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Robust stability criteria for uncertain genetic regulatory networks with time-varying delays

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Abstract—This paper presents the robust stability criteria for uncertain genetic regulatory networks with time-varying delays. One key point of the criterion is that the decomposition of the matrix $\tilde{D}$ into $\tilde{D} = \tilde{D}_1 + \tilde{D}_2$. This decomposition corresponds to a decomposition of the delayed terms into two groups: the stabilizing ones and the destabilizing ones. This technique enables one to take the stabilizing effect of part of the delayed terms into account. Meanwhile, by choosing an appropriate new Lyapunov functional, a new delay-dependent stability criteria is obtained and formulated in terms of linear matrix inequalities (LMIs). Finally, numerical examples are presented to illustrate the effectiveness of the theoretical results.

Keywords—Genetic regulatory network; Time-varying delay; Uncertain system; Lyapunov-Krasovskii functional

I. Introduction

GENETIC networks are biochemically dynamical systems, which are attracting more and more attention from biology, engineering and other research fields. Genetic regulatory networks (GRNs) are the mechanisms which have evolved to regulate the expression of genes, and the expression of a gene is regulated by its production. They have become an very important research area in the biological and biomedical sciences [1], [2], [3], [4], [5], [6], [7], [8].

Recently, the mathematical models are useful for studying the mechanisms of organisms and the behavior of gene networks from the data observed. Generally, there are two types of genetic regulatory network models: the Boolean model [1], [2], [3], [4] and the differential equation model [5], [6], [7], [8]. In Boolean models, the activity of each gene is expressed in one of two states: ON or OFF, and the state of a gene is described by a Boolean function of states of other related genes. On the other hand, the concentration of gene products are determined by variables, such as mRNAs, proteins and continuous values of the gene regulation systems in the differential equation model. In practical biological model, gene expression rates are usually continuous variables rather than ideal ON-OFF switches. Several typical GRNs have been modelled and studied, both in theories and in experiments (see [8], [9], [10]).

Due to the completion of the transcription and translation of DNA, mRNA, and the diffusion to a certain place of a protein need time, time delay is a common occurrence in modeling gene regulation processes (see [11], [12]). Therefore, mathematical models without addressing time delays may even provide the wrong predictions of the mRNA and protein concentrations. Furthermore, the gene regulation process is always subject to intrinsic noise which is due to the random births and deaths of individual molecules, and extrinsic noise which is derived from environment. Meanwhile, because of the use of an approximate system model for the purpose of simplifying models, the uncertainties are inevitable. This means that one has to investigate the robust stability of uncertain systems [13], [14], [20], [21], [22].

In the paper, we consider the stability problem of the uncertain genetic regulatory networks based on a descriptor model transformation and the decomposition technique of discrete delay term matrix which have been introduced for stability analysis of delayed systems. We construct a differential equation model for the uncertain gene regulation networks with time-varying delays. By choosing an appropriate new Lyapunov functional and employing control theory analysis methods, some less conservative delay-derivative-dependent stability criteria have been derived in LMIs forms, which can be easily checked in practice. Finally, two examples are also given to demonstrate the effectiveness and advantages of our analysis.

II. Problem formulation and some Preliminaries

Based on the structure of the genetic regulatory network , a single gene auto-regulatory genetic network with time delays containing n mRNAs and n proteins was considered by the following equations [15]:

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

where $m_i(t), p_i(t)$ are concentrations of mRNA and protein of the ith node at time t, respectively. a_i and c_i are the degradation rates of the mRNA and protein, d_i is the translation rate, and $b_i(\cdot)$ is the regulatory function of the ith gene, which is generally a nonlinear function of variables $(p_1(t), p_2(t), \cdots, p_n(t))$, but has a form of monotonicity with each variable, $\tau(t)$ and $\sigma(t)$ are the time-varying delays.

In this network, gene regulation function $b_i(\cdot)$ plays an important role in the dynamics. Typical regulatory logics include AND-like gates and OR-like gates [16], [17], [18] for $b_i(\cdot)$. Here, we focus on a model of genetic networks where each transcription factor acts additively to regulate the ith gene. The regulatory function is of the form

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$b_i(p_1(t), p_2(t), \cdots, p_n(t)) = \sum_{j=1}^{n} b_{ij}(p_j(t))$, which is called SUM logic [19], [23]. The function $b_{ij}(p_j(t))$ is a monotonic function of the Hill form, and if transcription factor j is an activator of gene i, $b_{ij}(p_j(t)) = \alpha_{ij}\frac{(p_j(t)/\beta_j)^{H_j}}{1+(p_j(t)/\beta_j)^{H_j}}$; if transcription factor j is a repressor of gene i, $b_{ij}(p_j(t)) = \alpha_{ij}\frac{1}{1+(p_j(t)/\beta_j)^{H_j}}$. where $H_j (j = 1, 2, \cdots, n)$ is the Hill coefficient, β_j is a positive constant, α_{ij} is the dimensionless transcriptional rate of transcription factor j to gene i, which is a bounded constant. Therefore, (1) can be rewritten as:

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

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

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

In compact matrix form, system (2) can be rewritten as

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

where $m(t) = [m_1(t),\ m_2(t),\ \cdots,\ m_n(t)]^T$,
$p(t) = [p_1(t),\ p_2(t),\ \cdots,\ p_n(t)]^T$,
$h(p(t)) = [h_1(p_1(t)),\ h_2(p_2(t)),\ \cdots,\ h_n(p_n(t))]^T$,
A =diag$(a_1, a_2, \cdots, a_n)$, $u = (u_1, u_2, \cdots, u_n)^T$,
C=diag$(c_1, c_2, \cdots, c_n)$, D =diag$(d_1, d_2, \cdots, d_n)$,
It should be noted that the definition of $h(\cdot)$ guarantee the existence of an equilibrium for system (3). Let $[(m^*)^T, (p^*)^T]^T$ be an equilibrium point of the system (3), and we always shift the intended equilibrium point to the origin by letting $\tilde{m}(t) = m(t) - m^*, \tilde{p}(t) = p(t) - p^*$. Thus, we have

