

# New Global Stability Conditions for Genetic Regulatory Networks with Time-Varying Delays

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**Abstract**—The study of the global stability is essential for designing and controlling genetic regulatory networks. Most existing results on this issue are based on linear matrix inequality (LMI) approach, which results in checking the existence of feasible solutions to high dimensional LMIs. In our previous study, we present several stability conditions for genetic regulatory networks with time-varying delays, based on M-matrix theory and the non-smooth Lyapunov function. In this paper, we design a smooth Lyapunov function and employ M-matrix theory to derive new stability conditions for genetic regulatory networks with time-varying delays. Theoretically, these conditions are less conservative than existing ones in some cases. For genetic regulatory networks with  $n$  genes and  $n$  proteins, these conditions become to check if an  $n \times n$  matrix is an M-matrix, which is much easier than existing results. To illustrate the effectiveness of our theoretical results, two genetic regulatory networks are analyzed.

**Keywords**—global stability, genetic regulatory network, time-varying delay, M-matrix

## I. INTRODUCTION

A genetic regulatory network is a dynamic system to describe interactions among products of genes: mRNAs and proteins. It has been proved that many diseases (such as cancer, diabetes, and AIDS) stem from the malfunctions of genetic regulatory networks of the corresponding cell lines. Therefore, it is indispensable in understanding the properties and functions of various genetic regulatory networks. However, since it is difficult (if not impossible) to fully understand genetic regulatory networks only through biological experiments, it is necessary to address this issue through modeling and analysis methods from the viewpoint of systems theory. Based on the statistic thermodynamics and

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biochemical reaction principles [1, 2], a genetic regulatory network can be model by a group of nonlinear differential

equations [3, 4]. In genetic regulatory networks, mRNAs and proteins may be synthesized at different locations (i.e. nucleus and cytoplasm, respectively), thus transportation or diffusion of mRNAs and proteins between these two locations results in sizeable delays [5-8]. This study is focusing on the global stability of genetic regulatory networks with time-varying delays.

In [5, 6], based on linear matrix inequality (LMI), some sufficient conditions of the global stability are derived for genetic regulatory networks with time-varying delays. To apply these conditions to a genetic regulatory network with  $n$  genes and  $n$  proteins, typically a couple of several  $5n \times 5n$  to  $7n \times 7n$ -dimensional LMIs must be solved. Although LMI can be solved by MatLab, the construction of large size LMIs is very annoying. In [7, 8], we study global stability of genetic regulatory networks with delays, based on M-matrix theory [9, 10]. In [7] we also consider the robust stability to parameter uncertainties. The derived conditions are to check if a  $2n \times 2n$  matrix is an M-matrix. In [8], we reduce the stability conditions to check if an  $n \times n$  matrix is an M-matrix

In [7, 8], the Lyapunov functions are non-smooth for deriving the stability conditions. In this study, we will design a smooth Lyapunov function and derive some new stability conditions for genetic regulatory networks with time-varying delays, based on M-matrix theory. Section II describes genetic regulatory networks with time-varying delays. Some properties of such systems are discussed too. In Section III, we derive sufficient conditions for the global stability of genetic regulatory networks with time-varying delays. We theoretically prove that the newly derived conditions are less conservative and simpler than those in [7]. To illustrate the effectiveness, two genetic regulatory networks are analyzed in Section IV. Section V gives our conclusion of this study.

## II. GENETIC REGULATORY NETWORKS WITH TIME-VARYING DELAYS

Genetic regulatory networks with time-varying delays consisting of  $n$  mRNAs and  $n$  proteins can be described by the following equations:

$$\begin{aligned} \dot{m}_i(t) &= -k_{m_i} m_i(t) + c_i(p(t - \tau_p(t))) \\ \dot{p}_i(t) &= -k_{p_i} p_i(t) + r_i m_i(t - \tau_{m_i}(t)) \end{aligned} \quad (1)$$

for  $i=1,2,\dots,n$ .

