Model Embedding
Combining Constraint-based & Kinetic Networks

Wolfram Liebermeister & Matthias König

Introduction

The main idea is the coupling of kinetic and constraint based models. Main test case will be the coupling of a kinetic model of hepatic glucose metabolism {Koenig2012a, Koenig2012b} into a highly curated subnetwork of HepatoNet1 {Gille2010}.

Model Description

GlucoNet - Human Hepatic Glucose Model

Kinetic model of the hepatic glucose metabolism comprising gluconeogenesis, glycolysis and glycogen metabolism integrated with the hormonal response via insulin and glucagon {Koenig2012a, Koenig2012b} (Figure 1). The model will be referred to as GlucoNet.

Simulations

The model can simulate the switch between hepatic glucose production (HGP) and hepatic glucose utilization (HGU) under varying external glucose concentrations. The set of test simulations will comprise the kinetic simulations under varying glucose concentrations.

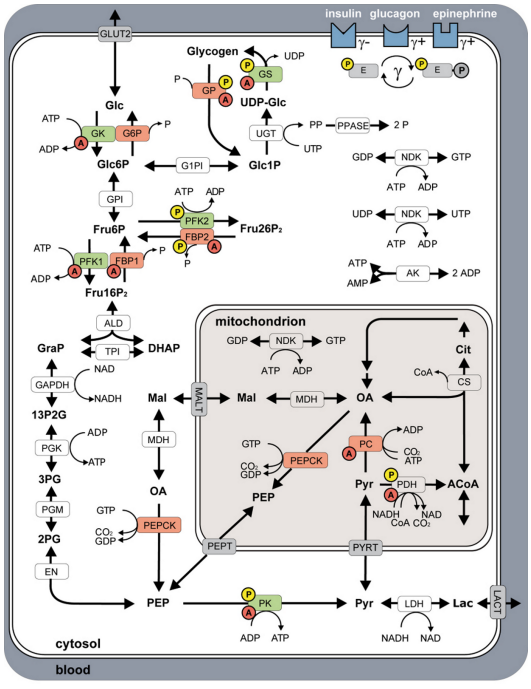

Figure 1 - GlucoNet model overview.

HepatoCore - Human Hepatic Core Metabolism

Highly curated subnetwork of HepatoNet1 {Gille2010} described in {Koenig2009}. The model will be referred to as HepatoCore.

The reconstruction contains the central metabolic pathways and functionality of the liver (Figure 2):

- glycolysis and gluconeogenesis
- glycogen metabolism
- pentose phosphate pathway (PPP)
- purine and pyrimidine metabolism
- TCA cycle
- synthesis and β-oxidation of fatty acids
- metabolism of amino acids
- glutathione and folate reactions
- NH_3 fixation and detoxification (urea cycle)
- ketone body synthesis

An overview over the network components is provided in Table 1.

Netzwerkobjekte	766	(100)
Prozesse	402	(52.5)
Reaktionen	296	(38.6)
Einmalige Reaktionen	274	
Zytosol	243	(31.7)
Mitochondrium	53	(6.9)
BlackboxEvents	24	(3.1)
Zytosol	7	(0.9)
Mitochondrium	14	(1.8)
Innere Mitochondrien Membran	3	(0.4)
Transportreaktionen	82	(10.7)
Zytosol ↔ Blut	48	(6.3)
Zytosol ↔ Mitochondrium	34	(4.4)
Metabolite	364	(47.5)
Einmalige Metabolite	199	
Zytosol	245	(32.0)
Mitochondrium	79	(10.3)
Blut	40	(5.2)

Table 1 - Overview network reconstruction of human core hepatocyte metabolism. Singular metabolites and reactions are network objects occuring only in a single compartment. BlackBox events are processes which combine multiple reaction steps into a single replacement process.

Simulations

HepatoCore was functionaly curated via testing the central metabolic functions associated with these pathways via FBA based simulations (see simulations list). Different functional aspects of the core metabolism are tested.

