

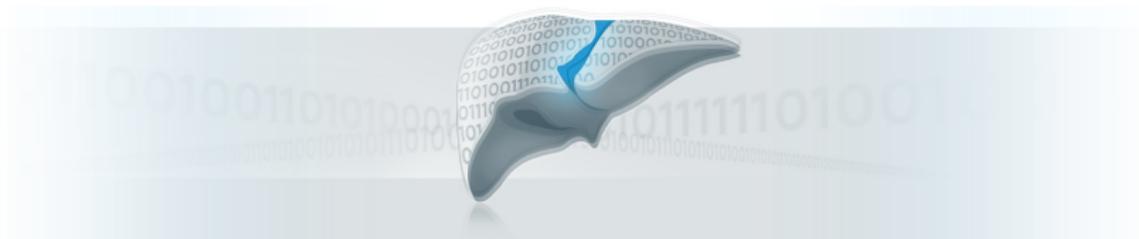
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# MULTI-SCALE SIMULATION OF ZONATED LIVER METABOLISM

Lars Ole Schwen

5th Conference on Systems Biology of Mammalian Cells  
Berlin, 2014-05-14

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# Outline

1. Motivation

2. Four-Scale Model

3. Applications and Results

4. Outlook

# 1. Motivation

## Contents

1. Motivation

2. Four-Scale Model

3. Applications and Results

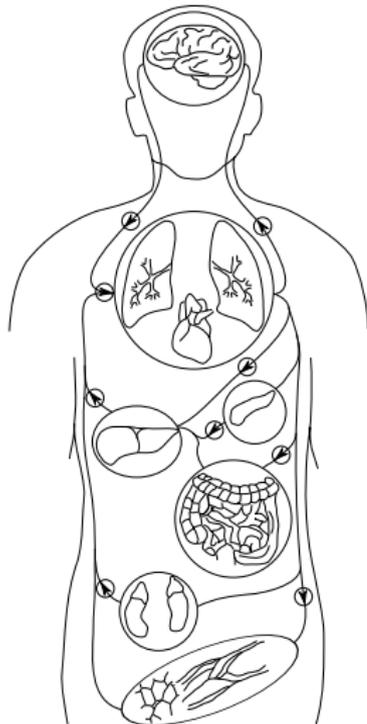
4. Outlook

# 1. Motivation

## Introduction: The Liver

Tasks (among others)

- metabolization
- detoxification



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[http://upload.wikimedia.org/wikipedia/en/2/22/WholeBody\\_wiki.svg](http://upload.wikimedia.org/wikipedia/en/2/22/WholeBody_wiki.svg)

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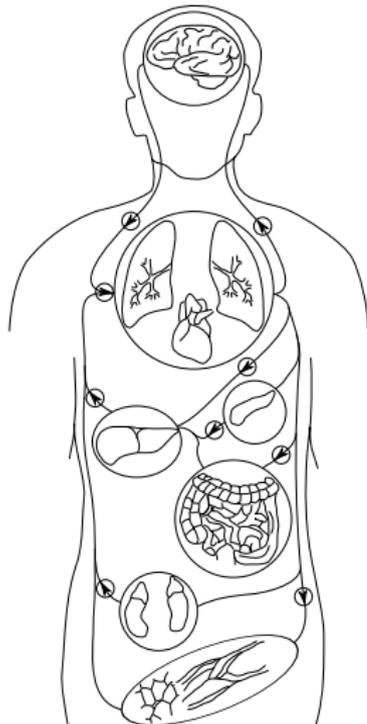
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- metabolization
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### Structure

- vascular systems for
  - blood supply
  - drainage



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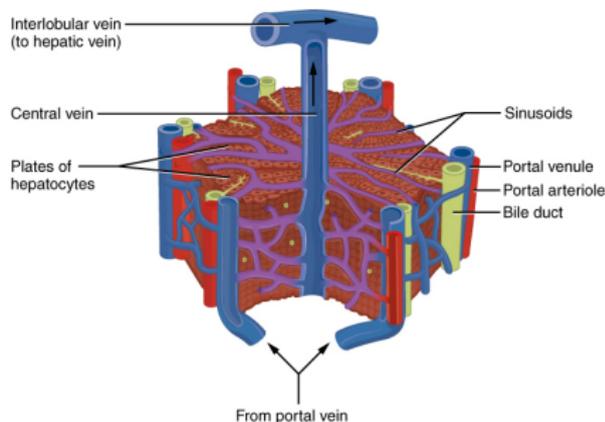
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- cells organized along sinusoids



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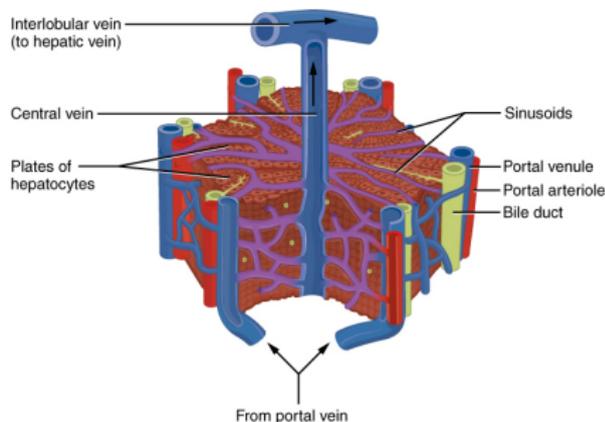
## Introduction: The Liver

### Tasks (among others)

- metabolization
- detoxification

### Structure

- vascular systems for
  - blood supply
  - drainage
- cells organized along sinusoids
- not necessarily homogeneous



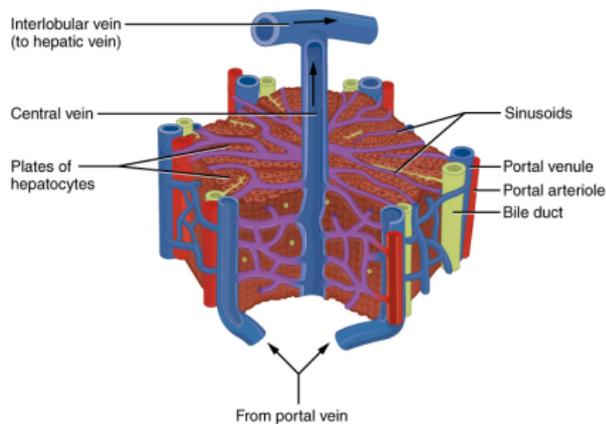
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# 1. Motivation

