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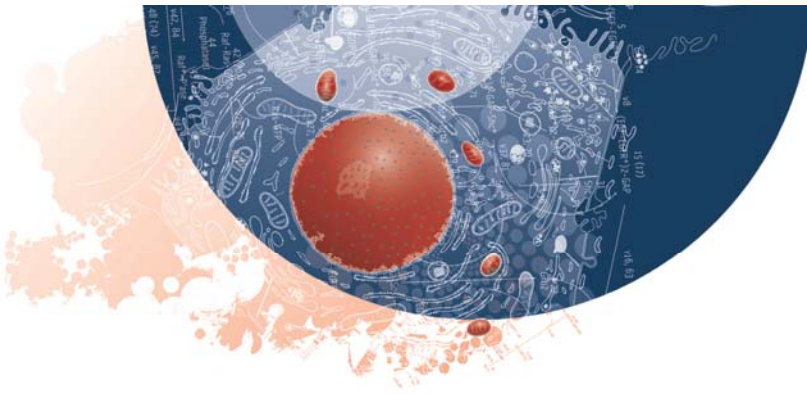

MATHEMATICAL MODELLING OF LIVER METABOLISM

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Hepatocytes possess the most versatile metabolism among all human cells. Precise coordination of a multitude of different cellular metabolic pathways enables an adequate metabolic response of the liver to a large variety of physiological conditions such as, unbalanced diets, physical exercise, drug administration, systemic inflammation or presence of enzyme deficiencies. We have reconstructed a metabolic network of the hepatocyte. The network includes 740 metabolites in six intracellular and two extracellular compartments and encompasses 2440 reactions, including 1435 transport reactions. All data have been manually curated using more than 1200 original scientific research publications to warrant a high-quality evidence-based model. The final ad-functionem network is the result of an iterative process of data compilation and rigorous testing of network consistency and functionality. Constraint-based modelling has been applied to align the model's functional properties with known physiological behaviour of the human liver for a large canon of biochemical functions and physiological conditions. Taking the hepatic detoxification of ammonia as an example, we show how the availability of nutrients and oxygen may modulate the interplay of various metabolic pathways to allow an efficient response of the liver to perturbations of the homeostasis of blood compounds.