$$\begin{cases} \dot{\tilde{m}}(t) = -A\tilde{m}(t) + W\tilde{h}(\tilde{p}(t-\sigma(t))) \\ \dot{\tilde{p}}(t) = -C\tilde{p}(t) + D\tilde{m}(t-\tau(t)) \end{cases} \tag{4}$$

where $\tilde{m}(t) = [\tilde{m}_1(t),\ \tilde{m}_2(t),\ \cdots,\ \tilde{m}_n(t)]^T$,
$\tilde{p}(t) = [\tilde{p}_1(t),\ \tilde{p}_2(t),\ \cdots,\ \tilde{p}_n(t)]^T$,
$\tilde{h}(\tilde{p}(t)) = [\tilde{h}_1(\tilde{p}_1(t)),\ \tilde{h}_2(\tilde{p}_2(t)),\ \cdots,\ \tilde{h}_n(\tilde{p}_n(t))]^T$, with $\tilde{h}_j(\tilde{p}_j(t)) = h_j(\tilde{p}_j(t) + p_j^*) - h_j(P_j^*)$.
Let $x(t) = [\tilde{m}^T(t), \tilde{p}^T(t)]^T$,the system (4) is equivalent to:

$$\dot{x}(t) = -\tilde{A}x(t) + \tilde{D}x(t-\tau(t)) + \tilde{W}f(x(t-\sigma(t))) \tag{5}$$

where $\tilde{A} = \left[\begin{smallmatrix} A & 0 \\ 0 & C \end{smallmatrix}\right]$, $\tilde{D} = \left[\begin{smallmatrix} 0 & 0 \\ D & 0 \end{smallmatrix}\right]$, $\tilde{W} = \left[\begin{smallmatrix} 0 & W \\ 0 & 0 \end{smallmatrix}\right]$, $f(x(t)) = \left[\begin{smallmatrix} \tilde{h}(\tilde{m}(t)) \\ \tilde{h}(\tilde{p}(t)) \end{smallmatrix}\right]$ $with$ $\tilde{h}(\tilde{m}(t)) = 0$.

Due to the modeling inaccuracies and changes in the environment, the parametric uncertainties may enters into GRN (5), the uncertain GRN can be formulated as follows:

$$\begin{aligned} \dot{x}(t) = &-(\tilde{A} + \Delta\tilde{A})x(t) + (\tilde{D} + \Delta\tilde{D})x(t-\tau(t)) \\ &+ (\tilde{W} + \Delta\tilde{W})f(x(t-\sigma(t))) \end{aligned} \tag{6}$$

where $\Delta\tilde{A} = \left[\begin{smallmatrix} \Delta A & 0 \\ 0 & \Delta C \end{smallmatrix}\right]$, $\Delta\tilde{D} = \left[\begin{smallmatrix} 0 & 0 \\ \Delta D & 0 \end{smallmatrix}\right]$, $\Delta\tilde{W} = \left[\begin{smallmatrix} 0 & \Delta W \\ 0 & 0 \end{smallmatrix}\right]$.

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

Assumption.1 The parametric uncertainties $\Delta A, \Delta W, \Delta C, \Delta D$ satisfy: $[\Delta A, \Delta W, \Delta C, \Delta D] = \bar{E}\tilde{F}(t)[H_a, H_w, H_c, H_d]$, where $\bar{E}, H_a, H_w, H_c$ and H_d are some given constant matrices with appropriate dimensions, and $\tilde{F}(t)$ satisfies : $\tilde{F}^T(t)\tilde{F}(t) \leq I$, for any $t \geq 0$. And let $[\Delta\tilde{A}, \Delta\tilde{W}, \Delta\tilde{D}] = \tilde{E}F(t)[\tilde{H}_a, \tilde{H}_w, \tilde{H}_d]$, where $\tilde{E} = \left[\begin{smallmatrix} \bar{E} & 0 \\ 0 & \bar{E} \end{smallmatrix}\right]$, $F(t) = \left[\begin{smallmatrix} \tilde{F}(t) & 0 \\ 0 & \tilde{F}(t) \end{smallmatrix}\right]$, $\tilde{H}_a = \left[\begin{smallmatrix} H_a & 0 \\ 0 & H_c \end{smallmatrix}\right]$, $\tilde{H}_w = \left[\begin{smallmatrix} 0 & H_w \\ 0 & 0 \end{smallmatrix}\right]$, $\tilde{H}_d = \left[\begin{smallmatrix} 0 & 0 \\ H_d & 0 \end{smallmatrix}\right]$.

Assumption.2 $\tau(t)$ and $\sigma(t)$ are the time-varying delays satisfying: $0 \leq \tau(t) \leq \tau_2$, $\dot{\tau}(t) \leq \tau_d < \infty$; $0 \leq \sigma(t) \leq \sigma_2$, $\dot{\sigma}(t) \leq \sigma_d < \infty$.

Assumption.3 Since h_j is a monotonically increasing function with saturation, and from the relationship of $f(\cdot)$ and $h(\cdot)$, we know that $f(\cdot)$ satisfies the sector condition: $l_j^- \leq \frac{f_j(x_j)}{x_j} \leq l_j^+$, for $j = 1, 2, \cdots, n$. which implies that $\frac{f_j(x_j) - l_j^- x_j}{x_j} \geq 0$, $\frac{l_j^+ x_j - f_j(x_j)}{x_j} \geq 0$, where l_j^- and l_j^+ are some constants. Let L_0=diag$(l_1^-, l_2^-, \cdots, l_n^-)$, L_1=diag$(l_1^+, l_2^+, \cdots, l_n^+)$.

Remark 1 It should be noted that the activation functions in [19],[24] need to satisfy the following condition: $0 \leq f_j(x)/x \leq k_j^*$, for $j = 1, 2, \cdots, n$. which is equivalent to $f_j(x)(f_j(x) - k_j^* x) \leq 0$. It is easy to see that the assumption 3 endows with less restriction than monotonically increasing condition in [19],[24], the constants l_j^- and l_j^+ are allowed to be positive, negative,or zero. Obviously, the class of functions satisfying the assumption 3 is larger than the class of functions satisfying the condition in [19],[24]. Hence, our results will be less restrictive than those given in the literature.

