Robust Stability for Uncertain Genetic Regulatory Networks with Interval Time-varying Delays

Pin- Lin Liu

Department of Automation Engineering Institute of Mechatronoptic System, Chienkuo Technology University, Changhua, 500, Taiwan, R.O.C., Tel: 886-7111155, Fax:886-7111129, Email:lpl@cc.ctu.edu.tw

Abstract

The paper is to study the continuous time genetic regulatory networks to probe into the related issue of system asymptotically stable, due to the system be existence of interval time-varying delays and norm-bounded parameter uncertainty. Gene networks are being used increasingly as models to represent phenomena at the level of gene expression, how to construct models for analyzing the interaction between genes from experimental data is becoming important. In recent years researchers have proposed many methods to reconstruct gene regulatory networks based on gene expression data, such as clustering, Boolean networks, linear and non-linear model, Bayesian Networks and differential equation. For each gene category, we find its regulation patterns. By using the regulation patterns found for each gene category, we can infer the gene regulation relationships by finding the inclusive and opposite patterns between gene categories. Accordingly, these key genes can be admitted as the centers, and the whole network can further be decomposed into smaller ones, according to these centers. Finally, in order to optimize this decomposition, the boundaries among sub-networks can be determined, based on the mutual-information among sub-networks. So must to use Lyapunov–Krasovskii function, and delay-dependent stability is solved according to the skill of linear matrix inequalities. Simulation examples are to prove the validity and applicability for suggested result

Keywords: Genetic regulatory networks, asymptotically stable, delay-dependent stability, linear matrix inequality (LMI)

1. Introduction

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. Genetic networks are biochemically dynamical systems, and it is natural to model genetic networks by using dynamical system models, which provide a powerful tool for studying gene regulation processes in living organisms. At present, GRN has become a new area of research in the fields of biological and biomedical sciences. Stability behavior of genetic regulatory networks has important biological implication and potential engineering application from both theoretical and experimental viewpoints [1, 2]. Therefore stability is a basic feature of genetic regulatory process. Many researchers have studied so far the stability of genetic regulatory networks by experiment, numerical simulation and theoretical analysis [2, 3, 5-8, 12-14].

On the other hand, there is no doubt that time delay play important role in dynamics of genetic networks, and theoretical models without consideration of these factors may even provide wrong results. To have the accurate results, time delay should be considered in the biological systems or artificial genetic networks due to the slow processes of transcription, translation, and translocation or the finite switching speed of amplifiers. However, the dynamics will be more complicated due to the incorporation of the time delay in the genetic networks. Recently, some researchers have paid attention to the issue concerning time delay stability analysis [5-8, 12-15]. In [5], the authors studied the stability of a general genetic network model with time delays by using local stability analysis and characteristic equation analysis. Although the method of characteristic equation analysis can provide an accurate local stability region, it is difficult to be verified, especially for large-scale genetic networks with time delays. By local stability analysis and characteristic equation, the authors have addressed the stability of a general GRNs model with time delays. In [7], the modelled GRNs with SUM regulatory functions and have proposed some stability criteria for GRNs with time delays and/or stochastic perturbations. In [8], the stability of GRNs with noise perturbations and time delays has been studied. The criteria in [7, 8] are obtained by LMIs and can be easily verified. To have the accurate predictions, time delay should be considered in the biological systems or artificial genetic networks due to the slow processes of transcription, translation and translocation or the finite switching speed of amplifiers; theoretical models without consideration delay may even provide wrong predictions [6, 12]. In [13], the authors investigated the robust asymptotical stability issues of the GRNs with time delays and norm bounded uncertainties. By choosing an appropriate new Lyapunov functional and employing some free-weighting matrices, [14] derived some less conservative delay dependent stability criteria. Besides, the proposed method is particularly useful when applied

to eukaryotic genetic networks. The numerical results show that the proposed criteria are valid, and are superior to some results in the existing literature. Furthermore, as mentioned in [13, 14], all the theoretical results can be used not only in the analysis and understanding of the biological mechanism of gene regulation in living organisms; but can also be applied to the design and modelling of synthetic gene circuits in the framework of the synthetic biology.Meanwhile, in the application and design of genetic networks, there are often some unavoidable uncertainties, such as modeling errors, external perturbations and parameters fluctuations. These uncertainties may cause the genetic networks unstable [15]. Thus, it is also of great importance to investigate the robust asymptotical stability.

Based on the above discussion, the main purpose of this paper is to analyze the stability of genetic networks in the forms of differential equations. The stability analysis of the genetic networks are based on the Lyapunov method and integral inequality (LMI) approach, and the results are represented in terms of linear matrix inequalities (LMIs), which are easy to be verified by convex optimization techniques, e.g., the interior point method, and by software packages, e.g., the MATLAB LMI Toolbox. Numerical examples have also been used to demonstrate the usefulness of the main result.

The rest of this paper is organized as follows. Preliminaries and assumptions are defined in section 2. In section 3 the main results of this paper for the uncertain genetic regulatory networks is established. Three examples are given in section 4 to show the effectiveness of the proposed method. Finally the paper is closed with the interpretation and discussion of the results.

2. Model description and assumptions

The differential equations for genetic regulatory networks with time delay can be described as [5]

$$
\begin{cases}
\dot{m}_i(t) = -a_i m_i(t) + \sum_{j=1}^{n} b_i(p_j(t-h)) \\
\dot{p}_i(t) = -c_i p_i(t) + d_i m_i(t-\tau), \ i = 1, 2, ..., n
\end{cases}
\tag{1}
$$

where $m_i(t), p_i(t) \in R^n$ are the concentrations of mRNA and protein of the ith node. In this network, there is one output and multiple inputs for a single node or gene. The degradation rates of mRNA and protein are denoted by a_i and c_i, respectively. d_i is a constant, and as a monotonic increasing or decreasing regulatory function, we usually take b_i as a Michaelis–Menten or Hill form [7]. Here, we take $b_i(p_1(t), p_2(t), ..., p_n(t)) = \sum_{j=1}^{n} b_{ij}(p_j(t))$, which is called SUM logic [16]. Thus each transcription factor acts additively to regulate the ith gene.

If transcription factor j is an activator of gene i, then

$$
b_{ij}(p_j(t)) = \alpha_{ij} \frac{(p_j(t)/\beta)^H}{1 + (p_j(t)/\beta)^H}
\tag{2}
$$

which is a positive feedback loop. Then the system may tend to settle in one of two stable states.

If transcription factor j is a repressor of gene i, then

$$
b_{ij}(p_j(t)) = \alpha_{ij} \frac{1}{1 + (p_j(t)/\beta)^H} = \alpha_{ij}(1 - \frac{(p_j(t)/\beta)^H}{1 + (p_j(t)/\beta)^H})
\tag{3}
$$

which is a negative feedback loop. Then the system may approach or oscillate around a single steady-state [1, 11], where H is a Hill coefficient, parameter β is a positive constant and a bounded constant α_{ij} is the dimensionless transcriptional rate of transcriptional factor j to gene i.

Hence, (1) can be rewritten as

$$
\begin{cases}
\dot{m}_i(t) = -a_i m_i(t) + \sum_{j=1}^{n} w_{ij} g_j(p_j(t-h)) + B_i \\
\dot{p}_i(t) = -c_i p_i(t) + d_i m_i(t-\tau), \ i = 1, 2, ..., n
\end{cases}
\tag{4}
$$

where $g_i(x) = (x/\beta)^H / [1 + (x/\beta)^H]$ is a monotonically increasing function, B_i is defined as a basal rate, $B_i = \sum_{j \in L}, \alpha_{ij}$ and L_i is a set of repressors of gene i. $W = (w_{ij}) \in R^{n \times n}$ is a coupling matrix of the genetic

regulatory networks, which is defined as

$$
w_{ij} = \begin{cases} \alpha_{ij} & \text{if transcription factor } j \text{ is activator of gene } i \\ 0 & \text{if there is no link from gene } j \text{ to } i \\ -\alpha_{ij} & \text{if transcription factor } j \text{ is repressor of gene } i \end{cases} \tag{5}
$$

In other words, the matrix $W = (w_{ij})$ defines the coupling topology, direction and the transcriptional rate of the genetic regulatory network.

