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An LPV based robust peak-to-peak state estimation for genetic regulatory networks with time varying delay

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ABSTRACT

This paper addresses the nonlinear observer design problem for gene regulatory networks with time-varying delay, focusing on the case of unstable GRNs with oscillatory behavior. Currently available approaches are conservative due to presence of nonlinear terms, which should be dealt with. In addition, nonlinear terms are only known approximately in practice and therefore previous works may lead to undesirable performance. To address conservativeness issue, we have provided an LPV approach. Besides, to diminish effects of uncertain nonlinear terms on observer performance, a peak-to-peak state estimation problem is considered. By defining appropriate Lyapunov–Krasovskii functional, sufficient conditions are derived that guarantee the desirable performance. The superiority of the proposed method to existing approaches is illustrated by means of a numerical example. Moreover, good performance of state estimation in presence of uncertainty is demonstrated by simulations.

1. Introduction

It is well known that gene regulation is responsible for the production of different amounts of diverse RNAs in different cell types which in turn produce different amounts of distinct proteins. This process is very complex in which a lot of elements such as transcription factors, RNA polymerase and their respective DNA bind sites interact with each other to determine whether the expression of particular genes in specific cell types should be activated or inhibited. Recently, a lot of research have been done to analyze these networks quantitatively and gain insight into the hidden mechanisms responsible for producing their behavior.

According to the crucial need to have descriptions of their behavior, it is very essential to model GRNs as accurate as possible. Several methods for design and analysis of GRN have been proposed: the Boolean and discrete approaches go back to works of Kauffman [1], the continuous differential approach was applied to GRN by Goodwin [2], and the piecewise affine models were first introduced by Glass and Kauffman [3]. In [4], GRNs are modeled by using differential equations in the form of Lur'e systems.

With respect to modeling the GRN, it should be considered that GRNs, just as other biological systems, exhibit time delays as intrinsic phenomenon which are demonstrated to play important roles. They are resulted from slow reactions such as transcription, translation, translocation, and diffusion with translational delay as the chief cause. Nowadays different types of time delays associated with GRNs are considered such as time-varying delays [5–7], probability-distribution-dependent delay [8–10], neutral delays [11] and unknown delays [12]. It is paramount to take into account time delays when dealing with GRNs since they can cause oscillations [13]. Furthermore, Mathematical models not incorporating time delay may provide inconsistent predictions of the network states, i.e. mRNA and protein concentrations.

To identify malfunctioning genes and design drugs, it is necessary to estimate the concentrations of the mRNA and protein. In spite of recent advances in measuring technologies such as microarray data that enable us to assess the cellular products concentration, time varying delays and noises cause network measurements to deviate from the true network states. Thus, these problems ask for methodologies aiming to estimate missing information from the available data.

There are generally two main methods to estimate states in GRNs. In [14–17], state estimation is performed by using linear filters; nevertheless, this approach cannot be used for state estimation for unstable systems showing oscillatory behavior. Thus, coming up with

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methods directed toward state estimation problem for unstable systems with periodically oscillatory feature is imperative. In the second approach, nonlinear terms are considered for state estimation [18–21]. For instance, a state estimator for delayed GRNs is designed in [18], which involves the use of the Lipschitz property of nonlinear terms in addition to the Young inequality. In another method, dealing with nonlinear terms was done with the sector bounded property being considered [19–21]. Recently, an Linear parameter varying (LPV) approach was proposed to reduce conservativeness in the design of nonlinear observers [22]. LPV based modeling and control has been used successfully in many applications [23–25].

Although persistently exciting disturbances may lead to poor performance results, these observers are exposed to such disturbances owing to the fact that we do not have access to the exact knowledge on nonlinear terms in the GRN. The first formulation on the rejection of persistent bounded disturbances was presented in [26]. Earlier solutions to this problem tend to high-order or non-recursive controllers [27,28]. In [29], a new method aimed to deal with the peak-to-peak minimization problem was given in which a set of LMIs was used to solve the problem. Moreover, robust peak-to-peak filtering problem was investigated for linear jump systems in [30].

