Automatica 48 (2012) 2945–2950

Contents lists available at SciVerse ScienceDirect

Automatica

journal homepage: www.elsevier.com/locate/automatica

Brief paper

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

Nader Motee [a,1], Bassam Bamieh [b], Mustafa Khammash [c]

[a] Department of Mechanical Engineering and Mechanics, Lehigh University, Bethlehem, PA 18015, USA

[b] Department of Mechanical Engineering, University of California, Santa Barbara, CA 93106, USA

[c] Department of Biosystems Science and Engineering, Swiss Federal Institute of Technology, Basel, Switzerland

ARTICLE INFO

Article history:
Received 17 March 2012
Accepted 7 June 2012
Available online 4 August 2012

Keywords:
Nonlinear systems
Interconnected systems
Stability analysis
Asymptotic stability
Complex systems

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.

☆ This work is supported by research funding from the National Science Foundation through Grants ECCS-0835847 and ECCS-0802008. The material in this paper was partially presented at the 2010 American Control Conference (ACC'10), June 30–July 2, 2010, Baltimore, Maryland, USA. This paper was recommended for publication in revised form by Associate Editor Juergen Hahn under the direction of Editor Frank Allgöwer.

E-mail addresses: motee@lehigh.edu (N. Motee), bamieh@engineering.ucsb.edu (B. Bamieh), mustafa.khammash@bsse.ethz.ch (M. Khammash).

[1] Tel.: +1 610 758 4547; fax: +1 610 758 4102.

0005-1098/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
doi:10.1016/j.automatica.2012.06.094

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)

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

in which z^* is a nontrivial equilibrium of (4) and $P = \text{diag}(p_1, \ldots, p_m) > 0$ satisfies (5) or (6). We refer to Kaszkurewicz and Bhaya (2000) for a thorough discussion on diagonal stability and the related diagonal-type Lyapunov functions.

Let us assume that the number of monomials m is greater than the number of state variables n in quasi-polynomial system (3). Thus, one can see that $\Delta = \Sigma A$ is a singular $m \times m$ matrix. By applying Theorem 2 to system (4), we can only hope to prove the boundedness of the solutions of (4), and therefore, the solutions of (3). In the following theorem, we propose sufficient conditions for asymptotic stability of the set of equilibrium points of (3).

Proposition 3. *Suppose that for system (3) matrix $\Delta = [\delta_{ij}]$ is diagonally dominant and $\delta_{ii} \leq 0$. If for every $x(0) \in \mathbb{R}^n_{++}$ the trajectory of system (3) converges asymptotically to the set of equilibria $\mathcal{E}(A, \Sigma, b)$, then $-M(\Delta)$ is an M-matrix.*

Proof. Suppose that $x(t; x(0))$ asymptotically converges to $x^* \in \mathcal{E}(A, \Sigma, b)$ and denote $z^* = F(x^*)$. We consider the corresponding Lotka–Volterra system (4) with initial condition $z(0) = F(x(0))$. The trajectory $z(t; z(0))$ also converges asymptotically to equilibrium point z^*. Consider linearization of (4) at z^*. The Jacobian matrix is given by $J = \text{diag}(z_1^*, \ldots, z_m^*)\Delta$. Since the set of equilibria $\mathcal{E}(A, \Sigma, b)$ is asymptotically stable for all $x(0) \in \mathbb{R}^n_{++}$, all the eigenvalues of J must have non-positive real parts. Therefore, all the eigenvalues of Δ must have non-positive real parts. From our assumption that Δ is diagonally dominant and according to the Gershgorin circle theorem, the eigenvalues of $M(\Delta)$ also belong to the Gershgorin discs of matrix Δ. Therefore, all the eigenvalues of $-M(\Delta)$ must have non-negative real parts. Since $-M(\Delta) \in \mathcal{D}_0$, we can conclude that $-M(\Delta)$ is an M-matrix. □

Theorem 4. *Suppose that $\mathcal{E}(A, \Sigma, b)$ is the set of all nontrivial equilibria of system (3) in $\mathbb{R}^n_{++}$ and $\Delta = \Sigma A$ is irreducible. Then every trajectory of the system $x(t; x(0))$ asymptotically converges to the set $\mathcal{E}(A, \Sigma, b)$ for all initial conditions $x(0) \in \mathbb{R}^n_{++}$ if $-M(\Delta)$ is an M-matrix.*

