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Analysis of a Nonlinear Delay Differential-Difference Biological Model [★]

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Abstract: Recently, a new model describing the cell dynamics in hematopoiesis was proposed. It can be described as an age-structured delay differential-difference model. Under some conditions on the biological parameters, it admits two equilibrium points. The first one is the 0-equilibrium and the second one, which does not always exist, is a strictly positive point. We propose a Lyapunov functional construction in order to investigate the stability properties of both equilibria. For the 0 equilibrium, we establish the global exponential stability when the positive equilibrium does not exist. For the positive equilibrium, we establish its local exponential stability, estimate the decay rate of solutions and provide an open subset of its basin of attraction.

Keywords: Lyapunov Functionals, Exponential Stability, Basin of attraction.

1. INTRODUCTION

Different research communities have been interested in the phenomenon of hematopoiesis over the last years. The complexity of the process of blood cells formation and the multiple diseases that affect this process, including leukemia, made mathematical modeling of these phenomena essential in order to understand both the healthy and unhealthy hematopoiesis. A significant work has been done by Adimy et al. (2008), improving the initial model proposed by Mackey (1978). Considerable works have followed thereafter covering both modeling and stability analysis of the dynamics of healthy and cancerous cells; see for instance: Özbay et al. (2008), Özbay et al. (2012), Avila et al. (2014), Fridman et al. (2015), Djema et al. (2015), Djema et al. (2016) and recently Adimy et al. (2015).

The present contribution is based on the latter work, where a new way to model the fast self-renewal dynamics of hematopoietic stem cells is introduced. The new model takes into account a subpopulation of cells that remains constantly active in the proliferating compartment. Its main interest is that it may explain the dynamics of cancer cells in the case of acute myeloid leukemia, where a high level production of abnormal immature white blood cells is observed.

The resulting model is a nonlinear delay differential-difference system. It is worth mentioning that it can have bounded or unbounded solutions. The first equilibrium of interest is the 0-equilibrium which always exists. Biologically, it means the extinction of all the blood cells. This situation becomes interesting in the case where the

studied model represents the dynamics of cancer cells that we want to eradicate. Under some conditions, a unique strictly positive steady state will exist. Biologically, the latter equilibrium reflects the **survival** of blood cells. The stability analysis of the positive equilibrium offers a way to maintain the density of cells at a desired level and avoid the unbounded or periodic behaviors observed in some hematopoietic diseases.

From a mathematical point of view, it is well known that theory of the Lyapunov functions offers some strong advantages when investigating the stability properties of time-delay systems, but unfortunately the construction of suitable Lyapunov functionals may be difficult. Some tools making possible to construct Lyapunov functionals for some nonlinear differential-difference equations are available (see, Pepe et al. (2008), Karafyllis et al. (2009), Gu and Liu (2009), and the references therein), or, when it is possible, one may formulate the problem in the neutral time-delay framework and take advantage of the existing literature in this field (see, for more information, Mazenc and Ito (2013) for nonlinear systems and Fridman (2001) for linear systems), but that does not apply when the trajectories are not differentiable. On the other hand, it is worth mentioning that even if an equilibrium is known to be asymptotically stable, we still need some explicit strict Lyapunov functionals in order to establish some robustness results (Malisoff and Mazenc, 2009). Besides the difficulties related to the construction of suitable functionals for nonlinear systems, the stability analysis may be more complicated due to some mathematical or practical considerations. Indeed, we wish to point out that it is more difficult to investigate the stability properties of piecewise solutions (see, Orlov (2009) and Filippov (1988)) than the uniformly continuous solutions. For instance, the Barbalat's lemma requires uniform continuity of solutions which is not the case of the studied model describing hematopoiesis. We

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also emphasize that, generally speaking, some robustness issues are expected when the studied models are dealing with living organisms, in contrast with other phenomena that are almost perfectly described by physical laws. It is worth mentioning that these obstacles are overcome by the knowledge of a strict Lyapunov functional.

In light of previous comments, in this paper, we develop a Lyapunov approach to analyze the differential-difference model of hematopoiesis. We construct two types of functionals that can be used to perform a robustness analysis.

The work is organized as follows: in the remainder of the introduction, the studied model is briefly introduced. In Section 2, we prove the global exponential stability of the 0-equilibrium via a linear functional, then, in Section 3, we use some quadratic functionals to analyze the local stability of the positive equilibrium and we provide an open subset of its basin of attraction.

The reader is invited to refer to the Sections 1-3 in Adimy et al. (2015) for the accurate presentation of the biological model which is represented in Figure 1. The differential-difference system studied in this paper is given by:

$$\begin{cases} \dot{x}(t) = -(\delta + \beta(x(t)))x(t) + 2Le^{-\gamma\tau}u(t - \tau), \\ u(t) = \beta(x(t))x(t) + 2Ke^{-\gamma\tau}u(t - \tau), \quad t > 0, \end{cases} \quad (1)$$

where we consider that the parameters δ , K , $L = 1 - K$, γ and τ are strictly positive real numbers and $K \in (0, 1)$. x represents the total density of resting cells and u is the density of the new proliferating cells. The function β is continuous, decreasing and $\lim_{x \rightarrow \infty} \beta(x) = 0$. We can prove that a unique piecewise continuous solution $(x(t), u(t))$ exists for all $t \geq 0$, when the system (1) is associated with the initial conditions $x(0) = x_0$ and $u(t) = \varphi_u \in \mathcal{C}([-\tau, 0], \mathbb{R})$. Moreover, System (1) is a positive system (i.e. the solutions of system (1) associated with positive initial conditions are positive). In this paper we consider only the positive solutions of (1).