## Inhomogeneity

### Mechanisms

- concentration gradients
- differences in cells
- pathologies



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# 1. Motivation

## Inhomogeneity

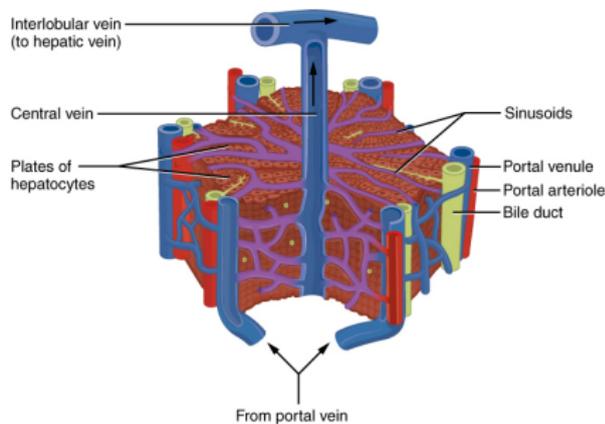
### Mechanisms

- concentration gradients
- differences in cells
- pathologies

### Scales

- zonation within lobuli (along sinusoids)
- heterogeneity across lobes

examples ...



adapted from OpenStax College: Anatomy & Physiology  
<http://cnx.org/content/col11496/1.6/>, p. 1072 (CC-BY 3.0)

# 1. Motivation

## Inhomogeneity Example I

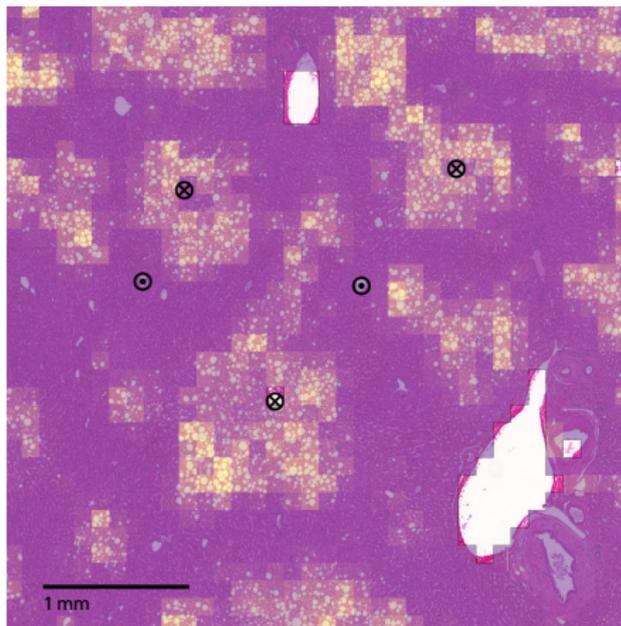


Uta Dahmen, André Homeyer

organ-scale heterogeneity of steatosis in a mouse liver

# 1. Motivation

## Inhomogeneity Example II



- ⊗ central veins
- ⊙ portal fields (selection)

Serene Lee, Wolfgang Thasler, André Homeyer

zonation of steatosis in a human liver

## 2. Four-Scale Model

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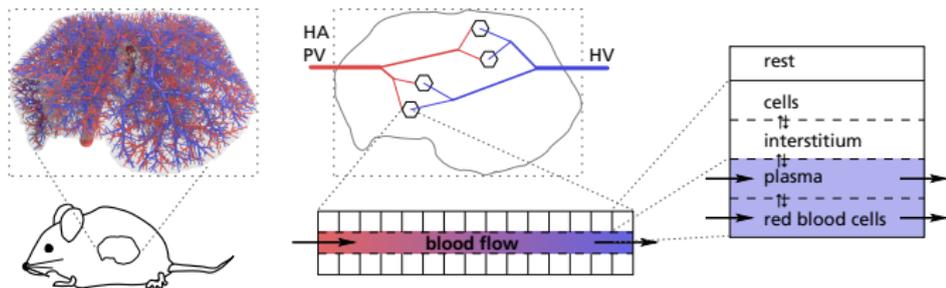
2. Four-Scale Model

3. Applications and Results

4. Outlook

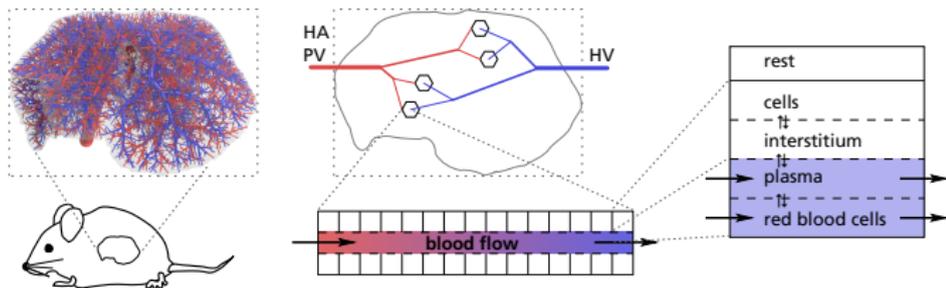
## 2. Four-Scale Model

### Liver Model Overview



## 2. Four-Scale Model

### Liver Model Overview

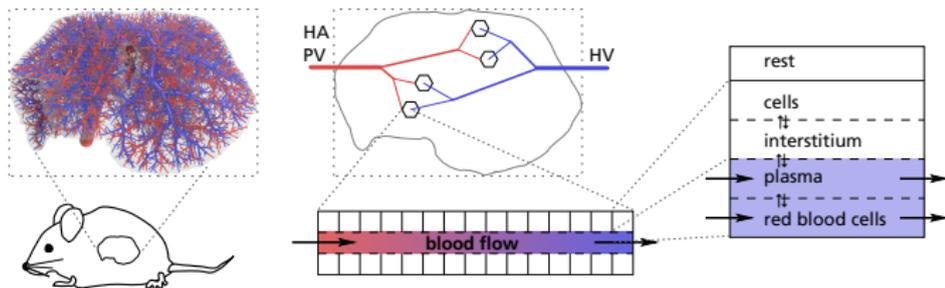


Key module: **representative sinusoids**

- blood flow and metabolization (advection–reaction)
- permit spatio-temporal simulation

## 2. Four-Scale Model

### Liver Model Overview



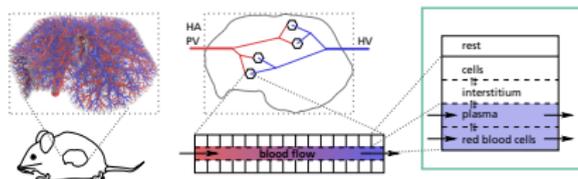
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Let us proceed from fine to coarse ...