Lemma 1. For any $x, y \in \mathbf{R}^n$ and a positive scalar ε,then we have

$$2x^T y \leq \varepsilon x^T x + \varepsilon^{-1} y^T y.$$

Lemma 2. (Schur complement). Given constant symmetric matrices S_1, S_2 and S_3,where $S_1 = S_1^T$, and $S_2 = S_2^T > 0$,then $S_1 + S_3^T S_2^{-1} S_3 < 0$ if and only if :

$$\begin{bmatrix} S_1 & S_3^T \\ S_3 & -S_2 \end{bmatrix} < 0, \text{ or } \begin{bmatrix} -S_2 & S_3 \\ S_3^T & S_1 \end{bmatrix} < 0.$$

Lemma 3.[25] For any positive definite matrix $M \in R^{n\times n}$, a scalar $\rho > 0$, vector function $w : [0, \rho] \mapsto R^n$ such that the integrations concerned are well defined, the following inequality holds:

$$[\int_0^\rho w(s)ds]^T M[\int_0^\rho w(s)\mathrm{d}s] \leq \rho \int_0^\rho w^T(s) M w(s)\mathrm{d}s$$

Lemma 4.(Lower bounds theorem [26]) Let $f_1, f_2, \cdots, f_N : R^m \mapsto R$ have positive values in an open subset D of R^m. Then, the reciprocally convex combination of f_i over D satisfies

$$\min_{\{\alpha_i | \alpha_i > 0, \sum_i \alpha_i = 1\}} \sum_i \frac{1}{\alpha_i} f_i(t) = \sum_i f_i(t) + \max_{g_{i,j}(t)} \sum_{i\neq j} g_{i,j}(t)$$

subject to

$$\left\{ g_{i,j} : R^m \mapsto R, g_{j,i}(t) = g_{i,j}(t), \begin{bmatrix} f_i(t) & g_{i,j}(t) \\ g_{i,j}(t) & f_j(t) \end{bmatrix} \geq 0 \right\}$$

Remark 2 To handle the integral terms, the Jensen inequality lemma [25] has been generally adopted. However, from the application to delayed systems in [26], we can see that the Lower bounds theorem which is based on the integral inequality lemma but with the less number of decision variables, comparable to those based on the Jensen inequality lemma.

III. Robust stability criteria for genetic regulatory networks

In this section, several theorems and corollaries are presented for the genetic regulatory networks with time-varying delays.

In order to derive discrete delay-dependent stability conditions, which include the information of time delay $\tau(t)$, we usually uses the fact: $x(t-\tau(t)) = x(t) - \int_{t-\tau(t)}^{t} \dot{x}(s)\mathrm{d}s$ to transform the system (6) into the following system with a distributed delay:

$$\begin{aligned}\dot{x}(t) =& -(\tilde{A}+\Delta\tilde{A}-\tilde{D}_1)x(t)+(\tilde{D}_2+\Delta\tilde{D})x(t-\tau(t))\\ &+(\tilde{W}+\Delta\tilde{W})f(x(t-\sigma(t)))-\tilde{D}_1\int_{t-\tau(t)}^{t}\dot{x}(s)\mathrm{d}s\end{aligned} \tag{7}$$

where $\tilde{D}=\tilde{D}_1+\tilde{D}_2$, $\tilde{D}_1, \tilde{D}_2$ are constant parameter matrix which make the stability result less restrictive to some degree. Such process is generically called a parameterized first-order model transformation [26] since only one-integration over one delay interval is used herein.

Firstly, a asymptotic stability result is developed for GRNs (7) with $\Delta\tilde{A}=\Delta\tilde{D}=\Delta\tilde{W}=0$, that is:

$$\begin{aligned}\dot{x}(t) =& -(\tilde{A}-\tilde{D}_1)x(t)+\tilde{D}_2x(t-\tau(t))\\ &+\tilde{W}f(x(t-\sigma(t)))-\tilde{D}_1\int_{t-\tau(t)}^{t}\dot{x}(s)\mathrm{d}s\end{aligned} \tag{8}$$

Theorem 1 For given constants τ_2, τ_d, σ_d, the system (8) is asymptotically stable, if there exist matrices $P_1>0$, $Q_i>0$, $i=1,2$; $R_i>0$, $i=1,2$; $\left[\begin{smallmatrix} R_1 & E_1 \\ * & R_2\end{smallmatrix}\right]\geq 0$, $\left[\begin{smallmatrix} Q_2 & \tilde{Q}_2 \\ * & Q_2\end{smallmatrix}\right]\geq 0$, $\Lambda_i = diag(\lambda_{1i},\lambda_{2i},\cdots,\lambda_{ni})>0$, $i=1,2$; $T_i = diag\,(t_{1i},t_{2i},\cdots,t_{ni})>0$, $i=1,2$; P_2, P_3, L_0, L_1, $\tilde{Q}_2$, J_1, J_2, J_3 and E_1 with appropriate dimensions respectively satisfying:

$$\Phi_1=\Phi_{11}+\Phi_{12}+\Phi_{12}^T<0 \tag{9}$$

where

$$\begin{aligned}\Phi_{11} =& -W_x^T(L_1T_1L_0+L_0T_1L_1-Q_1-R_1)W_x-W_y^T(P_2\\ &+P_2^T-\tau_2^2Q_2)W_y-W_f^T(2T_1-R_2)W_f-W_{x\tau}^T((1-\\ &\tau_d)Q_1)W_{x\tau}-W_{x\sigma}^T((1-\sigma_d)R_1+L_1T_2L_0+L_0T_2L_1)\\ &W_{x\sigma}-W_{f\sigma}^T((1-\sigma_d)R_2+2T_1)W_{f\sigma}-W_{s1}^TQ_2W_{s1}\\ &-W_{s2}^TQ_2W_{s2}\end{aligned} \tag{10}$$

$$\begin{aligned}\Phi_{12} =& W_x^T(P_1-P_3^T)W_y+W_x^T(P_3^T+L_1\Lambda_2-L_0\Lambda_1)W_{xy}\\ &+W_y^TP_2^TW_{xy}+W_f^T(\Lambda_1-\Lambda_2)W_{xy}+W_x^T(E_1+\\ &L_0T_1+L_1T_1)W_f+W_x^TJ_1W_{xs}+W_{x\tau}^TJ_2W_{xs}+W_s^T\\ &J_3W_{xs}+W_{x\sigma}^T(-(1-\sigma_d)E_1+L_0T_2+L_1T_2)W_{f\sigma}\\ &-W_{s1}^T\tilde{Q}_2W_{s2}\end{aligned} \tag{11}$$

