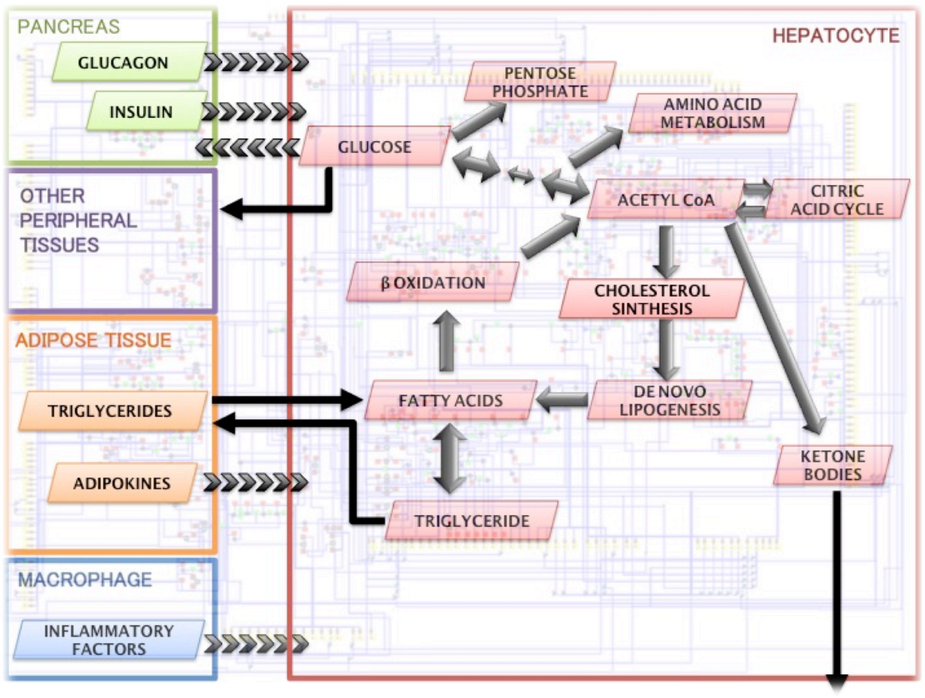
SteatoNet as a predictive and gender-based liver metabolic model

Tanja Cvitanović[1], Miha Moškon[2], Miha Mraz[2], Damjana Rozman[1]

Univerza v Ljubljani
Medicinska fakulteta

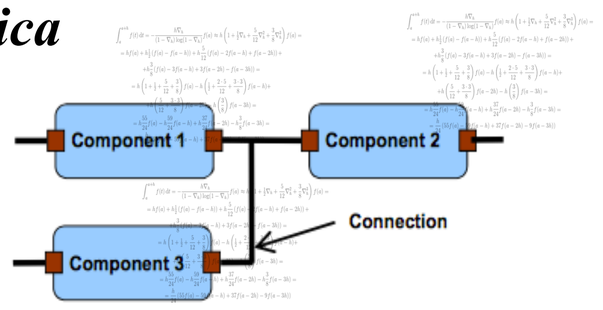
[1]*Centre for Functional Genomics and Bio-chips, Faculty of Medicine, University of Ljubljana, Slovenia*
[2] *Faculty of Computer and Information Science, University of Ljubljana, Slovenia*

About *SteatoNet*



SteatoNet is an object-oriented model, which addresses the dynamics of NAFLD from systems medicine perspective [1]. SteatoNet accounts for interactions between the liver and peripheral tissues and includes metabolic, gene regulatory, as well as signal transduction pathways. SteatoNet requires only a minimal set of parameters and can be used even in a case of sparse experimental data. Due to its object-oriented nature, it can be easily adapted to investigate different liver-associated pathologies.

Modelica



- Object oriented modeling language.
- Library SysBio implements basic systems biology objects.
- Each object represents a biological entity, i.e. biochemical reaction or biochemical compound.
- Connections among objects represent relations in the system.
- Physical behaviour of an objectis described by its equations.
- Hierarchical decomposition of objects.

