Model Embedding
Combining Constraint-based & Kinetic Networks

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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}.

Github

https://github.com/matthiaskoenig/model-embedding

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git clone https://github.com/matthiaskoenig/model-embedding.git
```

Google Doc

https://docs.google.com/document/d/10PNdH9KWvYQ4uMHNNM0UOEW_3d5U81kVyczS1OuSHLk/edit#

SBML models

`model-embedding/models/hepatocore/`**`HepatoCore2_v1.xml`**
`model-embedding/models/gluconet/`**`Koenig2014_Hepatic_Glucose_Model.xml`**
`model-embedding/models/gluconet/`**`Koenig2014_Hepatic_Glucose_Model_annotated.xml`**

Methods (model embedding)

See manuscript
https://drive.google.com/?authuser=0&usp=gmail#folders/0B53SD0wZtwprYmgyaGJSaE1relk

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.

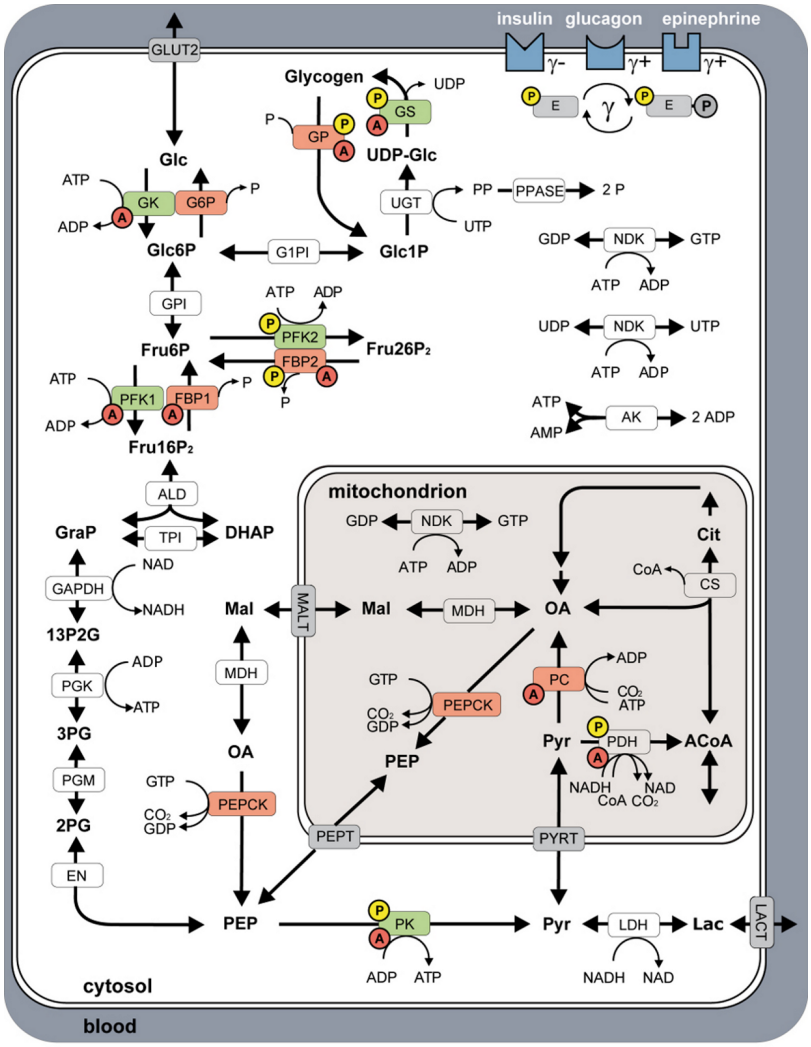

Figure 1 - GlucoNet model overview.

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.

