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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 a 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 a 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 mechanism 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 in addition to the 0-equilibrium. Biologically, the positive equilibrium reflects the survival of blood cells and its stability analysis 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 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, for instance, Michel et al. (2015)) 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 also emphasize that, generally speaking, some robustness

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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 delay 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 a subset of its basin of attraction.

The reader is invited to refer to Sections 1-3 in Adimy et al. (2015) to get the accurate presentation of the biological model represented in Figure 1, and analyzed in the present paper. The delay differential-difference system which interests us is given by:

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

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 $\lim_{x\to\infty}\beta(x) = 0$. 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 $x(0) \in \mathbb{R}$ and $\varphi_u \in \mathcal{PC}\left([-\tau, 0], \mathbb{R}\right)$ (Gu and Liu (2009)). Moreover, system (1) is positive (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

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

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).

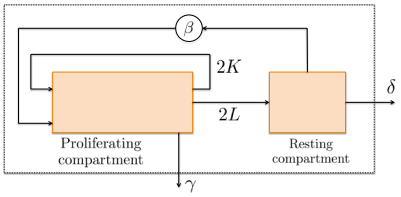

Fig. 1. Schematic representation of blood cells formation.

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

$$\overline{K} = \frac{1}{2}e^{\gamma\tau}, \tag{3}$$

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

$$\underline{K} = (\mu+1)\overline{K} - \mu. \tag{5}$$

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

2. STABILITY ANALYSIS OF THE 0-EQUILIBRIUM

We start by providing stability and instability results for the trivial equilibrium $E^0 = (0,0)$ of system (1).

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.

Theorem 1. For all

$$K \in (0, \overline{K}), \tag{6}$$

i) if the condition

$$s := \underline{K} - K > 0, \tag{7}$$

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

$$s := \underline{K} - K < 0, \tag{8}$$

then no positive trajectory converges to the origin of 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:

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

with

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

Notice that, since $K \in (0, \overline{K})$, then $\epsilon < 0$, when (7) is satisfied and $\epsilon > 0$ 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 $\epsilon > 0$, the functional $\mathcal{M}$ is positive on the positive orthant. Moreover, its derivative along the trajectories of (1) is

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

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

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

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 $t \geq t_1$,

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

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