Research Article

Analysis on Global Asymptotical Stability of Genetic Regulatory Networks with Time-Varying Delays via Convex Combination Method

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The global asymptotical stability analysis for genetic regulatory networks with time delays is concerned. By using Lyapunov functional theorem, LMIs, and convex combination method, a new delay-dependent stability criterion has been presented in terms of LMIs to guarantee the delayed genetic regulatory networks to be asymptotically stable. The restriction that the derivatives of the time-varying delays are less than one is removed. Our result is applicable to both fast and slow time-varying delays. The stability criterion has less conservative and wider application range. Experimental result has been used to demonstrate the usefulness of the main results and less conservativeness of the proposed method.

1. Introduction

Genetic regulatory networks (GRNs) play a key role in systems biology as they explain the interactions between genes (mRNA) and proteins. In a biological cell, genes may be expressed constantly (i.e., constitutive gene expression) or expressed based on molecular signals (i.e., regulated gene expression) [1–3]. The central dogma of molecular biology states that gene expression consists of two main processes, namely, transcription and translation for prokaryotes, and with the additional step of ribonucleic acid (RNA) splicing for eukaryotes. In the transcriptional process, messenger RNAs (mRNAs) are synthesized from genes by the regulations of transcript factors, which are proteins. In the translational process, the sequence of nucleotides in the mRNA is used in the synthesis of a protein. A genetic regulatory network (GRN) is a nonlinear dynamical system which describes the highly complex interactions between mRNAs and proteins—two main genetic products produced in the transcriptional and translational processes. Nowadays, in systems biology, one of the main challenges is to understand the genetic regulatory networks, for example, how biological activities are governed by the connectivity of genes and proteins. The study of the nature and functions of GRN has already aroused the interest of many researchers.

Since 1960s, many notable researchers have proposed various kinds of mathematical models to describe GRN. So far, during the past few years, there are two basic models for genetic network models: the Boolean model and the differential equation model [2, 3]. In Boolean models, the expression of each gene in the network is assumed to be either ON or OFF, no “intermediate” activity levels are ever taken into consideration, and the state of a gene is determined by a Boolean function of the states of other related genes. The differential equation model describes the rates of change of the concentrations of gene products, such as mRNAs and proteins, as continuous values. The differential equation model is often preferred over the Boolean model because its accuracy is more secured. In practical biological model, gene expression rates are usually continuous variables rather than ideal ON-OFF switches. Several typical genetic regulatory networks have been modelled and studied experimentally and/or theoretically; see [4–6] for some recent results.
On the other hand, time delays which usually exist in transcription, translation, diffusion, and translocation processes especially in a eukaryotic cell are one of the key factors affecting the dynamics of genetic regulatory network. The delays could be time invariant or time variant. The study of stability is essential for designing or controlling genetic regulatory networks. Up to now, there are already some sufficient conditions that have been proposed to guarantee the asymptotic or robust stability for genetic regulatory networks [7–20].

Motivated by the above discussions, we aim to analyze the stability of genetic regulatory networks with SUM logic in the form of differential equations. Besides the basic case, we will make contributions on the issues of asymptotical stability for genetic networks with time-varying delays. By choosing an appropriate new Lyapunov functional and employing convex combination method, new delay-derivative-dependent stability criterion is derived based on the consideration of ranges for the time-varying delays. The obtained criterion is given in terms of linear matrix inequalities (LMIs) and is applicable to both fast and slow time-varying delays. Finally, one numerical example is given to demonstrate the effectiveness and the merit of the proposed method.

2. Problem Description and Preliminaries

In [8, 9], the following differential equations have been used to describe GRNs containing n mRNAs and n proteins:

\[
\begin{align*}
m(t) &= -Am(t) + Wg(p(t - \sigma(t))) + U, \\
\dot{p}(t) &= -Cp(t) + Dm(t - \tau(t)),
\end{align*}
\]

