Title: Multi-scale modeling of liver regeneration: integrating molecular regulation, cell phenotype dynamics, and physiological response

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Description:
Following mechanical or chemical damage, the liver initiates a recovery program inducing hepatocytes to enter the cell cycle and recover lost mass. Dynamic molecular changes begin as early as 30 seconds after injury and continue for ~1 week, when liver mass is fully restored. Yet much remains to be understood about how regulation of multiple molecular factors is coordinated to control liver repair mechanisms. Additionally, cell types within the liver become activated to multiple distinct phenotypes contributing to or inhibiting repair. The present study takes a systems-based approach to investigate how multi-scale balances in cell phenotypes and molecular regulation impact liver regeneration.
We developed a computational model to synthesize the intrinsically multi-scale nature of liver regeneration by simulating connections between physiological-scale dynamics, activation phenotypes of non-parenchymal cells, and molecular signaling networks. Model analysis showed that shifting balances between populations of non-parenchymal cell activation phenotypes was sufficient to alter regeneration dynamics and overall tissue recovery following partial hepatectomy. As a perturbation to regeneration phenotype, we simulated alcohol-mediated suppression of liver regeneration by fitting our model to experimental data of liver recovery following chronic alcohol consumption and partial hepatectomy. Based on the model simulations, we predict that chronic alcohol consumption acts at a cellular-scale by shifting populations of non-parenchymal cells to anti-proliferative phenotypes. At a molecular-scale, these changes are paralleled by dynamic increases in anti-inflammatory cytokine production and high levels of anti-regenerative molecules. We validated these predictions by measuring mRNA levels following partial hepatectomy in alcohol-fed rats and controls using a high-throughput qPCR platform.