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AGE-STRUCTURED AND DELAY DIFFERENTIAL-DIFFERENCE MODEL OF HEMATOPOIETIC STEM CELL DYNAMICS

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Abstract. In this paper, we investigate a mathematical model of hematopoietic stem cell dynamics. We take two cell populations into account, quiescent and proliferating one, and we note the difference between dividing cells that enter directly to the quiescent phase and dividing cells that return to the proliferating phase to divide again. The resulting mathematical model is a system of two age-structured partial differential equations. By integrating this system over age and using the characteristics method, we reduce it to a delay differential-difference system, and we investigate the existence and stability of the steady states. We give sufficient conditions for boundedness and unboundedness properties for the solutions of this system. By constructing a Lyapunov function, the trivial steady state, describing cell's dying out, is proven to be globally asymptotically stable when it is the only equilibrium. The stability analysis of the unique positive steady state, the most biologically meaningful one, and the existence of a Hopf bifurcation allow the determination of a stability area, which is related to a delay-dependent characteristic equation. Numerical simulations illustrate our results on the asymptotic behavior of the steady states and show very rich dynamics of this model. This study may be helpful in understanding the uncontrolled proliferation of blood cells in some hematological disorders.

1. **Introduction.** The generation and regulation of blood cells (red cells, white cells and platelets) to maintain homeostasis (metabolic equilibrium) is called hematopoiesis. The different blood cells have a short life span of one day to several weeks. The hematopoiesis process must provide daily renewal with very high output (approximately $10^{11} - 10^{12}$ new blood cells are produced each day (see [16])). It is initiated in the bone morrow by a small population of cells called hematopoietic stem cells (HSCs), and controlled by a cascade of events, which have very complex

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features not all of which are completely clear. The HSCs have the unique ability to produce either cells engaged in a cell lineage (differentiation) or similar cells (self-renewal) to ensure their proliferative capacity (see [22]). Cell biologists (see [10]) classify HSCs as proliferating (cells in the cell cycle) and quiescent (cells withdrawn from the cell cycle and cannot divide). Quiescent cells are also called resting cells or G_0-cells. The vast majority of HSCs are in quiescent phase (see [10] and [22]). Provided they do not die, they eventually enter the proliferating phase. In the proliferating phase, if they do not die by apoptosis, the cells are committed to divide a certain time after their entrance in this phase. Then, they give birth to two daughter cells which, either enter directly into the quiescent phase (long-term proliferation) or return immediately to the proliferating phase (short-term proliferation) (see [12], [21] and [22]).

Due to the number of divisions and the quantity of cells involved in hematopoiesis, issues may arise at different cellular levels and sometimes result in disorders affecting blood cells. Among a wide variety of disorders affecting blood cells, myeloproliferative diseases are of great interest. They are characterized by a group of conditions that cause blood cells – red blood cells, white cells and platelets – to grow abnormally. They include chronic myelogenous leukemia, a cancer of white blood cells. In some cases, chronic myelogenous leukemia exhibits periodic oscillations in all blood cell counts (see [11]). Myeloproliferative disorders usually originate from the HSC compartment: an uncontrolled proliferation in the HSC compartment can perturb the entire system and leads to a quick proliferation, that invade the circulating blood.

Many authors have been interested in modeling the dynamics of HSCs. To our knowledge, the first mathematical model was proposed by Mackey in 1978, [17], and has been improved by many authors, including [1], [2], [3], [4], [5], [8], [9], [18] and [19]. In all these works, the authors assumed that after each division of HSCs, all daughter cells directly enter the quiescent phase. This hypothesis allows this phenomena to be modeled by a delay differential system (see for instance [1] and the references therein). The models mentioned above, cannot fully explain how high-output hematopoiesis is maintained, and how the uncontrolled proliferation of HSCs can perturb the entire system. In order to obtain a more realistic model, one has to take into account that there exists a fraction of HSCs that are always active in the cell cycle and they can induce a rapid production of blood cells (see [20]).

In this paper, based on the model of Mackey [17], we propose a more general system of HSC dynamics. As in [17], we take into account the fact that a cell cycle has two phases, that is, HSCs are either in a quiescent phase or actively proliferating. However, we do not suppose that after each division it is necessary for the two daughter cells to enter the quiescent phase. We suppose that only a fraction of daughter cells enter the quiescent phase (long-term proliferation) and the other fraction of cells return immediately to the proliferating phase to divide again (short-term proliferation) (see [20]). This assumption leads to a modification of Mackey's model, which cannot be reduced to a classical delay differential system. To our knowledge, this assumption has never been used in previous attempts to model hematopoiesis.

We obtain a system of two age-structured partial differential equations, describing the evolution of HSC population. By integrating it over the age variable and using the characteristics method, we reduce it to a coupled system of differential and difference equations. We focus our mathematical analysis on this delay differential-difference system. We show that the behavior of the system is related to both short and long proliferating terms. The model is relevant due to its ability to explain the maintenance of high level production of blood cells, and also explains how an uncontrolled proliferation of HSCs can lead either to an overproduction of blood cells, or instability of the production.

The paper is organized as follows. Section 2 is devoted to the presentation of the model. It is an age-structured system describing the dynamics of HSC population where cells can be either proliferating or quiescent. In Section 3, by using the characteristics method, we reduce this system to a coupled system of differential and difference equations. Then, we prove the existence and the positivity of solutions. In Section 4, we show the existence of steady states, a trivial one and a positive one. We then focus on properties of the system related to the boundedness and unboundedness of solutions. In Section 5, we prove the global asymptotic stability of the trivial steady state, by using a Lyapunov function. In Section 6, we linearize the system about its positive steady state and we deduce a delay-dependent characteristic equation. Then, we investigate the local asymptotic stability of this steady state, and we prove that it can be destabilized through a Hopf bifurcation that leads to the existence of periodic solutions. In Section 7, we numerically illustrate the asymptotic behavior results obtained in the previous sections. The numerical simulations allow us to identify the role of each parameter and its influence in stability switch of the positive steady state. A brief discussion is given in Section 8.

2. **Presentation of the model.**

Denote by $q(t,a)$ (respectively, $p(t,a)$) the population density of quiescent HSCs (respectively, proliferating HSCs) at time $t \geq 0$ and age $a \geq 0$. The age represents the time spent by a cell in one of the two phases quiescent or proliferating. Quiescent cells can either be lost randomly at a rate $\delta \geq 0$, which takes into account the cellular differentiation, or enter into the proliferating phase at a rate $\beta \geq 0$. A cell in the quiescent phase can stay its entire life, then its age a ranges from 0 to infinity. In the proliferating phase, cells stay a time $\tau \geq 0$, necessary to perform a series of process leading to division at mitosis. They can be lost by apoptosis (programmed cell death) at a rate $\gamma \geq 0$. At the end of proliferating phase (that is when cells have spent a time $a = \tau$), each cell divides in two daughter cells. A part ($K \in [0,1]$) of daughter cells returns immediately to the proliferating phase to go over a new cell cycle while the other part $(1-K)$ enters directly the resting phase. For a more clear understanding of the model, we give a schematic representation of this process in Figure 1. The dynamics of the HSC population (the cell densities $q(t,a)$ and $p(t,a)$) is described by the following system of age-structured partial differential equations

$$\begin{cases} \dfrac{\partial}{\partial t}q(t,a) + \dfrac{\partial}{\partial a}q(t,a) = -\left(\delta + \beta\left(Q(t)\right)\right)q(t,a), & a > 0, \ \ t > 0, \\ \dfrac{\partial}{\partial t}p(t,a) + \dfrac{\partial}{\partial a}p(t,a) = -\gamma p(t,a), & 0 < a < \tau, \ \ t > 0, \\ q(t,0) = 2(1-K)p(t,\tau), & t > 0, \\ p(t,0) = \beta(Q(t))Q(t) + 2Kp(t,\tau), & t > 0. \end{cases} \tag{1}$$

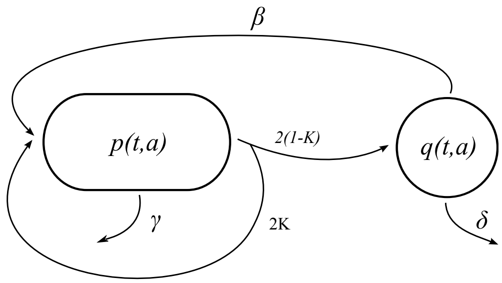

FIGURE 1. Schematic representation of the hematopoiesis process. We make a difference between dividing cells that enter immediately the quiescent phase (with a rate $1-K$) and dividing cells that return to the proliferating phase (with a rate K).

We assume that the introduction rate $\beta := \beta(Q(t))$ depends on the total population of quiescent cells (see [17]),

$$Q(t) = \int_0^{+\infty} q(t,a)\mathrm{d}a, \quad t \geq 0,$$

and it is a continuous, differentiable and strictly decreasing function with $\lim_{Q\to+\infty} \beta(Q) = 0$. Typically, β is a Hill function (see [17], [18] and [19]) given by

$$\beta(Q) = \frac{\beta_0 \theta^r}{\theta^r + Q^r}, \quad r > 1. \tag{2}$$

The coefficient $\beta_0 > 0$ is the maximum rate of reintroduction, θ is a threshold value for which β reaches half of its maximum β_0, and r is the so-called sensitivity of the introduction rate, it describes the reaction of β due to external stimuli, the action of a growth factor for example.

Parameters	Interpretation (units)	Values
δ	Resting cells mortality rate (day^{-1})	0.05
γ	Apoptosis rate (day^{-1})	0.2
β_0	Maximum introduction rate (day^{-1})	1.77
r	Sensitivity of the introduction rate (none)	5
θ	θ is such that $\beta(\theta) = \beta_0/2$ (cells.kg^{-1})	1.62×10^8
τ	Duration of proliferating phase (days)	1
K	Short proliferating rate (day^{-1})	$*$

TABLE 1. Model parameter values with their interpretation. All the parameter values come from the literature, except K which to our knowledge, has never been used in modeling hematopoiesis.

A table that contains the values of parameters used in [17], [18] and [19], is given in Table 1. In this paper, all fixed parameters are taken from this table. However, to verify some particular cases, some appropriate values of the parameters not corresponding to those in Table 1, are taken. The value of θ is usually $\theta = 1.62 \times 10^8$ cells.kg^{-1} (see [17]). However, here we explore the qualitative behavior of the HSC population, which can be normalized without loss of generality. Then, we put $\theta = 1$, and $Q(t)$, $u(t)$ and $P(t)$ are expressed in units of 1.62×10^8 cells.kg^{-1}.