We consider that the nonlinearity β is locally Lipschitz and its expression is given by

$$\beta(x) = \frac{\beta(0)}{1 + bx^n} \quad (2)$$

where b , n and $\beta(0)$ are strictly positive real numbers. (See, Mackey (1978) and Adimy et al. (2015) for some numerical values and their interpretation).

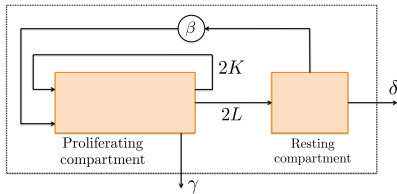


Fig. 1. Schematic representation of blood cells formation.

To ease the notation, let us define the following constants:

$$\bar{K} = \frac{1}{2}e^{\gamma\tau}, \quad (3)$$

$$\mu = \frac{\beta(0)}{\delta}, \quad (4)$$

$$\underline{K} = (\mu + 1)\bar{K} - \mu. \quad (5)$$

Notice that \bar{K} and μ are strictly positive.

2. STABILITY ANALYSIS OF THE 0-EQUILIBRIUM

We start by stability and instability results for the trivial equilibrium $E^0 = (0, 0)$. Biologically, E^0 reflects the extinction of all blood cells. In the case where the model (1) describes the dynamics of unhealthy hematopoietic stem cells, the stability analysis of E^0 may give a way to eradicate the cancerous cells. Our approach is slightly different from the one used in Adimy et al. (2015) in the sense that we prove the exponential stability, with an estimate of the rate of convergence, via a construction of a strict Lyapunov functional, without requiring the continuity of solutions. As mentioned in the Introduction, the strict functional may also be used to perform a robustness analysis.

Theorem 1. For all

$$K \in (0, \bar{K}), \quad (6)$$

i) if the condition

$$s := \underline{K} - K > 0, \quad (7)$$

is satisfied, the origin of the system (1) is globally exponentially stable.

ii) if

$$s := \underline{K} - K \leq 0, \quad (8)$$

then no positive trajectory converges to the origin of the system (1).

Remark 1. In Section 3, we shall prove that if (7) is satisfied, the origin is the unique equilibrium point of system (1). This explains why the stability results in Theorem 1 are global.

Proof. Let us introduce the following functional:

$$\mathcal{M}(x(t), u_t) = x(t) + \left(\frac{\mu + 1}{\mu} + \epsilon \right) \int_{t-\tau}^t u(l) dl, \quad (9)$$

with

$$\epsilon = -\frac{s}{2(\bar{K} - K)\mu}. \quad (10)$$

Notice that, since $K \in (0, \bar{K})$, then $\epsilon < 0$, when (7) is satisfied and $\epsilon \geq 0$ when (8) holds.

We start by proving ii). Let us proceed by contradiction. We assume that the condition (8) is satisfied and a positive solution $(x(t), u(t))$ converges to the origin.

Since $\epsilon \geq 0$, the functional \mathcal{M} is positive on the positive orthant. Moreover, its derivative along the trajectories of (1) is

$$\begin{aligned} \dot{\mathcal{M}}(t) = & \left[-\delta + \left(\frac{\mu + 1}{\mu} + \epsilon - 1 \right) \beta(x(t)) \right] x(t) \\ & + \left[-\frac{\mu + 1}{\mu} - \epsilon + \left(\frac{\mu + 1}{\mu} + \epsilon \right) \frac{K}{\bar{K}} \right. \\ & \left. + \frac{1 - K}{\bar{K}} \right] u(t - \tau). \end{aligned} \quad (11)$$

On the other hand, from (4), we notice that

$$-\delta + \left(\frac{\mu + 1}{\mu} + \epsilon - 1 \right) \beta(0) = \epsilon \beta(0) \geq 0. \quad (12)$$

Since $x(t)$ converges to zero, and β is continuous and decreasing, we conclude that there exists a time instant

$t_1 > 0$, such that for all $t \geq t_1$,

$$-\delta + \left(\frac{\mu+1}{\mu} + \epsilon - 1 \right) \beta(x(t)) \geq \frac{\epsilon\beta(0)}{2} \geq 0. \quad (13)$$

It follows from (11) and (13) that for all $t \geq t_1$,

$$\begin{aligned} \dot{\mathcal{M}}(t) &\geq \frac{\epsilon\beta(0)}{2}x(t) + \left[-\frac{\mu+1}{\mu} - \epsilon + \left(\frac{\mu+1}{\mu} + \epsilon \right) \frac{K}{\bar{K}} \right. \\ &\quad \left. + \frac{1-K}{\bar{K}} \right] u(t-\tau) \\ &= \frac{\epsilon\beta(0)}{2}x(t) + \frac{1}{\mu\bar{K}} \left[-(\mu+1)\bar{K} + \mu + K \right. \\ &\quad \left. + \epsilon\mu(K - \bar{K}) \right] u(t-\tau). \end{aligned}$$

Since $s = (\mu+1)\bar{K} - \mu - K$, the previous inequality rewrites as

$$\begin{aligned} \dot{\mathcal{M}}(t) &\geq \frac{\epsilon\beta(0)}{2}x(t) + \frac{1}{\mu\bar{K}} [-s + \epsilon\mu(K - \bar{K})] u(t-\tau) \\ &= \frac{\epsilon\beta(0)}{2}x(t) - \frac{s}{2\mu\bar{K}}u(t-\tau), \end{aligned}$$

where the last equality is a consequence of (10). Since $s \leq 0$ and $\epsilon \geq 0$, we conclude that for all $t \geq t_1$, $\dot{\mathcal{M}}(t) \geq 0$.

