HAL
open science

Stability of limit cycles in a pluripotent stem cell dynamics model

Mostafa Adimy, Fabien Crauste, Andrei Halanay, Mihaela Neamtu, Dumitru Opris

To cite this version:

Mostafa Adimy, Fabien Crauste, Andrei Halanay, Mihaela Neamtu, Dumitru Opris. Stability of limit cycles in a pluripotent stem cell dynamics model. Chaos, Solitons & Fractals, 2006, 27 (4), pp.1091-1107. 10.1016/j.chaos.2005.04.083 . hal-00376002

HAL Id: hal-00376002

https://hal.science/hal-00376002v1

Submitted on 16 Apr 2009

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Stability of Limit Cycles in a Pluripotent Stem Cell Dynamics Model

Mostafa Adimy*, Fabien Crauste*, Andrei Halanay†,
Mihaela Neamţu‡ and Dumitru Opriş◇

Year 2005

*Laboratoire de Mathématiques Appliquées, UMR 5142,
Université de Pau et des Pays de l'Adour,
Avenue de l'université, 64000 Pau, France.
ANUBIS project, INRIA–Futurs
Emails: mostafa.adimy@univ-pau.fr, fabien.crauste@univ-pau.fr

†Department of Mathematics 1, University Politehnica of Bucharest,
Splaiul Independenţei 313, RO-060042, Bucharest, Romania.
Email: halanay@vectron.mathem.pub.ro

‡Faculty of Economics, I.N. Pestalozzi 16, West University of Timişoara,
RO-300115, Timişoara, Romania.
Email: mihaela.neamtu@fse.uvt.ro

◇Department of Applied Mathematics, Faculty of Mathematics,
Bd. V. Parvan 4, West University of Timişoara,
RO-300223, Timişoara, Romania.
Email: opris@math.uvt.ro

Abstract

This paper is devoted to the study of the stability of limit cycles of a nonlinear delay differential equation with a distributed delay. The equation arises from a model of population dynamics describing the evolution of a pluripotent stem cells population. We study the local asymptotic stability of the unique nontrivial equilibrium of the delay equation and we show that its stability can be lost through a Hopf bifurcation. We then investigate the stability of the limit cycles yielded by the bifurcation using the normal form theory and the center manifold theorem. We illustrate our results with some numerics.

Keywords: Delay differential equations, distributed delay, Hopf bifurcation, stability, limit cycles, normal form, center manifold, blood production system, hematopoietic stem cells.

1 Introduction

This paper is devoted to the analysis of the nonlinear delay differential equation

$$x'(t) = -\big(\delta + \beta(x(t))\big)x(t) + \frac{2}{\tau}\int_0^\tau \beta(x(t-s))x(t-s)ds. \tag{1}$$

This equation arises from a model of pluripotent hematopoietic stem cells dynamics, that is stem cells at the root of the blood production process [1, 2]. It describes the fact that the cell density evolves according to mortality and cell division. One may stress that the cell density considered in equation (1) is in fact the density of resting cells, in opposition to the density of proliferating cells.

The distinction between these two stages of the cell cycle is now widely accepted. We can cite, for example, the works of Burns and Tannock [3] on the existence of a resting phase — also called G_0-phase — in the cell cycle. This phase is a quiescent stage in the cell development, contrary to the proliferating phase which represents the active part of the cell cycle: it is composed of the main stages of the cell development (e.g. DNA synthesis) and ends at mitosis with the cell division. Thus, proliferating pluripotent hematopoietic stem cells are committed to divide and give birth to two daughter cells which immediately enter the resting phase and complete the cycle.

Mathematical models describing the dynamics of hematopoietic stem cells population have been studied since the end of the seventies and the works of Mackey [4, 5]. For the reader interested in this topic, we mention the review articles by Haurie *et al.* [6] and Mackey *et al.* [7], and the references therein. Recently, Pujo-Menjouet *et al.* [8, 9] proved the existence of a Hopf bifurcation for the hematopoiesis model proposed in [4], described by a nonlinear differential equation with discrete delay. However, their results cannot be directly applied to (1) because of the nature of the delay.

Delay differential equations with distributed delay have been studied by many authors. We can cite, for example, the works in [10, 11, 12, 13, 14]. However, these studies mainly focused on stability conditions. In 2003, Liao *et al.* [15] showed the existence of a Hopf bifurcation for a Van der Pol equation with distributed delay and studied the stability of limit cycles, applying the normal form theory and the center manifold theorem. The characteristic equation in [15] is an exponential polynomial, similar to the one obtained in [8, 9] except that the degree is higher, which makes the study easier than with equation (1). In [2], Adimy *et al.* obtained the existence of a Hopf bifurcation for a nonlinear differential equation with a delay distributed according to a density, generalizing equation (1). However, these authors did not study the limit cycles of their model.

We consider a pluripotent hematopoietic stem cells population density $x(t)$, satisfying the nonlinear delay differential equation (1). The constant δ accounts for natural mortality and cellular differentiation. The nonlinear term $\beta(x(t))$ represents a rate of introduction in the proliferating phase. The last term appears to describe the amount of cells due to cell division: cells are assumed to divide uniformly on an interval $(0, \tau)$, with $\tau > 0$, and dividing cells are in fact cells introduced in the proliferating phase one generation earlier. The assumption on the cell division comes from the fact that, even though only a little is known about phenomena involved in hematopoiesis, there are strong evidences (see Bradford *et al.* [16]) indicating that cells do not divide at the same age. The factor 2 describes the division of each mother cell in two daughter cells.

The rate of reintroduction in the proliferating compartment β is taken to be a monotone and decreasing Hill function, given by

$$\beta(x) = \beta_0 \frac{\theta^n}{\theta^n + x^n} \qquad \text{for } x \geq 0. \tag{2}$$

The coefficient $\beta_0 > 0$ is the maximum rate of reintroduction, $\theta \geq 0$ is the resting phase population density for which the rate of re-entry β attains its maximum rate of change with respect to the resting phase population, and $n \geq 0$ describes the sensitivity of β with changes in the population. This function was firstly used in hematopoiesis models by Mackey [4] in 1978.

In [4, 5] Mackey gave values of the above parameters for a normal human body production. These values are

$$\delta = 0.05 \text{ d}^{-1} \quad \text{and} \quad \beta_0 = 1.77 \text{ d}^{-1}. \tag{3}$$

Usually, n is close to 1, but Mackey [4, 5] reports values of n around 3 in abnormal situations.

The value of θ is usually $\theta = 1.62 \times 10^8$ cells/kg. However, since we shall study the qualitative behavior of the pluripotent stem cells population, the value of θ is not really important and setting the scale change

$$x(t) \to \frac{x(t)}{\theta}$$

in (1), with the function β given by (2), we obtain

$$\frac{dx}{dt}(t) = -\delta x(t) - \beta_0 f\left(x(t)\right) + \frac{2\beta_0}{\tau} \int_{-\tau}^{0} f\left(x(t+s)\right) ds \tag{4}$$

with

$$f(x) = \frac{x}{1+x^n}, \qquad x \geq 0. \tag{5}$$

However, we mention that this special form of f will not be used in the following, except in computations in Section 4. We only assume that f is differentiable with $f(0) = 0$ and, for $x > 0$, $f(x)/x$ is decreasing and satisfies

$$\lim_{x \to +\infty} \frac{f(x)}{x} = 0.$$

An illustration of such a function is presented in Fig. 1.

Notice that equation (4) has at most two equilibria: the trivial equilibrium $x \equiv 0$ and a nontrivial positive equilibrium $x \equiv x^*$. The trivial equilibrium always exists and corresponds to the extinction of the population.

The nontrivial equilibrium exists if and only if

$$0 < \delta < \beta_0 f'(0) \tag{6}$$

and is then uniquely defined by

$$\delta x^* = \beta_0 f(x^*). \tag{7}$$

This can be easily shown by using the fact that the function $f(x)/x$ is decreasing on $[0, +\infty)$.

Our aim in this work is to show that the unique nontrivial equilibrium of equation (1) undergoes, in a particular case, a unique Hopf bifurcation and to show the stability of the limit cycles following the approach in [17, 18].

The paper is organized as follows. In Section 2, we establish some local stability results for the unique nontrivial equilibrium of (1) and prove that it undergoes a Hopf bifurcation. We study the stability of the limit cycles obtained at the bifurcation in Section 3. Our results are illustrated numerically in Section 4. We conclude with a discussion in Section 5.

