Mathematical Biosciences and Engineering

http://www.aimspress.com/journal/MBE

MBE, 18(4): 3448–3468.
DOI: 10.3934/mbe.2021173
Received: 17 February 2021
Accepted: 08 April 2021
Published: 19 April 2021

Research article

Dynamic behavior of the p53-Mdm2 core module under the action of drug Nutlin and dual delays

Juenu Yang, Fang Yan and Haihong Liu*

Department of Mathematics, Yunnan Normal University, Kunming 650500, China

* **Correspondence:** Email: lhhmath@aliyun.com; Tel: +8618687810297.

Supplementary

S1. Stability of the equilibrium and local Hopf bifurcation

This section, we discuss the stability of the positive equilibrium and the existence of local Hopf bifurcations of system (2.2) by considering the time delay τ as the bifurcation parameter. From a biological point of view, it is assumed that system (2.2) has a positive equilibrium $E_* = (X_*, Y_*, P_*, Q_*)$,which satisfies the following equation

$$\begin{cases} \sigma - \alpha p(t) - k_f p(t)m(t) + k_b c(t) + \gamma c(t) = 0, \\ k_t p^2(t-\tau) - \beta m_m(t) = 0, \\ k_{tl} m_m(t) - k_f p(t)m(t) + k_b c(t) + \delta c(t) - \gamma m(t) - k_{a3} n m(t) = 0, \\ k_f p(t)m(t) - k_b c(t) - \delta c(t) - \gamma c(t) = 0. \end{cases} \tag{S1.1}$$

By introducing $\bar{p}(t) = p(t) - P_*$, $\bar{m_m}(t) = m_m(t) - M_{M*}$, $\bar{m}(t) = m(t) - M_*$,$\bar{c}(t) = c(t) - C_*$, and still representing $\bar{p}$, $\bar{m_m}$, $\bar{m}$, $\bar{c}$ by p, m_m, m, c respectively. Then the linearized system of the system (2.2) in positive equilibrium is

$$\begin{cases} \dot{p}(t) = e_1 p(t) - k_f P_* m(t) + e_2 c(t), \\ \dot{m_m}(t) = 2k_t P_* p(t) - \beta m_m(t), \\ \dot{m}(t) = k_{tl} m_m(t) + e_3 m(t) - k_f M_* p(t) + e_4 c(t), \\ \dot{c}(t) = k_f P_* m(t) + k_f M_* p(t) + e_5 c(t). \end{cases} \tag{S1.2}$$

For the sake of simplicity, $\bar{p}$, $\bar{m_m}$, $\bar{m}$, $\bar{c}$ in the resultant equations have been represented p, m_m, m, c respectively,
where

$$e_1 = -\alpha - M_* k_f,$$

$$e_2 = k_b + \gamma, \quad e_3 = -k_f P_* - \gamma - k_{a3} n,$$
$$e_4 = k_b + \delta, \quad e_5 = -k_b - \delta - \gamma.$$

The characteristic equation corresponding to the linearized system (S1.2) can be written as

$$det \begin{pmatrix} \lambda - e_1 & 0 & k_f P_* & -e_2 \\ -2P_* k_t e^{-\lambda\tau} & \lambda + \beta & 0 & 0 \\ k_f M_* & -k_{tl} & \lambda - e_3 & -e_4 \\ -k_f M_* & 0 & -k_f P_* & \lambda - e_5 \end{pmatrix} = 0. \tag{S1.3}$$

Expanding Eq (S1.3) leads to the following exponential polynomial equation

$$D_4 + D_3\lambda + D_2\lambda^2 + D_1\lambda^3 + \lambda^4 + e^{-\lambda\tau}(D_5\lambda + D_6) = 0, \tag{S1.4}$$

where

$$\begin{aligned} D_1 &= -e_1 - e_3 - e_5 + \beta, \\ D_2 &= e_1e_3 + e_1e_5 + e_3e_5 - e_2k_fM_* - e_4k_fP_* - {k_f}^2 M_* P_* \\ &\quad - e_1\beta - e_3\beta - e_5\beta, \\ D_3 &= -e_1e_3e_5 + e_2e_3k_fM_* + e_1e_4k_fP_* + e_2{k_f}^2M_*P_* \\ &\quad + e_4{k_f}^2M_*P_* + e_5{k_f}^2M_*P_* + e_1e_3\beta + e_1e_5\beta \\ &\quad + e_3e_5\beta - e_2k_fM_*\beta - e_4k_fP_*\beta - {k_f}^2M_*P_*\beta, \\ D_4 &= -e_1e_3e_5\beta + e_2e_3k_fM_*\beta + e_1e_4k_fP_*\beta + e_2{k_f}^2M_*P_*\beta \\ &\quad + e_4{k_f}^2M_*P_*\beta + e_5{k_f}^2M_*P_*\beta, \\ D_5 &= 2k_fk_tk_{tl}{P_*}^2, \quad D_6 = -2e_2k_fk_tk_{tl}{P_*}^2 - 2e_5k_fk_tk_{tl}{P_*}^2. \end{aligned}$$

It is well known that $E_* = (P_*, M_{M*}, M_*, C_*)$ is locally asymptotically stable only if all roots of Eq (S1.4) have strictly negative real parts and the equilibrium will lose its stability if a pair of purely imaginary roots appears. Next, we take time delay as a parameter and discuss the distribution of roots of Eq (S1.4).

