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Stability and bifurcation analysis of a gene expression model with small RNAs and mixed delays

Fan Qing[1], Min Xiao[1,2*], Chengdai Huang[3], Guoping Jiang[1], Jianlong Qiu[4], Jinxing Lin[1], Zhengxin Wang[5] and Cong Zheng[5]

*Correspondence:
candymanxm2003@aliyun.com
[1]College of Automation, Nanjing
University of Posts and
Telecommunications, Nanjing,
China
[2]School of Mathematics and
Physics, Qingdao University of
Science and Technology, Qingdao,
China
Full list of author information is
available at the end of the article

Abstract

This paper investigates a gene expression model, which is mediated by sRNAs (small RNAs) and includes discrete and distributed delays. We take both the strong and weak kernel forms of distributed delay into consideration. The discrete time delay is chosen as the bifurcation parameter. By analyzing the distribution of characteristic values, we obtain the sufficient conditions of stability and examine the existence of periodic oscillations. When the discrete time delay is small and not greater than the threshold, the equilibrium of the gene expression model is asymptotically stable. When the bifurcation parameter exceeds the critical value, the model can produce limit cycles. Finally, numerical simulations are implemented to verify the correctness of our theoretical results.

Keywords: Hopf bifurcation; Local stability; Periodic oscillation; Distributed delay; Genetic expression model

1 Introduction

The study of bifurcation phenomena has aroused the interest of scientists in many fields. Both theoretical and experimental results show that the phenomenon of bifurcation is a common physical phenomenon in various disciplines [1, 2]. In system theory, bifurcation theory can be used to discuss the generation and disappearance of bifurcation phenomena in nonlinear systems [3–8]. For gene networks, the bifurcation theory is a useful tool for studying the dynamic performance in regulation process [9–15].

The gene regulatory network systematically studies the function and behavior of genes in the highly connected cell environment [16, 17], and it regards the gene as a whole organizational structure. With the development of information technology and computer science progress in recent years, the gene expression model has been widely addressed [18–20]. On the basis of a comprehensive interpretation of cell metabolism, it has played a great role in exploring the mechanism of life activities, the cause and treatment of the disease. A mathematical model of gene expression mediated by sRNAs is put forward in

[13–15]:

$$\begin{cases} \dot{x}(t) = -cx(t) - dy(t)x(t) + g(z(t - \tau_1)), \\ \dot{y}(t) = e - dy(t)x(t) - fy(t), \\ \dot{z}(t) = -bz(t) + ax(t - \tau_2), \end{cases} \tag{1}$$

where $x(t)$, $y(t)$, and $z(t)$ represent the densities of mRNA, sRNA, and protein, respectively. a represents the synthesis rate of protein. b, c, and f are the degradation rates of protein, mRNA, and sRNA. d is the matching rate of sRNA with mRNA. e is the transcription rate of sRNA. $g(p(t - \tau_1))$ denotes the generation rate of mRNA. τ_1 and τ_2 stand for the time delays. All of the above parameters are positive.

Due to the complexity of the interaction of gene information in reality, the time delay of the system is not invariable [21–23], and it may produce complicated nonlinear phenomena with the change of time. According to literature [24–28], we find that there may be more than one kind of time delay in practical engineering systems. Scholars usually neglect the existence of two kinds of time delay in order to obtain simple differential equations. In most cases, gene regulatory networks with sRNA have mixed delays due to their complex network models. In order to describe the genetic process of organisms more accurately, we introduce the distributed delays to exactly describe the change of the time delay in the reality. This paper takes the following gene expression model having distributed and discrete delays into consideration:

$$\begin{cases} \dot{x}(t) = -cx(t) - dy(t)x(t) + g[\int_{-\infty}^{t} T(t - x)z(x)\,dx], \\ \dot{y}(t) = e - dy(t)x(t) - fy(t), \\ \dot{z}(t) = -bz(t) + ax(t - \tau). \end{cases} \tag{2}$$

The time delay kernel function T is presumed to satisfy some conditions as follows:
   (i) $T : [0, \infty) \to [0, \infty)$;
   (ii) T is piecewise continuous;
   (iii) $\int_0^{\infty} T(x)\,dx = 1$, $\int_0^{\infty} xT(x)\,dx < \infty$.
The standard mathematical form of $T(x)$ is as follows:

$$T(x) = \sigma^{n+1}\frac{x^n e^{-\sigma x}}{n!}, \quad x \in (0, \infty), n = 0, 1, \tag{3}$$

where the positive real number σ stands for the rate of fading of past memories. $n = 0$ and $n = 0$ denote the weak and strong kernel, respectively. The forms of weak and strong kernel respectively read as follows:

$$T(x) = \sigma e^{-\sigma x}, \quad x \in (0, \infty), \tag{4}$$

$$T(x) = \sigma^2 x e^{-\sigma x}, \quad x \in (0, \infty). \tag{5}$$

Compared with the discrete time delay, the distributed time delay possesses a more complex mathematical form, and it may degenerate to the discrete time delay if taking the delta function as the kernel function [29]. This makes it unfavorable for theoretical analysis. There have been a great number of scholars who pay attention to bifurcation

dynamics for various models with distributed time delays, such as predator-prey models [30], neural network models [31], Kuramoto oscillators [32], turbidostat models [33], and virus dynamics models [34].

However, so far, there are few results on the study of bifurcation for gene expression processes which have distributed delays. Distributed delays in Gamma-type were incorporated in a cyclic gene expression network [35], and the bifurcation and oscillation were discussed. But their model does not take sRNAs into account, which is depicted in the second equation in system (2). The influence of distributed time delays on dynamical behaviors of a mathematical model of gene expression was studied [36]. Both the cases of the weak and strong delay kernels were addressed. But the model proposed in [36] includes only distributed delays, no discrete delays and sRNAs, while model (2) has mixed delays and is mediated by not only mRNAs and protein, but also sRNAs.

We summarize the main contributions of this article as follows: (1) We first incorporate distributed time delays into genetic expression processes with sRNAs and put forward a novel mathematical model with mixed delays. (2) The proposed model can capture the effects of the distributed delay on the temporal and spatial dynamics of gene expression process. (3) The Hopf bifurcation theory is applied to investigate the dynamic characteristics of a gene expression model with distributed and discrete time delays. (4) Our model and analysis method are applicable to the analysis of gene expression information.

Next, the organization of this paper is as follows. In the case of weak kernel, the stability and local bifurcation of the gene expression model with sRNAs and mixed delays are discussed in Sect. 2. We investigate the existence of periodic oscillations in the case of strong kernel in Sect. 3. In Sect. 4, we give some numerical simulations to support the theoretic results. In Sect. 5, the conclusion is drawn.