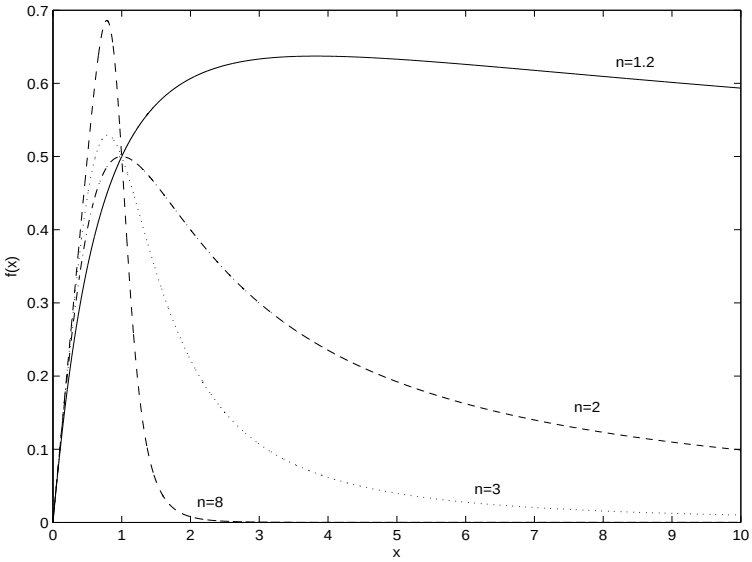


Figure 1: Graph of the function f given by (5) for different values of n.

2 Local Stability and Hopf Bifurcation Analysis

Part of the study presented in this section has been previously performed by Adimy *et al.* in [1]. However, for the reader convenience and to preserve the coherence of the present work, we detail the asymptotic behavior study of the nontrivial equilibrium $x \equiv x^*$ of equation (4), defined by (7). We first concentrate on the local asymptotic stability of this equilibrium. Then, we will show that it undergoes a Hopf bifurcation for some critical value of the time delay.

We assume that (6) holds in order to ensure the existence of x^*, that is

$$0 < \delta < \beta_0 f'(0).$$

The linearization of equation (4) around x^* leads to the characteristic equation

$$\Delta(\lambda, \tau) := \lambda + \delta + \beta_0\beta_1 - \frac{2\beta_0\beta_1}{\tau}\int_{-\tau}^{0} e^{\lambda s} ds = 0, \tag{8}$$

where we have set

$$\beta_1 := f'(x^*).$$

We recall that the nontrivial equilibrium x^* is locally asymptotically stable if and only if all eigenvalues of (8) have negative real parts.

The function f in (4) is not necessarily monotone so β_1 may be either positive or negative. We first study the case $\beta_1 \geq 0$.

Consider $\Delta(\lambda, \tau)$ as a function of real λ. Then Δ is differentiable with respect to λ and

$$\Delta_\lambda(\lambda, \tau) := \frac{\partial \Delta}{\partial \lambda}(\lambda, \tau) = 1 - \frac{2\beta_0\beta_1}{\tau}\int_{-\tau}^{0} s e^{\lambda s} ds. \tag{9}$$

Since $\int_{-\tau}^{0} se^{\lambda s}ds < 0$, we deduce that $\Delta_\lambda(\lambda,\tau) > 0$. Moreover, one can easily check that

$$\lim_{\lambda\to-\infty} \Delta(\lambda,\tau) = -\infty \qquad \text{and} \qquad \lim_{\lambda\to+\infty} \Delta(\lambda,\tau) = +\infty.$$

Consequently, $\Delta(\lambda,\tau)$ has a unique real eigenvalue, namely λ_0. From (8), we obtain

$$\Delta(0,\tau) = \delta - \beta_0\beta_1.$$

Writing

$$\beta_1 = x^*\left(\frac{f(x)}{x}\right)'\Big|_{x=x^*} + \frac{f(x^*)}{x^*} = x^*\left(\frac{f(x)}{x}\right)'\Big|_{x=x^*} + \frac{\delta}{\beta_0},$$

we deduce

$$\Delta(0,\tau) = -\beta_0 x^*\left(\frac{f(x)}{x}\right)'\Big|_{x=x^*} > 0.$$

Hence, λ_0 is strictly negative.

Let $\lambda = \nu + i\omega$ be an eigenvalue of (8) and assume that $\nu > \lambda_0$. Considering the real part of (8), we obtain

$$\nu + \delta + \beta_0\beta_1 - \frac{2\beta_0\beta_1}{\tau}\int_{-\tau}^{0} e^{\nu s}\cos(\omega s)ds = 0.$$

Therefore,

$$\nu - \lambda_0 = \frac{2\beta_0\beta_1}{\tau}\int_{-\tau}^{0}\left[e^{\nu s}\cos(\omega s) - e^{\lambda_0 s}\right]ds < 0,$$

which gives a contradiction. We deduce that every eigenvalue of (8) has negative real part. It follows that the nontrivial positive equilibrium x^* is locally asymptotically stable. This result is summed up in the following proposition.

Proposition 2.1. *Assume that $\beta_1 \geq 0$. Then the nontrivial equilibrium $x \equiv x^*$ of (4) is locally asymptotically stable for all $\tau \geq 0$.*

If the function f is given by (5) then (6) is equivalent to $0 < \delta < \beta_0$ and $x^* = (\beta_0/\delta - 1)^{1/n}$. The condition $\beta_1 \geq 0$ reduces to

$$n\frac{\beta_0 - \delta}{\beta_0} \leq 1.$$

We assume now that $\beta_1 < 0$. We are going to show that the equilibrium x^* undergoes a Hopf bifurcation. To that aim, we look for the existence of purely imaginary roots of (8).

We first check that x^* is locally asymptotically stable when $\tau = 0$. In this case, the characteristic equation (8) reduces to

$$\lambda + \delta - \beta_0\beta_1 = 0,$$

so

$$\lambda = -\delta + \beta_0\beta_1 < 0.$$

We have the following lemma.

Lemma 2.1. *Assume that $\beta_1 < 0$. Then the nontrivial equilibrium $x \equiv x^*$ of (4) is locally asymptotically stable when $\tau = 0$.*

Let $\lambda = i\omega$, $\omega \in \mathbb{R}$, be a purely imaginary eigenvalue of (8). One can check that

$$\Delta(-i\omega, \tau) = 0,$$

so we only look for positive ω. Moreover, $\omega \neq 0$ since

$$\Delta(0, \tau) = \delta - \beta_0\beta_1 > 0.$$

Thus, let us assume that $\omega > 0$ and $\tau > 0$ satisfy $\Delta(i\omega, \tau) = 0$. Separating real and imaginary parts of $\Delta(i\omega, \tau)$, we obtain

$$\left\{ \begin{array}{rcl} \delta + \beta_0\beta_1 - \dfrac{2\beta_0\beta_1}{\omega\tau}\sin(\omega\tau) & = & 0, \\ \omega + \dfrac{2\beta_0\beta_1}{\omega\tau}(1 - \cos(\omega\tau)) & = & 0. \end{array} \right. \tag{10}$$

We set

$$h(x) = \frac{\sin(x)}{x}, \qquad x > 0.$$

Then system (10) can be written

$$\left\{ \begin{array}{rcl} h(\omega\tau) & = & \dfrac{\delta + \beta_0\beta_1}{2\beta_0\beta_1}, \\ \dfrac{\cos(\omega\tau) - 1}{(\omega\tau)^2} & = & \dfrac{1}{2\beta_0\beta_1\tau}. \end{array} \right. \tag{11}$$

Since $\beta_1 < 0$ and $\delta > 0$, then

$$\frac{\delta + \beta_0\beta_1}{2\beta_0\beta_1} < \frac{1}{2}.$$

Let

$$x_0 = \min\{x > 0;\ x = \tan(x) \text{ and } h(x) > 0\} \simeq 7.725,$$

and assume that

$$h(x_0) < \frac{\delta + \beta_0\beta_1}{2\beta_0\beta_1}. \tag{12}$$

One can check that $h(x_0) \simeq 0.1284$. Then (12) is equivalent to

$$\beta_1 < -\frac{\delta}{\beta_0(1 - 2h(x_0))}.$$

On the interval $[0, \pi]$, the function h is strictly decreasing and nonnegative, with $0 \leq h(x) \leq 1$. Moreover, for $x \geq \pi$, $h(x) \leq h(x_0)$. Consequently, the equation

$$h(x) = \frac{\delta + \beta_0\beta_1}{2\beta_0\beta_1}$$

has a unique solution, denoted x_c, which belongs to the interval $(0, \pi)$. We then set

$$\tau_c = \frac{x_c^2}{2\beta_0\beta_1(\cos(x_c) - 1)}$$

and

$$\omega_c = \frac{x_c}{\tau_c}.$$

Therefore, (ω_c, τ_c) is the unique solution of (11) and $\pm i\omega_c$ are purely imaginary eigenvalues of (8) for $\tau = \tau_c$.

