Multi-scale simulation of zonated metabolism in steatotic livers

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Detoxification of the blood is one of the manifold tasks of the liver in the mammalian body. Hepatocytes, the major metabolizing cells in the liver, are organized along sinusoids where about 12 successive cells (in mouse livers) perform compound exchange with the blood and metabolization [1]. The sinusoids form one important length scale for clearance inhomogeneity due to zonated cellular properties (e.g., ammonia detoxification [2]) or pathologies (e.g., necrosis after CCl_4 intoxication [3]). Pathologies can also occur heterogeneously between different regions in the liver (e.g., fibrosis [4] or cirrhosis), introducing a second length scale. Steatosis, a common disease in which abnormal lipid droplets form in liver cells, can be observed to be inhomogeneous at both these length scales [5], see Figure 1 for an example in mice. We show how the extent of steatosis can be quantified with high spatial resolution and how this information can be used in pharmacokinetic simulations. As an extension of previous simulations [6], see Figures 2 and 3, we now use actual experimentally measured spatial steatosis distributions.

These steatosis measurements were obtained using optically imaged histological slices. For this purpose, mouse liver tissue with steatosis was embedded in paraffin, cut into 4µm thin sections and mounted to microscope slides. The slides were stained with haematoxylin and eosin and imaged with a Hamamatsu NanoZoomer 2.0-HT scanner (Hamamatsu Photonics K.K., Japan) at 0.46 µm/pixel resolution. In the images, steatosis becomes visible as thousands of bright, roundish fat droplets, surrounded by liver tissue appearing in various shades of red, pink and blue. Fat droplets, portal fields and central veins were fully annotated across entire tissue sections. Fat droplets were identified via automated image analysis [7], by segmenting all bright areas with thresholds to pixel intensities and then sorting out non-droplet areas, like vessels or tissue cracks, with respect to shape features. The annotation of portal fields and central veins, on the other hand, was performed manually in a graphical user interface.

Clearance effects of the liver (i.e., the removal of compounds from the blood stream) have been addressed by various modeling approaches in the literature [8], in particular by physiologically based pharmacokinetics (PBPK) models [9]. Based on these, we use a representative-sinusoid-based clearance modeling approach as part of a multiscale modeling framework. The simulation considers an individuum-specific organ geometry whose vascular structures connect model sinusoids to a whole-body pharmacokinetics model. In the sinusoids, blood flow along the sinusoid are considered as well as exchange between red blood cells, blood plasma, interstitium, and liver cells plus metabolization in the latter. Mathematically, these processes are described by an advection-reaction (PDE+ODE) problem for each sinusoid, each of which is representative for a certain region of the liver. This permits spatially resolved clearance simulations taking into account steatosis as the exemplary pathological condition considered here. Both zonation and organ-scale heterogeneity are determined as described above. The PBPK (ODE) parameters are correspondingly assumed to be influenced by steatosis as in [6]. We additionally take into account pathological perturbations of other model parameters such as the microcirculation.

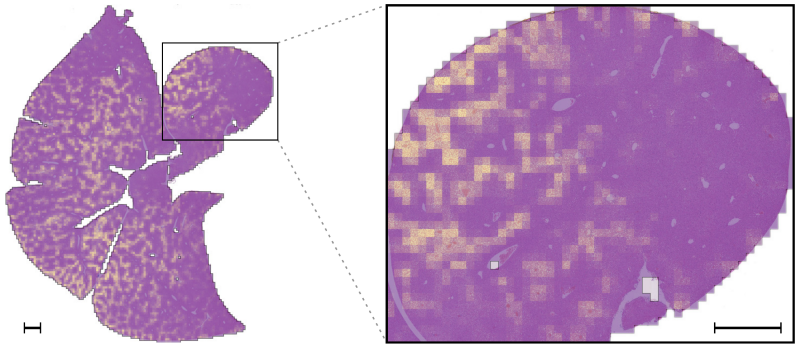

Figure 1. Steatosis heterogeneity in a mouse liver. In histological whole-slide-scans of a mouse liver, the amount of steatosis is analyzed and visualized on a color scale from violet (low) to yellow (high). Heterogeneity can be observed at two length scales: Within and between the different lobes (left image) as well as on a lobular scale (right image).

