Chapter 3
Mathematical Analysis of a Delayed Hematopoietic Stem Cell Model with Wazewska–Lasota Functional Production Type

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Abstract In this chapter, we consider a more general model describing the dynamics of a hematopoietic stem cell (HSC) model with Wazewska–Lasota functional production type describing the cycle of proliferating and quiescent phases. The model is governed by a system of two ordinary differential equations with discrete delay. Its dynamics are studied in terms of local stability and Hopf bifurcation. We prove the existence of the possible steady state and their stability with respect to the time delay and the apoptosis rate of proliferating cells. We show that a sequence of Hopf bifurcations occurs at the positive steady state as the delay crosses some critical values. We illustrate our results with some numerical simulations.

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A.C.J. Luo, H. Merdan (eds.), *Mathematical Modeling and Applications in Nonlinear Dynamics*, Nonlinear Systems and Complexity 14,
DOI 10.1007/978-3-319-26630-5_3

3.1 Biological Background

Hematopoietic stem cells (HSCs) are found in adult bone marrow, which is found in femurs, hips, ribs, sternum, and other bones. HSCs are precursor cells which give rise to all types of both the myeloid and lymphoid lineages of blood cells. HSCs have the ability to form multiple cell types (multipotency) and an ability to self-renew.

Multipotency: Individual HSCs can give rise to all of the end-stage blood cell types.

During differentiation, daughter cells derived from HSCs undertake a series of commitment decisions, retaining differentiation potential for some lineages while losing others. Intermediate cells become progressively more restrictive in their lineage potential until eventually, at the end stage, the cells are lineage-committed.

Self-Renewal: Some kinds of stem cells are thought to undertake asymmetric cell division to generate one daughter cell that remains a stem cell and one daughter cell that is differentiated. However, it is not known with certainty whether or not asymmetric cell division occurs during self-renewal. An alternative possibility is that hematopoiesis occurs via symmetric divisions that sometimes give rise to two HSC daughter cells, and sometimes to two daughter cells that are committed to differentiate. The balance between self-renewal and differentiation would then be determined by the control of these two distinct kinds of symmetric cell divisions (see Fig. 3.1).

HSCs are either proliferating or nonproliferating (quiescent or resting) cells. The majority of HSCs are actually in a quiescent stage [14].

Quiescent HSCs represent a pool of stem cells that are used to produce new blood cells.

Proliferating HSCs are actively involved in cell division (growth, DNA synthesis, etc.).

After entering the proliferating phase, a cell is committed to undergo cell division at a fixed time τ later. The generation time τ is assumed to consist of four phases: G_1, the presynthesis phase; S, the DNA synthesis phase; G_2, the postsynthesis phase; and M, the mitotic phase.

Just after the division, both daughter cells go into the resting (quiescent) phase called the G_0-phase. Once in this phase, they can either return to the proliferating phase and complete the cycle or die before ending the cycle (see Fig. 3.3).

The first mathematical model was introduced by Mackey [19] and Burns and Tannock [8]. Mackey's model is governed by a system of delay differential equations taking into account the proliferating and quiescent phases and the necessary time delay of cell division. It was also proposed to describe some periodic hematological diseases, such as periodic autoimmune hemolytic anemia [6, 22], cyclical thrombocytopenia [26, 28], cyclical neutropenia [17, 18], and periodic chronic myelogenous leukemia [14]. Periodic hematological disorders are classic examples of dynamic diseases. Because of their dynamic properties, they offer an almost unique opportunity to understand the nature of the regulatory processes involved in hematopoiesis. Periodic hematological disorders are characterized by

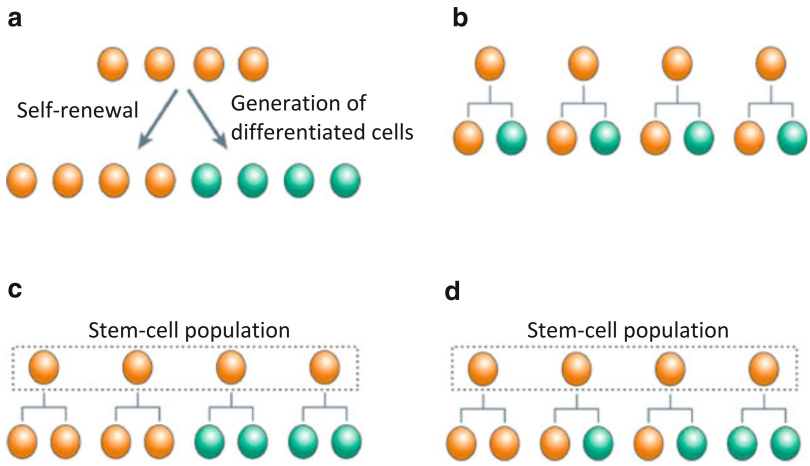

Fig. 3.1 (**a**) Stem cells (*orange*) must accomplish the dual task of self-renewal and generation of differentiated cells (*green*). (**b**)–(**d**) Possible stem cell strategies that maintain a balance of stem cells and differentiated progeny. (**b**) Asymmetric cell division: Each stem cell generates one daughter stem cell and one daughter destined to differentiate. (**c**), (**d**) Population strategies. A population strategy provides dynamic control over the balance between stem cells and differentiated cells—a capacity that is necessary for repair after injury or disease. In this scheme, stem cells are defined by their "potential" to generate both stem cells and differentiated daughters, rather than their actual production of a stem cell and a differentiated cell at each division. (**c**) Symmetric cell division: Each stem cell can divide symmetrically to generate either two daughter stem cells or two differentiated cells. (**d**) Combination of cell divisions: Each stem cell can divide either symmetrically or asymmetrically (courtesy of www.nature.com)

oscillations in the number of one or more of the circulating blood cells with periods on the order of days to months (see the figures in [17] for examples of experimental data for four hematological diseases. AIHA: Reticulocyte numbers ($\times 10^4$cells/μL) in an AIHA subject. Adapted from Orr et al. [23]. CT: Cyclical fluctuations in platelet counts ($\times 10^3$cells/μL). From Yanabu et al. [30]. CN: Circulating neutrophils ($\times 10^3$cells/μL), platelets ($\times 10^5$cells/μL), and reticulocytes ($\times 10^4$cells/μL) in a cyclical neutropenic patient. From Guerry et al. [15]. PCML: White blood cell (top) ($\times 10^4$cells/μL), platelet (middle) ($\times 10^5$cells/μL), and reticulocyte (bottom) ($\times 10^4$cells/μL) counts in a PCML patient. From Chikkappa et al. [9]. AIHA: Autoimmune hemolytic anemia. CT: cyclical thrombocytopenia. CN: cyclical neutropenia. PCML: periodic chronic myelogenous leukemia).

Recently, many authors have tried to reintroduce Mackey's model in the unstructured and structured versions. In the unstructured version with discrete and distributed time delays, the model was intensively studied by Adimy et al. [2]. They studied the dynamics of the model with respect to the time delay and occurrence and direction of Hopf bifurcation. It was also studied by Alaoui and Yafia [4] and Alaoui et al. [5] in terms of local stability, occurrence, and direction of Hopf bifurcation by proposing an approachable model. In recent years, Adimy et al. [1, 2] proposed the structured model of HSC dynamics in which the cell cycle duration depends on the cell maturity by reducing the model to a system of delay differential equations by the characteristic method. This is a way of indicating that cell cycles can be shortened for some types of cells, or in particular situations such as diseases or anemia.

In 2010, Adimy et al. [3] proposed the same Mackey model with a system of differential equations with state-dependent delay; they proved the global stability and the Hopf bifurcation occurrence.

