Stability and bifurcation analysis in leukopoiesis models with two delays

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***Abstract*—We consider a nonlinear system of two equations, describing the evolution of a stem cell population and the resulting white blood cell population. Two delays appear in this model to describe the cell cycle duration of the stem cell population and the time required to produce white blood cells. We establish sufficient conditions for the asymptotic stability of the unique nontrivial positive steady state of the model by analyzing roots of a second degree exponential polynomial characteristic equation with delay-dependent coefficients. We also prove the existence of Hopf bifurcations which leads to periodic solutions.**

Keywords-Leukopoiesis; Delay differential equations; Stability; Hopf bifurcation.

I. INTRODUCTION

The process that leads to the production and regulation of blood cells is called hematopoiesis. It consists of mechanisms triggering differentiation and maturation of hematopoietic stem cells. Mathematical modeling of hematopoietic stem cells dynamics has been extensively studied in the past 30 years, with attempts to determine causes leading to a number of periodic hematological diseases. In 1978, [1] proposed a mathematical model of hematopoietic stem cells dynamics inspired by the works of [2] and [3]. Formed by a system of two nonlinear delay differential equations, where the delay describes the average cell cycle duration, this model stressed the influence of some factors (such as the apoptotic rate, the introduction rate, the cell cycle duration) playing an important role in the appearance of periodic solutions. Many authors studied properties of the model introduced by [1] (see [4-7]).

In this paper, we analyze the leukopoiesis model with two delays proposed by [5] without the simplifying assumption. We want to point out that studying the case with both delays is biologically significant since it makes a clear link between the number of circulating leukocytes and the differentiation of hematopoietic stem cells. Mathematically, the difficulty resides in the presence of two independent delays and the fact that some coefficients in the model equations depend upon these delays. Consequently, the characteristic equation of the linearized system has delay-dependent coefficients. As mentioned by [8], models with delay-dependent coefficients often exhibit very rich dynamics as compared to models with constant coefficients. When analyzing the stability and bifurcation of planar systems with two delays, we need to study the second degree transcendental polynomials with two delays. The problem of determining the distribution of roots to such polynomials is very complex, in this paper, we use an analytical approach proposed by Wei and Ruan [9-10].

Our work is organized as follows. In section, we present the model of leukopoiesis dynamics, a system of two nonlinear delay differential equations with two delays, and give the existence conditions of positive equilibrium. In section III, we analyze the asymptotic stability of steady state and establish the existence of Hopf bifurcation.

II. MODEL AND EQUILIBRIUM

Our model, proposed by [7-8], is the following

$$\begin{cases} \dot{Q}(t) = -[K + k(W(t)) + \beta(Q(t))]Q(t) \\ \qquad + 2e^{-\gamma_1\tau_1}\beta(Q(t-\tau_1))Q(t-\tau_1), \\ \dot{W}(t) = -\gamma_2 W(t) + Ak(W(t-\tau_2))Q(t-\tau_2). \end{cases} \tag{2}$$

Where $Q(t)$ is the quiescent stem cell population, $W(t)$ is the population of white blood cells. γ_1 denotes the rate of apoptosis of hematopoietic stem cells. k denotes the rate of differentiation of hematopoietic stem cells in leukocytes and K denotes the rate of differentiation in other blood cells (red blood cells and platelets). We assume that k is a positive monotone decreasing function of W, which tends to zero as W tends to infinity. γ_2 denotes the natural mortality rate of white blood cells. When a hematopoietic stem cell differentiates in a committed stem cell, a certain number of generations, say i, is necessary to produce a leukocyte. We do not take into account the exact number of generations involved in this process, but only (see [5]) the time needed to perform these i generations, that we denote by τ_2, coupled to an amplification parameter, denoted by A. We assume that the proliferating phase duration is the same for all hematopoietic stem cells and denote it by τ_1. There is a feedback loop between the resting phase and the proliferating phase, which regulates the rate of reentrance in the proliferative compartment from the G_0 stage. We denote this rate by β. It is supposed to depend on the quiescent stem cell population $Q(t)$. Typically, β is a Hill function given by