2 Case of the weak kernel

For system (2), we consider the weak kernel form and let

$$u(t) = \int_{-\infty}^{t} \sigma e^{-\sigma(t-x)} p(x) \, dx.$$

Then we have

$$\begin{cases} \dot{x}(t) = -cx(t) - dy(t)x(t) + g(u(t)), \\ \dot{y}(t) = e - dy(t)x(t) - fy(t), \\ \dot{z}(t) = -bz(t) + ax(t - \tau), \\ \dot{u}(t) = \sigma z(t) - \sigma u(t). \end{cases} \tag{6}$$

Assume that (x^*, y^*, z^*, u^*) is the equilibrium point of system (6), and let $y_1 = x - x^*$, $y_2 = y - y^*$, $y_3 = z - z^*$, $y_4 = u - u^*$. Then the linearized system of (6) at (x^*, y^*, z^*, u^*) is as follows:

$$\begin{cases} \dot{y}_1(t) = -(c + dy^*)y_1(t) - dx^*y_2(t) + g'(u^*)y_4(t), \\ \dot{y}_2(t) = -dy^*y_1(t) - (f + dx^*)y_2(t), \\ \dot{y}_3(t) = -by_3(t) + ay_1(t - \tau), \\ \dot{y}_4(t) = \sigma y_3(t) - \sigma y_4(t). \end{cases} \tag{7}$$

Then we have the following characteristic equation of system (7):

$$\det \begin{pmatrix} \lambda + (c + dy^*) & dx^* & 0 & -g'(u^*) \\ dy^* & \lambda + (f + dx^*) & 0 & 0 \\ -ae^{-\lambda\tau} & 0 & \lambda + b & 0 \\ 0 & 0 & -\sigma & \lambda + \sigma \end{pmatrix} = 0. \tag{8}$$

From (8), we have

$$\lambda^4 + q_1\lambda^3 + q_2\lambda^2 + q_3\lambda + q_4 + (q_5\lambda + q_6)e^{-\lambda\tau} = 0, \tag{9}$$

where

$$q_1 = b + \sigma + c + f + dx^* + dy^*,$$

$$q_2 = b\sigma + bc + \sigma c + bf + \sigma f + cf + bdx^* + bdy^* + \sigma dx^* + \sigma dy^* + cdx^* + dfy^*,$$

$$q_3 = b\sigma c + b\sigma f + bcf + \sigma cf + b\sigma dx^* + b\sigma dy^* + bcdx^* + \sigma cdx^* + bdfy^* + \sigma dfy^*,$$

$$q_4 = b\sigma cf + b\sigma cdx^* + b\sigma dfy^*,$$

$$q_5 = -a\sigma g'(u^*),$$

$$q_6 = -a\sigma fg'(u^*) - a\sigma dg'(u^*)x^*.$$

If $i\omega$ ($\omega > 0$) is the pure imaginary root of (9), we have

$$\omega^4 - q_2\omega^2 + q_4 + q_6\cos\omega\tau + q_5\omega\sin\omega\tau$$

$$+ i\left(-q_1\omega^3 + q_3\omega + q_5\omega\cos\omega\tau - q_6\sin\omega\tau\right) = 0. \tag{10}$$

Combining the properties of trigonometric functions, we separate the real and imaginary parts and get

$$\begin{cases} q_6\cos\omega\tau + q_5\omega\sin\omega\tau = -\omega^4 + q_2\omega^2 - q_4, \\ q_5\omega\cos\omega\tau - q_6\sin\omega\tau = q_1\omega^3 - q_3\omega. \end{cases} \tag{11}$$

Then

$$\begin{cases} \cos\omega\tau = \frac{n_1\omega^4 + n_2\omega^2 + n_3}{n_4\omega^2 + n_5}, \\ \sin\omega\tau = \frac{n_6\omega^5 + n_7\omega^3 + n_8\omega}{n_4\omega^2 + n_5}, \end{cases} \tag{12}$$

where

$$n_1 = q_1q_5 - q_6, \qquad n_2 = q_2q_6 - q_3q_5,$$

$$n_3 = -q_4q_6, \qquad n_4 = q_5^2, \qquad n_5 = q_6^2,$$

$$n_6 = -q_5^2, \qquad n_7 = q_2q_5 - q_1q_6, \qquad n_8 = q_3q_6 - q_4q_5.$$

This leads to

$$d_1\omega^{10} + d_2\omega^8 + d_3\omega^6 + d_4\omega^4 + d_5\omega^2 + d_6 = 0, \tag{13}$$

with

$$d_1 = n_6^2, \qquad d_2 = 2n_6n_7 + n_1^2,$$
$$d_3 = 2n_1n_2 + n_7^2 + 2n_6n_8,$$
$$d_4 = n_2^2 - 2n_1n_3 + 2n_7n_8 - n_4^2,$$
$$d_5 = n_8 - 2n_2n_3 - 2n_4n_5, \qquad d_6 = n_3^2 - n_5^2.$$

Letting $z = \omega^2$, (13) becomes

$$d_1z^5 + d_2z^2 + d_3z^3 + d_4z^2 + d_5z + d_6 = 0. \tag{14}$$

Define

$$h(z) = d_1z^5 + d_2z^2 + d_3z^3 + d_4z^2 + d_5z + d_6. \tag{15}$$

Lemma 1 *If $d_6 < 0$, there exists at least one positive root for* (14).

Proof By simply calculating, we can easily get $h(0) = d_6 < 0$ and note that $\lim_{z \to +\infty} h(z) = +\infty$. Then there exists $h(z_a) = 0$ for $z_a \in (0, +\infty)$. □

We assume that (14) has five positive roots shown as $z_k, k = 1, 2, \ldots, 5$. Clearly, $\omega_k = \sqrt{z_k}$, $k = 1, 2, \ldots, 5$. Thus

$$\tau_k^{(j)} = \frac{1}{\omega_k}\left\{\arccos\left[\frac{n_1\omega^4 + n_2\omega^2 - n_3}{n_4\omega^2 + n_5}\right] + 2j\pi\right\},$$
$$k = 1, 2, \ldots, 5; j = 0, 1, 2, \ldots. \tag{16}$$

Assume that $\tau_0 = \tau_{k_0}^0 = \min\{\tau_k^0\}$, and $\omega_0 = \omega_{k_0}$. When $\tau = 0$, (9) turns to be

$$\lambda^4 + q_1\lambda^3 + q_2\lambda^2 + (q_3 + q_5)\lambda + q_4 + q_6 = 0. \tag{17}$$

We denote

$$D_1 = q_1, \qquad D_2 = q_1q_2 - q_3 - q_5,$$
$$D_3 = q_1\big[q_2(q_3 + q_5) - q_1(q_4 + q_6)\big] - (q_3 + q_5)^2,$$
$$D_4 = (q_4 + q_6)D_3,$$

and take the hypothesis as follows:

$$(H1) \qquad D_i > 0, \quad i = 1, 2, 3, 4.$$

It follows from the Routh–Hurwitz criterion that if $(H1)$ holds, all roots of (17) have negative real parts.

