GLOBAL ASYMPTOTIC STABILITY AND HOPF BIFURCATION FOR A BLOOD CELL PRODUCTION MODEL

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(Communicated by Yasuhiro Takeuchi)

ABSTRACT. We analyze the asymptotic stability of a nonlinear system of two differential equations with delay, describing the dynamics of blood cell production. This process takes place in the bone marrow, where stem cells differentiate throughout division in blood cells. Taking into account an explicit role of the total population of hematopoietic stem cells in the introduction of cells in cycle, we are led to study a characteristic equation with delay-dependent coefficients. We determine a necessary and sufficient condition for the global stability of the first steady state of our model, which describes the population's dying out, and we obtain the existence of a Hopf bifurcation for the only nontrivial positive steady state, leading to the existence of periodic solutions. These latter are related to dynamical diseases affecting blood cells known for their cyclic nature.

1. **Introduction.** The blood cell production process is based on the differentiation of so-called hematopoietic stem cells, located in the bone marrow. These undifferentiated and unobservable cells have unique capacities of differentiation (the ability to produce cells committed to one of the three blood cell types: red blood cells, white cells or platelets) and self-renewal (the ability to produce cells with the same properties).

Mathematical modelling of hematopoietic stem cell dynamics was introduced at the end of the seventies by Mackey [20]. He proposed a system of two differential equations with delay where the time delay describes the cell cycle duration. In this model, hematopoietic stem cells are separated in proliferating and nonproliferating cells, these latter being introduced in the proliferating phase with a nonlinear rate depending only upon the nonproliferating cell population. The resulting system of delay differential equations is then uncoupled, with the nonproliferating cells equation containing the whole information about the dynamics of the hematopoietic stem cell population. The stability analysis of the model in [20] highlighted the existence of periodic solutions, through a Hopf bifurcation, describing in some cases diseases affecting blood cells, characterized by periodic oscillations [18].

Mackey's model [20] has been studied by many authors, mainly since the beginning of the nineties. Mackey and Rey [22, 23, 24] numerically studied the behavior of a structured model based on the model in [20], stressing the existence of strange behaviors of the cell populations (such as oscillations or chaos). Mackey and Rudnicky [25, 26] developed the description of blood cell dynamics through an age-maturity structured model, stressing the influence of hematopoietic stem cells on blood production. Their model has been further developed by Dyson et al. [12, 13, 14], Adimy and Pujo-Menjouet [6], Adimy and Crauste [1, 2] and Adimy et al. [3]. Recently, Adimy et al. [4, 5] studied the model proposed in [20], taking into account that cells in cycle divide according to a density function (usually gamma distributions play an important role in cell cycle durations), contrary to what has been assumed in the works cited above, where the division has always been assumed to occur at the same time.

More recently, Pujo-Menjouet and Mackey [29] and Pujo-Menjouet et al. [28] gave a better insight into the Mackey's model [20], highlighting the role of each parameter of the model on the appearance of oscillations and, more particularly, of periodic solutions, when the model is applied to the study of chronic myelogenous leukemia [15].

Contrary to the assumption used in all of the works cited above, we study, in this paper, the model introduced by Mackey [20], considering that the rate of introduction in the proliferating phase, which contains the nonlinearity of this model, depends upon the total population of hematopoietic stem cells and not only upon the nonproliferating cell population. The introduction in cell cycle is partly known to be a consequence of activation of hematopoietic stem cells due to molecules fixing on them. Hence, the entire population is in contact with these molecules, and it is reasonable to think that the total number of hematopoietic stem cells plays a role in the introduction of nonproliferating cells in the proliferating phase.

The first consequence is that the model is not uncoupled, and the nonproliferating cell population equation does not contain all the information about the dynamics of blood cell production, contrary to the model in [20, 28, 29]. Therefore, we are led to the study of a modified system of delay differential equations (system (3)–(4)), where the delay describes the cell cycle duration, with a nonlinear part depending on one of the two populations.

Second, while studying the local asymptotic stability of the steady states of our model, we have to determine roots of a characteristic equation taking the form of a first-degree exponential polynomial with delay-dependent coefficients. For such equations, Beretta and Kuang [8] developed a very useful and powerful technique, which we will apply to our model.

Our aim is to show, through the study of the steady states' stability, that our model, described in (3)–(4), exhibits properties similar to those in [20] and that it can be used to model blood cell production dynamics with good results, particularly when one is interested in the appearance of periodic solutions in blood cell dynamics models. We want to point out that the usually accepted assumption about the introduction rate may be limitative and that our model can display interesting dynamics, such as stability switches, that have never been noted before.

The present work is organized as follows. In the next section we present our model, stated in equations (3) and (4). We then determine the steady states of this model. In section 3, we linearize the system (3)–(4) about a steady state, and we

deduce the associated characteristic equation. In section 4, we establish necessary and sufficient conditions for the global asymptotic stability of the trivial steady state (which describes the extinction of the hematopoietic stem cell population). In section 5, we focus on the asymptotic stability of the unique nontrivial steady state. By studying the existence of pure imaginary roots of a first degree exponential polynomial with delay-dependent coefficients, we obtain the existence of a critical value of the time delay for which a Hopf bifurcation occurs at the positive steady state, leading to the appearance of periodic solutions. Using numerical illustrations, we show how these solutions can be related to periodic hematological diseases in section 6, and we note the existence of a stability switch. We conclude with a discussion.

2. **A Nonlinear Model of Blood Cell Production.** Let us consider a population of hematopoietic stem cells located in the bone marrow. These cells actually perform a succession of cell cycles, to differentiate into blood cells (white cells, red blood cells and platelets). According to early works, Burns and Tannock [10] for example, we assume that cells in cycle are divided in two groups: proliferating and nonproliferating cells. The respective proliferating and nonproliferating cell populations are denoted by P and N.

All hematopoietic stem cells die with constant rates, namely $\gamma > 0$ for proliferating cells and $\delta > 0$ for nonproliferating cells. The latter are introduced in the proliferating phase, in order to mature and divide, with a rate β. At the end of the proliferating phase, cells divide into two daughter cells, which immediately enter the nonproliferating phase.

Then the populations P and N satisfy the following evolution equations (see Mackey [20] or Pujo-Menjouet and Mackey [29]):

$$\frac{dP}{dt}(t) = -\gamma P(t) + \beta N(t) - e^{-\gamma\tau}\beta N(t-\tau), \tag{1}$$

$$\frac{dN}{dt}(t) = -\delta N(t) - \beta N(t) + 2e^{-\gamma\tau}\beta N(t-\tau). \tag{2}$$

In each of the above equations, τ denotes the average duration of the proliferating phase. The term $e^{-\gamma\tau}$ then describes the survival rate of proliferating cells. The last terms in the right-hand side of equations (1) and (2) account for cells that have performed a whole cell cycle and leave the proliferating phase (in (1)) or enter the nonproliferating phase (in (2)). These cells are in fact nonproliferating cells introduced in the proliferating phase a time τ earlier. The factor 2 in equation (2) represents the division of each proliferating hematopoietic stem cell in two daughter cells.

We assume that the rate of introduction β depends on the total population of hematopoietic stem cells, which we denote by S. With our notations, $S = P + N$. This assumption stresses the fact that the nature of the trigger signal for introduction in the proliferating phase is the result of an action on the entire cell population. For example, it can be caused by molecules entering the bone marrow and fixing on hematopoietic stem cells, activating or inhibiting their proliferating capacity. This occurs in particular for the production of red blood cells. Their regulation is mainly mediated by a hormone (a growth factor, in fact) called erythropoietin, produced by the kidneys under a stimulation by circulating blood cells (see Bélair et al. [7], Mahaffy et al. [27]).

Hence we assume that

$$\beta = \beta(S(t)).$$

The function β is supposed to be continuous and positive on $[0, +\infty)$, and strictly decreasing. This latter assumption describes the fact that the fewer hematopoietic stem cells in the bone marrow, the more cells introduced in the proliferative compartment [20, 29]. Furthermore, we assume that

$$\lim_{S \to \infty} \beta(S) = 0.$$

Adding equations (1) and (2), we can then deduce an equation satisfied by the total population of hematopoietic stem cells $S(t)$. We assume, for the sake of simplicity, that proliferating and nonproliferating cells die with the same rate, that is $\delta = \gamma$. Then the populations N and S satisfy the following nonlinear system with time delay τ, corresponding to the cell cycle duration,

$$\frac{dS}{dt}(t) = -\delta S(t) + e^{-\delta\tau}\beta(S(t-\tau))N(t-\tau), \tag{3}$$

$$\frac{dN}{dt}(t) = -\delta N(t) - \beta(S(t))N(t) + 2e^{-\delta\tau}\beta(S(t-\tau))N(t-\tau). \tag{4}$$

From Hale and Verduyn Lunel [17], for each continuous initial condition, system (3)–(4) has a unique continuous solution $(S(t), N(t))$, well-defined for $t \geq 0$.

LEMMA 2.1. *For all nonnegative initial condition, the unique solution $(S(t), N(t))$ of (3)–(4) is nonnegative.*

Proof. First assume that there exists $\xi > 0$ such that $N(\xi) = 0$ and $N(t) > 0$ for $t < \xi$. Then, from (4) and since β is a positive function,

$$\frac{dN}{dt}(\xi) = 2e^{-\delta\tau}\beta(S(\xi-\tau))N(\xi-\tau) > 0.$$

Consequently, $N(t) \geq 0$ for $t > 0$.

