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Numerical bifurcation control of Mackey–Glass system

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ABSTRACT

In this paper, a mathematical physiological model, Mackey–Glass system of a delay differential equation, is considered. With a greater delay, a periodic solution arises, which characterizes the disease of chronic granulocytic leukemia (CGL). To treat such disease, a blood transfusion feedback control is considered, from the point of view of mathematical control. By using a nonstandard finite-difference (NSFD) scheme to the control system, we obtain a numerical discrete system and analyze its Neimark–Sacker and fold bifurcations. The results imply that the condition of the illness could be relieved by transfusing blood to the patient, if the control is a delay control. Finally, the effectiveness of the control are illustrated by several numerical simulations.

1. Introduction

Nowadays, since some results provided by mathematical physiological models are always much close to clinical manifestation, more and more mathematical models are applied to medical researches for providing some safe ways to explore the effects of novel techniques. With the building of the relation between the onset of some disease and the occurrence of some bifurcation, theories in dynamics of differential equations are used to analyze the state of illness and to provide therapeutic treatments.

In Mackey and Glass [1], Mackey and Glass described a physiological system as delay differential equation (DDE):

$$\dot{p}(t) = -\gamma p(t) + \frac{\beta\theta^n p(t-\tau)}{\theta^n + p^n(t-\tau)}, \quad t \geqslant 0, \tag{1}$$

in which $p(t)$ denotes the density of mature blood cells in circulation at time t, time delay $\tau > 0$ measures the time between the initial of cellular production in the bone marrow and the release of mature cells into the blood, $\beta, \theta, n \geqslant 3$ and γ are all positive constants. In fact, in normal healthy adults, the circulating levels of granulocytes are either constant or showing a mild oscillation with a period of 14 to 24 days. Cyclical neutropenia is a disease characterized by spontaneous oscillations in granulocyte numbers from normal to subnormal levels with a period of about 21 days. For some patients with chronic granulocytic leukemia (CGL), the circulation granulocyte numbers display large-amplitude oscillations with period ranging from 30 to 70 days, depending on the patients.

Meanwhile, the above phenomenon also could be interpreted by the dynamics of system (1), which could be gotten easily from [2]. It shows that, if $\beta/\gamma > n/(n-2)$, then a periodic solution will arise as τ increases and crosses a value, that is, system (1) will undergo a Hopf bifurcation. This reflects the fact that, if the time delay is long enough, then there is no adequate blood cells being released into circulating bloodstreams, thus the stability of the circulating level is destroyed and even CGL is caused.

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Although the qualitative properties of system (1) could be gotten by [2], considered the performance and a better monitor for the circulating levels of granulocytes, we must turn to the numerical simulation of system (1). In order to replicate exactly the dynamical behavior, dynamical consistent numerical methods are needed. In [3–5], some numerical methods which could preserve the Hopf bifurcation of DDEs are given. In [6], a nonstandard finite-difference (NSFD) scheme [7,8] for system (1) is constructed as follows:

$$p_{k+1} - p_k = \frac{1 - e^{-\gamma\tau h}}{\gamma\tau} f(p_k, p_{k-m}), \quad k = 0, 1, 2, \ldots, \tag{2}$$

where $h = 1/m (m \in \mathbb{Z}^+)$ is time step size, p_k is the numerical approximation of $p(kh)$, $f(p_k,p_{k-m})$ is an approximation of the right-hand side of system (1). Using NSFD scheme (2) to (1), it yields a numerical discrete system, whose dynamics has been studied in [6].

Lemma 1 [6]. *For the numerical discrete system of (1) with positive equilibrium* $p^* = \theta \sqrt[n]{\beta/\gamma - 1}$,

(i) *If* $1 < \beta/\gamma < n/n - 2$, *then* p^* *is asymptotically stable for any* $\tau \geqslant 0$.
(ii) *For* $\beta/\gamma > n/(n - 2)$, *there exists a sequence of* τ_k $(k = 0,1,2,\ldots, [(m - 1)/2])$ *such that the numerical discrete system undergoes a Neimark–Sacker (i.e. discrete Hopf) bifurcation at* p^* *when* $\tau = \tau_k$.
(iii) *If* $\beta/\gamma > n/(n - 2)$, *then* p^* *is asymptotically stable for* $\tau \in [0, \tau_0)$, *and there exists a unique closed invariant curve for* $\tau > \tau_0$.

Remark 1. Comparing Lemma 1 with the results in [2], we could see that the NSFD scheme could represent the asymptotical stability and the Hopf bifurcation with a mild restriction on time step size. Hence, in this paper, we will apply the scheme to simulate some systems. And we always believe that the dynamics of the numerical discrete system is topologically equivalent to the ones of the continuous system.

The purpose of this paper is to construct a feedback control for system (1) having a periodic solution, such that the physiological system could be stabilized at a positive equilibrium. In Section 2, the feedback control system is described by a DDE, and three types of control functions are given. The dynamics of the numerical discrete systems, derived by NSFD scheme (2), are studied by applying the bifurcation theorem (see [9–11]) in Section 3. The result shows that the positive fixed point cannot be stabilized by a linear non-delay control, but could be stabilized by a linear/nonlinear delay control. By analyzing the distribution of characteristic roots, we get the range of coefficients in the delay control functions, under which the positive fixed point is asymptotically stable. The main result in this paper implies that the circulating bloodstreams can be stabilized by transfusing blood with a suitable speed. Finally, some numerical experiments are illustrated to verify the theoretical results.

2. A control system with blood transfusion feedback

For the past years, bifurcation control theory has been used in more and more fields. Typical bifurcation control objectives include delaying the onset of an inherent bifurcation, stabilizing a bifurcation solution or branch, monitoring the multiplicity, amplitude, and frequency of more limit cycles emerging from bifurcation, etc. (see [12,13] and the references therein). By applying bifurcation control theory, Kramer et al. [14] made use of feedback controls to a model of human cortical electrical activity and discussed the types of bifurcation that both produce (subHopf/fold cycle) and destroy the large amplitude, stable oscillations characteristic of a seizure. In [15], an effective external pancreatic insulin production was introduced into a model of blood-glucose concentration to control the condition of diabetic patient.

Motivated by the observation that many physiologists cite control as a potential influence in the evolution of biological systems, and by the above analysis for the aetiology of CGL, we investigate whether the symptoms of CGL could be relieved by transfusing blood to the patient using a control equipment. In medical research, blood transfusion therapy is usually adopted to stabilize the patient's condition. In clinical research, besides what kind of blood, the speed and the volume of transfusing blood should be also considered to prevent adverse reactions. Since the amount of blood in a person is fixed, which takes 7% $\sim$ 8% of the person's weight. So as the blood is transfused, the excess plasma is discharged from the blood vessel and the mature blood cells are left in. Hence, roughly speaking, transfuse blood is equivalent to transfuse mature cells.