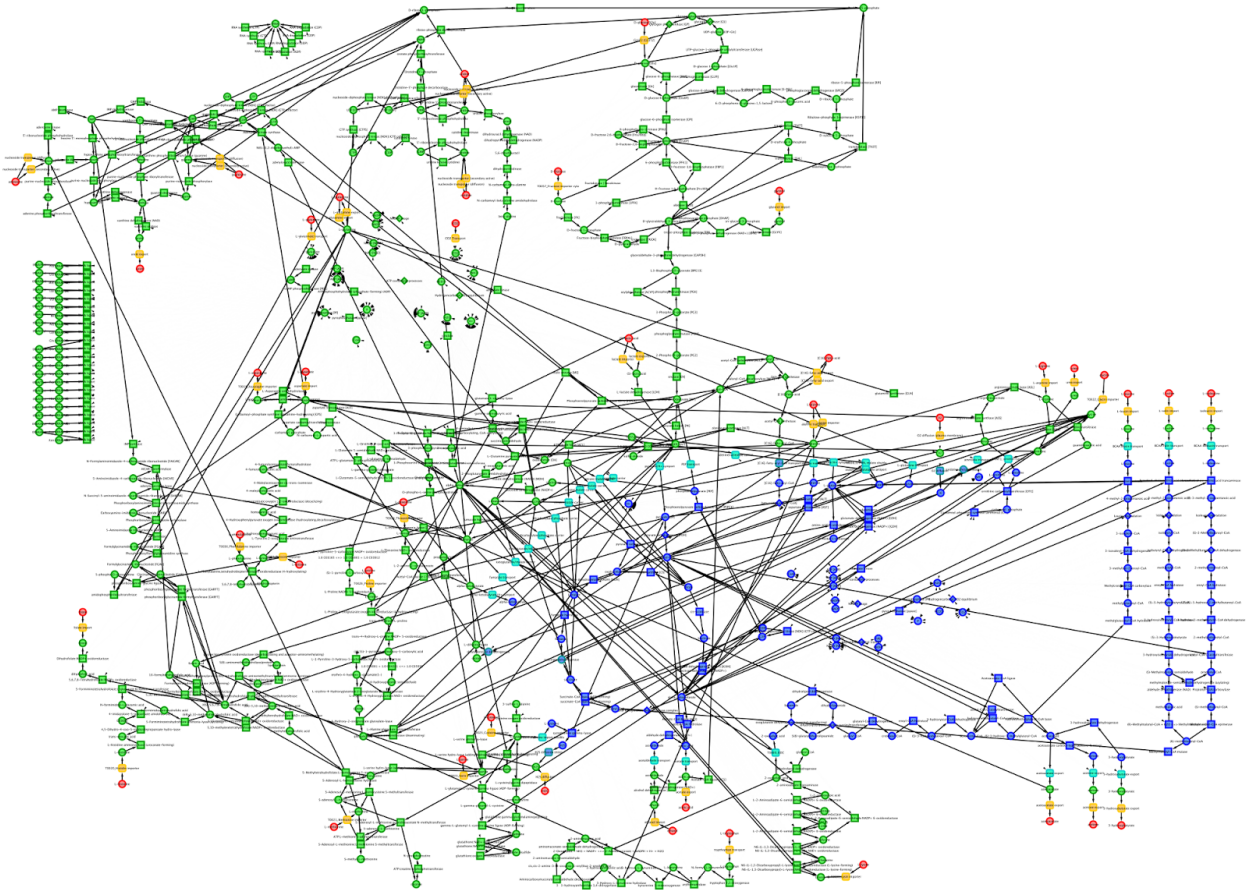

Figure 2 - HepatoCore model overview.

Flux rates

Process	Value	References
albumin synthesis rate (synthesis of proalbumin) + ID_22334_cyto	Mr(albumin) = 66500 g/mol 131±8 mg/day (rat, liver weight 8.18±0.14g) {Ruot1999} **v(alb) = 0.167nmol/min/g_lw ~ v(alb) ~ 0.167nmol/min/ml_lw** Albumin is manufactured in the liver at a rate 9-12g/day. The normal serum albumin is 30 to 40 grams per litre. 9-12g/day (human, liver weight 1500g) **v(alb) = 0.063-0.084nmol/min/g_lw ~ 0.063-0.084nmol/min/g_lw**	{Ruot1999}
hepatic glucose production (HGP) - GLUT2	Mr(glucose) = 180 g/mol 0-18µmol/min/kgbw (human, liver weight 1500g, bodyweight 70kg) {Koenig2012a} **v(HGP) = 0 - 0.84 µmol/min/glw = 840nmol/min/g_lw ~ 0.063-0.084nmol/min/ml_lw**	{Koenig2012a} & references within
hepatic glucose consumption (HGU) + GLUT2	0-20µmol/min/kgbw (human, liver weight 1500g, bodyweight 70kg) {Koenig2012a} **v(HGP) = 0 - 0.93 µmol/min/glw = 930nmol/min/g_lw ~930nmol/min/ml_lw**	{Koenig2012a} & references within

hepatic oxygen uptake (O2l) - ID_13638_extern	2.62 mmol/min (in vivo pig liver, liver weight 1.05kg, total liver blood flow 1.07L/min) {Tygstrup1970} 1.9µmol/min/glw (human liver with estimated liver weight) {Tygstrup1962} **v(O2l) = 1.9-2.5 µmol/min/glw = 1900-2500nmol/min/g_lw**	{Tygstrup1970} {Tygstrup1962}
ethanol consumption acetate production ID_14769_extern		{Lundquist1961}

Exchange Sets

+ [lb=0, ub=∞]
flux in direction of reaction (import or export depending on definition of reaction direction)
- [lb=-∞,ub=0]
flux against direction of reaction (import or export depending on definition of reaction direction)
= [lb=-∞,ub=∞]
import and export allowed

A Minimal Exchange Set

Core exchange for model consisting of uptake of essential amino acids, glucose, lactate, O_2, folate and basic exports like urea, urate, and ketone bodies

process			
ID_13886_extern	+	detox	urea export allowed
ID_15523_extern	+	detox	urate export allowed
ID_13809_extern	+	ketone body	acetoacetate export allowed
ID_13810_extern	+	ketone body	acetone export allowed
ID_13832_extern	+	ketone body	beta-hydroxybutyrate export allowed
ID_14035_extern	+	detox	H2S export for cysteine degradation
ID_15668_extern	=		lactate can be imported and exported
ID_13640_extern	=		CO_2 exchange
ID_14769_extern	=	ketone body	acetate exchange
ID_13638_extern	-		O_2 uptake
ID_14148_extern	=		glucose exchange
ID_15924_cyto	=		glycogen storage/usage
ID_14250_extern	-	essential cofactor	folate uptake
ID_14614_extern	-	essential AA	phenylalanine uptake
ID_14028_extern	-	essential AA	valine uptake
ID_13868_extern	-	essential AA	threonine uptake
ID_14082_extern	-	essential AA	trypthophan uptake
ID_15249_extern	-	essential AA	isoleucin uptake
ID_13695_extern	-	essential AA	methionine uptake
ID_14832_extern	-	essential AA	leucin uptake
ID_14958_extern	-	essential AA	lysin uptake
ID_13649_extern	+	nonessential AA	glutamine export allowed

B Full Exchange Set

In addition the nonessential amino acids and nucleotides.

ID_13885_extern	-	nonessential AA	arginine uptake