If there exists $\zeta > 0$ such that $S(\zeta) = 0$ and $S(t) > 0$ for $t < \zeta$, then the same reasoning, using (3), leads to

$$\frac{dS}{dt}(\zeta) = e^{-\delta\tau}\beta(S(\zeta-\tau))N(\zeta-\tau) > 0,$$

and we deduce that $S(t) \geq 0$ for $t > 0$. $\square$

REMARK 1. *The positivity of S and N, solutions of system (3)–(4), does not a priori imply that $P = S - N$ is nonnegative.*

Using a classical variation of constant formula, the solutions $P(t)$ of (1) are given, for $t \geq 0$, by

$$P(t) = e^{-\delta t}P(0) + e^{-\delta t}\int_0^t e^{\delta\theta}\beta(S(\theta))N(\theta) - e^{\delta(\theta-\tau)}\beta(S(\theta-\tau))N(\theta-\tau)d\theta.$$

Setting the change of variable $\sigma = \theta - \tau$, we obtain

$$P(t) = e^{-\delta t}\left[P(0) - \int_{-\tau}^0 e^{\delta\theta}\beta(S(\theta))N(\theta)d\theta\right] + e^{-\delta t}\int_{t-\tau}^t e^{\delta\theta}\beta(S(\theta))N(\theta)d\theta.$$

Consequently, $P(t) \geq 0$ for $t \geq 0$ if

$$P(0) \geq \int_{-\tau}^0 e^{\delta\theta}\beta(S(\theta))N(\theta)d\theta;$$

that is, if

$$S(0) \geq N(0) + \int_{-\tau}^{0} e^{\delta\theta}\beta(S(\theta))N(\theta)d\theta.$$

This condition is biologically relevant, since $\int_{-\tau}^{0} e^{\delta\theta}\beta(S(\theta))N(\theta)d\theta$ represents the population of cells that have been introduced in the proliferating phase at time $\theta \in [-\tau, 0]$ and that have survived at time $t = 0$. Hence, from a biological point of view, the population in the proliferating phase at time $t = 0$ should be larger than this quantity.

In the stability analysis of system (3)–(4), the existence of stationary solutions, called steady states, is relevant since these particular solutions are potential limits of system (3)–(4).

A steady state of system (3)–(4) is a solution $(\overline{S}, \overline{N})$ satisfying

$$\frac{d\overline{S}}{dt} = \frac{d\overline{N}}{dt} = 0.$$

Let $(\overline{S}, \overline{N})$ be a steady state of (3)–(4). Then

$$\delta\overline{S} = e^{-\delta\tau}\beta(\overline{S})\overline{N}, \tag{5}$$

$$(\delta + \beta(\overline{S}))\overline{N} = 2e^{-\delta\tau}\beta(\overline{S})\overline{N}. \tag{6}$$

We immediately notice that $(0,0)$ is a steady state of system (3)–(4), which we will denote, in the following, by E^0. This steady state always exists. It describes the extinction of the hematopoietic stem cell population.

Assume that $(\overline{S}, \overline{N})$ is a steady state of (3)–(4) with $\overline{S}, \overline{N} \neq 0$. Then, from (5) and (6),

$$(2e^{-\delta\tau} - 1)\beta(\overline{S}) = \delta \qquad \text{and} \qquad \overline{N} = \frac{\delta\overline{S}}{e^{-\delta\tau}\beta(\overline{S})}.$$

A necessary condition to obtain a nontrivial steady state is then $2e^{-\delta\tau} - 1 > 0$, that is

$$\tau < \frac{\ln(2)}{\delta}.$$

Under this condition, since the function β is decreasing, positive, and tends to zero at infinity, there exists $\overline{S} > 0$ satisfying

$$(2e^{-\delta\tau} - 1)\beta(\overline{S}) = \delta, \tag{7}$$

if and only if

$$(2e^{-\delta\tau} - 1)\beta(0) > \delta. \tag{8}$$

One can easily check that condition (8) is equivalent to

$$\delta < \beta(0) \qquad \text{and} \qquad 0 \leq \tau < \overline{\tau} := \frac{1}{\delta}\ln\left(\frac{2\beta(0)}{\delta + \beta(0)}\right). \tag{9}$$

In this case, $\overline{S} > 0$ solution of (7) is unique, and

$$\overline{N} = \frac{2e^{-\delta\tau} - 1}{e^{-\delta\tau}}\overline{S}.$$

One can check that $\overline{N} \leq \overline{S}$. These results are summed up in the next proposition.

PROPOSITION 2.1. *If inequality (8) holds true, the system (3)–(4) has exactly two steady states:* $E^0 = (0,0)$ *and* $E^* = (S^*, N^*)$, *where* $S^* > 0$ *is the unique solution of equation (7) and* $N^* = (2e^{-\delta\tau} - 1)e^{\delta\tau}S^*$.
If

$$(2e^{-\delta\tau} - 1)\beta(0) \leq \delta,$$

then system (3)–(4) has only one steady state, namely $E^0 = (0,0)$.

In the next section, we linearize the system (3)–(4) about one of its steady states to analyze its local asymptotic stability.

3. **Linearization and Characteristic Equation.** We are interested in the asymptotic stability of the steady states of system (3)–(4). To that aim, we linearize system (3)–(4) about one of its steady state and we determine the associated characteristic equation. We assume that β is continuously differentiable on $[0, +\infty)$.

Let $(\overline{S}, \overline{N})$ be a steady state of system (3)–(4). From Proposition 2.1, $(\overline{S}, \overline{N})$ is either E^0 or E^*.

The linearization of system (3)–(4) about $(\overline{S}, \overline{N})$ leads to the following system,

$$\frac{dS}{dt}(t) = -\delta S(t) + e^{-\delta\tau}\beta(\overline{S})N(t-\tau) + e^{-\delta\tau}\overline{N}\beta'(\overline{S})S(t-\tau), \qquad (10)$$

$$\frac{dN}{dt}(t) = -(\delta + \beta(\overline{S}))N(t) - \overline{N}\beta'(\overline{S})S(t)$$
$$+ 2e^{-\delta\tau}\left[\beta(\overline{S})N(t-\tau) + \overline{N}\beta'(\overline{S})S(t-\tau)\right], \qquad (11)$$

where we have used the notations $S(t)$ and $N(t)$ instead of $S(t) - \overline{S}$ and $N(t) - \overline{N}$ for the sake of simplicity.

The system (10)–(11) can be written

$$\begin{pmatrix} \dfrac{dS}{dt}(t) \\ \dfrac{dN}{dt}(t) \end{pmatrix} = \mathcal{A}_1 \begin{pmatrix} S(t) \\ N(t) \end{pmatrix} + \mathcal{A}_2 \begin{pmatrix} S(t-\tau) \\ N(t-\tau) \end{pmatrix},$$

where

$$\mathcal{A}_1 := \begin{pmatrix} -\delta & 0 \\ -\alpha & -(\delta + \beta(\overline{S})) \end{pmatrix}, \qquad \mathcal{A}_2 := e^{-\delta\tau}\begin{pmatrix} \alpha & \beta(\overline{S}) \\ 2\alpha & 2\beta(\overline{S}) \end{pmatrix},$$

and

$$\alpha = \alpha(\overline{N}, \overline{S}) := \overline{N}\beta'(\overline{S}). \qquad (12)$$

The characteristic equation of system (10)–(11) associated with the steady state $(\overline{S}, \overline{N})$ is defined by

$$\det(\lambda - \mathcal{A}_1 - e^{-\lambda\tau}\mathcal{A}_2) = 0.$$

After calculations, this equation reduces to

$$(\lambda + \delta)\left[\lambda + \delta + \beta(\overline{S}) - (2\beta(\overline{S}) + \alpha(\overline{N}, \overline{S}))e^{-\delta\tau}e^{-\lambda\tau}\right] = 0. \qquad (13)$$

We recall that the steady state $(\overline{S}, \overline{N})$ is locally asymptotically stable when all roots of (13) have negative real parts, and the stability can only be lost if eigenvalues cross the imaginary axis; that is, if pure imaginary roots appear.

One can notice that $\lambda = -\delta < 0$ is always an eigenvalue of (13). Therefore, we focus only on the equation

$$\lambda + \delta + \beta(\overline{S}) - (2\beta(\overline{S}) + \alpha(\overline{N}, \overline{S}))e^{-\delta\tau}e^{-\lambda\tau} = 0. \qquad (14)$$

We first analyze, in the next section, the stability of the trivial steady state E^0. We establish necessary and sufficient conditions for the population's dying out. Then, in section 5, we concentrate on the behavior of the positive steady state E^*.

4. Global Asymptotic Stability of the Trivial Steady State: Cells' Dying Out.

We concentrate, in this section, on the stability of the steady state $E^0 = (0, 0)$. From (12), $\alpha(0, 0) = 0$, so, for $\overline{S} = \overline{N} = 0$, the characteristic equation (14) becomes

$$\lambda + \delta + \beta(0) - 2\beta(0)e^{-\delta\tau}e^{-\lambda\tau} = 0. \tag{15}$$

It is straightforward to see that equation (15) has a unique real eigenvalue, say λ_0, and all other eigenvalues $\lambda \neq \lambda_0$ of (15) satisfy $\text{Re}(\lambda) < \lambda_0$.

