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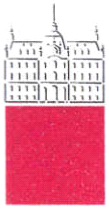

ANALYSIS OF SYSTEM DISORDERS IN LIVER METABOLISM WITH THE STEATONET MODEL

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Abstract

Systems approaches are crucial for understanding of complex biological systems, such as liver. With systems approaches based on the *SteatoNet* model, we gained novel insights into the liver metabolism and liver interactions with other tissues. Various adaptations of the *SteatoNet* to currently actual areas of hepatology research, have opened the door to understanding the biological processes that are not yet fully understood. With *SteatoNet*, we tested the *in silico* liver knock-out of the *Cyp51* gene from cholesterol biosynthesis. Simulation results showed that adipose tissue increases the synthesis of ketone bodies and reduces the triglyceride hydrolysis. For modeling the cholesterol synthesis we used our own experimental data as well as data from literature. During the validation, hormonal effects were also identified as extremely important factors. Therefore, we have adapted the *SteatoNet* to gender differences. Main differences are in expression of sex hormones and in the growth hormone release. The adapted model was named *LiverSex* and it represents the first mathematical model of hepatic metabolism related to gender differences. The *LiverSex* was validated with experimental data obtained from mice in which we examined the effect of diet with different laboratory chows. With the sensitivity analysis of the *LiverSex* we identified critical points in the development of non-alcoholic fatty liver in both sexes. The result of a sensitivity analysis of *LiverSex* emphasized that communication between the liver and adipose tissue is crucial at the first stage in the development of non-alcoholic fatty liver disease, and that this is a possible reason for a lower prevalence of disease in women before menopause. VLDL, the storage of triglycerides in fat droplets, and/or the decomposition of fatty acids into the ketone body are likely the mechanisms that protect women from the development of non-alcoholic fatty liver disease before menopause.

The liver has the main role in the decomposition of alcohol. We have adapted the *SteatoNet* to the hepatic effect of alcohol. *SteatoNet* was extended to *StAlco* model with the introduction of alcohol metabolism as well as inhibition of two gluconeogenesis steps: the reaction of pyruvate to lactate in oxaloacetate to malate. *StAlco* can describe the biochemical hepatic effects of excessive alcohol consumption and was validated with literature data.

The *LiverSex* and *StAlco* are the first computational models for exploring influences of sexual dimorphism and the alcohol on the liver. They represent an excellent starting point for an even better understanding of liver communication with other organs, in terms of liver-related disease. Such

adaptations give an opportunity to new applications, such as a personal approach to diagnose and treat complex liver related diseases.