Aims

➢Apply ***SteatoNet*** to increase understanding of complex communication between liver and adipose tissue in non-alcoholic fatty liver disease (NAFLD) pathologies

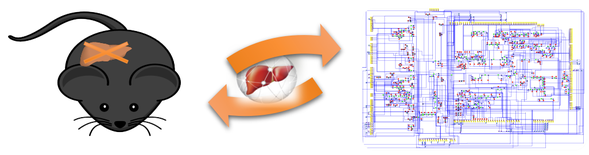
➢Adapt ***SteatoNet*** to gender based differences of liver metabolism

Model prediction

Lanosterol 14α- demethylase (CYP51) is a key regulatory enzyme in the late stage of cholesterol synthesis. Demethylation of lanosterol caused by CYP51 is regarded as a checkpoint in the transformation to cholesterol, whose metabolites and transcription regulators are linked to liver pathologies.

The deletion of *Cyp51* in the mouse liver (the conditional knockout) resulted in hepatomegaly with oval cell proliferation, fibrosis and inflammation, but without steatosis. The key trigger were the reduced cholesterol esters that induced cell cycle arrest, senescence-associated secretory phenotype and oval cell response, while elevated CYP51 substrates promoted the integrated stress response [2].

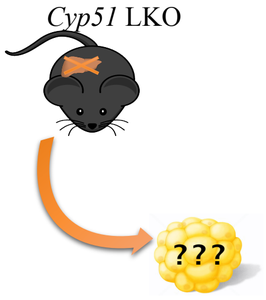
Cyp51 LKO

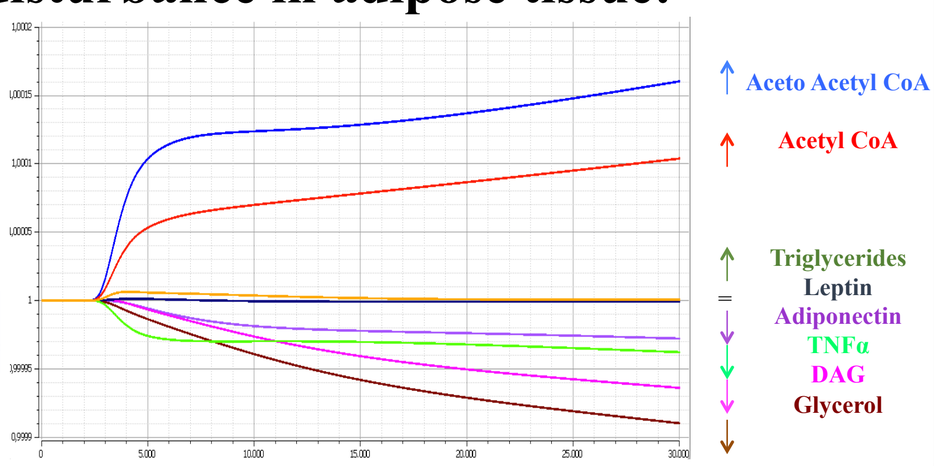


We applied *SteatoNet* to address the question of metabolic consequences after knocking out gene *Cyp51* from cholesterol synthesis in the liver. The experimental data for the *Cyp51* liver knockout are available [2]. The model simulations demonstrate the network disturbances in adipose tissue, which is an excellent starting point for further experimental testing on gene expression and protein levels.

Network disturbance in adipose tissue:

