Simulating Chemical-Induced Injury Using Virtual Hepatic Tissues

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Background. Chemical-induced liver injury involves a dynamic sequence of events that span multiple levels of biological organization. Current methods for testing the toxicity of a single chemical can cost millions of dollars, take up to two years and sacrifice thousands of animals. It is difficult to assess the health impact of long-term exposure to low levels of contaminants from animal studies. *In vitro* models offer a more efficient and humane alternative, however, translating chemical-induced molecular changes in cell cultures to clinical outcomes remains an open problem. A key research challenge in predicting many adverse outcomes is relating molecular changes with histopathologic lesions, which are the gold-standard for measuring toxicity.

Objective. The objective of the Virtual Liver (v-Liver^{TM}) is to develop an integrated *in vitro* and *in silico* framework to: (a) efficiently generate the plausible sequence of molecular, cellular and tissue events perturbed by a test chemical, and (b) quantitatively simulate the risk of these events in humans at environmentally relevant exposures. As a proof of concept we are focusing on 20 environmental chemicals that activate nuclear receptors (NR) and produce lesions of varying severity in rodents leading to cancer.

Approach: The Virtual Liver (v-Liver) is a multiscale cellular systems model designed to simulate the normal physiologic behviour hepatic tissues and adverse effects due to chemicals. We assume that: (a) adverse histopathologic effects arise from local interactions between thousands of spatially distributed cells, and (b) cellular phenotypes are an integrated response to molecular inputs from the microenvironment. We are investigating the role of NR activation in increased hepatic hyperplasia via mitogenic stimulation versus regenerative proliferation using experimental data.

Results. We reconstructed the microanatomic architecture of the classic hepatic lobule using a spatial graphical model. The topology of this graph is currently represents two key components of the lobule including: a cellular network of hepatocytes and macrophages, and a vascular network of sinusoids connected to hepatic circulation. The phenotypic response of each hepatocyte was simulated by a non-deterministic Boolean Network (BN) that integrates inputs from the microenvironment. Mass transfer in the sinusoidal network was approximated as one dimensional linear flow and coupled with a physiologically based pharmacokinetic model to estimate microdosimetry of orally ingested substances. We are calibrating the molecular, cellular and dosimetry prediction modules using published data and testing the system to investigate the dose, time and space-dependent effects of 20 environmental chemicals.