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Stability of Immature Cell Dynamics in Healthy and Unhealthy Hematopoiesis

Walid Djema, Frédéric Mazenc, Catherine Bonnet

Abstract—A nonlinear system with distributed delays is studied. The model takes into account the fast self-renewal dynamics observed in Acute Myeloid Leukemia (AML). In this case, stability and instability conditions are derived for the zero equilibrium of the model. Notice that, biologically, the zero equilibrium means the eradication of **all malignant** cells which is the aim of the anti-AML therapy. The novelty of this work is that we consider time-varying biological parameters reflecting the fact that the differentiating and self-renewing parameters become time-variant both under the effect of the disease and the drugs. A simpler case of the studied model describes the normal process of hematopoiesis. In the latter case we focus on the stability of the strictly positive equilibrium point since it reflects the surviving of all the generations of blood cells. Via a construction of a novel Lyapunov-Krasovskii functional, we derive sufficient conditions for the local exponential stability of the studied equilibrium and we propose an estimate of its basin of attraction.

Key Words: Time-delay Systems, Time-varying, Lyapunov functionals, basin of attraction.

I. INTRODUCTION

Through the process of hematopoiesis, in a healthy bone marrow, the hematopoietic stem cells (HSC) develop into red blood cells, white blood cells, platelets and all other blood cells. The HSC are immature cells able to produce cells with the same maturity level (self-renew) and to differentiate into specialized cells with specific functions. In the case of acute myelogenous leukemia (AML), there is an overproduction of abnormal myeloblasts. These cells are unable to develop further into mature white blood cells (a blockade in the maturation process). These abnormal blasts begin to take over the bone marrow (overproliferation) and prevent production of adequate numbers of other types of blood cells. The model that describes healthy or unhealthy hematopoiesis is given by nonlinear transport equations, which are transformed to a nonlinear system with distributed delays using the method of characteristics.

In Section II, we analyse the stability of the zero equilibrium for the multi-stage AML model introduced recently in [5], and widely analysed in [7]. We consider the case of time-varying differentiating, self-renewing and fast self-renewing rates and we derive from a novel Lyapunov-Krasovskii functional, conditions of global exponential stability. In Section III, we focus on the model without fast self-renewal dynamics describing the process of healthy

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hematopoiesis. This simpler model was proposed by Adimy in [2], [3] and analyzed by an input-output approach in [15]. In our previous contribution [6], we investigated the same model by a Lyapunov approach. Unfortunately, the complexity of the system led **only** to a local stability analysis of the positive equilibrium. However, this equilibrium is the most interesting from a practical point of view because it models the normal process of hematopoiesis where all the generations of cells survive. Added to this, several diseases may disrupt strongly the hematopoiesis process and a local stability analysis is insufficient. As mentioned in [15], estimates of the domain of attraction of the positive equilibrium point and of the exponential decay rate for the nonlinear full-order system have not been found and these are still important open problems. In the present paper, first we establish the exponential stability of the positive equilibrium with a given decay rate, then we determine an approximation of its basin of attraction via a construction of a novel Lyapunov-Krasovskii functional.

II. STABILITY OF THE MODEL WITH FAST SELF-RENEWAL DYNAMICS

A schematic representation of the cell dynamics is given in Figure 1 where the total population densities of resting cells x_i and of fast self-renewing cells \tilde{x}_i , which may have $n \geq 1$ stages of maturity, are described by the following time-delay system, for all $i \in I_n = \{1, \dots, n\}$,

$$\begin{cases} \dot{\tilde{x}}_i(t) = -(\delta_i + \beta_i(x_i(t)))\tilde{x}_i(t) + L_i(t)\mathfrak{S}_i(w_i, \tilde{w}_i) \\ \quad + 2K_{i-1}(t)\mathfrak{S}_{i-1}(w_{i-1}, \tilde{w}_{i-1}) \\ \dot{x}_i(t) = -\tilde{w}_i(\tilde{x}_i(t)) + \tilde{L}_i(t)\mathfrak{S}_i(w_i, \tilde{w}_i), \quad t \geq 0, \end{cases} \quad (1)$$

where, with an abuse of notation, $\mathfrak{S}_i(w_i, \tilde{w}_i) = \int_0^{\tau_i} g_i(a)[w_i(x_i(t-a)) + \tilde{w}_i(\tilde{x}_i(t-a))]da$, with a the age of cells. The constant δ_i is the death rate of quiescent cells. The function $g_i(a)$ are defined by $g_i(a) = e^{-\gamma_i a} f_i(a)$ where f_i is a density function describing the mitosis and is such that $\int_0^{\tau_i} f_i(a)da = 1$ and γ_i is the death rate of the proliferating cells (apoptosis).

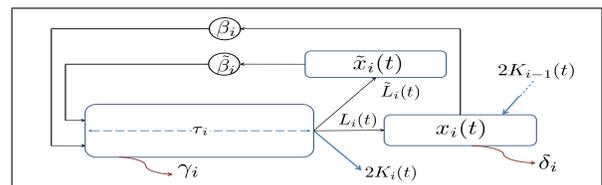


Fig. 1. Schematic representation of the age-structured model describing unhealthy hematopoiesis.

Proliferating cells can divide between the moment they enter the proliferating phase and a maximal age $\tau_i > 0$. The reintroduction functions are defined by $w_i(x_i) = x_i\beta_i(x_i)$ and $\tilde{w}_i(\tilde{x}_i) = \tilde{x}_i\tilde{\beta}_i(\tilde{x}_i)$, such that β_i and $\tilde{\beta}_i$ are a Locally Lipschitz, differentiable and uniformly decreasing functions with $\tilde{\beta}_i(0) \gg \beta_i(0) > 0$ and $\lim_{a \rightarrow +\infty} \tilde{\beta}_i(a) = \lim_{a \rightarrow +\infty} \beta_i(a) = 0$. We assume that the functions L_i and \tilde{L}_i are of class C^0 for all $i \in I_n$ and such that $L_i(t) := 2\sigma_i(t)(1-K_i(t))$, $\tilde{L}_i(t) := 2(1-\sigma_i(t))(1-K_i(t))$, $K_0 = 0$, for all $t > 0$. The rates $K_i(t)$ represent the proportion of cells that differentiate while the function $1 - \sigma_i(t)$ characterizes the probability of fast self-renewal at the time instant t . Moreover, we introduce for later use the parameters

$$C_i = \int_0^{\tau_i} g_i(a)da, \text{ for all } i \in I_n. \quad (2)$$

Originally, the model described by (1) was introduced in [5] with constant parameters K_i , L_i , \tilde{L}_i and σ_i , for all $i \in I_n$. Since AML is characterized by a blockade in the differentiation process, which becomes also a target for some drugs already used in the treatment of this disease, we consider in this paper the time-varying system (1). However, we invite the interested reader to refer to [5] for the introduction of the time-invariant model.