Such stem cells are released by the marrow to help with the regeneration of damaged bone and tissue. “Techniques already exist to increase the numbers of blood cell producing stem cells from the bone marrow, but the study focuses on two other types-endothelial, which produce the cells which make up our blood vessels, and mesenchymal, which can become bone or cartilage cells.” The scientists hope that the increased production rate could be used to greatly speed tissue repair and to allow recovery from wounds that would otherwise be too severe. “There are also hopes that the technique could help damp down autoimmune diseases such as rheumatoid arthritis, where the body’s immune system attacks its own tissues. Mesenchymal stem cells are known to have the ability to damp down the immune system (see Pitchford et al. [25]).

It is generally agreed that the production rate is a decreasing function over a wide range of cells levels. Indeed, we would expect the production rate to increase when the number of cells decreases. There are many functions that fit this description, for example the Hill function type $\beta(x) = \beta_0 \frac{\theta^n}{\theta^n + x^n}$ (see Mackey [19]) and the Lasota function type $l(x) = e^{-\gamma x}$ [29].

In this work, we focus on the influence of the necessary time delay (duration) of division and the apoptosis rate of the proliferating cells and the production rate of HSCs.

3.2 Description of Hematopoietic Stem Cells

The classic model of HSCs is as follows (see [8, 21, 27]):

$$\begin{cases} \frac{dN}{dt} = -\delta N - \beta(N)N + 2e^{-\gamma\tau}\beta(N_\tau)N_\tau \\ \\ \frac{dP}{dt} = -\gamma P + \beta(N)N - e^{-\gamma\tau}\beta(N_\tau)N_\tau, \end{cases} \tag{3.1}$$

where β is a monotone decreasing function of N which has the explicit form of a Hill function (see [7, 13, 19, 24]):

$$\beta(N) = \beta_0 \frac{\theta^n}{\theta^n + N^n}. \tag{3.2}$$

The symbols in Eq. (3.1) have the following interpretation. N is the number of cells in the nonproliferating phase, $N_\tau = N(t-\tau)$, P the number of cycling proliferating cells, γ the rate of cell loss from the proliferating phase (apoptosis rate), δ the rate of cell loss from the nonproliferating phase, τ the time spent in the proliferating phase, β the feedback function, the rate of recruitment from nonproliferating phase, $\beta_0 > 0$ the maximal rate of reentry in the proliferating phase, and $\theta \geq 0$ the number of resting cells at which β has its maximum rate of change with respect to the resting phase population; $n > 0$ describes the sensitivity of the reintroduction rate with changes in the population, and $e^{-\gamma\tau}$ accounts for the attenuation due to apoptosis (programmed cell death) at rate γ (or the survival function).

Low cell counts lead to quick reactions of the organism, in order to produce enough cells to return to a normal state, and this can then induce shorter cell cycles and a small rate of apoptosis (this is observed for red cells, where, following an anemia, immature cells enter the bloodstream and replace mature cells very quickly) [11]. To control this low cell count and increase the speed of production of HSCs, we replace the quantity $e^{-\gamma\tau}$ by the Wazewska–Lasota function $e^{-\gamma N_\tau}$ (Fig. 3.2). Let's denote the change in the levels of quiescent cells between $t-\tau$ and $t-\tau+\Delta t$ as

$$\Delta N(t-\tau) = N(t+\Delta t-\tau) - N(t-\tau).$$

The production stimulated of level of proliferating cells between $t-\tau$ and $t-\tau+\Delta t$ is given by

$$\Delta P(t) = P(t+\Delta t) - P(t).$$

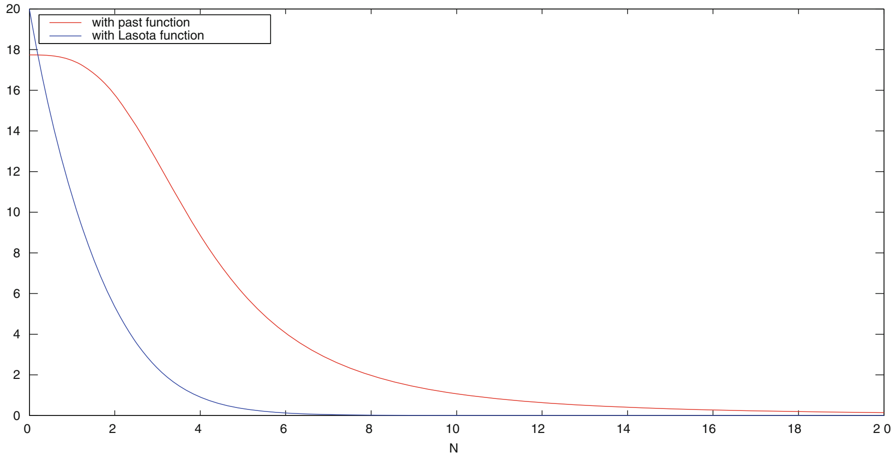

Fig. 3.2 From this figure, we observe that the new function $e^{-\gamma N}\beta(N)$ is much more decreasing than the old function $e^{-\gamma\tau}\beta(N)$

The number of quiescent cells is decreasing, and the production increases after the time delay τ. Therefore we look for a nonnegative function $l(t, \tau)$ such that

$$\Delta P(t) = -l(t, \tau)\Delta N(t - \tau).$$

We suppose there exists some kind of per capita increase. Therefore we choose simply $l(t, \tau) = \xi P(t)$:

$$P(t + \Delta t) - P(t) = -\xi P(t)N(t + \Delta t - \tau) - N(t - \tau),$$

where ξ characterizes the excitability of the HSCs. After dividing by Δt and choosing $\Delta t \longrightarrow 0^+$, we have

$$\frac{d}{dt}P(t) = -\xi P(t)\frac{d}{dt}N(t - \tau).$$

The solution of this equation with some constant υ is

$$P(t) = \upsilon e^{-\xi N(t-\tau)}.$$

υ is a medical constant.

We consider the case when $\upsilon = \gamma$; without loss of generality, we suppose that the survival function of the active cells takes the form $e^{-\gamma N(t-\tau)}$ instead of $e^{-\gamma\tau}$.

The model that is under consideration is governed by the following schematic representation (see Fig. 3.3):

The mathematical model is as follows:

$$\begin{cases} \frac{dN}{dt} = -\delta N - \beta(N)N + 2e^{-\gamma N_\tau}\beta(N_\tau)N_\tau \\ \\ \frac{dP}{dt} = -\gamma P + \beta(N)N - e^{-\gamma N_\tau}\beta(N_\tau)N_\tau. \end{cases} \tag{3.3}$$

Parameter estimation and their references appear in the following table.

