
ZONATED QUANTIFICATION OF STEATOSIS FOR PHARMACOKINETICS SIMULATIONS

Lars Ole Schwen

Joint work with

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20. Chirurgische Forschungstage

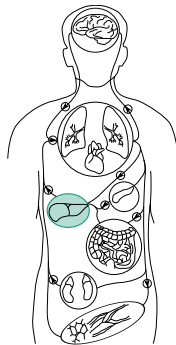
Systembiologie der (Fett-)Leber und Implikationen für chirurgische Forschung
Magdeburg, 2016-09-09



1. Introduction

Pharmacokinetics Simulations

- different organs
- compounds in blood
- model using ordinary differential equations (ODEs)
 - blood flow
 - exchange
 - metabolism
- here: focus on liver

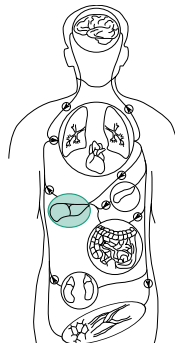


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http://upload.wikimedia.org/wikipedia/en/2/22/WholeBody_wiki.svg

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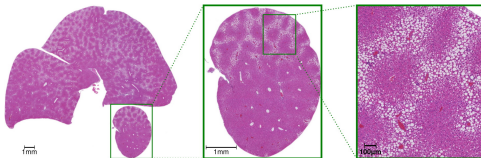


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http://upload.wikimedia.org/wikipedia/en/2/22/WholeBody_wiki.svg

Challenge:

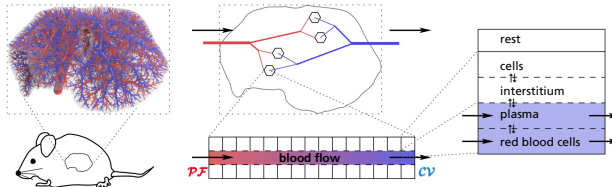
classical 'well stirred' models
cannot represent heterogeneity,
e.g., steatosis



[Zonated quantification of steatosis in an entire mouse liver. Comput Biol Med 73:108–118, 2016.]

2. Methods

Spatially Resolved PK Model

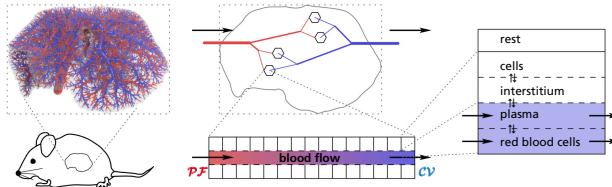


- mechanistic spatially resolved pharmacokinetics model

[Representative sinusoids for hepatic four-scale pharmacokinetics simulations. PLOS ONE, 10(7):e0133653, 2015.]

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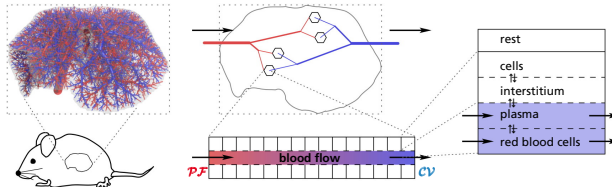


- mechanistic spatially resolved pharmacokinetics model
- four spatial scales
 - body
 - organ
 - sinusoid
 - cellular

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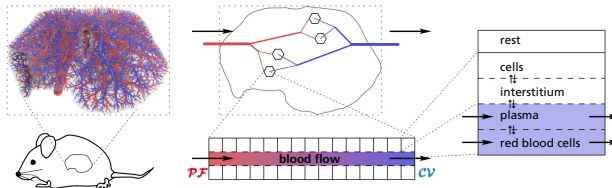


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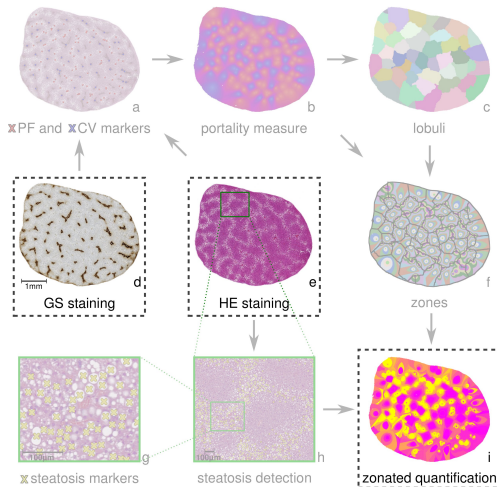