where  $m_i(t), p_i(t) \in R_+^n$  represent the concentrations of mRNA  $i$  and protein  $i$ , respectively.  $k_{m_i}$  and  $k_{p_i}$  are positive real numbers that represent the degradation rates of mRNA  $i$  and protein  $i$ , respectively.  $r_i$  is a positive constant representing the rate of translating mRNA  $i$  to protein  $i$ .  $c_i(p(t - \tau_p(t)))$  is a nonlinear function of  $p_1(t - \tau_{p_1}(t)), \dots, p_n(t - \tau_{p_n}(t))$  representing the regulation function of gene  $i$ . Both  $\tau_{m_i}(t)$  and  $\tau_{p_i}(t)$  are positive and piecewise differentiable functions indicating time-varying delays for mRNA  $i$  and protein  $i$ , respectively.

The bottom equation in model (1) describes the translational process. The term  $r_i m_i(t)$  reflects the fact that one kind of protein is translated only from one kind of mRNA molecule. The top equation in model (1) describes the transcriptional process.  $c_i(p(t))$  represents the relative promoter or repressor activity of all possible proteins to gene  $i$  as a function of the concentrations  $p(t)$  of all possible proteins. One gene or mRNA is generally activated or repressed by multiple proteins. In this paper, we take  $c_i(p(t)) = \sum_{j=1}^n c_{ij}(p_j(t))$ , which called the ‘‘SUM’’ logic [5,11].

That is, each transcription factor acts additively to regulate gene  $i$ . The SUM logic is applicable if one gene can be regulated by several proteins independently by binding with different promoters or by a family of similar proteins independently binding to one promoter. In many natural gene networks, this SUM logic does exist [11]. For example, in apoptosis [12] antiapoptotic proteins Bcl-2 and Bcl-x<sub>L</sub> identically and independently repress the activation of procaspase-9 while proapoptotic proteins Bax, Bad and Bik identically and independently repress the activation of Bcl-2 and Bcl-x<sub>L</sub>. The regulation function  $c_{ij}(p_j(t))$  is a function of the Hill form [1, 11] as follows:

$$c_{ij}(p_j(t)) = a_{ij} \frac{1}{1 + (p_j(t)/b_j)^{h_j}}$$

if transcription factor  $j$  is a repressor of gene  $i$ , or

$$c_{ij}(p_j(t)) = a_{ij} \frac{(p_j(t)/b_j)^{h_j}}{1 + (p_j(t)/b_j)^{h_j}}$$

if transcription factor  $j$  is an activator of gene  $i$ , where  $a_{ij}$  and  $b_j$  are nonnegative constants,  $h_j$  is the Hill coefficient representing the degree of cooperativity. In this study, assume that  $h_j \geq 1$ . Note that

$$\frac{1}{1 + (p_j(t)/b_j)^{h_j}} = 1 - \frac{(p_j(t)/b_j)^{h_j}}{1 + (p_j(t)/b_j)^{h_j}}$$

Then system (1) can be rewritten as follows

$$\begin{aligned} \dot{m}_i(t) &= -k_{m_i} m_i(t) + \sum_j^n f_{ij} g_j(p_j(t - \tau_{p_j}(t))) + l_i \\ \dot{p}_i(t) &= -k_{p_i} p_i(t) + r_i m_i(t - \tau_{m_i}(t)) \end{aligned} \quad (2)$$

for  $i=1,2,\dots,n$ .

where  $F = (f_{ij})$  is an  $n \times n$  matrix representing regulatory relationships of the network, which is defined as:  $f_{ij} = 0$  if transcription factor  $j$  does not regulate gene  $i$ ;  $f_{ij} = a_{ij}$  if transcription factor  $j$  activates gene  $i$ ; and  $f_{ij} = -a_{ij}$  if transcription factor  $j$  represses gene  $i$ .  $l_i$  is a constant and is defined as  $l_i = \sum_{j \in R} a_{ij}$ , where  $R$  is the set of repressors of gene  $i$ .