## 2. Four-Scale Model

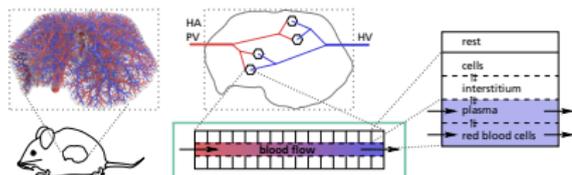
### Cellular Scale



- reflects organ subcompartments from PBPK model
- reaction term describes
  - exchange blood  $\leftrightarrow$  cells
  - metabolization within cells

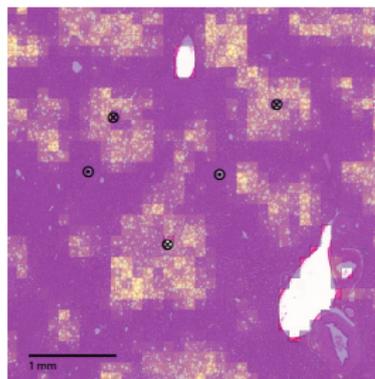
## 2. Four-Scale Model

### Sinusoid and Organ Scale



### Representative sinusoids

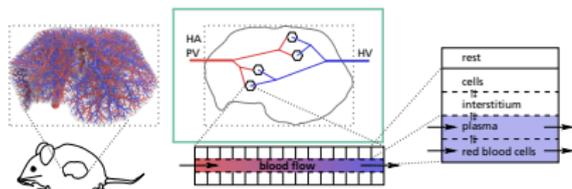
- zonation
  - ⇒ parameters depend on position along rep. sin.



Serene Lee, Wolfgang Thasler, André Homeyer

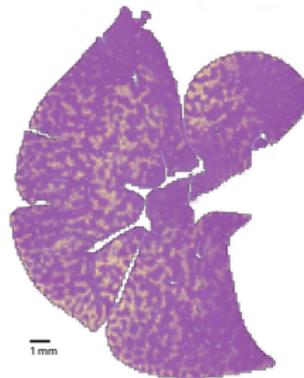
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### Sinusoid and Organ Scale



### Representative sinusoids

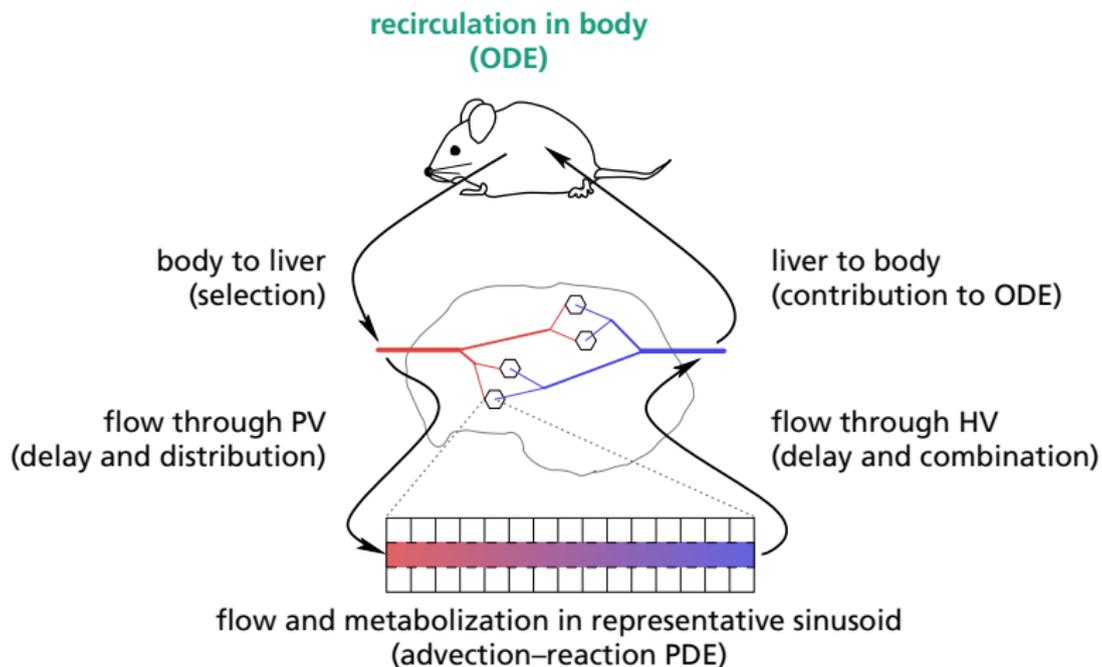
- zonation
  - ⇒ parameters depend on position along rep. sin.
- organ-scale heterogeneity
  - ⇒ one rep. sin. per 'region'



