A Note on the Robust Stability of Genetic Regulatory Networks with Time-Varying Delays

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***Abstract*—This paper is concerned the robust stability analysis problem for genetic regulatory networks with time-varying delays. By utilizing a Lyapunov-Krasovskii functional, we show that the addressed genetic regulatory networks are robustly, asymptotically stable if a convex optimization problem is feasible. A stability criterion is derived and formulated by means of the feasibility of a linear matrix inequality (LMI), which can be effectively solved by some standard numerical packages. A numerical example is given to demonstrate the usefulness of the proposed robust stability criterion.**

***Keywords*—genetic regulatory networks, robust stability, time-varying delays, Lyapunov-Krasovskii functional, LMI**

I. INTRODUCTION

In our post-genomic era, regulatory networks have become an important new area of research in the biological and biomedical sciences and been investigated [1,2,4,11,13,14]. A genetic regulatory network (GRN) consists of a number of genes that interact and regulate the expression of other genes by the gene derivatives, i.e. proteins. The change in expression of a gene is controlled by the stimulation and inhibition of proteins in transcriptional, translational and post-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.

Up to now, several simple genetic networks have been successfully constructed by means of experiments, for example, genetic switches [7], repressilator [10], and a single negative feedback loop network [3]. 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. The results in these experiments show that mathematical models can be a powerful tool 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. 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. In [3], the authors designed and constructed simple gene circuits consisting of a regulator and transcriptional repressor modules in *Escherichia coli* and they showed the gain of stability produced by negative feedback. In [6], 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. It is known that genetic networks are usually large-scale. In [4], a nonlinear model for GRNs with SUM regulatory functions was presented. The cases of genetic networks with time-varying delays and stochastic perturbations were studied and sufficient conditions of stability were derived in terms of LMIs. In [5], the authors investigated the robust asymptotical stability issues of the GRNs with time-varying delays and norm bounded uncertainties. The method combing Lyapunov stability theory and Lur'e system approach was adopted to study these issues and sufficient conditions were also given in terms of LMIs.

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 the Lur'e system approach, and the results are represented in terms of linear matrix inequalities (LMIs) [12], which are easy to be verified by convex optimization techniques, e.g., the interior point method [12], and by software packages, e.g., the MATLAB LMI Toolbox.

Notations: The notations are quite standard. Throughout this paper, $\mathbb{R}^n$ and $\mathbb{R}^{n\times n}$ denote, respectively, the n-dimensional Euclidean space and the set of all $n\times n$ real matrices. The superscript "T" denotes matrix transposition and the notation $X \geq Y$ (respectively, $X > Y$) where X and Y are symmetric matrices, means that $X - Y$ is positive semi-definite (respectively, positive definite). I_n is the $n\times n$ identity matrix. $|\cdot|$ is the Euclidean norm in $\mathbb{R}^n$. The shorthand $diag\{M_1, M_2, ..., M_n\}$ denotes a block diagonal matrix with diagonal blocks being the matrices $M_1, M_2, ..., M_n$. The notation $\star$ always denotes the symmetric block in one

symmetric matrix. Sometimes, the arguments of a function or a matrix will be omitted in the analysis when no confusion can arise.

II. PROBLEM DESCTIPTION

In [1,6], a genetic regulatory network model was described as follows:

$$\begin{cases} \dot{M}_i(t) = -a_i M_i(t) + G_i(P_1(t-\delta(t)), \\ \qquad P_2(t-\delta(t)),...,P_n(t-\delta(t))) \\ \dot{P}_i(t) = -c_i P_i(t) + d_i M_i(t-\tau(t))), \quad i = 1,2,...,n \end{cases} \tag{1}$$

where $\dot{M}_i(t), \dot{P}_i(t) \in \mathbb{R}$ are the concentrations of mRNA and protein of the ith node. In this network, there is one output but multiple inputs for a single node or gene. A direct edge is linked from node j to i if the transcriptional factor or protein j regulates gene i. In (1), a_i and c_i are the degradation rates of the mRNA and protein, d_i is a constant, and $G_i(\cdot)$ is the regulatory function of the ith gene, which is generally a nonlinear function of the variables $(p_1(t), p_2(t),..., p_n(t))$, but has a form of monotonicity with each variable.

