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Theoretical analysis of the delay on the p53 micronetwork

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Abstract

Time delay plays a crucial role in p53 dynamic. However, the theoretical understanding is still lower. Thus we construct a micro-differential equation model and introduce the time delay τ based on the regulation process. Firstly, we linearize the system and analyze the associated characteristic equation. We can conclude that there exists the delay threshold τ_0 such that when the delay τ is less than τ_0 , the system is asymptotically stable and otherwise stable oscillations occur. Secondly, we use the normal form method and the center manifold theorem to derive the direction and stability of the Hopf bifurcation. Finally, by numerical simulations we verify our theoretical results. We also find that the effect of noise on the amplitude is more severe than that of the period, which well agrees with the experimental results.

Keywords: Delays; Oscillations; Hopf bifurcation

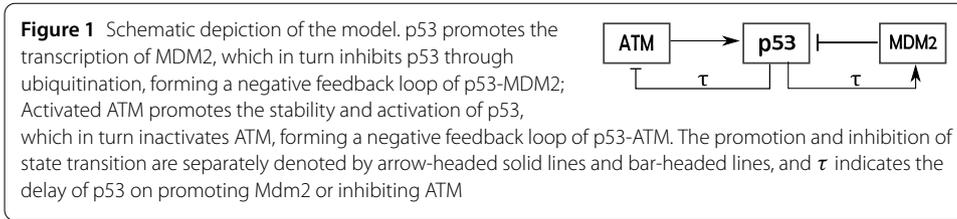
1 Introduction

The tumor suppressor p53 is located in the center of the cellular signaling networks and stress-activated signals networks [1]. In unstressed cells, wild-type p53 remains at low levels [2]. Upon DNA damage, p53 is stabilized and activated [3, 4]. p53 can induce different cellular outcomes such as cell cycle arrest and apoptosis [5–12]. It is very crucial to study the mechanism of p53 network dynamics [13].

Recently, it was experimentally shown that the concentration of p53 undergoes pulses upon ionization radiation in MCF7 cells [14]. Much work has explored the feedback mechanism of p53 oscillations [6, 7, 15, 16]. It has been suggested that the fate of cells between survival and death can be determined by counting the number of p53 pulses: cells can survive on the transient p53 pulses, but apoptosis under the action of continuous p53 pulse [7–10]. This may represent a reliable and flexible mechanism. For example, it can prevent premature apoptosis caused by drastic unexpected fluctuations in p53 levels [17].

The p53-Mdm2 negative feedback loop is recognized as the basis of p53 oscillation [6, 18], and the research has shown that the ATM (ataxia telangiectasia mutated)-p53-WIP1(wild-type p53-induced phosphatase1) negative feedback loop (NFL) is required for the generation of uniform p53 pulses [16]. Therefore it is important to further clarify how p53 pulses are regulated.

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Mathematical models are generally used to study dynamic processes [19], including, from the cell process point of view, a series of regulatory behaviors in biological cells, such as transcriptional translation, transmembrane transport, and so on [20–23]. All they possess a certain time delay [6, 10, 24, 25]. We construct p53-MDM2-ATM micro network with time delays to fit the biological facts. Based on the real networks modeling and theoretical research, we analyze the influence of time delay on the oscillation behavior of the simplified model and verify the correctness of the theoretical analysis by numerical simulations.

2 Models and assumptions

In resting cells, p53 is suppressed by MDM2 at low level [26]. When DNA is damaged by external stimulation, DNA double-strand breaks (DSBs) promote the activation of ATM, which make p53 transform to active state [6, 27]. Activated p53 is beneficial to the transcription of p53 target protein. WIP1 is one of the proteins that promoted by p53 [5, 9] can catalyze the dephosphorylation of ATM [28]. WIP1-ATM-p53 forms an NFL. To avoid the complexity of the model, we hide the WIP1 protein, that is, p53 can directly inhibit ATM with time delay τ . At the same time, p53 promotes the production of MDM2 in cytoplasm (MDM2c) [29]. When MDM2c is phosphorylated, it moves to the nucleus [29]. MDM2n (MDM2 in nucleus) in turn promotes the ubiquitin of p53, accelerates the degradation of p53 [9], and encloses the p53-MDM2 NFL. Due to the existence of transmembrane transport, here we add a time delay to the effect of p53 on MDM2. To simplify the numerical calculation and theoretical analysis, we choose the same time delay as shown in Fig. 1.

Through p53 mininetwork, we give system (1), where β is the phosphorylation rate constant of ATM under DSBS, γ and α are the maximum production rate constants of p53 and MDM2, respectively, ζ is the production rate of noise in protein. For simplicity, we take $\zeta = 1$ in the next theory study, that is, the ideal cell environment. η is the dephosphorylation rate constant of ATM dependent on p53, and $k\eta$ is the basal ATM dephosphorylation rate. We use $A(t), P(t), M(t)$ to denote the concentrations of ATM, p53, and Mdm2, respectively. All they are dimensionless concentrations. k_i ($i = 1, 2, 3, 4$) are Michaelis constants of the Michaelis–Menten function or Hill function.

$$\begin{cases} \dot{A}(t) = \beta - \eta(P(t - \tau) + k) \frac{A(t)}{k_1 + A(t)}, \\ \dot{P}(t) = \zeta \gamma \frac{A(t)}{k_2 + A(t)} - \mu M(t) \frac{P(t)}{k_3 + P(t)}, \\ \dot{M}(t) = \zeta \alpha \frac{P^4(t - \tau)}{k_4^4 + P^4(t - \tau)} - \mu \frac{A(t)}{k_2 + A(t)} M(t). \end{cases} \tag{1}$$

3 Local stability and Hopf bifurcation

In this part, we theoretically analyze the bifurcation and oscillation mechanism of system (1) under time delay. The equilibrium point of the system is $\hat{E} = (A^*, P^*, M^*)$. Let