It follows that

$$\mathcal{M}(x(t), u_t) \geq \mathcal{M}(x(t_1), u_{t_1}) > 0. \quad (14)$$

Therefore, \mathcal{M} does not converge to zero. On the other hand, \mathcal{M} converges to zero since $(x(t), u(t))$ converges to the origin. This yields a contradiction.

Next, let us prove i). We consider the case where the inequality (7) is satisfied. An immediate consequence is that $\epsilon < 0$.

First, to ensure that the functional \mathcal{M} is positive on the positive orthant, let us check that $\left(\frac{\mu+1}{\mu} + \epsilon \right) > 0$. From the definitions of ϵ and s , we get

$$\frac{\mu+1}{\mu} + \epsilon = \frac{2[(\mu+1)\bar{K} - \mu K] - 2K - s}{2(\bar{K} - K)\mu}. \quad (15)$$

Since $K \in (0, 1)$, we deduce that $(\mu+1)\bar{K} - \mu K > (\mu+1)\bar{K} - \mu = \underline{K}$. It follows that

$$\frac{\mu+1}{\mu} + \epsilon > \frac{2(\underline{K} - K) - s}{2(\bar{K} - K)\mu} = \frac{s}{2(\bar{K} - K)\mu} > 0. \quad (16)$$

Consequently, the functional \mathcal{M} is positive on the positive orthant. Moreover, its derivative along the trajectories of (1) satisfies

$$\begin{aligned} \dot{\mathcal{M}}(t) &= \left[-\delta + \left(\frac{\mu+1}{\mu} + \epsilon - 1 \right) \beta(x(t)) \right] x(t) \\ &\quad - \frac{s}{2\mu\bar{K}}u(t-\tau) \\ &\leq \left[-\delta + \left(\frac{\mu+1}{\mu} - 1 \right) \beta(0) \right] x(t) \\ &\quad + \epsilon\beta(x(t))x(t) - \frac{s}{2\mu\bar{K}}u(t-\tau) \\ &= \epsilon\beta(x(t))x(t) - \frac{s}{2\mu\bar{K}}u(t-\tau), \end{aligned} \quad (17)$$

where the last equality is a consequence of (4).

By integrating (17), we get, for all $t \geq 0$,

$$\begin{aligned} \mathcal{M}(x(t), u_t) &\leq \mathcal{M}(x_0, \varphi_u) + \epsilon \int_0^t \beta(x(m))x(m)dm \\ &\quad - \frac{s}{2\mu\bar{K}} \int_0^t u(m-\tau)dm. \end{aligned} \quad (18)$$

Since $\epsilon < 0$ and $s > 0$, it follows from (9) and (18) that for all $t \geq 0$, the trajectory $x(t)$ is bounded by a constant $x_b > 0$.

In order to complete the proof, let us introduce the following functional:

$$\begin{aligned} \mathcal{W}(x(t), u_t) &= \mathcal{M}(x(t), u_t) - \psi \int_{t-\tau}^t u(l)dl \\ &\quad + \tilde{\psi} \int_{t-\tau}^t \int_m^t e^{l-t}u(l)dldm, \end{aligned} \quad (19)$$

where ψ and $\tilde{\psi}$ are positive real numbers to be selected later. From (16), observe that if we choose

$$\psi = \min \left\{ \frac{s}{4(\bar{K} - K)\mu}, \frac{s}{2\mu\bar{K}} \right\}, \quad (20)$$

then the functional \mathcal{W} is positive on the positive orthant and its derivative along the trajectories of (1) is:

$$\begin{aligned} \dot{\mathcal{W}}(t) &= \dot{\mathcal{M}}(t) - \psi [u(t) - u(t-\tau)] \\ &\quad + \tilde{\psi} \left[-\int_{t-\tau}^t e^{l-t}u(l)dl + \tau u(t) \right] \\ &\quad - \tilde{\psi} \int_{t-\tau}^t \int_m^t e^{l-t}u(l)dldm. \end{aligned}$$

Selecting $\tilde{\psi} = \frac{\psi}{\tau}$, we obtain

$$\begin{aligned} \dot{\mathcal{W}}(t) &= \dot{\mathcal{M}}(t) + \psi u(t-\tau) - \tilde{\psi} \int_{t-\tau}^t e^{l-t}u(l)dl \\ &\quad - \tilde{\psi} \int_{t-\tau}^t \int_m^t e^{l-t}u(l)dldm \\ &\leq \dot{\mathcal{M}}(t) + \psi u(t-\tau) - \tilde{\psi} e^{-\tau} \int_{t-\tau}^t u(l)dl \\ &\quad - \tilde{\psi} \int_{t-\tau}^t \int_m^t e^{l-t}u(l)dldm. \end{aligned} \quad (21)$$