In order to show that x^* undergoes a Hopf bifurcation for $\tau = \tau_c$, we have to prove that $\pm i\omega_c$ are simple eigenvalues of $\Delta(\cdot, \tau_c)$ and satisfy the transversality condition

$$\left.\frac{d\mathrm{Re}(\lambda)}{d\tau}\right|_{\tau=\tau_c} > 0.$$

We first check that $\pm i\omega_c$ are simple eigenvalues of (8). Using (9), one can see that $i\omega_c$ is simple if

$$\mathrm{Re}\left(\Delta_\lambda(i\omega_c, \tau_c)\right) = 1 + \frac{2\beta_0\beta_1}{\tau_c}\ \frac{\omega_c\tau_c\sin(\omega_c\tau_c) + \cos(\omega_c\tau_c) - 1}{\omega_c^2} \neq 0 \tag{13}$$

or

$$\mathrm{Im}\left(\Delta_\lambda(i\omega_c, \tau_c)\right) = \frac{2\beta_0\beta_1}{\tau_c}\ \frac{\omega_c\tau_c\cos(\omega_c\tau_c) - \sin(\omega_c\tau_c)}{\omega_c^2} \neq 0. \tag{14}$$

We are going to show that, in fact, these two conditions are satisfied.

Lemma 2.2. *Assume that $\beta_1 < 0$ and (12) holds. Let (ω_c, τ_c) be the unique solution of (11), with $\omega_c\tau_c \in (0, \pi)$. Then*

$$Re\left(\Delta_\lambda(i\omega_c, \tau_c)\right) > 0 \qquad \text{and} \qquad Im\left(\Delta_\lambda(i\omega_c, \tau_c)\right) > 0. \tag{15}$$

In particularly, $\pm i\omega_c$ are simple eigenvalues of (8) for $\tau = \tau_c$.

Proof. First, one can check, using (11) and (13), that

$$\mathrm{Re}\left(\Delta_\lambda(i\omega_c, \tau_c)\right) = 2 + (\delta + \beta_0\beta_1)\tau_c.$$

Since

$$\frac{\cos(x) - 1}{x^2} = -\frac{h^2(x)}{1 + \cos(x)}, \qquad \text{for } x > 0,$$

then, from (11) it follows that

$$1 + \cos(x) = -(\delta + \beta_0\beta_1)\tau_c.$$

Consequently,

$$\mathrm{Re}\left(\Delta_\lambda(i\omega_c, \tau_c)\right) = 1 - \cos(\omega_c\tau_c) > 0.$$

Secondly, since $x\cos(x) < \sin(x)$ for $x \in (0, \pi)$ and $x_c = \omega_c\tau_c \in (0, \pi)$, then from (14) we obtain

$$\mathrm{Im}\left(\Delta_\lambda(i\omega_c, \tau_c)\right) > 0.$$

This concludes the proof. □

Consider now a branch of eigenvalues $\lambda(\tau) = \nu(\tau) + i\omega(\tau)$ of (8) such that $\nu(\tau_c) = 0$ and $\omega(\tau_c) = \omega_c$. Separating real and imaginary parts in (8) we obtain

$$\begin{cases} \nu(\tau) + \delta + \beta_0\beta_1 - \dfrac{2\beta_0\beta_1}{\tau}\displaystyle\int_{-\tau}^{0} e^{\nu(\tau)s}\cos(\omega(\tau)s)ds &= 0, \\ \omega(\tau) - \dfrac{2\beta_0\beta_1}{\tau}\displaystyle\int_{-\tau}^{0} e^{\nu(\tau)s}\sin(\omega(\tau)s)ds &= 0. \end{cases}$$

Then, by differentiating each of the above equalities with respect to τ, we get, for $\tau = \tau_c$,

$$\begin{aligned} &\mathrm{Re}\left(\Delta_\lambda(i\omega_c,\tau_c)\right)\nu'(\tau_c) \\ &= \mathrm{Im}\left(\Delta_\lambda(i\omega_c,\tau_c)\right)\omega'(\tau_c) + \frac{2\beta_0\beta_1}{\tau_c}\left(\cos(x_c) - \frac{\sin(x_c)}{x_c}\right) \end{aligned} \tag{16}$$

and

$$\begin{aligned} &\mathrm{Re}\left(\Delta_\lambda(i\omega_c,\tau_c)\right)\omega'(\tau_c) \\ &= -\mathrm{Im}\left(\Delta_\lambda(i\omega_c,\tau_c)\right)\nu'(\tau_c) + \frac{2\beta_0\beta_1}{\tau_c}\left(\frac{1-\cos(x_c)}{x_c} - \sin(x_c)\right). \end{aligned} \tag{17}$$

Using (15), (16) and (17), we can see that $\nu'(\tau_c)$ satisfies

$$\begin{aligned} &\left[\mathrm{Im}\left(\Delta_\lambda(i\omega_c,\tau_c)\right)^2 + \mathrm{Re}\left(\Delta_\lambda(i\omega_c,\tau_c)\right)^2\right]\nu'(\tau_c) \\ &= \frac{2\beta_0\beta_1}{\tau_c}\left[\left(\frac{1-\cos(x_c)}{x_c} - \sin(x_c)\right)\mathrm{Im}\left(\Delta_\lambda(i\omega_c,\tau_c)\right)\right. \\ &\qquad\qquad \left. + \left(\cos(x_c) - \frac{\sin(x_c)}{x_c}\right)\mathrm{Re}\left(\Delta_\lambda(i\omega_c,\tau_c)\right)\right]. \end{aligned}$$

Using the definitions in (13) and (14), simple computations give

$$\begin{aligned} &\left(\frac{1-\cos(x_c)}{x_c} - \sin(x_c)\right)\mathrm{Im}\left(\Delta_\lambda(i\omega_c,\tau_c)\right) \\ &+ \left(\cos(x_c) - \frac{\sin(x_c)}{x_c}\right)\mathrm{Re}\left(\Delta_\lambda(i\omega_c,\tau_c)\right) \quad = \quad \cos(x_c) - \frac{\sin(x_c)}{x_c}. \end{aligned}$$

Hence,

$$\left|\Delta_\lambda(i\omega_c,\tau_c)\right|^2\nu'(\tau_c) = \frac{2\beta_0\beta_1}{\tau_c}\,\frac{x_c\cos(x_c) - \sin(x_c)}{x_c} > 0.$$

It follows that

$$\nu'(\tau_c) > 0. \tag{18}$$

To conclude, when $\tau = \tau_c$, the characteristic equation $\Delta(\lambda,\tau)$ has a unique pair of purely imaginary simple eigenvalues satisfying $(d\mathrm{Re}(\lambda)/d\tau)(\tau = \tau_c) > 0$. Consequently, a Hopf bifurcation occurs at x^* when $\tau = \tau_c$. Moreover, applying Rouché's Theorem with Lemma 2.1, we easily check that every eigenvalue of $\Delta(\lambda,\tau)$, with $\tau < \tau_c$, has negative real part. It follows that x^* is locally asymptotically stable for $0 \le \tau < \tau_c$. These results are summed up in the following theorem.

Theorem 2.1. *Assume that $\beta_1 < 0$ and (12) holds. Then there exists a unique value $\tau_c > 0$ of the time delay such that the equilibrium $x \equiv x^*$ is locally asymptotically stable when $\tau \in [0,\tau_c)$ and becomes unstable when $\tau = \tau_c$ throughout a Hopf bifurcation. In particularly, periodic solutions appear for equation (4) when $\tau = \tau_c$.*

As an example, one can check that when f is given by (5) the assumptions in Theorem 2.1 are equivalent to

$$n > \frac{2(1-h(x_0))}{1-2h(x_0)}\,\frac{\beta_0}{\beta_0-\delta} \simeq 2.35\frac{\beta_0}{\beta_0-\delta}.$$

In particularly, these conditions are satisfied when β_0 and δ are given by (3) and $n \ge 2.42$.

The existence of a Hopf bifurcation in Theorem 2.1 leads to the existence of a limit cycle when the bifurcation occurs. In the next section, we focus on the stability of this limit cycle.

3 Stability of Limit Cycles

We study now the stability of the limit cycle yielded by Theorem 2.1. We follow the approach used in [17, 18]. This involves the description of a center manifold and subsequently the study of the normal form given by the restriction of the flow to this center manifold. The stability of the limit cycle will be decided by the sign of the first Lyapunov coefficient $l_1(0)$.

For general properties concerning delay equations and the theory of central manifolds for these equations, see [19]. For the existence and various properties of center manifolds we refer to [20, 21, 22, 23, 24, 25]. Also, in [23] and [26], a rigorous treatment of the operators involved in this approach is to be found. A similar problem is considered in [15].

