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ORIGINAL ARTICLE

Modelling Hematopoiesis Mediated by Growth Factors With Applications to Periodic Hematological Diseases

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Abstract Hematopoiesis is a complex biological process that leads to the production and regulation of blood cells. It is based upon differentiation of stem cells under the action of growth factors. A mathematical approach of this process is proposed to understand some blood diseases characterized by very long period oscillations in circulating blood cells. A system of three differential equations with delay, corresponding to the cell cycle duration, is proposed and analyzed. The existence of a Hopf bifurcation at a positive steady-state is obtained through the study of an exponential polynomial characteristic equation with delay-dependent coefficients. Numerical simulations show that long-period oscillations can be obtained in this model, corresponding to a destabilization of the feedback regulation between blood cells and growth factors, for reasonable cell cycle durations. These oscillations can be related to observations on some periodic hematological diseases (such as chronic myelogenous leukemia, for example).

Keywords Delay differential equations · Characteristic equation · Delay-dependent coefficients · Stability switch · Hopf bifurcation · Cell population models · Hematopoiesis · Stem cells

1. Introduction

Hematopoiesis is the process by which erythrocytes (red blood cells), leukocytes (white blood cells), and thrombocytes (platelets) are produced and regulated. These cells perform a variety of vital functions such as transporting oxygen,

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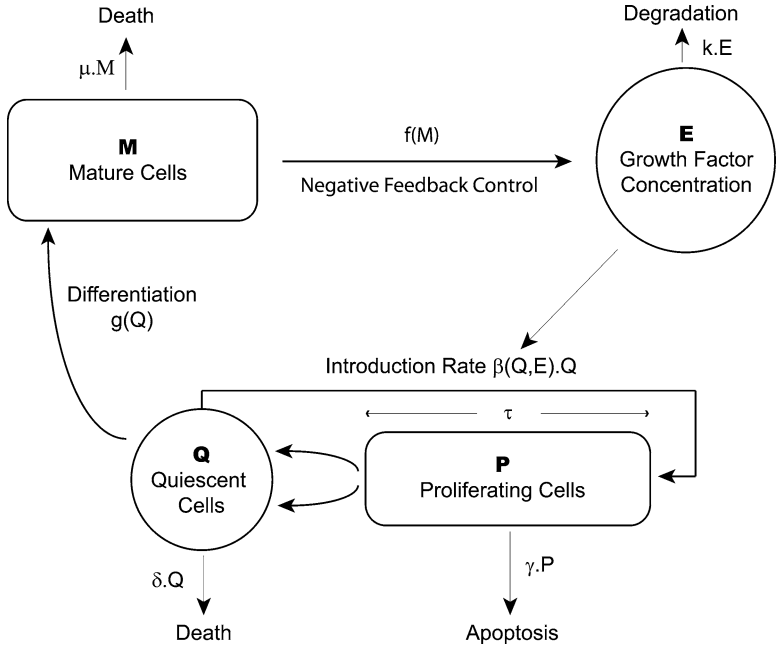

Fig. 1 Blood production process. Hematopoietic stem cells are divided in two groups: proliferating cells P and nonproliferating (or quiescent) cells Q. Proliferating cells actually perform the main stages of cell cycle (growth, division). They can die by apoptosis with a rate γ. The proliferating phase duration is assumed to be constant and equals τ. After division, each newborn cell enters the quiescent phase. Quiescent cells can die with a rate δ and can be introduced in the proliferating phase with a rate β which depends on Q and on the growth factor concentration E. Moreover, quiescent cells differentiate with a rate $g(Q)/Q$ in mature blood cells M, that can be found in the bloodstream. These cells are eliminated with a constant rate μ and trigger the production of growth factors by the mean of a negative feedback denoted by f. In turn, the growth factor concentration E acts on the introduction rate β of hematopoietic stem cells, from the quiescent phase to the proliferating phase. While in blood, growth factors are degraded with a rate k.

fighting infections, and repairing lesions. Therefore, the body must carefully regulate their production. For example, there are about 3.5×10^{11} erythrocytes for each kg of body weight, so almost 7% of the body mass is red blood cells. The turnover rate is about 3×10^9 erythrocytes/kg of body weight each day, which must be carefully regulated by several O_2 sensitive receptors and a collection of growth factors and hormones. Although understanding of blood production process evolves constantly, the main outlines are clear (see Fig. 1).

Blood cells, that can be observed in blood vessels, originate from a pool of hematopoietic pluripotent stem cells, located in the bone marrow of most of human bones. Hematopoietic pluripotent stem cells, which are undifferentiated cells with a high self-renewal and differentiation capacity, give rise to committed stem cells. These committed stem cells form bands of cells called colony forming units (CFU) and are specialized in the sense that they can only produce one of the three blood cell types: red blood cells, white cells, or platelets. Colony forming units

differentiate in precursor cells, which are not stem cells anymore, because they have lost their self-renewal capacity. These cells eventually give birth to mature blood cells which enter the bloodstream.

One can see that the hematopoiesis process is formed by a succession of complex differentiations from hematopoietic pluripotent stem cells to precursors. These different differentiations, occurring in the bone marrow, are mainly mediated by growth factors. They are proteins acting, in some way, like hormones playing an activator/inhibitor role. Each type of blood cell is the result of specific growth factors acting at specific moments during the hematopoiesis process.

The red blood cells production, for example, called erythropoiesis, is mainly mediated by erythropoietin (EPO), a growth factor produced at 90% by the kidneys. Erythropoietin is released in the bloodstream due to tissue hypoxia. It stimulates the erythropoiesis in the bone marrow, causing an increase in circulating red blood cells, and consequently an increase in the tissue pO_2 levels. Then the release of erythropoietin decreases and a regulation of the process is observed: there is a feedback control from the blood to the bone marrow. In extreme situations, like bleeding or moving to high altitudes, where needs in oxygen are important, erythropoiesis is accelerated.

White blood cells are produced during leukopoiesis and the main growth factors acting on their regulation are Granulocyte-CSF (Colony Stimulating Factor), Macrophage-CSF, Granulocyte-Macrophage-CSF, and different interleukins (IL-1, IL-2, IL-6, IL-8, etc.). Platelets are mainly regulated by thrombopoietin (TPO), which acts similarly to erythropoietin.

The hematopoiesis process sometimes exhibits abnormalities in blood cells production, causing the so-called dynamical hematological diseases Haurie et al. (1998). They are characterized by oscillations of circulating blood cell counts, with periods ranging from days (19–21 days for cyclical neutropenia, Haurie et al. (1998, 1999); Bernard et al. (2003a)) to months (periodic chronic myelogenous leukemia Fortin and Mackey (1999) may exhibit periods about 30–100 days, with a mean about 70–80 days). Most of these diseases seem to be due to a destabilization of the pluripotent hematopoietic stem cell compartment caused by the action of one or more growth factors. For erythropoiesis, abnormalities in the feedback loop between erythropoietin and the bone marrow production are suspected to cause periodic hematological disorders, such as autoimmune-induced hemolytic anemia Bélair et al. (1995); Haurie et al. (1998). Cyclical neutropenia Hearn et al. (1998); Haurie et al. (1999); Bernard et al. (2003a), one of the most intensively studied periodic hematological diseases, characterized by a fall of neutrophils (white blood cells) counts every 3 weeks, to sometimes barely detectable values, is now known to be due to a destabilization of the apoptotic (mortality) rate during the proliferating phase of the cell cycle.

Mathematical models of hematopoiesis have been intensively studied since the end of the 1970s. To our knowledge, Mackey (1978, 1979) proposed the first model of hematopoiesis, based on early works by Lajtha (1959) and Burns and Tannock (1970). This model takes the form of a delay differential equation, where the delay describes the cell cycle duration. Since then it has been modified and studied by many authors. The works of Mackey and Rudnicki (1994, 1999) and Mackey and Rey (1993, 1995a,b) deal with age-maturity structured models of

hematopoiesis based on the model of Mackey (1978). The authors stressed the role of pluripotent hematopoietic stem cells in hematopoiesis, pointing out in particular that the destabilization of this population surely led to the destabilization of the entire process. We also mention the works of Dyson et al. (1996, 2000a,b), Adimy and Pujo-Menjouet (2003), Adimy and Crauste (2003, 2005), and Adimy et al. (2005a) on this topic, taking into account different ways of cell division.

Recently, the model of Mackey (1978) has been used to bring some information about some periodic hematological diseases. Pujo-Menjouet and Mackey (2004) and Pujo-Menjouet et al. (2005) studied the model of Mackey (1978, 1979) and obtained the existence of periodic solutions, with long periods compared to the cell cycle duration, describing phenomena observed with periodic chronic myelogenous leukemia. Bernard et al. (2003a, 2004) considered a model of leukopoiesis (white cell production) based on the model of Mackey (1978), formed with two delay differential equations. Using a quasi steady-state assumption (that reduces their model to one delay differential equation, whose resolution is equivalent to the one proposed by Mackey (1978)), the authors applied their model to cyclical neutropenia and stressed the role of the rate of apoptosis in the appearance of this disease. More recently, Colijn and Mackey (2005a,b) tried to model the entire process of hematopoiesis (taking into account the three blood cell lineages) and dealt with a system of four differential equations with six time delays. They applied their model to the study of periodic chronic myelogenous leukemia and cyclical neutropenia. However, the influence of growth factors has never been explicitly incorporated in these models.

In the late 1990s, Bélair et al. (1995) and Mahaffy et al. (1998) considered a mathematical model for erythropoiesis. The model is a system of age and maturity structured equations that can be reduced to a system of delay differential equations. They showed that their model fitted well with experimental observations in normal erythropoiesis but they stressed some difficulties to reproduce pathological behaviors observed for periodic hematological diseases.