(1)

where \(m(t) = [m_1(t), m_2(t), \ldots, m_n(t)]^T\), \(p(t) = [p_1(t), p_2(t), \ldots, p_n(t)]^T\), and \(\dot{p}(t)\) are the concentrations of mRNA and protein of the \(i\)th node at time \(t\), respectively; \(A = \text{diag}(a_1, a_2, \ldots, a_n)\) and \(C = \text{diag}(c_1, c_2, \ldots, c_n)\) denote the degradation or dilution rates of mRNAs and proteins; \(D = \text{diag}(d_1, d_2, \ldots, d_n)\) and \(W = (w_{ij}) \in \mathbb{R}^{n \times n}\) are the coupling matrices, and \(W\) is defined as follows:

\[
w_{ij} = \begin{cases} 
\overline{w}_{ij} & \text{if transcription factor } j \text{ is an activator of gene } i, \\
0 & \text{if there is no link from node } j \text{ to } i, \\
-\overline{w}_{ij} & \text{if transcription factor } j \text{ is a repressor of gene } i.
\end{cases}
\]

(2)

Furthermore, nonlinear function \(g(\cdot) \in \mathbb{R}^n\) represents the feedback regulation of the protein on the transcription, which is the monotonic function in Hill form, \(g_j(x) = x^{H_j}/(1 + x^{H_j})\), \(H\) is the Hill coefficient, and \(\tau(t)\) and \(\sigma(t)\) are the time-varying delays satisfying \(0 \leq \tau(t) \leq \tau, 0 \leq \sigma(t) \leq \sigma\), respectively; \(U = [u_1, u_2, \ldots, u_n]^T\), where \(u_i = \sum_{j \in \mathcal{N}_i} \overline{w}_{ij}\) and \(\mathcal{N}_i\) is the set of all \(j\) nodes which are repressors of gene \(i\).

In the following, we will always shift an intended equilibrium point \((m^*, p^*)\) of the system (1) to the origin by letting \(x(t) = m(t) - m^*, y(t) = p(t) - p^*\). Hence, system (1) can be transformed into the following form:

\[
\begin{align*}
\dot{x}(t) &= -Ax(t) + Wf(y(t - \sigma(t))) , \\
\dot{y}(t) &= -Cy(t) + Dx(t - \tau(t)),
\end{align*}
\]

(3)

where \(f(y(t)) = g(y(t) + p^*) - g(p^*)\). Since \(g_i\) is a monotonically increasing function with saturation, it satisfies, for all, \(x, y \in \mathbb{R}\) with \(x \neq y\) and \(0 \leq (g_i(x) - g_i(y))/(x - y) \leq k_i\). From the relationship of \(f(\cdot)\) and \(g(\cdot)\), we know that \(f(\cdot)\) satisfies the sector condition

\[
0 \leq \frac{f_i(x)}{x} \leq k_i.
\]

(4)

Lemma 1 (Schur complement). Given constant symmetric matrices \(\Sigma_1, \Sigma_2,\) and \(\Sigma_3\), where \(\Sigma_1 = \Sigma^T_1\) and \(0 < \Sigma_2 = \Sigma^T_2\), then \(\Sigma_1 + \sum_{i=1}^{3} \Sigma_i < 0\) if and only if

\[
\begin{bmatrix}
\sum_{i=1}^{3} \sum_{j=1}^{3} \\
\sum_{i=1}^{3} -\sum_{j=1}^{3}
\end{bmatrix} < 0, \quad \text{or} \quad \begin{bmatrix}
-\sum_{i=1}^{2} \sum_{j=1}^{3} \\
\sum_{i=1}^{3} -\sum_{j=1}^{1}
\end{bmatrix} < 0.
\]

(5)

3. Main Result

Theorem 2. For given scalars \(0 < \tau, 0 < \sigma, \mu,\) and \(d\), system (1) is asymptotically stable, if there exist matrices \(R_k = R_k^T \geq 0, k = 1, 2, Q_k = Q_k^T \geq 0, r = 1, 2, Z_j = Z_j^T \geq 0, j = 1, 2, R_j = R_j^T \geq 0, i = 1, 2, 3, A = \text{diag}(\lambda_1, \lambda_2, \ldots, \lambda_n) \geq 0, T_j = \text{diag}(t_{1j}, t_{2j}, \ldots, t_{nj}) \geq 0, j = 1, 2, N_i, M_i, S_i, U_i, i = 1, 2, \ldots, 8\), such that the following LMIs (6) hold:

\[
\begin{bmatrix}
Y & \tau M & \sigma S \\
* & -\tau Z_1 & 0 \\
* & * & -\sigma Z_2
\end{bmatrix} < 0,
\]