Generally, A GRN consists of a number of genes that interact and regulate the expression of other genes by proteins (the gene derivatives). The change in expression of a gene is controlled by the stimulation and inhibition of proteins in transcriptional, translational, and post-translational processes. The gene activity is tightly controlled in a cell, and gene regulation function $G_i(\cdot)$ plays an important role in the dynamics. The form of may be very complicated, depending on all biochemical reactions involved in this regulation. Typical regulatory logics include AND-like gates and OR-like gates [11,13,14] for $G_i(\cdot)$. In this paper, we focus on the case that each transcription factor acts additively to regulate the ith gene. The regulatory function is of the form $G_i(P_1(t), P_2(t),..., P_n(t)) = \sum_{j=1}^{n} G_{ij}(P_j(t))$, which is also called SUM logic [11]. This SUM logic does exist in many natural gene networks.

The function $G_{ij}(p_j(t))$ is a monotonic function of the Hill form [9]. If transcription factor j is an activator of gene i, then

$$G_{ij}(p_j(t)) = \begin{cases} b_{ij} \dfrac{(P_j(t)/\beta_j)^{H_j}}{1+(p_j(t)/\beta_j)^{H_j}}, & \text{if transcription factor } j \\ & \text{is an activator of gene } i \\ b_{ij} \dfrac{1}{1+(P_j(t)/\beta_j)^{H_j}}, & \text{if transcription factor } j \\ & \text{is a repressor of gene } i \end{cases}$$

where H is the Hill coefficient, β_j is a positive constant, and b_{ij} is the dimensionless transcriptional rate of transcription factor j to gene i, which is a bounded constant. Hence, Eq.(1) can be rewritten into the following form:

$$\begin{cases} \dot{M}_i(t) = -a_i M_i(t) + \sum_{j=1}^{n} w_{ij} g_j(P_j(t-\delta(t)) + B_i, \\ \dot{P}_i(t) = -c_i P_i(t) + d_i M_i(t-\tau(t))), \quad i = 1,2,...,n \end{cases} \tag{2}$$

where $g_j(x) = (x/\beta_j)^{H_j} / (1+(x/\beta_j)^{H_j})$, $B_i = \sum_{j \in I_i} b_{ij}$ and 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 defined as follows:

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

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

$$\begin{cases} \dot{M}(t) = -AM(t) + Wg(P(t-\delta(t))) + B, \\ \dot{P}(t) = -CP(t) + DM(t-\tau(t)), \end{cases} \tag{3}$$

where $M(t) = [M_1(t), M_2(t),..., M_n(t)]^T$, $P(t) = [P_1(t), P_2(t),..., P_n(t)]^T$, $g(P(t-\delta(t))) = [g_1(P_1(t-\delta(t))), g_2(P_2(t-\delta(t))),..., g_n(P_n(t-\delta(t)))]^T$, $M(t-\tau(t)) = [M_1(t-\tau(t)), M_2(t-\tau(t)),..., M_n(t-\tau(t))]^T$, $B = [B_1, B_2,..., B_n]^T$, $A = diag\{a_1, a_2,..., a_n\}$, $C = diag\{c_1, c_2,..., c_n\}$, $D = diag\{d_1, d_2,..., d_n\}$. $(M^{*T}, P^{*T})^T$ are said to be an equilibrium point of the system (3) if they satisfy $-AM^* + Wg(P^*) + B = 0$, and $-CP^* + DM^* = 0$.