Uta Dahmen, André Homeyer

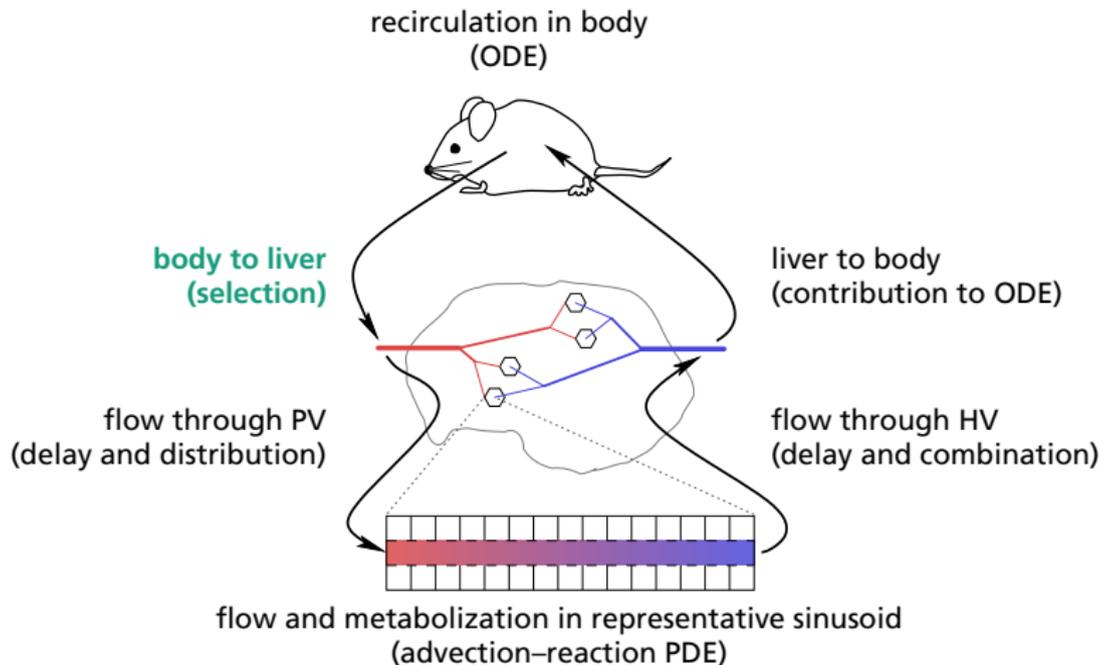
## 2. Four-Scale Model

### Integration to Body Scale



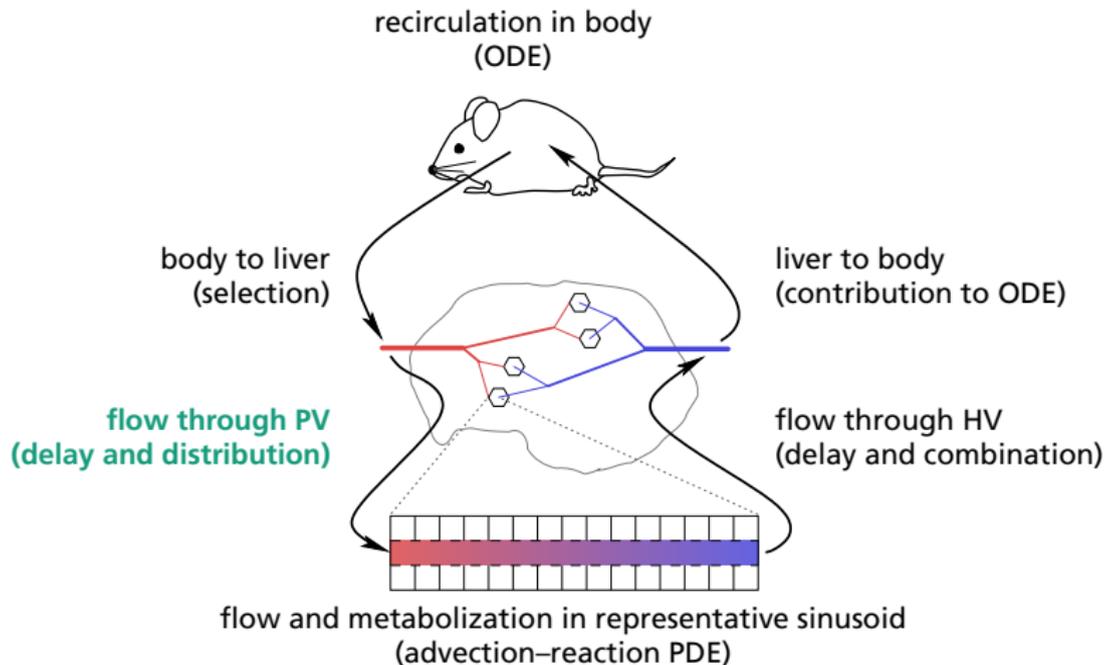
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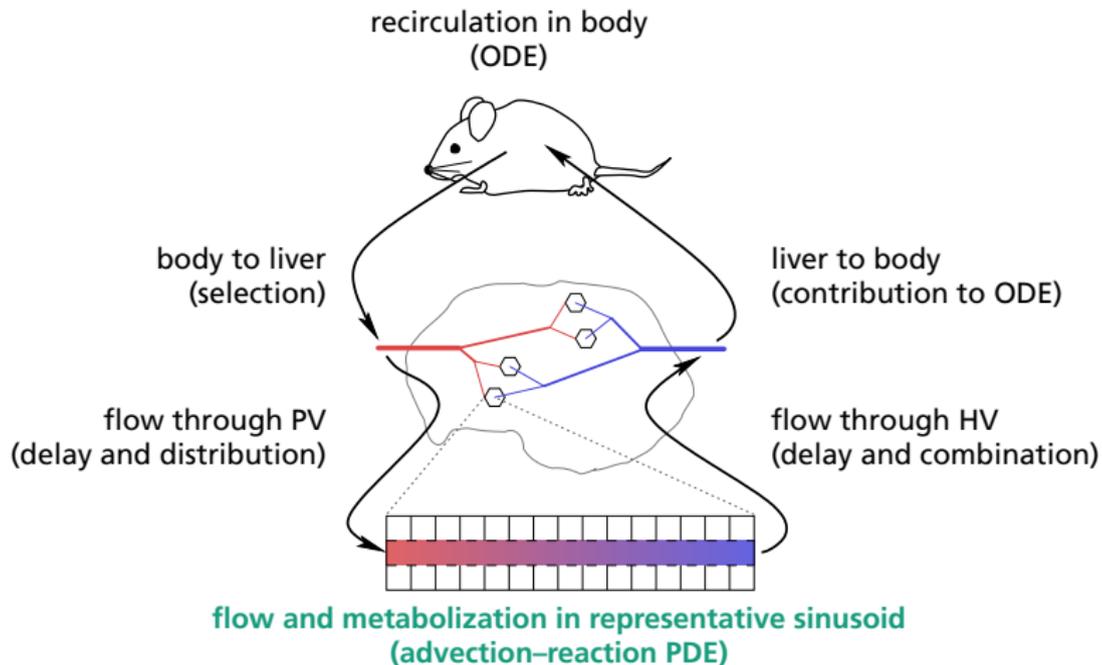
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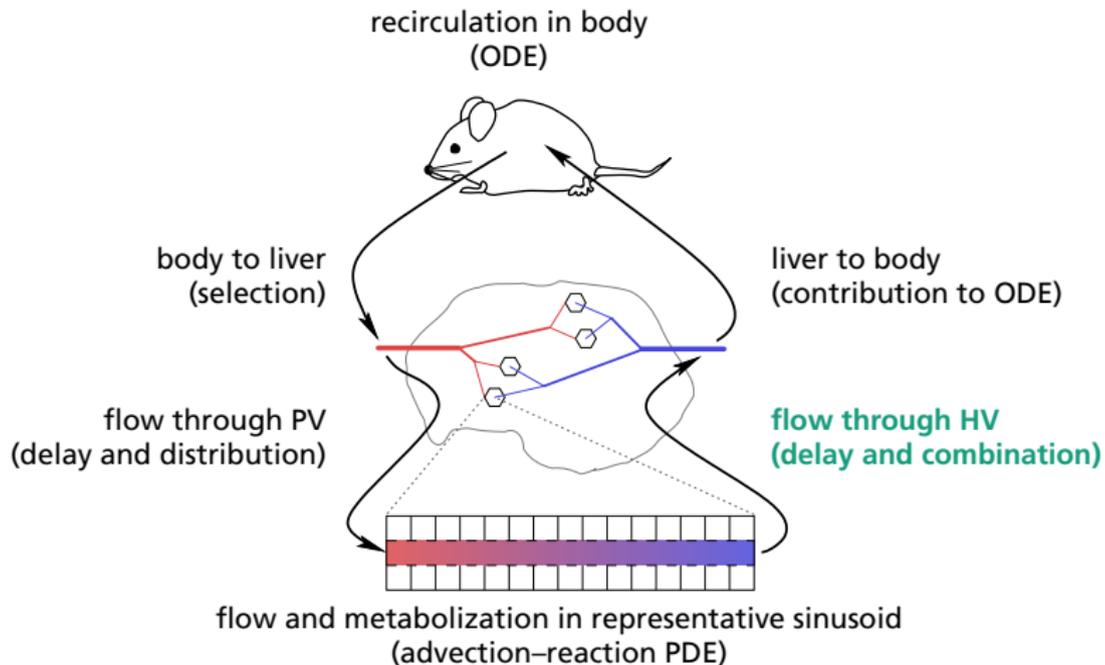
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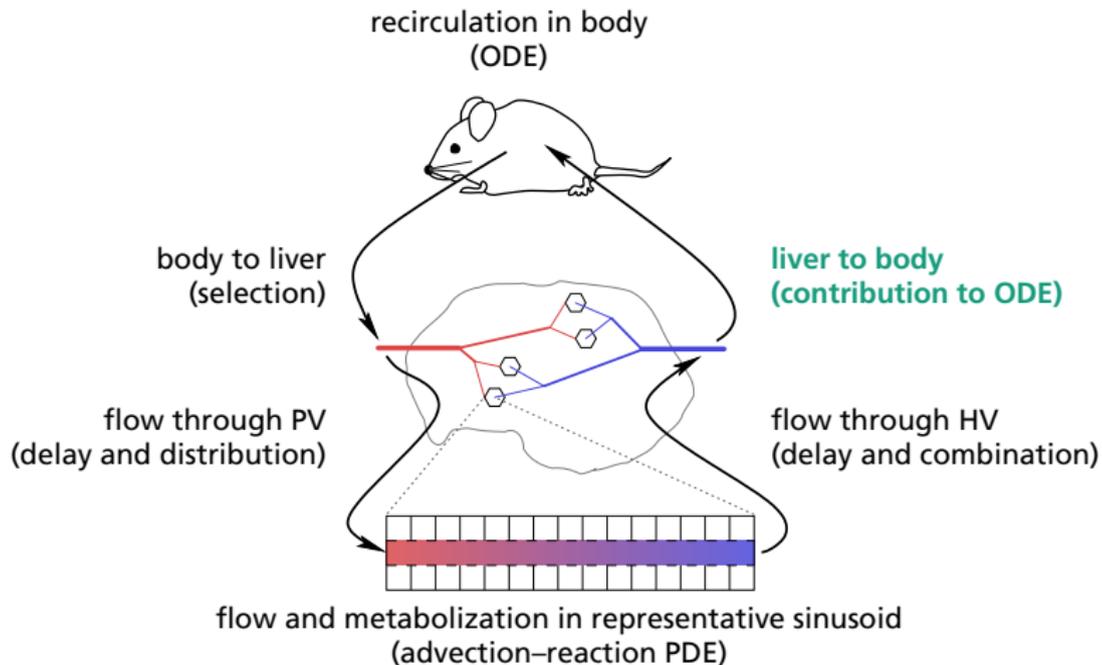
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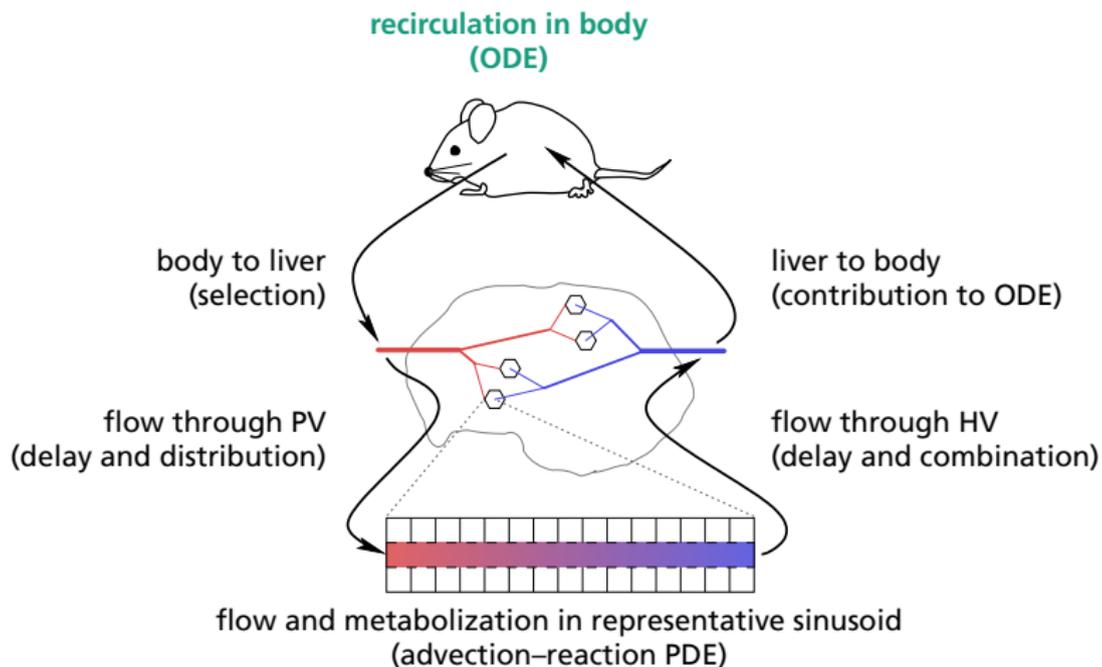
## 2. Four-Scale Model

