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Positive Quadratic System Approximate Representation of Nonlinear Systems

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Abstract: Our previous study proposed a positive quadratic system representation for molecular interaction in a cell, including a signal transduction pathway and a gene regulatory network, and also presented a method for estimating a positive invariant set depending on the initial state. As an extension towards wider applications of this approach, this paper proposes a system representation called here a singularly perturbed positive quadratic system, and shows that every positive rational system, which is used as a mathematical model expressing biological behavior, can be approximately represented by a quasi-steady state system of a singularly perturbed positive quadratic system. In addition, we prove that the singularly perturbed positive quadratic system preserves stability at an equilibrium point of the positive rational system.

Keywords: Positive systems, quadratic systems, systems biology, singular perturbation, stability analysis.

1. INTRODUCTION

Mathematical models expressing molecular interaction in a cell of protein and/or other molecular substances have been introduced in the field of systems biology and mathematical biology; S-system (Voit (2000); Savageau (1969, 1970)), differential equations with hill functions (Tony Yu-Chen Tsai et al. (2008); Shinohara et al. (2014); Kholodenko (2000); Angeli et al. (2004)), and so on. Those mathematical models have been derived on experimental data. However, the nonlinearity of those models is too complex to analyze the system behavior in a theoretical way.

We focus on fundamental molecular interactions in a cell, where association and dissociation in the signal transduction pathway, and the gene expression regulated by binding of transcription factors to DNA followed by activation of RNA polymerase are included (Alon (2006); Alberts et al. (2015)). Reaction rates of those molecular interactions are in general approximated by 2 dimensional systems of concentration of protein and/or other molecular substance. This motivated us to introduce a positive quadratic system representation as a mathematical model, and we proved that any molecular interaction in a cell can be approximately expressed by the positive quadratic system (Okamoto et al. (2015)). In addition, we proposed the relatively easier stability analysis for this positive quadratic systems, as developed by the so-called positive linear systems. However, this previous study has not found that various biological models derived in the field of systems biology except for fundamental molecular interactions can be approximately represented by positive quadratic systems.

Michaelis and Menten (1913) presented a simple nonlinear model of enzyme kinetics, which approximates complex biological phenomenon. If the velocity of some enzyme reaction is large, the dimension of the system is reduced by regarding that the corresponding behavior is in a steady state, namely, has no dynamics. In similar studies of Segel (1993); Sauro (2012), various phenomena of enzyme reaction in a cell have been approximately represented by various nonlinear models based on enzyme kinetics. It is not clear what type of biological model can be approximated by enzyme kinetics. These approaches are based on so-called singular perturbation theory (Kokotović et al. (1987)).

This paper also exploits this method and proposes a singularly perturbed positive quadratic system representation to show that every positive system composed of rational functions (positive rational system), which is used as a mathematical model expressing biological behavior, can be approximately expressed by a quasi-steady state system of a singularly perturbed positive quadratic system. As one possible approach, Ohtsuka (2000) has proved that the input-output behavior of any rational system can be represented by a higher dimensional quadratic system. However this approach extends the dimension of the invariant set of a nonlinear system with taking no account of the stability issue, and thus of the output of the extended quadratic systems are very sensitive to the initial state error. On the other hand, our approach is robust for the initial state errors because the state subspace extended by a singularly perturbed system is always stable.

The rest of this paper is organized as follows. In the next section, we define a singularly perturbed positive quadratic system, and we show that every positive system represented

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by rational functions can be approximated by a singularly perturbed positive quadratic system. In Section III, we prove that the manifold obtained by extending the state subspace in the proposed approach is stable. Finally, we show that the proposed method is effective by simple examples and the numerical simulations.

NOTATION The following notion is used in this paper.