In compact matrix form, (4) can be rewritten as

$$
\begin{cases} \dot{m}(t) = -Am(t) + Wg(p(t-h)) + B_i \\ \dot{p}(t) = -Cp(t) + Dm(t-\tau), \ i = 1,2,...,n \end{cases} \tag{6}
$$

where
$m(t) = [m_1(t), m_2(t),..., m_n(t)]^T$, $p(t) = [p_1(t), p_2(t),..., p_n(t)]^T$, $m(t-\tau) = [m_1(t-\tau), m_2(t-\tau),..., m_n(t-\tau)]^T$,
$g(p(t-h)) = [p_1(t-h), p_2(t-h),..., p_n(t-h)]^T$, $A = diag(a_1, a_2,..., a_n)$, $C = diag(c_1, c_2,..., c_n)$,
$D = diag(d_1, d_2,..., d_n)$, $B = [B_1, B_2,..., B_n]$.

It should be noted that, in model (4) and (6), B_i is dependent on the biological function of transcription factor j on gene i, that is, B_i is determined by whether j acts as an activator or a repressor of gene i. Once gene i has one or more repressors, then L_i, the set of all j which are repressors of gene i, is a non-empty set and B is relevant to W. Thus, once W is uncertain, B is also uncertain. Therefore either for this case or when all transcription factors are repressors of gene i, the variable equilibrium point is an unknown function about the uncertainty, and these variable equilibrium points cannot be calculated because they are the solution of a parameter-dependent non-linear system. As biological networks, genetic regulatory networks are usually non-identical, so it is necessary to introduce estimation errors into the genetic network model, which makes the mathematical model uncertain.

Let (m^*, p^*) be an equilibrium of Eq. (6). Then we shift an intended equilibrium point to the origin by letting $x(t) = m(t) - m^*, y(t) = p(t) - p^*$, Hence, it is easy to get:

$$
\begin{cases} \dot{x}(t) = -Ax(t) + Wf(y(t-h)) \\ \dot{y}(t) = -Cy(t) + Dx(t-\tau) \end{cases} \tag{7}
$$

where $x(t) = [x_1(t), x_2(t),..., x_n(t)]^T$, $y(t) = [y_1(t), y_2(t),..., y_n(t)]^T$,
$f(y(t)) = [f_1(y_1(t)), f_2(y_2(t)),..., f_n(y_n(t))]^T$, $f(y(t)) = g(y(t) + p^*) - g(p^*)$.

Since g_i is a monotonically increasing function with saturation, it satisfies, for all $x, y \in R$ with $x \neq y$:

$$
0 \leq \frac{g_i(x) - g_i(y)}{x - y} \leq k_i \tag{8}
$$

From the relationship between $f(\cdot)$ and $g(\cdot)$, we know that $f(\cdot)$ satisfies the sector condition:

$$
0 \leq \frac{f_i(x)}{x} \leq k_i, \quad f_i(0) = 0, \forall x \neq 0, i = 1, 2,..., n, \tag{9}
$$

which is equivalent to the following one:

$$
f_i(x)(f_i(x) - k_i x) \leq 0, \quad f_i(0) = 0, \forall x \neq 0, i = 1, 2,..., n. \tag{10}
$$

Next, we consider the following genetic regulatory network of N time-coupled non-identical nodes with parameter uncertainties.

$$
\begin{cases} \dot{x}(t) = -(A + \Delta A(t))x(t) + (W + \Delta W(t))f(y(t-h)) \\ \dot{y}(t) = -(C + \Delta C(t))y(t) + (D + \Delta D(t))x(t-\tau), \end{cases} \tag{11}
$$

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where $\Delta A(t)$, $\Delta W(t)$, $\Delta C(t)$, and $\Delta D(t)$ are unknown matrices representing time-varying parameter uncertainties, which are assumed to be of the form

$$[\Delta A(t) \quad \Delta W(t) \quad \Delta C(t) \quad \Delta D(t)] = MF(k)[N_1 \quad N_2 \quad N_3 \quad N_4], \tag{12}$$

where $M, N_1, N_2, N_3,$ and N_4 are known real constant matrices and $F(t)$ is an unknown matrix function with Lebesgue- measurable elements bounded by

$$F^T(t)F(t) \le I, \qquad \forall t, \tag{13}$$

where I is an appropriately dimensioned identity matrix.

The following lemmas will be used to prove the main results:

Lemma 1 [9, 10]. For any positive semi-definite matrices

$$X = \begin{bmatrix} X_{11} & X_{12} & X_{13} \\ X_{12}^T & X_{22} & X_{23} \\ X_{13}^T & X_{23}^T & X_{33} \end{bmatrix} \ge 0, \tag{14a}$$

the following integral inequality holds

$$-\int_{t-h(t)}^{t} \dot{x}^T(s)X_{33}\dot{x}(s)ds \le$$

$$\int_{t-h(t)}^{t} \begin{bmatrix} x^T(t) & x^T(t-h(t)) & \dot{x}^T(s) \end{bmatrix} \begin{bmatrix} X_{11} & X_{12} & X_{13} \\ X_{12}^T & X_{22} & X_{23} \\ X_{13}^T & X_{23}^T & 0 \end{bmatrix} \begin{bmatrix} x(t) \\ x(t-h(t)) \\ \dot{x}(s) \end{bmatrix} ds. \tag{14b}$$

Lemma 2 [4]. The following matrix inequality

$$\begin{bmatrix} Q(x) & S(x) \\ S^T(x) & R(x) \end{bmatrix} < 0, \tag{15a}$$

where $Q(x) = Q^T(x), R(x) = R^T(x)$ and $S(x)$ depend affine on x, is equivalent to

$$R(x) < 0 \tag{15b}$$
$$Q(x) < 0, \tag{15c}$$

and

$$Q(x) - S(x)R^{-1}(x)S^T(x) < 0. \tag{15d}$$

Finally, the following Lemma 3 will be used to handle the parametrical perturbation.

Lemma 3 [4]. Given symmetric matrices Ω and D, E of appropriate dimensions,

$$\Omega + DF(t)E + E^T F^T(t)D^T < 0 \tag{16a}$$

for all $F(t)$ satisfying $F^T(t)F(t) \le I$, if and only if there exists some $\varepsilon > 0$ such that

$$\Omega + \varepsilon DD^T + \varepsilon^{-1}E^TE < 0, \tag{16b}$$

3. Main results

In this section, we use the integral inequality approach (IIA) to obtain stability criterion for a genetic regulatory networks with time delay (7). Based on the Lyapunov-Krasovskii stability theorem and integral inequality approach (IIA), the following result is obtained.

Theorem 1. For given positive scalars h and τ, the genetic regulatory networks with time delay (7) is asymptotically stable if there exist symmetry positive-definite matrices $Q_i = Q_i^T > 0, R_i = R_i^T > 0, (i = 1, 2, 3)$,

$U = U^T > 0$, diagonal matrices $S \geq 0$, $\Lambda_1 \geq 0$, $\Lambda_2 \geq 0$, and $X = \begin{bmatrix} X_{11} & X_{12} & X_{13} \\ X_{12}^T & X_{22} & X_{23} \\ X_{13}^T & X_{23}^T & X_{33} \end{bmatrix} \geq 0$,

$Y = \begin{bmatrix} Y_{11} & Y_{12} & Y_{13} \\ Y_{12}^T & Y_{22} & Y_{23} \\ Y_{13}^T & Y_{23}^T & Y_{33} \end{bmatrix} \geq 0$, such that the following LMIs hold for

$$\Omega = \begin{bmatrix} \Omega_{11} & 0 & \Omega_{13} & \Omega_{14} & 0 & 0 & \Omega_{17} & 0 \\ 0 & \Omega_{22} & \Omega_{23} & 0 & \Omega_{25} & \Omega_{26} & 0 & \Omega_{28} \\ \Omega_{13}^T & \Omega_{23}^T & \Omega_{33} & 0 & \Omega_{35} & 0 & 0 & \Omega_{38} \\ \Omega_{14}^T & 0 & 0 & \Omega_{44} & 0 & \Omega_{46} & \Omega_{47} & 0 \\ 0 & \Omega_{25}^T & \Omega_{35}^T & 0 & \Omega_{55} & 0 & 0 & 0 \\ 0 & \Omega_{26}^T & 0 & \Omega_{46}^T & 0 & \Omega_{66} & 0 & 0 \\ \Omega_{17}^T & 0 & 0 & \Omega_{47}^T & 0 & 0 & \Omega_{77} & 0 \\ 0 & \Omega_{28}^T & \Omega_{38}^T & 0 & 0 & 0 & 0 & \Omega_{88} \end{bmatrix} < 0, \tag{17a}$$

and

$$Q_3 - X_{33} \geq 0, \tag{17b}$$
$$R_3 - Y_{33} \geq 0, \tag{17c}$$

where
$K = diag\{k_1, k_2, \ldots, k_n,\}, \Omega_{11} = -Q_1 A - A^T Q_1 + Q_2 + \tau X_{11} + X_{13} + X_{13}^T,$

