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Stability of the cell dynamics in acute myeloid leukemia[☆]

Emilia Fridman[a,*], Catherine Bonnet[b], Frederic Mazenc[b], Walid Djema[b]

[a] School of Electrical Engineering, Tel-Aviv University, Tel-Aviv 69978, Israel
[b] Inria, Université Paris-Saclay, L2S-CentraleSupélec, 3 rue Joliot Curie, 91192, Gif-sur-Yvette, France

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ABSTRACT

In this paper we analyze the global asymptotic stability of the trivial solution for a multi-stage maturity acute myeloid leukemia model. By employing the positivity of the corresponding nonlinear time-delay model, where the nonlinearity is locally Lipschitz, we establish the global exponential stability under the same conditions that are necessary for the local exponential stability. The result is derived for the multi-stage case via a novel construction of linear Lyapunov functionals. In a simpler model of hematopoiesis (without fast self-renewal) our conditions guarantee also global exponential stability with a given decay rate. Moreover, in this simpler case the analysis of the PDE model is presented via novel Lyapunov functionals for the transport equations.

1. Introduction

In order to better understand the dynamics of unhealthy hematopoiesis, and in particular to find theoretical conditions for the efficient delivery of drugs in acute myeloblastic leukemia, the stability of a system modeling its cell dynamics was studied in [1–5] and the references therein. The model is given by nonlinear transport equations, which are transformed by the characteristic method to nonlinear time-delay systems. In the above works either local asymptotic stability of the resulting time-delay systems is provided or some sufficient global asymptotic stability conditions are given. In the latter case these conditions for the trivial solutions are either sufficient only [2] or they are derived for the case of nonlinearity subject to a sector bound [3].

In this paper we analyze the global asymptotic stability of the trivial solution for the multi-stage acute myeloid leukemia model. By employing the positivity of the corresponding nonlinear time-delay model, where the nonlinearities are monotone functions, we establish the global asymptotic stability under the same conditions that are necessary for the local exponential stability. The result is derived via the construction of novel linear Lyapunov functionals for multi-stage case. For the Lyapunov-based analysis of positive linear time-delay systems, as well as nonlinear systems with the nonlinearities subject to a sector bound, we refer to [6–9]. In a simpler model of hematopoiesis (without fast self-renewal) our conditions guarantee global exponential stability with a given decay rate. Moreover, in this simpler case, the analysis of the PDE model is presented via novel Lyapunov functionals for the transport equations. These are linear in the state Lyapunov functionals with some weighting functions. Note that the idea of weighting functions in Lyapunov functionals for Euler equations was introduced in [10] and was used later for nonlinear systems of conservation laws in [11].

The structure of this paper is as follows. Section 2 provides the exponential stability analysis of hematopoiesis model, where the Lyapunov-based analysis is developed for both, the time-delay and the PDE model. Section 3 is devoted to the global asymptotic/regional exponential stability of the acute myeloid leukemia model via Lyapunov-based analysis of the corresponding time-delay model. Finally, in Section 4, concluding remarks are outlined.

Some preliminary sufficient conditions for local asymptotic stability of 1-stage Acute Myeloid Leukemia PDE model were presented in [12].

Notation and preliminaries: Throughout the paper the superscript 'T' stands for matrix/vector transposition, $\mathbb{R}_+$ denotes the set of nonnegative real numbers, $\mathbb{R}^n$ denotes the n-dimensional Euclidean space. For $a, b \in \mathbb{R}^n$ the inequality $a < b$ ($a \le b$) means componentwise inequality $a_i < b_i$ ($a_i \le b_i$) for all $i = 1, \ldots, n$. Similarly is defined the opposite vector inequality $a > b$ ($a \ge b$).

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* Corresponding author.
E-mail addresses: emilia@eng.tau.ac.il (E. Fridman), Catherine.Bonnet@inria.fr (C. Bonnet), Frederic.Mazenc@lss.supelec.fr (F. Mazenc), Walid.Djema@inria.fr (W. Djema).

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$\mathbb{R}^n_+$ denotes the set of vectors $a \in \mathbb{R}^n$ with nonnegative components, i.e. $a \geq 0$. The space of continuous functions $\phi_i : [-\tau_i, 0] \to \mathbb{R}$ $(i = 1, \ldots, n)$ with the norm $\|\phi\|_C = \sum_{i=1}^n \max_{s\in[-\tau_i,0]} |\phi_i(s)|$ is denoted by C^n_τ; $C^n_{\tau+} = \{\phi \in C^n_\tau : \phi_i(s) \geq 0\ s \in [-\tau_i, 0],\ i = 1, \ldots, n\}$; $x_t(s) = x(t+s), s \in [-\tau, 0]$ for $x_t : [-\tau, 0] \to \mathbb{R}^n$. The matrix $A \in \mathbb{R}^{n\times n}$ with nonnegative off-diagonal terms is called Metzler matrix, the matrix A is called nonnegative if all its entries are nonnegative.

2. Stability of the model of cell dynamics in hematopoiesis

A model of hematopoietic stem cell dynamics, that takes two cell populations into account, an immature and a mature one, was proposed and analyzed in [1]. Immature cells may have n different stages of maturity before they become mature. All cells are able to self-renew, and immature cells can be either in a proliferating or in a resting compartment. The resulting model for n stages of immature cells is given by

$$\begin{aligned} &\partial_t r_i + \partial_a r_i = -(\delta_i + \beta_i(x_i))r_i, \quad a > 0,\ t > 0,\ i = 1, \ldots, n, \\ &\partial_t p_i + \partial_a p_i = -(\gamma_i + g_i(a))p_i, \quad 0 < a < \tau_i,\ t > 0, \end{aligned} \tag{1}$$

where r_i are p_i are resting and proliferating cell densities, a is the age of the cells, τ_i is the maximum possible time spent by a cell in proliferation in compartment i before it divides, $\delta_i > 0$ and $\gamma_i > 0$ are the death rates for the quiescent and for the proliferating cell population, n is the number of compartments, $\beta_i > 0$ is the introduction rate that depends on the total density of resting cells

$$x_i(t) = \int_0^\infty r_i(t, a)da.$$

Boundary conditions, describing the flux between the two phases and two successive generations, are given by

$$\begin{aligned} r_i(t, 0) &= 2(1-K_i)\int_0^{\tau_i} g_i(a)p_i(t, a)da \\ &\quad + 2K_{i-1}\int_0^{\tau_{i-1}} g_{i-1}(a)p_{i-1}(t, a)da, \\ p_i(t, 0) &= \beta_i(x_i(t))x_i(t), \quad t > 0,\ i = 1, \ldots, n, \end{aligned} \tag{2}$$

where $K_0 = 0$ and $0 < K_i < 1$ is the probability of cell differentiation.

Following [1], we have taken into account the following assumptions:

- The division rates $g_i(a)$ are continuous functions such that $\int_0^{\tau_i} g_i(a)\, da = +\infty$. This property implies
$$\int_0^{\tau_i} g_i(t)\, e^{-\int_0^t g_i(w)dw} dt = 1.$$
- $\lim_{a\to+\infty} r_i(t, a) = 0$.
- The re-introduction term β_i is a Locally Lipschitz, differentiable and decreasing function with $\beta_i(0) > 0$ and $\beta_i(x) \to 0$ as $x \to \infty$. Typical selection of β_i is in the form of Hill function
$$\beta_i(x_i) = \frac{\beta_i(0)}{1 + b_i x_i^{N_i}},$$
where $b_i > 0$ and $N_i > 0$.