ID_13663_extern	-	nonessential AA	alanine uptake
ID_13795_extern	-	nonessential AA	cysteine uptake
ID_13704_extern	-	nonessential AA	serine uptake
ID_13787_extern	-	nonessential AA	histidine uptake
ID_13781_extern	-	nonessential AA	tyrosine uptake
ID_14131_extern	-	nonessential AA	glycine uptake
ID_14215_extern	-	nonessential AA	proline uptake
ID_15065_extern	-	nonessential AA	asparagine uptake
ID_14072_extern	-	nonessential AA	aspartate uptake

ID_13649_extern	-	nonessential AA	glutamine uptake
ID_13650_extern	-	nonessential AA	glutamate uptake

C Extended Exchange Set

Full exchange set and nucleotides

ID_13948_extern	-	nucleotide	uridine uptake
ID_14258_extern	-	nucleotide	cytidine uptake
ID_15327_extern	-	nucleotide	guanosine uptake
ID_13981_extern	-	nucleotide	adenosine uptake

TODO Matthias:

FBA

- Setup FBA simulations corresponding to {Koenig2009} (CobraPy, CBMPy)
- Literature research uptake & excretion rates + production of metabolites/bile, … Currently abstract function tests, make more physiological
- Integrate knockout information

Kinetic simulations

- Setup kinetic simulations, i.e. full range of HGP - HGP simulations

Visualization

- Get CySBML & CyFluxViz visualization running (interactive evaluation CyRest & Cy3)

Mapping

- fix rates between models & use identical time units, substance units and flux units
- fix the handling of compartments (especially the Vcell = Vcyto + Vmito part)
- consistent scaling to complete liver in both models

Model extension

- extend HepatoCore via insulin/glucagon constraints, i.e. integrate information about hormonal regulation (interconvertible enzymes) in Fat metabolism

Model annotation & integration of information

- get database with model information running & old code base
- add irreversibility and flux bound information to model & collect additional flux constraints (uptake rates, oxygen consumption, …) (see FBA)
- get all the annotation information for the model components from
- add the Delta G were available
- Annotate the units! in Hepatocore and make units consistent between networks

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

Lundquist, F., Tygstrup, N., Winkler, K., Mellemgaard, K., & Munck-Petersen, S. (1962). Ethanol metabolism and production of free acetate in the human liver. *Journal of Clinical Investigation*, *41*(5), 955.

Ruot, B., Breuillé, D., Rambourdin, F., Bayle, G., Capitan, P., & Obled, C. (2000). Synthesis rate of plasma albumin is a good indicator of liver albumin synthesis in sepsis. *American Journal of Physiology-Endocrinology And Metabolism*, *279*(2), E244-E251.

Tygstrup, N., Winkler, K., Mellemgaard, K., & Andreassen, M. (1962). Determination of the hepatic arterial blood flow and oxygen supply in man by clamping the hepatic artery during surgery. *Journal of Clinical Investigation*, *41*(3), 447.

Tygstrup, N., Funding, J., Juul-Nielsen, J., Keiding, S., Koudahl, G., Ramsöe, K., et al. (1970). The function of the isolated perfused and the in vivo pig liver. *Scandinavian journal of gastroenterology. Supplement*, *9*, 131-138.