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Periodic Solution for a Delayed Gene Expression Model

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ABSTRACT

In this paper, a modified gene expression model with discrete delays is studied. The oscillatory behavior of the solutions is investigated. Make the change of variables, and the model will be linearized to a time-delayed system. The instability of the trivial solution of the linearized system implies the instability of the equilibrium point of the original model. It will generate a periodic oscillatory solution in which the original system has only one equilibrium point. We extend the result in the literature from stability to oscillation of the model. Some sufficient conditions to guarantee the oscillation of the solutions are provided, and computer simulations are given to support the present result.

Keywords: delayed gene expression model, delay, instability, oscillation.

INTRODUCTION

Genetic regulatory networks are biochemical dynamical systems. There are many models that have been proposed. For example, Wang et al. investigated the following delayed gene regulatory model:

$$\begin{cases} x_1'(t) = r_1 - d_1x_1(t) + \beta_1 f_1\big(x_1(t-\tau_1)\big) - k_1 g_1\big(x_1(t)\big)x_2(t), \\ x_2'(t) = r_2 - d_2x_2(t) + \beta_2 f_2\big(x_2(t-\tau_2)\big) - k_2 g_2\big(x_2(t)\big)x_1(t), \end{cases} \tag{1}$$

where $x_1(t)$ and $x_2(t)$ represent the concentrations of mRNA and protein, respectively. $f_i(x_i)$ and $g_i(x_i)$ are Hill functions ($i = 1,2$). By using the normal form method and central manifold theorem, the hybrid control scheme was proposed, and the bifurcation properties of the controlled system were exhibited [1]. Gao and Li [2] proposed the following delayed gene regulatory model of the form

$$\begin{cases} x'(t) = dx(t) + f\big(y(t)\big) - bx(t-p)y(t-p), \\ y'(t) = my(t) + kx(t), \\ v'(t) = \lambda - nv(t) - bx(t-p)y(t-p). \end{cases} \tag{2}$$

The authors introduced a generalized hybrid control to control the unstable dynamical behavior induced by time delay. Firstly, the equilibrium point of the network model (2) was calculated. Then, a systematical dynamics analysis was performed to derive sufficient conditions to generate the Hopf bifurcation. Yue et al. established a discrete-time genetic model and obtained the conditions for the existence and stability of fixed points [3]. For stability, bifurcations, and chaos of various gene regulatory models, one can see [4-16]. Noting that the effect of distributed time delays on the dynamics of a model of gene expression is different from a discrete delayed model. Song et al. discussed the following model:

$$\begin{cases} m'(t) = \alpha_m/(1 + \int_0^{\infty} p(t-\xi)\, g(\xi) d\xi)^h - \mu_m m(t), \\ p'(t) = \alpha_p m(t) - \mu_p p(t). \end{cases} \tag{3}$$

Both the weak and strong delay kernels were discussed. Sufficient conditions for the local stability of the unique equilibrium were obtained. Taking the average delay as a bifurcation parameter, the direction of the Hopf bifurcations, and the stability of the bifurcating periodic solutions by using the method of multiple time scales were investigated [17]. Qing et al. extended model (3) to a three-dimensional system of the following:

$$\begin{cases} x'(t) = cx(t) - dy(t)x(t) + g\left(\int_{-\infty}^{t} T(t-x)\, z(x) dx\right), \\ y'(t) = c - dy(t)x(t) - fy(t), \\ z'(t) = -bz(t) + ax(t-\tau), \end{cases} \tag{4}$$

where time delay kernel function T is presumed to satisfy some conditions as follows: $T(x) = \sigma^{n+1}\frac{x^n e^{-\sigma x}}{n!}, x \in (0, +\infty), n = 0{,}1$. The discrete time delay τ is chosen as the bifurcation parameter. By analyzing the distribution of characteristic values, the sufficient conditions of the stability and the existence of periodic oscillations for model (4) were obtained [18]. In [19], Wang et al. investigated the Hopf bifurcation induced by time delay and the direction of the Hopf bifurcation for the following four-dimensional genetic regulatory network model:

$$\begin{cases} M_1'(t) = -a_1 M_1(t) + b_{11} f_1\big(P_1(t-\sigma_3)\big) + b_{12} f_2\big(P_2(t-\sigma_3)\big) + B_1, \\ M_2'(t) = -a_2 M_2(t) + b_{21} f_1\big(P_1(t-\sigma_4)\big) + b_{22} f_2\big(P_2(t-\sigma_4)\big) + B_2, \\ P_1'(t) = -c_1 P_1(t) + d_1 M_1(t-\sigma_1), \\ P_2'(t) = -c_2 P_2(t) + d_2 M_2(t-\sigma_2). \end{cases} \tag{5}$$

