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H_∞ mode-independent filter design for Markovian jump genetic regulatory networks with time-varying delays

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ABSTRACT

This paper investigates the problem of designing H_∞ filter for gene regulatory networks (GRNs) with time-varying delays and Markovian jumping parameters. Since in real gene networks the current jump mode is not easily accessible, the filter parameters are considered to be independent from the current system mode. By using mode-dependent Lyapunov–Krasovski functionals, appropriate conditions for the stochastic stability and disturbance attenuation of mixed GRN/filter system is derived. Mode independent filter gains are then obtained from some sufficient conditions in the form of linear matrix inequalities which are easy to solve by numerical methods. In the end, a numerical example and the relevant simulations are presented to evaluate the results.

1. Introduction

In recent years, the interaction between genes, proteins and molecules forming cellular systems have been one of the most important aspects of post-genomic biology. Specifically, stability and modeling problem of gene regulatory networks (GRNs), as a significant area of research in the biological and biomedical sciences, have attracted much attention [1–5]. GRNs are the mechanisms that regulate the expression of genes. The change in expression of genes is regulated negatively or positively by their own produced proteins. The main mathematical models proposed to model the genetic networks are Boolean networks [6,7] and differential equation models [2,8]. Examining gene expression data, it seems that the gene expression levels tend to be more continuous rather than binary.

In differential equation modeling of GRNs, similar to modeling other dynamical systems, the exact model can hardly be obtained. It is mostly because of the modeling errors, external perturbation and parameter fluctuations. So it is important to study the robust problem of such networks with noise, errors and perturbations. Also, It is shown in [9–11] that the time taken for the gene transcription and translation are not negligible in the dynamics of GRNs. The mathematical models without addressing the delay effects may provide wrong predictions of the mRNA and protein concentrations. The delays are usually considered as time-varying delays [9] and [10–12].

The existence of switching mechanisms in gene networks is a well known fact [13,14]. To address the switching nature, authors in [15,16] have proposed Markovian jump GRNs with the emphasis on quantitatively describing of gene regulation. Markovian jump GRNs are hybrid systems with their discrete state varying as a continuous-time finite state Markov process. So, GRNs can be assumed as a type of Markovian jump nonlinear systems with noise and delays. The stochastic stability and control problem of delayed nonlinear systems with and without Markovian jumps are investigated in [17–19].

To achieve some biological objectives such as identifying genes of interest and drugs extraction, biologists are interested in knowing the concentration values of mRNA and protein in gene networks. To this end, the problem of filtering has been investigated for nonlinear genetic regulatory networks in many recent works such as in [20–23]. In [20], authors have designed a filter for stochastic GRNs including noise and fixed transcription and translation delays. But the switching mechanism in GRNs has been disregarded. In [21], the problem of state estimation for Markovian jump GRNs with time-varying delays has been investigated but the noise in GRNs dynamics has not been considered. [22], [23] present the investigations on the filtering for the GRNs with distributed time delays.

In all above works on Markovian jump GRNs filtering, the complete access to present system mode is presumed. In other words, the filter gains are all obtained as mode-dependent values. Such an assumption may not hold in many real world situations.

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There are many situations in which the state of the Markov process is not available for observation. For instance, in a cancer treatment application, it is not possible to track the expression status of all genes in the network. The availability of the Markov states may be limited by cost, physical accessibility or other considerations. Clearly, in such a case the filtering techniques of previous works cannot be implemented. The control problem of GRNs with non-accessible Markov states in Probabilistic Boolean Networks is investigated in [24]. However, to the best knowledge of authors, all dynamical filters designed to monitor the states of GRNs need the switching status to be available. In the literature of Markovian Jump Systems (MJSs), the problem of mode-independent filtering is addressed in [25–27]. To design mode-independent and deterministic filters or controllers for MJSs, It is important to use mode-dependent Lyapunov functions. Using mode-independent Lyapunov functions, introduces very strong conservatism on the filter performance [26].

Even in the area of MJSs, there exist few numbers of studies on the mode-independent filtering in presence of noise and time-varying delays. According to that mentioned above, there is a strong motivation to design a mode independent filter based on mode dependent Lyapunov functions. Such filters have been neither investigated in the literature of MJLs and gene regulatory networks with time delays.