Lemma 2 *Premeditate the exponential polynomial*

$$R\big(\omega, e^{-\omega\sigma_1}, \ldots, e^{-\omega\sigma_m}\big)$$
$$= \omega^n + R_1^{(0)}\omega^{n-1} + \cdots + R_{n-1}^{(0)}\omega + R_n^{(0)}$$
$$+ \big[R_1^{(1)}\omega^{n-1} + \cdots + R_{n-1}^{(1)}\omega + R_n^{(1)}\big]e^{-\omega\sigma_1} + \cdots$$
$$+ \big[R_1^{(m)}\omega^{n-1} + \cdots + R_{n-1}^{(m)}\omega + R_n^{(m)}\big]e^{-\omega\sigma_m},$$

where $\sigma_i \geq 0$ $(j = 1, 2, \ldots, m)$ and R_i $(i = 1, 2, \ldots, m)$ are constant. As $(\sigma_1, \sigma_2, \ldots \sigma_m)$ change, the sum of the order of the zeros of $R(\omega, e^{-\omega\sigma}, \ldots, e^{-\omega\sigma_m})$ in the open right half plane can be modified only if a zero appears on or crosses the imaginary axis.

Considering the transversal condition, we give the following hypothesis:

$$(H2) \qquad \mathrm{Re}\left[\frac{d(\lambda(\tau))}{d\tau}\right]_{\tau=\tau_0} \neq 0.$$

We differentiate (9) and obtain the derivative of delay as follows:

$$\left[\frac{d\lambda}{d\tau}\right]^{-1} = \frac{(4\lambda^3 + 3q_1\lambda^2 + 2q_2\lambda + q_3)e^{\lambda\tau} + q_5}{q_5\lambda^2 + q_6\lambda} - \frac{\tau}{\lambda}.$$

Then

$$\mathrm{Re}\left[\frac{d\lambda}{d\tau}\right]^{-1}_{\tau=\tau_k^j} = \frac{1}{M}\Big\{\big[(3q_1q_5 - 4q_6)\omega_k^4 + (2q_2q_6 - q_3q_5)\omega_k^2\big]\cos\big(\omega_k\tau_k^j\big)$$
$$- q_5^2\omega_k^2 - \big[4q_5\omega_k^5 + (3q_1q_6 - 2q_2q_5)\omega_k^3 - q_3q_6\omega_k\big]\sin\big(\omega_k\tau_k^j\big)\Big\},$$

where $M = q_5 2\omega_k^4 + q_6^2\omega_k^2$. Note that

$$\mathrm{sign}\left\{\mathrm{Real}\left[\frac{d\lambda}{d\tau}\right]_{\tau=\tau_k^j}\right\} = \mathrm{sign}\left\{\mathrm{Real}\left[\frac{d\lambda}{d\tau}\right]^{-1}_{\tau=\tau_k^j}\right\}.$$

Next, we can derive the following theorem.

Theorem 1 *Under $(H1)$ and $(H2)$, we have the following results.*
  (i) *When $\tau \in (0, \tau_0)$, the trajectories of model (6) converge to the equilibrium point (x^*, y^*, z^*, u^*).*
  (ii) *When $\tau > \tau_0$, model (6) presents an oscillatory dynamic near the unstable equilibrium point (x^*, y^*, z^*, u^*). More concretely, there exists a Hopf bifurcation when $\tau = \tau_0$.*

Remark 1 For a gene expression model, it is challenging for us to construct the sufficient conditions of periodic oscillation and local stability when introducing the distributed delays, because the simplification of distributed delays with weak kernel can increase the

dimension of the system. The results indicate that the gene expression model with mixed time delay can also produce bifurcation.

3 Case of the strong kernel

In view of the complexity of system (2) with strong kernel, we let

$$u(t) = \int_{-\infty}^{t} \sigma e^{-\sigma(t-x)} p(x)\, dx,$$

$$v(t) = \int_{-\infty}^{t} \sigma^2 (t-x) e^{-\sigma(t-x)} p(x)\, dx.$$

Then system (2) becomes

$$\begin{cases} \dot{x}(t) = -cx(t) - dy(t)x(t) + g(v(t)), \\ \dot{y}(t) = e - dy(t)x(t) - fy(t), \\ \dot{z}(t) = -bz(t) + ax(t-\tau), \\ \dot{u}(t) = \sigma z(t) - \sigma u(t), \\ \dot{v}(t) = \sigma u(t) - \sigma v(t). \end{cases} \tag{18}$$

We assume $(x^*, y^*, z^*, u^*, v^*)$ is one equilibrium point of system (18), and let $y_1 = x - x^*$, $y_2 = y - y^*$, $y_3 = z - z^*$, $y_4 = u - u^*$, $y_5 = v - v^*$. Then the linearized system of (18) at $(x^*, y^*, z^*, u^*, v^*)$ is as follows:

$$\begin{cases} \dot{y}_1(t) = -(c + dy^*)y_1(t) - dx^* y_2(t) + g'(v^*)y_4(t), \\ \dot{y}_2(t) = -dy^* y_1(t) - (f + dx^*)y_2(t), \\ \dot{y}_3(t) = -by_3(t) + ay_1(t-\tau), \\ \dot{y}_4(t) = \sigma y_3(t) - \sigma y_4(t), \\ \dot{y}_5(t) = \sigma y_4(t) - \sigma y_5(t). \end{cases} \tag{19}$$

Then we have the following characteristic equation of system (19):

$$\det \begin{pmatrix} \lambda + (c + dy^*) & dx^* & 0 & -g'(v^*) & 0 \\ dy^* & \lambda + (f + dx^*) & 0 & 0 & 0 \\ -ae^{-\lambda\tau} & 0 & \lambda + b & 0 & 0 \\ 0 & 0 & -\sigma & \lambda + \sigma & 0 \\ 0 & 0 & 0 & -\sigma & \lambda + \sigma \end{pmatrix} = 0. \tag{20}$$

Then

$$\lambda^5 + q_1\lambda^4 + q_2\lambda^3 + q_3\lambda^2 + q_4\lambda + q_5 + \left(q_6\lambda^2 + q_7\lambda + q_8\right)e^{-\lambda\tau} = 0, \tag{21}$$

where

$$q_1 = b + 2\sigma + c + f + dx^* + dy^*,$$

$$q_2 = \sigma^2 + 2b\sigma + bc + 2\sigma c + bf + 2\sigma f + cf + bdx^* + bdy^* + 2\sigma dx^*$$
$$+ 2\sigma dy^* + cdx^* + dfy^*,$$

$$q_3 = b\sigma d^2 + \sigma^2 c + \sigma^2 f + 2b\sigma c + 2b\sigma f + bcf + 2\sigma cf + \sigma^2 dx^* + \sigma^2 dy^*$$

$$+ 2b\sigma dx^* + 2b\sigma dy^* + bcdx^* + 2\sigma cdx^* + bdfy^* + 2\sigma dfy^*,$$