In [20], a delayed mass action version of the gene model of the binding-site clearance delays for both the promoter and ribosome binding site (RBS) was formed:

$$\begin{cases} K_{in} \to S(t), \\ E(t) + S(t)\ \overrightarrow{K_1}\ C(t)\ \overrightarrow{K_{-2}}\ E(t) + Q(t), \\ E(t) + S(t)\ \overleftarrow{K_{-1}}\ C(t) \to E(t) + Q(t), \\ nS(t) + A(t)\, \overrightarrow{K_3}\, P(t), \\ nS(t) + A(t)\ \overleftarrow{K_{-3}}\ P(t), \\ P(t)\ \overrightarrow{K_4}\ P(t+\tau_1) + R(t+\tau_2), \\ R(t)\ \overrightarrow{K_5}\ R(t+\tau_3) + E(t+\tau_4), \\ R(t)\ \overrightarrow{K_6} \end{cases} \tag{6}$$

In this model, $S(t)$ is a substrate to be metabolized to a product $Q(t)$ by the enzyme $E(t)$. $E(t)$ is synthesized by the usual gene expression pathway. The active gene promoter, $P(t)$ is cleared and the RNA. Define the following dimensionless variables: $c(t) = \frac{C(t)}{K_m}$, $e(t) = \frac{E(t)}{K_m}$, $s(t) = \frac{S(t)}{K_m}$, $a(t) = \frac{A(t)}{K_m}$, $p(t) = \frac{P(t)}{K_m}$, $r(t) = \frac{R(t)}{K_m}$, where K_m is the Michaelis constant. Then a delayed gene expression model was given as follows:

$$\begin{cases} c'(t) = e(t)s(t) - c(t), \\ e'(t) = -e(t)s(t) - k_2 e(t) + c(t) + k_5 r(t-\tau_4), \\ s'(t) = k_{in} - e(t)s(t) + k_{-1}c(t) - nk_3 s^n(t)a(t) + nk_{-3}p(t), \\ a'(t) = -k_3 s^n(t)a(t) + k_{-3}p(t), \\ p'(t) = k_3 s^n(t)a(t) - (k_{-3} + k_4)p(t) + k_4 p(t-\tau_1), \\ r'(t) = -(k_5 + k_6)r(t) + k_4 p(t-\tau_2) + k_5 r(t-\tau_3), \end{cases} \tag{7}$$

where k_{in}, k_{-1}, k_{-3}, k_3, k_4, k_5 are real positive numbers. By using the "small-gain" theorem, the stability of the model (7) was analyzed, the existence of a positive equilibrium point and the boundedness of the solutions for model (7) were discussed. It is known that periodic oscillation is an important property for various gene models. This paper will study the periodic solution for a modified model (7) as the follows:

$$\begin{cases} c'(t) = e(t)s(t) - k_{10}c(t) - k_{11}c(t-\tau_5), \\ e'(t) = -e(t)s(t) - k_2 e(t) + c(t) + k_5 r(t-\tau_4), \\ s'(t) = k_{in} - e(t)s(t) + k_{-1}c(t-\tau_5) - nk_3 s^n(t)a(t) + nk_{-3}p(t), \\ a'(t) = -k_3 s^n(t)a(t) + k_{-3}p(t), \\ p'(t) = k_3 s^n(t)a(t) - (k_{-3} + k_4)p(t) + k_4 p(t-\tau_1), \\ r'(t) = -(k_5 + k_6)r(t) + k_4 p(t-\tau_2) + k_5 r(t-\tau_3), \end{cases} \tag{8}$$

where k_{10} , k_{11} are positive constants. The general bifurcation method can discuss the bifurcating periodic solution for model (8). However, there are five time delays in model (8). It is not easy to deal with model (8) by employing the bifurcation method if the five delays are different positive numbers, as in our simulation. In this paper, we will use the method of mathematical analysis to discuss the existence of periodic solutions for model (8). Assume that $(c^*, e^*, s^*, a^*, p^*, r^*)^T$ is an equilibrium point of the system (8), then we have

$$\begin{cases} e^*\, s^* - k_{10}c^* - k_{11}c^* = 0, \\ -e^*\, s^* - k_2 e^* + \ c^* + k_5\, r^* = 0, \\ k_{in} - \ e^*\, s^* + k_{-1}\, c^* - nk_3 (s^*)^n\, a^* + nk_{-3}\, p^* = 0, \\ -k_3 (s^*)^n\, a^* + k_{-3}\, p^* = 0, \\ k_3 (s^*)^n\, a^* - (k_{-3} + k_4)p^* + k_4 p^* = 0, \\ -(k_5 + k_6)r^* + k_4 p^* + k_5 r^* = 0. \end{cases} \tag{9}$$