with

$W_x=\begin{bmatrix}I_n & O_{n,7n}\end{bmatrix}$, $W_y=\begin{bmatrix}O_{n,n} & I_n & O_{n,6n}\end{bmatrix}$,
$W_f=\begin{bmatrix}O_{n,2n} & I_n & O_{n,5n}\end{bmatrix}$, $W_{x\tau}=\begin{bmatrix}O_{n,3n} & I_n & O_{n,4n}\end{bmatrix}$,
$W_{x\sigma}=\begin{bmatrix}O_{n,4n} & I_n & O_{n,3n}\end{bmatrix}$, $W_{f\sigma}=\begin{bmatrix}O_{n,5n} & I_n & O_{n,2n}\end{bmatrix}$,
$W_{s1}=\begin{bmatrix}O_{n,6n} & I_n & O_{n,n}\end{bmatrix}$, $W_{s2}=\begin{bmatrix}O_{n,7n} & I_n\end{bmatrix}$,
$W_{xs}=\begin{bmatrix}I_n & O_{n,2n} & -I_n & O_{n,2n} & -I_n & O_{n,n}\end{bmatrix}$,
$W_{xy}=\begin{bmatrix}-(\tilde{A}-\tilde{D}_1) & O_{n,2n} & \tilde{D}_2 & O_{n,n} & \tilde{W} & -\tilde{D}_1 & O_{n,n}\end{bmatrix}$.

Proof. Following [27], we represent (8) in the following equivalent descriptor system form:

$$\begin{cases}\dot{x}(t)=y(t),\\ y(t)=-(\tilde{A}-\tilde{D}_1)x(t)+\tilde{D}_2x(t-\tau(t))\\ \qquad +\tilde{W}f(x(t-\sigma(t)))-\tilde{D}_1\int_{t-\tau(t)}^{t}y(s)\mathrm{d}s\end{cases} \tag{12}$$

Then, take the following Lyapunov-Krasovskii functional for system (12):
$V(t)=V_1(t)+V_2(t)+V_3(t)+V_4(t)+V_5(t)$
where

$$\begin{aligned}V_1(t) =& x^T(t)P_1x(t)\\ =& \begin{bmatrix}x^T(t) & y^T(t)\end{bmatrix}\begin{bmatrix}I & 0\\ 0 & 0\end{bmatrix}\begin{bmatrix}P_1 & 0\\ P_3 & P_2\end{bmatrix}\begin{bmatrix}x(t)\\ y(t)\end{bmatrix}\\ V_2(t) =& 2\sum_{i=1}^{n}\lambda_{i1}\int_0^{x_i}(f_i(s)-l_i^-s)\,\mathrm{d}s\\ &+2\sum_{i=1}^{n}\lambda_{i2}\int_0^{x_i}(l_i^+s-f_i(s))\,\mathrm{d}s\\ V_3(t) =& \int_{t-\tau(t)}^{t}x^T(s)Q_1x(s)\mathrm{d}s+\int_{t-\sigma(t)}^{t}\begin{bmatrix}x(s)\\ f(x(s))\end{bmatrix}^T\\ &\times\begin{bmatrix}R_1 & E_1\\ * & R_2\end{bmatrix}\begin{bmatrix}x(s)\\ f(x(s))\end{bmatrix}\mathrm{d}s\\ V_4(t) =& \tau_2\int_{-\tau_2}^{0}\int_{t+\theta}^{t}y^T(s)Q_2y(s)\mathrm{d}s\mathrm{d}\theta\end{aligned}$$

Let $\xi^T(t)=[x^T(t)\ y^T(t)\ f^T(x(t))\ x^T(t-\tau(t))\ x^T(t-\sigma(t))\ f^T(x(t-\sigma(t)))\ (\int_{t-\tau(t)}^{t}y(s)ds)^T\ (\int_{t-\tau_2}^{t-\tau(t)}y(s)ds)^T\ ]$
Taking the derivative of V (t) along the trajectories of system (12) yields
$\dot{V}(t)=\dot{V}_1(t)+\dot{V}_2(t)+\dot{V}_3(t)+\dot{V}_4(t)+\dot{V}_5(t)$.
while

$$\begin{aligned}\dot{V}_1(t) =& 2\begin{bmatrix}x^T(t) & y^T(t)\end{bmatrix}\begin{bmatrix}P_1 & P_3^T\\ 0 & P_2^T\end{bmatrix}\begin{bmatrix}\dot{x}(t)\\ 0\end{bmatrix}\\ =& 2\begin{bmatrix}x^T(t) & y^T(t)\end{bmatrix}\begin{bmatrix}P_1 & P_3^T\\ 0 & P_2^T\end{bmatrix}\\ &\times\begin{bmatrix}y(t)\\ -y(t)-(\tilde{A}-\tilde{D}_1)x(t)+\tilde{D}_2x(t-\tau(t))\\ +\tilde{W}f(x(t-\sigma(t)))-\tilde{D}_1\int_{t-\tau(t)}^{t}y(s)\mathrm{d}s\end{bmatrix}\\ =& \xi^T(t)[2W_x^T(P_1-P_3^T)W_y-W_y^T(P_2+P_2^T)W_y\\ &+2W_x^TP_3^TW_{xy}+2W_y^TP_2^TW_{xy}]\xi(t)\end{aligned} \tag{13}$$

$$\begin{aligned}\dot{V}_2(t) =& 2[f(x(t))-L_0x(t)]^T\Lambda_1[-(\tilde{A}-\tilde{D}_1)x(t)+\tilde{D}_2\\ &x(t-\tau(t))+\tilde{W}f(x(t-\sigma(t)))-\tilde{D}_1\int_{t-\tau(t)}^{t}y(s)\mathrm{d}s]\\ &+2[L_1x(t)-f(x(t))]^T\Lambda_2[-(\tilde{A}-\tilde{D}_1)x(t)+\tilde{D}_2\\ &x(t-\tau(t))+\tilde{W}f(x(t-\sigma(t)))-\tilde{D}_1\int_{t-\tau(t)}^{t}y(s)\mathrm{d}s]\\ =& \xi^T(t)[2W_f^T(\Lambda_1-\Lambda_2)W_{xy}+2W_x^T(L_1\Lambda_2-L_0\Lambda_1)\\ &W_{xy}]\xi(t)\end{aligned} \tag{14}$$