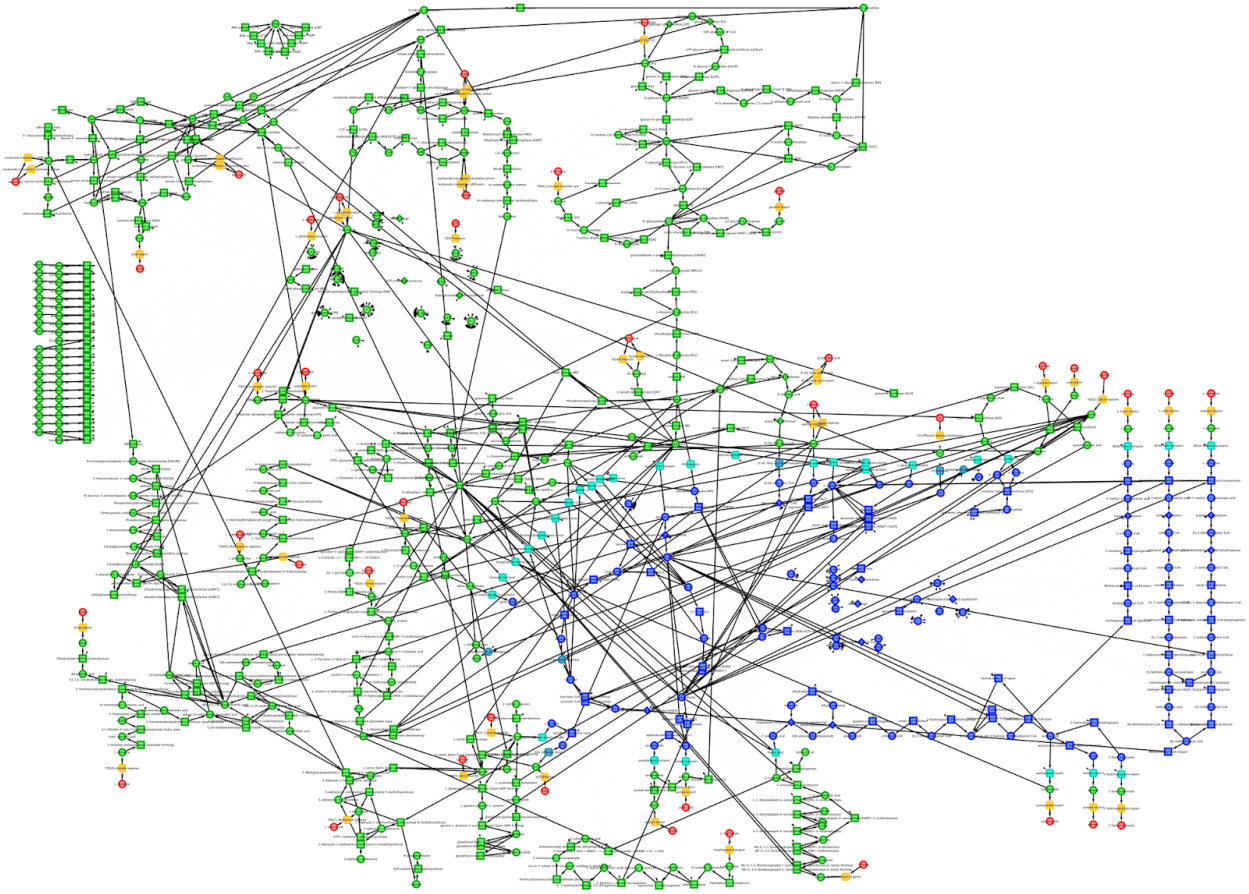

Figure 2 - HepatoCore model overview.

References

Gille, C., Bölling, C., Hoppe, A., Bulik, S., Hoffmann, S., Hübner, K., et al. (2010). HepatoNet1: a comprehensive metabolic reconstruction of the human hepatocyte for the analysis of liver physiology. *Molecular systems biology*, *6*(1).

König, M., Bulik, S., & Holzhütter, H. (2012a). Quantifying the contribution of the liver to glucose homeostasis: a detailed kinetic model of human hepatic glucose metabolism. *PLoS computational biology*, *8*(6), e1002577.

König, M., & Holzhütter, H. (2012b). Kinetic modeling of human hepatic glucose metabolism in type 2 diabetes mellitus predicts higher risk of hypoglycemic events in rigorous insulin therapy. *Journal of Biological Chemistry*, *287*(44), 36978-36989.

König, M (2009). Metabolic network reconstruction of the human hepatocyte core metabolism. Diploma thesis, Humboldt University Berlin