Neutral Network models for Biochemical Systems

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The major difficulty in modeling biological systems from multivariate time series is the identification of parameter sets that endow a model with dynamical behaviors sufficiently similar to the experimental data. Directly related to this parameter estimation issue is the task of identifying the structure and regulation of ill-characterized systems. Both tasks are simplified if the mathematical model is canonical, *i.e.*, if it is constructed according to strict guidelines. Here, we present a method for the identification of admissible parameter sets of canonical S-systems from biological time series. The method is based on a Monte Carlo process that is combined with our improved parameter optimization algorithm. The parameter space is mapped into the network space, which characterizes the connectivity among components, by creating an ensemble of decoupled S-system models that imitate the dynamical behavior of the time series with sufficient accuracy. The concept of sloppiness is revisited in the context of these S-system models with an exploration not only of different parameter sets that produce similar dynamical behaviors but also different network topologies that yield dynamical similarity. The proposed parameter estimation methodology was applied to actual time series data from the glycolytic pathway of the bacterium *Lactococcus lactis* and led to ensembles of models with different network topologies (Figure 1). In parallel, the parameter optimization algorithm was applied to the same dynamical data upon imposing a pre-specified network topology derived from prior biological knowledge, and the results from both strategies were compared. The results suggest that the proposed method may serve as a powerful exploration tool for testing hypotheses and the design of new experiments.

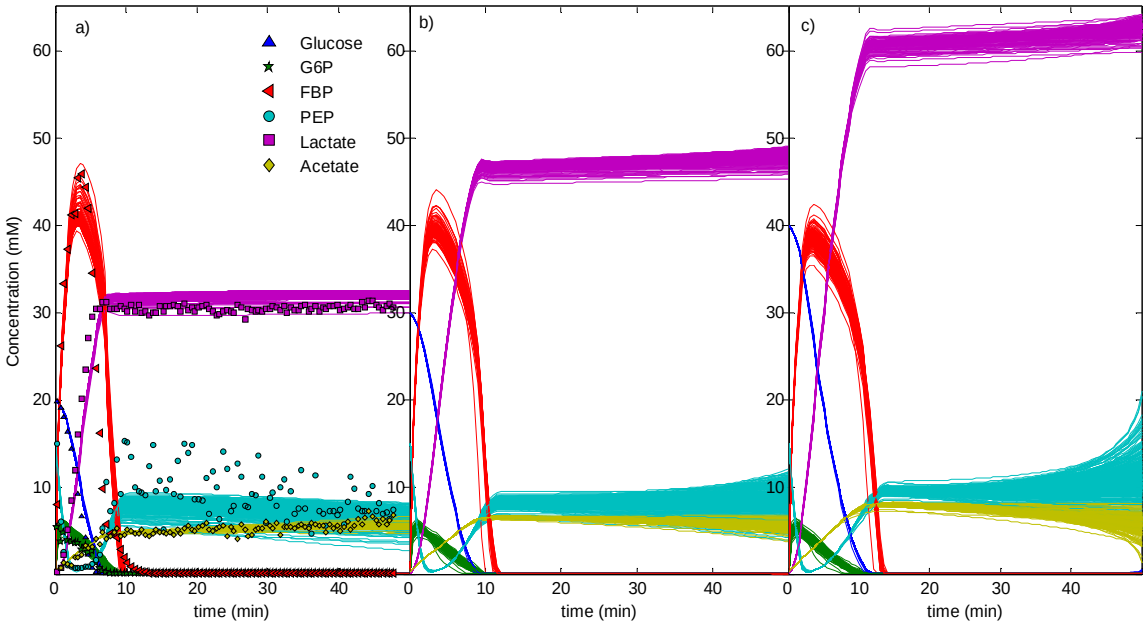

Figure 1 - Ensembles of 500 models. The systems were integrated with different initial concentrations for glucose substrate, namely with 20, 30 and 40 mM; results are shown, respectively, in panels a, b and c.