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A delay-differential equation model of the Signal Transduction Pathway

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Abstract

This paper studies the behavior of a signal transduction model with signal amplification delay. By choosing the delay as a bifurcation parameter, we show that the delay model exhibits a Hopf bifurcation at the positive equilibrium. Numerical simulations are also given to support the theoretical predictions.

1 Introduction

The signal transduction model is very famous and has been discussed by many authors [6, 9, 11-14]. In fact, the smallest unit of the living organism is called a cell. In order to perform the function of cells, they have to communicate with each other by releasing a signal molecule of a cell outside and act to another cell inside [1-4, 8]. This process is called the signal

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transduction whose pathway is separated in three steps [2,11]. In the first step (called detection), when a signal messenger of a particular ligand is coming in, it is detected and picked up by receptors at the cell membrane, typically G-protein which is composed of 3 subunits, α, β and γ subunits. At the time when the ligand attach the G-protein receptor, a change in the shape of G-protein happens. In the second step (called transduction), the activated receptor turns on the heterotrimetric G protein to exchange GDP (guanosine diphosphate) to GTP (guanosine triphosphate). After that the α-subunit is separated from the $\beta - \gamma$ group of the G protein. In the last step (called response), either or both of subunits move on and control the effector unit (the adenylate cyclase or AC), whose activity produces secondary messengers, tripically cAMP (cyclic adenosine monophosphate). Finally, the GTPase activity is running to convert bound GTP to GDP and then the G protein is eliminated.

Time delays have been incorporated into the signal transduction model by many authors (see for example [9,13,14]). In general, delayed differential equations could cause a stable steady state to become unstable. So the focus of this paper is to study nonlinear delayed differential equations under which a signal transduction pathway is described. We will apply the Routh-Hurwitz criterian for stability of the equilibrium. The existence of Hopf bifurcation for the model is shown in this work.

The present paper is organized as follows. In Section 2, the delay model is introduced. In Section 3, we study the corresponding characteristic equation of the linearized system at the positive equilibria. We obtain analytic conditions on the parameters under which the equilibrium point is locally asymptotically stable for all delay. We investigate a critical value of the delay and obtain necessary conditions so that the delay system exhibits a Hopf bifurcation at the steady state. Numerical results are provided to confirm the theoretical predictions in Section 4. Finally, a brief conclusion is provided.

2 The delay model

In this paper, we consider the signal transduction pathway model under signal amplification delay which is introduced in [9]. The model consists of three differential equations with $x_1(t)$ denoting the membrane surface density of the ligand bound receptors, $x_2(t)$ denoting the concentration of the second messenger or cAMP, which is synthesized as a result of the output signal of the transduction process and $x_3(t)$ denoting the concentration of the inhibiting agent. A time delay τ is taken before the signal amplification process can take effect on the production of the ligand-receptor complex as the following form:

$$\begin{aligned} \frac{dx_1}{dt} &= -ax_1 - \frac{bx_1}{c+x_1} + dx_2, \\ \frac{dx_2}{dt} &= -nx_2 + \frac{fx_1^2(t-\tau)}{(gx_1(t-\tau)+x_3)^2} + h, \\ \frac{dx_3}{dt} &= -kx_3 + mx_1 \end{aligned} \tag{2.1}$$

where $a, b, c, d, f, g, h, k, m$ and n are the positive constants.

The initial conditions for system (2.1) take the form of $x_1(\theta) = \phi(\theta)$ is continuous on $\theta \in [-\tau, 0]$ and $x_1(0), x_2(0), x_3(0) > 0$.

Describing the delay system (2.1), the first differential equation is formulated by the removal rate of the ligand receptor, the rate at which the ligand-receptor complexes are internalized through the cell membrane, the signal amplification arising from the synthesis of cAMP, respectively. All terms of the second equation are the removal rate of the secondary messenger, the amplification effect on the production of the ligand-receptor complexes due to the secondary hormone with a delay τ and the zero order production rate. The removal rate of the inhibiting protein and the production rate of the inhibiting protein in response to the increase in the ligand-receptor complexes are combined for the last equation.