$$\begin{aligned}\dot{V}_3(t) \leq & x^T(t)Q_1x(t) - (1-\tau_d)x^T(t-\tau(t))Q_1 \\ & x(t-\tau(t)) + \begin{bmatrix} x(t) \\ f(x(t)) \end{bmatrix}^T \begin{bmatrix} R_1 & E_1 \\ * & R_2 \end{bmatrix} \begin{bmatrix} x(t) \\ f(x(t)) \end{bmatrix} - (1 \\ & - \sigma_d) \begin{bmatrix} x(t-\sigma(t)) \\ f(x(t-\sigma(t))) \end{bmatrix}^T \begin{bmatrix} R_1 & E_1 \\ * & R_2 \end{bmatrix} \begin{bmatrix} x(t-\sigma(t)) \\ f(x(t-\sigma(t))) \end{bmatrix} \\ = & \xi^T(t)[W_x^T(Q_1+R_1)W_x - W_{x\tau}^T((1-\tau_d)Q_1) \\ & \times W_{x\tau} + W_f^T R_2 W_f + 2W_x^T E_1 W_f - W_{x\sigma}^T \\ & \times ((1-\sigma_d)R_1)W_{x\sigma} - W_{f\sigma}^T((1-\sigma_d)R_2)W_{f\sigma} \\ & - 2W_{x\sigma}^T((1-\sigma_d)E_1)W_{f\sigma}]\xi(t) \end{aligned} \tag{15}$$

$$\begin{aligned}\dot{V}_4(t) \leq & \tau_2^2 y^T(t)Q_2y(t) - \tau_2\int_{t-\tau_2}^{t} y^T(s)Q_2y(s)\mathrm{d}s \\ \leq & \tau_2^2 y^T(t)Q_2y(t) - \tau_2\int_{t-\tau_2}^{t-\tau(t)} y^T(s)Q_2y(s)\mathrm{d}s \\ & - \tau_2\int_{t-\tau(t)}^{t} y^T(s)Q_2y(s)\mathrm{d}s \\ \leq & \tau_2^2 y^T(t)Q_2y(t) - \frac{\tau_2}{\tau_2-\tau(t)}\int_{t-\tau_2}^{t-\tau(t)} y^T(s)\mathrm{d}s \\ & \times Q_2\int_{t-\tau_2}^{t-\tau(t)} y(s)\mathrm{d}s - \frac{\tau_2}{\tau(t)}\int_{t-\tau(t)}^{t} y^T(s)\mathrm{d}s \\ & \times Q_2\int_{t-\tau(t)}^{t} y(s)\mathrm{d}s \\ \leq & \tau_2^2 y^T(t)Q_2y(t) - \begin{bmatrix} \int_{t-\tau(t)}^{t} y(s)\mathrm{d}s \\ \int_{t-\tau_2}^{t-\tau(t)} y(s)\mathrm{d}s \end{bmatrix}^T \begin{bmatrix} Q_2 & \tilde{Q}_2 \\ * & Q_2 \end{bmatrix} \\ & \times \begin{bmatrix} \int_{t-\tau(t)}^{t} y(s)\mathrm{d}s \\ \int_{t-\tau_2}^{t-\tau(t)} y(s)\mathrm{d}s \end{bmatrix} \\ = & \xi^T(t)[W_y^T(\tau_2^2Q_2)W_y - W_{s1}^TQ_2W_{s1} \\ & - W_{s2}^TQ_2W_{s2} - W_{s1}^T\tilde{Q}_2W_{s2}]\xi(t) \end{aligned} \tag{16}$$

In addition, for any $T_j = \mathrm{diag}(t_{1j}, t_{2j}, \cdots, t_{2j}) \geq 0, \quad j = 1, 2$; it follows that:

$$\begin{aligned} & -2[f(x(t)) - L_1x(t)]^TT_1[f(x(t)) - L_0x(t)] \\ & -2[f(x(t-\sigma(t))) - L_1x(t-\sigma(t))]^TT_2 \\ & \times [f(x(t-\sigma(t))) - L_0x(t-\sigma(t))] \\ = & \xi^T(t)[-2W_x^TL_1T_1L_0W_x - 2W_f^TT_1W_f + 2W_x^T \\ & (L_0T_1 + L_1T_1)W_f - 2W_{x\sigma}^TL_1T_2L_0W_{x\sigma} - 2W_{f\sigma}^T \\ & \times T_1W_{f\sigma} + 2W_{x\sigma}^T(L_0T_2 + L_1T_2)W_{f\sigma}]\xi(t) \geq 0 \end{aligned} \tag{17}$$

Meanwhile, by the Leibniz-Newton formula, the following equality is true for any matrices J with appropriate dimension:

$$2\xi^T(t)J[x(t) - x(t-\tau(t)) - \int_{t-\tau(t)}^{t} y(s)\mathrm{d}s] = 0. \tag{18}$$

where $J = [J_1^T \ 0 \ 0 \ J_2^T \ 0 \ 0 \ J_3^T \ 0]^T$
Combing (13)-(18) ,we have

$$\dot{V}(t) \leq \xi^T(t)\Phi_1\xi(t) \tag{19}$$

Therefore, $\dot{V}(t) < 0$ holds if $\Phi_1 < 0$. From (9), we can see that the GRN (8) with time-varying delays is asymptotically stable. This complete the proof.

Remark 3 One key point of the criterion in Theorem 1 is that the decomposition of the matrix $\tilde{D}$ into $\tilde{D} = \tilde{D}_1 + \tilde{D}_2$. This decomposition corresponds to a decomposition of the delayed terms into two groups: the stabilizing ones and the destabilizing ones. This technique enables one to take the stabilizing effect of part of the delayed terms into account.