In this paper we consider a system of differential equations modelling the evolution of hematopoietic stem cells in the bone marrow, of mature blood cells in the bloodstream, and of the concentration of some growth factors acting on the stem cell population (see Fig. 1). A delay naturally appears in the model, describing the cell cycle duration. This approach is based on the early work of Mackey (1978, 1979) and the recent work of Bélair et al. (1995) and Mahaffy et al. (1998) dealing with erythropoiesis. Our aim is to show that oscillations with very long periods can appear in such models for reasonable values of the involved parameters, causing periodic hematological diseases, and that they are mainly due to the destabilization of the feedback loop between blood cells and growth factors.

The paper is organized as follows. We first describe the biological background leading to the mathematical model. After showing the existence of a positive equilibrium, we analyze its local asymptotic stability. This analysis is performed through the study of a characteristic equation which takes the form of a third-degree exponential polynomial with delay-dependent coefficients. Using the approach of Beretta and Kuang (2002), we show that the positive steady-state can

be destabilized through a Hopf bifurcation and stability switches can occur. We illustrate our results with numerical simulations and show that very long-period oscillations can be observed in this model, as can be observed in patients with some periodic hematological diseases (periodic chronic myelogenous leukemia for example).

2. The model

In the bone marrow, hematopoietic stem cells are divided into two groups: quiescent (or nonproliferating) and proliferating cells. The existence of a quiescent phase (also called G_0 phase) in the cell cycle is proved, for example, in Burns and Tannock (1970). Quiescent cells represent the major part of hematopoietic stem cells, that is about 90% of the hematopoietic stem cell population. Proliferating cells are cells actually in cycle: they are committed to divide during mitosis after, in particularly, having synthesized DNA. Immediately after division, proliferating cells enter the G_0 phase where they can stay their entire life.

We denote by $Q(t)$ and $P(t)$ the quiescent and proliferating cell populations at time t, respectively (see Fig. 1). In the proliferating phase, apoptosis, which is a programmed cell death, controls the cell population and eliminates deficient cells. We assume that the apoptosis rate, denoted by γ, is constant and nonnegative. In the G_0 phase, cells can disappear by natural death with a rate δ. They also differentiate in mature blood cells with a rate $g(Q)/Q$, where the function g is assumed to be nonnegative with $g(0) = 0$, because no cell can become mature when there is no hematopoietic stem cell, and continuously differentiable. Moreover, we assume that the function $Q \mapsto g(Q)/Q$ is nondecreasing for $Q \geq 0$, which is equivalent to

$$0 \leq g'(0) \leq \frac{g(Q)}{Q} \leq g'(Q) \qquad \text{for } Q > 0. \tag{1}$$

It follows, in particular, that g is nondecreasing and $\lim_{Q\to+\infty} g(Q) = +\infty$.

Quiescent cells can also be introduced into the proliferating phase in order to ensure the population renewal, at a nonconstant rate β. It is generally accepted that β depends on the total population of nonproliferating cells (Mackey, 1978; Sachs, 1993). However, the production of mature blood cells is also mediated by growth factors through the stem cell population: growth factors induce differentiation and maturation of hematopoietic cells via the stem cell compartment. Thus, the dependence of β on growth factors must be represented. We assume that β is continuously differentiable. Moreover, in the particular case of erythropoiesis, β is an increasing function of the erythropoietin concentration, because a release of erythropoietin increases the production of red blood cells. Hence, we assume that β is an increasing function of the growth factor concentration, with $\beta(Q, 0) = 0$, and a nonincreasing function of the G_0 phase population (Mackey, 1978).

Thus, the equations modelling the differentiation of hematopoietic stem cells in the bone marrow are

$$\frac{\mathrm{d}Q}{\mathrm{d}t} = -\delta Q(t) - g(Q(t)) - \beta(Q(t), E(t))Q(t) + 2\mathrm{e}^{-\gamma\tau}\beta(Q(t-\tau), E(t-\tau))Q(t-\tau), \tag{2}$$

$$\frac{\mathrm{d}P}{\mathrm{d}t} = -\gamma P(t) + \beta(Q(t), E(t))Q(t) - \mathrm{e}^{-\gamma\tau}\beta(Q(t-\tau), E(t-\tau))Q(t-\tau), \tag{3}$$

where $E(t)$ is the growth factor concentration at time t. The parameter $\tau > 0$ denotes the average time needed by a proliferating cell to divide, that is, τ is an average cell cycle duration. The last term in Eq. (2) represents the amount of cells coming from the proliferating phase at division. They are, in fact, quiescent cells introduced in the proliferating phase one generation earlier. The factor 2 represents the division of each proliferating cell in two daughter cells.

At the end of their development, precursors give birth to mature blood cells, which are introduced in the bloodstream. We denote by $M(t)$ the population of circulating mature blood cells (see Fig. 1). These cells only proceed from G_0 cells at the rate $g(Q)$. Mature blood cells are degraded, in the bloodstream, at a rate $\mu \geq 0$. Red blood cells usually live an average of 120 days, whereas platelets live about 1 week and white blood cells only few hours. Mature blood cell population satisfies the differential equation

$$\frac{\mathrm{d}M}{\mathrm{d}t} = -\mu M(t) + g(Q(t)).$$

The growth factor concentration is governed by a differential equation with an explicit negative feedback. This feedback describes the control of the bone marrow production on the growth factor production, explained in the previous section. This control acts by the mean of circulating blood cells: the more circulating blood cells the less growth factor produced. We denote by f the feedback control. The function f depends on the population of circulating cells M and is positive, decreasing, and continuously differentiable. Then

$$\frac{\mathrm{d}E}{\mathrm{d}t} = -kE(t) + f(M(t)),$$

where $k \geq 0$ is the disappearance rate of the growth factor. In fact, the action of the mature blood cell population on the production of growth factor is not

immediate: it is slightly delayed, but this delay is negligible compared with the cell cycle duration, so we do not consider it here.

At this point, one can notice that system (2)–(3) is not coupled: the population in the proliferating phase is not needed in the description of the hematopoiesis process, since circulating blood cells only come from quiescent cells. From a mathematical point of view, the solution of (2) does not depend on the solution of (3) whereas the converse is not true. Consequently, we concentrate on the following system of delay differential equations in $Q(t)$, $M(t)$, and $E(t)$:

$$\begin{cases} \dfrac{\mathrm{d}Q}{\mathrm{d}t} = -\delta Q(t) - g(Q(t)) - \beta(Q(t), E(t))Q(t) \\ \qquad\qquad +2\mathrm{e}^{-\gamma\tau}\beta(Q(t-\tau), E(t-\tau))Q(t-\tau), \\ \dfrac{\mathrm{d}M}{\mathrm{d}t} = -\mu M(t) + g(Q(t)), \\ \dfrac{\mathrm{d}E}{\mathrm{d}t} = -kE(t) + f(M(t)). \end{cases} \tag{4}$$

Using the results in Hale and Verduyn Lunel (1993), one can check that for any continuous initial conditions system (4) has a unique continuous solution $(Q(t), M(t), E(t))$. Moreover, we have the following conclusions.

First, solutions $Q(t)$, $M(t)$, and $E(t)$ of system (4) are nonnegative. In fact, let us suppose, by contradiction, that there exists $t_0 > 0$ such that $Q(t) > 0$ for $t < t_0$ and $Q(t_0) = 0$. Then, since $g(0) = 0$,

$$\frac{\mathrm{d}Q}{\mathrm{d}t}(t_0) = 2\mathrm{e}^{-\gamma\tau}\beta(Q(t_0-\tau), E(t_0-\tau))Q(t_0-\tau) > 0.$$

Hence $Q(t)$ is nonnegative. Since the functions g and f are nonnegative, we similarly obtain that $M(t)$ and $E(t)$ are nonnegative. Secondly, solutions of (4) are bounded when $\lim_{Q\to\infty}\beta(Q, E) = 0$ for all $E \geq 0$, and $\delta + g'(0) > 0$. This result is not straightforward, details of the proof are given in Appendix A.

Now, let us focus on the existence of steady states of system (4). A solution $(\bar{Q}, \bar{M}, \bar{E})$ of (4) is a steady-state or equilibrium if

$$\frac{\mathrm{d}\bar{Q}}{\mathrm{d}t} = \frac{\mathrm{d}\bar{M}}{\mathrm{d}t} = \frac{\mathrm{d}\bar{E}}{\mathrm{d}t} = 0,$$

that is

$$\begin{cases} \delta\bar{Q} + g(\bar{Q}) = (2\mathrm{e}^{-\gamma\tau} - 1)\beta(\bar{Q}, \bar{E})\bar{Q}, \\ \mu\bar{M} = g(\bar{Q}), \\ k\bar{E} = f(\bar{M}). \end{cases} \tag{5}$$

We make some remarks. It would be nonsense to suppose that the rates μ and k may vanish, because we cannot allow the blood cell population to grow indefinitely and the growth factor is necessarily degraded while in blood. Hence, we assume that $\mu > 0$ and $k > 0$.

Since $g(0) = 0$, it follows that $(0, 0, f(0)/k)$ is always a steady-state of (4) that we will call in the following the *trivial equilibrium* of (4). This steady-state corresponds to the extinction of the cell population with a saturation of the growth factor concentration.

From now on, we assume that

$$\lim_{Q\to+\infty} \beta\left(Q, \frac{1}{k} f\left(\frac{1}{\mu} g(Q)\right)\right) = 0. \tag{6}$$

Since $\lim_{Q\to+\infty} g(Q) = +\infty$ and $\lim_{M\to+\infty} f(M) = 0$, this property holds true if $\beta(Q, 0) = 0$ for all $Q \geq 0$, or $\lim_{Q\to+\infty} \beta(Q, E) = 0$ for all $E \geq 0$.

