**SteatoNet as a predictive and gender-based liver metabolic model**

Tanja Cvitanović1, Miha Moškon2, Miha Mráz2, Damjana Rozman1

1Centre for Functional Genomics and Bio-chips, Faculty of Medicine, University of Ljubljana, Slovenia  
2Faculty 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-associatedopathologies.

---

**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 objects 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.

---

**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.

---

**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].

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:**

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.

---

**Gender-based model validation based on literature data:**

**Growth hormone[3]:**

- **CD36 enzyme**
  - Input: **GROWTH HORMONE**
  - **CD36 - fatty acid uptake**
  - **CD36 mRNA**

**Androgen hormones[4]:**

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

---

**Current applications**

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

---

**Literature:**


**Funding:**