Proof. Consider the corresponding Lotka–Volterra system (7) with $z(0) = F(x(0))$ for a given $x(0) \in \mathbb{R}^n_{++}$. Let us assume that $z^* = F(x^*)$ for some $x^* \in \mathcal{E}(A, \Sigma, b)$. We show that one can choose parameters $p_i > 0$ such that the time derivative of (7) is non-positive along all trajectories $z(t; z(0))$ of system (4) with initial condition $z(0) = F(x(0))$. The time-derivative of (7) along a trajectory of (4) is given by

$$\dot{V} = \sum_{i=1}^{m} p_i \dot{z}_i \left(\frac{z_i - z_i^*}{z_i} \right). \tag{8}$$

We rewrite (4) in terms of new state variables $y_i = z_i - z_i^*$ as $\dot{z}_i = z_i \sum_{j=1}^m \delta_{ij} y_j$. By plugging this into (8) we get

$$\begin{aligned} \dot{V} &= \sum_{i=1}^{m} p_i y_i \sum_{j=1}^{m} \delta_{ij} y_j \\ &= \sum_{i=1}^{m} \sum_{j=1}^{m} p_i \delta_{ij} y_i y_j + \sum_{i=1}^{m} q_i y_i^2 - \sum_{i=1}^{m} q_i y_i^2. \end{aligned} \tag{9}$$

The assumption that $-M(\Delta)$ is an M-matrix and irreducible is equivalent to the fact that there exist positive vectors $\nu, \mu > 0$ such that $M(\Delta)\nu \leq 0$ and $\mu^T M(\Delta) \leq 0$ (see Poole and Boullion (1974) for more details), i.e., there exist $\nu_i, \mu_i > 0$ such that

$$\delta_{ii}\, \nu_i + \sum_{j \neq i} |\delta_{ij}|\, \nu_j \leq 0, \tag{10}$$

$$\mu_i\, \delta_{ii} + \sum_{j \neq i} \mu_j\, |\delta_{ji}| \leq 0. \tag{11}$$

By choosing $p_i = \frac{2\mu_i}{\nu_i}$ and $q_i = \frac{2}{\nu_i} \sum_{j \neq i} \mu_j |\delta_{ji}|$, we have

$$\begin{aligned} \dot{V} &= 2 \sum_{i=1}^{m} \sum_{j \neq i}^{m} \frac{\mu_i}{\nu_i} \delta_{ij}\, y_i\, y_j \\ &\quad + \sum_{i=1}^{m} \left(\sum_{j \neq i} \frac{\mu_j}{\nu_i} |\delta_{ji}| + 2 \frac{\mu_i}{\nu_i} \delta_{ii} \right) y_i^2 - \sum_{i=1}^{m} \sum_{j \neq i} \frac{\mu_j}{\nu_i} |\delta_{ji}| y_i^2. \end{aligned} \tag{12}$$

From (10) and (11), we have that

$$\frac{\mu_i}{\nu_i^2} \left(\delta_{ii} \nu_i + \sum_{j \neq i} |\delta_{ij}| \nu_j \right) + \frac{1}{\nu_i} \left(\mu_i \delta_{ii} + \sum_{j \neq i} \mu_j |\delta_{ji}| \right) \leq 0. \tag{13}$$

Therefore, it follows that

$$\sum_{j \neq i} \frac{\mu_j}{\nu_i} |\delta_{ji}| + 2 \frac{\mu_i}{\nu_i} \delta_{ii} \leq - \sum_{j \neq i} \frac{\mu_i}{\nu_i^2} \nu_j |\delta_{ij}|. \tag{14}$$

By applying (14) to (12), we get the following inequality

$$\dot{V} \leq - \sum_{\substack{i,j \\ i \neq j}} \frac{\mu_i}{\nu_j} |\delta_{ij}| \left(\frac{\nu_j}{\nu_i} \text{sgn}(\delta_{ij}) y_i - y_j \right)^2 \leq 0. \tag{15}$$

