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Integration of Representative Sinusoids into a Physiologically Based Whole-Body Model for a Detailed Description of Biliary Transport

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Introduction

- Enterohepatic circulation (EHC) important for distribution and clearance of drugs
- Transport mechanisms involve biliary transport
- Cholyl-lysyl-fluorescein (CLF), an analogon of natural bile acids, is used as probe molecule

Goals

- Quantify kinetics of transport processes
- Include them in physiologically based pharmacokinetics (PBPK) models
- Obtain parameters via fluorescence imaging [2]

Approach

- Combine well-stirred organism-scale model and detailed liver model
- Multi-scale, spatially resolved “representative sinusoid model” extended from [3, 4]

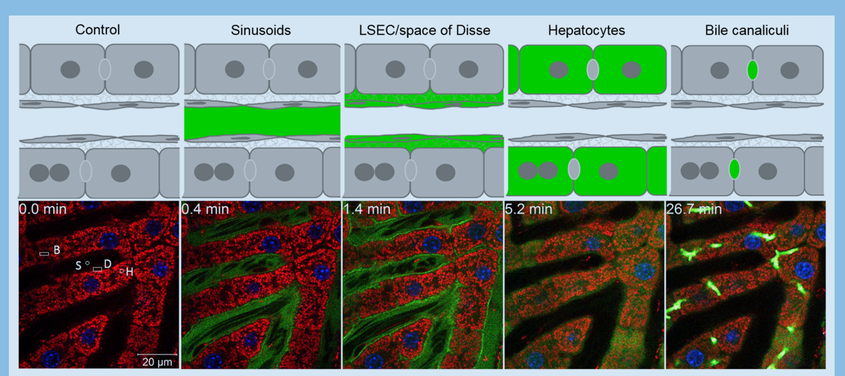

Fig. 1. CLF concentration measurements by intravital two-photon imaging [2] (CC-BY)

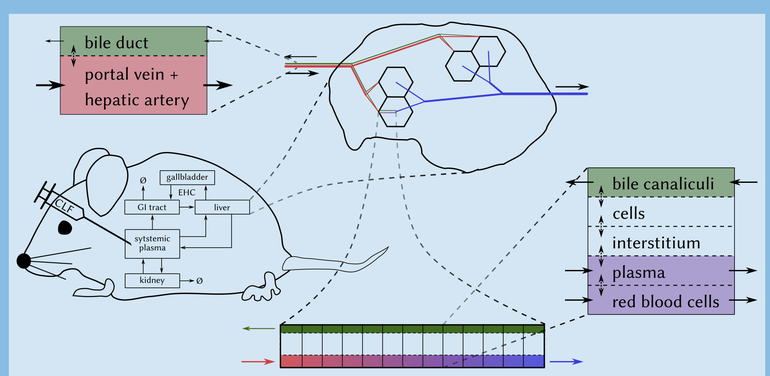

Fig. 2. Conceptual sketch of the multiscale CLF model including biliary transport

