Estimating the Hepatic Effects of Xenobiotic Perturbations in a Virtual Liver

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There are thousands of environmental chemicals and hundreds of new ones are introduced each year. Human health risk assessments for this number of chemicals is a challenge, and have been completed for only a fraction of these chemicals. The US EPA Virtual Liver (v-Liver^{TM}) project has created a cellular systems model of hepatic tissues integrating *in vitro* data for efficient prediction of hepatic effects from chronic exposure to chemicals. We developed an agent-based modeling (ABM) framework to reconstruct the cellular and vascular organization of the hepatic lobule in order to investigate chemical-induced lesions.

The v-Liver addresses two main challenges: (i) relating individual environmental exposures to cell-scale chemical concentrations in the liver, and (ii) modeling the key molecular, cellular and tissue-level consequences pertaining to injury. Our initial focus lies in the nuclear receptor (NR) mediated pathways leading to liver cancers from several non-genotoxic rodent carcinogens and other reference hepatotoxicants. We assume a Boolean framework for simulating the consequences of molecular receptor activation. Biological variability of the model is captured via asynchronous updating. Looking at the aggregate activity profile for key proteins across ensembles of these Boolean networks, and assuming activity of key proteins as a surrogate for changes in cell state/fate, we investigated concentration-dependent phenotypic changes in cell populations. Exploring cellular signalling in this way allows us to integrate dose-response data from toxicity studies in a modelling framework with a large emphasis on network topology.

The v-Liver *in silico* modeling approach attempts to capture critical components for risk analysis: chemical exposure, tissue dosimetry, and cellular dynamics. Backed by a knowledgebase populated with literature-curated information, the v-Liver is designed as a predictive tool for examining the link between chemical perturbations and human liver toxicity. [*This abstract does not necessarily reflect U.S. EPA policy*.]