Make the change of variables $c(t) \to c(t) - \ c^*, e(t) \to e(t) - \ e^*, s(t) \to s(t) - \ s^*, a(t) \to a(t) - a^*, p(t) \to p(t) - p^*, r(t) \to r(t) - r^*$, and the equilibrium point at system (8) will be shifted to the trivial equilibrium and we have the following system:

$$\begin{cases} c'(t) = -k_{10}c(t) - k_{11}c(t-\tau_5) + s^*e(t) + e^*s(t) + e(t)s(t), \\ e'(t) = c(t) - (s^* + k_2)e(t) - e^*s(t) - e(t)s(t) + k_5 r(t-\tau_4), \\ s'(t) = k_{-1}c(t-\tau_5) - s^*e(t) - (e^* + n^2k_3a^*(s^*)^{n-1})s(t) - nk_3a^*\left(s^*\right)^n a(t)\big) \\ +nk_{-3}p(t) - nk_3a(t)[s^n + ns^*s^{n-1} + \cdots + n(s^*)^{n-1}s(t)] - e(t)s(t), \\ a'(t) = -nk_3a^*(s^*)^{n-1}s(t) - k_3(s^*)^n a(t) + k_{-3}p(t) \\ -k_3a(t)[s^n + ns^*s^{n-1} + \cdots + n(s^*)^{n-1}s(t)], \\ p'(t) = nk_3a^*(s^*)^{n-1}s(t) + k_3(s^*)^n a(t) - (k_{-3} + k_4)p(t) + k_4p(t-\tau_1) \\ +k_3a(t)[s^n + ns^*s^{n-1} + \cdots + n(s^*)^{n-1}s(t)] \\ r'(t) = -(k_5 + k_6)r(t) + k_4p(t-\tau_2) + k_5r(t-\tau_3). \end{cases} \quad (10)$$

The system (10) can be expressed in the following matrix form:

$$y'(t) = My(t) + Ny(t-\tau) + g\big(y(t)\big), \quad (11)$$

where $y(t) = (c(t), e(t), s(t), a(t), p(t), r(t))^T$, $y(t-\tau) = (c(t-\tau_5), 0, p(t-\tau_1), p(t-\tau_2), r(t-\tau_3),\ r(t-\tau_4))^T$, M and N both are 6×6 matrices.

$$M = (m_{ij})_{6\times 6} = \begin{pmatrix} m_{11} & m_{12} & m_{13} & 0 & 0 & 0 \\ m_{21} & m_{22} & m_{23} & 0 & 0 & 0 \\ 0 & m_{32} & m_{33} & m_{34} & m_{35} & 0 \\ 0 & 0 & m_{43} & m_{44} & m_{45} & 0 \\ 0 & 0 & m_{53} & m_{54} & m_{55} & 0 \\ 0 & 0 & 0 & 0 & 0 & m_{66} \end{pmatrix},$$

$$N = (n_{ij})_{6\times 6} = \begin{pmatrix} -k_{11} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & k_3 \\ k_{-1} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & k_4 & 0 \\ 0 & 0 & 0 & 0 & k_4 & k_5 \end{pmatrix},$$

where $m_{11} = -k_{10}$, $m_{12} = s^*, m_{13} = e^*, m_{21} = 1, m_{22} = -(s^* + k_2), m_{23} = -e^*, m_{32} = -s^*, m_{33} = -(e^* + n^2k_3a^*(s^*)^{n-1}), m_{34} = -nk_3(s^*)^n, m_{35} = nk_{-3}, m_{43} = -nk_3a^*(s^*)^{n-1}, m_{44} = k_3(s^*)^n, m_{45} = -(k_{-3} + k_4), m_{53} = nk_3a^*(s^*)^{n-1}, m_{54} = k_3(s^*)^n, m_{55} = -(k_{-3} + k_4), m_{66} = -(k_5 + k_6)$. The nonlinear term $g\big(y(t)\big) = (e(t)s(t), -e(t)s(t), \cdots, k_3a(t)[s^n + ns^*s^{n-1} + \cdots + n(s^*)^{n-1}s(t)], 0)^T$. The linearized equation of (11) is as follows:

$$y'(t) = My(t) + Ny(t-\tau). \quad (12)$$

We first have the following two lemmas:

Lemma 1 If matrix $M + N$ is a nonsingular matrix for selected parameters, then there exists a unique equilibrium point for system (8).

Proof If system (12) has a unique trivial equilibrium point, then system (10) or (11) has a unique trivial equilibrium point, since $g(\mathbf{0}) = \mathbf{0}$, this suggests that system (9) has a unique trivial equilibrium point, implying that system (8) has a unique equilibrium point. Now, assume that $y^* = (c^*, e^*, s^*, a^*, p^*, r^*)^T$ is an equilibrium point of the system (12), then we have the following algebraic equations:

$$(M + N)y^* = \mathbf{0}. \tag{13}$$

According to the basic linear algebraic knowledge, system (13) has a unique trivial solution since $M + N$ is a nonsingular matrix, implying that there is a unique equilibrium point in the system (8).