The main idea in this paper is to design a mode-independent filter for dynamic GRN model including noise and time-varying delays while using mode-dependent Lyapunov functions. The designed asymptotically stable filter ensures mean square stability for the estimation error dynamics and a prescribed upper-bound on the $\mathscr{L}_2$ -induced gain from the disturbance signals to the estimation error. The design method is based on assuming a special form for Lyapunov matrices. To synthesize the filter gains from the stochastic stability conditions some techniques and transformations are applied. The filter designs are given in terms of linear matrix inequalities (LMIs). The effectiveness of results are tested via a simulation example.

This paper is organized as follows: Section 2 describes the model of Markovian jump Genetic regulatory networks and the filter structure and gives some definitions and preliminaries on stochastic stability of GRNs; Section 3 presents the main results on filter design, Section 4 gives a simulation example and finally Section 5 concludes the paper.

2. System description and preliminaries

In this paper, the following genetic regulatory networks are considered [2]:

$$\begin{aligned}&\dot m(t)=A_m m(t)+Bf(p(t-\sigma(t)))+L\\&\dot p(t)=A_p p(t)+Dm(t-\tau(t))\end{aligned}\tag{1}$$

in which $m(t)=[m_1(t),m_2(t),\ldots,m_n(t)]^T$, $p(t)=[p_1(t),p_2(t),\ldots,p_n(t)]^T$ and $m_i(t),p_i(t)\in R$ are the concentrations of mRNA and protein of ith node. The parameters in (1) are considered as follows:

$$\begin{aligned}&A_m=\mathrm{diag}(-a_{m1},-a_{m2},\ldots,-a_{mn}),\\&A_p=\mathrm{diag}(-a_{p1},-a_{p2},\ldots,-a_{pn}),\\&D=\mathrm{diag}(d_1,d_2,\ldots,d_n),\\&L=[l_1,l_2,\ldots,l_n]^T,\\&f(t)=[f_1(t),f_2(t),\ldots,f_n(t)]^T.\end{aligned}$$

in which, a_{mi}'s and a_{pi}'s are the degradation rates of mRNA and protein and d_i's represent the translation rates. $f_i(x)=((x/\beta)^H/1+(x/\beta)^H)$ is a monotonically increasing function, and $B\in\mathbb{R}^{n\times n}$ is the coupling matrix of the genetic networks. l_i's stand for the basal rates of degradation. Vectors m^*, p^* are said to be an equilibrium point of system (1) if they satisfy $A_m m^*+Bf(p^*)+L=0$ and $A_p p^*+Dm^*=0$. For convenience, we always shift an intended equilibrium point (p^*,m^*) to origin by letting $x_m(t)=m(t)-m^*$, $x_p(t)=p(t)-p^*$. Thus, the GRN dynamics could be rewritten as:

$$\begin{aligned}&\dot x_m(t)=A_m x_m(t)+Bg(x_p(t-\sigma(t)))\\&\dot x_p(t)=A_p x_p(t)+Dx_m(t-\tau(t))\end{aligned}\tag{2}$$

where $g(x_p(t))=f(x_p(t)+p^*)-f(p^*)$. Since f is monotonically increasing function with saturation, it satisfies for all $a,b\in R$ with $a\neq b$:

$$0\le\frac{f(a)-f(b)}{a-b}\le k.\tag{3}$$

When $g(.)$ is differentiable, the above inequality is equivalent to $0\le \mathrm{d}f(a)/\mathrm{d}a\le k$. From the relationship between $f(.)$ and $g(.)$, we know that $g(.)$ satisfies the sector condition $0\le g(a)/a\le k$, or equivalently:

$$g(a)(g(a)-ka)\le 0\tag{4}$$

$\tau(t)$ and $\sigma(t)$ are time-varying delays which satisfy the following constraints:

$$\begin{aligned}&0\le\sigma(t)\le\overline{\sigma},\quad \dot\sigma(t)\le\alpha_{\sigma i}<\infty\\&0\le\tau(t)\le\overline{\tau},\quad \dot\tau(t)\le\alpha_{\tau i}<\infty\end{aligned}\tag{5}$$

