Modelling progressive metabolic diseases with parameter transition trajectories

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Abstract

From a systems medicine perspective one could argue that the metabolite profile of a subject constitutes the interaction of the genotype with the environment and therefore is the molecular reflection of the clinical phenotype. Metabolic profiling of blood plasma, urine, but also tissues in vivo becomes increasingly feasible, e.g., using novel technologies such as NMR spectroscopy. Some point to metabolomics as the emerging 'omic', and one of today's hot trends in bioscience research. Especially for multi-factorial, progressive diseases, such as type 2 diabetes and metabolic syndrome, metabolic profiling provides many opportunities for approaches such as Systems Biology and the Virtual Physiological Human.

Modelling progressive metabolic diseases requires on one hand the integration of molecular data at the metabolome, proteome and transcriptome level of cells (systems biology) and at the other hand describing the dynamic interaction of metabolic organs and tissues (systems physiology, VPH). We report our developments regarding a mathematical and computational framework to bridge the scales and different levels of biological detail between these approaches.

The foundation of the modelling approach is a mathematical model of the metabolic networks in cells, between cells in different tissues and in the blood plasma connecting the tissues. The model is based on biochemical kinetics and can predict metabolite concentrations and fluxes under steady-state conditions. The model is parameterized using clinical metabolite profiling data (parameter estimation). By collecting data from patients that are in different stages of disease progression, including healthy control subjects, different realizations of the model are obtained, each representing a specific stage. Similarly, a collection of model can be developed for patients that underwent a certain therapeutic intervention (medication, lifestyle intervention, bariatric surgery) and are monitored in time. We refer to these models as 'phenotype snapshots'. We assume these phenotype snapshots are temporarily related in case of a progressive disease. The structure of the metabolic network is invariant, but the kinetic parameters can vary as function of time, reflected by changes in proteome and transcriptome. Using the constraints imposed by the network structure (mass balances and conservation of mass) and the multi-omics experimental data per snapshot we can infer trajectories of the model parameters which link the different phenotype models into a consistent description of disease progression. The underlying computational approach is based on advanced numerical optimization. Interestingly, multiple acceptable parameter transition trajectories are obtained. More detailed analyses of the differences in these scenarios might identify biologically different ways of disease progression, critical transition thresholds, and possible biomarkers for improved patient stratification. Ultimately such models could contribute to the development of novel and/or patient-specific interventions.

The concept and framework have been applied to disturbed lipoprotein metabolism, which is common in metabolic syndrome, obesity and type 2 diabetes.