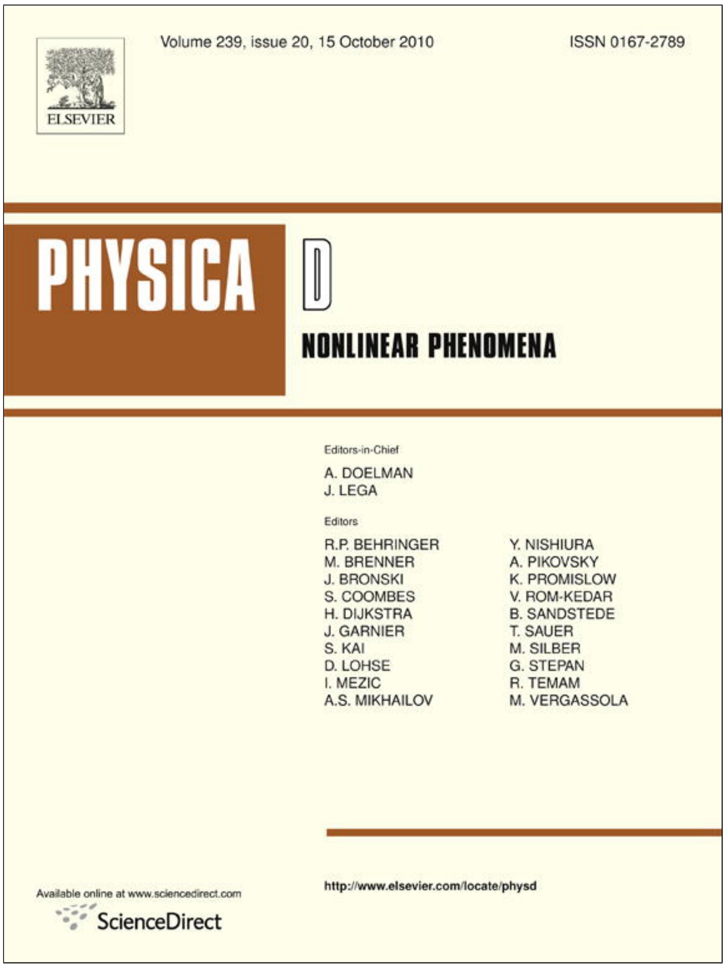

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Stability and bifurcation analysis in hematopoietic stem cell dynamics with multiple delays[☆]

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ABSTRACT

This paper is devoted to the analysis of a maturity structured system of hematopoietic stem cell (HSC) populations in the bone marrow. The model is a system of differential equations with several time delays. We discuss the stability of equilibria and perform the analysis of Hopf bifurcation. More precisely, we first obtain a set of improved sufficient conditions ensuring the global asymptotical stability of the zero solution using the Lyapunov method and the embedding technique of asymptotically autonomous semiflows. Then we prove that there exists at least one positive periodic solution for the n-dimensional system as a time delay varies in some region. This result is established by combining Hopf bifurcation theory, the global Hopf bifurcation theorem due to Wu [J. Wu, Symmetric functional differential equations and neural networks with memory, Trans. Amer. Math. Soc. 350 (1998) 4799–4838], and a continuation theorem of coincidence degree theory. Some numerical simulations are also presented to illustrate the analytic results.

1. Introduction

Hematopoietic stem cells (HSCs) are primitive cells that self-renew and differentiate into any of the hematopoietic cell lineages, which are crucial to maintain lifelong production of all blood cells. Although HSCs divide infrequently, it is believed that HSCs enter and exit the cell cycle regularly [1–3].

HSCs reside in the bone marrow in adult animals in a specialized micro-environment, called the niche. In the bone marrow niche, most HSCs remain in a quiescent state, also known as the G_0-phase, thereby preserving their capacity to self-renew. Other HSCs are in a proliferating phase, which is the so-called cell cycle. There, hematopoietic homeostasis is maintained throughout the lifetime of an animal through the self-renewal of HSCs. Self-renewal is a specialized cell division in which one or both of the daughter cells retain the same cellular potential as the parental stem cells. At last, the two daughter cells enter directly into the resting phase and complete the cycle. Throughout such divisions, HSCs produce an increasing number of differentiated cells until the process leads to mature cells. These latter cells finally reach the blood stream and become blood cells (see [4,3]).

Since the end of the 1970s, various mathematical models have been proposed to describe the dynamics of HSCs, in particularly by Mackey [1,2]. The model of Mackey [1] is an uncoupled system with two nonlinear delay differential equations which considers a stem cell population divided into two compartments, a proliferating and a nonproliferating phase. There is a time delay corresponding to the proliferating phase duration. Mackey's model has been studied and improved by many authors (see [5–11] and the references therein). However, most authors consider only systems of two differential equations to depict the whole process of differentiation.

Based on the idea of Bernard et al. [12] and the model of Mackey [1], Adimy et al. [4] proposed an n-dimensional model, which includes a finite number of stages during the production of blood cells corresponding to different maturity levels. They introduced a (discrete) maturity variable in their model and took into account the self-renewal capacity of HSCs, which allows some cells to stay in the same maturity compartment as their mother and commit them to go further in the differentiation process at each division. Thus each cell can be either in a proliferating phase, where it performs a series of processes such as growth, DNA synthesis, which ends with the cell division, or in a non-proliferating phase, where it can stay its entire life. Non-proliferating cells can reach the proliferating phase whenever during their life with a nonlinear rate β, in which a part of the cell population in a given compartment leaves it at division to go to the next one, and the other part stays in the compartment. The proportion of cells that leave is supposed to be constant in each compartment (see [4]).

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Adimy et al. [4] studied the boundedness and positivity of the solutions, investigated the existence as well as asymptotical behavior of steady states, and drew some stability conclusions of every equilibrium, respectively. Adimy et al. [5] further studied the model from the biological point of view. Though the model has been studied extensively by them, there are still some questions to be answered. For example, when zero is the unique equilibrium, does the locally asymptotical stability imply the globally asymptotical stability? This is an interesting and reasonable question from both mathematical and biological points of view. In addition, Adimy et al. did not give a clear stability description of the zero, when 0 is a root of the corresponding characteristic equation. Furthermore, there are some results on the stability of equilibria but few discussions for the existence of periodic solutions. The study of periodic solutions in such models is not only mathematically interesting but also biologically significant as it can help provide better understanding of some blood diseases. This motivates our study.

In this paper, we still consider the model proposed by Adimy et al. [4]. We begin with the investigation of a 1-dimensional equation for one stage and use an analytical approach proposed by Wei and Ruan [13] (see also [14]). Then, by applying the local Hopf bifurcation theory, we investigate the existence of periodic oscillations for this scalar equation. More precisely, we prove that the unique positive equilibrium loses its stability as the time delay τ increases and a sequence of Hopf bifurcations occur at this equilibrium. Whereafter, based on the normal form and center manifold theory due to [15,16], we derive sufficient conditions for determining the direction of Hopf bifurcation and the stability of the bifurcating periodic solutions. Furthermore, the existence of periodic solutions for τ far away from the Hopf bifurcation values is also established by using a global Hopf bifurcation result due to Wu [17], see also [18–21]. Finally, we return to the original n-dimensional system. On one hand, integrating the Lyapunov method with the embedding technique of asymptotically autonomous semiflows (see [22,23]), we prove that the zero equilibrium is globally asymptotically stable when it is the unique equilibrium. On the other hand, we discuss the existence of positive periodic solutions using the continuation theorem of coincidence degree theory [24–27].

We would like to mention that, when the stability and Hopf bifurcation at the positive equilibrium are considered, the difficulty resides in the presence of the dependent delay and the fact that some coefficients in the equations depend upon this delay. Consequently, the characteristic equation of the linearized system has delay-dependent coefficients. As mentioned by Beretta and Kuang [28], models with delay-dependent coefficients often exhibit very rich dynamics as compared to those with constant coefficients. In the analysis, we need to study a first degree transcendental polynomial with delay coefficients. The problem of determining the distribution of roots to such polynomials is very complex and there are very few studies on this topic (see [29,30, 14,11] and references therein).

This paper is organized as follows. After introducing the model in Section 2, the stability analysis of equilibria for the first equation, including the special and complex cases under which 0 is a root of the corresponding characteristic equation, are given in Section 3. Sections 4 and 5 are devoted to establishing the local and global Hopf bifurcations at the positive steady-state, respectively. We derive improved conditions on the global asymptotical stability of the zero solution in Section 6. Finally, in Section 7 conditions for the existence of positive periodic solutions for the n-dimensional model are given and some numerical simulations are carried out to illustrate the analytic results. A brief discussion is presented in Section 8.

2. The model

Firstly, we introduce the model proposed by Adimy et al. [4] in detail. Set

$$I_n := \{1, 2, \ldots, n\}, \quad n \in \mathbb{N},\ n \geq 3.$$

Let $x_i(t)$, $i \in I_n$, be the density of (nonproliferating) hematopoietic stem cells in the ith compartment at time t. Then x_i satisfies

$$\begin{aligned}
\frac{dx_1}{dt}(t) &= -[\delta_1 + \beta_1(x_1(t))x_1(t)] \\
&\quad + 2(1-K_1)e^{-\gamma_1\tau_1}\beta_1(x_1(t-\tau_1))x_1(t-\tau_1), \\
\frac{dx_i}{dt}(t) &= -[\delta_i + \beta_i(x_i(t))]x_i(t) \\
&\quad + 2(1-K_i)e^{-\gamma_i\tau_i}\beta_i(x_i(t-\tau_i))x_i(t-\tau_i) \\
&\quad + 2K_{i-1}e^{-\gamma_{i-1}\tau_{i-1}}\beta_{i-1}(x_{i-1}(t-\tau_{i-1}))x_{i-1}(t-\tau_{i-1}), \\
&\quad i = 2, \ldots, n-1, \\
\frac{dx_n}{dt}(t) &= -[\delta_n + \beta_n(x_n(t))]x_n(t) \\
&\quad + 2K_{n-1}e^{-\gamma_{n-1}\tau_{n-1}}\beta_{n-1}(x_{n-1}(t-\tau_{n-1}))x_{n-1}(t-\tau_{n-1}),
\end{aligned} \tag{2.1}$$

where, for i fixed, δ_i and γ_i are the mortality rates in the nonproliferating phase and proliferating phase, respectively, τ_i is the proliferating phase duration, K_i is the proportion of cells that leave the stage i to the stage $i+1$, and the introduction rate $\beta_i : [0, \infty) \to \mathbb{R}$ is a continuous function. Assume for $i \in I_{n-1}$ that

(H1) $0 < \delta_i \leq \delta_{i+1}$, $0 < \gamma_i \leq \gamma_{i+1}$, and $0 \leq \tau_i \leq \tau_{i+1}$;

(H2) $0 := K_0 < K_i \leq K_{i+1} < 1$.

Assumption (H1) implies that the proliferating phase duration τ_i is an increasing function of cell maturity (immature cells dividing faster than mature cells) as well as mortality rate. Assumption (H2) ensures that cells lose their self-renewal capacity gradually as they become more and more mature, thus the differentiation rate K_i increases and becomes closer to one.

More precisely, the function β_i satisfies:

(H3) $0 < \beta_{i+1}(0) \leq \beta_i(0)$ for $i \in I_{n-2}$ and $\beta_n \equiv 0$;

(H4) for $i \in I_{n-1}$, β_i is a positive and strictly decreasing function such that

$$\lim_{x\to\infty} \beta_i(x) = 0.$$

Typically, β_i is a Hill function given by

$$\beta_i(Q) = \frac{\beta_i^0\theta_i^{n_i}}{\theta_i^{n_i} + Q}. \tag{2.2}$$

The parameter β_i^0 represents the maximal rate of introduction in the proliferating phase, θ_i is the value for which β_i attains half of its maximum value, and n_i is the sensitivity of reintroduction rate which describes the reaction of β_i due to external stimuli and the action of a growth factor, for example (some growth factors are known to trigger the introduction of quiescent cells in the proliferating phase).

Remark 2.1. All the above assumptions are biologically reasonable (see [31,32]).

System (2.1) admits a unique solution for each continuous initial condition by the fundamental theory in [33]. Denote each of the solutions with initial condition $x_0 = \varphi$ as $x(0, \varphi)(t)$, where $\varphi \in C([-\tau, 0], \mathbb{R}^n)$, $\tau := \max_{i\in I_{n-1}}\{\tau_i\}$ and 0 is the initial time.

Proposition 2.2. *Each solution of (2.1) with nonnegative initial condition is nonnegative and bounded.*

Proof. For the nonnegativity, we first claim that the first element, x_1, of the solution of (2.1) associated with nonnegative initial condition is nonnegative. In particular, if $\varphi_1 \geq 0$ and there exists at least a $\theta \in [-\tau_1, 0]$ such that $\varphi_1(\theta) > 0$, then there exists a $t_0 \in [0, \tau_1)$ such that $x_1(t) > 0$ when $t > t_0$.

Notice that the first equation in (2.1) is independent of variables x_i, $i \geq 2$, we have that $x_1(t)$ is the solution of the initial value problem

$$\frac{dx_1}{dt}(t) = -[\delta_1 + \beta_1(x_1(t))]x_1(t) + 2(1-K_1)e^{-\gamma_1\tau_1}\beta_1(x_1(t-\tau_1))x_1(t-\tau_1), \quad (2.3)$$
$x_0 = \varphi_1$.

