Stability and Oscillation of Genetic Regulatory Networks with Time Delays

Fang-Xiang Wu, *Member, IEEE*

Abstract— From biochemical reaction principles, a genetic regulatory network can be described by a group of nonlinear differential equations with time delays. Previous studies have investigated delay-independent stability of genetic regulatory networks with time delays. However, if it is delay-independently stable, a genetic regulatory network loses other interesting properties such as oscillation. In this paper, we provide a computational method for computing the maximal delay interval over which the genetic regulatory network maintains stability, and beyond which the network will not be stable. Furthermore we prove that when its delay is exactly the maximal delay the network is oscillated. In addition, the formula for calculating the oscillation period is presented. The autoregulatory genetic network in zebrafish is used as an example to illustrate the presented method. The oscillation period calculated from our method is very close to that observed from the real-life of a zebrafish, which indicates the effectiveness of our method.

I. Introduction

A genetic regulatory network is a dynamic system to describe highly complex interactions among two main species of gene product: mRNAs and proteins, in the interactive processes of transcription and translation. In the transcriptional process, mRNAs are synthesized from genes by the regulations of transcription factors, which are proteins. In the translational process, mRNAs are used as templates to produce proteins. These complicated processes can be modeled by nonlinear differential equations according to biochemical reaction principles [1, 2]. Several typical genetic regulatory networks have been modeled and studied experimentally and/or theoretically [3, 4, 5, 6], separately. One of the key factors affecting dynamics of genetic regulatory networks is time delays, which usually exist in transcription, translation, and translocation processes especially in a eukaryotic cell. Time delays may significantly influence the overall properties of a dynamic system. Much attention has been paid to delay-independent stability of genetic regulatory networks [7-9]. However, if it is delay-independently stable, a genetic regulatory network loses other interesting properties such as oscillation.

In this paper we develop a method to compute the maximal delay interval over which a genetic regulatory network maintains stable and, beyond which the network may become unstable. Furthermore we prove that when its delay is exactly the maximal delay the network appears oscillated, and present a formula for calculating the oscillation period. Section II describes nonlinear differential equation models for genetic regulatory networks with time delays. The linearized model and its characteristic equations are also derived in this section. Using the essential properties of genetic regulatory networks, the characteristic equations are simplified. In addition, the concept of stability of a linear system with time delays is introduced in terms of characteristic equations. Section III contains our main results. We first develop a method to calculate the maximal delay for stability of gene regulatory networks with a single time delay. We show that when its delay is the exact maximal delay the network appears oscillated. The formula for calculating the oscillation period is also presented. Then we extend these results to gene regulatory networks with multiple time delays. Section IV illustrates the presented method by analyzing the autoregulatory genetic network in zebrafish. Section V draws the brief conclusion from this study.

Manuscript received July 2, 2008. This work was supported by Natural Sciences and Engineering Research council of Canada (NSERC).

F. X. Wu is with Department of Mechanical Engineering and associated with Division of Biomedical Engineering, University of Saskatchewan, Saskatoon, SK S7N5A9, Canada (e-mail: faw341@mail.usask.ca).

II. Genetic regulatory networks with time delays

Genetic regulatory networks with time delays consisting of n mRNAs and n proteins can be described by the following equations [7, 8]:

$$\begin{aligned} \dot{m}(t) &= -K_m m(t) + c(p(t,\tau_p)) \\ \dot{p}(t) &= -K_p p(t) + d(m(t,\tau_m)) \end{aligned} \tag{1}$$

where $m = (m_1, \Lambda, m_n) \in R^n$, and $p = (p_1, \Lambda, p_n) \in R^n$ represent the concentrations of mRNAs and proteins, respectively. $K_m = diag(k_{m_1}, \Lambda, k_{m_n}) \in R^{n\times n}$ and $K_p = diag(k_{p_1}, \Lambda, k_{p_n}) \in R^{n\times n}$ are positive real diagonal matrices that represent the degradation rates for mRNAs and proteins, respectively. $\tau_m = (\tau_{m_1}, \Lambda, \tau_{m_n}) \in R^n$ and $\tau_p = (\tau_{p_1}, \Lambda, \tau_{p_n}) \in R^n$ are positive real vectors indicating time delays for mRNAs and proteins, respectively, and $m(t,\tau_m) = (m_1(t-\tau_{m_1}), \Lambda, m_n(t-\tau_{mn}))$ and $p(t,\tau_p) = (p_1(t-\tau_{p_1}), \Lambda, p_n(t-\tau_{p_n}))$. $c(p(t,\tau_p)) = (c_1(p(t,\tau_p)), \Lambda, c_n(p(t,\tau_p))$ and $d(m(t,\tau_m)) = (d_1(m_1(t,\tau_{m_1})), \Lambda, d_1(m_1(t,\tau_{m_1})))$ are vector functions. Note that $d_i(m(t,\tau_m))$ is defined as the