$\Omega_{13} = \tau X_{12} - X_{13} + X_{23}^T, \Omega_{14} = Q_1 W, \Omega_{17} = \tau A^T Q_3,$

$\Omega_{22} = -R_1 C - C^T R_1 + R_2 + h Y_{11} + Y_{13} + Y_{13}^T, \Omega_{23} = R_1 D, \Omega_{25} = K \Lambda_1 - C^T S,$

$\Omega_{26} = h Y_{12} - X_{13} + Y_{23}^T, \Omega_{28} = h C^T R_3, \Omega_{33} = -Q_2 + \tau X_{22} - X_{23} - X_{23}^T, \Omega_{35} = D^T S,$

$\Omega_{38} = -h D^T R_3, \Omega_{44} = -U - 2\Lambda_2, \Omega_{46} = K \Lambda_2, \Omega_{47} = -\tau W^T Q_3, \Omega_{55} = U - 2\Lambda_1,$

$\Omega_{66} = h Y_{22} - Y_{23} - Y_{23}^T - R_2, \Omega_{77} = -\tau Q_3, \Omega_{88} = -h R_3.$

Proof: Choose the following Lyapunov-Kravoskii functional candidate to be

$$V(t) = V_1(t) + V_2(t) + V_3(t) + V_4(t), \tag{18}$$

where

$V_1(t) = x^T(t) Q_1 x(t) + y^T(t) R_1 y(t),$

$V_2(t) = 2 \sum_{i=1}^{n} s_i \int_0^{y_i(t)} f_i(s) ds + \int_{t-h}^{t} f^T(y(s)) U f(y(s)) ds,$

$V_3(t) = \int_{t-\tau}^{t} x^T(s) Q_2 x(s) ds + \int_{t-h}^{t} y^T(s) R_2 y(s) ds,$

$V_4(t) = \int_{-\tau}^{0} \int_{t+\theta}^{t} \dot{x}^T(s) Q_3 \dot{x}(s) ds d\theta + \int_{-h}^{0} \int_{t+\theta}^{t} \dot{y}^T(s) R_3 \dot{y}(s) ds d\theta.$

Then, taking the time derivative of $V(t)$ with respect to t along the system (18) yield

$$\dot{V}(t) = \dot{V}_1(t) + \dot{V}_2(t) + \dot{V}_3(t) + \dot{V}_4(t), \tag{19}$$

where

$\dot{V}_1(x_t) = 2 x^T(t) Q_1 \dot{x}(t) + 2 y^T(t) R_1 \dot{y}(t)$
$= 2 x^T(t) Q_1 [-Ax(t) + W f(y(t-h))] + 2 y^T(t) R_1 [-Cy(t) + Dx(t-\tau)] \tag{20}$

$\dot{V}_2(t) = 2 f^T(y(t)) S \dot{y}(t) + f^T(y(t)) U f(y(t)) - f^T(y(t-h(t))) U f(y(t-h(t)))$
$\leq 2 g^T(y(t)) S[-Cy(t) + Dx(t-\tau)] + f^T(x(t)) U f(x(t))$
$- f^T(y(t-h(t))) U f(y(t-h(t))), \tag{21}$

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$$\dot{V}_3(t) = x^T(t)Q_2x(t) - x^T(t-\tau)Q_2x(t-\tau) + y^T(t)R_2y(t) - y^T(t-h)R_2y(t-h) \tag{22}$$

and

$$\dot{V}_4(t) = \dot{x}^T(t)\tau Q_3\dot{x}(t) - \int_{t-\tau}^t \dot{x}^T(s)Q_3\dot{x}(s)ds + \dot{y}^T(t)hR_3\dot{y}(t) - \int_{t-h}^t \dot{y}^T(s)R_3\dot{y}(s)ds$$
$$= \dot{x}^T(t)\tau Q_3\dot{x}(t) + \dot{y}^T(t)hR_3\dot{y}(t) - \int_{t-\tau}^t \dot{x}^T(s)(Q_3 - X_{33})\dot{x}(s)ds - \int_{t-h}^t \dot{y}^T(s)(R_3 - Y_{33})\dot{y}(s)ds$$
$$-\int_{t-\tau}^t \dot{x}^T(s)X_{33}\dot{x}(s)ds - \int_{t-h}^t \dot{y}^T(s)Y_{33}\dot{y}(s)ds \tag{23}$$

Using Lemma 1, the term $-\int_{t-\tau}^t \dot{x}^T(s)X_{33}\dot{x}(s)ds$ can be written that

$$-\int_{t-\tau}^t \dot{x}^T(s)X_{33}\dot{x}(s)ds$$
$$\leq \int_{t-\tau}^t \begin{bmatrix} x^T(t) & x^T(t-\tau) & \dot{x}^T(s) \end{bmatrix} \begin{bmatrix} X_{11} & X_{12} & X_{13} \\ X_{12}^T & X_{22} & X_{23} \\ X_{13}^T & X_{23}^T & 0 \end{bmatrix} \begin{bmatrix} x(t) \\ x(t-\tau) \\ \dot{x}(s) \end{bmatrix} ds$$
$$\leq x^T(t)\tau X_{11}x(t) + x^T(t)\tau X_{12}x(t-\tau) + x^T(t)X_{13}\int_{t-\tau}^t \dot{x}(s)ds$$
$$+x^T(t-\tau)\tau X_{12}^T x(t) + x^T(t-\tau)\tau X_{22}x(t-\tau) + x^T(t-\tau)X_{23}\int_{t-\tau}^t \dot{x}(s)ds$$
$$+\int_{t-\tau}^t \dot{x}^T(s)ds X_{13}^T x(t) + \int_{t-\tau}^t \dot{x}^T(s)ds X_{23}^T x(t-\tau)$$
$$= x^T(t)[\tau X_{11} + X_{13}^T + X_{13}]x(t) + x^T(t)[\tau X_{12} - X_{13} + X_{23}^T]x(t-\tau)$$
$$+x^T(t-\tau)[\tau X_{12}^T - X_{13}^T + X_{23}]x(t) + x^T(t-\tau)[\tau X_{22} - X_{23} - X_{23}^T]x(t-\tau). \tag{24}$$

Similarly, we have

$$-\int_{t-h}^t \dot{y}^T(s)Y_{33}\dot{y}(s)ds$$
$$\leq y^T(t)[hY_{11} + Y_{13}^T + Y_{13}]y(t) + y^T(t))[hY_{12} - Y_{13} + Y_{23}^T]y(t-h)$$
$$+y^T(t-h)[hY_{12}^T - Y_{13}^T + Y_{23}]y(t)) + y^T(t-h)[hY_{22} - Y_{23} - Y_{23}^T]y(t-h). \tag{25}$$

Evaluating $\dot{x}^T(t)\tau Q_3\dot{x}(t) + \dot{y}^T(t)hR_3\dot{y}(t)$ along solution to (7), gives as follows:

$$\dot{x}^T(t)\tau Q_3\dot{x}(t) + \dot{y}^T(t)hR_3\dot{y}(t)$$
$$= [-Ax(t) + Wf(y(t-h))]^T(\tau Q_3)[-Ax(t) + Wf(y(t-h))]$$
$$+[-Cy(t) + Dx(t-\tau)]^T(hR_3)[-Cy(t) + Dx(t-\tau)] \tag{26}$$

