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On the estimation of robustness and filtering ability of dynamic biochemical networks under process delays, internal parametric perturbations and external disturbances

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ABSTRACT

Inherently, biochemical regulatory networks suffer from process delays, internal parametrical perturbations as well as external disturbances. Robustness is the property to maintain the functions of intracellular biochemical regulatory networks despite these perturbations. In this study, system and signal processing theories are employed for measurement of robust stability and filtering ability of linear and nonlinear time-delay biochemical regulatory networks. First, based on Lyapunov stability theory, the robust stability of biochemical network is measured for the tolerance of additional process delays and additive internal parameter fluctuations. Then the filtering ability of attenuating additive external disturbances is estimated for time-delay biochemical regulatory networks. In order to overcome the difficulty of solving the Hamilton Jacobi inequality (HJI), the global linearization technique is employed to simplify the measurement procedure by a simple linear matrix inequality (LMI) method. Finally, an example is given *in silico* to illustrate how to measure the robust stability and filtering ability of a nonlinear time-delay perturbative biochemical network. This robust stability and filtering ability measurement for biochemical network has potential application to synthetic biology, gene therapy and drug design.

1. Introduction

In living cells, the interactions of genes and proteins build up of dynamic genetic regulatory networks. In these networks, the internal parameter perturbations include kinetic parameter variations in molecular processes of transcriptional control, alternative splicing, translation, diffusion and chemical modification. In contrast, the external molecular disturbances come from the transmitted noise from upstream genes and the global noise affecting the expression of all genes. These processes also bring about the effect of process delays. A mixed integer linear programming framework has been discussed for inferring time delay in gene regulatory networks [1], and the stability of gene regulatory network with time delay has also been discussed [2,3]. Despite the process delays, intrinsic kinetic parameter variations and external disturbances, most cellular events are ordered and precisely regulated [4–9]. For example, development in *Caenorhabditis elegans* (*C. elegans*) is so regular that we can trace the differentiated states of nearly every cell [10]. In *Drosophila melanogaster* embryos, the transition from disorder to order has been measured [11]. Although the anterior-to-posterior gradient of the maternal morphogen bicoid in *D. melanogaster* embryo displays significant variability, the profile of the hunchback gap gene, which is regulated by bicoid, is precise. The need for order has led to the proposal that robust stability and filtering ability are inherent properties of biochemical networks [6–10,12,13].

Robust stability is a fundamental property of biological systems [8]. Given the importance of robustness in understanding the function principles of biochemical networks and their medical implications, it is important to formulate a mathematically solid and possibly unified theory for biological robustness that might serve as a basic organizational principle of biological systems. Such a unified theory could be a bridge between the fundamental principle of life, medical practice, engineering, physics and chemistry [8]. It is a difficult challenge in which a number of issues have to be solved for establishment of mathematically well-founded theories. However, the impact could be enormous [8].

In the last decade, robustness in bacterial chemotaxis, hox genes, neuron-genetic networks, circadian rhythms and biochemical networks has been widely discussed under kinetic parameter variation due to intracellular fluctuations [14]. Recently, the filtering ability of genetic networks to attenuate the effect of external disturbances has also been an important topic of signal

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transmission in systems biology [12–15]. Although examples of robust cellular process abound, how cells are able to function under process delays and biochemical fluctuations remains unclear [12,13]. These questions present one of the most challenging and fascinating problems for systems biologists, as they raise questions in physiology, development and evolutionary biology [7–9]. In order for biochemical networks to maintain their functions, they must be able to cope with these types of internal fluctuations, external noise and the effects of time delay [3,8,16,17]. The robustness is shown to arise from the systematic properties of regulatory networks rather than from a single mechanism [8,14,17]. Apparently, both the robustness against process delays and intrinsic parameter perturbations as well as the filtering ability against external disturbances arise from complex mechanisms involving multiple feedback loops. Recently, stability robustness of biochemical networks without time-delay has been investigated from the frequency domain perspective based on the linearized models [1–3,9,18] and from the steady state perspective based on S-system model [5,19,20].

In this study, new measures of robust stability and filtering ability are proposed for biochemical networks. Based on dynamic system models, we can estimate the robustness for linear and nonlinear time-delay biochemical regulatory networks. The kinetic parameter variations due to internal molecular fluctuations are modeled as additive state-dependent noise, which will influence the stability of the biochemical regulatory network. The environmental and extrinsic noises are modeled as additive external disturbances, which have fluctuation effects on the performance of biochemical regulatory network. The robustness to tolerate the process delays and intrinsic parameter perturbations is analyzed by Lyapunov (energy-like) stability theory [21], while the filtering ability to attenuate the effect of external disturbances on biochemical networks is examined by nonlinear robust filtering theory. Both linear and nonlinear time-delay biochemical perturbative regulatory networks are discussed in this study. The techniques of nonlinear stabilization, nonlinear filtering and constrained optimization are employed to efficiently measure the robust stability and the filtering ability of biochemical time-delay regulatory networks.