Remark 4 In [22], the stability conditions were obtained for the delays $\tau(t)$ and $\sigma(t)$ satisfying $\dot{\tau}(t) \leq \tau_\mu < 1$ and $\dot{\sigma}(t) \leq \sigma_\mu < 1$, however, in Theorem 1, the delays $\tau(t)$ and $\sigma(t)$ satisfy $\dot{\tau}(t) \leq \tau_d < \infty$ and $\dot{\sigma}(t) \leq \sigma_d < \infty$ respectively. Therefore the stability criteria derived turn out to be less conservative.

If there is no decomposition ($\tilde{D}_1 = 0, \ \tilde{D} = \tilde{D}_2$), the following Corollary can be turned for checking the stability of system (5).

Corollary 1 For given constants $\tau_2, \ \tau_d, \ \sigma_d$, the system (5) is asymptotically stable, if there exist matrices $P_1 > 0, \ Q_i > 0, \ i = 1, 2; \ R_i > 0, \ i = 1, 2; \ \begin{bmatrix} R_1 & E_1 \\ * & R_2 \end{bmatrix} \geq 0, \ \begin{bmatrix} Q_2 & \tilde{Q}_2 \\ * & Q_2 \end{bmatrix} \geq 0, \ \Lambda_i = diag(\lambda_{1i}, \lambda_{2i}, \cdots, \lambda_{ni}) > 0, \ i = 1, 2; \ T_i = diag(t_{1i}, t_{2i}, \cdots, t_{ni}) > 0, \ i = 1, 2; \ P_2, \ P_3, \ L_0, \ L_1, \ \tilde{Q}_2$ and E_1 with appropriate dimensions respectively satisfying:

$$\tilde{\Phi}_1 = \tilde{\Phi}_{11} + \tilde{\Phi}_{12} + \tilde{\Phi}_{12}^T < 0 \tag{20}$$

where

$$\begin{aligned} \Phi_{11} = & -W_x^T(L_1T_1L_0 + L_0T_1L_1 - Q_1 - R_1 + Q_2) \\ & \times W_x - W_y^T(P_2 + P_2^T - \tau_2^2Q_2)W_y - W_f^T(2T_1 \\ & - R_2)W_f - W_{x\tau}^T((1-\tau_d)Q_1 + Q_2)W_{x\tau} \\ & - W_{x\sigma}^T((1-\sigma_d)R_1 + L_1T_2L_0 + L_0T_2L_1)W_{x\sigma} \\ & - W_{f\sigma}^T((1-\sigma_d)R_2 + 2T_1)W_{f\sigma} - W_{s2}^TQ_2W_{s2} \end{aligned} \tag{21}$$

$$\begin{aligned} \Phi_{12} = & W_x^T(P_1 - P_3^T)W_y + W_x^T(P_3^T + L_1\Lambda_2 - L_0\Lambda_1) \\ & \times W_{xy} + W_y^TP_2^TW_{xy} + W_f^T(\Lambda_1 - \Lambda_2)W_{xy} \\ & + W_x^T(E_1 + L_0T_1 + L_1T_1)W_f + W_x^TQ_2W_{x\tau} \\ & + W_{x\sigma}^T(-(1-\sigma_d)E_1 + L_0T_2 + L_1T_2)W_{f\sigma} \\ & - W_x^T\tilde{Q}_2W_{s2} + W_{x\tau}^T\tilde{Q}_2W_{s2} \end{aligned} \tag{22}$$

with
$\tilde{W}_x = \begin{bmatrix} I_n & O_{n,6n} \end{bmatrix}, \ \tilde{W}_y = \begin{bmatrix} O_{n,n} & I_n & O_{n,5n} \end{bmatrix},$
$\tilde{W}_f = \begin{bmatrix} O_{n,2n} & I_n & O_{n,4n} \end{bmatrix}, \ \tilde{W}_{x\tau} = \begin{bmatrix} O_{n,3n} & I_n & O_{n,3n} \end{bmatrix},$
$\tilde{W}_{x\sigma} = \begin{bmatrix} O_{n,4n} & I_n & O_{n,2n} \end{bmatrix}, \ \tilde{W}_{f\sigma} = \begin{bmatrix} O_{n,5n} & I_n & O_{n,n} \end{bmatrix},$
$\tilde{W}_{s2} = \begin{bmatrix} O_{n,6n} & I_n \end{bmatrix},$
$\tilde{W}_{xy} = \begin{bmatrix} -\tilde{A} & O_{n,2n} & \tilde{D} & O_{n,n} & \tilde{W} & O_{n,n} \end{bmatrix}.$

Base on Theorem 1,we can perform the robust stability analysis for the uncertain genetic regulatory network (7).

Theorem 2 For given constants $\tau_2, \ \tau_d, \ \sigma_d, \ \varepsilon_i > 0$, i=1,2,3, the system (7) is robustly asymptotically stable, if there exist matrices $P_1 > 0, \ Q_i > 0, \ i = 1, 2; R_i > 0, \ i = 1, 2;$ $\begin{bmatrix} R_1 & E_1 \\ * & R_2 \end{bmatrix} \geq 0, \begin{bmatrix} Q_2 & \tilde{Q}_2 \\ * & Q_2 \end{bmatrix} \geq 0, \ \Lambda_i = diag(\lambda_{1i}, \lambda_{2i}, \cdots, \lambda_{ni}) > 0, \ i = 1, 2; \ T_i = diag \ (t_{1i}, t_{2i}, \cdots, t_{ni}) > 0, \ i = 1, 2; \ P_2, \ P_3, \ L_0, \ L_1, \ \tilde{Q}_2, \ J_1, \ J_2, \ J_3$ and E_1 with appropriate dimensions respectively satisfying:

$$\Xi_1 = \begin{bmatrix} \Phi_1 & P_2^T\tilde{E} & (\Lambda_1-\Lambda_2)\tilde{E} & (L_1\Lambda_2 - L_0\Lambda_1)\tilde{E} & W_{\Delta xy}^T \\ * & -\varepsilon_1^{-1} & 0 & 0 & 0 \\ * & * & -\varepsilon_2^{-1} & 0 & 0 \\ * & * & * & -\varepsilon_3^{-1} & 0 \\ * & * & * & * & -\varepsilon_4^{-1} \end{bmatrix} < 0 \tag{23}$$

with
$W_{\Delta xy} = \begin{bmatrix} -H_a & O_{n,2n} & H_d & O_{n,n} & H_w & O_{n,2n} \end{bmatrix}$ $\varepsilon_4 = \varepsilon_1^{-1} + \varepsilon_2^{-1} + \varepsilon_3^{-1}$ and the others have been defined in Theorem 1.