Since each proliferating cell which does not die by apoptosis and completes its mitosis gives birth to two daughter cells, we deduce that $K_i(t) \in [0, 1]$ for all $t \geq 0$. In fact, we assume that $K(t) \in [K_{i \min}, K_{i \max}] \subset (0, 1)$, for all $t \geq 0$, meaning that even for an unhealthy hematopoiesis the differentiating process will not completely vanish. More precisely, in the AML case, we have $\lim_{t \rightarrow \infty} K(t) = K_{i \min} \neq 0$. Similarly, we consider the case where for all $t \geq 0$, $\sigma_i(t) \in [\sigma_{i \min}, \sigma_{i \max}] \subseteq [0, 1]$. From medical practice we know that, in the AML case, a blockade in the differentiation process ($\lim_{t \rightarrow \infty} K_i(t) = K_{i \min}$) and a high rate of fast self-renewing ($\lim_{t \rightarrow \infty} \sigma_i(t) = \sigma_{i \min}$) are simultaneously observed. This fact yields to $\lim_{t \rightarrow \infty} \tilde{L}_i(t) = \tilde{L}_{i \max}$, in the AML case, with $\tilde{L}_{i \max} = 2(1 - \sigma_{i \min})(1 - K_{i \min})$.

Moreover, we define for all $i \in I_n$,

$$\hat{L}_i(t) := L_i(t) + \tilde{L}_i(t) = 2(1 - K_i(t)), \quad t \geq 0.$$

Notice that $\hat{L}(t) \in [\hat{L}_{i \min}, \hat{L}_{i \max}] \subset (0, 2)$, for all $t > 0$, where $\hat{L}_{i \max} = 2(1 - K_{i \min})$.

It is easy to prove that the nonlinear time-delay system (1) is a positive system (*i.e.*, for nonnegative initial conditions, the solutions are nonnegative). We will employ the positivity of the system to explicitly construct a suitable Lyapunov-Krasovskii functional in order to investigate the stability properties of the overall system. We start with the following Proposition:

Proposition 1: If the conditions

$$\tilde{L}_{i \max} C_i < 1, \quad (3)$$

for all $i \in I_n$, are not satisfied, then there exists a system in the family of systems (1) whose origin is not globally asymptotically stable.

Proof: We prove Proposition 1 by contradiction. Let us assume that (3) is not satisfied for a given $j \in I_n$ and that all the positive solutions of the system (1), with for all $i \in I_n$, $\tilde{L}_i(t) = \tilde{L}_{i \max}$, for all $t \geq 0$, converges to the origin.

Observe that

$$\dot{\tilde{x}}_i(t) \geq -\tilde{w}_i(\tilde{x}_i(t)) + \tilde{L}_{i \max} \int_{t-\tau_i}^t g_i(t-a)\tilde{w}_i(\tilde{x}_i(a))da \quad (4)$$

Let us introduce the functionals

$$h_i(\tilde{x}_{it}) = \int_{t-\tau_i}^t \int_m^t g_i(m-a+\tau_i)\tilde{w}_i(\tilde{x}_i(a))dadm. \quad (5)$$

Simple calculations give

$$\dot{h}_i(t) = C_i\tilde{w}_i(\tilde{x}_i(t)) - \int_{t-\tau_i}^t g_i(t-a)\tilde{w}_i(\tilde{x}_i(a))da. \quad (6)$$

From (4) and (6) it follows that the derivatives of the functionals

$$\hat{h}_i(x_{it}) = \tilde{x}_i(t) + \tilde{L}_{i \max} h_i(\tilde{x}_{it}), \quad (7)$$

along the trajectories of (1), satisfy

$$\dot{\hat{h}}_i(t) \geq (C_i\tilde{L}_{i \max} - 1)\tilde{w}_i(\tilde{x}_i(t)). \quad (8)$$

Since there exists $j \in I_n$ such that $\tilde{L}_j C_j > 1$, we have $\dot{\hat{h}}_j(t) \geq 0$. It follows that

$$\hat{h}_j(\tilde{x}_{jt}) \geq \hat{h}_j(0) > 0. \quad (9)$$

Therefore $\hat{h}_j(\tilde{x}_{jt})$ does not converge to zero. But we consider a solution which converges to the origin, which implies that $\hat{h}_j(\tilde{x}_{jt})$ converges to zero. This yields a contradiction. ■

Remark 1: If $\sigma_{i \min} = 0$, we have $\hat{L}_{i \max} = \tilde{L}_{i \max}$. Therefore, if the condition $C_i\hat{L}_{i \max} < 1$ is not satisfied for all $i \in I_n$, then there exists a system (1) such that its origin is not globally asymptotically stable.

We can establish the global exponential stability of the origin of system (1) under the following assumption.

Assumption 1: For all $i \in I_n$,

$$C_i\hat{L}_{i \max} < 1. \quad (10)$$

In fact, it is not difficult to prove that if the condition (10) is satisfied then the origin of (1) is globally asymptotically stable. This means that (10) is a necessary and sufficient condition so that all the trajectories of (1) (including the case where $L_i(t) = \hat{L}_i(t)$, for all $t > 0$) converge asymptotically to the origin. However, it is more challenging and interesting to establish the exponential stability with an estimate of the rate of convergence. That is what we are focusing on in this section. Let Assumption 1 hold and let us define the following positive constants

$$\theta_i = \frac{C_i\hat{L}_{i \max} + 1}{2C_i\hat{L}_{i \max}} \quad \text{and} \quad \tilde{\theta}_i = \frac{\theta_i + 1}{2C_i}. \quad (11)$$

Observe for later use that for all $i \in I_n$, θ_i and $\tilde{\theta}_i$ satisfy

$$1 < \tilde{\theta}_i C_i < \theta_i < \frac{1}{\hat{L}_{i \max} C_i}. \quad (12)$$

Now we are ready to prove the following result:

Theorem 1: Let Assumption 1 hold. The origin of the system (1) is globally exponentially stable if the inequalities

$$s_i = \delta_i - \left(C_i \bar{\theta}_i - 1\right) \beta_i(0) > 0, \quad (13)$$

are satisfied for all $i \in I_n$.

Proof: Let us introduce, for all $i \in I_n$, the functionals defined along the trajectories of system (1), by

$$v_i(x_{it}, \tilde{x}_{it}) = \bar{\theta}_i \int_{t-\tau_i}^t \int_m^t e^{\rho_i(m-t)} g_i(m-a+\tau_i) [w_i(x_i(a)) + \tilde{w}_i(\tilde{x}_i(a))] dadm, \quad (14)$$

where the constants $\rho_i > 0$, for all $i \in I_n$, satisfy

$$\frac{1}{\bar{\theta}_i C_i} < e^{-\rho_i \tau_i} < 1. \quad (15)$$

The derivatives of the functionals (14) along the trajectories of (1) are given by

$$\dot{v}_i(t) = -\rho_i v_i(x_{it}, \tilde{x}_{it}) - \bar{\theta}_i e^{-\rho_i \tau_i} \mathfrak{S}_i(w_i, \tilde{w}_i) + \bar{\theta}_i [w_i(x_i(t)) + \tilde{w}_i(\tilde{x}_i(t))] \int_{t-\tau_i}^t e^{\rho_i(m-t)} g_i(m-t+\tau_i) dm.$$

As an immediate consequence,

$$\dot{v}_i(t) \leq -\rho_i v_i(x_{it}, \tilde{x}_{it}) - \bar{\theta}_i e^{-\rho_i \tau_i} \mathfrak{S}_i(w_i, \tilde{w}_i) + \bar{\theta}_i [w_i(x_i(t)) + \tilde{w}_i(\tilde{x}_i(t))] C_i. \quad (16)$$