From (10) for appropriately dimensioned diagonal matrices $\Lambda_i(i=1,2)$, we have

$$-2f^T(y(t))\Lambda_1[f(y(t))-Ky(t)] \geq 0 \tag{27}$$

and

$$-2f^T(y(t-h))\Lambda_2[f(y(t-h)) - Ky(t-h)] \geq 0. \tag{28}$$

Substituting the above equations (20)-(28) into (19), we obtain

$$\dot{V}(t) \leq \xi^T(t)\Xi\xi(t) - \int_{t-\tau}^t \dot{x}^T(s)(Q_3 - X_{33})\dot{x}(s)ds - \int_{t-h}^t \dot{y}^T(s)(R_3 - Y_{33})\dot{y}(s)ds, \tag{29}$$

where $\xi^T(t) = \begin{bmatrix} x^T(t) & y^T(t) & x^T(t-\tau) & f^T(y(t-h)) & f^T(y(t)) & y^T(t-h) \end{bmatrix}$ and

$$\Xi = \begin{bmatrix} \Xi_{11} & 0 & \Xi_{13} & \Xi_{14} & 0 & 0 \\ 0 & \Xi_{22} & \Xi_{23} & 0 & \Xi_{25} & \Xi_{26} \\ \Xi_{13}^T & \Xi_{23}^T & \Xi_{33} & \Xi_{34} & \Xi_{35} & 0 \\ \Xi_{14}^T & 0 & \Xi_{34}^T & \Xi_{44} & 0 & \Xi_{46} \\ 0 & \Xi_{25}^T & \Xi_{35}^T & 0 & \Xi_{55} & 0 \\ 0 & \Xi_{26}^T & 0 & \Xi_{46}^T & 0 & \Xi_{66} \end{bmatrix} < 0, \text{ with}$$

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$K = diag\{k_1, k_2, ..., k_n\}, \Xi_{11} = -Q_1 A - A^T Q_1 + Q_2 + \tau X_{11} + X_{13} + X_{13}^T + \tau A^T Q_3 A,$

$\Xi_{13} = \tau X_{12} - X_{13} + X_{23}^T, \Xi_{14} = Q_1 W - \tau A^T Q_3 W,$

$\Xi_{22} = -R_1 C - C^T R_1 + R_2 + h Y_{11} + Y_{13} + Y_{13}^T + h C^T R_3 C,$

$\Xi_{23} = R_1 D - h C^T R_3 D, \Xi_{25} = K \Lambda_1 - C^T S, \Xi_{26} = h Y_{12} - X_{13} + Y_{23}^T,$

$\Xi_{33} = -Q_2 + \tau X_{22} - X_{23} - X_{23}^T + h D^T R_3 D, \Xi_{35} = D^T S,$

$\Xi_{44} = -U - 2\Lambda_2 + \tau W^T Q_3 W, \Xi_{46} = K \Lambda_2, \Xi_{55} = U - 2\Lambda_1, \Xi_{66} = h Y_{22} - Y_{23} - Y_{23}^T - R_2.$

Finally, using the Schur complements of Lemma 2, with some effort we can show that (29) guarantees of $\dot{V}(t) < -\delta \|x(t)\|^2$ for a sufficiently small $\delta > 0$. It is clear that if $\Xi < 0, \; Q_3 - X_{33} \geq 0, \;$ and $R_3 - Y_{33} \geq 0.$ Furthermore, (17) implies $\Omega < 0,$ which is equivalent to (29). Therefore, if LMIs (17) are feasible, the system (7) is asymptotically stable. This completes the proof. $\square$

Based on Theorem 1, we have the following result for uncertain genetic regulatory network with time delay (11).

Theorem 2. For given positive scalars h and τ, the genetic regulatory networks with time delay (11) is asymptotically stable if there exist symmetry positive-definite matrices $Q_i = Q_i^T > 0, R_i = R_i^T > 0, (i = 1, 2, 3),$

$U = U^T > 0,$ diagonal matrices $S \geq 0, \quad \Lambda_1 \geq 0, \quad \Lambda_2 \geq 0, \varepsilon > 0,$ and $X = \begin{bmatrix} X_{11} & X_{12} & X_{13} \\ X_{12}^T & X_{22} & X_{23} \\ X_{13}^T & X_{23}^T & X_{33} \end{bmatrix} \geq 0,$

$Y = \begin{bmatrix} Y_{11} & Y_{12} & Y_{13} \\ Y_{12}^T & Y_{22} & Y_{23} \\ Y_{13}^T & Y_{23}^T & Y_{33} \end{bmatrix} \geq 0,$ such that the following LMIs hold for

$$\overline{\Omega} = \begin{bmatrix} \overline{\Omega}_{11} & 0 & \Omega_{13} & \Omega_{14} & 0 & 0 & \Omega_{17} & 0 & \Omega_{19} & \Omega_{110} & 0 & 0 \\ 0 & \overline{\Omega}_{22} & \Omega_{23} & 0 & \Omega_{25} & \Omega_{26} & 0 & \Omega_{28} & 0 & 0 & \Omega_{211} & \Omega_{212} \\ \Omega_{13}^T & \Omega_{23}^T & \overline{\Omega}_{33} & 0 & \Omega_{35} & 0 & 0 & \Omega_{38} & 0 & 0 & 0 & 0 \\ \Omega_{14}^T & 0 & 0 & \overline{\Omega}_{44} & 0 & \Omega_{46} & \Omega_{47} & 0 & 0 & 0 & 0 & 0 \\ 0 & \Omega_{25}^T & \Omega_{35}^T & 0 & \Omega_{55} & 0 & 0 & 0 & 0 & 0 & \Omega_{511} & \Omega_{512} \\ 0 & \Omega_{26}^T & 0 & \Omega_{46}^T & 0 & \Omega_{66} & 0 & 0 & 0 & 0 & 0 & 0 \\ \Omega_{17}^T & 0 & 0 & \Omega_{47}^T & 0 & 0 & \Omega_{77} & 0 & \Omega_{79} & \Omega_{710} & 0 & 0 \\ 0 & \Omega_{28}^T & \Omega_{38}^T & 0 & 0 & 0 & 0 & \Omega_{88} & 0 & 0 & \Omega_{811} & \Omega_{812} \\ \Omega_{19}^T & 0 & 0 & 0 & 0 & 0 & \Omega_{79}^T & 0 & \Omega_{99} & 0 & 0 & 0 \\ \Omega_{110}^T & 0 & 0 & 0 & 0 & 0 & \Omega_{710}^T & 0 & 0 & \Omega_{1010} & 0 & 0 \\ 0 & \Omega_{211}^T & 0 & 0 & \Omega_{511}^T & 0 & 0 & \Omega_{811}^T & 0 & 0 & \Omega_{1111} & 0 \\ 0 & \Omega_{212}^T & 0 & 0 & \Omega_{512}^T & 0 & 0 & \Omega_{812}^T & 0 & 0 & 0 & \Omega_{1212} \end{bmatrix} < 0 \quad (30a)$$

and

$$Q_3 - X_{33} \geq 0, \quad (30b)$$

$$R_3 - Y_{33} \geq 0, \quad (30c)$$

where

$\overline{\Omega}_{11} = \Omega_{11} + \varepsilon_1 N_1^T N_1, \overline{\Omega}_{22} = \Omega_{22} + \varepsilon_3 N_3^T N_3, \overline{\Omega}_{33} = \Omega_{33} + \varepsilon_4 N_4^T N_4, \overline{\Omega}_{44} = \Omega_{44} + \varepsilon_2 N_2^T N_2, \Omega_{19} = Q_1 M_1, \Omega_{110} = Q_1 M_2,$

$\Omega_{211} = R_1 M_3, \Omega_{212} = R_1 M_4, \Omega_{511} = S M_3, \Omega_{511} = S M_4, \Omega_{79} = -\tau Q_3 M_1, \Omega_{710} = -\tau Q_3 M_2, \Omega_{811} = -h R_3 M_3,$

$\Omega_{812} = -h R_3 M_4, \Omega_{99} = -\varepsilon_1 I, \Omega_{1010} = -\varepsilon_2 I, \Omega_{1111} = -\varepsilon_3 I, \Omega_{1212} = -\varepsilon_4 I. \; \Omega_{ij}, (i, j = 1, ..., 8; i < j \leq 8)$ are defined in (17).

It is, incidentally, worth noting that the uncertain genetic regulatory network with time (11) is asymptotically stable, that is, the uncertain parts of the nominal system can be tolerated within allowable time delay h .