Let us assume that (4) has a nontrivial positive steady-state (Q^*, M^*, E^*), that is, $Q^* > 0$, $M^* > 0$, and $E^* > 0$ satisfy (5). Then

$$(2\mathrm{e}^{-\gamma\tau} - 1)\beta(Q^*, E^*) = \delta + \frac{g(Q^*)}{Q^*},\ M^* = \frac{1}{\mu} g(Q^*), \text{ and } \quad E^* = \frac{1}{k} f(M^*). \tag{7}$$

Necessarily, we have

$$2\mathrm{e}^{-\gamma\tau} - 1 > 0,$$

which is equivalent to

$$\tau < \frac{\ln(2)}{\gamma}. \tag{8}$$

We assume that (8) holds. Since $Q^* > 0$ and

$$E^* = \frac{1}{k} f(M^*) = \frac{1}{k} f\left(\frac{1}{\mu} g(Q^*)\right),$$

we must have

$$(2\mathrm{e}^{-\gamma\tau} - 1)\beta\left(Q^*, \frac{1}{k} f\left(\frac{1}{\mu} g(Q^*)\right)\right) = \delta + \frac{g(Q^*)}{Q^*}. \tag{9}$$

Let us define

$$\widetilde{\beta}(Q) := \beta\left(Q, \frac{1}{k} f\left(\frac{1}{\mu} g(Q)\right)\right). \tag{10}$$

Since f is decreasing, g is nondecreasing and $\beta(Q, E)$ is decreasing with respect to Q and increasing with respect to E, we deduce that $\widetilde{\beta}$ is decreasing with

$$\widetilde{\beta}(0) = \beta\left(0, \frac{1}{k} f(0)\right) \qquad \text{and} \qquad \lim_{Q\to+\infty} \widetilde{\beta}(Q) = 0.$$

Moreover, from (1), the function $Q \mapsto \delta + g(Q)/Q$ is nondecreasing. Consequently, Eq. (9) has a positive solution, which is unique if and only if

$$\delta + g'(0) < \left(2\mathrm{e}^{-\gamma\tau} - 1\right)\beta\left(0, \frac{1}{k}f(0)\right). \tag{11}$$

These results are summarized in the next proposition.

Proposition 1. *Assume that $\mu > 0$ and $k > 0$.*

(i) If

$$\delta + g'(0) > (2e^{-\gamma\tau} - 1)\beta\left(0, \frac{1}{k}f(0)\right), \tag{12}$$

then system (4) has a unique steady-state $(0, 0, f(0)/k)$;

(ii) If condition (11) holds, then system (4) has two steady-states: a trivial one $(0, 0, f(0)/k)$ and a nontrivial positive one (Q^*, M^*, E^*), where Q^* is the unique positive solution of (9), $M^* = g(Q^*)/\mu$ and $E^* = f(M^*)/k$.

The above proposition indicates that system (4) undergoes a transcritical bifurcation when $\delta + g'(0) = (2e^{-\gamma\tau} - 1)\beta(0, f(0)/k)$. Since the trivial steady-state $(0, 0, f(0)/k)$ corresponds, biologically, to the extinction of the cell population and a saturation of the growth factor concentration, it is not a biologically interesting equilibrium. It describes a pathological situation that can only lead to death without appropriate treatment. Therefore, we focus on the local stability analysis of the other steady-state (Q^*, M^*, E^*). One can check that condition (11), which ensures the existence of this steady-state, is equivalent to

$$\delta + g'(0) < \beta\left(0, \frac{f(0)}{k}\right) \quad \text{and} \quad 0 \le \tau < \tau_{\max} := \frac{1}{\gamma}\ln\left(\frac{2\beta\left(0, \frac{f(0)}{k}\right)}{\delta + g'(0) + \beta\left(0, \frac{f(0)}{k}\right)}\right). \tag{13}$$

Note that, using the implicit function theorem, we can easily show that the steady-states Q^*, M^*, and E^* are continuously differentiable with respect to the cell cycle duration $\tau \in [0, \tau_{\max})$. Moreover, Q^* and M^* are decreasing functions of τ and E^* is an increasing function of τ, with

$$\lim_{\tau \to \tau_{\max}} (Q^*(\tau), M^*(\tau), E^*(\tau)) = (0, 0, f(0)/k).$$

3. Local stability analysis

We concentrate on the study of the stability of the nontrivial equilibrium (Q^*, M^*, E^*). Hence, we assume throughout this section that $\mu, k > 0$ and condition (13) holds.

The delay is often seen as a destabilization parameter (see, for example, Metz and Diekmann (1986); Mackey and Milton (1990)). To compare the long periods of the bifurcating periodic solutions with the cell cycle duration, we then perform the stability analysis with respect to the delay parameter τ, which represents the cell cycle duration.

We recall that Q^*, M^*, and E^* satisfy (7). To linearize (4) around the equilibrium (Q^*, M^*, E^*), we set

$$q(t) = Q(t) - Q^*, \quad m(t) = M(t) - M^*, \quad \text{and} \quad e(t) = E(t) - E^*.$$

The linearized system is

$$\begin{cases} \dfrac{\mathrm{d}q}{\mathrm{d}t} = -Aq(t) + Bq(t-\tau) - Ce(t) + De(t-\tau), \\ \dfrac{\mathrm{d}m}{\mathrm{d}t} = -\mu m(t) + Gq(t), \\ \dfrac{\mathrm{d}e}{\mathrm{d}t} = -ke(t) - Hm(t), \end{cases} \tag{14}$$

where the real coefficients A, B, C, D, G, and H are defined by

$$\begin{aligned} A &= \delta + g'(Q^*) + \beta(Q^*, E^*) + \beta_1'(Q^*, E^*)Q^*, \\ B &= 2\mathrm{e}^{-\gamma\tau}\left[\beta(Q^*, E^*) + \beta_1'(Q^*, E^*)Q^*\right], \\ C &= \beta_2'(Q^*, E^*)Q^* > 0, \\ D &= 2\mathrm{e}^{-\gamma\tau}\beta_2'(Q^*, E^*)Q^* > 0, \\ G &= g'(Q^*) > 0, \\ H &= -f'(M^*) > 0. \end{aligned} \tag{15}$$

One can notice that these coefficients depend, explicitly or implicitly, on the parameter τ through the equilibrium values Q^*, M^*, and E^*. However, we do not stress this dependence when we write the coefficients. Moreover, from the assumptions on β, g, and f, the coefficients C, D, G, and H are strictly positive.

In the above definitions, we have used the notations

$$\beta_1'(Q, E) := \frac{\partial\beta}{\partial Q}(Q, E) \qquad \text{and} \qquad \beta_2'(Q, E) := \frac{\partial\beta}{\partial E}(Q, E).$$

Furthermore, one can notice that

$$A - B = g'(Q^*) - \frac{g(Q^*)}{Q^*} - (2\mathrm{e}^{-\gamma\tau} - 1)\beta_1'(Q^*, E^*)Q^* \geq 0$$

and

$$D - C = (2\mathrm{e}^{-\gamma\tau} - 1)\beta_2'(Q^*, E^*)Q^* > 0.$$

System (14) can be written in the matrix form

$$\frac{\mathrm{d}X}{\mathrm{d}t} = \mathcal{A}_1 X(t) + \mathcal{A}_2 X(t-\tau)$$

with

$$X(t) = \begin{pmatrix} q(t) \\ m(t) \\ e(t) \end{pmatrix}, \quad \mathcal{A}_1 = \begin{pmatrix} -A & 0 & -C \\ G & -\mu & 0 \\ 0 & -H & -k \end{pmatrix} \quad \text{and} \quad \mathcal{A}_2 = \begin{pmatrix} B & 0 & D \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}.$$

Consequently, the characteristic equation of (14) is given by

$$\det\left(\lambda I - \mathcal{A}_1 - \mathcal{A}_2 \mathrm{e}^{-\lambda\tau}\right) = 0,$$

which reduces to

$$(\lambda+\mu)(\lambda+k)(\lambda+A-B\mathrm{e}^{-\lambda\tau}) - GH(C-D\mathrm{e}^{-\lambda\tau}) = 0. \tag{16}$$

We recall the following result: the trivial solution of system (14), or equivalently the steady-state of system (4), is asymptotically stable if all roots of (16) have negative real parts, and the stability is lost only if characteristic roots cross the axis from left to right, or right to left, that is if pure imaginary roots appear.

Remark 2. If we linearize system (4) around its trivial steady-state $(0, 0, f(0)/k)$, we obtain a system similar to (14), with

$$\begin{aligned} A &= \delta + g'(0) + \beta(0, f(0)/k) > 0, & D &= 0, \\ B &= 2\mathrm{e}^{-\gamma\tau}\beta(0, f(0)/k) > 0, & G &= g'(0) > 0, \\ C &= 0, & H &= -f'(0) > 0. \end{aligned}$$

Therefore, the characteristic Eq. (16) of the linearized system, about the trivial steady-state, becomes

$$(\lambda+\mu)(\lambda+k)(\lambda+A-B\mathrm{e}^{-\lambda\tau}) = 0. \tag{17}$$

Studying the sign of the real parts of the roots of (17), we obtain the following proposition (whose proof is given in Appendix B) which deals with the local asymptotic stability of the trivial steady-state of (4).

Proposition 3. *Assume that $\mu > 0$ and $k > 0$. If condition (12) holds, then the trivial steady-state of system (4) is locally asymptotically stable for all $\tau \geq 0$, and if condition (11) holds, then it is unstable for all $\tau \geq 0$.*

The results stated in Proposition 3 indicate that the trivial steady-state of (4) is locally asymptotically stable when it is the only equilibrium and unstable as soon as the nontrivial equilibrium exists.