Here we suppose that $B > 0$ is the density of mature blood cells in the blood bag and the blood is transfused into the patient under a controllable speed $u(t)$ which will be designed later. For example, there is $u(t)$ blood is transfused at the time t, thus the amount of mature blood cells increases by $Bu(t)$ cells. Hence, the blood transfusion control system is gotten as:

$$\dot{p}(t) = -\gamma p(t) + \frac{\beta\theta^n p(t-\tau)}{\theta^n + p^n(t-\tau)} + Bu(t), \quad t \geqslant 0, \tag{3}$$

In the rest of this paper, we always assume that $\beta/\gamma > n/(n-2)$ and $\tau > \tau_0$, which guarantee that system (1) has a periodic solution. For the sake of simplicity, we restrict ourselves to three types of feedback control functions:

(1) linear non-delay control (LNDC):

$$u(t) = g(p(t)) = \tilde{k}(p(t) - p^*), \quad \tilde{k} > 0, \tag{4}$$

(2) linear delay control (LDC):

$$u(t) = g(p(t-\tau)) = a(p(t-\tau) - p^*), \quad a > 0, \tag{5}$$

(3) nonlinear delay control (NLDC) which could be expanded as:

$$u(t) = g(p(t-\tau)) = a(p(t-\tau) - p^*) + b(p(t-\tau) - p^*)^2 + c(p(t-\tau) - p^*)^3 + o((p(t-\tau) - p^*)^3), \tag{6}$$

where $\tilde{k}, a, b$ and c are coefficients to be determined.

3. Stabilization of control system

In this section, we mainly discuss the stability and bifurcation of the numerical discrete control systems according to (4)–(6), respectively. It is known that the fixed point is asymptotically stable if and only if all the characteristic roots of the linearization at the fixed point stay in the unit circle. However, from the analysis in [6], we see that if $u(t) = 0$, the characteristic equation of the numerical discrete system of (3) will have finite roots outside the unit circle and the others inside the unit circle. Hence we attempt to manipulate the control parameters such that all the characteristic roots are pulled back into the unit circle. At first, let us consider the simplest case.

3.1. Linear non-delay control

Under transformations

$$(T) := p(t) = \theta x(t), \quad z(t) = x(\tau t), \quad y(t) = z(t) - \sqrt[n]{\beta/\gamma - 1},$$

system (3) is equivalent to

$$\dot{y}(t) = \tau\left\{-\gamma\left(y(t) + \sqrt[n]{\frac{\beta}{\gamma} - 1}\right) + \frac{\beta\left(y(t-1) + \sqrt[n]{\frac{\beta}{\gamma} - 1}\right)}{1 + \left(y(t-1) + \sqrt[n]{\frac{\beta}{\gamma} - 1}\right)^n} + B\tilde{k}y(t)\right\}. \tag{7}$$

Applied NSFD scheme (2) to system (7), we get numerical discrete system:

$$y_{k+1} = \frac{1}{\gamma}\left[B\tilde{k} + (\gamma - B\tilde{k})e^{-\gamma\tau h}\right]y_k + (1 - e^{-\gamma\tau h})\left\{-\sqrt[n]{\frac{\beta}{\gamma} - 1} + \frac{\beta\left(y_{k-m} + \sqrt[n]{\frac{\beta}{\gamma} - 1}\right)}{\gamma\left[1 + \left(y_{k-m} + \sqrt[n]{\frac{\beta}{\gamma} - 1}\right)^n\right]}\right\}. \tag{8}$$

Clearly, the origin is a fixed point and the linearization at it is

$$y_{k+1} = \frac{1}{\gamma}\left[B\tilde{k} + (\gamma - B\tilde{k})e^{-\gamma\tau h}\right]y_k + \frac{1}{\beta}(1 - e^{-\gamma\tau h})[n\gamma + (1-n)\beta]y_{k-m},$$

whose characteristic equation is

$$\lambda^{m+1} - \frac{1}{\gamma}\left[B\tilde{k} + (\gamma - B\tilde{k})e^{-\gamma\tau h}\right]\lambda^m - \frac{1}{\beta}(1 - e^{-\gamma\tau h})[n\gamma + (1-n)\beta] = 0. \tag{9}$$

Now we suppose that $\lambda = re^{i\omega}$ is a root of Eq. (9). Differentiating both sides of (9) with respect to $\tilde{k}$, we get

$$\frac{d\lambda}{d\tilde{k}} = \frac{B(1 - e^{-\gamma\tau h})\lambda}{\gamma(1+m)\lambda - m\left[B\tilde{k} + (\gamma - B\tilde{k})e^{-\gamma\tau h}\right]}. \tag{10}$$

Therefore

$$\frac{d|\lambda|^2}{d\tilde{k}} = \bar{\lambda}\frac{d\lambda}{d\tilde{k}} + \lambda\frac{d\bar{\lambda}}{d\tilde{k}} = \frac{B(1 - e^{-\gamma\tau h})|\lambda|^2\sigma}{\left|\gamma(1+m)\lambda - m\left[B\tilde{k} + (\gamma - B\tilde{k})e^{-\gamma\tau h}\right]\right|^2}, \tag{11}$$

in which

$$\sigma = 2\left\{\gamma(1+m)\Re[\lambda] - m\left[B\tilde{k} + (\gamma - B\tilde{k})e^{-\gamma\tau h}\right]\right\}. \tag{12}$$

Here $\Re[\cdot]$ stands for the real part of a complex number. Inserting $\lambda = re^{i\omega}$ into (9) and separating the real and the imaginary parts, it yields

$$\begin{cases} r\cos\omega - \frac{1}{\gamma}\left[B\tilde{k} + (\gamma - B\tilde{k})e^{-\gamma\tau h}\right] = \frac{1}{\beta r^m}(1 - e^{-\gamma\tau h})[n\gamma + (1-n)\beta]\cos m\omega, \\ r\sin\omega = -\frac{1}{\beta r^m}(1 - e^{-\gamma\tau h})[n\gamma + (1-n)\beta]\sin m\omega. \end{cases} \tag{13}$$

Squaring both sides of the two equalities and adding them together, it deduces that

$$\Re[\lambda] = \frac{1}{2\gamma}\left[B\tilde{k} + (\gamma - B\tilde{k})e^{-\gamma\tau h}\right] + \frac{\gamma}{2}\frac{\beta^2 r^{2(m+1)} - (1 - e^{-\gamma\tau h})^2[n\gamma + (1-n)\beta]^2}{\beta^2 r^{2m}\left[B\tilde{k} + (\gamma - B\tilde{k})e^{-\gamma\tau h}\right]}. \tag{14}$$

Putting it into (12) and simplifying it, we have

$$\sigma = (1-m)\left[B\tilde{k} + (\gamma - B\tilde{k})e^{-\gamma\tau h}\right] + (1+m)\gamma^2\frac{\beta^2 r^{2(m+1)} - (1 - e^{-\gamma\tau h})^2[n\gamma + (1-n)\beta]^2}{\beta^2 r^{2m}\left[B\tilde{k} + (\gamma - B\tilde{k})e^{-\gamma\tau h}\right]}.$$

In view of $\lim_{h\to 0}\sigma = \gamma(1 + r^2) > 0$ for $r > 1$, we have

$$\left.\frac{d|\lambda|^2}{d\tilde{k}}\right|_{\lambda = re^{i\omega}, r>1} > 0$$

for sufficiently small $h > 0$.

The above analysis implies that, with the increasing of $\tilde{k} > 0$, the module of λ more than one becomes more and more larger, furthermore, there is no root outside coming into the unit circle. That is, the origin can not be stabilized by the LNDC.