### Integration to Body Scale



## 2. Four-Scale Model

### Integration to Body Scale



# 3. Applications and Results

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### 3. Applications and Results

#### Human Talinolol Model

- human model (20 hepatocytes)
- non-zonated metabolism for Talinolol, a beta blocker
- preliminary parameters for representative sinusoids
- 30 mg injected in portal vein in 2 s

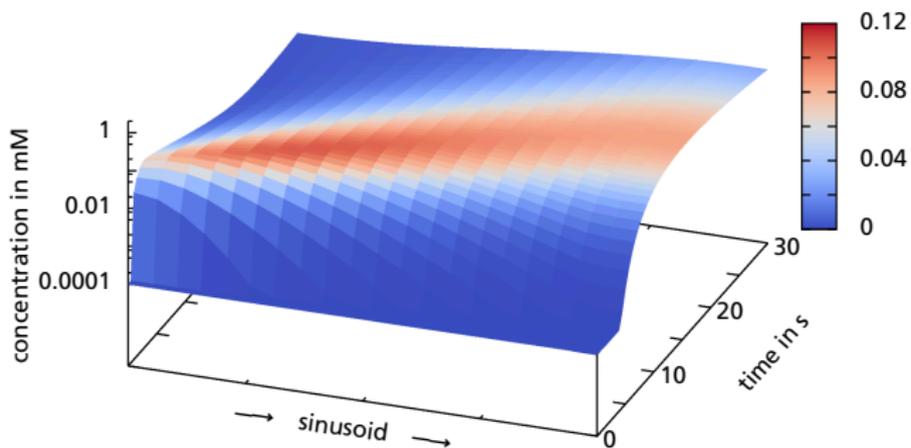
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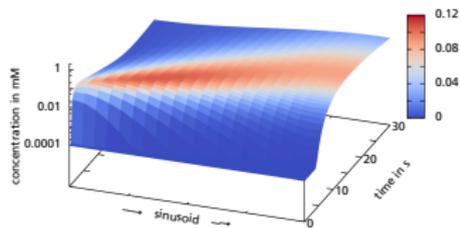
### 3. Applications and Results