By the fundamental theory of functional differential equation [10], system (2.1) has a unique solution $(x_1(t), x_2(t), x_3(t))$ satisfying the initial conditions. It is easy to show that all solutions of system (2.1) are defined on $[0, \infty)$ and remain positive for all $t \geq 0$.

3 Local stability and Existence of Hopf bifurcation

In this section, we investigate the conditions for the local stability of a positive equilibrium and the existence of Hopf bifurcation in the system (2.1).

Let $E = (x_1^*, x_2^*, x_3^*)$ be the unique positive equilibrium point of the system

(2.1). Then

$$\begin{aligned} x_1^* &= \frac{\beta + \sqrt{\beta^2 + \gamma}}{2a}, \\ x_2^* &= \frac{\alpha}{n}, \\ x_3^* &= \frac{m x_1^*}{k}, \end{aligned}$$

where $\alpha = h + \frac{fk^2}{(gk+m)^2}$, $\beta = \frac{d\alpha}{n} - b - ac$ and $\gamma = \frac{4adc\alpha}{n}$.

It is not difficult to see that the Jacobian of the system (2.1) at $E = (x_1^*, x_2^*, x_3^*)$ yields

$$J = \begin{bmatrix} -a - \frac{bc}{(c+x_1^*)^2} & d & 0 \\ \frac{2fmk^2 e^{-\lambda\tau}}{(gk+m)^3 x_1^*} & -n & \frac{-2fk^3}{(gk+m)^3 x_1^*} \\ m & 0 & -k \end{bmatrix}.$$

The characteristic equation about E is given by

$$\lambda^3 + A_1\lambda^2 + A_2\lambda + A_3 + A_4 - (A_4 + A_5\lambda)e^{-\lambda\tau} = 0 \qquad (3.2)$$

where

$$\begin{aligned} A_1 &= B_1 + n + k \\ A_2 &= (n+k)B_1 + nk \\ A_3 &= B_1 nk \\ A_4 &= kB_2 \\ A_5 &= B_2 \\ B_1 &= a + \frac{bc}{(c+x_1^*)^2} \\ B_2 &= \frac{2dfmk^2}{(gk+m)^3 x_1^*}. \end{aligned}$$

In what follows, we study the local stability of the equilibrium E of the system (2.1). We need to investigate the distribution of roots of equation (3.2).

When $\tau = 0$, equation (3.2) becomes

$$\lambda^3 + A_1\lambda^2 + (A_2 - A_5)\lambda + A_3 = 0 \qquad (3.3)$$

Next, we apply the Routh-Hurwitz criterion to obtain the results on the distribution of roots of equation (3.3). Thus, we have the following result.

Theorem 3.1. *Let* $\hat{B} = max\{(n+k)B_1, \frac{(n+k)(B_1+n)(B_1+k)}{B_1+n+k}\}$. *If* $B_2 < \hat{B}$, *then the equilibrium* E *is locally asymptotically stable when* $\tau = 0$.

Proof.
Consider

$$\begin{aligned}
A_1 &= B_1 + n + k > 0, \\
A_2 - A_5 &= (n+k)B_1 + nk - B_2 > (n+k)B_1 + nk - \hat{B} \geq 0 \\
A_1(A_2 - A_5) - A_3 &= (B_1 + n + k)((n+k)B_1 + nk - B_2) - B_1 nk \\
&= (n+k)(B_1^2 + (n+k)B_1 + nk) - (B_1 + n + k)B_2 \\
&= (B_1 + n + k)\left[\frac{(n+k)(B_1+n)(B_1+k)}{B_1+n+k} - B_2\right] \\
&> (B_1 + n + k)\left[\frac{(n+k)(B_1+n)(B_1+k)}{B_1+n+k} - \hat{B}\right] \\
&\geq 0.
\end{aligned}$$

Hence, $A_1 > 0$, $A_2 - A_5 > 0$ and $A_1(A_2 - A_5) > A_3$. By the Routh-Hurwitz criteria, all roots of equation (3.3) have negative real parts. Therefore, the equilibrium E is locally asymptotically stable. ■

We now analyze the Hopf bifurcation for the system (2.1), using the time delay τ as the bifurcation parameter.