3.2. Linear delay control

In view of that it is the delay τ causes the periodic solutions, therefore, we are interested in the time-delay feedback control. For simplicity let $u(t) = g(p(t - \tau))$ be a linear delay function as (5). Taking transformations (T), system (3) is rewritten as:

$$\dot{y}(t) = \tau\left\{-\gamma\left(y(t) + \sqrt[n]{\frac{\beta}{\gamma} - 1}\right) + \frac{\beta\left(y(t-1) + \sqrt[n]{\frac{\beta}{\gamma} - 1}\right)}{1 + \left(y(t-1) + \sqrt[n]{\frac{\beta}{\gamma} - 1}\right)^n} + Bay(t-1)\right\}. \tag{15}$$

Using NSFD scheme (2) to system (15), we get numerical discrete system

$$y_{k+1} = e^{-\gamma\tau h}y_k + \frac{1}{\gamma}(1 - e^{-\gamma\tau h})\left\{-\gamma\sqrt[n]{\frac{\beta}{\gamma} - 1} + \frac{\beta\left(y_{k-m} + \sqrt[n]{\frac{\beta}{\gamma} - 1}\right)}{1 + \left(y_{k-m} + \sqrt[n]{\frac{\beta}{\gamma} - 1}\right)^n} + Bay_{k-m}\right\}. \tag{16}$$

It is easy to see that the origin is a fixed point and the linearization of (16) at the origin is

$$y_{k+1} = e^{-\gamma\tau h}y_k + \frac{1}{\gamma}(1 - e^{-\gamma\tau h})(Ba - d_1)y_{k-m},$$

in which $d_1 = -[n\gamma^2 + (1-n)\gamma\beta]/\beta > \gamma$. Its characteristic equation is

$$d(\lambda) \triangleq \lambda^{m+1} - e^{-\gamma\tau h}\lambda^m - \frac{1}{\gamma}(1 - e^{-\gamma\tau h})(Ba - d_1) = 0. \tag{17}$$

It is known that when $a = 0$ characteristic Eq. (17) has finite roots outside the unit circle. In the following, we are going to study whether there exists a suitable a, such that all of the roots are in the unit circle. At first, let us give a useful lemma.

Lemma 2. *Suppose $\lambda = re^{i\omega}$ ($r \geqslant 1$, $\omega \in [0, \pi]$) is the root of Eq. (17). Then $d|\lambda|^2/da < 0$ if $Ba - d_1 < 0$, and $d|\lambda|^2/da > 0$ if $Ba - d_1 > 0$.*

Proof. From (17), we have

$$\frac{d\lambda}{da} = \frac{B(1 - e^{-\gamma\tau h})}{\gamma[(m+1)\lambda^m - me^{-\gamma\tau h}\lambda^{m-1}]}. \tag{18}$$

Then

$$\frac{d|\lambda|^2}{da} = \bar{\lambda}\frac{d\lambda}{da} + \lambda\frac{d\bar{\lambda}}{da} = \frac{B|\lambda|^2\Delta}{(Ba - d_1)|(m+1)\lambda - me^{-\gamma\tau h}|^2}, \tag{19}$$

in which

$$\Delta = 2\{(r - e^{-\gamma\tau h})[(m+1)r - me^{-\gamma\tau h}] + re^{-\gamma\tau h}(2m+1)(1 - \cos\omega)\} > 0$$

for any $r \geqslant 1$. Hence, $d|\lambda|^2/da < 0$ if $Ba - d_1 < 0$ and $d|\lambda|^2/da > 0$ if $Ba - d_1 > 0$. □

Theorem 1. *There exists an $a^* \in (0, d_1/B)$ such that for (16) the origin is asymptotically stable if $a \in (a^*, d_1/B)$.*

Proof. Let $\lambda(a)$ denote the root of characteristic Eq. (17) with respect to a. Without loss of generality, according to [6], we assume that when $a = 0$, (17) has s roots outside the unit circle and $(m + 1 - s)$ roots inside the unit circle, denoted by

$$|\lambda_j(0)| \geqslant 1 (j = 1, 2, \ldots, s) \quad \text{and } |\lambda_j(0)| < 1 \quad (j = s + 1, \ldots, m + 1).$$

Meanwhile, when $a = d_1/B$, (17) only has two roots 0 (m-multiple) and $e^{-\gamma\tau h} < 1$. From Lemma 2, we see that every $|\lambda_j(a)|$ ($j = 1,\ldots,s$) is monotone decreasing for $a \in (0, d_1/B)$. Hence, by the intermediate value theorem, there exist some $a_j^* \in (0, d_1/B)$ such that $|\lambda_j(a_j^*)| = 1$ and $|\lambda_j(a)| < 1$ for $a \in (a_j^*, d_1/B)$. Denote $a^* = \max_{1 \leqslant j \leqslant s} a_j^*$. Then if $a \in (a^*, d_1/B)$ all of the roots satisfy $|\lambda_j(a)| < 1$.

On the other hand, $d|\lambda|^2/da|_{|\lambda|=1} < 0$ for any $a \in (0, d_1/B)$. So the roots inside the unit circle will not pass through the unit circle. Hence, if $a \in (a^*, d_1/B)$ all of the characteristic roots will be in the unit circle. The assertion of the theorem follows immediately. □

Remark 2. The proof shows that with the increasing of a, the roots outside the unit circle will come into the unit circle in turn and the others will still stay in the unit circle. To describe this clearly, the routes of the characteristic roots are traced in Fig. 1. The left figure implies that the system will undergo a subcritical Neimark–Sacker bifurcation, and the right infers a supercritical fold bifurcation.

In order to find the bifurcation points of a, we have to calculate the eigenvalues on the unit circle. Suppose that the root on the unit circle is $e^{i\omega}$ for $\omega \in (-\pi, \pi]$. It is easily to solve that $a = (\gamma + d_1)/B$ for $\omega = 0$ and $a = [\gamma + d_1 + (\gamma - d_1)e^{-\gamma\tau h}]/B(1 - e^{-\gamma\tau h})$ (when m is an odd number) or $a = [d_1 - \gamma - (d_1 + \gamma)e^{-\gamma\tau h}]/B(1 - e^{-\gamma\tau h})$ (when m is an even number) for $\omega = \pi$. Moreover, considered the characteristic equation is a real polynomial equation, it only needs to look for ω in $(0, \pi)$.

$e^{i\omega}$ is a root of characteristic Eq. (17) if and only if

$$e^{\omega i} - e^{-\gamma\tau h} - \frac{1}{\gamma}(1 - e^{-\gamma\tau h})(Ba - d_1)e^{-m\omega i} = 0. \tag{20}$$

By separating the real and the imaginary parts of equality (20), it yields

$$\begin{cases} \cos\omega - \frac{1}{\gamma}(1 - e^{-\gamma\tau h})(Ba - d_1)\cos m\omega = e^{-\gamma\tau h}, \\ \sin\omega + \frac{1}{\gamma}(1 - e^{-\gamma\tau h})(Ba - d_1)\sin m\omega = 0. \end{cases} \tag{21}$$

Multiply the both sides of the first equation by $\sin m\omega$ and the second equation by $\cos m\omega$, and add them together, then we get

$$\sin(m+1)\omega - e^{-\gamma\tau h}\sin m\omega = 0. \tag{22}$$

For the sake of simplicity, we divide the discussion into two cases, m is an even number and an odd number. At first, let us consider the former case.