Let us introduce the following functional for the first compartment

$$\mathcal{V}_1(x_{1t}, \tilde{x}_{1t}) = x_1(t) + \theta_1 \tilde{x}_1(t) + v_1(x_{1t}, \tilde{x}_{1t}). \quad (17)$$

From (16), it follows that

$$\begin{aligned} \dot{\mathcal{V}}_1(t) &\leq -(\delta_1 + \beta_1(x_1(t))) x_1(t) - \rho_1 v_1(x_{1t}, \tilde{x}_{1t}) \\ &+ \left(L_1(t) + \theta_1 \tilde{L}_1(t) - \frac{1}{C_1}\right) \mathfrak{S}_1(w_1, \tilde{w}_1) \\ &- \theta_1 \tilde{w}_1(\tilde{x}_1(t)) + \bar{\theta}_1 C_1 [w_1(x_1(t)) + \tilde{w}_1(\tilde{x}_1(t))]. \end{aligned} \quad (18)$$

Since $\theta_i > 1$, we have $L_i(t) + \theta_i \tilde{L}_i(t) \leq \theta_i \hat{L}_{i\max}$, for all $i \in I_n$. Moreover, from (12), we have $C_i \bar{\theta}_i > 1$ and consequently (18) gives

$$\begin{aligned} \dot{\mathcal{V}}_1(t) &\leq -\left[\delta_1 - (C_1 \bar{\theta}_1 - 1) \beta_1(0)\right] x_1(t) \\ &- \bar{\theta}_1 \tilde{w}_1(\tilde{x}_1(t)) - \rho_1 v_1(x_{1t}, \tilde{x}_{1t}) \\ &- \lambda_1 \mathfrak{S}_1(w_1, \tilde{w}_1) \end{aligned} \quad (19)$$

with $\bar{\theta}_i = \theta_i - \bar{\theta}_i C_i$ and $\lambda_1 = \frac{1 - \theta_1 \hat{L}_{1\max} C_1}{C_1}$. We notice from (12) that $\bar{\theta}_i$ and λ_1 are strictly positive for all $i \in I_n$. It follows that

$$\dot{\mathcal{V}}_1(t) \leq -s_1 x_1(t) - \bar{\theta}_1 \tilde{w}_1(\tilde{x}_1(t)). \quad (20)$$

We conclude that if (13) is satisfied then the origin of the subsystem $i = 1$ is globally asymptotically stable. This means in particular that $\lim_{t \rightarrow +\infty} \tilde{x}_1(t) = 0$. Since the function $\tilde{\beta}_1$ is uniformly decreasing and $\beta_1(0)$ is its maximum, there exist a time instant $t' > 0$, and a small enough $\epsilon \in (0, 1)$,

such that for all $t > t'$, $\tilde{\beta}_1(\tilde{x}_1(t)) > \epsilon \tilde{\beta}_1(0)$. Then, for all $t > t'$, (19) gives

$$\begin{aligned} \dot{\mathcal{V}}_1(t) &\leq -s_1 x_1(t) - \bar{\theta}_1 \epsilon \tilde{\beta}_1(0) \tilde{x}_1(t) \\ &- \rho_1 v_1(x_{1t}, \tilde{x}_{1t}) - \lambda_1 \mathfrak{S}_1(w_1, \tilde{w}_1). \end{aligned} \quad (21)$$

We conclude that for all $t > t'$,

$$\dot{\mathcal{V}}_1(t) \leq -\tilde{s}_1 \mathcal{V}_1(x_{1t}, \tilde{x}_{1t}) - \lambda_1 \mathfrak{S}_1(w_1, \tilde{w}_1), \quad (22)$$

with $\tilde{s}_1 = \min\{s_1, \frac{\bar{\theta}_1 \epsilon \tilde{\beta}_1(0)}{\theta_1}, \rho_1\}$. It follows that the origin of the subsystem $i = 1$ is globally exponentially stable with a decay rate smaller than \tilde{s}_1 . Next, let us introduce the following functional

$$\begin{aligned} \mathcal{V}_2(X_{2t}) &= x_2(t) + \theta_2 \tilde{x}_2(t) + v_2(x_{2t}, \tilde{x}_{2t}) \\ &+ \frac{2K_{1\max}}{\lambda_1} \mathcal{V}_1(x_{1t}, \tilde{x}_{1t}), \end{aligned} \quad (23)$$

with $X_2 = (x_2, \tilde{x}_2, x_1, \tilde{x}_1)$. The derivative of the functional (23) along the trajectories of (1) satisfies

$$\begin{aligned} \dot{\mathcal{V}}_2(t) &\leq -s_2 x_2(t) - \bar{\theta}_2 \tilde{w}_2(\tilde{x}_2(t)) - \rho_2 v_2(x_{2t}, \tilde{x}_{2t}) \\ &- \lambda_2 \mathfrak{S}_2(w_2, \tilde{w}_2) + \frac{2K_{1\max}}{\lambda_1} \dot{\mathcal{V}}_1(t) \\ &+ 2K_1(t) \mathfrak{S}_1(w_1, \tilde{w}_1). \end{aligned} \quad (24)$$

Combining (24) and (22), we deduce that for all $t > t'$

$$\begin{aligned} \dot{\mathcal{V}}_2(t) &\leq -s_2 x_2(t) - \bar{\theta}_2 \tilde{w}_2(\tilde{x}_2(t)) - \lambda_2 \mathfrak{S}_2(w_2, \tilde{w}_2) \\ &- \rho_2 v_2(x_{2t}, \tilde{x}_{2t}) - \frac{2\tilde{s}_1 K_{1\max}}{\lambda_1} \mathcal{V}_1(x_{1t}, \tilde{x}_{1t}) \\ &- 2(K_{1\max} - K_1(t)) \mathfrak{S}_1(w_1, \tilde{w}_1). \end{aligned} \quad (25)$$

Since $K_1(t) \leq K_{1\max}$, for all $t > 0$, we conclude that

$$\begin{aligned} \dot{\mathcal{V}}_2(t) &\leq -s_2 x_2(t) - \bar{\theta}_2 \tilde{w}_2(\tilde{x}_2(t)) - \lambda_2 \mathfrak{S}_2(w_2, \tilde{w}_2) \\ &- \rho_2 v_2(x_{2t}, \tilde{x}_{2t}) - \frac{2\tilde{s}_1 K_{1\max}}{\lambda_1} \mathcal{V}_1(x_{1t}, \tilde{x}_{1t}). \end{aligned} \quad (26)$$

Finally, we straightforwardly deduce that there exists $\tilde{s}_2 > 0$ such that

$$\dot{\mathcal{V}}_2(t) \leq -\tilde{s}_2 \mathcal{V}_2(X_{2t}) - \lambda_2 \mathfrak{S}_2(w_2, \tilde{w}_2). \quad (27)$$

