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Hopf Bifurcation Direction in a Delayed Hematopoietic Stem Cells Model

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Abstract

The dynamics of Hematopoietic Stem Cells (HSC) model with one delay is widely investigated (see Mackey [21, 23] and Andersen and Mackey [1]). There are two possible stationary states in the model. One of them is trivial, the second $E^*(\tau)$, depending on the delay, may be non-trivial. The stability of the non trivial state as well as the occurrence of the Hopf bifurcation depending on time delay and the existence and uniqueness of a critical values τ_0 and τ of the delay, such that $E^*(\tau)$ is asymptotically stable for $\tau < \tau_0$ and unstable for $\tau_0 < \tau < \tau$, are recalled and a Hopf bifurcation may occurs at $\tau = \tau_0$. The main result of this paper is to establish an explicit algorithm for determining the direction of this Hopf bifurcation and the stability or instability of the bifurcating branch of periodic solutions, using the methods presented by O. Diekmann et al. in [10].

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Introduction and mathematical model of stem cell dynamics

Hematological diseases have attracted a significant amount of modelling attention because a number of them are periodic in nature (Haurie, Dale and Mackey (1998) [17]). Some of these diseases involve only one blood cell type and are due to the destabilization of peripheral control mechanisms, e.g., periodic auto-immune hemolytic anemia (Blair, Mackey and Mahaffy (1995) [3] ; Mahaffy, Blair and Mackey (1998) [28]), and cyclical thrombocytopenia (Swinburne and Mackey (2000) [39] ; Santillan et al. (2000) [37]). Typically, periodic hematological diseases of this type involve periodicity between two and four times the bone marrow production or maturation delay (which is different from the delay considered in this paper).

Other periodic hematological diseases involve oscillations in all of the blood cells (white cells, red cells and platelets). Examples include cyclical neutropenia (Haurie, Dale and Mackey (1999) [19] ; Haurie et al. (2000) [18]) and periodic chronic myelogenous leukemia (Fortin and Mackey (1999) [13]). These diseases involve very long periodic dynamics [14, 35] (on the order of weeks to months) and are thought to be due to a destabilization of haematopoietic stem cells (HSC) compartment from which all of these mature blood cell types are derived, see Fowler and Mackey (2002) [14].

The population of (HSC) give rise to all of the differentiated elements of the blood: the white blood cells, red blood cells, and platelets, which may be either actively proliferating or in a resting phase. 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 pre-synthesis phase, S the DNA synthesis phase, G_2 the post-synthesis phase and M the mitotic phase.

Just after the division, both daughter cells go into the resting phase called 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.

The (HSC) model that we consider is a classical G_0 model, see [9, 25, 38] and reference therein.

The full model for this situation consists of a pair of (age structured) reaction convection evolution equations with their associated boundary and initial conditions [21, 22, 36, 26]. Using the method of characteristics [40] these equations can be transformed into a pair of non-linear first order differential delay equations, see [1, 14, 21, 23], [24], see also [35] and references therin cited,

$$\begin{cases} \frac{dN}{dt} = -\delta N - \beta(N)N + 2e^{-\gamma\tau}\beta(N_\tau)N_\tau \\ \frac{dP}{dt} = -\gamma P + \beta(N)N - e^{-\gamma\tau}\beta(N_\tau)N_\tau \end{cases} \tag{1}$$

where β is a monotone decreasing function of N which has the explicit form of a Hill

function (see [8, 12, 21, 32]):

$$\beta(N) = \beta_0 \frac{\theta^n}{\theta^n + N^n} \tag{2}$$

The symbols in equation (1) have the following interpretation. N is the number of cells in non-proliferative phase, $N\tau = N(t - \tau)$, P the number of cycling proliferating cells, γ the rate of cells loss from proliferative phase, ∂ the rate of cells loss from non-proliferative phase, τ the time spent in the proliferative phase, β the feedback function, rate of recruitment from non-proliferative phase, $\beta_0 > 0$ the maximal rate of re-entry in the proliferating phase, $\theta \geq 0$ is 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 reintroduction rate with changes in the population, and $e^{-\gamma\tau}$ accounts for the attenuation due to apoptosis (programmed cell death) at rate γ.

The model (1) was intensively studied by many authors, see for example, [1, 6, 7, 12, 14, 21, 22, 23, 24, 34, 35], this list being not exhaustive.

For numerical study, typical values of the parameters for humans are given by Mackey (1978), (1997) [21, 23] as

$\partial = 0.05d^{-1}$, $\beta_0 = 1.77d^{-1}$, $\tau = 2.2d$, $n = 3$.

(The value of θ is 1.62×10^8 cells Kg^{-1}, but this is immaterial for dynamic considerations). For values of in the range $0.2d^{-1}$, the consequent steady state is unstable and there is a periodic solution whose period T at the bifurcation ranges from 20−40 days, see (Fowler and Mackey, 2002) [14]. In [21, 22] the author proves that the stability of the non trivial steady state depend on the value of γ. When $\gamma = 0$, this steady state cannot be destabilized to produce dynamics characteristic of periodic hematopoiesis. On the other hand, for $\gamma > 0$, increase in γ lead to a decrease in the (HSC) numbers and a consequent decrease in the cellular efflux (given by ∂N) into the differentiated cell lines. This diminished efflux becomes unstable when a critical value of γ is reached, $\gamma = \gamma_1$, at which a supercritical Hopf bifurcation occurs. For all values of γ satisfying $\gamma_1 < \gamma < \gamma_2$, there is a periodic solution of the above model whose period is in good agreement with that seen in periodic hematopoiesis. At $\gamma = \gamma^2$, a reverse bifurcation occurs and greatly diminished (HSC) numbers as well as cellular efflux again become unstable.