Cyp51 LKO



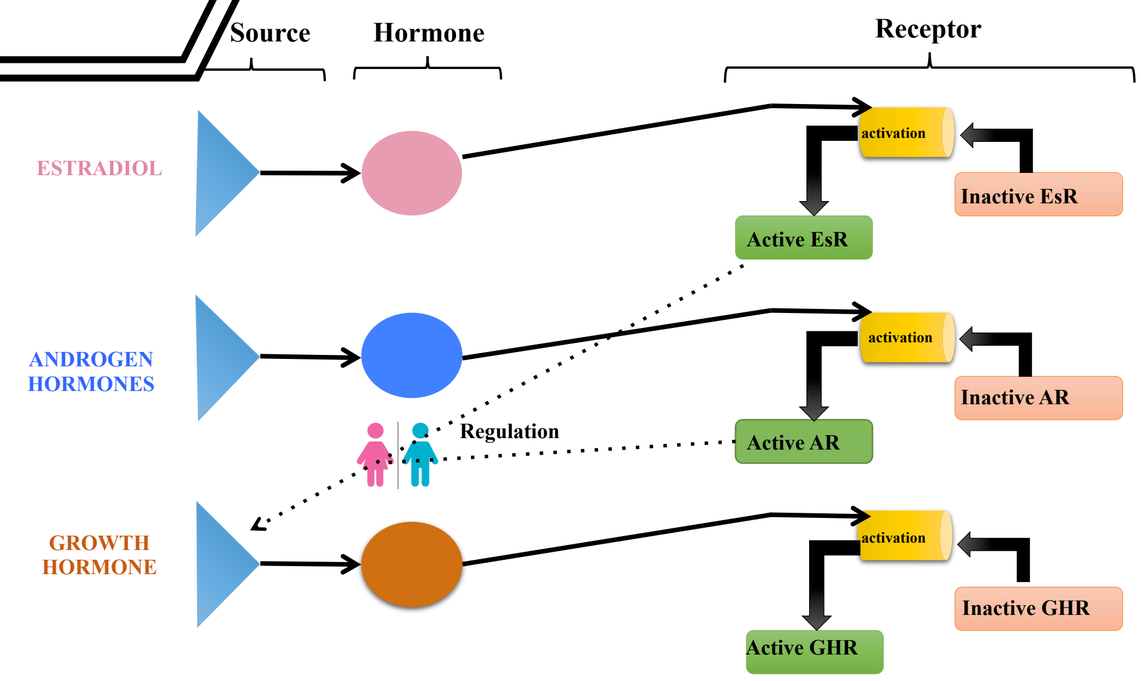


↑ Aceto Acetyl CoA
↑ Acetyl CoA
↑ Triglycerides
= Leptin
↓ Adiponectin
↓ TNFα
↓ DAG
↓ Glycerol

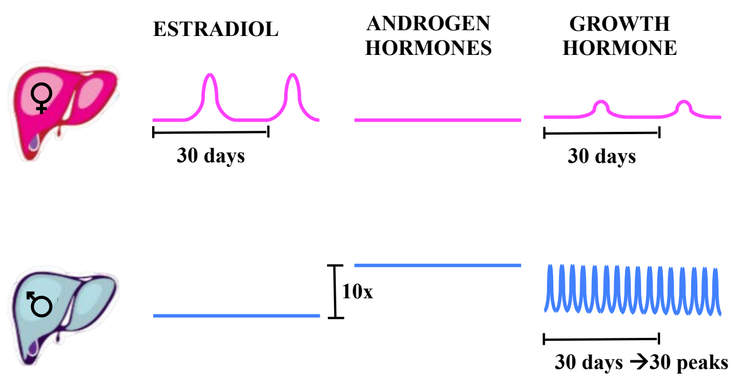
experimental validation in progress

Gender based model adaptation

Liver is known as a sexually dimorphic organ especially at the gene expression level. Gender-based differences were discovered also in the experimental *Cyp51* liver knockout responses. We extended *SteatoNet* to differentiate between genders based on literature data and expert based knowledge. To the best of our knowledge, described SteatoNet adaptation represents the first gender-based liver metabolic model.



