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Brief paper

Stability analysis of quasi-polynomial dynamical systems with applications to biological network models☆

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ABSTRACT

We study asymptotic stability properties of a class of quasi-polynomial dynamical systems. This class of nonlinear systems is a special class of interconnected systems arising in several biochemical and biological system applications and can be represented using quasi-polynomial dynamical systems. It is known that a special class of such systems can be embedded into a higher dimensional space and cast in Lotka–Volterra canonical form. We characterize a class of quasi-polynomial dynamical systems with asymptotic stability properties for all initial conditions in the positive orthant. The key advantage of the proposed method is that it is algebraic such that asymptotic stability conditions can be derived in terms of (as they are usually in biological network models) parameters of the system. We apply our results to parameterized models of three different biological systems: the generalized mass action (GMA) model, an oscillating biochemical network, and a reduced order model of the glycolysis pathway, and show that one can apply our proposed method to verify asymptotic stability for each case in terms of underlying parameters.

1. Introduction

Recent advances in systems biology have created a new trend to study network level properties of biological networks. Robustness with respect to changes in various parameters in a biological network is one such fundamental characteristic. There is an abundance of literature on how robustness is involved in various biological processes and mechanisms as well as living systems (cf. Kitano (2007) and references therein). Nonetheless, a mathematical framework to provide a unified perspective on robustness is sorely missing. Our aim is to provide a framework to study stability properties of a class of biological network models in terms of uncertain network parameters (e.g. the rate constants, etc.).

There has been recent interest in stability analysis of biochemical reaction network models, for instance see Arcak and Sontag (2006, 2008), Jovanović, Arcak, and Sontag (2008) and Ma and Iglesias (2002) and references therein. In Ma and Iglesias (2002), two different techniques are applied to reason about the robustness of an oscillatory model. Another method to quantify the robustness of oscillatory behavior of bio-molecular models to perturbations is presented in Ghaemi, Sun, Iglesias, and Del Vecchio (2009). The authors propose a method that is based on Hopf bifurcation and the Routh–Hurwitz stability criterion. In Arcak and Sontag (2008), a passivity-based stability criterion for a class of interconnected systems is discussed which extends the earlier work of the authors on the secant criterion for cyclic systems to a general interconnection structure (Arcak & Sontag, 2006). The main result of Arcak and Sontag (2008) establishes global asymptotic stability of an interconnected network from the diagonal stability of the corresponding dissipativity matrix.

In this paper, we consider a special class of quasi-polynomial dynamical systems that arises in modeling biochemical reaction networks. This class of nonlinear systems can be represented using power-law expansions in the variables of the system. The state variable of the (quasi-polynomial) system represents one of the variables of the model (metabolite concentrations, protein concentrations or levels of gene expression) and the coefficients are stoichiometric coefficients and kinetic orders. The main difference between quasi-polynomial models and other ODE models used in biochemical systems is that the kinetic orders can be non-integer numbers. A kinetic order can have even negative value when inhibition is modeled. In this way, power-law models have a higher flexibility to reproduce the nonlinearity of biochemical systems.

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It is known that a quasi-polynomial system can be transformed into a Lotka–Volterra system with some appropriate change of variables in higher dimensions (Hernandez-Bermejoa & Fairen, 1997). The dimension of the corresponding Lotka–Volterra system depends on the number of different quasi-monomials appearing in the right-hand side of the equations, which is usually greater than the number of state variables. Clearly, the resulting interaction matrix (Δ in (4)) is singular. We show that stability properties of a quasi-polynomial system can be studied through its mathematically equivalent counterpart (namely, the Lotka–Volterra system) that has much simpler form.

It is known that if the interaction matrix of a Lotka–Volterra system is diagonally stable, then one can conclude the global asymptotic stability of the equilibrium of the system in the positive orthant (Goh, 1977; Kaszkurewicz & Bhaya, 2000). For a singular interaction matrix, the existing diagonal stability results can only guarantee the boundedness of the solutions in the positive orthant. There is also some research that proposes methods to study the boundedness of solutions based on the existence of a Lyapunov function associated with a fixed point of a quasi-polynomial system (Figueiredo, Gléria, & Rocha Filho, 2000; Hernandez-Bermejo, 2002).

We show how to derive sufficient conditions to guarantee global asymptotic stability of the equilibria of the corresponding Lotka–Volterra systems and the quasi-polynomial system in the positive orthant. These sufficient conditions impose a rank condition on the matrix of kinetic orders (Σ in (3)) and require a comparison matrix constructed using the moduli of the entries of the interaction matrix to be an M-matrix (Horn & Johnson, 1990). We also provide necessary conditions for asymptotic stability of the equilibria of the corresponding Lotka–Volterra system. The main advantage of the proposed stability analysis is that it is algebraic in the sense that the procedure to embed a quasi-polynomial dynamical system into a Lotka–Volterra form is an algebraic procedure. Moreover, in order to verify that a matrix is an M-matrix one only needs to check whether the leading principal minors of the matrix are non-negative. This step is also algebraic and leads to a set of inequalities in terms of the system parameters. In Section 3, we apply our results to study stability properties of three parameterized biological network models in terms of their parameters. We show that one can follow the proposed algebraic procedures to find the range of parameters for which a given parameterized model is asymptotically stable.

