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New delay-dependent stability criteria for uncertain genetic regulatory networks with time-varying delays ☆

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ABSTRACT

This study is concerned with the problem of robust stability of uncertain genetic regulatory networks with time-varying delays. The parameter uncertainties are modeled as having a structured linear fractional form. By choosing an augmented novel Lyapunov–Krasovskii functional which contains some triple integral terms and using the lower bound lemma rather than the Jensen inequality lemma, less conservative condition are obtained. What's more, the criteria can be applicable to both fast and slow time-varying delays. Finally, two numerical examples are presented to illustrate the effectiveness of the theoretical results.

1. Introduction

Genetic regulatory networks have become an important new area of research in the biological and biomedical sciences and received great attention over past few years [1–17]. Due to the slow processes of transcription, translation, and translocation or the finite switching speed of amplifiers, time delay is a common occurrence in modeling gene regulation processes [11–17,24,25].

Besides, it should be noticed that the intrinsic noise and the extrinsic noise may bring parameter uncertainties during the constructing of genetic models. Meanwhile, because of the use of an approximate system model for the purpose of simplifying model, the uncertainties such as external perturbations, parameter fluctuations, data errors are inevitable. This means that one has to investigate the robust stability of uncertain systems [14–17,24,25].

What's more, the stability analysis of GRNs is an important area for understanding the living organisms at both molecular and cellular levels in the biological system. In real biological organisms, the GRNs regulate the mRNA and protein concentrations. And the steady stage of those molecular concentrations is often essential for normal life functions. Otherwise, the instability of those molecular concentrations may lead to very serious consequences.

In this study, we obtain new delay-dependent stability criteria for uncertain genetic regulatory networks with time-varying delays by choosing a new augmented Lyapunov functional which contains some triple integral terms. What's more, every rational nonlinear system possesses a linear fractional representation [18]. It is easy to see that the linear fractional uncertainty [19,20] can reduce to norm bounded one which has been investigated in [14–17,24,25].

Furthermore, the Jensen integral inequality lemma [21] has been generally adopted to handle the integral terms [11–17]. However, we use the lower bound lemma which is investigated for a linear combination of positive functions weighted by the inverses of convex parameters [22]. It can not only achieve performance behavior identical to approaches based on the integral inequality lemma but also decrease the number of decision variables, comparable to those based on the Jensen inequality lemma. From the examples in [22], it is easy to obtain that the lower bound theorem can achieve better results than those based on the Jensen integral inequality for the application to delayed systems. Therefore, the stability criteria derived in this study turn out to be less conservative than some recently reported ones. Finally, two numerical examples are also given to demonstrate the effectiveness and advantages of our analysis.

Notations: The notations used throughout the paper are fairly standard. The superscript 'T' stands for matrix transposition; R^n

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denotes the n-dimensional Euclidean space; $R^{n\times m}$ is the set of all $n\times m$ real matrices; the notation $P>0$ means that P is real symmetric and positive definite; I and 0 represent identity matrix and zero matrix, respectively. In symmetric block matrices, we use an asterisk ($*$) to represent a term that is induced by symmetry. Matrices, if their dimensions are not explicitly stated, are assumed to be compatible for algebraic operations.

2. Problem formulation and some preliminaries

Generally, a GRN consists of a group of genes which interact and regulate the expression of other genes by proteins. The change in expression of a gene is controlled by the stimulation and inhibition of proteins in transcriptional, translational, and post-translational processes. In [2], a single gene auto-regulatory genetic network with time delays containing n mRNAs and n proteins can be described by the following equations:

$$\begin{cases} \dot m_i(t) = -a_i m_i(t) + b_i(p_1(t-\sigma(t)),\quad p_2(t-\sigma(t)),\ldots,p_n(t-\sigma(t))) \\ \dot p_i(t) = -c_i p_i(t) + d_i m_i(t-\tau(t)),\quad i=1,2,\ldots,n \end{cases} \tag{1}$$

where $m_i(t),p_i(t)$ are concentrations of mRNA and protein of the ith node at time t, respectively. a_i and c_i are the degradation rates of the mRNA and protein. d_i is the translation rate, and $b_i(\cdot)$ is the regulatory function of the ith gene. The regulatory function is of the form $b_i(p_1(t),p_2(t),\ldots,p_n(t)) = \sum_{j=1}^{n} b_{ij}(p_j(t))$, which is called SUM logic [4]. The function $b_{ij}(p_j(t))$ is a monotonic function of the Hill form:

$$b_{ij}(p_j(t)) = \begin{cases} \alpha_{ij}\dfrac{(p_j(t)/\beta_j)^{H_j}}{1+(p_j(t)/\beta_j)^{H_j}} & \text{if transcription factor } j \text{ is an activator of gene } i \\ \alpha_{ij}\dfrac{1}{1+(p_j(t)/\beta_j)^{H_j}} & \text{if transcription factor } j \text{ is a repressor of gene } i \end{cases}$$

where H is the Hill coefficient, β_j is a positive constant, and α_{ij} is the dimensionless transcriptional rate of transcription factor j to gene i, which is a bounded constant. Therefore, (1) can be rewritten in the following form:

$$\begin{cases} \dot m_i(t) = -a_i m_i(t) + \sum_{j=1}^{n} w_{ij} h_j(p_j(t-\sigma(t))) + u_i \\ \dot p_i(t) = -c_i p_i(t) + d_i m_i(t-\tau(t)),\ i=1,2,\ldots,n \end{cases} \tag{2}$$

where $h_j(x) = (x/\beta_j)^{H_j}/(1+(x/\beta_j)^{H_j})$, u_i is defined as a basal rate, $u_i = \sum_{j\in I_i}\alpha_{ij}$ and I_i is the set of all the j which is a repressor of gene i. The matrix $W=(w_{ij})\in\mathbb{R}^{n\times n}$ of the genetic network is defined as follows:

$$w_{ij} = \begin{cases} \alpha_{ij} & \text{if transcription factor } j \text{ is an activator of gene } i \\ 0 & \text{if there is no link from node } j \text{ to node } i \\ -\alpha_{ij} & \text{if transcription factor } j \text{ is a repressor of gene } i \end{cases}$$

Rewriting system (2) into compact matrix form, we obtain

$$\begin{cases} \dot m(t) = -Am(t) + Wh(p(t-\sigma(t))) + u \\ \dot p(t) = -Cp(t) + Dm(t-\tau(t)) \end{cases} \tag{3}$$

where $A=\mathrm{diag}(a_1,a_2,\ldots,a_n)$, $u=col\{u_1,u_2,\ldots,u_n\}$, $C=\mathrm{diag}(c_1,c_2,\ldots,c_n)$, $D=\mathrm{diag}(d_1,d_2,\ldots,d_n)$, $m(t)=col\{m_1(t),m_2(t),\ldots,m_n(t)\}$, $p(t)=col\{p_1(t),p_2(t),\ldots,p_n(t)\}$, $h(p(t))=col\{h_1(p_1(t)),h_2(p_2(t)),\ldots,h_n(p_n(t))\}$.

In the following, we will always shift an intended equilibrium point (m^*,p^*) of the system (3) to the origin by letting $x(t)=m(t)-m^*, y(t)=p(t)-p^*$. Hence, system (3) can be transformed into the following form:

$$\begin{cases} \dot x(t) = -Ax(t) + Wf(y(t-\sigma(t))) \\ \dot y(t) = -Cy(t) + Dx(t-\tau(t)) \end{cases} \tag{4}$$

where $x(t)=col\{x_1(t),x_2(t),\ldots,x_n(t)\}$, $y(t)=col\{y_1(t),y_2(t),\ldots,y_n(t)\}$, $f(y(t))=col\{f_1(y_1(t)),f_2(y_2(t)),\ldots f_n(y_n(t))\}$ with $f_j(y_j(t)) = h_j(y_j(t)+p_j^*)-h_j(p_j^*)$.

$\tau(t)$ and $\sigma(t)$ are the time-varying delays satisfying $0\le\tau_1\le\tau(t)\le\tau_2$, $\dot\tau(t)\le\tau_d<\infty$; $0\le\sigma_1\le\sigma(t)\le\sigma_2$, $\dot\sigma(t)\le\sigma_d<\infty$; $\tau_{12}=\tau_2-\tau_1$, $\sigma_{12}=\sigma_2-\sigma_1, \tau_s=\frac{1}{2}(\tau_2^2-\tau_1^2)$, $\sigma_s=\frac{1}{2}(\sigma_2^2-\sigma_1^2)$, where τ_1,τ_2,τ_d and $\sigma_1,\sigma_2,\sigma_d$ are constants.