Dynamics of hormones in liver:

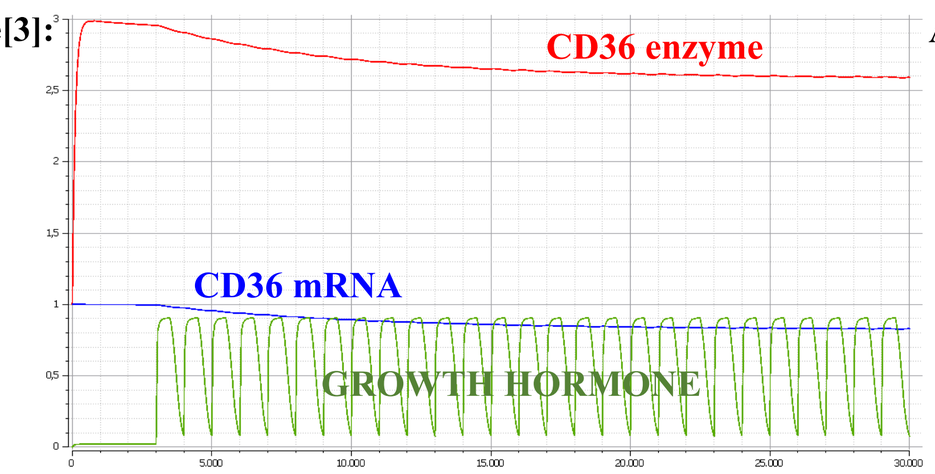


Current applications include simulations of sex hormone ratios in blood and their networking with gender-based differences in cholesterol synthesis and regulatory nodes.

Gender-based model validation based on literature data:

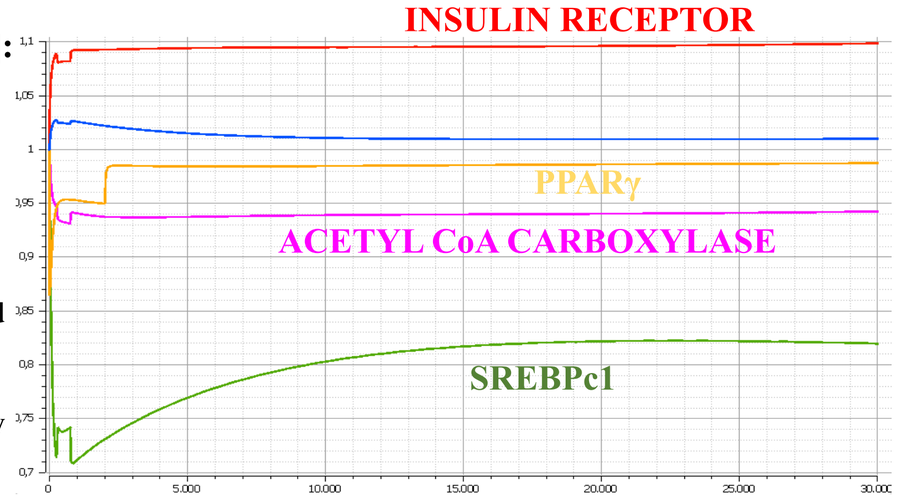
Growth hormone[3]:

Input:
↑ **GROWTH HORMONE**
↓
↓ **CD36 -** fatty acid uptake



Androgen hormones[4]:

Input:
↑ **ANDROGEN HORMONES**
↓
↑ **Insulin signaling**
↓ Fatty acid synthesis
↓ **Glucose homeostasis and denovo lipogenesis**
↓ Adipogenesis and inflammation regulated by PPARγ
↑ **Glucose uptake**



Literature:
1) Naik A. et al. **SteatoNet: the first integrated human metabolic model with multi-layered regulation to investigate liver-associated pathologies.** *PLoS Comput Biol* 2014;10(12)
2) Lorbek G. et al. **Lessons from hepatocyte-specific Cyp51 knockout mice: impaired cholesterol synthesis leads to oval cell-driven liver injury.** *Sci Rep.* 2015, 5:8777
3) Baik M., Yu J. H., & Hennighausen L. **Growth hormone–STAT5 regulation of growth, hepatocellular carcinoma and liver metabolism**. *Annals of the New York Academy of Sciences*. 2011, 1229, 29–37
4) Kelly D.M. and Jones T.H. **Testosterone: a metabolic hormone in health and disease**. *Journal of Endocrinology* . 2013, 217, R25- R45

Funding:
Coordinating Action Systems Medicine Implementation of Systems Medicine across Europe