At the beginning before discussing, we need to introduce the following lemma.

Theorem 1: The Routh-Hurwitz criterion [1].Consider the real coefficient polynomial equation

$$a_0\lambda^n + a_1\lambda^{n-1} + \cdots + a_{n-1}\lambda + a_n = 0.$$

Make determinants

$$\Delta_n = \begin{vmatrix} a_1 & a_0 & 0 & \cdots & 0 \\ a_3 & a_2 & a_1 & \cdots & 0 \\ a_5 & a_4 & a_3 & \cdots & 0 \\ \vdots & \vdots & \vdots & \cdots & \vdots \\ a_{2n-1} & a_{2n-2} & a_{2n-3} & \cdots & a_n \end{vmatrix}.$$

Assuming $a_0 > 0$, if $i > n$ regulations $a_i > 0$, the sufficient and necessary condition for all the roots of the equation to have a strictly negative real part is that the following inequality holds

$(H1)\Delta_1 > 0, \qquad \Delta_2 > 0, \qquad \cdots, \qquad \Delta_n > 0.$

Lemma 2: Consider the transcendental equation

$$p(\lambda, e^{-\lambda\tau_1}, \ldots, e^{-\lambda\tau_m}) = \lambda^n + p_1^{(0)}\lambda^{n-1} + \cdots + p_{n-1}^{(0)}\lambda + p_n^{(0)} + [p_1^{(1)}\lambda^{n-1} + \cdots + p_{n-1}^{(1)}\lambda + p_n^{(1)}]e^{-\lambda\tau_1} + \cdots + [p_1^{(m)}\lambda^{n-1} + \cdots + p_{n-1}^{(m)}\lambda + p_n^{(m)}]e^{-\lambda\tau_m},$$

where $\tau_i(i = 1, 2, \ldots, m)$ and $p_j^{(i)}(i = 1, 2, \ldots, m; j = 1, 2, \ldots, n)$ are constants. Then as $(\tau_1, \tau_2, \ldots, \tau_m)$ vary, the sum of the zeros on the right half-open plane changes only when the zero appears on the imaginary axis or intersects the imaginary axis [2].

Case I : When $\tau = 0$ Eq (S1.4) can be simplified to

$$\lambda^4 + D_1\lambda^3 + D_2\lambda^2 + (D_3 + D_5)\lambda + (D_4 + D_6) = 0. \tag{S1.5}$$

Based on the Routh-Hurwitz criterion, a set of sufficient and necessary conditions for all roots of Eq (S1.5) to have a negative real part can be expressed as

$$\begin{aligned}
&\Delta_1 = D_1 > 0,\\
&\Delta_2 = \begin{vmatrix} D_1 & 1 \\ D_3 + D_5 & D_2 \end{vmatrix} > 0,\\
&\Delta_3 = \begin{vmatrix} D_1 & 1 & 0 \\ D_3 + D_5 & D_2 & D_1 \\ 0 & D_4 + D_6 & D_3 + D_5 \end{vmatrix} > 0,\\
&\Delta_4 = \begin{vmatrix} D_1 & 1 & 0 & 0 \\ D_3 + D_5 & D_2 & D_1 & 1 \\ 0 & D_4 + D_6 & D_3 + D_5 & D_2 \\ 0 & 0 & 0 & D_4 + D_6 \end{vmatrix} > 0.
\end{aligned}$$

Then, when (H1) is established, the equilibrium point $E_* = (P_*, M_{M*}, M_*, C_*)$ is locally asymptotically stable.

Case II : When $\tau \neq 0$ is satisfied,multiplies $e^{\lambda\tau}$ at both ends of the Eq (S1.4). Then the characteristic Eq (S1.4) can be rewritten as follows:

$$(D_4 + D_3\lambda + D_2\lambda^2 + D_1\lambda^3 + \lambda^4)e^{\lambda\tau} + D_5\lambda + D_6 = 0. \tag{S1.6}$$

Then assume that $\pm i\omega(\omega > 0)$ is a pair of pure virtual roots of Eq (S1.6), which means that the following equation must be satisfied

$$(\omega^4 - D_1 i\omega^3 - D_2\omega^2 + D_3 i\omega + D_4)(\cos(\omega\tau) + i\sin(\omega\tau)) + D_5 i\omega + D_6. \tag{S1.7}$$

Separating the real and imaginary parts are

$$\begin{cases} D_6 + (D_4 - D_2\omega^2 + \omega^4)\cos(\tau\omega) + (D_1\omega^3 - D_3\omega)\sin(\tau\omega) = 0, \\ D_5\omega + (D_3\omega - D_1\omega^3)\cos(\tau\omega) + (D_4 - D_2\omega^2 + \omega^4)\sin(\tau\omega) = 0. \end{cases} \tag{S1.8}$$