$\bar{A}(t) = A(t) - A^*, \bar{P}(t) = P(t) - P^*, \bar{M}(t) = M(t) - M^*$. For simplicity, we still denote $\bar{A}, \bar{P}, \bar{M}$ by A, P, M . System (1) is deployed using Taylor’s formula. We obtain

$$\begin{cases} \dot{A}(t) = C_1A(t) + C_2P(t - \tau) - \eta P(t - \tau)G'(A^*)A(t) \\ \quad - \eta(P(t - \tau) + P^* + k) \sum_{i=2}^{\infty} \frac{1}{i!} G^i(A^*)A^i(t), \\ \dot{P}(t) = C_3A(t) + C_4P(t) + C_5M(t) - uP(t)M(t)f'(P^*) \\ \quad + \gamma \sum_{i=2}^{\infty} \frac{1}{i!} G_1^i(A^*)A^i(t) - u(M(t) + M^*) \sum_{i=2}^{\infty} \frac{1}{i!} G^i(A^*)A^i(t), \\ \dot{M}(t) = C_6A(t) + C_7P(t - \tau) + C_8M(t) - \mu A(t)M(t)G_1'(A^*) \\ \quad + \alpha \sum_{i=2}^{\infty} \frac{1}{i!} f_2^i(P^*)P^i(t - \tau) + (M(t) + M^*) \sum_{i=2}^{\infty} \frac{1}{i!} G_1^i(A^*)A^i(t), \end{cases} \tag{2}$$

where superscript i represents the i th-order derivative, and

$$\begin{aligned} C_1 &= -\eta(P^* + k)G'(A^*), & C_2 &= -\eta G(A^*), & C_3 &= \gamma G'(A^*), \\ C_4 &= -uM^*f'(P^*), & C_5 &= -uf(P^*), & C_6 &= -\mu M^*G'(A^*), \\ C_7 &= \alpha f_2'(P^*), & C_8 &= -\mu G_1(A^*), & G'(A) &= \frac{k_1}{(k_1 + A^*)^2}, \\ f'(P) &= \frac{k_3}{(k_3 + P^*)^2}, & G_1'(A) &= \frac{k_2}{(k_2 + A^*)^2}, \\ f_2'(P) &= \frac{4k_4^4 P^3(t - \tau)}{(k_4^4 + P^4(t - \tau))^2}. \end{aligned}$$

The stable point \hat{E} of system (1) is transformed into zero $E^0(0, 0, 0)$ of system (2), and we can get the linearized system

$$\begin{cases} \dot{A}(t) = C_1A(t) + C_2P(t - \tau), \\ \dot{P}(t) = C_3A(t) + C_4P(t) + C_5M(t), \\ \dot{M}(t) = C_6A(t) + C_7P(t - \tau) + C_8M(t), \end{cases} \tag{3}$$

and then we get the characteristic equation

$$\lambda^3 + A_1\lambda^2 + A_2\lambda + a_0 + a_1e^{-\lambda\tau}\lambda + a_2e^{-\lambda\tau} = 0, \tag{4}$$

where

$$\begin{aligned} A_1 &= -(C_1 + C_4 + C_8), & A_2 &= -(C_1C_8 + C_4C_8 - C_1C_4), & a_0 &= -C_1C_4C_8, \\ a_1 &= -(C_2C_3 + C_5C_7), & a_2 &= C_2C_3C_8 + C_1C_5C_7 - C_2C_5C_6. \end{aligned}$$

To obtain all the cases from the theoretical point of view, we assume that $i\omega$ ($\omega > 0$) is the root of Eq. (4) and ω satisfies the equation

$$\begin{aligned} -i\omega^3 - A_1\omega^2 + A_2i\omega + a_0 + a_1i\omega(\cos(\omega\tau) - i\sin(\omega\tau)) \\ + a_2(\cos(\omega\tau) - i\sin(\omega\tau)) = 0. \end{aligned} \tag{5}$$

The real and imaginary parts of Eq. (5) can be separated from each other, and we obtain

$$\begin{cases} -A_1\omega^2 + a_0 + a_1\omega \sin(\omega\tau) + a_2\omega \cos(\omega\tau) = 0, \\ -i\omega^3 + A_2i\omega + a_1i\omega \cos(\omega\tau) - a_2i\omega \sin(\omega\tau) = 0, \end{cases} \tag{6}$$

which leads to

$$a_1^2\omega^2 + a_2^2\omega^2 = (A_1\omega^2 - a_0)^2 + (\omega^3 - A_2\omega)^2. \tag{7}$$

Then we get the equation

$$b_0 + b_1\omega^2 + b_2\omega^4 + \omega^6 = 0, \tag{8}$$

where

$$b_0 = a_0^2, \quad b_1 = A_2^2 - a_1^2 - a_2^2 - 2a_0A_1, \quad b_2 = A_1^2 - 2A_2.$$

If there is at least one positive real root of Eq. (8), then Eq. (4) has a pair of purely imaginary roots at the critical value of τ . We define that the positive root of Eq. (8) is $\omega_l, 1 \leq l \leq 6$. For every fixed l , the corresponding critical value of time delay τ is

$$\begin{aligned} \tau_l^{(j)} &= \frac{2j\pi}{\omega_l} + \frac{1}{\omega_l} \times \arccos \left[\frac{(A_1\omega^2 - a_0)a_2 + \omega^3 a_1 - A_2 a_1 \omega^2}{a_1^2 \omega^2 + a_2^2} \right] \\ 1 \leq l \leq 6, j &= 0, 1, 2, \dots \end{aligned} \tag{9}$$

For simplicity, we record that the minimum value of $\tau_l^{(j)}$ is represented by τ_0 . When $\tau_l = \tau_0$, the corresponding $\omega_l = \omega_0$. Let $\lambda(\tau) = \nu(\tau) + i\omega(\tau)$ be the root of Eq. (4) that satisfies $\nu(\tau_0) = 0$ and $\omega(\tau_0) = 0$. We can prove that $[d(\text{Re}(\lambda)/d\tau)]|_{\tau=\tau_0} > 0$. Substituting $\lambda(\tau)$ into the left-hand side of the Eq. (4), we obtain

$$\begin{aligned} \left(\frac{d(\text{Re}(\lambda))}{d\tau} \right)^{-1} &= \text{Re} \left[\frac{(3\lambda^2 + 2A_1\lambda + A_2)e^{\lambda\tau} + a_1}{-a_1\lambda^2 - a_2\lambda} \right] \\ &= \frac{W_0R_1 + W_0^2R_2 + W_0^3R_3 + W_0^4R_4}{B_1^2 + B_2^2}, \end{aligned}$$

where

$$\begin{aligned} R_1 &= -A_2a_2\sin(\omega_0\tau_0), & R_2 &= A_2a_1\cos(\omega_0\tau_0) - 2A_1a_2\cos(\omega_0\tau_0) - 2A_1a_2\sin(\omega_0\tau_0) \\ R_3 &= 3a_2\sin(\omega_0\tau_0), & R_4 &= -3\cos(\omega_0\tau_0), & B_1 &= a_1\omega_0^2, & B_2 &= a_2\omega_0. \end{aligned}$$

