Falsification/Validation of Enzyme Induction Mechanisms within a Validated, Multiscale Liver Model

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A source of intra- and interindividual variability in drug responses (non-responses, adverse effects, toxicity, etc.) is variability in hepatic clearance and metabolism. That variability is caused in part by variability in zonation of enzyme expression within hepatic lobules, and complicated further because enzyme levels rise and fall in response to temporal fluctuations in enzyme induction signals (or lack thereof). A goal of our group is achieving an individualizable multiscale In Silico Livers (ISLs) in which components and modules within individual "cells" within lobule structures interact with (act on, respond to) objects representing drugs, and do so based on the physicochemical properties of the real drug counterparts. An important milestone, the focus of this poster, is that "hepatocytes" contain an autonomous "enzyme" induction (EI) mechanism that achieves qualitative and quantitative validation targets. An ISL design specification is that mechanisms be no more complicated (fine grained) than needed to achieve validation targets, but flexible enough to be easily revised (made more fine grain) when the set of validation targets is expanded. We used a previously validated ISL model family (discrete event, OO, agent oriented and agent directed): an iteratively developed suite of hypotheses about how rat livers function. We implemented a medium-grained Enzyme Induction (EI) mechanism that validated against the coarse grained measure of drug fraction in perfusate during single-pass perfusions. However, it was falsified against a medium grained measure of hepatic zonation. The validation (falsification) of complicated, knowledge-based models requires validation of multiple aspects. However, such integration may not be straightforward, especially with multiscale, multi-frequency, and/or hierarchical models like ISLs. Falsification (validation) can be crucial to the use of ISLs for the iterative process of formulating, testing, and evolving parsimonious hypotheses about liver mechanisms: falsification can guide the refinement of the hypothesis represented by the simulation. A somewhat more complicated mechanism was implemented (in which variables were replaced by components). It enabled achieving the key validation target: location dependent, increasing portal vein to central vein (PV-CV) EI that is inversely related with number of hepatocytes within a zone. A PV-CV (blood) gradient was needed to control both metabolism and induction. Multiscale validation efforts will be necessary for effective scientific use of knowledge-based computational models such as ISLs.