Parameters	Value used	Unit	Sources
β_0	3–3.5,	day^{-1}	Mackey et al. [20], Colijn et al. [10]
θ	1.38×10^8–0.5×10^6	cells kg^{-1}	Mackey et al. [20], Colijn et al. [10]
n	3–4		Mackey et al. [20], Colijn et al. [10]
δ	0.16	day^{-1}	Mackey et al. [20]
γ	0.1–0.36	day^{-1}	Mackey et al. [20], Colijn et al. [10]
τ	0.83–0.88	day^{-1}	Mackey et al. [20], Colijn et al. [10]

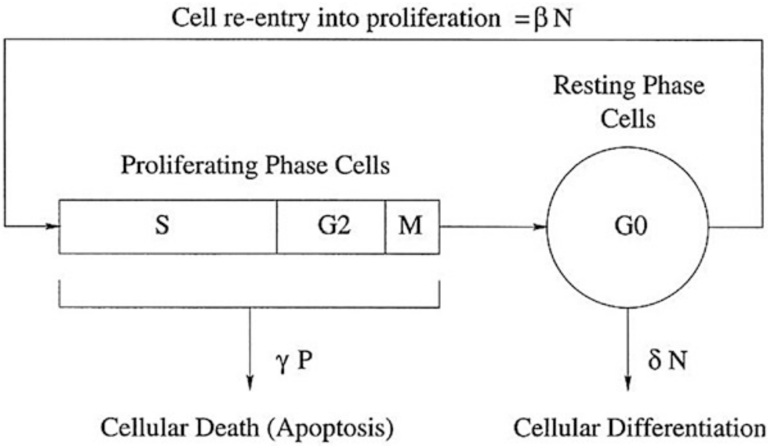

Fig. 3.3 A schematic representation of the $G0$ stem cell model. Proliferating phase cells P include those cells in S (DNA synthesis), $G2$, and M (mitosis), while the resting phase N cells are in the $G0$ phase. δ is the rate of differentiation into all of the committed stem cell populations, while γ represents a loss of proliferating phase cells due to apoptosis. $G(\gamma, N)$ is the rate of cell reentry from $G0$ into the proliferating phase, and τ is the duration of the proliferating phase. See Mackey [19] for further details

Remark by M. C. Mackey This term just tries to capture the fact that the production of erythrocytes is a decreasing function of the number of erythrocytes in the circulation. The delay τ takes into account the fact that it requires a number of days τ between the time the signal to produce erythrocyte precursors is felt in the bone marrow and when mature blood cells are ready for circulation.

This work is organized as follows. In Sect. 3.3, we prove the existence and stability of the possible steady states both with and without delay. Section 3.4 is devoted to the occurrence of Hopf bifurcation by considering the delay as a parameter bifurcation; we prove the occurrence of a sequence of Hopf bifurcation. In Sect. 3.5, we give an algorithm determining the stability and instability of periodic solutions bifurcating from the nontrivial steady state and the direction of bifurcation. At the end we illustrate our result with numerical simulations.

3.3 Steady States and Stability

In this section, we establish the conditions of the existence of the possible steady states. We prove their stability for the model without and with delay and show the influence of the delay and the rate of the apoptosis of the proliferating cells on the stability of the positive steady state.

3.3.1 Existence of Possible Steady States

Consider the following system:

$$\begin{cases} \frac{dN}{dt} = -\delta N - \beta(N)N + 2e^{-\gamma N_\tau}\beta(N_\tau)N_\tau \\ \\ \frac{dP}{dt} = -\gamma P + \beta(N)N - e^{-\gamma N_\tau}\beta(N_\tau)N_\tau. \end{cases} \tag{3.4}$$

The equilibrium points are given by resolving the equations

$$\begin{cases} \frac{dN}{dt} = 0 \\ \\ \frac{dP}{dt} = 0. \end{cases} \tag{3.5}$$

Let $d = \frac{\ln(2)}{\gamma}$ and define the function $F(N) = \beta(N)(2e^{-\gamma N} - 1)$.

As $F(0) = \beta_0$ and $F(d) = 0$, we have that F is a positive decreasing function on $]0, d[$ (Fig. 3.4).

From Eq. $(3.5)_1$, there exists $N^* \in]0, d[$ such that $F(N^*) = \delta$ if and only if (iff) $\delta \in]0, \beta_0[$, where $N^* = F^{-1}(\delta)$ (see, Fig. 3.4), and from Eq. $(3.5)_2$ we obtain

$$P^* = \frac{1}{\gamma}(1 - e^{-\gamma N^*})\beta(N^*)N^*.$$

Let

(H_1): $\delta > \beta_0$,
(H_2): $\delta \in]0, \beta_0[$,

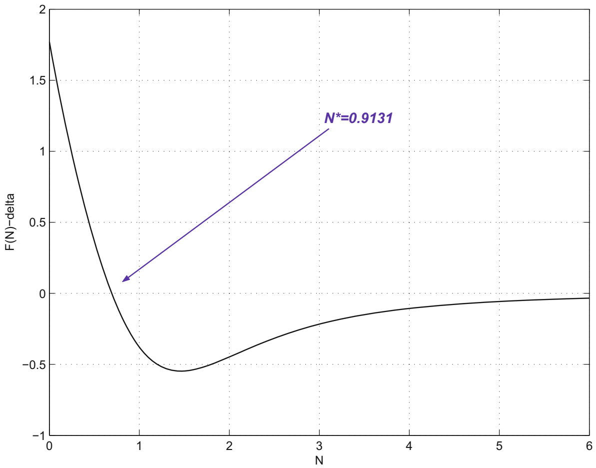

Fig. 3.4 The curve of the functional F showing the existence of N^*

(H_3): $\beta_0 > 0$,

(H_4): $N^* < \inf\left(d = \frac{\ln(2)}{\gamma}, (\frac{\gamma}{2})^{\frac{1}{n-1}}\right)$.

Proposition 1. *(1) If (H_1) is satisfied, system (3.4) has a unique trivial equilibrium point $E_0 = (0,0)$.*

(2) If (H_2) is satisfied, system (3.4) has two equilibrium points: The first is trivial, $E_0 = (0,0)$, and the second is nontrivial (positive), given by $E^* = (N^*, P^*)$, where $N^* = F^{-1}(\delta)$ and $P^* = \frac{1}{\gamma}(1 - e^{-\gamma N^*})\beta(N^*)N^*$.

The previous proposition gives a condition of the existence of two different equilibria. In fact, by definition δ is the differentiation rate of cells and β_0 is the maximal proliferation rate of reentry into the proliferating phase. Therefore, if the proliferation rate is small, then in addition to the trivial equilibrium we get another nontrivial equilibrium. The normal step is to investigate the condition of stability of each equilibrium; for this we will first use the case without delay $\tau = 0$; second, we will study the effect of increasing the delay $\tau > 0$ on the stability of our model.

3.3.2 Stability of Steady States for $\tau = 0$

For $\tau = 0$, system (3.4) becomes a system of ordinary differential equations (ODEs) given by the following system:

$$\begin{cases} \frac{dN}{dt} = -\delta N - \beta(N)N + 2e^{-\gamma N}\beta(N)N \\ \\ \frac{dP}{dt} = -\gamma P + \beta(N)N - e^{-\gamma N}\beta(N)N. \end{cases} \tag{3.6}$$

Proposition 2. *(1) If (H_1) is satisfied, the trivial equilibrium point $E_0 = (0,0)$ is asymptotically stable.*

(2) If (H_2) is satisfied, the equilibrium point $E_0 = (0,0)$ is unstable and the nontrivial (positive) $E^* = (N^*, P^*)$ is asymptotically stable.

Proof. (1) The steady states are the same given in Proposition 1. To study the stability of $E_0 = (0,0)$, we linearize system (3.6) around the concerned steady state E_0.

The linearized equation is given as follows:

$$\begin{cases} \frac{dN}{dt} = -\delta N + \beta(0)N \\ \\ \frac{dP}{dt} = -\gamma P, \end{cases} \tag{3.7}$$

and the characteristic equation associated to E_0 is

$$(\lambda + \delta - \beta(0))(\lambda + \gamma) = 0. \tag{3.8}$$

Then the characteristic roots are as follows: $\lambda_1 = -\gamma$ and $\lambda_2 = -\delta + \beta_0$.