Lemma 2 All solutions of system (8) are bounded.

Proof Since the time delay does not affect the boundedness of the solutions, the proof is similar to [20].

In the following, we provide two theorems to guarantee the existence of periodic solutions for model (8).

THE EXISTENCE OF PERIODIC OSCILLATORY SOLUTIONS

Theorem 1 Assume that the system (8) has a unique equilibrium point. Let $\rho_1, \rho_2, \cdots, \rho_6, \delta_1, \delta_2, \cdots, \delta_6$ be characteristic values of matrix M and N, respectively. If there is some ρ_i, say ρ_1 such that $Re(\rho_1) > 0$, or there exists some δ_i, say δ_1 such that $Re(\delta_1) > Re(\rho_1)$, then the unique equilibrium point of system (8) is unstable, implying that there exists a periodic oscillatory solution in the system (8).

Proof The trivial equilibrium of the system (12) corresponds to the equilibrium point $y^* = (c^*, e^*, s^*, a^*, p^*, r^*)^T$ of the system (8). Therefore, if the trivial equilibrium is unstable, then the equilibrium point $(c^*, e^*, s^*, a^*, p^*, r^*)^T$ is still unstable. To discuss the instability of the equilibrium point of the system (8), we only need to deal with the instability of the trivial solution of the system (12). Since $\rho_1, \rho_2, \cdots, \rho_6, \delta_1, \delta_2, \cdots, \delta_6$ are characteristic values of matrix M and N, respectively, we have at least one $\delta_i = 0$ from the matrix N. Then the characteristic equations corresponding to the system (12) are the following:

$$\prod_{i=1}^{5}\left(\lambda - \rho_i - \delta_i e^{-\lambda\tau_i}\right) = 0 \tag{14}$$

Or

$$\lambda - \rho_6 = 0 \tag{15}$$

Thus, we are led to investigate the nature of the roots of the equation (15) and the following equation:

$$\lambda - \rho_1 - \delta_1 e^{-\lambda\tau_1} = 0 \tag{16}$$

If $Re(\rho_6) > 0$, then equation (15) has a positive real part eigenvalue. If equation (16) holds, we show that there exists a positive real part eigenvalue of equation (16) under the assumptions of Theorem 1. Indeed, if $Re(\delta_1) > Re(\rho_1)$, setting $\lambda = \lambda_1 + i\lambda_2$, $\rho_1 = \rho_{11} + i\rho_{12}$, $\delta_1 = \delta_{11} + i\delta_{12}, \lambda_1 = Re(\lambda), \lambda_2 = Im(\lambda), \rho_{11} = Re(\rho_1), \rho_{12} = Im(\rho_1), \delta_{11} = Re(\delta_1), \delta_{12} = Im(\delta_1)$. Separating the real part and imaginary part of the equation (16), we get

$$\lambda_1 = \rho_{11} + \delta_{11}e^{-\lambda_1\tau_1}\cos(\lambda_2\tau_1) - \delta_{12}e^{-\lambda_1\tau_1}\sin(\lambda_2\tau_1). \tag{17}$$

We show that equation (17) has a positive root. Let

$$\phi(\lambda_1) = \lambda_1 - \rho_{11} - \delta_{11}e^{-\lambda_1\tau_1}\cos(\lambda_2\tau_1) + \delta_{12}e^{-\lambda_1\tau_1}\sin(\lambda_2\tau_1). \tag{18}$$

Obviously, $\phi(\lambda_1)$ is a continuous function of λ_1. Noting that $\delta_{11} > \rho_{11}$, then $\phi(0) = -\rho_{11} - \delta_{11}\cos(\lambda_2\tau_1) + \delta_{12}\sin(\lambda_2\tau_1) \le -\rho_{11} - \delta_{11} < 0$ as $\lambda_2\tau_1 \sim 2n\pi$, where n is an integer number. Since $\lim_{\lambda_1\to\infty} e^{-\lambda_1\tau_1} = 0$, so there exists a suitably large λ_1, say λ_1^* (> 0) such that

$$\phi(\lambda_1^*) = \lambda_1^* - \rho_{11} - \delta_{11}e^{-\lambda_1^*\tau_1}\cos(\lambda_2\tau_1) + \delta_{12}e^{-\lambda_1^*\tau_1}\sin(\lambda_2\tau_1) > 0. \tag{19}$$

By the Intermediate Value Theorem, there exists a λ_1, say $\lambda_{10} \in (0, \lambda_1^*)$ such that $\phi(\lambda_{10}) = 0$, implying that there is a positive real part characteristic value of equation (17). This means that the trivial solution of the system (12) is unstable, implying that the unique equilibrium point $(c^*, e^*, s^*, a^*, p^*, r^*)^T$ of the system (8) is unstable. This instability of the unique equilibrium point, together with the boundedness of the solutions, will force system (8) to generate an oscillatory solution [21, 22]. The proof is completed.