Lemma 3. *In each interval $((i - 1)\pi/m, i\pi/m)$, (22) has a unique root ω_i ($i = 1,2,\ldots,m$).*

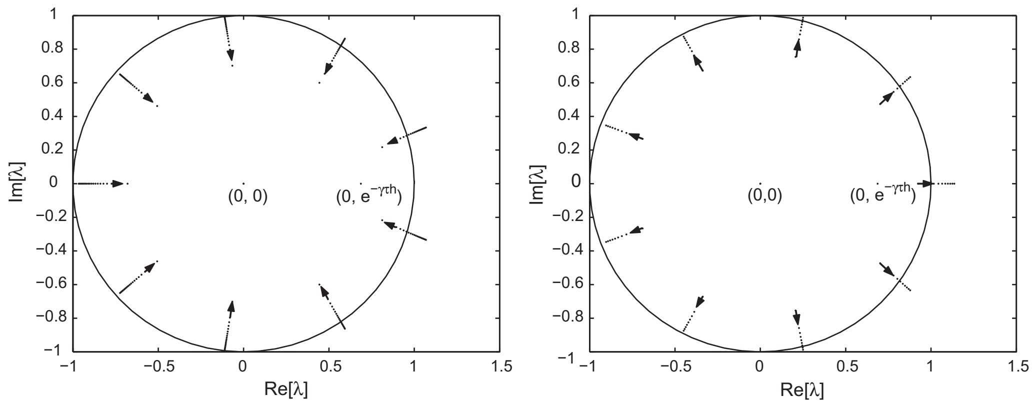

Fig. 1. Routes of the characteristic roots when a varies from 0 to d_1/B (left) and from d_1/B to $2d_1/B > (d_1 + \gamma)/B$ (right) for $m = 8$, $\beta = 0.2$, $\gamma = 0.1$, $n = 10$, $\tau = 30$ and $\tau_0 = 4.41861$.

Proof. Define a function $F(\omega) =: \sin(m+1)\omega - e^{-\gamma\tau h}\sin m\omega$ for $\omega \in (0,\pi)$. Then

$$F\left(\frac{k\pi}{m}\right) = \begin{cases} -\sin\frac{k\pi}{m} < 0, & k = 1,3,\ldots,m-1, \\ \sin\frac{k\pi}{m} > 0, & k = 2,4,\ldots,m-2. \end{cases}$$

By the intermediate value theorem, it infers that (22) has a root at least in each interval $I_i = ((i-1)\pi/m, i\pi/m)$ ($i = 2,3,\ldots, m-1$). In addition, since

$$F'(\omega) = (m+1)\cos(m+1)\omega - me^{-\gamma\tau h}\cos m\omega,$$

it follows that $F'(0+) = m(1-e^{-\gamma\tau h}) + 1 > 0$ and $F'(\pi-) = -(m+1) - me^{-\gamma\tau h} < 0$. As a consequence, $F(\epsilon) > 0$ and $F(\pi-\epsilon) > 0$ for sufficiently small $\epsilon > 0$. Hence, by the intermediate value theorem again, there exist roots in the intervals $(0,\pi/m)$ and $((m-1)\pi/m,\pi)$. Thus (22) has a root at least in each interval I_i ($i = 1,2,\ldots, m$).

Moreover, from the direct computation and (22), there is

$$F''(\omega) = -(m+1)^2\sin(m+1)\omega + m^2e^{-\gamma\tau h}\sin m\omega = -(2m+1)e^{-\gamma\tau h}\sin m\omega.$$

So

$$\begin{cases} F''(\omega) < 0, & \omega \in \left(\frac{2i\pi}{m}, \frac{(2i+1)\pi}{m}\right), \\ F''(\omega) > 0, & \omega \in \left(\frac{(2i+1)\pi}{m}, \frac{(2i+2)\pi}{m}\right), \end{cases} \quad i = 0,1,\ldots,\frac{m}{2}-1.$$

This indicates that $F'(\omega)$ is decreasing on $(2i\pi/m, (2i+1)\pi/m)$ and increasing on $((2i+1)\pi/m, (2i+2)\pi/m)$, which infers that $F'(\omega) = 0$ has one root at most. That is, function $F(\omega)$ has an extreme point at most in each interval $((i-1)\pi/m, i\pi/m)$. Therefore (22) has a unique root, denoted by ω_i, in each interval I_i. The graph of function $F(\omega)$ is sketched in Fig. 2. This completes the proof. $\square$

Solve ω_i from (22) and insert it into the second equation of (21), thus we have

$$Ba_i - d_1 = -\frac{\gamma\sin\omega_i}{(1-e^{-\gamma\tau h})\sin m\omega_i}.$$

It follows that $a_i < d_1/B$ for $i = 1,3,\ldots,m-1$, and $a_i > d_1/B$ for $i = 2,4,\ldots,m$. On the other hand, squaring both sides of (21) and adding them together, we deduce that

$$Ba - d_1 = \pm\frac{\gamma\sqrt{1+e^{-2\gamma\tau h} - 2e^{-\gamma\tau h}\cos\omega}}{1-e^{-\gamma\tau h}}, \quad \omega \in (0,\pi),$$

which implies that

$$a_i = \frac{1}{B}\left(-\frac{\gamma\sqrt{1+e^{-2\gamma\tau h} - 2e^{-\gamma\tau h}\cos\omega_i}}{1-e^{-\gamma\tau h}} + d_1\right) < \frac{d_1}{B}, \quad i = 1,3,\ldots,m-1,$$

and

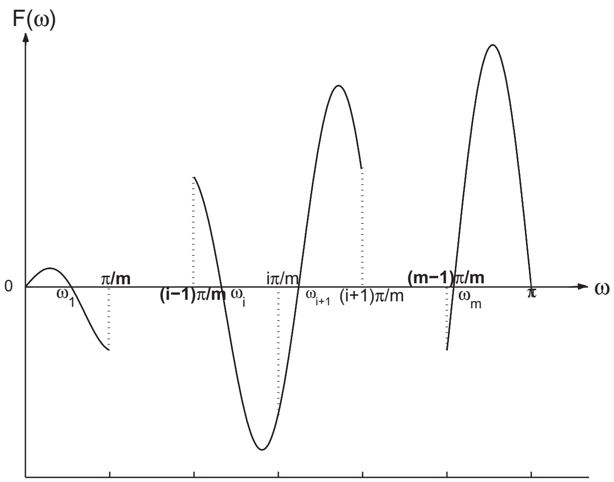

Fig. 2. The graph of function $F(\omega)$.

$$a_i = \frac{1}{B}\left(\frac{\gamma\sqrt{1+e^{-2\gamma\tau h}-2e^{-\gamma\tau h}\cos\omega_i}}{1-e^{-\gamma\tau h}} + d_1\right) \geqslant \frac{\gamma+d_1}{B}, \quad i = 2,4,\ldots,m.$$

So $[d_1-\gamma-(d_1+\gamma)e^{-\gamma\tau h}]/[B(1-e^{-\gamma\tau h})] = a_{m+1} < a_{m-1} < \cdots < a_3 < a_1 < d_1/B < (\gamma+d_1)/B = a_0 < a_2 < \cdots < a_m$, which means $a^* = a_1$ by Theorem 1.