(2) Suppose now that $0 < \delta < \beta_0$ and let $N = x + N^*$ and $P = y + P^*$. We linearize system (3.6) around the equilibrium point E^* and the linearized system is given as follows:

$$\begin{cases} \frac{dx}{dt} = -\delta x + \left\{ -\beta'(N^*)N^* - 2\gamma e^{-\gamma N^*}\beta(N^*)N^* + 2e^{-\gamma N^*}\beta'(N^*)N^* \right\} x \\ \frac{dy}{dt} = -\gamma y + \left\{ \gamma \frac{P^*}{N^*} + \gamma \frac{P^*\beta'(N^*)}{\beta(N^*)} + \gamma e^{-\gamma N^*}\beta(N^*)N^* \right\} x. \end{cases} \tag{3.9}$$

The characteristic equation is given by

$$(\lambda + \gamma)(\lambda + \beta'(N^*)N^* + 2\gamma e^{-\gamma N^*}\beta(N^*)N^* - 2e^{-\gamma N^*}\beta'(N^*)N^*) = 0 \tag{3.10}$$

and the associated characteristic roots are $\lambda_1 = (2e^{-\gamma N^*} - 1)\beta'(N^*)N^* - 2\gamma e^{-\gamma N^*}\beta(N^*)N^*$ and $\lambda_2 = -\gamma$. As β is a decreasing positive function and $2e^{-\gamma N^*} - 1 > 0$, we have $\lambda_i < 0$, $i = 1, 2$.

Then the steady states E^* are asymptotically stable.

It is clear from the previous results for a nondelay model that when the trivial equilibrium exists and is unique, then it is asymptotically stable; otherwise, the nontrivial equilibrium exists and is asymptotically stable. Next, we will study the stability of our delay model and the effect of the delay on the stability of these equilibria.

3.3.3 Stability of Steady States for $\tau > 0$

Proposition 3. *(1) If (H_1) is satisfied, the trivial equilibrium point $E_0 = (0, 0)$ is asymptotically stable for all $\tau > 0$.*

(2) If (H_2)–(H_4) are satisfied, there exists $\tau_0 > 0$ such that the nontrivial (positive) steady state $E^* = (N^*, P^*)$ is asymptotically stable for $\tau < \tau_0$ and unstable for $\tau > \tau_0$ and the equilibrium point $E_0 = (0, 0)$ is unstable for all $\tau > 0$.

Proof. (1) By linearizing system (3.3) around the steady state E_0, we obtain the following linearized equation:

$$\begin{cases} \frac{dN}{dt} = -\delta N - \beta_0 N + 2\beta_0 N_\tau \\ \frac{dP}{dt} = -\gamma P + \beta_0 N - \beta_0 N_\tau. \end{cases} \tag{3.11}$$

The characteristic equation is

$$(\lambda + \gamma)(\lambda + \delta + \beta_0 - 2\beta_0 e^{-\lambda\tau}) = 0. \tag{3.12}$$

For the stability of E_0, one needs to study the position of the characteristic roots of the following equation:

$$(\lambda + \delta + \beta_0 - 2\beta_0 e^{-\lambda\tau}) = 0. \tag{3.13}$$

From Proposition 3, E_0 is asymptotically stable. For a change of stability, replacing $\lambda = i\omega$ in (3.13) and separating the real and imaginary parts gives us

$$\begin{cases} \delta + \beta_0 - 2\beta_0 \cos(\omega\tau) = 0 \\ \\ \quad \omega + 2\beta_0 \sin(\omega\tau) = 0. \end{cases} \tag{3.14}$$

From (3.14), we have $\omega^2 = (\beta_0 - \delta)(3\beta_0 + \delta)$. As $\beta_0 < \delta$, there exists any value of τ in which E_0 changes the stability. Then we conclude that E_0 is asymptotically stable for all $\tau > 0$.

(2) Suppose now that $\tau > 0$ and $\delta < \beta_0$, and by linearizing system (3.3) around the nontrivial steady state we have the following linearized system:

$$\begin{cases} \frac{dx(t)}{dt} = -\delta x(t) - h(N^*)x(t) + 2g(N^*)x(t-\tau) \\ \\ \frac{dy(t)}{dt} = -\gamma y(t) + h(N^*)x(t) - g(N^*)x(t-\tau), \end{cases} \tag{3.15}$$

where

$$h(N^*) = \beta(N^*) + \beta'(N^*)N^* = (\beta(N)N)'_{N=N^*} = H^{'}(N)_{/N=N^*},$$

$$\begin{aligned} g(N^*) &= e^{-\gamma N^*}\beta(N^*) - \gamma e^{-\gamma N^*}\beta(N^*)N^* + e^{-\gamma N^*}\beta'(N^*)N^* \\ &= (e^{-\gamma N}\beta(N)N)'_{N=N^*} == G^{'}(N)_{/N=N^*}, \end{aligned}$$

and

$$x = N - N^* \qquad\qquad y = P - P^*.$$

The characteristic equation is

$$\Delta(\lambda,\tau) = (\lambda + \gamma)(\lambda + \delta + h(N^*) - g(N^*)e^{-\lambda\tau}) = 0. \tag{3.16}$$

To study the change of stability, replacing $\lambda = i\omega$ and separating the real and imaginary parts gives us $\delta + h(N^*) - g(N^*)\cos(\omega\tau) = 0$ and $\omega + g(N^*)\sin(\omega\tau) = 0$.

Then

$$\omega^2 = g(N^*)^2 - (\delta + h(N^*))^2 = (g(N^*) - \delta - h(N^*)).$$

From the expressions of h and g, we have

$$g(N^*) - \delta - h(N^*) = (2e^{-\gamma N^*} - 1)\beta'(N^*)N^* - 2\gamma e^{-\gamma N^*}\beta(N^*)N^* < 0.$$

By calculations, we obtain

$$g(N^*) + \delta + h(N^*) = 2e^{-\gamma N^*}\beta(N^*)(2 - \gamma N^*) + \beta'(N^*)N^* + 2e^{-\gamma N^*}\beta'(N^*)N^*.$$

From the expression of β, we have

$$\begin{aligned} &2e^{-\gamma N^*}\beta(N^*)(2 - \gamma N^*) + 2e^{-\gamma N^*}\beta'(N^*)N^* \\ &= 2e^{-\gamma N^*}\beta(N^*)(2 - \gamma N^* - \frac{\beta_0\theta^n}{\theta^n + N^{*n}}) \\ &= 2e^{-\gamma N^*}\beta(N^*)(2N^{*n} - \gamma N^* + (2 - \beta_0)\theta^n). \end{aligned}$$

As $\beta_0 < 2$ and $N^* < \inf\left(\frac{\ln(2)}{2}, (\frac{\gamma}{2})^{\frac{1}{n-1}}\right)$, and from the expression of the function β, we have

$$g(N^*) + \delta + h(N^*) < 0$$

and the quantity of ω^2 is positive.

As

$$\mid \frac{\delta + h(N^*)}{g(N^*)} \mid < 1,$$

let

$$\tau_k = \frac{1}{\omega_0}\left\{\arccos\left(\frac{\delta + h(N^*)}{g(N^*)}\right) + 2k\pi\right\}, k = 0, 1, 2, 3, \ldots, \tag{3.17}$$

and

$$\omega_0 = \sqrt{g(N^*)^2 - (\delta + h(N^*))^2}. \tag{3.18}$$

Then Eq. (3.16) has a pair of purely imaginary roots $\pm i\omega_0$ at $\tau = \tau_k,\ k = 0, 1, 2, 3, \ldots$.

Let $\lambda(\tau) = \eta(\tau) + \omega(\tau)$ denote a root of (3.16) near $\tau = \tau_k$ such that $\eta(\tau_k) = 0,\ \omega(\tau_k) = \omega_0$.