By using the method of characteristics, the following explicit formulation for $p_i(t, a)$ was derived in [1]:

$$p_i(t, a) = \begin{cases} p_i(0, a-t)e^{-\int_{a-t}^a(\gamma_i + g_i(s))ds}, & t \leq a, \\ p_i(t-a, 0)e^{-\int_0^a(\gamma_i+g_i(s))ds}, & t > a, \end{cases} \tag{3}$$

where $p_i(0, a) \geq 0$. Then, the authors obtained the following time-delay model for the total population densities of resting cells

$$\begin{aligned} \dot{x}_i(t) &= -(\delta_i + \beta_i(x_i(t)))x_i(t) + 2(1-K_i)\int_0^{\tau_i} e^{-\gamma_i a}f_i(a) \\ &\quad \times \beta_i(x_i(t-a))x_i(t-a)da + 2K_{i-1}\int_0^{\tau_{i-1}} e^{-\gamma_{i-1}a} \\ &\quad \times f_{i-1}(a)\beta_{i-1}(x_{i-1}(t-a))x_{i-1}(t-a)da, \\ &\quad t > 0, \quad i = 1, \ldots, n, \end{aligned} \tag{4}$$

where

$$f_i(a) := g_i(a)e^{-\int_0^a g_i(s)ds}, \quad 0 < a < \tau_i$$

is a density function with $\int_0^{\tau_i} f_i(a)da = 1$. We denote for a later use

$$f_i^* = \sup_{a\in[0,\tau_i]} g_i(a)e^{-\int_0^a g_i(s)ds}, \quad i = 1, \ldots, n. \tag{5}$$

It is easy to see that nonlinear time-delay system (4) with a nonnegative initial condition

$$x_i(s) = \phi_i(s) \geq 0, \quad \forall s \in [-\tau_i, 0],\ \phi_i \in C^1_{\tau_i+}$$

has nonnegative solutions, meaning that (4) is a positive system. Assume also nonnegativity of the initial function $p(0, a)$. Then, taking into account that $p_i(t-a, 0) = \beta_i(x_i(t-a))x_i(t-a) \geq 0$, (3) implies $p_i(t, a) \geq 0$ for all $t \geq 0$ and $a \in [0, \tau_i]$.

Local asymptotic stability of (4) was studied in [1,2,5,4,3] by the analysis of the linearized system. For systems with nonlinearities satisfying sector condition, the stability conditions for the strictly positive steady state were found in [3] by using Popov, circle and nonlinear small gain criteria. More recently, sufficient stability conditions for the 0-equilibrium and the strictly positive equilibrium were derived in [5] by a Lyapunov approach. Notice that knowing Lyapunov functionals allows us, for instance, to estimate rates of convergence and to determine approximations of the basin of attraction of a locally stable equilibrium point.

In the present paper, we focus on the stability analysis of the 0-equilibrium and we will show that necessary conditions for the local exponential stability are also sufficient for the global exponential stability of the trivial solution by using the direct Lyapunov method developed for the time-delay models and, for the first time, for the PDE model. We will also present estimates on the exponential decay rate for the nonlinear full-order system.

2.1. *Global exponential stability of the zero solution of the time-delay model*

We will start with the time-delay model (4). The linearized around the zero solution model has the following form

$$\begin{aligned} \dot{x}_i(t) &= -(\delta_i + \beta_i(0))x_i(t) + 2(1-K_i)\int_0^{\tau_i} e^{-\gamma_i a}f_i(a) \\ &\quad \times \beta_i(0)x_i(t-a)da + 2K_{i-1}\int_0^{\tau_{i-1}} e^{-\gamma_{i-1}a}f_{i-1}(a) \\ &\quad \times \beta_{i-1}(0)x_{i-1}(t-a)da, \quad t > 0,\ i = 1, \ldots, n. \end{aligned} \tag{6}$$

This is a positive linear system that can be presented as

$$\begin{aligned} &\dot{x}(t) = Ax(t) + \sum_{i=1}^n \int_0^{\tau_i} A_i(a)x(t-a)da, \\ &x = col\{x_1, \ldots, x_n\} \end{aligned} \tag{7}$$

where A is Metzler (since it is diagonal) and each A_i is non-negative. Note that for such a system the following holds:

Lemma 1 ([6,8]). *Consider (7), where A is Metzler and A_i is non-negative. Then the following conditions are equivalent:*

(i) *The system (7) is asymptotically stable;*
(ii) *$A + \sum_{i=1}^n \int_0^{\tau_i} A_i(s)ds$ is Hurwitz;*

(iii) *There exists a vector* $0 < \lambda \in \mathbb{R}^n$ *such that*

$$\lambda^T \left(A + \sum_{i=1}^{n} \int_0^{\tau_i} A_i(s) ds \right) < 0.$$

Note that sufficiency of (iii) for the asymptotic stability of (7) can be derived by using the following Lyapunov functional [6,8]

$$V(x_t) = \lambda^T \left[x(t) + \sum_{i=1}^{n} \int_0^{\tau_i} A_i(a) \int_{t-a}^{t} x(s) ds da \right]. \quad (8)$$

Due to "triangular" structure of (4), the condition (ii) for this system is equivalent to the following inequalities

$$\left[2(1-K_i) \int_0^{\tau_i} e^{-\gamma_i a} f_i(a) da - 1 \right] \beta_i(0) < \delta_i, \quad i = 1, \dots, n. \quad (9)$$

The inequalities (9) are also necessary and sufficient conditions for the *local* exponential stability of the nonlinear system (4) (see e.g. Proposition 3.17 in [13]). The conditions (9) for the local asymptotic stability were derived in [2]. Sufficient K_i-independent conditions

$$\left[\int_0^{\tau_i} e^{-\gamma_i a} f_i(a) da - 1 \right] \beta_i(0) < \delta_i, \quad i = 1, \dots, n$$

for the *global* asymptotic stability of (4) were derived in [2] via the linear in state Lyapunov functional

$$V(x_t) = \sum_{i=1}^{n} \left[x_i(t) + 2 \int_0^{\tau_i} e^{-\gamma_i a} f_i(a) \int_{t-a}^{t} \beta_i(x_i(s)) x_i(s) ds da \right].$$

Keeping in mind the Lyapunov candidate (8) and a special triangular structure of (4), we suggest the following Lyapunov functional for the global exponential stability of (4):

$$V(x_t) = \sum_{i=1}^{n} \varepsilon^i [x_i(t) + V_{2i}(x_t)], \quad \varepsilon > 0,$$
$$V_{2i}(x_t) = 2[1 - K_i(1-\varepsilon)] \int_0^{\tau_i} \int_{t-a}^{t} e^{-\eta(t-a-s)-\gamma_i a} \times f_i(a) \beta_i(x_i(s)) x_i(s) ds da, \quad (10)$$

where ε is small enough and where $\eta > 0$ is a decay rate for the exponential stability. We will find conditions that guarantee

$$\dot{V}(x_t) + \eta V(x_t) \le 0, \quad (11)$$

implying the exponential stability of (4) with a decay rate $\eta > 0$ in the "norm" defined by V:

$$V(x_t) \le e^{-\eta t} V(x_0), \quad t \ge 0. \quad (12)$$

Proposition 1. *Let there exist* $\eta \in (0, \min\{\delta_1, \dots, \delta_n\})$ *such that the following inequalities are satisfied:*

$$\left[2(1-K_i) \int_0^{\tau_i} e^{-(\gamma_i - \eta)a} f_i(a) da - 1 \right] \beta_i(0) < \delta_i - \eta, \quad i = 1, \dots, n. \quad (13)$$

