NEW RESULTS ON ASYMPTOTIC AND ROBUST STABILITY OF GENETIC REGULATORY NETWORKS WITH TIME-VARYING DELAYS

Ruixia Yan¹ and Jinliang Liu^{2,*}

¹Glorious Sun School of Business and Management Donghua University No. 1882, Yan'an West Road, Changning Dist., Shanghai 200051, P. R. China yanruixia@gmail.com

²Department of Applied Mathematics Nanjing University of Finance and Economics No. 3, Wenyuan Road, Yadong Xincheng Dist., Nanjing 210046, P. R. China *Corresponding author: liujinliang@vip.163.com

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ABSTRACT. The robust asymptotic stability problem of genetic regulatory networks with time-varying delays is investigated. Based on a piecewise analysis method, the variation interval of the time delay is firstly divided into two subintervals, and then the convexity property of the matrix inequality and the free weighting matrix method are fully used in this paper. By using a Lyapunov functional approach and linear matrix inequality techniques, the stability criteria for the delayed genetic regulatory networks are expressed as a set of linear matrix inequalities (LMIs), which can lead to much less conservative analysis results. A genetic network example is given to illustrate that the results in this paper are more effective and less conservative than some existing ones.

Keywords: Genetic regulatory networks, Piecewise analysis method, Time-varying delays, Linear matrix inequality (LMI)

1. Introduction. During the past decades, genetic regulatory networks have drawn increasing attention in the biological and biomedical sciences [1, 2], but few results have been carried out in this area [3, 4, 5, 6, 7, 8]. Nowadays, one of the main challenges in systems biology is to understand the genetic regulatory networks, for example, how genes and proteins interact to form a complex network that performs complicated biological functions. Recent mathematical modeling of genetic networks as dynamical system models provides a powerful tool for studying gene regulation processes in living organisms, and genetic network models in literature can be roughly classified into two types, i.e., the Boolean model (or discrete model) and the differential equation model (or continuous model) [9, 10]. In Boolean models, the activity of each gene is functioned in one of two states: ON or OFF, and the state of a gene is interacted by a Boolean function of the states of other related genes. In the differential equation models, the variables describe the concentrations of gene products, such as mRNAs and proteins, as continuous values of the gene regulation systems. Using continuous values, the second approach is viewed more accurate, and being able to provide more detailed understanding and insights of the dynamic behavior demonstrated by biological systems.

Recently, studies on genetic regulatory networks are considerable, and many important results have been obtained in the literature [11, 12, 13, 14]. These results make significant

contribution for discovering higher order structure of an organism and for gaining deep insights into both static and dynamic behaviors of genetic networks by extracting functional information from observation data. Based on the theoretical analysis, several simple genetic networks have been successfully constructed by means of experiments, for example, genetic switches [15], repressilator [16] and a single negative feedback loop network [17]. 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 [10, 16].

This paper aims to investigate the robust stability of the regulatory networks with timevarying delays, and time delays are assumed to belong to the given intervals. Combining the piecewise analysis method in [18, 19] and employing the convexity property of the matrix inequality, sufficient conditions of the asymptotic stability and robust stability are derived in terms of LMIs which are easy to be verified via the LMI toolbox. An example is employed to show the effectiveness and less conservativeness of the proposed method.

2. Model and Preliminaries. In this paper, based on the structure of the genetic regulatory network presented in [20, 21], we consider a functional differential equation model described by

$$\begin{cases} \dot{M}_i(t) = -a_i M_i(t) + W_i(P_1(t), P_2(t), \cdots, P_n(t)) \\ \dot{P}_i(t) = -c_i P_i(t) + d_i M_i(t) \quad (i = 1, 2, \cdots, n) \end{cases}$$
(1)

where $M_i(t), P_i(t) \in R$ denote the concentrations of mRNA and protein of the *i*th node, respectively; $a_i, c_i \in R$ are the degradation rates of the mRNA and protein, respectively; $d_i \in R$ is the translation rate, and the function W_i represents the feedback regulation of the protein on the transcription, which is generally a nonlinear function but has a form of monotonicity with each variable [9, 22, 23]. From (1), for any single gene *i*, there is only one output $P_i(t)$ to other genes, but multiple inputs $P_j(t)$ $(j = 1, 2, \dots, n)$ from other genes. Being a monotonic increasing or decreasing regulatory function, W_i is usually of the Michaelis-Menten or Hill form. In this paper, the function W_i is taken as $W_i(P_1(t), P_2(t), \dots, P_n(t)) = \sum_{j=1}^n W_{ij}(P_j(t))$, which is called SUM logic [24, 25]. That is, each transcription factor acts additively to regulate the *i*th gene, the functional $W_{ij}(P_j(t))$ is generally expressed by a monotonic function of the Hill form [26]. If transcription factor *j* is an activator of gene *i*, then

$$W_{ij}(P_j(t)) = \alpha_{ij} \frac{(P_j(t)/\beta_j)^{H_j}}{1 + (P_j(t)/\beta_j)^{H_j}}$$
(2)

if transcription factor j is repressor of gene i, then

$$W_{ij}(P_j(t)) = \alpha_{ij} \frac{1}{1 + (P_j(t)/\beta_j)^{H_j}} = \alpha_{ij} \left(1 - \frac{(P_j(t)/\beta_j)^{H_j}}{1 + (P_j(t)/\beta_j)^{H_j}} \right)$$
(3)