If the middle term in inequality (15) is nonzero, then $\dot{V} < 0$ which implies asymptotic stability of the equilibrium. According to LaSalle's theorem, the Φ-limit set of the system is contained in the maximal invariant subset of $\mathcal{M} = \{z \in \mathbb{R}^n \mid \dot{V}(z) \equiv 0\}$. From (15), one can see that if $\dot{V} \equiv 0$, then $y_j = \frac{\nu_j}{\nu_i} \text{sgn}(\delta_{ij}) y_i$ if $\delta_{ij} \neq 0$ for all $j \neq i$. By substituting this into (9), we can find the function form of $\dot{V}$ as follows

$$\dot{V} = \sum_{i=1}^{m} \left(\frac{2\mu_i}{\nu_i^2} \right) \left(\delta_{ii} \nu_i + \sum_{j \neq i} |\delta_{ij}| \nu_j \right) y_i^2. \tag{16}$$

Let us assume that $z_i(t) \not\equiv z_i^*$ whenever $\dot{V} \equiv 0$. From inequalities (10), we can conclude that $\dot{V} \equiv 0$ if and only if $\delta_{ii}\nu_i + \sum_{j \neq i} |\delta_{ij}| \nu_j = 0$. This implies that

$$\dot{z}_i = z_i \left(\delta_{ii} \nu_i + \sum_{j \neq i} |\delta_{ij}| \nu_j \right) \frac{y_i}{\nu_i} = 0. \tag{17}$$

Hence $z(t)$ must be a constant solution of (4), i.e., an equilibrium point z^{**} of (4). Since $z(0) \in \mathbb{R}^m_{++}$ and $\dot{V} \leq 0$ along the trajectory of the system, this constant solution z^{**} must be in $\mathbb{R}^m_{++}$ as well. Therefore, this constant solution z^{**} is a nontrivial equilibrium point of system (4), i.e., $z^{**} \in \{z \in \mathbb{R}^m_{++} \big| \lambda + \Delta z = 0\}$. Since $\text{rank}(\Sigma) = n$, we have that $b + Az^{**} = 0$. Therefore, there is $x^{**} \in \mathcal{E}(A, \Sigma, b)$ such that $z^{**} = F(x^{**})$. This implies that the maximal invariant set of system (4) only contains the set of equilibria $\mathcal{E}(A, \Sigma, b)$ and that $x(t; x(0))$ for all $x(0) \in \mathbb{R}^n_{++}$ converges asymptotically to $\mathcal{E}(A, \Sigma, b)$. □

Theorem 4 characterizes sufficient conditions for the stability of the set of equilibria of system (3). The condition that $-M(\Delta)$ is an M-matrix is equivalent to the following feasibility condition: there is a non-negative diagonal matrix D such that

$$DM(\Delta) + M(\Delta)^T D \leq 0. \tag{18}$$

The sufficient condition provided by Theorem 4 is more conservative than that of Theorem 2. However, it guarantees asymptotic stability of the set of equilibria. We note that matrix $M(\Delta)$ is parameterized in terms of system parameters. The system parameters can be uncertain but with known variability ranges. We refer the reader to Feron, Boyd, El Ghaoui, and Balakrishnan (1997) and Kaszkurewicz and Bhaya (2000) for an extensive discussion on how to check the feasibility and solve linear matrix inequality (18) with uncertain matrix $M(\Delta)$.

3. Application to biological network models

3.1. Generalized Mass Action (GMA) model

We consider stability conditions for the following Generalized Mass Action model for biochemical reactions (Irving, Voit, & Savageau, 1991)

$$\dot{x}_1 = b_1 x_1 - a_1 x_1^{\sigma_3} x_2^{\sigma_1} \tag{19}$$

$$\dot{x}_2 = -b_2 x_2 + a_2 x_1^{\sigma_1} x_3^{\sigma_2} \tag{20}$$

$$\dot{x}_3 = -b_3 x_3 + a_3 x_2^{\sigma_1}. \tag{21}$$

The state variables $x_i > 0$ are concentrations, parameters σ_i are kinetic orders of different processes, and $b_i, a_i > 0$ are the reaction rate constants. This system can be cast as (3) with the following matrices

$$b = \begin{bmatrix} b_1 \\ -b_2 \\ -b_3 \end{bmatrix}, \qquad A = \begin{bmatrix} -a_1 & 0 & 0 \\ 0 & a_2 & 0 \\ 0 & 0 & a_3 \end{bmatrix},$$
$$\Sigma = \begin{bmatrix} \sigma_3 - 1 & \sigma_1 & 0 \\ \sigma_1 & -1 & \sigma_2 \\ 0 & \sigma_1 & -1 \end{bmatrix}. \tag{22}$$