In [34], authors numerically investigate the influence of each parameter (τ , ∂, γ, β_0 and n) on the oscillation characteristics, see [35]. In [35], authors consider the limiting case ($n = +\infty$) of the above model in order to compute an explicit solution, give an exact form of the period and the amplitude of oscillations. They illustrate these results numerically and show that the main parameters controlling the period are (τ , ∂, γ, β_0 and n) mainly influence the amplitude. These authors consider $n = 12$ as a good approximation of high Hill coefficient for their numerical simulations. The Hill coefficient n is often regarded as a cooperativity coefficient, describing the number of agents (molecules, proteins or complexes) required to activate or deactivate a given process. If n was interpreted to be the number of ligand molecules required to active or deactivate a receptor site, then values of $n = 12$ or larger would not biologically realistic. However, there are other situations in which cascade effects are known to create switch like phenomena [12]. In these circumstances, both experimental data and theoretical modelling suggest that the large values of n considered are quite realistic [6, 7, 35].

It is generally believed that normal and malignant cell population have different cell cycle times (Andersen and Mackey (2000) [1], Baserga (1981) [2]) and thus they will be described by different parameters in the above model. In particular, in untreated leukemic cells the apoptotic rate γ is significantly smaller than in normal cells (Macnamara et al., (1999) [27] ; Okita et al., (2000) [30] ; Ong et al., (2000) [31] ; Parker et al., (2000) [33]), and the time spent τ in the proliferating phase is longer relative to normal cells in the bone morrow, see also (Andersen and Mackey 2001) [1].

In this paper, the influence of the delay parameter τ on the change of stability of the non-trivial steady state (depending on the delay) of the above model (1) (when γ is close to 0, see [1, 21, 22], e.g. the case of untreated leukemic cells) and the existence of a family of periodic solutions of the model (1) bifurcating from the non-trivial steady state via Hopf bifurcation theorem are given. We mainly prove (in section 3) that the analysis of some of the coefficients of the expansion of the delay function gives a systematic criteria to decide about the direction and stability or instability of the bifurcating branch of periodic solutions. Our analytical study of model (1) is based on the theory of functional differential equations [10, 15].

The informed reader can pass directly in section 3. Section 2 brings anything new, we put it just for the reader's convenience.

This paper is organized as follows. In section 2, we recall and give some clarification results on the stability of trivial and non-trivial steady state (depending on delay) of (1). The existence of a critical value τ_0 of the delay in which the non-trivial steady state, the most biologically meaningful one, becomes unstable via a Hopf bifurcation for γ close to 0 and $n \geq 2$ is investigated. Main and new results of this paper are given in section 3. Based on the analysis of some of the coefficients of the expansion of the delay function, we establish a systematic criteria for determining the direction of Hopf bifurcation and the stability or instability of the bifurcating branch of periodic solutions. Section 4 gives a short conclusion.

Local stability and Hopf bifurcation

In [1, 35] a study of stability properties of the steady states of (1) is considered. In this section, we reconsider this study with respect to the delay τ . Therefore, if the trivial steady state is unstable for $\tau = 0$, then it is unstable for any positive delay. If the non-trivial steady state is stable for $\tau = 0$, then it looses its stability for some $\tau_0 > 0$ of delay via a Hopf bifurcation and cannot be stable for larger delay τ .

2.1 **Stability without delay** $\tau = 0$. For $\tau = 0$, equation (1) reads as :

$$\begin{cases} \frac{dN}{dt} = -\delta N + \beta(N)N \\ \frac{dP}{dt} = -\gamma P \end{cases} \tag{3}$$

Theorem 1. *Assume $\partial \in (0, \beta_0]$. System (3) has a positive equilibrium $(N^*, 0) = (\beta^{-1}(\partial), 0)$ which is asymptotically stable. The trivial one (0, 0) is unstable.*

Proof. The characteristic equation of the linearized equation of (3) around $E^* = (N^*, 0)$, has two roots given by $\lambda_1 = -\partial + \alpha'(N^*)$ and $\lambda_2 = -\gamma$,

where

$$\alpha(N) = \beta(N)N \tag{4}$$

and $\alpha'(N)$ its derivative.

As β is a decreasing function, E^* is asymptotically stable.

For the trivial equilibrium, the roots of the characteristic equation of the linearized equation of (3) around (0, 0) are $\lambda_1 = -\partial + \alpha'(0)$ and $\lambda_2 = -\gamma$.

As $\alpha'(0) = \beta_0 > \partial$, (0, 0) is unstable.

2.2 **Stability for positive delay**. Normalizing the delay τ by the time scaling $t \to \frac{t}{\tau}$, effecting the change of variables $u(t) = N(t\tau)$ and $v(t) = P(t\tau)$, the system (1) is transformed into

$$\begin{cases} \dot{u}(t) = \tau[-\delta u(t) - \alpha(u(t)) + 2e^{-\gamma\tau}\alpha(u(t-1))] \\ \dot{v}(t) = \tau[-\gamma v(t) + \alpha(u(t)) - e^{-\gamma\tau}\alpha(u(t-1))] \end{cases} \quad (5)$$

where α is given by equation (4)

Let:

$$(\mathbf{H_0}): \qquad \delta < \frac{\beta_0}{3}$$

and denote by $\overline{\tau} = \frac{1}{\gamma}\ln\left(\frac{2}{1+\frac{2\delta}{\beta_0}}\right)$.