In system (1), the first boundary condition describes the dividing cells that immediately enter the resting phase, and the second boundary condition describes both the flux of cells coming from the resting phase and the dividing cells that immediately return to the proliferating phase. The coefficient 2 represents the division. The model is completed with initial conditions, that are nonnegative L^1-functions,

$$\begin{cases} q(0,a) = q_0(a), & a > 0, \\ p(0,a) = p_0(a), & 0 < a < \tau, \end{cases}$$

and the following natural condition

$$\lim_{a \to +\infty} q(t,a) = 0, \quad t \geq 0.$$

3. **Reduction to a delay differential-difference system.** The age-structured partial differential system (1) can be reduced to a delay differential-difference system. The method of characteristics allows us to write

$$p(t,a) = \begin{cases} e^{-\gamma t} p(0, a-t) = e^{-\gamma t} p_0(a-t), & 0 \leq t \leq a, \\ e^{-\gamma a} p(t-a, 0), & t > a. \end{cases} \tag{3}$$

By integrating the system (1) over the age variable, we obtain, for $t > 0$

$$\begin{cases} Q'(t) &=& -\left(\delta + \beta\left(Q(t)\right)\right) Q(t) + \begin{cases} 2(1-K)e^{-\gamma\tau} u(t-\tau), & t > \tau, \\ 2(1-K)e^{-\gamma t} p_0(\tau - t), & t \leq \tau, \end{cases} \\ P'(t) &=& -\gamma P(t) + \beta\left(Q(t)\right) Q(t) - \begin{cases} (1-2K)e^{-\gamma\tau} u(t-\tau), & t > \tau, \\ (1-2K)e^{-\gamma t} p_0(\tau - t), & t \leq \tau, \end{cases} \\ u(t) &=& \beta(Q(t))Q(t) + \begin{cases} 2Ke^{-\gamma\tau} u(t-\tau), & t > \tau, \\ 2Ke^{-\gamma t} p_0(\tau - t), & t \leq \tau, \end{cases} \end{cases} \tag{4}$$

where $u(t) = p(t,0)$ is the density of new proliferating cells and $P(t) = \int_0^\tau p(t,a)\mathrm{d}a$ is the total population of proliferating cells. The initial conditions for (4) are

$$Q(0) = Q_0 := \int_0^{+\infty} q_0(a)\mathrm{d}a \quad \text{and} \quad P(0) = P_0 := \int_0^\tau p_0(a)\mathrm{d}a.$$

Note that, the function $u(t) = p(t,0)$ is defined for $t \geq 0$. To write the system (4) in a convenient form, we put

$$u(t) = \phi(t) := e^{-\gamma t} p_0(-t), \quad \text{for } -\tau \leq t \leq 0. \tag{5}$$

Therefore, (4) can be written, for $t > 0$

$$\begin{cases} Q'(t) &=& -\left(\delta + \beta\left(Q(t)\right)\right) Q(t) + 2(1-K)e^{-\gamma\tau} u(t-\tau), \\ P'(t) &=& -\gamma P(t) + \beta\left(Q(t)\right) Q(t) - (1-2K)e^{-\gamma\tau} u(t-\tau), \\ u(t) &=& \beta(Q(t))Q(t) + 2Ke^{-\gamma\tau} u(t-\tau), \end{cases} \tag{6}$$

with initial conditions

$$Q(0) = Q_0, \ P(0) = P_0 \ \text{ and } \ u(t) = \phi(t) \text{ for } t \in [-\tau, 0].$$

Thanks to (3) and (5), we have

$$P(t) = \int_0^\tau e^{-\gamma a} u(t-a)\mathrm{d}a.$$

Then, the asymptotic behavior of P is related to u and since the first and the third equation of (6) do not depend on P, we will focus on the study of the system

$$\begin{cases} Q'(t) = -\left(\delta + \beta\left(Q(t)\right)\right) Q(t) + 2(1-K)e^{-\gamma\tau}u(t-\tau), & t > 0, \\ u(t) = \beta(Q(t))Q(t) + 2Ke^{-\gamma\tau}u(t-\tau), & t > 0, \end{cases} \tag{7}$$

with initial conditions

$$Q(0) = Q_0, \text{ and } u(t) = \phi(t) \text{ for } t \in [-\tau, 0]. \tag{8}$$

For the sake of simplicity, we assume that the initial condition p_0 of the age-structured system (1) is continuous on $[0, \tau]$. Thereby, the initial conditions (8) of the system (7) are such that $\phi \in C([-\tau, 0], \mathbb{R})$.

Let us observe that, by the method of steps we can solve the system (7) in each interval $[k\tau, (k+1)\tau]$, for $k = 0, 1, 2 \dots$. Thus, we can check the existence and uniqueness of a piecewise function (Q, u) solution of (7). Moreover, the function Q is continuous for $t \geq 0$. Q has a continuous first derivative for all $t > 0$ and the function u is continuous for all $t \geq -\tau$ if and only if the initial condition $(Q_0, \phi) \in \mathbb{R} \times C([-\tau, 0], \mathbb{R})$ satisfies the compatibility condition

$$\phi(0) = \beta(Q_0)Q_0 + 2Ke^{-\gamma\tau}\phi(-\tau). \tag{9}$$

The following proposition deals with the nonnegativity of solutions of system (7).

Proposition 1. *All solutions of system (7) with initial conditions $(Q_0, \phi) \in \mathbb{R}^+ \times C([-\tau, 0], \mathbb{R}^+)$ are nonnegative.*

Proof. Let $(Q(t), u(t))$ be a solution of (7). We prove the nonnegativity on the interval $[0, \tau]$, and we apply the same reasoning by steps on each interval $[k\tau, (k+1)\tau]$, for $k = 1, 2 \dots$. Indeed, we suppose by contradiction that there exists $s \in [0, \tau]$ and $\epsilon > 0$ such that $Q(t) > 0$ for $t < s$, $Q(s) = 0$ and $Q(t) < 0$ for $t \in (s, s + \epsilon)$. Since $s - \tau \in [-\tau, 0]$, we have $u(s - \tau) = \phi(s - \tau) > 0$ and

$$\begin{cases} Q'(s) = 2(1-K)e^{-\gamma\tau}\phi(s-\tau), \\ u(s) = 2Ke^{-\gamma\tau}\phi(s-\tau). \end{cases}$$

This yields $Q'(s) > 0$ and $u(s) > 0$, which give a contradiction. The result is that, both functions Q and u are non-negative on $[0, \tau]$. Hence, by steps Q and u are non-negative on $[0, +\infty)$. □

We assume throughout this paper that $(Q_0, \phi) \in \mathbb{R}^+ \times C([-\tau, 0], \mathbb{R}^+)$, the parameters δ, β_0, γ, τ, with $\beta_0 := \beta(0)$, are nonnegative and $0 \leq K \leq 1$.

Many authors (see [6], [9], [10], [11] and the references therein), stressed the influence of the cell cycle duration τ, playing an important role in the appearance of periodic oscillations, characterizing many hematological disorders. The short-term proliferation represented by the parameter K, plays also (as it was explained in Sections 1 and 2), an important role in the hematopoiesis process (see [20], [21] and [22]). Then, among all the parameters, we consider the asymptotic behavior of steady states based on the (τ, K)-plane (see Figure 2). In the next section, we investigate the existence of steady states of system (7), and we give some properties related to boundedness and unboundedness of solutions.

4. **Existence of steady states and properties.** Let $(\overline{Q},\overline{u})$ be a steady state of (7). It satisfies

$$\left\{\begin{array}{lcl} \left(\delta+\beta\left(\overline{Q}\right)\right)\overline{Q} &=& 2(1-K)e^{-\gamma\tau}\overline{u}, \\ \left(1-2Ke^{-\gamma\tau}\right)\overline{u} &=& \beta(\overline{Q})\overline{Q}. \end{array}\right. \tag{10}$$

The steady state $\overline{P}$ related to the proliferating population $P(t)$ is given in terms of $\overline{u}$ by

$$\overline{P}=\left\{\begin{array}{ll} \tau\overline{u}, & \text{if } \gamma=0, \\ \dfrac{1}{\gamma}\left(1-e^{-\gamma\tau}\right)\overline{u}, & \text{if } \gamma>0. \end{array}\right.$$

One can note that $(0,0)$ is always a steady state of (7), describing the cell population's dying out. We will refer to this steady state as the trivial one.

The function β is strictly decreasing on $[0,+\infty)$ with $\lim_{Q\to+\infty}\beta(Q)=0$. Therefore, from (10), a nontrivial steady state $(\overline{Q},\overline{u})$, with $\overline{Q}\neq 0$, $\overline{u}\neq 0$, is given by

$$(\overline{Q},\overline{u})=\left(\beta^{-1}\left(\delta\left(\frac{1-2Ke^{-\gamma\tau}}{2e^{-\gamma\tau}-1}\right)\right),\frac{\delta}{2e^{-\gamma\tau}-1}\beta^{-1}\left(\delta\left(\frac{1-2Ke^{-\gamma\tau}}{2e^{-\gamma\tau}-1}\right)\right)\right). \tag{11}$$

The existence of positive steady state $(\overline{Q},\overline{u})$ depends on the parameters τ, K, γ and $\mu=\beta_0/\delta$ (see Proposition 2). To determine in (τ,K)-plane, the zone of existence of steady states, we define for $\gamma>0$, the following thresholds for the parameter τ

$$\tau_\mu=\left\{\begin{array}{ll} \dfrac{1}{\gamma}\ln\left(\dfrac{2\mu}{1+\mu}\right), & \mu>1, \\ 0, & 0\le\mu\le 1, \end{array}\right. \qquad \tau_\infty=\frac{1}{\gamma}\ln(2),$$

and, for $\gamma=0$

$$\tau_\mu=\left\{\begin{array}{ll} +\infty, & \mu>1, \\ 0, & 0\le\mu\le 1, \end{array}\right. \qquad \tau_\infty=+\infty.$$

In particular, for $\mu=0$, which corresponds to the case $\beta_0=0$ and $\delta>0$, we have $\tau_0=0$. The notation $\mu=\infty$ corresponds to the case $\delta=0$ and $\beta_0>0$.
The special case $\delta=\beta_0=0$ can be treated directly, and will not be considered here.

To introduce thresholds for the parameter K, we consider the function $K_\mu\colon[0,+\infty)\to[0,1]$, defined by

$$K_\mu(\tau)=\left\{\begin{array}{ll} 0, & \tau<\tau_\mu, \\ (1+\mu)\,K_0(\tau)-\mu, & \tau\ge\tau_\mu, \end{array}\right.$$

and in particular the functions, for $\mu=0$ and $\mu=\infty$,

$$\begin{array}{rcl} K_0\colon[0,+\infty) & \to & [0,1], \\ \tau & \mapsto & K_0(\tau)=\left\{\begin{array}{ll} \dfrac{1}{2}e^{\gamma\tau}, & \tau<\tau_\infty, \\ 1, & \tau\ge\tau_\infty, \end{array}\right. \end{array}$$

and

$$\begin{array}{rcl} K_\infty\colon[0,+\infty) & \to & [0,1], \\ \tau & \mapsto & K_\infty(\tau)=\left\{\begin{array}{ll} 0, & \tau<\tau_\infty, \\ 1, & \tau\ge\tau_\infty. \end{array}\right. \end{array}$$

The functions $K_\mu(\tau)$ and $K_0(\tau)$ are represented in Figure 2, for $\mu>1$ and $0<\mu<1$.

The next proposition deals with the existence and uniqueness of steady states.

Proposition 2. *Assume that*

$$\left\{\begin{array}{l} K_\mu(\tau)<K<K_0(\tau), \\ \tau_\mu\le\tau<\tau_\infty, \end{array}\right. \quad \textit{or} \quad \left\{\begin{array}{l} 0\le K<K_0(\tau), \\ 0\le\tau<\tau_\mu. \end{array}\right. \tag{12}$$

Then, the system (7) *has two distinct finite steady states:* $(0,0)$ *and* $(\overline{Q},\overline{u})$ *given explicitly by* (11). *If* (12) *does not hold, then* $(0,0)$ *is the only finite steady state of the system* (7).