function of only $m_i(t,\tau_{m_i})$, and that in general $c_i(p(t,\tau_p))$ is defined as the function of the concentrations of several proteins.

The bottom equation in model (1) describes the translational process. Although one mRNA molecule (by splicing alternatives) could correspond to multiple proteins, this study does not take the splicing alternatives of an mRNA molecule into consideration. The definition of $d_i(m(t))$ reflects the fact that one mRNA molecule presumably corresponds just to one protein. On the other hand, one gene or mRNA is generally activated or repressed by multiple proteins in the transcriptional process indicated in the definition of $c(p(t))$. The top equation in model (1) describes the transcriptional process. $c_i(p(t))$ represents the relative activator or repressor activity of all proteins to gene i as a function of the concentrations $p(t)$ of all proteins. In this paper, we take $c_i(p(t)) = \sum_{j=1}^{n} c_{ij}(p_j(t))$, which is called SUM logic [10]. That is, each transcription factor acts additively to regulate gene i. c_{ij} is a monotonic function of the Hill form [1]. If transcription factor (protein) j is a activator of gene i, then

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

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

$$c_{ij}(p_j(t)) = a_{ij}\frac{1}{1+(p(t)/b_j)^{h_j}} = a_{ij}\left(1-\frac{(p(t)/b_j)^{h_j}}{1+(p(t)/b_j)^{h_j}}\right),$$

where h_j is the Hill coefficient representing the degree of cooperativity, b_j (j=1,2,…,n) are positive constants, and a_{ij} (i, j=1,2, …, n) are nonnegative constants

Assume that $(\overline{m},\overline{p})$ is an equilibrium state of model (1). That is, they are satisfied the following equations:

$$0 = -K_m\overline{m} + c(\overline{p})$$
$$0 = -K_p\overline{p} + d(\overline{m})$$

The linearized system of genetic regulatory network (1) around the equilibrium state $(\overline{m},\overline{p})$ follows as:

$$\begin{aligned}\dot{\tilde{m}}(t) &= -K_m\tilde{m}(t) + J_c\tilde{p}(t-\tau_p)\\ \dot{\tilde{p}}(t) &= -K_p\tilde{p}(t) + J_d\tilde{m}(t-\tau_m)\end{aligned} \quad (2)$$

where $\tilde{m}(t) = m(t)-\overline{m}$ and $\tilde{p}(t) = p(t)-\overline{p}$ are the differences between the state at time t and the equilibrium state $(\overline{m},\overline{p})$. $J_c = \frac{\partial c}{\partial p}\Big|_{(\overline{m},\overline{p})}$ and $J_d = \frac{\partial d}{\partial m}\Big|_{(\overline{m},\overline{p})}$ are $n\times n$ Jacobian matrices of vector functions $c(p)$ and $d(m)$, respectively. Note that J_d is a diagonal matrix because of the definition of $d(m)$ in model (1). Further we obtain the characteristic matrix equation of linear system (2)

$$\det\left(\begin{bmatrix}\lambda I_n + K_m & 0\\ 0 & \lambda I_n + K_p\end{bmatrix} - \begin{bmatrix}0 & J_c E^{-\lambda\tau_p}\\ J_d E^{-\lambda\tau_m} & 0\end{bmatrix}\right) = 0 \quad (3)$$

where $\lambda \in C$ is the characteristic value of (2), and C is the set of all complex numbers. I_n is an identity matrix, and $E^{-\lambda\tau_m} = diag(e^{-\lambda\tau_{m_1}},\Lambda\ ,e^{-\lambda\tau_{m_n}})$ and $E^{-\lambda\tau_p} = diag(e^{-\lambda\tau_{p_1}},\Lambda\ ,e^{-\lambda\tau_{p_n}})$ are diagonal matrices.

