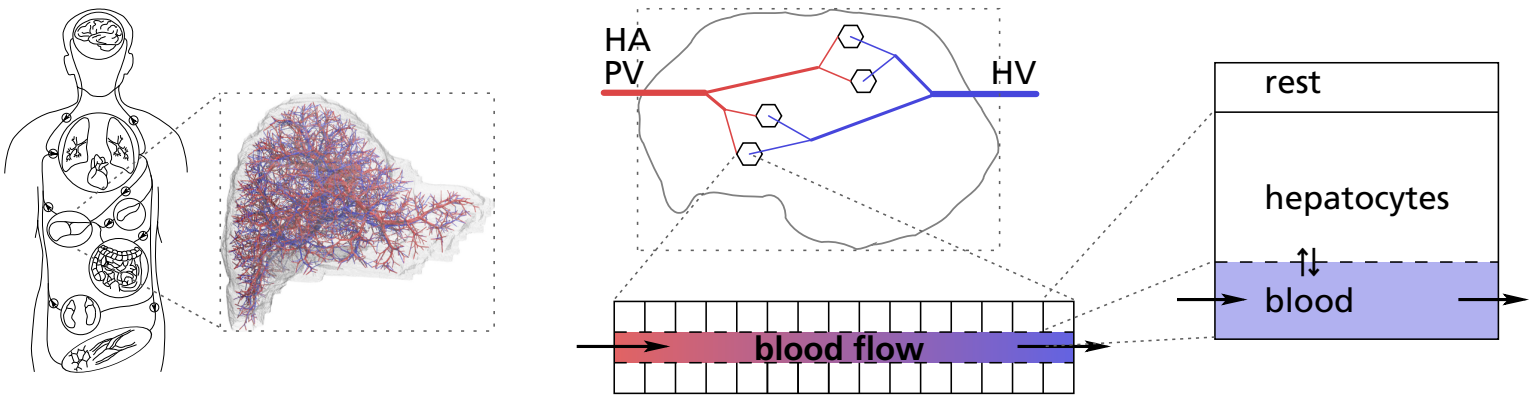
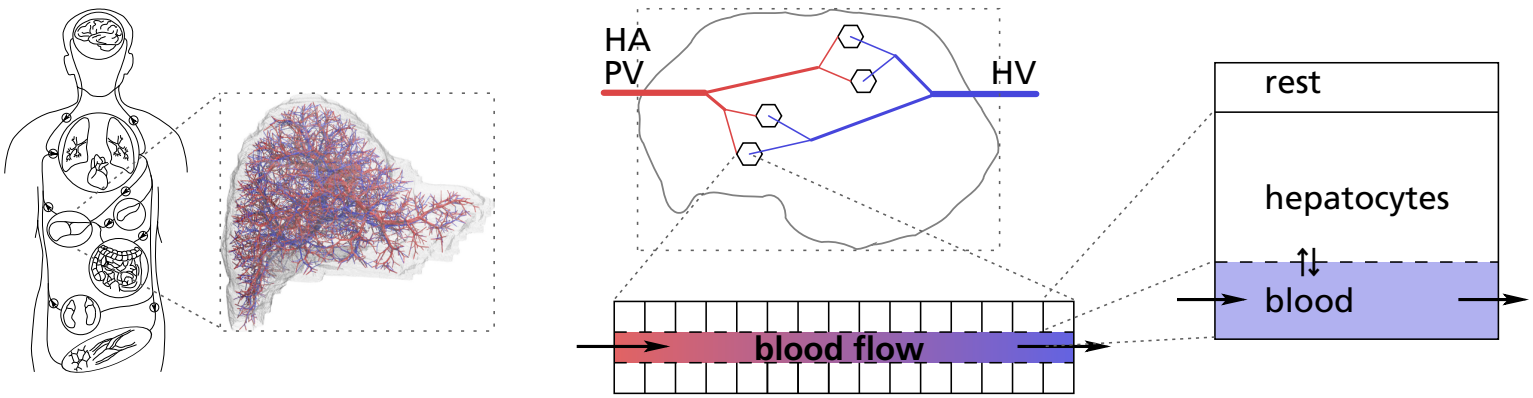
Summary



Four-scale liver model based on representative sinusoids

- mechanistic metabolism model
- can deal with inhomogeneity at different scales
- glucose metabolism