Next, by induction, one can readily determine constants $\tilde{\lambda}_i > 0$ and $\tilde{s}_n > 0$, such that the derivative of the functional

$$\mathcal{V}_n(X_t) = \sum_{i=1}^n \left[x_i(t) + \theta_i \tilde{x}_i(t) + \tilde{\lambda}_i v_i(x_{it}, \tilde{x}_{it}) \right], \quad (28)$$

with $X = (x_1, \tilde{x}_1, \dots, x_n, \tilde{x}_n)$, satisfies

$$\dot{\mathcal{V}}_n(t) \leq -\tilde{s}_n \mathcal{V}_n(X_t). \quad (29)$$

From the inequality (29) and the properties of the functional \mathcal{V}_n , we conclude that the origin of the system (1) is globally exponentially stable with a decay rate smaller than \tilde{s}_n . ■

III. STABILITY OF THE MODEL DESCRIBING HEALTHY HEMATOPOIESIS

In this section we focus on a simpler form of system (1) which fits well with the healthy hematopoiesis. The model

of interest describing the dynamics of immature quiescent cells is in the form

$$\begin{aligned} \dot{x}_i(t) = & -(\delta_i + \beta_i(x_i(t)))x_i(t) + 2L_i\mathfrak{S}_i(w_i) \\ & + 2K_{i-1}\mathfrak{S}_{i-1}(w_{i-1}), \end{aligned} \quad (30)$$

with $\mathfrak{S}_i(w_i) = \int_{t-\tau_i}^t g_i(t-a)w_i(x_i(a))da$ to ease the notation of the distributed delayed terms. Observe that the system (1) is equivalent to the system (30) when $\tilde{x}_i \equiv 0$, for all $i \in I_n$, as illustrated in Figure 2, since we consider that the fast self-renewal process is a phenomenon observed only in leukemic cell dynamics. Compared to Section II, the analysis now is different since the objectives are not the same. Indeed, in this section we will focus on the stability analysis of the strictly positive equilibrium $X^e = (x_1^e, \dots, x_n^e)$, $x_i^e > 0$, $i \in I_n$, since the survival of all the healthy cells is the purpose of normal hematopoiesis.

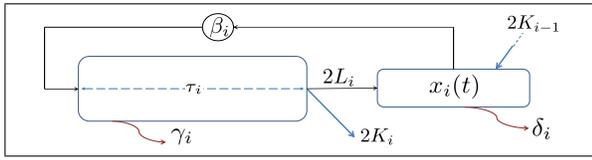


Fig. 2. Schematic representation of the age-structured model describing healthy hematopoiesis.

All the biological parameters involved in (30) are strictly positive constants with the same definitions introduced in Section II. Furthermore, we introduce for later use the following parameters:

$$\alpha_i = 2L_i C_i - 1. \quad (31)$$

where C_i are the constants defined in (2). The model described by (30) was first proposed in [2], widely analysed by an input-output approach in [15] and recently by a Lyapunov approach in [6]. We revisit it in this paper by a new Lyapunov approach. We extend the results of [6] and the novelty of the present work is that, for the strictly positive equilibrium X^e , we establish first the local exponential stability under the same conditions that are sufficient for the local asymptotic stability proposed in [6]. Then, we determine a subset of the basin of attraction of the strictly positive equilibrium of the nonlinear system. This region depends on the different biological parameters involved in the biological process of hematopoiesis.

Now, let us recall some results from [6]:

i) The solutions of system (30) associated with positive initial conditions are positive. Throughout our work, we consider only positive solutions of (30).

ii) We assume that $\alpha_i > 0$ is satisfied for $i \in I_n$. Then a unique strictly positive equilibrium X^e may exist. The following proposition gives a necessary and sufficient condition that ensures its existence.

Proposition 2: Under the previous assumptions, the system (30) admits a strictly positive equilibrium $X^e = (x_1^e, \dots, x_n^e)$ if and only if

$$\beta_1(0) > \frac{\delta_1}{\alpha_1}. \quad (32)$$

In the remainder of this work, we assume that $\alpha_i > 0$ and that the condition (32) is satisfied.

Assumption 2: The reintroduction functions from the resting to the proliferating stages are given by

$$\beta_i(x_i) = \frac{\beta_i(0)}{1 + b_i x_i^{n_i}}, \quad (33)$$

with $\beta_i(0) > 0$, $b_i > 0$ and n_i is an integer greater than 2.

Remark 2: The typical choice of the functions β_i proposed in Assumption 2 was first justified by Mackey in [10], then assumed in [17], [2] and [15].

From assumption 2, we have

$$w_i(x_i) = x_i \beta_i(x_i) = \frac{\beta_i(0)x_i}{1 + b_i x_i^{n_i}}. \quad (34)$$

Next, we give sufficient conditions that ensure the exponential stability of X^e . This preliminary result will allow us to determine an approximation of the basin of attraction of the positive equilibrium point of the nonlinear system (30). We perform the change of coordinates: $\hat{x}_i = x_i - x_i^e$, for $i \in I_n$. It follows from (30) that

$$\begin{aligned} \dot{\hat{x}}_i(t) = & -\delta_i [\hat{x}_i(t) + x_i^e] - w_i(\hat{x}_i(t) + x_i^e) \\ & + 2L_i\mathfrak{S}_i(w_i) + 2K_{i-1}\mathfrak{S}_{i-1}(w_{i-1}), \end{aligned} \quad (35)$$

with $\mathfrak{S}_i(w_i) = \int_{t-\tau_i}^t g_i(t-a)w_i(\hat{x}_i(a) + x_i^e) da$. We observe that it is difficult to investigate the stability properties of the system (35) written in this form. Therefore we propose a new representation of (35) which eases the analysis of its origin. Using the Taylor-Lagrange formula, we obtain

$$w_i(\hat{x}_i + x_i^e) = w_i(x_i^e) + \mu_i \hat{x}_i + R_i(\hat{x}_i), \quad (36)$$

where

$$\mu_i = \left[\frac{\partial w_i}{\partial x_i} \right]_{x_i=x_i^e} = \beta_i(x_i^e) + \beta_i'(x_i^e)x_i^e, \quad (37)$$

and

$$R_i(\hat{x}_i) = \int_{x_i^e}^{x_i^e + \hat{x}_i} [\hat{x}_i + x_i^e - l] w_i^{(2)}(l) dl. \quad (38)$$

As an immediate consequence,

$$\begin{aligned} \dot{\hat{x}}_i(t) = & -\beta_{i*} \hat{x}_i(t) + 2L_i \mu_i \int_{t-\tau_i}^t g_i(t-a) \hat{x}_i(a) da \\ & - R_i(\hat{x}_i(t)) + 2L_i \int_{t-\tau_i}^t g_i(t-a) R_i(\hat{x}_i(a)) da \\ & + 2K_{i-1} \mu_{i-1} \int_{t-\tau_{i-1}}^t g_{i-1}(t-a) \hat{x}_{i-1}(a) da \\ & + 2K_{i-1} \int_{t-\tau_{i-1}}^t g_{i-1}(t-a) R_{i-1}(\hat{x}_{i-1}(a)) da, \end{aligned} \quad (39)$$

with $\beta_{i*} = \delta_i + \mu_i$.