#### Talinolol, Sinusoid-Scale

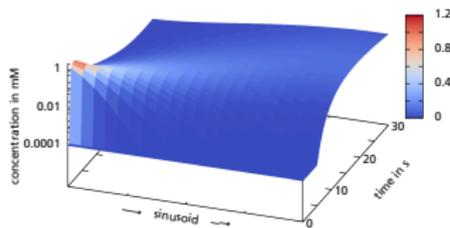


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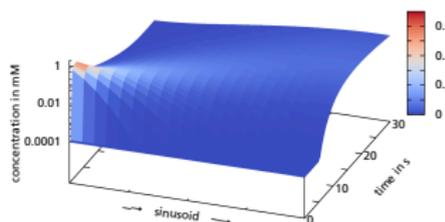
## Talinolol, Sinusoid-Scale



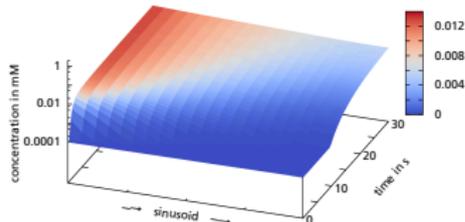
red blood cells



plasma



interstitium

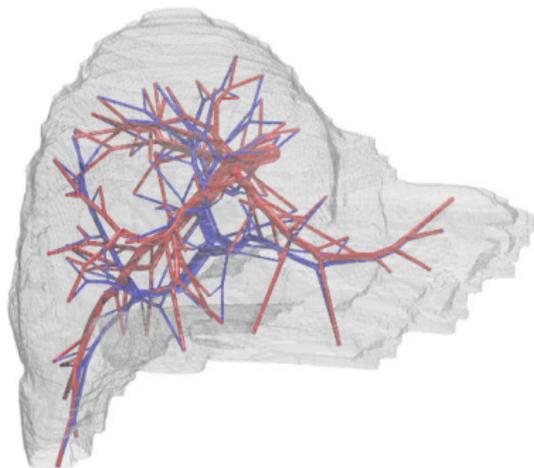


cells

### 3. Applications and Results

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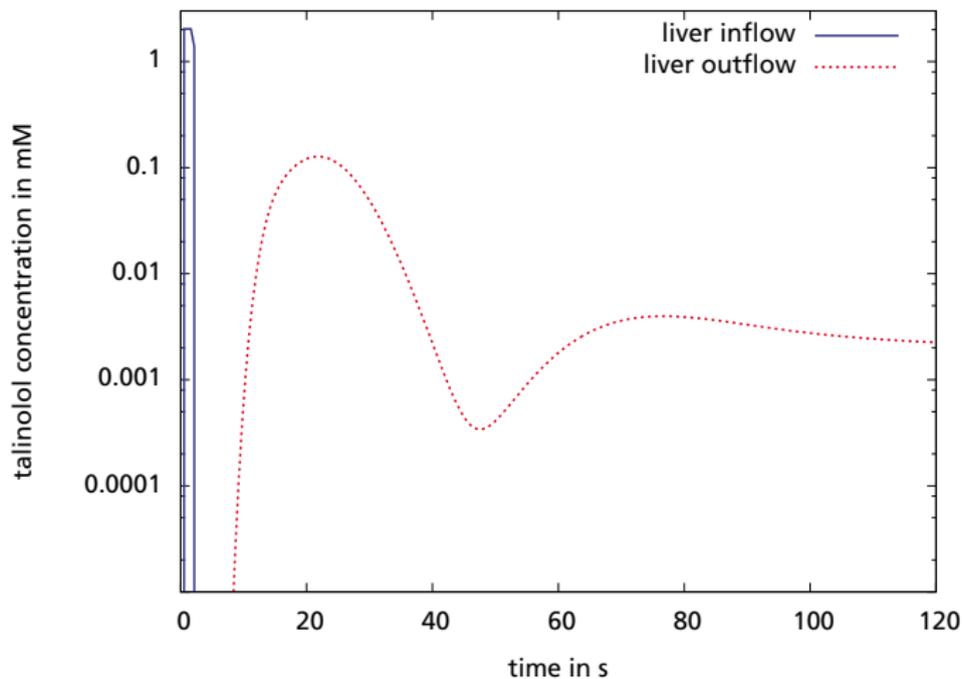
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  - preliminary parameters for representative sinusoids
  - 30 mg injected in portal vein in 2 s
1. single representative sinusoid
  2. organ scale (multiple representative sinusoids) with recirculation delay



supply/drainage for 100 regions

### 3. Applications and Results

#### Talinolol, Organ-Scale

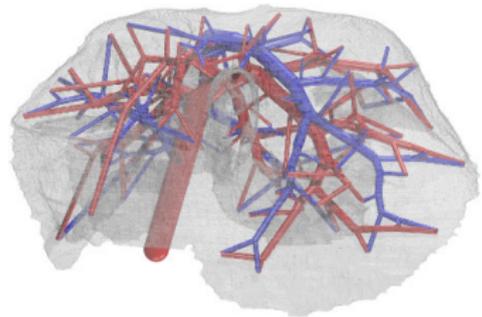


### 3. Applications and Results

#### Murine Caffeine Model

[Schenk et al., Poster P4.4]

- mouse model

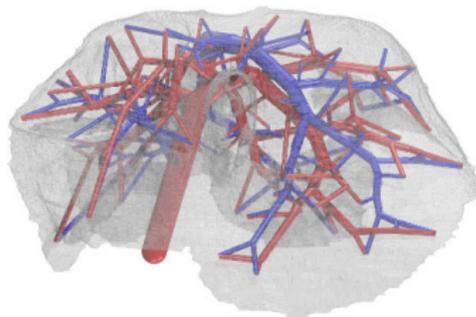


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- zoned metabolism: enzyme only present in pericentral hepatocytes



metabolization:

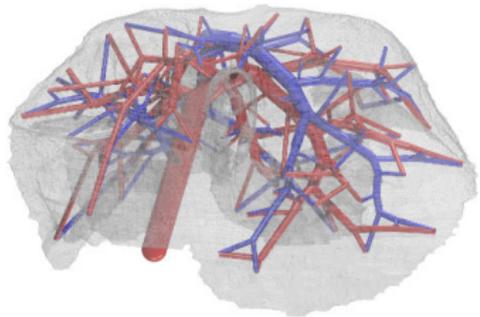


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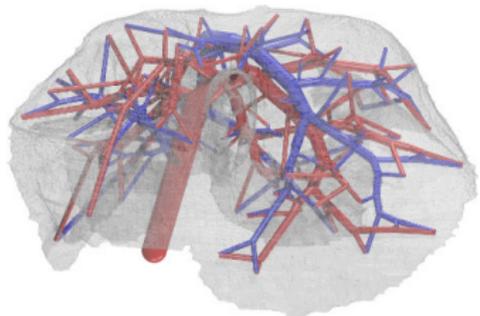