Then from (17) and (21), we deduce that

$$\begin{aligned} \dot{\mathcal{W}}(t) &\leq \epsilon\beta(x(t))x(t) - \left[\frac{s}{2\mu\bar{K}} - \psi \right] u(t-\tau) \\ &\quad - \tilde{\psi} e^{-\tau} \int_{t-\tau}^t u(l)dl - \tilde{\psi} \int_{t-\tau}^t \int_m^t e^{l-t}u(l)dldm \\ &\leq \epsilon\beta(x(t))x(t) - \tilde{\psi} e^{-\tau} \int_{t-\tau}^t u(l)dl \\ &\quad - \tilde{\psi} \int_{t-\tau}^t \int_m^t e^{l-t}u(l)dldm, \end{aligned} \quad (22)$$

where the last inequality is a consequence of (20).

Combining the facts that $\epsilon < 0$, β is a continuous decreasing function and $x(t)$ is bounded by $x_b > 0$, for all $t \geq 0$, we deduce that

$$\begin{aligned} \dot{\mathcal{W}}(t) &\leq \epsilon\beta(x_b)x(t) - \tilde{\psi} e^{-\tau} \int_{t-\tau}^t u(l)dl \\ &\quad - \tilde{\psi} \int_{t-\tau}^t \int_m^t e^{l-t}u(l)dldm. \end{aligned} \quad (23)$$

Finally, we conclude that there exists a strictly positive \tilde{s} , such that

$$\dot{W}(t) \leq -\tilde{s}W(x(t), u_t). \quad (24)$$

We deduce that

$$W(x(t), u_t) \leq e^{-\tilde{s}t}W(x_0, \varphi_u). \quad (25)$$

Therefore,

$$x(t) \leq e^{-\tilde{s}t}W(x_0, \varphi_u). \quad (26)$$

It follows that x converges exponentially to zero. Consequently, from the second equation in (1), u converges exponentially to zero (the proof of this simple result is omitted here).

Remark 2. Notice that Theorem 1 gives a necessary and sufficient condition for the exponential stability of the trivial steady state when $K \in (0, \bar{K})$ (Eq. (6)). In the case where \bar{K} is greater than 1, it follows that Theorem 1 is available for all $K \in (0, 1)$. However, if $\bar{K} \leq 1$, the conditions (6) and (7) give stability/instability conditions only for $K \in (0, \bar{K})$. In order to complete the analysis, we show that if $\bar{K} \leq 1$, then no positive trajectory converges to the origin for all $K \in (\bar{K}, 1)$, by similar arguments as in ii) in Theorem 1, where we consider the functional \mathcal{M} , defined in (11) with ϵ any strictly positive constant.

3. ANALYSIS OF THE POSITIVE EQUILIBRIUM

Contrary to the trivial equilibrium, $E^0 = (0, 0)$, studied in the previous part, the strictly positive equilibrium $E = (x_e, u_e)$ does not always exist. In this section, first, we recall the conditions for its existence then we investigate its stability properties by a Lyapunov approach.

In order to analyze the stability of the positive equilibrium, the authors in Adimy et al. (2015) develop a method which consists in writing the model (1) as a special case of a neutral differential system and then investigating the local stability properties of the linear approximation of the neutral system by a frequency approach. Notice that the latter procedure requires the solutions of the system (1) to be differentiable.

In the present contribution, without extra assumptions on the system (1), which may admit discontinuous solutions, we prove under suitable sufficient conditions that E is locally exponentially stable by a direct Lyapunov approach, which allows us to determine an approximation of its basin of attraction.

3.1 Existence of a strictly positive equilibrium point

If a positive equilibrium $E = (x_e, u_e)$ exists, then it satisfies:

$$\begin{cases} (\delta + \beta(x_e))x_e = 2Le^{-\gamma\tau}u_e, \\ \beta(x_e)x_e = (1 - 2Ke^{\gamma\tau})u_e. \end{cases} \quad (27)$$

From the second equation in (27), it follows that

$$u_e = \frac{\bar{K}}{\bar{K} - K}\beta(x_e)x_e. \quad (28)$$

From the previous equation, observe that the existence of E implies necessarily that $K < \bar{K}$. By substituting u_e in the first equation in (27), and since x_e is not zero, we get

$$\left(\frac{1 - \bar{K}}{\bar{K} - K}\right)\beta(x_e) = \delta.$$

Since $\delta > 0$ and $K < \bar{K}$, we deduce that

$$\bar{K} < 1. \quad (29)$$

Since β is continuous, decreasing and $\lim_{a \rightarrow \infty} \beta(a) = 0$, it follows from (28) that the existence and uniqueness of E are guaranteed by

$$\frac{1 - \bar{K}}{\bar{K} - K} > \frac{1}{\mu}.$$

Since $1 - \bar{K} > 0$, $\bar{K} - K > 0$ and $\underline{K} = (\mu + 1)\bar{K} - \mu$, the previous inequality is equivalent to

$$\underline{K} < K. \quad (30)$$

We conclude that the condition $K \in (\underline{K}, \bar{K})$ is necessary for the existence of E . This statement justifies what we have mentioned in Remark 1. We can easily check that if (29) holds, then $\underline{K} < \bar{K}$, and consequently E may exist. Next, since \underline{K} may be positive or negative, and using the fact that $K > 0$, we conclude that we have proved the following:

Proposition 2. A **strictly positive steady state** $E = (x_e, u_e)$ exists if and only if the conditions:

$$0 < K < \bar{K} < \frac{\mu}{\mu + 1}, \quad (31)$$

or,

$$0 < \underline{K} < K < \bar{K} < 1, \quad (32)$$

are satisfied.