Let us consider the mapping $\lambda \mapsto \lambda + \delta + \beta(0) - 2\beta(0)e^{-\delta\tau}e^{-\lambda\tau}$ as a function of real λ. Then it is an increasing function from $-\infty$ to $+\infty$, yielding the existence and uniqueness of λ_0.

Assume that $\lambda = \mu + i\omega \neq \lambda_0$ satisfies (15). Then, considering the real part of (15), we get

$$\mu - \lambda_0 = 2\beta(0)e^{-\delta\tau}\left[e^{-\mu\tau}\cos(\omega\tau) - e^{-\lambda_0\tau}\right].$$

By contradiction, we assume that $\mu > \lambda_0$. Then $e^{-\mu\tau}\cos(\omega\tau) - e^{-\lambda_0\tau} < 0$ and we obtain a contradiction. So $\mu \leq \lambda_0$. Now if $\mu = \lambda_0$, then the previous equality implies that

$$\cos(\omega\tau) = 1, \qquad \text{for } \tau \geq 0.$$

It follows that $\sin(\omega\tau) = 0$ and, considering the imaginary part of (15) with $\lambda = \mu + i\omega$, given by

$$\omega + 2\beta(0)e^{-\delta\tau}e^{-\mu\tau}\sin(\omega\tau) = 0,$$

we obtain $\omega = 0$ and $\lambda = \lambda_0$, which gives a contradiction. Therefore, $\mu < \lambda_0$.

The real root λ_0 is negative if

$$(2e^{-\delta\tau} - 1)\beta(0) < \delta,$$

and all eigenvalues of (15) have negative real parts in this case. When condition (8) holds, λ_0 is positive. We can then conclude in the next proposition to the stability of E^0.

PROPOSITION 4.1. *The trivial steady state $E^0 = (0, 0)$ of system (3)–(4) is locally asymptotically stable when*

$$(2e^{-\delta\tau} - 1)\beta(0) < \delta, \tag{16}$$

and unstable when

$$(2e^{-\delta\tau} - 1)\beta(0) > \delta.$$

REMARK 2. *When*

$$(2e^{-\delta\tau} - 1)\beta(0) = \delta,$$

then the unique real root of (15) is $\lambda_0 = 0$, and all other eigenvalues have negative real parts. One can easily check that $\lambda_0 = 0$ is a simple root of (15), since the first derivative of the mapping $\lambda \mapsto \lambda + \delta + \beta(0) - 2\beta(0)e^{-\delta\tau}e^{-\lambda\tau}$ at $\lambda_0 = 0$ is

$$1 + 2\beta(0)\tau e^{-\delta\tau} > 0.$$

Then the linear system is stable, but we cannot conclude to the asymptotic stability of the trivial steady state $E^0 = (0, 0)$ of system (3)–(4) without further analysis. This is done in Proposition 4.2.

When condition (16) holds true, E^0 is in fact the only steady state of system (3)–(4) (see Proposition 2.1). In this case, we can show that E^0 is globally asymptotically stable.

We first show the following result.

LEMMA 4.1. *Let $(S(t), N(t))$ be a solution of (3)–(4). If $\lim_{t \to +\infty} N(t) = 0$, then $\lim_{t \to +\infty} S(t) = 0$.*

Proof. Using (3), a classical variation of constant formula gives us, for $t \geq 0$,

$$S(t) = e^{-\delta t} S(0) + e^{-\delta t} \int_0^t e^{\delta(\theta - \tau)} \beta(S(\theta - \tau)) N(\theta - \tau) d\theta.$$

Setting $\sigma = \theta - \tau$, this expression becomes

$$S(t) = e^{-\delta t} S(0) + e^{-\delta t} \int_{-\tau}^{t - \tau} e^{\delta \sigma} \beta(S(\sigma)) N(\sigma) d\sigma.$$

Let $\varepsilon > 0$ be fixed. Since N is assumed to tend to zero when t tends to ∞, there exists $T > 0$ such that

$$N(t) < \varepsilon \frac{\delta e^{\delta \tau}}{2 \beta(0)}, \qquad \text{for } t \geq T. \tag{17}$$

Then, for $t \geq T + \tau$,

$$S(t) = e^{-\delta t} \left[S(0) + \int_{-\tau}^{T} e^{\delta \sigma} \beta(S(\sigma)) N(\sigma) d\sigma \right] + e^{-\delta t} \int_{T}^{t - \tau} e^{\delta \sigma} \beta(S(\sigma)) N(\sigma) d\sigma.$$

Using (17) and the fact that $\beta(0)$ is a bound of β, we obtain, for $t \geq T + \tau$,

$$
\begin{aligned}
S(t) &\leq e^{-\delta t} \left[S(0) + \int_{-\tau}^{T} e^{\delta \sigma} \beta(S(\sigma)) N(\sigma) d\sigma \right] + \varepsilon \frac{\delta e^{\delta \tau}}{2} e^{-\delta t} \int_{T}^{t - \tau} e^{\delta \sigma} d\sigma, \\
&\leq e^{-\delta t} \left[S(0) + \int_{-\tau}^{T} e^{\delta \sigma} \beta(S(\sigma)) N(\sigma) d\sigma \right] + \varepsilon \frac{e^{\delta \tau}}{2} \left(e^{-\delta \tau} - e^{-\delta(t - T)} \right), \\
&\leq e^{-\delta t} \left[S(0) + \int_{-\tau}^{T} e^{\delta \sigma} \beta(S(\sigma)) N(\sigma) d\sigma \right] + \frac{\varepsilon}{2}.
\end{aligned}
$$

Let $\bar{t} > 0$ be such that

$$e^{-\delta t} \left[S(0) + \int_{-\tau}^{T} e^{\delta \sigma} \beta(S(\sigma)) N(\sigma) d\sigma \right] < \frac{\varepsilon}{2}, \qquad \text{for } t \geq \bar{t}.$$

Then, for $t \geq \max\{\bar{t}, T + \tau\}$, we obtain

$$S(t) < \varepsilon.$$

Thus, $S(t)$ tends to zero as t tends to $+\infty$, and the proof is complete. $\qquad \square$

We recall a very useful lemma, proved by Barbălat (see Gopalsamy [16]).

LEMMA 4.2. *Let $f : [a, +\infty) \to \mathbb{R}$, $a \in \mathbb{R}$, be a differentiable function. If $\lim_{t \to +\infty} f(t)$ exists and $f'(t)$ is uniformly continuous on $(a, +\infty)$, then*

$$\lim_{t \to +\infty} f'(t) = 0.$$

We then prove the following result, dealing with the global asymptotic stability of E^0.

PROPOSITION 4.2. *Assume that*

$$(2e^{-\delta\tau} - 1)\beta(0) \leq \delta. \tag{18}$$

Then all solutions $(S(t), N(t))$ of system (3)–(4) converge to the trivial solution $(0, 0)$. Hence E^0 is globally asymptotically stable and the cell populations die out.

Proof. Let $(S(t), N(t))$ be a solution of (3)–(4). We define, for $t \geq 0$,

$$Y(t) = N(t) + 2e^{-\delta\tau} \int_{t-\tau}^{t} \beta(S(\theta))N(\theta)d\theta.$$

Using (4), we can check that

$$Y'(t) = N(t) \left[(2e^{-\delta\tau} - 1)\beta(S(t)) - \delta \right]. \tag{19}$$

From condition (18) and the fact that β is decreasing, it follows that

$$Y'(t) \leq 0 \qquad \text{for } t > 0.$$

Thus, Y is decreasing. Since Y is a nonnegative function, we deduce that there exists $y \geq 0$ such that

$$\lim_{t \to +\infty} Y(t) = y.$$

In particular, Y is bounded, and consequently N is also bounded.

We then deduce, with (4), that N' is bounded and, using a similar technique as the one used in the proof of Lemma 4.1, that S is bounded. Consequently, with (3), we obtain that S' is bounded.

From (19), since N, S, N' and S' are bounded, Y' is uniformly continuous.

Since $\lim_{t \to +\infty} Y(t)$ exists and Y' is uniformly continuous on $(0, +\infty)$, Lemma 4.2 implies that

$$\lim_{t \to +\infty} Y'(t) = 0.$$

Consequently, from (19), we obtain either

$$\lim_{t \to +\infty} N(t) = 0 \qquad \text{or} \qquad \lim_{t \to +\infty} (2e^{-\delta\tau} - 1)\beta(S(t)) = \delta.$$

First, assume that (16) holds true, that is,

$$(2e^{-\delta\tau} - 1)\beta(0) < \delta.$$

If $2e^{-\delta\tau} - 1 > 0$, then, since β is a decreasing function satisfying (16), we deduce that $(2e^{-\delta\tau}-1)\beta(S(t)) \leq (2e^{-\delta\tau}-1)\beta(0) < \delta$. If $2e^{-\delta\tau}-1 \leq 0$, then $(2e^{-\delta\tau}-1)\beta(S(t)) \leq 0 < \delta$. Consequently, if it exists, $\lim_{t \to +\infty}(2e^{-\delta\tau} - 1)\beta(S(t))$ cannot be equal to δ and it follows that

$$\lim_{t \to +\infty} N(t) = 0.$$

From Lemma 4.1, we deduce that $\lim_{t \to +\infty} S(t) = 0$, and the conclusion follows.