Then the system (4) *is globally exponentially stable with the decay rate* η. *Moreover, if the inequalities* (13) *are satisfied with* $\eta = 0$ *(i.e. if* (9) *are satisfied), then* (4) *is globally exponentially stable with a small enough decay rate.*

Proof. We have along (4)

$$\sum_{i=1}^{n} \varepsilon^i \dot{x}_i(t) = \sum_{i=1}^{n} \varepsilon^i \Big[-(\delta_i + \beta_i(x_i(t))) x_i(t) + 2[1-K_i] \times \int_0^{\tau_i} e^{-\gamma_i a} f_i(a) \beta_i(x_i(t-a)) x_i(t-a) da + 2K_{i-1} \times \int_0^{\tau_{i-1}} e^{-\gamma_{i-1} a} f_{i-1}(a) \beta_{i-1}(x_{i-1}(t-a)) x_{i-1}(t-a) da \Big]$$
$$\le \sum_{i=1}^{n} \varepsilon^i \Big[-(\delta_i + \beta_i(x_i(t))) x_i(t) + 2[1 - K_i(1-\varepsilon)] \times \int_0^{\tau_i} e^{-\gamma_i a} f_i(a) \beta_i(x_i(t-a)) x_i(t-a) da \Big].$$

Then differentiating V of (10) along (4) we obtain

$$\dot{V}(x_t) + \eta V(x_t) \le \sum_{i=1}^{n} \varepsilon^i \left[-\delta_i + \eta + \left[2(1 - K_i(1-\varepsilon)) \times \int_0^{\tau_i} e^{-(\gamma_i - \eta)a} f_i(a) da - 1 \right] \beta_i(x_i(t)) \right] x_i(t). \quad (14)$$

For each $i = 1, \dots, n$ and for small enough $\varepsilon > 0$ we have either

$$2(1 - K_i(1-\varepsilon)) \int_0^{\tau_i} e^{-(\gamma_i - \eta)a} f_i(a) da < 1$$

or due to $0 \le \beta_i(x_i) \le \beta_i(0)$

$$\left[2(1 - K_i(1-\varepsilon)) \int_0^{\tau_i} e^{-(\gamma_i - \eta)a} f_i(a) da - 1 \right] \beta_i(x_i(t)) \le \left[2(1 - K_i(1-\varepsilon)) \int_0^{\tau_i} e^{-(\gamma_i - \eta)a} f_i(a) da - 1 \right] \beta_i(0) < \delta_i - \eta.$$

Note that the latter inequality holds for small enough ε due to (13). Therefore, in both cases, for small enough ε Eq. (14) implies (11).

Now, if inequalities (13) are satisfied with $\eta = 0$, we can always find a small enough $\eta_1 > 0$ such that (13) are satisfied. The latter guarantees global exponential stability of (4) with a decay rate $\eta_1 > 0$. □

Summarizing, the inequalities (9) are necessary for the local and sufficient for the global exponential stability of the trivial solution of (4).

Remark 1. In [4] the division rates g_i, $i = 1, \dots, n$ were chosen as

$$g_i(a) = \frac{m_i}{e^{m_i(\tau_i - a)} - 1}, \quad 0 \le a \le \tau_i,$$

where $m_i \ge \gamma_i$ are integers. It was found that $f_i(a) = g_i(a) e^{-\int_0^a g_i(s) ds}$ has a form

$$f_i(a) = \frac{m_i}{e^{m_i \tau_i} - 1} e^{m_i a}, \quad 0 \le a \le \tau_i.$$

Here the term $f_i^\star$ is well-defined, although $\lim_{a \to \tau_i} g_i(a) = \infty$, and

$$f_i^\star = \frac{m_i}{e^{m_i \tau_i} - 1} e^{m_i \tau_i}.$$

Example 1. Choosing $f_i(a) = \frac{m_i}{e^{m_i \tau_i} - 1} e^{m_i a}$, with $m_i > 0$ for all $i \in [1, n]$, the following parameters satisfy (13).

For $i = 1$: $\delta_1 = 1$, $L_1 = 1 - K_1 = 0.95$, $m_1 = 1$, $\tau_1 = 1$, $\gamma_1 = 0.8$ and $\beta_1(x) = \frac{1}{1+x^2}$.

For $i = 2$: $\delta_2 = 0.8$, $L_2 = 1 - K_2 = 0.95$, $m_2 = 1$, $\tau_2 = 1.2$, $\gamma_2 = 0.7$ and $\beta_2(x) = \frac{1}{1+x^3}$.

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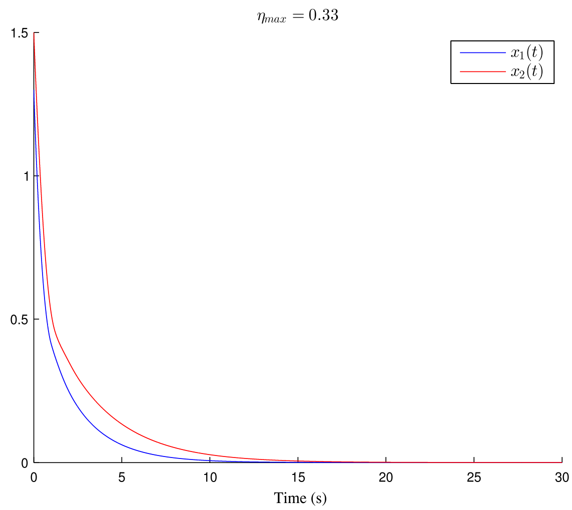

Fig. 1. Trajectories of the states x_1 and x_2 for the parameters of Example 1.

These parameters yield to $\left[2(1-K_1)\int_0^{\tau_1} e^{-\gamma_1 a} f_1(a)da - 1\right]\beta_1(0) = 0.2241 < \delta_1$ and consequently no positive equilibrium exists.

According to Proposition 1, $\eta \in (0, \min\{\delta_1, \delta_2\}) = (0, 0.8)$. Numerically, we find that the largest value $\eta_{\max}$ which verifies (13) is $\eta_{\max} \approx 0.33$.

- Choosing $\eta = \eta_{\max}$:

$$\left[2(1-K_1)\int_0^{\tau_1} e^{-(\gamma_1-\eta_{\max})a} f_1(a)da - 1\right]\beta_1(0) - \delta_1 + \eta_{\max} = -0.2118 < 0$$

and

$$\left[2(1-K_2)\int_0^{\tau_2} e^{-(\gamma_2-\eta_{\max})a} f_2(a)da - 1\right]\beta_2(0) - \delta_2 + \eta_{\max} = -0.0015 < 0.$$

The trajectories x_1 and x_2 are illustrated in Fig. 1.

