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Continuous-switch piecewise quadratic models of biological networks: Application to bacterial growth☆

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ABSTRACT

An extension of the class of piecewise linear (PL) systems is proposed to model gene expression dynamics dependent on dilution due to cell growth rate. The growth rate is modeled as the weighted minimum of two or more limiting gene products responsible for bacterial growth. The production terms are still piecewise constant, but now the degradation terms are piecewise quadratic (PQ). This new mathematical formalism exhibits continuous switches between PQ modes. We first study the novel dynamical behavior generated by the nonlinear terms at the regions of discontinuity of the vector fields, showing that the sliding motion configurations occurring in PL systems can further lead to damped convergent oscillations or periodic behavior in PQ systems. As an application, a core model of the bacterial gene expression machinery is studied with the goal of externally tuning the growth rate of cells. This system may exhibit several behaviors including bi-mode bistability or damped oscillatory behavior.

1. Introduction

The concepts and methods from systems and control theory have a large potential to significantly help in systems and synthetic biology research, where the goal is to develop and apply engineering tools to control cellular behavior and achieve desired functions (Mukherji & Van Oudenaarden, 2009). Synthetic biology aims at constructing novel biological circuits in the cell and most recent designs focus on assembling components from the cell transcription machinery, which includes the genes to be expressed, their promoters, RNA polymerase, ribosomes and transcription factors, all serving as potential individual engineering components (Elowitz & Leibler, 2000; Gardner, Cantor, & Collins, 2000; Wang, Kitney, Joly, & Buck, 2011).

In this context, control-based approaches are increasingly being used in synthetic biology (Ang, Bagh, Ingalls, & McMillen, 2010; LeDuc, Messner, & Wikswo, 2011; Menolascina, di Bernardo, & di Bernardo, 2011; Yang, Lenaghan, Wikswo, & Zhang, 2011) where some control theoretical results are applicable, although with various limitations due to biological constraints (Chaves & Gouzé, 2011; Sontag, 2004).

Here, our goal is to introduce a novel mathematical formalism to qualitatively model gene expression and dilution due to cell growth. In fact, one of the aims of systems and synthetic biology is to link molecular-level mechanisms (e.g. gene expression) to cell-level behavior (e.g. growth rate) (Mukherji & Van Oudenaarden, 2009). To this aim, we introduce a model where bacterial growth rate is limited by different factors, which ultimately lead to a *continuous-switch piecewise quadratic* (CSPQ) formalism—derived from *piecewise linear* (PL) systems (de Jong, 2002; Gouzé & Sari, 2002).

An application of this modeling formalism is the control of the cells' growth rate by designing appropriate laws. Growth control is essential in industrial biotechnology and fundamental research of this kind could pave the way to novel types of antimicrobial strategies (Khalil & Collins, 2010). We analyze a core model of the gene expression machinery of the bacterium *Escherichia coli*, where the growth rate is controlled externally by tuning the synthesis of a component of the gene expression machinery (RNA Polymerase). This type of control can be easily implemented, for instance, by means of inducers that activate synthetic inducible promoters (Kaern, Blake, & Collins, 2003).

A first formulation and preliminary results on CSPQ systems were introduced in Carta, Chaves, and Gouzé (2013). Here, new

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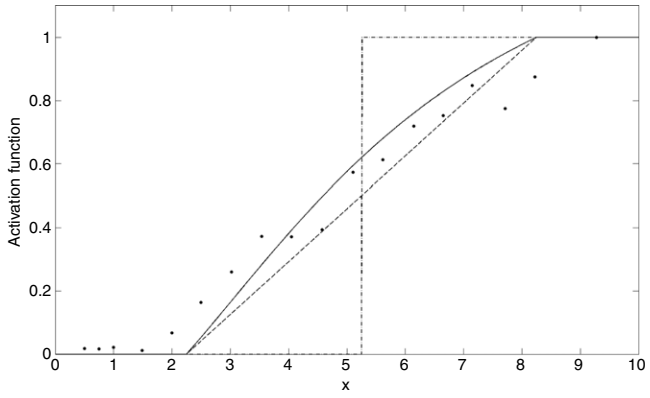

Fig. 1. Example of gene expression data points (Brewster et al., 2014) and possible activation functions. Step (dash-dotted), logoid (dashed), or a C^1 Hill-type function (solid).

properties of these systems are investigated. Section 2 recalls and extends the formulation of CSPQ systems. In Section 3 we state and prove some theorems on the stability of each piecewise quadratic (PQ) subsystem; in particular, new results are given on the properties of sliding modes and their differences with respect to the "standard" PL system. Section 4 studies local stability of the CSPQ system. Section 5 discusses an application to an open-loop control system of bacterial gene expression. Section 6 summarizes our results and conclusions.

2. Continuous-switch piecewise quadratic systems

As introduced in Carta et al. (2013), the switched piecewise quadratic systems are an extension of piecewise linear (PL) systems, a class of well known qualitative models originally introduced by Glass and Kauffman (1973) and further studied in Casey, De Jong, and Gouzé (2006), de Jong et al. (2004), Gouzé and Sari (2002). The PL systems are very useful to study genetic networks in the absence of detailed data or parameter knowledge (see, for instance, (Ropers, de Jong, Page, Schneider, & Geiselmann, 2006)) due to their suitableness for theoretical analysis and simulations using algorithmic tools and software. However, PL systems consider only linear protein degradation without taking into account cell growth, required to represent the connections between molecular and cellular mechanisms.