In the following, we simplify the characteristic equation (3) by taking the properties of genetic regulatory network (1) into account. Since $\lambda I_n + K_m$, $\lambda I_n + K_p$, and $J_d E^{-\lambda\tau_m}$ are $n\times n$ diagonal matrices, by Schur's theorem equation (3) becomes

$$\det((\lambda I_n + K_m)(\lambda I_n + K_p) - JE^{-\lambda\overline{\tau}}) = 0 \quad (4)$$

where $\overline{\boldsymbol{\tau}} = (\overline{\tau}_1,\ \Lambda\ ,\overline{\tau}_n) \in R^n$ is the total delay vector and $\overline{\tau}_i = \tau_{m_i} + \tau_{p_i}$, and $J = J_c J_d$. Clearly, in equation (4) $2n$ delays (τ_m,τ_p) is reduced to n delays $(\boldsymbol{\tau})$. Actually, without linearization, delays in regulatory networks (1) can also be reduced to n delays [6-9], provided that $\frac{dd_i(x)}{d(x)} \neq 0$ for $x \geq 0$ and $i = 1,\Lambda\ ,n$

In this study, assume that the values of all delays $\overline{\tau}_i$ (i=1, … , n) are rational numbers. Therefore there exists a maximal positive constant τ and r ($\leq n$) integers q_k (k = 1,2, …, r) such that $\overline{\tau}_i = q_k\tau$. Let $q = \max_{1\leq k\leq r}\{q_k\}$. Then we can rewrite the equation as

$$\det((\lambda I_n + K_m)(\lambda I_n + K_p) - \sum_{k=1}^{q} J_k e^{-k\tau\lambda}) = 0 \quad (5)$$

where each matrix J_k is derived from matrix J by replacing the i-th row with a zero row vector if $\overline{\tau}_i \neq k\tau$. Some matrices J_k may be zero matrices if $\overline{\tau}_i \neq k\tau$ for all i = 1,2,..., n.

The local stability of model (1) depends on the roots of characteristic equation (5) and can be defined as follows

***Definition** [8, 9]*: Genetic regulatory network (1) is said to be locally stable for some time delay $\tau \geq 0$ if

$$\det((sI_n + K_m)(sI_n + K_p) - \sum_{k=1}^{q} J_k e^{-k\tau s}) \neq 0\ ,\ \forall s \in \overline{C}_+ \quad (6)$$

where $C_+ := \{s = \alpha + j\omega, \mathrm{Re}(s) = \alpha > 0\}$ denotes the open right half of the complex number plane, $\overline{C}_+$ denotes its closure. Matrix J is calculated at the equilibrium state $(\overline{m},\overline{p})$.

In other words, for a given delay constant $\tau \geq 0$, genetic regulatory network (1) is locally stable if the characteristic equation (6) has no roots in the closed right-half plane. If the genetic regulatory network is stable for all $\tau \geq 0$, then it is said to be delay-independently locally stable. If there exists a root with the nonnegative real part, linear system (2) is unstable and thus genetic regulatory network (1) is unstable.

Suppose that genetic regulatory network (1) is locally stable for some $\tau \geq 0$. By the continuity of roots of equation (6), there must exist a neighborhood around τ such that over it network (1) remains locally stable. Knowing that network (1) is stable for some $\tau \geq 0$, one may naturally ask what is the largest interval around τ over which the network remains locally stable. Specifically, in this study, assume that genetic regulatory network (1) is locally stable for $\tau = 0$, we would like to find an interval $[0, \tau^+)$ such that for all $\tau \in [0, \tau^+)$ genetic regulatory network (1) is locally stable and over $\tau > \tau^+$ it is unstable. Furthermore, we would also like to study the oscillation of gene regulatory network (1) at $\tau = \tau^+$

III. Stability and Oscillation

To derive our results, we need the following lemmas.

Lemma 3.1: Let $K(s) = (sI_n + K_m)(sI_n + K_p)$, K_m and K_p be defined as in genetic regulatory network (1). Then $K^{-1}(s)$ is analytic in $\overline{C}_+$.