Proof. Following Theorem 1, we represent (7) in the following equivalent descriptor system form:

$$\begin{cases} \dot{x}(t) = y(t), \\ y(t) = -(\tilde{A} + \Delta\tilde{A} - \tilde{D}_1)x(t) + (\tilde{D}_2 + \Delta\tilde{D})x(t-\tau(t)) \\ \quad +(\tilde{W} + \Delta\tilde{W})f(x(t-\sigma(t))) - \tilde{D}_1 \int_{t-\tau(t)}^{t} y(s)\mathrm{d}s \end{cases} \tag{24}$$

Consider the same Lyapunov-Krasovskii functional in the proof of Theorem 1, do the differential along the trajectory of (24).

Noting that, for any constants $\varepsilon_i > 0$ i=1,2,3, it is clearly true that:

$$\begin{aligned} &2y^T(t)P_2^T[-\Delta\tilde{A}x(t) + \Delta\tilde{D}x(t-\tau(t)) \\ &\quad + \Delta\tilde{W}f(x(t-\sigma(t)))] = 2y^T(t)P_2^T\tilde{E}F(t)W_{\Delta xy}\xi(t) \\ &\leq \varepsilon_1\xi^T(t)W_y^T P_2^T\tilde{E}\tilde{E}^T P_2 W_y\xi(t) \\ &\quad + \varepsilon_1^{-1}\xi^T(t)W_{\Delta xy}^T W_{\Delta xy}\xi(t) \end{aligned} \tag{25}$$

$$\begin{aligned} &2f^T(x(t))(\Lambda_1 - \Lambda_2)[-\Delta\tilde{A}x(t) + \Delta\tilde{D}x(t-\tau(t)) \\ &\quad + \Delta\tilde{W}f(x(t-\sigma(t)))] \\ &\leq \varepsilon_2\xi^T(t)W_f^T(\Lambda_1 - \Lambda_2)\tilde{E}\tilde{E}^T(\Lambda_1 - \Lambda_2)W_f\xi(t) \\ &\quad + \varepsilon_2^{-1}\xi^T(t)W_{\Delta xy}^T W_{\Delta xy}\xi(t) \end{aligned} \tag{26}$$

$$\begin{aligned} &2x^T(t)(L_1\Lambda_2 - L_0\Lambda_1)[-\Delta\tilde{A}x(t) + \Delta\tilde{D}x(t-\tau(t)) \\ &\quad + \Delta\tilde{W}f(x(t-\sigma(t)))] \\ &\leq \varepsilon_3\xi^T(t)W_x^T(L_1\Lambda_2 - L_0\Lambda_1)\tilde{E}\tilde{E}^T(L_1\Lambda_2 - L_0\Lambda_1) \\ &\quad \times W_x\xi(t) + \varepsilon_3^{-1}\xi^T(t)W_{\Delta xy}^T W_{\Delta xy}\xi(t) \end{aligned} \tag{27}$$

Combing (13)-(19),and the above inequalities, by Schur complements (Lemma 2), we have:

$$\dot{V}(t) \leq \xi^T(t)\Xi_1\xi(t) \tag{28}$$

From (23), we can see that the uncertain system (7) is robust asymptotically stable. This complete the proof. □

Similarly to Corollary 1, If there is no decomposition ($\tilde{D}_1 = 0,\ \tilde{D} = \tilde{D}_2$), the following Corollary can be turned for checking the stability of system (6).

Corollary 2 For given constants $\tau_2,\ \tau_d,\ \sigma_d,\ \varepsilon_i > 0$ i=1,2,3, the system (6) is asymptotically stable, if there exist matrices $P_1 > 0,\ Q_i > 0,\ i = 1,2;\ R_i > 0,\ i = 1,2;\ \begin{bmatrix} R_1 & E_1 \\ * & R_2 \end{bmatrix} \geq 0,\ \begin{bmatrix} Q_2 & \tilde{Q}_2 \\ * & Q_2 \end{bmatrix} \geq 0,\ \Lambda_i = diag(\lambda_{1i}, \lambda_{2i}, \cdots, \lambda_{ni}) > 0,\ i = 1,2;$ $T_i = diag\ (t_{1i}, t_{2i}, \cdots, t_{ni}) > 0,\ i = 1,2;\ P_2,\ P_3,\ L_0,\ L_1,$ $\tilde{Q}_2$ and E_1 with appropriate dimensions respectively satisfying:

$$\tilde{\Xi}_1 = \begin{bmatrix} \tilde{\Phi}_1 & P_2^T\tilde{E} & (\Lambda_1-\Lambda_2)\tilde{E} & (L_1\Lambda_2 - L_0\Lambda_1)\tilde{E} & W_{\Delta xy}^T \\ * & -\varepsilon_1^{-1} & 0 & 0 & 0 \\ * & * & -\varepsilon_2^{-1} & 0 & 0 \\ * & * & * & -\varepsilon_3^{-1} & 0 \\ * & * & * & * & -\varepsilon_4^{-1} \end{bmatrix} < 0 \tag{29}$$

with $\tilde{W}_{\Delta xy} = \begin{bmatrix} -H_a & O_{n,2n} & H_d & O_{n,n} & H_w & O_{n,n} \end{bmatrix}$

IV. Illustrative Examples

In this section, two numerical examples will be presented to illustrate the effectiveness of our results.

Example.1 Firstly, let us consider the genetic regulatory network (5)with time-varying delays. The parameters are listed as follows:

$\tilde{A}$ =diag $\begin{bmatrix} 6 & 0 & 0 \\ 0 & 6 & 0 \\ 0 & 0 & 6 \end{bmatrix}$, $\tilde{C}$ =diag $\begin{bmatrix} 2.5 & 0 & 0 \\ 0 & 2.5 & 0 \\ 0 & 0 & 2.5 \end{bmatrix}$,
$\tilde{D}$=diag $\begin{bmatrix} 0.8 & 0 & 0 \\ 0 & 0.8 & 0 \\ 0 & 0 & 0.8 \end{bmatrix}$, $\tilde{W} = \begin{bmatrix} 0 & 0 & -2.5 \\ -2.5 & 0 & 0 \\ 0 & -2.5 & 0 \end{bmatrix}$

And $f(x) = x^2/(x^2+1)$, $L_0 = \text{diag}\ (0.1, 0.1, 0.1)$ $L_1 = \text{diag}\ (0.65, 0.65, 0.65)$. The time delays $\tau(t)$ and $\sigma(t)$ are assumed to be: $\tau_d = 0.7,\ \sigma_d = 0.5$ [24] .