3.2 Stability properties of the positive equilibrium point

In this section, we assume that the positive equilibrium E exists. First, the changes of coordinates $\tilde{x} = x - x_e$ and $\tilde{u} = u - u_e$ give

$$\begin{cases} \dot{\tilde{x}}(t) = -(\delta + \beta(\tilde{x}(t) + x_e))(\tilde{x}(t) + x_e) \\ \quad + 2Le^{-\gamma\tau}(\tilde{u}(t - \tau) + u_e), \\ \tilde{u}(t) = -u_e + \beta(\tilde{x}(t) + x_e)(\tilde{x}(t) + x_e) \\ \quad + 2Ke^{-\gamma\tau}(\tilde{u}(t - \tau) + u_e), \quad t > 0, \end{cases} \quad (33)$$

or, equivalently,

$$\begin{cases} \dot{\tilde{x}}(t) = -\delta\tilde{x}(t) - \beta(\tilde{x}(t) + x_e)(\tilde{x}(t) + x_e) \\ \quad + 2Le^{-\gamma\tau}\tilde{u}(t - \tau) - \delta x_e + 2Le^{-\gamma\tau}u_e, \\ \tilde{u}(t) = \beta(\tilde{x}(t) + x_e)(\tilde{x}(t) + x_e) + 2Ke^{-\gamma\tau}\tilde{u}(t - \tau) \\ \quad + (2Ke^{-\gamma\tau} - 1)u_e, \quad t > 0. \end{cases} \quad (34)$$

Analyzing the **stability properties of the origin** of (34) seems to be a difficult task. We write the model (34) in an equivalent form that eases its analysis. Using the Taylor formula, we can write

$$\beta(\mathfrak{z} + x_e)(\mathfrak{z} + x_e) = \beta(x_e)x_e + \theta\mathfrak{z} + I(\mathfrak{z}), \quad (35)$$

with

$$\theta = \beta(x_e) + \beta'(x_e)x_e \quad (36)$$

and

$$I(\mathfrak{z}) = \int_{x_e}^{x_e + \mathfrak{z}} (\mathfrak{z} + x_e - l)\tilde{\theta}(l)dl, \quad (37)$$

where $\tilde{\theta}(\mathfrak{z}) = [\beta(\mathfrak{z})\mathfrak{z}]^{(2)}$. We deduce that for all $t > 0$, the system (34) is equivalent to

$$\begin{cases} \dot{\tilde{x}}(t) = -\delta\tilde{x}(t) - \beta(x_e)x_e - \theta\tilde{x}(t) - I(\tilde{x}(t)) \\ \quad + 2Le^{-\gamma\tau}\tilde{u}(t - \tau) - \delta x_e + 2Le^{-\gamma\tau}u_e, \\ \tilde{u}(t) = \beta(x_e)x_e + \theta\tilde{x}(t) + I(\tilde{x}(t)) \\ \quad + 2Ke^{-\gamma\tau}\tilde{u}(t - \tau) + (2Ke^{-\gamma\tau} - 1)u_e. \end{cases} \quad (38)$$

Using (27), we get for all $t > 0$,

$$\begin{cases} \dot{\tilde{x}}(t) = -(\delta + \theta)\tilde{x}(t) - I(\tilde{x}(t)) + 2Le^{-\gamma\tau}\tilde{u}(t - \tau), \\ \dot{\tilde{u}}(t) = \theta\tilde{x}(t) + I(\tilde{x}(t)) + 2Ke^{-\gamma\tau}\tilde{u}(t - \tau). \end{cases} \quad (39)$$

Observe that, **due to the shifting**, the trajectories are no longer positive ($\tilde{x} > -x_e$, $\tilde{u} > -u_e$, where $x_e > 0$ and $u_e > 0$). To analyze the model (39), we introduce the quadratic function

$$Q(a) = \frac{1}{2}a^2, \quad (40)$$

and the functionals,

$$\Theta(\tilde{u}_t) = \int_{t-\tau}^t Q(\tilde{u}(l))dl, \quad (41)$$

$$\Lambda(\tilde{u}_t) = \int_{t-\tau}^t \int_m^t e^{l-t} Q(\tilde{u}(l))dl dm. \quad (42)$$

For later use, let us state the following result:

Claim 3. For all $x_e > 0$ and $\tilde{x} > -x_e$, there exist two strictly positive constants z_1 and z_2 , such that

$$|I(\tilde{x})| \leq z_1 Q(\tilde{x}) \quad \text{and} \quad |I(\tilde{x})| \leq z_2 |\tilde{x}|, \quad (43)$$

where,

$$z_1 = 2\mathbf{c}_4\beta(0), \quad (44)$$

$$z_2 = \beta(0) \max\{\mathbf{c}_4, 2 \max\{b, b^{-1}\} + |\mathbf{c}_1|\}, \quad (45)$$

with $\mathbf{c}_1 = \frac{1}{h} - \frac{nbx_e^n}{h^2}$, $\mathbf{c}_2 = x_e$, $\mathbf{c}_3 = \left(1 - \frac{nbx_e^n}{h}\right)$, $h = 1 + bx_e^n$, and

$$\mathbf{c}_4 = \frac{nb(n-1)(1 + b(2x_e)^n)(|\mathbf{c}_2| + |\mathbf{c}_3|) \max\{b, b^{-1}\}}{2h} + \frac{nbx_e^{n-1}(1 + b(2x_e)^n)|\mathbf{c}_3|}{h^2}.$$

Proof. The proof of this simple result is omitted here.