The proof of this lemma is straightforward [8]. For a given matrix $M \in C^{n\times n}$, let $\lambda_i(M)$ denote its *i*-th eigenvalue and $\rho(M)$ denote its spectral radius.

Lemma 3.2 *[12, 13]:* Let $M(s) \in C^{n\times n}$ be analytic in $\overline{C}_+$. Then its absolute values of n eigenvalues $|\lambda_i(M(s))|$ (*i* = 1, …, *n*) are continuous and sub-harmonic in $\overline{C}_+$, and therefore equation $|\lambda_i(M(j\omega))| = 1$ has only a finite number of solutions.

In the following, we first examine a simple case, which corresponds to the case $q = 1$. It will be seen that the results for this case can be extended to the case $q > 1$ in a straightforward manner. The case $q = 1$ biologically means that the total delay $\bar{\tau}$ of the transcriptional and translational processes for each gene product has the same value. i.e. $\tau \equiv \tau_{m_1} + \tau_{p_1} = \Lambda = \tau_{m_n} + \tau_{p_n}$. For this case equation (6) can be simplified as:

$$\det((sI_n + K_m)(sI_n + K_p) - Je^{-s\tau}) \neq 0, \ \forall s \in \overline{C}_+,$$

From Lemma 3.1, the above equation is equivalent to

$$\det(I - K^{-1}(s)Je^{-s\tau}) \neq 0, \ \forall s \in \overline{C}_+ \qquad (7)$$

***Theorem 3.1*:** Assume that genetic regulatory network (1) is locally stable for $\tau = 0$. Define $\tau^+ = \min_{1\leq i\leq n} \tau_i^+$ and τ_i^+ by the formulas at the bottom of this page. Then genetic regulatory network (1) is stable for any $\tau \in [0, \tau^+)$. If $\tau^+ < \infty$, the network becomes unstable at $\tau = \tau^+$.

Proof: From [8, 9], if $\rho(K^{-1}(j\omega)J) < 1$, $\forall \omega > 0$, the genetic regulatory network is delay-independent locally stable, that is, $\tau^+ = \infty$. Now suppose that $\tau^+ < \infty$, for any $\tau \in [0, \tau^+)$, we claim that for $\forall \omega \geq 0$

$$\det(I - K^{-1}(j\omega)Je^{-j\omega\tau}) \neq 0, \qquad (8)$$

In the case $\omega \neq \omega_k^i$, $|\lambda_i(K^{-1}(j\omega)Je^{-j\omega\tau})| = |\lambda_i(K^{-1}(j\omega)J)| \neq 1$, and thus inequality (8) is true. In addition, from the definition of τ^+, only if $\omega_k^i\tau = \alpha_k^i$, we have

$$\det(I - K^{-1}(j\omega_k^i)Je^{-j\omega_k^i\tau}) = \det(I - K^{-1}(j\omega_k^i)Je^{-j\alpha_k^i}) = 0,$$

However, in case $\omega = \omega_k^i$, we have $\omega_k^i\tau < \alpha_k^i$ for any $\tau \in [0, \tau^+)$, and thus again inequality (8) is true. This proves the claim. As genetic regulatory network (1) is locally stable for $\tau = 0$, by continuity of the characteristic roots, we establish the local stability of network (1).

On the other hand, if $\tau = \tau^+$, then there exists a pair of (ω_k^i, α_k^i) such that $\tau^+ = \alpha_k^i / \omega_k^i$, and

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$$\tau_i^+ = \begin{cases} \min_{|\lambda_i(K^{-1}(j\omega_k^i)J)|=1} \{\alpha_k^i / \omega_k^i\} & \text{if } \lambda_i(K^{-1}(j\omega_k^i)J) = e^{j\alpha_k^i}, \text{for some } \omega_k^i > 0, \alpha_k^i \in (0, 2\pi) \\ \infty & \text{if } \rho(K^{-1}(j\omega)J) < 1, \forall \omega > 0 \end{cases}$$

where $\lambda_i(M)$ stands for the *i*-th eigenvalues of matrix M, and $\rho(M)$ for the spectral radius of matrix M, which is defined as the largest absolute value of the eigenvalues of matrix M

$$\det(I - K^{-1}(j\omega_k^i)Je^{-j\omega_k^i\tau^+}) = \det(I - K^{-1}(j\omega_k^i)Je^{-j\alpha_k^i})$$
$$\left[e^{-j\alpha_k^i}\right]^n \det(e^{j\alpha_k^i} I - K^{-1}(j\omega_k^i)J) = 0,$$

