A Virtual Liver for Simulating Chemical-Induced Injury

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The US EPA Virtual Liver – vLiver™ --is a tissue simulator that is designed to predict histopathologic lesions – the gold-standard for toxicity. We have developed an approach for a biologically motivated model of a canonical liver lobule. The simulated lobule is composed of discrete representations of hepatic cells that can each determine their state and fate in response to their local environment, which is determined by a dynamic graph of the interactions between cells and vascular segments.

We are simultaneously developing two interacting models – one model for the cellular dynamics that drives how an individual hepatocyte responds to its local environment, including local concentrations of endogenous and xenobiotic compounds, and a second, tissue model that determines the local environment of each simulated hepatocyte, including the impact of whole-organism environmental exposure. The two interacting models provide a working framework in which research focusing on refining specific aspects of a single scale, *i.e.* cellular or tissue, can determine consequences on both scales.

We are investigating the molecular mechanisms underlying chemically-induced physiological changes in hepatocytes. Specifically, we are focusing on the roles of a subset of the nuclear receptor superfamily – the so-called adopted orphan nuclear receptors. Through *in silico* models, we hope to elucidate the biochemical processes governing the important hepatocellular processes associated with the diseases and disorders of liver toxicity. The chemical induction of nuclear receptors has been linked to a variety of important cellular processes in the liver, including proliferation, steatosis, apoptosis, necrosis, and hyperplasia. Nuclear receptor-mediated effects can have drastic consequences in rodent hepatocytes. Building *in silico* models will help to reveal the differences between the human and rodent cell behavior with respect to nuclear receptor activation/inhibition.

The Virtual Liver cellular dynamics model requires two modules of cellular signaling networks: one for the effects of chemicals on nuclear receptor activation, crosstalk, and regulation of gene expression, and a second describing the effects of nuclear receptor-mediated gene expression on the cell signaling pathways, ultimately predicting changes in cellular phenotypes. Whereas the first module is an investigation into gene expression, the second module is the realization of that gene expression within the context of normal cellular function. The second module provides a causal link between nuclear receptor-mediated gene expression and cellular changes – including, proliferation, survival, death, and disease (cancer).

This poster will present preliminary aspects of the of the first cellular dynamics module. Literature curation, the ToxCast™ data set, and the v-Liver™ Knowledgebase are being used to establish a nuclear receptor crosstalk and gene expression simulation model. We are interested in modeling these activities with a threshold networks approach to

Boolean networks that, while relatively simple, is capable of capturing the dynamics of cellular processes with very low computational overhead.

The Virtual Liver tissue model for microdosimetry makes use of a modified physiologically-based pharmacokinetic (PBPK) approach to determining local concentrations throughout the simulated lobule. Based upon ordinary differential equations, this microdosimetry approach bypasses computationally-intensive fluid dynamics to rapidly determine the impact of environmental exposure to individual hepatocytes within the simulated lobule. By providing a spatially-extended environment, the tissue model is intended to allow physiologically based models for inter-cellular communication and lesion progression as allowed by the cellular dynamics model. We will also be presenting results of our microdosimetry model as they pertain to lobule layout, hetergeniety of the hepatocellular environment, and the consequences of oral vs. inhalation exposure.

The Virtual Liver ultimately provides a framework for making predictions of *in vivo* consequences based upon *in vitro* data. The cellular dynamics model is intended to be calibrated with *in vitro* measures of chemical activity, while the tissue model can be calibrated with histopathology slides and pharmacokinetic data. As a chemically-perdurable simulation of a homeostatic tissue function, virtual tissues will be powerful tools for 21st Century Toxicology.

This work was reviewed by EPA and approved for publication but does not necessarily reflect official Agency policy.