Firstly, we know that $x(0, \varphi_1)(t)$ is well defined in $[-\tau, \infty)$ from [33]. Hence, $x_1(t)$ is well defined in $[-\tau_1, \infty)$ and expressed in the following form:

$$x_1(t) = e^{-\int_0^t [\delta_1+\beta_1(x_1(s))]ds}\varphi_1(0) + \int_0^t e^{-\int_s^t [\delta_1+\beta_1(x(\sigma))]d\sigma} \times \left[2(1-K_1)e^{-\gamma_1\tau_1}\beta_1(x_1(s-\tau_1))x(s-\tau_1)\right] ds. \quad (2.4)$$

There are three cases for φ_1:
(I) $\varphi_1(0) > 0$;
(II) $\varphi_1(0) = 0$ and $\varphi_1(-\tau_1) = 0$;
(III) $\varphi_1(0) = 0$ and $\varphi_1(-\tau_1) > 0$.

In case (I), (2.4) and $\varphi_1 \geq 0$ imply that $x_1(t) > 0$ when $t \in [0, \tau_1]$. By induction, one can verify that $x_1(t) > 0$ holds for all $t \in [0, \infty)$.

In case (II), (2.4) becomes

$$x_1(t) = \int_0^t e^{-\int_s^t [\delta_1+\beta_1(x(\sigma))]d\sigma} \times \left[2(1-K_1)e^{-\gamma_1\tau_1}\beta_1(x_1(s-\tau_1))x(s-\tau_1)\right] ds. \quad (2.5)$$

Let

$$\theta_0 = \inf_{\theta\in[-\tau_1,0]}\{\theta : \varphi_1(\theta) > 0\}.$$

Then θ_0 is well defined, and there exists a $\varepsilon > 0$ such that $[\theta_0, \theta_0+\varepsilon] \subset [-\tau_1, 0)$, and $\varphi_1(\theta) > 0$ when $\theta \in (\theta_0, \theta_0+\varepsilon]$, and $\varphi_1(\theta) = 0$ when $\theta \in [-\tau_1, \theta_0]$. Hence, (2.5) implies that $x_1(t) > 0$ when $t \in (\tau_1+\theta_0, \tau_1]$ and $x_1(t) = 0$ when $t \in [0, \tau_1+\theta_0]$. The rest of the proof is similar to that in case (I), so we omit it.

In case (III), note that there exists a $\epsilon > 0$ such that $[-\tau_1, -\tau_1+\epsilon] \subset [-\tau_1, 0)$ and $\varphi_1(\theta) > 0$ when θ is in the interval. The rest of the proof is similar to that in case (II). This completes the proof of our claim.

Now assume that x_{i-1}, $i \geq 2$, is nonnegative. We have for the ith equation of (2.1),

$$\frac{dx_i}{dt}(t) = -[\delta_i + \beta_i(x_i(t))]x_i(t) + 2(1-K_i)e^{-\gamma_i\tau_i}\beta_i(x_i(t-\tau_i))x_i(t-\tau_i) + 2K_{i-1}e^{-\gamma_{i-1}\tau_{i-1}}\beta_{i-1}(x_{i-1}(t-\tau_{i-1}))x_{i-1}(t-\tau_{i-1}).$$

Using the similar method as for x_1, we can show that x_i is nonnegative.

For the boundedness, we refer to [4, Proposition 2.2]. □

We would like to mention that most results in Sections 2–4 were obtained by Adimy et al. [4,6–8,34] and Mackey et al. [2,10] using various methods. However, for the sake of completeness, we introduce these results and provide detailed proofs here.

3. Stability analysis

Notice that the first equation of (2.1) is uncoupled with the other $n-1$ equations. Therefore, we begin with the investigation of a 1-dimensional equation:

$$\frac{dx}{dt}(t) = -[\delta + \beta(x(t))]x(t) + 2(1-K)e^{-\gamma\tau}\beta(x(t-\tau))x(t-\tau). \quad (3.1)$$

Here, the subscript of x_1's equation is omitted for convenience.

Let $\bar{x}$ be an equilibrium of (3.1). Then $\bar{x}$ satisfies

$$\bar{x}[(2(1-K)e^{-\gamma\tau} - 1)\beta(\bar{x}) - \delta] = 0.$$

Denote

$$\xi := [2(1-K)e^{-\gamma\tau} - 1]\beta(0) - \delta. \quad (3.2)$$

In the following, ξ will be regarded as a parameter. Obviously, zero is always an equilibrium point and corresponds to the extinction of the population. Besides, (3.1) has a positive steady-state denoted by x^* when $\xi > 0$, and 0 as its unique equilibrium when $\xi \leq 0$, which is ensured by the monotonicity of $\beta(x)$.

It is possible and reasonable that inequality $\xi \leq 0$ is satisfied. For example, the mortality rate δ or γ is large, or the introduction rate $\beta(0)$ is small, which in fact describes a situation that mortality has advantage over cell renewal for immature cells. From assumptions (H1)–(H3), this situation is valid for all cells and thus the extinction becomes unavoidable.

The corresponding characteristic equation of Eq. (3.1) at $\bar{x}$ is given by,

$$\Delta(\lambda, \tau, \bar{x}) \overset{def}{=} \lambda + [\delta + \alpha(\bar{x})] - 2(1-K)e^{-\gamma\tau}\alpha(\bar{x})e^{-\lambda\tau} = 0 \quad (3.3)$$

with $\alpha(\bar{x}) := \frac{d(\beta(\bar{x})\bar{x})}{dx} = \beta'(\bar{x})\bar{x} + \beta(\bar{x})$.

We say that $\bar{x} = 0$ is globally asymptotically stable if it is stable and

$$\lim_{t\to\infty} x(0, \varphi)(t) = 0$$

for all $\varphi \in C^+ := C([-\tau, 0], \mathbb{R}^+)$ with $\mathbb{R}^+ := \{x \in \mathbb{R} : x \geq 0\}$.

Theorem 3.1. *If $\xi < 0$, then $\bar{x} = 0$ is globally asymptotically stable. If $\xi > 0$, then $\bar{x} = 0$ is unstable, where ξ is defined by (3.2).*

Proof. When $\bar{x} = 0$, (3.3) turns into

$$\Delta(\lambda, \tau, 0) = \lambda + \delta - [2(1-K)e^{-\gamma\tau}e^{-\lambda\tau} - 1]\beta(0) = 0. \quad (3.4)$$

Hence, the last conclusion follows from $\Delta(0, \tau, 0) = -\xi < 0$ and $\Delta(\infty, \tau, 0) = \infty$.

To prove the first assertion on local stability, notice that when $\xi < 0$, $\Delta(\lambda, \tau, 0) = 0$ is equivalent to

$$[\tau\lambda + \tau(\delta + \beta(0))]e^{\tau\lambda} - 2\tau(1-K)e^{-\gamma\tau}\beta(0) = 0.$$

Then, we use the sufficient and necessary conditions given by Hayes [35] regarding the distribution of all roots of (3.4). In fact, note that $a := \tau(\delta+\beta(0)) > 0$ and $b := -2\tau(1-K)e^{-\gamma\tau}\beta(0) < 0$, it follows that $a + b = -\tau\xi > 0$ and thus $b \in (-a, 0)$. Let us check the condition $b < \eta\sin\eta - a\cos\eta$, where η is the root of $\eta = -a\tan\eta$, $0 < \eta < \pi$.

Suppose, by contradiction, that $b \geq \eta\sin\eta - a\cos\eta$. Then from the definition of η, we obtain

$$b \geq -\frac{a}{\cos\eta}.$$

Since $a > 0$ and $b \in (-a, 0)$, it is deduced that $\cos\eta \geq 0$ and thus $\eta \in (0, \frac{\pi}{2})$. Consequently, $\tan\eta > 0$ and

$$\eta > 0 > -a\tan\eta.$$

This contradicts the definition of η, so we have verified our inequality.

Finally, to show the global asymptotical stability, we consider the following function:

$$V(\varphi) = \varphi(0) + 2(1-K)e^{-\gamma\tau}\int_{-\tau}^{0}\beta(\varphi(\theta))\varphi(\theta)d\theta$$

with $\varphi \in C^+$. The derivative of V along the solutions of (3.1) is given by

$$\frac{dV}{dt} = \dot{x}(t) + 2(1-K)e^{-\gamma\tau}\beta(x(t))x(t) - 2(1-K)e^{-\gamma\tau}\beta(x(t-\tau))x(t-\tau).$$

Using (3.1), it follows that

$$\dot{V}(\varphi) = [(2(1-K)e^{-\gamma\tau} - 1)\beta(\varphi(0)) - \delta]\varphi(0) \leq \max\{-\delta, \xi\} \cdot \varphi(0).$$

Therefore, when $\xi < 0$, $\dot{V}(\varphi) \leq 0$ for any $\varphi \in C^+$. Thus, V is a Lyapunov function on C^+. Moreover, $\dot{V}(\varphi) = 0$ is equivalent to $\varphi(0) = 0$. Set

$$S = \{\varphi \in C^+ : \varphi(0) = 0\},$$

and let $M \in S$ be the largest invariant set in S of (3.1). Then M is nonempty since $0 \in M$. In fact, we have $M = \{0\}$. Otherwise, there exists a $\varphi \in M$ so that $\varphi \neq 0$. This means that $\varphi(0) = 0$ and there is a $\theta_0 \in [-\tau, 0)$ such that $\varphi(\theta_0) > 0$. By the invariance of M we have that $x_t(0, \varphi) \in M$ for every $t \geq 0$. From the proof of Proposition 2.2, we know that $x(0, \varphi)(t) > 0$ when $t > \tau + \theta_0$. This implies that $x_t(0, \varphi)$ with $t > \tau + \theta_0$ does not belong to M. This contradiction proves the fact that $M = \{0\}$. Therefore, solutions of (3.1) with nonnegative initial conditions ultimately tend to zero as time increases by using the Lasalle invariance principle. The proof is complete. □

Theorem 3.1 shows that $\xi = 0$ a critical value for the stability of $\bar{x} = 0$. Clearly, $\lambda = 0$ is a simple root of (3.4) with $\xi = 0$ from

$$\frac{d\Delta(0, \tau, 0)}{d\lambda} = 1 + 2(1-K)\tau\beta(0)e^{-\gamma\tau} > 0.$$

The following result is to describe the stability of zero equilibrium when $\xi = 0$.

Theorem 3.2. *If $\xi = 0$, then $\bar{x} = 0$ is unstable.*

Proof. From Theorem 3.1 we know that all roots of (3.4) with $\xi = 0$, except $\lambda = 0$, have negative real parts. In order to investigate the stability of $\bar{x} = 0$ for Eq. (3.1), we employ the center manifold theory and normal form method. Here, we shall use the method of computing normal forms for FDEs introduced by Faria et al. [36].

Following the same algorithms as those in [36], let $\Lambda = \{0\}$ and $B = 0$. Clearly, the non-resonance conditions relative to Λ are satisfied. Therefore, there exists a 1-dimensional ODE which governs the dynamics of Eq. (3.1) near the origin (see [15]).

Firstly, Eq. (3.1) can be written in $C := C([-\tau, 0], \mathbb{R})$ of the form

$$\frac{d}{dt}x(t) = L(x_t) + F(x_t), \tag{3.5}$$

where,

$$L(\varphi) = -[\delta + \beta(0)]\varphi(0) + 2(1-K)\beta(0)e^{-\gamma\tau}\varphi(-\tau)$$

and

$$F(\varphi) = -\beta'(0)[\varphi^2(0) - 2(1-K)e^{-\gamma\tau}\varphi^2(-\tau)] - \frac{1}{2}\beta''(0)[\varphi^3(0) - 2(1-K)e^{-\gamma\tau}\varphi^3(-\tau)] + O(\varphi^4(0), \varphi^4(-\tau))$$

for any $\varphi \in C$.

Choosing

$$\eta(\theta) = \begin{cases} 0, & \theta = -\tau \text{ or } 0 \\ \delta + \beta(0), & \theta \in (-\tau, 0), \end{cases}$$

we obtain

$$L(\varphi) = \int_{-\tau}^{0} d\eta(\theta)\varphi(\theta).$$

Using the formal adjoint theory for FDEs (see [33]), we decompose C by Λ as $C = P \oplus Q$, where $P = \text{span}\{\Phi(\theta)\}$ with $\Phi(\theta) = 1$ being the center space for $\frac{d}{dt}x_t = L(x_t)$. Choose a basis Ψ for the adjoint space P^* such that $\langle\Psi, \Phi\rangle = 1$, where $\langle\cdot, \cdot\rangle$ is the bilinear form on $C^* \times C$ defined by

$$\langle\psi, \varphi\rangle = \psi(0)\varphi(0) - \int_{-\tau}^{0}\int_{\theta=0}^{s}\psi(\theta - s)d\eta(s)\varphi(\theta)d\theta.$$

Thus, $\Psi(s) = (1 + 2\tau(1-K)\beta(0)e^{-\gamma\tau})^{-1}$.

