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Stability analysis and robustness results for a nonlinear system with distributed delays describing hematopoiesis☆

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ABSTRACT

A nonlinear system with distributed delays describing cell dynamics in hematopoiesis is analyzed – in the time-domain – via a construction of suitable Lyapunov–Krasovskii functionals (LKFs). Two interesting biological situations lead us to re-investigate the stability properties of two meaningful steady states: the 0-equilibrium for unhealthy hematopoiesis and the positive equilibrium for the healthy case. Biologically, convergence to the 0-equilibrium means the extinction of all the generations of blood cells while the positive equilibrium reflects the normal process where blood cells survive. Their analyses are slightly different in the sense that we take advantage of positivity of the system to construct linear functionals to analyze the 0-equilibrium, while we use some quadratic functionals to investigate the stability properties of the positive equilibrium. For both equilibria, we establish the exponential stability of solutions and we provide an estimate of their rates of convergence. Moreover, a robustness analysis is performed when the model is subject to some nonvanishing perturbations. Numerical examples are provided.

1. Introduction

With the ultimate goal of determining a model describing cell dynamics in acute myeloid leukemia, which will be of use for the optimization of polychemotherapies, we start here with a model describing the process of fabrication of blood which was studied in [1] and revisited by input–output methods in [2]. Using an alternative approach, our aim here is to deepen the analysis as well as to solve some open issues which are of importance in practice.

Through the process of hematopoiesis, the Hematopoeitic Stem Cells (HSCs) develop into red blood cells, white blood cells, platelets and all other blood cells. HSCs are immature unspecialized cells able to produce cells with the same maturity level and to differentiate into specialized cells. This is a simplified development scheme, which does not take into account other cell fates – increasingly highlighted in recent years – such as cell dedifferentiation [3]. In fact, the complex cascade of signals regulating hematopoiesis is not currently clearly identified. Therefore, the importance of this biological process has motivated many theoretical and experimental works that focus on the earliest generations of immature cells since they play a critical role in blood formation, and because they are the source of several hematological disorders. The long list of works devoted to blood cells dynamics includes [1,4–6,2,7–9], and [10].

Acute Myelogenous Leukemia (AML) is a serious type of cancer, which is characterized by an overproduction of abnormal myeloblasts, simultaneously with an inability to develop further into mature white blood cells (a blockade in the maturation process). Due to their overproliferation, blasts invade the bone marrow and even – sometimes – the blood circulation (Fig. 1(a)), which prevents adequate production of mature healthy blood cells. Since we want to emphasize on AML, we consider that the model that we focus on describes the development hierarchy leading to white cell production in the myeloid lineage.

Relying on several essential contributions by Mackey and his colleagues ([8,9,6], to name but a few), Adimy et al. introduced and analyzed in [1] a nonlinear system with distributed delays to model cell dynamics in several maturity stages. This is the model we study here, considering that it describes a cancer state when some of its biological parameters are abnormal (i.e. being different from healthy parameters, or becoming time-varying to model the effect of appropriate infused drugs) and it reflects a healthy situation when all its parameters are normal. Using a Lyapunov technique we improve some existing results in two different contexts: (i) we provide theoretical conditions to eradicate cancer cells in

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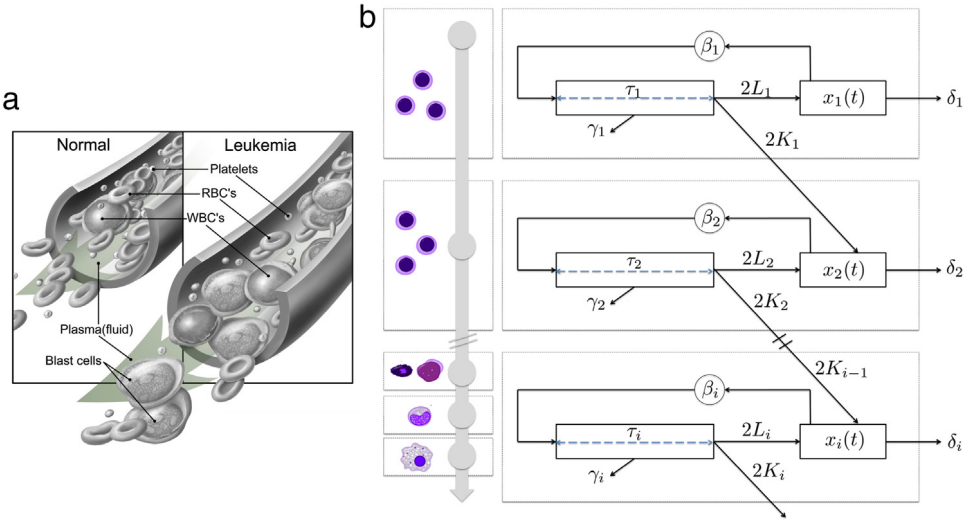

Fig. 1. (a) Blast cells are not typically found in the circulating blood of healthy individuals. The picture is from the National Cancer Institute. (b) Schematic representation of the earliest stages in the myeloid lineage [1].

what we assume to be a basic unhealthy situation, and, (ii) we ensure the survival of healthy cells in normal hematopoiesis. A key point that we emphasize here is that the Lyapunov direct method offers strong tools to study exponential convergence of solutions, estimates on their decay rates (for both steady states), as well as estimating the basin of attraction of the positive equilibrium point and this, in our opinion, improves the way to study the phenomenon of hematopoiesis (see the concluding remarks in [2]). On the other hand, the search for a suitable Lyapunov functional is generally quite difficult, since no systematic methods apply [11,12], and that is the challenging problem that we are dealing with in this contribution.