Next, let us we define the following constants which depend on the biological parameters:

$$\xi = (|\theta| + 2z_2 + 2Ke^{-\gamma\tau})|\theta| + (2Ke^{-\gamma\tau} + 1)z_2^2, \quad (46)$$

$$\mathfrak{K} = 2Ke^{-\gamma\tau}(2Ke^{-\gamma\tau} + |\theta| + 1) - 1, \quad (47)$$

$$\bar{\omega} = \frac{2(\delta + \theta - Le^{-\gamma\tau})}{\xi}, \quad (48)$$

and

$$\underline{\omega} = -\frac{2Le^{-\gamma\tau}}{\mathfrak{K}}, \quad \text{for } \mathfrak{K} \neq 0. \quad (49)$$

Now we are ready to prove the following result:

Theorem 4. If the conditions

$$0 < \underline{\omega} < \bar{\omega}, \quad (50)$$

are satisfied, then the positive equilibrium E of the non-linear system (1) is locally exponentially stable. Moreover, an open subset of the basin of attraction of E can be determined.

Proof. The derivative of the functional $Q(\tilde{x}(t))$ along the trajectories of (39) satisfies

$$\begin{aligned} \dot{Q}(t) &= -2(\delta + \theta)Q(\tilde{x}(t)) - \tilde{x}(t)I(\tilde{x}(t)) \\ &\quad + 2Le^{-\gamma\tau}\tilde{x}(t)\tilde{u}(t - \tau) \\ &\leq -2(\delta + \theta)Q(\tilde{x}(t)) + z_1|\tilde{x}(t)|Q(\tilde{x}(t)) \\ &\quad + 2Le^{-\gamma\tau}\tilde{x}(t)\tilde{u}(t - \tau), \end{aligned} \quad (51)$$

where the last inequality is a consequence of (43). Using the inequality $\tilde{x}(t)\tilde{u}(t - \tau) \leq Q(\tilde{x}(t)) + Q(\tilde{u}(t - \tau))$, it follows that

$$\begin{aligned} \dot{Q}(t) &\leq -2(\delta + \theta - Le^{-\gamma\tau})Q(\tilde{x}(t)) \\ &\quad + z_1|\tilde{x}(t)|Q(\tilde{x}(t)) + 2Le^{-\gamma\tau}Q(\tilde{u}(t - \tau)). \end{aligned} \quad (52)$$

On the other hand, observe that,

$$\begin{aligned} Q(\tilde{u}(t)) &= \theta^2 Q(\tilde{x}(t)) + \theta\tilde{x}(t)I(\tilde{x}(t)) + \frac{1}{2}I^2(\tilde{x}(t)) \\ &\quad + (2Ke^{-\gamma\tau})^2 Q(\tilde{u}(t - \tau)) \\ &\quad + 2K\theta e^{-\gamma\tau}\tilde{u}(t - \tau)\tilde{x}(t) \\ &\quad + 2Ke^{-\gamma\tau}I(\tilde{x}(t))\tilde{u}(t - \tau) \\ &\leq (|\theta| + 2z_2)|\theta|Q(\tilde{x}(t)) + z_2^2 Q(\tilde{x}(t)) \\ &\quad + (2Ke^{-\gamma\tau})^2 Q(\tilde{u}(t - \tau)) \\ &\quad + 2K|\theta|e^{-\gamma\tau}Q(\tilde{u}(t - \tau)) + 2K|\theta|e^{-\gamma\tau}Q(\tilde{x}(t)) \\ &\quad + 2Ke^{-\gamma\tau}z_2^2 Q(\tilde{x}(t)) + 2Ke^{-\gamma\tau}Q(\tilde{u}(t - \tau)), \end{aligned}$$

where the last inequality is a consequence of the inequalities $|I(\tilde{x}(t))| \leq z_2|\tilde{x}(t)|$, $\tilde{u}(t - \tau)\tilde{x}(t) \leq Q(\tilde{u}(t - \tau)) + Q(\tilde{x}(t))$ and $I(\tilde{x}(t))\tilde{u}(t - \tau) \leq \frac{1}{2}I^2(\tilde{x}(t)) + Q(\tilde{u}(t - \tau))$.