(6)

\[
\begin{bmatrix}
Y & \tau M & \sigma U \\
* & -\tau Z_1 & 0 \\
* & * & -\sigma Z_2
\end{bmatrix} < 0,
\]

}\[
\begin{bmatrix}
Y & \tau N & \sigma S \\
* & -\tau Z_1 & 0 \\
* & * & -\sigma Z_2
\end{bmatrix} < 0,
\]

(6)
with 

\[
Y = \begin{bmatrix}
Y_{11} & Y_{12} & Y_{13} & S_1 + M_4 & M_5 & P_W + M_6 \\
Y_{21} & Y_{22} & Y_{23} & Y_{24} & Y_{25} & Y_{26} & Y_{27} & Y_{28} & Y_{29} \\
Y_{31} & Y_{32} & Y_{33} & Y_{34} & Y_{35} & Y_{36} & Y_{37} & Y_{38} & Y_{39} \\
Y_{41} & Y_{42} & Y_{43} & Y_{44} & Y_{45} & Y_{46} & Y_{47} & Y_{48} & Y_{49} \\
Y_{51} & Y_{52} & Y_{53} & Y_{54} & Y_{55} & Y_{56} & Y_{57} & Y_{58} & Y_{59} \\
Y_{61} & Y_{62} & Y_{63} & Y_{64} & Y_{65} & Y_{66} & Y_{67} & Y_{68} & Y_{69} \\
Y_{71} & Y_{72} & Y_{73} & Y_{74} & Y_{75} & Y_{76} & Y_{77} & Y_{78} & Y_{79} \\
Y_{81} & Y_{82} & Y_{83} & Y_{84} & Y_{85} & Y_{86} & Y_{87} & Y_{88} & Y_{89} \\
Y_{91} & Y_{92} & Y_{93} & Y_{94} & Y_{95} & Y_{96} & Y_{97} & Y_{98} & Y_{99}
\end{bmatrix}
\]

\[
< 0,
\]

\[
Y_{11} = -P_1 A - A^T P_1 + Q_1 + Q_2 + 2 M_1,
\]

\[
Y_{12} = N_1 - M_1 + M_2,
\]

\[
Y_{13} = -N_1 + M_3,
\]

\[
Y_{15} = U_1 + M_5,
\]

\[
Y_{22} = -(1 - \mu) Q_2 + N_2 + N_2^T - M_2 - M_2^T,
\]

\[
Y_{23} = -N_2 + N_3 - M_3,
\]

\[
Y_{24} = S_2 + P_2 D - M_4,
\]

\[
Y_{25} = U_2 - S_2 - M_5 + N_5,
\]

\[
Y_{26} = U_2 - M_6 + N_6,
\]

\[
Y_{27} = -M_7 + \Lambda D + N_7,
\]

\[
Y_{28} = U_3 - S_3 - N_8,
\]

\[
Y_{33} = -Q_1 - M_3 - M_3^T,
\]

\[
Y_{44} = -P_1 C - C^T P_1 + R_1 + R_2,
\]

\[
Y_{45} = U_4 - S_4 + S_5,
\]

\[
Y_{47} = K T_1 - \Lambda C + S_7,
\]

\[
Y_{55} = -(1 - d) R_2 + U_5 + U_5^T - S_5 - S_5^T,
\]

\[
Y_{56} = -U_5 + U_6 - S_6 - N_6,
\]

\[
Y_{57} = U_7 - S_7 - N_7,
\]

\[
Y_{77} = R_3 - 2 T_1,
\]

\[
Y_{88} = -(1 - d) R_3 - 2 T_2.
\]

\[
V(t) = V_1(t) + V_2(t) + V_3(t) + V_4(t),
\]

\[
V_1(t) = x^T(t) P_1 x(t) + y^T(t) P_2 y(t) + \sum_{i=1}^{8} \lambda_i \int_0^t f_i(s) ds,
\]

\[
V_2(t) = \int_{t-\tau}^t x^T(s) Q_1 x(s) ds + \int_{t-\tau}^t y^T(s) R_1 y(s) ds,
\]

\[
V_3(t) = \int_{t-\tau(t)}^t x^T(s) Q_2 x(s) ds + \int_{t-\alpha(t)}^{t-\tau(t)} y^T(s) R_2 y(s) ds + \int_{t-\alpha(t)}^{t-\tau(t)} y^T(s) R_3 f(y(s)) ds,
\]

\[
V_4(t) = \int_0^t \int_{t-\tau(t)}^t x^T(s) Z_1 x(s) ds d\theta + \int_0^t \int_{t-\alpha(t)}^{t-\tau(t)} x^T(s) Z_2 y(s) ds d\theta.
\]