Hence, genetic network becomes unstable. This completes the proof of Theorem 3.1

To have a bounded delay interval for stability, it is necessary that $\rho(K^{-1}(j\omega^*)J) \geq 1$ for some $\omega^* \in (0,\infty)$. Actually, only under this condition, there exists $\omega_k^i \in (0,\infty)$ such that $\left|\lambda_i(K^{-1}(j\omega_k^i)J)\right| = 1$ for some $1 \leq i \leq n$ because of Lemma 3.2 and the factor that $\lim_{\omega\to\infty} \rho(K^{-1}(j\omega)J) = 0$. Therefore, to compute the delay interval for stability, the eigenvalues of $K^{-1}(j\omega)J$ should first be calculated. If for $\forall \omega > 0$, $\rho(K^{-1}(j\omega)J) < 1$, then one may conclude that genetic regulatory network (1) is locally delay-independently stable. Otherwise computing ω_k^i and α_k^i, one may immediately determine the value of τ^+. By Lemma 3.2, to find the maximal delay τ^+ for stability, only a finite number of frequencies ω_k^i are required to check.

From the proof of Theorem 3.1 and the definition of τ^+, if there exists a unique pair of (ω^+, α^+) such that $\tau^+ = \alpha^+ / \omega^+$, then $s = j\omega^+$ is the root of the characteristic equation

$$\det((sI_n + K_m)(sI_n + K_p) - Je^{-s\tau^+}) = 0 \qquad (9)$$

As all constants are real numbers, $s = -j\omega^+$ is also a root of the characteristic equation. Now we have the following theorem about the oscillation of genetic regulatory networks.

***Theorem 3.2*:** If (ω^+, α^+) is a unique pair such that $\tau^+ = \alpha^+ / \omega^+$, then characteristic equation (9) has two simple roots $s = \pm j\omega^+$ and the remaining roots have negative real parts. Furthermore, genetic regulatory network (1) with time delay τ^+ oscillates locally with a fundamental period of $T = 2\pi / \omega^+$.

The proof of the first part of Theorem 3.2 has been discussed in the previous paragraph. The second part can be proved according to the first part and results in [13].

In the remainder of this section we extend Theorems 3.1 and 3.2 to the general case $q > 1$. The strategy in this extension to transform the problem to the one similar to the case $q = 1$.

***Theorem** 3.3:* Assume that genetic regulatory network (1) is locally stable for $\tau = 0$. For the case $q > 1$, define $\tau^+ = \min_{1\leq i\leq n} \tau_i^+$ and τ_i^+ by the formulas at the bottom of this page where

$$M(s) := \begin{bmatrix} K^{-1}(s)J_1 & \Lambda & K^{-1}(s)J_{q-1} & K^{-1}(s)J_q \\ I & \Lambda & 0 & 0 \\ \mathrm{M} & \mathrm{O} & \mathrm{M} & \mathrm{M} \\ 0 & & I & 0 \end{bmatrix}$$

Then genetic regulatory network (1) is stable for any $\tau \in [0, \tau^+)$. If $\tau^+ < \infty$, the network becomes unstable at $\tau = \tau^+$. Furthermore, if (ω^+, α^+) is a unique pair such that $\tau^+ = \alpha^+ / \omega^+$, then genetic regulatory network (1) with time delay τ^+ oscillates locally with a fundamental period of $T = 2\pi / \omega^+$.

Proof: From Lemma 3.1, equation (6) is equivalent to

$$\det(I - \sum_{k=1}^{q} K^{-1}(s)J_k e^{-k\tau s}) \neq 0 \qquad (10)$$

By repeating to use Schur's complement identity [14], it follows that

$$\det(I - \sum_{k=1}^{q} K^{-1}(s)J_k e^{-k\tau s}) = \det(I - M(s)e^{-\tau s}) \qquad (11)$$

Comparing equations (11) and (7), the proof of Theorem 3.3 can be completed by following the proof of Theorems 3.1 and 3.2 in which matrix $K^{-1}(s)J$ is replaced by matrix $M(s)$.