Though calculation, the following equations are obtained

$$\begin{cases} \cos(\omega\tau) = -\dfrac{D_5\omega(-D_3\omega + D_1\omega^3) - D_6(D_4 - D_2\omega^2 + \omega^4)}{(D_3\omega - D_1\omega^3)(-D_3\omega + D_1\omega^3) - (D_4 - D_2\omega^2 + \omega^4)^2}, \\ \sin(\omega\tau) = -\dfrac{\omega(D_4D_5 - D_3D_6 - D_2D_5\omega^2 + D_1D_6\omega^2 + D_5\omega^4)}{D_4^2 + C_1\omega^2 + C_2\omega^4 + C_3\omega^6 + \omega^8}, \end{cases} \tag{S1.9}$$

where

$$\begin{aligned} C_1 &= D_3^2 - 2D_2D_4, \\ C_2 &= D_2^2 - 2D_1D_3 + 2D_4, \\ C_3 &= D_1^2 - 2D_2. \end{aligned}$$

Square and addition both ends of the Eq (S1.9). The algebraic equation about ω is get

$$H(\omega) = h_1 + h_2\omega^2 + h_3\omega^4 + h_4\omega^6 - \omega^8 = 0, \tag{S1.10}$$

where

$$\begin{aligned} h_1 &= -D_1^2 + 2D_2, \\ h_2 &= -D_2^2 + 2D_1D_3 - 2D_4, \\ h_3 &= -D_3^2 + 2D_2D_4 + {D_5}^2, \\ h_4 &= -D_4^2 + D_6^2. \end{aligned}$$

Here, we make the following assumptions aim of getting the main results.
(H2) Eq (S1.10) has no positive roots.
If (H2) holds, all roots of Eq (S1.10) have negative real parts when $\tau \in (0, \infty)$.
(H3) Eq (S1.10) has at least one positive real root.
If (H3) holds and substituting $\omega_i (0 \leq i \leq 8)$ into (S1.9), we can get the following sets of critical values of the time delay

$$\tau_i^j = \frac{1}{\omega_i}\arccos[-\frac{D_5\omega(-D_3\omega + D_1\omega^3) - D_6(D_4 - D_2\omega^2 + \omega^4)}{(D_3\omega - D_1\omega^3)(-D_3\omega + D_1\omega^3) - (D_4 - D_2\omega^2 + \omega^4)^2}] + \frac{2j\pi}{\omega_i}, \tag{S1.11}$$

where $i = 1, 2, \ldots, 8$; $j = 0, 1, 2, \ldots$.

Denote $\tau_0 = min(\tau_i^j \mid i = 1, 2, \cdots, 8, j = 0, 1, 2, \cdots)$. When $\tau = \tau_0$, $\omega_0 = \omega_i$ is satisfied, the equation has a pair of pure virtual roots $\pm i\omega$.

Next, let us assume

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

Let $\lambda_\tau = \alpha_\tau + i\omega_\tau$ be a root of a characteristic Eq (S1.7) that satisfies $\alpha(\tau_0^j) = 0, \omega(\tau_0) = \omega_0$, then we get

$$(\lambda'(\tau))^{-1} = \frac{D_5}{D_6\lambda + D_5\lambda^2} - \frac{D_3 + \lambda(2D_2 + 3D_1\lambda + 4\lambda^2)}{D_4\lambda + \lambda^2(D_3 + \lambda(D_2 + \lambda(D_1 + \lambda)))} - \frac{\tau}{\lambda}. \tag{S1.12}$$

Therefore, we can easily find

$$Re(\lambda'(\tau))^{-1} \mid_{\tau=\tau_0} = -\frac{P_1}{P_2} + \frac{P_3}{P_4} \neq 0, \tag{S1.13}$$

where

$$\begin{aligned}
P_1 &= D_5^2,\\
P_2 &= D_6^2 + D_5^2\omega_0^2,\\
P_3 &= D_3^2 - 2D_2k_4 + 2D_2^2\omega_0^2 - 4D_1k_3\omega_0^2 + 4D_4\omega_0^2 + 3D_1^2\omega_0^4 - 6D_2\omega_0^4 + 4\omega_0^6,\\
P_4 &= \omega_0^2(D_3 - D_1\omega_0^2)^2 + (D_4 - D_2\omega_0^2 + \omega_0^4)^2.
\end{aligned}$$

Based on the correlation results of the functional differential equation [3] and the Hopf bifurcation theorem, the following theorem can be obtained.

Theorem 3: For $\tau = 0$, assume (H1) is satisfied. The following conclusions can be drawn.
(i) If (H2) are true, the equilibrium point $E^* = (P_*, M_{M*}, M_*, C_*)$ of system (2.2) is asymptotically stable for an arbitrary time delay $\tau > 0$.
(ii) If (H3) and (H4) are true, the equilibrium point $E^* = (P_*, M_{M*}, M_*, C_*)$ of system (2.2) is asymptotically stable for time delay $\tau\epsilon[0, \tau_0)$ and unstable when $\tau_1 > \tau_0$. In addition, system (2.2) undergoes Hopf bifurcation when $\tau = \tau_0$ at the unique positive equilibrium point. That is, system (2.2) has a branch of periodic solutions bifurcating from the equilibrium point when τ crosses through the critical value τ_0.

The above theorem can be proved by the theory of Hopf bifurcation, which is similar to the proof of Mao et al. [4].Consequently, the process of proof is omitted here for brevity.

S2. The direction and stability of Hopf bifurcation

In the previous section we studied the stability and the emergence of Hopf bifurcation of the system at positive equilibrium. In this section, we will further investigate the Hopf bifurcation direction and the bifurcating periodic solution stability though using the normal form and the central manifold theorem proposed by Hässard et al. [5].

