A Model for Micro-Dosimetry in Virtual Liver Tissues

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Motivation: Humans are potentially exposed to over 6,000 environmental chemicals. The liver is the primary organ for metabolism and often the first site of chemical-induced toxicity in animal testing, but it remains difficult to translate these outcomes to humans. To address this issue the US Environmental Protection Agency is developing a Virtual Liver – v-Liver™ – in order to computationally simulate clinically-relevant effects in humans. As a proof of concept, the Virtual Liver Project is focusing on tissue lesions caused by 20 non-genotoxic rodent carcinogens including: pesticides, persistent toxic substances, and plasticizers. Currently, we are modeling a canonical hepatic lobule (~ 1 mm diameter) as a complex cellular system in which parenchymal and non-parenchymal cells are spatially organized according to lobular morphology around a network of vessels, called sinusoids. In our model lesions arise from cellular alterations, which are caused by concentration-dependent perturbations in molecular pathways. Here we describe our initial approach for estimating the micro-anatomic distribution to hepatocytes of environmental chemicals in the lobule.

Approach: Organ-level concentrations are computed from environmental exposure via inhalation, ingestion, or dermal transport using physiologically-based pharmacokinetic (PBPK) models. Exact approaches for estimating cell-scale chemical concentrations within the liver are difficult because the sinusoidal structure is complex, highly permeable, and dynamic. To address this issue we propose a discrete, graph-based method for quantitatively approximating the transport of blood as it flows in from the portal triad, filters through the sinusoidal network, and ultimately leaves the lobule through the central vein. We represent lobular microanatomy as a graphical structure composed of two main node types: cell-nodes and vascular-nodes corresponding to roughly cell-sized regions through which blood can flow. The model of the lobule is synthesized geometrically using physiologic parameters in two steps: (i) layout the vascular-nodes as a connected vascular-graph along whose edges blood flows through the lobule, and then (ii) organize cell-nodes around the vascular-graph. We reduce the vascular-graph by aggregating vascular nodes into well-mixed sinusoids. Using the reduced sinusoidal-graph **G,** network flow algorithms, and mass balance we derive the concentration distribution across the hepatic lobule, $\frac{d\vec{\mathbf{C}}^i}{dt} = \ddot{\mathbf{E}} \cdot \vec{\mathbf{C}}^i - \vec{\mathbf{M}}^i \cdot \ddot{\mathbf{I}} \cdot \vec{\mathbf{C}}^i$, where **E** is the adjacency matrix of **G** and vectors $\mathbf{C}^i(t)$ and $\mathbf{M}^i(t)$ are the concentration and aggregated metabolic clearance of compound *i* in each sinusoid.

In this poster we describe our methods and initial results for connecting organism-level exposure to cellular concentrations.