Assume that $\lambda(\tau) = i\omega(\tau), (\omega > 0)$ is a root of characteristic equation (3.2). Then

$$(i\omega)^3 + A_1(i\omega)^2 + A_2(i\omega) + A_3 + A_4 - (A_4 + A_5 i\omega)e^{-i\omega\tau} = 0$$
$$-i\omega^3 - A_1\omega^2 + iA_2\omega + A_3 + A_4 - (A_4 + A_5 i\omega)(cos\omega\tau - isin\omega\tau) = 0.$$

By separating real part and imaginary part, we get

$$A_4 cos\omega\tau + \omega A_5 sin\omega\tau = -A_1\omega^2 + A_3 + A_4 \qquad (3.4)$$
$$-A_4 sin\omega\tau + \omega A_5 cos\omega\tau = -\omega^3 + \omega A_2. \qquad (3.5)$$

By squaring both sides of equations (3.4) and (3.5) and summing them up, we get

$$\omega^6 + g_1\omega^4 + g_2\omega^2 + g_3 = 0, \qquad (3.6)$$

where

$$\begin{aligned} g_1 &= A_1^2 - 2A_2 = B_1^2 + n^2 + k^2 > 0 \\ g_2 &= A_2^2 - A_5^2 - 2A_1(A_3 + A_4) \\ g_3 &= (A_3 + A_4)^2 - A_4^2 = B_1nk(B_1nk + 2kB_2) > 0. \end{aligned}$$

Let $v = \omega^2$. Then equation (3.6) becomes

$$h(v) = v^3 + g_1v^2 + g_2v + g_3 = 0. \tag{3.7}$$

We can see that

$$\lim_{v\to-\infty} h(v) = -\infty, \lim_{v\to\infty} h(v) = \infty, h(0) = g_3 > 0.$$

Since g_2 can either be negative or positive value. So, we will discuss the roots of equation (3.7) and establish the next Lemmas.

Lemma 3.2. *Suppose that $g_2 > 0$. The equation (3.7) has no positive real roots.*

Proof.

From the expression of $h(v)$, we have

$$h'(v) = 3v^2 + 2g_1v + g_2, \tag{3.8}$$

and the zeros of equation (3.8) are

$$v_1 = \frac{-g_1 - \sqrt{g_1^2 - 3g_2}}{3} \tag{3.9}$$

$$v_2 = \frac{-g_1 + \sqrt{g_1^2 - 3g_2}}{3}. \tag{3.10}$$

Since $g_1, g_2 > 0$, $\sqrt{g_1^2 - 3g_2} < g_1$. Hence, v_1 and v_2 are negative; that is, the equation $\frac{dh(v)}{dv} = 0$ has no positive roots. Since,

$$h(0) = g_3 > 0,$$

it follows that $h(v) = 0$ has no positive roots. ■

Remark 3.3. *Suppose that $B_2 < \hat{B}$ and $g_2 > 0$ hold. Then the equilibrium point E is locally asymptotically stable for all $\tau \geq 0$.*

Next, we will discuss the distribution of equation (3.7) when $g_2 < 0$. Since $g_1 > 0$, $\sqrt{g_1^2 - 3g_2} > g_1$. So, equation (3.8) has one negative and the other positive real root. Thus, $h(v)$ must have two real turning points, and the first turning point must occur at negative value v_1, another occur at positive value v_2 as shown in figure 1.