For convenience, we will always shift an intended equilibrium point of the system (3) to the origin by letting $m(t) = M(t) - M^*$, $p(t) = P(t) - P^*$. Hence, system (3) can be transformed into the following form:

$$\begin{cases} \dot{m}(t) = -Am(t) + Wf(p(t-\delta(t))), \\ \dot{p}(t) = -Cp(t) + Dm(t-\tau(t)), \end{cases} \tag{4}$$

where $m(t) = [m_1(t), m_2(t),..., m_n(t)]^T$, $p(t) = [p_1(t), p_2(t),..., p_n(t)]^T$, $f(p(t)) = [f_1(p_1(t)), f_2(p_2(t)),..., f_n(p_n(t))]^T$ with $f_i(p_i(t)) = g_i(p_i(t) + P_i^*) - g_i(P_i^*)$. Since g_i is a monotonically increasing function with saturation, it satisfies, for all $a, b \in R$ with $a \neq b$

$$0 \le \frac{g_i(x) - g_i(y)}{x - y} \le k_i.$$

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

$$0 \le \frac{f_i(x)}{x} \le k_i \tag{5}$$

which is equivalent to the following condition

$$f_i(x)(f_i(x)-k_i x)\le 0. \tag{6}$$

Recall that a Lur'e system is a linear dynamic system, feedback interconnected to a static nonlinearity that satisfies a sector condition (6) [8].Hence, the genetic networks (3) can be seen as a kind of Lur'e system, which can be investigated by using the fruitful Lur'e system method in control theory [9]. Motivated by the above discussion, we consider robust stability for genetic networks with time-varying delays as following:

$$\begin{cases}\dot{M}(t)=-AM(t)+Wf(P(t-\delta(t))),\\ \dot{P}(t)=-CP(t)+DM(t-\tau(t)),\end{cases} \tag{7}$$

where $\delta(t)$, $\tau(t)$ are the are the time-varying delays satisfying $0\le\delta(t)\le\overline{\delta}$, $0\le\tau(t)\le\overline{\tau}$, $\dot{\delta}(t)\le\delta_d$ and $\dot{\tau}(t)\le\tau_d$ respectively, where $\overline{\delta}$ and $\overline{\tau}$ are positive constants.

Before ending this section, we give the following lemmas that are useful in deriving our LMI-based stability criterion in the next section.

Lemma 1. *For any vectors $a,b\in\mathbb{R}^n$, the following inequality*
$2a^Tb\le a^T\mathfrak{D}a+b^T\mathfrak{D}^{-1}b$
holds, in which $\mathfrak{D}>0$ is any positive define matrix.

Lemma 2. *For any constant matrix $M\in\mathbb{R}^{n\times n}$, $M=M^T>0$, a scalar $\rho>0$, vector function $\omega:[0,\rho]\to\mathbb{R}^n$ such that the integrations are well defined, the following inequality holds:*
$\left[\int_0^\rho\omega(s)\mathrm{d}s\right]^T M\left[\int_0^\rho\omega(s)\mathrm{d}s\right]\le\rho\int_0^\rho\omega^T(s)M\omega(s)\mathrm{d}s$.

III. STABILITY CONDITION OF GENETIC NETWORKS WITH TIME-VARYING DELAYS

In this section, we will perform robust stability analysis of the genetic network with time-varying delays described by (7) by using the Lyapunov-Krasovskii stability theorem. We have the following main theorem which can be expressed as the feasibility of a linear matrix inequality.

Theorem 1. *System (7) is robustly asymptotically stable for any $0\le\delta(t)\le\overline{\delta}$ and $0\le\tau(t)\le\overline{\tau}$, if there exist symmetric positive definite matrices $R_i,S_i(i=1,2,3)$, and K, and positive scalar λ such that the LMI holds:*

$$\Xi=\begin{bmatrix}-2R_1A+R_1+R_2+\overline{\tau}R_3 & 0 & 0\\ \star & D^{\mathrm{T}}S_1D-(1-\tau_d)R_2 & 0\\ \star & \star & -\overline{\tau}^{-1}R_3\end{bmatrix}<0,$$

$$\Sigma=\begin{bmatrix}\Sigma_{11} & 0 & 0 & 0\\ \star & \Sigma_{22} & 0 & 0\\ \star & \star & W^TR_1W-\lambda I & 0\\ \star & \star & \star & -\overline{\delta}^{-1}S_3\end{bmatrix}<0, \tag{8}$$

with

$$\Sigma_{11}=-2S_1C+S_1+S_2+\overline{\delta}S_3,$$
$$\Sigma_{22}=-(1-\delta_d)S_2+\lambda K^TK,$$

where $K=diag\{k_1,k_1,...,k_n\}$.