2.2. Stability of the PDE model

In this section we will develop the direct Lyapunov method to the PDE model. Consider first the following Lyapunov functional

$$V(t) = \sum_{i=1}^{n} \varepsilon^i [x_i(t) + V_{2i}(t)], \quad \varepsilon > 0,$$
$$V_{2i}(t) = \frac{1}{q_i}\int_0^{\tau_i} e^{\int_0^a g_i(s)ds} p_i(t,a)\,da, \quad i = 1,\dots,n,\ q_i > 0. \tag{15}$$

Differentiating $x_i(t)$ along (1) and taking into account the boundary conditions we have

$$\dot{x}_i(t) = \int_0^{\infty} (-\partial_a r_i(t,a) - (\delta_i + \beta_i(x_i(t)))\, r_i(t,a))\, da$$
$$= -[\delta_i + \beta_i(x_i(t))]x_i(t) + 2(1-K_i)\int_0^{\tau_i} g_i(a)p_i(t,a)da + 2K_{i-1}\int_0^{\tau_{i-1}} g_{i-1}(a)p_{i-1}(t,a)da.$$

Then

$$\int_0^{\tau_i} g_i(a)p_i(t,a)da = \int_0^{\tau_i} g_i(a)e^{-\int_0^a g_i(s)ds}e^{\int_0^a g_i(s)ds}p_i(t,a)da \le q_i f_i^* V_{2i}(t),$$

implying

$$\sum_{i=1}^{n}\varepsilon^i \dot{x}_i(t) \le -\sum_{i=1}^{n}\varepsilon^i[\delta_i + \beta_i(x_i(t))]x_i(t) + 2\sum_{i=1}^{n}\varepsilon^i q_i(1-K_i(1-\varepsilon))f_i^* V_{2i}(t). \tag{16}$$

Differentiating $V_{2i}(t)$ along (1) and taking into account the boundary conditions we obtain

$$\dot{V}_{2i}(t) = \frac{1}{q_i}\int_0^{\tau_i}[-\partial_a p_i(t,a) - (\gamma_i + g_i(a))p_i(t,a)]e^{\int_0^a g_i(s)ds}da$$
$$= -\gamma_i V_{2i}(t) - \frac{1}{q_i}\int_0^{\tau_i}\frac{d}{da}\left[p_i(t,a)e^{\int_0^a g_i(s)ds}\right]da$$
$$= -\gamma_i V_{2i}(t) - \frac{p_i(t,a)}{q_i}e^{\int_0^a g_i(s)ds}\Big|_0^{\tau_i}$$
$$\le -\gamma_i V_{2i}(t) + \frac{\beta_i(x_i)}{q_i}x_i(t).$$

Therefore,

$$\dot{V}(t) + \eta V(t) \le -\sum_{i=1}^{n}\varepsilon^i\Big[[\delta_i - \eta + (1-1/q_i)\beta_i(x_i)]x_i(t) + [\gamma_i - \eta - 2q_i(1-K_i(1-\varepsilon))f_i^*]V_{2i}(t)\Big] \le 0$$

if

$$\delta_i - \eta + (1-1/q_i)\beta_i(x_i) \ge 0,$$
$$\gamma_i - \eta - 2q_i(1-K_i(1-\varepsilon))f_i^* \ge 0. \tag{17}$$

Choosing from the second inequality of (17)

$$q_i = \frac{\gamma_i - \eta}{2(1-K_i(1-\varepsilon))f_i^*}$$

and substituting the latter expression to the first inequality of (17) we arrive at

$$\delta_i - \eta + \left[1 - \frac{2(1-K_i(1-\varepsilon))f_i^*}{\gamma_i - \eta}\right]\beta_i(x_i) \ge 0.$$

For small enough ε the latter inequality is feasible if

$$\left[\frac{2(1-K_i)f_i^*}{\gamma_i - \eta} - 1\right]\beta_i(0) < \delta_i - \eta, \quad \eta < \delta_i,\ i = 1,\dots,n. \tag{18}$$

Note that the exponential stability conditions (18) are sufficient for the time-delay model-based conditions (13). However, convergence is guaranteed in a different norm defined by a different Lyapunov functional.

We summarize the result in the following

Proposition 2. *Let there exist $\eta \in (0, \min\{\delta_1,\dots,\delta_n\})$ such that the inequalities (18) are satisfied. Then the system (1), (2) is globally exponentially stable with a decay rate η. Moreover, if the inequalities are satisfied with $\eta = 0$, then the system is globally exponentially stable with a small enough decay rate.*

- ***Recovering the stability conditions for the time-delay model via the PDE model***:

It is interesting to recover the exponential stability result by developing the direct Lyapunov approach to the PDE model (1), (2). Inspired by the construction of (10), consider the following Lyapunov functional:

$$V(t) = \sum_{i=1}^{n}\varepsilon^i\Big[x_i(t) + 2[1-K_i(1-\varepsilon)]\int_0^{\tau_i} g_i(a) \times \int_t^{t+a} e^{-\eta(t-s)}p_i(s,a)dsda\Big], \quad \varepsilon > 0. \tag{19}$$

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Then

$$\dot V(t) = \sum_{i=1}^{n} \varepsilon^i \dot x_i(t) + \sum_{i=1}^{n} 2\varepsilon^i[1-K_i(1-\varepsilon)] \times \int_0^{\tau_i} e^{\eta a} g_i(a)p_i(t+a,a)da - \sum_{i=1}^{n} 2\varepsilon^i[1-K_i(1-\varepsilon)] \int_0^{\tau_i} g_i(a)p_i(t,a)da.$$

Taking into account (4) and the boundary conditions we have

$$p_i(t+a,a) = p_i(t,0)e^{-\int_0^a(\gamma_i+g_i(s))ds} = \beta_i(x_i(t))x_i(t)e^{-\int_0^a(\gamma_i+g_i(s))ds}.$$

Therefore, by the arguments of Proposition 1 we arrive at the following

Proposition 3. *Let there exist $\eta > 0$ such that the strict inequalities (13) are satisfied. Then the zero solution of the system (1) is globally exponentially stable with a decay rate η in the sense that for all $t \geq 0$ $V(t) \leq e^{-\eta t}V(0)$, where V is defined by (19). Moreover if the inequalities (9) are satisfied, then (1) is globally exponentially stable with a small enough decay rate (meaning that there exists a small enough $\eta_0 > 0$ such that for all $t \geq 0$ $V(t) \leq e^{-\eta_0 t}V(0)$).*