We now return to the analysis of the local asymptotic stability of the nontrivial steady-state (Q^*, M^*, E^*) of system (4).

Equation (16) takes the general form

$$P(\lambda, \tau) + Q(\lambda, \tau)e^{-\lambda\tau} = 0 \tag{18}$$

with

$$P(\lambda, \tau) = \lambda^3 + a_1(\tau)\lambda^2 + a_2(\tau)\lambda + a_3(\tau),$$
$$Q(\lambda, \tau) = a_4(\tau)\lambda^2 + a_5(\tau)\lambda + a_6(\tau),$$

where

$$a_1(\tau) = \mu + k + A, \qquad a_4(\tau) = -B,$$
$$a_2(\tau) = \mu k + A(\mu + k), \qquad a_5(\tau) = -B(\mu + k),$$
$$a_3(\tau) = \mu kA - GHC, \qquad a_6(\tau) = -B\mu k + GHD.$$

We can check that, for all $\tau \in [0, \tau_{\max})$,

$$a_1(\tau) + a_4(\tau) = \mu + k + A - B > 0,$$

$$a_2(\tau) + a_5(\tau) = \mu k + (A - B)(\mu + k) > 0,$$

and

$$a_3(\tau) + a_6(\tau) = \mu k(A - B) + GH(D - C) > 0.$$

We will remember, in the following, that

$$a_i(\tau) + a_{i+3}(\tau) > 0 \qquad \text{for } i = 1, 2, 3. \tag{19}$$

Let us examine the case $\tau = 0$. This case is of importance, because it can be necessary that the nontrivial positive steady-state of (4) is stable when $\tau = 0$ to be able to obtain the local stability for all nonnegative values of the delay, or to find a critical value which could destabilize the steady-state (see Theorem 8).

When $\tau = 0$, the characteristic Eq. (18) reduces to

$$\lambda^3 + [a_1(0) + a_4(0)]\lambda^2 + [a_2(0) + a_5(0)]\lambda + a_3(0) + a_6(0) = 0. \tag{20}$$

The Routh–Hurwitz criterion says that all roots of (20) have negative real parts if and only if

$$a_1(0) + a_4(0) > 0,$$
$$a_3(0) + a_6(0) > 0,$$

and

$$[a_1(0) + a_4(0)][a_2(0) + a_5(0)] > a_3(0) + a_6(0). \tag{21}$$

From (19), it follows that all characteristic roots of (20) have negative real parts if and only if (21) holds.

Proposition 4. *When $\tau = 0$, the nontrivial steady-state (Q^*, M^*, E^*) of (4) is locally asymptotically stable if and only if*

$$(\mu + k)\,[\mu k + (A - B)(\mu + k + A - B)] > GH(D - C), \tag{22}$$

where A, B, C, D, G, and H are given by (15).

In the following, we investigate the existence of purely imaginary roots $\lambda = i\omega$, $\omega \in \mathbb{R}$, of (18). Equation (18) takes the form of a third-degree exponential polynomial in λ. In 2001, Ruan and Wei (2001) gave sufficient conditions for the existence of zeros for such an equation, but only in the case where the coefficients of the polynomial functions P and Q do not depend on the delay τ, that is when the characteristic Eq. (18) is given by $P(\lambda) + Q(\lambda)e^{-\lambda\tau} = 0$. Since all the coefficients of P and Q depend on τ, we cannot apply their results directly. In 2002, however, Beretta and Kuang (2002) established a geometrical criterion which gives the existence of purely imaginary roots for a characteristic equation with delay dependent coefficients. We are going to apply this criterion to Eq. (18) in order to obtain stability results for Eq. (14). In the following, we use the same notations as inBeretta and Kuang (2002).

We first have to verify the following properties, for all $\tau \in [0, \tau_{\max})$:

(i) $P(0, \tau) + Q(0, \tau) \neq 0$;
(ii) $P(i\omega, \tau) + Q(i\omega, \tau) \neq 0$;
(iii) $\limsup \left\{ \left| \frac{Q(\lambda,\tau)}{P(\lambda,\tau)} \right| ; |\lambda| \to \infty, \mathrm{Re}\lambda \geq 0 \right\} < 1$;
(iv) $F(\omega, \tau) := |P(i\omega, \tau)|^2 - |Q(i\omega, \tau)|^2$ has a finite number of zeros.

Properties (i), (ii), and (iii) can be easily verified. Let $\tau \in [0, \tau_{\max})$. Using (19), a simple computation gives

$$P(0, \tau) + Q(0, \tau) = a_3(\tau) + a_6(\tau) > 0.$$

Moreover,

$$P(\mathrm{i}\omega,\tau)+Q(\mathrm{i}\omega,\tau)=[-(a_1(\tau)+a_4(\tau))\omega^2+a_3(\tau)+a_6(\tau)] \\ +\mathrm{i}[-\omega^3+(a_2(\tau)+a_5(\tau))\omega],$$

so (ii) is true. Finally,

$$\left|\frac{Q(\lambda,\tau)}{P(\lambda,\tau)}\right|\underset{|\lambda|\to\infty}{\sim}\left|\frac{a_4(\tau)}{\lambda}\right|,$$

therefore (iii) is also true.

Now, let F be defined as in (iv). Since

$$|P(\mathrm{i}\omega,\tau)|^2=\omega^6+\left[a_1^2(\tau)-2a_2(\tau)\right]\omega^4+\left[a_2^2(\tau)-2a_1(\tau)a_3(\tau)\right]\omega^2+a_3^2(\tau)$$

and

$$|Q(\mathrm{i}\omega,\tau)|^2=a_4^2(\tau)\omega^4+\left[a_5^2(\tau)-2a_4(\tau)a_6(\tau)\right]\omega^2+a_6^2(\tau),$$

we have

$$F(\omega,\tau)=\omega^6+b_1(\tau)\omega^4+b_2(\tau)\omega^2+b_3(\tau)$$

with

$$b_1(\tau)=a_1^2(\tau)-2a_2(\tau)-a_4^2(\tau),$$
$$b_2(\tau)=a_2^2(\tau)+2a_4(\tau)a_6(\tau)-2a_1(\tau)a_3(\tau)-a_5^2(\tau),$$
$$b_3(\tau)=a_3^2(\tau)-a_6^2(\tau).$$

One can check that

$$b_1(\tau)=\mu^2+k^2+A^2-B^2,$$

and

$$b_2(\tau)=\mu^2k^2+(A^2-B^2)(\mu^2+k^2)+2GH\left[C(\mu+k+A)-BD\right],$$
$$b_3(\tau)=\mu^2k^2(A^2-B^2)+G^2H^2(C^2-D^2)+2\mu kGH(BD-AC),$$

where A, B, C, D, G, and H are given by (15). It is obvious that property (iv) is satisfied.

Now assume that $\lambda=\mathrm{i}\omega$, $\omega\in\mathbb{R}$, is a purely imaginary characteristic root of (18). Separating real and imaginary parts, we can show that (ω,τ) satisfies

$$-a_1(\tau)\omega^2+a_3(\tau)=-\left[-a_4(\tau)\omega^2+a_6(\tau)\right]\cos(\omega\tau)-a_5(\tau)\omega\sin(\omega\tau), \quad (23)$$
$$-\omega^3+a_2(\tau)\omega=-a_5(\tau)\omega\cos(\omega\tau)+\left[-a_4(\tau)\omega^2+a_6(\tau)\right]\sin(\omega\tau). \quad (24)$$

One can check that, if (ω, τ) is a solution of system (23)–(24), then so is $(-\omega, \tau)$. Hence, if $i\omega$ is a purely imaginary characteristic root of (18), its conjugate has the same property. Consequently, we only look in the following for purely imaginary roots of (18) with positive imaginary part.

Adding the squares of both sides of system (23)–(24), a necessary condition for this system to have solutions (ω, τ) is that

$$[-a_1(\tau)\omega^2 + a_3(\tau)]^2 + [-\omega^3 + a_2(\tau)\omega]^2 = [-a_4(\tau)\omega^2 + a_6(\tau)]^2 + a_5^2\omega^2,$$

that is

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

The polynomial function F can be written as

$$F(\omega, \tau) = h(\omega^2, \tau),$$

where h is a third-degree polynomial, defined by

$$h(z, \tau) := z^3 + b_1(\tau)z^2 + b_2(\tau)z + b_3(\tau). \tag{25}$$

We set

$$\Delta(\tau) = b_1^2(\tau) - 3b_2(\tau), \tag{26}$$

and, when $\Delta(\tau) \geq 0$,

$$z_0(\tau) = \frac{-b_1(\tau) + \sqrt{\Delta(\tau)}}{3}. \tag{27}$$

We then have the following lemma (details of the proof are given in Ruan and Wei (2001), Lemma 2.1).

Lemma 5. *Let $\tau \in [0, \tau_{\max})$ and $\Delta(\tau)$ and $z_0(\tau)$ be defined by (26) and (27), respectively. Then $h(\cdot, \tau)$, defined in (25), has positive roots if and only if*

$$b_3(\tau) < 0 \quad \text{or} \quad b_3(\tau) \geq 0,\ \Delta(\tau) \geq 0,\ z_0(\tau) > 0 \text{ and } h(z_0(\tau), \tau) < 0. \tag{28}$$

Conditions $\Delta(\tau) \geq 0$, $z_0(\tau) > 0$, and $h(z_0(\tau), \tau) < 0$ cannot be easily checked. However, we express them using the coefficients $b_i, i = 1, 2, 3$, which can be useful. Details of the easy but tedious computations are given in Appendix C.