Now setting $\mu(M) = \max_{1\le j\le 6}\left(m_{jj} + \sum_{i=1,i\ne j}^{6}|m_{ij}|\right)$, $\sigma = \max\{k_{11} + k_{-1}, 2k_{4,}, k_3 + k_5\}$ [23]. Then we have

Theorem 2 Assume that the conditions of Lemma 1 and Lemma 2 hold. If the following inequality holds

$$\mu(M) + \sigma > 0. \tag{20}$$

Then the unique trivial equilibrium point in system (12) is unstable, implying that the system (8) generates a periodic oscillatory solution.

Proof Let $\tau_* = \min\{\tau_1, \tau_2, \cdots, \tau_5\}$. To prove the instability of the trivial solution in system (12), let $w(t) = |c(t)| + |e(t)| + |s(t)| + |a(t)| + |p(t)| + |r(t)|$. So $w(t) > 0$ and we have:

$$w'(t) \le \mu(M)w(t) + \sigma w(t - \tau_*). \tag{21}$$

Specifically, consider the equation

$$z'(t) = \mu(M)z(t) + \sigma z(t - \tau_*). \tag{22}$$

Obviously, $w(t) \leq z(t)$. If the trivial solution of equation (22) is unstable, then the trivial solution of (21) is still unstable. The characteristic equation associated with equation (22) is given by

$$\lambda = \mu(M) + \sigma e^{-\lambda\tau_*} \tag{23}$$

We claim that there exists a positive root of (23) under the condition (20). Let $\varphi(\lambda) = \lambda - \mu(M) - \sigma e^{-\lambda\tau_*}$. Thus, $\varphi(\lambda)$ is a continuous function of λ. When λ = 0, we have $\varphi(0) = -\mu(M) - \sigma = -(\mu(M) + \sigma) < 0$, since $\mu(M) + \sigma > 0$. On the other hand, there exists a suitably large λ, say $\lambda_0 > 0$ such that $\varphi(\lambda_0) = \lambda_0 - \mu(M) - \sigma e^{-\lambda_0\tau_*} > 0$, since $e^{-\lambda_0\tau_*} \to 0$ as $\lambda_0 \to +\infty$. Again, based on the Intermediate Value Theorem, there exists a λ, say $\lambda_* \in (0, \lambda_0)$ such that $\varphi(\lambda_*) = \lambda_* - \mu(M) - \sigma e^{-\lambda_*\tau_*} = 0$. In other words, λ_* is a positive characteristic root of the equation (23). So the trivial solution of the equation (22) is unstable. According to the property of the delayed differential equation, when $\tau_i \geq \tau_*$ $(i = 1, 2, \cdots, 5)$, the trivial solution of the equation (22) is still unstable, implying that the unique equilibrium point $(c^*, e^*, s^*, a^*, p^*, r^*)^T$ of the system (8) is unstable. Similar to Theorem 1, there exists a periodic solution of the system (8). The proof is completed.