Proof: Replacing $A, W, C,$ and D in (17) with $A + M_1 F(t) M_1, W + M_2 F(t) N_2, \quad C + M_3 F(t) N_3,$ and $D + M_4 F(t) N_4,$ respectively, we apply Lemma 2 for system (17) is equivalent to the following condition:

$$\Omega + \Gamma_{1d}F(t)\Gamma_{1e} + \Gamma_{1e}^T F(t)\Gamma_{1d}^T + \Gamma_{2d}F(t)\Gamma_{2e} + \Gamma_{2e}^T F(t)\Gamma_{2d}^T + \Gamma_{3d}F(t)\Gamma_{3e} + \Gamma_{3e}^T F(t)\Gamma_{3d}^T + \Gamma_{4d}F(t)\Gamma_{4e} + \Gamma_{4e}^T F(t)\Gamma_{4d}^T < 0 \tag{31}$$

where

$$\Gamma_{1d} = \begin{bmatrix} Q_1 M_1 & 0 & 0 & 0 & 0 & 0 & -\tau Q_3 M_1 & 0 \end{bmatrix}^T, \Gamma_{1e} = \begin{bmatrix} -N_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix},$$

$$\Gamma_{2d} = \begin{bmatrix} Q_1 M_2 & 0 & 0 & 0 & 0 & 0 & -\tau Q_3 M_2 & 0 \end{bmatrix}^T, \Gamma_{2e} = \begin{bmatrix} 0 & 0 & 0 & N_2 & 0 & 0 & 0 & 0 \end{bmatrix},$$

$$\Gamma_{3d} = \begin{bmatrix} 0 & R_1 M_3 & 0 & 0 & S M_3 & 0 & 0 & -h R_3 M_3 \end{bmatrix}^T, \Gamma_{3e} = \begin{bmatrix} 0 & 0 & N_4 & 0 & 0 & 0 & 0 & 0 \end{bmatrix},$$

$$\Gamma_{4d} = \begin{bmatrix} 0 & R_1 M_4 & 0 & 0 & S M_4 & 0 & 0 & -h R_3 M_4 \end{bmatrix}^T, \Gamma_{4e} = \begin{bmatrix} 0 & 0 & N_4 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}.$$

According to Lemma 3, (31) is true if there exist a scalar $\varepsilon_i > 0 (i = 1,2,3,4)$ such that the following inequality holds

$$\Omega + \varepsilon_1^{-1}\Gamma_{1d}\Gamma_{1d}^T + \varepsilon_1\Gamma_{1e}^T\Gamma_{1e} + \varepsilon_2^{-1}\Gamma_{2d}\Gamma_{2d}^T + \varepsilon_2\Gamma_{2e}^T\Gamma_{2e} + \varepsilon_3^{-1}\Gamma_{3d}\Gamma_{3d}^T + \varepsilon_3\Gamma_{3e}^T\Gamma_{3e} + \varepsilon_4^{-1}\Gamma_{4d}\Gamma_{4d}^T + \varepsilon_4\Gamma_{4e}^T\Gamma_{4e} < 0. \tag{32}$$

Applying the Schur complement shows that (32) is equivalent to (30a). This completes the proof.

Base on that, a convex optimization problem is formulated to find the bound on the allowable delay time h and τ which maintains the genetic regulatory network time delay with parameter uncertainties systems (11).

Remark 2. It is interesting to note that h and τ appear linearly in (17) and (30). Thus a generalized eigenvalue problem (GEVP) as defined in Boyd, *et al.* [4] can be formulated to solve the minimum acceptable $1/h$ (or $1/\tau$) and therefore the maximum h (or τ) to maintain robust stability as judged by these conditions.

In this way, our optimization problem becomes a standard generalized eigrnvalue problem, then which can be solved using GEVP technique. From this discussion, we have the following Remark 2.

Remark 2: Theorem 2 provides delay-dependent robust asymptotic stability criterion for the genetic regulatory network time delay with parameter uncertainties systems (11) in terms of solvability of LMIs [4]. Based on them, we can obtain the maximum allowable delay bound (MADB) $\bar{h}(\text{ or } \bar{\tau})$ such that (11) is stable by solving the following convex optimization problem

$$\begin{cases} \text{Maximize} & \bar{h}(\text{or } \bar{\tau}) \\ \text{Subject to} & (30) \end{cases} \tag{33}$$

Inequality (33) is a convex optimization problem and can be obtained efficiently using the MATLAB LMI Toolbox.

4. Examples

Example 1: Consider an uncertain genetic regulatory network (11) with the following parameters

$$\begin{cases} \dot{x}(t) = -(A + \Delta A(t))x(t) + (W + \Delta W(t))f(y(t - h)) \\ \dot{y}(t) = -(C + \Delta C(t))y(t) + (D + \Delta D(t))x(t - \tau), \end{cases} \tag{34}$$

where

$A = diag(1,1,1), C = diag(1,1,1), D = diag(0.3,0.2,0.4), K = diag(0.65,0.65,0.65),$

$$W = \begin{bmatrix} 0 & -1 & -1 \\ -1 & 0 & 0 \\ 0 & 1 & 0 \end{bmatrix}, M_1 = \begin{bmatrix} 0.04 & 0.01 & -0.02 \\ 0.01 & 0.04 & -0.01 \\ -0.02 & -0.01 & 0.03 \end{bmatrix}, M_2 = \begin{bmatrix} 0.2 & 0 & 0 \\ 0 & 0.2 & 0 \\ 0 & 0 & 0.2 \end{bmatrix},$$

$$M_3 = \begin{bmatrix} 0.4 & 0.1 & -0.2 \\ 0.1 & 0.4 & -0.1 \\ -0.2 & -0.1 & 0.3 \end{bmatrix}, M_4 = \begin{bmatrix} 0.040 & 0.02 & -0.04 \\ 0.020 & 0.03 & -0.02 \\ -0.040 & -0.02 & 0.06 \end{bmatrix}, N_1 = M_1, N_2 = diag(0.2,0.2,0.2),$$

$N_3 = M_3, N_4 = M_4, B = \begin{bmatrix} 2 & 1 & 0 \end{bmatrix}^T, \Delta B = \begin{bmatrix} 0.08 & 0.04 & 0 \end{bmatrix}^T,$

$F_1(t) = diag(\sin(t), \cos(2t), -\sin(t)), F_3(t) = diag(-0.01\sin(t), -0.01\cos(2t), -0.01\sin(t)),$

$F_2(t)=F_4(t)=I, f(x)=\dfrac{x^2}{1+x^2}$, that is, the Hill coefficient is 2. It is obvious that the derivative of $f(x)$ is less than 0.65, and assumption (9) is satisfied.

Solution: Using Theorem 2, the MADB $\bar{\tau}$ and $\bar{h}$ for the system (34) to be asymptotically stable are $\bar{\tau}=5.8895,$ and $\bar{h}=6.4654.$ Applying the criterion in [13], the system is asymptotically stable for $\bar{\tau}$ and $\bar{h}$ that satisfies $\bar{\tau}=0.2$ and $\bar{h}=0.3,$ respectively. Hence, for this example, the criteria proposed here significantly improve the estimate of the stability limit compared for the result of [13].In case of $\bar{\tau}=5.8895, \bar{h}=6.4654,$ by using the MATLAB LMI toolbox, we can easily obtain the following feasible solutions of LMIs (30) in terms of Theorem 2.

$$Q_1=\begin{bmatrix}24.1477 & 0.4063 & 7.3111 \\ 0.4063 & 25.9010 & -0.1794 \\ 7.3111 & -0.1794 & 35.2756\end{bmatrix}, Q_2=\begin{bmatrix}18.0469 & 0.4554 & 6.5921 \\ 0.4554 & 18.5387 & 1.5321 \\ 6.5921 & 1.5321 & 29.5817\end{bmatrix}, Q_3=\begin{bmatrix}3.1722 & 0.0414 & 0.0439 \\ 0.0414 & 3.1751 & -0.4772 \\ 0.0439 & -0.4772 & 3.3921\end{bmatrix},$$

$$R_1=\begin{bmatrix}29.1748 & -1.2044 & 4.2439 \\ -1.2044 & 36.0465 & 1.0496 \\ 4.2439 & 1.0496 & 28.5873\end{bmatrix}, R_2=\begin{bmatrix}5.5993 & -1.0400 & 2.1852 \\ -1.0400 & 7.7781 & 0.8754 \\ 2.1852 & 0.8754 & 6.0608\end{bmatrix}, R_3=\begin{bmatrix}2.4865 & 0.0030 & 0.4955 \\ 0.0030 & 3.8168 & 0.1010 \\ 0.4955 & 0.1010 & 2.3132\end{bmatrix},$$