IV. ILLUSTRATIVE EXAMPLE

Lewis [6] proposed the auto-regulatory genetic circuit with time delay for both her1 and her7 of zebrafish described by the following equation:

$$\tau_i^+ = \begin{cases} \min_{|\lambda_i(M(j\omega_k^i))|=1} \{\alpha_k^i / \omega_k^i\} & \text{if } \lambda_i(M(j\omega_k^i)) = e^{j\alpha_k^i}, \text{for some } \omega_k^i > 0, \alpha_k^i \in (0, 2\pi) \\ \infty & \text{if } \rho(M(j\omega)) < 1, \forall \omega > 0 \end{cases}$$

where $\lambda_i(M)$ stands for the *i*-th eigenvalues of matrix M, and $\rho(M)$ for the spectral radius of matrix M, which is defined as the largest absolute value of the eigenvalues of matrix M

$$\begin{aligned} \dot{m}(t) &= -k_m m(t) + f(p(t-\tau_p)) \\ \dot{p}(t) &= -k_p p(t) + am(t-\tau_m) \end{aligned} \tag{12}$$

where $f(p(t)) = k/(1+p^2/p_0^2)$. k_m and k_p are the decay rates (inverse lifetime) of mRNA and protein molecules [1/min], respectively, a is the rate of production new mRNA molecules [1/min], k is the number of mRNA molecules per diploid cell [1/min], and p_0 is the number of initial protein molecules.

For network (12), we have that $K(s) = (s+k_m)(s+k_p)$. As parameters and variables in network (12) are nonnegative real numbers, it has a unique equilibrium state $(\overline{m}, \overline{p}) = (k_p u/a, u)$ where u is the unique positive solution of the following nonlinear equation

$$u^3 + p_0^2 u - p_0^2 ak/(k_p k_m) = 0 \tag{13}$$

At the equilibrium state, we have

$$J_c = -2kp_0^2 u/(p_0^2+u^2)^2 \text{ and } J_d = a$$

thus $J = J_c J_d = -2kap_0^2 u/(p_0^2+u^2)^2$, and $K^{-1}(j\omega)J$ has a single eigenvalue

$$\lambda(K^{-1}(j\omega)J) = J/[(j\omega+k_m)(j\omega+k_p)] \tag{14}$$

and a spectral radius

$$\rho(K^{-1}(j\omega)J) = |J|/\sqrt{(\omega^2+k_m^2)(\omega^2+k_p^2)}$$

From Theorem 3.1, regulatory network (12) is delay-independently locally stable if inequality $|J| < k_m k_p$ holds

To have the finite delay for stability, let's assume that $|J| > k_m k_p$. From equation $|\lambda(K^{-1}(j\omega)J)| = 1$, it follows

$$\omega^4 + (k_m^2+k_p^2)\omega^2 + k_m^2 k_p^2 - J^2 = 0$$

Solving the above equation for ω, we get the unique positive solution

$$\omega = \sqrt{\left[\sqrt{(k_m^2-k_p^2)^2+4J^2} - (k_m^2+k_p^2)\right]/2} \tag{15}$$

Substituting the above value of ω into equation (14) leads

$$\lambda(K^{-1}(j\omega)J) = e^{j(\pi-\theta)}$$

where $\theta = a\tan((k_m+k_p)\omega/(k_m k_p - \omega^2))$ and $0 \le \theta < \pi$. Therefore, we have

$$\tau^+ = (\pi-\theta)/\omega \tag{16}$$

and from Theorem 3.2 network (12) with time delay τ^+ should locally oscillate with the fundamental period of

$$T = 2\pi/\omega = 2\tau^+ + 2\theta/\omega. \tag{17}$$

In paper [6], Lewis took the values of parameters in network (12) as $k_m = k_p = 0.23$ molecules per minute, $a = 4.5$ protein molecules per mRNA molecule per minute, $k = 33$ mRNA molecules per diploid per cell per minute, and $p_0 = 40$ molecules. Those values were estimated according to the real-life regulatory network of a zebrafish. In regulatory network model (12), for gene her1 he estimated the values of delay between 13.0 and 34.3 minutes, and then estimated the period of oscillation as 47 minutes which is far from the period of 30 minutes observed in a real-life zebrafish. For gene her7 he estimated the values of delay between 7.6 and 21.8 minutes, and then estimated the period of oscillation as about 30 minutes which is the same as the observed period.