Furthermore, in system (2) function

$$g_j(u) = \frac{(u/b_j)^{h_j}}{1 + (u/b_j)^{h_j}}$$

is a monotonically increasing function in variable  $u$ . Obviously these functions with  $h_j \geq 1$  have the continuous derivatives for  $u \geq 0$ . From calculus, we have

$$\alpha_j = \max_{u \geq 0} g'_j(u) = \frac{(h_j - 1)^{(h_j-1)/h_j} (h_j + 1)^{(h_j+1)/h_j}}{4b_j h_j} > 0 \quad (3)$$

Assume that  $(\bar{m}, \bar{p})$  is an equilibrium state of genetic regulatory network (2). That is, they are satisfied the following equations:

$$0 = -k_{m_i} \bar{m}_i + \sum_j^n f_{ij} g_j(\bar{p}_j) + l_i$$

$$0 = -k_{p_i} \bar{p}_i + r_i \bar{m}_i$$

for  $i=1,2,\dots,n$ .

To shift equilibrium  $(\bar{m}, \bar{p})$  to the origin, let  $x(t) = m(t) - \bar{m}$  and  $y(t) = p(t) - \bar{p}$ , then we have the following equations:

$$\dot{x}_i(t) = -k_{m_i} x_i(t) + \sum_j^n f_{ij} \tilde{g}_j(y_j(t - \tau_{p_j}(t))) \quad (4)$$

$$\dot{y}_i(t) = -k_{p_i} y_i(t) + r_i x_i(t - \tau_{m_i}(t))$$

for  $i=1,2,\dots,n$ .

where  $\tilde{g}_j(y_j(t - \tau_{p_j}(t))) = g_j(y_j(t - \tau_{p_j}(t)) + \bar{p}_j) - g_j(\bar{p}_j)$ . From (3), we have

$$0 \leq \tilde{g}_j(y_j(t - \tau_{p_j}(t))) \leq \alpha_j y_j(t - \tau_{p_j}(t)) \quad (5)$$

Let  $\sup_{t \geq 0} D\tau_{pj}(t) = \sigma_{pj}$  and  $\sup_{t \geq 0} D\tau_{mj}(t) = \sigma_{mj}$ , where  $D$  represents any kind of well-defined (e.g., right, left or ordinary) derivatives. In this paper assume that  $\sigma_{pj} < 1$  and  $\sigma_{mj} < 1$  for  $j=1, 2, \dots, n$ . In addition, inequalities  $0 \leq \sigma_{pj}$  and  $0 \leq \sigma_{mj}$  are true. Actually, if  $\sigma_{pj}$  (or  $\sigma_{mj}$ ) is strictly less than 0,  $\tau_{pj}(t)$  (or  $\tau_{mj}(t)$ ) will be a negative after some time point  $t \geq 0$ , which contradicts with the meaning of time delay. Therefore in this paper we consider that  $0 \leq \sigma_{pj}, \sigma_{mj} < 1$  for  $j=1, 2, \dots, n$ .

### III. GLOBAL STABILITY OF GENETIC REGULATORY NETWORKS WITH TIME-VARYING DELAYS

In this section we will derive some novel sufficient conditions for the global stability of genetic regulatory network (2) or (4) based on M-matrix theory. To this end, define a  $2n \times 2n$  matrix associated with genetic regulatory network (4)

$$L = \begin{bmatrix} K_m^2 & -E^2 \\ -D^2 & K_p^2 \end{bmatrix} \quad (6)$$

where  $K_m^2 = \text{diag}(k_{m1}^2, \dots, k_{mn}^2)$

$$K_p^2 = \text{diag}(k_{p1}^2, \dots, k_{pn}^2)$$

$$D^2 = \text{diag}(d_i) = \text{diag}(r_1^2/(1-\sigma_{m1}), \dots, r_n^2/(1-\sigma_{mn}))$$

$$E^2 = (e_j) = (n_j f_{ij}^2 \alpha_j^2 / (1-\sigma_{pj}))$$

and  $n_i$  is the number of non-zero elements in row  $i$  of matrix  $F$ .

To derive our main results, we need some results about M-matrices. Let  $F_n$  denote the set of all  $n \times n$  real-valued matrices whose off-diagonal entries are non-positive. There are more than 50 equivalent statements for nonsingular M-matrices [9]. In this study, we adopt the following definition.