Note that ($\mathbf{H}_0$) implies that for each $0 < \tau < \tau$, $\alpha'(u^*(\tau)) < 0(b(\tau)$ and β_0 $(2c^{-\gamma\tau}-1) > \partial$ system (5) has a unique positive equilibrium $E^*(\tau) = (u^*(\tau), v^*(\tau))$ with

$$u^*(\tau) = \theta\left(\frac{\beta_0(2e^{-\gamma\tau}-1)-\delta}{\delta}\right)^{\frac{1}{n}} \text{ and } v^*(\tau) = \frac{\delta u^*}{\gamma}\left(\frac{1-e^{-\gamma\tau}}{2e^{-\gamma\tau}-1}\right)$$

By the translation $z(t) = (u(t), v(t)) - (u^*(\tau), v^*(\tau))$, system (5) is written as a functional differential equation (FDE) in $C := C([-1,0], \mathbb{R}^{\nvDash})$:

$$\dot{z}(t) = L(\tau)z_t + f_0(z_t, \tau) \quad (6)$$

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

$$L(\tau)\varphi = \tau\begin{pmatrix} -(\delta + \alpha'(u^*(\tau))\varphi_1(0) + 2e^{-\gamma\tau}\alpha'(u^*(\tau))\varphi_1(-1) \\ -\gamma\varphi_2(0) + \alpha'(u^*(\tau))\varphi_1(0) - e^{-\gamma\tau}\alpha'(u^*(\tau))\varphi_1(-1) \end{pmatrix}$$

$$f_0(\varphi,\tau) = \tau\begin{pmatrix} -\alpha(\varphi_1(0) + u^*(\tau)) + \alpha'(u^*(\tau))\varphi_1(0) - 2e^{-\gamma\tau}\alpha'(u^*(\tau))\varphi_1(-1) \\ +2e^{-\gamma\tau}\alpha(\varphi_1(-1) + u^*(\tau)) - \delta u^*(\tau) \\ \alpha(\varphi_1(0) + u^*(\tau)) - \alpha'(u^*(\tau))\varphi_1(0) - e^{-\gamma\tau}\alpha(\varphi_1(-1) + u^*(\tau)) \\ +e^{-\gamma\tau}\alpha'(u^*(\tau))\varphi_1(-1) - \gamma v^*(\tau). \end{pmatrix}$$

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

The characteristic equation of the linear equation $z(t) = L(\tau)_{zt}$ is given by

$$W(\lambda,\tau) = (\lambda + \tau\gamma)(\lambda - \tau a(\tau) - \tau b(\tau)e^{-\lambda}) = 0, \quad (7)$$

with $\alpha(\tau) = -(\partial + \alpha'(u^*(\tau)))$ and $b(\tau) = 2e^{-\gamma\tau}\alpha'(u^*(\tau))$ and

$$\alpha'(u^*(\tau)) = \frac{\delta}{\beta_0(2e^{-\gamma\tau}-1)^2}\left[\beta_0(1-n)(2e^{-\gamma\tau}-1) + n\delta\right].$$

As $\tau\gamma > 0$, the stability of the equilibrium $z = 0$ follows from the study of roots of the following equation:

$$\nabla(\lambda,\tau) = \lambda - \tau\alpha(\tau) - \tau b(\tau)\, e^{-\lambda} = 0 \quad (8)$$

corresponding to the characteristic equation associated to the first equation in (5). To obtain the switch of stability of $z = 0$ one needs to find the imaginary root of equation (8). Let $\lambda = i\zeta$, then $\Delta(i\zeta, \tau) = 0$ if and only if

$$\begin{cases} \zeta = \arccos\left(-\frac{a(\tau)}{b(\tau)}\right) \in (0,\pi) \text{ for } 0 \le \left|\frac{a(\tau)}{b(\tau)}\right| \le 1 \\ \text{and} \\ \tau\sqrt{b^2(\tau)-a^2(\tau)} = \arccos(-\frac{a(\tau)}{b(\tau)}) \text{ for } 0 \le \left|\frac{a(\tau)}{b(\tau)}\right| < 1. \end{cases} \quad (9)$$

Let:

$(\mathbf{H_1})$: $a(\tau) < 0$ and $|b(\tau)| < -a(\tau)$ for all $\tau > 0$.

$(\mathbf{H_2})$: $\tau a(\tau) < 1$, and $|a(\tau)| < |b(\tau)|$ for all $\tau > 0$.

Theorem 2. *Assume* ($\mathbf{H_0}$). *Then,*

(1) *The trivial equilibrium* (0, 0) *of system* (5) *is unstable for* $0 < \tau < \tau$.

(2) *(i) If a and b satisfy* ($\mathbf{H_1}$), *then the equilibrium point* $z = 0$ *of* (6) *is asymptotically*
stable for $0 < \tau < \tau$.

(ii) *If a and b satisfy* ($\mathbf{H_2}$), $n \ge 2$ *and* γ *close enough to* 0, *there exists a unique* τ_0 *in* $]0, \tau[$ *such that the equilibrium point* $z = 0$ *of* (6) *is asymptotically stable for* $\tau \in]0, \tau0[$ *and unstable for* $\tau \in (\tau_0, \tau)$.