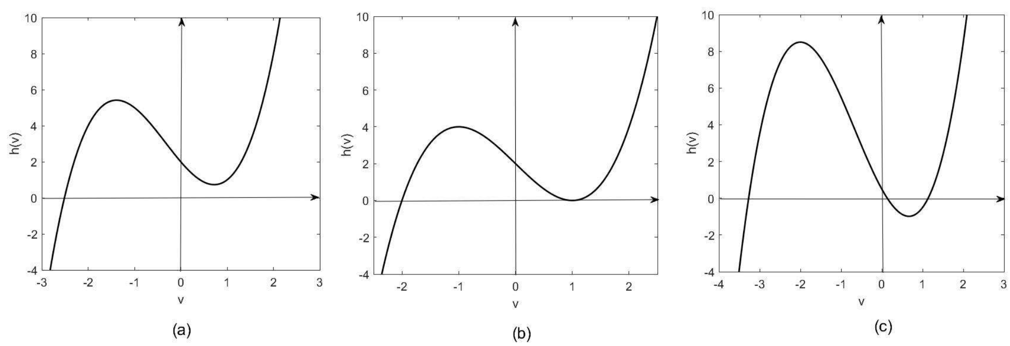

Figure 1: The possible roots of equation (3.7) when $g_2 < 0$.

In addition, we obtain

$$\begin{aligned} v_1+v_2 &= \frac{-2g_1}{3} \\ v_1v_2 &= \frac{g_2}{3} \\ v_1^2+v_2^2 &= (v_1+v_2)^2-2v_1v_2 = \frac{4g_1^2}{9}-\frac{2g_2}{3} \\ v_1^3+v_2^3 &= (v_1+v_2)^3-3v_1v_2(v_1+v_2) = \frac{-8g_1^3}{27}+\frac{2g_1g_2}{3}. \end{aligned}$$

By using the above equations, we have

$$\begin{aligned} \Delta &= h(v_1)h(v_2) \\ &= (v_1^3+g_1v_1^2+g_2v_1+g_3)(v_2^3+g_1v_2^2+g_2v_2+g_3) \\ &= (v_1v_2)^3+g_1(v_1v_2)^2(v_1+v_2)+g_2v_1v_2(v_1^2+v_2^2)+g_3(v_1^3+v_2^3) \\ &+ g_1^2(v_1v_2)^2+g_1g_2v_1v_2(v_1+v_2)+g_1g_3(v_1^2+v_2^2) \\ &+ g_2g_3(v_1+v_2)+g_3^2+g_2^2(v_1v_2); \end{aligned}$$

that is,

$$\Delta = \frac{4g_2^3}{27}-\frac{g_1^2g_2^2}{27}+\frac{4g_1^3g_3}{27}-\frac{2g_1g_2g_3}{3}+g_3^2. \tag{3.11}$$

Substituting $v = y - \frac{g_1}{3}$ into equation (3.7), we obtain the normal from of cubic equation

$$y^3+ay+b=0,$$

where $a = g_2 - \frac{g_1^2}{3} < 0$ and $b = \frac{2g_1^3}{27} - \frac{g_1g_2}{3} + g_3 > 0$. It can be shown that $\Delta = h(v_1)h(v_2) = 4\Big(\frac{b^2}{4}+\frac{a^3}{27}\Big)$. From [7] and Cardano's formula for the third degree algebra equation, we obtain the following lemma about the roots of equation (3.7).

Lemma 3.4. *Suppose that* $g_2 < 0$ *and* $\Delta = \frac{4g_2^3}{27}-\frac{g_1^2g_2^2}{27}+\frac{4g_1^3g_3}{27}-\frac{2g_1g_2g_3}{3}+g_3^2$.
(i) If $\Delta > 0$, *then equation (3.7) does not have positive roots.*
(ii) If $\Delta = 0$, *then equation (3.7) has one positive root at the positive turning point* v_2.
(iii) If $\Delta < 0$, *then equation (3.7) has two positive roots.*

Moreover, when $\Delta > 0$, none of $v = \omega^2$ is positive; that is, the characteristic equation (3.2) does not have purely imaginary roots. Also, Theorem 3.1 ensures that the equilibrium E is locally asymptotically stable for all $\tau \geq 0$. When $\Delta = 0$, equation (3.6) has a positive root ω_+^2. When $\Delta < 0$, equation (3.6) has two positive roots $\omega_\pm^2$. In both cases, the characteristic equation (3.2) has purely imaginary roots when τ takes certain values.