$$q_4 = b\sigma^2 c + b\sigma^2 f + \sigma^2 cf + 2b\sigma cf + b\sigma^2 dx^* + b\sigma^2 dy^* + \sigma^2 cdx^*$$

$$+ \sigma^2 dfy^* + 2b\sigma cdx^* + 2b\sigma dfy^*,$$

$$q_5 = b\sigma^2 cf + b\sigma^2 cdx^* + b\sigma^2 dfy^*,$$

$$q_6 = -a\sigma g'(v^*),$$

$$q_7 = -a\sigma^2 g'(v^*) - a\sigma fg'(v^*) - a\sigma dg'(v^*),$$

$$q_8 = -a\sigma fg'(v^*) - a\sigma^2 dg'(v^*)x^*.$$

In order to solve the crossing frequency, we let $\lambda = i\omega$ $(\omega > 0)$ and (21) turns to

$$\omega^5 i - q_1\omega^4 - q_2\omega^3 i - q_3\omega^2 + q_4\omega i + q_5$$

$$+ \left(q_7\omega i - q_6\omega^2 + q_8\right)(\cos\omega\tau - i\sin\omega\tau) = 0. \tag{22}$$

It follows that

$$\begin{cases} (-q_6\omega^2 + q_8)\cos\omega\tau + q_7\omega\sin\omega\tau = -q_1\omega^4 + q_3\omega^2 - q_5, \\ q_7\omega\cos\omega\tau - (-q_6\omega^2 + q_8)\sin\omega\tau = -\omega^5 + q_2\omega^3 - q_4\omega. \end{cases} \tag{23}$$

Thus,

$$\begin{cases} \cos\omega\tau = \dfrac{n_1\omega^6 + n_2\omega^4 + n_3\omega^2 + n_4}{n_5\omega^4 + n_6\omega^2 + n_7}, \\ \sin\omega\tau = \dfrac{n_8\omega^7 + n_9\omega^5 + n_{10}\omega^3 + n_{11}\omega}{n_5\omega^4 + n_6\omega^2 + n_7}. \end{cases} \tag{24}$$

This leads to

$$d_1\omega^{14} + d_2\omega^{12} + d_3\omega^{10} + d_4\omega^8 + d_5\omega^6 + d_6\omega^4 + d_7\omega^2 + d_8 = 0, \tag{25}$$

in which

$$d_1 = n_8^2, \qquad d_2 = 2n_8 n_9 + n_1^2,$$

$$d_3 = 2n_1 n_2 + n_9^2 + 2n_8 n_{10},$$

$$d_4 = n_2^2 + 2n_1 n_3 + 2n_8 n_{11} + 2n_9 n_{10} - n_5^2,$$

$$d_5 = 2n_1 n_4 + 2n_2 n_3 + n_{10}^2 + 2n_9 n_{11} - 2n_5 n_6,$$

$$d_6 = 2n_2 n_4 + n_3^2 + 2n_{10} n_{11} - n_6^2 - 2n_5 n_7,$$

$$d_7 = 2n_3 n_4 + n_{11}^2 - 2n_6 n_7,$$

$$d_8 = n_4^2 - n_7^2.$$

Letting $z = \omega^2$, (25) becomes

$$d_1 z^7 + d_2 z^6 + d_3 z^5 + d_4 z^4 + d_5 z^3 + d_6 z^2 + d_7 z + d_8 = 0. \tag{26}$$

Define

$$l(z) = d_1 z^7 + d_2 z^6 + d_3 z^5 + d_4 z^4 + d_5 z^3 + d_6 z^2 + d_7 z + d_8. \tag{27}$$

Lemma 3 *If $d_8 < 0$, there exists at least one positive root for* (26).

Proof By simply calculating, we can easily get $l(0) = d_8 < 0$ and note that $\lim_{z \to +\infty} l(z) = +\infty$. Therefore, there exists $l(z_0) = 0$ for $z_0 \in (0, +\infty)$. □

Suppose that (26) has seven roots with positive real parts defined as $z_k, k = 1, 2, \ldots, 7$. Clearly, $\omega_k = \sqrt{z_k}, k = 1, \ldots, 7$. Thus

$$\tau_k^{(j)} = \frac{1}{\omega_k} \left\{ \arccos\left[\frac{n_1 \omega^6 + n_2 \omega^4 + n_3 \omega^2 + n_4}{n_5 \omega^4 + n_6 \omega^2 + n_7} \right] + 2j\pi \right\},$$
$$k = 1, 2, \ldots, 7; j = 0, 1, 2, \ldots. \tag{28}$$

Define $\tau_0 = \tau_{k_0}^0 = \min\{\tau_k^0\}$, and $\omega_0 = \omega_{k_0}$. When $\tau = 0$, (21) turns to be

$$\lambda^5 + q_1 \lambda^4 + q_2 \lambda^3 + (q_3 + q_6)\lambda^2 + (q_4 + q_7)\lambda + q_5 + q_8 = 0. \tag{29}$$

Define

$$D_1 = q_1, \qquad D_2 = q_1 q_2 - q_3 - q_6,$$
$$D_3 = (q_3 + q_6)(q_1 q_2 - q_3 - q_6) - q_1[q_1(q_4 + q_7) - q_5 - q_8],$$
$$D_4 = (q_4 + q_7)D_3 - (q_5 + q_8)\{q_1(q_2^2 - q_4 - q_7) - [(q_3 + q_6)q_2 - q_5 - q_8]\},$$
$$D_5 = (q_5 + q_8)D_4.$$

For the correctness of the theory, we give the following necessary assumption:

$$(H3) \qquad D_i > 0, \quad i = 1, 2, \ldots, 5.$$

It complies with the Routh–Hurwitz criterion that the equilibrium point of system (18) without delays is asymptotically stable if $(H3)$ holds.

We give the following hypothesis:

$$(H4) \qquad \mathrm{Re}\left[\frac{d(\lambda(\tau))}{d\tau} \right]_{\tau = \tau_0} \neq 0.$$

Consider the derivative of (21) with the respect to τ:

$$\left[\frac{d\lambda}{d\tau} \right]^{-1} = \frac{(5\lambda^4 + 4q_1\lambda^3 + 3q_2\lambda^2 + 2q_3\lambda + q_4)e^{\lambda\tau} + 2q_6\lambda + q_7}{q_6\lambda^3 + q_7\lambda^2 + q_8\lambda} - \frac{\tau}{\lambda}. \tag{30}$$