To overcome this problem, we consider a general model structure to describe the dynamics of the concentrations of a system of n species, $x = (x_1, \ldots, x_n)^T \in \mathbb{R}^n_{\geq 0}$:

$$\dot{x}_i = f_i(x) - (\mu(x) + \gamma_i)\, x_i, \quad 1 \leq i \leq n \tag{1}$$

where $f_i(x)$ is the synthesis rate and γ_i represents the typical linear degradation constant for species i, and $\mu(x)$ represents dilution in the concentrations, proportional to the bacterial growth rate and equal for all species. These terms are next defined.

The function $f_i : \mathbb{R}^n_{\geq 0} \to \mathbb{R}_{\geq 0}$ represents the expression rate of the gene i depending on state x. Several experiments (Brewster et al., 2014; Wang et al., 2011) show that gene expression often follows an increasing (or decreasing) curve $h(x)$ as a function of an activator (or inhibitor) x, between two essentially flat regions:

$$h(x) = \begin{cases} 0, & x < x_{low} \\ \tilde{h}(x), & x_{low} < x < x_{high} \\ 1, & x > x_{high} \end{cases} \tag{2}$$

where $\tilde{h}(x)$ may take any form. The *logoid* (linear $\tilde{h}$) is studied in Mestl, Plahte, and Omholt (1995). A C^1 alternative is a Hill-type function $b + ax^2/(x^2 + \theta^2)$ (see Fig. 1). To facilitate theoretical analysis, in the class of piecewise linear systems, activation functions are approximated by step functions, so that the function f_i has the general form:

$$f_i(x) = \sum_{l=1}^{n} k_{il} b_{il}(x)$$

where $k_{il} \geq 0$ is a rate parameter and $b_{il}(x)$ is a sum of products of step functions, s^+, s^-. These are defined in terms of a threshold parameter $\theta > 0$:

$$s^+(x_i, \theta) = \begin{cases} 1 & \text{if } x_i > \theta \\ 0 & \text{if } x_i < \theta \end{cases}; \qquad s^-(x_i, \theta) = 1 - s^+(x_i, \theta).$$

Note that, in the case $\mu(x) \equiv 0$, system (1) recovers the classical piecewise linear (PL) systems (de Jong, 2002). Assuming that bacterial growth rate is limited by the amount of one or more generic cellular components (Carta et al., 2013) which are necessary to sustain the gene expression machinery of the cell, let the growth rate $\mu : \mathbb{R}^n_{\geq 0} \to \mathbb{R}_{\geq 0}$ be given as:

$$\mu(x) = \min_{1 \leq i \leq n} \{\, \mu_i x_i \,\} \tag{3}$$

where $\mu_i \geq 0$ are proportion factors depending, for instance, on the carbon source used. If $\mu_k = 0$, then growth does not depend on species k. Similar expressions have been used recently for ribosomal regulation in *E. coli* (Shachrai, Zaslaver, Alon, & Dekel, 2010). This formulation appears also in other contexts, such as in ecology where the specific growth rate of species is often determined by the resource that is most limiting according to Liebig's "law of the minimum" (Huisman & Weissing, 1999).

System (1) belongs to the class of *switched systems* (Liberzon & Morse, 1999) in which the growth rate μ acts as the rule that orchestrates the switching between the different subsystems (4):

$$\text{mode-}r\text{: } \dot{x}_i = f_i(x) - [\mu_r x_r + \gamma_i]\, x_i, \quad 1 \leq i \leq n. \tag{4}$$

Each mode is piecewise quadratic (PQ), hence to study the dynamics of the (full) CSPQ system (1) we will first characterize the dynamics of its PQ modes (4), and then investigate the properties arising from the switching condition.

3. The PQ subsystem: dynamical study

A dynamical study is provided for mode-r in (4), that is when $\mu(x) = \mu_r x_r$. The PQ system can be written as:

$$\dot{x} = f(x) - d(x_r)x, \tag{5}$$

where $f = (f_1, \ldots, f_n)$ and $d(x_r) = diag(\mu_r x_r + \gamma_1, \ldots, \mu_r x_r + \gamma_n)$, where *diag* is the diagonal matrix corresponding to the vector.

First, note that the non-negative orthant remains invariant, since $x_i = 0$ implies $\dot{x}_i \geq 0$. Second, note that all solutions remain bounded, since $f_i(x) - d_i(x_r)x_i < \max_{x \in \mathbb{R}^n_{\geq 0}} f_i(x) - \gamma_i x_i$, where $\max_{x \in \mathbb{R}^n_{\geq 0}} f_i(x) < \infty$, by definition of f. Without loss of generality, the dynamics of the PQ subsystem can be studied in the n-dimensional state-space $\Omega = \Omega_1 \times \Omega_2 \times \cdots \times \Omega_n$, where each Ω_i is defined by $\Omega_i = \{x_i \in \mathbb{R}_{\geq 0} | 0 \leq x_i \leq \max_i\}$ with $max_i = \max_{x \in \mathbb{R}^n_{\geq 0}} f_i(x)/\gamma_i$. The set Ω is thus invariant for system (5). Each protein will be involved in different interactions at different concentration thresholds so, for each variable x_i, we assume there are p_i ordered thresholds $\theta_i^1, \ldots, \theta_i^{p_i}$ and let $\theta_i^0 = 0$, $\theta_i^{p_i+1} = \max_i$. These thresholds partition Ω into hyper-rectangular regions called *domains*. Specifically, a domain $D \subset \Omega$ is defined to be a set $D = D_1 \times \cdots \times D_n$, where D_i is one of the following:

$$D_i = \left\{ x_i \in \Omega_i | \theta_i^{j_i} < x_i < \theta_i^{j_i+1} \right\}, \quad \text{for } j_i \in \{0, \ldots, p_i\}$$

$$D_i = \left\{ x_i \in \Omega_i | x_i = \theta_i^{j_i} \right\}, \quad \text{for } j_i \in \{1, \ldots, p_i\}.$$