where H_j is the Hill coefficient, β_j is a positive constant, and α_{ij} is a bounded constant, which is the dimensionless transcriptional rate of transcription factor j to i. Based on (2) and (3), (1) can be rewritten in the following form:

$$\begin{cases} \dot{M}_i(t) = -a_i M_i(t) + \sum_{j=1}^n W_{ij}(P_j(t)) f(P_i(t)) + b_i \\ \dot{P}_i(t) = -c_i P_i(t) + d_i M_i(t) \quad (i = 1, 2, \cdots, n) \end{cases}$$
(4)

where $f(x) = \frac{(x/\beta_j)^{H_j}}{1 + (x/\beta_j)^{H_j}}$ is a monotonically increasing function; $b_i = \sum_{j \in I_i} \alpha_{ij}$, I_i is the set of all the *j* which is a repressor of gene *i*; $W = (W_{ij}) \in \mathbb{R}^{n \times n}$ is the coupling matrix of the genetic network, W_{ij} is defined as follows:

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

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

$$\begin{cases} \dot{M}(t) = -AM(t) + Wf(P(t)) + B\\ \dot{P}(t) = -CP(t) + DM(t) \end{cases}$$
(6)

where

$$M(t) = \begin{bmatrix} M_1(t) \\ M_2(t) \\ \vdots \\ M_n(t) \end{bmatrix}, \quad P(t) = \begin{bmatrix} P_1(t) \\ P_2(t) \\ \vdots \\ P_n(t) \end{bmatrix}, \quad B = \begin{bmatrix} b_1 \\ b_2 \\ \vdots \\ b_n \end{bmatrix}, \quad f(P(t)) = \begin{bmatrix} f_1(P_1(t)) \\ f_2(P_2(t)) \\ \vdots \\ f_n(P_n(t)) \end{bmatrix}, \\ A = diag(a_1, a_2, \cdots, a_n), \quad C = diag(c_1, c_2, \cdots, c_n), \quad D = diag(d_1, d_2, \cdots, d_n).$$

Let M^* and P^* be an equilibrium of (6), that is (M^*, P^*) is the solution of equation

$$\begin{cases} -AM^* + Wf(P^*) + B = 0\\ -CP^* + DM^* = 0 \end{cases}$$
(7)

For convenience, we will always shift an intended equilibrium point (M^*, P^*) of the system (6) to the origin by letting

$$m(t) = M(t) - M^*, \quad p(t) = P(t) - P^*$$

then, we have

$$\begin{cases} \dot{m}(t) = -Am(t) + Wg(p(t))\\ \dot{p}(t) = -Cp(t) + Dm(t) \end{cases}$$
(8)

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

$$0 \le \frac{f(a) - f(b)}{a - b} < k$$

where f(x) is the differentiable, the above inequality is equivalent to $0 \leq \frac{df(a)}{da} \leq k$, from the relationship of $f(\cdot)$ and $g(\cdot)$, we know that $g(\cdot)$ satisfies the sector condition $0 \leq \frac{g(a)}{a} \leq k$, or equivalently

$$g(a)(g(a) - ka) \le 0 \tag{9}$$

Recall that a lur'e system is linear dynamic system, feedback interconnected to a static nonlinearity $f(\cdot)$ that satisfies a sector condition [20]. Hence, the genetic network (8) can be seen as a kind of lur'e system, and can be investigated by using fruitful lur'e system theory. In the following, we consider asymptotically stability of genetic networks with time-varying delays

$$\begin{cases} \dot{m}(t) = -Am(t) + Wg(p(t - \sigma(t))) \\ \dot{p}(t) = -Cp(t) + Dm(t - \tau(t)) \end{cases}$$
(10)

where $\tau(t)$, $\sigma(t)$ are the time-varying delays, which satisfy the following conditions:

$$0 \le \tau_m \le \tau(t) \le \tau_M,\tag{11}$$

$$0 \le \sigma_m \le \sigma(t) \le \sigma_M. \tag{12}$$

To obtain the main results, the following lemmas are needed.

Lemma 2.1. [27] Suppose $\tau_m \leq \tau(t) \leq \tau_M$ and $x(t) \in \mathbb{R}^n$, for any positive matrix $R \in \mathbb{R}^{n \times n}$, $R = \mathbb{R}^T > 0$, then

$$-(\tau_M - \tau_m) \int_{t-\tau_M}^{t-\tau_m} \dot{x}^T(s) R \dot{x}(s) ds \le \begin{bmatrix} x(t-\tau_m) \\ x(t-\tau_M) \end{bmatrix}^T \begin{bmatrix} -R & R \\ R & -R \end{bmatrix} \begin{bmatrix} x(t-\tau_m) \\ x(t-\tau_M) \end{bmatrix}$$
(13)