It is straightforward to verify that the equilibrium of the corresponding Lotka–Volterra system is given by $z_1^* = \frac{b_1}{a_1}, z_2^* = \frac{b_2}{a_2}, z_3^* = \frac{b_3}{a_3}$. According to Theorem 4, sufficient conditions for stability of system (19)–(21) are $\operatorname{rank}(\Sigma) = 3$ and

$$-M(\Delta) = \begin{bmatrix} (\sigma_3 - 1)a_1 & -|\sigma_1||a_2| & 0 \\ -|\sigma_1||a_1| & a_2 & -|\sigma_2||a_3| \\ 0 & -|\sigma_1||a_2| & a_3 \end{bmatrix} \tag{23}$$

is an M-matrix. Thus, one can easily compute all the principal minors of the above matrix and find the set of parameters for which system (19)–(21) is globally asymptotically stable in the positive orthant. Under the assumption that $a_i > 0$, the sufficient condition that $-M(\Delta)$ is an M-matrix is equivalent to the parameter space defined by the following feasible inequalities

$$\sigma_3 - 1 \geq 0 \tag{24}$$

$$\sigma_3 - 1 - \sigma_1^2 \geq 0 \tag{25}$$

$$(\sigma_3 - 1)(1 - |\sigma_1\sigma_2|) - \sigma_1^2 \geq 0. \tag{26}$$

It follows that system (19)–(21) is asymptotically stable for $\sigma_1 = 0$, $\sigma_3 = 1$, and all $\sigma_2 \in \mathbb{R}$.

3.2. Oscillating biochemical network

In our next example, we consider a model of the molecular network underlying 3′, 5′-cyclic adenosine monophosphate (cAMP) oscillations observed in homogenous populations of *Dictyostelium* cells (Laub & Loomis, 1998). The proposed model exhibits the spontaneous oscillations in cAMP observed during the early development of *Dictyostelium discoideum*. The robustness properties of this model were studied in Ghaemi et al. (2009) and Ma and Iglesias (2002). The variations in the enzymatic activities of these proteins are described by the following autonomous dynamical system

$$\begin{cases} \dot{x}_1 = k_1 x_7 - k_2 x_1 x_2 \\ \dot{x}_2 = k_3 x_5 - k_4 x_2 \\ \dot{x}_3 = k_5 x_7 - k_6 x_2 x_3 \\ \dot{x}_4 = k_7 - k_8 x_3 x_4 \\ \dot{x}_5 = k_9 x_1 - k_{10} x_4 x_5 \\ \dot{x}_6 = k_{11} x_1 - k_{12} x_6 \\ \dot{x}_7 = k_{13} x_6 - k_{14} x_7 \end{cases} \tag{27}$$

in which the state variable $x = [x_1, \ldots, x_7]^T$ represents the concentration of the various proteins (Laub & Loomis, 1998). Since this system has a S-system representation, the equilibrium can be calculated analytically. The unique equilibrium of the system in $\mathbb{R}_+^7$ in terms of parameters k_i can be calculated analytically (see Ghaemi et al. (2009) for more details). It is straightforward to see that one can reformulate (27) in the form of (3) with quasi-monomials $x_2, x_3, x_4, x_4^{-1}, x_1^{-1}x_7, x_2^{-1}x_5, x_3^{-1}x_7, x_1x_4^{-1}, x_1x_6^{-1}, x_6x_7^{-1}$ and find the corresponding system matrices b, A, and Σ. The matrix Σ has full-column rank. Also, the matrix $-M(\Delta)$ in which $\Delta = \Sigma A$ is given by the equation in Box I.

The set of all parameters k_i for which $-M(\Delta)$ is an M-matrix is defined by the feasible solutions of the following inequalities

$$k_1k_3k_6k_7k_8k_{10} \leq 0 \quad \text{and} \quad k_5 \geq 0. \tag{28}$$

The dynamical system (27) represents the model of an oscillator when the values of parameters k_i vary within some specific sets (cf. Laub and Loomis (1998) and Ma and Iglesias (2002)). The set of parameters defined by inequalities (28) guarantees asymptotic stability of (27).