Remark 3: Once we perform the proposed change of coordinates, the analysis of the positive equilibrium point of (30) is equivalent to the analysis of the origin of the new system (39). It seems similar to what we did in Section II. However, the fundamental difference between the two analyses is that now we can no longer take advantage of

the positivity of the system under study for constructing suitable Lyapunov functionals. This observation motivates the introduction of these following functions and functionals:

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

$$\Omega_i(\varphi_{it}) = \int_{t-\tau_i}^t \int_l^t g_i(l-a+\tau_i)Q(\varphi_i(a))dadl, \quad (41)$$

$$\Lambda_i(\varphi_{it}) = \int_{t-\tau_i}^t e^{l-t} \int_l^t g_i(l-a+\tau_i)Q(\varphi_i(a))dadl, \quad (42)$$

and the following constants

$$\varsigma_i = \beta_{i*} - 2L_i|\mu_i|C_i = \delta_i + \mu_i - 2L_i|\mu_i|C_i. \quad (43)$$

We observe the similarity between the functionals Ω_i and Λ_i , which are an extension of the construction of Kolmanovskii and Myshkis [9]. For technical reasons we use a weighted combination between them to compensate the distributed delayed terms and estimate the exponential decay rate.

A. Exponential stability of the linear approximation

In [6], we have already proposed sufficient conditions for the local asymptotic stability of the positive steady state of the system (39). In this paper, we will extend this result by designing a novel Lyapunov-Krasovskii functional implying local exponential stability under the same previous sufficient conditions and making possible to estimate the rate of convergence. For technical reasons that will appear along our constructions, the analytic expression of the novel functional is slightly different from the one proposed in [6]. This functional will allow us to achieve our next objective, which is to determine an approximation of the basin of attraction of the positive equilibrium of the nonlinear system (39).

Let us state and prove the following result:

Theorem 2: The conditions

$$\varsigma_i > 0, \quad (44)$$

for all $i \in I_n$, ensure that the origin of (39) is locally exponentially stable.

Proof: The linear approximation of the system (39) at the origin (which is obtained by neglecting the terms where R_i is present for all $i \in I_n$) is

$$\begin{aligned} \dot{z}_i(t) = & -\beta_{i*}z_i(t) + 2L_i\mu_i \int_{t-\tau_i}^t g_i(t-a)z_i(a)da \\ & + 2K_{i-1}\mu_{i-1} \int_{t-\tau_{i-1}}^t g_{i-1}(t-a)z_{i-1}(a)da. \end{aligned} \quad (45)$$

Let us define for all $i \in I_n$ the following functionals

$$S_i(z_{it}) = \frac{1}{2}Q(z_i(t)) + L_i|\mu_i|\Omega_i(z_{it}), \quad (46)$$

$$N_1(z_{1t}) = S_1(z_{1t}) + \frac{\varsigma_1}{2C_1}\Lambda_1(z_{1t}), \quad (47)$$

and for all $i \in \{2, \dots, n\}$,

$$N_i(z_{it}, z_{i-1t}) = S_i(z_{it}) + \frac{\varsigma_i}{2C_i}\Lambda_i(z_{it}) + \psi_i\Lambda_{i-1}(z_{i-1t}), \quad (48)$$

where ψ_i is an appropriate strictly positive constant to be determined later for all $i \in \{2, \dots, n\}$.

First of all, observe for later use that the derivatives of the functionals Ω_i and Λ_i , for all $i \in I_n$, along the trajectories of (45) satisfy,

$$\dot{\Omega}_i(t) = C_iQ(z_i(t)) - \int_{t-\tau_i}^t g_i(t-a)Q(z_i(a))da, \quad (49)$$

$$\begin{aligned} \dot{\Lambda}_i(t) = & -\Lambda_i(z_{it}) - e^{-\tau_i} \int_{t-\tau_i}^t g_i(t-a)Q(z_i(a))da \\ & + \int_0^{\tau_i} e^{l-\tau_i} g_i(l)dlQ(z_i(t)) \\ \leq & -\Lambda_i(z_{it}) - e^{-\tau_i} \int_{t-\tau_i}^t g_i(t-a)Q(z_i(a))da \\ & + C_iQ(z_i(t)), \end{aligned} \quad (50)$$

where the last inequality is a consequence of the definition of the constants C_i given by (2).

For the sake of clarity, we will decompose now the proof of Theorem 2 in two parts: we start the construction of a Lyapunov functional for the first compartment and next we generalize this construction to any number of compartments.

1) *Lyapunov-Krasovskii functional for the first compartment:* Using the inequality $|z_1(t)z_1(a)| \leq \frac{1}{2}|z_1(t)|^2 + \frac{1}{2}|z_1(a)|^2$, one can readily check that the derivative along the trajectories of (45) of $Q(z_1)$, where Q is the function defined in (40), satisfies the inequality

$$\begin{aligned} \frac{1}{2}\dot{Q}(t) \leq & [-\beta_{1*} + L_1|\mu_1|C_1]Q(z_1(t)) \\ & + L_1|\mu_1| \int_{t-\tau_1}^t g_1(t-a)Q(z_1(a))da. \end{aligned} \quad (51)$$

The derivative of the functional N_1 , defined in (47), along the trajectories of (45) satisfies

$$\dot{N}_1(t) \leq -\frac{\varsigma_1}{2}Q(z_1(t)) - \frac{\varsigma_1}{2C_1}\Lambda_1(z_{1t}). \quad (52)$$

On the other hand, observe that

$$\begin{aligned} N_1(z_{1t}) \leq & \frac{1}{2}Q(z_1(t)) \\ & + \frac{\varsigma_1}{2C_1} \int_{t-\tau_1}^t e^{l-t} \int_l^t g_1(l-a+\tau_1)Q(z_1(a))dadl \\ & + L_1|\mu_1| \int_{t-\tau_1}^t \int_l^t e^{(l-(t-\tau_1))} g_1(l-a+\tau_1)Q(z_1(a))dadl. \end{aligned}$$

Then

$$N_1(z_{1t}) \leq \frac{1}{2}Q(z_1(t)) + \left(\frac{\varsigma_1 + 2L_1C_1|\mu_1|e^{\tau_1}}{2C_1} \right) \Lambda_1(z_{1t}). \quad (53)$$

From (52) and (53) we deduce that

$$\dot{N}_1(t) \leq -\tilde{\varsigma}_1N_1(z_{1t}) - \frac{\varsigma_1}{4}Q(z_1(t)), \quad (54)$$

for all $\tilde{\zeta}_1 \in \left(0, \min \left\{ \frac{\varsigma_1}{2}, \frac{\varsigma_1}{\varsigma_1 + 2L_1 C_1 |\mu_1| e^{\tau_1}} \right\} \right)$.