Second, assume that

$$(2e^{-\delta\tau} - 1)\beta(0) = \delta.$$

Then, $\lim_{t \to +\infty}(2e^{-\delta\tau} - 1)\beta(S(t)) = \delta$ is equivalent to $\lim_{t \to +\infty} \beta(S(t)) = \beta(0)$. Since β is positive and decreasing, this is equivalent to $\lim_{t \to +\infty} S(t) = 0$. It follows that either

$$\lim_{t \to +\infty} N(t) = 0 \qquad \text{or} \qquad \lim_{t \to +\infty} S(t) = 0.$$

If $\lim_{t \to +\infty} N(t) = 0$, we conclude similarly to the previous case with Lemma 4.1. So we assume that $\lim_{t \to +\infty} S(t) = 0$.

From (3), we deduce that

$$\lim_{t \to +\infty} \beta(S(t-\tau))N(t-\tau) = 0.$$

Consequently, either

$$\lim_{t \to +\infty} \beta(S(t-\tau)) = 0 \qquad \text{or} \qquad \lim_{t \to +\infty} N(t-\tau) = 0.$$

Since $\lim_{t \to +\infty} S(t) = 0$, then $\lim_{t \to +\infty} \beta(S(t-\tau)) = \beta(0) > 0$. Hence, $\lim_{t \to +\infty} N(t-\tau) = 0$, and it follows that $\lim_{t \to +\infty} N(t) = 0$.

This concludes the proof. $\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad$ $\square$

REMARK 3. *Let C denote the set of continuous functions mapping $[-\tau, 0]$ into $\mathbb{R}^+$. One can check that the function V, defined for $(\varphi, \psi) \in C^2$ by*

$$V(\varphi, \psi) = \psi(0) + 2e^{-\delta\tau} \int_{-\tau}^{0} \beta(\varphi(\theta))\psi(\theta)d\theta,$$

satisfies

$$\dot{V}(\varphi, \psi) = \psi(0) \left[(2e^{-\delta\tau} - 1)\beta(\varphi(0)) - \delta \right].$$

Hence, V is a Lyapunov functional (see Hale and Verduyn Lunel [17]) on the set

$$G = \left\{ (\varphi, \psi) \in C^2; \ \psi(0) \left[(2e^{-\delta\tau} - 1)\beta(\varphi(0)) - \delta \right] \le 0 \right\}.$$

With assumption (18), $G = C^2$. In the proof of Proposition 4.2, we did not directly use the properties of Lyapunov functionals, but the function Y is defined by

$$Y(t) = V(S_t, N_t), \qquad \text{for } t \ge 0,$$

where S_t (respectively, N_t) is defined by $S_t(\theta) = S(t+\theta)$ (respectively, $N_t(\theta) = N(t+\theta)$), $\theta \in [-\tau, 0]$.

Through Propositions 4.1 and 4.2, we obtained necessary and sufficient conditions for the global asymptotic stability of E^0. Therefore, in the next section, we concentrate on the behavior of E^*, the unique positive steady state of (3)–(4).

5. **Local Asymptotic Stability of the Positive Steady State.** We now turn our considerations on the stability of the unique nontrivial steady state of system (3)–(4), namely $E^* = (S^*, N^*)$, where, from Proposition 2.1, S^* is the unique solution of (7), and $N^* = (2e^{-\delta\tau} - 1)e^{\delta\tau}S^*$.

To ensure the existence of this steady state, we assume that condition (8), or equivalently condition (9), holds true. That is,

$$\delta < \beta(0) \qquad \text{and} \qquad 0 \le \tau < \bar{\tau} := \frac{1}{\delta} \ln \left(\frac{2\beta(0)}{\delta + \beta(0)} \right).$$

In particular, $2e^{-\delta\tau} - 1 > 0$.

In this case, Proposition 4.1 indicates that the unique other steady state E^0 is unstable.

From their definitions in Proposition 2.1, the steady states S^* and N^* depend on the time delay τ. In fact,

$$S^* = S^*(\tau) = \beta^{-1} \left(\frac{\delta}{2e^{-\delta\tau} - 1} \right) \quad \text{and} \quad N^* = N^*(\tau) = \frac{2e^{-\delta\tau} - 1}{e^{-\delta\tau}} S^*(\tau),$$

where $\beta^{-1} : (0, \beta(0)] \to [0, +\infty)$ is a decreasing function.

Using these expressions, we can stress that S^* and N^* are positive decreasing continuous functions of $\tau \in [0, \overline{\tau})$, continuously differentiable, such that $S^*(0) = N^*(0) = \beta^{-1}(\delta)$, and $\lim_{\tau \to \overline{\tau}} (S^*(\tau), N^*(\tau)) = (0, 0) = E^0$.

The characteristic equation (14), with $\overline{S} = S^*$ and $\overline{N} = N^*$, is then given by

$$\lambda + A(\tau) - B(\tau)e^{-\lambda \tau} = 0, \tag{20}$$

with

$$A(\tau) := \delta + \beta(S^*(\tau)) \qquad \text{and} \qquad B(\tau) := [2\beta(S^*(\tau)) + N^*(\tau)\beta'(S^*(\tau))]e^{-\delta \tau}.$$

Notice that $A(\tau) > 0$ for all $\tau \in [0, \overline{\tau})$. Moreover, from (7), we obtain

$$B(\tau) = A(\tau) + (2e^{-\delta \tau} - 1)S^*(\tau)\beta'(S^*(\tau)), \quad \text{for } \tau \in [0, \overline{\tau}). \tag{21}$$

In particular, $B(\tau) < A(\tau)$ for $\tau \in [0, \overline{\tau})$.

Taking $\tau = 0$ in (20), we obtain

$$\lambda + A(0) - B(0) = 0,$$

that is

$$\lambda = \beta^{-1}(\delta)\beta'(\beta^{-1}(\delta)).$$

Since β is decreasing, we deduce that the only eigenvalue of (20) is then negative. The ensuing lemma follows.

LEMMA 5.1. *When $\delta < \beta(0)$ and $\tau = 0$, the nontrivial steady-state E^* of system (3)–(4) is locally asymptotically stable, and the system (3)–(4) undergoes a transcritical bifurcation.*

When τ increases and remains in the interval $[0, \overline{\tau})$, the stability of the steady state can only be lost if purely imaginary roots appear. Therefore, we investigate the existence of purely imaginary roots of (20).

Let $\lambda = i\omega$, $\omega \in \mathbb{R}$, be a pure imaginary eigenvalue of (20). Separating real and imaginary parts, we obtain

$$A(\tau) - B(\tau)\cos(\omega \tau) = 0, \tag{22}$$
$$\omega + B(\tau)\sin(\omega \tau) = 0. \tag{23}$$

One can notice, first, that if ω is a solution of (22)–(23) then $-\omega$ also satisfies this system. Second, $\omega = 0$ is not a solution of (22)–(23). Otherwise, we would obtain $A(\tau) = B(\tau)$ for some $\tau \in [0, \overline{\tau})$, which contradicts $B(\tau) < A(\tau)$ for $\tau \in [0, \overline{\tau})$. Therefore $\omega = 0$ cannot be a solution of (22)–(23). Thus, in the following, we will look only for positive solutions ω of (22)–(23).

From (22), a necessary condition for equation (20) to have purely imaginary roots is that

$$A(\tau) < |B(\tau)|.$$

Since $B(\tau) < A(\tau)$, this implies in particularly that $B(\tau)$ must be negative. Moreover, from (21), the above condition is equivalent to

$$2A(\tau) + (2e^{-\delta \tau} - 1)S^*(\tau)\beta'(S^*(\tau)) < 0.$$

Using the definitions of $A(\tau)$, $N^*(\tau)$, $S^*(\tau)$ and equality (5), this inequality becomes the following condition on τ,

$$\frac{4\delta e^{-\delta \tau}}{2e^{-\delta \tau} - 1} + (2e^{-\delta \tau} - 1)\beta^{-1}\left(\frac{\delta}{2e^{-\delta \tau} - 1}\right)\beta'\left(\beta^{-1}\left(\frac{\delta}{2e^{-\delta \tau} - 1}\right)\right) < 0. \tag{24}$$

LEMMA 5.2. *Let $\chi : [0, +\infty) \to (-\infty, 0]$ be defined, for $y \geq 0$, by*

$$\chi(y) = y\beta'(y).$$

Assume that

> *(H_1) χ is decreasing on the interval $\left[0, \beta^{-1}(\delta)\right]$.*
> *(H_2) $\chi\left(\beta^{-1}(\delta)\right) < -4\delta$.*

Then there exists a unique $\tau^* \in (0, \overline{\tau})$ such that condition (24) is satisfied if and only if $\tau \in [0, \tau^*)$.

Proof. Consider the negative functions $f_1(\tau)$ and $f_2(\tau)$, defined for $\tau \in [0, \overline{\tau}]$ by

$$f_1(\tau) = \chi\left(\beta^{-1}\left(\frac{\delta}{2e^{-\delta\tau} - 1}\right)\right) \quad \text{and} \quad f_2(\tau) = -\frac{4\delta e^{-\delta\tau}}{(2e^{-\delta\tau} - 1)^2}.$$

Then

$$\{\tau \in [0, \overline{\tau}) \, ; \text{condition (24) is satisfied}\} = \{\tau \in [0, \overline{\tau}) \, ; f_1(\tau) < f_2(\tau)\}.$$

The function f_2 satisfies

$$f_2(0) = -4\delta \quad \text{and} \quad f_2(\overline{\tau}) = -2\frac{\delta + \beta(0)}{\delta}\beta(0),$$

and, for $\tau \in [0, \overline{\tau}]$,

$$f_2'(\tau) = -\frac{4\delta^2 e^{-\delta\tau}(2e^{-\delta\tau} + 1)}{(2e^{-\delta\tau} - 1)^3} < 0.$$

Hence f_2 is decreasing from -4δ to $-2(\delta + \beta(0))\beta(0)/\delta$.

