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Model of Spatio-temporal Xenobiotic Distribution and Metabolism in an in Silico Mouse Liver Lobule¹ XIAO FU, JAMES SLUKA, SHERRY CLENDENON, JAMES GLAZIER, Indiana Univ - Bloomington, JENNIFER RYAN, KENNETH DUNN, Indiana Univ - Indianapolis, ZEMIN WANG, JAMES KLAUNIG, Indiana Univ - Bloomington - Our study aims to construct a structurally plausible in silico model of a mouse liver lobule to simulate the transport of xenobiotics and the production of their metabolites. We use a physiologically-based model to calculate blood-flow rates in a network of mouse liver sinusoids and simulate transport, uptake and biotransformation of xenobiotics within the in silico lobule. Using our base model, we then explore the effects of variations of compound-specific (diffusion, transport and metabolism) and compound-independent (temporal alteration of blood flow pattern) parameters, and examine their influence on the distribution of xenobiotics and metabolites. Our simulations show that the transport mechanism (diffusive and transporter-mediated) of xenobiotics and blood flow both impact the regional distribution of xenobiotics in a mouse hepatic lobule. Furthermore, differential expression of metabolic enzymes along each sinusoids portal to central axis, together with differential cellular availability of xenobiotics, induce non-uniform production of metabolites. Thus, the heterogeneity of the biochemical and biophysical properties of xenobiotics, along with the complexity of blood flow, result in different exposures to xenobiotics for hepatocytes at different lobular locations.

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