Lemma 2.2. [28] Suppose $0 \le \tau_m \le \tau(t) \le \tau_M$, Ξ_1 , Ξ_2 and Ω are constant matrices of appropriate dimensions, then

$$(\tau(t) - \tau_m)\Xi_1 + (\tau_M - \tau(t))\Xi_2 + \Omega < 0$$
(14)

if and only if the following inequalities hold

$$(\tau_M - \tau_m)\Xi_1 + \Omega < 0 \tag{15}$$

$$(\tau_M - \tau_m)\Xi_2 + \Omega < 0 \tag{16}$$

3. Asymptotic Stability Condition of Genetic Networks with Time-Varying Delays. In this paper, we divided the variation of the delay into two parts with equal length. Define

$$\tau_1 = \frac{\tau_m + \tau_M}{2}, \quad \delta_1 = \frac{\tau_M - \tau_m}{2}, \quad \sigma_1 = \frac{\sigma_m + \sigma_M}{2}, \quad \delta_2 = \frac{\sigma_M - \sigma_m}{2}$$
(17)

then

$$\tau_1 = \tau_m + \delta_1, \quad \sigma_1 = \sigma_m + \delta_2. \tag{18}$$

Based on (17) and (18), a sufficient condition for delay-dependent asymptotic stability of system (10) is given as follows.

Theorem 3.1. System (10) is asymptotically stable for any $0 \leq \tau_m \leq \tau(t) \leq \tau_M$, $0 \leq \sigma_m \leq \sigma(t) \leq \sigma_M$ and scalar k, if there exist positive definite matrices Q_i , R_i $(i = 1, 2, \dots, 7)$, $\Lambda = diag(\lambda_1, \lambda_2, \dots, \lambda_n) > 0$ and M_i , N_i , T_i , V_i (i = 1, 2, 3, 4) of appropriate dimensions such that the following LMIs hold:

$$\Pi_{1}(i,j) = \begin{bmatrix} \Xi_{11} & * & * & * \\ \Xi_{21} & \Xi_{22} & * & * \\ \Xi_{31}(i) & 0 & -Q_{6} & * \\ 0 & \Xi_{42}(j) & 0 & -R_{6} \end{bmatrix} < 0, \ (i,j=1,2)$$
(19)

$$\Pi_{2}(i,j) = \begin{bmatrix} \Sigma_{11} & * & * & * \\ \Xi_{21} & \Sigma_{22} & * & * \\ \Sigma_{31}(i) & 0 & -Q_{6} & * \\ 0 & \Sigma_{42}(j) & 0 & -R_{7} \end{bmatrix} < 0, \ (i,j=1,2)$$
(20)

$$\Pi_{3}(i,j) = \begin{bmatrix} \Psi_{11} & * & * & * \\ \Xi_{21} & \Psi_{22} & * & * \\ \Psi_{31}(i) & 0 & -Q_{7} & * \\ 0 & \Psi_{42}(j) & 0 & -R_{6} \end{bmatrix} < 0, \ (i,j=1,2)$$
(21)

$$\Pi_4(i,j) = \begin{bmatrix} \Theta_{11} & * & * & * \\ \Xi_{21} & \Theta_{22} & * & * \\ \Theta_{31}(i) & 0 & -Q_7 & * \\ 0 & \Theta_{42}(j) & 0 & -R_7 \end{bmatrix} < 0, \ (i,j=1,2)$$
(22)

