Qualitative Analysis of Nonlinear Biochemical Networks with Piecewise-Affine Functions

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Abstract. Nonlinearities and the lack of accurate quantitative information considerably hamper modeling and system analysis of biochemical networks. Here we propose a procedure for qualitative mathematical analysis of piecewise-affine (PWA) approximations of these networks. First the biochemical model size was reduced with quasi-steady state approaches by taking *a priori* information into account. Second, a conversion of a nonlinear model into a PWA approximation and subsequent qualitative analysis of this model was performed. This resulted in different sets of transition graphs that depend on the parameter values, which enables reduction of the parameter search space.

1 Introduction

Understanding biological processes is essential and a challenging task in which computer modeling and analysis have become indispensable, but simulation and analysis are seriously hampered by a lack of accurate experimental data and the complexity of the mathematical models. Certain biochemical networks show switch-like behavior. For instance, genetic regulatory networks can be described as a collection of discrete switches that react on continuous fluctuations in protein concentration. An obvious choice would be to model these networks with a framework that can handle both discrete and continuous components, i.e. the hybrid approach. This hybrid systems paradigm is therefore appropriate and has been applied to various biological systems with distinct switches, e.g. [1–3]. However, the field of biology is much larger, covering other nonlinear biochemical networks that contain non-switch-like components, e.g. [4]. In this short paper, we use hybrid systems to analyze a more general class of nonlinear biochemical networks.

2 Systematic Approach for Biological System Analysis

We will present a methodology that consists of four consecutive steps: 1) model reduction by quasi-steady state approximation, 2) conversion of the nonlinear

model into a hybrid system, in a piecewise-affine (PWA) form, 3) determination of the symbolic equilibrium points and transitions, and 4) transition graph construction. The procedure will be illustrated with a biologically relevant biochemical network, the Transforming Growth Factor-β_1 (TGF-β_1) pathway. We remark explicitly that this method is not limited to this example, but is applicable to other biochemical networks with nonlinear terms as well.

2.1 Step I: Model Reduction

A nonlinear mathematical model can be formulated by means of standard kinetic modeling in biochemistry. Typical biological models are composed of many nonlinear differential equations. The analysis procedure presented here is not automated yet; for manual analysis, a reduced model is required. A suitable model reduction method is the quasi-steady-state approximation, which leads to a more condensed set of state equations by means of timescale separation. The original model of the example consists of a seventh order ODE and is reduced to a second order set:

$$\begin{aligned} \dot{x}_4 &= k_4 \frac{1 - x_4}{K_{\mathrm{m}_2}\left(1 + \frac{x_7}{K_{\mathrm{I}}}\right) + 1 - x_4} - k_6 x_4, \\ \dot{x}_7 &= k_8 \frac{x_4^r}{K_{\mathrm{m}_3}^r + x_4^r} - k_9 x_7, \end{aligned} \tag{1}$$

with k_4, K_{m_2}, K_{I}, k_6, k_8, K_{m_3}, r and k_9: eight parameters (positive values); x_4 and x_7: two states (not negative).

2.2 Step II: PWA Approximation of the Nonlinear Model

Subsequently, the nonlinear terms in Eq. (1) are approximated by PWA functions by applying the rules in [5], which have been extended to deal with multivariable functions. In Eq. (1), the PWA approximation results in a hybrid system f of maximally four regular modes $(q_1, \ldots, q_4)$ containing two states $x = [x_4; x_7]^T$:

$$f = \begin{cases} [-k_6 x_4 + \beta(1 - x_7); -k_9 x_7]^T & \text{if } x_4 - \alpha x_7 < 1 - \alpha \wedge x_4 < K_{\mathrm{m}_3}, \\ [-k_6 x_4 + \frac{\beta}{\alpha}(1 - x_4); -k_9 x_7]^T & \text{if } x_4 - \alpha x_7 > 1 - \alpha \wedge x_4 < K_{\mathrm{m}_3}, \\ [-k_6 x_4 + \beta(1 - x_7); \gamma - k_9 x_7]^T & \text{if } x_4 - \alpha x_7 < 1 - \alpha \wedge x_4 > K_{\mathrm{m}_3}, \\ [-k_6 x_4 + \frac{\beta}{\alpha}(1 - x_4); \gamma - k_9 x_7]^T & \text{if } x_4 - \alpha x_7 > 1 - \alpha \wedge x_4 > K_{\mathrm{m}_3}, \end{cases} \tag{2}$$

with α, β, and γ: parameters required for the PWA approximation, which could be linked to the parameters in the nonlinear model with Eq. (1).