Proof. (1) The characteristic equation of the linearized equation associated to (5) around (0, 0) is given by,

$$\lambda + \tau(\partial + \beta_0) - 2\tau e^{-\gamma\tau}\beta_0 e^{-\lambda} = 0 \quad (10)$$

From ($\mathbf{H_0}$), we have $\beta_0(2e^{-\gamma\tau} - 1) > \partial$, thus equation (10) has a real root which is positive. Then (0, 0) is unstable.

(2) (*i*) Let $\lambda = \mu + i\nu$ be a root of equation $\Delta(\lambda,\tau) = 0$ for $0 < \tau < \tau$. We have:

$$\begin{cases} \mu - \tau a(\tau) - \tau b(\tau)e^{-\mu}\cos(\nu) = 0 \\ \nu + \tau b(\tau)e^{-\mu}\sin(\nu) = 0 \end{cases} \quad (11)$$

If there exists a root $\mu_0 \ge 0$ of (11), then $-\alpha(\tau) \le b(\tau)e^{-\mu 0}\cos(\nu)$.

As $-1 \le \cos(\nu) \le 1$ and $0 < e^{-\mu 0} < 1$ and $b(\tau) < 0$ for $0 < \tau < \tau$, we have $b(\tau) \le \alpha(\tau)$, which contradicts the assumption ($\mathbf{H_1}$). So for all $0 < \tau < \tau$, the roots of the equation (8) have negative real parts, and therefore $z = 0$ is asymptotically stable.

For the proof of the stability in (2) (*ii*) , we need the following lemmas.

Lemma 1. *(Hale 1993 [15]) All roots of the equation* $(z + c)e^z + d = 0$*, where c and d are real, have negative real parts if and only if,*

(i) $c > -1$

(ii) $c + d > 0$

(iii) $\sqrt{d^2 - c^2} < \zeta$

where ζ *is the root of* $\zeta = -c\tan\zeta$, $0 < \zeta < \pi$, *if* $c \neq 0$ *and* $\zeta = \frac{\pi}{2}$ *if* $c = 0$.

Lemma 2. *Under hypotheses* ($\mathbf{H_0}$) *and* ($\mathbf{H_2}$), *for* $n \ge 2$ *and* γ *close enough to* 0, *there exists a unique solution* τ_0 *of the second equation of (9) in* $]0, \tau[$, *such that* $i\zeta 0$ *is a purely imaginary root of equation (8), with* ζ_0 = arccos$(-a\frac{a(\tau_0)}{b(\tau_0)})$. *Furthermore, the following inequalities hold:*

$$\begin{cases} \tau\sqrt{b^2(\tau)-a^2(\tau)} < \arccos(-\frac{a(\tau)}{b(\tau)}) \ \textit{for}\ \tau \in (0,\tau_0) \\ \tau\sqrt{b^2(\tau)-a^2(\tau)} > \arccos(-\frac{a(\tau)}{b(\tau)}) \ \textit{for}\ \tau \in (\tau_0,\overline{\tau}) \end{cases} \quad (12)$$

Lemma 3. *Let* $f : (0, \pi) \to \mathbb{R}$ *be defined by* $f(x) = \alpha \tan x$, $\alpha < 1$ *and* $\alpha \neq 0$. *Then, f has a unique fixed point* $\zeta \in (0, \pi)$, *such that:*

$$\textit{for}\ 0<\alpha<1,\ f(x)<x\ \textit{if}\ x\in(0,\zeta)\cup(\tfrac{\pi}{2},\pi)\ \textit{and}\ f(x)>x\ \textit{if}\ x\in(\zeta,\tfrac{\pi}{2}),$$
$$\textit{and for}\ \alpha<0,\ f(x)<x\ \textit{if}\ x\in(0,\tfrac{\pi}{2})\cup(\zeta,\pi)\ \textit{and}\ f(x)>x\ \textit{if}\ x\in(\tfrac{\pi}{2},\zeta).$$

Proof of (2)(ii) of theorem 2.

We only have to verify the three conditions (i), (ii) and (iii) of lemma 1. The assertions (i) and (ii) follow from (**H$_2$**) with $c = -\tau\,\alpha(\tau)$ and $d = -\tau\, b(\tau)$.

For (iii), let $\tau \in (0, \tau_0)$ and $f(\zeta) = \tau\alpha(\tau) \tan \zeta$. From the first equation of (12):

if $\alpha(\tau) = 0$, the first inequality of (12) becomes $-\tau b(\tau) < \frac{\pi}{2}$, and (iii) is satisfied. If $0 < \tau\alpha(\tau) < 1$ or $\alpha(\tau) < 0$, as

$$f\left(\arccos(-\frac{a(\tau)}{b(\tau)})\right) = \tau\sqrt{b(\tau)^2 - a(\tau)^2},$$

the first equation of (12) implies that

$$f\left(\arccos(-\frac{a(\tau)}{b(\tau)})\right) < \arccos(-\frac{a(\tau)}{b(\tau)}),$$

with arccos $\left(-\frac{a(\tau)}{b(\tau)}\right) \in (0,\pi)$.

From lemma 3 and the graph of *f*, if ζ is the fixed point of *f* in $(0, \pi)$, we have,

$$f\left(\arccos(-\frac{a(\tau)}{b(\tau)})\right) < \zeta, \quad (13)$$

that is

$$\sqrt{(\tau b(\tau))^2 - (\tau a(\tau))^2} < \zeta,$$

which leads to the desired assertion. This complete the stability of $z = 0$ for $0 < \tau < \tau_0$. To prove the instability of $z = 0$ in (2) (*ii*), for $\tau_0 < \tau < \tau$, we will show that the characteristic equation (8) has at least one root with positive real part.