Solving equations (3.4) and (3.5) simultaneously, we obtain

$$cos(\omega\tau) = \frac{A_4(-A_1\omega^2 + A_3 + A_4) + A_5\omega^2(-\omega^2 + A_2)}{A_4^2 + A_5^2\omega^2}.$$

Therefore, these values $\tau_j^\pm$ of τ can be determined and are given by

$$\tau_j^\pm = \frac{1}{\omega_\pm} arccos\left(\frac{A_4(-A_1\omega_\pm^2 + A_3 + A_4) + A_5\omega_\pm^2(-\omega_\pm^2 + A_2)}{A_4^2 + A_5^2\omega_\pm^2}\right) + \frac{2\pi j}{\omega_\pm}, \tag{3.12}$$

where $j = 0, 1, 2, ...$

The above analysis can be summarized in the following lemma.

Lemma 3.5. *(i) If $B_2 < \hat{B}$ and $\Delta = 0$ hold and $\tau = \tau_j^+$, then equation (3.2) has a pair of purely imaginary roots $\pm i\omega_+$.*
(ii) $B_2 < \hat{B}$ and $\Delta < 0$ hold and $\tau = \tau_j^+ (\tau = \tau_j^-$ respectively), then equation (3.2) has a pair of imaginary roots $\pm i\omega_+ (\pm i\omega_-$ respectively).

We would expect that the real part of some root of equation (3.2) becomes positive when $\tau > \tau_j^+$ and $\tau < \tau_j^-$.

Denote

$$\lambda_j^\pm = \eta_j^\pm(\tau) + i\omega_j^\pm(\tau),$$

when $j = 0, 1, 2, ...$ The root of equation (3.2) satisfying

$$\eta_j^\pm(\tau_j^\pm) = 0, \quad \omega_j^\pm(\tau_j^\pm) = \omega_\pm.$$

Differentiating both sides of equation (3.2) with respect to τ, we get

$$(3\lambda^2 + 2A_1\lambda + A_2)\frac{d\lambda}{d\tau} - A_5\frac{d\lambda}{d\tau}e^{-\lambda\tau} - (A_4 + A_5\lambda)e^{-\lambda\tau}(-\lambda - \tau\frac{d\lambda}{d\tau}) = 0,$$

$$\frac{d\lambda}{d\tau} = \frac{-(A_4\lambda + A_5\lambda^2)e^{-\lambda\tau}}{3\lambda^2 + 2A_1\lambda + A_2 - A_5e^{-\lambda\tau} + \tau(A_4 + A_5\lambda)e^{-\lambda\tau}},$$

$$\left(\frac{d\lambda(\tau)}{d\tau}\right)^{-1} = \frac{A_5e^{-\lambda\tau} - (3\lambda^2 + 2A_1\lambda + A_2)}{\lambda(A_4 + A_5\lambda)e^{-\lambda\tau}} - \frac{\tau}{\lambda}.$$

One can verify the following transversality condition [5]. So

$$\begin{aligned}
\left(\frac{dRe\lambda(\tau)}{d\tau}\bigg|_{\tau=\tau_0^{\pm}}\right)^{-1} &= Re\left[\left(\frac{d\lambda(\tau)}{d\tau}\right)^{-1}\bigg|_{\tau=\tau_0^{\pm}}\right] \\
&= Re\left[\frac{A_5(cos\omega_0\tau_0^{\pm} - isin\omega_0\tau_0^{\pm}) + 3\omega_0^2 - 2A_1\omega_0 i - A_2}{(A_4\omega_0 i - A_5\omega_0^2)(cos\omega_0\tau_0^{\pm} - isin\omega_0\tau_0^{\pm})} + \frac{\tau_0^{\pm} i}{\omega_0}\right] \\
&= \frac{3\omega_0^4 + 2g_1\omega_0^2 + g_2}{A_5^2\omega_0^2 + A_4^2} \\
&= \frac{h'(\omega_0^2)}{A_5^2\omega_0^2 + A_4^2}.
\end{aligned}$$