Let $C([-\tau_0, 0], R^4)$ be a Banach space continuously mapped from $[-\tau_0, 0]$ to R^4, fitted out the supremum norm $||\phi|| = sup_{-\tau_0 \le \theta \le 0}|\phi(\theta)|$ for $\phi \in C([-\tau_0, 0], R^4)$. For the sake of simplicity, let $\tau = \tau_0 + \gamma(\gamma \in R)$. Then $\gamma = 0$ is the bifurcation value of system (2.2). Standardized time scale $t \to \frac{t}{\tau}$, system (2.2) can be written as an operator differential equation in $C([-\tau_0, 0], R^4)$. Then we can get

$$\begin{cases}
\dot{p}(t) = (\tau_0 + \gamma)[e_1 p(t) - k_f P_* m(t) + e_2 c(t) + f_1],\\
\dot{m}_m(t) = (\tau_0 + \gamma)[2P_* p(t-1) - \beta m_m(t) + f_2],\\
\dot{m}(t) = (\tau_0 + \gamma)[k_{tl} m_m(t) + e_3 m(t) - k_f M_* p(t) + e_4 c(t) + f_3],\\
\dot{c}(t) = (\tau_0 + \gamma)[k_f P_* m(t) + k_f M_* p(t) + e_5 c(t) + f_4],
\end{cases} \tag{S2.1}$$

where

$$f_1 = -k_f p(t) m(t),$$

$$f_2 = k_t p^2(t),$$
$$f_3 = -k_f p(t) m(t),$$
$$f_4 = -k_f p(t) m(t).$$

Let $U = (u_1(t), u_2(t), u_3(t), u_4(t))^T \in C([-1,0], R^4)$, system (S2.1) can be converted into

$$\dot{U} = L_\gamma(U_t) + F(\gamma, U_t). \tag{S2.2}$$

Then define the linear operator $L_\gamma : C \to R^4$ and the nonlinear operator $F : R \times C \to R^4$ are represented by the following equation

$$L_\gamma \phi = (\tau_0 + \gamma)[M_1 \phi(0) + M_2 \phi(-1)], \tag{S2.3}$$

and

$$F(\gamma, \phi) = (\tau_0 + \gamma)(f_1, f_2, f_3, f_4)^T, \tag{S2.4}$$

where

$$M_1 = \begin{pmatrix} e_1 & 0 & -k_f P_* & e_2 \\ 0 & -\beta & 0 & 0 \\ -k_f M_* & k_{tl} & e_3 & e_4 \\ k_f M_* & 0 & k_f P_* & e_5 \end{pmatrix}, M_2 = \begin{pmatrix} 0 & 0 & 0 & 0 \\ 2P_* k_t & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix},$$

And

$$F(\gamma, \phi) = (\tau_0 + \gamma) \begin{pmatrix} -k_f \phi_1(0) \phi_3(0) \\ k_t \phi_1(0)^2 \\ -k_f \phi_1(0) \phi_3(0) \\ -k_f \phi_1(0) \phi_3(0), \end{pmatrix}. \tag{S2.5}$$

where $\phi = (\phi_1(\theta), \phi_2(\theta), \phi_3(\theta), \phi_4(\theta))^T \in C$. According to the Riesz representation theorem, there is a 4×4 matrix function composed of the bounded variation function $\eta(\theta, \gamma)$ in $\theta \in [-1, 0] \to R^4$ as follows

$$L_\gamma \phi = \int_{-1}^{0} \mathrm{d}\eta(\theta, \gamma) \phi(\theta). \tag{S2.6}$$

We can choose

$$\eta(\theta, \gamma) = (\tau_0 + \gamma) M_1 \delta(\theta) + (\tau_0 + \gamma) M_2 \delta(\theta + 1), \tag{S2.7}$$

where $\delta(\theta)$ is the Dirac function.

For $\phi \in C^1([-1, 0], R^4)$, define operators

$$A(\gamma)\phi = \begin{cases} \dfrac{d\phi(\theta)}{d\theta}, & \theta \in [-\tau_0, 0), \\ \displaystyle\int_{-1}^{0} \mathrm{d}\eta(\gamma, \theta)\phi(\theta), & \theta = 0, \end{cases} \tag{S2.8}$$

$$R(\gamma)\phi = \begin{cases} 0, & \theta \in [-1, 0), \\ F(\gamma, \theta), & \theta = 0. \end{cases} \tag{S2.9}$$

To study the characteristics of Hopf bifurcation, we transform system (S2.1) into an operator equation of this form

$$\dot{U}_t = A(\gamma)U_t + R(\gamma)U_t, \tag{S2.10}$$

where $U_t = U(t + \theta)$.

The adjoint operator A^* of A for $\psi \in C^1[0, 1], R^4)$ is defined as

$$A^*(\gamma)\psi(\theta^*) = \begin{cases} -\dfrac{d\psi(\theta^*)}{d\theta^*}, & \theta^* \in (0, 1], \\ \displaystyle\int_{-1}^{0} d\eta^T(\theta^*, \gamma)\psi(-\theta^*), & \theta^* = 0, \end{cases} \tag{S2.11}$$

where $\eta^T(\theta^*, \gamma)$ is the transpose of the matrix $\eta(\theta^*, \gamma)$.