Proof. First, it is clear that $(0,0)$ is always a steady state.
Second, from the second equation of (10), we deduce that

$$\overline{u} = \frac{K_0(\tau)}{K_0(\tau)-K}\beta(\overline{Q})\overline{Q}, \quad \text{for} \quad 0 \leq K < K_0(\tau).$$

We substitute $\overline{u}$ in the first equation of (10) and we get

$$\left(\left(\frac{1-K_0(\tau)}{K_0(\tau)-K}\right)\beta(\overline{Q})-\delta\right)\overline{Q}=0, \quad \text{for} \quad 0 \leq K < K_0(\tau).$$

β is a decreasing function and satisfies $\lim_{Q\to+\infty}\beta(Q)=0$. Then, the existence of a finite positive steady state is equivalent to

$$0 \leq K < K_0(\tau) \quad \text{and} \quad K > (\mu+1)K_0(\tau)-\mu.$$

This means that, the existence and uniqueness of positive steady state is equivalent to (12). □

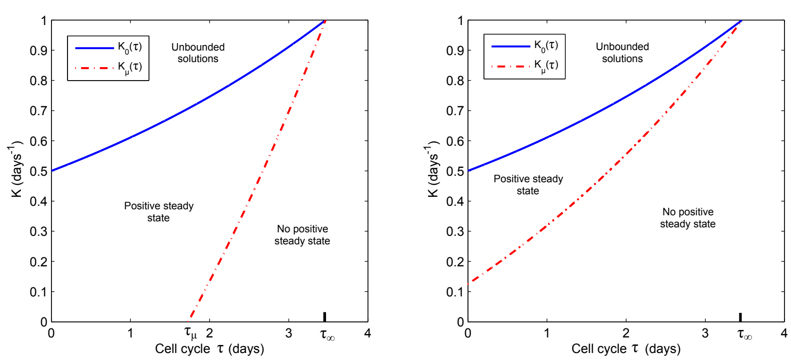

FIGURE 2. $K_0(\tau)$ and $K_\mu(\tau)$ are plotted to show in the $(\tau,\, K)$-plane the region of existence of steady states of system (7). Fixed parameter is $\gamma = 0.2$ day^{-1}. Left: $\mu = 2.40$. Right: $\mu = 0.75$. The zone of existence of finite positive steady state is between the dashed curve $K_\mu(\tau)$ and the solid curve $K_0(\tau)$. Outside this area, the positive steady state does not exist. The zone of unbounded solutions is above the curve $K_0(\tau)$. That is the zone of existence of infinite steady state. The intersection of $K_\mu(\tau)$ with the τ-axis, for $\mu > 1$, is $\frac{1}{\gamma}\ln\left(\frac{2\mu}{\mu+1}\right)$, and with the K-axis, for $0<\mu<1$, is $\frac{1}{2}(1-\mu)$.

Remark 1. 1. If $\gamma = 0$, the conditions (12) are independent of τ and become

$$\begin{cases} \frac{1}{2}(1-\mu) < K < \frac{1}{2}, \\ 0 \leq \mu \leq 1, \end{cases} \qquad \text{or} \qquad \begin{cases} 0 \leq K < \frac{1}{2}, \\ \mu > 1. \end{cases}$$

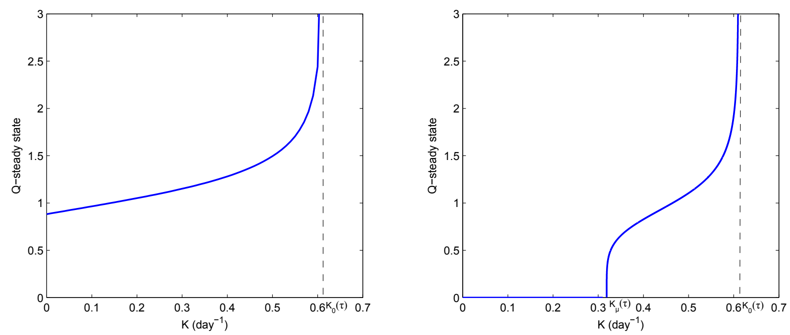

FIGURE 3. The function $K \mapsto \overline{Q}(K)$ is plotted to show the monotonicity of the steady state $\overline{Q}$ in terms of the parameter K. Fixed parameters are $r = 5$, $\theta = 1$, $\gamma = 0.2$ day^{-1} and $\tau = 1$ day. Left: $\mu = 2.40$. Right: $\mu = 0.75$.

2. Let $\delta > 0$, $\beta_0 > 0$, $\gamma \geq 0$ and $0 \leq \tau < \tau_\infty$. Then, $\lim\limits_{K \to K_0(\tau)} \overline{Q} = \lim\limits_{K \to K_0(\tau)} \overline{u} = +\infty$. In fact, if $K \geq K_0(\tau)$ system (7) has an infinite steady state.
3. If $\delta = 0$ the trivial equilibrium is the only finite steady state. Moreover, for $0 \leq \tau < \tau_\infty$, system (7) has an infinite equilibrium.
4. The positive steady state $\overline{Q}$ is a decreasing function with respect to δ, γ, τ, and an increasing function with respect to β_0, μ, K.

We now study the boundedness and unboundedness of solutions of system (7). First, we consider the case $\delta > 0$. The particular case $\delta = 0$ is treated in the next proposition.

Proposition 3. *1. Assume that $\delta > 0$, $\tau \geq \tau_\mu$ and $0 \leq K \leq K_\mu(\tau)$. Then, all solutions of system (7) are bounded.*

2. Assume that $K > K_0(\tau)$. Then, all nontrivial solutions of system (7) are unbounded.

Proof. Let $(Q(t), u(t))$ be a solution of (7) with initial condition $(Q_0, \phi) \in \mathbb{R}^+ \times C([-\tau, 0], \mathbb{R}^+)$.

Consider the function defined by

$$W(t) = Q(t) + \rho(\tau) \int_{t-\tau}^{t} u(\theta) \mathrm{d}\theta, \quad t > 0,$$

where

$$\rho(\tau) = \frac{1 - K}{K_0(\tau) - K} \quad \text{and} \quad 0 \leq K < K_0(\tau). \tag{13}$$

By differentiating the function W on $(0,+\infty)$, and using (7) we obtain

$$\begin{aligned}
W'(t) &= Q'(t)+\rho(\tau)[u(t)-u(t-\tau)],\\
&= -(\delta+\beta(Q(t)))Q(t)+2(1-K)e^{-\gamma\tau}u(t-\tau)+\rho(\tau)\beta(Q(t))Q(t)\\
&\quad +2K\rho(\tau)e^{-\gamma\tau}u(t-\tau)-\rho(\tau)u(t-\tau),\\
&= -\left(\delta+\beta(Q(t))-\rho(\tau)\beta(Q(t))\right)Q(t)\\
&\quad +u(t-\tau)[2(1-K)e^{-\gamma\tau}+2K\rho(\tau)e^{-\gamma\tau}-\rho(\tau)],\\
&= -\left[\delta-\left(\rho(\tau)-1\right)\beta(Q(t))\right]Q(t),\\
&= -\left[\delta-\left(\frac{1-K_0(\tau)}{K_0(\tau)-K}\right)\beta(Q(t))\right]Q(t),\\
&= -\chi(Q(t))Q(t),
\end{aligned}$$

with

$$\chi(Q)=\delta-\left(\frac{1-K_0(\tau)}{K_0(\tau)-K}\right)\beta(Q), \quad \text{for} \quad Q\geq 0.$$

Since β is decreasing and $0\leq K<K_0(\tau)\leq 1$, it follows that χ is an increasing function and

$$\chi(0)=\frac{\delta}{K_0(\tau)-K}\left[(\mu+1)\,K_0(\tau)-\mu-K\right]$$

is nonnegative for $\tau\geq\tau_\mu$ and $0\leq K\leq K_\mu(\tau)$. Consequently, $W'(t)\leq 0$. Then $W(t)\leq W(0)$. This leads to the boundedness of the function $Q(t)$ on $[0,+\infty)$. Furthermore, thanks to [14], Theorem 3.5 - page 275, there exist constants $C>0$ and $\alpha>0$ such that

$$|u(t)|\leq C\left[\|\phi\|e^{-\alpha t}+\beta_0\sup_{0\leq s\leq t}|Q(s)|\right], \quad t>0,$$

where $\|\phi\|=\sup_{-\tau\leq\theta\leq 0}|\phi(\theta)|$. As a consequence, we conclude that u is also bounded on $[0,+\infty)$.

Now, we will prove the unboundedness of the solutions $(Q(t),u(t))$ of system (7) for $K>K_0(\tau)$. In the first place, let us focus on the component $u(t)$. Let $t>0$. Consider the integer part $n=\lfloor\frac{t}{\tau}\rfloor$ of $\frac{t}{\tau}$. Then, $-\tau\leq t-(n+1)\tau<0$. Thanks to the expression of $u(t)$ in (7), we obtain

$$\begin{aligned}
u(t) &> 2Ke^{-\gamma\tau}u(t-\tau)\geq(2Ke^{-\gamma\tau})^{n+1}u\left(t-(n+1)\tau\right),\\
&\geq (2Ke^{-\gamma\tau})^{n+1}\inf_{-\tau\leq\theta\leq 0}(\phi(\theta)),\\
&\geq \left(\frac{K}{K_0(\tau)}\right)^{n+1}\inf_{-\tau\leq\theta\leq 0}(\phi(\theta)).
\end{aligned}$$

By using the hypothesis $\frac{K}{K_0(\tau)}>1$, we have $\lim_{t\to+\infty}u(t)=+\infty$.

In the second place, let us prove that $Q(t)$ is unbounded. Assume by contradiction that $Q(t)$ is bounded. Then, the first equation of system (7) implies that $\lim_{t\to+\infty}Q'(t)=+\infty$. This means that $Q(t)$ is an increasing function on an interval $[t_0,+\infty)$. Consequently, $\lim_{t\to+\infty}Q(t)=+\infty$ which is a contradiction with our hypothesis. We conclude that $Q(t)$ is also unbounded. □

Let $\delta > 0$. When $K = 0$ (Mackey's model [17]), all nontrivial solutions are bounded. But, in our model when K approaches $K_0(\tau)$ the positive equilibrium (then, the solutions of (7)) approaches the infinity. So, contrary to Mackey's model, the introduction of the parameter K can explain the maintenance of high level of production of blood cells.

We now consider the particular case $\delta = 0$. Recall that in that case, the trivial equilibrium is the only finite steady state and $\lim_{\delta\to 0} \overline{Q} = +\infty$. Note that assertion 2 of proposition 3 is still valid for $\delta = 0$. Remark also that, for all $\tau \geq 0$, $1 - K_0(\tau) \leq K_0(\tau)$. The goal of the next proposition is to prove the existence of unbounded solutions for $0 < K < 1 - K_0(\tau)$.

Proposition 4. *Assume that $\delta = 0$ and $0 < K < 1 - K_0(\tau)$. Let (Q, u) be a solution of (7). Suppose that there exists $\overline{x} \geq 0$ such that the function $\beta(x)x$ is decreasing for $x \geq \overline{x}$. If there exists $\overline{t} \geq 0$ such that $Q(\overline{t}) > \overline{x}$ and Q is increasing on $[\overline{t}, \overline{t} + \tau]$. Then, Q is increasing for all $t \geq \overline{t}$ and $\lim_{t\to+\infty} Q(t) = +\infty$.*

Proof. We have $Q(\overline{t} + \tau) \geq Q(\overline{t}) > \overline{x}$. It follows that $\beta(Q(\overline{t} + \tau))Q(\overline{t} + \tau) \leq \beta(Q(\overline{t}))Q(\overline{t})$. Then

$$\begin{aligned}
Q'(\overline{t}+\tau) &= -\beta(Q(\overline{t}+\tau))Q(\overline{t}+\tau) + 2(1-K)e^{-\gamma\tau}u(\overline{t}),\\
&= -\beta(Q(\overline{t}+\tau))Q(\overline{t}+\tau) + 2(1-K)e^{-\gamma\tau}\beta(Q(\overline{t}))Q(\overline{t})\\
&\quad +4K(1-K)e^{-2\gamma\tau}u(\overline{t}-\tau),\\
&\geq \beta(Q(\overline{t}+\tau))Q(\overline{t}+\tau)\left(\frac{1-K-K_0(\tau)}{K_0(\tau)}\right),\\
&> 0.
\end{aligned}$$

Hence Q is increasing on $[\overline{t}, \overline{t}+\tau+\varepsilon]$ for some $\varepsilon > 0$. We repeat the same reasoning, we get $Q'(\overline{t} + \tau + \varepsilon) \geq 0$. Then, we obtain that Q is increasing on $[\overline{t}, +\infty)$.
We now show that $\lim_{t\to+\infty} Q(t) = +\infty$. Suppose by contradiction that Q is bounded. Hence, the limit $L = \lim_{t\to+\infty} Q(t)$ exists. Then, we obtain from (7) that $\beta(L)L(1 - 2e^{-\gamma\tau}) = 0$. Consequently, $L = 0$. This leads to a contradiction. □

The condition $K < 1 - K_0(\tau)$ in proposition 4 is in fact equivalent to $2(1 - K)e^{-\gamma\tau} > 1$, and the coefficient $2(1-K)e^{-\gamma\tau}$ is the proportion of proliferating cells entering the resting phase. So, it is no surprise that $\lim_{t\to+\infty} Q(t) = +\infty$.