Calculating the derivative of $V(t)$ along the solutions of system (1), one can get

\[
\dot{V}_1(t) = 2x^T(t) P_1 [-Ax(t) + WF(y(t - \sigma(t)))]
+ 2y^T(t) P_2 [-Cy(t) + DX(t - \tau(t))]
+ 2f^T(y(t)) \Lambda [-Cy(t) + DX(t - \tau(t))],
\]

\[
\dot{V}_2(t) = x^T(t) Q_1 x(t) - x^T(t - \tau) Q_1 x(t - \tau)
+ y^T(t) R_1 y(t) - y^T(t - \sigma) R_1 y(t - \sigma),
\]

\[
\dot{V}_3(t) = x^T(t) Q_2 x(t) - (1 - \mu) x^T(t - \tau(t))
\times Q_2 x(t - \tau(t)) + y^T(t) R_2 y(t)
- (1 - d) y^T(t - \sigma(t)) R_2 y(t - \sigma(t))
+ f^T(y(t)) R_3 f(y(t))
- (1 - d) f^T(y(t - \sigma(t))) R_3 f(y(t - \sigma(t))),
\]

\[
\dot{V}_4(t) = x^T(t) T_x(t - \tau) - \int_{t-\tau}^{t-\tau(t)} x^T(s) Z_1 x(s) ds
ds + \int_{t-\alpha(t)}^{t-\tau(t)} y^T(s) Z_2 y(s) ds
\]

\[
= x^T(t) h_2 Z_1 x(t) - \int_{t-\tau(t)}^{t-\tau(t)} x^T(s) Z_1 x(s) ds
- \int_{t-\alpha(t)}^{t-\tau(t)} x^T(s) Z_1 x(s) ds
+ \int_{t-\alpha(t)}^{t-\alpha(t)} y^T(s) Z_2 y(s) ds
- \int_{t-\alpha(t)}^{t-\alpha(t)} y^T(s) Z_2 y(s) ds.
\]

From the Leibniz-Newton formula, the following equations are true for any matrices $N_i, M_i, U_i, S_i, i = 1, 2, \ldots, 8$ with appropriate dimensions:

\[
0 = 2\xi(t)^T N \left[ x(t - \tau(t)) - x(t - \tau_2) - \int_{t-\tau}^{t-\tau(t)} x(s) ds \right],
\]

\[
0 = 2\xi(t)^T M \left[ x(t) - x(t - \tau(t)) - \int_{t-\tau(t)}^{t-\tau(t)} x(s) ds \right],
\]

\[
0 = 2\xi(t)^T U \left[ y(t - \sigma(t)) - y(t - \alpha(t)) - \int_{t-\alpha(t)}^{t-\sigma(t)} y(s) ds \right],
\]

\[
0 = 2\xi(t)^T S \left[ y(t) - y(t - \sigma(t)) - \int_{t-\sigma(t)}^{t} y(s) ds \right].
\]
with $\xi(t) = \begin{bmatrix} \xi_1^T(t) \\ \xi_2^T(t) \end{bmatrix}^T,$
$\xi_1^T(t)$
\begin{equation}
\xi_2^T(t) = [y^T(t) y^T(t - \tau(t)) y^T(t - \sigma(t)) f^T(y(t)) f^T(y(t - \sigma(t)))]^T.
\end{equation}

(17)