- mechanistic spatially resolved pharmacokinetics model
- four spatial scales $\Rightarrow$ reflect zonation and organ-scale heterogeneity
 - body
 - organ
 - sinusoid
 - cellular
- parameterized partial differential equations (PDEs)

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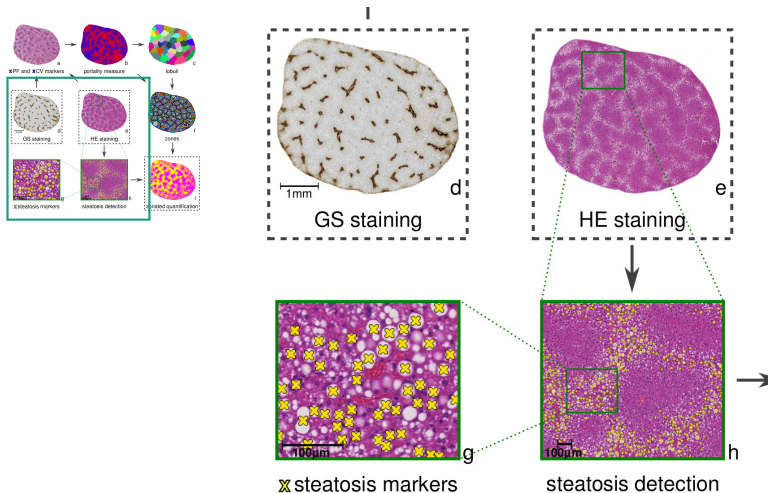
Heterogeneity Quantification from Histo Images



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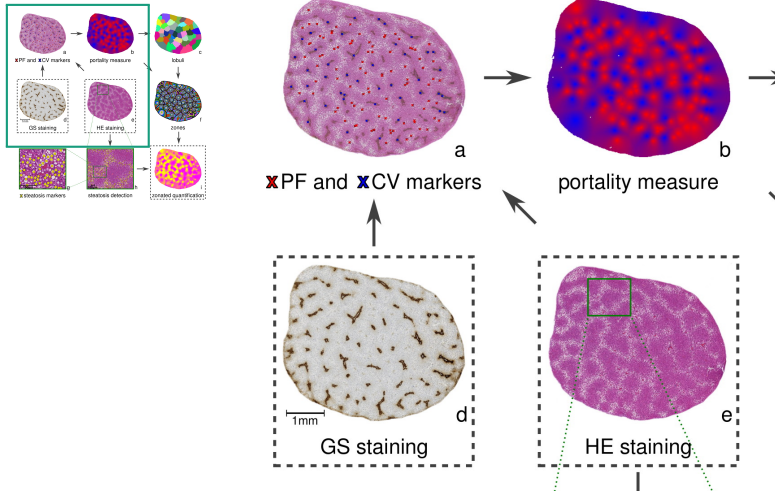
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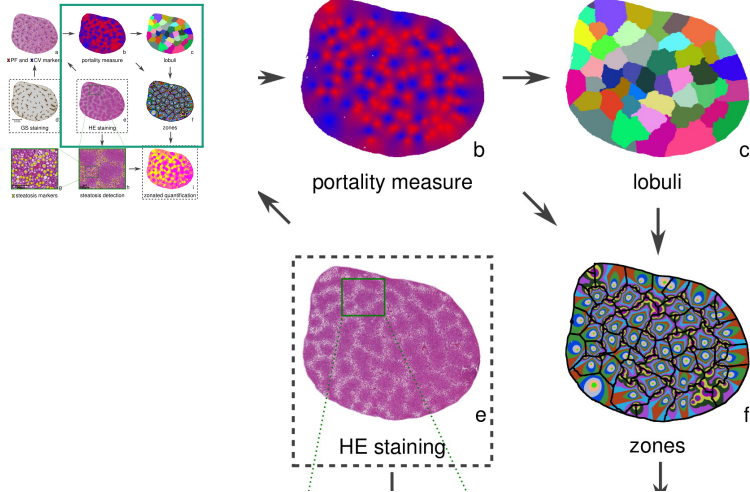
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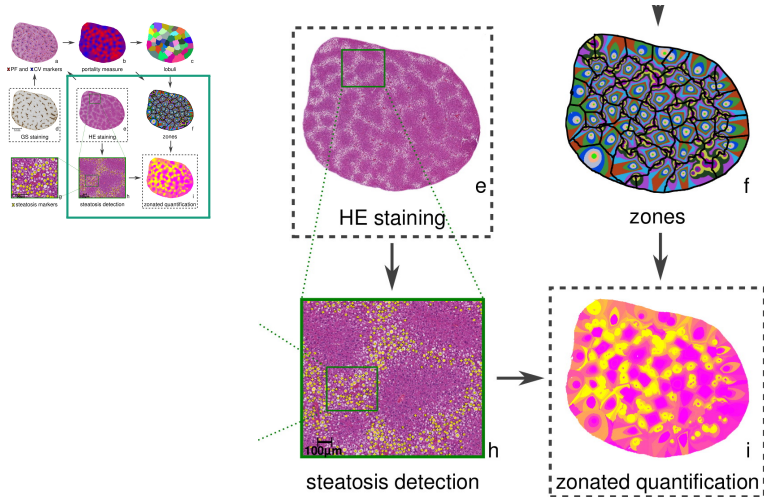
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2. Methods