Lemma 6. *Let $\tau \geq 0$ be such that $b_3(\tau) \geq 0$. Then $\Delta(\tau) \geq 0$, $z_0(\tau) > 0$, and $h(z_0(\tau), \tau) < 0$ if and only if*

$$(i)\ b_2(\tau) < 0 \quad or \quad b_1(\tau) < 0 \le b_2(\tau) < \frac{b_1^2(\tau)}{3},\ and$$
$$(ii)\ 2\Delta(\tau)z_0(\tau) + b_1(\tau)b_2(\tau) - 9b_3(\tau) > 0.$$

From the previous lemma, condition (28) is equivalent to

$$b_3(\tau) < 0 \qquad \text{or} \qquad b_3(\tau) \ge 0 \text{ and (i)-(ii) hold true.} \tag{29}$$

Let us show on an example that condition (29) is satisfied.

Note that b_3 can be expressed as

$$b_3(\tau) = \mu^2k^2(A-B)(A+B) + G^2H^2(C-D)(C+D) + 2\mu kGH(B(D-C) + C(B-A)),$$

where A, B, C, D, G, and H are defined by (15). Since $C - D < 0$ and $B - A \le 0$, then $b_3(\tau) < 0$ if $A + B \le 0$ and $B \le 0$. Moreover, from the definition of B, it follows that $B \le 0$ if $A + B \le 0$. Consequently, a sufficient condition for $b_3(\tau) < 0$ is $A + B \le 0$.

Let us assume that g is a linear function given by $g(Q) = GQ$ with $G > 0$, $\beta(Q, E) = \beta_1(Q)\beta_2(E)$ with $\beta_1(Q) = 1/(1 + Q^n)$, $n > 0$, and β_2 an increasing function satisfying $\beta_2(0) = 0$. Then, for $\tau = 0$,

$$A + B = [4\beta_1(Q^*) + 3\beta_1'(Q^*)Q^*]\beta_2(E^*).$$

Since $E^* > 0$, $\beta_2(E^*) > 0$ and $A + B \le 0$ if and only if

$$4\beta_1(Q^*) + 3\beta_1'(Q^*)Q^* = \frac{4 + (4-3n)(Q^*)^n}{(1 + (Q^*)^n)^2} \le 0,$$

that is

$$n > \frac{4}{3} \qquad \text{and} \qquad Q^* \ge \left(\frac{4}{3n-4}\right)^{1/n}.$$

Let δ and G be such that

$$\delta + G < \widetilde{\beta}(1) = \frac{1}{2}\beta_2\left(\frac{1}{k}f\left(\frac{G}{\mu}\right)\right),$$

where $\widetilde{\beta}$ is defined by (10), and let $\bar{n} > 4/3$ be the unique solution of

$$\frac{3\bar{n}}{3\bar{n}-4} + \ln\left(\frac{4}{3\bar{n}-4}\right) = 0.$$

Then, for $n > \bar{n} \approx 6.12$,

$$\widetilde{\beta}\left(\left(\frac{4}{3n-4}\right)^{1/n}\right) > \widetilde{\beta}(1) > \delta + G,$$

so $Q^* \geq (4/(3n-4))^{1/n}$ and it follows that $A + B \leq 0$.

Consequently, $b_3(0) < 0$ and, using the continuity of b_3 with respect to τ, we deduce that there exists $\bar{\tau} > 0$ such that (29) is verified for $\tau \in [0, \bar{\tau})$.

When the reintroduction rate β only depends on the growth factor concentration E, condition (29) is also satisfied for τ close to zero. This is numerically obtained in Section 4.

We set $I := [0, \bar{\tau})$ an interval in which (29) is satisfied, with $0 < \bar{\tau} \leq \tau_{\max}$. From the above remarks, we can find functions β, g, and f, and parameter values such that $\bar{\tau}$ exists. For $\tau \in I$ there exists at least $\omega = \omega(\tau) > 0$ such that $F(\omega(\tau), \tau) = 0$.

Then, let $\theta(\tau) \in [0, 2\pi]$ be defined for $\tau \in I$ by

$$\cos(\theta(\tau)) = \frac{(a_5 - a_1 a_4)\,\omega^4 + (a_1 a_6 + a_3 a_4 - a_2 a_5)\,\omega^2 - a_3 a_6}{a_4^2 \omega^4 + (a_5^2 - 2a_4 a_6)\,\omega^2 + a_6^2},$$

$$\sin(\theta(\tau)) = \frac{a_4 \omega^5 + (a_1 a_5 - a_2 a_4 - a_6)\,\omega^3 + (a_2 a_6 - a_3 a_5)\,\omega}{a_4^2 \omega^4 + (a_5^2 - 2a_4 a_6)\,\omega^2 + a_6^2},$$

where $\omega = \omega(\tau)$, and we deliberately omit the dependence of the a_i on τ. Since $F(\omega(\tau), \tau) = 0$ for $\tau \in I$, it follows that θ is well and uniquely defined for all $\tau \in I$.

One can check, using (23)–(24), that $\mathrm{i}\omega^*$ with $\omega^* = \omega(\tau^*) > 0$ is a purely imaginary characteristic root of (18) if and only if τ^* is a root of the function S_n, defined by

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

The following theorem is due to Beretta and Kuang (2002).

Theorem 7. *Assume that the function $S_n(\tau)$ has a positive root $\tau^* \in I$ for some $n \in \mathbb{N}$. Then a pair of simple purely imaginary roots $\pm\mathrm{i}\omega(\tau^*)$ of (18) exists at $\tau = \tau^*$ and*

$$\operatorname{sign}\left\{\frac{\mathrm{d}\operatorname{Re}(\lambda)}{\mathrm{d}\tau}\bigg|_{\lambda=\mathrm{i}\omega(\tau^*)}\right\} = \operatorname{sign}\left\{\frac{\partial F}{\partial \omega}(\omega(\tau^*), \tau^*)\right\} \operatorname{sign}\left\{\frac{\mathrm{d}S_n(\tau)}{\mathrm{d}\tau}\bigg|_{\tau=\tau^*}\right\}. \tag{30}$$

Since

$$\frac{\partial F}{\partial \omega}(\omega, \tau) = 2\omega \frac{\partial h}{\partial z}(\omega^2, \tau),$$

condition (30) is equivalent to

$$\operatorname{sign}\left\{\frac{\mathrm{dRe}(\lambda)}{\mathrm{d}\tau}\bigg|_{\lambda=\mathrm{i}\omega(\tau^*)}\right\} = \operatorname{sign}\left\{\frac{\partial h}{\partial z}(\omega^2(\tau^*), \tau^*)\right\} \operatorname{sign}\left\{\frac{\mathrm{d}S_n(\tau)}{\mathrm{d}\tau}\bigg|_{\tau=\tau^*}\right\}.$$

We can easily observe that $S_n(0) < 0$. Moreover, for all $\tau \in I$, $S_n(\tau) > S_{n+1}(\tau)$, with $n \in \mathbb{N}$. Therefore, if S_0 has no root in I, then the S_n functions have no root in I and, if the function $S_n(\tau)$ has positive roots $\tau \in I$ for some $n \in \mathbb{N}$, there exists at least one root satisfying

$$\frac{\mathrm{d}S_n}{\mathrm{d}\tau}(\tau) > 0.$$

Using Proposition 4, we can conclude the existence of a Hopf bifurcation as stated in the next theorem.

Theorem 8. *Assume that μ, $k > 0$, condition (11) is satisfied and (22) holds true.*

(i) If the function $S_0(\tau)$ has no positive root in I, then the steady-state (Q^*, M^*, E^*) is locally asymptotically stable for all $\tau \geq 0$.

(ii) If the function $S_0(\tau)$ has at least one positive root in I, then there exists $\tau^* \in I$ such that the steady-state (Q^*, M^*, E^*) is locally asymptotically stable for $0 \leq \tau < \tau^*$ and becomes unstable for $\tau \geq \tau^*$, with a Hopf bifurcation occurring when $\tau = \tau^*$, if and only if

$$\frac{\partial h}{\partial z}(\omega^2(\tau^*), \tau^*) > 0.$$

The bifurcation diagram given in Fig. 2 describes the situation of Theorem 8 (ii). A Hopf bifurcation occurs for a certain value of τ ($\tau = 1.4$ day), destabilizing the system. A stability switch that is not predicted by Theorem 8 occurs for a larger value of the time delay ($\tau = 2.82$ days). These results are detailed in the next section, where we illustrate the results established in Theorem 8. We show, in particular, that our model can exhibit long-period oscillations, compared to the delay, that can be related to experimental observations in patients with periodic chronic myelogenous leukemia.