Taking the enlarged phase space

$$BC = \left\{\varphi : [-\tau, 0] \to \mathbb{C}, \varphi \text{ is continuous on } [-\tau, 0) \text{ and } \lim_{\theta\to 0}\varphi(\theta) \text{ exists}\right\},$$

we obtain the abstract differential equation with the form

$$\frac{d}{dt}x_t = Ax_t + X_0F(x_t). \tag{3.6}$$

Here, for any $\varphi \in C^1([-\tau, 0], \mathbb{R})$,

$$A\varphi = \dot{\varphi}(\theta) + X_0[L(\varphi) - \dot{\varphi}(0)],$$

and $X_0 = X_0(\theta)$ is given by

$$X_0(\theta) = \begin{cases} I, & \theta = 0 \\ 0, & \theta \in [-\tau, 0). \end{cases}$$

Consider the projection

$$\pi : BC \mapsto P, \qquad \pi(\varphi + X_0\alpha) = \Phi[\langle\Psi, \varphi\rangle + \psi(0)\alpha],$$

which leads to the decomposition $BC = P \oplus \text{Ker}\,\pi$. Then, using the decomposition $x_t = \Phi x(t) + y$, $x(t) \in \mathbb{C}$, $y = y(\theta) \in Q^1$, we decompose (3.6) as

$$\begin{aligned} \dot{x} &= Bx + \Psi(0)F(\Phi x + y), \\ \dot{y} &= A_{Q^1}y + (I - \pi)X_0F(\Phi x + y). \end{aligned} \tag{3.7}$$

Note that

$$\Psi(0)F(\Phi x + y) = \frac{-\beta'(0)}{1 + 2\tau(1-K)\beta(0)e^{-\gamma\tau}} \times \left[(x + y(0))^2 - 2(1-K)e^{-\gamma\tau}(x + y(-\tau))^2\right] + O(3). \tag{3.8}$$

Therefore, the locally invariant manifold for Eq. (3.1) tangent to P at zero satisfies $y(\theta) = 0$ and the flow on this manifold is given by the following 1-dimensional ODE

$$\begin{aligned} \dot{x} &= \frac{\beta'(0)}{1 + 2\tau(1-K)\beta(0)e^{-\gamma\tau}}\left[2(1-K)e^{-\gamma\tau} - 1\right]x^2 + O(3) \\ &= \frac{\beta'(0)}{1 + 2\tau(1-K)\beta(0)e^{-\gamma\tau}} \cdot \frac{\delta}{\beta(0)}x^2 + O(3). \end{aligned} \tag{3.9}$$

Clearly, when $\xi = 0$, the zero solution of Eq. (3.9) is unstable, so is the zero solution of Eq. (3.1). The proof is completed. □

4. Hopf bifurcation analysis

From the above analysis, it is known that there exists a positive equilibrium point x^* of (3.1) bifurcated from zero when $\xi > 0$ and $x = 0$ becomes unstable. In this section, we are going to investigate the stability of x^* and show that it can be destabilized via Hopf bifurcation. The time delay τ will be used as a bifurcation parameter.

In this section, we always assume $\xi > 0$. Linearizing (3.1) around x^*, we obtain the corresponding characteristic equation

$$\Delta(\lambda, \tau, x^*) = \lambda + [\delta + \alpha(x^*)] - 2(1-K)e^{-\gamma\tau}\alpha(x^*)e^{-\lambda\tau} = 0. \tag{4.1}$$

Note that some of these coefficients depend on the time delay τ. We rewrite Eq. (4.1) in the general form

$$P(\lambda,\tau)+Q(\lambda,\tau)\mathrm{e}^{-\lambda\tau}=0, \tag{4.2}$$

where

$$P(\lambda,\tau):=\lambda+\delta+\alpha(x^*),\qquad Q(\lambda,\tau):=-2(1-K)\mathrm{e}^{-\gamma\tau}\alpha(x^*). \tag{4.3}$$

When $\tau=0$,

$$\Delta(\lambda,0,x^*)=\lambda-(1-2K)\beta'(x^*)x^*=0.$$

This implies that $\lambda=(1-2K)\beta'(x^*)x^*$. Thus the following conclusion holds.

Proposition 4.1. *The positive equilibrium x^* of (3.1) with $\tau=0$ is asymptotically stable if $K<\frac{1}{2}$.*

Proposition 4.1 tells that, at the beginning of HSC's division, the pluripotent stem cell population stays at a stable state if K is less than $\frac{1}{2}$. However, the assumption $\tau=0$ seems to be not biologically realistic. Now we assume $\tau>0$ and regard it as a parameter to obtain finer results on the stability of the positive equilibrium of (3.1). Here, we use the method introduced by Beretta and Kuang [28], which gives the existence of purely imaginary roots of a characteristic equation with delay dependant coefficients. We discuss the existence of purely imaginary roots $\lambda=\mathrm{i}\omega$ ($\omega\in\mathbb{R}^+$) to Eq. (4.2) which takes the form of a first-degree exponential polynomial equation in λ, with the coefficients of P and Q depending on τ.

In order to apply the geometrical criterion due to Beretta and Kuang [28], we need to verify the following properties for $\tau\ge 0$.

(i) $P(0,\tau)+Q(0,\tau)\neq 0$;
(ii) $P(\mathrm{i}\omega,\tau)+Q(\mathrm{i}\omega,\tau)\neq 0$;
(iii) $\limsup\{|\frac{Q(\lambda,\tau)}{P(\lambda,\tau)}|;|\lambda|\to\infty,\operatorname{Re}\lambda\ge 0\}<1$;
(iv) $F(\omega,\tau):=|P(\mathrm{i}\omega,\tau)|^2-|Q(\mathrm{i}\omega,\tau)|^2$ has a finite number of zeros;
(v) Each positive root $\omega(\tau)$ of $F(\omega,\tau)=0$ is continuous and differentiable in τ whenever it exists.

Let $\tau\in[0,\tau_{\max})$, given the fact that

$$P(0,\tau)+Q(0,\tau)=-[2(1-K)\mathrm{e}^{-\gamma\tau}-1]\beta'(x^*)x^*>0$$

and

$$P(\mathrm{i}\omega,\tau)+Q(\mathrm{i}\omega,\tau)=\mathrm{i}\omega-[2(1-K)\mathrm{e}^{-\gamma\tau}-1]\beta'(x^*)x^*,$$

(i) and (ii) are satisfied.

From (4.3) we know that

$$\lim_{|\lambda|\to\infty}\left|\frac{Q(\lambda,\tau)}{P(\lambda,\tau)}\right|=0.$$

Therefore (iii) follows.

Let F be defined as in (iv) with the following expression

$$F(\omega,\tau)=\omega^2+(\delta+\alpha(x^*))^2-(2(1-K)\alpha(x^*)\mathrm{e}^{-\gamma\tau})^2.$$

It is obvious that property (iv) is satisfied, and by the Implicit Function Theorem, (v) is also satisfied.

Now let $\lambda=\mathrm{i}\omega$ ($\omega>0$) be a root of Eq. (4.2). Substituting it into Eq. (4.2) and separating the real and imaginary parts, we have

$$\sin\omega\tau=-\frac{\omega}{2(1-K)\alpha(x^*)\mathrm{e}^{-\gamma\tau}}\quad\text{and}\quad \cos\omega\tau=\frac{\delta+\alpha(x^*)}{2(1-K)\alpha(x^*)\mathrm{e}^{-\gamma\tau}}. \tag{4.4}$$

This deduces

$$F(\omega,\tau)=0.$$

Observe that

$$[2(1-K)\mathrm{e}^{-\gamma\tau}-1]\alpha(x^*)-\delta=[2(1-K)\mathrm{e}^{-\gamma\tau}-1]\beta'(x^*)x^*<0.$$

For convenience, we further make the following hypothesis:

(P1) $[2(1-K)\mathrm{e}^{-\gamma\tau}+1]\alpha(x^*)+\delta<0$.

Then $F(\omega,\tau)=0$ has a unique positive real root given by

$$\omega^*=\omega^*(\tau):=\sqrt{(2(1-K)\alpha(x^*)\mathrm{e}^{-\gamma\tau})^2-(\delta+\alpha(x^*))^2}$$

if and only if (P1) is satisfied.

Set

$$I=\{\tau\mid\tau\in\mathbb{R}_0^+\text{ satisfies (P1)}\}.$$

Assume that I is nonempty. Then for $\tau\in I$, there exists a unique $\omega^*=\omega^*(\tau)>0$ such that $F(\omega^*,\tau)=0$. In the sequel, let $\theta(\tau)\in[0,2\pi]$ be defined for $\tau\in I$ by

$$\sin\theta(\tau)=-\frac{\omega^*(\tau)}{2(1-K)\alpha(x^*)\mathrm{e}^{-\gamma\tau}}\quad\text{and}\quad \cos\theta(\tau)=\frac{\delta+\alpha(x^*)}{2(1-K)\alpha(x^*)\mathrm{e}^{-\gamma\tau}} \tag{4.5}$$

with $\sin\theta(\tau)\ge 0$ by the fact that (P1) implies $\alpha(x^*)<0$. From the above definitions, it follows that $\theta(\tau)$ is well and uniquely defined for all $\tau\in I$.

One can check that $\mathrm{i}\omega^*$ ($\omega^*>0$) is a purely imaginary root of (4.2) if and only if τ^* is a root of the function S_n, defined by

$$S_n(\tau)=\tau-\frac{\theta(\tau)+2n\pi}{\omega^*(\tau)},\quad \tau\in I,\ \text{with } n\in\mathbb{N}. \tag{4.6}$$

Obviously, $S_n(0^+)<0$. Observing that when τ is close to the right border of I, $\omega^*(\tau)\to 0$ as well as $\sin\theta(\tau)\to 0$ and $\cos\theta(\tau)\to -1$ imply $\theta(\tau)\to\pi$, therefore, $S_n(\tau)\to-\infty$.

The following is the result introduced by Beretta and Kuang [28].

Lemma 4.2. *Assume that the function $S_n(\tau)$ has a positive root $\tau^*\in I$ for some $n\in\mathbb{N}$, then a pair of simple purely imaginary roots $\pm\mathrm{i}\omega^*(\tau^*)$ of (4.2) exists at $\tau=\tau^*$ and*

$$\operatorname{Sign}\left\{\left.\frac{\mathrm{d}\operatorname{Re}\lambda(\tau)}{\mathrm{d}\tau}\right|_{\lambda=\mathrm{i}\omega^*(\tau^*)}\right\}=\operatorname{Sign}\left\{\frac{\partial F}{\partial\omega^*}(\omega^*(\tau^*),\tau^*)\right\}\times\operatorname{Sign}\left\{\left.\frac{\mathrm{d}S_n(\tau)}{\mathrm{d}\tau}\right|_{\tau=\tau^*}\right\}. \tag{4.7}$$

Since $\frac{\partial F}{\partial\omega^*}(\omega^*,\tau)=2\omega^*$, condition (4.7) is equivalent to

$$\delta(\tau^*)=\operatorname{Sign}\left\{\left.\frac{\mathrm{d}\operatorname{Re}\lambda(\tau)}{\mathrm{d}\tau}\right|_{\lambda=\mathrm{i}\omega^*(\tau^*)}\right\}=\operatorname{Sign}\left\{\left.\frac{\mathrm{d}S_n(\tau)}{\mathrm{d}\tau}\right|\tau=\tau^*\right\}.$$

Therefore, this pair of simple conjugate purely imaginary roots crosses the imaginary axis from left to right if $\delta(\tau^*)>0$ and from right to left if $\delta(\tau^*)<0$.

It can be easily observed that, for all $\tau\in I$, $S_n(\tau)>S_{n+1}(\tau)$ with $n\in\mathbb{N}$. Therefore, if S_0 has no zero in I, then for any $n\in\mathbb{N}$, S_n have no zeros in I, and if $S_n(\tau)$, $n\ge 1$, has positive zeros for some $n\in\mathbb{N}^+$, then there exists at least one zero $\tilde{\tau}\in I$ satisfying $S'_{\tilde{n}}(\tilde{\tau})>0$.

Remark 4.3. Denote the zeros of S_n, if they exist, by τ_{n_j} for $n\in\mathbb{N}$. In what follows, we always assume $S'_n(\tau_{n_j})\neq 0$. Rearrange these roots in the set

$$J:=\{\tau_0,\tau_1,\ldots,\tau_m\}\quad\text{with } \tau_j<\tau_{j+1}.$$

Applying Proposition 4.1 and Lemma 4.2 as well as Corollary 2.4 in [14], we can draw the conclusion: If $\xi>0$ and $K<\frac{1}{2}$, then all roots of Eq. (4.1) have negative real parts when $\tau\in[0,\tau_0)$ and at least a pair of roots has positive real parts when $\tau\in(\tau_0,\tau_m)$. Furthermore, all other roots of Eq. (4.1), except a pair of purely imaginary roots, have negative real parts when $\tau=\tau_0$.

Now we can state the following theorem on the existence of a Hopf bifurcation at the positive steady-state.

Theorem 4.4. *Assume $\xi > 0$. Then*

(i) *If either I is empty or the function $S_0(\tau)$ has no positive zero in I ($\neq \emptyset$), then for all $\tau \geq 0$, the steady-state x^* is asymptotically stable (unstable) when $K < \frac{1}{2}$ ($K > \frac{1}{2}$).*

(ii) *If $J \neq \emptyset$, then the equilibrium x^* is asymptotically stable (unstable) for $0 \leq \tau < \tau_0$ when $K < \frac{1}{2}$ ($K > \frac{1}{2}$) and unstable for τ lies between τ_0 and τ_m, with a Hopf bifurcation occurring at x^* when $\tau = \tau_j \in J$.*

Theorem 4.4 gives some sufficient conditions to ensure that Eq. (3.1) undergoes a Hopf bifurcation at x^*. Next, under the conditions of Theorem 4.4(ii), we shall use the center manifold and normal form theories presented by Hassard et al. [16] to study the direction of Hopf bifurcation and the stability of the bifurcating periodic solutions from x^*. As the details are given in the Appendix, we summarize the results in the following theorem and corollary.