Now, we consider the existence of the solutions mentioned in the previous proposition.

Corollary 1. *Assume that $\delta = 0$ and $0 < K < 1 - K_0(\tau)$. Let $\overline{x}$ be as defined in proposition 4 and consider $v \in \mathbb{R}^+ \setminus \{0\}$ such that $v \geq \overline{x}$. We take the following initial condition for system (1)*

$$\begin{cases}
q_0(a) = exp\left(-\dfrac{a}{v}\right), & a \geq 0,\\
p_0(a) = \dfrac{1}{1-2K}\beta(v)v, & 0 \leq a \leq \tau.
\end{cases}$$

Then, the solution Q of (7) is an increasing function for all $t \geq 0$ and $\lim_{t\to+\infty} Q(t) = +\infty$.

Proof. Remark that $0 \leq 1 - K_0(\tau) < \dfrac{1}{2}$. Then, the function p_0 is well defined for $K < 1 - K_0(\tau)$. Moreover, the initial condition $(Q_0, \phi) \in \mathbb{R}^+ \times C([-\tau, 0], \mathbb{R}^+)$ of

(7) is given, for $t \in [-\tau, 0]$, by

$$Q_0 = \int_0^{+\infty} exp\left(-\frac{a}{v}\right) da = v \quad \text{and} \quad \phi(t) = e^{-\gamma t} p_0(-t) = \frac{1}{1-2K}\beta(v) v e^{-\gamma t}.$$

It satisfies the compatibility condition (9). On the interval $[0, \tau]$, the first equation of system (7) becomes

$$\begin{aligned} Q'(t) &= -\beta\left(Q(t)\right) Q(t) + 2(1-K) e^{-\gamma\tau} \phi(t-\tau), \\ &= -\beta\left(Q(t)\right) Q(t) + \frac{2(1-K)}{1-2K}\beta(v) v e^{-\gamma t}. \end{aligned}$$

Then,

$$\begin{aligned} Q'(0) &= -\beta(v) v + \frac{2(1-K)}{1-2K}\beta(v) v, \\ &= \frac{1}{1-2K}\beta(v) v > 0. \end{aligned}$$

So, there exists $\varepsilon \in (0, \tau]$ such that Q is an increasing function on $[0, \varepsilon]$ and $Q(\varepsilon) > Q(0) = v \geq \overline{x}$. With the same manner, we prove that $Q'(\varepsilon) \geq 0$. Repeating this argument, we get an increasing function on the interval $[0, \tau]$. By direct application of the previous proposition, the results hold. □

Remark 2. One can notice that if β is given by the Hill function (2) with $r > 1$, the function $Q \mapsto \beta(Q)Q$ is decreasing on $[\overline{x}, +\infty)$, with

$$\overline{x} := \frac{\theta}{(r-1)^{1/r}}.$$

In Figure 4, we represent a Hill function $Q \mapsto \beta(Q)$ and the function $Q \mapsto \beta(Q)Q$.

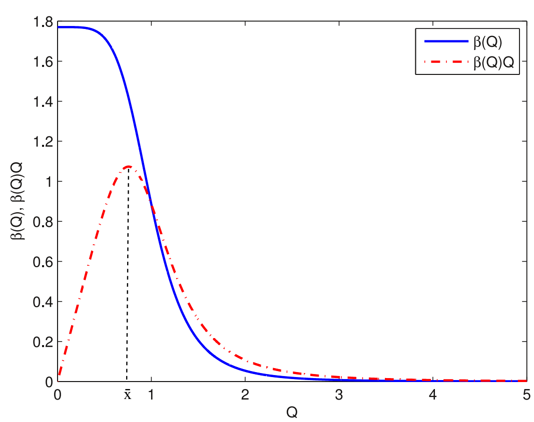

FIGURE 4. A Hill function $Q \mapsto \beta(Q)$ and the function $Q \mapsto \beta(Q)Q$ are plotted with the parameters $r = 5$, $\theta = 1$ and $\beta_0 = 1.77$ day^{-1}.

5. **Global asymptotic stability of the trivial steady state.** In this section, we deal with the asymptotic stability of the trivial steady state of system (7): we show that it is globally asymptotically stable when it is the only steady state. Recall that the differential-difference system (7) can be written, for $t > 0$, in the following form

$$\left\{\begin{array}{lcl} Q'(t) & = & f\left(Q(t), u_t\right), \\ u(t) & = & g\left(Q(t), u_t\right), \end{array}\right. \tag{14}$$

with initial condition $Q(0) = Q_0 \in \mathbb{R}^+$ and $u_0 = \phi \in C([-\tau, 0], \mathbb{R}^+)$. For every $t \geq 0$ and every continuous function $u\colon [-\tau, +\infty) \to \mathbb{R}^+$, the function $u_t \in C([-\tau, 0], \mathbb{R}^+)$ is defined by

$$u_t(\theta) = u(t+\theta), \quad \text{for } \ \theta \in [-\tau, 0].$$

The functions $f, g\colon \mathbb{R}^+ \times C([-\tau, 0], \mathbb{R}^+) \to \mathbb{R}^+$ are defined, for $(Q_0, \psi) \in \mathbb{R}^+ \times C([-\tau, 0], \mathbb{R}^+)$, by

$$\left\{\begin{array}{lcl} f(Q_0, \psi) & = & -\left(\delta + \beta\left(Q_0\right)\right) Q_0 + 2(1-K)e^{-\gamma\tau}\psi(-\tau), \\ g(Q_0, \psi) & = & \beta(Q_0)Q_0 + 2Ke^{-\gamma\tau}\psi(-\tau). \end{array}\right.$$

The idea is to use a Lyapunov type method to prove the global asymptotic stability of the trivial steady state of system (7).

Definition 5.1. The system (7) (or (14)) is said to be input-to-state stable if there exist two continuous functions $\eta\colon \mathbb{R}^+ \times \mathbb{R}^+ \to \mathbb{R}^+$, $(\nu, t) \mapsto \eta(\nu, t)$ and $\kappa\colon \mathbb{R}^+ \to \mathbb{R}^+$, $\nu \mapsto \kappa(\nu)$ such that

1. η is strictly increasing with respect to ν, strictly decreasing with respect to t, and satisfies $\eta(0, t) = 0$, for all $t \geq 0$, and $\lim\limits_{t \to +\infty} \eta(\nu, t) = 0$, for all $\nu \geq 0$,
2. κ is strictly increasing and $\kappa(0) = 0$,

the solutions (Q, u) of (7) (or (14)) with initial conditions $u_0 = \phi \in C([-\tau, 0], \mathbb{R}^+)$ satisfy

$$|u(t)| \leq \eta(\|\phi\|, t) + \kappa(\|Q_{[0,t]}\|), \quad \text{for } \ t \geq 0, \tag{15}$$

where $Q_{[0,t]}$ is the restriction of the function Q to the interval $[0, t]$ and $\|.\|$ is the supremum norm of continuous functions.

The inequality (15) plays an essential role in studying the stability of the component u of solutions (Q, u) of (7). By the last definition, we give a Lyapunov-type result for (7).

Theorem 5.2. *Suppose that the system (7) is input-to-state stable, and* $v, \vartheta, w\colon \mathbb{R}^+ \to \mathbb{R}^+$ *are continuous nondecreasing functions,* $v(s)$, $\vartheta(s)$, $w(s) > 0$, *for* $s > 0$, $v(0) = \vartheta(0) = 0$, *and* $\lim\limits_{s \to +\infty} v(s) = +\infty$. *If there is a continuous function* $V\colon \mathbb{R}^+ \times C([-\tau, 0], \mathbb{R}^+) \to \mathbb{R}^+$ *such that*

$$\left\{\begin{array}{l} v(Q_0) \leq V(Q_0, \psi) \leq \vartheta\left(\|(Q_0, \psi)\|\right), \\ \dot{V}(Q_0, \psi) \leq -w(Q_0), \end{array}\right.$$

where

$$\dot{V}(Q_0, \psi) = \limsup_{h \to 0^+} \frac{1}{h}\left[V\left(Q(h), u_h\right) - V(Q_0, \psi)\right],$$

and $(Q(t), u(t))$ *is the solution of system (7) through* (Q_0, ψ), *then the trivial steady state of (7) is globally asymptotically stable.*

Proof. The proof of this theorem can be found in [13]. □

We use this fundamental theorem to prove the global asymptotic stability of the trivial steady state of (7).

Lemma 5.3. *If $0 \leq K < K_0(\tau)$ then, the system (7) is input-to-state stable. More precisely, there exist constants $C > 0$ and $\alpha > 0$ such that the solution (Q, u) of (7) satisfies*

$$|u(t)| \leq C \left[\|\phi\| e^{-\alpha t} + \beta_0 \sup_{0 \leq s \leq t} |Q(s)| \right],$$

where ϕ is the initial condition for u on the interval $[-\tau, 0]$.

Proof. This is an immediate consequence of (see [14], theorem 3.5 - page 275). □

Remark 3. Consider the linear homogeneous difference equation

$$D(u_t) = 0, \tag{16}$$

where the operator $D\colon C([-\tau, 0], \mathbb{R}^+) \to \mathbb{R}^+$ is defined by $D(\psi) = \psi(0) - 2Ke^{-\gamma\tau}\psi(-\tau)$. Then, the condition

$$0 \leq K < K_0(\tau)$$

is equivalent to say that the zero solution of (16) is globally asymptotically stable (see [14]).

Suppose that $\delta > 0$. The following theorem gives a necessary and sufficient condition for the trivial steady state of (7) to be globally asymptotically stable.

Theorem 5.4. 1. *Assume that*

$$\tau \geq \tau_\mu \quad \text{and} \quad 0 \leq K < K_\mu(\tau). \tag{17}$$

Then, the trivial steady state of system (7) is globally asymptotically stable.

2. *Assume that*

$$\tau \geq \tau_\mu \ \text{ and } \ K > K_\mu(\tau), \quad \text{or} \quad \tau < \tau_\mu. \tag{18}$$

Then, the trivial steady state of system (7) is unstable.