And define the following bilinear inner product

$$\langle \psi, \phi \rangle = \bar{\psi}(0)\phi(0) - \int_{-1}^{0} \int_{\xi=0}^{\theta} \bar{\psi}(\xi - \theta)d\eta(\theta)\phi(\xi)d\xi, \tag{S2.12}$$

where $\eta(\theta) = \eta(\theta, 0)$. $A^*(0)$ and $A(0)$ are adjoint operators. Corresponding to the discussion in the section 2, $\pm i\omega_0$ is the eigenvalue of $A(0)$ and the other eigenvalues have strictly negative real parts. They are also the eigenvalues of $A^*(0)$. Then, we will calculate the eigenvector $q(\theta)$ of the corresponding eigenvalue $i\omega_0$ and the eigenvector $q^*(s)$ of the corresponding eigenvalue $-i\omega_0$. We can get

$$\begin{cases} A(0)q(0) = i\omega_0 q(\theta), \\ A^*(0)q^*(0) = -i\omega_0 q^*(\theta^*), \end{cases} \tag{S2.13}$$

where $\theta \in [-1, 0]$, $\theta^* \in [0, 1]$.

Define

$$q(\theta) = q(0)e^{i\omega_0\tau_0\theta} = (1, v_1, v_2, v_3)e^{i\omega_0\tau_0\theta}, q^*(s) = q^*(0)e^{i\omega_0\tau_0 s} = G(1, v_1^*, v_2^*, v_3^*)e^{i\omega_0\tau_0 s}. \tag{S2.14}$$

Simple calculations can have

$$v_1 = -\frac{2k_{tl}P_*}{-\beta - i\omega_0}e^{-i\tau_0\omega_0}, \qquad v_2 = \frac{B_2}{B_1}e^{-i\tau_0\omega_0}, \qquad v_3 = \frac{B_3}{iB_1}e^{-i\tau_0\omega_0},$$
$$v_1^* = -\frac{k_{tl}B_4}{iB_5}, \qquad v_2^* = -\frac{B_4(i\beta + \omega_0)}{B_5}, \qquad v_3^* = \frac{B_6}{-k_f B_5},$$

where

$$B_1 = (-i\beta + \omega_0)(ie_2e_3 + ie_4k_fP_* + e_2\omega_0),$$
$$B_2 = -2e_2{k_{tl}}^2P_* + e^{i\tau_0\omega_0}(\beta + i\omega_0)(e_1e_4 + e_2k_fM_* - ie_4\omega_0),$$

$$B_3 = 2ik_f k_{tl}^2 P_*^2 + e^{i\tau_0\omega_0}(-i\beta + \omega_0)(k_f^2 M_* P_* + (ie_1 + \omega_0)(ie_3 + \omega_0)),$$
$$B_4 = P_*(e_1 + k_f M_* + i\omega_0),$$
$$B_5 = 2ie^{i\tau_0\omega_0} k_{tl}^2 P_*^2 - iM_*(\beta - i\omega_0)(e_3 + k_f P_* + i\omega_0),$$
$$B_6 = -2ie^{i\tau_0\omega_0} k_f k_{tl}^2 P_*^2 + (i\beta + \omega_0)(-e_1 e_3 + k_f^2 M_* P_* - i(e_1 + e_3)\omega_0 + \omega_0^2).$$

The normalization conditions of q and q^* are

$$< q^*, q >= 1, \quad < q^*, \bar{q} >= 0. \tag{S2.15}$$

To guarantee $< q^*, q >= 1$, we need to determine the value of G by the definition of the bilinear inner product of (S2.12). Substituting (S2.14) into the first equation in (S2.15) obtains

$$\begin{aligned}
\langle q^*, q\rangle =& \bar{q}^*(0)\cdot q(0) - \int_{-1}^{0}\int_{\xi=0}^{\theta} \bar{q}^*(\xi-\theta)d\eta(\theta)q(\xi)d\xi \\
=& \bar{q}^*(0)\cdot q(0) - \int_{-1}^{0}\int_{\xi=0}^{\theta} \bar{G}(1, \bar{v_1}^*, \bar{v_2}^*, \bar{v_3}^*)e^{-i\omega_0\tau_0(\xi-\theta)}d\eta(\theta)(1, v_1, v_2, v_3)^T e^{i\omega_0\tau_0\xi}d\xi \\
=& \bar{q}^*(0)\cdot q(0) - \bar{q}^*(0)\int_{-1}^{0}\theta e^{i\omega_0\tau_0\theta}d\eta(\theta)q(0) \\
=& \bar{q}^*(0)\cdot q(0) + \bar{q}^*(0)\tau_0 \begin{bmatrix} 0 & 0 & 0 & 0 \\ 2P_*k_t & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix} e^{-i\omega_0\tau_0\theta}q(0) \\
=& \bar{G}[(1 + v_1\bar{v_1}^* + v_2\bar{v_2}^* + v_3\bar{v_3}^*) + \tau_0 2P_*k_t\bar{v_1}^* e^{-i\omega_0\tau_0}] \\
=& 1.
\end{aligned} \tag{S2.16}$$

Then we can determine

$$\bar{G} = \frac{1}{(1 + v_1\bar{v_1}^* + v_2\bar{v_2}^* + v_3\bar{v_3}^*) + \tau_0 2P_*k_t v_1^* e^{-i\omega_0\tau_0}}. \tag{S2.17}$$

Using the same method as Hassard et al. [5], we first calculate the coordinates to describe the central manifold Ω_0 at $\gamma = 0$, defined

$$z(t) = \langle q^*, x_t\rangle, \tag{S2.18}$$

and

$$W(t, \theta) = U_t - 2Re[z(t)q(\theta)], \tag{S2.19}$$

where U_t is a solution of (S2.10).

