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Metabolic network structure analysis: a case study on glycolysis in Lactococcus lactis

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***short abstract**
The dynamic modeling of metabolic networks constitutes a major challenge in systems biology. The time evolution of metabolite concentration in cells is modeled by complex systems of non-linear differential equations with a large number of parameters. A case study of the stability analysis based on the Jacobian matrix of the model equations combined with singular value decomposition of output sensitivities is presented for glycolysis in L. lactis. This approach shows how a preliminary structural model can be reformulated in simplified form to substantially improve the parameter estimation task.

***extended abstract**
The dynamic modeling of metabolic networks constitutes a major challenge in systems biology. The development of experimental techniques for data acquisition is producing at growing rate high quality biochemistry information. The time evolution of metabolite concentration in living cells is usually modeled by complex systems of non-linear differential equations with a large number of parameters which are very difficult to infer in practice. The reverse engineering step of inferring the parameters and model structure from these experimental time series data is still a major bottleneck to correctly identify the network dynamical behavior. There is currently no automatic and straightforward solution that guarantees convergence to a global optimum.

A case study of application of the traditional stability analysis based on the Jacobian matrix of the model equation, combined with the approach of singular value decomposition of model output sensitivities is presented. Local identifiabiliy analysis evaluates linear dependencies among parameter sensitivities of model outputs. This analysis is conducted on glycolysis in Lactococcus lactis for which several multivariate time series of in vivo metabolic concentrations are available.

This approach shows how a preliminary structural model can be reformulated in simplified form to substantially improve the parameter estimation task. In fact, by performing the preliminary analysis of the structural model it is possible to identify a cluster of state variables with fast equilibration dynamics that can be lumped into a single state variable. This procedure eliminates practically unidentifiable fast modes and allows estimating a reduced parameter set that accurately reproduces, upon simulation, the original experimental time series.

The structural analysis of the network allows identifying which parameters are redundant and significantly improves model identification and parameters inference. The network structural simplification causes the system to be more easily integrated and allowed the convergence of a standard non-linear least squares algorithm for parameter optimization. Prior structural analysis of the model that addresses parameter sensitivity and identifiability issues can thus significantly improve the subsequent reverse engineering step. The application of established model building and analysis procedures can consequently have a positive impact in the development of complex biological systems models.