The first contribution of the following article is to incorporate LPV approach to designing state estimator for gene regulatory networks with a special care to the case of time-varying delays. To do so, appropriate Lyapunov–Krasovskii functionals are used to derive sufficient conditions guaranteeing the asymptotic stability of estimation errors. This gives less conservativeness concerning the Lipschitz constants which is particularly important in oscillatory networks with hard nonlinearities. In addition, previous studies assume precise knowledge of the nonlinear terms when designing the state estimator. Hence, the second objective of this note would be not to make such unrealistic assumption. Therefore, it is shown how this problem can be formulated as peak-to-peak state estimation. The sufficient conditions for achieving the prescribed performance are provided in terms of LMIs. Finally, several examples are studied to show the validity of the presented method. In these examples, it is illustrated that the new method provides less conservative results than the previous ones.

This paper consists of following sections: Section 2 introduces the GRN's model, describes the observer structure, and gives some definitions and preliminaries; Section 3 presents the main theorems on observer design; Section 4 demonstrates several examples and compares the results with previous works and at the end, Section 5 gives the conclusion.

2. System description and preliminaries

The compact form of gene regulatory networks is given by the following equations [4]:

$$\begin{aligned}\frac{dm(t)}{dt}&=Am(t)+Gg(p(t-\tau(t)))+l,\\ \frac{dp(t)}{dt}&=Cp(t)+Dm(t-\sigma(t)),\end{aligned}\tag{1}$$

in which the states of the system are $m(t)=[m_1(t),m_2(t),\dots,m_n(t)]^T$, $P(t)=\left[p_1(t),p_2(t),\dots,p_n(t)\right]^T$. $m_i(t),p_i(t)\in\mathbb{R}$, represent concentrations of mRNAs and proteins in the cell respectively. Also, we have the following structures:

$$A=diag(-a_1,-a_2,\dots,-a_n),\quad a_i>0$$

$$C=diag(-c_1,-c_2,\dots,-c_n),\qquad c_i>0$$

$$D=diag(d_1,d_2,\dots,d_n),$$

$$l=\begin{bmatrix} l_1 & l_2 & \cdots & l_n\end{bmatrix}^T,$$

$$g(p(t))=\begin{bmatrix} g_1(p_1(t)) & g_2(p_2(t)) & \dots & g_n(p_n(t))\end{bmatrix}^T,$$

degradation process of mRNAs and proteins are designated by $-a_im_i(t)$ and $-c_ip_i(t)$, and $d_im_i(t-\sigma(t))$ terms stand for translation. $G\in\mathbb{R}^{n\times n}$ shows the interaction graph of the genetic network. The effect of protein on gene transcription is taken into account by the nonlinear function $g_i(x)=\left(x/\beta_j\right)^{H_j}/\left(1+\left(x/\beta_j\right)^{H_j}\right)$. In addition, $l_i=\sum_{j\in\varpi_i}a_{ij}$, where ϖ_i is the set of inhibitors pertained to the gene i.

Eq. (2), which holds true for all $a,b\in\mathbb{R}$ with $\neq b$, states that the derivative of g_i is positive and bounded. This property is obvious since g_i is an increasing function with rate constraint, as follows:

$$0\le\frac{g_i(a)-g_i(b)}{a-b}\le k_i.\tag{2}$$

The main goal of this article is to design an observer so that one is able to estimate network's states from available measurements as in equations below

$$\begin{aligned}y_m(t)&=H_mm(t)\\ y_p(t)&=H_pp(t)\end{aligned}\tag{3}$$

Considering the nonlinear observer with the structure specified by

$$\begin{aligned}\dot{\tilde{m}}(t)&=A\tilde{m}(t)+Gg(\tilde{p}(t-\tau(t)))+l+K_m\left(y_m(t)-H_m\tilde{m}(t)\right)\\ \dot{\tilde{p}}(t)&=C\tilde{p}(t)+D\tilde{m}(t-\sigma(t))+K_p\left(y_p(t)-H_p\tilde{p}(t)\right)\end{aligned}\tag{4}$$

and by defining $e_m(t)=m(t)-\tilde{m}(t)\,\tilde{p}$ and $e_p(t)=p(t)-\tilde{p}(t)$, we get

$$\begin{aligned}\dot{e}_m(t)&=(A-K_mH_m)e_m(t)+G(f(p(t-\tau(t)),\tilde{p}(t-\tau(t))))\\ \dot{e}_p(t)&=\left(C-K_pH_p\right)e_p(t)+De_m(t-\sigma(t))\end{aligned}\tag{5}$$