where

$$\begin{split} \Psi_{42}(1) &= \left[\sqrt{\delta_2} T_{41}^{31} \quad \sqrt{\delta_2} T_{22}^{3} \quad \sqrt{\delta_2} T_{31}^{3} \quad \sqrt{\delta_2} T_{31}^{3} \quad \sqrt{\delta_2} T_{32}^{3} \quad 0 \right] \\ \Psi_{42}(2) &= \left[\sqrt{\delta_2} V_{31}^{31} \quad \sqrt{\delta_2} V_{32}^{3} \quad \sqrt{\delta_2} V_{31}^{3} \quad \sqrt{\delta_2} V_{32}^{3} \quad 0 \right] \\ \Psi_{22} &= \left[\begin{matrix} T_{1} & * & * & * & * & * & * \\ T_{31}^{1} + V_{31}^{3} \quad T_{10} & * & * & * & * & * & * \\ T_{22} \quad T_{31} - V_{33}^{3} \quad T_{23} \quad T_{23} \quad T_{43} & * & * & * \\ 0 & -T_{33} + V_{33}^{3} \quad T_{33} & -V_{35} \quad T_{23}^{2} & -R_{4} - \frac{R_{2}}{\delta_{2}} & * & * \\ 0 & KA & 0 & 0 & 0 & 0 & T_{10} \right] \\ \\ \Theta_{11} &= \left[\begin{matrix} T_{1} & * & * & * & * & * & * \\ -M_{41}^{1} + N_{41}^{1} \quad T_{24} & * & * & * & * \\ -M_{41}^{1} - -M_{44} + N_{44} + M_{42}^{1} & M_{43}^{1} - T_{33}^{2} & N_{25} & * & * \\ -N_{41}^{1} & -M_{44} + N_{44} + M_{42}^{1} & M_{43}^{1} - T_{33}^{2} & N_{25} & * & * \\ -N_{41}^{1} & -M_{44} + N_{44} - R_{5}^{1} & -R_{2}^{1} - \frac{R_{5}}{\delta_{2}} & * & * & * \\ R_{5} & -T_{43} + V_{43} - R_{5} & -R_{2}^{1} - \frac{R_{5}}{\delta_{3}} & * & * & * \\ R_{5} & -T_{43} + V_{43} - R_{5} & -R_{2}^{1} - \frac{R_{5}}{\delta_{3}} & V_{53} & V_{50}^{2} & * \\ 0 & kA & 0 & 0 & 0 & 0 & T_{10} \\ \\ \Theta_{31}(1) &= \left[\sqrt{\delta_{1}} M_{41}^{1} & \sqrt{\delta_{1}} M_{12}^{1} & \sqrt{\delta_{1}} M_{43}^{1} & \sqrt{\delta_{1}} M_{45}^{1} & \sqrt{\delta_{1}} M_{45}^{1} \\ \Theta_{42}(1) &= \left[\sqrt{\delta_{2}} N_{11}^{1} & \sqrt{\delta_{2}} M_{12}^{2} & \sqrt{\delta_{2}} T_{43}^{2} & \sqrt{\delta_{2}} V_{55}^{2} & 0 \\ \Theta_{42}(2) &= \left[\sqrt{\delta_{2}} V_{11}^{1} & \sqrt{\delta_{2}} M_{12}^{2} & \sqrt{\delta_{2}} V_{35}^{2} & \sqrt{\delta_{2}} V_{45}^{2} & \sqrt{\delta_{2}} V_{55}^{2} \\ \Theta_{42}(1) &= \left[\sqrt{\delta_{2}} N_{11}^{1} & \sqrt{\delta_{2}} M_{12}^{2} & \sqrt{\delta_{2}} V_{35}^{2} & \sqrt{\delta_{2}} V_{45}^{2} & \sqrt{\delta_{2}} V_{55}^{2} \\ \Theta_{42}(2) &= \left[\sqrt{\delta_{2}} V_{11}^{1} & \sqrt{\delta_{2}} M_{12}^{2} & \sqrt{\delta_{2}} V_{35}^{2} & \sqrt{\delta_{2}} V_{45}^{2} & 0 \\ \Theta_{42}(2) &= \left[\sqrt{\delta_{2}} V_{11}^{1} & \sqrt{\delta_{2}} V_{12}^{2} & \sqrt{\delta_{2}} V_{35}^{2} & \sqrt{\delta_{2}} V_{45}^{2} & 0 \\ \Gamma_{1} &= -Q_{1} - M_{12}^{2} + N_{12} + N_{12}^{2} + D^{2} RD \\ T_{1} &= -Q_{1} - M_{12}^{2} + N_{12} + N_{12}^{2} + D^{2} RD \\ T_{1} &= -Q_{1} - M_{12}^{2} + N_{12} + N_{12}^{2} + D^{2} RD \\ T_{1} &= -R_{12} - T_{12}^{2} + V_{12}$$

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$$\begin{split} \Upsilon_{26} &= -Q_3 + M_{44} + M_{44}^T - \frac{Q_6}{\delta_1}, \quad \Upsilon_{27} = -Q_4 - N_{45} - N_{45}^T \\ \Upsilon_{28} &= T_{44} + T_{44}^T - \frac{R_6}{\delta_2} - R_3, \quad \Upsilon_{29} = -R_4 - V_{45} - V_{45}^T \\ Q &= \tau_m^2 Q_5 + \delta_1 Q_6 + \delta_1 Q_7, \quad R = \sigma_m^2 R_5 + \delta_2 R_6 + \delta_2 R_7 \end{split}$$

Proof: Construct a Lyapunov-Krasovskii candidate as:

$$V(t) = V_1(t) + V_2(t) + V_3(t)$$
(23)

where

$$\begin{aligned} V_{1}(t) &= m^{T}(t)Q_{1}m(t) + p^{T}(t)R_{1}p(t) \\ V_{2}(t) &= \int_{t-\tau_{m}}^{t} m^{T}(s)Q_{2}m(s)ds + \int_{t-\tau_{1}}^{t} m^{T}(s)Q_{3}m(s)ds + \int_{t-\tau_{M}}^{t} m^{T}(s)Q_{4}m(s)ds \\ &+ \int_{t-\sigma_{m}}^{t} p^{T}(s)R_{2}p(s)ds + \int_{t-\sigma_{1}}^{t} p^{T}(s)R_{3}p(s)ds + \int_{t-\sigma_{M}}^{t} p^{T}(s)R_{4}p(s)ds \\ V_{3}(t) &= \tau_{m}\int_{t-\tau_{m}}^{t} \int_{s}^{t} \dot{m}^{T}(v)Q_{5}\dot{m}(v)dvds + \int_{t-\tau_{1}}^{t-\tau_{m}} \int_{s}^{t} \dot{m}^{T}(v)Q_{6}\dot{m}(v)dvds \\ &+ \int_{t-\tau_{M}}^{t-\tau_{1}} \int_{s}^{t} \dot{m}^{T}(v)Q_{7}\dot{m}(v)dvds + \sigma_{m}\int_{t-\sigma_{m}}^{t} \int_{s}^{t} \dot{p}^{T}(v)R_{5}\dot{p}(v)dvds \\ &+ \int_{t-\sigma_{1}}^{t-\sigma_{m}} \int_{s}^{t} \dot{p}^{T}(v)R_{6}\dot{p}(v)dvds + \int_{t-\sigma_{M}}^{t-\sigma_{1}} \int_{s}^{t} \dot{p}^{T}(v)R_{7}\dot{p}(v)dvds \end{aligned}$$