2) *Lyapunov-Krasovskii functional for the overall system:*
Now observe that for $i > 1$, the derivatives of the functions $Q(z_i(t))$ along the trajectories of (45) satisfy

$$\begin{aligned} \dot{Q}(t) \leq & -\beta_{i*} z_i^2(t) + 2L_i |\mu_i| \int_{t-\tau_i}^t g_i(t-a) |z_i(t) z_i(a)| da \\ & + 2K_{i-1} |\mu_{i-1}| \int_{t-\tau_{i-1}}^t g_{i-1}(t-a) |z_i(t) z_{i-1}(a)| da. \end{aligned}$$

Using the inequalities: $|z_i(t) z_i(a)| \leq Q(z_i(t)) + Q(z_i(a))$, for all $i \in I_n$, and $|z_i(t) z_{i-1}(a)| \leq \xi_i Q(z_i(t)) + \frac{1}{\xi_i} Q(z_{i-1}(a))$, with $\xi_i > 0$, for all $i > 1$, it follows that

$$\begin{aligned} \dot{Q}(t) \leq & 2[-\beta_{i*} + L_i |\mu_i| C_i] Q(z_i(t)) \\ & + 2L_i |\mu_i| \int_{t-\tau_i}^t g_i(t-a) Q(z_i(a)) da \\ & + 2\xi_i K_{i-1} |\mu_{i-1}| C_{i-1} Q(z_i(t)) \\ & + \frac{2K_{i-1} |\mu_{i-1}|}{\xi_i} \int_{t-\tau_{i-1}}^t g_{i-1}(t-a) Q(z_{i-1}(a)) da. \end{aligned}$$

We keep in mind the inequality (54), and we observe that, for $i > 1$, the derivatives of the functionals N_i , defined in (48), along the trajectories of (45) satisfy

$$\begin{aligned} \dot{N}_i(t) \leq & [-\beta_{i*} + 2L_i |\mu_i| C_i] Q(z_i(t)) \\ & + \xi_i K_{i-1} |\mu_{i-1}| C_{i-1} Q(z_i(t)) \\ & + \frac{K_{i-1} |\mu_{i-1}|}{\xi_i} \int_{t-\tau_{i-1}}^t g_{i-1}(t-a) Q(z_{i-1}(a)) da \\ & - \frac{\varsigma_i}{2C_i} \Lambda_i(z_{it}) + \frac{\varsigma_i}{2} Q(z_i(t)) + \psi_i \dot{\Lambda}_i(t). \end{aligned} \quad (55)$$

Choosing

$$\psi_i = \frac{K_{i-1} |\mu_{i-1}| e^{\tau_{i-1}}}{\xi_i} + m_i e^{\tau_{i-1}}, \quad (56)$$

with $m_i > 0$, the inequality (55) gives

$$\begin{aligned} \dot{N}_i(t) \leq & -\frac{\varsigma_i}{2} Q(z_i(t)) - \frac{\varsigma_i}{2C_i} \Lambda_i(z_{it}) \\ & - \psi_i \Lambda_{i-1}(z_{i-1t}) + \psi_i C_{i-1} Q(z_{i-1}(t)) \\ & + \xi_i K_{i-1} |\mu_{i-1}| C_{i-1} Q(z_i(t)) \\ & - m_i \int_{t-\tau_{i-1}}^t g_{i-1}(t-a) Q(z_{i-1}(a)) da. \end{aligned} \quad (57)$$

Remark 4: In the remainder of the proof of Theorem 2, one can choose $m_i = 0$ for all $i \in \{2, \dots, n\}$. The interest of these parameters will appear along our constructions in the proof of Theorem 3 in the next section.

Now, observe that if we select $\xi_i = \frac{\varsigma_i}{4K_{i-1} |\mu_{i-1}| C_{i-1}}$, for all $i \in \{2, \dots, n\}$, then

$$\begin{aligned} \dot{N}_i(t) \leq & -\frac{\varsigma_i}{4} Q(z_i(t)) - \frac{\varsigma_i}{2C_i} \Lambda_i(z_{it}) \\ & - \psi_i \Lambda_{i-1}(z_{i-1t}) + \psi_i C_{i-1} Q(z_{i-1}(t)). \end{aligned} \quad (58)$$

One can readily check that there exists a strictly positive real number $\tilde{\zeta}_i$ such that

$$\dot{N}_i(t) \leq -\tilde{\zeta}_i N_i(z_{it}, z_{i-1t}) - \frac{\varsigma_i}{8} Q(z_i(t)) + \frac{\theta_i \varsigma_{i-1}}{8} Q(z_{i-1}(t)), \quad (59)$$

with

$$\theta_i = \frac{8\psi_i C_{i-1}}{\varsigma_{i-1}}. \quad (60)$$

In order to establish that the conditions (44), for all $i \in I_n$, are sufficient to ensure that the origin of the cascaded system (45) is exponentially stable, we introduce the functional:

$$W(Z_t) = p_1 N_1(z_{1t}) + \sum_{i=2}^n p_i N_i(z_{it}, z_{i-1t}), \quad (61)$$

with

$$p_i = 2^{n-i} \prod_{k=i+1}^n \theta_k, \quad p_n = 1. \quad (62)$$

From (54) and (59), we conclude that

$$\begin{aligned} \dot{W}(t) \leq & -\sum_{i=1}^n p_i \tilde{\zeta}_i N_i(z_{it}, z_{i-1t}) - \frac{p_1 \varsigma_1}{4} Q(z_1(t)) \\ & - \sum_{i=2}^n \frac{p_i \varsigma_i}{8} Q(z_i(t)) + \sum_{i=2}^n \frac{p_i \theta_i \varsigma_{i-1}}{8} Q(z_{i-1}(t)). \end{aligned} \quad (63)$$

On the other hand

$$p_i \theta_i = 2^{n-i} \prod_{k=i+1}^n \theta_k \theta_i = \frac{1}{2} p_{i-1}. \quad (64)$$

By combining (63) and (64), we deduce that

$$\begin{aligned} \dot{W}(t) \leq & -\sum_{i=1}^n p_i \tilde{\zeta}_i N_i(z_{it}, z_{i-1t}) - \frac{\varsigma_n}{8} Q(z_n(t)) \\ & - \frac{1}{2} \sum_{i=1}^{n-1} \frac{p_i \varsigma_i}{8} Q(z_i(t)) - \frac{p_1 \varsigma_1}{8} Q(z_1(t)) \\ & \leq -\tilde{\zeta} W(Z_t), \end{aligned} \quad (65)$$

with $\tilde{\zeta} > 0$. From the features of the functional W and the inequality (65) we conclude that the origin of the system (45) is exponentially stable. The next step in this work consists in determining an approximation of the basin of attraction of the strictly positive equilibrium of the nonlinear system (39). ■

B. Exponential stability of the nonlinear system

The importance of the phenomenon of hematopoiesis has motivated many theoretical works that are particularly interested in the analysis of the earliest generations of immature cells. In contrast with the methods already used, the Lyapunov approach allows us to address more general statements, as the case of some time-varying parameters studied in Section II. Now, we will use the Lyapunov-Krasovskii functional proposed in Theorem 2 in order to answer to another open question, which is the estimation of the basin of attraction of the positive steady state. So, we focus here on the nonlinear system (35), written in the

form (39). First of all, let us observe that

$$R_i(\hat{x}_i) = -\hat{x}_i w_i'(x_i^e) + w_i(x_i^e + \hat{x}_i) - w_i(x_i^e). \quad (66)$$

