Falsifying an Enzyme Induction Mechanism within a Validated, Multiscale Liver Model

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ABSTRACT

The focus is an In Silico Liver (ISL) model family and an evolving suite of mechanistic hypotheses about (rat) liver-drug interactions. ISLs are multiscale and hierarchical. A medium grain Enzyme Induction mechanism was implemented. Validation (falsification) of complicated, knowledge-based models requires integrating distinct aspects and methods for multi-aspect validation. For ISLs, such integration has not been straightforward. Falsification is crucial for formulating, testing, and iteratively evolving hypotheses about liver mechanisms. During multi-aspect falsification, the authors can falsify a hypothesis in one aspect while simultaneously validating it in another aspect. The authors demonstrate a multi-scalar validation/falsification event in which they validate the mechanism against coarse grain measures of liver perfusate drug levels and falsify it against a medium grained measure of hepatic zonation. The authors also discuss how falsification is guiding mechanism (hypothesis) refinement. The ability to scale validation efforts is necessary for effective scientific use models such as ISLs.

Keywords: Agent-Based, Falsification, Hepatic Zonation, In Silico Liver, Mechanisms, Multiscale, Simulation

INTRODUCTION

The In Silico Liver (ISL) is part of a proof of principle project demonstrating exploratory experimental methods on synthetic, computational analogs. The project explores concrete hypotheses for potential wet-lab experiments on rat livers, the analog’s referent. Liver was chosen as referent because of its complex phenotype, which at some scales and in some aspects, is well behaved and well characterized. At other scales and in other aspects, livers can be complex without any feasible modeling methods. Aspect is defined as the perspective taken when an analog is observed (including the phenomena on which we focus); one of many functional effects that result and can be observed when an analog executes.

Agent-based modeling was chosen as the base ISL platform because it is an extensible
method that facilitates multi-models across all spectra: homogenous to heterogeneous, continuous to discrete, shallow to deep, regular to chaotic, and across all representation paradigms including equation-based, rule-based, cellular, lattice-free, etc.

Liver is an excellent demonstration referent for hierarchical, multiscale modeling. Hepatic tissue consists of many nearly polyhedral lobules packed together to form secondary units. The lobules, in turn, consist of vascular tubes (sinusoids) lined with endothelial cells, through which blood flows from exterior portal ducts to a central venule. Some solute in blood filters through the endothelial layer into the surrounding Space of Disse, where it contacts and can enter hepatocytes. Various enzymes within hepatocytes bind and metabolize endogenous and exogenous compounds. Liver plays essential roles in the organism and exhibits a broad phenotype at several scales.

**USE CASE**

The target of this study is hepatocytes’ ability to regulate (up or down) their enzymes in response to encountered compounds and other physiological signals (Hung, Chang, Cheung, McWhinney, Masci, Weiss & Roberts, 2005; Hunt, Ropella, Lam, Tang, Kim, Engelberg, & Sheikh-Bahaei, 2009; Hunt, Ropella, Yan, Hung, & Roberts, 2006). The use case is the experimental protocol for a single-pass, in situ, isolated perfused rat liver. The liver is first perfused with an oxygenated fluid. A bolus of compound is then added to the perfusate and a fraction collector protocol is next used to measure perfusate contents as it flows out of the liver. This use case exercises many of the steady state and fast transient aspects of hepatic function and was used to study the in situ clearance of cationic drugs (Kim, Park, Ropella, & Hunt, 2010). That study’s results provide the coarse-grained validation aspect on which we focus: the fraction of compound exiting in relation to the amount of compound in the bolus. Validation of various ISLs against data from the cited experiments is presented in several previous reports (Lam & Hunt, 2010; Le-parpetritou, Georgopoulos, Roth, & Androulakis, 2009; Mankowski & Ekins, 2003; Oinonen, & Lindros, 1998; Park, Ropella, Kim, Roberts, & Hunt, 2009; Park, Kim, Ropella, Kim, Roberts, & Hunt, 2010).

The output fraction is a cumulative response based on the topological, geometrical, and biochemical attributes of the liver tissue, making it an excellent baseline aspect against which to validate. The output fraction aspect provides the ISL project with a whole organ regression test to guide the development of refined, falsifiable, and mechanistic hypotheses. More refined hypotheses have been validated in the contexts of intrinsic clearance (Ropella, Park, & Hunt, 2008) and diseased livers (Oinonen & Lindros, 1998; Park, Ropella, Kim, Roberts, & Hunt, 2009; Park, Kim, Ropella, Kim, Roberts, & Hunt, 2010) and falsified in the distribution of enzyme induction (Santostefano et al., 1999).

The influential mechanisms reveal themselves in different aspects of ISL phenotype. Consequently, specific measures were designed to take observations from ISLs during simulations. For example, in Oinonen and Lindros (1998), Park, Ropella, Kim, Roberts, and Hunt (2009), and Park, Kim, Ropella, Kim, Roberts, and Hunt (2010) tracing instrumentation was added to the ISL code to take very specific measurements of compounds (which refer to drug, the extracellular marker sucrose, and metabolite in Kim, Park, Ropella, & Hunt, 2010) at different locations within the ISL lobule at any given time. Obviously, such aspects are easier to measure during simulations than during liver perfusion experiments, if the latter is even feasible. It is important to note that adding a new measure or changing a measure usually changes the wet-lab use case, but not necessarily the analog. This point is made clearly with Ropella, Park, and Hunt (2008) where intrinsic clearance is measured with an entirely different use case (experimental apparatus and protocol) than in situ clearance.
A Programming Language for Normative Multi-Agent Systems
www.igi-global.com/chapter/programming-language-normative-multi-agent/21108?camid=4v1a