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]

First Step: Isolated Perfused Liver

\[
\begin{align*}
\frac{\partial}{\partial t} \begin{bmatrix}
c_{\text{bc}} \\
c_{\text{pl}} \\
c_{\text{int}} \\
c_{\text{cell}} \\
c_{\text{bile}}
\end{bmatrix} &= \\
&= \begin{bmatrix}
-k_{\text{bc,pl}} + k_{\text{pl,bc}} & k_{\text{bc,pl}} & 0 & 0 & 0 \\
0 & -k_{\text{pl,bc}} + k_{\text{bc,pl}} & k_{\text{pl,cell}} & 0 & 0 \\
0 & 0 & -k_{\text{int,cell}} & k_{\text{int,bc}} & 0 \\
0 & 0 & 0 & -k_{\text{cell,bile}} & k_{\text{cell,pl}} \\
0 & 0 & 0 & 0 & -k_{\text{bile,bc}}
\end{bmatrix} \\
&\text{+ active transport} \begin{bmatrix}
0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0
\end{bmatrix} \\
&\text{+ blood/bile flow} \begin{bmatrix}
0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0
\end{bmatrix}
\end{align*}
\]

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

First Results

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

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 physiology 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