SIMULATION RESULT

This simulation is based on the system (8). Firstly, the parameters are selected as follows: $k_{in} = 5.5, k_{10} = 0.16, k_{11} = 0.658, k_{-1} = 0.24, k_{-3} = 0.15, n = 3, k_2 = 0.76, k_3 = 0.068, k_4 = 0.32, k_5 = 0.18, k_6 = 0.44$, then the unique positive equilibrium point is $(c^*, e^*, s^*, a^*, p^*, r^*)^T = (10.8823, 3.8123, 5.9598, 0.2236, 1.5014, 1.9598)^T$. Thus, $m_{11} = -0.16, m_{12} = 5.9598, m_{13} = 3.8123, m_{21}$ =1, $m_{22} = -6.7198, m_{23} = -3.8123, m_{32} = -5.9598, m_{33} = -5.8022, m_{34} = -11.3118, m_{35} = 0.45, m_{43} = -0.6633, m_{44} = -3.7706, m_{45} = -0.47, m_{53} = -5.8022, m_{54} = 3.7706, m_{55} = -0.47, m_{66} = -0.62$. Then the eigenvalues of matrix M and N are $-11.9368, -4.4368, -0.7653, -0.62, 0.1071 \pm 1.7505\, i$, and $0.32, -0.16, 0, 0, 0, 0$, respectively. We see that matrix M has a positive real part eigenvalue $0.1071 + 1.7505\, i$. Also matrix N has a positive eigenvalue $0.32 > 0.1071$. The conditions of Theorem 1 are satisfied. When time delays are selected as 1. 71, 1.72, 1.73, 1.74, 1.75, there is a periodic solution (see Fig.1). Then we change the parameter k_{in} as 4 and 2.5, respectively, the other parameters are the same as in Fig.1, the oscillatory behavior is maintained (see Fig.2 and Fig.3). Then we select another set of parameters as $k_{in} = 3.5, k_{10} = 0.16, k_{11} = 0.45, k_{-1} = 0.032, k_{-3} = 1.65, n = 3, k_2 = 0.86, k_3 = 0.68, k_4 = 0.65, k_5 = 0.28, k_6 = 0.72$, the equilibrium point is $(c^*, e^*, s^*, a^*, p^*, r^*)^T = (6.7601, 3.6639, 2.1642, 1.1384, 0.9442, 1.0164)^T$. We get $m_{11} = -0.16, m_{12} = 2.1642, m_{13} = 3.6639, m_{21}$ =1, $m_{22} = -3.0242, m_{23} = -3.6639, m_{32} = -2.1642, m_{33} = -36.2414, m_{34} = -20.6271, m_{35} = 4.95, m_{43} = -10.8592, m_{44} = -6.8757, m_{45} = -2.3, m_{53} = 10.8592, m_{54} = 6.8757, m_{55} = -2.3, m_{66} = -1$. Then $\mu(M) + \sigma$ = 21.9271 > 0. The conditions of Theorem 2 are satisfied. When time delays are selected as 2.15, 2.20, 2.25, 2.30, 2.35, there exists a periodic solution (see Fig.4). Then the value of k_{in} is changed from $k_{in} = 3.5$ to $k_{in} = 3$, the other parameters are the same as in Fig.4, we see that the oscillatory behavior is kept (see Fig.5). In Fig.6, the parameters $k_{in} = 3, n = 5, k_{-1} = 0.045$, the other parameters are the same as in Fig.4. Then we select another set of parameters as $k_{in} = 2, k_{10} = 0.16, k_{11} = 0.434, k_{-1} = 0.065, k_{-3} = 1.25, n = 2, k_2 = 0.85, k_3 = 0.78, k_4 = 0.68, k_5 = 0.28, k_6 = 0.82$, the equilibrium point is $(c^*, e^*, s^*, a^*, p^*, r^*)^T =$

$(4.0434, 2.3256, 1.4764, 1.1164, 0.9538, 0.7949)^T$. Thus, $m_{11} = -0.16, m_{12} = 1.4764, m_{13} = 2.3256, m_{21}$ =1, $m_{22} = -2.3264, m_{23} = -2.3256, m_{32} = -1.4764, m_{33} = -7.4681, m_{34} = -3.4104, m_{35} = 2.5, m_{43} = -2.5713, m_{44} = -1.7102,$ $m_{45} = -1.93, m_{53} = 2.5713, m_{54} = 1.7102, m_{55} = -1.93, m_{66} = -1.10.$

Fig.1 Oscillation of the solutions, Kin=5.5, n=3, delays: 1.71, 1.72, 1.73, 1.74, 1.75.

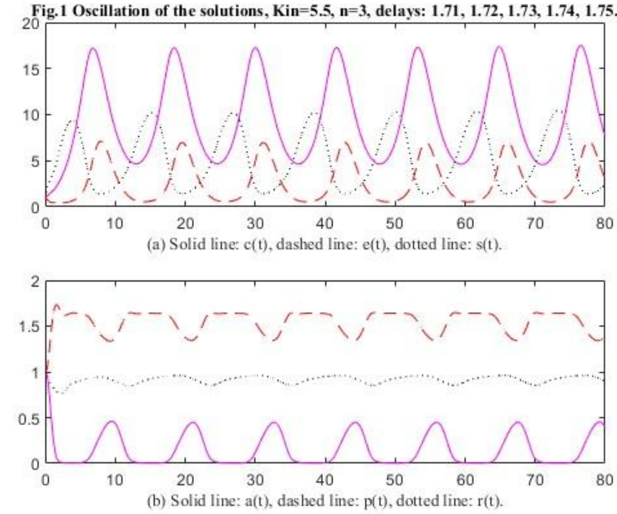


Fig.2 Oscillation of the solutions, Kin=4, n=3, delays: 1.71, 1.72, 1.73, 1.74, 1.75.