Proof. To obtain the result, the Lyapunov-Krasovskii functional of system (7) is defined by:

$$\begin{aligned}V(t)&=m^T(t)R_1m(t)+p^T(t)S_1p(t)\\&\quad+\int_{t-\tau(t)}^t m^T(s)R_2m(s)\mathrm{d}s+\int_{t-\delta(t)}^t P^T(s)S_2P(s)\mathrm{d}s\\&\quad+\int_{t-\overline{\tau}}^t\int_s^t m^T(\theta)R_3m(\theta)\mathrm{d}\theta\mathrm{d}s+\int_{t-\overline{\delta}}^t\int_s^t p^T(\theta)S_3p(\theta)\mathrm{d}\theta\mathrm{d}s\end{aligned}$$

Now we give some inequalities which will be used in the following proof. An application of Lemma 1 yields

$$-\int_{t-\overline{\tau}}^t m^T(s)R_3m(s)\mathrm{d}s\le-\frac{1}{\overline{\tau}}\left[\int_{t-\overline{\tau}}^t m(s)\mathrm{d}s\right]^T R_3\left[\int_{t-\overline{\tau}}^t m(s)\mathrm{d}s\right], \tag{9}$$

$$-\int_{t-\overline{\delta}}^t p^T(s)S_3p(s)\mathrm{d}s\le-\frac{1}{\overline{\delta}}\left[\int_{t-\overline{\delta}}^t p(s)\mathrm{d}s\right]^T S_3\left[\int_{t-\overline{\delta}}^t p(s)\mathrm{d}s\right], \tag{10}$$

The inequalities follow from Lemma 2

$$\begin{aligned}2m^T(t)R_1Wf(p(t-\delta(t)))&\le m^T(t)R_1m(t)\\&\quad+f^T(p(t-\delta(t)))W^TR_1Wf(p(t-\delta(t))),\\2p^T(t)S_1Dm(t-\tau(t))&\le p^T(t)S_1p(t)\\&\quad+m^T(t-\tau(t))D^TS_1Dm(t-\tau(t)).\end{aligned} \tag{11}$$

Noting the sector condition (5), we can get

$$\begin{aligned}-\lambda\big[&f^T(p(t-\delta(t)))f(p(t-\delta(t)))\\&-p^T(t-\delta(t))K^TKp(t-\delta(t))\big]\ge0,\ \lambda>0.\end{aligned} \tag{12}$$

Calculating the time derivative of $V(t)$ along the system (7), then we have

$$\begin{aligned}\dot{V}(t)&=-2m^T(t)R_1Am(t)+2m^T(t)R_1Wf(p(t-\delta(t)))\\&\quad-2p^T(t)S_1Cp(t)+2p^T(t)S_1Dm(t-\tau(t))\\&\quad+m^T(t)R_2m(t)-(1-\dot{\tau}(t))m^T(t-\tau(t))R_2m(t-\tau(t))\\&\quad+p^T(t)S_2p(t)-(1-\dot{\delta}(t))p^T(t-\delta(t))S_2p(t-\delta(t))\\&\quad+\overline{\tau}m^T(t)R_3m(t)-\int_{t-\overline{\tau}}^t m^T(s)R_3m(s)\mathrm{d}s\\&\quad+\overline{\delta}p^T(t)S_3p(t)-\int_{t-\overline{\delta}}^t p^T(s)S_3p(s)\mathrm{d}s\\&\le-2m^T(t)R_1Am(t)+2m^T(t)R_1Wf(p(t-\delta(t)))\\&\quad-2p^T(t)S_1Cp(t)+2p^T(t)S_1Dm(t-\tau(t))\\&\quad+m^T(t)R_2m(t)-(1-\tau_d)m^T(t-\tau(t))R_2m(t-\tau(t))\\&\quad+p^T(t)S_2p(t)-(1-\delta_d)p^T(t-\delta(t))S_2p(t-\delta(t))\\&\quad+\overline{\tau}m^T(t)R_3m(t)-\int_{t-\overline{\tau}}^t m^T(s)R_3m(s)\mathrm{d}s\\&\quad+\overline{\delta}p^T(t)S_3p(t)-\int_{t-\overline{\delta}}^t p^T(s)S_3p(s)\mathrm{d}s\end{aligned} \tag{13}$$