3. Stability of the model with a fast self-renewal

Consider two cell subpopulations of immature cells with age $a \geq 0$ at time $t \geq 0$: proliferating cells denoted by $p(t,a)$ and quiescent cells denoted by $r_i(t,a)$. Furthermore, we model here cells which do not go in the standard quiescent phase before self-renewing (the fast dynamics) by $\tilde r_i(t,a)$. The dynamics of the cell populations are governed by the following system of PDEs:

$$\begin{aligned} &\partial_t p_i + \partial_a p_i = -(\gamma_i + g_i(a))\,p_i, && 0 < a < \tau_i, \\ & && t > 0,\ i = 1,\dots,n, \\ &\partial_t r_i + \partial_a r_i = -(\delta_i + \beta_i(x(t)))\,r_i && a > 0, t > 0, \\ &\partial_t \tilde r_i + \partial_a \tilde r_i = -\tilde\beta_i\left(\tilde x(t)\right)\tilde r_i, && a > 0, t > 0, \end{aligned} \tag{20}$$

where as in the previous section $\delta_i > 0$ stands for the death rate in the resting phase, the re-introduction function from the resting subpopulation into the proliferative subpopulation is β_i, the death rate in the proliferating phase is $\gamma_i > 0$; the time elapsed in the proliferating phase is $\tau_i > 0$; and the division rate of the proliferating phases is $g_i(a)$. Finally, we complete the model by defining

$$x_i(t) = \int_0^{+\infty} r_i(t,a)\,da, \qquad \tilde x_i(t) = \int_0^{+\infty} \tilde r_i(t,a)\,da$$

which represent the total populations of resting and fast-self renewing cells at the time t, respectively. Boundary conditions associated with (20) are given by

$$\begin{aligned} p_i(t,0) &= \beta_i(x_i(t))\,x_i(t) + \tilde\beta\left(\tilde x_i(t)\right)\tilde x_i(t) \\ r_i(t,0) &= L_i\int_0^{\tau_i} g_i(a)\,p_i(t,a)\,da \\ &\quad + 2K_{i-1}\int_0^{\tau_{i-1}} g_{i-1}(a)\,p_{i-1}(t,a)\,da \\ \tilde r_i(t,0) &= \tilde L_i\int_0^{\tau_i} g_i(a)\,p_i(t,a)\,da, \end{aligned} \tag{21}$$

$$L_i := 2\sigma_i(1-K_i), \qquad \tilde L_i := 2(1-\sigma_i)(1-K_i), \qquad K_0 = 0,$$

where K_i and σ_i are probability rates such that $0 < K_i < 1$ and $0 < \sigma_i < 1$ $(i = 1,\dots,n)$. At the end of the proliferating phase, a cell gives birth to two daughter cells. Each daughter cell may have the same maturity as its parents or may differentiate (may be more advanced in the maturation process). The coefficients K_i represent the proportion of cells that differentiate. The constant $1-\sigma_i$ represents the probability of fast self-renewal.

The following assumptions complete the mathematical model (20), (21):

- The division rate g_i is continuous function such that $\int_0^{\tau_i} g_i(a)\,da = +\infty$.
- For any fixed $t \geq 0$
$$\lim_{a\to+\infty} r_i(t,a) = 0, \qquad \lim_{a\to+\infty} \tilde r(t,a) = 0, \qquad \lim_{a\to+\infty} \bar r(t,a) = 0.$$
- The re-introduction terms $\beta_i \geq 0$ and $\tilde\beta_i > 0$ (for $x_i < \infty$) are differentiable and decreasing functions.

Note that in the literature the functions β_i and $\tilde\beta_i$ are usually Hill functions with $\tilde\beta_i(0) \gg \beta_i(0)$.

By using the method of characteristics, the following time-delay model for the total population densities of resting cells x_i and of fast self-renewing cells $\tilde x_i$ has been derived in [14]:

$$\begin{aligned} \dot x_i(t) &= -[\delta_i + \beta_i(x_i(t))]x_i(t) + L_i\int_0^{\tau_i} e^{-\gamma_i a}f_i(a)[\beta_i(x_i(t-a)) \\ &\quad \times x_i(t-a) + \tilde\beta_i(\tilde x_i(t-a))\tilde x_i(t-a)]da \\ &\quad + 2K_{i-1}\int_0^{\tau_{i-1}} e^{-\gamma_{i-1}a}f_{i-1}(a)[\beta_{i-1}(x_{i-1}(t-a)) \\ &\quad \times x_{i-1}(t-a) + \tilde\beta_{i-1}(\tilde x_{i-1}(t-a))\tilde x_{i-1}(t-a)]da, \\ \dot{\tilde x}_i(t) &= -\tilde\beta_i(\tilde x_i(t))\tilde x_i(t) + \tilde L_i\int_0^{\tau_i} e^{-\gamma_i a}f_i(a)[\beta_i(x_i(t-a)) \\ &\quad \times x_i(t-a) + \tilde\beta_i(\tilde x_i(t-a))\tilde x_i(t-a)]da, \\ &\quad t > 0, \quad i = 1,\dots,n, \end{aligned} \tag{22}$$

where $f_i(a) = g_i(a)e^{-\int_0^a g_i(s)ds}$ is a density function with $\int_0^{\tau_i} f_i(a)da = 1$.

By arguments of Section 2 it can be shown that (22) is a positive system (having nonnegative solutions provided initial functions are nonnegative). Note that only nonnegative solutions of (22) have a physical (biological) meaning. As in the previous section, this property will be exploited to find suitable Lyapunov functionals.

The linearized around the zero time-delay model has the following form

$$\begin{aligned} \dot x_i(t) &= -(\delta_i + \beta_i(0))x_i(t) + L_i\int_0^{\tau_i} e^{-\gamma_i a}f_i(a)[\beta_i(0) \\ &\quad \times x_i(t-a) + \tilde\beta_i(0)\tilde x_i(t-a)]da \\ &\quad + 2K_{i-1}\int_0^{\tau_{i-1}} e^{-\gamma_{i-1}a}f_{i-1}(a)[\beta_{i-1}(0)x_{i-1}(t-a) \\ &\quad + \tilde\beta_{i-1}(0)\tilde x_{i-1}(t-a)]da, \\ \dot{\tilde x}_i(t) &= -\tilde\beta_i(0)\tilde x_i(t) + \tilde L_i\int_0^{\tau_i} e^{-\gamma_i a}f_i(a)[\beta_i(0)x_i(t-a) \\ &\quad + \tilde\beta_i(0)\tilde x_i(t-a)]da \\ &\quad t > 0, \quad i = 1,\dots,n. \end{aligned} \tag{23}$$

This is a positive linear system that can be presented as (7), where $x = col\{x_1, \tilde x_1, \dots, x_n, \tilde x_n\}$. Due to "block-triangular" structure of (23), the condition (ii) of Lemma 1 for this system is equivalent to the fact that the matrices

$$H_i^0 = \begin{bmatrix} -\delta_i - \beta_i(0)\left[1 - L_i\int_0^{\tau_i} e^{-\gamma_i a}f_i(a)da\right] & \tilde\beta_i(0)L_i\int_0^{\tau_i} e^{-\gamma_i a}f_i(a)da \\ \beta_i(0)\tilde L_i\int_0^{\tau_i} e^{-\gamma_i a}f_i(a)da & -\tilde\beta_i(0)\left[1 - \tilde L_i\int_0^{\tau_i} e^{-\gamma_i a}f_i(a)da\right] \end{bmatrix},$$
$$i = 1,\dots,n. \tag{24}$$

are Hurwitz. Since H_i^0 is Metzler, this matrix is Hurwitz if and only if there exists a vector $0 < \lambda_i \in \mathbb{R}^2$ such that $\lambda_i^T H_i^0 < 0$. Clearly λ_i can be chosen as $\lambda_i = col\{1, \lambda_i^1\}$ with a positive scalar λ_i^1 leading to the following inequalities (since $\tilde{\beta}_i(0) > 0$):

$$\begin{aligned}&\left[(L_i + \lambda_i^1 \tilde{L}_i)\int_0^{\tau_i} e^{-\gamma_i a} f_i(a)da - 1\right]\beta_i(0) < \delta_i,\\ &(L_i + \lambda_i^1 \tilde{L}_i)\int_0^{\tau_i} e^{-\gamma_i a} f_i(a)da - \lambda_i^1 < 0, \quad i = 1, \dots, n.\end{aligned} \tag{25}$$