Proof. Assume that (17) holds true. Thanks to $K_\mu(\tau) \leq K_0(\tau)$ and lemma 5.3, system (7) is input-to-state stable. On the other hand, consider the following continuous function

$$\begin{array}{rcl} V \colon \mathbb{R}^+ \times C([-\tau, 0], \mathbb{R}^+) & \to & \mathbb{R}^+, \\ (Q_0, \psi) & \mapsto & V(Q_0, \psi), \end{array}$$

defined by

$$V(Q_0, \psi) = Q_0 + \rho(\tau) \int_{-\tau}^{0} \psi(\theta) \mathrm{d}\theta,$$

where $\rho(\tau)$ is given by (13). Remark that V is the same function as that used in the proof of proposition 3. It is not difficult to see that

$$Q_0 \leq V(Q_0, \psi) \leq 2 \max\{1, \tau\rho(\tau)\} \max\{Q_0, \|\psi\|\}.$$

Furthermore, by differentiating the function $t \mapsto V(Q(t), u_t)$ along the solution (Q, u) of system (7), we obtain

$$\frac{d}{dt} V(Q(t), u_t) = -\left(\delta - \frac{1 - K_0(\tau)}{K_0(\tau) - K} \beta(Q(t)) \right) Q(t) = -\chi(Q(t)) Q(t), \quad t > 0,$$

with

$$\chi(Q) = \delta - \frac{1 - K_0(\tau)}{K_0(\tau) - K} \beta(Q), \quad \text{for } Q \geq 0.$$

Remember that, for $0 \leq K < K_0(\tau)$ the function χ is strictly increasing and

$$\chi(0) = \frac{\delta}{K_0(\tau) - K}\left[(1+\mu)K_0(\tau) - \mu - K\right].$$

Moreover, (17) is equivalent to $\chi(0) > 0$. Consequently,

$$\frac{d}{dt}V(Q(t), u_t) \leq -\chi(0)Q(t) = -w(Q(t)), \quad t > 0.$$

Then, we conclude by theorem 5.2 that the trivial steady state is globally asymptotically stable.

We now study the instability of the trivial steady state. The linearization of system (7) around the trivial steady state leads to the characteristic equation

$$\Delta_0(\lambda) \coloneqq \lambda + \delta + \beta_0 - 2\left(K\lambda + K\delta + \beta_0\right)e^{-(\lambda+\gamma)\tau} = 0. \tag{19}$$

The details for the linearization of system (7) around a steady state and the condition for the local asymptotic stability are given in Section 6. Recall that the trivial steady state of system (7) is locally asymptotically stable if all roots of (19) have negative real parts, and it is unstable if roots of (19) with positive real parts exist. We consider Δ_0 as a real function. Then,

$$\lim_{\lambda\to+\infty}\Delta_0(\lambda) = +\infty \quad \text{and} \quad \Delta_0(0) = \delta + \beta_0 - 2(K\delta + \beta_0)e^{-\gamma\tau}.$$

One can note that

$$\Delta_0(0) = 2e^{-\gamma\tau}\delta\left[(1+\mu)K_0(\tau) - \mu - K\right].$$

Then, $\Delta_0(0) < 0$ if and only if (18) holds true. Furthermore, $\Delta_0(0) < 0$ implies that the equation $\Delta_0(\lambda) = 0$ has a positive root. Consequently, condition (18) leads to the instability of the trivial steady state. □

Remark 4.
1. If $\gamma = 0$, then (17) is equivalent to $K < \frac{1}{2}(1-\mu)$, and (18) is equivalent to $K > \frac{1}{2}(1-\mu)$.
2. Assume that $\delta = 0$. If $\tau > \tau_\infty$ the trivial steady state is globally asymptotically stable, and if $\tau < \tau_\infty$ it is unstable.

The assumption (17) of theorem 5.4 is satisfied when δ, γ (the mortality rates) or τ (the duration of the cell division) are large, or when β_0 or K (the reintroduction rates into the proliferating phase) are small. Biologically, this condition corresponds to a population which cannot survive, because the mortality rates are too large, the cell cycle duration is too long or, simply, because not enough cells are introduced in the proliferating phase and, then, the population renewal is not supplied.

6. **Local asymptotic stability of the positive steady state.**

The purpose of this section is to study the local asymptotic stability of the positive steady state $(\overline{Q}, \overline{u})$. We treat the delayed differential-difference system (7) as a special case of neutral differential system. Then, we get the following system

$$\begin{cases} Q'(t) = -\left(\delta + \beta\left(Q(t)\right)\right)Q(t) + 2(1-K)e^{-\gamma\tau}u(t-\tau), \\ \dfrac{d}{dt}\left[u(t) - 2Ke^{-\gamma\tau}u(t-\tau) - \beta\left(Q(t)\right)Q(t)\right] = 0, \end{cases} \tag{20}$$

with initial condition $Q(0) = Q_0 \in \mathbb{R}^+$ and $u_0 = \phi \in C([-\tau, 0], \mathbb{R}^+)$. It has the form

$$\begin{cases} \dfrac{d}{dt} G(Q(t), u_t) = F(Q(t), u_t), & t > 0, \\ Q(0) = Q_0 \quad \text{and} \quad u_0 = \phi, \end{cases} \tag{21}$$

with

$$\begin{cases} G(Q, \phi) = \left(Q, \phi(0) - 2Ke^{-\gamma\tau}\phi(-\tau) - \beta(Q)Q\right), \\ F(Q, \phi) = \left(-(\delta + \beta(Q))Q + 2(1-K)e^{-\gamma\tau}\phi(-\tau), 0\right). \end{cases}$$

A qualitative theory for system (21) is available in the literature (see for instance, [14] and [15]). We apply this theory to the set of initial data characterized by the condition (9),

$$\left\{(Q_0, \phi) \in \mathbb{R}^+ \times C\left([-\tau, 0], \mathbb{R}^+\right) : \phi(0) - 2Ke^{-\gamma\tau}\phi(-\tau) = \beta(Q_0)Q_0\right\}.$$

The compatibility condition (9) makes the system (7) equivalent to (21). Remember that (9) was taken, in Section 3, to get a classic solution (Q, u) of (7) in the sense that Q has a continuous first derivative for all $t > 0$ and u is continuous for all $t \geq -\tau$.

We introduce the linearized system of (20) about the equilibrium $(\overline{Q}, \overline{u})$:

$$\begin{cases} \dfrac{d}{dt} D(Q(t), u_t) = L(Q(t), u_t), & t > 0, \\ Q(0) = Q_0, \; u_0(\theta) = \phi(\theta), & \theta \in [-\tau, 0], \end{cases} \tag{22}$$

with

$$\begin{cases} D(Q, \phi) = \left(Q, \phi(0) - 2Ke^{-\gamma\tau}\phi(-\tau) - \left(\beta'(\overline{Q})\overline{Q} + \beta(\overline{Q})\right)Q\right), \\ L(Q, \phi) = \left(-\left(\delta + \beta'(\overline{Q})\overline{Q} + \beta(\overline{Q})\right)Q + 2(1-K)e^{-\gamma\tau}\phi(-\tau), 0\right), \end{cases}$$

restricted to the set of initial conditions $(Q_0, \phi) \in \mathbb{R}^+ \times C([-\tau, 0], \mathbb{R}^+)$ such that

$$\phi(0) - 2Ke^{-\gamma\tau}\phi(-\tau) = \left(\beta'(\overline{Q})\overline{Q} + \beta(\overline{Q})\right)Q_0. \tag{23}$$

The characteristic equation of system (22) is given by

$$\det \Gamma(\lambda) = 0, \quad \Gamma(\lambda) = \lambda D\left(e^{\lambda \cdot} I\right) - L\left(e^{\lambda \cdot} I\right),$$

with

$$D\left(e^{\lambda \cdot} I\right) = \begin{pmatrix} 1 & 0 \\ -\overline{\beta}(\tau) & 1 - 2Ke^{-(\gamma+\lambda)\tau} \end{pmatrix},$$

$$L\left(e^{\lambda \cdot} I\right) = \begin{pmatrix} -\left(\delta + \overline{\beta}(\tau)\right) & 2(1-K)e^{-(\gamma+\lambda)\tau} \\ 0 & 0 \end{pmatrix}$$

and

$$\overline{\beta}(\tau) = \frac{d}{dQ}\left[\beta(Q)Q\right]_{Q=\overline{Q}} = \beta'(\overline{Q})\overline{Q} + \beta(\overline{Q}). \tag{24}$$

Thanks to the compatibility condition (23), the characteristic equation $\det \Gamma(\lambda) = 0$ becomes

$$\Delta(\tau, \lambda) := \lambda + \delta + \overline{\beta}(\tau) + (\overline{\alpha}(\tau)\lambda + \overline{\gamma}(\tau))e^{-\lambda\tau} = 0, \tag{25}$$

where

$$\overline{\alpha}(\tau) = -2Ke^{-\gamma\tau} \quad \text{and} \quad \overline{\gamma}(\tau) = -2(K\delta + \overline{\beta}(\tau))e^{-\gamma\tau}. \tag{26}$$

We recall that the steady state $(\overline{Q}, \overline{u})$ of (7) is locally asymptotically stable if all roots of the characteristic equation (25) have negative real parts, and unstable if roots with positive real parts exist.

Remark 5. We verify that, for the positive steady state $(\overline{Q},\overline{u})$, $\lambda=0$ is not a root of (25). Indeed,

$$\begin{aligned}\Delta(\tau,0) &= \delta+\overline{\beta}(\tau)+\overline{\gamma}(\tau),\\ &= \delta(1-2Ke^{-\gamma\tau})-(2e^{-\gamma\tau}-1)\overline{\beta}(\tau),\\ &= \delta(1-2Ke^{-\gamma\tau})-(2e^{-\gamma\tau}-1)\left[\delta\left(\frac{1-2Ke^{-\gamma\tau}}{2e^{-\gamma\tau}-1}\right)+\beta'(\overline{Q})\overline{Q}\right],\\ &= -(2e^{-\gamma\tau}-1)\beta'(\overline{Q})\overline{Q}.\end{aligned}$$

The existence of positive steady state means that $\tau<\tau_\infty:=\dfrac{1}{\gamma}\ln(2)$. Then, $\Delta(\tau,0)>0$.

We investigate the local asymptotic stability of the positive steady state $(\overline{Q},\overline{u})$. We recall that this steady state exists if the condition (12) holds true. Note that $(\overline{Q},\overline{u})$ depends on the time delay τ. Therefore, coefficients of the characteristic equation depend, explicitly (the term with $e^{-\gamma\tau}$) or implicitly, upon the delay τ. This particularity adds a complexity in studying the asymptotic stability of $(\overline{Q},\overline{u})$. The analysis of the sign of the real parts of eigenvalues is very complicated, and a direct approach cannot be considered. We will use the method consisting of determining the stability of $(\overline{Q},\overline{u})$ when the delay is equal to zero, and, using the analytic arguments that the stability of $(\overline{Q},\overline{u})$ can only be lost if pure imaginary roots appear.