**Definition 3.1** [9]: A matrix  $A$  in  $F_n$  is a nonsingular M-matrix if there exists a non-negative matrix  $B$  with the maximal eigenvalue  $r$  and a positive number  $c > r$  such that  $A = cI - B$

**Lemma 3.2** [9, 10]: The following five statements are equivalent

- a) a matrix  $A$  in  $F_n$  is a nonsingular M-matrix;
- b)  $A^T$  is in  $F_n$  and is a nonsingular M-matrix;
- c) there exists an  $n$ -dimensional vector  $\gamma > 0$  such that

$$A\gamma > 0$$

where  $\gamma > 0$  means that all components of  $\gamma$  are positive.

- d) all real eigenvalues of  $A$  in  $F_n$  are positive.
- e) the real part of all eigenvalues of  $A$  in  $F_n$  are positive.

In Lemma 3.2, the first three statements are used to derive theorems while the last two statements are used to check if a matrix is an M-matrix.

**Theorem 3.3:** If the matrix  $L$  defined in (6) associated with network (4) is a nonsingular M-matrix, the equilibrium state of

genetic regulatory network (2) is unique and is globally asymptotically stable.

*Proof:* From Lemma 3.2,  $L^T$  is a nonsingular M-matrix if  $L$  is a nonsingular M-matrix, and there exists a  $2n$ -dimensional vector  $\gamma > 0$  such that  $L^T \gamma > 0$ , that is

$$k_{mi}^2 \gamma_i - d_i \gamma_{n+i} > 0, k_{pi}^2 \gamma_{n+i} - \sum_{j=1}^n e_{ji} \gamma_j > 0 \quad (7)$$

for  $i=1, 2, \dots, n$ . Let

$$\delta = \min_{1 \leq i \leq n} \left\{ k_{pi}^2 \gamma_{n+i} - \sum_{j=1}^n e_{ji} \gamma_j, k_{mi}^2 \gamma_i - d_i \gamma_{n+i} \right\}$$

From Equation (7), we have  $\delta > 0$ . In [7,8], the Lyapunov functions adopted contains the absolute functions of  $x(t)$  and  $y(t)$  and thus are not smooth. Differently from [7, 8], in this study we consider the following smooth Lyapunov function:

$$V(x(t), y(t)) = \sum_{i=1}^n [\gamma_i k_{mi} x_i^2(t) + \gamma_{n+i} k_{pi} y_i^2(t)] + \sum_{i=1}^n d_i \gamma_{n+i} \int_{t-\tau_{mi}(t)}^t x_i^2(s) ds + \sum_{i=1}^n \gamma_i \sum_{j=1}^n e_{ij} \int_{t-\tau_{pj}(t)}^t y_j^2(s) ds \quad (8)$$

Calculating derivative of  $V(x(t), y(t))$  defined in Equation (8) with respect to  $t$  along with network (4) yields

$$\begin{aligned} \dot{V}(x(t), y(t)) &= \sum_{i=1}^n [2\gamma_i k_{mi} x_i(t) \dot{x}_i(t) + 2\gamma_{n+i} k_{pi} y_i(t) \dot{y}_i(t)] + \\ &+ \sum_{i=1}^n d_i \gamma_{n+i} [x_i^2(t) - (1 - \dot{\tau}_{mi}(t)) x_i^2(t - \tau_{mi}(t))] \\ &+ \sum_{i=1}^n \gamma_i \sum_{j=1}^n e_{ij} [y_j^2(t) - (1 - \dot{\tau}_{pj}(t)) y_j^2(t - \tau_{pj}(t))] \end{aligned}$$