Summarizing, we formulate the stability conditions for (23) in the following

Lemma 2. *The linear system (23) is exponentially stable if and only if there exist scalars $\lambda_i^1 > 0$, $i = 1, \dots, n$ that satisfy the inequalities (25), or, equivalently, if the Metzler matrices H_i^0 are Hurwitz.*

Remark 2. Note that if the inequalities (25) are satisfied with $\lambda_i^1 = 1$, then the resulting inequalities (25) are equivalent to

$$2(1 - K_i)\int_0^{\tau_i} e^{-\gamma_i a} f_i(a)da < 1, \quad i = 1, \dots, n. \tag{26}$$

It was shown in [14] that the nonlinear time-delay model has a non-zero (positive) equilibrium point if

$$1 < 2(1 - K_i)\int_0^{\tau_i} e^{-\gamma_i a} f_i(a)da < \frac{1}{1 - \sigma_i}, \quad i = 1, \dots, n \tag{27}$$

and

$$\beta_1(0) > \delta_1 \frac{1 - 2(1 - \sigma_1)(1 - K_1)\int_0^{\tau_1} e^{-\gamma_1 a} f_1(a)da}{2(1 - K_1)\int_0^{\tau_1} e^{-\gamma_1 a} f_1(a)da - 1}.$$

Summarizing, the inequalities (25) are necessary and sufficient conditions for the *local* exponential stability of (22) (see e.g. Proposition 3.17 in [13]). Note that in the case of equality in (25) there may be local asymptotic stability of the nonlinear system (22).

3.1. Global asymptotic/regional exponential stability of the nonlinear time-delay model

Our next objective is to show that inequalities (25) are sufficient for the global asymptotic stability of the zero solution of (22). We will also derive regional exponential stability conditions (for positive solutions starting from a bounded region). An extension of the Lyapunov functional construction (10) to a more general system (22) (that takes into account conditions (25)) has a form

$$\begin{aligned}V(x_t, \tilde{x}_t) &= \sum_{i=1}^n \varepsilon^i [x_i(t) + \lambda_i^1 \tilde{x}_i(t)\\ &\quad + (L_i + 2\varepsilon K_i + \lambda_i^1 \tilde{L}_i)(V_{2i}(x_t) + V_{3i}(\tilde{x}_t))],\\ &\quad \varepsilon > 0,\ \lambda_i^1 > 0,\\ V_{2i}(x_t) &= \int_0^{\tau_i}\int_{t-a}^t e^{-\eta(t-a-s)-\gamma_i a} f_i(a)\beta_i(x_i(s))x_i(s)dsda,\\ V_{3i}(\tilde{x}_t) &= \int_0^{\tau_i}\int_{t-a}^t e^{-\eta(t-a-s)-\gamma_i a} f_i(a)\tilde{\beta}_i(\tilde{x}_i(s))\tilde{x}_i(s)dsda,\\ &\quad i = 1, \dots, n.\end{aligned} \tag{28}$$

We have along (22)

$$\begin{aligned}\sum_{i=1}^n \varepsilon^i \dot{x}_i(t) &= \sum_{i=1}^n \varepsilon^i \Big[-(\delta_i + \beta_i(x_i(t)))x_i(t)\\ &\quad + L_i \int_0^{\tau_i} e^{-\gamma_i a} f_i(a)[\beta_i(x_i(t-a))x_i(t-a)\\ &\quad + \tilde{\beta}_i(\tilde{x}_i(t-a))\tilde{x}_i(t-a)]da + 2K_{i-1}\\ &\quad \times \int_0^{\tau_{i-1}} e^{-\gamma_{i-1} a} f_{i-1}(a)[\beta_{i-1}(x_{i-1}(t-a))x_{i-1}(t-a)da\\ &\quad + \tilde{\beta}_{i-1}(\tilde{x}_{i-1}(t-a))\tilde{x}_{i-1}(t-a)]da\Big]\\ &\le \sum_{i=1}^n \varepsilon^i \Big[-(\delta_i + \beta_i(x_i(t)))x_i(t)\\ &\quad + [L_i + 2\varepsilon K_i]\int_0^{\tau_i} e^{-\gamma_i a} f_i(a)[\beta_i(x_i(t-a))x_i(t-a)\\ &\quad + \tilde{\beta}_i(\tilde{x}_i(t-a))\tilde{x}_i(t-a)]da\Big]\end{aligned}$$

and

$$\begin{aligned}\sum_{i=1}^n \varepsilon^i \lambda_i^1 \dot{\tilde{x}}_i(t) &= \sum_{i=1}^n \varepsilon^i \lambda_i^1 \Big[-\tilde{\beta}_i(\tilde{x}_i(t))\tilde{x}_i(t)\\ &\quad + \tilde{L}_i \int_0^{\tau_i} e^{-\gamma_i a} f_i(a)[\beta_i(x_i(t-a))x_i(t-a)\\ &\quad + \tilde{\beta}_i(\tilde{x}_i(t-a))\tilde{x}_i(t-a)]da\Big].\end{aligned}$$

Then differentiating V defined in (28) along (22) and taking into account that

$$\begin{aligned}\dot{V}_{2i}(x_t) + \eta V_{2i}(x_t) &= \int_0^{\tau_i} e^{-(\gamma_i - \eta)a} f_i(a)da\beta_i(x_i(t))x_i(t)\\ &\quad - \int_0^{\tau_i} e^{-\gamma_i a} f_i(a)\beta_i(x_i(t-a))x_i(t-a)da,\\ \dot{V}_{3i}(x_t) + \eta V_{3i}(x_t) &= \int_0^{\tau_i} e^{-(\gamma_i - \eta)a} f_i(a)da\tilde{\beta}_i(\tilde{x}_i(t))\tilde{x}_i(t)\\ &\quad - \int_0^{\tau_i} [e^{-\gamma_i a}\tilde{\beta}_i(\tilde{x}_i(t-a))\tilde{x}_i(t-a)]da\end{aligned}$$

we obtain

$$\begin{aligned}&\dot{V}(x_t, \tilde{x}_t) + \eta V(x_t, \tilde{x}_t)\\ &\le \sum_{i=1}^n \varepsilon^i \left[\eta + \left[[L_i + 2\varepsilon K_i + \lambda_i^1 \tilde{L}_i]\right.\right.\\ &\quad \left.\left.\times \int_0^{\tau_i} e^{-(\gamma_i - \eta)a} f_i(a)da - 1\right]\beta_i(x_i(t)) - \delta_i\right]x_i(t)\\ &\quad + \sum_{i=1}^n \varepsilon^i \left[\lambda_i^1 \eta + \left[[L_i + 2\varepsilon K_i + \lambda_i^1 \tilde{L}_i]\right.\right.\\ &\quad \left.\left.\times \int_0^{\tau_i} e^{-(\gamma_i - \eta)a} f_i(a)da - \lambda_i^1\right]\tilde{\beta}_i(\tilde{x}_i(t))\right]\tilde{x}_i(t).\end{aligned} \tag{29}$$

We start with the boundedness of the solutions of (22) (non-asymptotic stability):