Then we deduce the result.

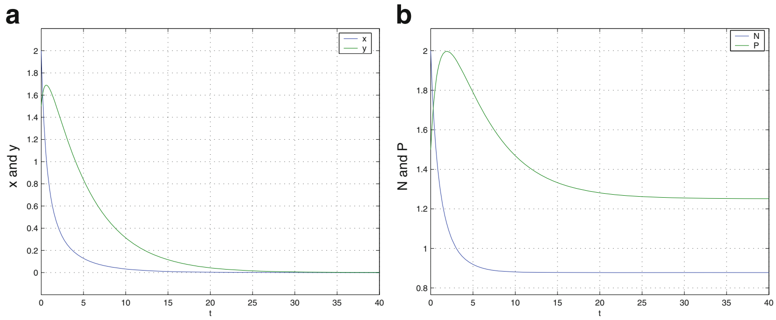

Fig. 3.5 (**a**) Stability of $E_0 = (0, 0)$ and the nonexistence of E^* for $\delta > \beta_0$. (**b**) Instability of $E_0 = (0, 0)$ and stability of E^* for $\tau = 0$ and $\delta < \beta_0$

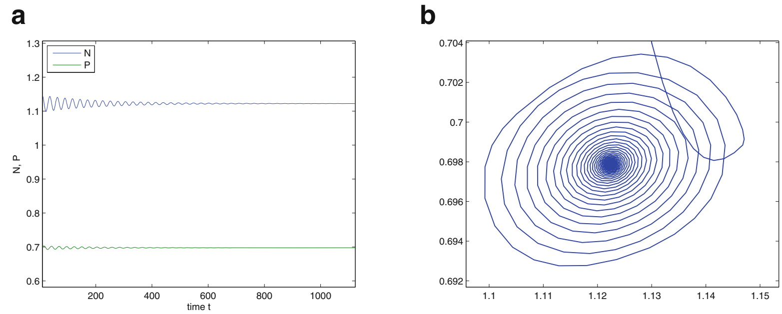

Fig. 3.6 Stability of E^* for $n = 3$, $\tau = 10$ in (t,P) and (t,N) planes (a) and in (P,N) plane

From this result, we showed that the condition of stability of the trivial solution is the same for the delay and nondelay models (see Fig. 3.5). On the other hand, we have additional conditions for the stability of the nontrivial solution (see, Figs. 3.6 and 3.8); there exists a threshold delay τ_0 under which the local asymptotic stability holds if $0 < \sup(\delta, 2) < \beta_0$ ($2 < \beta_0$ means that the maximal rate of proliferation is greater than the rate of division of one cell into two daughters) and $N^* < \inf\left(\frac{\ln(2)}{\gamma}, (\frac{\gamma}{2})^{\frac{1}{n-1}}\right)$ and beyond this threshold the system goes to Hopf bifurcation and becomes unstable (see, Figs. 3.7, 3.9, and 3.10).

It is worth mentioning that $\inf\left(\frac{\ln(2)}{\gamma}, (\frac{\gamma}{2})^{\frac{1}{n-1}}\right)$ is determined by the order of $\gamma^{\frac{n}{n-1}}$ and $2^{\frac{1}{n-1}}\ln(2)$. This can be determined by knowing the range of possible values of γ.

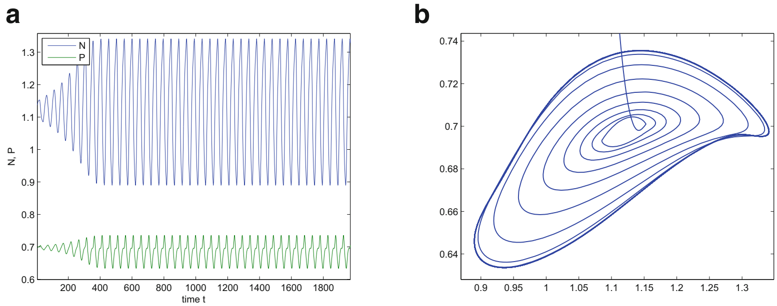

Fig. 3.7 Periodic solutions for $n = 3$, $\tau = 20$ in (t,P) and (t,N) planes (a) and in (P,N) plane

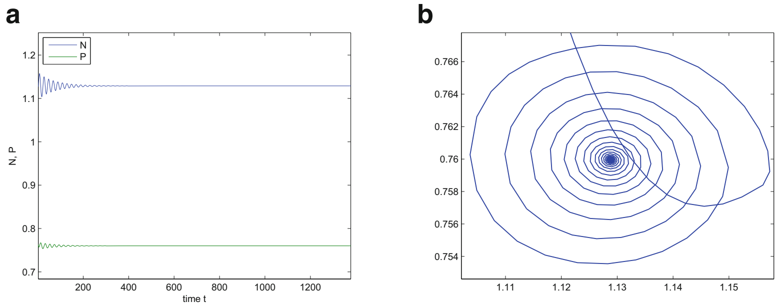

Fig. 3.8 Stability of E^* for $n = 4$, $\tau = 7$ in (t,P) and (t,N) planes (a) and in (P,N) plane

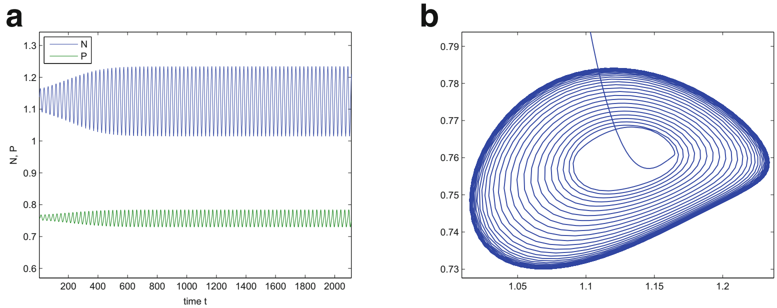

Fig. 3.9 Periodic solutions for $n = 4$, $\tau = 10$ in (t,P) and (t,N) planes (a) and in (P,N) plane

3.4 Branch of Bifurcating Periodic Solutions

We apply the Hopf bifurcation theorem to show the existence of a nontrivial periodic solution of system (3.4), for suitable values of parameter delay, used as a bifurcation parameter. Therefore, the periodicity is a result of changing the type of stability, from a stable stationary solution to a limit cycle.

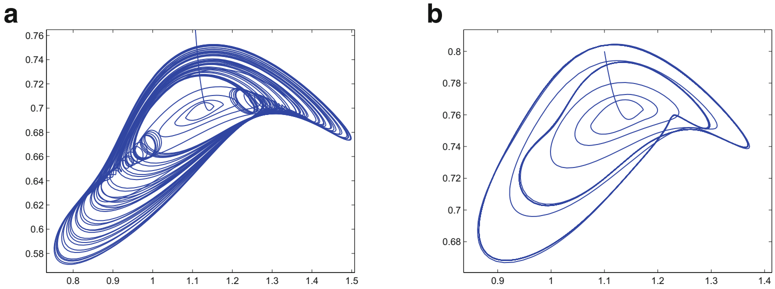

Fig. 3.10 Chaotic solutions for $n = 3$, $\tau = 30$ (**a**) and $n = 4$, $\tau = 16$ (**b**)

In what follows, we recall the formulation of the Hopf bifurcation theorem for delayed differential equations. Let

$$\frac{dx(t)}{dt} = F(\alpha, x_t), \tag{3.19}$$

with $F : \mathbb{R} \times C \longrightarrow \mathbb{R}^n$, F of class $\mathscr{C}^k$, $k \geq 2$, $F(\alpha, 0) = 0$ for all $\alpha \in \mathbb{R}$, and $C = C([-r, 0], \mathbb{R}^n)$ the space of continuous functions from $[-r, 0]$ into $\mathbb{R}^n$. As usual, x_t is the function defined from $[-r, 0]$ into $\mathbb{R}^n$ by $x_t(\theta) = x(t + \theta)$, $r \geq 0$, and $n \in \mathbb{N}^*$.