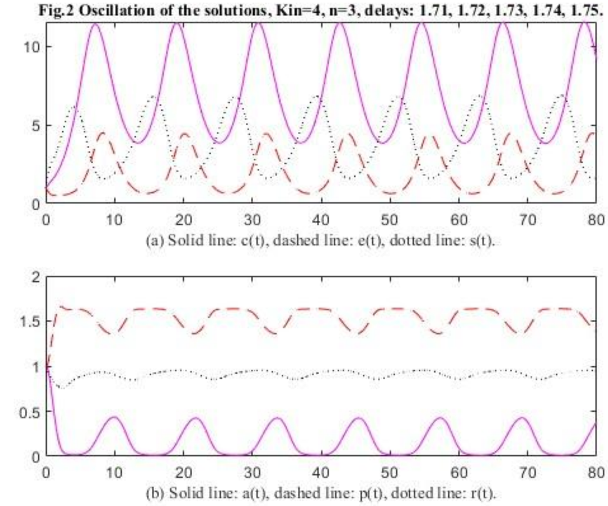
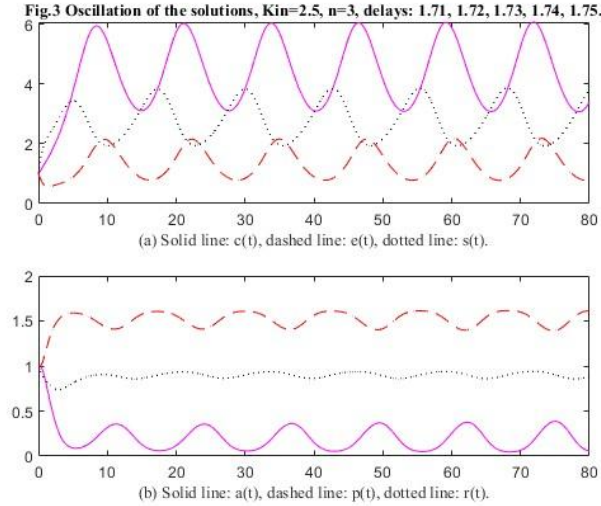


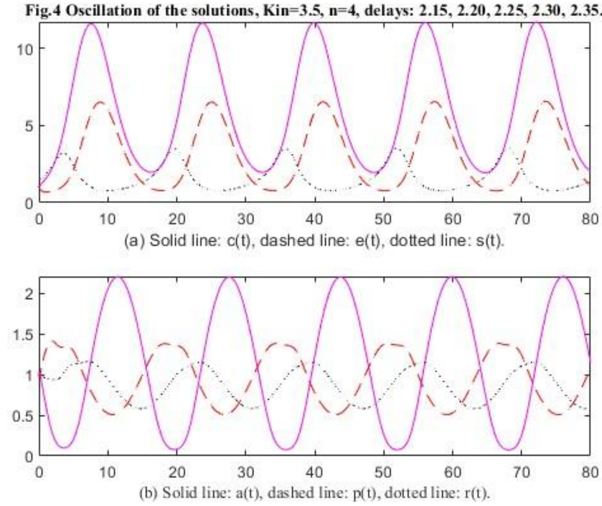
Fig.3 Oscillation of the solutions, Kin=2.5, n=3, delays: 1.71, 1.72, 1.73, 1.74, 1.75.



(a) Solid line: c(t), dashed line: e(t), dotted line: s(t).

(b) Solid line: a(t), dashed line: p(t), dotted line: r(t).

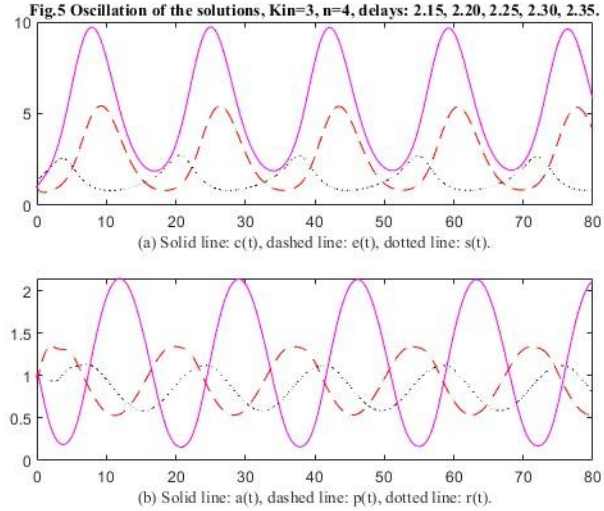
Fig.4 Oscillation of the solutions, Kin=3.5, n=4, delays: 2.15, 2.20, 2.25, 2.30, 2.35.



(a) Solid line: c(t), dashed line: e(t), dotted line: s(t).

(b) Solid line: a(t), dashed line: p(t), dotted line: r(t).