Let $\tau_0 < \tau < \tau$. If all the roots of the characteristic equation (8) have negative real parts, the properties (i), (ii) and (iii) of lemma 1 are satisfied. From the second equation of (12) and from (13) we have,

$$\begin{cases} f\left(\arccos(-\frac{a(\tau)}{b(\tau)})\right) > \arccos(-\frac{a(\tau)}{b(\tau)}) \\ \qquad\qquad \text{and} \\ f\left(\arccos(-\frac{a(\tau)}{b(\tau)})\right) < \overline{\zeta} \end{cases}$$

Henceforth, from lemma 3 and the graph of f, we have

$$\begin{cases} \arccos(-\frac{a(\tau)}{b(\tau)}) < \overline{\zeta} \\ \text{and} \\ \arccos(-\frac{a(\tau)}{b(\tau)}) > \overline{\zeta} \end{cases}$$

which is impossible.

Now, suppose that there is one root with zero real part with all the remaining roots having negative real parts. From (9) and lemma 2 we deduce that $\tau = \tau_0$, which contradicts the assumption $\tau > \tau_0$. Then $z = 0$ is unstable for $\tau_0 < \tau < \tau$.

Proof. (of lemma 2)

In view of (**H$_0$**) and (**H$_2$**), to find a root of second equation of (9) is equivalent to find a root of the equation

$$\tau = -\frac{\arccos(-\frac{a(\tau)}{b(\tau)})}{b(\tau)\sin(\arccos(-\frac{a(\tau)}{b(\tau)}))}. \tag{14}$$

Let: $y(\tau) = \arccos(-\frac{a(\tau)}{b(\tau)})$, and $F(\tau) = -\frac{y(\tau)}{b(\tau)\sin(y(\tau))}$.

Besides, in the hypotheses (**H$_0$**) and (**H$_2$**), F is continuously differentiable on $\tau \in [0,\tau]$. As $y(0) \in (0, \pi)$ and $b(0) < 0$, we have $F(0) > 0$ for $n \geq 2$ and $F(\tau) < \tau$ for γ close enough to 0 (because $F(\tau)$ is independent of γ and τ is larger when γ is small), then there exits at least one solution τ_0 of equation (14) in $]0,\tau[$. Now, for the uniqueness of τ_0, let $g(\tau) = \tau - F(\tau)$, then

$$g'(\tau) = 1 - \frac{y'(\tau)b(\tau)\sin(y(\tau)) - y(\tau)b'(\tau)\sin(y(\tau))}{(b(\tau)\sin(y(\tau)))^2}$$
$$- \frac{y(\tau)b(\tau)\cos((\tau))y'(\tau)}{(b(\tau)\sin(y(\tau)))^2}$$

where

$$y'(\tau) = -\sqrt{1 - \left(\frac{a(\tau)}{b(\tau)}\right)^2}\frac{a'(\tau)b(\tau) - a(\tau)b'(\tau)}{b^2(\tau)}.$$

As

$$\lim_{\gamma \to 0} \frac{d}{d\tau}\alpha'(u^*) = 0$$

from (7), we have:

$$\lim_{\gamma \to 0} b'(\tau) = 0 \quad \text{and} \quad \lim_{\gamma \to 0} a'(\tau) = 0.$$

Then

$$\lim_{\gamma \to 0} g'(\tau) = 1 > 0, \text{ for all } 0 \leq \tau \leq \overline{\tau}$$

so as, $g' > 0$ and g is an increasing function on the interval $]0, \tau[$ for γ close enough to 0, τ_0 is unique in $]0,\tau[$. By the continuity property of F, we have $F(\tau) > \tau$ for τ

$\in]0,\tau_0[$ and $F(\tau) < \tau$ for $\tau \in]\tau_0,\tau[$.

The proof of lemma 3 is obvious.

2.3. **Hopf bifurcation**. From theorem 2, we deduce that the Hopf bifurcation may occurs at the critical value $\tau = \tau_0$ (see [5, 35]) and we have the following result.

Theorem 3. Assume (**H$_0$**), (**H$_2$**), $n \geq 2$ and γ sufficiently small. There exists $\varepsilon 0 > 0$ such that, for each $0 \leq \varepsilon < \varepsilon_0$, equation (6) has a family of periodic solutions $p(\varepsilon)$ with period $T = T(\varepsilon)$, for the parameter values $\tau = \tau(\varepsilon)$ such that $p(0) = 0$, $T(0) = \frac{2\pi}{\zeta_0}$ and $\tau(0) = \tau_0$, where τ_0 stated in lemma 2 and $\zeta 0 = \arccos\left(-\frac{a(\tau_0)}{b(\tau_0)}\right)$.

Proof. We apply the Hopf bifurcation theorem (see [10, 11, 15, 16, 29]). From the expression of $f0$ in (6), we have,

$f_0(0, \tau) = 0$ and $\frac{\partial f_0(0,\tau)}{\partial\varphi} = 0$, for all $\tau > 0$

From (8) and lemma 2, we have:

$$\Delta(i\zeta,\tau) = 0 \quad \Leftrightarrow \quad \begin{cases} \zeta = \zeta_0 = \arccos\left(-\frac{a(\tau_0)}{b(\tau_0)}\right) \\ \text{and} \\ \tau = \tau_0 \end{cases}$$

Thus, characteristic equation (7) has a pair of simple imaginary roots $\lambda_0 = i\zeta_0$ and $\lambda_0 = -i\zeta_0$ at $\tau = \tau_0$.