Obviously, when $\omega_0R_1 + \omega_0^2R_2 + \omega_0^3R_3 + \omega_0^4R_4 > 0$, we have

$$\text{sign} \left\{ \left[\frac{d(\text{Re}(\lambda))}{d\tau} \right] \Big|_{\tau=\tau_0} \right\} = \text{sign} \left\{ \text{Re} \left[\frac{d(\lambda)}{d\tau} \right]^{-1} \Big|_{\tau=\tau_0} \right\} > 0.$$

Therefore the conclusion is that when $0 \leq \tau < \tau_0$, the equilibrium point \hat{E} of system (1) is asymptotically stable; when $\tau > \tau_0$, the system is unstable; obviously, when $\tau = \tau_0$, the system experiences Hopf bifurcation at the equilibrium point. From this conclusion we can clearly realize that τ_0 is a very important value; when the system delay is greater than τ_0 , the system is oscillatory, and otherwise it remains stable. The influence mechanism of time delay on the oscillation of p53-MDM2-ATM system can be obtained by studying τ_0 .

4 Direction and stability of the Hopf bifurcation

In this section, we continue to study the Hopf bifurcation through the normal form theory and the center manifold reduction theory. Define $\tau = \gamma + \tau_0$. When $\gamma = 0$, as in the third part of the study, we normalize the time scale by $t \rightarrow (\frac{t}{\tau})$, rewriting the system as follows:

$$\begin{cases} \dot{A}(t) = (\tau_0 + \gamma)[C_1A(t) + C_2P(t - \tau) - \eta P(t - \tau)G'(A^*)A(t) \\ \quad - \eta(P(t - \tau) + P^* + k) \sum_{i=2}^{\infty} \frac{1}{i!} G^i(A^*)A^i(t)], \\ \dot{P}(t) = (\tau_0 + \gamma)[C_3A(t) + C_4P(t) + C_5M(t) - uP(t)M(t)f'(P^*) \\ \quad + \gamma \sum_{i=2}^{\infty} \frac{1}{i!} G_1^i(A^*)A^i(t) - u(M(t) + M^*) \sum_{i=2}^{\infty} \frac{1}{i!} G^i(A^*)A^i(t)], \\ \dot{M}(t) = (\tau_0 + \gamma)[C_6A(t) + C_7P(t - \tau) + C_8M(t) - \mu A(t)M(t)G_1'(A^*) \\ \quad + \alpha \sum_{i=2}^{\infty} \frac{1}{i!} f_2^i(P^*)P^i(t - \tau) + (M(t) + M^*) \sum_{i=2}^{\infty} \frac{1}{i!} G_1^i(A^*)A^i(t)]. \end{cases} \tag{10}$$

Let $U = (A(t), P(t), M(t))^T$ and $U_t = U(t + \theta), \theta \in [-1, 0]$. We denote $C = C([-1, 0], R^3)$. Then system (10) can be transformed to

$$\dot{U} = L_\gamma(U_t) + f(\gamma, U_t). \tag{11}$$

Equation (12) can be obtained by defining the linear operator $L_\gamma : C \rightarrow R^3$ and the non-linear operator $f : R \times C \rightarrow R^3$ as follows:

$$L_\gamma(\phi) = (\tau_0 + \gamma) \begin{pmatrix} C_1 & 0 & 0 \\ C_3 & C_4 & C_5 \\ C_6 & 0 & C_8 \end{pmatrix} \begin{pmatrix} \phi_1(0) \\ \phi_2(0) \\ \phi_3(0) \end{pmatrix} + (\tau_0 + \gamma) \begin{pmatrix} 0 & C_2 & 0 \\ 0 & 0 & 0 \\ 0 & C_7 & 0 \end{pmatrix} \begin{pmatrix} \phi_1(-1) \\ \phi_2(-1) \\ \phi_3(-1) \end{pmatrix}, \tag{12}$$

and

$$f(\gamma, \phi) = (\tau_0 + \gamma) \begin{pmatrix} F_1 \\ F_2 \\ F_3 \end{pmatrix}, \tag{13}$$

where

$$\begin{aligned} F_1 &= -\eta\phi_2(-1)G'(A^*)\phi_1(0) - \eta(\phi_2(-1) + P^* + k) \sum_{i=2}^{\infty} \frac{1}{i!} G^i(A^*)\phi_1(0)^i, \\ F_2 &= \gamma \sum_{i=2}^{\infty} \frac{1}{i!} G^i(A^*)\phi_1(0)^i - u\phi_2(0)\phi_3(0)f'(P^*) - u(\phi_3(0) + M^*) \sum_{i=2}^{\infty} \frac{1}{i!} f^i(P^*)\phi_2(0)^i, \\ F_3 &= \alpha \sum_{i=2}^{\infty} \frac{1}{i!} f_2^i(P^*)\phi_2(-1)^i - \mu\phi_3(0)G_1'(A^*)\phi_1(0) + \sum_{i=2}^{\infty} \frac{1}{i!} G_1^i(A^*)\phi_1(0)^i(\phi_3(0) + M^*), \end{aligned}$$

and $U_t = \phi = (\phi_1(t), \phi_2(t), \phi_3(t))^T \in C$. Through Riesz representation theorem, there is a coefficient 3×3 matrix function $\eta(\theta, \gamma), -1 \leq \theta \leq 0$, whose elements are bounded-variation functions, and

$$L_\gamma(\phi) = \int_{-1}^0 d\eta(\theta, \gamma)\phi(\theta). \tag{14}$$

We can choose

$$\eta(\theta, \gamma) = (\tau_0 + \gamma) \begin{pmatrix} C_1 & 0 & 0 \\ C_3 & C_4 & C_5 \\ C_6 & 0 & C_8 \end{pmatrix} \delta(\theta) + (\tau_0 + \gamma) \begin{pmatrix} 0 & C_2 & 0 \\ 0 & 0 & 0 \\ 0 & C_7 & 0 \end{pmatrix} \delta(\theta + 1), \tag{15}$$

where $\delta(\theta)$ is the Dirac function. When $\phi \in C^1([-1, 0], R^3)$, we define

$$A(\gamma)\phi = \begin{cases} \frac{d\phi(\theta)}{d\theta}, & \theta \in [-1, 0), \\ \int_{-1}^0 d\eta(\gamma, \theta)\phi(\theta), & \theta = 0, \end{cases} \tag{16}$$

and

$$R(\gamma)\phi = \begin{cases} 0, & \theta \in [-1, 0), \\ f\eta(\gamma, \theta), & \theta = 0. \end{cases} \tag{17}$$

