SteatoNet as a predictive and gender-based liver metabolic model

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Several large-scale computational models of liver metabolism address the liver dynamics from systems biology/medicine perspective. Herein we describe applications of the state-of-the-art model *SteatoNet* designed by the object-oriented approach (Naik et al., PLOS Comput. Biol. 2014). *SteatoNet* accounts for interactions between the liver and peripheral tissues and includes metabolic as well as gene regulatory and signal transduction pathways describing the dynamics of non-alcoholic fatty liver disease. *SteatoNet* requires only a minimal set of parameters and can be used even in a case of sparse experimental data. Furthermore, due to its object-oriented nature, it can be easily adapted to investigate different liver-associated pathologies. This makes the model an excellent starting point for testing biological hypotheses prior to experimentation.

We applied *SteatoNet* to address the question of metabolic consequences in adipose tissue after knocking out gene *Cyp51* from cholesterol synthesis in the liver. The experimental data for the *Cyp51* liver knockout are available (Lorbek et al., Sci. Rep. 2015). 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.

Another important application is the gender-based model adaptation. Liver has been known for decades 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. As far as we can tell this represents the first gender-based liver metabolic model. Current applications include simulations of sex hormone ratios in blood and their networking with gender-based differences in cholesterol synthesis and regulatory nodes. The future *SteatoNet* adaptation will be guided towards personalization, aimed at predicting the network effects of liver disease – related polymorphisms in individuals.