Lastly, we need to verify the transversality condition.

From (8), $W(\lambda_0, \tau_0) = 0$ and $\frac{\partial}{\partial\lambda} W(\lambda_0, \tau_0) = (\lambda_0+\gamma\tau_0)(1-\tau_0 a(\tau_0)+\lambda_0) \neq 0$. According to the implicit function theorem, there exists a complex function $\lambda = \lambda(\tau)$ defined in a neighborhood of τ_0, such that $\lambda(\tau_0) = \lambda_0$ and $\Delta_0(\lambda(\tau), \tau) = 0$ and

$\lambda'(\tau) = -\frac{\partial W(\lambda,\tau)/\partial\tau}{\partial W(\lambda,\tau)/\partial\lambda}$, for τ in a neighborhood of τ_0. (15)

Let $\lambda(\tau) = p(\tau) + iq(\tau)$. From (15) we have:

$$p'(\tau)_{/\tau=\tau_0} = \frac{1}{\tau_0}\frac{\zeta_0^2}{(1-\tau_0 a(\tau_0))^2+\zeta_0^2} \text{ for } \gamma = 0$$

By the continuity property, we conclude that, $p'(\tau)_{/\tau=\tau 0} > 0$, for γ close to 0.

In this last section we have verified that, system (6) has a Hopf bifurcation at the critical value τ_0 of the delay. Another interesting problem is to determine the direction and stability of the bifurcating branch. In the next, we give an explicit algorithm to decide about the direction and stability of the bifurcating branch of periodic solutions of (6).

Direction of Hopf Bifurcation

In this section we follow methods presented in [10], 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 3).

Namely, this direction and stability are determined by the sign of the first non zero term of Taylor expansion, i.e.

$\tau(\varepsilon) = \tau_0 + \tau_2\varepsilon^2 + o(\varepsilon^2)$ (16)

and the sign of τ_2 determines 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 [10], using the formula,

$$\tau_2 = \frac{Re(c)}{Re(qD_2M_0(i\zeta_0, \tau_0)p)}, \tag{17}$$

where M_0 is the characteristic matrix of (6) given by:

$$M_0(\lambda, \tau) = \begin{pmatrix} \lambda - \tau a(\tau) - \tau b(\tau)e^{-\lambda} & 0 \\ \tau\alpha'(u^*(\tau))(-1 + e^{-\gamma\tau}e^{-\lambda}) & \lambda + \gamma\tau \end{pmatrix},$$

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

$$c = \frac{1}{2}qD_1^3 f_0(0, \tau_0)(P^2(\theta), \overline{P}(\theta))$$
$$+qD_1^2 f_0(0, \tau_0)(e^{0\cdot}M_0^{-1}(0, \tau_0)D_1^2 f_0(0, \tau_0)(P(\theta), \overline{P}(\theta)), P(\theta))$$
$$+\frac{1}{2}qD_1^2 f_0(0, \tau_0)(e^{2i\zeta_0\cdot}M_0^{-1}(2i\zeta_0, \tau_0)D_1^2 f_0(0, \tau_0)(P(\theta), P(\theta)), \overline{P}(\theta))$$

where f_0 is the nonlinear part of (6), $D_1^i f_0, i$ f_0, i = 2, 3, denotes the $i - th$ derivative of f_0 with respect to φ, $P(\theta)$ denotes the eigenvector of A, $P(\theta)$ denotes the conjugate eigenvector, and p and q are defined later.

Now, we describe all the above operators and vectors precisely. Let

$L := L(\tau_0) : C([-1, 0], \mathbb{R}^{\not{k}}) \longrightarrow \mathbb{R}^{\not{k}}$

denotes the linear part of (6). Using the Riesz representation theorem one obtain, see [15]:

$$L\varphi = \int_{-1}^{0} d\eta(\theta)\varphi(\theta) \tag{18}$$

where,

$$d\eta(\theta) = \tau_0 \begin{pmatrix} -(\delta + \alpha'(u^*))\delta(\theta) + 2e^{-\gamma\tau_0}\alpha'(u^*)\delta(\theta + 1) & 0 \\ \alpha'(u^*)\delta(\theta) - e^{-\gamma\tau_0}\alpha'(u^*)\delta(\theta + 1) & -\gamma\delta(\theta) \end{pmatrix} \tag{19}$$

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

Let A denotes the generator of semigroup generated by the linear part of (6).

Then,

$$A\varphi(\theta) = \begin{cases} \frac{d\varphi}{d\theta}(\theta) \text{ for } \theta \in [-1, 0) \\ L\varphi \text{ for } \theta = 0 \end{cases} \tag{20}$$

where $\varphi \in C([-1, 0], \mathbb{R}^{\not{k}})$.