By grouping the terms we obtain:

$$Q(\tilde{u}(t)) \leq \xi Q(\tilde{x}(t)) + (\mathfrak{K} + 1)Q(\tilde{u}(t - \tau)) \quad (53)$$

where ξ and \mathfrak{K} are the constants defined in (46) and (47). Using (53), we deduce that the derivative of the functional Θ , defined in (41), along the trajectories of (39) satisfies

$$\dot{\Theta}(t) \leq \xi Q(\tilde{x}(t)) + \mathfrak{K}Q(\tilde{u}(t - \tau)) \quad (54)$$

Now, let us assume that the condition (50) is satisfied. Observe that, from the definition of $\underline{\omega}$, we have $\mathfrak{K} < 0$. Furthermore, we introduce the strictly positive constant

$$\omega = \frac{\bar{\omega} + \underline{\omega}}{2}. \quad (55)$$

By combining (52) and (54), we conclude that the derivative of the functional:

$$V(\tilde{x}(t), \tilde{u}_t) = Q(\tilde{x}(t)) + \omega\Theta(\tilde{u}_t), \quad (56)$$

along the trajectories of (39), satisfies the inequality,

$$\begin{aligned} \dot{V}(t) &\leq -\xi[\bar{\omega} - \omega]Q(\tilde{x}(t)) + z_1|\tilde{x}(t)|Q(\tilde{x}(t)) \\ &\quad + \mathfrak{K}[\omega - \underline{\omega}]Q(\tilde{u}(t - \tau)), \end{aligned} \quad (57)$$

with $\xi > 0$ and $\mathfrak{K} < 0$. From (55), we conclude that

$$\begin{aligned} \dot{V}(t) &\leq -\mathfrak{q}[Q(\tilde{x}(t)) + Q(\tilde{u}(t - \tau))] \\ &\quad + z_1|\tilde{x}(t)|Q(\tilde{x}(t)). \end{aligned} \quad (58)$$

where

$$\mathfrak{q} = \min\{\xi(\bar{\omega} - \omega), -\mathfrak{K}(\omega - \underline{\omega})\} \quad (59)$$

On the other hand, the derivative of the functional Λ , introduced in (42), along the trajectories of (39), satisfies

$$\begin{aligned} \dot{\Lambda}(t) &= \tau Q(\tilde{u}(t)) - \int_{t-\tau}^t e^{l-t} Q(\tilde{u}(l))dl - \Lambda(\tilde{u}_t) \\ &\leq \tau Q(\tilde{u}(t)) - e^{-\tau}\Theta(\tilde{u}_t) - \Lambda(\tilde{u}_t) \\ &\leq \tau\xi Q(\tilde{x}(t)) + \tau(\mathfrak{K} + 1)Q(\tilde{u}(t - \tau)) \\ &\quad - e^{-\tau}\Theta(\tilde{u}_t) - \Lambda(\tilde{u}_t) \end{aligned} \quad (60)$$

where the last inequality is a consequence of (53).

Now, by combining (60) and (58), we straightforwardly conclude that the derivative of the functional

$$\mathcal{U}(\tilde{x}(t), \tilde{u}_t) = V(\tilde{x}(t), \tilde{u}_t) + \mathfrak{p}\Lambda(\tilde{u}_t), \quad (61)$$

where

$$\mathfrak{p} = \frac{\mathfrak{q}}{2\tau \max\{\xi, \mathfrak{K} + 1\}}, \quad (62)$$

along the trajectories of (39), satisfies

$$\begin{aligned} \dot{\mathcal{U}}(t) \leq & -\frac{\mathfrak{q}}{2}Q(\tilde{x}(t)) + z_1|\tilde{x}(t)|Q(\tilde{x}(t)) \\ & - \mathfrak{p}e^{-\tau}\Theta(\tilde{u}_t) - \mathfrak{p}\Lambda(\tilde{u}_t), \end{aligned} \quad (63)$$

Since $|\tilde{x}(t)| \leq \sqrt{2\mathcal{U}(\tilde{x}(t), \tilde{u}_t)}$, we deduce that

$$\begin{aligned} \dot{\mathcal{U}}(t) \leq & -\left[\frac{\mathfrak{q}}{2} - z_1\sqrt{2\mathcal{U}(\tilde{x}(t), \tilde{u}_t)}\right]Q(\tilde{x}(t)) \\ & - \mathfrak{p}e^{-\tau}\Theta(\tilde{u}_t) - \mathfrak{p}\Lambda(\tilde{u}_t). \end{aligned} \quad (64)$$

Therefore, for all $\tilde{x}(0)$ and $\tilde{\varphi}_u$, satisfying

$$\mathcal{U}(\tilde{x}_0, \tilde{\varphi}_u) < \left(\frac{\mathfrak{q}}{4\sqrt{2}z_1}\right)^2, \quad (65)$$

the derivative of the functional \mathcal{U} satisfies:

$$\begin{aligned} \dot{\mathcal{U}}(t) \leq & -\frac{\mathfrak{q}}{4}Q(\tilde{x}(t)) - \mathfrak{p}e^{-\tau}\Theta(\tilde{u}_t) - \mathfrak{p}\Lambda(\tilde{u}_t) \\ \leq & -\mathfrak{r}\mathcal{U}(\tilde{x}(t), \tilde{u}_t), \end{aligned} \quad (66)$$

with

$$\mathfrak{r} = \min\left\{1, \frac{\mathfrak{p}e^{-\tau}}{\omega}, \frac{\mathfrak{q}}{4}\right\}. \quad (67)$$