$$\begin{aligned}
&= \sum_{i=1}^n \left[ -2\gamma_i k_{mi}^2 x_i^2(t) + 2\gamma_i k_{mi} x_i(t) \sum_j^n f_{ij} \tilde{g}_j(y_j(t - \tau_{pj}(t))) \right] \\
&+ \sum_{i=1}^n \left[ -2\gamma_{n+i} k_{pi}^2 y_i^2(t) + 2\gamma_{n+i} k_{pi} r_i y_i(t) x_i(t - \tau_{mi}(t)) \right] \\
&+ \sum_{i=1}^n d_i \gamma_{n+i} [x_i^2(t) - (1 - \dot{\tau}_{mi}(t)) x_i^2(t - \tau_{mi}(t))] \\
&+ \sum_{i=1}^n \gamma_i \sum_{j=1}^n e_{ij} [y_j^2(t) - (1 - \dot{\tau}_{pj}(t)) y_j^2(t - \tau_{pj}(t))] \\
&\leq \sum_{i=1}^n \left[ -\gamma_i k_{mi}^2 x_i^2(t) + \gamma_i n_i \sum_j^n f_{ij}^2 \alpha_j^2 y_j^2(t - \tau_{pj}(t)) \right] \\
&+ \sum_{i=1}^n \left[ -\gamma_{n+i} k_{pi}^2 y_i^2(t) + \gamma_{n+i} r_i^2 x_i^2(t - \tau_{mi}(t)) \right] \\
&+ \sum_{i=1}^n d_i \gamma_{n+i} x_i^2(t) - \sum_{i=1}^n \gamma_{n+i} r_i^2 x_i^2(t - \tau_{mi}(t)) \\
&+ \sum_{i=1}^n \gamma_i \sum_{j=1}^n e_{ij} y_j^2(t) - \sum_{i=1}^n \gamma_i n_i \sum_{j=1}^n f_{ij}^2 \alpha_j^2 y_j^2(t - \tau_{pj}(t)) \\
&= \sum_{i=1}^n \left[ -\gamma_i k_{mi}^2 x_i^2(t) + d_i \gamma_{n+i} x_i^2(t) \right] \\
&+ \sum_{i=1}^n \left[ -\gamma_{n+i} k_{pi}^2 y_i^2(t) + \sum_{i=1}^n \gamma_i \sum_{j=1}^n e_{ij} y_j^2(t) \right] \\
&\leq -\delta \sum_{i=1}^n [x_i^2(t) + y_i^2(t)]
\end{aligned}$$

Therefore, from Lyapunov stability theory [13, 14], genetic regulatory network (2) is globally asymptotically stable. To prove the uniqueness of the equilibrium state of genetic regulatory network, we will use proof-by-contradiction technique. Note that matrix  $L$  associated with genetic regulatory network (2) is independent of the equilibrium state. Therefore, if genetic regulatory network (2) has another equilibrium state, it is also globally asymptotically stable, which is not possible.

Combining Theorem 3.3 above and Lemma 4 in [8], we have the following main result of this study

**Theorem 3.4:** If the  $n \times n$  matrix

$$Ln = K_m^2 K_p^2 - D^2 E^2$$

is a nonsingular M-matrix, the equilibrium state of genetic regulatory network (2) is unique and is globally asymptotically stable.

In [7], we have derived the following global stability condition for system (2).

**Theorem 3.5 [7]:** If the following matrix  $\bar{L}$

$$\bar{L} = \begin{bmatrix} K_m & -|\bar{E}| \\ -\bar{D} & K_p \end{bmatrix} \quad (9)$$

is a nonsingular M-matrix, the equilibrium state of genetic regulatory network (2) is unique and is globally asymptotically stable. Where

$$\begin{aligned}
K_m &= \text{diag}(k_{m1}, \dots, k_{mn}), \\
K_p &= \text{diag}(k_{p1}, \dots, k_{pn}), \\
\bar{D} &= \text{diag}(r_1/(1 - \sigma_{m1}), \dots, r_n/(1 - \sigma_{mn})), \\
\bar{E} &= (\bar{e}_{ij}) = (f_{ij} \alpha_j / (1 - \sigma_{pj}))
\end{aligned}$$

Combining Theorem 3.5 and Lemma 4 in [8], we have

**Theorem 3.6:** If the  $n \times n$  matrix  $\bar{L}n = K_m K_p - \bar{D} |\bar{E}|$  is a nonsingular M-matrix, the equilibrium state of genetic regulatory network (2) is unique and is globally asymptotically stable.