According to what is said about stochastic switching mechanism in gene networks, the model perturbations, external noise and disturbances, we consider gene regulation networks as follows:

$$\begin{aligned}&\mathrm{d}x_m(t)=A_m(r(t))x_m(t)\mathrm{d}t+B(r(t))g(x_p(t-\sigma(t)))\mathrm{d}t\\&\qquad+\Sigma(r(t),x_m(t-\tau(t)),x_p(t))\mathrm{d}\omega(t)+H_1(r(t))v_1(t)\mathrm{d}t,\\&\mathrm{d}x_p(t)=A_p(r(t))x_p(t)\mathrm{d}t+D(r(t))x_m(t-\tau(t))\mathrm{d}t+H_2(r(t))v_2(t)\mathrm{d}t,\\&y_m(t)=C_m(r(t))x_m(t)+E_m(r(t))v_1(t),\\&y_p(t)=C_p(r(t))x_p(t)+E_p(r(t))v_2(t),\\&z(t)=\begin{bmatrix}z_m(t)\\z_p(t)\end{bmatrix}=(t)\begin{bmatrix}L_m(r(t))x_m(t)\\L_p(r(t))x_p(t)\end{bmatrix}\end{aligned}\tag{6}$$

where $y_m(t)$, $y_p(t)$ represent the expression levels of mRNA and protein of the ith node at time t, $H_1(r(t)),H_2(r(t))$ are input matrices and $v_1(t),v_2(t)$ are input disturbances which belongs to $L_2[0,\infty)$, $\omega(t)$ is scalar Brownian motion with zero mean value and unit variance and $z(t)$ is the concentration of intended genes or proteins. $r(t),t\ge 0$ is a right-continuous Markov chain on the probability space taking values in a finite state space $S=\{1,2,\ldots,\chi\}$ with generator $\Pi=(\pi_{ij})_{N\times N}$ given by:

$$\begin{cases}P[r_{t+h}=i|r_t=j]=\begin{cases}\pi_{ij}h+o(h) & i\neq j\\1+\pi_{ii}h+o(h) & \text{otherwise}\end{cases}\\\lim\limits_{h\to 0}\frac{o(h)}{h}=0,\quad \pi_{ij}\ge 0,\quad \pi_{ii}=-\sum_{j\neq i}\pi_{ij}\end{cases}\tag{7}$$

For simplicity in notation, we refer to $r(t)$ with the i index. $g(\cdot)$ is a vector function of $g_1(\cdot),\ldots,g_n(\cdot)$'s in the following form:

$$g(\cdot)=[g_1(\cdot)\quad\ldots\quad g_n(\cdot)]^T\tag{8}$$

where all of $g_i(\cdot)$'s satisfy (4) for $k=k_1,\ldots,k_n$. Also define matrix K as:

$$K=\mathrm{diag}(k_1,\ldots,k_n)\tag{9}$$

$\Sigma(\cdot)$ is the nonlinear function describing noise intensity and satisfies the following condition:

$$\begin{aligned}&\mathrm{trace}[\Sigma_i^T(x_m(t-\tau(t)),x_p(t))\Sigma_i(x_m(t-\tau(t)),x_p(t))]\\&\quad\le x_m^T(t-\tau(t))\Omega_{1i}x_m(t-\tau(t))+x_p^T(t)\Omega_{2i}x_p(t)\end{aligned}\tag{10}$$

So, the Markovian jump GRN can be rewritten as:

$$\begin{aligned}&\mathrm{d}x_m(t)=A_{mi}x_m(t)\mathrm{d}t+B_i g(x_p(t-\sigma(t)))\mathrm{d}t+\Sigma_i(x_m(t-\tau(t)),x_p(t))\mathrm{d}\omega(t)\\&\qquad+H_{1i}v_1(t)\mathrm{d}t,\\&\mathrm{d}x_p(t)=A_{pi}x_p(t)\mathrm{d}t+D_i x_m(t-\tau(t))\mathrm{d}t+H_{2i}v_2(t)\mathrm{d}t,\\&y_m(t)=C_{mi}x_m(t)+E_{mi}v_1(t),\end{aligned}$$