In the central manifold Ω_0: $W(t, \theta) = W(z(t), \bar{z}(t), \theta)$, where

$$W(z, \bar{z}, \theta) = W_{20}(\theta)\frac{z^2}{2} + W_{11}(\theta)z\bar{z} + W_{02}(\theta)\frac{\bar{z}^2}{2} + \cdots . \tag{S2.20}$$

Obviously, $z(t)$ and $\bar{z}(t)$ are the local coordinates of the central manifold Ω_0 in the q^* and $\bar{q}^*$ directions, respectively. Note that if $U_t(\theta)$ is a real, we only need to find a real root. For the solution $U_t \in \Omega_0$ of (S2.10), due to $\gamma = 0$, we can have:

$$\begin{aligned}\dot{z}(t) &= < q^*, \dot{U}_t > \\ &= < q^*, AU_t + RU_t > \\ &= < A^* q^*, U_t > + < \bar{q}^*(0), F(0, U_t) > \\ &= i\omega_0\tau_0 z(t) + \bar{q}^*(0)F_0(z, \bar{z}),\end{aligned} \tag{S2.21}$$

i.e.

$$\dot{z}(t) = i\omega_0\tau_0 z(t) + g(z, \bar{z}), \tag{S2.22}$$

where

$$g(z, \bar{z}) = \bar{q}^*(0)F_0(z, \bar{z}) = g_{20}\frac{z^2}{2} + g_{11}z\bar{z} + g_{02}\frac{\bar{z}^2}{2} + g_{21}\frac{z^2\bar{z}}{2} + \cdots . \tag{S2.23}$$

In addition, available from (S2.10) and (S2.21), we get

$$\begin{aligned}\dot{W} &= \dot{U}_t - \dot{z}q - \dot{\bar{z}}\bar{q} \\ &= AU_t + RU_t - [i\omega_0\tau_0 z + \bar{q}^*(0)F_0(z, \bar{z})]q(\theta) - [-(i\omega_0\tau_0\bar{z} + q^*(0)\bar{F}_0(z, \bar{z}))]\bar{q}(\theta) \\ &= AW - 2Re[\bar{q}^*(0)F_0(z, \bar{z})q(\theta)] + RU_t \\ &= \begin{cases} AW - 2Re[\bar{q}^*(0)F_0(z, \bar{z})q(\theta)], & \theta \in [-1, 0) \\ AW - 2Re[\bar{q}^*(0)F_0(z, \bar{z})q(0)] + F_0, & \theta = 0 \end{cases} \\ &= AW + H(z, \bar{z}, \theta),\end{aligned} \tag{S2.24}$$

where

$$H(z, \bar{z}, \theta) = H_{20}(\theta)\frac{z^2}{2} + H_{11}(\theta)z\bar{z} + H_{02}(\theta)\frac{\bar{z}^2}{2} + \cdots . \tag{S2.25}$$

Taking the derivative of W with respect to t in Eq (S2.20) leads to

$$\dot{W} = W_z\dot{z} + W_{\bar{z}}\dot{\bar{z}}. \tag{S2.26}$$

Substituting (S2.20) and (S2.22) into (S2.26) yields

$$\dot{W} = (W_{20}z + W_{11}\bar{z} + \cdots)(i\omega_0\tau_0 z + g) + (W_{11}z + W_{02}\bar{z} + \cdots)(-i\omega_0\tau_0\bar{z} + \bar{g}). \tag{S2.27}$$

Then substituting (S2.20) and (S2.25) into (S2.24) gives rise to

$$\dot{W} = (AW_{20} + H_{20})\frac{z^2}{2} + (AW_{11} + H_{11})z\bar{z} + (AW_{02} + H_{02})\frac{\bar{z}^2}{2} + \cdots . \tag{S2.28}$$

Compare the coefficients of (S2.27) and (S2.28) lead to

$$(A - 2i\omega_0\tau_0 I)W_{20}(\theta) = -H_{20}(\theta), \tag{S2.29}$$

$$AW_{11}(\theta) = -H_{11}(\theta). \tag{S2.30}$$

According to Eq (S2.19), we obtain $U_t(\theta) = W(z, \bar{z}, \theta) + zq + \bar{z}\bar{q}$ and $q(\theta) = (1, v_1, v_2, v_3)e^{i\omega_0\tau_0\theta}$. It follows together with (S2.5) that

$$g(z, \bar{z})) = \bar{q}^*(0)F_0(z, \bar{z}) = \bar{q}^*(0)F(0, U_t) = \bar{G}\tau_0(1, \bar{v_1}^*, \bar{v_2}^*, \bar{v_3}^*) \times \begin{pmatrix} -k_f\phi_1(0)\phi_3(0) \\ k_t\phi_1(0)^2 \\ -k_f\phi_1(0)\phi_3(0) \\ -k_f\phi_1(0)(\phi_3(0)) \end{pmatrix} \tag{S2.31}$$