4. Numerical illustrations: Long-period oscillations

Let us assume that the introduction of resting cells in the proliferating phase is only triggered by the growth factor concentration $E(t)$, that is $\beta = \beta(E(t))$. This assumption is based on the hypothesis made by Bélair et al. (1995) for an erythropoiesis model. It describes, for example, the fact that the cell population may only react to external stimuli and cannot be directly sensitive to its own size. We assume that β is given by

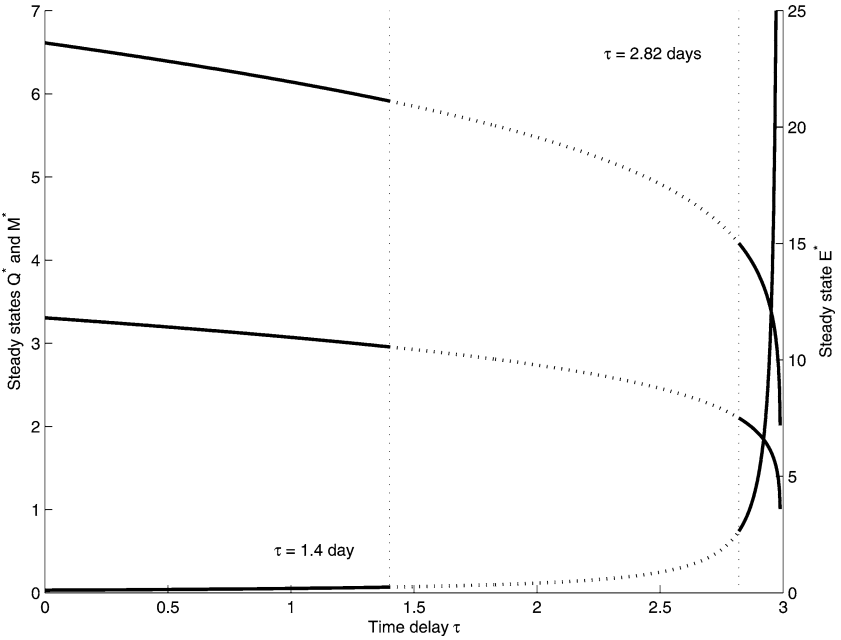

Fig. 2 Bifurcation diagram. With parameters given by Table 1, values of the steady states Q^*, M^*, and E^* are drawn for $\tau \in [0, \tau_{\max})$, with $\tau_{\max} = 2.99$ days. The *upper line* is for M^*, the *middle* one for Q^*, and the *lower* one for E^* (the scale for E^* is given on the right vertical axis). When $\tau = 2.99$, $E^* \approx 2346$ but we have stopped the scale on the vertical axis at 25 to improve the illustration clarity. When τ is close to zero, the steady states are stable, and a Hopf bifurcation occurs for $\tau = 1.4$ day. Then, the steady states become unstable. A stability switch (whose existence is not established by Theorem 8) stabilizes the steady states for $\tau \geq 2.82$ days.

$$\beta(E) = \beta_0 \frac{E}{1+E}, \qquad \beta_0 > 0.$$

The functions g and f are defined by

$$g(Q) = GQ \qquad \text{with } G > 0,$$

and

$$f(M) = \frac{a}{1+KM^r}, \qquad a, K > 0, r > 0.$$

This latter function often occurs in enzyme kinetics. It has been used by Mackey (1978, 1979) to describe the rate of introduction in the proliferating phase and by Bélair et al. (1995) to define the feedback from the blood to the growth factor production.

With these choices for the functions β, g, and f, our model involves 10 parameters, including the delay τ. Most of the values of these parameters can be found in the literature. The values we used are listed in Table 1.

Table 1 Table of parameters.

Parameter	Value used	Range (d^{-1})	References
δ	0.01 day^{-1}	0–0.09	(Mackey (1978, 1997); Pujo-Menjouet and Mackey (2004))
G	0.04 day^{-1}	0–0.09	(Mackey (1978, 1997); Pujo-Menjouet and Mackey (2004))
β_0	0.5 day^{-1}	0.08–2.24	(Mackey (1997); Bernard et al. (2003b))
γ	0.2 day^{-1}	0–0.9	(Mackey (1978, 2001); Bernard et al. (2003b); Pujo-Menjouet et al. (2005))
μ	0.02 day^{-1}	0.001–0.1	(Bélair et al. (1995))
k	2.8 day^{-1}	—	(Bélair et al. (1995); Mahaffy et al. (1998); Erslev (1990, 1991))
a	6570	—	(Bélair et al. (1995); Mahaffy et al. (1998); Erslev (1990, 1991))
K	0.0382	—	(Bélair et al. (1995); Mahaffy et al. (1998); Erslev (1990, 1991))
r	7	—	(Bélair et al. (1995); Mahaffy et al. (1998); Erslev (1990, 1991))

Note. Values indicated in the second column are the ones used in the simulations.

According to Mackey (1978) and Pujo-Menjouet and Mackey (2004), the rate of differentiation and death of hematopoietic stem cells is about 0.05 per day. Considering that mortality of hematopoietic stem cells is very low, we choose $\delta = 0.01\,\text{day}^{-1}$ and $G = 0.04\,\text{day}^{-1}$, so $\delta + G = 0.05\,\text{day}^{-1}$. The stem cells apoptosis rate γ is given by Mackey (1978) and Pujo-Menjouet and Mackey (2004). We choose $\gamma = 0.2\,\text{day}^{-1}$.

In Bélair et al. (1995) and Mahaffy et al. (1998), the authors claim that the mortality rate of mature blood cells μ ranges from 0.001 to 0.1 per day. In our simulations, we use the value $\mu = 0.02\,\text{day}^{-1}$ to fit the model with experimental data.

The coefficient β_0 represents the maximum rate of introduction in the proliferating phase and also the value of $\beta'(0)$. It strongly depends on the nature of the growth factor. Using data about erythropoiesis Mackey (1997), we choose $\beta_0 = 0.5\,\text{day}^{-1}$, which is less than the maximal rate of introduction proposed by Mackey (1978), but seems sufficiently large for erythropoiesis modelling.

The coefficients of the function f and the disappearance rate k are given by Bélair et al. (1995) and Mahaffy et al. (1998), according to Erslev (1990, 1991). So we use $k = 2.8\,\text{day}^{-1}$ and $a = 6570$, $K = 0.0382$ and $r = 7$.

With the above choices for the functions β, g, and f, we can explicitly compute the steady-states of system (4), Q^*, M^*, and E^*. In particular, one can check that condition (6) holds true. Condition (13) becomes

$$(\delta + G)(a + k) < \beta_0 a \quad \text{and} \quad 0 \leq \tau < \frac{1}{\gamma} \ln\left(\frac{2\beta_0 a}{(\delta + G)(a + k) + \beta_0 a}\right) := \tau_{\max}.$$

We set

$$\alpha(\tau) = 2\mathrm{e}^{-\gamma\tau} - 1 \qquad \text{for } \tau \in [0, \tau_{\max}).$$

The function α is positive and decreasing on $[0, \tau_{\max})$ and satisfies

$$\frac{(\delta + G)(a + k)}{a\beta_0} < \alpha(\tau) \leq 1 \qquad \text{for } \tau \in [0, \tau_{\max}).$$

The steady-states of (4) are then defined by

$$\begin{aligned} Q^* &= \frac{\mu}{G} \frac{1}{K^{1/r}} \left(\frac{a\beta_0\alpha(\tau) - (\delta + G)(a + k)}{k(\delta + G)}\right)^{1/r}, \\ M^* &= \frac{G}{\mu} Q^*, \\ E^* &= \frac{\delta + G}{\beta_0\alpha(\tau) - (\delta + G)}. \end{aligned}$$

For $\tau \in [0, \tau_{\max})$, Q^* and M^* are decreasing with

$$0 < Q^* \leq \frac{\mu}{G} \frac{1}{K^{1/r}} \left(\frac{a\beta_0 - (\delta + G)(a + k)}{k(\delta + G)}\right)^{1/r}$$

and

$$0 < M^* \leq \frac{1}{K^{1/r}} \left(\frac{a\beta_0 - (\delta + G)(a + k)}{k(\delta + G)} \right)^{1/r},$$

and E^* is increasing with

$$\frac{\delta + G}{\beta_0 - (\delta + G)} \leq E^* < \frac{a}{k}.$$

For the parameters given in Table 1, the steady-states are drawn on the interval $[0, \tau_{\max})$ in Fig. 2. In this case, $\tau_{\max} = 2.99$ days.

The coefficients A, B, C, and D, defined in (15), become

$$A = \delta + G + \beta(E^*) > 0, \qquad C = \beta'(E^*)Q^* > 0,$$
$$B = 2e^{-\gamma\tau}\beta(E^*) > 0, \qquad D = 2e^{-\gamma\tau}\beta'(E^*)Q^* > 0,$$

and are all strictly positive. The coefficient G is constant and H is still given by $H = -f'(M^*) > 0$. One can also check that E^* is the unique solution of

$$\left(2e^{-\gamma\tau} - 1\right)\beta\left(E^*\right) = \delta + G.$$

Thus,

$$A = B = (\delta + G)\frac{\alpha(\tau) + 1}{\alpha(\tau)}.$$

In particular, we deduce that

$$b_1(\tau) = \mu^2 + k^2 > 0,$$
$$b_2(\tau) = \mu^2 k^2 + 2GH\left[C(\mu + k + A) - AD\right],$$
$$b_3(\tau) = GH(D - C)\left(2\mu kA - GH(C + D)\right).$$

One can notice that b_1 is now independent of the delay τ. Moreover, since $b_1 > 0$, the polynomial function h, defined in (25), has strictly positive roots if and only if (see Lemma 5 and Lemma 6) $b_3(\tau) < 0$ or $b_3(\tau) \geq 0$, $b_2(\tau) < 0$ and

$$2\Delta(\tau)z_0(\tau) + b_1(\tau)b_2(\tau) - 9b_3(\tau) > 0.$$

Using Maple 9, we compute the coefficients b_2 and b_3 for the values in Table 1. Results are presented in Fig. 3. Since $b_3 < 0$ on $[0, 2.92)$ and b_2 is always positive, h has positive roots if and only if $\tau \in I := [0, 2.92)$. In this case, h has exactly one positive root for each $\tau^* \in [0, 2.92)$, denoted by z^*, and, since $h(0, \tau) < 0$, z^* satisfies

$$\frac{\partial h}{\partial z}(z^*, \tau^*) > 0.$$

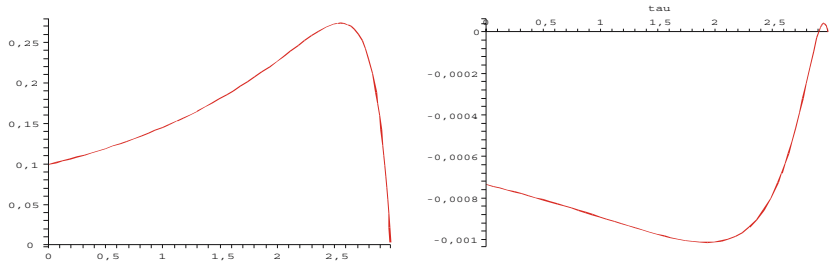

Fig. 3 Coefficients $b_2(\tau)$ (*left*) and $b_3(\tau)$ (*right*) are represented for $\tau \in [0, \tau_{\max})$ with $\tau_{\max} = 2.99$.