Lemma 3. *Let there exist $\lambda_1^1 > 0, \dots, \lambda_n^1 > 0$ such that the inequalities (25) hold. Then there exists a small enough $\varepsilon > 0$ such that*

$$\begin{aligned}&\left[(L_i + 2\varepsilon K_i + \lambda_i^1 \tilde{L}_i)\int_0^{\tau_i} e^{-\gamma_i a} f_i(a)da - 1\right]\beta_i(0) \le \delta_i,\\ &(L_i + 2\varepsilon K_i + \lambda_i^1 \tilde{L}_i)\int_0^{\tau_i} e^{-\gamma_i a} f_i(a)da \le \lambda_i^1, \quad i = 1, \dots, n.\end{aligned} \tag{30}$$

Moreover, given $\varepsilon \in (0, 1)$ that satisfies (30), the following bound holds for solutions of (22) starting from the initial functions $\phi \in$

$C^n_{\tau+}, \tilde{\phi} \in C^n_{\tau+}$:

$$\sum_{i=1}^{n}[x_i(t)+\tilde{x}_i(t)] \le K\{\|\phi\|_C + \|\tilde{\phi}\|_C\} \quad \text{for all } t \ge 0,$$
$$K = \frac{\max\{1, \lambda_1^1, \dots, \lambda_n^1\} + \max_{i=1,\dots,n}\{\tau_i\lambda_i^1\beta_i(0), \tau_i\lambda_i^1\tilde{\beta}_i(0)\}}{\varepsilon^{n-1}\min\{1, \lambda_1^1, \dots, \lambda_n^1\}}. \tag{31}$$

Proof. The implication (25) ⇒ (30) that holds for small enough $\varepsilon > 0$ is straightforward.

Under (30), it follows from (29) that $\dot{V}(x_t, \tilde{x}_t)_{|\eta=0} \le 0$, implying

$$\sum_{i=1}^{n}\varepsilon^i[x_i(t) + \lambda_i^1\tilde{x}_i(t)] \le V(x_t, \tilde{x}_t)_{|\eta=0} \le V(\phi, \tilde{\phi})_{|\eta=0}. \tag{32}$$

Note that β_i and $\tilde{\beta}_i$ are monotonically decreasing. Then

$$\begin{aligned} V_{2i}(\phi)_{|\eta=0} &= \int_0^{\tau_i}\int_{-a}^{0} e^{-\gamma_i a} f_i(a)\beta_i(x_i(s))x_i(s)dsda \\ &\le \tau_i\beta_i(0)\cdot \max_{s\in[-\tau_i,0]}|\phi_i(s)| \cdot \int_0^{\tau_i} e^{-\gamma_i a} f_i(a)da, \\ V_{3i}(\tilde{\phi})_{|\eta=0} &= \int_0^{\tau_i}\int_{-a}^{0} e^{-\gamma_i a} f_i(a)\tilde{\beta}_i(\tilde{x}_i(s))\tilde{x}_i(s)dsda \\ &\le \tau_i\tilde{\beta}_i(0)\cdot \max_{s\in[-\tau_i,0]}|\tilde{\phi}_i(s)| \cdot \int_0^{\tau_i} e^{-\gamma_i a} f_i(a)da. \end{aligned}$$

Therefore, taking into account the second inequality (30), we arrive at

$$\begin{aligned} &\varepsilon^n \min\{1, \lambda_1^1, \dots, \lambda_n^1\}\cdot \sum_{i=1}^{n}[x_i(t)+\tilde{x}_i(t)] \\ &\le V(\phi, \tilde{\phi})_{|\eta=0} \le \epsilon\Big[\max\{1, \lambda_1^1, \dots, \lambda_n^1\} \\ &\quad + \max_{i=1,\dots,n}\{\tau_i\lambda_i^1\beta_i(0), \tau_i\lambda_i^1\tilde{\beta}_i(0)\}\Big]\Big[\|\phi\|_C + \|\tilde{\phi}\|_C\Big] \end{aligned}$$

that yields (31). □

Given $\tilde{x}^* \in \mathbb{R}^n_+$, denote by

$$\mathcal{A}(\tilde{x}^*) = \{\phi \in C^n_{\tau+}, \tilde{\phi} \in C^n_{\tau+} : \tilde{x}(t, \phi, \tilde{\phi}) \le \tilde{x}^* \ \forall t \ge 0\},$$

where $\tilde{x}(t, \phi, \tilde{\phi})$ satisfies (22) with the initial conditions $x_0 = \phi$, $\tilde{x}_0 = \tilde{\phi}$.

We are in a position to state our main result on the global asymptotic stability and on regional exponential stability of the zero solution of (22):

Theorem 1. (i) *Let there exist* $\eta \in (0, \min\{\delta_1, \dots, \delta_n\})$, $\lambda_1^1 > 0, \dots, \lambda_n^1 > 0$ *and* $\tilde{x}_1^* > 0, \dots, \tilde{x}_n^* > 0$ *such that the following inequalities are satisfied:*

$$\begin{aligned} &\left[(L_i + \lambda_i^1\tilde{L}_i)\int_0^{\tau_i} e^{-(\gamma_i-\eta)a} f_i(a)da - 1\right]\beta_i(0) < \delta_i - \eta, \\ &\left[(L_i + \lambda_i^1\tilde{L}_i)\int_0^{\tau_i} e^{-(\gamma_i-\eta)a} f_i(a)da - \lambda_i^1\right]\tilde{\beta}_i(\tilde{x}_i^*) \\ &\quad < -\lambda_i^1\eta, \quad i = 1, \dots, n, \end{aligned} \tag{33}$$

or, equivalently, let the Metzler matrices

$$\begin{aligned} H_i &= \begin{bmatrix} -\delta_i - \beta_i(0)[1 - L_i\int_0^{\tau_i} e^{-(\gamma_i-\eta)a} f_i(a)da] & \tilde{\beta}_i(0)L_i\int_0^{\tau_i} e^{-(\gamma_i-\eta)a} f_i(a)da \\ \beta_i(0)\tilde{L}_i\int_0^{\tau_i} e^{-(\gamma_i-\eta)a} f_i(a)da & -\tilde{\beta}_i(\tilde{x}_i^*)\left[1 - \tilde{L}_i\int_0^{\tau_i} e^{-(\gamma_i-\eta)a} f_i(a)da\right] \end{bmatrix} \\ &\quad + \mathrm{diag}\{\eta, \eta\}, \quad i = 1, \dots, n \end{aligned} \tag{34}$$

be Hurwitz. Then the zero solution of the system (22) is regionally exponentially stable with a decay rate η *for all initial conditions* $(\phi, \tilde{\phi}) \in \mathcal{A}(\tilde{x}^*)$.