The result of the second case can be studied easily in a similar fashion. We could obtain that $a_m < \cdots < a_3 < a_1 < d_1/B < [\gamma+d_1]/B = a_0 < a_2 < \cdots < a_{m-1} < a_{m+1} = [\gamma+d_1+(\gamma-d_1)e^{-\gamma\tau h}]/[B(1-e^{-\gamma\tau h})]$ when m is an odd number.

Theorem 2. *Suppose that $\beta/\gamma > n/(n-2)$ and $\tau > \tau_0$. Then system (16) undergoes a Hopf bifurcation at the origin when $a = a_1$, and a fold bifurcation when $a = a_0$. Furthermore, there exists a closed invariant curve when $a \in [0, a_1)$, and the origin is asymptotically stable for $a \in (a_1, a_0)$ and unstable for $a \in (a_0, +\infty)$.*

Proof. From the above analysis we see that there is a pair of characteristic roots $\lambda = e^{\pm i\omega_1}$ when $a = a_1$ and, from Lemma 2, $d|\lambda|^2/da|_{|\lambda|=1} < 0$ for $a = a_1 < d_1/B$. Applying the Neimark–Sacker bifurcation theorem (Theorem 3.2.3 in [11]), it is proved that $a = a_1$ is a Neimark–Sacker bifurcation point. Similarly, when $a = a_0$, $\lambda = 1$ is a simple characteristic root and $d|\lambda|^2/da|_{|\lambda|=1} > 0$ for $a = a_0 > d_1/B$. Therefore $a = a_0$ is a fold bifurcation point [10].

Hence all roots of characteristic Eq. (17) have model less than one for $a \in (a_1, a_0)$ and there exists a characteristic root having model more than one for $a > a_0$. Thus for system (16) the origin is asymptotically stable for $a \in (a_1, a_0)$ and unstable for $a > a_0$. □

Remark 3. This theorem shows that system (16) could be stabilized by choosing $a \in (a_1, a_0)$.

3.3. Nonlinear delay control

Now we consider NLDC (6). Under transformations (T), system (3) is equivalent to

$$\dot{y}(t) = -\tau\gamma\left(y(t) + \sqrt[n]{\frac{\beta}{\gamma}-1}\right) + \frac{\tau\beta\left(y(t-1)+\sqrt[n]{\frac{\beta}{\gamma}-1}\right)}{1+\left(y(t-1)+\sqrt[n]{\frac{\beta}{\gamma}-1}\right)^n} + \tau B[ay(t-1) + b\theta y^2(t-1) + c\theta^2 y^3(t-1)]. \tag{23}$$

By using NSFD scheme (2) to system (23), we have numerical discrete system

$$y_{k+1} = e^{-\gamma\tau h}y_k + \frac{(1-e^{-\gamma\tau h})}{\gamma}\left[-\gamma\sqrt[n]{\frac{\beta}{\gamma}-1} + \frac{\beta\left(y_{k-m}+\sqrt[n]{\frac{\beta}{\gamma}-1}\right)}{1+\left(y_{k-m}+\sqrt[n]{\frac{\beta}{\gamma}-1}\right)^n} + B\left(ay_{k-m} + b\theta y_{k-m}^2 + c\theta^2 y_{k-m}^3\right)\right]. \tag{24}$$

Clearly, the origin is a fixed point.

By the comparison between systems (24) and (16), we see that they have the same linearization at the origin. Hence, the asymptotical stability of the origin of systems (24) and (16) is completely same. This determines that the origin could be stabilized by choosing parameter $a \in (a_1, a_0)$. Besides that, parameters b and c could decide another dynamics of system (24) e.g. the direction of the bifurcation, the stability and the amplitude of the closed invariant curve (see [4,12,13,9]). Followed the similar way in [4,6], the explicit formula of a critical value which decides the direction of the bifurcation and the stability of the closed invariant curve could be gotten.

Set $a = a_1 + \mu$, $\mu \in R$. Then $\mu = 0$ is a Neimark–Sacker bifurcation value for system (24). The expansion of system (24) at the origin is

$$y_{k+1} = \tilde{a}_m y_k + \tilde{a}_0 y_{k-m} + \frac{\tilde{b}}{2}y_{k-m}^2 + \frac{\tilde{c}}{6}y_{k-m}^3 + \mathcal{O}(|y_{k-m}^4|), \tag{25}$$

in which

$$\begin{aligned}
\tilde{a}_m &= e^{-\gamma\tau h},\\
\tilde{a}_0 &= \frac{1}{\gamma}(1-e^{-\gamma\tau h})(Ba-d_1),\\
\tilde{b} &= (1-e^{-\gamma\tau h})\left\{\frac{1}{u_*\beta^2}n(\beta-\gamma)[(n-1)\beta-2n\gamma] + \frac{2}{\gamma}Bb\theta\right\},\\
\tilde{c} &= (1-e^{-\gamma\tau h})\left\{-\frac{1}{u_*^2\beta^3}n(\beta-\gamma)[(n^2-1)\beta^2-6n^2\beta\gamma+6n^2\gamma^2] + \frac{6}{\gamma}Bc\theta^2\right\},
\end{aligned}$$

where $u_* = \sqrt[n]{\beta/\gamma-1}$. By introducing a new variable $Y_k = (y_k, y_{k-1}, \ldots, y_{k-m})^T$, system (25) is equivalently rewritten as

$$Y_{k+1} = \widetilde{A}Y_k + \frac{1}{2}\widetilde{B}(Y_k, Y_k) + \frac{1}{6}\widetilde{C}(Y_k, Y_k, Y_k) + O(\|Y_k\|^4),$$

where

$$\widetilde{A} = \begin{pmatrix} \tilde{a}_m & 0 & \cdots & 0 & \tilde{a}_0 \\ 1 & 0 & & & \\ & \ddots & \ddots & & \\ & & & 1 & 0 \end{pmatrix},$$

and

$$\widetilde{B}(Y_k, Y_k) = (b_0(Y_k, Y_k), 0, \ldots, 0)^T,$$
$$\widetilde{C}(Y_k, Y_k, Y_k) = (c_0(Y_k, Y_k, Y_k), 0, \ldots, 0)^T.$$

Here for vectors $\phi = (\phi_0, \ldots, \phi_m)^T$, $\psi = (\psi_0, \ldots, \psi_m)^T$ and $\eta = (\eta_0, \ldots, \eta_m)^T$, $b_0(\phi, \psi) = \tilde{b}\phi_m\psi_m$ and $c_0(\phi, \psi, \eta) = \tilde{c}\phi_m\psi_m\eta_m$.

Let $q = q(a_1) \in C^{m+1}$ be an eigenvector of $\widetilde{A}$ corresponding to $e^{i\omega_1}$, then $\widetilde{A}q = e^{i\omega_1}q$ and $\widetilde{A}\bar{q} = e^{-i\omega_1}\bar{q}$. We also introduce an adjoint eigenvector $q^* = q^*(\tau) \in C^{m+1}$, which satisfies $\widetilde{A}^T q^* = e^{-i\omega_1}q^*$, $\widetilde{A}^T\bar{q}^* = e^{i\omega_1}\bar{q}^*$ and $\langle q^*, q\rangle = 1$, where $\langle q^*, q\rangle = \sum_{i=0}^{m}\bar{q}_i^* q_i$.