$$X_{11}=\begin{bmatrix}0.8000 & 0.0285 & 0.6659 \\ 0.0285 & 0.9915 & 0.1126 \\ 0.6659 & 0.1126 & 1.5381\end{bmatrix}, X_{12}=\begin{bmatrix}-0.0727 & 0.0001 & 0.0212 \\ 0.0185 & -0.0661 & 0.0115 \\ -0.0017 & -0.0115 & -0.0624\end{bmatrix}, X_{13}=\begin{bmatrix}-0.2771 & -0.0075 & 0.0185 \\ -0.0060 & -0.2648 & 0.0452 \\ 0.0183 & 0.0442 & -0.2742\end{bmatrix},$$

$$X_{22}=\begin{bmatrix}0.6849 & 0.0034 & 0.4510 \\ 0.0034 & 0.9369 & 0.0604 \\ 0.4510 & 0.0604 & 1.1611\end{bmatrix}, X_{23}=\begin{bmatrix}0.2792 & 0.0078 & -0.0150 \\ 0.0061 & 0.2657 & -0.0449 \\ -0.0141 & -0.0439 & 0.2810\end{bmatrix}, X_{33}=\begin{bmatrix}1.7163 & 0.0378 & -0.0386 \\ 0.0378 & 1.6597 & -0.2699 \\ -0.0386 & -0.2699 & 1.7803\end{bmatrix},$$

$$Y_{11}=\begin{bmatrix}1.4205 & -0.3446 & 0.7114 \\ -0.3446 & 2.1812 & 0.2834 \\ 0.7114 & 0.2834 & 1.5612\end{bmatrix}, Y_{12}=\begin{bmatrix}-0.0661 & 0.0012 & -0.0120 \\ 0.0006 & -0.1028 & -0.0027 \\ -0.0135 & -0.0040 & -0.0611\end{bmatrix}, Y_{13}=\begin{bmatrix}-0.2611 & -0.0108 & -0.0411 \\ -0.0066 & -0.3901 & -0.0081 \\ -0.0392 & -0.0038 & -0.2370\end{bmatrix},$$

$$Y_{22}=\begin{bmatrix}0.0652 & -0.0001 & 0.0134 \\ -0.0001 & 0.0998 & 0.0024 \\ 0.0134 & 0.0024 & 0.0606\end{bmatrix}, Y_{23}=\begin{bmatrix}0.2884 & 0.0016 & 0.0578 \\ 0.0016 & 0.4502 & 0.0133 \\ 0.0578 & 0.0134 & 0.2651\end{bmatrix}, Y_{33}=\begin{bmatrix}1.8715 & 0.0101 & 0.3758 \\ 0.0101 & 2.9252 & 0.0870 \\ 0.3758 & 0.0870 & 1.7202\end{bmatrix},$$

$$U=\begin{bmatrix}34.0247 & -2.1175 & 3.2784 \\ -2.1175 & 51.8903 & 9.0948 \\ 3.2784 & 9.0948 & 33.9774\end{bmatrix}, S=\begin{bmatrix}19.3547 & 0 & 0 \\ 0 & 25.0042 & 0 \\ 0 & 0 & 20.942\end{bmatrix}, \Lambda_1=\begin{bmatrix}25.8591 & 0 & 0 \\ 0 & 36.5520 & 0 \\ 0 & 0 & 27.0943\end{bmatrix},$$

$$\Lambda_2=\begin{bmatrix}1.1653 & 0 & 0 \\ 0 & 1.5273 & 0 \\ 0 & 0 & 1.1798\end{bmatrix}, \varepsilon_1=16.1286, \varepsilon_2=19.0746, \varepsilon_3=23.9381, \varepsilon_4=16.3011.$$

Example 2: In this example, we consider a five-node genetic regulatory network in order to show how to test our theoretical results in detail. In Fig. 1, each ellipse represents a node, and the lines represent regulatory links, in which $\uparrow$ denotes activation. According to the definition of links in Section 2, we can obtain the coupling matrix of this genetic regulatory network as follows

$$\begin{cases}\dot{x}(t)=-(A+\Delta A(t))x(t)+(W+\Delta W(t))f(y(t-h)) \\ \dot{y}(t)=-(C+\Delta C(t))y(t)+(D+\Delta D(t))x(t-\tau),\end{cases} \tag{35}$$

where
$\quad A=diag(3,4,5,4,4), C=diag(5,4,5,4.5,4), D=diag(0.3,0.2,0.4,0.2,0.2),$
$\quad K=diag(0.65,0.65,0.65,0.65,0.65),$

$$W = \begin{bmatrix} 0 & 1 & 1 & 0 & 0 \\ 1 & 0 & 0 & 1 & 1 \\ 0 & 1 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \end{bmatrix}, M_1 = \begin{bmatrix} 0.04 & 0.01 & -0.02 & -0.01 & 0.01 \\ 0.01 & 0.04 & -0.01 & 0.01 & 0.02 \\ -0.02 & -0.01 & 0.03 & 0.01 & 0 \\ -0.01 & 0.01 & 0.01 & 0.04 & 0.01 \\ 0.01 & 0.02 & 0 & 0.01 & 0.04 \end{bmatrix}, M_2 = \begin{bmatrix} 0 & 0.2 & 0.2 & 0 & 0 \\ 0.2 & 0 & 0 & 0.2 & 0.2 \\ 0 & -0.2 & 0 & 0 & 0 \\ 0.2 & 0.2 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0.2 & 0 \end{bmatrix},$$

$$M_3 = \begin{bmatrix} 0.4 & 0.1 & -0.2 & -0.1 & 0.1 \\ 0.1 & 0.4 & -0.1 & 0.1 & 0.2 \\ -0.2 & -0.1 & 0.3 & 0.1 & 0 \\ -0.1 & 0.1 & 0.1 & 0.4 & 0.1 \\ 0.1 & 0.2 & 0 & 0.1 & 0.4 \end{bmatrix}, M_4 = \begin{bmatrix} 0.04 & 0.02 & -0.04 & -0.02 & 0.02 \\ 0.02 & 0.03 & -0.02 & 0.02 & 0.04 \\ -0.04 & -0.02 & 0.06 & 0.02 & 0 \\ -0.02 & 0.02 & 0.02 & 0.02 & 0.02 \\ 0.02 & 0.04 & 0 & 0.02 & 0.02 \end{bmatrix},$$

$N_1 = M_1, N_2 = diag(0.2,0.2,0.2,0.2,0.2), N_3 = M_3, N_4 = M_4, B = 0, F_1(t) = diag(\sin(t), \cos(2t), \cos(t), \cos(t^2), -\sin(t)),$
$F_3(t) = diag(-0.01\sin(t), -0.01\cos(2t), -0.01\cos(t), -0.01\cos(t)/2, -0.01\sin(t)),$

$F_2(t) = F_4(t) = I, f(x) = \dfrac{x^2}{1+x^2},$ that is, the Hill coefficient is 2. It is obvious that the derivative of $f(x)$ is less than 0.65, and assumption (9) is satisfied.

Solution: The MADB $\bar{\tau}$ and $\bar{h}$ that guarantee the system (35) to be asymptotically stable are calculated to be $\bar{\tau} = 2, \bar{h} = 3$ in [13], which is $\bar{\tau} = 4.6665, \bar{h} = 5.5435,$ by using Theorem 2 in this paper. It is seen that our results improve the existing results [13]. In case of $\bar{\tau} = 4.6665, \bar{h} = 5.5435,$ solving Theorem 2 yields the following set of feasible solutions

$$Q_1 = \begin{bmatrix} 1.5001 & -0.0105 & -0.0727 & -0.1414 & -0.0166 \\ -0.0105 & 1.4413 & 0.0094 & -0.0675 & -0.1032 \\ -0.0727 & 0.0094 & 1.5978 & -0.0523 & 0.0062 \\ -0.1414 & -0.0675 & -0.0523 & 1.5754 & 0.0008 \\ -0.0166 & -0.1032 & 0.0062 & 0.0008 & 1.6490 \end{bmatrix}, Q_2 = \begin{bmatrix} 2.2963 & 0.0194 & -0.0933 & -0.1429 & 0.0158 \\ 0.0194 & 2.5388 & -0.0040 & -0.0886 & -0.1183 \\ -0.0933 & -0.0040 & 3.0592 & -0.0633 & 0.0077 \\ -0.1429 & -0.0886 & -0.0633 & 2.6282 & 0.0103 \\ 0.0158 & -0.1183 & 0.0077 & 0.0103 & 2.75437 \end{bmatrix},$$