Substituting (9)-(12) in (13), we get

$$\begin{aligned}\dot{V}(t) &\le m^T(t)\left[-2R_1A+R_1+R_2+\overline{\tau}R_3\right]m(t)\\ &+m^T(t-\tau(t))\left[D^TS_1D-(1-\tau_d)R_2\right]m(t-\tau(t))\\ &+\left(\int_{t-\overline{\tau}}^{t}m(s)\mathrm{d}s\right)^T\left[-\frac{1}{\overline{\tau}}R_3\right]\left(\int_{t-\overline{\tau}}^{t}m(s)\mathrm{d}s\right)\\ &+p^T(t)\left[-2S_1C+S_1+S_2+\overline{\delta}S_3\right]p(t)\\ &+p^T(t-\delta(t))\left[-(1-\delta_d)S_2+\lambda K^TK\right]p(t-\delta(t))\\ &+f^T(p(t-\delta(t)))\left[W^TR_1W-\lambda I\right]f(p(t-\delta(t)))\\ &+\left(\int_{t-\overline{\delta}}^{t}p(s)\mathrm{d}s\right)^T\left[-\frac{1}{\overline{\delta}}S_3\right]\left(\int_{t-\overline{\delta}}^{t}p(s)\mathrm{d}s\right)\\ &\le \xi_1^T(t)\Xi\xi_1(t)+\xi_2^T(t)\Sigma\xi_2(t)\\ &\le 0, \end{aligned}\tag{14}$$

where

$$\xi_1^T=\left[m^T(t)\quad m^T(t-\tau(t))\quad \left(\int_{t-\overline{\tau}}^{t}m(s)\mathrm{d}s\right)^T\right],$$

$$\xi_2^T=\left[p^T(t)\quad p^T(t-\delta(t))\quad f(p^T(t-\delta(t)))\quad \left(\int_{t-\delta(t)}^{t}p(s)\mathrm{d}s\right)^T\right].$$

Hence for ensuring negativity of $\dot{V}(t)$ for any possible state, it suffices to require Ξ,Σ be a negative definite matrix. This implies that the equilibrium point of genetic regulatory network (7) is robustly asymptotically stable. The proof is completed.

IV. ILLUSTRATIVE EXAMPLE

In this section, we illustrate the effectiveness and correctness of our result with the genetic networks composed of three nodes with time-varying delays.

Example 1. Consider the dynamics of repressilator, which has been theoretically predicted and experimentally investigated in *Escherichia coli* [10]. The repressilator is a cyclic negative-feedback loop comprising three repressor genes (*lacI*, *tetR*, and *cI*) and their promoters. The kinetics of the system are determined by six coupled first-order differential equations

$$\begin{cases}\dot{m}_i=-m_i+\dfrac{\alpha}{1+p_j^n},\\ \dot{p}_j=-\beta(p_j-m_i),\end{cases}$$

Where $i=lacI,tetR,cI;\ \ j=cI,lacI,tetR.$ m_i and p_j are the concentrations of the three mRNAs and repressor-proteins, and $\beta>0$ denotes the ratio of the protein decay rate to mRNA decay rate. Taking into account the transcriptional time delay, we rewrite the above equations into vector form with adjusting some parameters:

$$\begin{cases}\dot{M}(t)=-AM(t)+Wg(P(t-\delta(t)))+B,\\ \dot{P}(t)=-CP(t)+DM(t-\tau(t)),\end{cases}\tag{15}$$

where

$A=diag\{3,4,5\}$, $C=diag\{5,4,5\}$, $A=diag\{0.3,0.2,0.4\}$,

$$B=\begin{bmatrix}2.5 & 2.5 & 2.5\end{bmatrix}^T,\qquad W=\begin{bmatrix}0 & -1 & -1\\ -1 & 0 & 0\\ 0 & 1 & 0\end{bmatrix},$$

