Title: Blood Flow and Oxygen Distribution in a Simulated 3D Liver Lobule

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Previously we described a multiscale modeling framework for xenobiotic metabolism in the liver. The framework incorporates a PBPK whole body representation, a tissue level (multicell), representation of a liver sinusoid and subcellular signaling and metabolic pathways. The sub-models at each of these three scales communicate with the model(s) at higher or lower scales. Here we describe a refinement of the liver portion of our multiscale model consisting of a multi-cell 3D liver lobule. The human liver is constructed of approximately one million lobules "plumbed" with blood vessels in a parallel arrangement. The parallel nature of the lobules within the liver makes it possible to simulate the entire liver by simulating a small number of lobules. We have used Compucell3D to construct representative portions of a 3D lobule consisting of portal arterial plus venous blood sources, a network of sinusoids (liver capillaries) lined with hepatocytes and a central vein drain. The lobule is stochastically constructed but directed by parameters derived from the analysis of mouse livers. The resulting network is then used to simulate flow of oxygenated blood though the lobule using Kirchhoff's law. A critical assumption in the generation of the model is that the diameter of the sinusoids is constant throughout a lobule. This assumption, and Kirchhoff's law, results in the requirement that the blood velocity increases from the pericentral region to the central vein of a liver lobule. We have also modeled the diffusion of oxygen, using a PDE solver, out of the sinusoidal blood and its consumption by hepatocytes. The combination of the stochastic sinusoid structure, and the changes in blood velocity in different regions of a lobule, give rise to localized differences in oxygen availability.