Note that matrix  $\bar{L}$  in (9) is an M-matrix iff there exists a  $2n$ -dimensional vector  $\mu > 0$  such that the following two inequalities is true.

$$k_{mi} \mu_i - \bar{d}_i \mu_{n+i} > 0, \quad k_{pi} \mu_{n+i} - \sum_{j=1}^n |\bar{e}_{ji}| \mu_j > 0 \quad (10)$$

From (10) we can have

$$k_{mi}^2 \mu_i^2 > \bar{d}_i^2 \mu_i^2 = d_i \mu_i^2 / (1 - \sigma_{mi})$$

and

$$k_{pi}^2 \mu_{n+i}^2 > \left( \sum_{j=1}^n |\bar{e}_{ji}| \mu_j \right)^2 \geq \sum_{j=1}^n |\bar{e}_{ji}|^2 \mu_j^2 = \sum_{j=1}^n e_{ji} \mu_j^2 / [(1 - \sigma_{pj}) n_i]$$

From the above, if  $(1 - \sigma_{pj}) n_i \leq 1$ ,  $\mu^2$  is one of the vectors that satisfy (7). Therefore we obtain

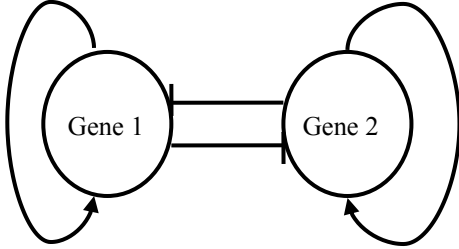
**Corollary 3.7:** If  $\sigma_{pj} \geq 1 - 1/n_i$ , the stability conditions in Theorems 3.3 and 3.4 are less conservative than that in Theorems 3.5 or 3.6.

For genetic regulatory networks with ring structure [15], we have  $n_i = 1$  and thus  $\sigma_{pj} \geq 1 - 1/n_i = 0$  is trivial. Therefore, from Corollary 3.7, the stability conditions in Theorems 3.3 and 3.4 are always less conservative than those in [7] for genetic regulatory networks with ring structure.

#### IV. ILLUSTRATIVE EXAMPLES

To illustrate the effectiveness of the presented theoretical results in previous sections, the globally delay-independent stability of two genetic regulatory networks is analyzed in this section. Comparisons with some existing results [6, 7] are made too.

**Example 1:** We first consider gene toggle switch network shown in Figure 1. In this network, two genes are repressed by each other and activated by their own proteins. Gene toggle switch network has been studied theoretically and experimentally at mRNA level without consideration of self-activation and time-invariant delays [4, 7, 16].



**Figure 1.** Structure of gene toggle switch network (→: activation, —|: repression)

This study considers gene toggle switch network with time-varying delays as follows:

$$\begin{aligned} \dot{m}_1(t) &= -1.5m_1(t) + \frac{p_1(t - \tau_{p1}(t))}{1 + p_1(t - \tau_{p1}(t))} \\ &\quad + \frac{1/4}{1 + 256(p_2(t - \tau_{p2}(t)))^2 / 27} \\ \dot{m}_2(t) &= -1.5m_2(t) + \frac{1}{1 + p_1(t - \tau_{p1}(t))} \\ &\quad + \frac{64(p_2(t - \tau_{p2}(t)))^2 / 27}{1 + 256(p_2(t - \tau_{p2}(t)))^2 / 27} \\ \dot{p}_1(t) &= -2p_1(t) + 0.8m_1(t - \tau_{m1}(t)) \\ \dot{p}_2(t) &= -2p_2(t) + 0.6m_2(t - \tau_{m2}(t)) \end{aligned} \quad (11)$$

where delays  $\tau_{mj}(t) = [\sin(t)+1]/2$  and  $\tau_{pj}(t) = [\cos(t)+1]/2$  for  $j=1, 2$ . Comparing to network (2), for this system we have  $h_1=1$  and  $b_1=1$ ;  $h_2=2$ ,  $b_2 = 3\sqrt{3}/16$ , and

$$\begin{aligned} K_m &= \begin{bmatrix} 1.5 & 0 \\ 0 & 1.5 \end{bmatrix}, K_p = \begin{bmatrix} 2 & 0 \\ 0 & 2 \end{bmatrix} \\ R &= \begin{bmatrix} 0.8 & 0 \\ 0 & 0.6 \end{bmatrix}, F = \begin{bmatrix} 1 & -1/4 \\ -1 & 1/4 \end{bmatrix} \\ \alpha_1 &= 1, \alpha_2 = 2 \end{aligned}$$