$g_i(P_i)=P_i^2/(1+P_i^2)$, which means $n=2,\alpha=2.5$ in the above equations, where n is the Hill coefficient. It is easy to know that the maximal value of the derivative of $g_i(p_i)$ less than $k=0.65$, which means $K=diag\{0.65,0.65,0.65\}$. Let $\tau(t)=0.4+0.4\sin(t)$, $\delta(t)=0.2+0.2\cos(t)$. Obviously, we have $\tau(t)\le\overline{\tau}=0.8$, $\dot{\tau}(t)\le\tau_d=0.4$, $\delta(t)\le\overline{\delta}=0.4$ and $\dot{\delta}(t)\le\delta_d=0.2$. Using Matlab LMI Control Toolbox, by our Theorem 1, we can find that the feasible solution of LMI (8) is obtained as

$$R_1=\begin{bmatrix}6.9721 & 0 & 0.4694\\ 0 & 5.9812 & 0\\ 0.4694 & 0 & 4.5606\end{bmatrix},$$

$$R_2=\begin{bmatrix}16.0664 & 0 & 1.3365\\ 0 & 18.8674 & 0\\ 1.3365 & 0 & 18.6713\end{bmatrix},$$

$$R_3=\begin{bmatrix}7.9825 & 0 & 0.1650\\ 0 & 8.3385 & 0\\ 0.1650 & 0 & 8.2854\end{bmatrix},$$

$$S_1=\begin{bmatrix}4.8996 & 0 & 0.0021\\ 0 & 6.3402 & 0\\ 0.0021 & 0 & 4.8946\end{bmatrix},$$

$$S_2=\begin{bmatrix}21.4125 & 0 & 0.0064\\ 0 & 21.5107 & 0\\ 0.0064 & 0 & 21.3972\end{bmatrix},$$

$$S_3=\begin{bmatrix}15.7336 & 0 & 0.0042\\ 0 & 15.7980 & 0\\ 0.0042 & 0 & 15.7235\end{bmatrix},\qquad \lambda=19.2003.$$

Figure 1 shows the trajectories of variable $M_i(t)$ and $P_i(t)$ with the following initial condition (16), respectively.

$$\begin{cases}m_1(\theta)=0.2,m_2(\theta)=0.4,m_3(\theta)=0.6\quad(\theta\in[-\overline{\tau},0]),\\ p_1(\phi)=0.1,p_2(\phi)=0.2,p_3(\phi)=0.3\quad(\phi\in[-\overline{\delta},0]).\end{cases}\tag{16}$$

Hence, the genetic regulatory networks (15) with time-varying delays is robustly, asymptotically stable. In the meanwhile, we can get that the unique equilibrium point of this network is $m^*=[0.7930\ 0.6225\ 0.5077]^T$, $p^*=[0.2476\ 0.2811\ 0.2406]^T$.

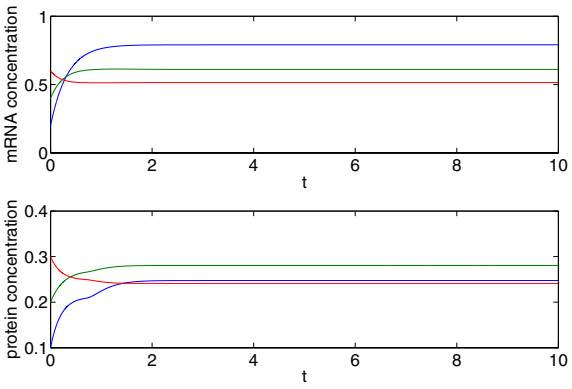

Figure 1. Transient response of $M_i(t)$ and $P_i(t)(i=1,2,3)$.

V. CONCLUSIONS

In this paper, we have dealt with the problem of robust stability analysis for a class of genetic regulatory networks with time-varying delays. 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). A numerical example has also been used to demonstrate the usefulness of the main result.

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