Notations. We denote the set of real numbers by $\mathbb{R}$. The positive orthant of $\mathbb{R}^n$ is defined as

$$\mathbb{R}^n_{++} = \{x \in \mathbb{R}^n \mid x_i > 0 \text{ forall } i = 1, \ldots, n\}. \tag{1}$$

The set of all matrices $\Delta = [\delta_{ij}]$ for which $\delta_{ii} \geq 0$ for all i and $\delta_{ij} \leq 0$ for all $i \neq j$ are shown by $\mathcal{D}_0$. For a given matrix $\Delta = [\delta_{ij}]$, we define matrix $M(\Delta) = [m_{ij}]$ as follows

$$m_{ij} = \begin{cases} \delta_{ij} & \text{if } j = i \\ |\delta_{ij}| & \text{if } j \neq i. \end{cases} \tag{2}$$

Definition 1. A matrix $\Delta \in \mathcal{D}_0$ is called an M-matrix if all the leading principal minors of Δ are non-negative, or equivalently, if the real part of each nonzero eigenvalue of Δ is positive.

2. Global stability of quasi-polynomial systems

The primary motivation for our study is biological network models where most of the biochemical processes can be represented using power-law expansions in the variables of the system. In this paper, we consider the following class of quasi-polynomial dynamical systems:

$$\dot{x}_i = b_i x_i + x_i \sum_{j=1}^{m} a_{ij} \prod_{k=1}^{n} x_k^{\sigma_{jk}} \tag{3}$$

for $i = 1, \ldots, n$. The state variables x_i represents one of the n variables of the model (metabolite concentrations, protein concentrations or levels of gene expression), b_i and a_{ij} are stoichiometric coefficients, and σ_{jk} are kinetic orders. The principal difference of quasi-polynomial models with respect to other ODE models used in biochemical systems is that the kinetic orders can be non-integer numbers. A kinetic order can have even negative value when inhibition is modeled. In this way, quasi-polynomial models have a higher flexibility to capture nonlinear behavior of biochemical systems. For fixed parameters, we denote the trajectory of system (3) at time instant t with initial condition x_0 by $x(t; x_0)$.

Let us denote by $A = [a_{ij}]$ the $n \times m$ interaction matrix, by $\Sigma = [\sigma_{ij}]$ the $m \times n$ matrix of kinetic orders, and by $b = [b_i]$ the $n \times 1$ vector of coefficients. For a given set of parameters, we denote the set of nontrivial equilibria of system (3) by $\mathcal{E}(A, \Sigma, b)$, i.e., the set of all strictly positive vectors $x^* = (x_1^*, \ldots, x_n^*)$ for which $b_i + \sum_{j=1}^{m} a_{ij} \prod_{k=1}^{n} (x_k^*)^{\sigma_{jk}} = 0$ and for all $i = 1, \ldots, n$. Define nonlinear map $F : \mathbb{R}^n \to \mathbb{R}^m$ componentwise as $z_j = F_j(x_1, \ldots, x_n) = \prod_{k=1}^{n} x_k^{\sigma_{jk}}$ for all $j = 1, \ldots, m$. The projection of the positive orthant $\mathbb{R}^n_{++}$ under F is denoted by $\Phi = \left\{z \mid z = F(x), \forall x \in \mathbb{R}^n_{++}\right\}$. The class of quasi-polynomial dynamical systems defined by (3) can be cast as a (usually with higher dimension) Lotka–Volterra system with the following canonical form (Hernandez-Bermejoa & Fairen, 1997)

$$\dot{z}_i = \lambda_i z_i + z_i \sum_{j=1}^{m} \delta_{ij} z_j \tag{4}$$

for $i = 1, \ldots, m$, where the system matrices are given by $\Delta = [\delta_{ij}] = \Sigma A$ and $\lambda = [\lambda_i] = \Sigma b$. Throughout the paper, we assume that $\text{rank}(\Sigma) = n$ (Magyar, Szederknyi, & Hangos, 2005). This assumption implies that dynamical systems (4) with initial condition $z(0)$ and (3) with initial condition $x(0)$ exhibit the same dynamical behavior if $z(0) = F(x(0))$. We denote the trajectory of system (4) starting at $z(0)$ by $z(t; z(0))$.

One of the early works on the stability properties of Lotka–Volterra system (4) was reported in Goh (1977). For a recent reference on the subject, we refer to Kaszkurewicz and Bhaya (2000) for a comprehensive discussion. The following theorem from Goh (1977) gives a sufficient condition for the global stability of system (4).

Theorem 2. *If there exists a constant positive diagonal matrix* $P = \text{diag}(p_1, \ldots, p_m) > 0$ *such that*

$$\Delta^T P + P\Delta < 0, \tag{5}$$

then the nontrivial equilibrium $z^* \in \mathbb{R}^m_{++}$ *of the Lotka–Volterra model (4) is globally stable for all* $z(0) \in \mathbb{R}^m_{++}$.

We refer to Goh (1977) for a proof. The existence of a positive diagonal matrix in Theorem 2 implies that Δ is non-singular and that the unique nontrivial equilibrium is asymptotically stable. In order to handle singular Δ, the sufficient condition in Theorem 2 can be relaxed to the following form

$$\Delta^T P + P\Delta \leq 0 \tag{6}$$

for a positive diagonal matrix P. The existence of a solution for (6) implies the boundedness of the solutions and stability of the nontrivial equilibrium points. It is straightforward to verify that the following function which is defined on $\mathbb{R}^m_{++}$ serves as a Lyapunov candidate for system (4)

$$V(z) = \sum_{i=1}^{m} p_i \left(z_i - z_i^* - z_i^* \ln \left(\frac{z_i}{z_i^*} \right) \right) \tag{7}$$