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    - 1.1 healthy



steatosis:

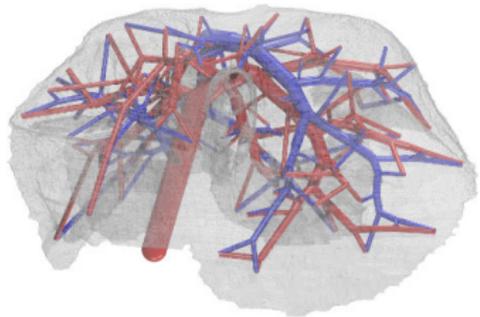


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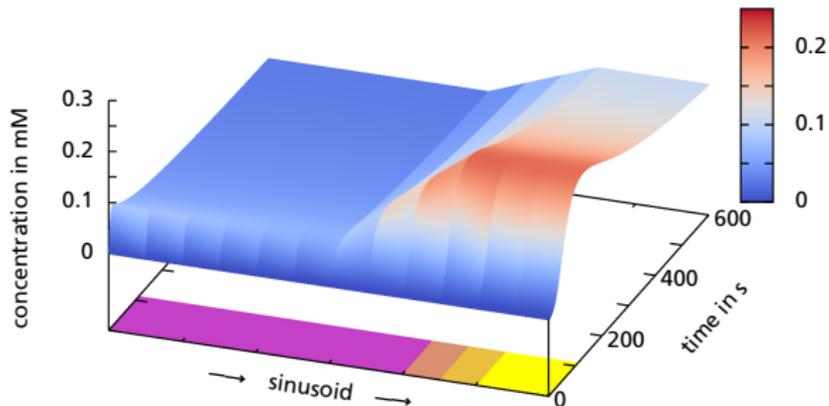
steatosis:



### 3. Applications and Results

## Caffeine, Sinusoid-Scale

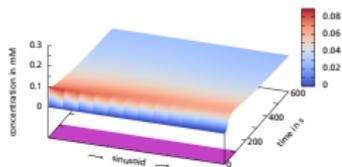
cellular concentrations



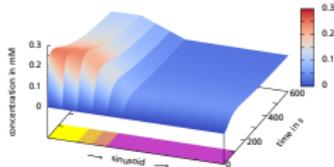
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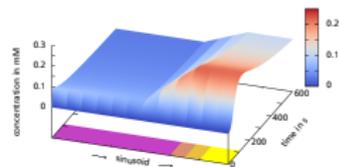
cellular concentrations



healthy



periportal steatosis



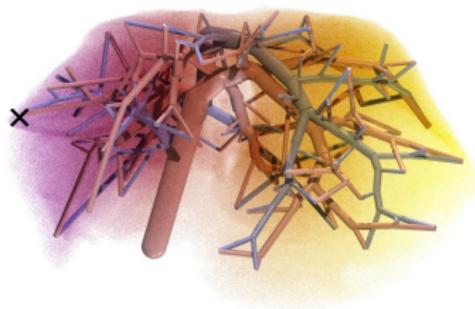
pericentral steatosis

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    - 1.2 periportal and pericentral steatosis
  2. organ-scale heterogeneous case (steatosis)



steatosis:

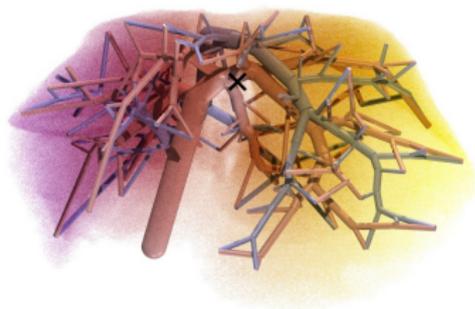


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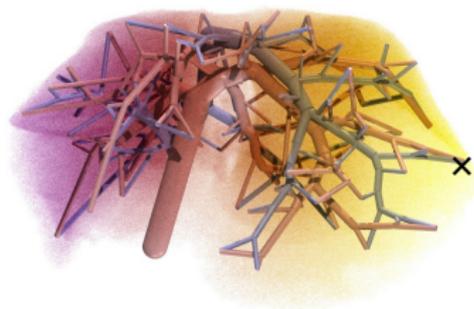


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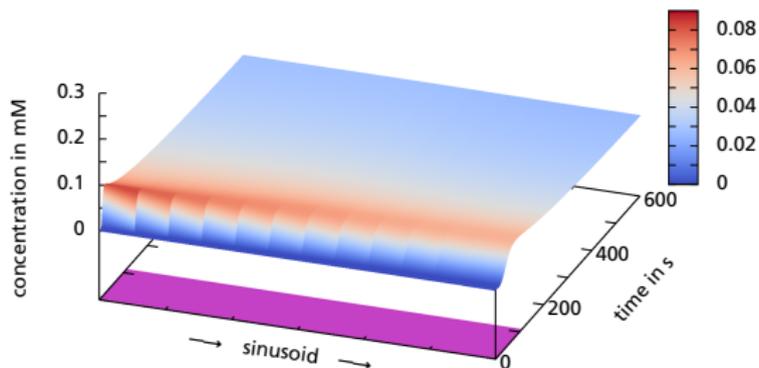
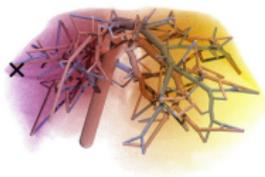


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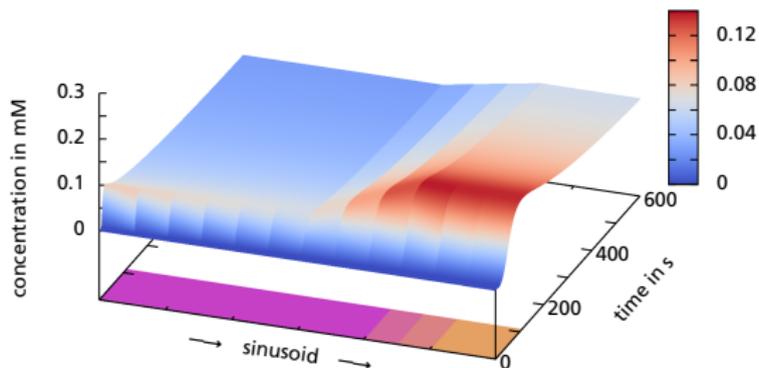
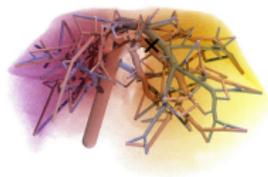
### 3. Applications and Results