$$Q_3 = \begin{bmatrix} 0.0737 & -0.0028 & 0.0006 & -0.0037 & -0.0024 \\ -0.0028 & 0.0618 & 0.0005 & 0.0012 & 0.0003 \\ 0.0006 & 0.0005 & 0.0506 & 0.0010 & -0.0001 \\ -0.0037 & 0.0012 & 0.0010 & 0.0654 & -0.0019 \\ -0.0024 & 0.0003 & -0.0001 & -0.0019 & 0.0644 \end{bmatrix}, R_1 = \begin{bmatrix} 1.4703 & 0.0032 & -0.0101 & -0.0075 & 0.0040 \\ 0.0032 & 1.8503 & -0.0039 & 0.0017 & 0.0051 \\ -0.0101 & -0.0039 & 1.4255 & 0.0026 & 0.0005 \\ -0.0075 & 0.0017 & 0.0026 & 1.6924 & 0.0034 \\ 0.0040 & 0.0051 & 0.0005 & 0.0034 & 1.8690 \end{bmatrix},$$

$$R_2 = \begin{bmatrix} 1.2730 & -0.0054 & 0.0076 & 0.0035 & -0.0040 \\ -0.0054 & 1.2607 & 0.0052 & -0.0044 & -0.0099 \\ 0.0076 & 0.0052 & 1.2604 & -0.0045 & 0.0023 \\ 0.0035 & -0.0044 & -0.0045 & 1.2841 & -0.0039 \\ -0.0040 & -0.0099 & 0.0023 & -0.0039 & 1.2627 \end{bmatrix}, R_3 = \begin{bmatrix} 0.0408 & -0.0003 & -0.0001 & -0.0004 & -0.0003 \\ -0.0003 & 0.0693 & -0.0003 & -0.0002 & -0.0004 \\ -0.0001 & -0.0003 & 0.0391 & -0.0001 & 0.0000 \\ -0.0004 & -0.0002 & -0.0001 & 0.0552 & -0.0003 \\ -0.0003 & -0.0004 & 0.0000 & -0.0003 & 0.0706 \end{bmatrix},$$

$$X_{11} = \begin{bmatrix} 0.4503 & 0.0240 & -0.0943 & -0.1173 & 0.0085 \\ 0.0240 & 0.6672 & 0.0085 & -0.1083 & -0.1544 \\ -0.0943 & 0.0085 & 1.2161 & -0.1033 & 0.0128 \\ -0.1173 & -0.1083 & -0.1033 & 0.8161 & 0.0308 \\ 0.0085 & -0.1544 & 0.0128 & 0.0308 & 0.9260 \end{bmatrix}, X_{12} = \begin{bmatrix} -0.0021 & -0.0002 & -0.0004 & 0.0000 & 0.0001 \\ 0.0000 & -0.0016 & -0.0000 & -0.0003 & -0.0005 \\ -0.0001 & -0.0000 & -0.0008 & -0.0001 & 0.0000 \\ -0.0002 & -0.0004 & 0.0000 & -0.0016 & 0.0001 \\ 0.0001 & -0.0001 & 0.0000 & -0.0001 & -0.0015 \end{bmatrix},$$

$$X_{13} = \begin{bmatrix} -0.0053 & 0.0003 & -0.0004 & -0.0003 & 0.0002 \\ 0.0004 & -0.0034 & 0.0000 & -0.0006 & -0.0008 \\ -0.0005 & 0.0000 & -0.0006 & -0.0005 & 0.0001 \\ -0.0005 & -0.0006 & -0.0005 & -0.0028 & 0.0003 \\ 0.0002 & -0.0008 & 0.0001 & 0.0002 & -0.0022 \end{bmatrix}, X_{22} = \begin{bmatrix} 0.2688 & 0.0030 & -0.0137 & -0.0224 & 0.0025 \\ 0.0030 & 0.3164 & 0.0006 & -0.0147 & -0.0199 \\ -0.0137 & 0.0006 & 0.3639 & -0.0108 & 0.0015 \\ -0.0224 & -0.0147 & -0.0108 & 0.3400 & 0.0018 \\ 0.0025 & -0.0199 & 0.0015 & 0.0018 & 0.3514 \end{bmatrix},$$

$$X_{23} = \begin{bmatrix} 0.0063 & -0.0003 & 0.0001 & -0.0002 & -0.0002 \\ -0.0003 & 0.0051 & 0.0000 & 0.0002 & 0.0001 \\ 0.0001 & 0.0000 & 0.0040 & 0.0001 & -0.0000 \\ -0.0002 & 0.0002 & 0.0001 & 0.0052 & -0.0002 \\ -0.0002 & 0.0001 & -0.0000 & -0.0002 & 0.0051 \end{bmatrix}, X_{33} = \begin{bmatrix} 0.0370 & -0.0014 & 0.0003 & -0.0018 & -0.0012 \\ -0.0014 & 0.0309 & 0.0002 & 0.0006 & 0.0001 \\ 0.0003 & 0.0002 & 0.0253 & 0.0005 & -0.0001 \\ -0.0018 & 0.0006 & 0.0005 & 0.0327 & -0.0010 \\ -0.0012 & 0.0001 & -0.0001 & -0.0010 & 0.0322 \end{bmatrix},$$

$$Y_{11} = \begin{bmatrix} 0.9886 & -0.0160 & 0.0217 & 0.0109 & -0.0119 \\ -0.0160 & 0.9543 & 0.0157 & -0.0145 & -0.0311 \\ 0.0217 & 0.0157 & 0.9454 & -0.0137 & 0.0068 \\ 0.0109 & -0.0145 & -0.0137 & 1.0312 & -0.0126 \\ -0.0119 & -0.0311 & 0.0068 & -0.0126 & 0.9606 \end{bmatrix}, Y_{12} = \begin{bmatrix} -0.0010 & -0.0000 & 0.0000 & 0.0000 & -0.0000 \\ 0.0000 & -0.0018 & 0.0000 & -0.0000 & -0.0000 \\ 0.0000 & 0.0000 & -0.0010 & -0.0000 & 0.0000 \\ 0.0000 & -0.0000 & -0.0000 & -0.0014 & -0.0000 \\ 0.0000 & -0.0000 & 0.0000 & -0.0000 & -0.0019 \end{bmatrix},$$

$$Y_{13} = \begin{bmatrix} -0.0013 & -0.0001 & 0.0001 & 0.0001 & -0.0001 \\ -0.0000 & -0.0027 & 0.0001 & -0.0001 & -0.0002 \\ 0.0001 & 0.0001 & -0.0014 & -0.0001 & 0.0001 \\ 0.0001 & -0.0001 & -0.0001 & -0.0017 & -0.0001 \\ -0.0000 & -0.0002 & 0.0000 & -0.0001 & -0.0027 \end{bmatrix}, Y_{22} = \begin{bmatrix} 0.0014 & -0.0000 & -0.0000 & -0.0000 & -0.0000 \\ -0.0000 & 0.0024 & -0.0000 & -0.0000 & -0.0000 \\ -0.0000 & -0.0000 & 0.0013 & -0.0000 & -0.0000 \\ -0.0000 & -0.0000 & -0.0000 & 0.0019 & -0.0000 \\ -0.0000 & -0.0000 & -0.0000 & -0.0000 & 0.0025 \end{bmatrix},$$

$$Y_{23} = \begin{bmatrix} 0.0050 & -0.0001 & -0.0000 & -0.0001 & -0.0000 \\ -0.0001 & 0.0091 & -0.0001 & -0.0000 & -0.0000 \\ -0.0000 & -0.0001 & 0.0048 & 0.0000 & 0.0000 \\ -0.0001 & -0.0000 & 0.0000 & 0.0071 & -0.0000 \\ -0.0000 & -0.0000 & 0.0000 & -0.0000 & 0.0094 \end{bmatrix}, Y_{33} = \begin{bmatrix} 0.0280 & -0.0003 & -0.0002 & -0.0005 & -0.0002 \\ -0.0003 & 0.0507 & -0.0004 & -0.0001 & -0.0003 \\ -0.0002 & -0.0004 & 0.0267 & 0.0000 & 0.0000 \\ -0.0005 & -0.0001 & 0.0000 & 0.0395 & -0.0003 \\ -0.0002 & -0.0003 & 0.0000 & -0.0003 & 0.0522 \end{bmatrix},$$