Due to the modeling inaccuracies and changes in the environment, the parametric uncertainties may enters into GRNs (4), the uncertain GRNs can be considered as follows [6,14]:

$$\begin{cases} \dot x(t) = -(A+\Delta A(t))x(t) + (W+\Delta W(t))f(y(t-\sigma(t))) \\ \dot y(t) = -(C+\Delta C(t))y(t) + (D+\Delta D(t))x(t-\tau(t)) \\ x_0 = x(\theta)=\varphi(\theta),\quad y_0 = y(\theta)=\phi(\theta),\quad \forall\theta\in[-\omega,0] \end{cases} \tag{5}$$

where $\omega=\max\{\tau_2,\sigma_2\}$, $\varphi(\cdot)$ and $\phi(\cdot)$ are the initial functions which are continuously differentiable on $[-\omega,0]$. And we extend the $\varphi(\theta),\phi(\theta)$ on $\theta\in[-2\omega,0]$ to satisfy $\|\varphi\|_\omega=\|\varphi\|_{2\omega}$, $\|\phi\|_\omega=\|\phi\|_{2\omega}$ with $\|\varphi\|_\omega=\sup_{\theta\in[-\omega,0]}\|\varphi(\theta)\|$, $\|\phi\|_\omega=\sup_{\theta\in[-\omega,0]}\|\phi(\theta)\|$, $\|\varphi\|_{2\omega}=\sup_{\theta\in[-2\omega,0]}\|\varphi(\theta)\|$, $\|\phi\|_{2\omega}=\sup_{\theta\in[-2\omega,0]}\|\phi(\theta)\|$.

The parametric uncertainties $\Delta A(t)$, $\Delta W(t)$, $\Delta C(t)$ and $\Delta D(t)$ satisfy: $[\Delta A(t),\Delta W(t),\Delta C(t),\Delta D(t)]=\tilde E\Delta(t)[H_a,H_w,H_c,H_d,]$, where $\tilde E$, H_a, H_w, H_c and H_d are some given constant matrices with appropriate dimensions. Besides, $\Delta(t)=[I-F(t)J]^{-1}F(t)$, where J are known real constant matrices of appropriate dimensions, $F(t)$ are uncertain matrices satisfying $I-JJ^T>0$ and $F(t)F^T(t)\le I$, respectively.

Remark 1. Since every rational nonlinear system possesses a linear fractional representation [18], the linear fractional parametric uncertainties have been investigated in the robust control setting as in [19,20]. It is easy to see that when $J=0$, the linear fractional uncertainty reduces to norm bounded one.

In order to conduct the stability analysis for the above genetic networks, the following assumption and lemmas are necessary.

Assumption 1. Since h_j is a monotonically increasing function with saturation, and from the relationship of $f(\cdot)$ and $h(\cdot)$, we know that $f(\cdot)$ satisfies the sector condition: $l_j^-\le f_j(x_j)/x_j\le l_j^+$, for $j=1,2,\ldots,n$. which implies that $(f_j(x_j)-l_j^-x_j)/x_j\ge 0$, $(l_j^+x_j-f_j(x_j))/x_j\ge 0$ where l_j^- and l_j^+ are some constants. Let $L_0=\mathrm{diag}\,(l_1^-,l_2^-,\ldots,l_n^-)$, $L_1=\mathrm{diag}\,(l_1^+,l_2^+,\ldots,l_n^+)$.

Remark 2. Assumption 1 endows with less restriction than monotonically increasing condition in [16,17], the constants l_j^- and l_j^+ are allowed to be positive, negative, or zero.

Lemma 2.1 (*Gu [21]*). *For any positive definite matrix $M\in R^{n\times n}$, scalars $h_2>h_1>0$, vector function $w:[h_1,h_2]\mapsto R^n$ such that the integrations concerned are well defined, the following inequality holds*:

$$\begin{aligned} &-(h_2-h_1)\int_{t-h_2}^{t-h_1} w^T(s)Mw(s)\,ds \\ &\quad\le -\left(\int_{t-h_2}^{t-h_1} w(s)\,ds\right)^T M\left(\int_{t-h_2}^{t-h_1} w(s)\,ds\right) \end{aligned}$$

$$\begin{aligned} &-\frac{1}{2}(h_2^2-h_1^2)\int_{-h_2}^{-h_1}\int_{t+\theta}^{t} w^T(s)Mw(s)\,ds \\ &\quad\le -\left(\int_{-h_2}^{-h_1}\int_{t+\theta}^{t} w(s)\,ds\right)^T M\left(\int_{-h_2}^{-h_1}\int_{t+\theta}^{t} w(s)\,ds\right) \end{aligned}$$

Lemma 2.2 (*Lower bounds theorem [22]*). *Let $f_1,f_2,\ldots,f_N: R^m\mapsto R$ have positive values in an open subset D of R^m. Then, the reciprocally*