#### Caffeine, Organ-Scale



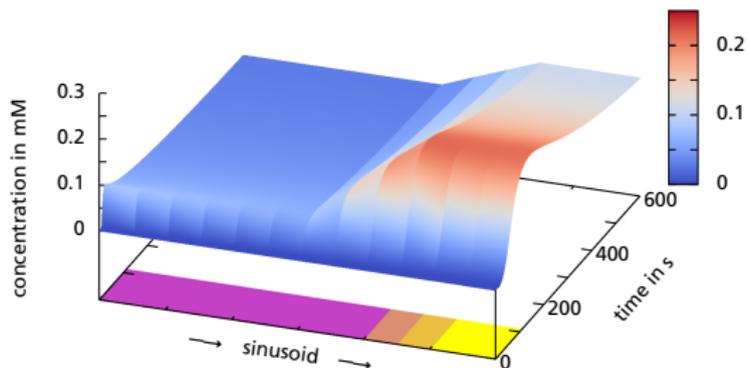
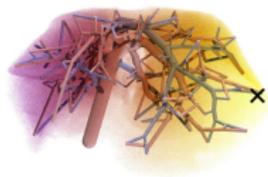
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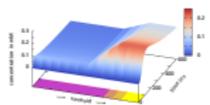
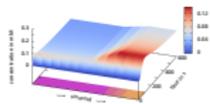
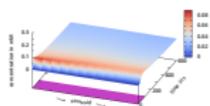
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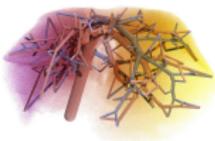


### 3. Applications and Results

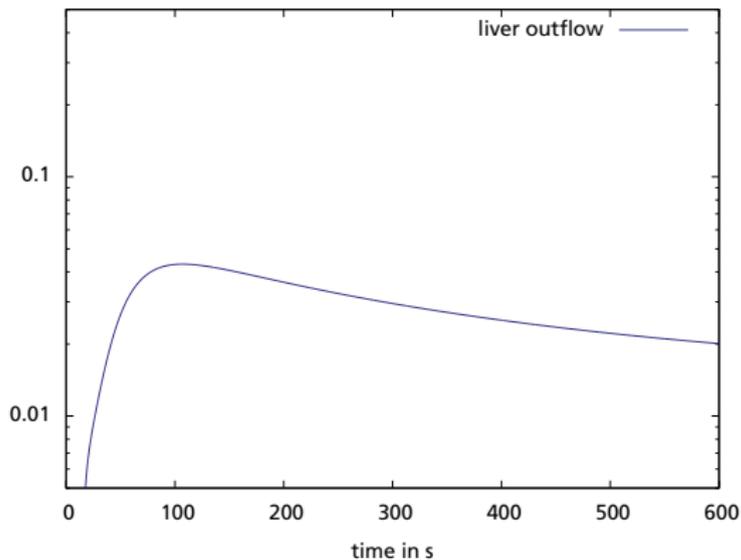
## Caffeine, Organ-Scale



...



caffeine concentration in mM



## 4. Outlook

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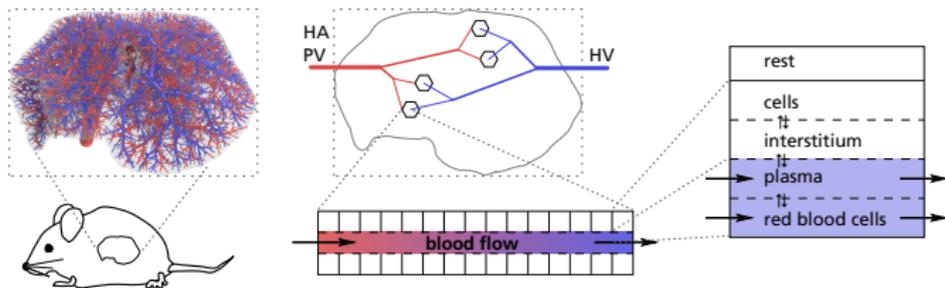
3. Applications and Results

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## 4. Outlook

- experimental input and validation
- refined model
  - pharmacokinetics parameters
  - blood flow delays
  - influence of steatosis

# Summary



Four-scale liver model based on representative sinusoids

- mechanistic metabolism model
- inhomogeneity at different scales

# Contributions

## Experiments (IfADO Dortmund)

- Ahmed Ghallab
- Jan Hengstler

## Data Analysis (IKP, Stuttgart)

- Ute Hofmann

## PBPK Modeling (BTS, Leverkusen)

- Arne Schenk
- Markus Krauss
- Lars Küpfer

## $\mu$ CT Imaging (ExMI, RWTH Aachen)

- Felix Gremse
- Fabian Kiessling

## MR Imaging (MEVIS, Bremen)

- Benjamin Knowles

## Image Processing (MEVIS, Bremen)

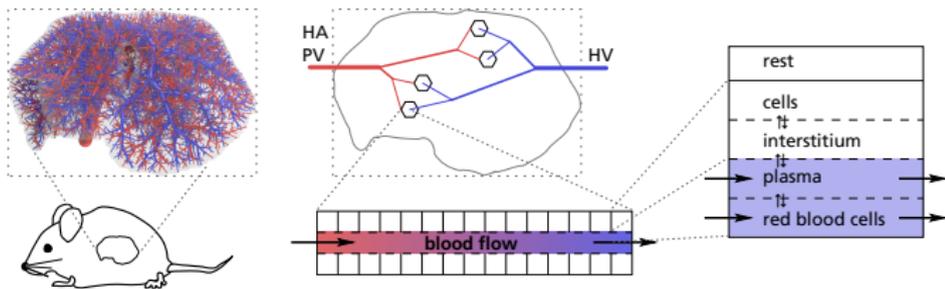
- Andrea Schenk

## Modeling (MEVIS, Bremen)

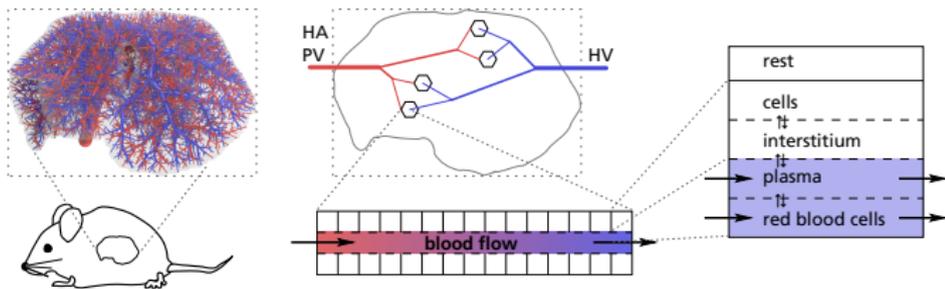
- Tobias Preusser

## Discussion, Images, ...

Uta Dahmen, Serene Lee, André Homeyer, Hergo Holzhütter



**Contact:** Ole Schwen <ole.schwen@mevis.fraunhofer.de>



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