Theorem 4.5. *Assume that the conditions ensuring that Hopf bifurcation at x^* occurs in Theorem 4.4 are fulfilled. Then when $\tau = \tau_j \in J$, the periodic solutions bifurcated from x^* are asymptotically stable (unstable) on the center manifold if $\mathrm{Re}(c_1(0)) < 0$ (> 0). In particular, if $\xi > 0$ and $K < \frac{1}{2}$, then the bifurcating periodic solution at the first bifurcation value $\tau = \tau_0$ is stable (unstable) if $\mathrm{Re}(c_1(0)) < 0$ (> 0). Here $c_1(0)$ is derived in the Appendix.*

Corollary 4.6. *When $\tau = \tau_0$, x^* is stable (unstable) if* $\mathrm{Re}(c_1(0)) < 0$ (> 0).

Proof. We have known that the normal form of the restriction of Eq. (3.1) with $\tau = \tau_0$ on the center manifold is given by

$$\dot{z}(t) = \mathrm{i}\omega^* \tau_0 z + c_1(0) z^2 \bar{z} + \cdots. \tag{4.8}$$

It is not difficult to obtain that the zero solution of Eq. (4.8) is stable (unstable) via Lyapunov's second method, and hence so is x^*. □

Remark 4.7. See the Appendix for and explanation of $c_1(0)$ appeared in Theorem 4.5 and Corollary 4.6.

In [1], Mackey gave a set of parameter values for a normal human body production: $\delta = 0.05d^{-1}$, $\beta(0) = 1.77d^{-1}$ and $n = 3$ for β in the Hill function referred before. According to these data, we choose the Hill function with $n_i = 3$ and $\theta_{n_i} = 1$ as the nonlinear introduction functions β_i (here and in all simulations of this paper) and set $\gamma_1 = 0.02d^{-1}$, $K_1 = 0.05$, $\delta_1 = 0.05d^{-1}$ and $\beta_1^0 = 1.77d^{-1}$. Under this parameter set, $\xi > 0$ is equivalent to $\tau_1 \in [0, 30.7)$. From Fig. 4.1, we obtain the existence interval $I = [0, 29.996)$ of $S_n(\tau)$. Accordingly, the pictures of S_n on I can be drawn clearly. It follows from Fig. 4.2 that there exists 4 roots denoted by τ_j ($j = 0, 1, 2, 3$) for S_i ($i = 0, 1$) on I, and $S_i'(\tau_j) \neq 0$. Therefore, the unique positive equilibrium x^* is asymptotically stable when $\tau \in [0, 5.6149)$ and becomes unstable when $\tau \in (5.6149, 29.9726)$, with Hopf bifurcation takes place when $\tau = \tau_j$ ($j = 0, 1, 2, 3$).

By using the algorithm given in the Appendix, we can obtain $c_1^j(0)$ corresponding to $\tau_j, j = 0, 1, 2, 3$, as $c_1^0(0) \approx -0.0566 - 0.3849\mathrm{i}$, $c_1^1(0) \approx -0.6941 - 0.2016\mathrm{i}$, $c_1^2(0) \approx -13.9347 + 5.1485\mathrm{i}$ and $c_1^3(0) \approx -1250.5 - 1250.8\mathrm{i}$. This implies that the direction of Hopf bifurcation is forward at τ_0 and τ_1 and backward at τ_2 and τ_3, respectively; The bifurcating periodic solutions at $\tau_j, j = 0, 1, 2, 3$ on the center manifold are all stable. Particularly, the bifurcating periodic solutions at $\tau_j, j = 0, 3$ are stable in phase space.

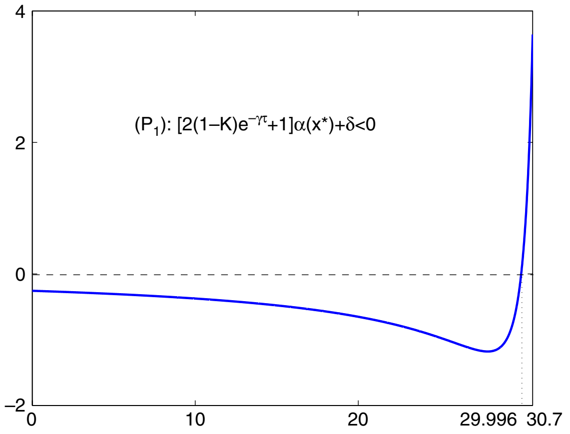

Fig. 4.1. The graph of the existence interval I for S_n given in condition (P1).

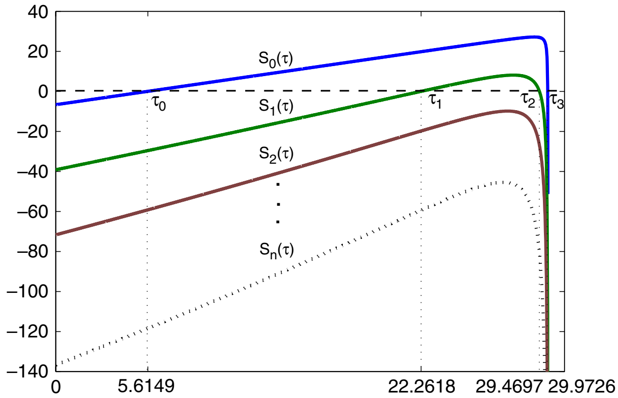

Fig. 4.2. The graphs of S_n on I: S_n has no zeros on I if $n \geq 2$.

Remark 4.8. The above analysis concentrates on the existence of Hopf bifurcation at the positive equilibrium x^*. In fact, using a similar process, it can be obtained that when $\xi > 0$, there exists

$$J^0 = \{\tau^j > 0 : \tau^j \text{ is the Hopf bifurcation point of (3.1) at } 0\}, \quad \text{with } \tau^j < \tau^{j+1},$$

here, τ^j is the zero of $S_n^0(\tau)$ on $I^0 := \{\tau : \xi > 0\}$ with

$$S_n^0(\tau) := \tau - \frac{\theta^0(\tau) + 2n\pi}{\omega^0(\tau)}, \quad \tau \in I, \; n \in \mathbb{N},$$

where

$$\omega^0(\tau) := \sqrt{\xi \cdot \left[(2(1-K)\mathrm{e}^{-\gamma\tau} + 1)\beta(0) + \delta\right]}$$

and $\theta^0(\tau) \in (\frac{3}{2}\pi, 2\pi)$ is defined by

$$\sin\theta^0(\tau) = -\frac{\omega^0(\tau)}{2(1-K)\beta(0)\mathrm{e}^{-\gamma\tau}} < 0 \quad \text{and} \quad \cos\theta^0(\tau) = \frac{\delta + \beta(0)}{2(1-K)\beta(0)\mathrm{e}^{-\gamma\tau}} > 0. \tag{4.9}$$

5. Global Hopf bifurcation analysis

Assume $\xi > 0$ and $J \neq \emptyset$. Then from Theorem 4.4 we know that Hopf bifurcation occurs at x^* and nontrivial periodic solutions exist when τ is near τ_j, $\tau_j \in J$. Denote

$$J_0 := \{\tau \in J : S_0(\tau) = 0\}$$

and

$$J_+ := J - J_0.$$

Assume further that $J_+ \neq \emptyset$. In this section, we will discuss the global continuation of periodic solutions bifurcated from the point (x^*, τ_j) $(\tau_j \in J_+)$ as the bifurcation parameter τ varies.

For the sake of convenience, we copy Eq. (3.1) as follows:

$$\frac{dx}{dt}(t) = -[\delta + \beta(x(t))]x(t) + 2(1-K)e^{-\gamma\tau}\beta(x(t-\tau))x(t-\tau).$$

Adopting the technique of Wu [17], we will show that some Hopf bifurcation branches through (x^*, τ_j) for some $\tau_j \in J_+$ can be continued to a larger extension. We first introduce the following notations:

$$X = C([-1, 0], \mathbb{R}),$$
$$\Sigma = \text{Cl}\{(x, \tau, T) : x \text{ is a } T\text{-periodic solution of (3.1)}\} \subset X \times \mathbb{R}_+ \times \mathbb{R}_+,$$
$$N = \{(\hat{x}, \tau, T) : (2(1-K)e^{-\gamma\tau} - 1)\beta(\hat{x}) = \delta \text{ or } \hat{x} = 0\}.$$

Let $C(x^*, \tau_j, 2\pi/\omega_j^*)$ be the connected component of $(x^*, \tau_j, 2\pi/\omega_j^*)$ in Σ, and denote $\text{Proj}_\tau(x^*, \tau_j, 2\pi/\omega_j^*)$ its projection on τ component, where $\omega_j^* = \omega^*(\tau_j)$ and $\tau_j \in J_+$ is defined as before, and $\pm i\omega_j^*$ is a pair of purely imaginary roots of Eq. (4.1) with $\tau = \tau_j$. By Theorem 4.4, we know that $C(x^*, \tau_j, 2\pi/\omega_j^*)$ is nonempty.

Lemma 5.1. *All bifurcating periodic solutions of (3.1) from Hopf bifurcation are positive if $\tau \in \text{Proj}_\tau(x^*, \tau_j, 2\pi/\omega_j^*) \cap (A_j, B_j)$. Here τ_j satisfies $A_j < \tau_j < B_j$, A_j and B_j are defined respectively as:*

$$A_j \overset{def}{=} \begin{cases} \max\{\tau^j \in J^0 : \tau^j < \tau_j\}, & J^0 \neq \emptyset \\ 0, & \textit{else} \end{cases}$$

and

$$B_j \overset{def}{=} \begin{cases} \min\{\tau^j \in J^0 : \tau^j > \tau_j\}, & J^0 \neq \emptyset \\ \sup_{\tau \in I} I, & \textit{else}, \end{cases}$$

where τ^j and J^0 are defined in Remark 4.8.

Proof. For each $\tau \in \text{Proj}_\tau(x^*, \tau_j, 2\pi/\omega_j^*) \cap (A_j, B_j)$, denote $X(t, \tau)$ the corresponding nontrivial periodic solution, with its minimum value $\inf_{t\in\mathbb{R}^+} X(t, \tau)$. From the fact that the periodic solutions bifurcated from the positive equilibrium are continuous with respect to τ and $\lim_{\tau\to\tau_j} X(t, \tau) = x^*$ uniformly in $t \in \mathbb{R}$, we have that $\inf_{t\in\mathbb{R}} X(t, \tau)$ is continuous with respect τ, and the bifurcating periodic solutions are positive when τ varies in a small neighborhood of τ_j. To prove the positivity, it is equivalent to proving $\inf_{t\in\mathbb{R}} X(t, \tau) > 0$ when $\tau \in \text{Proj}_\tau(x^*, \tau_j, 2\pi/\omega_j^*) \cap (A_j, B_j)$. Otherwise, there exists a $\tau^* \in \text{Proj}_\tau(x^*, \tau_j, 2\pi/\omega_j^*) \cap (A_j, B_j)$ such that $\inf_{t\in\mathbb{R}} X(t, \tau^*) = 0$. Without loss of generality, we assume that $\tau^* > \tau_j$ and $\inf_{t\in\mathbb{R}^+} X(t, \tau) > 0$ when $\tau \in (\tau_j, \tau^*)$. Similar to the proof of Proposition 2.2 we can obtain $X(t, \tau^*) \equiv 0$. This implies that $(0, \tau^*, 2\pi/\omega)$ is a center of (3.1) for some $\omega > 0$, and hence, $\tau^* \in J^0$. This contradicts the fact that $\tau^* \in \text{Proj}_\tau(x^*, \tau_j, 2\pi/\omega_j^*) \cap (A_j, B_j)$ and completes the proof. $\square$

Remark 5.2. The motivation of restricting τ on $\text{Proj}_\tau(x^*, \tau_j, 2\pi/\omega_j^*) \cap (A_j, B_j)$ is that we can exclude $(0, \tau^j, 2\pi/\omega^0)$ from the branch $C(x^*, \tau_j, 2\pi/\omega_j^*)$.

Lemma 5.3. *All positive periodic solutions of (3.1) are uniformly bounded under the assumption:*

(P2) *$\beta(x)x$ is bounded.*

More precisely, if there exists a $B > 0$ such that $\beta(x)x < B$, then any positive periodic solution $x(t)$ satisfies $0 < x(t) < \frac{2B}{\delta}$.

Proof. Let $y(t)$ be a positive periodic solution to (3.1) with $y(t_1) = M$ be its maximum. Then $\dot{y}(t_1) = 0$. Therefore,

$$M = \frac{1}{\delta}[-\beta(M)M + 2(1-K)e^{-\gamma\tau}\beta(y(t_1-\tau))y(t_1-\tau)].$$

It follows that

$$M < \frac{2B}{\delta}$$

from $\beta(x)x < B$. The proof is complete. $\square$

Remark 5.4. Condition (P2) is biologically reasonable and can be easily satisfied. For example, when $\beta(x)$ is the Hill function defined by (2.2) with $n > 1$.