Define, for $t \geq 0$,

$$y(t) = x(t) - x^*, \qquad \mu = \tau - \tau_c$$

with x^* the nontrivial equilibrium of (4) that bifurcates into a limit cycle for the critical value $\tau = \tau_c$ (see Theorem 2.1). The equilibrium x^* is defined by (6) and (7). Equation (4) turns into

$$y'(t) = -\delta(y(t) + x^*) - \beta_0 f(y(t) + x^*) + \frac{2\beta_0}{\mu + \tau_c} \int_{-\mu-\tau_c}^{0} f\left(y(t+s) + x^*\right) ds. \tag{19}$$

Thanks to this formulation, we now concentrate on the trivial equilibrium $y \equiv 0$ of (19) which bifurcates when $\mu = 0$.

For an interval $I \subset \mathbb{R}$, denote $C(I, \mathbb{K}) = \{f : I \to \mathbb{K}, f \text{ continuous }\}$ where $\mathbb{K} = \mathbb{R}$ or $\mathbb{C}$. When $I = [-\mu - \tau_c, 0]$, we set

$$C_\mu := C([-\mu - \tau_c, 0], \mathbb{K}).$$

Considering, for $t \geq 0$, the function $y_t : [-\mu - \tau_c, 0] \to \mathbb{K}$ defined by $y_t(s) = y(t+s)$, we can reformulate equation (19) as the following abstract functionnal differential equation

$$\frac{d}{dt} y(t) = G_\mu(y_t), \qquad t \geq 0, \tag{20}$$

where, for $\varphi \in C_\mu$,

$$G_\mu(\varphi) = -\delta\left[\varphi(0) + x^*\right] - \beta_0 f\left(\varphi(0) + x^*\right) + \frac{2\beta_0}{\mu + \tau_c} \int_{-\mu-\tau_c}^{0} f\left(\varphi(s) + x^*\right) ds.$$

Assume that f is $\mathcal{C}^4$ on $[0, +\infty)$ (remark that G_μ is then $\mathcal{C}^4(C_\mu, \mathbb{R})$).

Consider the linearized equation of (20), corresponding to the Fréchet derivative $D_\varphi G_\mu(0) := L_\mu$, given by

$$\frac{d}{dt} z(t) = L_\mu z_t, \qquad t \geq 0. \tag{21}$$

In fact, L_μ is given explicitly by

$$L_\mu \varphi = -c_1 \varphi(0) + c_2(\mu) \int_{-\mu-\tau_c}^{0} \varphi(\theta) d\theta, \qquad \varphi \in C_\mu, \tag{22}$$

where

$$c_1 := \delta + \beta_0 \beta_1, \qquad c_2(\mu) := \frac{2\beta_0\beta_1}{\tau_c + \mu}, \qquad \beta_1 := f'(x^*). \tag{23}$$

Setting

$$F_\mu := G_\mu - L_\mu,$$

equation (20) becomes

$$\frac{d}{dt}y(t) = L_\mu y_t + F_\mu(y_t), \qquad t \geq 0, \tag{24}$$

with $F_\mu(0) = 0$ and $D_\varphi F_\mu(0) = 0$.

In order to develop a normal form associated to equation (21), we write this latter as an abstract ordinary differential equation.

First, we know from [24] that the linear equation (21) gives a C_0-semigroup $(T(t))_{t\geq 0}$ on C_μ, with generator A_μ defined by

$$\left\{ \begin{array}{rcl} \mathcal{D}(A_\mu) & = & \left\{\varphi \in C^1([-\mu-\tau_c, 0], \mathbb{R});\ \varphi'(0) = L_\mu\varphi\right\}, \\ A_\mu\varphi & = & \varphi', \qquad \varphi \in \mathcal{D}(A_\mu). \end{array} \right.$$

To write equation (24) as an ODE we need to extend the problem (21) to the Banach space $\widetilde{C}_\mu := C_\mu \oplus \langle X_0 \rangle$, where

$$\langle X_0 \rangle = \{X_0 c;\ c \in \mathbb{R} \text{ and } (X_0 c)(\theta) = X_0(\theta)c\}$$

and X_0 denotes the function defined on $[-\mu-\tau_c, 0]$ by

$$X_0(\theta) = \left\{ \begin{array}{ll} 0, & \text{if } -\mu-\tau_c \leq \theta < 0, \\ 1, & \text{if } \theta = 0. \end{array} \right.$$

Adimy proved in [27] that this extension determines a Hille-Yosida operator. This result is recalled in the next lemma.

Lemma 3.1. *The continuous extension $\widetilde{A}_\mu$ of the operator A_μ defined on $\widetilde{C}_\mu$ by*

$$\left\{ \begin{array}{rcl} \mathcal{D}(\widetilde{A}_\mu) & = & C^1([-\mu-\tau_c, 0], \mathbb{R}), \\ \widetilde{A}_\mu\varphi & = & \varphi' + X_0\left(L_\mu\varphi - \varphi'(0)\right), \qquad \varphi \in \mathcal{D}(\widetilde{A}_\mu), \end{array} \right. \tag{25}$$

is a Hille-Yosida operator on $\widetilde{C}_\mu$; that is: there exists $\omega_0 \in \mathbb{R}$ such that $(\omega_0, +\infty) \subset \rho(\widetilde{A}_\mu)$ and

$$\sup\left\{(\lambda-\omega_0)^n \|(\lambda I - \widetilde{A}_\mu)^{-n}\|, n \in \mathbb{N}, \lambda > \omega_0\right\} < \infty.$$

It follows that if y is a solution of (24) on $[0, T]$, $T > 0$, with an initial condition $\varphi \in C_\mu$ on the interval $[-\mu-\tau_c, 0]$, then the function $t \in [0, T] \mapsto y_t \in C_\mu$ satisfies

$$\left\{ \begin{array}{rcl} \dfrac{d}{dt}y_t & = & \widetilde{A}_\mu y_t + X_0 F_\mu(y_t), \qquad t \in [0, T], \\ y_0 & = & \varphi. \end{array} \right. \tag{26}$$

Conversely, if there exists a function $t \in [0, T] \mapsto u(t) \in C_\mu$ such that

$$\left\{ \begin{array}{rcl} \dfrac{du}{dt}(t) & = & \widetilde{A}_\mu u(t) + X_0 F_\mu(u(t)), \qquad t \in [0, T], \\ u(0) & = & \varphi, \end{array} \right. \tag{27}$$

then $u(t) = y_t$, $t \in [0, T]$, where

$$y(t) = \left\{ \begin{array}{ll} u(t)(0), & \text{if } t \in [0, T], \\ \varphi(t), & \text{if } t \in [-\mu-\tau_c, 0], \end{array} \right.$$

and y is a solution of (24). This handles in particularly the problems arising from the fact that $\widetilde{A}_\mu$ does not preserve the space of $\mathcal{C}^1$-functions.

Thanks to results by Arendt [28] and Da Prato and Sinestrari [29], the ODE (27) is well-posed for initial conditions in $\overline{\mathcal{D}(\widetilde{A}_\mu)} = C_\mu$.

Now we can reformulate the problem (24) as the abstract ODE (26).

Another important step towards the description of a center manifold is the definition of a bilinear form related to the equation (21).

From now on, we set $\mathbb{K} = \mathbb{C}$. For $\varphi \in C_\mu$ and $\psi \in C_\mu^* := C([0, \mu+\tau_c], \mathbb{C})$, define according to [23] or [24],

$$\langle \psi, \varphi \rangle = \overline{\psi(0)}\varphi(0) - \int_{-\mu-\tau_c}^{0} \left(\int_0^s \overline{\psi(\xi - s)}\varphi(\xi) d\xi \right) d\eta(s) \tag{28}$$

where $d\eta(s) = c_2(\mu)ds - c_1 X_0(s)$. Thus (28) becomes

$$\langle \psi, \varphi \rangle = \overline{\psi(0)}\varphi(0) - c_2(\mu) \int_{-\mu-\tau_c}^{0} \left(\int_0^s \overline{\psi(\xi - s)}\varphi(\xi) d\xi \right) ds. \tag{29}$$

We build a natural extension of this bilinear form to the space $\widetilde{C}_\mu^* \times \widetilde{C}_\mu$ where

$$\widetilde{C}_\mu^* = C_\mu^* \oplus \langle X_0^* \rangle$$

and

$$\langle X_0^* \rangle = \{X_0^* c;\ c \in \mathbb{C} \text{ and } (X_0^* c)(\theta) = X_0^*(\theta)c\}$$

with X_0^* the function defined on $[0, \mu + \tau_c]$ by

$$X_0^*(\theta) = \begin{cases} 0, & \text{if } 0 < \theta \leq \mu + \tau_c, \\ 1, & \text{if } \theta = 0. \end{cases}$$

We obtain, for $\psi \in C_\mu^*$, $\varphi \in C_\mu$ and $a, c \in \mathbb{C}$,

$$\langle \psi + X_0^* a, \varphi + X_0 c \rangle = \langle \psi, \varphi \rangle + \overline{a}c.$$