Based on the previous steps, to study the Hopf bifurcation problem, we transform Eq. (11) into an operator equation of the form

$$\dot{U} = A(\gamma)_\gamma U_t + R(\gamma)_\gamma U_t. \tag{18}$$

For $\phi \in C^1([0, 1], (R^3)^*)$, define

$$A^*\psi(s) = \begin{cases} -\frac{d\psi(s)}{ds}, & s \in (0, 1], \\ \int_{-1}^0 d\eta(0, s)\phi(s), & s = 0, \end{cases} \tag{19}$$

and the bilinear inner product

$$\langle \psi(s), \phi(\theta) \rangle = \overline{\psi}(0)\phi \cdot q(0) - \int_{-1}^0 \int_{\xi=0}^\theta \overline{\psi}(\xi - \theta) d\eta(\theta)\phi(\xi) d\xi, \tag{20}$$

where $\gamma = 0, \eta(\theta) = \eta(\theta, 0)$, and $A(0)$ and $A^*(0)$ are adjoint operators. From the previous part we know that $\pm i\omega_0 \tau_0$ are the eigenvalues of $A(0)$ and $A^*(0)$. Let $q(\theta)$ be the eigenvector of $A(0)$ corresponding to $i\omega_0 \tau_0$, and let $q^*(s)$ be the eigenvector of $A^*(0)$ corresponding to $-i\omega_0 \tau_0$. When $q(\theta) = (1, v_1, v_2)e^{i\omega_0 \tau_0 \theta}$ and $q^*(\theta) = (1, v_1^*, v_2^*)e^{i\omega_0 \tau_0 \theta}$, we have $A(0)q(0) = i\omega_0 \tau_0 q(0)$ and $A^*(0)q^*(0) = -i\omega_0 \tau_0 q^*(0)$. Then we get

$$q(\theta) = e^{i\omega_0 \tau_0 \theta} \left(1, \frac{i\omega_0 \tau_0 - C_1}{C_2 e^{-i\omega_0}}, \frac{C_2 C_3 e^{-i\omega_0 \tau_0} + (i\omega_0 \tau_0 - C_1)(i\omega_0 \tau_0 - C_4)}{C_2 C_5 e^{-i\omega_0}} \right),$$

$$q^*(s) = G e^{-i\omega_0 \tau_0 s} \left(1, \frac{-i\omega_0 - C_1}{C_3}, \frac{(i\omega_0 \tau_0 + C_1)C_5}{C_3 C_7} - \frac{C_8}{C_7} \right),$$

since

$$\begin{aligned} \langle q^*, q \rangle &= \bar{q}^*(0) \cdot q(0) - \int_{-1}^0 \int_{\xi=0}^{\theta} \bar{q}^*(\xi - \theta) d\eta(\theta) q(\xi) d\xi \\ &= \bar{G}[(1 + \nu_1 \bar{\nu}_1^* + \nu_2 \bar{\nu}_2^*) + \tau_0 e^{-i\omega_0 \tau_0} (C_2 \nu_1 + C_6 \nu_1 \bar{\nu}_2^*)]. \end{aligned}$$

To ensure $\langle q^*, q \rangle = 1$, we get the values of \bar{G} and G :

$$\begin{aligned} \bar{G} &= \frac{1}{(1 + \nu_1 \bar{\nu}_1^* + \nu_2 \bar{\nu}_2^*) + \tau_0 e^{-i\omega_0 \tau_0} (C_2 \nu_1 + C_6 \nu_1 \bar{\nu}_2^*)}, \\ G &= \frac{1}{(1 + \bar{\nu}_1 \nu_1^* + \bar{\nu}_2 \nu_2^*) + \tau_0 e^{i\omega_0 \tau_0} (C_2 \bar{\nu}_1 + C_6 \bar{\nu}_1 \nu_2^*)}. \end{aligned} \tag{21}$$

Furthermore, the coordinates of the center manifold C_0 at $\gamma = 0$ can be calculated. Let U_t be the solution of the Eq. (11) and define

$$z(t) = \langle q^*, x_t \rangle, \quad W(t, \theta) = U_t(\theta) - 2\text{Re}\{z(t)q(\theta)\}. \tag{22}$$

On the center manifold C_0 , we have $W(t, \theta) = W(z(t), \bar{z}(t), \theta)$, where

$$W(t, \theta) = W_{20}(\theta) \frac{z^2}{2} + W_{11}(\theta) z\bar{z} + W_{02}(\theta) \frac{\bar{z}^2}{2} + \dots \tag{23}$$

In fact, $z(t)$ and $\bar{z}(t)$ are the local coordinates for the center manifold C_0 in the directions of q^* and \bar{q}^* , respectively. It is worth noting that $W(t, \theta)$ is treated as a real part, and the solution of the Eq. (11) is $u_t \in C_0$. Because $\gamma = 0$, by (22) we obtain

$$\begin{aligned} \dot{z}(t) &= i\omega_0 \tau_0 z(t) + \bar{q}^*(0) f(0, W(z, \bar{z}, \theta) + 2\text{Re}\{z(t)q(\theta)\}) \\ &= i\omega_0 \tau_0 z(t) + \bar{q}^*(0) f_0. \end{aligned} \tag{24}$$

We rewrite it as

$$\dot{z}(t) = i\omega_0 \tau_0 z(t) + g(z, \bar{z}). \tag{25}$$

According to the nature of W , we can define

$$g(z, \bar{z}) = g_{20} \frac{z^2}{2} + g_{11} z\bar{z} + g_{02} \frac{\bar{z}^2}{2} + g_{21} \frac{z^2 \bar{z}}{2} + \dots \tag{26}$$

By (22) and (23) we have

$$\begin{aligned} U_t &= W_{20}(\theta) \frac{z^2}{2} + W_{11}(\theta) z\bar{z} + W_{02}(\theta) \frac{\bar{z}^2}{2} \\ &\quad + (1, \nu_1, \nu_2) e^{i\omega_0 \tau_0 \theta} z + (1, \bar{\nu}_1, \bar{\nu}_2) e^{-i\omega_0 \tau_0 \theta} \bar{z}. \end{aligned} \tag{27}$$