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$$\beta(Q)=\beta_0\theta^n/(\theta^n+Q^n). \quad (1)$$

The parameter β_0 represents the maximal rate of introduction in the proliferating phase, θ is the value for which β attains half of its maximum value, and n is the sensitivity of the rate of reintroduction. One can easily check, from [11], that system (2) has a unique continuous solution $(Q(t),W(t))$, which is well-defined for all t_0 and for a continuous initial condition. Moreover, we easily see that, for nonnegative initial conditions, the solutions of (2) remain nonnegative for t_0. Now, let us turn our considerations on the existence of steady states for system (2). Steady states of (2) are stationary solutions (Q^*,W^*) of (2), that is,

$$\begin{cases}[K+k(W^*)+\beta(Q^*)]Q^*=2e^{-\gamma_1\tau_1}\beta(Q^*)Q^*,\\ \gamma_2W^*=Ak(W^*)Q^*.\end{cases} \quad (3)$$

Firstly, notice that $(0,0)$ is always a steady state of (2). It describes the extinction of the cell populations. Searching for nonzero steady states of (2), that is $(Q^*,W^*)\neq(0,0)$. [7] had given the existence of the positive equilibrium of system (2).

Lemma 1 Assume that

(**H**1) $(2e^{-\gamma_1\tau}-1)\beta(0)>k(0)+K$ and

(**H**2) the function $Q\to Q\beta(Q)$ is decreasing on the interv -al (Q_0,Q_1), where $Q_0=\beta^{-1}(\frac{k(0)+K}{2e^{-\gamma_1\tau}-1})$ and $Q_1=\beta^{-1}(\frac{K}{2e^{-\gamma_1\tau}-1})$.

Then system (2) has a unique nontrivial positive steady state (Q^*,W^*) a solution of system (3).

III. Stability Analysis

A. Stability of the steady state (0,0)

The characteristic equation of the linearization of system (2) at (0,0) is given by

$$\Delta(\lambda,\tau_1)=\lambda^2+[K+k(0)+\beta(0)+\gamma_2]\lambda$$
$$+[K+k(0)+\beta(0)]\gamma_2-2e^{-\gamma_1\tau_1}\beta(0)(\lambda+\gamma_2)e^{-\lambda\tau_1}=0 \quad (4)$$

From (4), we have that $\Delta(\lambda,0)=\lambda^2+[K+k(0)-\beta(0)+\gamma_2]\lambda+[K+k(0)-\beta(0)]\gamma_2$ and $\Delta(0,\tau_1)=[K+k(0)-\beta(0)+2(1-e^{-\gamma_1\tau_1})\beta(0)]\gamma_2$. Hence the following lemma holds.

lemma 2 If

(**H**3) $K+k(0)-\beta(0)>0$

holds, then all roots of the equation $\Delta(\lambda,0)=0$ have negative real parts and $\Delta(0,\tau_1)>0$; If

(**H**4) $K+k(0)-\beta(0)<0$

holds, then the equation $\Delta(\lambda,0)=0$ has at least a root with positive real parts.

In the following, we assume that $\tau_1>0$ and investigate the existence of imaginary roots of (4). Let $i\omega(\omega>0)$ be a root of (4), then separating real and imaginary parts, ω satisfies

$$\begin{aligned}&\omega^4+[(K+k(0)+\beta(0))^2-4e^{-2\gamma_1\tau_1}\beta^2(0)+\gamma_2^2]\omega^2\\&+[(K+k(0)+\beta(0))^2-4e^{-2\gamma_1\tau_1}\beta^2(0)]\gamma_2^2=0.\end{aligned} \quad (5)$$

Under the condition (H3), we know that the equation (5) has no positive real roots. Therefore, we have the following lemma and theorem.

Lemma 3 For $\tau_1\geq 0$, then all roots of (4) have negative real parts when (H3) holds. Under the condition (H4), the equation (4) has at least a root with positive real parts.