From this equality and (33), we deduce that

$$R_i(\hat{x}_i) = [r_{1i}(\hat{x}_i) + r_{2i}(\hat{x}_i)] \beta_i(0),$$

with

$$r_{1i}(\hat{x}_i) = -\hat{x}_i \frac{1 + b_i(1 - n_i)(x_i^e)^{n_i}}{(1 + b_i(x_i^e)^{n_i})^2},$$

and

$$r_{2i}(\hat{x}_i) = \frac{\hat{x}_i(1 + b_i(x_i^e)^{n_i}) + b_i x_i^e ((x_i^e)^{n_i} - (x_i^e + \hat{x}_i)^{n_i})}{(1 + b_i(x_i^e + \hat{x}_i)^{n_i})(1 + b_i(x_i^e)^{n_i})}.$$

Notice that

$$R_i(\hat{x}_i) = \tilde{R}_i(\hat{x}_i) \hat{x}_i^2, \quad (67)$$

with $\tilde{R}_i(\hat{x}_i) = [\tilde{r}_{1i}(\hat{x}_i) + \tilde{r}_{2i}(\hat{x}_i)] \beta_i(0)$ such that

$$\tilde{r}_{1i}(\hat{x}_i) = \frac{1}{\hat{x}_i(1 + b_i(x_i^e + \hat{x}_i)^{n_i})} - \frac{1 + b_i(1 - n_i)(x_i^e)^{n_i}}{\hat{x}_i(1 + b_i(x_i^e)^{n_i})^2},$$

$$\tilde{r}_{2i}(\hat{x}_i) = -\frac{b_i(x_i^e)^{n_i+1} \left(\left(\frac{\hat{x}_i + x_i^e}{x_i^e} \right)^{n_i} - 1 \right)}{(1 + b_i(x_i^e + \hat{x}_i)^{n_i})(1 + b_i(x_i^e)^{n_i}) \hat{x}_i^2}.$$

Noticing that

$$\lim_{\hat{x}_i \rightarrow 0} \tilde{R}_i(\hat{x}_i) = \frac{b_i \beta_i(0) n_i x_i^{e n_i - 1} (n_i (b_i x_i^{e n_i}) - b_i x_i^{e n_i} - 1)}{2(1 + b_i x_i^{e n_i})^3},$$

one can easily check that the function \tilde{R}_i is bounded on $[-x_i^e, +\infty)$. For later use, let us denote

$$\hat{s}_i = 2 \max_{x_i^e < \hat{x}_i} |\tilde{R}_i(\hat{x}_i)|, \quad (68)$$

and observe that \hat{s}_i depends on the biological parameters of the model and on the strictly positive equilibrium x_i^e for all $i \in I_n$. From (68) and (67) we conclude that, for all $i \in I_n$,

$$R_i(\hat{x}_i) \leq \hat{s}_i Q(\hat{x}_i). \quad (69)$$

Let us consider the functionals S_i and N_i defined in (46), (47) and (48). In order to ease the notation, we denote

$$I_i(\hat{x}_{it}) = \int_{t-\tau_i}^t g_i(t-a) Q(\hat{x}_i(a)) da. \quad (70)$$

Finally, we define the constants

$$\tilde{k}_i = \frac{S_i}{8\hat{s}_i}, \quad \hat{k}_i = \frac{S_i}{4C_i L_i \hat{s}_i e^{\tau_i}} \text{ and } \bar{N}_i = \min \left\{ \tilde{k}_i^2, \hat{k}_i^2 \right\}. \quad (71)$$

Notice that for all $i \in I_n$, \tilde{k}_i and \hat{k}_i are only dependent on the constant biological parameters of the model.

Now we are ready to state and prove the following theorem:

Theorem 3: Let the system (39) be such that

$$s_i > 0 \quad (72)$$

for all $i \in I_n$. Therefore all the solutions of (39) with initial conditions $\hat{\varphi}_i \in \mathcal{C}([-\tau_i, 0], \mathbb{R})$ satisfying

$$N_i(\hat{\varphi}_i, \hat{\varphi}_{i-1}) < \bar{N}_i, \quad (73)$$

converge exponentially to the origin.

Remark 5: Notice that if the conditions (72) are satisfied then $\bar{N}_i > 0$, for all $i \in I_n$.

Proof:

1) *Lyapunov-Krasovskii functional for the first compartment:* Using (69), One can prove that the derivative of the function $Q(\hat{x}_1(t))$, introduced in (40), along the trajectories of (39) satisfies

$$\begin{aligned} \dot{Q}(t) &\leq 2[-\beta_{1*} + L_1 |\mu_1| C_1] Q(\hat{x}_1(t)) \\ &\quad + 2L_1 (|\mu_1| + \hat{s}_1 |\hat{x}_1(t)|) I_1(\hat{x}_{1t}) \\ &\quad + \hat{s}_1 |\hat{x}_1(t)| Q(\hat{x}_1(t)). \end{aligned} \quad (74)$$

The derivative of the functional N_1 , introduced in (47), along the trajectories of (39) satisfies

$$\begin{aligned} \dot{N}_1(t) &\leq - \left[\frac{s_1}{8} Q(\hat{x}_1(t)) + \frac{s_1}{2C_1} \Lambda_1(\hat{x}_{1t}) \right] \\ &\quad + \left[\frac{\hat{s}_1}{2} |\hat{x}_1(t)| - \frac{s_1}{4} \right] Q(\hat{x}_1(t)) - \frac{s_1}{8} Q(\hat{x}_1(t)) \\ &\quad + \left[L_1 \hat{s}_1 |\hat{x}_1(t)| - \frac{s_1 e^{-\tau_1}}{2C_1} \right] I_1(\hat{x}_{1t}). \end{aligned} \quad (75)$$

Similarly to (53), one can observe that

$$N_1(\hat{x}_{1t}) \leq \frac{1}{2} Q(\hat{x}_1(t)) + \left(\frac{s_1 + 2L_1 C_1 |\mu_1| e^{\tau_1}}{2C_1} \right) \Lambda_1(\hat{x}_{1t}). \quad (76)$$

From (76) and (75) we deduce that for all

$$\tilde{\zeta}_1 \in \left(0, \min \left\{ \frac{s_1}{4}, \frac{s_1}{s_1 + 2L_1 C_1 |\mu_1| e^{\tau_1}} \right\} \right),$$

$$\begin{aligned} \dot{N}_1(t) &\leq -\tilde{\zeta}_1 N_1(\hat{x}_{1t}) + \left[\frac{\hat{s}_1}{2} |\hat{x}_1(t)| - \frac{s_1}{4} \right] Q_1(\hat{x}_1(t)) \\ &\quad + \left[L_1 \hat{s}_1 |\hat{x}_1(t)| - \frac{s_1 e^{-\tau_1}}{2C_1} \right] I_1(\hat{x}_{1t}) - \frac{s_1}{8} Q(\hat{x}_1(t)). \end{aligned} \quad (77)$$

Since $|\hat{x}_1(t)| \leq 2\sqrt{N_1(\hat{x}_{1t})}$ (from the definition of N_1 in (47)), we deduce that

$$\begin{aligned} \dot{N}_1(t) &\leq -\tilde{\zeta}_1 N_1(\hat{x}_{1t}) + \left[\hat{s}_1 \sqrt{N_1(\hat{x}_{1t})} - \frac{s_1}{4} \right] Q_1(\hat{x}_1(t)) \\ &\quad + \left[2L_1 \hat{s}_1 \sqrt{N_1(\hat{x}_{1t})} - \frac{s_1 e^{-\tau_1}}{2C_1} \right] I_1(\hat{x}_{1t}) - \frac{s_1}{8} Q(\hat{x}_1(t)). \end{aligned} \quad (78)$$

Now observe that if, for $i = 1$, the condition (73) is satisfied then

$$\dot{N}_1(t) \leq -\tilde{\zeta}_1 N_1(\hat{x}_{1t}) - \frac{s_1}{8} Q(\hat{x}_1(t)). \quad (79)$$

This allows us to conclude that the origin of (39) is exponentially stable with a decay rate smaller than $\tilde{\zeta}_1$ when $i = 1$.