By virtue of the functional \mathcal{U} , we conclude that \tilde{x} converges exponentially to its origin with a decay rate smaller or equal to \mathfrak{r} . Using the second equation in (39), one can prove that \tilde{u} converges exponentially to its origin. Notice that the set of all initial conditions satisfying the condition (65) provides an estimate of the basin of attraction of the origin of the shifted system (39). Since the initial system ((1)) is positive, we conclude that the set

$$\begin{aligned} \mathcal{A} = & \left\{x_0 \in \mathbb{R}^+, \varphi_u \in \mathcal{C}([-\tau, 0], \mathbb{R}^+), \right. \\ & \left. \mathcal{U}(x_0 - x_e, \varphi_u - u_e) < \left(\frac{\mathfrak{q}}{4\sqrt{2}z_1}\right)^2\right\}, \end{aligned} \quad (68)$$

is an open subset of the basin of attraction of the strictly positive equilibrium E of the system (1).

4. CONCLUSION

We studied the exponential stability of the 0-equilibrium of a differential-difference biological model by constructing a suitable linear functional. The local exponential stability of a positive equilibrium was performed via quadratic functionals and a subset of its basin of attraction was determined. [Future work will concern the analysis of more refined models that take into account the coexistence of healthy and unhealthy cells.](#)

REFERENCES

- M. Adimy, A. Chekroun, T. M. Touaoula. *Age-Structured and Delay Differential-Difference Model Of Hematopoietic Stem Cell Dynamics*. Discret And Continuous Dynamical Systems Series B, Volume 20, Number 9, pp. 2765-2791, November 2015.
- M. Adimy, F. Crauste, A. Abdllaoui, *Discrete Maturity-Structured Model of Cells Differentiation with Applications to Acute Myelogenous Leukemia*, J. Biological Systems, No. 3, pp. 395-424, 2008.

- J.L. Avila, C. Bonnet, J. Clairambault, H. Özbay, S. Niculescu, F. Merhi, A. Ballesta, R. Tang, and J.-P. Marie. *Analysis of a new model of cell population dynamics in acute myeloid leukemia*. In Delay Systems, pp. 315–328. Springer, 2014.
- W. Djema, F. Mazenc, C. Bonnet, *Lyapunov Stability Analysis of a Model Describing Hematopoiesis*. European Control Conference, Linz, Austria, pp. 2711-2716, 2015.
- W. Djema, F. Mazenc, C. Bonnet, *Stability of Immature Cell Dynamics in Healthy and Unhealthy Hematopoiesis*. (To appear in) American Control Conference, Boston, USA, 2016.
- A.F. Filippov, *Differential equations with discontinuous right-hand sides*, Kluwer Academic Publisher, Dordrecht, 1988.
- E. Fridman, *New Lyapunov-Krasovskii functionals for stability of linear retarded and neutral type systems*. Systems & Control Letters 43, No 4, 309-319, 2001.
- E. Fridman, C. Bonnet, F. Mazenc, W. Djema, *Stability of the cell dynamics in Acute Myeloid Leukemia*. To appear in Systems & Control Letters.
- K. Gu, Y. Liu. *Lyapunov-Krasovskii Functional for Uniform Stability of Coupled Differential-Functional Equations*. Automatica, Vol 45, No. 3, pp. 798-804, 2009.
- J.K. Hale, *Sufficient conditions for stability and instability of autonomous functional-differential equations*, Journal of Differential Equations, vol. 1, pp. 452-482, 1965.
- I. Karafyllis, P. Pepe, Z.P. Jiang, *Stability results for systems described by coupled retarded functional differential equations and functional difference equations*, Nonlinear Anal. Theory Methods Appl. 71, 3339–3362, 2009.
- V. Kolmanovskii, A. Myshkis, *Introduction to the Theory and Applications of Functional Differential Equations*, Kluwer Academic Publishers, Dordrecht, 1999.
- M.C. Mackey, *Unified hypothesis of the origin of plastic anemia and periodic hematopoiesis*, Blood, 51: pp. 941-956, 1978.
- M. Malisoff, F. Mazenc, *Constructions of Strict Lyapunov Functions*, Serie : Communications and Control Engineering. Springer-Verlag London Ltd, U.K., 2009.
- F. Mazenc, H. Ito. *Lyapunov Technique and Backstepping for Nonlinear Neutral Systems*, IEEE Transactions on Automatic Control, Volume 58, Issue 2, pp. 512-517, Feb. 2013.
- Y.V. Orlov, *Discontinuous Systems: Lyapunov Analysis and Robust Synthesis Under Uncertainty Conditions*, Serie : Communications and Control Engineering. Springer-Verlag London Ltd, 2009.
- H. Özbay, C. Bonnet, H. Benjelloun, J. Clairambault, *Stability analysis of cell dynamics in leukemia*, Math. Model Nat. Phenom., Vol. 7, No. 1, pp. 203-234, 2012.
- H. Özbay, C. Bonnet, J. Clairambault, *Stability analysis of systems with distributed delays and application to hematopoietic cell maturation dynamics*, IEEE Conference on Decision and Control, Cancun, Mexico, pp. 2050-2055, Dec. 2008.
- P. Pepe, I. Karafyllis, Z.P. Jiang, *On the Liapunov-Krasovskii methodology for the ISS of systems described by coupled delay differential and difference equation*, Automatica, 44. pp. 2266-2273, 2008.