Summary



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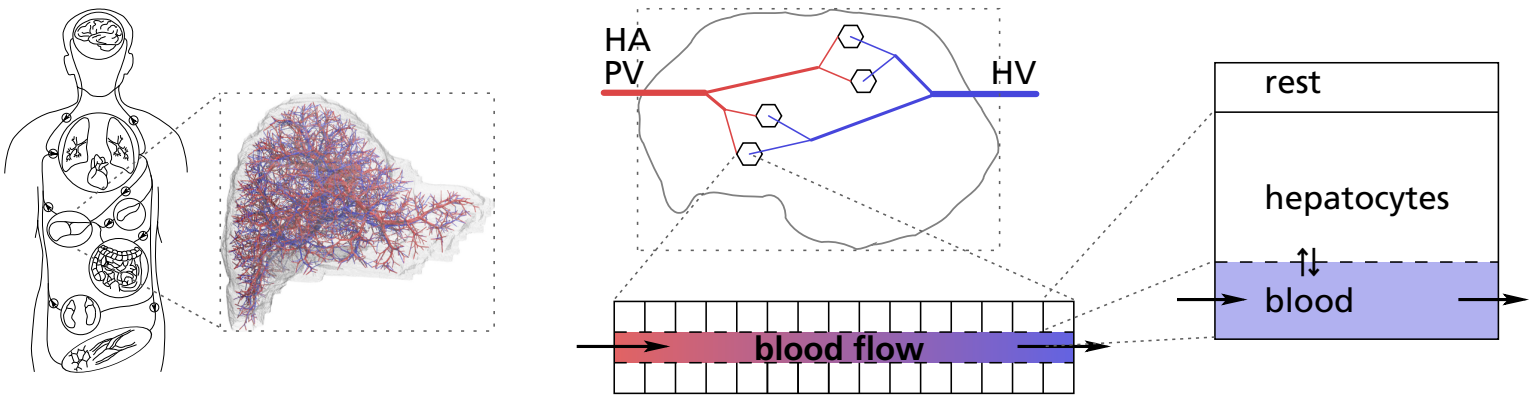

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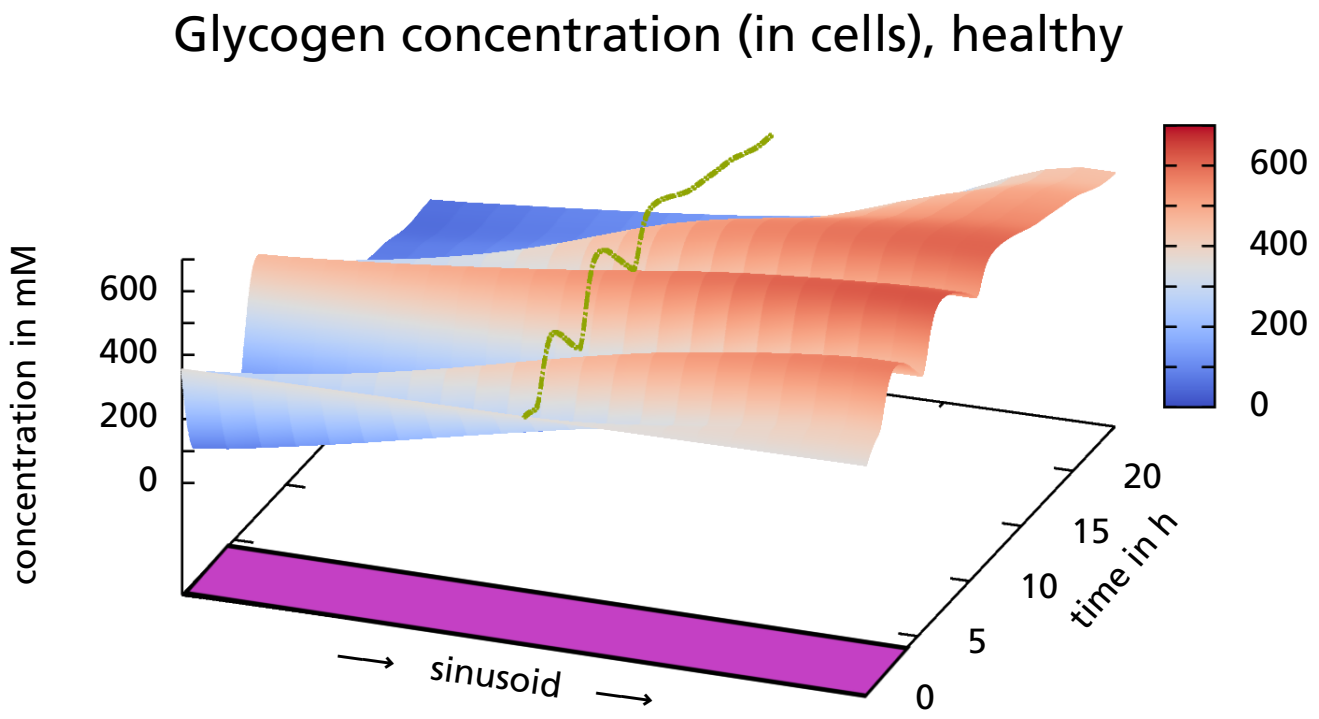
Influence of Steatosis (Single Representative Sinusoid)