The function S_0 is drawn for $\tau \in I = [0, 2.92)$ in Fig. 4. One can see that there are two critical values of the delay τ for which stability switches occur. In particularly, from Theorem 8, a Hopf bifurcation occurs when τ is approximately equal to 1.4. Thus, periodic solutions appear.

In Fig. 4, one can also check that S_1 has no positive root on I. Therefore, there exist only two critical values of the delay for which stability switches occur, $\tau = 1.4$ and $\tau = 2.82$ days.

Using dde23 Shampine and Thompson (2001), a MATLAB solver for delay differential equation, we can compute the solutions of (4) for the above mentioned values of the parameters. Illustrations are showed in Figs. 5–7.

Before the Hopf bifurcation occurs, solutions are stable and converge to the equilibrium, although they oscillate transiently (see Fig. 5). When the bifurcation occurs, periodic solutions appear with periods about 100 days (see Fig. 6). These are very long periods compared to the delay τ (the cell cycle duration), which is about 1.4 day.

When τ increases, longer periods oscillations exist. For $\tau = 2.82$ days, a stability switch occurs: the steady-state becomes asymptotically stable again and solutions converge to the equilibrium (see Fig. 7).

5. Periodic hematological diseases

Periodic hematological diseases Haurie et al. (1998) represent one kind of diseases affecting blood cells. They are characterized by significant oscillations in the num-

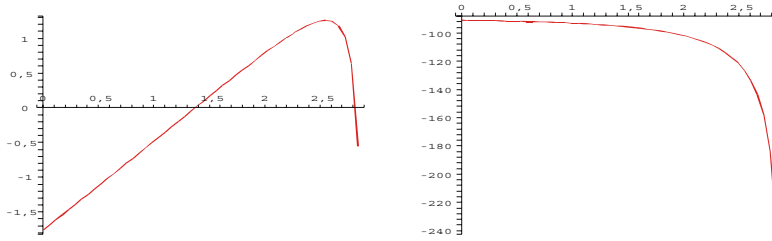

Fig. 4 Graphs of the functions $S_0(\tau)$ and $S_1(\tau)$. *Left*: Graph of the function $S_0(\tau)$ for $\tau \in [0, \tau_{\max})$ with parameters given by Table 1, and $\tau_{\max} \approx 2.99$. Two critical values of τ, for which stability switches can occur, appear. *Right*: Graph of the function $S_1(\tau)$ for the same values; the function has no positive root.

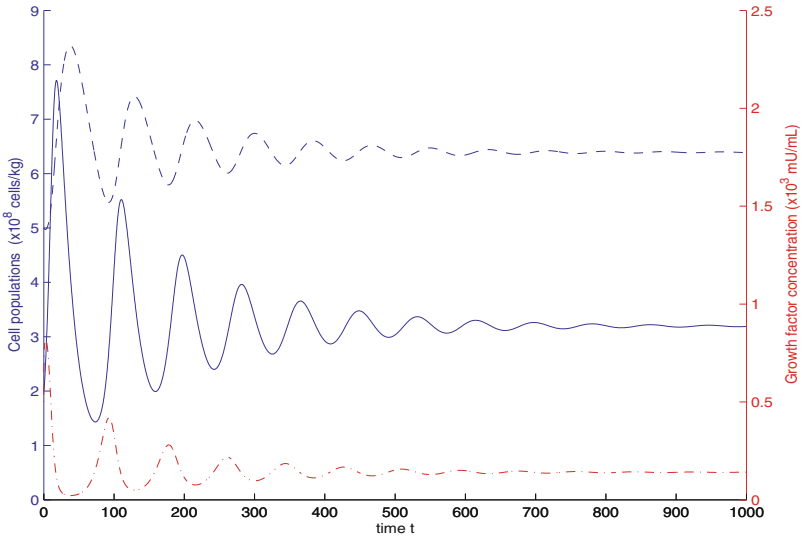

Fig. 5 Solutions $Q(t)$ (*solid line*), $M(t)$ (*dashed line*) and $E(t)$ (*dotted line*) of (4) are asymptotically stable and converge to the steady-state values. Damped oscillations can be observed. Parameters values are given by Table 1, with $\tau = 0.5$.

ber of circulating cells, with periods ranging from weeks (19–21 days for cyclical neutropenia Haurie et al. (1998)) to months (30–100 days for chronic myelogenous leukemia Haurie et al. (1998)) and amplitudes varying from normal to low levels or normal to high levels, depending on cell types. Because of their dynamic character, periodic hematological diseases offer an opportunity to understand some of the regulating processes involved in the production of blood cells.

Some periodic hematological diseases involve only one type of blood cells, for example, red blood cells in periodic autoimmune hemolytic anemia Bélair et al. (1995) or platelets in cyclical thrombocytopenia Santillan et al. (2000). In these cases, periods of the oscillations are usually between two and four times the cell cycle duration. However, other periodic hematological diseases, such as cyclical neutropenia Haurie et al. (1998) or chronic myelogenous leukemia Fortin and Mackey (1999), show oscillations in all of the circulating blood cells, i.e., white blood cells, red blood cells, and platelets. These diseases involve oscillations with quite long periods (on the order of weeks to months). A destabilization of the pluripotential stem cell population induced by growth factors seems to be at the origin of these diseases.

Recently, Pujo-Menjouet and Mackey (2004) and Pujo-Menjouet et al. (2005) considered models for the regulation of stem cell dynamics, based on the model of Mackey (1978, 1979), and noticed that long-period oscillations could be observed in hematopoiesis models. These long-period oscillations were obtained without taking into account the influence of growth factors on the regulation process, and for values of the parameters that are not so consistent with experimental data. Adimy et al. (2005b,c) analyzed a model of hematopoietic stem cells regulation

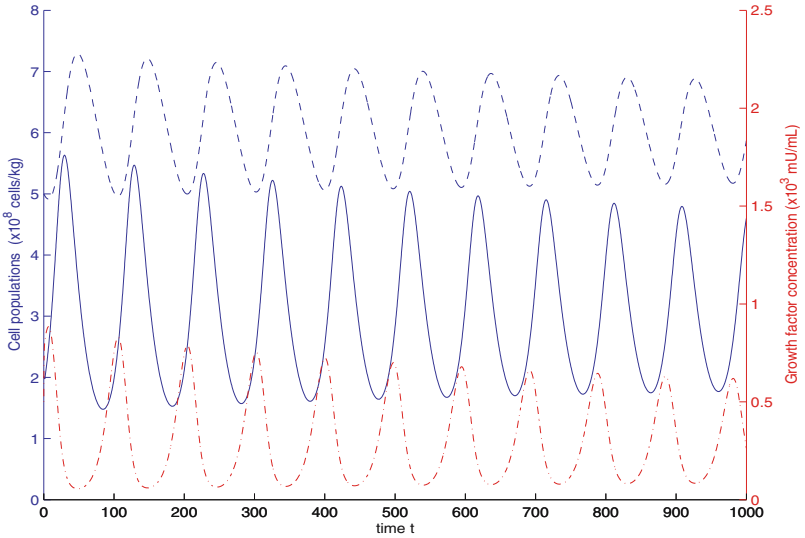

Fig. 6 When $\tau = 1.4$, a Hopf bifurcation occurs and periodic solutions appear, with the same period for the three solutions $Q(t)$ (*solid line*), $M(t)$ (*dashed line*), and $E(t)$ (*dotted line*) of (4). Periods are about 100 days. Parameters values are given by Table 1.

with a nonconstant cell cycle duration and established the existence of long-period oscillations (in the order of 70 days) when applying their model to the case of chronic myelogenous leukemia Fortin and Mackey (1999). However, longer periods oscillations could not be obtained in their model without using nonrealistic values of the parameters.

In this work, we have taken into account the role of growth factors on the regulation of the hematopoietic stem cell population. We have been able to obtain very long-period oscillations, in the order of 100 days, for very short cell cycle durations (less than 2 days). This may be compared to oscillations observed by Umemura et al. (1986) and Morley et al. (1967) with periods more than 80 and 100 days, respectively, for cases of chronic myelogenous leukemia. To our knowledge, up to now all other mathematical models of hematopoiesis have not been able to produce such long-period oscillations with reasonable data (especially for cell cycle durations and introduction rates). Our results indicate that growth factors and, in particular the destabilization of the feedback loop from blood to growth factors, may be considered as primarily responsible for such oscillations.