Substituting (13) and (27) into (26), we have

$$g(z, \bar{z}) = \bar{q}^* f_0(z, \bar{z}) = \bar{q}^* f(0, U_t) = \bar{G} \tau_0 (1, \bar{\nu}_1^*, \bar{\nu}_2^*) \begin{pmatrix} T_1 \\ T_2 \\ T_3 \end{pmatrix}, \tag{28}$$

where

$$\begin{aligned}
 T_1 &= -\eta\phi_2(-1)G'(A^*)\phi_1(0) - \eta(\phi_2(-1) + P^* + k) \sum_{i=2}^{\infty} \frac{1}{i!} G^i(A^*)\phi_1(0)^i, \\
 T_2 &= \gamma \sum_{i=2}^{\infty} \frac{1}{i!} G^i(A^*)\phi_1(0)^i - u\phi_2(0)\phi_3(0)f'(P^*) - u(\phi_3(0) + M^*) \sum_{i=2}^{\infty} \frac{1}{i!} f^i(P^*)\phi_2(0)^i, \\
 T_3 &= \alpha \sum_{i=2}^{\infty} \frac{1}{i!} f_2^i(P^*)\phi_2(-1)^i - \mu\phi_3(0)G_1'(A^*)\phi_1(0) + \sum_{i=2}^{\infty} \frac{1}{i!} G_1^i(A^*)\phi_1(0)^i(\phi_3(0) + M^*).
 \end{aligned}$$

Comparing the coefficients with (26), we obtain

$$\begin{aligned}
 g_{20} &= \bar{G}\tau_0(-\bar{G}\tau_0\eta(P^* + k)G_1''(A^*) - 2\eta G_1'(A^*)e^{-i\omega_0\tau_0}v_1 + [\gamma G_1''(A^*) - 2uv_1v_2f'(P^*)]v_1^* \\
 &\quad - uM^*f''(P^*)v_1^* + [\alpha f_2''(P^*)e^{-2i\omega_0\tau_0}v_1 - 2\mu v_2 + G_1''(A^*)M^*]v_2^*), \\
 g_{11} &= \bar{G}\tau_0(-\bar{G}\tau_0\eta(P^* + k)G_1''(A^*) - 2\eta G_1'(A^*)(v_1 + \bar{v}_1) + [\gamma G_1''(A^*) - 2u(\bar{v}_1v_2)f'(P^*)]v_1^* \\
 &\quad - 2u(v_1\bar{v}_2)f'(P^*)v_1^* - uM^*f''(P^*)\bar{v}_1v_1^* + [\alpha v_1\bar{v}_1f_2''(P^*) \\
 &\quad - 2\mu(v_2 + \bar{v}_2) + G_1''(A^*)M^*]v_2^*), \\
 g_{02} &= \bar{G}\tau_0(-\bar{G}\tau_0\eta(P^* + k)G_1''(A^*) - 2\eta G_1'(A^*)e^{i\omega_0\tau_0}\bar{v}_1 + \gamma G_1''(A^*)v_1^* - 2u\bar{v}_1\bar{v}_2f'(P^*)v_1^* \\
 &\quad - uM^*f''(P^*)v_1^* + [\alpha f_2''(P^*)e^{2i\omega_0\tau_0}\bar{v}_1 - 2\mu\bar{v}_2 + G_1''(A^*)M^*]v_2^*), \\
 g_{21} &= \bar{G}\tau_0(-\bar{G}\tau_0\eta G'(A^*)\bar{v}_1e^{i\omega_0\tau_0} - \eta G'(A^*)W_{20}^{(2)}(-1) - \eta W_{11}^{(1)}(0)G''(A^*)\bar{v}_1e^{i\omega_0\tau_0} \\
 &\quad - \eta(P^* + k)G_1''(A^*) - \eta G''(A^*)v_1e^{-i\omega_0\tau_0} - \frac{2!}{3!}\eta(P^* + k)G_1'''(A^*) \\
 &\quad + \left[\frac{2!}{3!}\gamma G_1'''(A^*) - uf''(P^*)v_1\bar{v}_2 - uf''(P^*)v_1\bar{v}_1v_2 - \frac{2!}{3!}um^*f'''(P^*)v_2\bar{v}_2 \right. \\
 &\quad \left. - 2uM^*f''(P^*)W_{20}^{(2)}(0)\bar{v}_1 + \gamma G_1''(A^*)W_{20}^{(1)}(0) - uW_{20}^{(2)}(0)\bar{v}_2f'(P^*) \right]v_1^* \\
 &\quad + \left[\frac{1}{2}\alpha f_2''(P^*)W_{20}^{(2)}(-1)v_1e^{-i\omega_0\tau_0} + \frac{2!}{3!}\alpha f_2'''(P^*)W_{20}^{(2)}(-1)v_1\bar{v}_1e^{-2i\omega_0\tau_0} \right. \\
 &\quad \left. - \mu(w_{20}^{(3)}(0) + w_{20}^{(1)}(0)\bar{v}_2) + \frac{1}{2}G_1''(A^*)M^*W_{20}^{(1)}(0) \right. \\
 &\quad \left. + G_1''(A^*)(\bar{v}_2 + v_2) + \frac{1}{3!}G_1'''(A^*)M^* \right]v_2^*).
 \end{aligned}$$

Note that there are unknown quantities W_{20} and W_{11} in the coefficients, and we continue to calculate from the Eq. (11) and (22):

$$\begin{aligned}
 \dot{W} &= U_t - z\dot{q} - z\dot{\bar{q}} \\
 &= \begin{cases} A(0)W - 2\text{Re}q^*(0)f_0q(\theta), & \theta \in [-1, 0), \\ A(0)W - 2\text{Re}q^*(0)f_0q(\theta) + f_0, & \theta = 0. \end{cases} \\
 &= A(0)W + K(z, \bar{z}, \theta), \tag{29}
 \end{aligned}$$

where

$$K(z, \bar{z}, \theta) = K_{20}(\theta) \frac{z^2}{2} + K_{11}(\theta) z\bar{z} + K_{02}(\theta) \frac{\bar{z}^2}{2} + \dots \tag{30}$$

From Eq. (23) we have

$$\begin{aligned} \dot{W} = & (W_{20}(\theta)z + W_{11}(\theta)\bar{z} + \dots)(i\omega_0\tau_0 z(t) + g(z, \bar{z})) \\ & + (W_{11}(\theta)z + W_{02}(\theta)\bar{z} + \dots)(-i\omega_0\tau_0 \bar{z}(t) + g(z, \bar{z})). \end{aligned} \tag{31}$$