3.3. Reduced biological models

In this example, we show that our proposed method can also be applied to a biological network model with fractional terms in the right hand side. For differential systems arising from generalized chemical reaction systems, there exists a standard way to perform the quasi-steady state approximation, provided that the set of chemical reactions is divided into two parts: the fast ones and the slow ones. One can obtain a set of algebraic equations by ignoring the fast dynamics (by setting the time derivative of the fast dynamics equal to zero). There is a standard procedure by which one can obtain a reduced model which only contains the slow dynamics. These reduced models usually contain the Hill functions of the form $\frac{ax^\alpha}{1+bx^\beta}$ for some positive real numbers a, b, α, β. In this example, we consider the nominal regulated autocatalytic glycolysis model, which is studied in Chandra, Buzi, and Doyle (2009), as follows

$$\dot{x} = -q\frac{Vx^q}{1+\gamma x^h} + (1+q)k_2 y - k_1 \tag{29}$$

$$\dot{y} = \frac{Vx^q}{1+\gamma x^h} - k_2 y \tag{30}$$

in which x is the ATP level, y the lumped variable of intermediate metabolites downstream of the autocatalytic reaction, q captures the strength of autocatalysis, k_2 represents the lumped metabolic reactions that generate ATP, k_1 represents the ATP demand of the cell, and h is the gain of the inhibition of the enzymes by ATP. The parameter γ is determined by the enzyme and regulates the strength of feedback inhibition. The parameter V is related to the availability of precursors such as F6P. In the following, we show that by a suitable change of variable, one can cast a nonlinear system with Hill functions in the form of (3). For example, we consider the auxiliary variable defined by $z = \frac{xy}{1+\gamma x^h}$. This new variable does not have a biological interpretation. However, it helps us to reformulate the glycolysis model in the following quasi-polynomial representation

$$\dot{x} = x\left(-qVx^{q-2}y^{-1}z + (q+1)k_2x^{-1}y - k_1x^{-1}\right) \tag{31}$$

$$\dot{y} = y\left(Vx^{q-1}y^{-2}z - k_2\right) \tag{32}$$

$$\begin{aligned} \dot{z} \;=\; & z(-qVx^{q-2}y^{-1}z + (q+1)k_2x^{-1}y - k_1x^{-1} \\ & + Vx^{q-1}y^{-2}z - k_2 + \gamma qhVx^{q+h-3}y^{-2}z^2 \\ & - \gamma h(q+1)k_2x^{-1}z + \gamma hk_1x^{h-2}y^{-1}z). \end{aligned} \tag{33}$$

$$-M(\Delta)=\begin{bmatrix} 0 & 0 & 0 & 0 & 0 & -k_3 & 0 & 0 & 0 & 0\\ -k_6 & 0 & 0 & 0 & 0 & 0 & -k_5 & 0 & 0 & 0\\ 0 & -k_8 & 0 & -k_7 & 0 & 0 & 0 & 0 & 0 & 0\\ 0 & -k_8 & 0 & k_7 & 0 & 0 & 0 & 0 & 0 & 0\\ -k_2 & 0 & 0 & 0 & k_1 & 0 & 0 & 0 & 0 & -k_{13}\\ 0 & 0 & -k_{10} & 0 & 0 & k_3 & 0 & -k_9 & 0 & 0\\ -k_6 & 0 & 0 & 0 & 0 & 0 & k_5 & 0 & 0 & -k_{13}\\ -k_2 & -k_8 & 0 & -k_7 & -k_1 & 0 & 0 & 0 & 0 & 0\\ -k_2 & 0 & 0 & 0 & -k_1 & 0 & 0 & 0 & k_{11} & 0\\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -k_{11} & k_{13} \end{bmatrix}.$$

Box I.

$$\Delta=\begin{bmatrix} k_1 & -(q+1)k_2 & qV & 0 & 0 & 0 & 0\\ k_1 & -(q+1)k_2 & qV & V & 0 & 0 & 0\\ -k_1q+k_1 & k_2q^2-k_2 & -q^2V+qV & 0 & \gamma qhV & -\gamma h(q+1)k_2 & \gamma hk_1\\ -k_1q & k_2q^2+k_2q & -q^2V & -V & \gamma qhV & -\gamma h(q+1)k_2 & \gamma hk_1\\ -k_1q-k_1h+k_1 & k_2q^2+k_2hq+k_2h-k_2 & -q^2V-qVh+qV & 0 & 2\gamma qhV & -2\gamma h(q+1)k_2 & 2\gamma hk_1\\ 0 & 0 & 0 & V & \gamma qhV & -\gamma h(q+1)k_2 & \gamma hk_1\\ -k_1h+k_1 & k_2hq+k_2h-k_2q-k_2 & -qVh+qV & 0 & \gamma qhV & -\gamma h(q+1)k_2 & \gamma hk_1 \end{bmatrix}$$

Fig. 1. The Δ matrix of the nominal regulated autocatalytic glycolysis model.