For $\tau \in [0, \overline{\tau})$,

$$\delta \leq \frac{\delta}{2e^{-\delta\tau} - 1} < \beta(0).$$

Since β^{-1} is decreasing on $(0, \beta(0)]$ and, from (H_1), χ is decreasing on $[0, \beta^{-1}(\delta)]$, we deduce that f_1 is increasing. Moreover,

$$f_1(0) = \chi\left(\beta^{-1}(\delta)\right) \quad \text{and} \quad f_1(\overline{\tau}) = 0.$$

From (H_2),

$$f_1(0) < f_2(0).$$

Since $f_1(\overline{\tau}) > f_2(\overline{\tau})$, there exists $\tau^* \in (0, \overline{\tau})$, which is unique since f_1 is increasing and f_2 decreasing, such that

$$\{\tau \in [0, \overline{\tau}) \, ; f_1(\tau) < f_2(\tau)\} = [0, \tau^*).$$

This concludes the proof.   □

REMARK 4. *Assumption (H_1) is not necessary for the existence of τ^*; it just implies the uniqueness. This latter can be achieved with weaker conditions, as we will check in an example in section 6.*

We assume, in the following, that (H_1) and (H_2) are fulfilled and $\tau \in [0, \tau^*)$.
System (22)–(23) is equivalent to

$$\cos(\omega\tau) = \frac{A(\tau)}{B(\tau)}, \qquad \sin(\omega\tau) = -\frac{\omega}{B(\tau)}. \tag{25}$$

Note that for $\tau \in [0, \tau^*)$, $B(\tau) < 0$.

Therefore, adding the squares of both sides of (25), purely imaginary eigenvalues $i\omega$ of (20), with $\omega > 0$, must satisfy

$$\omega = \sqrt{B^2(\tau) - A^2(\tau)}. \tag{26}$$

So, in the following, we will think of ω as $\omega(\tau)$.

Substituting this expression for ω in (25), we obtain

$$\begin{aligned}
\cos\left(\tau\sqrt{B^2(\tau) - A^2(\tau)}\right) &= \frac{A(\tau)}{B(\tau)}, \\
\sin\left(\tau\sqrt{B^2(\tau) - A^2(\tau)}\right) &= -\frac{\sqrt{B^2(\tau) - A^2(\tau)}}{B(\tau)}.
\end{aligned} \tag{27}$$

From the above reasoning, values of $\tau \in [0, \tau^*)$ solutions of system (27) generate positive $\omega(\tau)$, given by (26), and hence yield imaginary eigenvalues of (20). Consequently, we look for positive solutions τ of (27) in the interval $(0, \tau^*)$.

Positive solutions $\tau \in (0, \tau^*)$ of (27) satisfy

$$\tau\sqrt{B^2(\tau) - A^2(\tau)} = \arccos\left(\frac{A(\tau)}{B(\tau)}\right) + 2k\pi, \qquad k \in \mathbb{N}_0,$$

where $\mathbb{N}_0$ denotes the set of all nonnegative integers. We set

$$\tau_k(\tau) = \frac{\arccos\left(\frac{A(\tau)}{B(\tau)}\right) + 2k\pi}{\sqrt{B^2(\tau) - A^2(\tau)}}, \qquad k \in \mathbb{N}_0, \tau \in [0, \tau^*).$$

Values of τ for which $\omega(\tau) = \sqrt{B^2(\tau) - A^2(\tau)}$ is a solution of (25) are roots of the functions

$$Z_k(\tau) = \tau - \tau_k(\tau), \qquad k \in \mathbb{N}_0, \tau \in [0, \tau^*). \tag{28}$$

The roots of Z_k can be found using popular software like Maple, but are hard to determine with analytical tools [8]. The following lemma states some properties of the Z_k functions.

LEMMA 5.3. *For $k \in \mathbb{N}_0$,*

$$Z_k(0) < 0 \qquad and \qquad \lim_{\tau \to \tau^*} Z_k(\tau) = -\infty.$$

Therefore, provided that no root of Z_k is a local extremum, the number of positive roots of Z_k, $k \in \mathbb{N}_0$, on the interval $[0, \tau^*)$ is even.

Moreover, if Z_k has no root on the interval $[0, \tau^*)$, then Z_j, with $j > k$, does not have positive roots.

Proof. Notice first that $\tau_k(0) > 0$ and, second, that

$$\lim_{\tau \to \tau^*} \arccos\left(\frac{A(\tau)}{B(\tau)}\right) = \pi \qquad and \qquad \lim_{\tau \to \tau^*} \sqrt{B^2(\tau) - A^2(\tau)} = 0,$$

so $\lim_{\tau \to \tau^*} \tau_k(\tau) = +\infty$. Then the first statement holds.

To prove the second statement, one can notice that $\tau_{k+1}(\tau) > \tau_k(\tau)$, for $\tau \in [0, \tau^*)$ and $k \in \mathbb{N}_0$, so

$$Z_{k+1}(\tau) < Z_k(\tau), \qquad \tau \in [0, \tau^*), k \in \mathbb{N}_0.$$

Using the fact that $Z_k(0) < 0$, we conclude. This ends the proof. $\qquad \square$

REMARK 5. *The second statement in Lemma 5.3 implies, in particular, that, if Z_0 has no positive root, then (25) has no positive solution, and equation (20) does not have pure imaginary roots.*

In the following proposition, we establish some properties of pure imaginary roots of equation (20) using a method described in [19].

PROPOSITION 5.1. *Let* $\pm i\omega(\tau_c)$, *with* $\omega(\tau_c) > 0$, *be a pair of pure imaginary roots of equation (20) when* $\tau = \tau_c$. *Then* $\pm i\omega(\tau_c)$ *are simple roots of (20) such that*

$$sign\left\{ \frac{dRe(\lambda)}{d\tau}\bigg|_{\tau=\tau_c} \right\} = sign\left\{ -B^3 - B^2 B'\tau_c + B(A^2 + A' + AA'\tau_c) - B'A \right\}, \quad (29)$$

where $A = A(\tau_c)$, $B = B(\tau_c)$, $A' = A'(\tau_c)$ *and* $B' = B'(\tau_c)$.

Proof. We set

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

Let $\lambda(\tau)$ be a family of roots of (20), so $\Delta(\lambda(\tau), \tau) = 0$, such that $\lambda(\tau_c)$ is a pure imaginary root of (20), given by $\lambda(\tau_c) = i\omega(\tau_c)$. Then,

$$\frac{d\lambda}{d\tau}(\tau)\Delta_\lambda(\lambda, \tau) + \Delta_\tau(\lambda, \tau) = 0, \quad (30)$$

where

$$\Delta_\lambda(\lambda, \tau) := \frac{d\Delta}{d\lambda}(\lambda, \tau) = 1 + B(\tau)\tau e^{-\lambda\tau},$$

and

$$\Delta_\tau(\lambda, \tau) := \frac{d\Delta}{d\tau}(\lambda, \tau) = A'(\tau) + [B(\tau)\lambda - B'(\tau)]e^{-\lambda\tau}.$$

Assume, by contradiction, that $\lambda(\tau_c) = i\omega(\tau_c)$ is not a simple root of (20). Then, from (30), $\Delta_\tau(i\omega(\tau_c), \tau_c) = A'(\tau_c) + [iB(\tau_c)\omega(\tau_c) - B'(\tau_c)]e^{-i\omega(\tau_c)\tau_c} = 0$. Separating real and imaginary parts in this equality, we deduce

$$B'(\tau_c)\cos(\omega(\tau_c)\tau_c) - B(\tau_c)\omega(\tau_c)\sin(\omega(\tau_c)\tau_c) = A'(\tau_c),$$
$$B(\tau_c)\omega(\tau_c)\cos(\omega(\tau_c)\tau_c) + B'(\tau_c)\sin(\omega(\tau_c)\tau_c) = 0.$$

We recall that $B(\tau_c)$ is necessarily strictly negative. Using (25), the above system is equivalent to

$$\omega(\tau_c)^2 = \frac{A(\tau_c)B'(\tau_c) - B(\tau_c)A'(\tau_c)}{B(\tau_c)},$$
$$\omega(\tau_c)\left[A(\tau_c) + \frac{B'(\tau_c)}{B(\tau_c)}\right] = 0.$$

Since $\omega(\tau_c) > 0$ and satisfies, from (26), $\omega(\tau_c)^2 = B(\tau_c)^2 - A(\tau_c)^2$, we obtain

$$B(\tau_c)^2 - A(\tau_c)^2 = \frac{A(\tau_c)B'(\tau_c) - B(\tau_c)A'(\tau_c)}{B(\tau_c)},$$
$$A(\tau_c)B(\tau_c) = -B'(\tau_c).$$

Substituting the second equation in the first one, this yields $B(\tau_c)^2 - A(\tau_c)^2 = -A'(\tau_c) - A(\tau_c)^2$, so

$$B(\tau_c)^2 = -A'(\tau_c).$$

Since $B(\tau_c)^2 > 0$ and $A'(\tau_c) > 0$, we obtain a contradiction. Hence $\lambda(\tau_c) = i\omega(\tau_c)$ is a simple root of (20).

In the following, we do not mention the dependence of the coefficients A and B (and their derivatives) with respect to τ.

