

Qualitative Analysis of Nonlinear Biochemical Networks

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Introduction

The deterministic modeling approach with nonlinear ordinary differential equations (ODEs) is most widely applied to describe biochemical networks based on the underlying kinetic mechanisms:

$$\frac{dx_i}{dt} = \sum_j f_j(x, \theta), \quad i = 1 \dots N_x, \quad j = 1 \dots N_f \quad (1)$$

with $x: [x_1, \dots, x_{N_x}]^T \geq 0$, vector with state variables; $f_j(x, \theta) \geq 0$, linear and/or nonlinear rate equations; θ : vector with (kinetic) parameters; N_x : total number of states; N_f : total number of rate equations; and t : time.

For certain specific biochemical networks, e.g. [1], accurate experimental data are available and a quantitative model can be developed according to Eq(1) (i.e. the topology, type of kinetic interactions and kinetic parameters are known). However, the general lack in accurate and sufficient quantitative data has driven systems biologists towards alternative ways to describe and analyze biochemical networks. The novelty of our work is the *general* approach for the analysis and simulation of nonlinear biochemical networks for which *no* quantitative information is required [2].

Methods and Results

The mutual interaction and relative contribution of the components determine the global system dynamics; qualitative information is sufficient to analyze and predict the potential types of system behavior [3]. We propose a three-step procedure:

1. *Approximation of nonlinear functions with piecewise-affine (PWA) functions.* PWA functions are a collection of linear functions separated by switching planes. PWA functions can be used to approximate the typical nonlinearities arising in protein kinetics. Fig. 1 shows an example of a PWA approximation of a standard Michaelis-Menten equation.
2. *Detection of equilibrium points and performing stability analysis.* Equilibrium points give an indication of the qualitative behavior of the system and are determined for the complete PWA system.
3. *Construction of qualitative transition graphs.* The transitions on the vertices of the switching planes reconstruct several possible transition graphs. The different transition

graphs correspond to qualitatively different system behavior (e.g., whether it contains a limit cycle, or one or several stable nodes). Certain transitions, and therefore certain dynamic behavior, can only occur if the parameter values satisfy specific constraints, which are obtained from the analysis. The transition graphs can be compared with experimentally observed system dynamics to select the most appropriate transition graph and provide corresponding requirements on the parameters.

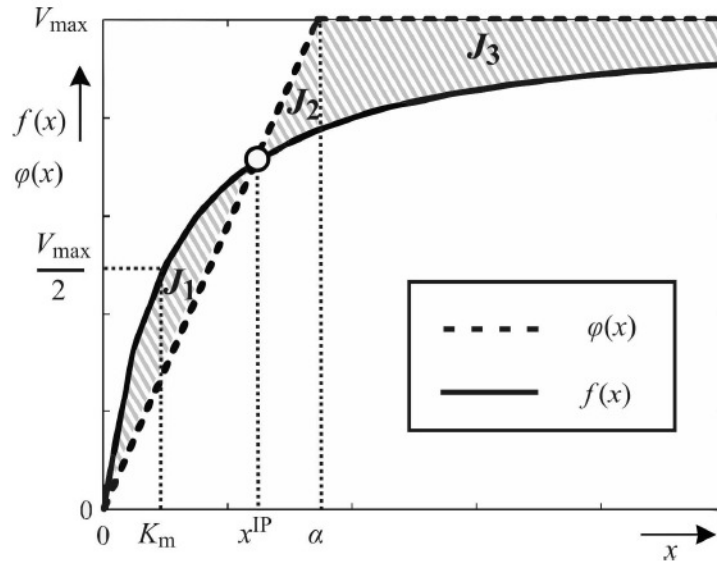


Figure 1 Standard Michaelis-Menten equation ($f(x)$, solid line) and its PWA approximation ($\varphi(x)$, dashed line). The functions $f(x)$ and $\varphi(x)$ intersect at x^{IP} . This approximation can be performed for multivariable nonlinear equations as well [2].

This procedure has successfully been applied to mathematical models of the Transforming Growth Factor- β_1 (TGF- β_1) signal transduction pathway [4] and Unfolded Protein Response (UPR) [2]. The restrictions on the parameter values assist in reducing the parameter search space, which leads to improved parameter estimation compared to conventional methods [2].

Discussion

Qualitative PWA analysis is a general procedure that covers an extensive class of nonlinear biochemical networks, without requiring quantitative information. It can predict the system behavior of a nonlinear model and contributes to experimental design and parameter estimation. Therefore, we consider qualitative PWA analysis as practically very relevant in understanding complex nonlinear biochemical networks with few experimental data.

References

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