First Step: Isolated Perfused Liver

$$\partial_t \begin{bmatrix} c^{\mathrm{rbc}} \\ c^{\mathrm{pls}} \\ c^{\mathrm{int}} \\ c^{\mathrm{cell}} \\ c^{\mathrm{bile}} \end{bmatrix} = \underbrace{\begin{bmatrix} \frac{-P_{\mathrm{rbc,pls}}}{\kappa_{\mathrm{rbc,pls}}\varphi^{\mathrm{rbc}}} & \frac{+P_{\mathrm{rbc,pls}}}{\varphi^{\mathrm{rbc}}} & 0 & 0 & 0 \\ \frac{+P_{\mathrm{rbc,pls}}}{\kappa_{\mathrm{rbc,pls}}\varphi^{\mathrm{pls}}} & \frac{-P_{\mathrm{rbc,pls}}}{\varphi^{\mathrm{pls}}} + \frac{-P_{\mathrm{pls,int}}}{\varphi^{\mathrm{pls}}} & \frac{+P_{\mathrm{pls,int}}}{\kappa_{\mathrm{pls,int}}\varphi^{\mathrm{pls}}} & 0 & 0 \\ 0 & \frac{+P_{\mathrm{pls,int}}}{\varphi^{\mathrm{int}}} & \frac{-P_{\mathrm{pls,int}}}{\kappa_{\mathrm{pls,int}}\varphi^{\mathrm{int}}} + \frac{-P_{\mathrm{int,cell}}\kappa^{\mathrm{int}}}{\varphi^{\mathrm{int}}} & \frac{+P_{\mathrm{int,cell}}\kappa^{\mathrm{cell}}}{\varphi^{\mathrm{int}}} & 0 \\ 0 & 0 & \frac{+P_{\mathrm{int,cell}}\kappa^{\mathrm{int}}}{\varphi^{\mathrm{cell}}} & \frac{-P_{\mathrm{int,cell}}\kappa^{\mathrm{cell}}}{\varphi^{\mathrm{cell}}} & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}}_{\text{passive diffusion}} \begin{bmatrix} c^{\mathrm{rbc}} \\ c^{\mathrm{pls}} \\ c^{\mathrm{int}} \\ c^{\mathrm{cell}} \\ c^{\mathrm{bile}} \end{bmatrix} + \underbrace{\begin{bmatrix} 0 \\ 0 \\ -\frac{V_{\max}^{\mathrm{int,cell}}\kappa^{\mathrm{int}}c^{\mathrm{int}}}{\varphi^{\mathrm{int}}\left(K_m^{\mathrm{int,cell}}+\kappa^{\mathrm{int}}c^{\mathrm{int}}\right)} \\ +\frac{V_{\max}^{\mathrm{int,cell}}\kappa^{\mathrm{int}}c^{\mathrm{int}}}{\varphi^{\mathrm{cell}}\left(K_m^{\mathrm{int,cell}}+\kappa^{\mathrm{int}}c^{\mathrm{int}}\right)} \\ 0 \end{bmatrix}}_{\text{active transport}} + \underbrace{\begin{bmatrix} 0 \\ 0 \\ 0 \\ -\frac{V_{\max}^{\mathrm{cell,bile}}\kappa^{\mathrm{cell}}c^{\mathrm{cell}}}{\varphi^{\mathrm{cell}}\left(K_m^{\mathrm{cell,bile}}+\kappa^{\mathrm{cell}}c^{\mathrm{cell}}\right)} \\ +\frac{V_{\max}^{\mathrm{cell,bile}}\kappa^{\mathrm{cell}}c^{\mathrm{cell}}}{\varphi^{\mathrm{bile}}\left(K_m^{\mathrm{cell,bile}}+\kappa^{\mathrm{cell}}c^{\mathrm{cell}}\right)} \end{bmatrix}}_{\text{active transport}} + \underbrace{\begin{bmatrix} +v_{\mathrm{blood}}\nabla_x c^{\mathrm{rbc}} \\ +v_{\mathrm{blood}}\nabla_x c^{\mathrm{pls}} \\ 0 \\ 0 \\ -v_{\mathrm{bile}}\nabla_x c^{\mathrm{bile}} \end{bmatrix}}_{\text{blood/bile flow}}$$

rbc: red blood cells, pls: plasma, int: interstitium, cell: hepatocytes, bile: bile canaliculi
P: permeabilities, κ: partition coefficients, φ: volume fractions, v: flow velocities, parameters partially from [1]