We can extract the corresponding matrices in the canonical representation of the system from (31)–(33) and obtain matrix Δ which is shown in Fig. 1. It is straightforward to verify that $\text{rank}(\Sigma) = 3$. Therefore, a sufficient condition for the positive equilibrium of the system (29)–(30) to be globally asymptotically stable is for $-M(\Delta)$ to be an M-matrix. We should emphasize that the representation (31)–(33) is not unique. Therefore, one may be able to find a suitable equivalent quasi-polynomial representation of (29)–(30) that can provide more insight into the stability properties of the glycolysis model. Moreover, we should emphasize that glycolysis model (29)–(30) induces oscillations when its parameters take values within a specific set. The above analysis quantifies a range of parameters for which system (29)–(30) is asymptotically stable.

Remark 5. The above examples show that one can directly apply our results to derive sufficient (and sometimes necessary, see Proposition 3) conditions for asymptotic stability of parameterized models arising in biological network models. The proposed method is easy to apply as one only needs to follow some specific algebraic procedures to derive the conditions. We should also emphasize that the resulting inequalities (which specify the asymptotic stability region) can be conservative, in the sense that the actual asymptotic stability region can be larger than the one our method suggests.

4. Conclusion

The primary objective of this paper is to propose a purely algebraic method to study polynomial dynamical systems arising in biological network models. To this end, we study stability properties of a special class of quasi-polynomial system. By first embedding a quasi-polynomial dynamical system into a Lotka–Volterra form in higher dimensions, we prove that under some sufficient conditions the trajectories of a quasi-polynomial dynamical system can asymptotically converge to the corresponding set of equilibria. We apply our results to three different biological network models and show that one can find the range of parameters for which a given parameterized model is stable. The future work in this area will focus on developing multi-parametric optimization techniques to find regions in the parameter space for which the system is asymptotically stable.

References

Arcak, M., & Sontag, E. (2006). Diagonal stability of a class of cyclic systems and its connection with the secant criterion. *Automatica*, *42*(9), 1531–1537.

Arcak, M., & Sontag, E. (2008). A passivity-based stability criterion for a class of biochemical reaction networks. *Mathematical Biosciences and Engineering*, *5*(1), 1–19.

Chandra, F.A., Buzi, G., & Doyle, J.C. (2009). Linear control analysis of the autocatalytic glycolysis system. In *Proceedings of the American control conference*.

Feron, E., Boyd, S., El Ghaoui, L., & Balakrishnan, V. (1997). *Linear matrix inequalities in system and control theory*. Society for Industrial Mathematics.

Figueiredo, A., Gléria, I. M., & Rocha Filho, T. M. (2000). Boundedness of solutions and Lyapunov functions in quasi-polynomial systems. *Physics Letters A*, *268*, 335–341.

Ghaemi, R., Sun, J., Iglesias, P., & Del Vecchio, D. (2009). A method for determining the robustness of bio-molecular oscillator models. *BMC Systems Biology*, *3*, 95.

Goh, B. S. (1977). Global stability in many-species systems. *The American Naturalist*, *111*(977), 135–143.

Hernandez-Bermejo, B. (2002). Stability conditions and Liapunov functions for quasi-polynomial systems. *Applied Mathematics Letters*, *15*(1), 25–28.

Hernandez-Bermejoa, B., & Fairen, V. (1997). Lotka–Volterra representation of general nonlinear systems. *Mathematical Biosciences*, *140*(1), 1–32.

Horn, R. A., & Johnson, C. R. (1990). *Matrix analysis*. Cambridge University Press.

Irving, D. H., Voit, E. O., & Savageau, M. A. (1991). Analysis of complex dynamic networks with ESSYNS. In E. O. Voit (Ed.), *Canonical non-linear modelling S-systems approach to understanding complexity*. Von Nostrand Reinhold.