$\mathbb{R}$	set of real numbers
$\mathbb{R}_{>0}$	set of positive real numbers
$\mathbb{R}_{\geq 0}$	set of nonnegative numbers
$\mathbb{H}^n$	set of symmetric matrices of order n
x_i	the ith element of vector x
x_{-i}	vector excluding the ith element from $x \in \mathbb{R}^n$, i.e., $x_{-i} := [x_1, \dots, x_{i-1}, x_{i+1}, \dots, x_n]^{\mathrm{T}}$
$[A]_{i,j}$	the (i,j)th element of matrix A
$x \preceq y$	$x_i \leq y_i$ for all i
$\mathrm{row}_i(A)$	the ith row vector of matrix A
$O(\varepsilon^n)$	a n order function of ε
∇_z	a partial differential operator of z

This paper introduces the Einstein law for simple notation. For two tensors $a \in \mathbb{R}^{n\times m}, b \in \mathbb{R}^m$, the multiplication of these tensors is denoted as

$$a_i^j b_j := \sum_{j=1}^n a_i^j b_j.$$

2. SINGULARLY PERTURBED POSITIVE QUADRATIC SYSTEMS AND QUASI-STEADY STATE SYSTEMS

Consider a singularly perturbed system given by, for a small positive constant ε,

$$\Sigma^\varepsilon : \begin{cases} \dot{x} = f_1(x,z,\varepsilon) + G_1(x,z,\varepsilon)u, & x(0) = x_0, \\ \varepsilon\dot{z} = f_2(x,z,\varepsilon) + G_2(x,z,\varepsilon)u, & z(0) = z_0, \end{cases} \tag{1}$$

where the dimension of x, z, and u are denoted as n_x, n_z, and m, respectively, and $n := n_x + n_z$.

If $\varepsilon = 0$, the system (1) satisfies

$$f_2(x,z,0) + G_2(x,z,0)u = 0. \tag{2}$$

Then if the condition (2) can be rewritten as

$$z = \phi(x,u), \tag{3}$$

for a function ϕ, the system (1) is reduced into the following system

$$\Sigma^0 : \dot{x} = f_1(x,\phi(x,u),0) + G_1(x,\phi(x,u),0)u, \tag{4}$$

The state z satisfying (3) is called the *quasi-steady state*, and the system Σ^0 is called the *quasi-steady state system* of (1) (Kokotović et al. (1987)). This relationship between Σ^ε and Σ^0 is denoted as

$$\Sigma^0 = \overset{\phi}{\lim_{\varepsilon\to 0}} \Sigma^\varepsilon.$$

If $\varepsilon > 0$ is sufficient small, the behavior of the slow speed state of a singularly perturbed system is approximated by the quasi-steady state system.

Next, we define three kinds of positive systems included in singularly perturbed systems.

Definition 1. For a nonnegative integer t, a *positive polynomial function* $h : \mathbb{R}^n_{\geq 0} \to \mathbb{R}_{>0}$ is defined as

$$h(x) = b_0 + b_1^{j_1} x_{j_1} + \cdots + b_t^{j_1,\dots,j_t} x_{j_1} \dots x_{j_t},$$

where x_{j_i} is the j_ith element of $x \in \mathbb{R}_{\geq 0}$, and the set of positive polynomial functions is denoted as $\mathbb{P}_{>0}[x]$, where

$$b_0 > 0, \quad b_k^{j_1,\dots,j_k} \geq 0, \quad (k = 1,\dots,t). \tag{5}$$

Furthermore, a *Metzler polynomial function* is defined as $f : \mathbb{R}^n_{\geq 0} \to \mathbb{R}^n_{\geq 0}$, if the ith element satisfies

$$f_i(x) = a_{0i} + a_{1i}^{j_1} x_{j_1} + \cdots + a_{ti}^{j_1,\dots,j_t} x_{j_1} \dots x_{j_t}, \tag{6}$$

and the set of Metzler polynomial functions is denoted as $\mathbb{M}_{\mathrm{P}}[x]$, where

$$a_{ki}^{j_1,\dots,j_k} \geq 0, \quad (i \neq j_s,\ s = 1,\dots,k,\ k = 0,\dots,t). \tag{7}$$

In particular, if the coefficient of the Metzler polynomial function satisfies

$$a_{ki}^{j_1,\dots,j_k} = 0, \quad (k < m \text{ or } l < k), \tag{8}$$

then the function f is called a (m,l) *Metzler function*, and the corresponding set is denoted as $\mathbb{M}_m^l[x]$.