Theorem 1. For all $\tau_1\geq 0,\tau_2\geq 0$, the following results hold.

(i) If (H3) holds, then the steady state (0,0) of system (2) is local asymptotically stable;

(ii) If (H4) holds, then the steady state (0,0) of system (2) is unstable.

B. Stability of the steady state (Q^*,W^*)

Throughout this section, we assume that condition (H1) and (H2) hold. Thus, the unique nontrivial steady state (Q^*,W^*), with $Q^*>0,W^*>0$, of (2) is well defined from lemma 1 by (3).

Let $x(t)=Q(t)-Q^*$, $y(t)=W(t)-W^*$, then (2) becomes

$$\begin{cases}\dot{x}(t)=-[K+k(W^*)+\beta(Q^*)+Q^*\beta'(Q^*)]x(t)\\ -Q^*k'(W^*)y(t)+2e^{-\gamma_1\tau_1}[\beta(Q^*)+Q^*\beta'(Q^*)]x(t-\tau_1)\\ \dot{y}(t)=-\gamma_2y(t)+A[k(W^*)x(t-\tau_2)+Q^*k'(W^*)y(t-\tau_2)].\end{cases} \quad (6)$$

The characteristic equation associated with (6) is given by

$$\begin{aligned}&\Delta(\lambda,\tau_1,\tau_2)=\lambda^2+[K+k(W^*)+\beta(Q^*)+Q^*\beta'(Q^*)\\&+\gamma_2]\lambda+[K+k(W^*)+\beta(Q^*)+Q^*\beta'(Q^*)]\gamma_2\\&-2e^{-\gamma_1\tau_1}[\beta(Q^*)+Q^*\beta'(Q^*)](\lambda+\gamma_2)e^{-\lambda\tau_1}\\&-AQ^*k'(W^*)[\lambda+K+\beta(Q^*)+Q^*\beta'(Q^*)]e^{-\lambda\tau_2}\\&+2Ae^{-\gamma_1\tau_1}Q^*k'(W^*)[\beta(Q^*)+Q^*\beta'(Q^*)]e^{-\lambda(\tau_1+\tau_2)}=0.\end{aligned} \quad (7)$$

This is a second degree exponential polynomial in λ. The local asymptotic stability analysis of the steady state (Q^*,W^*) is performed through the study of the sign of the real parts of roots of (7). We recall that (Q^*,W^*) is locally asymptotically stable if and only if all roots of (7) have negative real parts, and its stability can only be lost if roots cross the vertical axis, that is if purely imaginary roots appear. Because of the presence of two different delays, τ_1 and τ_2, in (7), the analysis of the sign of the real parts of eigenvalues is very complicated, and a direct approach cannot be considered. We will use a method consisting of determining the stability of the steady state when one delay is equal to zero, and, using similar analytic arguments as in [10], we will deduce conditions for the stability of the steady state when both time delays are nonzero. Note also that the steady state (Q^*,W^*) implicitly depends on the time delay

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τ_1, through (3). Therefore, coefficients of the characteristic (7) depend, explicitly (the term with $e^{-\gamma_1\tau_1}$) or implicitly, upon the delay τ_1. This particularity adds a complexity to the resolution of (7). Hence we firstly study the stability of the steady state when $\tau_2 = 0$ and $\tau_1 > 0$ by using the methods in [8], then investigate that both time delays are nonzero.

1) The case $\tau_1 = 0, \tau_2 = 0.$

Assume that $\tau_1 = \tau_2 = 0$. Then the characteristic equation (7) is written as a second degree polynomial equation

$$\begin{aligned}\Delta(\lambda,0,0) &= \lambda^2 + [K + k(W^*) + \gamma_2 - \beta(Q^*) - Q^*\beta'(Q^*)\\ &-AQ^*k'(W^*)]\lambda + [K + k(W^*) - \beta(Q^*) - Q^*\beta'(Q^*)]\gamma_2\\ &-AQ^*k'(W^*)[K - \beta(Q^*) - Q^*\beta'(Q^*)] = 0.\end{aligned} \quad (8)$$