$$U = \begin{bmatrix} 2.3045 & 0.1737 & -0.0078 & 0.1829 & 0.1802 \\ 0.1737 & 2.4622 & 0.2437 & 0.0002 & -0.0138 \\ -0.0078 & 0.2437 & 2.1719 & 0.0007 & 0.0036 \\ 0.1829 & 0.0002 & 0.0007 & 2.2224 & 0.1711 \\ 0.1802 & -0.0138 & 0.0036 & 0.1711 & 1.9564 \end{bmatrix}, S = \begin{bmatrix} 0.3542 & 0 & 0 & 0 & 0 \\ 0 & 0.4323 & 0 & 0 & 0 \\ 0 & 0 & 0.3523 & 0 & 0 \\ 0 & 0 & 0 & 0.3794 & 0 \\ 0 & 0 & 0 & 0 & 0.4119 \end{bmatrix},$$

$$\Lambda_1 = \begin{bmatrix} 1.9558 & 0 & 0 & 0 & 0 \\ 0 & 2.0052 & 0 & 0 & 0 \\ 0 & 0 & 1.8888 & 0 & 0 \\ 0 & 0 & 0 & 1.9048 & 0 \\ 0 & 0 & 0 & 0 & 1.7987 \end{bmatrix}, \Lambda_2 = \begin{bmatrix} 0.0706 & 0 & 0 & 0 & 0 \\ 0 & 0.0822 & 0 & 0 & 0 \\ 0 & 0 & 0.0699 & 0 & 0 \\ 0 & 0 & 0 & 0.0772 & 0 \\ 0 & 0 & 0 & 0 & 0.087 \end{bmatrix},$$

$\varepsilon_1 = 16.1286, \varepsilon_2 = 19.0746, \varepsilon_3 = 23.9381, \varepsilon_4 = 16.3011.$

Example 3: Consider a genetic regulatory network (7) with the following parameters

$$\begin{cases} \dot{x}(t) = -Ax(t) + Wf(y(t-h)) \\ \dot{y}(t) = -Cy(t) + Dx(t-\tau), \end{cases} \tag{36}$$

where
$A = diag(3,3,3), C = diag(2.5,2.5,2.5), D = diag(0.8,0.8,0.8), K = diag(0.65,0.65,0.65),$

$$W = \begin{bmatrix} 0 & 0 & -2.5 \\ -2.5 & 0 & 0 \\ 0 & -2.5 & 0 \end{bmatrix},$$

$F_2(t) = F_4(t) = I, f(x) = \dfrac{x^2}{1+x^2}$, that is, the Hill coefficient is 2. It is obvious that the derivative of $f(x)$ is less than 0.65, and assumption (9) is satisfied.

Solution: Using Theorem 1, the MADB $\bar{\tau}$ and $\bar{h}$ for the system (36) can be calculated as $\bar{\tau} = 5.5467$ and $\bar{h} = 6.2368$. Applying the criterion in [14], the system (36) is asymptotically stable for $\bar{\tau}$ and $\bar{h}$ that satisfies $\bar{\tau} = 1.2$ and $\bar{h} = 1.7$ respectively. Hence, for this example, the criteria proposed here significantly improve the estimate of the stability limit compared for the result of [14].

5. Conclusions

In this paper, we have worked out some new stability criteria for uncertain genetic networks with time delays by choosing an appropriate Lyapunov functional and employing integral inequality approach. A new stability criterion has been presented to guarantee that genetic regulatory networks are robustly, asymptotically stable, and the stability criterion has been given in terms of linear matrix inequality (LMI). Finally, three numerical examples are presented to illustrate the effectiveness and the less conservativeness of the developed results.

References

1. Angeli D., Sontag ED. Monotone control systems. IEEE Transactions on Automatic Control 2003; 48 (10): 1684-1698.
2. Becskei A., Serrano L. Engineering stability in gene networks by autoregulation. Nature 2000; 405 (6786): 590-593.
3. Bolouri H., Davidson E. Modeling transcriptional regulatory networks, BioEssays 2002;24(12):1118-1129.
4. Boyd S., Ghaoui LE., Feron E., Balakrishnan V. Linear Matrix Inequalities in System and Control Theory, SIAM, PA: Philadelphia, 1994.
5. Chen L., Aihara K. Stability of genetic regulatory networks with time delay. IEEE Transactions on Circuits and Systems-I, Fundamental Theory Application 2002; 49(5): 602-608.
6. Elowitz M., Leibler, S. A synthetic oscillatory network of transcriptional regulators, Nature 2000;403(6767):335-338.
7. Li C., Chen L., Aihara K. Stability of genetic networks with SUM regulatory logic: Lur'e system and LMI approach. IEEE Transactions on Circuits and Systems I-Regular Papers 2006; 53(11): 2451-2458.
8. Li C., Chen L., Aihara K. Stochastic stability of genetic networks with disturbance attenuation. IEEE Transactions on Circuits and Systems II 2007;54 : 892-896.
9. Liu PL. Robust exponential stability for uncertain time-varying delay systems   with delay dependence. Journal of Franklin Institute 2009; 346(10): 958-968.
10. Liu PL. A delay decomposition approach to robust stability analysis of uncertain systems with time-varying delay. ISA Transactions 2012;51(6):694-701.
11. Pfeuty B., Kaneko K. The combination of positive and negative feedback loops confers exquisite flexibility to biochemical switches. Physical Biology 2008; 6(4): 046013.
12. Smolen P., Baxter D., Byrne J. Mathematical modeling of gene networks, Neuron 2000; 26(3):567-580.
13. Wang Z., Liao X. Guo S., Liu G. Stability analysis of genetic regulatory network with time delays and parameter uncertainties. IET Control Theory Applications 2010;4(10): 2018-2028.
14. Wu HX., Liao XF., Feng W., Guo ST., Zhang W. Robust stability for uncertain genetic regulatory networks with interval time-varying delays. Information Sciences 2010;180: 3532-3545.
15. Xu S., Lam J., Ho, DWC. Global robust exponential stability analysis for interval recurrent neural networks. Physics Letters A 2004; 325:124-133.
16. Yuh C., Bolouri H., Davidson E. Genomic cis-regulatory logic: experimental and computational analysis of a sea urchin gene. Science 1998;279(5358):1896-1902.
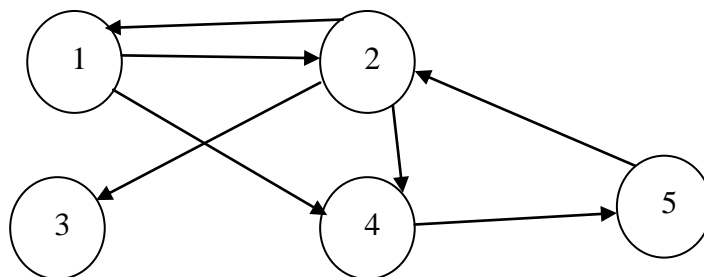
Figure 1 Genetic regulatory network model ($\uparrow$: activation)

具區間時變延遲基因調節網路強健穩定度分析

劉柄麟

建國科技大學自動化暨機電光系統研究所

lpl@ctu.edu.tw

　　本論文主要藉由連續時間的基因調控網路，探討時延系統漸進穩定的相關問題。基因網路是一種描述基因表達水準現象的模型，從實驗資料來構建模型的研究越來越普遍。近幾年來相繼提出了幾種基於基因表達資料構建基因調節網路的方法，其中包括聚類技術、布林型網路、線性非線性模型、貝葉斯網路模型和微分模型方程等。對於每個基因群，我們尋找基因群內的調節樣式。然後由這些調節樣式，我們尋找基因群和基因群之間包含與相反的調節樣式，以推論基因群之間的調節關係，並建立基因群之間的調節網路。實驗結果顯示我們所提出的方法具有效率性與擴充性，可以讓我們從一個全觀的角度去瞭解基因調節網路。通過對模型的標準化分析，找出關鍵節點，以各關鍵節點為中心，對網路劃分，通過計運算元網絡間交互資訊，確定各子網絡邊界，以達到對網路的最佳分解。由於系統具有間隔時變延遲和範數有界參數之不確定性，因此必須利用 Lyapunov- Krasovskii 函數與延遲相依穩定性，再根據線性矩陣不等式的技巧，解決此問題。模擬實例證明提出方法之有效性與適應性。

關鍵字: 基因調控網絡，漸進穩定，延遲相依，線性矩陣不等式。