The following assumptions are stated:

(M_0) F of class $\mathscr{C}^k$, $k \geq 2$, $F(\alpha, 0) = 0$ for all $\alpha \in \mathbb{R}$, and the map $(\alpha, \varphi) \longrightarrow D^k_\varphi F(\alpha, \varphi)$ sends bounded sets into bounded sets.

(M_1) The characteristic equation

$$\Delta(\alpha, \lambda) = \det(\lambda Id - D_\varphi F(\alpha, 0) \exp(\lambda(.)Id)) \tag{3.20}$$

of the linearized equation of (3.19) around the equilibrium $v = 0$,

$$\frac{dv(t)}{dt} = D_\varphi F(\alpha, 0) v_t, \tag{3.21}$$

has in $\alpha = \alpha_0$ a simple imaginary root $\lambda_0 = \lambda(\alpha_0) = i$. All others roots λ satisfy $\lambda \neq m\lambda_0$ for $m \in \mathbb{Z}$.

As $[(M_2)]$ $\lambda(\alpha)$ is the branch of roots passing through λ_0, we have

$$\frac{\partial}{\partial \alpha} Re\lambda(\alpha)_{/\alpha=\alpha_0} \neq 0. \tag{3.22}$$

Theorem 1 ([16]). *Under the assumptions* (M_0), (M_1), *and* (M_2), *there exist constants* $\varepsilon_0 > 0$ *and* δ_0 *and functions* $\alpha(\varepsilon)$, $T(\varepsilon)$, *and a* $T(\varepsilon)$*-periodic function* $x^*(\varepsilon)$ *such that* *(a) All of these functions are of class* $\mathscr{C}^{k-1}$ *with respect to* ε*, for* $\varepsilon \in [0, \varepsilon_0[$, $\alpha(0) = \alpha_0$, $T(0) = 2\pi$, $x^*(0) = 0$.

(b) $x^*(\varepsilon)$ *is a* $T(\varepsilon)$*-periodic solution of* (3.19)*, for the parameter values equal* $\alpha(\varepsilon)$.

(c) For $| \alpha - \alpha_0 | < \delta_0$ *and* $| T - 2\pi | < \delta_0$*, any T-periodic solution p, with* $\| p \| < \delta_0$*, of* (3.19) *for the parameter value* α*, there exists* $\varepsilon \in [0, \varepsilon_0[$ *such that* $\alpha = \alpha(\varepsilon)$, $T = T(\varepsilon)$*, and p is up to a phase shift equal to* $x^*(\varepsilon)$.

Normalizing the delay τ by the time scaling $t \to \frac{t}{\tau}$, effecting the change of variables $u(t) = N(t\tau)$ and $v(t) = P(t\tau)$, system (3.3) is transformed into

$$\begin{cases} \dot{u}\ (t) = \tau[-\delta u(t) - \alpha(u(t)) + 2e^{-\gamma u(t-1)}\alpha(u(t-1))] \\ \dot{v}\ (t) = \tau[-\gamma v(t) + \alpha(u(t)) - e^{-\gamma u(t-1)}\alpha(u(t-1))], \end{cases} \tag{3.23}$$

where $\alpha(x) = \beta(x)x$.

By the translation $z(t) = (u(t), v(t)) - (N^*, P^*)$, system (3.23) is written as a functional differential equation (FDE) in $C := C([-1, 0], \mathbb{R}^2)$:

$$\dot{z}\ (t) = L(\tau)z_t + f_0(z_t, \tau), \tag{3.24}$$

where $L(\tau) : C \longrightarrow \mathbb{R}^2$ is a linear operator and $f_0 : C \times \mathbb{R} \longrightarrow \mathbb{R}^2$ are respectively given by

$$L(\tau)\varphi = \tau \begin{pmatrix} -(\delta + h(N^*))\varphi_1(0) + 2g(N^*)\varphi_1(-1) \\ -\gamma\varphi_2(0) + h(N^*)\varphi_1(0) - g(N^*)\varphi_1(-1) \end{pmatrix}$$

$$f_0(\varphi, \tau) = \tau \begin{pmatrix} -H(\varphi_1(0)+N^*)+h(N^*)\varphi_1(0)+2G(\varphi_1(-1)+N^*)-\delta N^*-2g(N^*)\varphi_1(-1) \\ H(\varphi_1(0)+N^*)-h(N^*)\varphi_1(0)-G(\varphi_1(-1)+N^*)-\gamma P^*+g(N^*)\varphi_1(-1). \end{pmatrix}$$

for $\varphi = (\varphi_1, \varphi_2) \in C$.

The following theorem gives the existence of bifurcating periodic solutions.

Theorem 2. *Suppose* (H_2)–(H_4)*. Then Eq.* (3.23) *has a family of periodic solutions* $p_l(\varepsilon)$ *with period* $T_l = T_l(\varepsilon)$ *for the parameter values* $\tau = \tau(\varepsilon)$ *such that* $p_l(0) = 0$ ($p_l(0) = (N^*, P^*)$ *for system* (3.3)), $T_l(0) = \frac{2\pi}{\omega_0}$*, and* $\tau(0) = \tau_k$, $k = 0, 1, 2, \ldots$*. In this case* τ_k, $k = 0, 1, 2, \ldots$*, and* ω_0 *are respectively given by Eqs.* (3.17) *and* (3.18).

Proof. We apply the Hopf bifurcation theorem. From the expression of f in (3.24), we have

$$f(0,\tau) = 0 \qquad \text{and} \qquad \frac{\partial f(0,\tau)}{\partial \varphi} = 0, \text{ for all } \tau > 0.$$

From (3.16), we have

$$\Delta(i\omega,\tau) = 0 \qquad \Leftrightarrow \qquad \begin{cases} \omega = \omega_0 \\ \text{and} \\ \tau = \tau_k, k = 0, 1, 2, \ldots. \end{cases}$$

Thus, characteristic equation (3.16) has a pair of simple imaginary roots $\lambda_0 = i\omega_0$ and $\overline{\lambda}_0 = -i\omega_0$ at $\tau = \tau_k$, $k = 0, 1, 2, \ldots$.

Lastly, we need to verify the transversality condition.

From (3.16), $\Delta(\lambda_0, \tau_k) = 0$ and $\frac{\partial}{\partial\lambda}\Delta(\lambda_0, \tau_k) = (\lambda_0 + \gamma)(1 - \tau_k g(N^*) e^{-\lambda\tau_k}) \neq 0$. According to the implicit function theorem, there exists a complex function $\lambda = \lambda(\tau)$ defined in a neighborhood of τ_k such that $\lambda(\tau_k) = \lambda_0$ and $\Delta(\lambda(\tau), \tau) = 0$ and

$$\lambda^{'}(\tau) \;= -\frac{\partial\Delta(\lambda,\tau)/\partial\tau}{\partial\Delta(\lambda,\tau)/\partial\lambda}, \text{ for } \tau \text{ in a neighborhood of } \tau_k,\ k = 0, 1, 2, \ldots. \tag{3.25}$$

Let $\lambda(\tau) = \eta(\tau) + \omega(\tau)$. From (3.25) we have

$$\eta(\tau)^{'}(\tau)_{/\tau=\tau_k} = -\frac{\omega_0^2}{\cos(\omega_0\tau_k) + \tau_k g(N^*))^2 + \sin^2(\omega_0\tau_k)} \text{ for } k = 0, 1, 2, \ldots.$$

By the continuity property, we conclude that $\eta^{'}(\tau)_{/\tau=\tau_k} < 0$, for $k = 0, 1, 2, \ldots$.

