# Comparison of Models of Hepatic Lobules at Varying Levels of Detail

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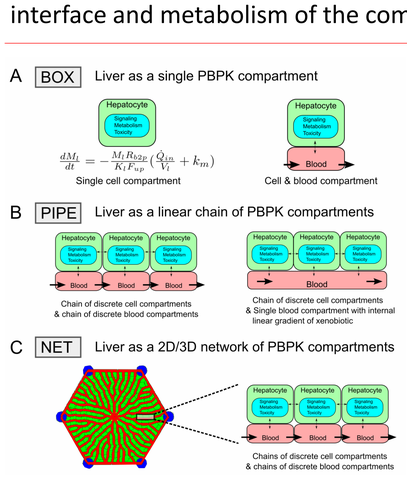
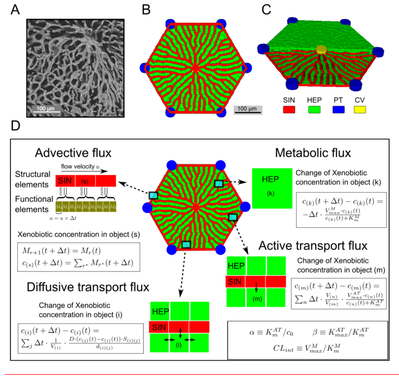
**Introduction:** Normal liver function and xenobiotics-induced liver damage often show zonal patterns. The local dose of both endogenous and exogenous compounds may vary spatially within the liver due to both compound-dependent factors (e.g., diffusion, transport and metabolism) and compound-independent 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.



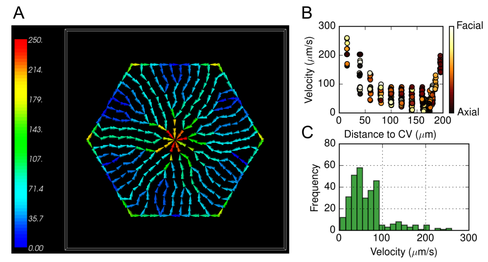

**1. Schematics of model representations of the liver.** Representations of the liver in ***BOX*** (A), ***PIPE*** (B), and ***NET*** (C) models. ***BOX*** models represent the liver as either a single PBPK compartment containing both the blood and tissue of the organ (left in (A)) or separate blood and tissue compartments (right in (A)). ***PIPE*** models represent the parenchyma as a linear chain of compartments (liver zones or hepatocytes) and model blood as either a chain of blood compartments (left in (B)) or as a continuous medium for compound transport solved using convection-diffusion equation (right in (B)). ***NET*** models represent the liver sinusoid network as spatially anastomotic chains of compartments and represent hepatocytes as individual compartments alongside the sinusoid network (C).




**2. Construction of a 3D *NET* model.** (A) *M*icrograph of rat liver sinusoids. A central vein is visible near the upper right. Scale bar is 100um and the width of the individual sinusoids is approx. 8μm. (B) 2D view of the virtual mouse liver lobule. Hepatocyte, sinusoids, central vein and portal triads are colored green, red, yellow and blue, respectively. (C) 3D cutaway view of the virtual mouse liver lobule. (D) Schematics and mathematics of the xenobiotic transport and metabolism processes included in the model.

**References**
[1] Hammand S, *et al.* Protocols for staining of bile canalicular and sinusoidal networks of human, mouse and pig livers… *Archives of Toxicology* (2014).
[2] MacPhee P, *et al.* Microcirculatory changes in livers of mice infected with murine hepatitis virus. *Microvasc. Res.* (1988).

Poster #2:36 IMAG/MSM 10th Anniversary Meeting, Bethesda MD, March 2017

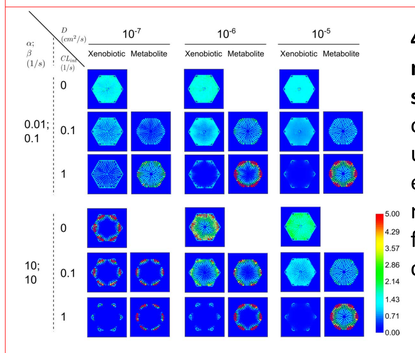



**Select features of the virtual mouse liver *NET* lobule.**

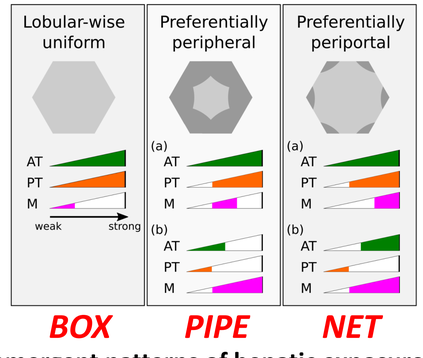
| Feature | Value | Comparator |
|---|---|---|
| Sinusoid volume fraction in tissue excluding CV and PT | 12.9% | 15.3% ± 3.9% [1] |
| Sinusoid-parenchyma interfacial area per unit volume (μm²/μm³) | 0.122 | 0.163 ± 0.087 [1] |
| Average flow velocity within sinusoid network (μm/s) | 67.5 | 69.2 [2] |

**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 are um/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 rate constant ***D***, the Michaelis-Menten parameters $V_{max}^{AT}$ and $K_m^{AT}$ for active (saturable) import and the metabolic rate parameters, also treated as saturable, $V_{max}^{M}$ and $K_m^{M}$. 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.




**4. (Left) Typical transient xenobiotic and metabolite concentrations in select simulations.** α β pairs (see bottom right of 2D) are (0.01, 0.1/s) and (10, 10/s) in upper and lower panels, respectively. In each panel, $CL_{int}$, from top to bottom row, are 0, 0.1, and 1/s, respectively. D's, from left to right, are $10^{-7}$, $10^{-6}$, and $10^{-5}$ $cm^2/s$. The color bar scale is mmol/L.




**5. (Above Right) Schematics of the parameter domains and the three emergent patterns of hepatic exposure.** Schematics of exposure patterns are shown in gray scale, qualitatively indicating high (dark) or low (light) steady state xenobiotic concentrations. Parameter domains, colored region in "**AT**" (active transport), "**PT**" (passive transport) and "**M**" (metabolism) magnitude bars, define the range of transport and metabolism parameters that give rise to the corresponding spatial exposure patterns. The suitable level of model detail for each of the three cases is given in red. We found that there are sets of conditions that give higher periportal xenobiotic exposures, a limited number that gave azimuthal distributions but no biologically practical conditions that gave higher pericentral vs. periportal xenobiotic exposures.

**CONCLUSION:** In the absence of any zonal differences 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 of type 1 are incapable of reproducing the complex local microdosimetry that may be critical to understanding dosimetry in the liver.