With respect to this bilinear form, we define the adjoint of the operator $\widetilde{A}_\mu$, denoted $\widetilde{A}_\mu^*$, and its domain $\mathcal{D}(\widetilde{A}_\mu^*)$. It satisfies, for $\varphi \in \mathcal{D}(A_\mu) = C^1([-\mu - \tau_c, 0], \mathbb{C})$ and $\psi \in \mathcal{D}(\widetilde{A}_\mu^*)$,

$$\langle \psi, \widetilde{A}_\mu \varphi \rangle = \langle \widetilde{A}_\mu^* \psi, \varphi \rangle.$$

From (25) and (29), we obtain

$$\langle \psi, \widetilde{A}_\mu \varphi \rangle = \overline{\psi(0)} L_\mu \varphi - c_2(\mu) \int_{-\mu-\tau_c}^{0} \left(\int_0^s \overline{\psi(\xi - s)}\varphi'(\xi) d\xi \right) ds.$$

Using an integration by parts and (22), we deduce

$$\begin{aligned}
\langle \psi, \widetilde{A}_\mu \varphi \rangle &= \overline{\psi(0)} \left[-c_1\varphi(0) + c_2(\mu) \int_{-\mu-\tau_c}^{0} \varphi(\theta) d\theta \right] \\
&\quad - c_2(\mu) \int_{-\mu-\tau_c}^{0} \left(\overline{\psi(0)}\varphi(s) - \overline{\psi(-s)}\varphi(0) - \int_0^s \overline{\psi'(\xi - s)}\varphi(\xi) d\xi \right) ds, \\
&= \left[-c_1 \overline{\psi(0)} + c_2(\mu) \int_0^{\mu+\tau_c} \overline{\psi(\theta)} d\theta \right] \varphi(0) \\
&\quad + c_2(\mu) \int_{-\mu-\tau_c}^{0} \left(\int_0^s \overline{\psi'(\xi - s)}\varphi(\xi) d\xi \right) ds, \\
&= \langle \widetilde{A}_\mu^* \psi, \varphi \rangle,
\end{aligned}$$

where

$$\begin{cases} \mathcal{D}(\widetilde{A}_\mu^*) &= C^1([0,\mu+\tau_c],\mathbb{R}), \\ \widetilde{A}_\mu^*\psi &= -\psi' + X_0^*\left[c_2(\mu)\displaystyle\int_0^{\mu+\tau_c}\psi(s)ds - c_1\psi(0) + \psi'(0)\right]. \end{cases}$$

We consider now the purely imaginary eigenvalues of (8) denoted $\pm i\omega_c$, with $\omega_c > 0$, which exist when $\tau = \tau_c$, that means when the bifurcation occurs (see Section 2 and, in particularly, Theorem 2.1). From the definition of the characteristic equation in (8) and the notations introduced in (23), we have

$$\Delta(i\omega_c,\tau_c) = i\omega_c + c_1 - c_2(0)\int_{-\tau_c}^0 e^{i\omega_c s}ds = 0.$$

It follows that

$$c_2(0)\frac{(e^{-i\omega_c\tau_c}-1)}{\omega_c}i - c_1 = i\omega_c. \tag{30}$$

Then, with definition (25), the function $q(s) = e^{i\omega_c s} \in C^1([-\tau_c,0],\mathbb{C})$ is an eigenvector of $\widetilde{A}_0$ associated with $i\omega_c$.

Hence, $q^*(s) = de^{i\omega_c s} \in C^1([0,\tau_c],\mathbb{C})$, $d \neq 0$, is an eigenvector for $\widetilde{A}_0^*$ associated with $-i\omega_c$. Moreover, we can choose $d \in \mathbb{C}$ so that the norming condition $\langle q^*, q\rangle = 1$ is satisfied. It follows that

$$\bar{d} = \left[1 + c_2(0)\left(\frac{\tau_c e^{-i\tau_c\omega_c}}{\omega_c}i - \frac{1-e^{-i\tau_c\omega_c}}{\omega_c^2}\right)\right]^{-1}.$$

One can check that in fact $\overline{d} = (\Delta_\lambda(i\omega_c,\tau_c))^{-1}$. Since $i\omega_c$ is a simple root of $\Delta(\cdot,\tau_c)$, then $\overline{d}$ is well-defined.

From (29) and (30) we infer also that

$$\langle q^*, \overline{q}\rangle = 0. \tag{31}$$

We are interested in the center manifold corresponding to the eigenvalue $\lambda = i\omega_c$ of $\widetilde{A}_0$ and to the system (26). Such a center manifold exists (see [17, 21]): it is a locally invariant, locally attracting manifold containing the origin and tangent at the origin to the subspace spanned by the eigenvectors corresponding to the eigenvalues $\pm i\omega_c$ of $\widetilde{A}_0$. In fact, to reach our aim, we only need information on the section of the center manifold, denoted $\mathcal{C}_0$, corresponding to $\mu = 0$ (see [17]).

Let y_t be a solution of

$$\frac{dy_t}{dt} = \widetilde{A}_0 y_t + X_0 F_0(y_t). \tag{32}$$

We compute the coordinates of the section $\mathcal{C}_0$ of the center manifold corresponding to $\mu = 0$. Following the notations in [17], we define

$$z(t) = \langle q^*, y_t\rangle, \qquad \text{for } t \geq 0. \tag{33}$$

We will use z and $\overline{z}$ as local coordinates of $\mathcal{C}_0$ in the directions q^* and $\overline{q}^*$ respectively. We also define, for $t \geq 0$ and $s \in [-\tau_c, 0]$,

$$\begin{aligned} w(t,s) &= y_t(s) - z(t)q(s) - \overline{z}(t)\overline{q}(s), \\ &= y_t(s) - 2\mathrm{Re}[z(t)q(s)]. \end{aligned}$$

We have

$$w(t,s) = W\left(z(t),\overline{z}(t),s\right), \quad t \geq 0,\ s \in [-\tau_c, 0],$$

with

$$W(z,\overline{z},s) = w_{20}(s)\frac{z^2}{2} + w_{11}(s)z\overline{z} + w_{02}(s)\frac{\overline{z}^2}{2} + \dots \tag{34}$$

One can notice that, for real solution y, w is real so $w_{02} = \overline{w_{20}}$. Moreover, (31) and (33) imply that $\langle q^*, w\rangle = 0$.

The section $\mathcal{C}_0$ of the center manifold is locally invariant under equation (32): any solution that starts in it will stay in it for any time t in some nontrivial interval; therefore, if $y_t \in \mathcal{C}_0$ we have

$$\frac{d}{dt}z(t) = \langle q^*, \widetilde{A}_0 y_t + X_0 F_0(y_t)\rangle$$

so, from (33), it follows that

$$\begin{aligned}\frac{d}{dt}z(t) &= i\omega_c z(t) + \overline{d}F_0\left(W(z(t),\overline{z}(t),\cdot) + 2\mathrm{Re}[z(t)q]\right),\\ &= i\omega_c z(t) + g(z(t),\overline{z}(t)),\end{aligned} \tag{35}$$

with

$$g(z,\overline{z}) = \overline{d}F_0\left(W(z,\overline{z},\cdot) + 2\mathrm{Re}[zq]\right).$$

We use the Taylor expansion of f around x^* to rewrite F_0 as

$$\begin{aligned}F_0(\varphi) &= c_3\int_{-\tau_c}^{0}\left[\frac{\beta_2}{2!}\varphi(\theta)^2 + \frac{\beta_3}{3!}\varphi(\theta)^3 + \mathcal{O}(\varphi(\theta)^4)\right]d\theta\\ &\quad -\beta_0\left[\frac{\beta_2}{2!}\varphi(0)^2 + \frac{\beta_3}{3!}\varphi(0)^3 + \mathcal{O}(\varphi(0)^4)\right],\end{aligned}$$

where

$$c_3 := \frac{2\beta_0}{\tau_c}, \qquad \beta_2 := f''(x^*) \qquad \text{and} \qquad \beta_3 := f'''(x^*). \tag{36}$$

If we denote, for convenience, $w(s) = W(z,\overline{z},s)$, we then obtain

$$\begin{aligned}g(z,\overline{z}) &= \overline{d}c_3\left\{\frac{\beta_2}{2}\int_{-\tau_c}^{0}[w(s) + ze^{i\omega_c s} + \overline{z}e^{-i\omega_c s}]^2 ds\right.\\ &\qquad +\frac{\beta_3}{6}\int_{-\tau_c}^{0}[w(s) + ze^{i\omega_c s} + \overline{z}e^{-i\omega_c s}]^3 ds\\ &\qquad \left.+\int_{-\tau_c}^{0}\mathcal{O}([w(s) + ze^{i\omega_c s} + \overline{z}e^{-i\omega_c s}]^4)ds\right\}\\ &\quad -\beta_0\overline{d}\left(\frac{\beta_2}{2}[w(0) + z + \overline{z}]^2\right.\\ &\qquad \left.+\frac{\beta_3}{6}[w(0) + z + \overline{z}]^3 + \mathcal{O}([w(0) + z + \overline{z}]^4)\right).\end{aligned} \tag{37}$$

Equation (35) is called the normal form obtained by the restriction of the flow to the center manifold. Our next goal is to compute some coefficients in the Taylor series of g and to use them to study stability of the limit cycle by computing also the Lyapunov coefficient. This latter is given by some coefficients in the Taylor expansion of $g(z,\overline{z})$ given by (37). This means, in fact, that stability of the limit cycle is determined by the normal form obtained through the restriction of the flow to the center manifold.