Lemma 4 [4]. *Define a vector valued function $p(\xi) = (\xi^m, \xi^{m-1}, \ldots, 1)^T$. If ξ is an eigenvalue of $\widetilde{A}$, then $\widetilde{A}p(\xi) = \xi p(\xi)$.*

In view of Lemma 4, we have

$$q = p(e^{i\omega_1}) = (e^{im\omega_1}, e^{i(m-1)\omega_1}, \ldots, e^{i\omega_1}, 1)^T. \tag{26}$$

Lemma 5. *Suppose $q^* = (q_0^*, q_1^*, \cdots, q_m^*)^T$ is the eigenvector of $\widetilde{A}^T$ corresponding to eigenvalue $e^{-i\omega_1}$, and $\langle q^*, q\rangle = 1$. Then*

$$q^* = \overline{K}(1, \tilde{a}_0 e^{im\omega_1}, \tilde{a}_0 e^{i(m-1)\omega_1}, \ldots, \tilde{a}_0 e^{i2\omega_1}, \tilde{a}_0 e^{i\omega_1})^T, \tag{27}$$

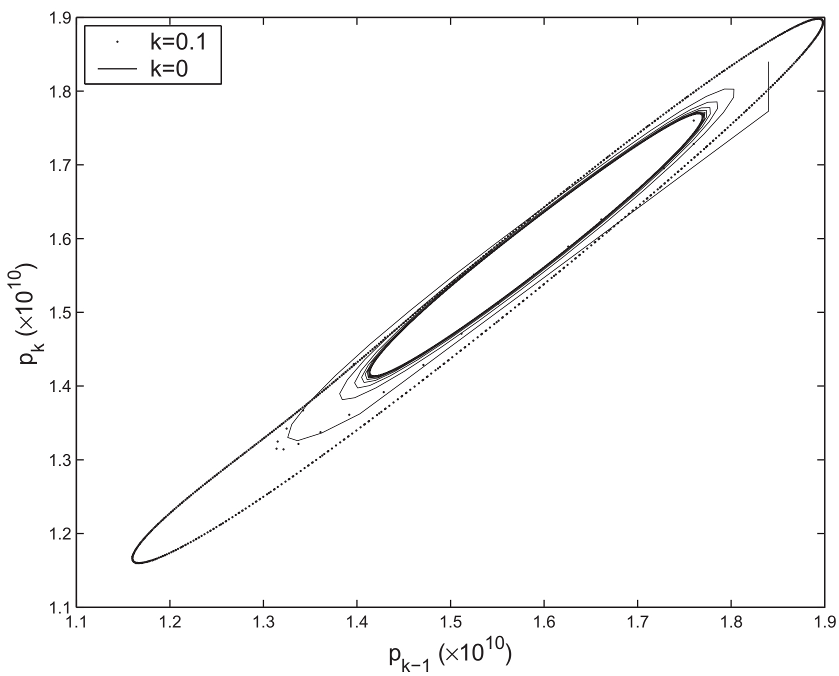

Fig. 3. Unstable solutions of LNDC (3).

Table 1
The roots of Eq. (21) for $\omega \in [0, \pi]$ when $\tau = 5$.

k	0	1	2	3	4	5	6	7	8	9
ω_k	0	0.217	0.566	0.931	1.29	1.66	2.03	2.40	2.77	3.14
$a_k(10^{-10})$	0.3125	0.0241	0.813	−0.650	1.46	−1.23	1.95	−1.62	2.22	−1.75

where

$$K = \frac{1}{e^{im\omega_1} + m\tilde{a}_0 e^{-i\omega_1}}. \tag{28}$$

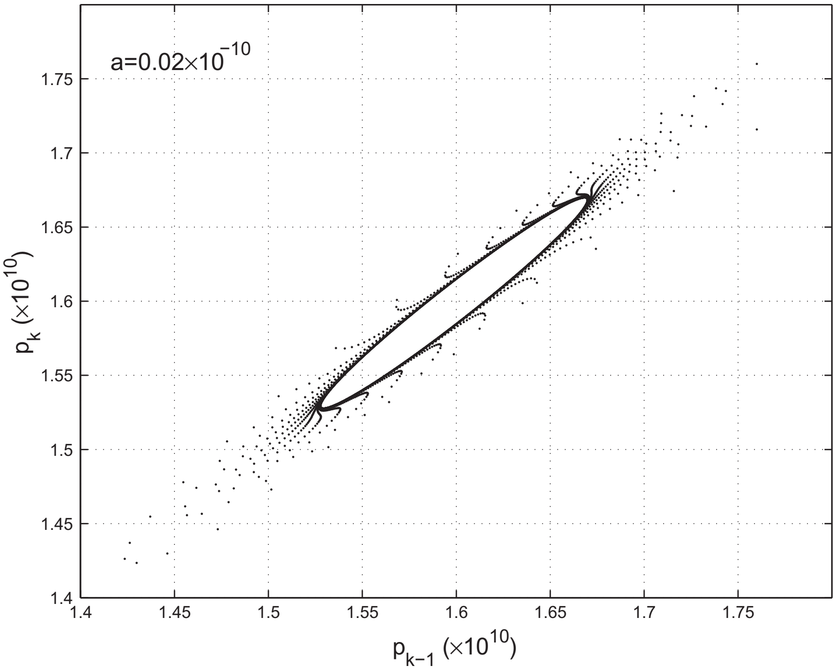

Fig. 4. Unstable solution of LDC system for $a = 0.02 \times 10^{-10}$.

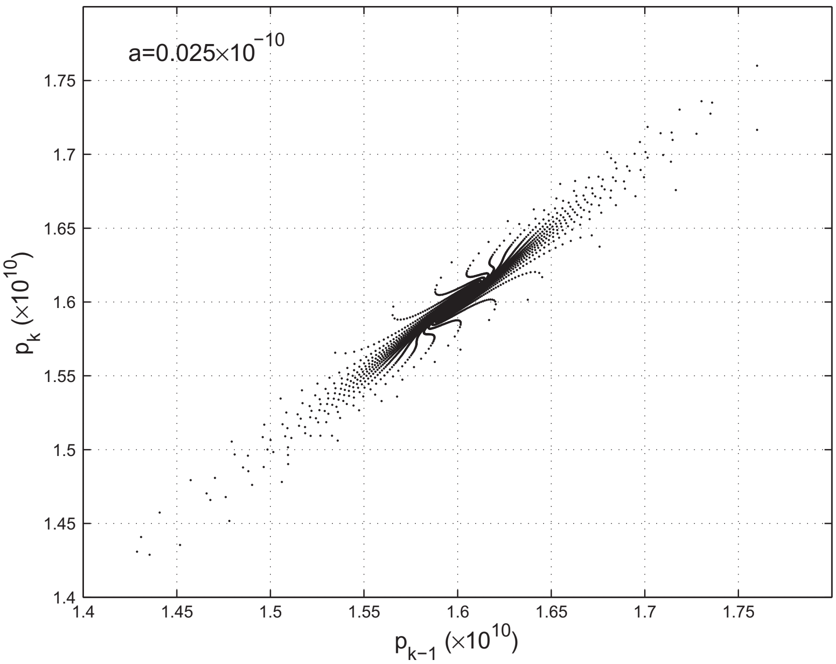

Fig. 5. Stable solution of LDC system for $a = 0.025 \times 10^{-10}$.