Comparing the coefficients in (S2.23) and (S2.31) according to the method of Wagner [6], there are

$$\begin{aligned}
g_{20} &= 2\bar{G}\tau_0[-k_f v_2 + k_t v_{11}{}^* - k_f v_2 v_{22}{}^* + k_f v_2 v_{33}], \\
g_{11} &= 2\bar{G}\tau_0[-k_f v_2 - k_f v_{22} + 2k_t v_{11}{}^* - k_f v_2 v_{22}{}^* - k_f v_{22} v_{22}{}^* + k_f v_2 v_{33}{}^* + k_f v_{22} v_{33}], \\
g_{02} &= 2\bar{G}\tau_0[-k_f v_{22} + k_t v_{11}{}^* - k_f v_{22} v_{22}{}^* + k_f v_{22} v_{33}{}^*], \\
g_{21} &= 2\bar{G}\tau_0[-k_f v_2 W_{1110}(0) - k_f W_{1130}(0) - \frac{k_f v_{22} W_{2010}(0)}{2} - \frac{k_f W_{2030}(0)}{2} + 2k_t W_{1110}(0)v_{11}{}^* - k_f W_{1130}(0)v_{22}{}^*, \\
&\quad - \frac{k_f v_{22} W_{2010}(0)v_{22}{}^*}{2} - \frac{k_f W_{2030}(0)v_{22}{}^*}{2} + k_f v_2 W_{1110}(0)v_{33}{}^* + k_f W_{1130}(0)v_{33}{}^* + \frac{k_f v_{22} W_{2010}(0)v_{33}{}^*}{2}, \\
&\quad + \frac{k_f W_{2030}(0)v_{33}{}^*}{2} - k_f v_2 W_{1110}(0)v_{22}{}^* + k_t W_{2010}(0)v_{11}{}^*].
\end{aligned} \tag{S2.32}$$

According to (S2.24), we know that for $\theta \in [-1, 0)$

$$\begin{aligned}
H(z, \bar{z}, \theta) &= -2Re[\bar{q}^*(0)^T \cdot F_0(z, \bar{z})q(\theta)] \\
&= -g(z, \bar{z})q(\theta) - \bar{g}(z, \bar{z})\bar{q}(\theta) \\
&= -(g_{20}\frac{z^2}{2} + g_{11}z\bar{z} + g_{02}\frac{\bar{z}^2}{2} + g_{21}\frac{z^2\bar{z}}{2} + \cdots)q(\theta) \\
&\quad - (\bar{g}_{20}\frac{\bar{z}^2}{2} + \bar{g}_{11}z\bar{z} + \bar{g}_{02}\frac{z^2}{2} + \bar{g}_{21}\frac{\bar{z}^2 z}{2} + \cdots)\bar{q}(\theta).
\end{aligned} \tag{S2.33}$$

Compare the coefficient with (S2.25) to get

$$H_{20}(\theta) = -g_{20}q(\theta) - \bar{g}_{02}\bar{q}(\theta), \tag{S2.34}$$

$$H_{11}(\theta) = -g_{11}q(\theta) - \bar{g}_{11}\bar{q}(\theta). \tag{S2.35}$$

Substituting (S2.34) and (S2.35) into (S2.29) and (S2.30) respectively,

$$\begin{cases} \dot{W}_{20}(\theta) = 2i\omega_c W_{20}(\theta) + g_{20}q(\theta) + \bar{g}_{02}\bar{q}(\theta), \\ \dot{W}_{11}(\theta) = g_{11}q(\theta) + \bar{g}_{11}\bar{q}(\theta). \end{cases} \tag{S2.36}$$

We can easily obtain the solution of (S2.36)

$$\begin{cases} W_{20}(\theta) = \dfrac{ig_{20}}{\omega_0} q(0) e^{i\omega_0\tau_0\theta} + \dfrac{i\bar{g}_{02}}{3\omega_0\tau_0} \bar{q}(0) e^{-i\omega_0\tau_0\theta} + E_1 e^{2i\omega_0\tau_0\theta}, \\ W_{11}(\theta) = -\dfrac{ig_{11}}{\omega_0} q(0) e^{i\omega_0\tau_0\theta} + \dfrac{i\bar{g}_{11}}{\omega_0\tau_0} \bar{q}(0) e^{-i\omega_0\tau_0\theta} + E_2, \end{cases} \tag{S2.37}$$

where $E_1 = (E_1^{(1)}, E_1^{(2)}, E_1^{(3)}, E_1^{(4)}) \in R^4$ and $E_2 = (E_2^{(1)}, E_2^{(2)}, E_2^{(3)}, E_2^{(4)}) \in R^4$ are constant vectors.We can determine the appropriate E_1 and E_1 by setting $\theta = 0$ in $H(z, \bar{z}, \theta)$.
From Eq (S2.24), we have

$$\begin{aligned} H_{20}(0) =& - g_{20} q(0) - \bar{g}_{02} \bar{q}(0) \\ & - \tau_0 \begin{pmatrix} -2k_f v_3 \\ 2k_t \\ -2k_f v_3 \\ -2k_f v_3 \end{pmatrix}, \end{aligned} \tag{S2.38}$$

and

$$\begin{aligned} H_{11}(0) =& - g_{11} q(0) - \bar{g}_{11} \bar{q}(0) \\ & - 2\tau_0 \begin{pmatrix} -k_f v_3 - k_f \bar{v}_3 \\ k_t \\ -k_f v_3 - k_f \bar{v}_3 \\ -k_f v_3 - k_f \bar{v}_3 \end{pmatrix}. \end{aligned} \tag{S2.39}$$