Our model still needs some improvements, in particular to take into account the influence of nonconstant cell cycle durations (see Adimy et al. (2005b,c)). One can notice that by assuming that the cell cycle duration is constant, values of τ for which a nontrivial steady-state exists are limited and cannot be too large. This does not appear in a model with distributed delay, as studied by Adimy et al. (2005b,c). Moreover, the long-period oscillations observed in Fig. 6 could describe other hematological diseases (cyclic pancytopenia, for example, for which

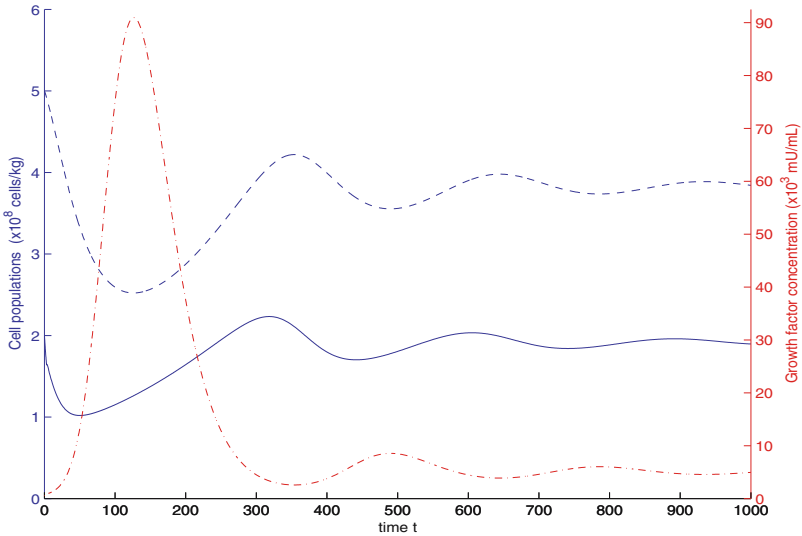

Fig. 7 When $\tau = 2.9$, the steady-state is asymptotically stable and solutions $Q(t)$ (solid line), $M(t)$ (*dashed line*) and $E(t)$ (*dotted line*) of (4) converge to the equilibrium. Parameter values are given by Table 1.

oscillations with periods about 100 days have been reported by Birgens and Karl (1993)). This phenomenon probably needs further analysis.

Appendix A: Bounded solutions of system (4)

Assume that $\lim_{Q\to\infty} \beta(Q, E) = 0$, for all $E \geq 0$, and that $\delta + g'(0) > 0$. Then the solutions of system (4) are bounded.

We first concentrate on the solution $E(t)$. Using a classical variation of constant formula, we obtain, for $t \geq 0$,

$$E(t) = \mathrm{e}^{-kt} E(0) + \mathrm{e}^{-kt} \int_0^t \mathrm{e}^{ks} f(M(s))\, \mathrm{d}s.$$

Since the function f is decreasing and bounded, we have

$$E(t) \leq \mathrm{e}^{-kt} E(0) + \frac{f(0)}{k}(1 - \mathrm{e}^{-kt}) \leq \max\left\{E(0), \frac{f(0)}{k}\right\}.$$

Consequently, $E(t)$ is bounded.

Now we focus on the solution $Q(t)$. If Q is bounded then the mapping $t \mapsto g(Q(t))$ is bounded so we will obtain that $M(t)$ is bounded using similar arguments than for the above case.

Let $C > 0$ be a bound of E and assume that $\lim_{Q\to\infty} \beta(Q, E) = 0$, for all $E \geq 0$, and that $\delta + g'(0) > 0$. Then, since the mapping $Q \mapsto \beta(Q, C)$ is decreasing, there exists $Q_0 \geq 0$ such that

$$2e^{-\gamma\tau}\beta(Q, C) < \delta + g'(0), \qquad \text{for } Q > Q_0.$$

We then set

$$Q_1 := 2e^{-\gamma\tau}\frac{\beta(0, C)Q_0}{\delta + g'(0)}.$$

Let $Q \geq Q_1$ be fixed and let $0 \leq y \leq Q$. If $y \leq Q_0$, then

$$2e^{-\gamma\tau}\beta(y, C)y \leq 2e^{-\gamma\tau}\beta(0, C)Q_0 = (\delta + g'(0))Q_1 \leq (\delta + g'(0))Q.$$

On the other hand, if $y > Q_0$, then

$$2e^{-\gamma\tau}\beta(y, C)y < (\delta + g'(0))y < (\delta + g'(0))Q.$$

Thus,

$$2e^{-\gamma\tau}\max_{0\leq y\leq Q}\beta(y, C)y \leq (\delta + g'(0))Q, \qquad \text{for } Q \geq Q_1.$$

We assume now, by contradiction, that $\limsup Q(t) = +\infty$. Then there exists $t_0 > \tau$ such that

$$Q(t) \leq Q(t_0), \quad \text{for } t \in [t_0 - \tau, t_0], \qquad \text{and} \qquad Q(t_0) > Q_1.$$

Since the function $E \mapsto \beta(Q, E)$ is increasing, we deduce, from (1), that

$$Q'(t_0) \leq g'(0)Q(t_0) - g(Q(t_0)) - \beta(Q(t_0), E(t_0))Q(t_0) < 0.$$

We obtain a contradiction so Q is bounded.

Appendix B: Local asymptotic stability of the trivial equilibrium: Proof of proposition 3

Let us recall that the trivial steady-state of system (4) is locally asymptotically stable if all roots of Eq. (17) have negative real parts and that it is unstable if roots with positive real parts exist.

Roots of (17) are $\lambda = -\mu < 0$, $\lambda = -k < 0$, and the roots of

$$\lambda + A - Be^{-\lambda\tau} = 0, \tag{B.1}$$

with

$$A = \delta + g'(0) + \beta(0, f(0)/k) > 0, \qquad \text{and} \qquad B = 2e^{-\gamma\tau}\beta(0, f(0)/k) > 0.$$

Then we focus on the roots of (B.1).

We also recall that condition (11) is equivalent to $B > A$ and condition (12) is equivalent to $A > B$.

First notice that, when $\tau = 0$, $\lambda = B - A$ so $\lambda > 0$ if condition (11) holds and $\lambda < 0$ if condition (12) holds.

Let $\tau > 0$ be fixed. Setting $\nu = \lambda\tau$, the characteristic Eq. (B.1) is equivalent to

$$(\nu + A\tau)e^{\nu} - B\tau = 0.$$

From Hayes (1950), we know that $\mathrm{Re}(\nu) < 0$ if and only if

$$A\tau > -1, \quad A\tau - B\tau > 0, \quad \text{and} \quad B\tau < \zeta \sin(\zeta) - A\tau \cos(\zeta),$$

where ζ is the unique solution of

$$\zeta = -A\tau \tan(\zeta), \qquad \zeta \in (0, \pi).$$

Since $A > 0$ and $\tau > 0$, condition $A\tau > -1$ is satisfied.

If we assume that condition (12) holds, then $A > B$ so $A\tau - B\tau > 0$. By contradiction, suppose that $B\tau > \zeta \sin(\zeta) - A\tau \cos(\zeta)$. Then, from the definition of ζ,

$$B\tau > -\frac{A\tau}{\cos(\zeta)}.$$

Since A>B>0, it follows that

$$1 > -\frac{1}{\cos(\zeta)}.$$

Consequently, $\cos(\zeta) > 0$ and $\zeta \in (0, \pi/2)$. We deduce that $\tan(\zeta) > 0$ so

$$-A\tau \tan(\zeta) < 0 < \zeta.$$

This gives a contradiction. Therefore $B\tau < \zeta \sin(\zeta) - A\tau \cos(\zeta)$, and all roots of (B.1) have negative real parts. The trivial steady-state is then locally asymptotically stable for all $\tau > 0$.

Assume now that condition (11) holds. Then $A < B$ and $A\tau - B\tau < 0$. Consequently, for all $\tau > 0$, (B.1) has roots with nonnegative real parts and the trivial steady-state is unstable.

Appendix C: Proof of lemma 6

Let τ be given such that $b_3(\tau) \geq 0$. We do not mention, in the following, the dependence of the coefficients b_i on τ.

We have

$$\Delta \geq 0 \qquad \text{if and only if} \qquad b_1^2 \geq 3b_2.$$

If $b_2 < 0$, this result holds true. Otherwise, it is necessary that $b_1^2 \geq 3b_2$. In this latter case, if $b_1 < 0$, then $z_0 > 0$ and, if $b_1 \geq 0$, then $z_0 > 0$ if and only if $b_2 < 0$. Therefore $z_0 > 0$ if and only if

$$b_2 < 0 \qquad \text{or} \qquad b_1 < 0 \leq b_2 < \frac{b_1^2}{3}. \tag{C.1}$$

Under the assumption (C.1), h', given by

$$h'(z) = 3z^2 + 2b_1 z + b_2,$$

has two roots,

$$z_- = -\frac{1}{3}(b_1 + d) \quad \text{and} \quad z_+ = -\frac{1}{3}(b_1 - d)$$

with $z_- < z_+$ and $d = \sqrt{b_1^2 - 3b_2}$ (in fact $z_+ = z_0 > 0$). A simple computation gives

$$h(z_+) = \frac{2}{27}\left(b_1^3 - d^3\right) - \frac{b_1 b_2}{3} + b_3.$$

Noticing that

$$b_1^3 - d^3 = (b_1 - d)\left(2b_1^2 - 3b_2 + b_1 d\right) = -3z_+\left(b_1^2 + b_1 d + d^2\right),$$

we obtain

$$h(z_+) < 0 \quad \Leftrightarrow \quad \frac{2}{3} z_+\left(b_1^2 + b_1 d + d^2\right) + b_1 b_2 - 3b_3 > 0.$$

Moreover,

$$b_1^2 + b_1 d + d^2 = d^2 + b_1(b_1 + d) = d^2 - 3b_1 z_-.$$

So

$$h(z_+) < 0 \quad \Leftrightarrow \quad \frac{2}{3} d^2 z_+ - 2b_1 z_+ z_- + b_1 b_2 - 3b_3 > 0.$$

Since $z_+ z_- = b_2/3$, we eventually obtain

$$h(z_+) < 0 \quad \Leftrightarrow \quad 2d^2 z_+ + b_1 b_2 - 9b_3 > 0.$$

This ends the proof.

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