Proof. From the assumption for q^*, there is $\widetilde{A}^T q^* = e^{-i\omega_1} q^*$. As a consequence,

$$\begin{cases} \tilde{a}_m q_0^* + q_1^* = e^{-i\omega_1} q_0^*, \\ q_k^* = e^{-i\omega_1} q_{k-1}^*, \quad k = 2, \ldots, m, \\ \tilde{a}_0 q_0^* = e^{-i\omega_1} q_m^*, \end{cases} \tag{29}$$

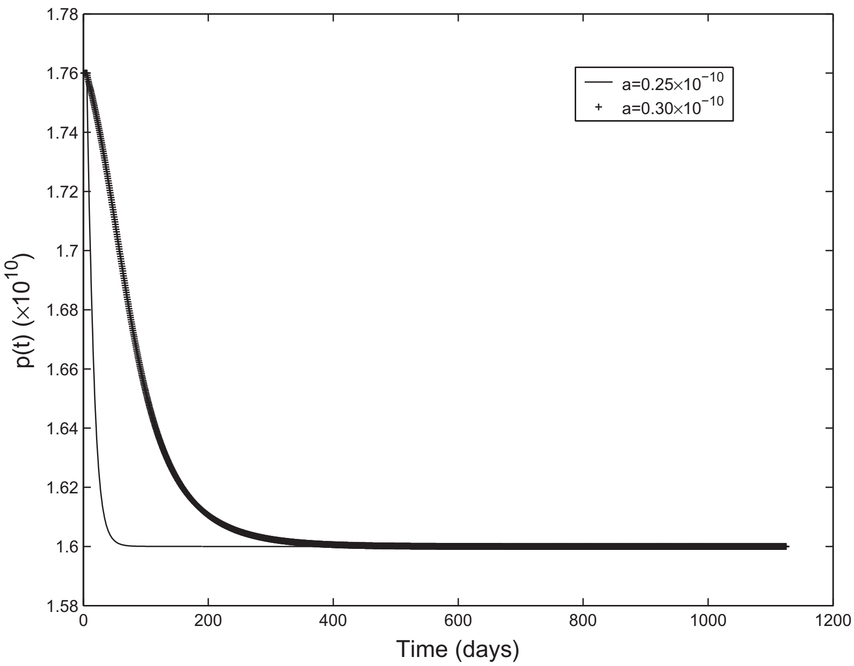

Fig. 6. Stable solutions of LDC system for $a = 0.25 \times 10^{-10}$ and 0.30×10^{-10}.

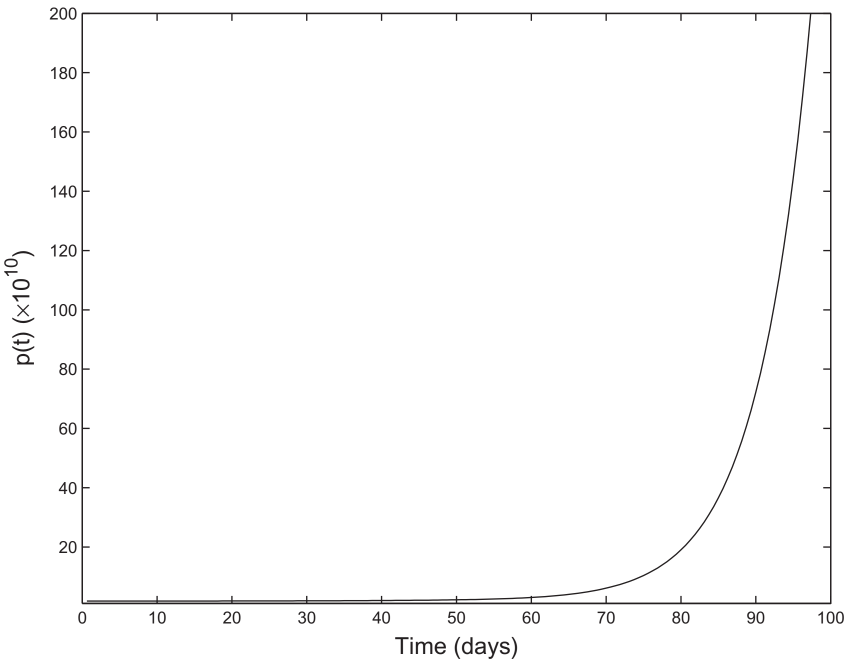

Fig. 7. Exploding solution of LDC system for $a = 0.32 \times 10^{-10}$.

Let $q_m^* = \tilde{a}_0 \overline{K} e^{i\omega_1}$, then $q_j^* = \tilde{a}_0 \overline{K} e^{i\omega_1 (m-j+1)} (j = 1, 2, \dots, m-1)$ and $q_0^* = \overline{K}$. Therefore, we get (27). From normalization $\langle q^*, q \rangle = 1$ and direct computation, equality (28) follows. □

Denote $\lambda^* = e^{i\omega_1}$. On the basis of the algorithms and the computation process in [4,10], we can compute

$$
\begin{aligned}
g_{20} &= \langle q^*, \widetilde{B}(q, q) \rangle, \\
g_{11} &= \langle q^*, \widetilde{B}(q, \bar{q}) \rangle, \\
g_{02} &= \langle q^*, \widetilde{B}(\bar{q}, \bar{q}) \rangle, \\
g_{21} &= \langle q^*, \widetilde{B}(\bar{q}, \omega_{20}) \rangle + 2\langle q^*, \widetilde{B}(q, \omega_{11}) \rangle + \langle q^*, \widetilde{C}(q, q, \bar{q}) \rangle,
\end{aligned}
$$

in which

$$
\begin{aligned}
\omega_{20} &= \frac{b_0(q,q)}{d(\lambda^{*2})} p(\lambda^{*2}) - \frac{\langle q^*, \widetilde{B}(q,q) \rangle}{\lambda^{*2} - \lambda^*} q - \frac{\langle \bar{q}^*, \widetilde{B}(q,q) \rangle}{\lambda^{*2} - \bar{\lambda}^*} \bar{q}, \\
\omega_{11} &= \frac{b_0(q,\bar{q})}{d(1)} p(1) - \frac{\langle q^*, \widetilde{B}(q,\bar{q}) \rangle}{1 - \lambda^*} q - \frac{\langle \bar{q}^*, \widetilde{B}(q,\bar{q}) \rangle}{1 - \bar{\lambda}^*} \bar{q}.
\end{aligned}
$$

Substituting these into

$$
c_1(a_1) = \frac{g_{20} g_{11} (1 - 2\lambda^*)}{2(\lambda^{*2} - \lambda^*)} + \frac{|g_{11}|^2}{1 - \bar{\lambda}^*} + \frac{|g_{02}|^2}{2(\lambda^{*2} - \bar{\lambda}^*)} + \frac{g_{21}}{2}, \tag{30}
$$

yields an expression of the critical coefficient $c_1(a_1)$.

Lemma 2 shows that $dr(a_1)/da < 0$. Therefore, by a straightforward application of the Naimark–Sacker bifurcation theorem and Theorem 2, we have the following result.

Theorem 3. *For system (24),*

(i) *when $a \in [0, a_1)$ there exists a unique closed invariant curve, which is attracting if $\Re[e^{-i\omega_1} c_1(a_1)] < 0$ and repelling if $\Re[e^{-i\omega_1} c_1(a_1)] > 0$;*
(ii) *the origin is asymptotically stable for $a \in (a_1, a_0)$ and unstable for $a \in (a_0, +\infty)$.*

Remark 4. From this theorem, we see that although it is enough to use linear delay control to stabilize the positive fixed point, it is more effective to exploit the NLDC to get the expected property of bifurcation.