From the Routh-Hurwith criterion, all roots of (8) have negative real parts if and only if

$$K + k(W^*) + \gamma_2 > \beta(Q^*) + Q^*\beta'(Q^*) + AQ^*k'(W^*) \quad (9)$$

and

$$\begin{aligned}&[K + k(W^*) - \beta(Q^*) + Q^*\beta'(Q^*) + AQ^*k'(W^*)]\gamma_2\\ &> AQ^*k'(W^*)[K - \beta(Q^*) - Q^*\beta'(Q^*)].\end{aligned}$$

From (3), the condition (9) is equivalent to

$$\gamma_2 > Q^*\beta'(Q^*) + AQ^*k'(W^*). \quad (10)$$

The functions β and k are decreasing, so $\beta'(Q) \le 0$ and $k'(W) \le 0$. Consequently, (10) holds true, and (9) is satisfied. We can then conclude to the asymptotic stability of (Q^*, W^*) when $\tau_1 = \tau_2 = 0$ in the next lemma.

Lemma 4**.** Assume that

(**H**5) $[K + k(W^*) - \beta(Q^*) + Q^*\beta'(Q^*) + AQ^*k'(W^*)]\gamma_2$
$> AQ^*k'(W^*)[K - \beta(Q^*) - Q^*\beta'(Q^*)].$

Then all eigenvalues of (8) have negative real parts, and the steady state (Q^*, W^*) of system (2) is locally asymptotically stable.

2) The case $\tau_1 > 0, \tau_2 = 0.$

We now consider the case $\tau_1 > 0$ and $\tau_2 = 0$. Since we want to estimate the critical delay values, then, with $\tau_1 > 0$, using the results of [8] to analyse the characteristic equation. Setting $\tau_2 = 0$ in (7), the characteristic equation becomes

$$\Delta(\lambda, \tau_1, 0) = \lambda^2 + p\lambda + q + (r + s\lambda)e^{-\lambda\tau_1} = 0, \quad (11)$$

where

$$\begin{aligned}p &= K + k(W^*) + \beta(Q^*) + Q^*\beta'(Q^*) + \gamma_2 - AQ^*k'(W^*),\\ q &= [K + k(W^*) + \beta(Q^*) + Q^*\beta'(Q^*)]\gamma_2\\ &-AQ^*k'(W^*)[K + \beta(Q^*) + Q^*\beta'(Q^*)],\\ r &= 2e^{-\gamma_1\tau_1}[\beta(Q^*) + Q^*\beta'(Q^*)](AQ^*k'(W^*) - \gamma_2),\\ s &= -2e^{-\gamma_1\tau_1}[\beta(Q^*) + Q^*\beta'(Q^*)].\end{aligned} \quad (12)$$

Equation (12) takes the general form

$$P(\lambda, \tau_1) + Q(\lambda, \tau_1)e^{-\lambda\tau_1} = 0, \quad (13)$$

where

$$P(\lambda, \tau_1) = \lambda^2 + p\lambda + q, \ \ Q(\lambda, \tau_1) = r + s\lambda. \quad (14)$$

In the following, we shall investigate the existence of purely imaginary roots $\lambda = i\omega\ (\omega > 0)$ to (13). Equation (13) takes the form of a second degree exponential polynomial in λ, with all the coefficients of P and Q depending on τ_1. [8] established a geometrical criterion which gives the existence of purely imaginary roots of a characteristic equation with delay dependent coefficients. We use the same notations as in [8] and we can verify the following conclusions:

(i) $P(0, \tau_1) + Q(0, \tau_1) \ne 0$; (ii) $P(i\omega, \tau_1) + Q(i\omega, \tau_1) \ne 0$;

(iii) $\lim sup\{|Q(\lambda, \tau_1)P(\lambda, \tau_1)| : |\lambda| \to \infty, Re\lambda \ge 0\} < 1$;

(iv) $F(\omega, \tau_1) = |P(i\omega, \tau_1)|^2 - |Q(i\omega, \tau_1)|^2$ has a finite number of zeros; (v) Each positive root $\omega(\tau_1)$ of $F(\omega, \tau_1) = 0$ is continuous and differentiable in τ_1 whenever it exists.