Through the previous calculation of (28), we get

$$\begin{aligned} \dot{W} = & (A(0)W_{20}(\theta) + K_{20}(\theta)) \frac{z^2}{2} + (A(0)W_{11}(\theta) \\ & + K_{11}(\theta))z\bar{z} + (A(0)W_{02}(\theta) + K_{02}(\theta)) + \dots \end{aligned} \tag{32}$$

Comparing the coefficients of (30) and (31), we obtain

$$(A(0) - 2i\omega_0\tau_0)W_{20}(\theta) = -K_{20}(\theta), \quad A(0)W_{11}(\theta) = -K_{11}(\theta). \tag{33}$$

Based on (28), when $\theta \in [-1, 0)$, we get

$$\begin{aligned} K(z, \bar{z}, \theta) = & -\left(g_{20} \frac{z^2}{2} + g_{11}z\bar{z} + g_{02} \frac{\bar{z}^2}{2} + g_{21} \frac{z^2\bar{z}}{2} + \dots\right)q(\theta) \\ & - \left(\bar{g}_{20} \frac{\bar{z}^2}{2} + \bar{g}_{11}z\bar{z} + \bar{g}_{02} \frac{z^2}{2} + \bar{g}_{21} \frac{\bar{z}^2z}{2} + \dots\right)\bar{q}(\theta). \end{aligned} \tag{34}$$

The coefficients at z^2 and $z\bar{z}$ are

$$K_{20}(\theta) = -g_{20}q(\theta) - \bar{g}_{02}\bar{q}(\theta) \tag{35}$$

and

$$K_{11}(\theta) = -g_{11}q(\theta) - \bar{g}_{11}\bar{q}(\theta). \tag{36}$$

From (32) and (34) we get

$$A(0)W_{20}(\theta) = 2i\omega_0\tau_0 W_{20}(\theta) - H_{20}(\theta).$$

By the definition of $A(0)$ we have

$$\dot{W}_{20}(\theta) = 2i\omega_0\tau_0 W_{20}(\theta) + g_{20}q(\theta) + \bar{g}_{02}\bar{q}(\theta).$$

Note that $q(\theta) = q(0)e^{i\omega_0\tau_0\theta}$, and therefore

$$W_{20}(\theta) = \frac{ig_{20}}{\omega_0\tau_0}q(0)e^{i\omega_0\tau_0\theta} + \frac{i\bar{g}_{02}}{\omega_0\tau_0}\bar{q}(0)e^{-i\omega_0\tau_0\theta} + D_1e^{2i\omega_0\tau_0\theta}, \tag{37}$$

where $D_1 = (D_1^{(1)}, D_1^{(2)}, D_1^{(3)})^T$ is a constant factor, and from (32) and (35) we obtain

$$\dot{W}_{11}(\theta) = g_{11}q(\theta) + \bar{g}_{11}\bar{q}(\theta)$$

and

$$W_{11}(\theta) = -\frac{ig_{11}}{\omega_0\tau_0}q(0)e^{i\omega_0\tau_0\theta} + \frac{i\bar{g}_{11}}{\omega_0\tau_0}\bar{q}(0)e^{-i\omega_0\tau_0\theta} + D_2, \tag{38}$$

where $D_2 = (D_2^{(1)}, D_2^{(2)}, D_2^{(3)})^T$ is a constant factor. We can find approximate values of D_1 and D_2 in (36) and (37), respectively. It follows from the form defined by A and (32) that

$$\int_{-1}^0 d\eta(\theta)W_{20}(\theta) = 2i\omega_0W_{20}(\theta) - K_{20}(\theta) \tag{39}$$

and

$$\int_{-1}^0 d\eta(\theta)W_{11}(\theta) = -K_{11}(\theta), \tag{40}$$

where $\eta(\theta) = \eta(0, \theta)$. From (28) we have

$$K_{20}(0) = -g_{20}q(\theta) - \bar{g}_{02}\bar{q}(\theta) + \tau_0 \begin{pmatrix} R_{11} \\ R_{12} \\ R_{13} \end{pmatrix},$$

$$R_{11} = -\bar{G}\tau_0\eta(P^* + k)G_1''(A^*) - 2\eta G_1'(A^*)e^{-i\omega_0\tau_0}v_1, \tag{41}$$

$$R_{12} = \gamma G_1''(A^*) - 2uv_1v_2f'(P^*) - uM^*f''(P^*),$$

$$R_{13} = \alpha f_2''(P^*)e^{-2i\omega_0\tau_0}v_1 - 2\mu v_2 + G_1''(A^*)M^*,$$

and

$$K_{11}(0) = -g_{11}q(\theta) - \bar{g}_{11}\bar{q}(\theta) + 2\tau_0 \begin{pmatrix} R_{21} \\ R_{22} \\ R_{23} \end{pmatrix}, \tag{42}$$

where

$$R_{21} = -\bar{G}\tau_0\eta(P^* + k)G_1''(A^*) - 2\eta G_1'(A^*)v_1\bar{v}_1,$$

$$R_{22} = [\gamma G_1''(A^*) - 2u(\bar{v}_1v_2 + v_1\bar{v} - 2)f'(P^*) - uM^*f''(P^*)\bar{v}_1]v_1^*,$$

$$R_{23} = [\alpha v_1\bar{v}_1f_2''(P^*) - 2\mu(v_2 + \bar{v}_2) + G_1''(A^*)M^*]v_2^*.$$

Because $i\omega_0\tau_0$ is an eigenvalue of $A(0)$ and $q(0)$, we have

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

and

$$\left(-i\omega_0\tau_0 I - \int_{-1}^0 e^{-i\omega_0\tau_0\theta} d\eta(\theta)\right)\tilde{q}(0) = 0. \tag{44}$$

Therefore we obtain

$$\begin{pmatrix} 2i\omega_0 - C_1 & -C_2 & 0 \\ -C_3 & 2i\omega_0 - C_4 & -C_5 \\ -C_6 & -C_7 & 2i\omega_0 - C_8 \end{pmatrix} \times D_1 = \begin{pmatrix} R_{11} \\ R_{12} \\ R_{13} \end{pmatrix} \tag{45}$$

and

$$\begin{pmatrix} -C_1 & -C_2 & 0 \\ -C_3 & -C_4 & -C_5 \\ -C_6 & -C_7 & -C_8 \end{pmatrix} \times D_2 = \begin{pmatrix} R_{21} \\ R_{22} \\ R_{23} \end{pmatrix}. \tag{46}$$