Then

$$
\operatorname{Re}\left[\frac{d(\lambda(\tau))}{d\tau}\right]_{\tau=\tau_k^j}^{-1} = \frac{1}{N}\Big\{\big[\big(5\omega_k^4\cos\big(\omega_k\tau_k^j\big) + 4q_1\omega_k^3\sin\big(\omega_k\tau_k^j\big) - 3q_2\omega_k^2\cos\big(\omega_k\tau_k^j\big)
$$

$$
- 2q_3\omega_k\sin\big(\omega_k\tau_k^j\big) + q_4\cos\big(\omega_k\tau_k^j\big)\big]\big(-q_7\omega_k^2\big) + \big[5\omega_k^4\sin\big(\omega_k\tau_k^j\big)
$$

$$
- 4q_1\omega_k^3\cos\big(\omega_k\tau_k^j\big) - 3q_2\omega_k^2\sin\big(\omega_k\tau_k^j\big) + 2q_3\omega_k\cos\big(\omega_k\tau_k^j\big)
$$

$$
+ q_4\sin\big(\omega_k\tau_k^j\big)\big]\big(q_8\omega_k - q_6\omega_k^3\big) + 2q_6\omega_k\big(q_8\omega_k - q_6\omega_k^3\big) - q_7^2\omega_k^2\Big\},
$$

where $N = q_7^2\omega_k^4 + (q_8\omega_k - q_6\omega_k^3)^2$. Note that

$$
\operatorname{sign}\left\{\operatorname{Real}\left[\frac{d\lambda}{d\tau}\right]_{\tau=\tau_k^j}\right\} = \operatorname{sign}\left\{\operatorname{Real}\left[\frac{d\lambda}{d\tau}\right]_{\tau=\tau_k^j}^{-1}\right\}.
$$

Combining with the above theoretical analysis, we can draw the following theorem.

Theorem 2 *Under the conditions of (H3) and (H4), we have the following results.*

(i) *When $\tau \in (0, \tau_0)$, the trajectories of model (18) converge to the equilibrium point $(x^*, y^*, z^*, u^*, v^*)$.*

(ii) *When $\tau > \tau_0$, model (18) shows an oscillatory dynamic. Furthermore, a Hopf bifurcation takes place at the equilibrium point $(x^*, y^*, z^*, u^*, v^*)$ when $\tau = \tau_0$.*