Now let $\lambda = i\omega(\omega > 0)$ be a root of (13). Substituting it into (13) and separating the real and imaginary parts yields

$$\sin\omega\tau_1 = Im(\frac{P(i\omega, \tau_1)}{Q(i\omega, \tau_1)}), \cos\omega\tau_1 = -Re(\frac{P(i\omega, \tau_1)}{Q(i\omega, \tau_1)}), \quad (15)$$

which yields

$$F(\omega, \tau_1) = \omega^4 + a_1(\tau_1)\omega^2 + a_2(\tau_1) = 0, \quad (16)$$

and its roots are given by

$$\omega_+^2 = \frac{1}{2}[-a_1(\tau_1) + \sqrt{\Delta}], \ \ \omega_-^2 = \frac{1}{2}[-a_1(\tau_1) - \sqrt{\Delta}], \quad (17)$$

where

$a_1(\tau_1) = p^2 - 2q - s^2, a_2(\tau_1) = q^2 - r^2, \Delta = a_1^2(\tau_1) - 4a_2(\tau_1).$

We know that $q^2 - r^2 > 0$ holds when $\beta(Q^*) + Q^*\beta'(Q^*) > 0$. Let

$$I = \{\tau_1 : \tau_1 \ge 0, \ \beta(Q^*) + Q^*\beta'(Q^*) > 0, a_1^2(\tau_1) \ge 4a_2(\tau_1) \ and \ a_1(\tau_1) < 0\}.$$

Then for all $\tau_1 \in I$, $\omega(\tau_1)$ satisfies (16), and for any $\tau_1 \notin I$, $\omega(\tau_1)$ is not definited. Let $\theta(\tau_1) \in [0, 2\pi]$ be defined for $\tau_1 \in I$ by

$$\sin\theta(\tau_1) = [(\omega^2 - q)s\omega + \omega pr]/[\omega^2 s^2 + r^2],$$
$$\cos\theta(\tau_1) = -[(q - \omega^2)r + \omega^2 ps]/[\omega^2 s^2 + r^2].$$

Since $F(\omega, \tau_1) = 0$ for $\tau_1 \in I$, it follows that $\theta(\tau_1)$ is well and uniquely defined for all $\tau_1 \in I$. Hence, we can define the maps $\tau_{1n} : I \to R_{+0}$ given by

$$\tau_{1n} := [\theta(\tau_1) + 2n\pi]/\omega(\tau_1), n \in N_0, \tau_1 \in I.$$

Let us introduce the functions

$$S_{1n} := \tau_1 - \tau_{1n}(\tau_1), \tau_1 \in I, n \in N_0,$$

which are continuous and differentiable in τ_1. The following theorems are due to [8].

Theorem 2. The equation (11) has a pair of simple and conjugate pure imaginary roots $\lambda = \pm i\omega(\tau_1^*)$, $\omega(\tau_1^*)$ real for $\tau_1 \in I, I \subseteq R_{+0}$, and at some $\tau_1^* \in I$,