For $\Delta < 0$, equation (3.7) has two positive real roots, denoted by $v_+ = \omega_+^2$ and $v_- = \omega_-^2$. We see that $h'(\omega_+^2) > 0$ and $h'(\omega_-^2) < 0$. Thus, the following transversality conditions hold:

$$\left(\frac{dRe\lambda(\tau)}{d\tau}\bigg|_{\tau=\tau_0^{+}}\right)^{-1} > 0$$

and

$$\left(\frac{dRe\lambda(\tau)}{d\tau}\bigg|_{\tau=\tau_0^{-}}\right)^{-1} < 0$$

It follows that $\tau_j^{\pm}$ are bifurcation values when $\Delta < 0$. Thus, we have the following theorem.

Theorem 3.6. *Suppose that the equilibrium point E exists. If the conditions $B_2 < \hat{B}$ and $\Delta < 0$ hold, then there is a positive integer k such that $0 < \tau_0^+ < \tau_0^- < \tau_1^+ < ... < \tau_{k-1}^- < \tau_k^+$ and there are k switches from stability to instability to stability; that is,*
(i) when $\tau \in [0, \tau_0^+), (\tau_0^-, \tau_1^+), ..., (\tau_{k-1}^-, \tau_k^+)$, the steady state E is locally asymptotically stable,
(ii) when $\tau \in [\tau_0^+, \tau_0^-), (\tau_1^+, \tau_1^-), ..., (\tau_{k-1}^+, \tau_{k-1}^-)$ and $\tau > \tau_k^+$, the steady state E is unstable and system (2.1) undergoes a Hopf bifurcation.

4 Numerical Results

In this section, we give some numerical simulations of our system to demonstrate the above analytic results.

Example 1. Let $a = 1.9, b = 0.5, c = 0.1, d = 0.3, n = 0.5, f = 0.5, g = 0.5, h = 0.16, k = 0.9, m = 0.16$. We consider the following system

$$\begin{aligned}
\frac{dx_1}{dt} &= -1.9x_1 - \frac{0.5x_1}{0.1 + x_1} + 0.3x_2, \\
\frac{dx_2}{dt} &= -0.5x_2 + \frac{0.5x_1^2(t-\tau)}{(0.5x_1(t-\tau) + x_3)^2} + 0.16, \\
\frac{dx_3}{dt} &= -0.9x_3 + 0.16x_1
\end{aligned}$$

For this case, we obtain a positive equilibrium $E = (0.2147, 2.4968, 0.0382)$. By direct calculation, we have $g_2 = 0.2323 > 0, B_2 = 0.7978, \hat{B} = 3.5324$ such that $B_2 < \hat{B}$. The equilibrium is locally asymptotically stable for $\tau = 2.5$ as shown in figure 2.

