



A COMPUTATIONAL MODEL OF HEPATIC LIPID METABOLISM: IDENTIFYING PERSISTENT BEHAVIOR

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The liver plays a major role in lipid metabolism by means of production and secretion of triglyceride-rich lipoproteins that critically determine steady-state lipid levels in liver and plasma. An imbalance in hepatic lipid metabolism is associated with cardiovascular diseases and hepatic steatosis. Although much progress has been achieved in better understanding the mechanisms involved in hepatic lipid metabolism, there is controversy as to how the liver responds to various stimuli, e.g. the observed responses to hepatic lipid loading vary widely. Our aim was to explore these differences in hepatic lipid metabolism, hereby analyzing different possible scenarios and identifying persistent behavior present irrespective of kinetic variations.

A computational model was constructed including reactions representing lipogenesis, cholesterol synthesis, as well as lipoprotein assembly, secretion and remodeling. Different murine datasets were used for model parameterization. To explore the complete potential set of system behaviors, a large-scale search in parameter space was carried out by performing a million simulations with random parameter sets, sampled from a log-uniform distribution, hereby locating regions of high likelihood. The parameter sets were subsequently optimized by applying a nonlinear least squares parameter estimation method. A parameter set was accepted if corresponding residuals were within the 95% confidence interval of the data.

We were able to quantitatively integrate data of different experiments into a consistent model and identify persistent behavior from acceptable parameter sets. Furthermore, the model was used to study a mouse phenotype, in which the LXR gene was induced, resulting in severe hepatic steatosis. Parameters were identified that changed consistently from the healthy to the diseased phenotype. In future research, the model will be used to study hepatic lipid metabolism in murine for different physiological conditions.

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