Now, from (30), we obtain

$$\left(\frac{d\lambda}{d\tau}\right)^{-1} = \frac{e^{\lambda\tau} + B\tau}{B' - B\lambda - A'e^{\lambda\tau}}.$$

Since $\Delta(\lambda, \tau) = 0$, we deduce

$$e^{\lambda\tau} = \frac{B}{\lambda + A}.$$

Therefore,

$$\left(\frac{d\lambda}{d\tau}\right)^{-1} = \frac{B + B\tau(\lambda + A)}{(B' - B\lambda)(\lambda + A) - A'B}.$$

For $\tau = \tau_c$, we obtain

$$\left.\left(\frac{d\lambda}{d\tau}\right)^{-1}\right|_{\tau = \tau_c} = \frac{B + B\tau_c(i\omega(\tau_c) + A)}{(B' - iB\omega(\tau_c))(i\omega(\tau_c) + A) - A'B},$$

$$= \frac{B(1 + A\tau_c) + iB\omega(\tau_c)\tau_c}{B'A - AB' + B\omega^2(\tau_c) + i(B' - AB)\omega(\tau_c)}.$$

Then,

$$\left.\mathrm{Re}\left(\frac{d\lambda}{d\tau}\right)^{-1}\right|_{\tau = \tau_c} = \frac{[B^2(1 + A\tau_c) + B\tau_c(B' - AB)]\omega(\tau_c)^2 + B(1 + A\tau_c)(B'A - A'B)}{[B'A - A'B + B\omega(\tau_c)^2] + [B' - AB]^2\omega(\tau_c)^2}.$$

Noticing that

$$\mathrm{sign}\left\{\frac{d\mathrm{Re}(\lambda)}{d\tau}\right\} = \mathrm{sign}\left\{\mathrm{Re}\left(\frac{d\lambda}{d\tau}\right)^{-1}\right\},$$

we get

$$\mathrm{sign}\left\{\left.\frac{d\mathrm{Re}(\lambda)}{d\tau}\right|_{\tau = \tau_c}\right\} = \mathrm{sign}\left\{[B^2(1 + A\tau_c) + B\tau_c(B' - AB)]\omega(\tau_c)^2 \right.$$
$$\left. + B(1 + A\tau_c)(B'A - A'B)\right\}. \qquad (31)$$

Since $i\omega(\tau_c)$ is a purely imaginary root of (20), then, from (26),

$$\omega(\tau_c)^2 = B^2 - A^2.$$

Substituting this expression in (31), we obtain, after simplifications

$$\mathrm{sign}\left\{\left.\frac{d\mathrm{Re}(\lambda)}{d\tau}\right|_{\tau = \tau_c}\right\} = \mathrm{sign}\left\{B\left[B^3 + B^2B'\tau_c - B(A^2 + A' + AA'\tau_c) + B'A\right]\right\}.$$

As we already noticed, if equation (20) has pure imaginary roots then necessarily $B < 0$. We then deduce (29) and the proof is complete. □

Using this last proposition and the previous results about the existence of purely imaginary roots of (13), we can state and prove the following theorem, dealing with the asymptotic stability of E^*.

THEOREM 5.1. *Assume that (9) holds true and (H_1) and (H_2) are fulfilled.*

(i) *If Z_0 (defined in (28)) has no root on the interval $[0, \tau^*)$, τ^* defined in Lemma 5.2, then the positive steady state $E^* = (S^*, N^*)$ of (3)–(4) is locally asymptotically stable for $\tau \in [0, \overline{\tau})$.*

(ii) *If Z_0 has at least one positive root $\tau_c \in (0, \tau^*)$, then E^* is locally asymptotically stable for $\tau \in [0, \tau_c)$ and a Hopf bifurcation occurs at E^* for $\tau = \tau_c$ if*

$$B(A^2 + A' + AA'\tau_c) - B^3 - B^2 B'\tau_c - B'A \neq 0, \qquad (32)$$

where $A = A(\tau_c)$, $B = B(\tau_c)$, $A' = A'(\tau_c)$ and $B' = B'(\tau_c)$.

Proof. First, from Lemma 5.1, we know that E^* is locally asymptotically stable when $\tau = 0$.

If Z_0 has no positive root on the interval $(0, \tau^*)$, then the characteristic equation (13) has no pure imaginary root (see Remark 5 and Lemma 5.3). Consequently, the stability of E^* cannot be lost when τ increases. We obtain the statement in (i).

Now, if Z_0 has at least one positive root, say $\tau_c \in (0, \tau^*)$, then equation (13) has a pair of simple conjugate pure imaginary roots $\pm i\omega(\tau_c)$ for $\tau = \tau_c$. From (32) together with Proposition 5.1, we have either

$$\frac{d\text{Re}(\lambda)}{d\tau}\bigg|_{\tau=\tau_c} > 0 \qquad \text{or} \qquad \frac{d\text{Re}(\lambda)}{d\tau}\bigg|_{\tau=\tau_c} < 0.$$

By contradiction, we assume that there exists a branch of characteristic roots $\lambda(\tau)$ such that $\lambda(\tau_c) = i\omega_c$ and

$$\frac{d\text{Re}(\lambda(\tau))}{d\tau} < 0$$

for $\tau < \tau_c$, τ close to τ_c. Then there exists a characteristic root $\lambda(\tau)$ such that $\text{Re}(\lambda(\tau)) > 0$ and $\tau < \tau_c$. Since E^* is locally asymptotically stable when $\tau = 0$, applying Rouché's Theorem [11], we obtain that all characteristic roots of (13) have negative real parts when $\tau \in [0, \tau_c)$, and we obtain a contradiction. Thus,

$$\frac{d\text{Re}(\lambda)}{d\tau}\bigg|_{\tau=\tau_c} > 0.$$

In this case, a Hopf bifurcation occurs at E^* when $\tau = \tau_c$. $\square$

The result stated in (ii) leads, through the Hopf bifurcation, to the existence of periodic solutions for system (3)–(4).

In the next section, we apply the above-mentioned results of stability to a particular introduction rate β and we present some numerical illustrations.

6. **Example and Numerical Simulations.** We develop, in this section, numerical illustrations of the above mentioned results (mainly the ones stated in Theorem 5.1).

Let us define (see [20, 21, 28, 29]) the introduction rate β by

$$\beta(S) = \beta_0 \frac{\theta^n}{\theta^n + S^n}, \qquad \beta_0, \theta \geq 0, \ n > 1.$$

The parameter β_0 represents the maximal rate of introduction in the proliferating phase, θ is the value for which β attains half of its maximum value, and n is the sensitivity of the rate of reintroduction. The coefficient n describes the reaction of β due to external stimuli, the action of a growth factor for example (some growth factors are known to trigger the introduction of nonproliferating cells in the proliferating phase [7, 27]).

Then, from (9), the unique positive steady state of (3)–(4) exists if and only if

$$\delta < \beta_0 \qquad \text{and} \qquad 0 \leq \tau < \overline{\tau} = \frac{1}{\delta} \ln\left(\frac{2\beta_0}{\delta + \beta_0}\right).$$

From (5)–(6), it is defined by

$$S^* = \theta \left(\frac{(2e^{-\delta\tau} - 1)\beta_0}{\delta} - 1 \right)^{1/n} \quad \text{and} \quad N^* = \theta \frac{2e^{-\delta\tau} - 1}{e^{-\delta\tau}} \left(\frac{(2e^{-\delta\tau} - 1)\beta_0}{\delta} - 1 \right)^{1/n}$$

Note that the function β^{-1} is defined by $\beta^{-1}(x) = \theta(\beta_0/x - 1)^{1/n}$ for $x \in (0, \beta_0]$.

After computations, we can state that condition (24) is equivalent to

$$\tau < \tau^* := \frac{1}{\delta} \ln \left(\frac{2\beta_0(n - 2)}{n(\beta_0 + \delta)} \right),$$

provided that

$$n > \frac{4\beta_0}{\beta_0 - \delta}. \tag{33}$$

Noticing that the function χ, defined in Lemma 5.2, is given by

$$\chi(y) = -n\beta_0 \frac{\theta^n y^n}{(\theta^n + y^n)^2},$$

one can check that (33) is equivalent to (H_2).

However, the function χ does not necessarily satisfy (H_1), which is too strong (as mentioned in Remark 4). For $y \geq 0$,

$$\chi'(y) = \frac{\beta_0 n^2 \theta^n y^{n-1}}{(\theta^n + y^n)^3} (y^n - \theta^n).$$

Consequently, χ is decreasing for $y \leq \theta$ and increasing for $y > \theta$. Taking $y = \beta^{-1}(\delta)$, we find that χ is decreasing on $[0, \beta^{-1}(\delta)]$ if and only if $\beta_0 < 2\delta$. In this case, (H_1) is fulfilled. If $\beta_0 > 2\delta$, then χ is decreasing on the interval $[0, \theta]$ and increasing on $[\theta, \beta^{-1}(\delta)]$, yet τ^* is uniquely defined.