From (36), (37), (44), and (45), we can express g_{21} . Furthermore, we can calculate the following values:

$$\begin{aligned} C_1(0) &= \frac{i}{2\omega_0\tau_0} \left(g_{11}g_{20} - 2|g_{11}|^2 - \frac{|g_{02}|^2}{3}\right) + \frac{g_{21}}{2}, \\ \mu_2 &= \frac{\text{Re}(C_1(0))}{\text{Re}(\lambda'(\tau_0))}, \\ T_2 &= -\frac{\text{Im}C_1(0) + \mu_2\text{Im}\lambda'(\tau_0)}{\omega_0\tau_0}, \\ \beta_2 &= 2\text{Re}C_1(0). \end{aligned} \tag{47}$$

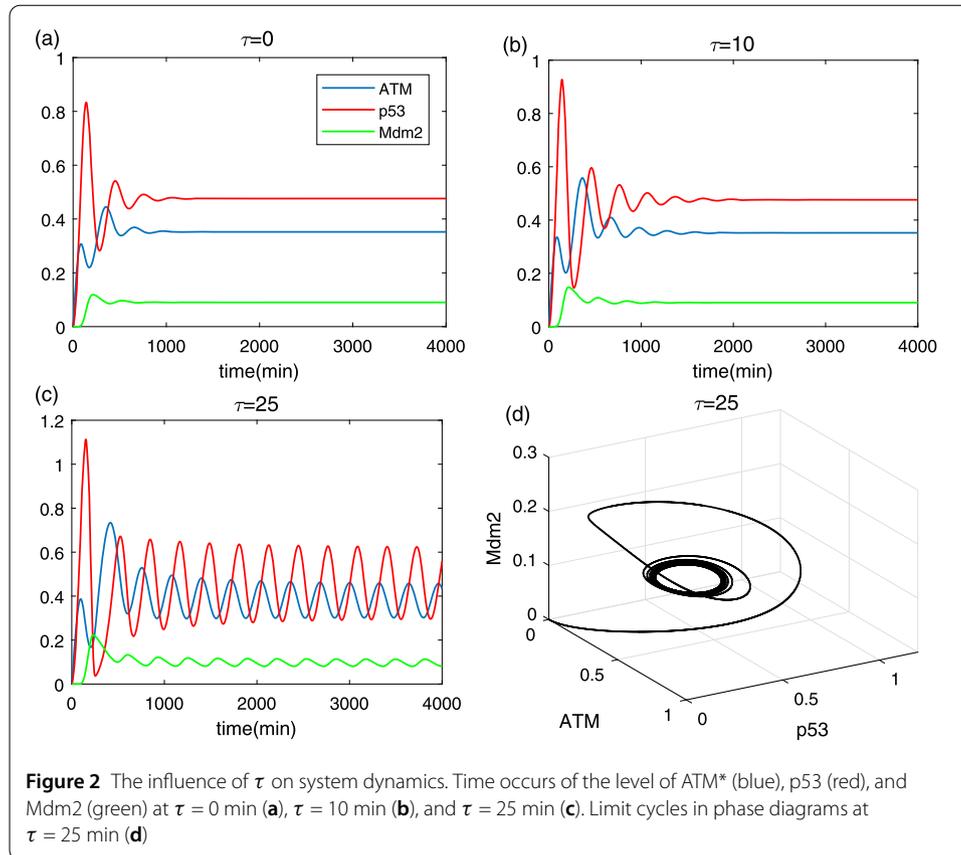
According to the Hassard theory, we can obtain the following theorem.

Theorem 4.1 *The bifurcating periodic solution of (11) from the trivial equilibrium has the following features:*

- (1) μ_2 determines the direction of the Hopf bifurcation: if $\mu_2 > 0$ ($\mu_2 < 0$), then the Hopf bifurcation is supercritical (subcritical), and the bifurcating periodic solutions exist for $\tau > \tau_0$ ($\tau < \tau_0$);
- (2) β_2 determines the stability of the bifurcating periodic solutions: the bifurcating periodic solutions are stable (unstable) if $\beta_2 < 0$ ($\beta_2 > 0$);
- (3) T_2 determines the period of the bifurcating periodic solutions: the period increases (decreases) if $T_2 > 0$ ($T_2 < 0$).

5 Numerical simulation

The numerical calculation is carried out by using the software Matlab. We choose the same proportion set of parameters as those in [9]: $\beta = 0.006$, $\eta = 0.04$, $u = 0.14$, $\mu = 0.01$, $\alpha = 0.0048$, $\gamma = 0.004$, $k_1 = 1$, $k_2 = 1$, $k_3 = 0.1$, $k_4 = 1$, $k = 0.1$. We can obtain that the steady-state solution of the equation is $\hat{E}(0.352, 0.476, 0.090)$. By using the derivation in Sect. 3 we conclude that the critical value of Hopf bifurcation τ_0 is equal to 23.237. From the conclusion of Sect. 4 we find that the obtained Hopf bifurcation point is supercritical, and