In addition, from (4), we have $f_i(y_i(t)) - k_i y_i(t)$ for $i = 1, 2, \ldots, n$. Using LMI Control Toolbox, by our Theorem 2, we can find that system (1) described by Example 1 is asymptotically stable. Notice that $Y_1(t)$ is a convex combination of matrices $N\Sigma^{-1}N^T$ and $MZ^{-1}M^T$ on $\tau(t)$ satisfying $0 \leq \tau_1 < \tau(t) < \tau_2$, and $Y_2(\sigma(t))$ is a convex combination of matrices $U\Sigma^{-1}U^T$ and $SZ^{-1}S^T$ on $\sigma(t)$ satisfying $0 \leq \sigma_1 < \sigma(t) < \sigma_2$. Then $Y(\tau(t), \sigma(t)) < 0$ only if

\begin{align*}
Y(\tau, \sigma) &= Y + \tau MZ^{-1}M^T + \sigma S\Sigma^{-1}S^T < 0, \\
Y(\tau, 0) &= Y + \tau MZ^{-1}M^T + \sigma UZ^{-1}U^T < 0, \\
Y(0, \sigma) &= Y + \tau NZ^{-1}N^T + \sigma S\Sigma^{-1}S^T < 0, \\
Y(0, 0) &= Y + \tau NZ^{-1}N^T + \sigma UZ^{-1}U^T < 0.
\end{align*}

(20)

Applying Lemma 1 (Schur complement) to the four inequalities above, we arrive at LMI (6).

Remark 3. In [7, 13], additional information regarding the derivatives of the time-varying delays is needed; that is $\dot{\tau}(t) \leq d_1$, $\ddot{\tau}(t) \leq d_2 < 1$. From Theorem 2, one can see that the restrictions are removed. In this case, the results in [13] may produce conservative results. Our result is applicable to both fast and slow time-varying delays.

4. Numerical Example

Example 1. Consider the following genetic regulatory networks with time-varying delays, borrowed from [8, 9]:

\begin{align*}
\dot{m}(t) &= -Am(t) + Wg(\psi(t - \sigma(t))) + u, \\
\dot{p}(t) &= -Cp(t) + Dm(t - \tau(t)),
\end{align*}

(23)
in which

\begin{align*}
A &= \text{diag} \{3, 3, 3\}, \\
C &= \text{diag} \{2.5, 2.5, 2.5\}, \\
D &= \text{diag} \{0.8, 0.8, 0.8\}, \\
W &= \begin{bmatrix} 0 & 0 & -2.5 \\ -2.5 & 0 & 0 \\ 0 & -2.5 & 0 \end{bmatrix}, \\
\sigma &= 5.61, \\
\mu &= 1.1, \\
d &= 0.8.
\end{align*}

(24)

Using LMI Control Toolbox, by our Theorem 2, we can find that system (1) described by Example 1 is asymptotically stable.

stable. Limited to the length of the paper, we only show a part of the feasible solution here:

$$P_1 = \begin{bmatrix} 1.3083 & 0.0011 & 0.0011 \\ 0.0011 & 1.3083 & 0.0011 \\ 0.0011 & 0.0011 & 1.3083 \end{bmatrix},$$

$$P_2 = \begin{bmatrix} 0.7230 & -0.0006 & -0.0006 \\ -0.0006 & 0.7230 & -0.0006 \\ -0.0006 & -0.0006 & 0.7230 \end{bmatrix}. \tag{25}$$

It should be pointed out that Theorem 1 in [8] and Corollary 3.2 in [9] are not feasible when employing the LMI Toolbox, but using Theorem 2 in this paper, we can find that system (1) is asymptotically stable. Therefore, our method is less conservative than that in [8, 9].

5. Conclusions

This paper presents some new results of stability analysis for genetic regulatory networks with time-varying delays. An appropriate Lyapunov functional is proposed to investigate the delay-derivative-dependent stability problem. The present results improve the existing ones due to a method to estimate the upper bound of the derivative of Lyapunov functional without ignoring some useful terms and the introduction of convex combination method into the proposed Lyapunov functional, which takes into account the relationship between the time-varying delays and their lower and upper bounds. The supplementary requirements that the time derivatives of time-varying delays must be less than one are removed. As a result, the new stability criterion in terms of LMIs is applicable to both fast and slow time-varying delays. One numerical example shows that the proposed criterion is an improvement over some existing results in the literature. In the future, our work will include the problems of filter design and state estimation for genetic networks.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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