To study the direction of Hopf bifurcation, one needs to calculate the second and third

derivatives of nonlinear part of (6):

$$D_1^2 f_0(\varphi,\tau)\psi\chi = \tau \begin{pmatrix} -\alpha''(u^*(\tau)+\varphi_1(0))\psi_1(0)\chi_1(0) \\ +2e^{-\gamma\tau_0}\alpha''(u^*(\tau)+\varphi_1(-1))\psi_1(-1)\chi_1(-1) \\ \\ \alpha''(u^*(\tau)+\varphi_1(0))\psi_1(0)\chi_1(0) \\ -e^{-\gamma\tau_0}\alpha''(u^*(\tau)+\varphi_1(-1))\psi_1(-1)\chi_1(-1) \end{pmatrix} \quad (21)$$

and

$$D_1^3 f_0(\varphi,\tau)\psi\chi v = \tau \begin{pmatrix} -\alpha'''(u^*(\tau)+\varphi_1(0))\psi_1(0)\chi_1(0)v_1(0) \\ +2e^{-\gamma\tau_0}\alpha'''(u^*(\tau)+\varphi_1(-1))\psi_1(-1)\chi_1(-1)v_1(-1) \\ \\ \alpha'''(u^*(\tau)+\varphi_1(0))\psi_1(0)\chi_1(0)v_1(0) \\ -e^{-\gamma\tau_0}\alpha'''(u^*(\tau)+\varphi_1(-1))\psi_1(-1)\chi_1(-1)v_1(-1) \end{pmatrix} \quad (22)$$

Then

$$D_1^2 f_0(0,\tau_0)\psi\chi = \tau_0\alpha''(u^*)\Big[\psi_1(0)\chi_1(0)\begin{pmatrix} -1 \\ 1 \end{pmatrix} + e^{-\gamma\tau_0}\psi_1(-1)\chi_1(-1)\begin{pmatrix} 2 \\ -1 \end{pmatrix}\Big] \quad (23)$$

and

$$D_1^3 f_0(0,\tau_0)\psi\chi v = \tau_0\alpha'''(u^*)\Big[\psi_1(0)\chi_1(0)v_1(0)\begin{pmatrix} -1 \\ 1 \end{pmatrix} + e^{-\gamma\tau_0}\psi_1(-1)\chi_1(-1)v_1(-1)\begin{pmatrix} 2 \\ -1 \end{pmatrix}\Big] \quad (24)$$

$$\psi = (\psi_1,\psi_2),\ \chi = (\chi_1,\chi_2),\ v = (v_1,v_2) \in C([-1,0],\mathbb{R}^{\not k}).$$

As $(i\zeta_0, \tau_0)$ is a solution of (7), 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:

$M\,p = 0$

with

$$M = M_0(i\zeta_0,\tau_0) = \begin{pmatrix} 0 & 0 \\ \tau_0\alpha'(u^*)(-1+e^{-\gamma\tau_0}e^{-i\zeta_0}) & i\zeta_0+\gamma\tau_0 \end{pmatrix}. \quad (25)$$

Then one may assume

$p_1 = 1$,

and calculate

$$p_2 = \tau_0\alpha'(u^*)\frac{1-e^{-\gamma\tau_0}e^{-i\zeta_0}}{i\zeta_0+\gamma\tau_0}.$$

Now, consider A^*, i.e. an operator conjugated to $A,\ A^* : C([0,1],\mathbb{R}^{\not k}) \longrightarrow \mathbb{R}^{\not k}$, defined by,

$$A^*\psi(s) = \begin{cases} -\frac{d\psi}{ds}(s) \text{ for } s \in (0,1] \\ -\int_{-1}^{0}\psi(-s)d\eta(s) \text{ for } s = 0 \end{cases} \quad (26)$$

$$\psi = (\psi_1,\psi_2) \in C([0,1],\mathbb{R}^{\not k}).$$

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 [15],

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

be equals to 1. Therefore
$q_2 = 0$
leads to
$$q_1 = \frac{1}{1 - \tau_0 a + i\zeta_0},$$

where $a = a(\tau_0)$, $b = b(\tau_0)$.

From (23) and (24) we have

$$D_1^2 f_0(0,\tau_0)(P(\theta), \overline{P}(\theta)) = \tau_0 \alpha''(u^*) \left[\begin{pmatrix} -1 \\ 1 \end{pmatrix} + e^{-\gamma\tau_0} \begin{pmatrix} 2 \\ -1 \end{pmatrix} \right] \quad (27)$$

$$D_1^2 f_0(0,\tau_0)(P(\theta), P(\theta)) = \tau_0 \alpha''(u^*) \left[\begin{pmatrix} -1 \\ 1 \end{pmatrix} + e^{-\gamma\tau_0} e^{-2i\zeta_0} \begin{pmatrix} 2 \\ -1 \end{pmatrix} \right] \quad (28)$$

and

$$D_1^3 f_0(0,\tau_0)(P^2(\theta), \overline{P}(\theta)) = \tau_0 \alpha'''(u^*) \left[\begin{pmatrix} -1 \\ 1 \end{pmatrix} + e^{-\gamma\tau_0} e^{-i\zeta_0} \begin{pmatrix} 2 \\ -1 \end{pmatrix} \right]. \quad (29)$$

and

$$\frac{1}{2} q D_1^3 f_0(0,\tau_0)(P^2(\theta), \overline{P}(\theta)) = q_1 \frac{\alpha'''(u^*)}{2\alpha'(u^*)} (i\zeta_0 + \tau_0 \delta) \quad (30)$$

From the expression of M_0 and the hypothesis (**H$_3$**), we have

$$M_0^{-1}(0,\tau_0) = -\frac{1}{\gamma\tau_0(a+b)} \begin{pmatrix} \gamma & 0 \\ \alpha'(u^*)(1 - e^{-\gamma\tau_0}) & -(a+b) \end{pmatrix} \quad (31)$$

and

$$M_0^{-1}(2i\zeta_0,\tau_0) = W_0^{-1}(2i\zeta_0,\tau_0) \begin{pmatrix} 2i\zeta_0 + \gamma\tau_0 & 0 \\ \tau_0 \alpha'(u^*)(1 - e^{-\gamma\tau_0} e^{-2i\zeta_0}) & 2i\zeta_0 - \tau_0 a - \tau_0 b e^{-2i\zeta_0} \end{pmatrix} \quad (32)$$