Lemma 5.5. *Eq. (3.1) has no non-constant periodic solution of period τ.*

Proof. Eq. (3.1) has no non-constant periodic solution of period τ is equivalent to the fact that Eq. (3.1) with $\tau = 0$ has no non-constant periodic solution. It is well known that a first order autonomous ODE has no non-constant periodic solutions. Eq. (3.1) with $\tau = 0$ is a first order autonomous ODE, which proves the lemma. $\square$

For convenience, we introduce the following notations:

$$\underline{A}_j = \max\{\tau_i | \tau_i \in J^0 \cup J_+, \tau_i < \tau_j \in J_+\}$$

and

$$\underline{B}_j = \min\{\tau_i | \tau_i \in J^0 \cup J_+, \tau_i > \tau_j \in J_+\}.$$

Obviously, $\underline{A}_j$ and $\underline{B}_j$ are both accessible by the definition of J_+. Up to now, we have prepared sufficiently to state the following global Hopf bifurcation result.

Theorem 5.6. *Assume that $\xi > 0$ and (P1)–(P2) are fulfilled. Then for each $\tau_j \in J_+$, there exists $\tau_i \in J^0 \cup J_+ - \{\tau_j\}$, such that Eq. (3.1) has at least one positive periodic solution for τ varies between τ_i and τ_j.*

Proof. First note that

$$F(x^\tau, \tau, T) := -[\delta + \beta(x(t))]x(t) + 2(1-K)e^{-\gamma\tau}\beta(x(t-\tau))x(t-\tau)$$

satisfies the hypotheses (A1)–(A3) in [17, p. 4813] with

$$(\hat{x}_0, \alpha_0, p_0) = \left(x^*, \tau_j, \frac{2\pi}{\omega_j^*}\right),$$

$$\Delta_{\left(x^*, \tau_j, \frac{2\pi}{\omega_j^*}\right)}(\lambda) = \lambda + [\delta + \alpha(x^*)] - 2(1-K)e^{-\gamma\tau}\alpha(x^*)e^{-\lambda\tau}.$$

It can be verified that for any $\tau_j \in J_+$, the stationary points $(x^*, \tau_j, 2\pi/\omega_j^*)$ of (3.1) are nonsingular and isolated centers (see [17]) under the assumption $\xi > 0$.

By Lemma 4.2 and $S_n'(\tau_j) \neq 0$, there exist constants $\epsilon > 0$ and $\delta > 0$ as well as a smooth curve $\lambda : (\tau_j - \delta, \tau_j + \delta) \to \mathbb{C}$ such that,

$$\Delta(\lambda(\tau)) = \Delta_{\left(x^*, \tau_j, \frac{2\pi}{\omega_j^*}\right)}(\lambda(\tau)) = 0, \quad |\lambda(\tau) - i\omega_j^*| < \epsilon,$$

for all $\tau \in [\tau_j - \delta, \tau_j + \delta]$, and

$$\lambda(\tau_j) = i\omega_j^*, \qquad \left.\frac{d\text{Re}(\lambda(\tau))}{d\tau}\right|_{\tau=\tau_j} \neq 0.$$

Denote $T_j = \frac{2\pi}{\omega_j^*}$ and let

$$\Omega_\epsilon = \left\{(u, T) : 0 < u < \epsilon, |T - T_j| < \epsilon\right\}.$$

Clearly, if $|\tau - \tau_j| \leq \delta$ and $(u, T) \in \Omega_\epsilon$ such that $\Delta_{(\hat{x}, \tau, T)}(u + i\frac{2\pi}{T}) = 0$, then $\tau = \tau_j$, $u = 0$ and $T = T_j$, which verify the assumption (A4) in Wu [17]. Moreover, if we put

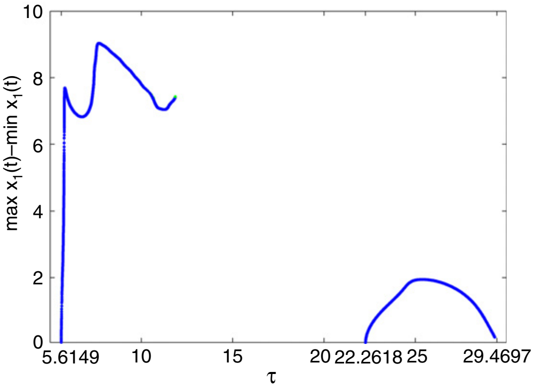

Fig. 5.1. Hopf bifurcation branches starting from τ_0, τ_1 and τ_2 on the (τ, d)-plane. In particular, the branch connects τ_1 and τ_2, where $d = \max x_1(t) - \min x_1(t)$.

$$H^{\pm}\left(x^*, \tau_j, \frac{2\pi}{\omega_j^*}\right)(u, T) = \Delta_{(x^*,\tau_j\pm\delta,T)}\left(u + \mathrm{i}\frac{2\pi}{T}\right),$$

then we have the crossing number

$$\begin{aligned}\gamma_1\left(x^*, \tau_j, \frac{2\pi}{\omega_j^*}\right) &= \deg_B\left(H^-\left(x^*, \tau_j, \frac{2\pi}{\omega_j^*}\right), \Omega_\epsilon\right) \\ &\quad - \deg_B\left(H^+\left(x^*, \tau_j, \frac{2\pi}{\omega_j^*}\right), \Omega_\epsilon\right) \\ &= \begin{cases}-1, & S_n'(\tau_j) > 0 \\ 1, & S_n'(\tau_j) < 0.\end{cases}\end{aligned}$$

By Theorem 3.2 of Wu [17], we conclude that the connected component $C(x^*, \tau_j, 2\pi/\omega_j^*)$ through $(x^*, \tau_j, 2\pi/\omega_j^*)$ in Σ is nonempty. Meanwhile, we have by Theorem 3.3 of Wu [17] that either

(i) $C(x^*, \tau_j, \frac{2\pi}{\omega_j^*})$ is unbounded or

(ii) $C(x^*, \tau_j, \frac{2\pi}{\omega_j^*})$ is bounded, $C(x^*, \tau_j, \frac{2\pi}{\omega_j^*}) \cap N$ is finite and $\sum_{(\hat{y},\tau,T)\in C(x^*,\tau_j,\frac{2\pi}{\omega_j^*})\cap N} \gamma_1(\hat{y}, \tau, T) = 0$.

By the definition of τ_j, we know that

$$2\pi < \tau_j\omega_j^* < 2(j+1)\pi, \quad \tau_j \in J_+,$$

which implies that

$$\frac{\tau_j}{j+1} < \frac{2\pi}{\omega_j^*} < \tau_j.$$

Therefore, we have that $\frac{\tau}{j+1} < T < \tau$ if $(x, \tau, T) \in C(x^*, \tau_j, 2\pi/\omega_j^*)$. This fact and Lemma 5.5 show that the projection of $C(x^*, \tau_j, 2\pi/\omega_j^*)$ onto the T-space is bounded. On the other hand, Lemmas 5.1 and 5.3 imply that the projection of $C(x^*, \tau_j, 2\pi/\omega_j^*)$ onto the x-space is uniformly bounded for $\tau \in \mathrm{Proj}_\tau(x^*, \tau_j, 2\pi/\omega_j^*) \cap (A_j, B_j)$, where A_j and B_j are defined in Lemma 5.1. Therefore, either $[\underline{A}_j, \tau_j] \in \mathrm{Proj}_\tau(x^*, \tau_j, 2\pi/\omega_j^*)$ or $[\tau_j, \underline{B}_j] \in \mathrm{Proj}_\tau(x^*, \tau_j, 2\pi/\omega_j^*)$ holds. Otherwise, $C(x^*, \tau_j, 2\pi/\omega_j^*)$ is unbounded and $\mathrm{Proj}_\tau(x^*, \tau_j, 2\pi/\omega_j^*) \subset (A_j, B_j)$, which contradict the fact that $\{X(t, \tau)\}$ and $\{T\}$ are both uniformly bounded for $\tau \in \mathrm{Proj}_\tau(x^*, \tau_j, 2\pi/\omega_j^*) \cap (A_j, B_j)$. The proof is complete. □

With the same parameters as in Figs. 4.1–4.2, the following Fig. 5.1 describes the phenomenon stated in Theorem 5.6. We would like to mention that the graph in Fig. 5.1 is drawn by using DDE-BIFTOOL developed by Engelborghs et al. [37,38].

6. Global stability of the *n*-dimensional model

So far, we have investigated the stability and Hopf bifurcation for the first equation of (2.1). Our objectives of the upcoming two sections are to study the dynamical behavior of the original n-dimensional HSCs model, mainly focusing on the global attractivity of the zero solution and existence of positive periodic solutions.

Denote

$$\xi_i := [2(1 - K_i)\mathrm{e}^{-\gamma_i\tau_i} - 1]\beta_i(0) - \delta_i, \quad i \in I_{n-1},$$

with $\xi_1 = \xi$ defined as before. The purpose of this section is to derive sufficient conditions for the global asymptotical stability of the zero solution by embedding the asymptotically autonomous systems into autonomous semiflows. We introduce a few notations (see [22] and also [23]) as follows.

Let X be a metric space with metric d. We consider a mapping

$$\Phi : \Delta \times X \to X, \quad \Delta = \{(t, s) : t_0 \le s \le t < \infty\}.$$

Φ is called a continuous (non-autonomous) semiflow if Φ is continuous as a mapping from $\Delta \times X$ to X and

$$\begin{aligned}&\Phi(t, s, \Phi(s, r, x)) = \Phi(t, r, x), \quad t \ge s \ge r \ge t_0, \\ &\Phi(s, s, x) = x, \quad s \ge t_0, \ x \in X.\end{aligned} \tag{6.1}$$

A semiflow is called autonomous if $\Phi(t + r, s + r, x) = \Phi(t, s, x)$. Setting $\Theta(t, x) = \Phi(t + t_0, t_0, x)$ one obtains $\Theta(t - s, x) = \Phi(t, s, x)$ with an autonomous continuous semiflow $\Theta : [0, \infty) \times X \to X$, i.e., it is a continuous mapping satisfying:

$$\begin{aligned}&\Theta(t, \Theta(s, x)) = \Theta(t + s, x), \quad t, s \ge 0, \\ &\Theta(0, x) = x, \quad x \in X.\end{aligned} \tag{6.2}$$

Definition 6.1. Let Φ be a (non-autonomous) continuous semiflow and Θ an autonomous continuous semiflow on X. Then Φ is called *asymptotically autonomous* – with *limit-semiflow* Θ – if and only if

$$\Phi(t_j + s_j, s_j, x_j) \to \Theta(t, x), \quad j \to \infty,$$

or equivalently,

$$d(\Phi(t_j + s_j, s_j, x_j), \quad \Theta(t, x)) \to 0, \quad j \to \infty,$$

for any three sequences $t_j \to t$, $s_j \to \infty$, $x_j \to x$ $(j \to \infty)$, with elements $x, x_j \in X$, $0 \le t, t_j < \infty$, and $s_j \ge t_0$.

Let Φ be an asymptotically autonomous continuous semiflow on the metric space X and Θ its continuous limit-semiflow. A Θ-equilibrium (or fixed point) is an element $e \in X$ such that $\Theta(t, e) = e$ for all $t \ge 0$. The following lemma which generalizes Markus's Theorem [39] is given by Thieme [23].

Lemma 6.2 ([23, Theorem 4.1]). *Let e be a locally asymptotically stable equilibrium of Θ and $W_s(e) = \{x \in X : \Theta(t, x) \to e, t \to \infty\}$ its basin of attraction (or stable set). Then every pre-compact Φ-orbit whose ω-Φ-limit set intersects $W_s(e)$ converges to e.*

Define $C := C([-\tau, 0], \mathbb{R})$ and

$$d(x, y) = \max_{\theta\in[-\tau_i,0]} |x(\theta) - y(\theta)|$$

for any $x, y \in C$. Suppose Ω is an open subset in C, $F \in C(\Omega, \mathbb{R})$ and F is Lipschitzian in each compact set in Ω. Consider the following equation

$$\begin{aligned}&\dot{x}(t) = F(x_t) + G(t), \quad t \ge \sigma \\ &x_\sigma = \phi\end{aligned} \tag{6.3}$$

with $(\sigma, \phi) \in \mathbb{R} \times C$. (6.3) is a 1-dimensional non-autonomous retarded differential equation and has a unique solution (see [33]). Let $x(s, \phi)(t)$ be the unique solution through (σ, ϕ) and well defined for all $t \in [\sigma - \tau, \sigma + \alpha]$. Here, we assume further that the maximal existence interval of solutions is $[\sigma - \tau, \infty)$. From

[33, Theorem 2.2 of Section 2.2], we know that $x(s,\phi)(t)$ is continuous in σ,ϕ,t for $\sigma\in\mathbb{R}$, $\phi\in C$ and $t\in[\sigma-\tau,\infty)$.

Consider a mapping $\Phi:\Delta\times C\to C$, which is defined as $\Phi(t,s,\phi)=x_t(s,\phi)\in C$, with $x_t(s,\phi)(\theta)=x(s,\phi)(t+\theta)$. It can be verified that Φ is continuous on $\Delta\times C$ and satisfies (6.1) by the existence and uniqueness of solutions. Therefore, Φ is a continuous non-autonomous semiflow.

Furthermore, we consider the corresponding autonomous equation:

$$\begin{aligned}&\dot{x}(t)=F(x_t)\\&x_0=\psi,\end{aligned}\qquad(6.4)$$

for $\psi\in C$. Under the same assumptions, let $y(\psi)(t)$ be the unique solution of (6.4) through $(0,\psi)$ and define $\Theta:[0,\infty)\times C\to C$ as $\Theta(t,\psi)=y(\psi)$, with $y_t(\psi)(\theta)=y(\psi)(t+\theta)$. Similarly, we obtain that Θ is continuous semiflow satisfying (6.2). Before stating the main theorem, we give the following property for Φ and Θ which are defined above.