Setting $\tau=0$, the condition of existence of positive steady state $(\overline{Q}(0),\overline{u}(0))$ is equivalent to

$$\left\{\begin{array}{l}0\le\mu\le1,\\ \frac{1}{2}(1-\mu)<K<\frac{1}{2},\end{array}\right.\qquad\text{or}\qquad\left\{\begin{array}{l}\mu>1,\\ 0\le K<\frac{1}{2}.\end{array}\right.\tag{27}$$

Under (27), we can define the positive steady state $(\overline{Q}(\tau),\overline{u}(\tau))$ as a function of τ, on the interval $[0,\tau_{\max})$ with

$$\tau_{\max}=\frac{1}{\gamma}\ln\left(\frac{2(K+\mu)}{1+\mu}\right),\tag{28}$$

and

$$\left\{\begin{array}{lcl}(\overline{Q}(0),\overline{u}(0)) &=& \left(\beta^{-1}\left(\delta(1-2K)\right),\delta\beta^{-1}\left(\delta(1-2K)\right)\right),\\ \lim\limits_{\tau\to\tau_{\max}}(\overline{Q}(\tau),\overline{u}(\tau)) &=& (0,0).\end{array}\right.$$

Throughout this section, we assume that condition (27) holds true and $\tau\in[0,\tau_{\max})$. When $\tau=0$, the characteristic equation (25) becomes

$$\Delta(0,\lambda)=\lambda+\delta+\overline{\beta}(0)+(\overline{\alpha}(0)\lambda+\overline{\gamma}(0))=0.$$

It has only one root

$$\lambda_0=-\frac{\delta+\overline{\beta}(0)+\overline{\gamma}(0)}{1+\overline{\alpha}(0)}\in\mathbb{R}.$$

Furthermore,

$$\begin{aligned}\delta+\overline{\beta}(0)+\overline{\gamma}(0) &= \delta+\beta'(\overline{Q}(0))\overline{Q}(0)+\beta(\overline{Q}(0))-2(K\delta+\beta'(\overline{Q}(0))\overline{Q}(0)+\beta(\overline{Q}(0))),\\ &= -\beta'(\overline{Q}(0))\overline{Q}(0)>0,\end{aligned}$$

and

$$1+\overline{\alpha}(\tau)=1-2K>0.$$

Then, $\lambda_0 < 0$. We conclude that the positive steady state $(\overline{Q}(0), \overline{u}(0))$ is locally asymptotically stable for $\tau = 0$. Thus, it is straightforward that there exists $\varrho \in (0, \tau_{\max})$, with $\tau_{\max}$ given by (28), such that $(\overline{Q}, \overline{u})$ is locally asymptotically stable for $\tau \in [0, \varrho)$. Consequently, when $\tau \in [0, \tau_{\max})$ increases, the stability of $(\overline{Q}, \overline{u})$ can only be lost if characteristic roots cross on the imaginary axis. Hence, we look for purely imaginary roots $\pm i\omega$, $\omega \in \mathbb{R}$. Remark that if λ is a characteristic root then its conjugate $\overline{\lambda}$ is also a characteristic root. Then, we can look for purely imaginary roots $i\omega$ with $\omega > 0$. Then, by separating real and imaginary parts in the characteristic equation (25), we obtain

$$\begin{cases} \overline{\alpha}(\tau)\omega\cos(\omega\tau) - \overline{\gamma}(\tau)\sin(\omega\tau) = -\omega, \\ \overline{\alpha}(\tau)\omega\sin(\omega\tau) + \overline{\gamma}(\tau)\cos(\omega\tau) = -(\delta + \overline{\beta}(\tau)), \end{cases} \tag{29}$$

where $\overline{\alpha}(\tau)$, $\overline{\beta}(\tau)$ and $\overline{\gamma}(\tau)$ are given by (24) and (26). The system (29) is equivalent to

$$\begin{cases} \cos(\omega\tau) &= \dfrac{-(\delta + \overline{\beta}(\tau))\overline{\gamma}(\tau) - \overline{\alpha}(\tau)\omega^2}{\overline{\alpha}(\tau)^2\omega^2 + \overline{\gamma}(\tau)^2}, \\ \sin(\omega\tau) &= \dfrac{\left(\overline{\gamma}(\tau) - \overline{\alpha}(\tau)(\delta + \overline{\beta}(\tau))\right)\omega}{\overline{\alpha}(\tau)^2\omega^2 + \overline{\gamma}(\tau)^2}. \end{cases}$$

Adding the squares of both hand sides of the last system, it follows that ω must satisfy

$$\omega^2 = \frac{\overline{\gamma}^2(\tau) - (\overline{\beta}(\tau) + \delta)^2}{1 - \overline{\alpha}^2(\tau)}.$$

Thanks to (11) and (26), we obtain

$$\begin{cases} \overline{\gamma}^2(\tau) - \left(\overline{\beta}(\tau) + \delta\right)^2 = -(2e^{-\gamma\tau} - 1)\beta'(\overline{Q})\overline{Q}\left[\overline{\gamma}(\tau) - \left(\overline{\beta}(\tau) + \delta\right)\right], \\ 1 - \overline{\alpha}^2(\tau) = (1 + 2Ke^{-\gamma\tau})(1 - 2Ke^{-\gamma\tau}). \end{cases}$$

Observe that, condition (27) and $\tau \in [0, \tau_{\max})$, yield to

$$-(2e^{-\gamma\tau} - 1)\beta'(\overline{Q})\overline{Q} > 0 \quad \text{and} \quad 1 - \overline{\alpha}(\tau)^2 > 0.$$

Hence, for the existence of $\omega > 0$, it is necessary to have

$$\overline{\gamma}(\tau) > \delta + \overline{\beta}(\tau).$$

Then, as a direct consequence, we have the following proposition.

Proposition 5. *Assume that* (27) *holds true and*

$$\overline{\gamma}(\tau) < \delta + \overline{\beta}(\tau), \quad \text{for all} \quad \tau \in [0, \tau_{\max}). \tag{30}$$

Then all roots of (25) *have negative real parts, and the steady state* $(\overline{Q}, \overline{u})$ *is locally asymptotically stable for all* $\tau \in [0, \tau_{\max})$.

Remark that if $\overline{\beta}(\tau) \geq 0$, then (30) is satisfied. This means that the steady state $(\overline{Q}, \overline{u})$ is locally asymptotically stable. For the Hill function (2), $\overline{\beta}(\tau) \geq 0$ if and only if $\overline{Q} \leq \overline{x}$, where $\overline{x}$ is given in remark 2 (see Figure 4).

Suppose now that there exists $\overline{\tau} \in (0, \tau_{\max}]$ such that

$$\overline{\gamma}(\tau) > \delta + \overline{\beta}(\tau), \quad \text{for all } \tau \in [0, \overline{\tau}). \tag{31}$$

Note that $\overline{\tau} \in (0, \tau_{\max}]$ may be chosen such that $\overline{\gamma}(\overline{\tau}) = \delta + \overline{\beta}(\overline{\tau})$ (see Figure 5 for an example of existence of $\overline{\tau}$).

Thanks to (26), the condition (31) implies that

$$-\overline{\beta}(\tau)\left(2e^{-\gamma\tau} + 1\right) > \delta\left(2Ke^{-\gamma\tau} + 1\right) > 0, \quad \text{for all } \tau \in [0, \overline{\tau}).$$

This means that $\overline{\beta}(\tau) < 0$, for all $\tau \in [0, \overline{\tau})$.
Consider the function $\varpi\colon [0, \overline{\tau}) \to (0, +\infty)$ defined by

$$\varpi(\tau) = \sqrt{\frac{\overline{\gamma}^2(\tau) - (\overline{\beta}(\tau) + \delta)^2}{1 - \overline{\alpha}^2(\tau)}}, \quad \text{for all } \tau \in [0, \overline{\tau}). \tag{32}$$

Then, for each $\tau \in [0, \overline{\tau})$, there is a unique solution $\Theta(\tau) \in [0, 2\pi)$ of the system

$$\left\{ \begin{array}{lcl} \cos(\Theta(\tau)) & = & \dfrac{-(\delta + \overline{\beta}(\tau))\overline{\gamma}(\tau) - \overline{\alpha}(\tau)\varpi^2(\tau)}{\overline{\alpha}^2(\tau)\varpi^2(\tau) + \overline{\gamma}^2(\tau)}, \\ \sin(\Theta(\tau)) & = & \dfrac{\left(\overline{\gamma}(\tau) - \overline{\alpha}(\tau)(\delta + \overline{\beta}(\tau))\right)\varpi(\tau)}{\overline{\alpha}(\tau)^2\varpi^2(\tau) + \overline{\gamma}^2(\tau)}. \end{array} \right.$$

As $\overline{\beta}(\tau) < 0$, we state that

$$\overline{\gamma}(\tau) - \overline{\alpha}(\tau)\left(\delta + \overline{\beta}(\tau)\right) = -2(1-K)e^{-\gamma\tau}\overline{\beta}(\tau) > 0, \quad \text{for all } \tau \in [0, \overline{\tau}).$$

Consequently,

$$\sin(\Theta(\tau)) = \frac{\left(\overline{\gamma}(\tau) - \overline{\alpha}(\tau)(\delta + \overline{\beta}(\tau))\right)\varpi(\tau)}{\overline{\alpha}(\tau)^2\varpi^2(\tau) + \overline{\gamma}^2(\tau)} > 0, \quad \text{for all } \tau \in [0, \overline{\tau}).$$

Then, $\Theta(\tau) \in [0, \pi)$ and it is given by

$$\Theta(\tau) = \arccos\left(\frac{-(\delta + \overline{\beta}(\tau))\overline{\gamma}(\tau) - \overline{\alpha}(\tau)\varpi^2(\tau)}{\overline{\alpha}^2(\tau)\varpi^2(\tau) + \overline{\gamma}^2(\tau)}\right). \tag{33}$$

We conclude that the system (29) is equivalent to find $\tau \in [0, \overline{\tau})$ solution of

$$\tau\varpi(\tau) = \Theta(\tau) + 2k\pi, \quad k \in \mathbb{N}, \tag{34}$$

with $\varpi(\tau)$ given by (32) and $\Theta(\tau)$ by (33). One can check that (34) is equivalent to solve

$$Z_k(\tau) \coloneqq \tau - \frac{1}{\varpi(\tau)}\left[\Theta(\tau) + 2k\pi\right] = 0, \quad k \in \mathbb{N}, \quad \tau \in [0, \overline{\tau}). \tag{35}$$

The functions $Z_k(\tau)$ are given implicitly. They do not provide analytic criteria to determine their roots. The roots can be found using popular software (see [7]). The following lemma states some straightforward properties of Z_k.

Lemma 6.1. *For all $k \in \mathbb{N}$ and $\tau \in [0, \overline{\tau})$,*

$$Z_k(0) < 0, \quad Z_{k+1}(\tau) < Z_k(\tau) \quad \text{and} \quad \lim_{\tau \to \overline{\tau}} Z_k(\tau) = -\infty.$$

Therefore, provided that no root of Z_k is a local extremum, the number of positive roots of Z_k, $k \in \mathbb{N}$, on the interval $[0, \overline{\tau})$ is even.

This lemma implies, in particular, that, if Z_k has no root on $[0, \overline{\tau})$, then no function Z_j, with $j > k$, has roots on $[0, \overline{\tau})$. The next proposition is a direct consequence of lemma 6.1.

Proposition 6. *Assume that there exists $\overline{\tau} \in (0, \tau_{\max})$ such that (31) holds true on $[0, \overline{\tau})$. If Z_0, defined by (35), has no root on the interval $[0, \overline{\tau})$, then the positive steady state $(\overline{Q}, \overline{u})$ of (7) is locally asymptotically stable for all $\tau \in [0, \tau_{\max})$.*

We now suppose that Z_0 has at least one positive root on the interval $[0, \overline{\tau})$. Let $\tau^* \in (0, \overline{\tau})$ be the smallest root of Z_0. Then, $(\overline{Q}, \overline{u})$ is locally asymptotically stable for $\tau \in [0, \tau^*)$, and loses its stability when $\tau = \tau^*$. A finite number of stability switch may occurs as τ increases and passes through roots of the Z_k functions.