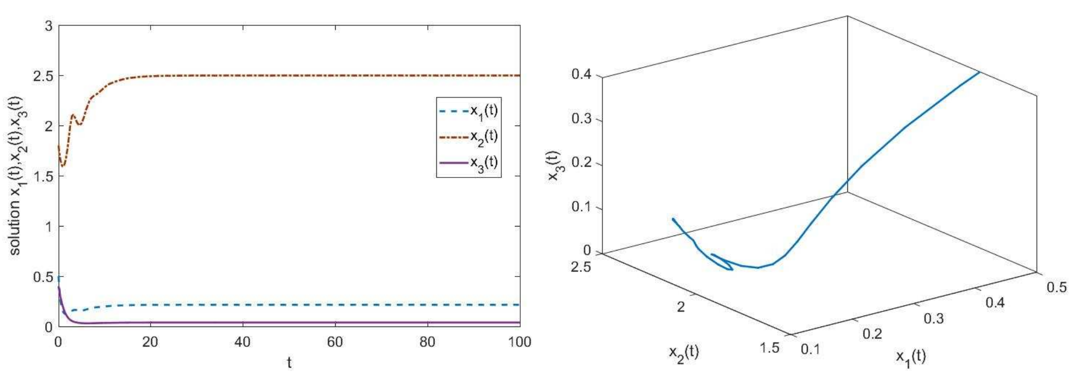

Figure 2: The behavior of $x_1(t), x_2(t)$, and $x_3(t)$ with $\tau = 2.5$.

Example 2. Let $a = 1.2, b = 0.5, c = 0.7, d = 0.3, n = 0.5, f = 4.2, g = 0.09, h = 0.16, k = 1.01, m = 1.1$. We consider the following system

$$\begin{aligned}
\frac{dx_1}{dt} &= -1.2x_1 - \frac{0.5x_1}{0.7 + x_1} + 0.3x_2, \\
\frac{dx_2}{dt} &= -0.5x_2 + \frac{4.2x_1^2(t-\tau)}{(0.09x_1(t-\tau) + x_3)^2} + 0.16, \\
\frac{dx_3}{dt} &= -1.01x_3 + 1.1x_1
\end{aligned}$$

We obtain a positive equilibrium $E = (1.3183, 6.3619, 1.4358)$. By direct calculation, the parameter values which satisfy the Hopf bifurcation discussion are $g_2 = -6.43 < 0, B_2 = 1.27, \hat{B} = 2.2145$ such that $B_2 < \hat{B}$ and $\Delta = -14.2237 < 0$. Figures 3 and 4 show the behavior of the solutions as τ varies.

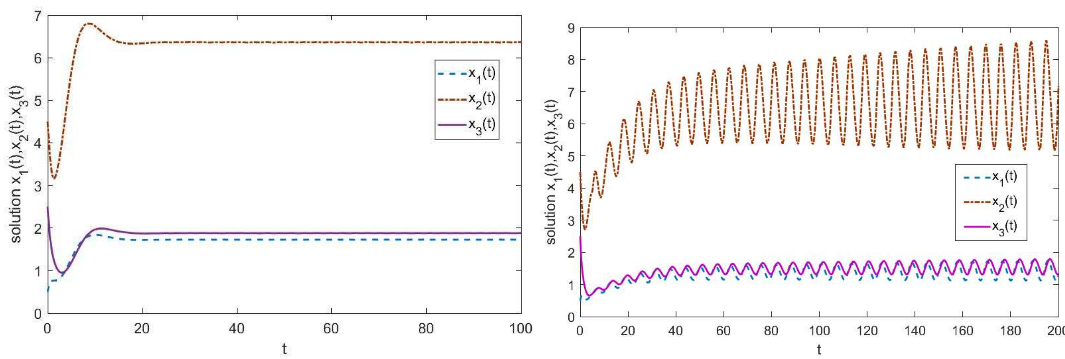

Figure 3: The behavior of $x_1(t), x_2(t)$, and $x_3(t)$ with $\tau = 0.5$ (left) and $\tau = 5$ (right).