Lemma 6.3. *If $G(t)\to 0$, $t\to\infty$, then Φ is asymptotically autonomous—with limit-semiflow Θ.*

Proof. For any three sequences $t_j\to t$, $s_j\to\infty$, $\varphi_j\to\varphi$ $(j\to\infty)$, with $\varphi,\varphi_j\in C_i$, $0\le t,t_j<\infty$ and $s_j\ge t_0$, let

$$u(\theta):=\Phi(t_j+s_j,s_j,\varphi_j)(\theta)-\Theta(t,\varphi)(\theta).$$

Then

$$\begin{aligned}u(\theta)&=x_{t_j+s_j}(s_j,\varphi_j)(\theta)-y_{t+s_j}(s_j,\varphi)(\theta)\\&=x(t_j+s_j+\theta)-y(t+s_j+\theta).\end{aligned}$$

Without loss of generality, we assume $t_j+\theta>0$. Otherwise,

$$u(\theta)=\varphi_j(t_j+s_j+\theta)-\varphi(t+s_j+\theta).$$

Obviously, the conclusion is obtained. Then

$$\begin{aligned}u(\theta)&=[\varphi_j(0)-\varphi(0)]+\int_{s_j}^{t_j+s_j+\theta}G(s)\mathrm{d}s\\&\quad-\int_{t_j+s_j+\theta}^{t+s_j+\theta}F(y(s+\bar{\theta}))\mathrm{d}s+I,\quad\bar{\theta}\in[-\tau,0].\end{aligned}$$

Here,

$$\begin{aligned}I&=\int_{s_j}^{t_j+s_j+\theta}\left[F(x(s+\bar{\theta}))-F(y(s+\bar{\theta}))\right]\mathrm{d}s\\&=\int_{s_j+\bar{\theta}}^{t_j+s_j+\theta+\bar{\theta}}\left[F(x(s))-F(y(s))\right]\mathrm{d}s\\&\le L\int_{s_j+\bar{\theta}}^{t_j+s_j+\theta}|x(s)-y(s)|\,\mathrm{d}s\\&\le L\int_{-t_j}^{\theta}\left|x(t_j+s_j+s)-y(t_j+s_j+s)\right|\mathrm{d}s\\&\quad+L\int_{s_j+\bar{\theta}}^{s_j}|x(s)-y(s)|\,\mathrm{d}s,\end{aligned}$$

where $0<L<\infty$ is the Lipschitz constant w.r.t. F. Therefore,

$$\begin{aligned}|u(\theta)|&\le(1-\bar{\theta}L)d(\varphi_j(\theta),\varphi(\theta))+\left|\int_{s_j}^{t_j+s_j+\theta}G(s)\mathrm{d}s\right|\\&\quad+\left|\int_{t_j+s_j+\theta}^{t+s_j+\theta}\left[F(y(s+\bar{\theta}))\right]\mathrm{d}s\right|+L\int_{-t_j}^{\theta}|u(s)|\mathrm{d}s.\end{aligned}$$

Using Gronwall's inequality, it is obtained that

$$\begin{aligned}|u(\theta)|\le&\left[(1-\bar{\theta}L)d(\varphi_j(\theta),\varphi(\theta))+\left|\int_{s_j}^{t_j+s_j+\theta}G(s)\mathrm{d}s\right|\right.\\&\left.+\left|\int_{t_j+s_j+\theta}^{t+s_j+\theta}\left[F(y(s+\bar{\theta}))\right]\mathrm{d}s\right|\right]\cdot\exp\left[L(\theta+t_j)\right].\end{aligned}$$

Letting $j\to\infty$, we prove the assertion. □

We are now in a position to state and prove our main result on global asymptotical stability.

Theorem 6.4. *If $\xi_1<0$, then the zero solution of Eq. (2.1) is globally asymptotically stable.*

Proof. Consider the second equation of (2.1) as follows,

$$\begin{aligned}\frac{\mathrm{d}x_2}{\mathrm{d}t}(t)&=-[\delta_2+\beta_2(x_2(t))]x_2(t)+2(1-K_2)\mathrm{e}^{-\gamma_2\tau_2}\\&\quad\times\beta_2(x_2(t-\tau_2))x_2(t-\tau_2)\\&\quad+2K_1\mathrm{e}^{-\gamma_1\tau_1}\beta_1(x_1(t-\tau_1))x_1(t-\tau_1)\\&\overset{def}{=}F(x_t)+G(t)\end{aligned}\qquad(6.5)$$

and the corresponding autonomous equation:

$$\begin{aligned}\frac{\mathrm{d}x_2}{\mathrm{d}t}(t)&=-[\delta_2+\beta_2(x_2(t))]x_2(t)\\&\quad+2(1-K_2)\mathrm{e}^{-\gamma_2\tau_2}\beta_2(x_2(t-\tau_2))x_2(t-\tau_2).\end{aligned}\qquad(6.6)$$

From Theorem 3.1, it is known that the zero solution of Eq. (3.1) is globally asymptotically stable if $\xi_1<0$. This implies that $G(t)\to 0$ for $t\to\infty$, with any given nonnegative initial condition for x_1. Therefore, Φ defined by (6.5) is asymptotically autonomous with limit-semiflow Θ defined by (6.6), where Lemma 6.3 is used. Next, we begin to investigate the asymptotical behavior of Eq. (6.6) in order to capture a message for (6.5). Similar to Theorem 3.1, it can be proved that the zero of (6.6) is globally asymptotically stable under the assumption that $\xi_2<0$.

Our first assertion is that the zero of (6.5) is globally asymptotically stable under the assumption that $\xi_i<0$, $i=1,2$. Let $e=0$ be the stable equilibrium of Θ on $C([-\tau_2,0],\mathbb{R})$ and denote $C_2^+:=C([-\tau_2,0],\mathbb{R}^+)$. Using Proposition 2.2, we know C_2^+ is a positively invariant set and is a subset of e's basin of attraction. On the other hand, it is known that every Φ-orbit through the point of C_2^+ is pre-compact by the Ascoli–Arzela theorem. Therefore, Lemma 6.2 implies our assertion.

Proceed in the same way, we can obtain similar conclusions for the next $n-3$ equations, that is, $x_i=0$ is globally asymptotically stable if $\xi_j<0, j\in I_i$ for $i=3,\ldots,n-1$. In particular, for the last one in Eq. (2.1), we can define an autonomous semiflow Θ_n for an ODE equation:

$$\frac{\mathrm{d}x_n}{\mathrm{d}t}(t)=-[\delta_n+\beta_n(x_n(t))]x_n(t).\qquad(6.7)$$

Obviously, the zero of (6.7) is globally asymptotically stable. Therefore, the same property holds for the equation of x_n.

Finally, notice that

$$2(1-K_i)\mathrm{e}^{-\gamma_i\tau_i}\le 2(1-K_1)\mathrm{e}^{-\gamma_1\tau_1}\quad\text{for all } i\in I_n,$$

where (H1) and (H2) are used. This implies by (H3) that $\xi_j<0$ if $\xi_1<0$ for all $j\in I_{n-1}$, thus the proof is complete. □

Remark 6.5. In fact, the condition $\xi_1<0$ in Theorem 6.4 is the one that ensures that (2.1) has a unique trivial equilibrium (see [4]). In [4, Theorem 10], Adimy et al. studied the global asymptotical stability of the zero solution under the assumption that $(2\mathrm{e}^{-\gamma_1\tau_1}-1]\beta_1(0)<\delta_1$ by constructing a Lyapunov function. Actually, our theorem is an improved result, which indicates that all solutions of (2.1) with positive initial conditions tend to zero as long as zero is the unique steady-state.

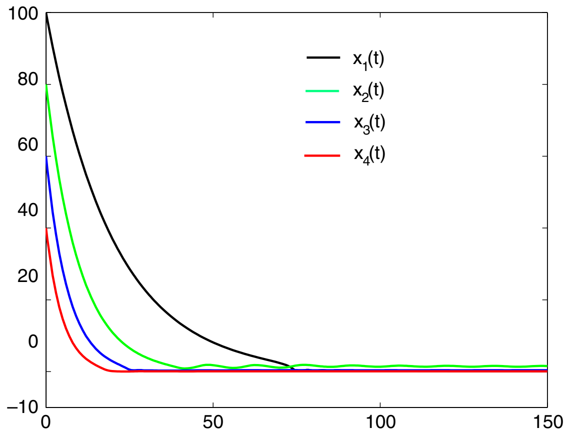

Fig. 6.1. Four sub-populations are considered. The initial condition in the form (x_1, x_2, x_3, x_4) with $x_i > 0$ $(i = 1, 2, 3, 4)$ describes an intermediate process of haemopoiesis, the cell populations are stable and converge toward the unique nontrivial steady state of the system. Parameters values: $\gamma_1 = 0.17$, $\gamma_2 = 0.18$, $\gamma_3 = 0.19$, $K_1 = 0.05$, $K_2 = 0.1$, $K_3 = 0.15$, $\beta_1^0 = 1.77$, $\beta_2^0 = 1.5$, $\beta_3^0 = 1$, $\beta_4^0 = 0.5$, $\delta_1 = 0.05$, $\delta_2 = 0.1$, $\delta_3 = 0.15$, $\delta_4 = 0.2$, $\tau_1 = 4$, $\tau_2 = 2$, $\tau_3 = 3$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Fig. 6.1 describes the HSCs populations with four stages: the pluripotent hematopoietic stem cell population x_1 (black line), the progenitor cell population x_2 (green line), the precursor cell population x_3 (blue line), and the mature cell population x_4 (red line). With the parameters $\gamma_1 = 0.17$, $K_1 = 0.05$, $\beta_1^0 = 1.77$ and $\delta_1 = 0.05$, we know from Theorem 6.4 that (0, 0, 0, 0) is globally asymptotically stable if $\xi_1 < 0$, which implies $\tau_1 > 3.6117$. We choose $\tau_1 = 4$ in this simulation. We should mention that the solution curve of x_2 in Fig. 6.1 ultimately tends to zero after a long time. Here, we only truncate the graph for t between 0 and 150.

7. Existence of periodic solutions in the *n*-dimensional model

Pujo-Menjouet and Mackey [10] showed that long period oscillations could be observed within the hematopoietic stem cell compartment and associated with hematological diseases [40], such as neutropenias and leukemias, which sometimes exhibit oscillations in all blood cell counts. Accordingly, for both biological and mathematical interests, our next objective is to study when the periodic oscillations occur in (2.1) as τ_1 varies.

Results in Sections 4 and 5 imply that under certain conditions, there exist nonconstant periodic solutions of (3.1) due to Hopf bifurcation when τ_1 lies in some neighborhood of each bifurcation value. Specially, some nonconstant periodic solutions can also exist when τ_1 varies in a larger interval under further assumptions. In the following, we assume that these conditions ensuring the appearance of (global) Hopf bifurcation are met. For the sake of convenience, we denote by D the region where τ_1 lies and (global) Hopf bifurcation for (2.1) takes place. Our purpose is to obtain sufficient conditions for the existence of positive periodic solutions to Eq. (2.1) by employing the coincidence degree method.

Let X, Y be the real Banach spaces, $L : \mathrm{Dom}\, L \subset X \to Y$ be a Fredholm mapping of index zero, and $P : X \to X$, $Q : Y \to Y$ be continuous projectors such that $\mathrm{Im}\, P = \mathrm{Ker}\, L$, $\mathrm{Ker}\, Q = \mathrm{Im}\, L$ and $X = \mathrm{Ker}\, L \oplus \mathrm{Ker}\, P$, $Y = \mathrm{Im}\, L \oplus \mathrm{Im}\, Q$. Denote by L_p the restriction of L to $\mathrm{Dom}\, L \cap \mathrm{Ker}\, P$, $K_p : \mathrm{Im}\, L \to \mathrm{Ker}\, P \cap \mathrm{Dom}\, L$ the inverse of L_p, and $J : \mathrm{Im}\, Q \to \mathrm{Ker}\, L$ an isomorphism of $\mathrm{Im}\, Q$ onto $\mathrm{Ker}\, L$. The following lemma is given by Gaines and Mawhin [41, p. 40].