Calculating the derivative of V(t) leads to the following equality:

$$\dot{V}(t) = 2m^{T}(t)Q_{1}\dot{m}(t) + 2p^{T}(t)R_{1}\dot{p}(t) + m^{T}(t)(Q_{2} + Q_{3} + Q_{4})m(t) -m^{T}(t - \tau_{m})Q_{2}m(t - \tau_{m}) - m^{T}(t - \tau_{1})Q_{3}m(t - \tau_{1}) - m^{T}(t - \tau_{M})Q_{4}m(t - \tau_{M}) +p^{T}(t)(R_{2} + R_{3} + R_{4})p(t) - p^{T}(t - \sigma_{m})R_{2}p(t - \sigma_{m}) - p^{T}(t - \sigma_{1})R_{3}p(t - \sigma_{1}) -p^{T}(t - \sigma_{M})R_{4}p(t - \sigma_{M}) + \dot{m}^{T}(t)\left(\tau_{m}^{2}Q_{5} + \delta_{1}Q_{6} + \delta_{1}Q_{7}\right)\dot{m}(t) +\dot{p}^{T}(t)\left(\sigma_{m}^{2}R_{5} + \delta_{2}R_{6} + \delta_{2}R_{7}\right)\dot{p}(t) - \tau_{m}\int_{t - \tau_{m}}^{t}\dot{m}^{T}(s)Q_{5}\dot{m}(s)ds -\sigma_{m}\int_{t - \sigma_{m}}^{t}\dot{p}^{T}(s)R_{5}\dot{p}(s)ds - \int_{t - \tau_{1}}^{t - \tau_{m}}\dot{m}^{T}(s)Q_{6}\dot{m}(s)ds - \int_{t - \tau_{M}}^{t - \tau_{1}}\dot{m}^{T}(s)Q_{7}\dot{m}(s)ds -\int_{t - \sigma_{1}}^{t - \sigma_{m}}\dot{p}^{T}(s)R_{6}\dot{p}(s)ds - \int_{t - \sigma_{M}}^{t - \sigma_{1}}\dot{p}^{T}(s)R_{7}\dot{p}(s)ds$$
(24)

Using Lemma 2.1, we can obtain

$$-\tau_m \int_{t-\tau_m}^t \dot{m}^T(s) Q_5 \dot{m}(s) ds \le \begin{bmatrix} m(t) \\ m(t-\tau_m) \end{bmatrix}^T \begin{bmatrix} -Q_5 & Q_5 \\ Q_5 & -Q_5 \end{bmatrix} \begin{bmatrix} m(t) \\ m(t-\tau_m) \end{bmatrix}$$
(25)

$$-\sigma_m \int_{t-\sigma_m}^t \dot{p}^T(s) R_5 \dot{p}(s) ds \le \begin{bmatrix} p(t) \\ p(t-\sigma_m) \end{bmatrix}^T \begin{bmatrix} -R_5 & R_5 \\ R_5 & -R_5 \end{bmatrix} \begin{bmatrix} p(t) \\ p(t-\sigma_m) \end{bmatrix}$$
(26)

Noting the sector condition, for any $\lambda_i > 0$ $(i = 1, 2, \dots, n)$, we have

$$-2\sum_{i=1}^{n} \lambda_{i} g(p_{i}(t-\sigma(t))) \left[g(p_{i}(t-\sigma(t))) - kp_{i}(t-\sigma(t))\right] \ge 0$$
(27)

Rewriting above inequalities into compact matrix form, we obtain

$$-2g^{T}(p(t-\sigma(t)))\Lambda g(p(t-\sigma(t))) + 2kg^{T}(p(t-\sigma(t)))\Lambda p(t-\sigma(t)) \ge 0$$
(28)

where $\Lambda = diag(\lambda_1, \lambda_2, \cdots, \lambda_n) > 0.$

It is noted that, for any $t \in R_+$, $\tau(t) \in [\tau_m, \tau_1]$ or $\tau(t) \in (\tau_1, \tau_M]$; $\sigma(t) \in [\sigma_m, \sigma_1]$ or $\sigma(t) \in (\sigma_1, \sigma_M]$. Define four sets

$$\Omega_1 = \{ t : \tau(t) \in [\tau_m, \tau_1] \}, \quad \Omega_2 = \{ t : \tau(t) \in (\tau_1, \tau_M] \}$$
(29)

$$\Omega_3 = \{t : \sigma(t) \in [\sigma_m, \sigma_1]\}, \quad \Omega_4 = \{t : \sigma(t) \in (\sigma_1, \sigma_M]\}$$
(30)

In the following, we will discuss the variation of $\dot{V}(t)$ for four cases, that is

Case 1:
$$\tau(t) \in \Omega_1, \sigma(t) \in \Omega_3$$
, Case 2: $\tau(t) \in \Omega_1, \sigma(t) \in \Omega_4$
Case 3: $\tau(t) \in \Omega_2, \sigma(t) \in \Omega_3$, Case 4: $\tau(t) \in \Omega_2, \sigma(t) \in \Omega_4$