Heterogeneity Quantification: Result



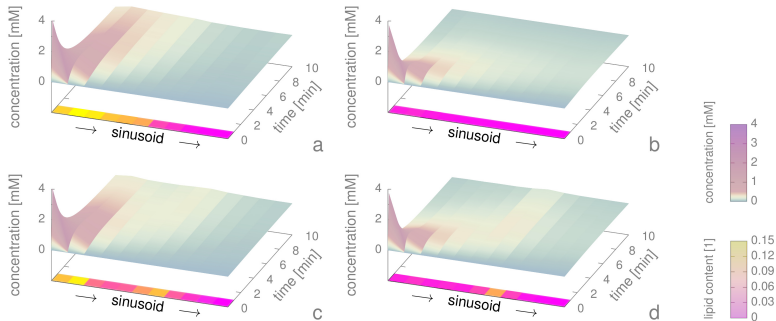
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3. Results

Example Simulation Results

Different 'representative' steatosis patterns

↪ cellular concentration of dextrometorphan



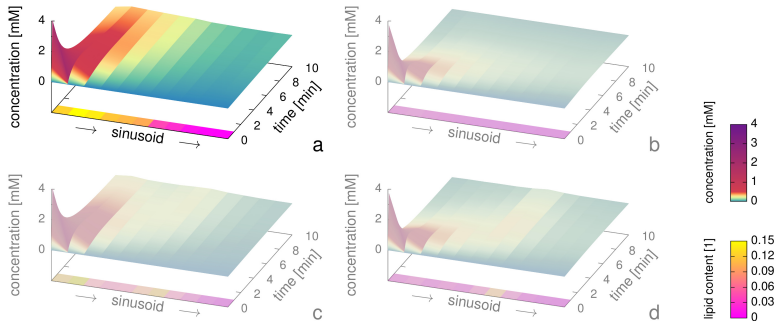
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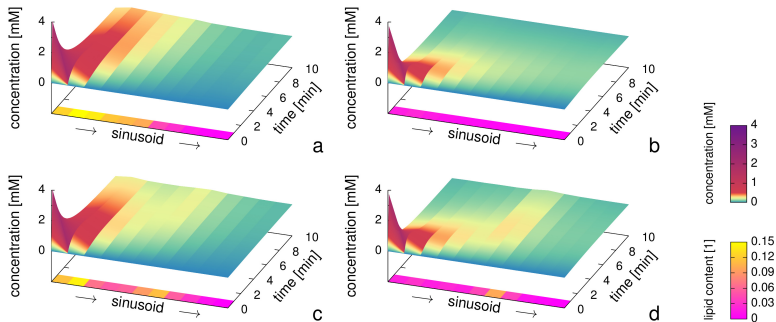
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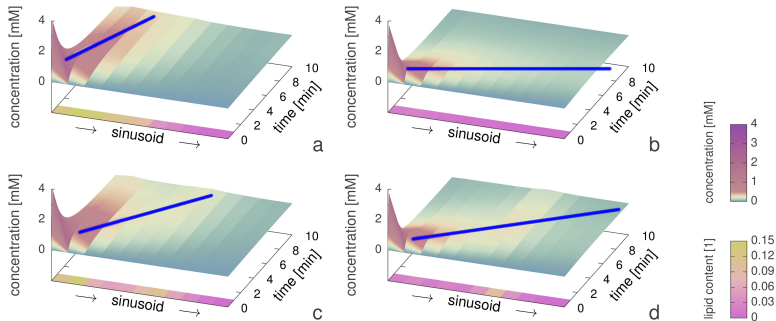
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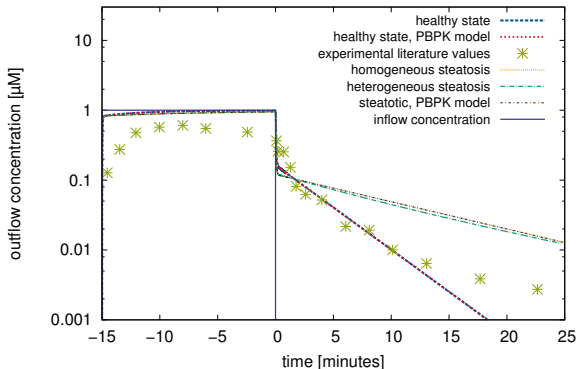