The paper is organized as follows. In Section 2 we briefly present the model of interest. Section 3 is devoted to the study of the 0-equilibrium of the system. We establish global exponential stability even when some parameters are time-varying, then we perform a robustness analysis. The strictly positive equilibrium X^e of the nominal system is discussed in Section 4. An estimate of its basin of attraction is proposed via a construction of a novel Lyapunov functional, that also allows us to perform a robustness analysis of the perturbed system.

2. Description of the model and known results

We revisit from [1] the model described in Fig. 1(b), where for all $i \in I_n = \{1, \dots, n\}, n \geq 1, x_i$ denotes the total density of resting cells of generation i. A resting cell is a cell that is not actively in the process of dividing. The re-introduction function from resting into proliferating subpopulation of the ith generation is denoted $\beta_i(\cdot)$. Proliferating cells can divide between the moment they enter the proliferating phase and a maximal age $\tau_i > 0$, while the apoptosis rate, γ_i, represents the death rate of proliferating cells of the ith generation. At each division, a proportion K_i of dividing cells goes to the next resting stage of the development hierarchy of interest, while the other part ($L_i = 1 - K_i$) stays at the same level i (self-renewing process), with the convention that $K_0 = 0$. The constant δ_i covers both the death rate of the resting cells of the ith generation, together with their differentiation into lineages that we do not focus on.

Finally, the dynamical system equation is in the form:

$$\dot{x}_i(t) = -\delta_i x_i(t) - w_i(x_i(t)) + 2L_i \int_0^{\tau_i} g_i(a) w_i(x_i(t-a))da + 2K_{i-1} \int_0^{\tau_{i-1}} g_{i-1}(a) w_{i-1}(x_{i-1}(t-a))da + \epsilon_i(t), \qquad (1)$$

for each compartment $i \in I_n$, and $t \geq 0$, with $w_i(x_i) = \beta_i(x_i)x_i$, $g_i(a) = e^{-\gamma_i a} f_i(a)$, where the f_is are $\mathcal{C}^1$ functions representing the cell division probability densities, such that $f_i(a) \geq 0$ for all $a \in [0, \tau_i]$, and $\int_0^{\tau_i} f_i(a)da = 1$, since it is assumed in [1] that the mitosis occurs before the age-limit τ_i. Moreover, biological facts induce that the parameters δ_i, L_i, K_i, τ_i and γ_i are positive for all $i \in I_n$, with $K_0 = 0$ and $K_i \in (0, 1)$ for all $i \in I_n$. The functions $\beta_i(\cdot)$ are assumed to be differentiable and decreasing functions such that $\lim_{a \to +\infty} \beta_i(a) = 0$. For a later use, we introduce the following parameters:

$$C_i = \int_0^{\tau_i} g_i(l)dl, \quad \text{and,} \quad \alpha_i = 2L_i C_i - 1, \qquad (2)$$

where α_i is assumed to be strictly positive, for all $i \in I_n$ (see [2], Assumption 2). We will perform a robustness analysis of (1) under nonvanishing perturbation terms $\epsilon_i(t) \in [0, \overline{\epsilon}_i]$, where $\overline{\epsilon}_i > 0$, for all $i \in I_n$ and $t \geq 0$. It is well-known that disturbances are in general due to the lack of accuracy when modeling the laws governing complex living organisms. More precisely, in the model that we study, uncertainty comes from the biological parameters and functions (e.g. the nonlinearity β_i, introduced in [8]), and from more complex phenomena which are difficult to model. In particular, the ability of differentiated cells to undergo lineage reversion (including dedifferentiation – the mechanism whereby differentiated cells regress to a less mature state [3] – and transdifferentiation from different types of cells and hierarchies) is not covered by the model illustrated in Fig. 1(b). A basic representation of cells plasticity features is achieved by considering dedifferentiation and transdifferentiation as perturbation inputs. In fact, it can be proven that nonvanishing perturbations arise from cell plasticity, and uncertain re-introduction functions β_i, leading to system (1) with $\epsilon_i(t) \in (0, \overline{\epsilon}_i]$, for all $t \geq 0$.

Notation and definitions:

Throughout the paper, we analyze the stability of the model described by (1), where for all $i \in I_n = \{1, \dots, n\}, x_i(t) \in \mathbb{R}^n$. The state of the system (1) at a time instant t is defined as the restriction of each component $x_i(t)$ of the solution $x(t) = (x_1(t), \dots, x_n(t))$, on the segment $[t - \tau_i, t]$, for all $i \in I_n$. We let $x = (x_1, \dots, x_n)$ and $\mathcal{C}_{\text{in}} = \mathcal{C}([-\tau_i, 0], \mathbb{R})$ denote the space of all continuous $\mathbb{R}$-valued functions defined on a given interval $[-\tau_i, 0]$, for all $i \in I_n$, and for all $t \geq 0$, the function x_{it} is defined by $x_{it}(m) = x_i(t + m)$ for all $m \in [-\tau_i, 0]$.

Finally, we notice that negative steady states are excluded from this study, as well as equilibria belonging to the boundaries of