From (23),(27), (28),(31), (32) and **(H$_3$)**, we have,

$$q D_1^2 f_0(0,\tau_0)(e^0 M_0^{-1}(0,\tau_0) D_1^2 f_0(0,\tau_0)(P(\theta), \overline{P}(\theta)), P(\theta)) = -q_1 \frac{\alpha''(u^*)^2}{\alpha'(u^*)(a+b)} (2e^{-\gamma\tau_0} - 1)(i\zeta_0 + \tau_0 \delta) \quad (33)$$

and

$$q D_1^2 f_0(0,\tau_0)(e^{2i\zeta_0} M_0^{-1}(2i\zeta_0,\tau_0) D_1^2 f_0(0,\tau_0)(P(\theta), P(\theta)), \overline{P}(\theta)) = q_1 \tau_0 \frac{\alpha''(u^*)^2}{\alpha'(u^*)} \Delta^{-1}(2i\zeta_0,\tau_0)(i\zeta_0 + \tau_0 \delta)(2e^{-\gamma\tau_0} e^{2i\zeta_0} - 1) \quad (34)$$

Then

$$c = \frac{1}{2} q_1 \frac{i\zeta_0 + \tau_0\delta}{\alpha'(u^*)} \Big[\alpha'''(u^*) - 2\alpha''(u^*)^2 \frac{2e^{-\gamma\tau_0} - 1}{a+b} + \tau_0 \alpha''(u^*)^2 \Delta^{-1}(2i\zeta_0, \tau_0)(2e^{-\gamma\tau_0} e^{-2i\zeta_0} - 1)\Big]$$

and

$$Re(c) = \frac{1}{2\alpha'(u^*)\left[(1-\tau_0 a)^2 + \zeta_0^2\right]} \times \Big\{ \Big((1-\tau_0 a)\tau_0\delta + \zeta_0^2\Big)\Big(\alpha'''(u^*) - 2\alpha''(u^*)^2 \frac{2e^{-\gamma\tau_0} - 1}{a+b} + \frac{\tau_0 \alpha''(u^*)^2 X}{\|\Delta(2i\zeta_0, \tau_0)\|^2}\Big) - \zeta_0(1 - \tau_0 a - \tau_0\delta)\frac{\tau_0\alpha''(u^*)^2 Y}{\|\Delta(2i\zeta_0, \tau_0)\|^2}\Big\} \quad (35)$$

where

$$X = (1 - 2e^{-\gamma\tau_0}\cos(2\zeta_0))(\tau_0 a + \tau_0 b\cos(2\zeta_0)) - 2e^{-\gamma\tau_0}\sin(2\zeta_0)(2\zeta_0 + \tau_0 b\sin(2\zeta_0))$$
$$Y = 2e^{-\gamma\tau_0}\sin(2\zeta_0)(\tau_0 a + \tau_0 b\cos(2\zeta_0)) + (1 - 2e^{-\gamma\tau_0}\cos(2\zeta_0))(2\zeta_0 + \tau_0 b\sin(2\zeta_0)).$$

As

$Re({}_qD_2M_0(i\xi_0, \tau_0)p) > 0$, for τ close to 0

we deduce the folowing result :

Theorem 4. *Let Re(c) be given in (35) 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; and (b) the bifurcating periodic solutions is stable if Re(c) > 0 and unstable if Re(c) < 0.

Note that, Theorem 4 provides an explicit algorithm for detecting the direction and stability of Hopf bifurcation.

Discussions

It is well known (Mackey (1997) [23]) that when taking γ as a bifurcation parameter and allowing γ to increase, a supercritical Hopf bifurcation of (1) is followed by an inverse Hopf bifurcation.

In [1] the following conditions of stability of the non-trivial steady state of (1) were proposed (Beretta and Kuang (2002) [4] and Hayes (1950) [20])

$$\left| \frac{a(\tau)}{b(\tau)} \right| > 1 \text{ or } \left(\left| \frac{a(\tau)}{b(\tau)} \right| \leq 1 \text{ and } \tau < \frac{\arccos(-\frac{a(\tau)}{b(\tau)})}{\sqrt{b(\tau)^2 - a(\tau)^2}} \right),$$
$$\text{where } 0 < \tau < \frac{1}{\gamma}\ln\left(\frac{2}{1+\frac{\delta}{\beta_0}}\right), \delta < \beta_0.$$

In sections 2.1 and 2.2 of this paper it is shown that if the loss rate γ from proliferating cells is smaller and the control shape satisfies $n \geq 2$, then the steady state $E^*(\tau)$ may be stable for $\tau = 0$, hence it is stable for $0 < \tau < \tau_0$ and unstable for $\tau_0 < \tau <$

τ , where
$\overline{\tau} = \frac{1}{\gamma}\ln(\frac{2}{1+\frac{2\delta}{\beta_0}}), 3\delta < \beta_0$ and at $\tau = \tau_0$ a Hopf bifurcation occurs.

In the rest of the paper we study the direction of Hopf bifurcation and we give a criteria for determining the stability or instability of the bifurcating branch of periodic solutions of (6)

The results proposed in this paper should hopefully improve the understanding of the qualitative properties of the description delivered by model (1). So far we have now a description of stability properties and direction of Hopf bifurcation with a detailed analysis of the influence of delays terms.

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