Jovanović, M. R., Arcak, M., & Sontag, E. D. (2008). A passivity-based approach to stability of spatially distributed systems with a cyclic interconnection structure. *IEEE Transactions on Automatic Control: Special Issue on Systems Biology*, *53*, 75–86.

Kaszkurewicz, E., & Bhaya, A. (2000). *Matrix diagonal stability in systems and computation*. Boston: Birkhauser.

Kitano, H. (2007). Towards a theory of biological robustness. *Molecular Systems Biology*, *3*, 137.

Laub, M. T., & Loomis, W. F. (1998). A molecular network that produces spontaneous oscillations in excitable cells of dictyostelium. *Molecular Biology of the Cell*, *9*, 3521–3532.

Magyar, A., Szederknyi, G., & Hangos, K.M. (2005). Quasi-polynomial system representation for the analysis and control of nonlinear systems. In *16th IFAC world congress*. Prague, Czech Republic.

Ma, L., & Iglesias, P. A. (2002). Quantifying robustness of biochemical network models. *BMC Bioinformatics*, *3*(38), 38–50.

Poole, G., & Boullion, T. (1974). A survey on *m*-matrices. *SIAM Review*, *16*(4), 419–427.

Nader Motee received his B.Sc. degree in Electrical Engineering from Sharif University of Technology in 2000, his M.Sc. degree in Mechanical Engineering from Louisiana State University in 2003, and his M.Sc. and Ph.D. degrees from the University of Pennsylvania in Electrical and Systems Engineering in 2006 and 2007 respectively. During 2008–2011, he was a postdoctoral scholar in the Control and Dynamical Systems Department at Caltech and Mechanical Engineering Department at the University of California at Santa Barbara. He is currently an Assistant Professor in the Department of Mechanical Engineering and Mechanics at Lehigh University. Dr. Motee's group is currently developing theoretical foundations for analysis and synthesis of networks of dynamical and control systems with particular focus on biological networks, integrated networks for electricity, and robotics. He is a past recipient of the AACC Hugo Schuck best paper award, the ACC best student paper award, the Joseph and Rosaline Wolf best thesis award, and a finalist for the best paper award in several conferences.

Bassam Bamieh received his Electrical Engineering and Physics degree from Valparaiso University in 1983, and his M.Sc. and Ph.D. degrees from Rice University in Electrical and Computer Engineering in 1986 and 1992 respectively. During 1991–1998 he was with the department of Electrical and Computer Engineering and the Coordinated Science Laboratory at the University of Illinois at Urbana-Champaign. He is currently a Professor of Mechanical Engineering at the University of California at Santa Barbara. His current research interests are in distributed systems, shear flow turbulence modeling and control, and thermo-acoustic energy conversion devices. He is a Fellow of the IEEE and IFAC, a Control Systems Society Distinguished Lecturer, a past recipient of the AACC Hugo Schuck best paper award, the IEEE CSS Axelby outstanding paper award, and an NSF CAREER award.

Mustafa Khammash is Professor of Control Theory and Systems Biology in the Department of Biosystems Science and Engineering (D-BSSE) at ETH-Zurich. He received his B.S. degree from Texas A&M University in 1986 and his Ph.D. from Rice University in 1990, both in Electrical Engineering. In 1990, he joined the Electrical Engineering Department at Iowa State University. While at Iowa State University, he created the Dynamics and Control Program and led that control group until 2002, when he became a member of the Mechanical Engineering faculty at the University of California, Santa Barbara. In Santa Barbara, he served as Vice Chair of the Mechanical Engineering Department from 2003 to 2006 and as the Director of the Center for Control, Dynamical Systems and Computation from 2005 to 2011. In 2011 Prof. Khammash moved with his group to Switzerland, joining the Department of Biosystems Science and Engineering at ETH Zurich.

Dr. Khammash works in the areas of control theory, systems biology, and synthetic biology. His research aims to understand the role of dynamics, feedback, and randomness in biology, and to develop the tools needed to aid in this understanding. Work in his lab focuses on the creation of novel computational methods for the modeling, simulation, analysis, and control of biological networks, with particular attention to stochastic systems. Prof. Khammash's group is currently developing the theory, computational methods, and experimental tools for the computer control of living cell populations.