Lemma 7.1. *Let $\Omega \subset X$ be an open bounded set and let $N : X \to Y$ be a continuous operator which is L-compact on $\bar{\Omega}$ (i.e., $QN : \bar{\Omega} \to Y$ and $K_p(I - Q)N : \bar{\Omega} \to Y$ are compact). Assume*

(i) *for each $\lambda \in (0, 1)$, $x \in \partial\Omega \cap \mathrm{Dom}\, L$, $Lx \neq \lambda Nx$;*
(ii) *for each $x \in \partial\Omega \cap \mathrm{Ker}\, L$, $QNx \neq 0$, and $\deg\{JQN, \Omega \cap \mathrm{Ker}\, L, 0\} \neq 0$. Then $Lx = Nx$ has at least one solution in $\bar{\Omega} \cap \mathrm{Dom}\, L$.*

To use the continuation Lemma 7.1, we take $X = Y = \{u(t) \in C(\mathbb{R}, \mathbb{R}) : u(t + \omega) = u(t)\}$, with the maximum norm $|\cdot|_0$ defined as $|u|_0 = \max_{t \in [0,\omega]} |u(t)|$ for any $u \in X$ or Y. Hence, X and Y are Banach spaces. Set

$$L : \mathrm{Dom}\, L \cap X, \qquad Lu = \dot{u},$$

where $\mathrm{Dom}\, L = \{u(t) \in C^1(\mathbb{R}, \mathbb{R})\}$. Define two projectors P and Q as

$$Pu = Qu = \frac{1}{\omega} \int_0^\omega u(s) \mathrm{d}s, \quad u \in X.$$

Obviously, $\mathrm{Ker}\, L = \mathbb{R}$, $\mathrm{Im}\, L = \{u \in X : \int_0^\omega u(t) \mathrm{d}t = 0\}$ is closed in Y. Therefore, $\dim \mathrm{Ker}\, L = \mathrm{codim} \mathrm{Im}\, L = 1$. These imply that L is a Fredholm mapping of index 0. Moreover, we can derive that the inverse K_p of L_p has the form

$$K_p : \mathrm{Im}\, L \to \mathrm{Dom}\, L \cap \mathrm{Ker}\, P,$$

$$K_p(u) = \int_0^t u(s) \mathrm{d}s - \frac{1}{\omega} \int_0^\omega \int_0^\tau u(s) \mathrm{d}s \mathrm{d}\tau, \quad t \in [0, \omega].$$

We are now in a position to state and prove our main result.

Theorem 7.2. *Assume that $\xi_1 > 0$ and the condition*

(P3) *$\beta_i(x)x$ is bounded, $i \in I_n$, $x \in \mathrm{R}^+$*

is satisfied. Then Eq. (2.1) has at least one positive periodic solution for $\tau_1 \in D$.

Proof. Let B_M be such that $0 < \beta_i(x)x < B_M$ for each $i \in I_n$ and $x \in \mathbb{R}^+$. We analyze the n-dimensional system one by one. To start with, consider (6.5) again,

$$\frac{\mathrm{d}x_2}{\mathrm{d}t}(t) = -[\delta_2 + \beta_2(x_2(t))]x_2(t) + 2(1 - K_2)\mathrm{e}^{-\gamma_2\tau_2} \times \beta_2(x_2(t - \tau_2))x_2(t - \tau_2) + 2K_1\mathrm{e}^{-\gamma_1\tau_1}\beta_1(x_1(t - \tau_1))x_1(t - \tau_1).$$

For any given $\tau_1 \in D$, we have known that there exists a positive periodic solution of (3.1) bifurcated from x^* and denoted by $X(t)$. Let $I(t) := 2K_1\mathrm{e}^{-\gamma_1\tau_1}\beta_1(X(t - \tau_1))X(t - \tau_1)$, then $I(t)$ is a periodic function with the same period as $X(t)$. From the above analysis and the boundedness of $X(t)$, we obtain that there exist I_m and I_M such that $0 < I_m < I(t) < I_M < \infty$ for $t \in \mathbb{R}^+$.

Let $x_2(t) = \mathrm{e}^{y(t)}$, then Eq. (6.5) becomes

$$\frac{\mathrm{d}y}{\mathrm{d}t}(t) = -[\delta_2 + \beta_2(\mathrm{e}^{y(t)})] + 2(1 - K_2)\mathrm{e}^{-\gamma_2\tau_2} \times \beta_2(\mathrm{e}^{y(t-\tau_2)})\mathrm{e}^{y(t-\tau_2)-y(t)} + \mathrm{e}^{-y(t)}I(t). \tag{7.1}$$

It is easy to see that if Eq. (7.1) has an ω-periodic solution $y^*(t)$, then $x_2^*(t) = \mathrm{e}^{y^*(t)}$ is a positive ω-periodic solution of Eq. (6.5). Thus, our next objective is to show that Eq. (6.5) has a periodic solution with the period denoted by ω. Define $N : X \to X$ as

$$Ny = -[\delta_2 + \beta_2(\mathrm{e}^{y(t)})] + 2(1 - K_2)\mathrm{e}^{-\gamma_2\tau_2}\beta_2(\mathrm{e}^{y(t-\tau_2)})\mathrm{e}^{y(t-\tau_2)-y(t)} + \mathrm{e}^{-y(t)}I(t).$$

Then by some computation, we can show that $QN : X \to X$ takes the form

$$QN(y) = -\delta_2 - \frac{1}{\omega} \int_0^\omega [\beta_2(\mathrm{e}^{y(t)}) - 2(1 - K_2)\mathrm{e}^{-\gamma_2\tau_2}\beta_2(\mathrm{e}^{y(t-\tau_2)}) \times \mathrm{e}^{y(t-\tau_2)-y(t)}]\mathrm{d}t + \frac{1}{\omega} \int_0^\omega \mathrm{e}^{-y(t)}I(t)\mathrm{d}t,$$

and $K_p(I-Q)N : X \to X$ takes the form

$$K_p(I-Q)N(y) = \int_0^t \left[\beta_2(e^{y(s)}) - 2(1-K_2)e^{-\gamma_2\tau_2}\beta_2(e^{y(s-\tau_2)}) \times e^{y(s-\tau_2)-y(s)} + e^{-y(s)}I(s)\right]dt - \frac{1}{\omega}\int_0^\omega\int_0^\tau \left[\beta_2(e^{y(s)}) - 2(1-K_2) \times e^{-\gamma_2\tau_2}\beta_2(e^{y(s-\tau_2)})e^{y(s-\tau_2)-y(s)} + e^{-y(s)}I(s)\right]ds d\tau + \left(\frac{t}{\omega}-\frac{1}{2}\right)\int_0^\omega \left[\beta_2(e^{y(t)}) - 2(1-K_2) \times e^{-\gamma_2\tau_2}\beta_2(e^{y(t-\tau_2)})e^{y(t-\tau_2)-y(t)} + e^{-y(t)}I(t)\right]dt.$$

The integral terms in both QN and $K_p(I-Q)N$ imply that they are continuously differentiable with respect to t and that they map bounded continuous functions to bounded continuous functions. By the Ascoli–Arzela theorem, we see that $QN(\bar{\Omega})$ and $K_p(I-Q)N(\bar{\Omega})$ are relatively compact for any open bounded set $\Omega \subset X$. Therefore, N is L-compact on $\bar{\Omega}$ for any open bounded set $\Omega \subset X$. Corresponding to the operator equation $Ly = \lambda Ny$, $\lambda \in (0, 1)$, we have

$$\frac{dy}{dt}(t) = \lambda\left[-\delta_2 - \beta_2(e^{y(t)}) + 2(1-K_2)e^{-\gamma_2\tau_2}\beta_2(e^{y(t-\tau_2)}) \times e^{y(t-\tau_2)-y(t)} + e^{-y(t)}I(t)\right]. \quad (7.2)$$

Suppose that $y(t) \in X$ is a solution of Eq. (7.2) for some $\lambda \in (0, 1)$. On one hand, we choose $t_M \in [0, \omega]$ such that $y(t_M) = \max_{t\in[0,\omega]} y(t)$. Then it is clear that $\dot{y}(t_M) = 0$. From this and Eq. (7.2), we obtain

$$\begin{aligned}\delta_2 e^{y(t_M)} &< \left[\delta_2 + \beta_2(e^{y(t_M)})\right]e^{y(t_M)} \\ &= 2(1-K_2)e^{-\gamma_2\tau_2}\beta_2(e^{y(t_M-\tau_2)})e^{y(t_M-\tau_2)} + I(t_M) \\ &\le 2B_M + I_M.\end{aligned}$$

Thus, it is obtained that

$$y(t_M) < \ln\frac{2B_M + I_M}{\delta_2}.$$

On the other hand, choose $t_m \in [0, \omega]$ such that $y(t_m) = \min_{t\in[0,\omega]} y(t)$. Similarly, we obtain

$$[\delta_2 + \beta_2(0)]\,e^{y(t_m)} \ge \left[\delta_2 + \beta_2(e^{y(t_m)})\right]e^{y(t_m)} > I_m,$$

which implies

$$y(t_m) > \ln\frac{I_m}{\delta_2 + \beta_2(0)}.$$

Hence, we obtain

$$|y(t)|_0 < \max\left\{\left|\ln\frac{I_m}{\delta_2+\beta_2(0)}\right|, \left|\ln\frac{2B_M+I_M}{\delta_2}\right|\right\}.$$

Denote

$$A = \max\left\{\left|\ln\frac{I_m}{\delta_2+\beta_2(0)}\right|, \left|\ln\frac{2B_M+I_M}{\delta_2}\right|\right\} + A_0,$$

where

$$A_0 = \max\left\{\left|\ln\frac{I_m}{\delta_2+\beta(0)|1-2(1-K_2)e^{-\gamma_2\tau_2}|}\right|, \left|\ln\frac{I_M + B_M|1-2(1-K_2)e^{-\gamma_2\tau_2}|}{\delta_2}\right|\right\}.$$

Take $\Omega = \{y(t) \in X : |y|_0 < A\}$. Then it is clear that Ω satisfies condition (i) in Lemma 7.1. When $y \in \partial\Omega \cap \mathbb{R}$, y is a constant with $|y| = A$. Thus,

$$QN(y) = -\delta_2 - \beta_2(e^y) + 2(1-K_2)e^{-\gamma_2\tau_2}\beta_2(e^y) + \frac{e^{-y}}{\omega}\int_0^\omega I(t)dt \neq 0.$$

Furthermore, take $J = I : \mathrm{Im}\,Q \to \mathrm{Ker}\,L$, $x \mapsto x$, we obtain through a computation that

$$\deg\{JQN, \ \Omega \cap \mathrm{Ker}\,L, \ 0\} \neq 0.$$

Therefore, there exists at least one periodic solution for (7.1), which is therefore equivalent to the existence of a positive periodic solution for (6.5). We proceed in the same way and obtain the expected result. This completes the proof. □

Remark 7.3. Actually, from the above proof it is shown that the amplitude of the periodic solution of (2.1) depends on τ_1. In addition, we can conclude that the origin of oscillations for (2.1) lies in the pluripotent hematopoietic stem cell populations.

As an example, we describe the asymptotic behavior of the HSCs population model with four stages as described in Section 6. Under the same parameter values for x_1 as in Section 4: $\gamma_1 = 0.02$, $K_1 = 0.05$, $\delta_1 = 0.05$, $\beta_1^0 = 1.77$ and x_i $(i = 2, 3, 4)$ as in Section 6:

$$\begin{aligned}&\gamma_2 = 0.18, \quad \gamma_3 = 0.19, \quad K_2 = 0.1, \quad K_3 = 0.15, \\ &\beta_2^0 = 1.5, \quad \beta_3^0 = 1, \\ &\beta_4^0 = 0.5, \quad \delta_2 = 0.1, \quad \delta_3 = 0.15, \quad \delta_4 = 0.2, \\ &\tau_2 = 2, \quad \tau_3 = 3,\end{aligned}$$

we let $\tau_1 = 6$. By Theorem 7.2, there exists at least one positive periodic solution $(X_1(t), x_2(t), x_3(t), x_4(t))$ for Eq. (2.1) (see Fig. 7.1).

8. Discussion

From Sections 6 and 7, we know that zero is the unique equilibrium of (2.1) and is globally asymptotically stable when $\xi_1 < 0$. On the other hand, when $\xi_1 > 0$, it becomes unstable. At the same time, a positive equilibrium bifurcated from zero is stable when τ_1 is small. As τ_1 increases and varies in region D, there exists at least one positive periodic solution for (2.1).

Noticing the expression of ξ_1 defined in (3.2), we obtain a threshold δ_1^0 for the death rate:

$$\delta_1^0 := [2(1-K_1)e^{-\gamma_1\tau_1} - 1]\beta_1(0).$$

If the death rate δ_1 for the pluripotent hematopoietic stem cells exceeds δ_1^0, then all cells in each stage will die out. Meanwhile, the phenomenon of extinction would be avoided if $\delta_1 < \delta_1^0$. In this case, when the proliferating phase duration τ_1 is small, the amount of HSCs will keep relatively stable.

In addition, there may exist some hematological diseases in human body if τ_1 varies between some values. On the other hand, it is known that the threshold is a decreasing function of K_1, the proportion of dividing cells go to the next nonproliferating phase, and a increasing function of $\beta_1(0)$, the maximal rate of introduction in the proliferating phase. This implies that extinction becomes more likely if either the quantity of the pluripotent hematopoietic stem cells entering the next stage increases or the maximal rate of introduction in the proliferating phase is smaller. It is concluded that the variation of the pluripotent hematopoietic stem cells plays a fundamental and important role to the dynamic behavior of whole HSCs.