3.5 Direction of Hopf Bifurcation

In this section we follow methods presented in [12], where the direction and stability of the bifurcating branch are obtained by the Taylor expansion of the delay function τ that describes the parameter of bifurcation near the critical value τ_0 (see Theorem 2). Namely, this direction and stability are determined by the sign of the first nonzero term of Taylor expansion, that is,

$$\tau(\varepsilon) = \tau_0 + \tau_2\varepsilon^2 + o(\varepsilon^2), \tag{3.26}$$

and the sign of τ_2 determines that either the bifurcation is supercritical (if $\tau_2 > 0$) and periodic orbits exist for $\tau > \tau_0$, or it is subcritical (if $\tau_2 < 0$) and periodic orbits exist for $\tau < \tau_0$. The term τ_2 may be calculated (see [12]) using the formula

$$\tau_2 = \frac{Re(c)}{Re(qD_2M_0(i\zeta_0, \tau_0)p)}, \tag{3.27}$$

where M_0 is the characteristic matrix of (3.24) given by

$$M_0(\lambda, \tau) = \begin{pmatrix} \lambda - \tau a(\tau) - \tau b(\tau)e^{-\lambda} & 0 \\ -\tau h(N^*) + \tau g(N^*)e^{-\lambda}) & \lambda + \gamma\tau \end{pmatrix},$$

where $a = a(\tau) = -(\delta + h(N^*))$ and $b = b(\tau) = 2g(N^*)$.

$D_2M_0(i\zeta_0, \tau_0)$ denotes the derivative of M_0 with respect to τ at the critical point $(i\zeta_0, \tau_0)$, and the constant c is defined as follows:

$$c = \frac{1}{2}qD_1^3f_0(0, \tau_0)(P^2(\theta), \overline{P}(\theta))$$

$$+qD_1^2f_0(0, \tau_0)(e^{0\cdot}M_0^{-1}(0, \tau_0)D_1^2f_0(0, \tau_0)(P(\theta), \overline{P}(\theta)), P(\theta))$$

$$+\frac{1}{2}qD_1^2f_0(0, \tau_0)(e^{2i\zeta_0\cdot}M_0^{-1}(2i\zeta_0, \tau_0)D_1^2f_0(0, \tau_0)(P(\theta), P(\theta)), \overline{P}(\theta)),$$

where f_0 is the nonlinear part of (3.24), $D_1^if_0, i = 2, 3$, denotes the ith derivative of f_0 with respect to φ, $P(\theta)$ denotes the eigenvector of A, $\overline{P}(\theta)$ denotes the conjugate eigenvector, and p and q are defined later.

Now, we will describe all the preceding operators and vectors precisely. Let $L := L(\tau_0) : C([-1, 0], \mathbb{R}^2) \longrightarrow \mathbb{R}^2$ denote the linear part of (3.24). Using the Riesz representation theorem, one obtains (see [16])

$$L\varphi = \int_{-1}^{0} d\eta(\theta)\varphi(\theta), \tag{3.28}$$

where

$$d\eta(\theta) = \tau_0 \begin{pmatrix} -(\delta + h(N^*))\delta(\theta) + 2g(N^*)\delta(\theta + 1) & 0 \\ h(N^*)\delta(\theta) - g(N^*)\delta(\theta + 1) & -\gamma\delta(\theta); \end{pmatrix} \tag{3.29}$$

δ denotes the Dirac function and $u^* = u^*(\tau_0)$.

Let A denote the generator of a semigroup generated by the linear part of (3.24). Then

$$A\varphi(\theta) = \begin{cases} \frac{d\varphi}{d\theta}(\theta) \text{ for } \theta \in [-1, 0) \\ \\ L\varphi \text{ for } \theta = 0, \end{cases} \tag{3.30}$$

where $\varphi \in C([-1, 0], \mathbb{R}^2)$.

To study the direction of Hopf bifurcation, one needs to calculate the second and third derivatives of the nonlinear part of (3.24):

$$D_1^2 f_0(\varphi, \tau)\psi\chi = \tau \begin{pmatrix} -H^{''}(N^* + \varphi_1(0))\psi_1(0)\chi_1(0) \\ +2G^{''}(N^* + \varphi_1(-1))\psi_1(-1)\chi_1(-1) \\ \\ H^{''}(N^* + \varphi_1(0))\psi_1(0)\chi_1(0) \\ -G^{''}(N^* + \varphi_1(-1))\psi_1(-1)\chi_1(-1) \end{pmatrix} \tag{3.31}$$

and

$$D_1^3 f_0(\varphi, \tau)\psi\chi\upsilon = \tau \begin{pmatrix} -H^{'''}(N^* + \varphi_1(0))\psi_1(0)\chi_1(0)\upsilon_1(0) \\ +2G^{'''}(N^* + \varphi_1(-1))\psi_1(-1)\chi_1(-1)\upsilon_1(-1) \\ \\ H^{'''}(N^* + \varphi_1(0))\psi_1(0)\chi_1(0)\upsilon_1(0) \\ -G^{'''}(N^* + \varphi_1(-1))\psi_1(-1)\chi_1(-1)\upsilon_1(-1). \end{pmatrix} \tag{3.32}$$

Then

$$\begin{aligned} D_1^2 f_0(0, \tau_0)\psi\chi = \tau_0 H^{''}(N^*)\psi_1(0)\chi_1(0)\begin{pmatrix} -1 \\ 1 \end{pmatrix} \\ +\tau_0 G^{''}(N^*)\psi_1(-1)\chi_1(-1)\begin{pmatrix} 2 \\ -1 \end{pmatrix} \end{aligned} \tag{3.33}$$

and

$$\begin{aligned} D_1^3 f_0(0, \tau_0)\psi\chi\upsilon = \tau_0 H^{'''}(N^*)\psi_1(0)\chi_1(0)\upsilon_1(0)\begin{pmatrix} -1 \\ 1 \end{pmatrix} \\ +\tau_0 G^{'''}(N^*)\psi_1(-1)\chi_1(-1)\upsilon_1(-1)\begin{pmatrix} 2 \\ -1 \end{pmatrix}; \end{aligned} \tag{3.34}$$

$\psi = (\psi_1, \psi_2), \chi = (\chi_1, \chi_2), \upsilon = (\upsilon_1, \upsilon_2) \in C([-1, 0], \mathbb{R}^2)$.

As $(i\zeta_0, \tau_0)$ is a solution of (3.16), then $i\zeta_0$ is an eigenvalue of A and there is an eigenvector of the form $P(\theta) = pe^{i\zeta_0\theta}$ and $p_i, i = 1, 2$ are complex numbers which satisfy the following system of equations:

$$Mp = 0$$

with

$$M = M_0(i\zeta_0, \tau_0) = \begin{pmatrix} 0 & 0 \\ -\tau_0 h(N^*) + \tau_0 g(N^*)e^{-i\zeta_0} & i\zeta_0 + \gamma\tau_0. \end{pmatrix}. \tag{3.35}$$

Then one may assume

$$p_1 = 1$$

and calculate

$$p_2 = \tau_0 \frac{h(N^*) - g(N^*)e^{-i\zeta_0}}{i\zeta_0 + \gamma\tau_0}.$$

Now, consider A^*, namely, an operator conjugated to A, $A^* : C([0, 1], \mathbb{R}^2) \longrightarrow \mathbb{R}^2$, defined by

$$A^*\psi(s) = \begin{cases} -\frac{d\psi}{ds}(s) \text{ for } s \in (0, 1] \\ -\int_{-1}^{0} \psi(-s)d\eta(s) \text{ for } s = 0, \end{cases} \tag{3.36}$$

and $\psi = (\psi_1, \psi_2) \in C([0, 1], \mathbb{R}^2)$.

