Poster No. X

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SteatoNet as a computational model for prediction of gender-based liver-related diseases

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SteatoNet has been developed by the object-oriented approach to address the dynamics of non-alcoholic fatty liver disease from systems biology/medicine perspective [1]. *SteatoNet* accounts for interactions between the liver and peripheral tissues and includes metabolic, gene regulatory and 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.

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.

Another important application is the 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 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 adaptation will be guided towards personalization, aimed at predicting the network effects of liver disease–related polymorphisms in individuals.

References:
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[2] G. Lorbek, et al., *Lessons from hepatocyte-specific cyp51 knockout mice: impaired cholesterol synthesis leads to oval cell-driven liver injury.* Sci Rep, 2015. 5: p. 8777.