By the definition of A and (S2.29) and (S2.30), we can write

$$\int_{-1}^{0} d\eta(\theta) W_{20}(\theta) = 2i\omega_0 W_{20}(0) - H_{20}(0), \tag{S2.40}$$

and

$$\int_{-1}^{0} d\eta(\theta) W_{11}(\theta) = -H_{11}(0), \tag{S2.41}$$

where $\eta(\theta) = \eta(0, \theta)$.
In particular,

$$\left(i\omega_0\tau_0 I - \int_{-1}^{0} e^{i\omega_0\tau_0\theta} d\eta(\theta) \right) q(0) = 0, \tag{S2.42}$$

$$\left(-i\omega_0\tau_0 I - \int_{-1}^{0} e^{-i\omega_0\tau_0\theta} d\eta(\theta) \right) \bar{q}(0) = 0. \tag{S2.43}$$

Therefore,

$$\begin{pmatrix} 2i\omega_0 - e_1 & 0 & k_f P_* & -e_2 \\ -2k_t P_* e^{-2i\omega_0\tau_0} & 2i\omega_0 + \beta & 0 & 0 \\ k_f M_* & -k_{tl} & 2i\omega_0 - e_3 & -e_4 \\ -k_f M_* & 0 & -k_f P_* & 2i\omega_0 - e_5 \end{pmatrix} \times E_1$$

$$= \begin{pmatrix} -2k_f v_3 \\ 2k_t \\ -2k_f v_3 \\ -2k_f v_3 \end{pmatrix}, \tag{S2.44}$$

and

$$\begin{pmatrix} -e_1 & 0 & k_f P_* & -e_2 \\ -2k_t P_* e^{-2i\omega_0\tau_0} & \beta & 0 & 0 \\ k_f M_* & -k_{tl} & -e_3 & -e_4 \\ -k_f M_* & 0 & -k_f P_* & -e_5 \end{pmatrix} \times E_2$$
$$= 2 \begin{pmatrix} -k_f v_3 - k_f \bar{v_3} \\ k_t \\ -k_f v_3 - k_f \bar{v_3} \\ -k_f v_3 - k_f \bar{v_3} \end{pmatrix}. \tag{S2.45}$$

For review, we can get all values of g_{ij}. Further, the following values can be calculated.

$$\begin{aligned} C_1(0) &= \frac{i}{2\omega_0\tau_0}\left(g_{11}g_{20} - 2|g_{11}|^2 - \frac{|g_{02}|^2}{3}\right) + \frac{g_{21}}{2}, \\ \mu_2 &= -\frac{Re(C_1(0))}{Re(\lambda'(\tau_0))}, \\ T_2 &= -\frac{Im\{C_1(0)\} + \mu_2 Im\{\lambda'(\tau_0)\}}{\omega_0}, \\ \beta_2 &= 2Re\{C_1(0)\}. \end{aligned} \tag{S2.46}$$

Based on the above discussion, we can gain the following results:

Theorem 4: From the equilibrium point, the bifurcating periodic solution of the system (S2.1) has the following properties:
(i) The sign of μ_2 determines the direction of the Hopf bifurcation: if $\mu_2 > 0(\mu_2 < 0)$, the Hopf bifurcation is supercritical (subcritical) and the bifurcation periodic solution exists in $\tau > \tau_0(\tau < \tau_0)$.
(ii) The sign of $\beta_2 < 0(\beta_2 > 0)$ the stability of the bifurcating period solutions: if $\beta_2 < 0(\beta_2 > 0)$, the bifurcating solution of the central manifold is stable (unstable).
(iii)The sign of T_2 determines the period of the bifurcating periodic solution: if $T_2 > 0(T_2 < 0)$, the period increases (decreases).

References

1. H. Hu, Z. Wang, *Dynamics of Controlled Mechanical Systems with Delayed Feedback*, Springer-Verlag, 1989.
2. S. Ruan, J. Wei, On the zeroes of transcendental functions with applications to the stability of delay differential equations, *Dyn. Contin. Discrete Impulsive Syst.*, **10** (2003), 863–874.
3. H. O. Walther, Book Review: Introduction to functional differential equations, *B. Am. Math. Soc.*, **32** (1995), 132–137.

4. X. C. Mao, H. Y. Hu, H. H. Yan, Hopf bifurcation analysis of a four-neuron network with multiple time delays, *Nonlinear Dynam.*, **55** (2008), 95–112.

5. H. D. Brian, B. D. Hassard, K. D. Nicholas, Y. H. Wan, W. Y. Wah, *Theory and Applications of Hopf Bifurcation*, CUP Archive, 1981.

6. V. E. Wagner, D. Bushnell, L. Passador, A. I. Brooks, B. H. Iglewski, Microarray analysis of Pseudomonas aeruginosa quorum-sensing regulons: effects of growth phase and environment, *J. Bacteriol.*, **185** (2003), 2080.