Remark 2 The appearance of strong kernel may greatly increase the dimension of the gene model, which makes the dynamic characteristics of the model more complicated. As the bifurcation parameters change, the phase diagrams of u and v can also produce limit cycles.
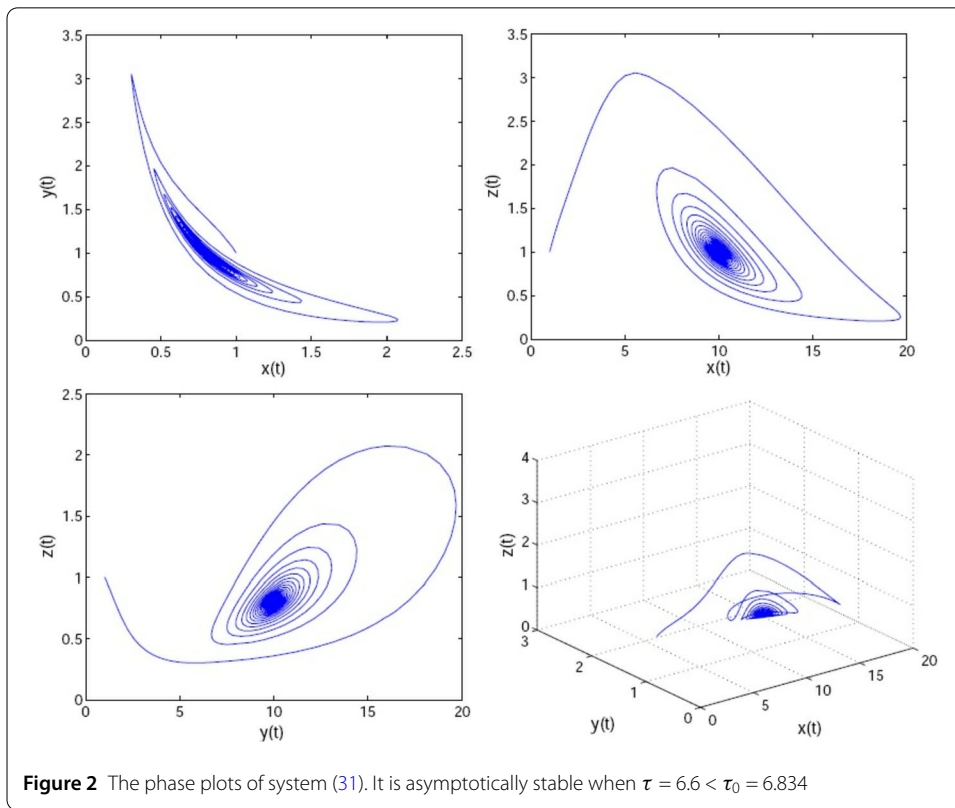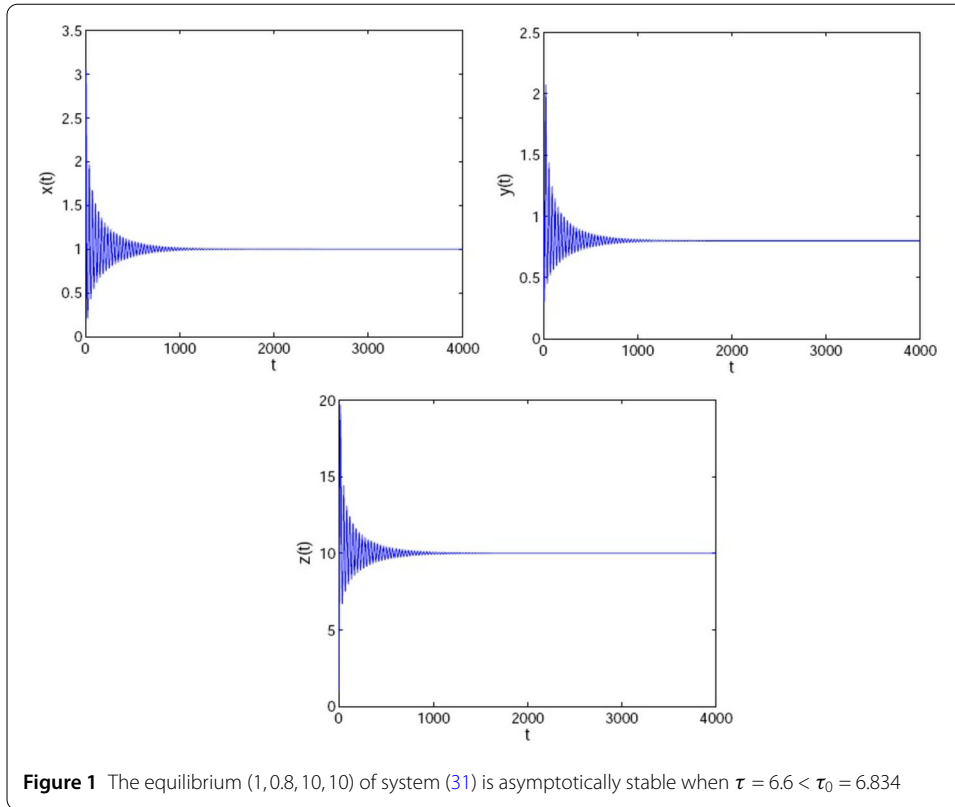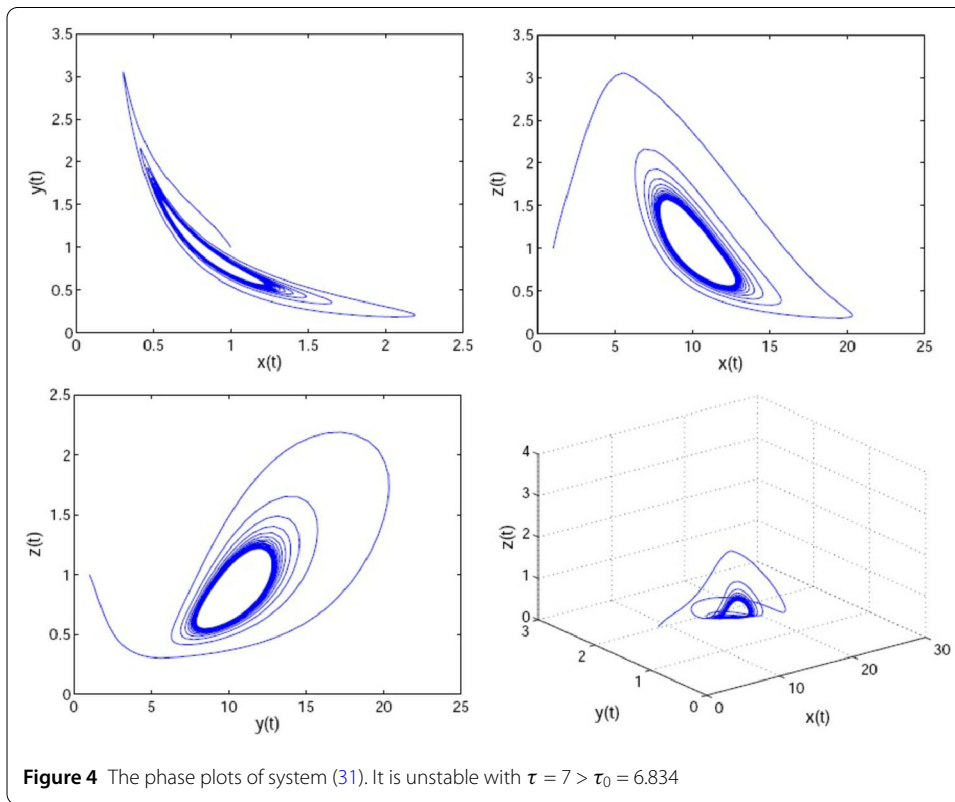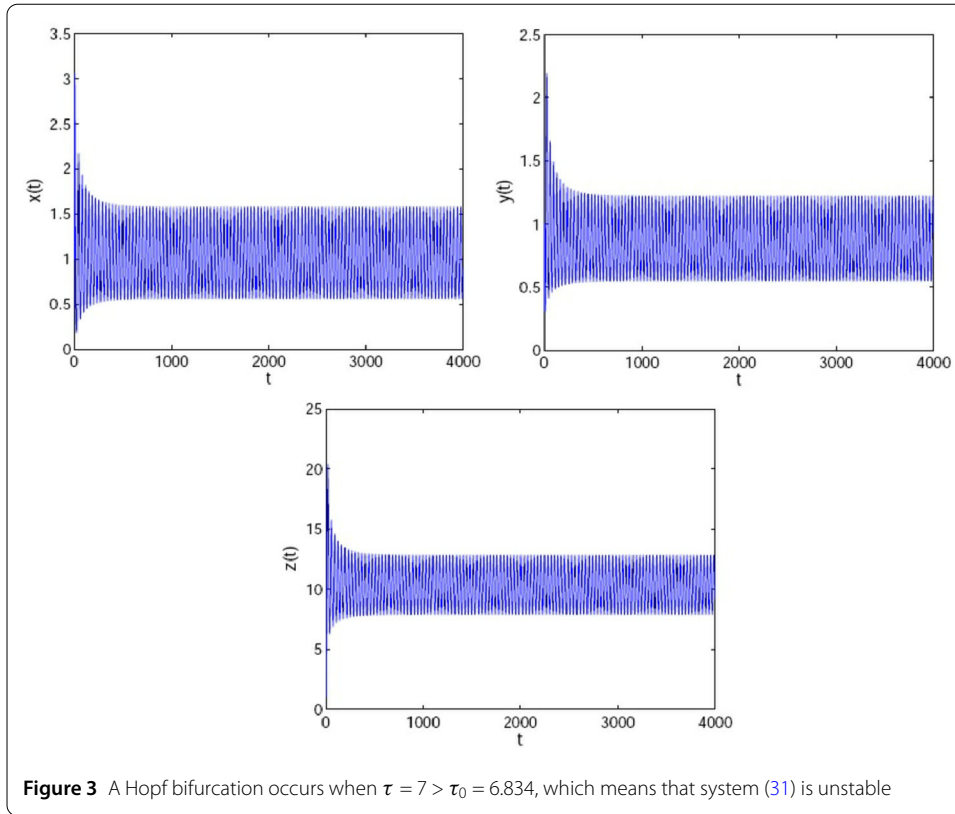
4 Numerical example

We will make some MATLAB simulations of the gene expression model to support the theoretical analysis obtained above in this section.

We take the following model with weak kernel form into consideration:

$$
\begin{cases}
\dot{x}(t) = -0.2x(t) - y(t)x(t) + \frac{200}{100+u^2}, \\
\dot{y}(t) = 1 - y(t)x(t) - 0.25y(t), \\
\dot{z}(t) = -0.1z(t) + x(t-\tau), \\
\dot{u}(t) = 1.2z(t) - 1.2u(t),
\end{cases}
\tag{31}
$$

which includes an equilibrium point $(x^*, y^*, z^*, u^*) = (1, 0.8, 10, 10)$. By calculating, we can obtain that $\tau_0 = 6.834$. It is known from Theorem 1 that system (31) is asymptotically stable at the equilibrium point when $\tau \in (0, \tau_0)$ (see Figs. 1 and 2), while system (31) produces a limit cycle when $\tau > \tau_0$ (see Figs. 3 and 4).