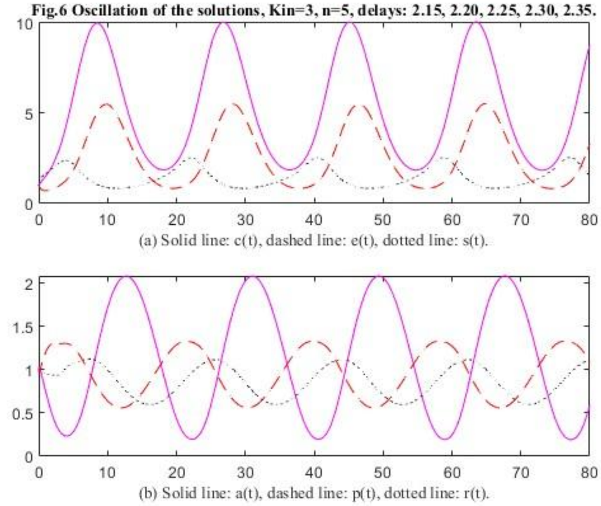
Fig.5 Oscillation of the solutions, Kin=3, n=4, delays: 2.15, 2.20, 2.25, 2.30, 2.35.



(a) Solid line: c(t), dashed line: e(t), dotted line: s(t).

(b) Solid line: a(t), dashed line: p(t), dotted line: r(t).

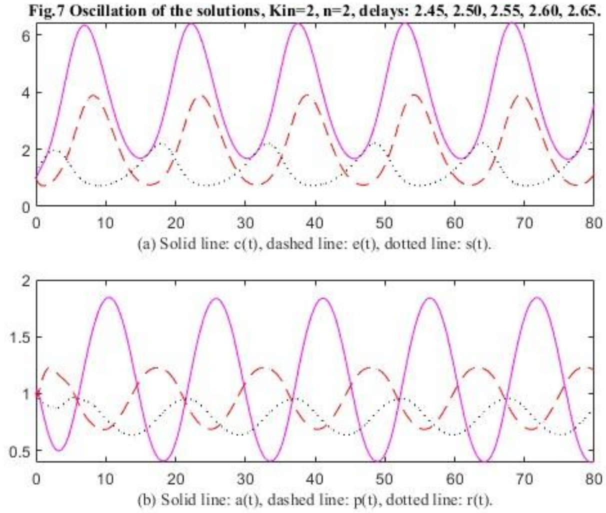
Fig.6 Oscillation of the solutions, Kin=3, n=5, delays: 2.15, 2.20, 2.25, 2.30, 2.35.



(a) Solid line: c(t), dashed line: e(t), dotted line: s(t).

(b) Solid line: a(t), dashed line: p(t), dotted line: r(t).

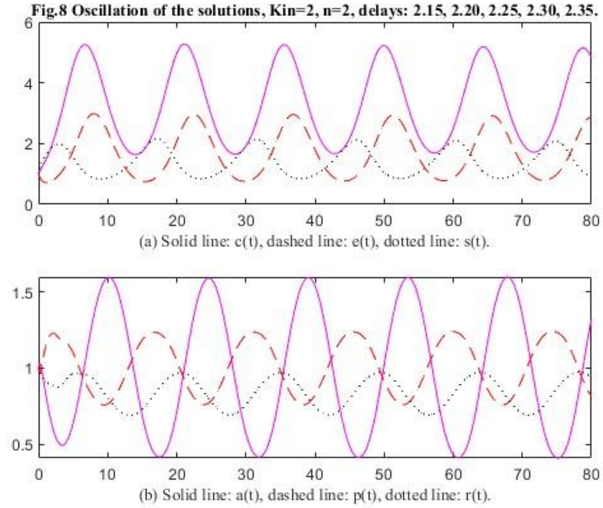
Fig.7 Oscillation of the solutions, Kin=2, n=2, delays: 2.45, 2.50, 2.55, 2.60, 2.65.



(a) Solid line: c(t), dashed line: e(t), dotted line: s(t).

(b) Solid line: a(t), dashed line: p(t), dotted line: r(t).

Fig.8 Oscillation of the solutions, Kin=2, n=2, delays: 2.15, 2.20, 2.25, 2.30, 2.35.



(a) Solid line: c(t), dashed line: e(t), dotted line: s(t).

(b) Solid line: a(t), dashed line: p(t), dotted line: r(t).

We see Then $\mu(M) + \sigma$ = 4.7701 > 0. The conditions of Theorem 2 are satisfied. When time delays are selected as 2.45, 2.50, 2.55, 2.60, 2.65, oscillation of the solutions appeared (see Fig.7). In Fig.8, time delays are selected as 2.15, 2.20, 2.25, 2.30, 2.35, we only change the values of k_{-1} from 0.065 to 0.018, k_{11} from 0.434 to 0.471, the other parameters are the same as in Fig.7, oscillation of the solutions still occurred (see Fig.8).

CONCLUSION

In this paper, we have discussed the oscillatory behavior of the solutions for a modified gene expression model with delays. Based on the method of mathematical analysis, we provided two theorems that those are only sufficient conditions to guarantee the oscillation of the solutions. Some simulations are provided to indicate the effectiveness of the criteria.

Competing Interests

The author has declared that no competing interests exist.

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