$$S_{1n}(\tau_1^*) = 0 \ \ for \ \ some \ \ n \in N_0.$$

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If $\omega(\tau_1^*)=\omega_+(\tau_1^*)$, this pair of simple conjugate pure imaginary roots crosses the imaginary axis from left to right if $\delta_+(\tau_1^*)>0$ and crosses the imaginary axis from right to left if $\delta_+(\tau_1^*)<0$, where $\delta_+(\tau_1^*):=Sign\{dRe\lambda/d\tau_1|_{\lambda=i\omega_+(\tau_1^*)}\}$ $=Sign\{dS_{1n}(\tau_1)/d\tau_1|_{\tau_1=\tau_1^*}\}$. If $\omega(\tau_1^*)=\omega_-(\tau_1^*)$, this pair of simple conjugate pure imaginary roots crosses the imaginary axis from left to right if $\delta_-(\tau_1^*)>0$ and crosses the imaginary axis from right to left if $\delta_-(\tau_1^*)<0$, where $\delta_-(\tau_1^*):=Sign\{dRe\lambda/d\tau_1|_{\lambda=i\omega_-(\tau_1^*)}\}=-Sign\{dS_{1n}(\tau_1)/d\tau_1|_{\tau_1=\tau_1^*}\}$. Besides, if $\omega(\tau_1^*)=\omega_+(\tau_1^*)=\omega_-(\tau_1^*)$, then $Sign\{dRe\lambda/d\tau_1|_{\lambda=i\omega(\tau_1^*)}\}=0$. The same is true when $S'_{1n}(\tau_1^*)=0$.

Under the conditions (H1), (H2) and (H5), we have the following theorem.

Theorem 3 For system (2) and $\tau_2=0$, the following conclusions hold.

(i) If $S_{1n}(\tau_1)$ has no positive zero in I, then (0,0) is asymptotically stable for all $\tau_1\geq 0$;

(ii) If the function S_{1n} has positive zeros in I, for $n\in N_0$, and let $\tau_1^0=min\{\tau_1:S_{1n}=0\}$, then (0,0) is asymptotically stable for $0\leq\tau_1<\tau_1^0$. When $\tau_1>\tau_1^0$, the stability switches follow Theorem 2. Here τ_1^0 is Hopf bifurcation value.

3) The case $\tau_1>0,\tau_2>0$.

Next, we consider the equation (7) when $\tau_1\in[0,\tau_1^0)$ and regard τ_2 as a parameter. Let $i\omega\,(\omega>0)$ be a root of (7), we have that ω satisfies the following equations

$$\begin{cases}-\omega^2+[K+k(W^*)+\beta^*]\gamma_2-2e^{-\gamma_1\tau_1}\beta^*(\gamma_2\cos\omega\tau_1+\omega\sin\omega\tau_1)\\ =[2e^{-\gamma_1\tau_1}\beta^*\sin\omega\tau_1+\omega]AQ^*k'(W^*)\sin\omega\tau_2-[2e^{-\gamma_1\tau_1}\beta^*\cos\omega\tau_1\\ -\beta^*-K]AQ^*k'(W^*)\cos\omega\tau_2, \\ (K+k(W^*)+\beta^*+\gamma_2)\omega-2e^{-\gamma_1\tau_1}\beta^*(\omega\cos\omega\tau_1-\gamma_2\sin\omega\tau_1)\\ =[2e^{-\gamma_1\tau_1}\beta^*\sin\omega\tau_1+\omega]AQ^*k'(W^*)\cos\omega\tau_2+[2e^{-\gamma_1\tau_1}\beta^*\cos\omega\tau_1\\ -\beta^*-K]AQ^*k'(W^*)\sin\omega\tau_2,\end{cases}\tag{18}$$

where $\beta^*=\beta(Q^*)+Q^*\beta'(Q^*)$.

Adding up the squares of both equations, we obtain that

$$\begin{aligned}&[-\omega^2+(K+k(W^*)+\beta^*)\gamma_2-2e^{-\gamma_1\tau_1}\beta^*(\gamma_2\cos\omega\tau_1+\omega\sin\omega\tau_1)]^2\\ &+[(K+k(W^*)+\beta^*+\gamma_2)\omega-2e^{-\gamma_1\tau_1}\beta^*(\omega\cos\omega\tau_1-\gamma_2\sin\omega\tau_1)]^2\\ &-[2e^{-\gamma_1\tau_1}\beta^*\cos\omega\tau_1-\beta^*-K]^2(AQ^*k'(W^*))^2\\ &-[2e^{-\gamma_1\tau_1}\beta^*\sin\omega\tau_1+\omega]^2(AQ^*k'(W^*))^2=0.\end{aligned}\tag{19}$$

From (25), we can obtain $\cos\omega\tau_2$.