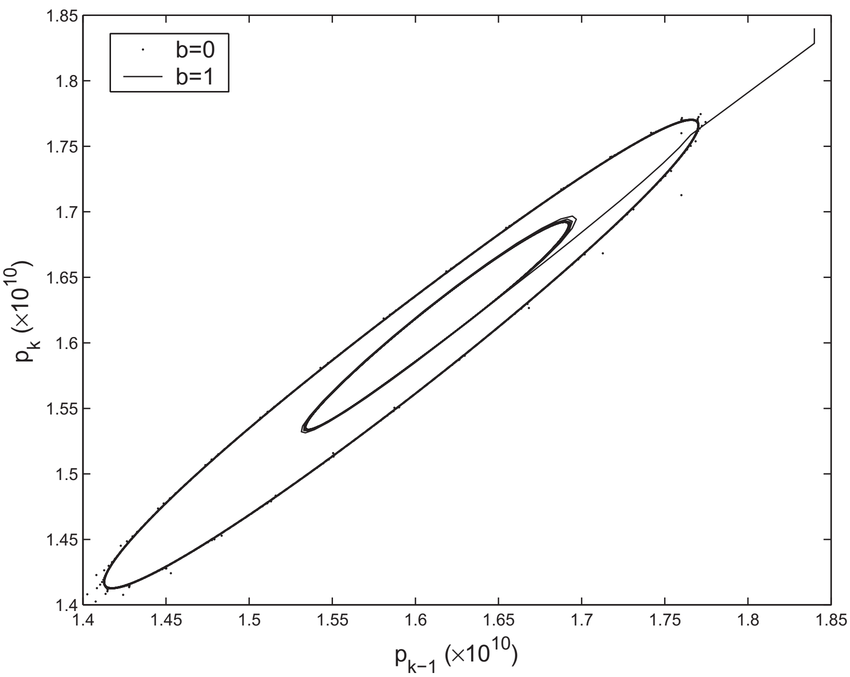

Fig. 8. A large and a small amplitude solutions of NLDC system when $a = 0$ and $c = 0$.

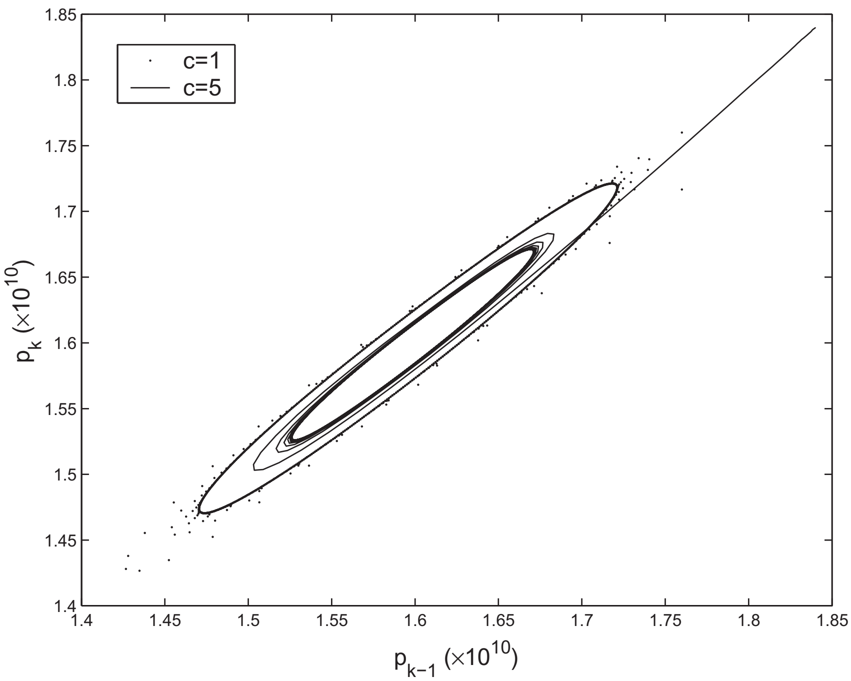

Fig. 9. A large and a small amplitude solutions of NLDC system when $a = 0$ and $b = 0$.

4. Numerical test

In this section, we present some numerical results to verify the analytical predictions obtained in the previous sections. Here we choose parameters as: $\beta = 0.2$/day, $\gamma = 0.1$/day, $n = 10$, $\theta = 1.6 \times 10^{10}$cells/kg, and the density of mature cells in blood bag $B = 1.6 \times 10^{10}$cells/kg. So the steady-state circulating levels of granulocytes is $p^* = 1.6 \times 10^{10}$cells/kg. We fix $m = 8$ in method (2). From Lemma 1 and [6], we know that for system (1) there exists a Hopf bifurcation point $\tau_0 = 4.41861$ and a bifurcation periodic solution occurs for $\tau > \tau_0$. In the following, we always choose $\tau = 5$.

Firstly, let us see the LNDC. The dynamical behaviors of the model with LNDC ($k = 0.1$) and without control ($k = 0$) are illustrated in Fig. 3, which shows that with the increasing of k the amplitude of the closed invariant curve is more and more large, that is, LNDC can not stabilize the fixed point.

Secondly, go to test the LDC. By solving Eq. (21), we compute the following values in Table 1. Table 1 and Theorem 2 infer that there exists closed invariant curve for $a \in [0, 0.0241 \times 10^{-10})$ (see Fig. 4); positive fixed point p^* is asymptotically stable for $a \in (0.0241 \times 10^{-10}, 0.3125 \times 10^{-10})$ (see Figs. 5 and 6); and p^* is unstable for $a > 0.32 \times 10^{-10}$ (see Fig. 7).

Finally, in order to obtain attracting closed invariant curve, it only needs $\Re[e^{-i\omega_1}c_1(a^*)] < 0$. By formula (30), we calculate the critical coefficient $\Re[e^{-i\omega_1}c_1(a_1)] = -3.196 + 2.926 \times 10^{20}b - 1.498 \times 10^{41}b^2 < 0$ when $c = 0$; and $\Re[e^{-i\omega_1}c_1(a^*)] = -3.196 - 2.943 \times 10^{30}c < 0$ when $c > -1.086 \times 10^{-30}$ and $b = 0$ (see Figs. 8 and 9). On the other hand, Figs. 8 and 9 suggest that the amplitude of the close invariant curve could be eliminated by choosing appropriate b and c.

5. Conclusion

In this paper, the problem of numerical bifurcation control for a physiological system is studied. To treat the disease of CGL, three types of feedback controls are proposed. We have shown that the LDC and the NLDC can not only delay the normal time between the production of immature cells in the bone marrow and their maturation for release in circulating bloodstreams, but also stabilize the density of mature cells in blood circulation. In addition, the NLDC also can change the amplitude of periodic solution. Numerical simulations have shown that the analytical predictions are correct.

Here we provide a reasonable therapy of CGL only based on mathematical consideration. From this point of view, the patient should make periodic blood tests and be transfused blood frequently according to the rule given in the paper. However, the study on the prophylaxis and treatment of CGL is a extremely complex work. This needs the mathematicians, medical scientists and other experts work hard together.

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