Note that

$$A(\tau) = \frac{2\delta e^{-\delta\tau}}{2e^{-\delta\tau} - 1} \quad \text{and} \quad B(\tau) = \frac{2\delta\beta_0 e^{-\delta\tau} - n\delta[(2e^{-\delta\tau} - 1)\beta_0 - \delta]}{(2e^{-\delta\tau} - 1)\beta_0},$$

with

$$A'(\tau) = \frac{2\delta^2 e^{-\delta\tau}}{(2e^{-\delta\tau} - 1)^2} \quad \text{and} \quad B'(\tau) = \frac{2\delta^2 e^{-\delta\tau}(\beta_0 + n\delta)}{(2e^{-\delta\tau} - 1)^2 \beta_0}.$$

Then, assuming that (33) holds true, we define the Z_k functions, as in (28), for $\tau \in [0, \tau^*)$ by

$$Z_k(\tau) = \tau - \frac{\arccos\left(\frac{A(\tau)}{B(\tau)} \right) + 2k\pi}{\sqrt{B^2(\tau) - A^2(\tau)}}, \quad k \in \mathbb{N}_0, \tau \in [0, \tau^*).$$

We choose the parameters according to [20, 28, 29]:

$$\delta = 0.05 \text{ days}^{-1}, \quad \beta_0 = 1.77 \text{ days}^{-1}, \quad \theta = 1. \tag{34}$$

Notice that the value of θ is in fact normalized and does not influence the stability of system (3)–(4) since all coefficients actually do not depend on θ. The value of θ only influences the shape of the oscillations and the values of the steady states.

Using Maple to determine the roots of Z_n, we first check that Z_0 (and consequently all Z_k functions) is strictly negative on $[0, \tau^*)$ for $n \leq 10$. Hence, from Theorem 5.1, the positive steady state $E^* = (S^*, N^*)$ of (3)–(4) is locally asymptotically stable for $\tau \in [0, \bar{\tau})$.
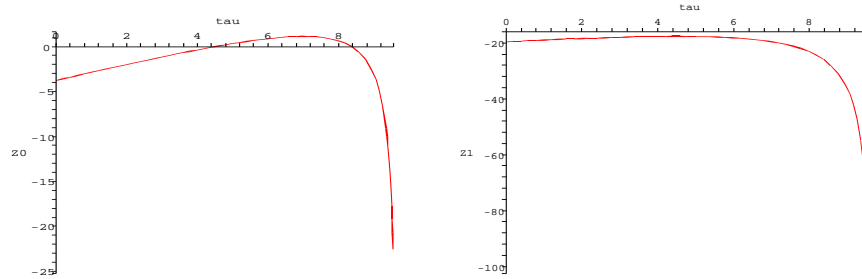
FIGURE 1. The functions Z_0 (left) and Z_1 (right) are drawn on the interval $[0, \tau^*)$ for parameters given by (34) and $n = 12$. One can see that Z_0 has exactly two roots, $\tau_1 \simeq 4.52$ and $\tau_2 \simeq 8.36$, and Z_1 has no root.
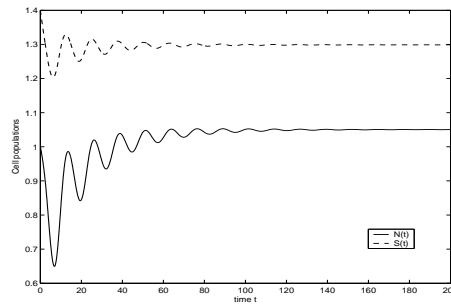

FIGURE 2. For $\tau = 3.5$ days and the other parameters given by (34) with $n = 12$, the solutions $S(t)$ (dashed line) and $N(t)$ (solid line) oscillate transiently to the steady state, which is asymptotically stable. Damped oscillations are observed.

For $n \geq 10$, Pujo-Menjouet et al. [28, 29] noticed, for the model (1)–(2) with the introduction rate β depending only upon the nonproliferating phase population $N(t)$, that oscillations may be observed.

We choose $n = 12$, in keeping with values in [28, 29]. Then, we find that

$$\overline{\tau} \simeq 13.3 \text{ days} \qquad \text{and} \qquad \tau^* \simeq 9.66 \text{ days.}$$

One can see in Figure 1 that Z_0 has two positive roots in this case, $\tau_1 \simeq 4.52$ days and $\tau_2 \simeq 8.36$ days, and that Z_1 is strictly negative, so all Z_k functions with $k \geq 1$ have no roots. Consequently, there exist two critical values, τ_1 and τ_2, for which a stability switch can occur at E^*.

For $\tau < \tau_1$, one can check that the populations are asymptotically stable on Figure 2. In this case $\tau = 3.5$ days and the solutions of (3)–(4) oscillate transiently to the steady state. Numerical simulations of the solutions of (3)–(4) are carried out with dde23 [30], a MATLAB solver for delay differential equations.

When $\tau = \tau_1$, one can check that

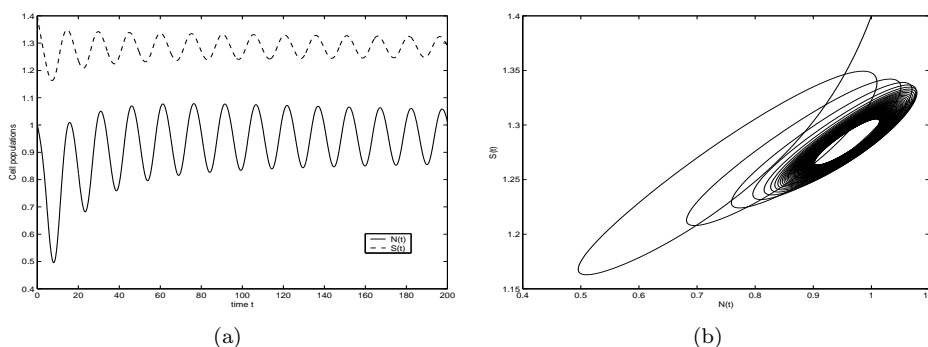$$B(A^2 + A' + AA'\tau_c) - B^3 - B^2 B'\tau_c - B'A \simeq 0.053,$$

(a) (b)

FIGURE 3. For $\tau = 4.52$ days and the other parameters given
by (34) with $n = 12$, a Hopf bifurcation occurs and the steady
state (S^*, N^*) of (3)–(4) is unstable. The periodic solutions $S(t)$
(dashed line) and $N(t)$ (solid line) are represented in (a), and we
can observe the solutions in the (S, N)-plane in (b). Periods of the
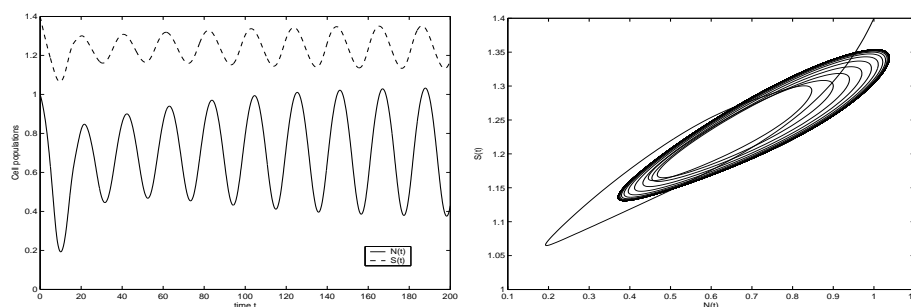oscillations are about 15 days.

FIGURE 4. For $\tau = 7$ days and the other parameters given by (34)
with $n = 12$, long periods oscillations are observed, with periods
about 20-25 days. The steady state E^* is unstable.

so condition (32) holds, and a Hopf bifurcation occurs at (S^*, N^*), from Theorem
5.1. This is illustrated on Figure 3. Periodic solutions with periods about 15 days
are observed at the bifurcation, and the steady state E^* becomes unstable.

When τ increases after the bifurcation, one can observe oscillating solutions with
longer periods (in the order of 20 to 30 days), as it can be seen in Figure 4.

This phenomenon has already been observed by Pujo-Menjouet et al. [28, 29]. It
can be related to diseases affecting blood cells, the so-called periodic hematological
diseases [18], which are characterized by oscillations of circulating blood cell counts
with long periods compared to the cell cycle duration. Among the wide variety of
periodic hematological diseases, we can cite chronic myelogenous leukemia [5, 15,
28], a cancer of white blood cells with periods usually falling in the range of 70
to 80 days, and cyclical neutropenia [9, 18], which is known to exhibit oscillations
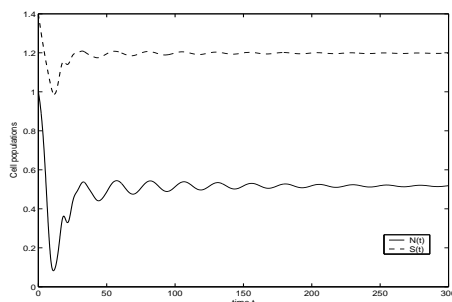around 3 weeks of circulating neutrophils (white cells), as observed in Figure 4.

FIGURE 5. For $\tau = 9$ days and the other parameters given by (34)
with $n = 12$, damped oscillations are observed and the steady state
is stable.

Eventually, one can note that when τ passes through the second critical value
τ_2, stability switches, and then the steady state (S^*, N^*) becomes stable again (see
Figure 5).

7. **Discussion.** We considered a nonlinear model of blood cell dynamics in which
the nonlinearity depends upon the entire hematopoietic stem cell population, con-
trary to the common assumption used in previous works [4, 5, 9, 20, 21, 28, 29]
dealing with blood cell production models. Then we were led to the study of a new
nonlinear system of two differential equations with delay (describing the cell cycle
duration) modelling the hematopoietic stem cells dynamics.

