Parameter Estimation in Biochemical Reaction Networks: An Observer-based Approach

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An important bottleneck in the modelling of biological systems is the scarcity of experimental data on kinetic parameters. Recent advances in measurement technologies increase the feasibility of infer ring these parameters from time series data (Anguelova *et al.*, 2007; Voit and Almeida, 2004). We present a methodology for estimating kinetic parameters from time series data, in a way that is particularly tailored to biological models consisting of nonlinear ordinary differential equations, in particular for systems in which the nonlinearities are polynomial, such as in mass action or generalised mass action kinetics, or rational functions of the states, as in Michaelis-Menten or Hill kinetics.

The proposed approach consists of three steps. First, the system is transformed into an extended system in observer normal form. The extended system does only depend on structural information, not on the value of the parameters (Xia and Zeitz, 1997; Fey *et al.*, 2008). This allows to design a high-gain observer estimating the states of the extended system (Vargas and Moreno, 2005). As the extended system is not observable everywhere, but only trajectory observable, the observer can only be an approximate observer. However, the observer error can be chosen to be arbitrarily small.

In a final step, the parameters are determined based on the observer states, as the unique solutions of simple nonlinear functions of these states. Thus, the proposed parameter scheme estimates is a global estimation algorithm.

The parameter estimation methodology is illustrated on a simple model of the circadian rhythm in neurospora (Leloup *et al.*, 1999). The model contains three species, six reactions and exhibits autonomous oscillations corresponding to the day-night cycle The proposed observer-based parameter estimation method is able to recover all parameters, even if the trajectory comes close to singularities of the observability.

References

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