2.3 Step III: Equilibrium Points

Analysis of system dynamics requires knowledge about the equilibrium points in the system. The equilibrium points have to satisfy the invariants and biochemical

constraints, e.g. all concentrations are larger than zero. Symbolic expressions of the equilibrium points in each mode $(q_1, ..., q_4)$ are derived with $\dot{x} = 0$. For the example, all equilibrium points and their associated existence conditions are listed in Table 1. The equilibrium points are mutually exclusive, which implies that no multiple equilibrium points can occur. Furthermore, a common Lyapunov function can be found for all modes, which guarantees that the complete system is globally uniformly asymptotically stable (GUAS), regardless of the parameter values. Note that switching modes are also present in this model, but omitting these modes will not influence the conclusions of the analysis.

Table 1. Equilibrium points and corresponding existence conditions

	Equilibrium point	Existence condition
q_1 :	$\left(\frac{\beta}{k_6}, 0\right)$	$0 < \frac{\beta}{k_6} < \min\left(1-\alpha, K_{\mathrm{m}_3}\right)$
q_2 :	$\left(\frac{\beta}{\alpha k_6+\beta}, 0\right)$	$1-\alpha < \frac{\beta}{k_6} < K_{\mathrm{m}_3}$
q_3 :	$\left(\frac{\beta(k_9-\gamma)}{k_6 k_9}, \frac{\gamma}{k_9}\right)$	$K_{\mathrm{m}_3}\frac{k_9}{k_9-\gamma} < \frac{\beta}{k_6} < \frac{k_9}{k_9-\gamma} - \alpha$
q_4 :	$\left(\frac{\beta}{\alpha k_6+\beta}, \frac{\gamma}{k_9}\right)$	$\max\left(K_{\mathrm{m}_3}\frac{k_9}{k_9-\gamma}, \frac{k_9}{k_9-\gamma} - \alpha\right) < \frac{\beta}{k_6} < 1$

2.4 Step IV: Transition Graph Construction

Mode transitions occur if the inner product of the model equations f and the normal n of the guard condition, i.e. the inequality in Eq. (2), is larger than zero [5]:

$$f^T \cdot n > 0. \tag{3}$$

Eq. (3) is applied for all transitions on the guard conditions, for each equilibrium point. Since the equilibria are bounded by existence conditions (Table 1) and transitions have to comply with Eq. (3), a transition has to satisfy specific inequalities of parameter values in order to be feasible. For the example it has been shown that multiple transition graphs can exist. With experimental information from the literature, one can exclude specific system behavior and, consequently, impose additional constraints on the parameter values. However, due to limitations in space, the plots of these transition graphs and corresponding restrictions on the parameter values have been omitted.

3 Discussion and Conclusion

The qualitative analysis method described above has been tailored for processes that are typically observed in biochemical networks, e.g. Michaelis-Menten and Hill kinetics, but can be applied to other research fields outside biology as well. A model of a biochemical network was used to illustrate our method. Since the

approach was partially based on model reduction, a relatively small model was constructed as a result, which simplifies qualitative analysis [5, 6]. Such small models can of course be analyzed with standard phase plane techniques, but larger biochemical networks are currently under study. Automation of our qualitative hybrid approach with quantifier elimination [7] will be done in the near future, enabling the analysis of larger systems. Comparison of the transition graphs of the example with preliminary experimental data shows qualitative similarities: the system converges to a single, stable steady-state and contains neither a limit cycle nor exhibits multistability, exactly according to the model predictions. The next step is to link the parameters of the PWA model to their nonlinear counterparts. The hybrid analysis procedure could fulfill an important role in obtaining an initial estimate for nonlinear parameter estimation [8] and support the parameter estimator to select a more appropriate solution that satisfies both the limited amount of measurement data and the *a priori* qualitative information.

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