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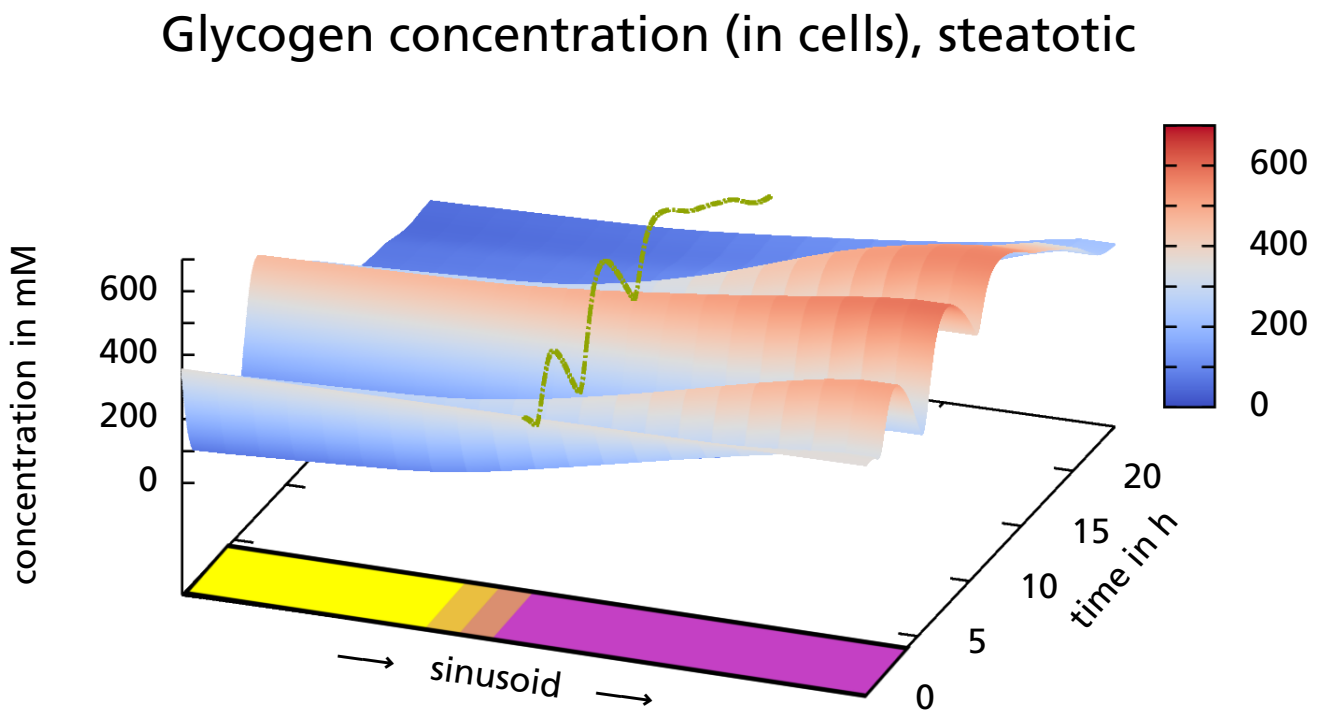

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