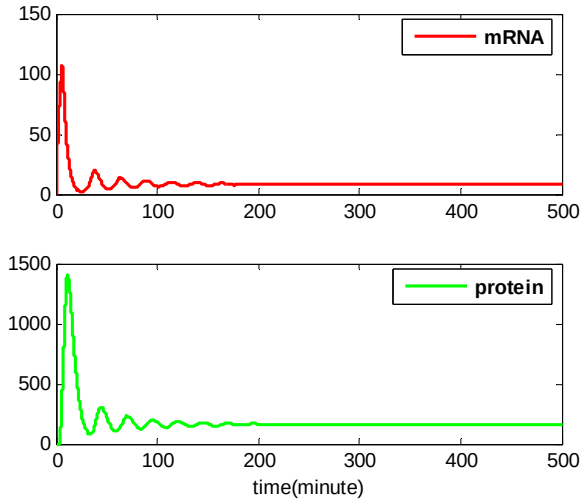

Figure 1. Simulation of gene regulatory network (12) with time delay of 5.55 minutes

However, from our study the values of time delay and oscillation period solely depend on the values of parameters k_m, k_p, a, k, and p_0, seeing equations (13) - (17). Substituting the same values of these parameters as used by Lewis [6] into equations (13) – (17), we calculate out that the maximal time delay for stability of network (12) is 7.55 minutes. By Theorem 3.1, when the time delay is less than 7.55 minutes, gene regulatory network will be stable. Figure 1 shows the simulation of gene regulatory network (12) with time delay of 5.55 minutes. It shows that the network is stable and converges to the equilibrium state $(\overline{m}, \overline{p})$ = (8.27, 161.76). We also simulate gene regulatory network (12) with time delay of 7.55 minutes and show the simulation results in Figure 2. From Figure 2, we can see that network (12) with this time delay oscillates around the equilibrium state $(\overline{m}, \overline{p})$ = (8.27, 161.76). By using formula (17), the oscillation period is calculated as 29.04 minutes, which is very close to the observed period. Compared to the results from Lewis [6], our method can accurately estimate the oscillation period and the time delay from parameters k_m, k_p, a, k, and p_0.

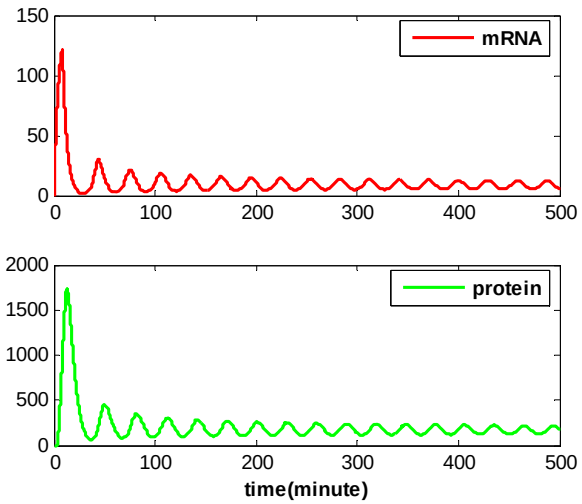

Figure 2. Simulation of gene regulatory network (12) with time delay of 7.55 minutes

V. Conclusion

In this paper, we have developed a method for computing the maximal delay interval over which a genetic regulatory network maintains stability. Furthermore we have proved that the network becomes unstable, but locally oscillated when its delay is equal to the maximal delay for stability. In addition, the formula for computing the oscillation period has been provided. The analysis of genetic regulatory network in a zebrafish has illustrated that the oscillation period can be accurately calculated by using our method. Compared to study in [6], this study is more rigorous and more general. The results of this study are expected to apply to synthesis of gene regulatory networks, which also is one direction of our future work.

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