It should be pointed out that, the delay-dependent conditions in [24] are not feasible when $\tau_2 > 1.1$. However, it can be checked that system (5) is asymptotically stable from Corollary 1 and the feasible solution of LMIs $(24) - (26)$ is obtained when $\tau_2 = 5$. Due to the limitation of the length of this paper, we only provide a part of the feasible solution here:

$$P_1 = \begin{bmatrix} 28.1396 & 16.5614 & -0.7061 \\ 16.5614 & 32.1684 & -1.5847 \\ -0.7061 & -1.5847 & 6.8041 \end{bmatrix}$$

$$Q_1 = \begin{bmatrix} 39.0312 & 14.2313 & -2.0212 \\ 14.2313 & 37.5365 & -1.3875 \\ -2.0212 & -1.3875 & 20.1990 \end{bmatrix}$$

Figure.1 shows the trajectories of variables $x(t)$ and $y(t)$ with the initial condition $[0.6\ 0.5\ 0.4\ 0.5\ 0.4\ 0.3]^T$.

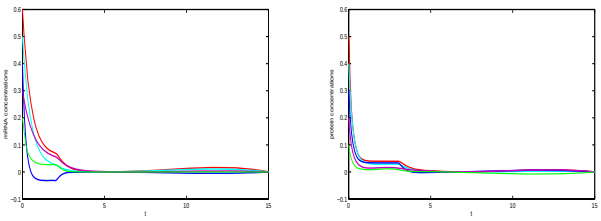

Fig. 1. Trajectories of x(t) and y(t) of the genetic network (5)

Example.2 In this example, we consider system (6) with the parameters listed as follows:

A =diag $(5, 5, 5, 5, 5)$, C =diag $(2.5, 2.5, 2.5, 2.5, 2.5)$,
D=diag $(0.3, 0.2, 0.4, 0.2, 0.2)$, $H_a = H_w = H_c = H_d$
$= \tilde{E} = \begin{bmatrix} 0 & 0.2 & 0.2 & 0 & 0 \\ 0.2 & 0 & 0 & 0.2 & 0.2 \\ 0 & -0.2 & 0 & 0 & 0.2 \\ 0.2 & 0 & 0.2 & 0 & 0 \\ 0 & 0 & -0.2 & 0.2 & 0 \end{bmatrix}$, $W = \begin{bmatrix} 0 & -1 & -1 & 0 & 0 \\ -1 & 0 & 0 & -1 & -1 \\ 0 & 1 & 0 & 0 & -1 \\ -1 & 0 & -1 & 0 & 0 \\ 0 & 0 & 1 & -1 & 0 \end{bmatrix}$
$F(t) = I_{5\times 5},\ f(x) = x^2/(x^2+1)$,

$L_0 = (0.1, 0.1, 0.1, 0.1, 0.1)$, $L_1 = \text{diag}\ (0.65, 0.65, 0.65, 0.65, 0.65)$. The time delays $\tau(t)$ and $\sigma(t)$ are assumed to be: $\tau_d = 0.7,\ \sigma_d = 0.5,\ \tau_2 = 5$. It can be checked that system (6) is asymptotically stable from Corollary 2 and the feasible solution of LMIs (29) is obtained. A part of the feasible solution is listed as follows:

$$P_1 = \begin{bmatrix} 1.6413 & 1.0595 & 1.3013 & -1.3011 & -0.1889 \\ 1.0595 & 1.5594 & 1.2432 & -1.4562 & -1.0437 \\ 1.3013 & 1.2432 & 2.5833 & -1.3414 & -0.8862 \\ -1.3011 & -1.4562 & -1.3414 & 4.8820 & 2.1172 \\ -0.1889 & -1.0437 & -0.8862 & 2.1172 & 4.0938 \end{bmatrix}$$

$$P_2 = \begin{bmatrix} 0.8154 & 0.2097 & 0.2271 & -0.2486 & -0.0553 \\ 0.2410 & 0.6797 & 0.2799 & -0.3028 & -0.2069 \\ 0.2842 & 0.2908 & 1.0518 & -0.2983 & -0.2139 \\ -0.2787 & -0.2849 & -0.2732 & 1.4173 & 0.4174 \\ -0.0318 & -0.1866 & -0.1947 & 0.4058 & 1.2281 \end{bmatrix}$$

Figure.2 shows the trajectories of variables $x(t)$ and $y(t)$ with the initial condition $[0.6\ 0.5\ 0.4\ 0.3\ 0.2\ 0.5\ 0.4\ 0.3\ 0.2\ 0.1]^T$.

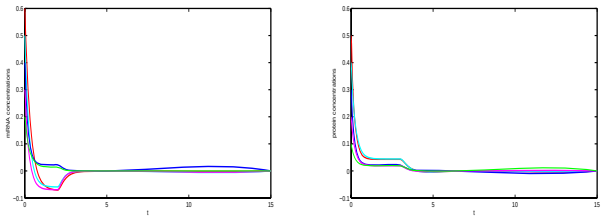

Fig. 2. Trajectories of x(t) and y(t) of the genetic network (6)

V. Conclusions

In this paper, we have worked out some new stability criteria for genetic regulatory networks with time-varying delays via the Lyapunov functional method. We consider the stability problem of the uncertain genetic regulatory networks based on a descriptor model transformation and the decomposition technique of discrete delay term matrix which have been introduced for stability analysis of delayed systems. This decomposition corresponds to a decomposition of the delayed terms into two groups: the stabilizing ones and the destabilizing ones and it enables one to take the stabilizing effect of part of the delayed terms into account. Finally, the feasibility and effectiveness of the developed methods have been shown by numerical simulation.

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