Our next objective is to prove that $(\overline{Q},\overline{u})$ can be destabilized through a Hopf bifurcation as τ increases. We start by proving that if an imaginary characteristic root $i\omega$ exists then, it is simple. Suppose, by contradiction, that $\lambda = i\omega$ is not a simple characteristic root. Then, λ is a solution of $\Delta(\tau,\lambda)=0$ and $\dfrac{\partial}{\partial\lambda}\Delta(\tau,\lambda)=0$. This yields

$$\left\{\begin{array}{l} e^{\lambda\tau}\left[\lambda+\delta+\overline{\beta}(\tau)\right]+\overline{\alpha}(\tau)\lambda+\overline{\gamma}(\tau)=0,\\ e^{\lambda\tau}+\overline{\alpha}(\tau)-\tau\left(\overline{\alpha}(\tau)\lambda+\overline{\gamma}(\tau)\right)=0.\end{array}\right. \tag{36}$$

The two equations of system (36) lead to

$$\begin{array}{l}\tau\overline{\alpha}(\tau)\lambda^2+\tau\left(\overline{\gamma}(\tau)+\overline{\alpha}(\tau)(\delta+\overline{\beta}(\tau))\right)\lambda\\ -\overline{\alpha}(\tau)\delta+\tau\delta\overline{\gamma}(\tau)-\overline{\alpha}(\tau)\overline{\beta}(\tau)+\tau\overline{\beta}(\tau)\overline{\gamma}(\tau)+\overline{\gamma}(\tau)=0.\end{array} \tag{37}$$

As $\lambda = i\omega$, the imaginary part of (37) implies

$$\overline{\gamma}(\tau)+\alpha(\tau)(\delta+\overline{\beta}(\tau))=0.$$

Then, as $0\le\alpha^2(\tau)<1$, we obtain

$$\overline{\gamma}^2(\tau)=\alpha^2(\tau)(\delta+\overline{\beta}(\tau))^2<(\delta+\overline{\beta}(\tau))^2.$$

This leads to a contradiction.

As τ^* is the smallest root of Z_0 then, from the definition of Z_0, the characteristic equation (25) has purely imaginary roots $\pm i\varpi(\tau^*)$, where ϖ is defined by (32). The stability of the positive steady state switches from stable to unstable as τ passes through τ^*. Other stability switch occur when τ passes through roots of the Z_k functions (see [7]).

As in [7], we rewrite the characteristic equation (25) in the following form

$$\Delta(\tau,\lambda) := A(\tau,\lambda)+B(\tau,\lambda)e^{-\lambda\tau}=0.$$

We define the polynomial function

$$H(\tau,\omega)=|A(\tau,i\omega)|^2-|B(\tau,i\omega)|^2.$$

Then

$$H(\tau,\omega) := \left(1-\overline{\alpha}^2(\tau)\right)\omega^2-\left(\overline{\gamma}^2(\tau)-(\overline{\beta}(\tau)+\delta)^2\right).$$

Let $\lambda(\tau)$ be a branch of roots of (25) such that $\lambda(\tau^*)=i\varpi(\tau^*)$. The Hopf bifurcation theorem says that a Hopf bifurcation occurs at $(\overline{Q},\overline{u})$ when $\tau=\tau^*$ if

$$\text{sign}\left[\left(\frac{\mathrm{d}\,\mathrm{Re}(\lambda(\tau))}{\mathrm{d}\tau}\right)_{\tau=\tau^*}\right]>0.$$

But, from [7], we know that

$$\text{sign}\left[\left(\frac{\mathrm{d}\,\mathrm{Re}(\lambda(\tau))}{\mathrm{d}\tau}\right)_{\tau=\tau^*}\right]=\text{sign}\left(\frac{\partial h}{\partial z}(\tau^*,\varpi^2(\tau^*))\right)\text{sign}\left(\frac{\mathrm{d}Z_0(\tau^*)}{\mathrm{d}\tau}\right),$$

with

$$h(\tau,\omega^2) := H(\tau,\omega).$$

That is to say

$$h(\tau,z)=\left(1-\overline{\alpha}^2(\tau)\right)z-\left(\overline{\gamma}^2(\tau)-(\overline{\beta}(\tau)+\delta)^2\right).$$

Then,

$$\frac{\partial h}{\partial z}(\tau^*,\varpi^2(\tau^*))=1-\overline{\alpha}^2(\tau^*).$$

It follows

$$\operatorname{sign}\left[\left(\frac{\mathrm{d}\operatorname{Re}(\lambda(\tau))}{\mathrm{d}\tau}\right)_{\tau=\tau^*}\right] = \left(1-\overline{\alpha}^2(\tau^*)\right)\operatorname{sign}\left(\frac{\mathrm{d}Z_0(\tau^*)}{\mathrm{d}\tau}\right).$$

As

$$1-\overline{\alpha}^2(\tau^*) = (1-2Ke^{-\gamma\tau^*})(1+2Ke^{-\gamma\tau^*}) > 0,$$

we get

$$\operatorname{sign}\left[\left(\frac{\mathrm{d}\operatorname{Re}(\lambda(\tau))}{\mathrm{d}\tau}\right)_{\tau=\tau^*}\right] = \operatorname{sign}\left(\frac{\mathrm{d}Z_0(\tau^*)}{\mathrm{d}\tau}\right).$$

The following proposition states the existence of a Hopf bifurcation that destabilizes the positive steady state $(\overline{Q},\overline{u})$.

Proposition 7. *Assume that (27) and (31) hold true. If $Z_0(\tau)$ has at least one positive root on the interval $(0,\overline{\tau})$, then the positive steady state $(\overline{Q},\overline{u})$ is locally asymptotically stable for $\tau\in[0,\tau^*)$, where τ^* is the smallest root of $Z_0(\tau)$ on $(0,\overline{\tau})$, and $(\overline{Q},\overline{u})$ loses its stability when $\tau=\tau^*$. A finite number of stability switch may occur as τ passes through roots of the Z_k functions. Moreover, if*

$$\frac{\mathrm{d}Z_0(\tau^*)}{\mathrm{d}\tau} > 0,$$

then a Hopf bifurcation occurs at $(\overline{Q},\overline{u})$ for $\tau=\tau^*$.

We are going now to check that the condition (31) can be satisfied for τ in an interval containing zero. First, notice that thanks to (11), (24) and (26), the expression (31) is equivalent to

$$\eta_1(\tau) := \frac{4(1-K)}{4e^{-\gamma\tau}-e^{\gamma\tau}} < \eta_2(\tau) := -\frac{1}{\delta}\beta'(\overline{Q}(\tau))\overline{Q}(\tau).$$

The function η_1 is increasing on $[0,\tau_{\max})$ and satisfies

$$\eta_1(0) = \frac{4}{3}(1-K) \ < \lim_{\tau\to\tau_{\max}}\eta_1(\tau) = \frac{2(1+\mu)(K+\mu)}{(1+K+2\mu)}.$$

The monotonicity of η_2 depends on the function β'. However, we are able to confirm that

$$\lim_{\tau\to\tau_{\max}}\eta_2(\tau) = 0 \ < \lim_{\tau\to\tau_{\max}}\eta_1(\tau).$$

This means that the condition (31) is not satisfied for $\tau\in[0,\tau_{\max})$ large. Remark also that

$$\eta_2(0) = -\frac{1}{\delta}\beta'\left[\beta^{-1}\left(\delta(1-2K)\right)\right]\beta^{-1}\left(\delta(1-2K)\right) > 0.$$

Then, the following proposition state a sufficient condition for the existence of an interval $[0,\overline{\tau})$ on which the condition (31) is satisfied.

Proposition 8. *Assume that (27) holds true, and*

$$\frac{4}{3}(1-K) < -\frac{1}{\delta}\beta'\left[\beta^{-1}\left(\delta(1-2K)\right)\right]\beta^{-1}\left(\delta(1-2K)\right). \tag{38}$$

Then, there exists $\overline{\tau}\in(0,\tau_{\max})$ such that (31) is satisfied for all $\tau\in[0,\overline{\tau})$.

Example 1. Let β be the Hill function

$$\beta(Q) = \frac{\beta_0\theta^r}{\theta^r+Q^r}, \quad r>1.$$

We calculate the derivative and the inverse of β,

$$\beta'(Q) = -r\beta_0\theta^r \frac{Q^{r-1}}{(\theta^r + Q^r)^2} \quad \text{and} \quad \beta^{-1}(Q) = \theta \left(\frac{\beta_0 - Q}{Q}\right)^{1/r}.$$

Consequently,

$$\eta_2(0) = \frac{r}{\mu}(\mu - (1-2K))(1-2K),$$

with $\mu = \beta_0/\delta$. Thanks to (27), we confirm that $(\mu-(1-2K))(1-2K) > 0$. Hence, (38) becomes

$$r > \frac{4\mu(1-K)}{3(\mu - (1-2K))(1-2K)}. \tag{39}$$

In fact, for β a Hill function, we have the following property: when $\mu > 2(1-2K)$, the function η_2 is increasing on $\left[0, \frac{1}{\gamma}\ln\left(\frac{2(\mu+2K)}{\mu+2}\right)\right]$ and decreasing on $\left[\frac{1}{\gamma}\ln\left(\frac{2(\mu+2K)}{\mu+2}\right), \tau_{\max}\right)$ (see Figure 5-(a)), and when $\mu \le 2(1-2K)$, the function η_2 is decreasing on $[0, \tau_{\max})$ (see Figure 5-(b)).

In the next theorem, we summarize our results dealing with the asymptotic stability of the positive steady state $(\overline{Q}, \overline{u})$ of system (7).

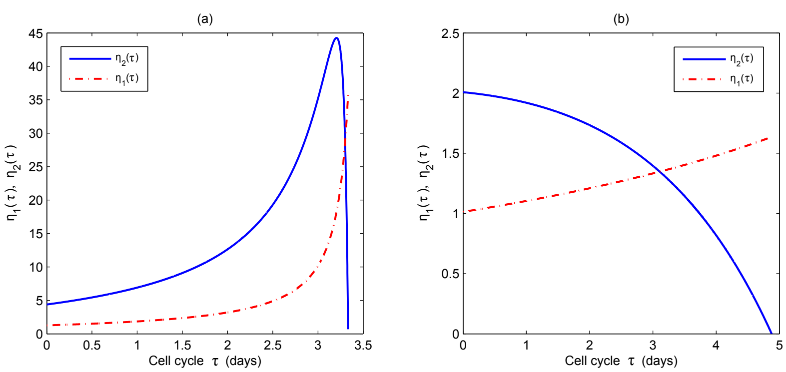

FIGURE 5. Functions η_1 and η_2 are drawn in $[0, \tau_{\max})$, with $r = 5$, $\theta = 1$, $\gamma = 0.2$ day^{-1} and $K = 0.05$ day^{-1}. *(a)* $\mu = 35.40$, $\tau_{\max} = 3.33$ days and the intersection of η_1 and η_2 is $\overline{\tau} = 3.30$ days. *(b)* $\mu = 1.62$, $\tau_{\max} = 4.87$ days and the intersection of η_1 and η_2 is $\overline{\tau} = 3.10$ days.

Theorem 6.2. *Assume that (27) holds true.*

1. *If no $\tau \in [0, \tau_{\max})$ satisfies (31), then the positive steady state $(\overline{Q}, \overline{u})$ is locally asymptotically stable for all $\tau \in [0, \tau_{\max})$.*
2. *Assume there exists $\overline{\tau} \in (0, \tau_{\max})$ such that (31) is fulfilled for all $\tau \in [0, \overline{\tau})$ (for instance, if (38) is satisfied). Then, the following hold true:*
   - *(a) If $Z_0(\tau)$, defined by (35), has no root on the interval $[0, \overline{\tau})$, then the positive steady state $(\overline{Q}, \overline{u})$ is locally asymptotically stable for all $\tau \in [0, \tau_{\max})$.*
   - *(b) If $Z_0(\tau)$ has at least one root on $(0, \overline{\tau})$, then $(\overline{Q}, \overline{u})$ is locally asymptotically stable for $\tau \in [0, \tau^*)$, where $\tau^* \in (0, \overline{\tau})$ is the smallest root of $Z_0(\tau)$ on*

$(0,\overline{\tau})$, and $(\overline{Q},\overline{u})$ is unstable for $\tau \geq \tau^*$, τ in a neighborhood of τ^*, and a Hopf bifurcation occurs at $(\overline{Q},\overline{u})$ for $\tau = \tau^*$ if

$$\frac{\mathrm{d}Z_0(\tau^*)}{\mathrm{d}\tau} > 0.$$

The asymptotic stability of the positive steady state of system (7) has been analyzed with respect to the parameter τ. One may notice that it can, however, be analyzed with respect to every parameter in the model. In particular, one can analyze the asymptotic stability of the positive steady state with respect to the parameter K. The role of some parameters on the stability of the positive steady state is numerically determined in the next section, which is devoted to numerical simulation.