Restricting the Taylor expansion in (37) to terms of order less or equal to three, we get

$$g(z,\overline{z}) = \frac{1}{2}g_{20}z^2 + g_{11}z\overline{z} + \frac{1}{2}g_{02}\overline{z}^2 + \frac{1}{2}g_{21}z^2\overline{z} + \dots \tag{38}$$

with

$$\begin{aligned}
g_{20} &= -\bar{d}\beta_2\left(\beta_0 + \frac{c_3(1-e^{-2i\omega_c\tau_c})}{2\omega_c}i\right),\\
g_{11} &= \bar{d}\beta_2(c_3\tau_c - \beta_0),\\
g_{02} &= -\bar{d}\beta_2\left(\beta_0 - \frac{c_3(1-e^{2i\omega_c\tau_c})}{2\omega_c}i\right),\\
g_{21} &= \overline{d}\Bigg(c_3\left\{\beta_2\int_{-\tau_c}^{0}[w_{20}(s)e^{-i\omega_c s} + 2w_{11}(s)e^{i\omega_c s}]ds - \beta_3\frac{(1-e^{-i\omega_c\tau_c})}{\omega_c}i\right\}\\
&\qquad -\beta_0\beta_2[w_{20}(0) + 2w_{11}(0)] - \beta_0\beta_3\Bigg).
\end{aligned} \tag{39}$$

With the definition of c_3 given in (36), one can see that

$$g_{11} = \overline{d}\beta_0\beta_2.$$

One can note that we do not need the coefficients g_{ij} with $i+j>2$ except g_{21} (see [17]).

At this point, we still need to compute $w_{20}(s)$ and $w_{11}(s)$ for $s \in [-\tau_c, 0]$. It follows directly from (32), (33) and (35), that

$$\begin{aligned}
\frac{d}{dt}w(t,\cdot) &= \frac{d}{dt}y_t - \frac{d}{dt}\left[z(t)q - \overline{z}(t)\overline{q}\right],\\
&= \widetilde{A}_0 w(t,\cdot) + X_0F_0\left(w(t,\cdot) + 2\mathrm{Re}(z(t)q)\right)\\
&\quad -2\mathrm{Re}\left(g(z(t),\overline{z}(t))q\right),\\
&= \widetilde{A}_0 w(t,\cdot) + H(z(t),\overline{z}(t),\cdot),
\end{aligned} \tag{40}$$

where, for $s \in [-\tau_c, 0]$,

$$H(z,\overline{z},s) = -2\mathrm{Re}\left(g(z,\overline{z})q(s)\right) + X_0(s)F_0\left(W(z,\overline{z},\cdot) + 2\mathrm{Re}(zq)\right). \tag{41}$$

Let $s \in [-\tau_c, 0)$ be fixed. From (41) with (38) we have

$$\begin{aligned}
H(z,\overline{z},s) &= -2\mathrm{Re}\left(g(z,\overline{z})q(s)\right),\\
&= -g(z,\overline{z})q(s) - \bar{g}(z,\overline{z})\bar{q}(s),\\
&= -\left(g_{20}\frac{z^2}{2} + g_{11}z\overline{z} + g_{02}\frac{\overline{z}^2}{2} + \dots\right)q(s)\\
&\quad -\left(\overline{g}_{20}\frac{\overline{z}^2}{2} + \overline{g}_{11}z\overline{z} + \overline{g}_{02}\frac{z^2}{2} + \dots\right)\overline{q}(s).
\end{aligned} \tag{42}$$

Considering the expansion

$$H(z,\overline{z},s) = H_{20}(s)\frac{z^2}{2} + H_{11}(s)z\overline{z} + H_{02}(s)\frac{\overline{z}^2}{2} + \dots$$

and comparing the coefficients with those in (42) yields

$$\begin{aligned}
H_{20}(s) &= -g_{20}q(s) - \overline{g}_{02}\overline{q}(s),\\
H_{11}(s) &= -g_{11}q(s) - \overline{g}_{11}\overline{q}(s),\\
H_{02}(s) &= \overline{H}_{20}(s).
\end{aligned} \tag{43}$$

From (34), (38) and (40), we obtain

$$\begin{aligned}
&(\widetilde{A}_0 - 2i\omega_c)w_{20}(s) = -H_{20}(s),\\
&\widetilde{A}_0 w_{11}(s) = -H_{11}(s),\\
&(\widetilde{A}_0 + 2i\omega_c)w_{02}(s) = -H_{02}(s).
\end{aligned} \tag{44}$$

Using (25) and (43), (44) becomes

$$\begin{aligned}
\frac{dw_{20}}{ds}(s) &= 2i\omega_c w_{20}(s) + g_{20}q(s) + \overline{g}_{02}\overline{q}(s),\\
\frac{dw_{11}}{ds}(s) &= g_{11}q(s) + \overline{g}_{11}\overline{q}(s).
\end{aligned}$$

Solving the above system, we obtain:

$$w_{20}(s) = -\frac{g_{20}}{i\omega_c}e^{i\omega_c s} - \frac{\overline{g}_{02}}{3i\omega_c}e^{-i\omega_c s} + E_1 e^{2i\omega_c s}, \tag{45}$$

$$w_{11}(s) = \frac{g_{11}}{i\omega_c}e^{i\omega_c s} - \frac{\overline{g}_{11}}{i\omega_c}e^{-i\omega_c s} + E_2, \tag{46}$$

where E_1 and E_2 can be determined by setting $s = 0$ in (41). In fact, we have

$$H(z, \overline{z}, 0) = -2\mathrm{Re}\left(g(z, \overline{z})\right) + F_0\left(W(z, \overline{z}, \cdot) + 2\mathrm{Re}(zq)\right),$$

so we deduce

$$\begin{aligned}
H_{20}(0) &= -g_{20} - \overline{g}_{02} + \beta_2\left(c_3\int_{-\tau_c}^{0} e^{2i\omega_c s}ds - \beta_0\right),\\
H_{11}(0) &= -g_{11} - \overline{g}_{11} + \beta_2\left(c_3\int_{-\tau_c}^{0} ds - \beta_0\right).
\end{aligned}$$

From (25) and (44), we have:

$$c_2(0)\int_{-\tau_c}^{0} w_{20}(s)ds - (c_1 + 2i\omega_c)w_{20}(0) = -H_{20}(0), \tag{47}$$

$$c_2(0)\int_{-\tau_c}^{0} w_{11}(s)ds - c_1 w_{11}(0) = -H_{11}(0). \tag{48}$$

Substituting (45) in (47) and using (30) we eventually get

$$E_1 = -\frac{\beta_2(c_3(1 - e^{-2i\omega_c\tau_c}) - 2i\omega_c\beta_0)}{c_2(0)(1 - e^{-2i\omega_c\tau_c}) - 2c_1 i\omega_c + 4\omega_c^2}. \tag{49}$$

Similarly, substituting (46) in (48) we get

$$E_2 = -\frac{\beta_2(c_3\tau_c - \beta_0)}{c_2(0)\tau_c - c_1}. \tag{50}$$

Using the definitions given in (23) and (36), we can write

$$E_2 = \frac{\beta_0\beta_2}{\delta - \beta_0\beta_1}.$$

We are now able to complete the calculation of g_{21} in (39) using the above values of w_{20}, w_{11}, E_1 and E_2. We set

$$K := \int_{-\tau_c}^{0} \left[w_{20}(s) e^{-i\omega_c s} + 2 w_{11}(s) e^{i\omega_c s} \right] ds.$$

Then, from (45) and (46), we obtain

$$K = \frac{(\overline{g}_{02} + 6g_{11})(1 - e^{-2i\omega_c\tau_c})}{6\omega_c^2} + \frac{\tau_c(g_{20} + 2\overline{g}_{11}) - (E_1 + 2E_2)(1 - e^{-i\omega_c\tau_c})}{\omega_c} i \tag{51}$$

where E_1 and E_2 are given respectively by (49) and (50).