Case 1. For $\tau(t) \in \Omega_1$, $\sigma(t) \in \Omega_3$. By using Lemma 2.1, we have

$$-\int_{t-\tau_M}^{t-\tau_1} \dot{m}^T(s) Q_7 \dot{m}(s) \le \frac{1}{\delta_1} \begin{bmatrix} m(t-\tau_1) \\ m(t-\tau_M) \end{bmatrix}^T \begin{bmatrix} -Q_7 & Q_7 \\ Q_7 & -Q_7 \end{bmatrix} \begin{bmatrix} m(t-\tau_1) \\ m(t-\tau_M) \end{bmatrix}$$
(31)

$$-\int_{t-\sigma_M}^{t-\sigma_1} \dot{p}^T(s) R_7 \dot{p}(s) \le \frac{1}{\delta_2} \begin{bmatrix} p(t-\sigma_1) \\ p(t-\sigma_M) \end{bmatrix}^T \begin{bmatrix} -R_7 & R_7 \\ R_7 & -R_7 \end{bmatrix} \begin{bmatrix} p(t-\sigma_1) \\ p(t-\sigma_M) \end{bmatrix}$$
(32)

Employing the free matrix method, we have

$$2\xi_1^T(t)M_1\left[m(t-\tau_m) - m(t-\tau(t)) - \int_{t-\tau(t)}^{t-\tau_m} \dot{m}(v)dv\right] = 0$$
(33)

$$2\xi_1^T(t)N_1\left[m(t-\tau(t)) - m(t-\tau_1) - \int_{t-\tau_1}^{t-\tau(t)} \dot{m}(v)dv\right] = 0$$
(34)

$$2\xi_{2}^{T}(t)T_{1}\left[p(t-\sigma_{m})-p(t-\sigma(t))-\int_{t-\sigma(t)}^{t-\sigma_{m}}\dot{p}(v)dv\right]=0$$
(35)

$$2\xi_2^T(t)V_1\left[p(t-\sigma(t)) - p(t-\sigma_1) - \int_{t-\sigma_1}^{t-\sigma(t)} \dot{p}(v)dv\right] = 0$$
(36)

where

$$\begin{split} \xi_1^T(t) &= \begin{bmatrix} m^T(t) & m^T(t-\tau(t)) & m^T(t-\tau_m) & m^T(t-\tau_1) & m^T(t-\tau_M) \end{bmatrix} \\ \xi_2^T(t) &= \begin{bmatrix} p^T(t) & p^T(t-\sigma(t)) & p^T(t-\sigma_m) & p^T(t-\sigma_1) & p^T(t-\sigma_M) \end{bmatrix} \\ M_1^T &= \begin{bmatrix} M_{11}^T & M_{12}^T & M_{13}^T & M_{14}^T & M_{15}^T \end{bmatrix}, \quad N_1^T &= \begin{bmatrix} N_{11}^T & N_{12}^T & N_{13}^T & N_{14}^T & N_{15}^T \end{bmatrix} \\ T_1^T &= \begin{bmatrix} T_{11}^T & T_{12}^T & T_{13}^T & T_{14}^T & T_{15}^T \end{bmatrix}, \quad V_1^T &= \begin{bmatrix} V_{11}^T & V_{12}^T & V_{13}^T & V_{14}^T & V_{15}^T \end{bmatrix} \end{split}$$

Adding (33)-(36) to the right of (24) and using some well-known inequalities, we have

$$\dot{V}(t) \leq \xi^{T}(t) \begin{bmatrix} \Xi_{11} & * \\ \Xi_{21} & \Xi_{22} \end{bmatrix} \xi(t) + (\tau(t) - \tau_{m}) \xi_{1}^{T}(t) M_{1} Q_{6}^{-1} M_{1}^{T} \xi_{1}(t) + (\tau_{1} - \tau(t)) \xi_{1}^{T}(t) N_{1} Q_{6}^{-1} N_{1}^{T} \xi_{1}(t) + (\sigma(t) - \sigma_{m}) \xi_{2}^{T}(t) T_{1} R_{6}^{-1} T_{1}^{T} \xi_{2}(t) + (\sigma_{1} - \sigma(t)) \xi_{2}^{T}(t) V_{1} R_{6}^{-1} V_{1}^{T} \xi_{2}(t)$$
(37)

where $\xi^{T}(t) = [\xi_{1}^{T}(t) \ \xi_{2}^{T}(t) \ g^{T}(p(t - \sigma(t)))].$

Using Lemma 2.2 and Schur complement, it is easy to see that (19) with i, j = 1, 2 can lead $\dot{V}(t) \leq 0$.

The proof of Case 2, Case 3 and Case 4 are similar to that in Case 1, we ommit details here for brevity.

From the above discussion, we can see that for all $t \in R_+$, (19)-(22) with i, j = 1, 2 can lead $\dot{V}(t) \leq 0$. Then, by using the Lyapunov stability theory, we know that the System (10) is asymptotically stable, the proof is completed.