We obtained the existence of two steady states for this model: a trivial one and a
positive delay-dependent steady state. Through sections 4 and 5, we performed the
stability analysis of our model. We determined necessary and sufficient conditions
for the global asymptotic stability of the trivial steady state of system (3)–(4), which
describes the population's dying out. Using an approach proposed by Beretta and
Kuang [8], we analyzed a first-degree exponential polynomial characteristic equation
with delay-dependent coefficients to obtain the existence of a Hopf bifurcation for
the positive steady state (see Theorem 5.1) leading to the existence of periodic
solutions.

In the example presented in the previous section, we obtained long-period oscil-
lations, which can be related to some periodic hematological diseases (in particular,
to cyclical neutropenia [9]). This result is in keeping with previous analysis of blood
cell dynamics models (as can be found in [20, 28, 29]). Periodic hematological dis-
eases are particular diseases mostly originated from the hematopoietic stem cell
compartment. The appearance of periodic solutions in our model with periods that
can be related to the ones observed in some periodic hematological diseases stresses
the interesting properties displayed by our model. Periods of oscillating solutions
can for example be used to determine the length of cell cycles in hematopoietic
stem cell populations that cannot be directly determined experimentally.

Moreover, stability switches have been observed, due to the structure of the
equations (nonlinear equations with delay-dependent coefficients). Such a behavior
had been noted in previous works dealing with blood cell production models (see
[28, 29]), but it had never been mathematically explained.

We can note that our assumption, that proliferating and nonproliferating cells
die at the same rate, may be too limitative, since Pujo-Menjouet et al. [28, 29]

already noticed that the apoptotic rate (the proliferating phase mortality rate γ) plays an important role in the appearance of oscillating solutions. However, by assuming that the two populations die with different rates, we are led to a second-order exponential polynomial characteristic equation, and the calculations are more difficult than the ones carried out in the present work. We leave it for further analysis.

REFERENCES

[1] M. Adimy and F. Crauste, GLOBAL STABILITY OF A PARTIAL DIFFERENTIAL EQUATION WITH DISTRIBUTED DELAY DUE TO CELLULAR REPLICATION, Nonlinear Analysis 54 (2003) 1469–1491.

[2] M. Adimy and F. Crauste, EXISTENCE, POSITIVITY AND STABILITY FOR A NONLINEAR MODEL OF CELLULAR PROLIFERATION, Nonlinear Analysis: Real World Applications 6(2) (2005) 337–366.

[3] M. Adimy, F. Crauste and L. Pujo-Menjouet, ON THE STABILITY OF A MATURITY STRUCTURED MODEL OF CELLULAR PROLIFERATION, Discret. Cont. Dyn. Sys. Ser. A 12(3) (2005) 501–522.

[4] M. Adimy, F. Crauste and S. Ruan, A MATHEMATICAL STUDY OF THE HEMATOPOIESIS PROCESS WITH APPLICATIONS TO CHRONIC MYELOGENOUS LEUKEMIA, SIAM J. Appl. Math. 65(4) (2005) 1328–1352.

[5] M. Adimy, F. Crauste and S. Ruan, STABILITY AND HOPF BIFURCATION IN A MATHEMATICAL MODEL OF PLURIPOTENT STEM CELL DYNAMICS, Nonlinear Analysis: Real World Applications 6(4) (2005) 651–670.

[6] M. Adimy and L. Pujo-Menjouet, ASYMPTOTIC BEHAVIOUR OF A SINGULAR TRANSPORT EQUATION MODELLING CELL DIVISION, Discret. Cont. Dyn. Syst. Ser. B 3 (2003) 439–456.

[7] J. Bélair, M.C. Mackey and J.M. Mahaffy, AGE-STRUCTURED AND TWO-DELAY MODELS FOR ERYTHROPOIESIS, Math. Biosci. 128 (1995) 317–346.

[8] E. Beretta and Y. Kuang, GEOMETRIC STABILITY SWITCH CRITERIA IN DELAY DIFFERENTIAL SYSTEMS WITH DELAY DEPENDENT PARAMETERS, SIAM J. Math. Anal. 33(5) (2002) 1144–1165.

[9] S. Bernard, J. Bélair and M.C. Mackey, OSCILLATIONS IN CYCLICAL NEUTROPENIA: NEW EVIDENCE BASED ON MATHEMATICAL MODELING, J. Theor. Biol. 223 (2003) 283–298.

[10] F.J. Burns and I.F. Tannock, ON THE EXISTENCE OF A G_0 PHASE IN THE CELL CYCLE, Cell Tissue Kinet. 19 (1970) 321–334.

[11] J. Dieudonné, FOUNDATIONS OF MODERN ANALYSIS, Academic Press, New-York, 1960.

[12] J. Dyson, R. Villella-Bressan and G.F. Webb, A NONLINEAR AGE AND MATURITY STRUCTURED MODEL OF POPULATION DYNAMICS. I: BASIC THEORY., J. Math. Anal. Appl. 242(1) (2000) 93–104.

[13] J. Dyson, R. Villella-Bressan and G.F. Webb, A NONLINEAR AGE AND MATURITY STRUCTURED MODEL OF POPULATION DYNAMICS. II: CHAOS., J. Math. Anal. Appl. 242(2) 255–270.

[14] J. Dyson, R. Villella-Bressan and G.F. Webb, ASYNCHRONOUS EXPONENTIAL GROWTH IN AN AGE STRUCTURED POPULATION OF PROLIFERATING AND QUIESCENT CELLS, Math. Biosci. 177–178 (2002) 73–83.

[15] P. Fortin and M.C. Mackey, PERIODIC CHRONIC MYELOGENOUS LEUKEMIA: SPECTRAL ANALYSIS OF BLOOD CELL COUNTS AND ETIOLOGICAL IMPLICATIONS, Brit. J. Haematol. 104 (1999) 336–345.

[16] K. Gopalsamy, STABILITY AND OSCILLATIONS IN DELAY DIFFERENTIAL EQUATIONS OF POPULATION DYNAMICS, Mathematics and its Applications 74, Kluwer Academic Publishers Group, Dordrecht, 1992.

[17] J. Hale and S.M. Verduyn Lunel, INTRODUCTION TO FUNCTIONAL DIFFERENTIAL EQUATIONS, Applied Mathematical Sciences 99, Springer-Verlag, New York, 1993.

[18] C. Haurie, D.C. Dale and M.C. Mackey, CYCLICAL NEUTROPENIA AND OTHER HEMATOLOGICAL DISORDERS: A REVIEW OF MECHANISMS AND MATHEMATICAL MODELS, Blood 92(8) (1998) 2629–2640.

[19] Y. Kuang, DELAY DIFFERENTIAL EQUATIONS WITH APPLICATIONS IN POPULATION DYNAMICS, Mathematics in Science and Engineering 191, Academic Press, New York, 1993.

[20] M.C. Mackey, UNIFIED HYPOTHESIS OF THE ORIGIN OF APLASTIC ANAEMIA AND PERIODIC HEMATOPOIESIS, Blood 51 (1978) 941–956.

[21] M.C. Mackey, DYNAMIC HEMATOLOGICAL DISORDERS OF STEM CELL ORIGIN, in J.G. Vassileva-Popova and E.V. Jensen (Eds), Biophysical and biochemical information transfer in recognition, Plenum Press, New York, 941–956, 1979.

[22] M.C. Mackey and A. Rey, MULTISTABILITY AND BOUNDARY LAYER DEVELOPMENT IN A TRANS-PORT EQUATION WITH RETARDED ARGUMENTS, Can. Appl. Math. Quart. 1 (1993) 1–21.

[23] M.C. Mackey and A. Rey, PROPAGATION OF POPULATION PULSES AND FRONTS IN A CELL REPLICATION PROBLEM: NON-LOCALITY AND DEPENDENCE ON THE INITIAL FUNCTION, Physica D 86 (1995) 373–395.

[24] M.C. Mackey and A. Rey, TRANSITIONS AND KINEMATICS OF REACTION-CONVECTION FRONTS IN A CELL POPULATION MODEL, Physica D 80 (1995) 120–139.

[25] M.C. Mackey and R. Rudnicki, GLOBAL STABILITY IN A DELAYED PARTIAL DIFFERENTIAL EQUATION DESCRIBING CELLULAR REPLICATION, J. Math. Biol. 33 (1994) 89–109.

[26] M.C. Mackey and R. Rudnicki, A NEW CRITERION FOR THE GLOBAL STABILITY OF SIMULTA-NEOUS CELL REPLICATION AND MATURATION PROCESSES, J. Math. Biol. 38 (1999) 195–219.

[27] J.M. Mahaffy, J. Bélair and M.C. Mackey, HEMATOPOIETIC MODEL WITH MOVING BOUNDARY CONDITION AND STATE DEPENDENT DELAY, J. Theor. Biol. 190 (1998) 135–146.

[28] L. Pujo-Menjouet, S. Bernard and M.C. Mackey, LONG PERIOD OSCILLATIONS IN A G_0 MODEL OF HEMATOPOIETIC STEM CELLS, SIAM J. Appl. Dyn. Systems 4(2) (2005) 312–332.

[29] L. Pujo-Menjouet and M.C. Mackey, CONTRIBUTION TO THE STUDY OF PERIODIC CHRONIC MYELOGENOUS LEUKEMIA, C. R. Biologies 327 (2004) 235–244.

[30] L.F. Shampine and S. Thompson, SOLVING DDEs IN MATLAB, Appl. Numer. Math. 37 (2001) 441–458. http://www.radford.edu/ thompson/webddes/

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