Finally, the set of *Metzler rational functions* is defined as

$$\mathbb{M}_{\mathrm{R}}[x] := \left\{ \tfrac{1}{h(x)} f(x) \;\middle|\; h \in \mathbb{P}_{>0}[x],\ f \in \mathbb{M}_{\mathrm{P}}[x] \right\}.$$

Definition 2. For a singularly perturbed nonlinear system (1), suppose that every initial state x_0 and z_0 is nonnegative, and the nonlinear system (1) satisfies

$$\begin{bmatrix} f_1 \\ f_2 \end{bmatrix} \in \mathbb{M}_{\mathrm{R}} \begin{bmatrix} x \\ z \end{bmatrix}, \quad \begin{bmatrix} G_1 \\ G_2 \end{bmatrix} \in \mathbb{M}_{\mathrm{R}} \begin{bmatrix} x \\ z \end{bmatrix}^m.$$

Then, the system (1) is called a singularly perturbed *positive rational system*, and the set of this class of systems is denoted as $\mathbb{S}^\varepsilon_{\mathrm{PR}}$. In particular, if $z \equiv 0$, the system (1) does not depend on the small parameter ε. Then the system is called a positive rational system simply, and the corresponding set is denoted as $\mathbb{S}_{\mathrm{PR}}$.

Similarly, if f_1, f_2, G_1, and G_2 are Metzler polynomial functions, (1) is called a singularly perturbed *positive polynomial system*, and its set is denoted as $\mathbb{S}^\varepsilon_{\mathrm{PP}}$. If $z \equiv 0$, the system is called a positive polynomial system, and its set is denoted as $\mathbb{S}_{\mathrm{PP}}$.

Finally, if the system (1) satisfies

$$\begin{bmatrix} f_1 \\ f_2 \end{bmatrix} \in \mathbb{M}_1^2 \begin{bmatrix} x \\ z \end{bmatrix}, \quad \begin{bmatrix} G_1 \\ G_2 \end{bmatrix} \in \mathbb{M}_0^1 \begin{bmatrix} x \\ z \end{bmatrix}^m,$$

the system (1) is called a singularly perturbed *positive quadratic system*, and its set is denoted as $\mathbb{S}^\varepsilon_{\mathrm{PQ}}$. If $z \equiv 0$, the system is called a positive quadratic system, and its set is denoted as $\mathbb{S}_{\mathrm{PQ}}$.

Remark 3. Differential equations with hill functions (Tony Yu-Chen Tsai et al. (2008); Shinohara et al. (2014); Kholodenko (2000); Angeli et al. (2004)) belong to positive rational systems, and S-system (Voit (2000); Savageau (1969, 1970)) can be approximately represented by a positive rational systems using a Taylor series.

Remark 4. The set of the defined system satisfies

$$\begin{aligned} \mathbb{S}^\varepsilon_{\mathrm{PQ}} &\subset \mathbb{S}^\varepsilon_{\mathrm{PP}} \subset \mathbb{S}^\varepsilon_{\mathrm{PR}}, \\ \mathbb{S}_{\mathrm{PQ}} &\subset \mathbb{S}_{\mathrm{PP}} \subset \mathbb{S}_{\mathrm{PR}}, \\ \mathbb{S}_* &\subset \mathbb{S}^\varepsilon_*, \end{aligned} \tag{9}$$

where $*$ denotes PR, PP, or PQ.

Remark 5. A positive quadratic system without inputs has been proposed by Okamoto et al. (2015), and the system is written as

$$\dot{x}_i = \mathrm{row}_i(A_0)x + x^{\mathrm{T}} A_i x, \quad x_i(0) \in \mathbb{R}_{\geq 0}, \quad i \in \{1,\dots,n\},$$