Lemma 5. If (19) has positive roots, then (7) has purely imaginary roots.

Let

(**H**6)

$$[(K+k(W^*)+\beta^*)-2e^{-\gamma_1\tau_1}\beta^*]^2\gamma_2^2-[(2e^{-\gamma_1\tau_1}-1)\beta^*-K]^2(AQ^*k'(W^*))^2<0$$

Lemma 6. If (H6) is satisfied, then (19) has at most finite positive roots.

Lemma 7. Suppose that (H1), (H2), (H5), (H6) and $\tau_1\in[0,\tau_1^0)$ are satisfied. Then (7) has a pair purely imaginary roots $\pm i\omega_j$ when $\tau_2=\tau_2^0$. Moreover, all roots of (7) have negative real parts when $\tau_2\in[0,\tau_2^0)$, and all the roots of (7) with $\tau_2=\tau_2^j$, except $\pm i\omega_0$, have negative real parts.

Let $\lambda(\tau_2)=\alpha(\tau_2)+i\omega(\tau_2)$ be the root of (7) satisfying $\alpha(\tau_2^j)=0$ and $\omega(\tau_2^j)=\omega_j$. From (7), we can obtain

Lemma 8 $Sign\{\alpha'(\tau_2^j)\}=Sign\{AC+BD\}$,

where $B_1=\omega_j\{2e^{-\gamma_1\tau_1}\beta^*AQ^*k'(W^*)\sin\omega_j(\tau_1+\tau_2^j)$ $+AQ^*k'(W^*)[\omega_j\cos\omega_j\tau_2^j-(\beta^*+K)\sin\omega_j\tau_2^j]\}$, $B_2=\omega_j\{2e^{-\gamma_1\tau_1}\beta^*AQ^*$ $k'(W^*)\cos\omega_j(\tau_1+\tau_2^j)-AQ^*k'(W^*)[\omega_j\sin\omega_j\tau_2^j+(\beta^*+K)\cos\omega_j\tau_2^j]\}$,

$$\begin{aligned}B_3&=K+k(W^*)+\beta^*+\gamma_2-2e^{-\gamma_1\tau_1}\beta^*[(1-\tau_1\gamma_2)\cos\omega_j\tau_1-\tau_1\omega_j\sin\omega\tau_1]\\ &-AQ^*k'(W^*)[(1-(\tau_2^j(\beta^*+K)))\cos\omega_j\tau_2^j-\tau_2^j\omega_j\sin\omega_j\tau_2^j]\\ &-2(\tau_1+\tau_2^j)e^{-\gamma_1\tau_1}A\beta^*Q^*k'(W^*)\cos\omega_j(\tau_1+\tau_2^j),\end{aligned}$$

$$\begin{aligned}B_4&=2\omega_j+2e^{-\gamma_1\tau_1}\beta^*[(1-\tau_1\gamma_2)\sin\omega_j\tau_1+\tau_1\omega_j\cos\omega_j\tau_1]\\ &+AQ^*k'(W^*)[(1-(\tau_2^j(\beta^*+K)))\sin\omega_j\tau_2^j+\tau_2^j\omega_j\cos\omega_j\tau_2^j]\\ &+2(\tau_1+\tau_2^j)e^{-\gamma_1\tau_1}A\beta^*Q^*k'(W^*)\sin\omega_j(\tau_1+\tau_2^j).\end{aligned}$$

Theorem 4. Suppose that (H1), (H2), (H5), (H6) and $\tau_1\in[0,\tau_1^0)$ are satisfied.

(i) If $\tau_2\in[0,\tau_2^0)$, then the positive equilibrium $E^*(x^*,y^*)$ of (2) is asymptotically stable;

(ii) If $\alpha'(\tau_2^j)\neq 0$, then (2) undergoes a Hopf bifurcation at E^* when $\tau_2=\tau_2^j$, $j=1,2,3,\cdots,n$.

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