From Theorems 3.5 and 3.6, we can figure out

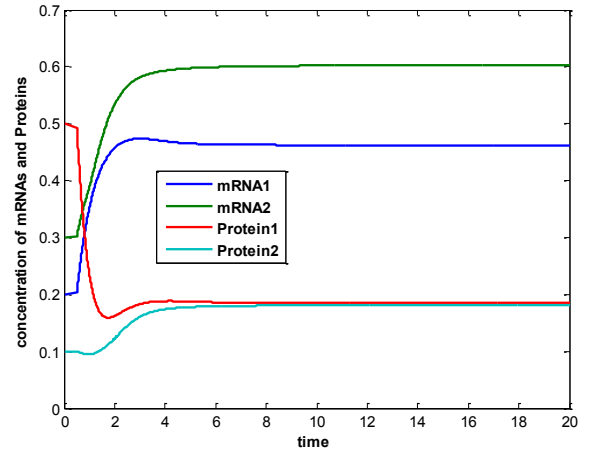
$$\bar{L}n = \begin{bmatrix} -0.2 & -1.2 \\ -3.2 & 1.8 \end{bmatrix}$$

and has the eigenvalues: -1.4 and 3.0, which indicates that  $\bar{L}n$  is not an M-matrix [9,10]. Therefore, Theorem 3.6 and thus theorems in [7] is invalid for this example.

On the other hand, from Theorems 3.3 and 3.4, we can figure out

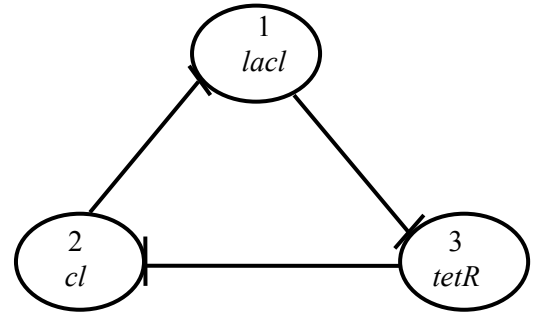
$$Ln = \begin{bmatrix} 3.88 & -0.72 \\ -5.12 & 8.28 \end{bmatrix}$$

and has the eigenvalues: 3.16 and 9.0, which indicates that  $Ln$  is an M-matrix [9,10]. Therefore, according to Theorems 3.4, gene toggle network (11) is globally stable. The trajectory of mRNA and protein concentrations in system (11) is plotted in Figure 4 which indicates that this system is indeed globally stable.



**Figure 2.** Trajectories of mRNA and protein concentrations of system (11) in Example 1

From this example, we can conclude that our newly derived sufficient condition in Theorems 3.3 and 3.4 is less conservative than those in Theorems 3.5 and 3.6 which are from [7].



**Figure 3.** Structure of gene repressilatory network

**Example 2:** The gene repressilatory network consists of three genes and three proteins (lacI, tetR, cl) in a ring topology structure, each repressing the transcription of its downstream partner [3] as shown in Figure 3. This network without time

delays has been studied theoretically and experimentally in [3]. The mathematical model of this gene repressilatory network with time-varying delays is described by the following equations:

$$\begin{aligned} \dot{m}_i(t) &= -am_i(t) + \frac{b}{1 + p_j^h(t - \tau_{pj}(t))} \\ \dot{p}_i(t) &= -c(p_i(t) + dm_i(t - \tau_{mi}(t))) \end{aligned} \quad (12)$$

where  $i = \text{lacI, tetR, cl}; j = \text{cl, lacI, tetR}$ ;  $a, b, c,$  and  $d$  are positive constants.