Let $Q(s) = qe^{i\zeta_0 s}$ be the eigenvector for A^* associated to eigenvalue $i\zeta_0$, $q = (q_1, q_2)^T$. One needs to choose q such that the inner product (see [16])

$$< Q, \overline{P} >= Q(0)\overline{P}(0) - \int_{-1}^{0}\int_{0}^{\theta} Q(\xi - \theta)d\eta(\theta)\overline{P}(\xi)d\xi$$

is equal to 1. Therefore

$$q_2 = 0$$

leads to

$$q_1 = \frac{1}{1 - 2\tau_0 a + i\zeta_0}.$$

From (3.33) and (3.34) we have

$$D_1^2 f_0(0,\tau_0)(P(\theta),\overline{P}(\theta)) = \tau_0 \left[H''(N^*) \begin{pmatrix} -1 \\ 1 \end{pmatrix} + G''(N^*) \begin{pmatrix} 2 \\ -1 \end{pmatrix} \right] \tag{3.37}$$

$$D_1^2 f_0(0,\tau_0)(P(\theta),P(\theta)) = \tau_0 \left[H''(N^*) \begin{pmatrix} -1 \\ 1 \end{pmatrix} + G''(N^*) e^{-2i\zeta_0} \begin{pmatrix} 2 \\ -1 \end{pmatrix} \right] \tag{3.38}$$

and

$$D_1^3 f_0(0,\tau_0)(P^2(\theta),\overline{P}(\theta)) = \tau_0 \left[H'''(N^*) \begin{pmatrix} -1 \\ 1 \end{pmatrix} + e^{-i\zeta_0} G'''(N^*) \begin{pmatrix} 2 \\ -1 \end{pmatrix} \right]. \tag{3.39}$$

and

$$\frac{1}{2} q D_1^3 f_0(0,\tau_0)(P^2(\theta),\overline{P}(\theta)) = \frac{\tau_0 q_1}{2} \left(H'''(N^*) + 2e^{-i\zeta_0} G'''(N^*) \right). \tag{3.40}$$

From the expression of M_0, we have

$$M_0^{-1}(0,\tau_0) = -\frac{1}{\gamma\tau_0(a+b)} \begin{pmatrix} \gamma & 0 \\ h(N^*) - g(N^*) & -(a+b) \end{pmatrix} \tag{3.41}$$

and

$$M_0^{-1}(2i\zeta_0,\tau_0) = \Delta^{-1}(2i\zeta_0,\tau_0) \begin{pmatrix} 2i\zeta_0 + \gamma\tau_0 & 0 \\ \tau_0 h(N^*) + \tau_0 g(N^*) e^{-2i\zeta_0} & 2i\zeta_0 - \tau_0 a - \tau_0 b e^{-2i\zeta_0} \end{pmatrix}. \tag{3.42}$$

From (3.33), (3.37), (3.38), (3.41), and (3.42) we have

$$\begin{aligned} qD_1^2 f_0(0,\tau_0)(e^0 M_0^{-1}(0,\tau_0) D_1^2 f_0(0,\tau_0)(P(\theta),\overline{P}(\theta)),P(\theta)) = \\ q_1 \tau_0 M_1 \left(-H''(N^*) + 2G''(N^*) e^{-i\zeta_0} \right), \end{aligned} \tag{3.43}$$

where

$$M_1 = -\frac{1}{\gamma\tau_0(a+b)} \gamma\tau_0(-H''(N^*) + 2G''(N^*))$$

and

$$\begin{aligned} qD_1^2 f_0(0,\tau_0)(e^{2i\zeta_0} M_0^{-1}(2i\zeta_0,\tau_0) D_1^2 f_0(0,\tau_0)(P(\theta),P(\theta)),\overline{P}(\theta)) = \\ q_1 \tau_0 N_1 \left(-H''(N^*) + 2G''(N^*) e^{-i\zeta_0} \right), \end{aligned} \tag{3.44}$$

where

$$N_1 = \tau_0 \Delta^{-1}(2i\zeta_0, \tau_0)(2i\zeta_0 + \gamma\tau_0)(-H^{''}(N^*) + 2G^{''}(N^*)).$$

Then

$$c = \frac{\tau_0 q_1}{2}\left(-H^{'''}(N^*) + 2e^{-i\zeta_0}G^{'''}(N^*)\right) + q_1\tau_0 M_1\left(-H^{''}(N^*) + 2G^{''}(N^*)e^{-i\zeta_0}\right)$$
$$\frac{q_1\tau_0 N_1}{2}\left(-H^{''}(N^*) + 2G^{''}(N^*)e^{-i\zeta_0}\right)$$

and

$$Re(c) = \frac{\tau_0}{2}\left(\frac{(1-\tau_0 a)}{(1-2\tau_0 a)^2 + \zeta_0^2}X + \frac{-\zeta_0}{(1-2\tau_0 a)^2 + \zeta_0^2}Y\right), \tag{3.45}$$

where

$$X = -H^{'''}(N^*) + 2\cos(\zeta_0)G^{'''}(N^*) - 2M_1 H^{''}(N^*) + 4\cos(\zeta_0)M_1 G^{''}(N^*)$$
$$+ \tau_0\frac{4\zeta_0^2 + \gamma^2\tau_0^2}{\|\Delta(2i\zeta_0, \tau_0)\|^2}\Big(-(\tau_0 a - \tau_0 b\cos(\zeta_0))(-H^{''}(N^*)$$
$$+2\cos(\zeta_0)M_1 G^{''}(N^*)) - 2\sin(\zeta_0)G^{''}(N^*)(2\zeta_0 + \tau_0 b\sin(\zeta_0))\Big)$$
$$Y = -2\sin(\zeta_0)G^{'''}(N^*) - 4\sin(\zeta_0)M_1 G^{''}(N^*)$$
$$+ \tau_0\frac{4\zeta_0^2 + \gamma^2\tau_0^2}{\|\Delta(2i\zeta_0, \tau_0)\|^2}\Big((\tau_0 a - \tau_0 b\cos(\zeta_0))\sin(\zeta_0)G^{''}(N^*)$$
$$-(2\zeta_0 + \tau_0 b\sin(\zeta_0))(-H^{''}(N^*) + 2\cos(\zeta_0)M_1 G^{''}(N^*)).\Big)$$

Then we deduce the following result:

Theorem 3. *Let* $Re(c)$ *be given in (3.45) and* γ *sufficiently small. Then*

(a) The Hopf bifurcation occurs as τ *crosses* τ_0 *to the right (supercritical Hopf bifurcation) if* $Re(c) > 0$ *and to the left (subcritical Hopf bifurcation) if* $Re(c) < 0$.
(b) Also, the bifurcating periodic solutions are stable if $Re(c) > 0$ *and unstable if* $Re(c) < 0$.

Note that Theorem 3 provides an explicit algorithm for detecting the direction and stability of Hopf bifurcation (Figs. 3.7, 3.9, and 3.10).

Acknowledgements We are very grateful to the editors and to Professor M. C. Mackey for their valuable discussions.

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