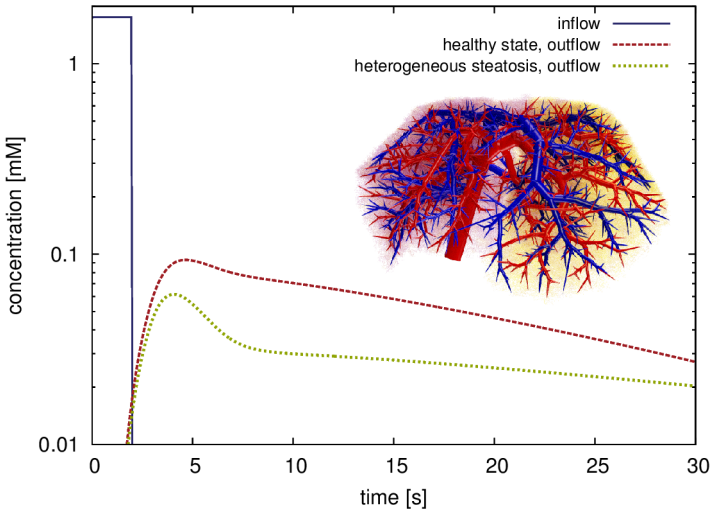

Figure 2. Simulating the impact of steatosis on hepatic detoxification capacity (adapted from [8]).

Using a 2s bolus injection of the drug midazolam (blue solid line in the plot), the simulation for an isolated perfused mouse liver predicts an increase of metabolization capacity in steatotic livers (green dotted line; artificial amount of steatosis visualized in the volume rendering on a color scale from cyan to yellow) compared to the healthy state (red dashed line). This model prediction is in qualitative agreement with pharmacokinetic studies in a high-fat emulsion-induced rat model [10].

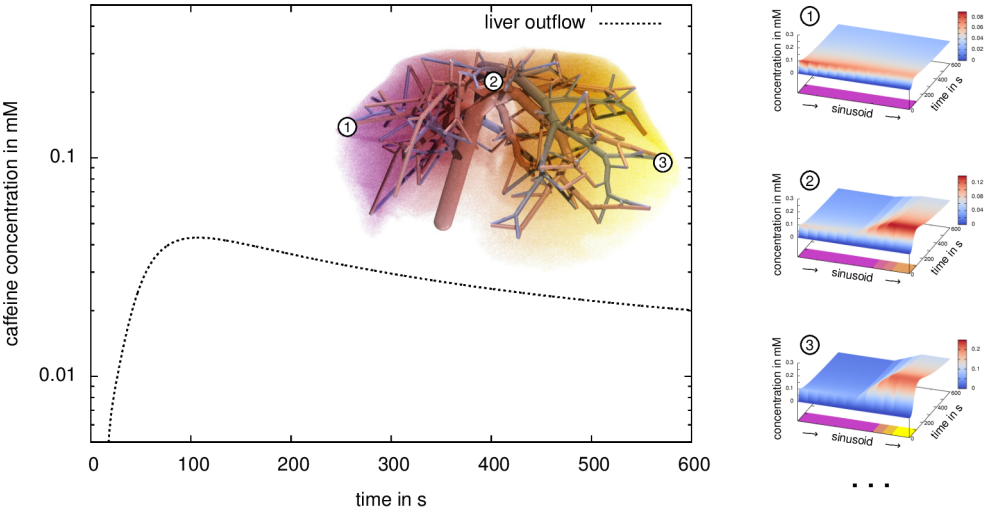

Figure 3. Simulating the impact of steatosis on hepatic detoxification capacity (adapted from [11]). For an instantaneous injection of caffeine in the arterial blood pool, an organism-scale simulation using a heterogeneously and zonated steatotic liver (here based on artificial pericentral steatosis was performed. Besides the liver outflow (large plot) as the connection to the organism, this approach permits a detailed insight into the local compound distributions in representative sinusoids for different regions of the liver. The smaller surface plots show the spatio-temporal cellular caffeine concentrations for three exemplary locations.

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