Remark 3.1. To further reduce the conservatism, we can divide the variation of the delay into $k \ (k \ge 3)$ parts with equal length. Defining

$$\tau_i = \tau_m + \frac{i(\tau_M - \tau_m)}{k} \quad (i = 1, 2, \cdots, k)$$
 (38)

$$\sigma_i = \tau_m + \frac{i\left(\sigma_M - \sigma_m\right)}{k} \quad (i = 1, 2, \cdots, k) \tag{39}$$

then $[\tau_m, \tau_M] = [\tau_m, \tau_1] \cup \bigcup_{i=1}^{k-1} (\tau_i, \tau_{i+1}], \ [\sigma_m, \sigma_M] = [\sigma_m, \sigma_1] \cup \bigcup_{i=1}^{k-1} (\sigma_i, \sigma_{i+1}].$

4. Robust Asymptotic Stability Condition of Genetic Networks with Time-Varying Delays. Consider robust stability for stochastic genetic networks with timevarying delays

$$\begin{cases} \dot{m}(t) = -(A + \Delta A(t))m(t) + (W + \Delta W(t))g(P(t - \sigma(t))) \\ \dot{p}(t) = -(C + \Delta C(t))P(t) + (D + \Delta D(t))m(t - \tau(t)) \end{cases}$$
(40)

where the time-varying delay $\tau(t)$, $\sigma(t)$ satisfy (11) and (12). The time-varying uncertain matrices $\Delta A(t)$, $\Delta W(t)$, $\Delta C(t)$ and $\Delta D(t)$ are defined as follows:

$$\triangle A(t) = E_1 F_1(t) T_1, \ \triangle W(t) = E_2 F_2(t) T_2, \ \triangle C(t) = E_3 F_3(t) T_3, \ \triangle D(t) = E_4 F_4(t) T_4(41)$$

where E_1 , E_2 , E_3 , E_4 , T_1 , T_2 , T_3 and T_4 are known constant real matrices with appropriate dimensions, $F_1(t)$, $F_2(t)$, $F_3(t)$ and $F_1(t)$ are unknown time-varying matrices satisfying

$$F_1^T(t)F_1(t) \le I, \ F_2^T(t)F_2(t) \le I, \ F_3^T(t)F_3(t) \le I, \ F_4^T(t)F_4(t) \le I$$
 (42)

Based on (40)-(42), we can get the following theorem:

Theorem 4.1. System (40) is asymptotically robust stable for any $0 \le \tau_m \le \tau(t) \le \tau_M$, $0 \le \sigma_m \le \sigma(t) \le \sigma_M$, if there exist positive definite matrices Q_i , R_i $(i = 1, 2, \dots, 7)$, $\Lambda = diag(\lambda_1, \lambda_2, \dots, \lambda_n) > 0$, M_i , N_i , T_i , V_i (i = 1, 2, 3, 4) and scalars $l_i > 0$ (i = 1, 2, 3, 4) of appropriate dimensions such that the following LMIs hold:

$$\hat{\Pi}_{1}(i,j) = \begin{bmatrix} \Xi_{11} + \Phi_{1} & * & * & * & * \\ \Xi_{21} & \Xi_{22} + \Phi_{2} & * & * & * \\ \Phi_{3} & \Phi_{4} & \Phi_{5} & * & * \\ \Xi_{31}(i) & 0 & 0 & -Q_{6} & * \\ 0 & \Xi_{42}(j) & 0 & 0 & -R_{6} \end{bmatrix} < 0, \ (i,j=1,2)$$
(43)

$$\hat{\Pi}_{2}(i,j) = \begin{bmatrix} \Sigma_{11} + \Phi_{1} & * & * & * & * \\ \Xi_{21} & \Sigma_{22} + \Phi_{2} & * & * & * \\ \Phi_{3} & \Phi_{4} & \Phi_{5} & * & * \\ \Sigma_{31}(i) & 0 & 0 & -Q_{6} & * \\ 0 & & \Sigma_{32}(i) & 0 & 0 & -R_{7} \end{bmatrix} < 0, \ (i,j=1,2)$$
(44)

$$\hat{\Pi}_{3}(i,j) = \begin{bmatrix} 0 & 2_{42}(j) & 0 & 0 & -R_{7} \end{bmatrix} \\ \begin{bmatrix} \Psi_{11} + \Phi_{1} & * & * & * & * \\ \Xi_{21} & \Psi_{22} + \Phi_{2} & * & * & * \\ \Phi_{3} & \Phi_{4} & \Phi_{5} & * & * \\ \Psi_{31}(i) & 0 & 0 & -Q_{7} & * \\ 0 & \Psi_{42}(j) & 0 & 0 & -R_{6} \end{bmatrix} < 0, \ (i,j=1,2)$$
(45)

$$\hat{\Pi}_{4}(i,j) = \begin{bmatrix} \Theta_{11} + \Phi_{1} & * & * & * & * \\ \Xi_{21} & \Theta_{22} + \Phi_{2} & * & * & * \\ \Phi_{3} & \Phi_{4} & \Phi_{5} & * & * \\ \Theta_{31}(i) & 0 & 0 & -Q_{7} & * \\ 0 & \Theta_{42}(j) & 0 & 0 & -R_{7} \end{bmatrix} < 0, \ (i,j=1,2)$$
(46)