In this example we consider gene repressilatory network (12) with the values of parameters specified as follows:  $h=2, a=2, b=2.5, c=1,$  and  $d=0.8,$  time delays  $\tau_{mj}(t) = (|\sin(t)|+1)/4$  and  $\tau_{pj}(t) = (|\cos(t)|+1)/8$ . For system (12) with these parameter specifications, we have

$$\begin{aligned} K_m &= \begin{bmatrix} 1.5 & 0 & 0 \\ 0 & 1.5 & 0 \\ 0 & 0 & 1.5 \end{bmatrix}, F = \begin{bmatrix} 0 & 2.5 & 0 \\ 0 & 0 & 2.5 \\ 2.5 & 0 & 0 \end{bmatrix} \\ K_p &= \begin{bmatrix} 1.2 & 0 & 0 \\ 0 & 1.2 & 0 \\ 0 & 0 & 1.2 \end{bmatrix}, R = \begin{bmatrix} 0.8 & 0 & 0 \\ 0 & 0.8 & 0 \\ 0 & 0 & 0.8 \end{bmatrix} \\ \alpha_j &= 3\sqrt{3}/8, \sigma_{pj} = 1/8, \sigma_{mj} = 1/4 \quad \text{for all } j=1,2,3 \end{aligned}$$

and thus matrix  $Ln$  associated with system (12) can be calculated as follows:

$$Ln = \begin{bmatrix} 3.24 & -18/7 & 0 \\ 0 & 3.24 & -18/7 \\ -18/7 & 0 & 3.24 \end{bmatrix}$$

Matrix  $Ln$  has three following eigenvalues:  $4.5257 \pm 2.2269i$  and  $0.6686,$  and thus is a nonsingular M-matrix. From Theorem 3.4, system (12) with this group of parameters is globally stable. The trajectory of protein concentrations in system (15) is plotted in Figure 4 which indicates that this system is indeed globally stable.

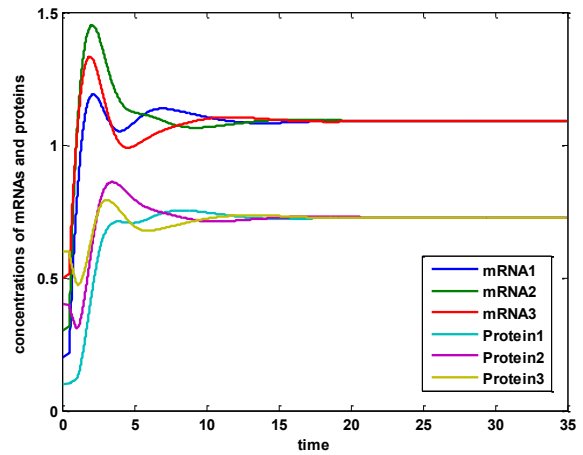


Figure 4. Trajectories of protein concentrations of system (12) with parameters specified in Example 2

On the other hand, matrix  $\bar{L}n$  associated with system (12) can be calculated as follows:

$$\bar{L}n = \begin{bmatrix} 1.8 & -8\sqrt{3}/7 & 0 \\ 0 & 1.8 & -8\sqrt{3}/7 \\ -8\sqrt{3}/7 & 0 & 1.8 \end{bmatrix}$$

Matrix  $\bar{L}n$  has three following eigenvalues:  $2.7897 \pm 1.7143i$  and  $-0.1795,$  and thus is not a nonsingular M-matrix. Therefore, Theorem 3.6 and thus theorems in [7] is invalid for this example.

## V. CONCLUSION

In this paper, we have derived new conditions for global stability of genetic regulatory networks with time-varying delays. The sufficient conditions are developed through M-matrix theory, which are easy to be verified. Differently from our previous study [7], in this study a smooth Lyapunov function is employed, which is the quadratic functional in states of networks. By applying the results in [8], the stability condition derived in this paper is to check if an  $n \times n$  matrix is an M-matrix, which is much easier than the existing results. Theoretically we have proved that the stability condition derived in this paper is less conservative than those in previous studies for some genetic regulatory networks with time-varying delays, especially for those with ring structure [15]. The theories presented in this paper are illustrated by two example genetic regulatory networks. The simulations have shown that the sufficient conditions derived in this study are effective.

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