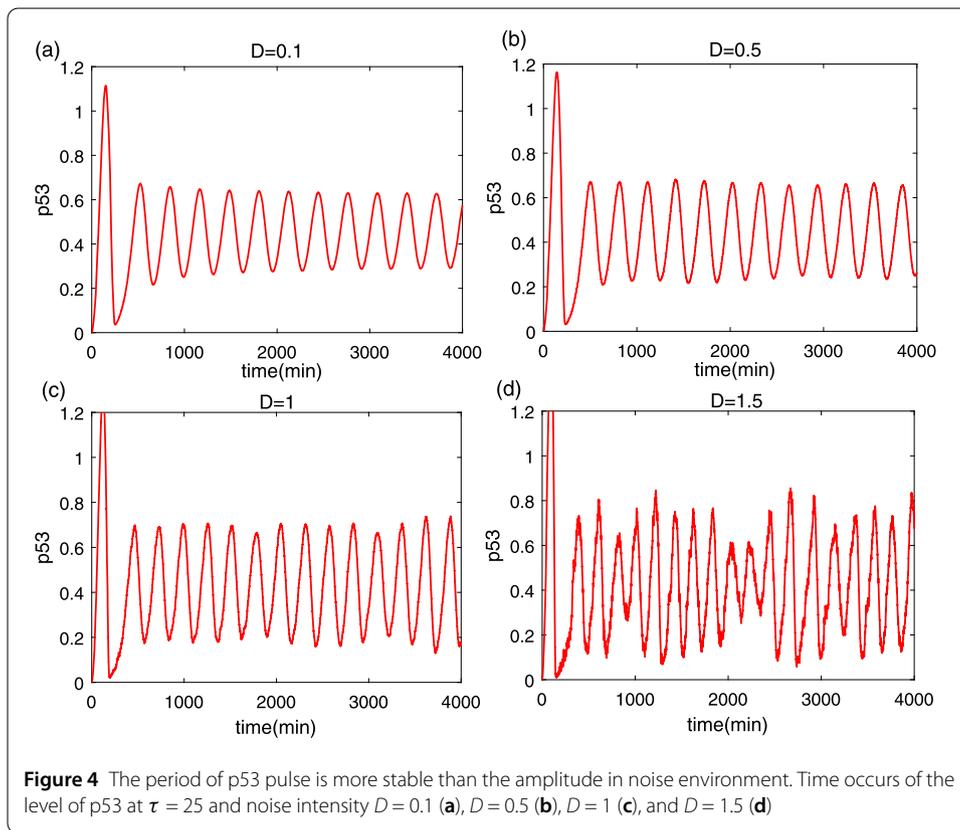
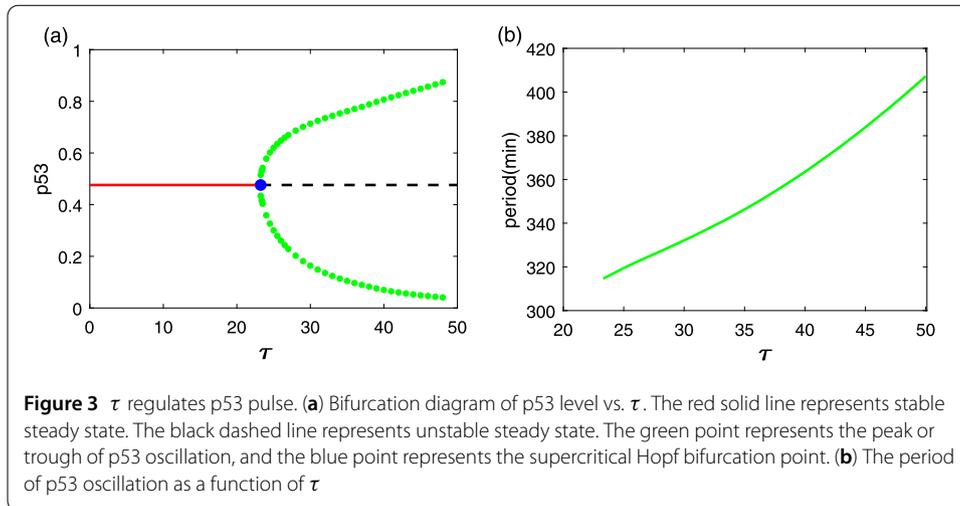


the period of oscillation increases with the increase of τ . Next, we use a time evolution diagram and bifurcation diagram to illustrate our theoretical results.

The units of time is minute, and the units of other parameters ensure that the concentrations of proteins are dimensionless. The initial values of the system are $A(0) = P(0) = M(0) = 0$. The numerical simulation results of time occurs are shown in Fig. 2. When τ is equal to 0 or 10 ($< \tau_0$) in Fig. 2(a) or (b), the system has damping oscillations and finally tends to steady state. When the value of τ is 25 ($> \tau_0$) in Fig. 2(c), the system has stable oscillations with a period of 4–7 hours [30]. Therefore the time delay is a necessary condition for p53 to oscillate. The phase diagram in Fig. 2(d) shows that the system finally converges to a stable limit cycle.

We further draw a bifurcation diagram to study the effect of τ on the p53 pulse. The functional relationship between p53 level and time delay τ is displayed in bifurcation graph Fig. 3(a). The coordinates of the Hopf bifurcation point are (23.237, 0.476). With the increase of τ , the steady state loses its stability. After the supercritical Hopf bifurcation point, system enters the oscillation state. With the increase of τ , the amplitude first sharply increases and then slowly increases. In Fig. 3(b), the relationship between the period of the oscillation and the time delay τ is almost linear after the Hopf bifurcation point. The results of numerical simulation are consistent with those of our theoretical analysis.

In addition, we theoretically analyze the network dynamics in the deterministic case. Noise always exists in biological systems [20, 21], and it is essential to explore the effect of noise on system dynamics. We use the multiplier exponential Gaussian white noise, that is, $\zeta = \exp(\epsilon)$, where ϵ obeys the Gaussian distribution with mean 0 and standard deviation D ,



which characterize the noise intensity; we write this as $\epsilon \sim N(0, D)$. The system oscillation is stable under weak noise in Figs. 4(a), 4(b), and 4(c), which indicate that at moderate noise intensity, the period of oscillation is stable. Figure 4(d) implies that at high noise intensity, the system amplitude is unstable. Our numerical simulation is consistent with experimental results, that is, the period of the p53 pulse is more robust than the amplitude, and not all cells have stable pulses [30].

6 Discussion

In this paper, we constructed a minimodel to explore how time delay affected the oscillation behavior of p53 in response to DNA damage. We find that if time delay τ is greater than τ_0 , then the system is oscillatory; otherwise, it is asymptotically stable. We also use the normal form method and the central manifold theorem to further analyze the effect of parameter τ on the kinetics of p53 and predict the direction and stability of the bifurcation diagram.

The correctness of the theory is verified by numerical simulation. The bifurcation diagram of p53 level versus τ vividly shows that the oscillation of p53 can be regulated by changing the parameter τ . Our model indicates that the effect of noise on the amplitude is more severe than the period. Because the p53 pulse is closely related to cell fate decision, it may be a good idea to consider the time delay in the treatment of cancer.

Acknowledgements

The authors are grateful to the referee for carefully reading the manuscript and for providing some comments and suggestions, which led to improvements in the paper.

Funding

This work was supported by grant from National Natural Science Foundation of China (11762011).

Availability of data and materials

All authors declare that all the data can be accessed in our paper in the numerical simulation section.

Competing interests

The authors declare that there is no conflict of interests.

Authors' contributions

All authors read and approved the final manuscript.

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Received: 3 February 2020 Accepted: 24 June 2020 Published online: 08 July 2020

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