Figure 1 The equilibrium $(1, 0.8, 10, 10)$ of system (31) is asymptotically stable when $\tau = 6.6 < \tau_0 = 6.834$

Figure 2 The phase plots of system (31). It is asymptotically stable when $\tau = 6.6 < \tau_0 = 6.834$

Figure 3 A Hopf bifurcation occurs when $\tau = 7 > \tau_0 = 6.834$, which means that system (31) is unstable

Figure 4 The phase plots of system (31). It is unstable with $\tau = 7 > \tau_0 = 6.834$

Next, we consider the case of strong kernel. The model is as follows:

$$\begin{cases} \dot{x}(t) = -0.2x(t) - y(t)x(t) + \frac{200}{100+v^2}, \\ \dot{y}(t) = 1 - y(t)x(t) - 0.25y(t), \\ \dot{z}(t) = -0.1z(t) + x(t-\tau), \\ \dot{u}(t) = 1.2z(t) - 1.2u(t), \\ \dot{v}(t) = 1.2u(t) - 1.2v(t). \end{cases} \tag{32}$$

There is an equilibrium point $(x^*, y^*, z^*, u^*, v^*) = (1, 0.8, 10, 10, 10)$ for system (32). A Hopf bifurcation occurs and a periodic oscillation appears around the equilibrium point when τ crosses the critical value $\tau_0 = 6.153$ which is calculated by (28). From Theorem 2, when $\tau \in (0, \tau_0)$, the equilibrium $(x^*, y^*, z^*, u^*, v^*)$ is stable (see Figs. 5 and 6). When τ passes through an appropriate value, it can cause the loss of stability of equilibrium $(x^*, y^*, z^*, u^*, v^*)$, and system (32) produces an oscillation phenomenon (see Figs. 7 and 8).

Remark 3 From the aforementioned simulation, we can clearly observe that the bifurcation parameter τ_0 in system (31) is smaller than that in system (32). This phenomenon indicates that the system with strong kernel can advance the generation of bifurcation, which means the stable domain of the system can shrink accordingly. Seen from long-term, it may play an important role in analyzing the stability of gene expression processes.

Remark 4 It can be found that after the coordinate transformations, the dimension of the gene network with the strong kernel is higher than that of the weak kernel. However, the genetic models with strong kernel or weak kernel are asymptotically stable when the
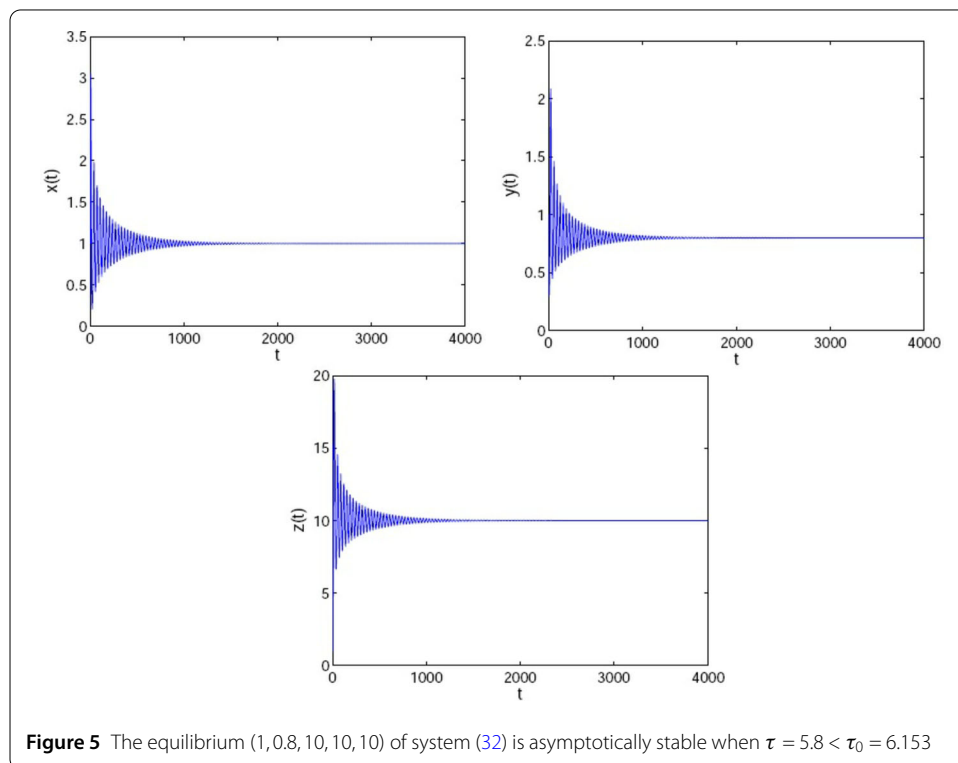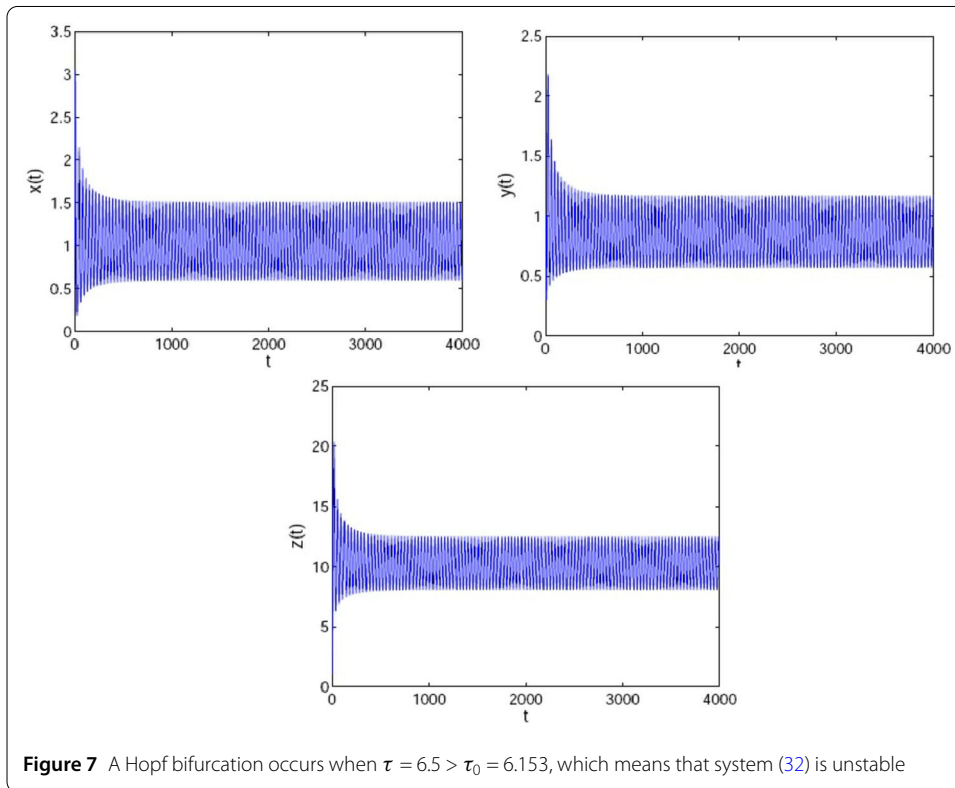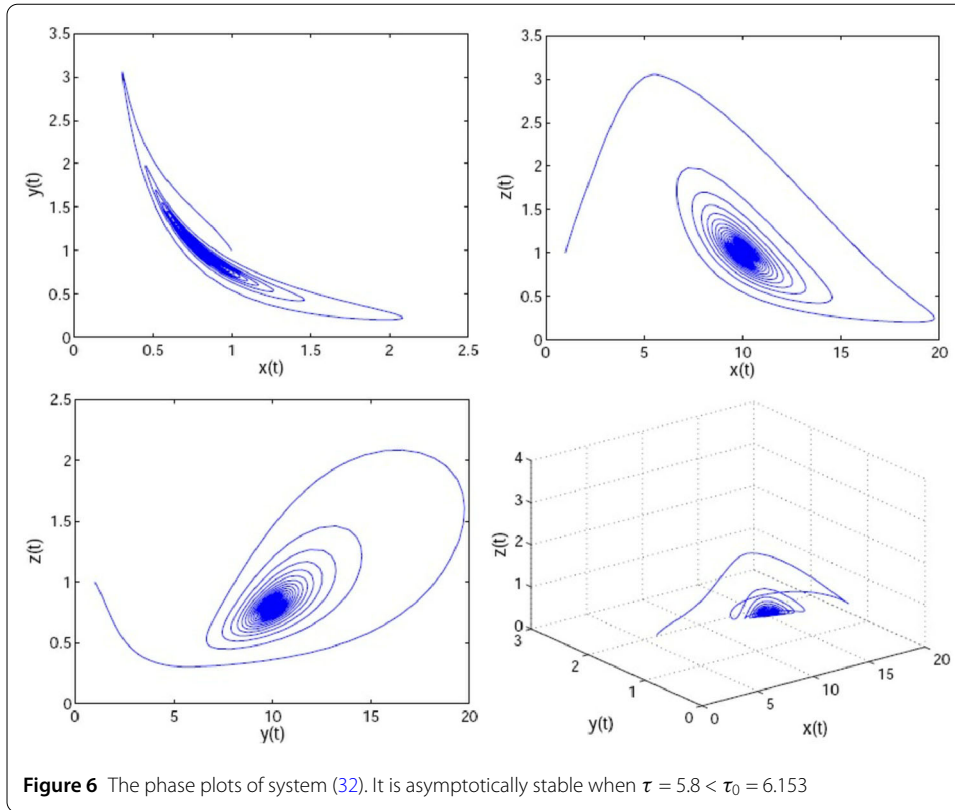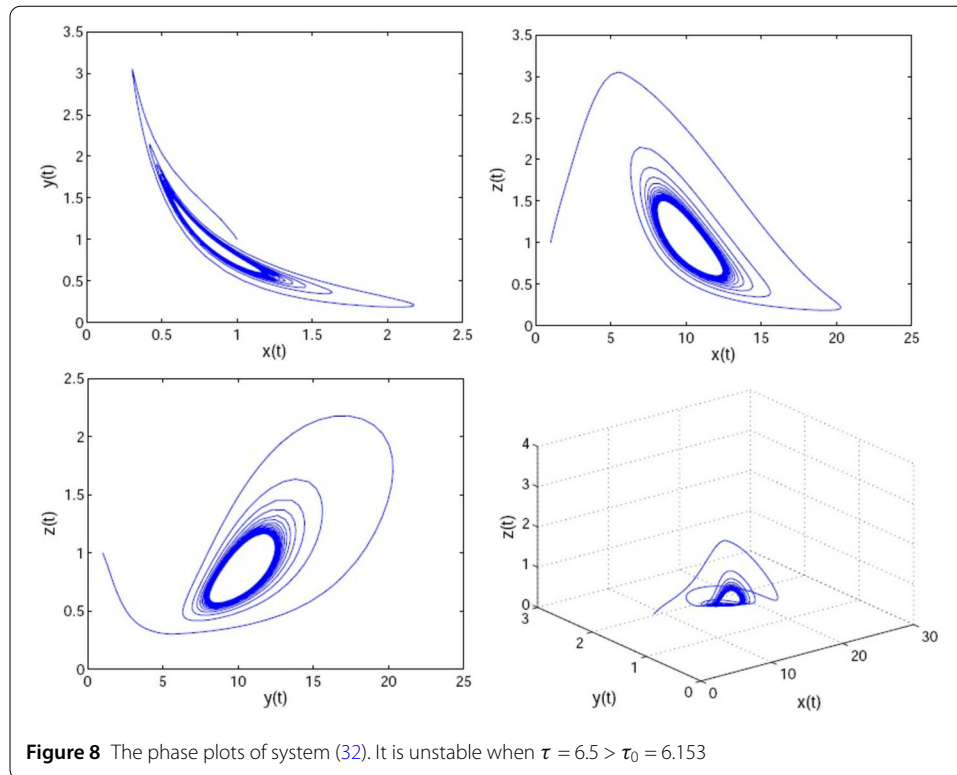

