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Emergent patterns of hepatic zonation of xenobiotic clearance and hepatotoxicity: a plausible role for cell learning

Hepatic zonation is conspicuous periportal (afferent) to perivenous (efferent) attribute gradients within lobules. Zonal differences occur in the clearance of a variety of endogenous compounds and xenobiotics, and are evident for a number of normal hepatic functions. However, no concrete, causal, mechanistic theory is available to explain how, for example, different hepatic zonation patterns of P450 isozyme levels and hepatotoxicity emerge following dosing with different compounds. We used the synthetic method of modeling and simulation to discover, explore, and experimentally challenge concrete mechanisms that show how and why biomimetic zonation patterns emerge and change within agent-based analogues. Synthetic methods enable teasing apart complex systems in contrast to inductive methods, which target prediction. Following an iterative Refinement Protocol enabled construction of real (not conceptual), strictly defined, biomimetic mechanisms while also accounting for considerable uncertainty. Even though abstract, the mechanisms and their spatial context are flexible and sufficiently concrete to instantiate mechanistic hypotheses and test their plausibility experimentally. Our working hypothesis was that those mechanisms have counterparts in rats. Mobile objects map to compounds. One analogue is comprised of 460 identical, quasi-autonomous functional units called sinusoidal segments (SSs). SSs detect and respond to compound-generated response signals and the local level of an endogenous gradient. Each SS used a learning algorithm to adapt to new information with the objective of improving efficiency. Upon compound exposure, analogues developed a variety of patterns that were strikingly similar to those reported in the literature. A degree of quantitative validation was achieved against data on hepatic zonation of CYP1A2 mRNA expression caused by three different doses of TCDD (2,3,7,8-tetracholorodibenzo-p-dioxone).