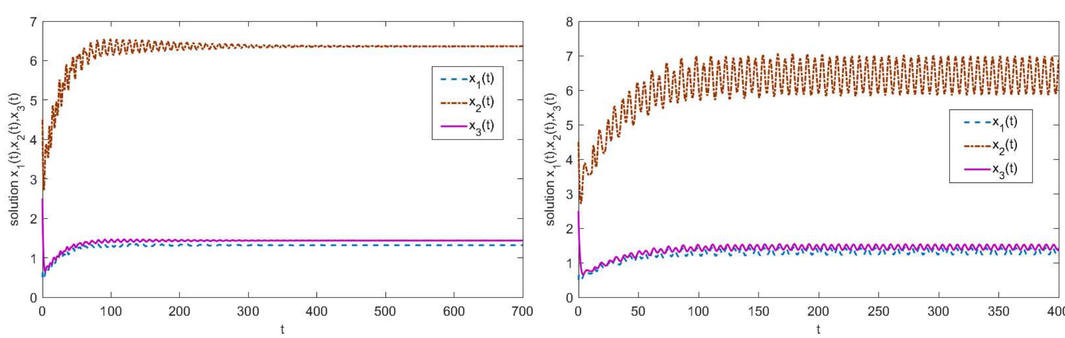

Figure 4: The behavior of $x_1(t), x_2(t)$, and $x_3(t)$ with $\tau = 8.5$ (left) and $\tau = 11$ (right).

Example 3. Let $a = 0.9, b = 3.5, c = 0.7, d = 0.3, n = 0.5, f = 4.2, g = 0.09, h = 0.16, k = 0.3, m = 1.8$. We consider the following system

$$\begin{aligned}\frac{dx_1}{dt} &= -0.9x_1 - \frac{3.5x_1}{0.7 + x_1} + 0.3x_2, \\ \frac{dx_2}{dt} &= -0.5x_2 + \frac{4.2x_1^2(t-\tau)}{(0.09x_1(t-\tau) + x_3)^2} + 0.16, \\ \frac{dx_3}{dt} &= -0.3x_3 + 1.8x_1\end{aligned}$$

We obtain a positive equilibrium $E = (0.0287, 0.5465, 0.1725)$. By direct calculation, we have $g_2 = -3.8852 < 0$ and $\Delta > 0$. The equilibrium is locally asymptotically stable for $\tau = 2.5$ as shown in figure 5.

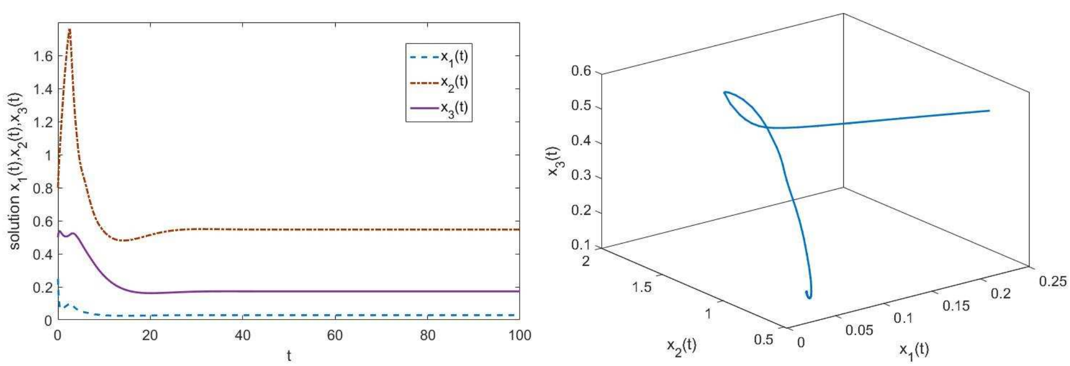

Figure 5: The behavior of $x_1(t), x_2(t)$, and $x_3(t)$ with $\tau = 2.5$.

5 Conclusion

In this paper, we have presented the conditions on the positive parameters of the signaling pathway model under the impact of delay. We found that the system could exhibit complex dynamics behavior and the stability of the equilibrium point E depends on the time delay τ. If $B_2 < \hat{B}$ and $g_2 > 0$, then the equilibrium point is locally asymptotically stable for $\tau \geq 0$. Under another set of assumptions on the parameters, the stability is verified in two cases. First, when the time delay increases to the critical value τ_0^+, the system changes its behavior from being stable to unstable. Secondly, the behavior of the system switches from unstable to stable when the time delay increases to the critical value τ_0^-. These mean that Hopf bifurcation can occur. Finally, some examples are given to confirm our analysis.

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