Introduction: Normal liver function and xenobiotics-induced liver damage often show zonal patterns. The local dose of both endogenous and exogenous compounds may vary spatially within the liver due to both compound-dependent factors (e.g., diffusion, transport and metabolism) and compound-independent factors (e.g., the complex hepatocyte-sinusoid architecture and heterogeneous blood flow rates). In this study we asked the question “is the complex vasculature and resulting flow pattern alone sufficient to give rise to zonally different xenobiotic concentrations?” To focus on the network and flow characteristics of the lobule we assumed that the hepatocytes themselves do not show zonal-dependence in their basic transport and metabolic capabilities and that any zonation is an emergent property of the lobule’s structure.

The degree of variation in localized hepatocyte exposures may guide the selection of a coarser (e.g., a simple model with a single “well-stirred” compartment) versus a more complex model that includes detailed vasculature architecture and blood flow representations. We examine three representative architectures for the liver lobule. (1) A simple single well-stirred compartment model similar to standard PBPK representations of the liver. (2) A linear sinusoidal capillary lined with hepatocytes and (3) a multi-cell virtual liver lobule composed of hepatocytes, complex microvasculature and hydrodynamic simulation of blood flow. For each of the three models we simulated active and passive transport of compound at the hepatocyte-sinusoid interface and metabolism of the compound within individual hepatocytes.

3. Spatial map and quantitative analysis of calculated flow velocities within the virtual sinusoid network. Left: (A) Spatial map of flow velocities. Warmer color represents greater flow velocity. Color bar has units of cm/s. (B) Calculated flow velocities in individual sinusoids segments with respect to their distances to the central vein. Color codes angular positions with black indicating axial (vertex-PT to CV) and white facial (center of lobule face to CV) flows. (C) Histogram of calculated flow velocities. Right: Comparison of selected model descriptors and outputs with values observed in rat livers.

Choice of Parameter Ranges: The xenobiotic’s behavior in the NET model is described by three sets of parameters: (Fig. 2D) the diffusive constant D, the Michaelis-Menten parameters \( V_{max} \) and \( K_{M} \), and the metabolic rate parameter, also treated as saturable, \( \alpha \) and \( \beta \). Ranges for each of these parameters were chosen based on the characteristic time constant for blood flow through the network. In particular, the values were chosen to span the range of time scales from about 10x faster to 0.01x the characteristic time. This range of parameter focuses on the domain where the model is most sensitive to the parameters and zonal differences in dosimetry are most pronounced.

CONCLUSION: In the absence of any zonations between hepatocytes, interactions between passive and active transport and metabolism, in the context of a complex liver sinusoid architecture, leads to three basic patterns of hepatic exposure within the liver lobule: 1) lobular-wise uniform, 2) radially varying and 3) both radially and azimuthally varying. We propose to use these emergent patterns to guide selection of the most suitable model representation for a particular compound based on compound-specific estimates of transport and metabolism. In some cases, models of type 1 are adequate to represent the liver compartment and more complex simulations do not provide additional information. In other cases models type 1 are incapable of reproducing the complex local microdosimetry that may be critical to understanding dosimetry in the liver.