Figure 5 The equilibrium $(1, 0.8, 10, 10, 10)$ of system (32) is asymptotically stable when $\tau = 5.8 < \tau_0 = 6.153$

Figure 6 The phase plots of system (32). It is asymptotically stable when $\tau = 5.8 < \tau_0 = 6.153$

Figure 7 A Hopf bifurcation occurs when $\tau = 6.5 > \tau_0 = 6.153$, which means that system (32) is unstable

Figure 8 The phase plots of system (32). It is unstable when $\tau = 6.5 > \tau_0 = 6.153$

bifurcation parameters are less than the critical value, and generate limit cycles when the bifurcation parameters are greater than the critical value.

5 Conclusion

We introduce distributed time delays into a gene expression model with sRNA in this paper. Specifically, we take two forms of distributed delays into consideration. The introduction of distributed time delay increases the dimension of the network and makes the dynamic behaviors more complex. However, it can describe the time delay of the actual genetic express process more accurately. Here, we take the time delay as the bifurcation parameter to reveal the dynamic behavior of the model. Based on the bifurcation analysis of the gene expression model, we obtain that the model is asymptotically stable when the time delay is suitable. Meanwhile, when the delay is greater than the critical value, the model will lose the stability and produce limit cycles.

This paper mainly discusses the effects of distributed delay of the strong kernel and the weak kernel on the stability and periodic oscillation of gene regulatory networks. We consider the case where the delay core is 0 and 1. Our future work will be devoted to the dynamical analysis of genetic regulatory networks having a delay core greater than 1. The dimension of the network may increase greatly, which makes the analysis more challenging.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
All authors contributed equally to the writing of this paper. All authors read and approved the final manuscript.

Author details
[1]College of Automation, Nanjing University of Posts and Telecommunications, Nanjing, China. [2]School of Mathematics and Physics, Qingdao University of Science and Technology, Qingdao, China. [3]School of Mathematics and Statistics, Xinyang Normal University, Xinyang, China. [4]School of Automation and Electrical Engineering, Linyi University, Linyi, China. [5]College of Science, Nanjing University of Posts and Telecommunications, Nanjing, China.

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