Because of the nonlinearity of the time-delay biochemical networks, estimations of both the robust stability and filtering ability need to be done by solving a nonlinear Hamilton-Jacobi inequality (HJI), which can not be easily solved except in some special cases. In this study, global linearization [22,23] is employed to simplify the measurement procedure by solving the corresponding linear matrix inequalities (LMIs) instead. Estimations of both the robust stability and filtering ability in a time-delay perturbative biochemical network are potential for robust designs of synthetic gene networks [4,8,16,17,20,24–26] and for therapeutic drug designs [15]. For example, a prescribed robust stability and a desired filtering ability must be specified before designing a synthetic gene network which is suffered from intrinsic parameter variation due to DNA mutation and evolution and from external disturbance due to the context in the host cells, and a prescribed robust stability and a desired filtering ability must be specified before synthesis circuit design [4,8,17,27]. Besides, a cause of diseases can be considered as the loss of robust stability and the reduction of filtering ability of biochemical networks. In this way, the stability of the biochemical network is violated by intrinsic parameter perturbations, the external disturbances such as pathogens cannot be efficiently attenuated, and the performance of the biochemical network is deteriorated [28,29]. Therefore, by the estimation method in this study, the designer could complete their genetic therapy and drug designs by filling in the blanks of how the robust stability and filtering ability of the corresponding biochemical networks can be improved [15,28,29]. Finally, a time-delay perturbative biochemical network example is given *in silico* to estimate the robust stability to parameter fluctuation and the filtering ability to external disturbance.

2. Preliminaries of time-delay perturbative biochemical networks

For simplicity of analysis, the robust stability of linear time-delay perturbative biochemical network is discussed first. It is also useful to highlight the global linearization approach for the robustness measure of nonlinear time-delay biochemical system in the sequel. The linear biochemical network with process delays can be suitably modeled by the following dynamic system [1,20]

$$\dot{X}(t) = A_0 X(t) + \sum_{l=1}^{L} A_{d,l} X(t-\tau_l), \quad X(t) = X_0(t), \quad \forall t \in [-\tau \quad 0] \tag{1}$$

In (1), the state vector $X(t)$ denotes the expression vector of the concentrations of the molecules, e.g. mRNAs, proteins, or other chemical complexes in the biochemical network at time t. A_0 and $A_{d,l}$ denote the real-time and delay-time interactive matrices among these molecules (see Fig. 1). The index τ_l indicates that these regulations are associated with time delays of τ_l for $l = 1 \cdots L$ due to the time needed for transcription, translation, post-translation, signal transduction or molecular diffusion in the biochemical process while the maximum time delay is $\tau = \max\{\tau_l, l \in [1 \quad L]\}$. In real dynamic biochemical processes, process delays always exist and will influence the stability of the biochemical network [4]. In this situation, the process delays should be considered in a dynamic biochemical model to mimic the real biochemical process. Suppose the biochemical network consists of n molecules with stoichiometric matrices as follows

$$X(t) = \begin{bmatrix} x_1(t) \\ x_2(t) \\ \vdots \\ x_i(t) \\ \vdots \\ x_n(t) \end{bmatrix}, \quad A_0 = \begin{bmatrix} a_{0,11} & a_{0,12} & \cdots & \cdots & a_{0,1n} \\ a_{0,21} & \ddots & & & \vdots \\ \vdots & & & a_{0,ij} & \vdots \\ \vdots & & & & \ddots \\ a_{0,n1} & \cdots & \cdots & \cdots & a_{0,nn} \end{bmatrix},$$

$$A_{d,l} = \begin{bmatrix} a_{d,l,11} & a_{d,l,12} & \cdots & \cdots & a_{d,l,1n} \\ a_{d,l,21} & \ddots & & & \vdots \\ \vdots & & a_{d,l,ij} & & \vdots \\ \vdots & & & \ddots & \vdots \\ a_{d,l,n1} & \cdots & \cdots & \cdots & a_{d,l,nn} \end{bmatrix} \tag{2}$$

where $x_i(t), i = 1 \cdots n$ are the concentrations of different molecules (mRNAs, proteins and other complexes) in the biochemical network; the diagonal component $a_{0,ii}$ of A_0 denotes the degradation of biochemical process of the i^{th} molecule; the kinetic parameter $a_{0,ij}$ means the interaction from molecule j to molecule i. So does the term of $a_{d,l,ij}$.

Remark 0. For a linear biochemical network, the interactive parameter $a_{0,ij} > 0$ means that molecule j activates the biochemical process of molecule i; the interactive parameter $a_{0,ij} < 0$ means that molecule$j$ inhibits the biochemical process of molecule i; the kinetic parameter $a_{0,ij} = 0$ means that there is no interaction between molecule j and molecule i; and so does the term of $a_{d,l,ij}$.

Suppose the kinetic parameters of a biochemical network are affected by the following real-time and delay-time intrinsic perturbations (see Fig. 1)