From (39), (45) and (46), we have

$$\begin{aligned} g_{21} &= \overline{d}\Bigg(c_3\beta_2 K - c_3\beta_3 \frac{(1 - e^{-i\omega_c\tau_c})}{\omega_c} i \\ &\quad -\beta_0\beta_2 \left(E_1 + 2E_2 + \frac{3g_{20} + \overline{g}_{02}}{3\omega_c} i + \frac{2(\overline{g}_{11} - g_{11})}{\omega_c} i \right) - \beta_0\beta_3 \Bigg), \end{aligned}$$

where K is given by (51).

Based on the above analysis and calculation, we can see that each g_{ij} in (39) is determined by the parameters and delay in equation (4). Thus we can explicitly compute the following quantities:

$$\begin{aligned} L_1(0) &= \frac{i}{2\omega_c} \left(g_{20}g_{11} - 2|g_{11}|^2 - \frac{1}{3}|g_{02}|^2 \right) + \frac{1}{2} g_{21}, \\ l_1(0) &= \mathrm{Re}\left(L_1(0)\right), \\ \mu_2 &= -\frac{l_1(0)}{\mathrm{Re}(\lambda'(\tau_c))}, \\ b_2 &= 2l_1(0), \\ T_2 &= -\frac{\mathrm{Im}(L_1(0)) + \mu_2 \mathrm{Im}\lambda'(\tau_c)}{\omega_c}. \end{aligned} \tag{52}$$

One knows from [17] that the following properties hold: if $\mu_2 > 0$ (< 0) then the Hopf bifurcation is supercritical (subcritical) and the bifurcating periodic solutions exist for $\tau > \tau_c$ ($\tau < \tau_c$); solutions are orbitally stable (unstable) if $b_2 < 0$ (> 0); and the period of bifurcating periodic solution increases (decreases) if $T_2 > 0$ (< 0).

The coefficient $\lambda'(\tau_c)$ in (52) is given by (16) and (17). In particularly, we have proved in Section 2, property (18), that

$$\mathrm{Re}(\lambda'(\tau_c)) > 0.$$

In summary, this leads to the following result:

Theorem 3.1. *If the Lyapunov coefficient $l_1(0)$, defined in (52), is negative (resp. positive) then the Hopf bifurcation is supercritical (subcritical) and the bifurcating periodic solutions exist for $\tau > \tau_c$ ($\tau < \tau_c$), and solutions are orbitally stable (unstable); The coefficient T_2 determines the period of the bifurcating periodic solutions: the period increases (decreases) if $T_2 > 0$ (< 0).*

4 Numerical results and simulations

We numerically compute, in this section, the formulas obtained above to determine the behavior of the periodic solutions of equation (4).

We choose f as in (5). In order to satisfy the assumptions of Theorem 2.1, we have to choose δ, β_0 and n such that $\beta_1 < 0$ and (12) holds true; that is

$$n > \frac{2(1-h(x_0))}{1-2h(x_0)} \frac{\beta_0}{\beta_0 - \delta}.$$

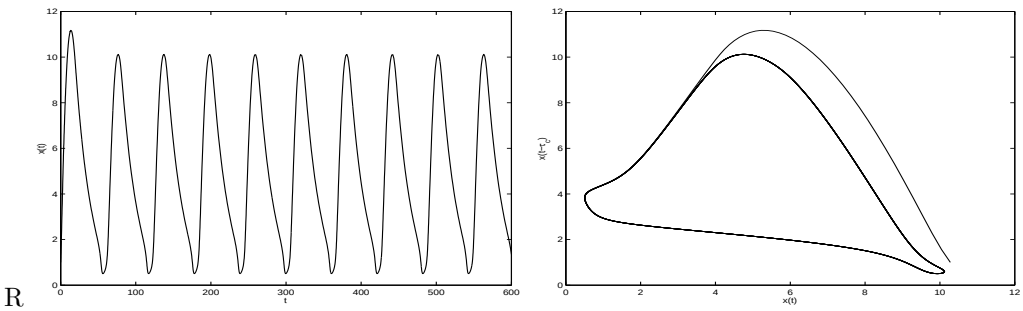
We take δ and β_0 as given in (3). Then the above conditions are in fact satisfied for $n \geq 2.42$.

Using Maple 9, we are able to compute the coefficients in (52), listed in the following table for $n \in \{3, 4, 5, 6, 7, 8\}$:

n	x^*	τ_c	ω_c	$l_1(0)$	T_2
3	3.2523	18.1270	0.1380	-0.0026	0.1540
4	2.4218	10.9688	0.2091	-0.0375	0.8083
5	2.0291	7.8748	0.2785	-0.1504	2.2097
6	1.8034	6.1447	0.3472	-0.3975	4.5441
7	1.6577	5.0385	0.4155	-0.8399	7.9335
8	1.5562	4.2702	0.4836	-1.5412	12.4589

Even though we do not give values of $l_1(0)$ and T_2 for all $n \geq 2.42$, we can notice that observations indicate that $l_1(0)$ is strictly negative and T_2 strictly positive for $n \geq 2.42$. Hence the unique Hopf bifurcation of equation (4) seems to be supercritical and solutions orbitally stable, with increasing periods.

Using the MATLAB solver dde23 [30], we can compute the solutions of equation (4) for the above-mentioned values of the parameter n and for any positive initial condition. Solutions of (4) are shown versus time t and in the phase plane in Fig 2 to 7.



R

Figure 2: Solutions of (4) are displayed when $n = 3$. Periods of the oscillations are close to 46 days.

5 Discussion

Many hematological diseases involve oscillations about a steady-state during the chronic period. These oscillations give rise to instability in the hematopoietic stem cell count. Chronic

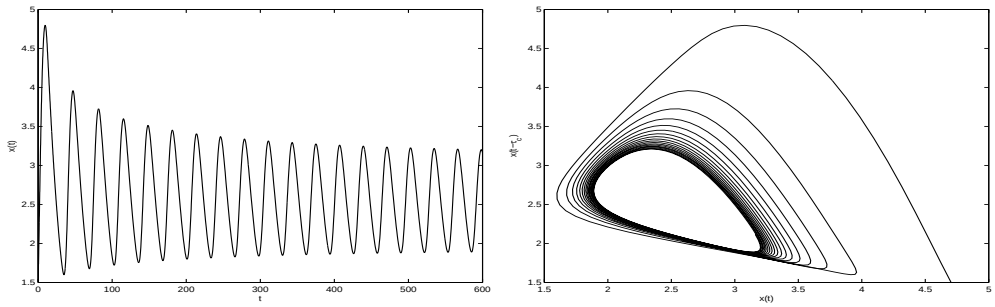


Figure 3: Solutions of (4) are displayed when $n = 4$. Periods of the oscillations are close to 30 days.

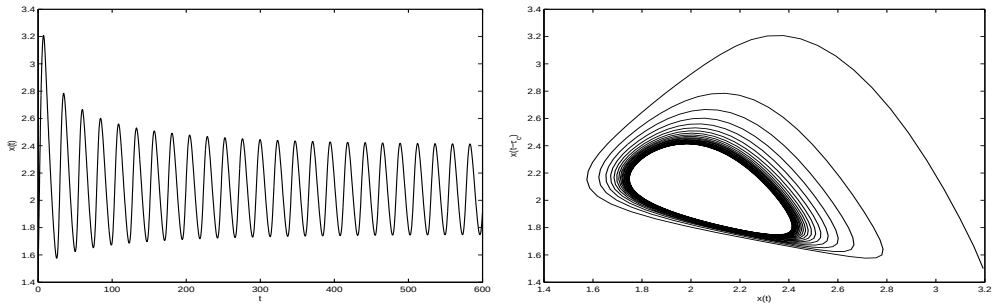


Figure 4: Solutions of (4) are displayed when $n = 5$. Periods of the oscillations are close to 23 days.

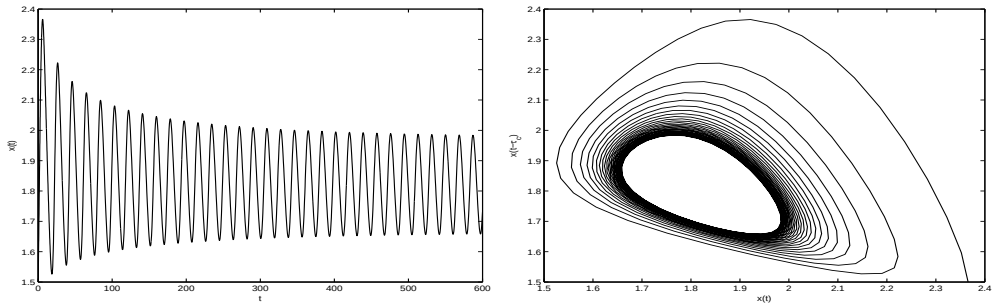


Figure 5: Solutions of (4) are displayed when $n = 6$. Periods of the oscillations are close to 18 days.