Periodic hematological diseases are characterized by significant oscillations in the number of circulating cells with periods ranging from weeks to months [42,43]. Based on the model of Mackey [1,2],

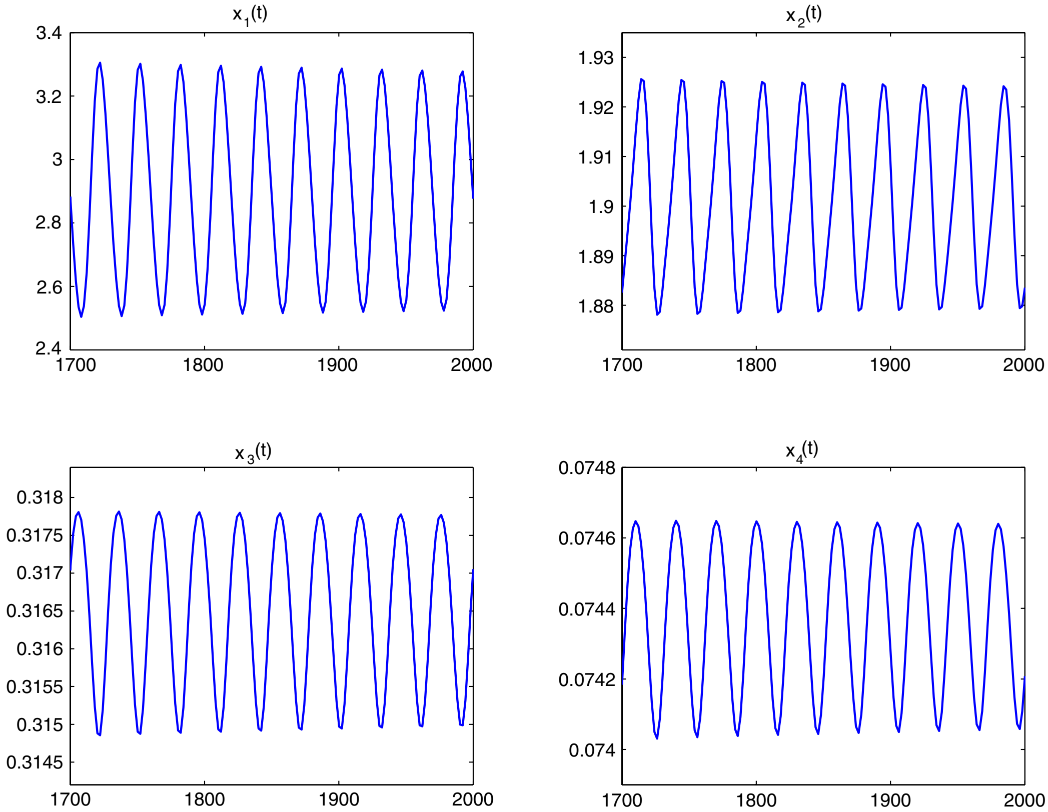

Fig. 7.1. Periodic solutions of the HSCs model (2.1) with four stages and $\tau_1 = 6$, where the initial condition is $(3, 0, 0, 0)$.

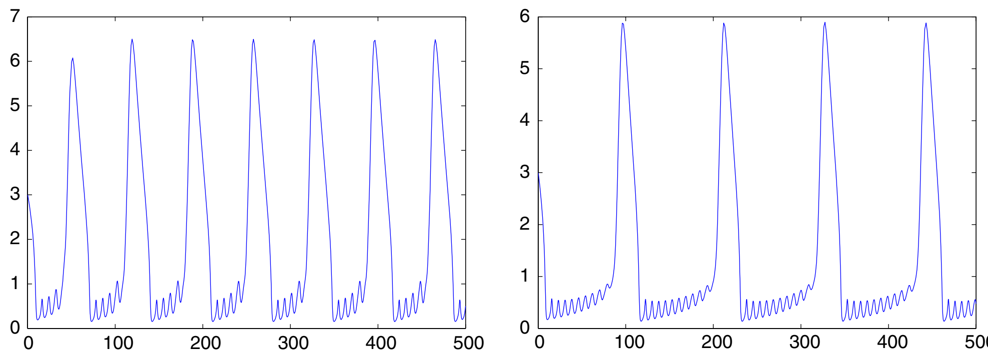

Fig. 8.1. Long-period oscillatory solutions of the multiple-stage HSCs model (2.1) with multiple delays. Left: $K = 0.3$, $T = 69$. Right: $K = 0.36$, $T = 116$.

Pujo-Menjouet and Mackey [10] considered models for the regulation of stem cell dynamics and noticed that long-period oscillations could be observed in hematopoiesis models. Adimy et al. [6] analyzed a model of hematopoietic stem cells regulation with a nonconstant cell cycle duration and established the existence of long-period oscillations (in the order of 70 days) when applying their model to the case of chronic myelogenous leukemia [43]. However, longer periods oscillations could not be obtained in their model without using nonrealistic values of the parameters. Taking into account the role of growth factors on the regulation of the hematopoietic stem cell population, Adimy et al. [34] were able to obtain very long-period oscillations, in the order of 100 days, for very short cell cycle durations. Numerical simulations demonstrate that long-period oscillations could be observed in HSCs model (2.1) with multiple stages and multiple delays (see Fig. 8.1).

Appendix. Properties of Hopf bifurcation

In this section, we use the center manifold and normal form theories presented in [16] to study the direction of Hopf bifurcation and stability of the bifurcating periodic solutions from x^* under the conditions of Theorem 4.4(ii).

By normalizing the delay τ by the time scaling $t \mapsto (t/\tau)$ and using the change of variables $x(t) = x(t\tau)$, system (3.1) is transformed into

$$\frac{dx}{dt}(t) = -\tau[\delta + \beta(x(t))]x(t) + 2\tau(1-K)e^{-\gamma\tau}\beta(x(t-1))x(t-1). \tag{3.1$'$}$$

Without loss of generality, we denote the critical value τ^* at which Eq. (3.1′) undergoes a Hopf bifurcation at x^*. Let $\tau = \tau^* + \mu$, then $\mu = 0$ is the Hopf bifurcation value of Eq. (3.1′).

Let $x_1(t) = x(t) - x^*$ and still denote $x_1(t)$ by $x(t)$, so that Eq. (3.1′) can be written in the form:

$$\begin{aligned}\frac{dx}{dt}(t) &= -(\tau^* + \mu)[\delta + \alpha(x^*)]x(t)\\ &+ 2\alpha(x^*)(\tau^* + \mu)(1-K)e^{-\gamma\tau}x(t-1)\\ &- \frac{1}{2}\alpha'(x^*)(\tau^*+\mu)[x^2 - 2(1-K)e^{-\gamma\tau}x^2(t-1)]\\ &- \frac{1}{3!}\alpha''(x^*)(\tau^*+\mu)[x^3 - 2(1-K)e^{-\gamma\tau}x^3(t-1)] + O(4),\end{aligned} \tag{A.1}$$

where

$$\alpha^{(n)}(x^*) := (n+1)\beta^{(n)}(x^*) + \beta^{(n+1)}(x^*)x^*, \quad n = 0, 1, 2.$$

Here, $\alpha^{(n)}(x^*)$ and $\beta^{(n)}(x^*)$ express the nth derivatives at x^* of $\alpha(x)$ and $\beta(x)$, respectively.

For $\phi \in C([-1, 0], \mathbb{R})$, define

$$\begin{aligned}L_\mu(\phi) &= -(\tau^*+\mu)[\delta + \alpha(x^*)]\phi(0)\\ &\quad + 2\alpha(x^*)(\tau^*+\mu)(1-K)e^{-\gamma(\tau^*+\mu)}\phi(-1).\end{aligned}$$

By the Riesz representation theorem, there exists a bounded variation function $\eta(\theta, \mu)$ ($\theta \in [-1, 0]$) such that

$$L_\mu(\phi) = \int_{-1}^{0}[d\eta(\theta,\mu)]\phi(\theta) \quad \text{for } \phi \in C([-1,0],\mathbb{R}).$$

In fact, we can choose

$$\eta(\theta,\mu) = \begin{cases} -(\tau^*+\mu)[\delta+\alpha(x^*)], & \theta = 0\\ 0, & \theta \in (-1,0)\\ -2\alpha(x^*)(\tau^*+\mu)(1-K)e^{-\gamma(\tau^*+\mu)}, & \theta = -1.\end{cases}$$

Define

$$A(\mu)\phi(\theta) = \begin{cases} \dfrac{d\phi(\theta)}{d\theta}, & \theta \in [-1,0)\\ \displaystyle\int_{-1}^{0}[d\eta(\xi,\mu)]\phi(\xi), & \theta = 0\end{cases}$$

and

$$\begin{aligned}h(\mu,\phi) &= -\frac{1}{2}\alpha'(x^*)(\tau^*+\mu)\\ &\quad\times[\phi^2(0) - 2(1-K)e^{-\gamma(\tau^*+\mu)}\phi^2(-1)]\\ &\quad - \frac{1}{3!}\alpha''(x^*)(\tau^*+\mu)[\phi^3(0) - 2(1-K)\\ &\quad\times e^{-\gamma(\tau^*+\mu)}\phi^3(-1)] + O(4).\end{aligned}$$

Furthermore, define the operator $R(\mu)$ as

$$R(\mu)\phi(\theta) = \begin{cases} 0, & \theta \in [-1,0)\\ h(\mu,\phi), & \theta = 0,\end{cases}$$

then Eq. (A.1) is equivalent to the following operator equation

$$\dot{x_t} = A(\mu)x_t + R(\mu)x_t,$$

where $x_t = x(t+\theta)$ for $\theta \in [-1, 0]$.

For $\psi \in C^1([0, 1], \mathbb{R})$, define a operator

$$A^*\psi(s) := \begin{cases} -\dfrac{d\psi(s)}{ds}, & s \in (0,1]\\ \displaystyle\int_{-1}^{0}\psi(-\xi)d\eta(\xi,0), & s = 0\end{cases}$$

and a bilinear form

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

where $\eta(\theta) = \eta(\theta, 0)$. Then $A(0)$ and A^* are adjoint operators.

From the before discussions, we know that $\pm i\omega^*\tau^*$ are eigenvalues of $A(0)$ and therefore they are also eigenvalues of A^*. It is not difficult to verify that the vectors $q(\theta) = e^{i\omega^*\tau^*\theta}$ ($\theta \in [-1, 0]$) and $q^*(s) = \bar{l}e^{i\omega^*\tau^*s}$ ($s \in [0, 1]$) are the eigenvectors of $A(0)$ and A^* corresponding to the eigenvalues $i\omega^*\tau^*$ and $-i\omega^*\tau^*$, respectively, where

$$l = (1 + 2\tau^*(1-K)\alpha(x^*)e^{-\gamma\tau^*}e^{-i\omega^*\tau^*})^{-1}.$$

Following the same algorithms as in [16] and using a computation process similar to that in [16], we can obtain the coefficients which will be used in determining the important quantities:

$$\begin{aligned}g_{20} &= l\tau^*\alpha'(x^*)[2(1-K)e^{-\gamma\tau^*}e^{-2i\omega^*\tau^*} - 1],\\ g_{11} &= l\tau^*\alpha'(x^*)[2(1-K)e^{-\gamma\tau^*} - 1],\\ g_{02} &= l\tau^*\alpha'(x^*)[2(1-K)e^{-\gamma\tau^*}e^{2i\omega^*\tau^*} - 1],\\ g_{21} &= -l\tau^*\alpha'(x^*)\big[2W_{11}(0) + W_{20}(0) - 2(1-K)e^{-\gamma\tau^*}\\ &\quad\times(2W_{11}(-1)e^{-i\omega^*\tau^*} + W_{20}(-1)e^{i\omega^*\tau^*})\big]\\ &\quad - l\tau^*\alpha''(x^*)[1 - 2(1-K)e^{-\gamma\tau^*}e^{-i\omega^*\tau^*}],\end{aligned}$$

where

$$\begin{aligned}W_{20}(\theta) &= \frac{ig_{20}}{\omega^*\tau^*}q(\theta) + \frac{i\bar g_{02}}{3\omega^*\tau^*}\bar q(\theta) + E_1e^{2i\omega^*\tau^*\theta},\\ W_{11}(\theta) &= -\frac{ig_{11}}{\omega^*\tau^*}q(\theta) + \frac{i\bar g_{11}}{\omega^*\tau^*}\bar q(\theta) + E_2\end{aligned}$$

and

$$\begin{aligned}E_1 &= \frac{\alpha'(x^*)[2(1-K)e^{-\gamma\tau^*}e^{-2i\omega^*\tau^*} - 1]}{2i\omega^* + \delta + \alpha(x^*) - 2\alpha(x^*)(1-K)e^{-\gamma\tau^*}e^{-2i\omega^*\tau^*}},\\ E_2 &= \frac{\alpha'(x^*)[2(1-K)e^{-\gamma\tau^*} - 1]}{\delta + \alpha(x^*) - 2\alpha(x^*)(1-K)e^{-\gamma\tau^*}}.\end{aligned}$$

Consequently, g_{21} can be expressed explicitly.

Thus, we can compute the following values:

$$\begin{aligned}c_1(0) &= \frac{i}{2\omega^*\tau^*}\left(g_{11}g_{20} - 2|g_{11}|^2 - \frac{|g_{02}|^2}{3}\right) + \frac{g_{21}}{2},\\ \mu_2 &= -\frac{\mathrm{Re}(c_1(0))}{\mathrm{Re}(\lambda'(\tau^*))},\\ \beta_2 &= 2\mathrm{Re}(c_1(0)),\\ T_2 &= -\frac{\mathrm{Im}\,(c_1(0)) + \mu_2\mathrm{Im}\,(\lambda'(\tau^*))}{\omega^*\tau^*},\end{aligned}$$

which determine the properties of bifurcating periodic solutions at the critical value τ^*, i.e., μ_2 determines the directions of the Hopf bifurcation: if $\mu_2 > 0$ ($\mu_2 < 0$), then the bifurcating periodic solutions are forward (backward); β_2 determines the stability of bifurcating periodic solutions: the bifurcating periodic solutions on the center manifold are stable (unstable) if $\beta_2 < 0$ ($\beta_2 > 0$); and T_2 determines the period of the bifurcating periodic solutions: the period increases (decreases) if $T_2 > 0$ ($T_2 < 0$).

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