↪ different **apparent velocity** of peak ($\neq$ flow velocity!)

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3. Results

First Validation and Model Prediction: Spiramycin



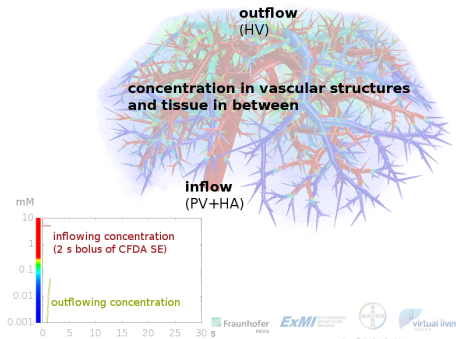
- isolated perfused mouse liver
- earlier continuum-based PK model variant

[Spatio-Temporal Simulation of First Pass Drug Perfusion in the Liver PLOS Comp Biol, 10(3):e1003499, 2014]

3. Results

Further Simulation Results

First-pass perfusion of the tracer CFDA-SE
(carboxyfluorescein diacetate succinimidyl ester)



→ Video

[Spatio-Temporal Simulation of First Pass Drug Perfusion in the Liver PLOS Comp Biol, 10(3):e1003499, 2014]

4. Perspective

Further Applications

- other species: human models

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- other species: human models
- other relevant compounds

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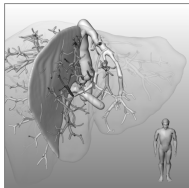
Further Applications

- other species: human models
- other relevant compounds
- other diseases

4. Perspective

Further Applications

- other species: human models
- other relevant compounds
- other diseases
- post-surgery conditions

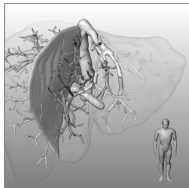


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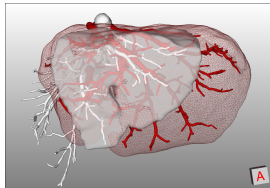
4. Perspective

Further Applications

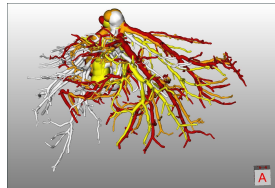
- other species: human models
- other relevant compounds
- other diseases
- post-surgery conditions
- time-dependent input parameters ($\Leftarrow$ progression/regeneration)



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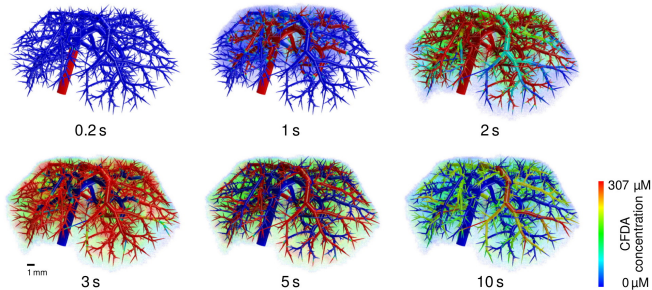


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5. Contact



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