2) *Lyapunov-Krasovskii functional for the overall system:* Similarly to the previous section where we analysed the linear approximation (45), using the inequality $|\hat{x}_i(t) \hat{x}_{i-1}(a)| \leq \xi_i Q(\hat{x}_i(t)) + \frac{1}{\xi_i} Q(\hat{x}_{i-1}(a))$, with $\xi_i > 0$ for $i > 1$, and the inequality $|\hat{x}_i(t) \hat{x}_i(a)| \leq Q(\hat{x}_i(t)) +$

$Q(\hat{x}_i(a))$, for $i \in I_n$, we show after elementary calculations that the derivatives of the functions $Q(\hat{x}_i(t))$, for $i > 1$, along the trajectories of (39) satisfy

$$\begin{aligned} \dot{Q}(t) &\leq 2[-\beta_{i*} + L_i|\mu_i|C_i]Q(\hat{x}_i(t)) \\ &+ \hat{s}_i|\hat{x}_i(t)|Q(\hat{x}_i(t)) \\ &+ 2L_i(|\mu_i| + \hat{s}_i|\hat{x}_i(t)|)I_i(\hat{x}_{it}) \\ &+ 2K_{i-1}|\mu_{i-1}|C_{i-1}\xi_i Q(\hat{x}_i(t)) \\ &+ 2K_{i-1}\left(\hat{s}_{i-1}|\hat{x}_i(t)| + \frac{|\mu_{i-1}|}{\xi_i}\right)I_{i-1}(\hat{x}_{i-1t}). \end{aligned} \quad (80)$$

By following similar steps to those in the proof of Theorem 2, grouping the terms and choosing now $m_i = \frac{\varsigma_i e^{-\tau_i} K_{i-1} \hat{s}_{i-1}}{2L_i \hat{s}_i C_i}$ and $\xi_i = \frac{\varsigma_i}{4K_{i-1}|\mu_{i-1}|C_{i-1}}$, we prove that the derivatives of the functionals N_i along the trajectories of (39) satisfy

$$\begin{aligned} \dot{N}_i(t) &\leq -\tilde{\varsigma}_i N_i(\hat{x}_i, \hat{x}_{i-1}) + \psi_i C_{i-1} Q(\hat{x}_{i-1}(t)) \\ &- \left[\frac{\varsigma_i}{8} - \frac{1}{2} \hat{s}_i |\hat{x}_i(t)| \right] Q(\hat{x}_i(t)) - \frac{\varsigma_i}{16} Q(\hat{x}_i(t)) \\ &+ L_i \hat{s}_i \left[|\hat{x}_i(t)| - \frac{\varsigma_i e^{-\tau_i}}{2L_i \hat{s}_i C_i} \right] I_i(\hat{x}_{it}) \\ &+ K_{i-1} \hat{s}_{i-1} \left[|\hat{x}_i(t)| - \frac{\varsigma_i e^{-\tau_i}}{2L_i \hat{s}_i C_i} \right] I_{i-1}(\hat{x}_{i-1t}), \end{aligned} \quad (81)$$

with $\tilde{\varsigma}_i > 0$. Finally we conclude that if the conditions (73) are satisfied for all $i \in I_n$ then

$$\begin{aligned} \dot{N}_i(t) &\leq -\tilde{\varsigma}_i N_i(\hat{x}_{it}, \hat{x}_{i-1t}) - \frac{\varsigma_i}{16} Q(\hat{x}_i(t)) \\ &+ \psi_i C_{i-1} Q(\hat{x}_{i-1}(t)). \end{aligned} \quad (82)$$

Then we easily verify that the derivative of the functional

$$W(\hat{X}_t) = \sum_{i=1}^n p_i N_i(\hat{x}_{it}, \hat{x}_{i-1t}), \quad (83)$$

with $\hat{X} = (\hat{x}_1, \dots, \hat{x}_n)$ and p_i the constants defined in (62), along the trajectories of (39), satisfies

$$\begin{aligned} \dot{W}(t) &\leq -\sum_{i=1}^n p_i \tilde{\varsigma}_i N_i(\hat{x}_{it}, \hat{x}_{i-1t}) - \frac{\varsigma_1}{8} Q(\hat{x}_1(t)) \\ &- \frac{\varsigma_n}{16} Q(\hat{x}_n(t)) - \frac{1}{2} \sum_{i=1}^{n-1} \frac{p_i \varsigma_i}{8} Q(\hat{x}_i(t)). \end{aligned} \quad (84)$$

Finally, we obtain

$$\dot{W}(t) \leq -\varsigma W(\hat{X}_t), \quad (85)$$

with $\varsigma = \min\{\tilde{\varsigma}_1, \dots, \tilde{\varsigma}_n\} > 0$. Moreover, we observe that for any function $\varphi_i \in \mathcal{C}([-\tau_i, 0], \mathbb{R})$ satisfying (73),

$$W(\varphi) < \overline{W}, \quad (86)$$

with $\varphi = (\varphi_1, \dots, \varphi_n)$ and $\overline{W} = \sum_{i=1}^n p_i \overline{N}_i > 0$.

To summarize, by virtue of the properties of the functionals N_i , for all $i \in I_n$, and since the original system (30) is a

positive system, we straightforwardly conclude that the set

$$\mathcal{A} = \{(\phi_i, \tilde{\phi}_i) \in \mathcal{C}([-\tau_i, 0], \mathbb{R}_+) \times \mathcal{C}([-\tau_i, 0], \mathbb{R}_+) : \mathcal{N}_i(\phi_i - x_i^e, \tilde{\phi}_i - x_i^e) < \overline{N}_i\}, \quad (87)$$

intersection between the set of initial conditions satisfying (73) and the set of all initial conditions $\varphi_i \in \mathcal{C}([-\tau_i, 0], \mathbb{R})$ such that $\varphi_i > -x_i^e$, for all $i \in I_n$, is an estimate of the basin of attraction of the origin of system (39). ■

IV. CONCLUSIONS

Lyapunov theory offers strong tools when investigating time-delay systems. However, the construction of strict Lyapunov-Krasovskii functionals is a challenging problem. In this work we proposed explicit constructions of suitable Lyapunov functionals for nonlinear systems with distributed delays. Much remains to be done in the theoretical analysis of hematopoiesis and leukemia. We think that the recent model proposed by Adimy in [1] in conjunction with infinite distributed delays [18] will allow the models to reproduce further biological phenomena observed in hematopoiesis.

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