where

$$\begin{split} \Phi_{1} &= diag \left(l_{1}T_{1}^{T}T_{1}, l_{2}T_{4}^{T}T_{4}, 0, 0, 0 \right), \ \Phi_{2} &= diag \left(l_{3}T_{3}^{T}T_{3}, 0, 0, 0, 0, l_{4}T_{2}^{T}T_{2} \right) \\ \Phi_{3} &= \begin{bmatrix} -E_{1}^{T}Q_{1} + E_{1}^{T}QA & 0 & 0_{n*3n} \\ 0 & E_{4}^{T}RD & 0_{n*3n} \\ 0 & -E_{3}^{T}RD & 0_{n*3n} \\ E_{2}^{T}Q_{1} - E_{2}^{T}QA & 0 & 0_{n*3n} \end{bmatrix}, \\ \Phi_{4} &= \begin{bmatrix} 0 & 0_{n*4n} & -E_{1}^{T}QW \\ E_{4}^{T}R_{1} - E_{4}^{T}RC & 0_{n*4n} & 0 \\ -E_{3}^{T}R_{1} + E_{3}^{T}RC & 0_{n*4n} & 0 \\ 0 & 0_{n*4n} & E_{2}^{T}QW \end{bmatrix} \\ \Phi_{5} &= \begin{bmatrix} -l_{1}I + E_{1}^{T}QE_{1} & * & * & * \\ 0 & -l_{2}I + E_{4}^{T}RE_{4} & * & * \\ 0 & -E_{3}^{T}RE_{4} & -l_{3}I + E_{3}^{T}RE_{3} & * \\ -E_{2}^{T}QE_{1} & 0 & 0 & -l_{4}I + E_{2}^{T}QE_{2} \end{bmatrix} \end{split}$$

Proof: Take the same Lyapunov functional as that in proof of Theorem 3.1, and replace A, W, C and D by $A + E_1F_1(t)T_1, W + E_2F_2(t)T_2, C + E_3F_3(t)T_3$ and $D + E_4F_4(t)T_4$. Note that

$$l_1 m^T(t) T_1^T T_1 m(t) - l_1 \left[F_1(t) T_1 m(t) \right]^T \left[F_1(t) T_1 m(t) \right] \ge 0$$
(47)

$$l_2 m^T (t - \tau(t)) T_4^T T_4 m(t - \tau(t)) - l_2 \left[F_4(t) T_4 m(t - \tau(t)) \right]^T \left[F_4(t) T_4 m(t - \tau(t)) \right] \ge 0$$
(48)

$$l_{3}p^{T}(t)T_{3}^{T}T_{3}p(t) - l_{3}[F_{3}(t)T_{3}p(t)]^{T}[F_{3}(t)T_{3}p(t)] \ge 0$$

$$l_{4}g^{T}(p(t-\sigma(t)))T_{2}^{T}T_{2}g(p(t-\sigma(t))) - l_{4}[F_{2}(t)T_{2}g(p(t-\sigma(t)))]^{T}[F_{2}(t)T_{2}g(p(t-\sigma(t)))] \ge 0 (50)$$

Using the above inequalities, for Case 1, Case 2, Case 3 and Case 4, by using Lemma 2.2 and Schur complement, it is easy to see that the system (40) is asymptotically robust stable.

5. Example.

Example 5.1. In order to show in detail how to test our theoretical results, we consider a small size genetic network with five nodes in Figure 1, each ellipse represents a gene, and the lines between two genes represent regulatory links, in which the solid line and dashed line denote activation and repression respectively. It is assumed that the dimensionless transcriptional rates are all 0.5. According to the definition of links in Section 2, we can obtain the coupling matrix W of this network as

$$W = 0.5 \times \begin{bmatrix} 0 & -1 & 1 & 0 & 0 \\ -1 & 0 & 0 & 1 & 1 \\ 0 & 1 & 0 & 0 & 0 \\ 1 & -1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \end{bmatrix}$$

We consider the genetic network (Figure 1) with time-varying delays, and take into account the transcriptional time delays, and also shift the equilibrium point to the origin, we have

$$\begin{cases} \dot{m}(t) = -Am(t) + Wg(P(t - \sigma(t)))\\ \dot{p}(t) = -CP(t) + Dm(t - \tau(t)) \end{cases}$$
(51)



FIGURE 1. A genetic network model

where $A = C = I_5$, $D = 0.8I_5$, $f(x) = \frac{x^2}{1+x^2}$, $g(p(t)) = f(p(t) + P^*) - f(P^*)$ and $\sigma(t) = 0.5 + 0.1 \sin(t)$, $\sigma_m = 0.4$, $\sigma_M = 0.6$. It is easy to check k less than 0.65 in the sector condition, the unique equilibrium point of this network

$$M^* = \begin{bmatrix} 0.4320 & 0.5126 & 0.0742 & 0.4816 & 0.0657 \end{bmatrix}^T,$$

$$P^* = \begin{bmatrix} 0.3459 & 0.4109 & 0.0651 & 0.3860 & 0.0553 \end{bmatrix}^T.$$

According to Theorem 3.1, and by using the MATLAB LMI Toolbox, we can easily find feasible solutions of the LMIs (19)-(22), which indicates that the network with timevarying delays is asymptotic stable. Moreover, we can easily obtain Table 1, which lists the maximum allowable bounds for different τ_m . Compared with [21], it is clear that our method produces significantly better results.

$ au_m$	0	0.1	0.4	0.7	1
[21]	3.49	3.59	3.89	4.19	4.49
Theorem 3.1	6.55	6.65	6.95	7.25	7.55

TABLE 1. Maximum allowable τ_M for different τ_m

6. **Conclusion.** In this paper, we have studied the robust asymptotical stability of genetic networks with time-varying delays. To analyze the robust asymptotical stability of the genetic networks system, a piecewise analysis method is used by using the convexity of the matrix function. Based on the free-weighting matrix method and the LMI method, stability conditions have been developed in terms of LMIs. An example with simulation results has been carried out to demonstrate the effectiveness of the proposed method.

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