First Results

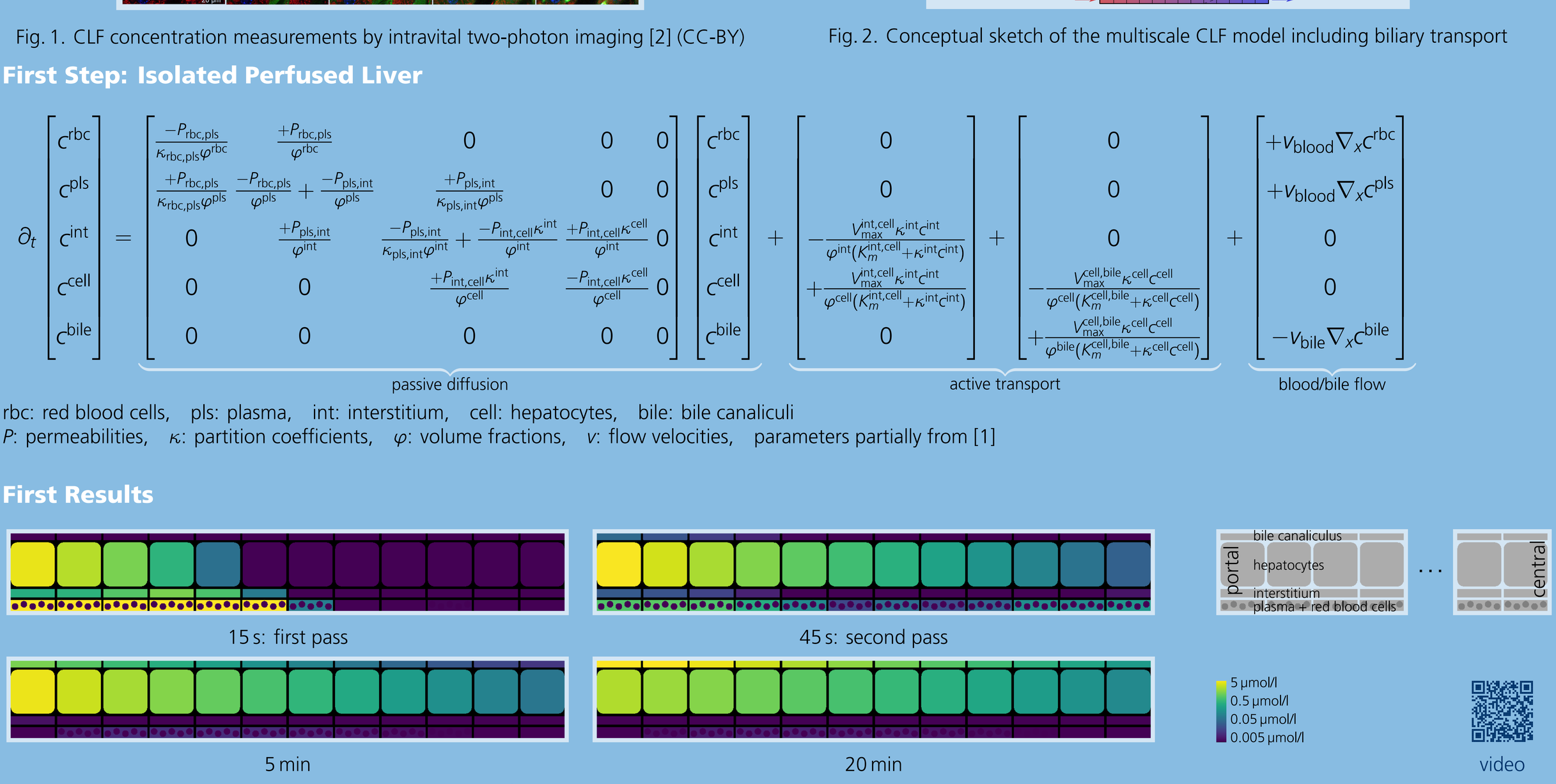

Fig. 3. Simulation of CLF distribution after bolus injection, representing the liver by a single sinusoid and the organism only by a blood pool.

Next Steps

- refine phyiology and physicochemistry in model structure and parameters
  - at sinusoidal scale
  - at organ-scale, including vascular systems and heterogeneity
  - at organism-scale, including excretion
- calibrate model parameters
- validate by comparison to experiments

Literature

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