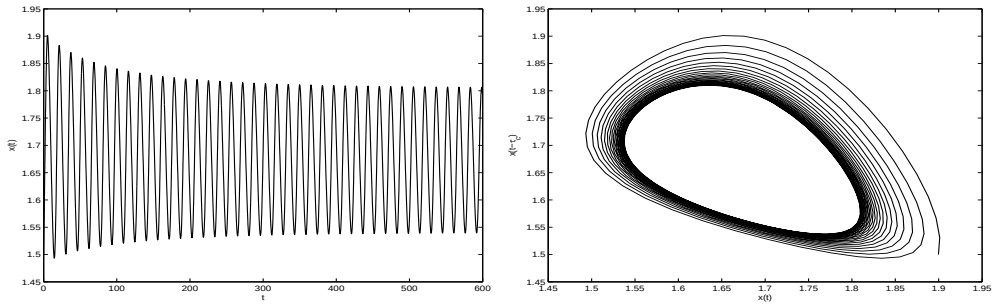


Figure 6: Solutions of (4) are displayed when $n = 7$. Periods of the oscillations are close to 15 days.

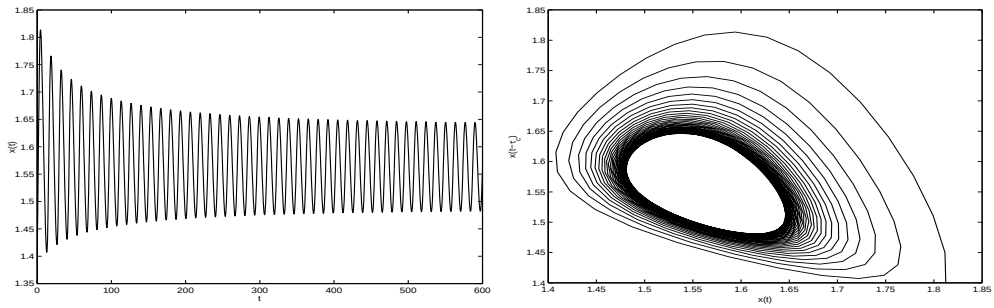


Figure 7: Solutions of (4) are displayed when $n = 8$. Periods of the oscillations are close to 13 days.

myelogenous leukemia (see Fortin and Mackey [31]) is one of the most common types of hematological disease characterized by the existence of periodic oscillations (oscillations of leukocytes with periods from 30 to 100 days). Experimental observations have led to the conclusion that this dynamic instability is located in the hematopoietic stem cells compartment.

We have studied, in this paper, a mathematical model of pluripotent hematopoietic stem cells dynamics in which the length of the proliferating phase is uniformly distributed on an interval. We have shown that instability can occur in this model via a Hopf bifurcation, leading to periodic solutions usually orbitally stable with increasing periods. This has been obtained throughout the description of a center manifold and the subsequently study of the normal form.

Periods of the oscillations obtained in numerical simulations, in Section 4, may be in the order of 30 to 50 days (at the bifurcation) when the parameter n is not too large, corresponding to what can be observed with chronic myelogenous leukemia. It has already been noticed by Pujo-Menjouet and Mackey [9] that this parameter n, which describes the sensitivity of the rate of reintroduction β, plays a crucial role in the appearance of periodic solutions when the delay is constant. The sensitivity n describes the way the rate of introduction in the proliferating phase reacts to changes in the resting phase population produced by external stimuli: a release of erythropoietin, for example, or the action of some growth factors. Since periodic hematological diseases are supposed to be due to hormonal control destabilization (see [31]), then n seems to be appropriate to identify causes leading to periodic solutions.

References

[1] Adimy M, Crauste F and Ruan S. Stability and Hopf Bifurcation in a Mathematical Model of Pluripotent Stem Cell Dynamics, Nonlinear Analysis: Real World Applications, 2005; 6: 651-670.

[2] Adimy M, Crauste F and Ruan S. A Mathematical Study of the Hematopoiesis Process with Applications to Chronic Myelogenous Leukemia, accepted in SIAM J. Appl. Math.

[3] Burns FJ and Tannock IF. On the existence of a G_0 phase in the cell cycle. Cell. Tissue Kinet, 1970; 19: 321–334.

[4] Mackey MC. A unified hypothesis on the origin of aplastic anaemia and periodic hematopoiesis. Blood, 1978; 51:946–956.

[5] Mackey MC. Dynamic hematological disorders of stem cell origin, in Biophysical and Biochemical Information Transfer in Recognition (J. G. Vassileva-Popova and E. V. Jensen, eds), Plenum Press, New York, 1979, pp. 373–409.

[6] Haurie C, Dale DC and Mackey MC. Cyclical neutropenia and other periodic hematological diseases: A review of mechanisms and mathematical models. Blood, 1998; 92: 2629–2640.

[7] Mackey MC, Haurie C and Bélair J. Cell replication and control, in Nonlinear Dynamics in Physiology and Medicine (A, Beuter, L. Glass, M. C. Mackey and M. S. Titcombe, eds), Springer, New York, 2003, pp. 233-269.

[8] Pujo-Menjouet L, Bernard S and Mackey MC. Long period oscillations in a G_0 model of hematopoietic stem cells. SIAM J. Appl. Dynam. Sys. (in press).

[9] Pujo-Menjouet L and Mackey MC, Contribution to the study of periodic chronic myelogenous leukemia. C. R. Biologies, 2004; 327: 235–244.

[10] Anderson RFV. Geometric and probabilistic stability criteria for delay systems. Math. Biosci., 1991; 105: 81–96.

[11] Anderson RFV. Intrinsic parameters and stability of differential-delay equations. J. Math. Anal. Appl., 1992; 163: 184–199.

[12] Bernard S, Belair J and Mackey MC. Sufficient conditions for stability of linear differential equations with distributed delay. Disc. Cont. Dyn. Syst. Ser. B, 2001; 1: 233–256.

[13] Boese FG. The stability chart for the linearized Cushing equation with a discrete delay and Gamma-distributed delays. J. Math. Anal. Appl., 1989; 140: 510–536.

[14] Kuang Y. Nonoccurrence of stability switching in systems of differential equations with distributed delays. Quart. Appl. Math., 1994; LII (3): 569–578.

[15] Liao X, Wong K and Wu Z. Stability of bifurcating periodic solutions for van der Pol equation with continuous distributed delay. Appl. Math. and Computation, 2003; 146: 313–334.

[16] Bradford G, Williams B, Rossi R and Bertoncello I, Quiescence, cycling, and turnover in the primitive haematopoietic stem cell compartment. Exper. Hematol., 1997; 25: 445–453.

[17] Hassard BD, Kazarinoff ND and Wan YH. Theory and Applications of Hopf Bifurcation. London Mathem. Soc. Lecture Note Series 41, Cambridge University Press, 1981.

[18] Stepan G. Retarded dynamical systems: stability and characteristic functions. Pitman Research Notes in Math. Ser., Longman, Harlow, 1989.

[19] Halanay A. Differential Equations; Stability, Oscillations, Time Lags. Academic Press, New York, 1966.

[20] Carr J. Applications of Center Manifold Theory. Springer, Berlin, 1981.

[21] Chafee N. A bifurcation problem for a functional differential equation of finitely retarded type. J. Math. Anal. Appl., 1991; 35: 312–348.

[22] Chow SN and Mallet-Paret J. Integral averaging and Hopf bifurcation. J. Diff. Eq., 1977; 26 (1): 112–159.

[23] Faria T and Magalhaes L. Normal Forms for Retarded Functional Differential Equations and Applications to Bogdanov-Takens singularity. J. Diff. Eq., 1995; 122 (2): 201–224.

[24] Hale J. Theory of Functional Differential Equations. Springer, New York, 1977.

[25] Marsden JE and McCraken M. The Hopf Bifurcation and its Applications. Springer, New York, 1976.

[26] Sri Namachchivaya N and van Roessel HJ. A centre-manifold analysis of variable speed machines. Dynamical Systems; an International Journal, 2003; 18 (3): 245–270.

[27] Adimy M. Integrated semigroups and delay differential equations. J. Math. Anal. Appl., 1993; 177 (1): 125–124.

[28] Arendt W. Resolvent positive operators. Proc. London. Math. Soc. (3), 1987; 54 (2): 321–349.

[29] Da Prato G and Sinestri E. Differential operators with non-dense domains. Ann. Scuola Norm. Sup. Pisa Cl. Sci., 1987; 14: 285–344.

[30] Shampine LF and Thompson S. Solving DDEs in MATLAB. Appl. Numer. Math., 2001; 37: 441–458. http://www.radford.edu/˜thompson/webddes/.

[31] Fortin P and Mackey MC. Periodic chronic myelogenous leukemia: Spectral analysis of blood cell counts and etiological implications. Brit. J. Haematol., 1999; 104: 336–345.