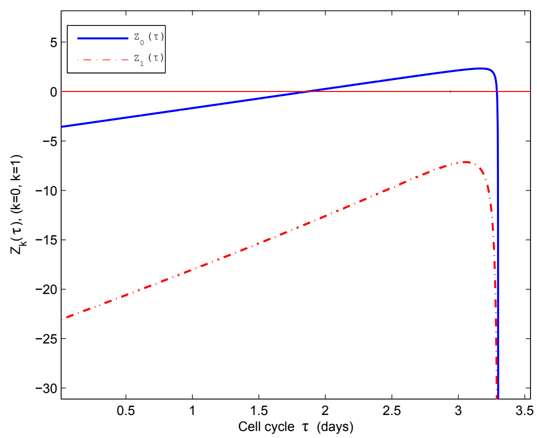

FIGURE 6. Functions Z_0 and Z_1 are drawn in $[0,\overline{\tau})$. Parameters are given by $r = 5$, $\theta = 1$, $\gamma = 0.2$ day^{-1}, $\delta = 0.05$ day^{-1}, $\beta_0 = 1.77$ day^{-1} ($\mu = 35.40$), $K = 0.05$ day^{-1}, $\tau_{\max} = 3.33$ days and $\overline{\tau} = 3.30$ days. The function Z_0 exhibits two positive roots, $\tau_1 = 1.86$ days, $\tau_2 = 3.29$ days, and the function Z_1 is negative.

7. **Numerical simulations.** In this section, we carry out some simulations to corroborate different results obtained in the previous sections, mainly in theorem 6.2. We give also some numerical simulations of the solutions in the case stable and unstable positive steady state. All fixed parameters are taken from Table 1. However, to verify some particular cases, some appropriate values of the parameters not corresponding to those in Table 1, are taken.

The stability area delimited by the roots of the Z_k functions (see Figure 6), can be computed as function of given parameters. Then, the stability and instability regions are plotted in the (τ, K)-plane for different values of the parameter $\mu = \beta_0/\delta$ (see Figure 7).

According to the result stated in theorem 6.2, under the conditions (31) and (38), when the value of the parameter $\tau \in [0, \tau_{\max})$ is small or large, the positive steady state $(\overline{Q},\overline{u})$ of system (7) is always locally asymptotically stable. As showed

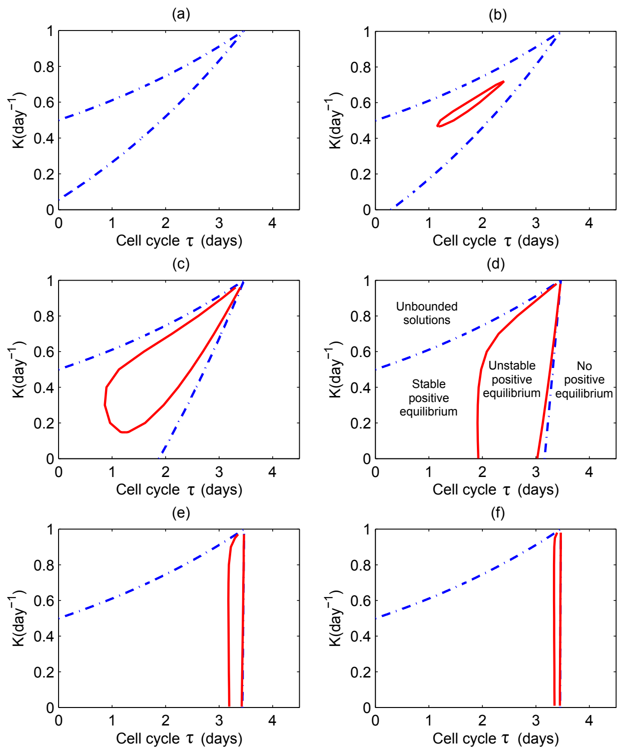

FIGURE 7. Stability region in the (τ, K)-plane, for different values of μ. Fixed parameters are given by $r = 5$, $\theta = 1$ and $\gamma = 0.2$ day^{-1}. The zone of existence of the positive steady state is between the two dashed curves: $K_0(\tau)$ and $K_\mu(\tau)$ (see proposition 2 and Figure 2). Outside this zone, the positive steady state does not exist. Above the upper dashed curve $(K_0(\tau))$, all nontrivial solutions of system (7) are unbounded (see proposition 3). Under the lower dashed curve $(K_\mu(\tau))$, the trivial equilibrium is globally asymptotically stable and it is unstable outside this zone (see theorem 5.4). The zone in which stability of the positive equilibrium switch can occur is delimited by a solid line (see theorem 6.2). Outside this area, the positive steady state is locally asymptotically stable. The values of the parameter μ are: (a) $\mu_1 = 0.88$, (b) $\mu_2 = 1.12$, (c) $\mu_3 = 2.66$, (d) $\mu_4 = 16$, (e) $\mu_5 = 160$, and (f) $\mu_6 = 400$.

in Figure 7, when $\mu > 1$ increases the area of existence of positive steady state increases and a zone of instability appears. As the parameter μ continues to increase, this zone of instability also increases. When μ becomes large, the instability zone becomes a strip with a decreasing width when μ continue to increases. The boundary of the instability zone represents the threshold at which the solutions become periodic. This result was proven previously for $K = 0$ through the existence of a Hopf bifurcation (see [17]). In fact, when μ is large, for each fixed value of $K \geq 0$

the function Z_0 has two roots $\tau_1 < \tau_2$ and the function Z_1 has no root (see Figure 6). Then, according to the result of theorem 6.2, the positive steady state is locally asymptotically stable for $\tau < \tau_1$ and $\tau > \tau_2$ and unstable when $\tau \in [\tau_1, \tau_2]$. In this latter case, the positive steady state undergoes a Hopf bifurcation when $\tau = \tau_1$. We can also notice that when μ varies then the zone of unbounded solutions remains fixed (this corresponds to the area of the existence of infinite steady state).

The instability of the positive steady state corresponds to oscillating solutions (see Figure 8-right). Hence, it appears relevant to investigate the influence of the parameters involved in the problem (for instance, the delay) on periods and amplitudes of the oscillations observed when the positive steady state is unstable. In Figure 9, amplitudes and periods of the oscillations are displayed when τ varies. One can consider that amplitudes in the instability region do not really vary: they quickly reach some plateau and finally decrease rapidly before the stability switches. In contrast, the delay promotes a regular increase of the periods of oscillating solutions.

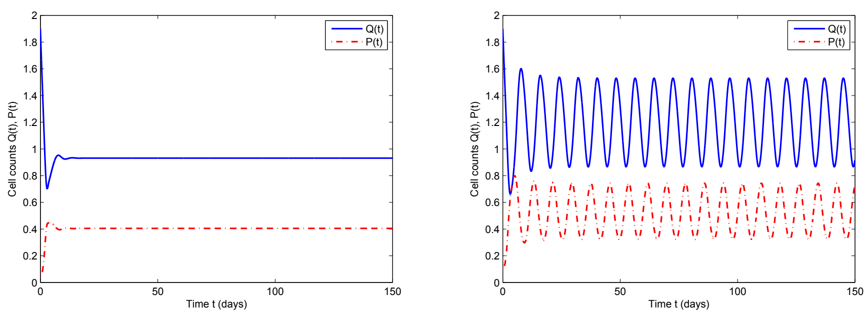

FIGURE 8. Parameters are $r = 5$, $\theta = 1$, $\gamma = 0.2$ day^{-1}, $\mu = 2.66$ and $\tau = 1$ day. In the left: Asymptotic stability of the positive steady state for $K = 0$ day^{-1} (Mackey's model). The positive steady state is locally asymptotically stable. In the right: Oscillating solution about the positive steady state for $K = 0.3$ day^{-1}. The positive steady state is unstable.

8. **Discussion.** We proposed and analyzed a mathematical model describing the dynamics of HSC population, in order to understand the behavior of the blood cell production system in normal and pathological cases. Our model extends previous HSC models (see [1], [2], [3], [4], [5], [8], [9], [17], [18] and [19]) by allowing a fraction of the daughter HSCs to return immediately to the proliferating phase to divide again (short-term proliferation represented by the parameter K), rather than all of the daughter cells entering the quiescent phase directly. We stressed that the behavior of the system is strongly related, not only to cell cycle duration τ, as was proved previously (see [1], [2], [3], [4], [5], [8], [9], [17], [18] and [19]), but also to the short proliferating term K and the parameter $\mu := \beta_0/\delta$. We proved the ability of our model to explain the maintenance of high level production of blood cells (when K approach the threshold $K_0(\tau)$, see Figure 3). We noticed also that the parameter K plays a crucial role in the appearance of periodic solutions (see Figures 7, 8 and 9) when the other parameters are not too large. Periods of the

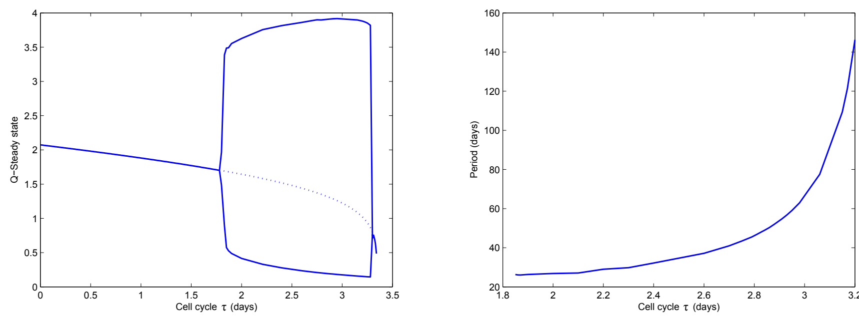

FIGURE 9. Positive steady state bifurcation diagram. Parameters are given by $r = 5$, $\theta = 1$, $\gamma = 0.2$ day^{-1}, $\delta = 0.05$ day^{-1}, $\beta_0 = 1.77$ day^{-1} ($\mu = 35.40$) and $K = 0.05$ day^{-1}. Positive steady state $\overline{Q}$ is plotted as function of τ. The solid curve (left) is for stable and the dashed curve is for unstable. When τ is close to zero or close to $\tau_{\max}$, the positive steady state is stable. When τ increases from zero, the positive steady state becomes unstable for $\tau = 1.86$ days (a Hopf bifurcation occurs for this critical value). A stability switch destabilizes the steady state for τ between 1.86 days and 3.29 days. Between these two critical values of τ, amplitudes (left) and periods (right) of oscillating solutions are plotted. The amplitudes (left) correspond to solid curves up and down of the unstable positive steady state.

oscillations obtained in numerical simulations, in Section 7, may be in the order of $26-146$ days when the delay varies between 1.86 and 3.29 days (Figure 9) (the other parameters are not too large), corresponding to what can be observed with chronic myelogenous leukemia (see [18] and [19]). Since periodic hematological diseases are supposed to be due to destabilization of the production of cells, then K seems to be appropriate to identify causes leading to periodic solutions. However, when μ is large, we observe that the parameter K has no influence on the stability of the positive steady state (Figure 7).

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