Moreover, if the above conditions hold with $\tilde{x}_1^* = \cdots = \tilde{x}_n^* = 0$, *then the zero solution of the system (22) is exponentially stable with a decay rate* η *for all small enough initial functions* $\phi \in C^n_{\tau+}, \tilde{\phi} \in C^n_{\tau+}$ *(i.e. the system is locally exponentially stable with a decay rate* η*).*

(ii) *Let there exist* $\lambda_1^1 > 0, \dots, \lambda_n^1 > 0$ *such that the inequalities (25) are satisfied, or, equivalently, let the Metzler matrices* $H_1^0, \dots, H_n^0$ *given by (24) be Hurwitz. Then the zero solution of (22) is globally asymptotically stable.*

Proof. (i) For each $i = 1, \dots, n$ we have either

$$[L_i + 2\varepsilon K_i + \lambda_i^1\tilde{L}_i]\int_0^{\tau_i} e^{-(\gamma_i-\eta)a} f_i(a)da < 1$$

or, due to $0 \le \beta_i(x_i) \le \beta_i(0)$,

$$\begin{aligned} &\left[[L_i + 2\varepsilon K_i + \lambda_i^1\tilde{L}_i]\int_0^{\tau_i} e^{-(\gamma_i-\eta)a} f_i(a)da - 1\right]\beta_i(x_i(t)) \\ &\le \left[[L_i + 2\varepsilon K_i + \lambda_i^1\tilde{L}_i]\int_0^{\tau_i} e^{-(\gamma_i-\eta)a} f_i(a)da - 1\right]\beta_i(0). \end{aligned}$$

Then, under the first inequality (33), for small enough ε Eq. (29) implies

$$\begin{aligned} &\eta + \left[[L_i + 2\varepsilon K_i + \lambda_i^1\tilde{L}_i]\int_0^{\tau_i} e^{-(\gamma_i-\eta)a} f_i(a)da - 1\right] \\ &\quad \times \beta_i(x_i(t)) - \delta_i < 0. \end{aligned} \tag{35}$$

Under the second inequality (33) we have for small enough $\varepsilon > 0$

$$[L_i + 2\varepsilon K_i + \lambda_i^1\tilde{L}_i]\int_0^{\tau_i} e^{-(\gamma_i-\eta)a} f_i(a)da - \lambda_i^1 < 0.$$

Then due to

$$\tilde{x}_i \le \tilde{x}_i^* \Rightarrow \tilde{\beta}_i(\tilde{x}_i^*) \le \tilde{\beta}_i(\tilde{x}_i)$$

we obtain under the second inequality (33)

$$\begin{aligned} &\lambda_i^1\eta + \left[[L_i + 2\varepsilon K_i + \lambda_i^1\tilde{L}_i]\int_0^{\tau_i} e^{-(\gamma_i-\eta)a} f_i(a)da - \lambda_i^1\right] \\ &\quad \times \tilde{\beta}_i(\tilde{x}_i(t)) < 0. \end{aligned} \tag{36}$$

Therefore, the inequalities (29), (35) and (36) imply (11).

(ii) If the inequalities (25) are satisfied, then for all $\tilde{x}^* \in \mathbb{R}^n_+$ there exists $\eta = \eta(\tilde{x}^*)$ such that (33) holds. The latter guarantees due to (i) that for all $\{\phi, \tilde{\phi}\} \in \mathcal{A}(\tilde{x}^*)$ the corresponding solutions $x(t)$ and $\tilde{x}(t)$ of (22) approach zero as $t \to \infty$. For $\tilde{x}_i^* \to \infty$ $(i = 1, \dots, n)$ by employing Lemma 3 we have $\|\phi\|_C + \|\tilde{\phi}\|_C \to \infty$ (cf. the inequality (31)) meaning that $\mathcal{A}(\tilde{x}^*) = \{C^n_{\tau+}, C^n_{\tau+}\}$. Therefore, the zero solution of (22) is globally asymptotically stable. □

Example 2. Choosing $f_i(a) = \frac{m_i}{e^{m_i\tau_i}-1}e^{m_i a}$, with $m_i > 0$ for all $i \in [1, n]$, the following parameters satisfy (25).

For $i = 1$: $\delta_1 = 2$, $\sigma_1 = 0.8$, $K_1 = 0.02$, $L_1 = 2\sigma_1(1 - K_1) = 1.5680$, $\tilde{L}_1 = 2(1 - \sigma_1)(1 - K_1) = 0.3920$, $m_1 = 1$, $\tau_1 = 0.9$, $\gamma_1 = 0.18$, $\beta_1(x_1) = \frac{1}{1+x_1^2}$ and $\tilde{\beta}_1(\tilde{x}_1) = \frac{10}{1+1.2\tilde{x}_1^3}$.

For $i = 2$: $\delta_2 = 4.2$, $\sigma_2 = 0.5$, $K_2 = 0.05$, $L_2 = 2\sigma_2(1 - K_2) = 0.95$, $\tilde{L}_2 = 2(1 - \sigma_2)(1 - K_2) = 0.95$, $m_2 = 1$, $\tau_2 = 1$, $\gamma_2 = 0.3$, $\beta_2(x_2) = \frac{0.7}{1+x_2^2}$ and $\tilde{\beta}_2(\tilde{x}_2) = \frac{10}{1+\tilde{x}_2^2}$.

- Choosing $\lambda_1^1 = 3$:

$$\left[(L_1 + \lambda_1^1\tilde{L}_1)\int_0^{\tau_1} e^{-\gamma_1 a} f_1(a)da - 1\right]\beta_1(0) = 1.5030 < 2 = \delta_1$$

and

$$(L_1 + \lambda_1^1 \tilde{L}_1) \int_0^{\tau_1} e^{-\gamma_1 a} f_1(a) da - \lambda_1^1 = -0.4970 < 0.$$

- Choosing $\lambda_2^1 = 5$:

$$\left[(L_2 + \lambda_2^1 \tilde{L}_2) \int_0^{\tau_2} e^{-\gamma_2 a} f_2(a) da - 1\right] \beta_2(0) = 2.6629 < 4.2 = \delta_2$$

and

$$(L_2 + \lambda_2^1 \tilde{L}_2) \int_0^{\tau_2} e^{-\gamma_2 a} f_2(a) da - \lambda_2^1 = -0.1959 < 0.$$

- We can also verify that the positive steady state does not exist:

$$\beta_1(0) = 0.7 < 1.6309 = \delta_1 \frac{1 - 2(1-\sigma_1)(1-K_1) \int_0^{\tau_1} e^{-\gamma_1 a} f_1(a) da}{2(1-K_1) \int_0^{\tau_1} e^{-\gamma_1 a} f_1(a) da}.$$

According to (ii) of Theorem 1, the origin of the nonlinear system (22) is globally asymptotically stable (see Fig. 2 with trajectories of the system).

Example 3. Choosing the same functions f_i's as in the previous examples, we observe that the following parameters satisfy (33) with $\tilde{x}^* = col\{3, 3\}$.

For $i = 1$: $\delta_1 = 1.5, \sigma_1 = 0.8, K_1 = 0.02, L_1 = 2\sigma_1(1 - K_1) = 1.5680, \tilde{L}_1 = 2(1 - \sigma_1)(1 - K_1) = 0.3920, m_1 = 1, \tau_1 = 0.8, \gamma_1 = 0.2, \beta_1(x_1) = \frac{0.5}{1+x_1^3}$ and $\tilde{\beta}_1(\tilde{x}_1) = \frac{10}{1+2\tilde{x}_1^2}$.

For $i = 2$: $\delta_2 = 2, \sigma_2 = 0.7, K_2 = 0.02, L_2 = 2\sigma_2(1 - K_2) = 1.3720, \tilde{L}_2 = 2(1 - \sigma_2)(1 - K_2) = 0.5880, m_2 = 1, \tau_2 = 0.8, \gamma_2 = 0.3, \beta_2(x_2) = \frac{0.5}{1+x_2^3}$ and $\tilde{\beta}_2(\tilde{x}_2) = \frac{10}{1+\tilde{x}_2^2}$.

- Choosing $\lambda_1^1 = \lambda_2^1 = 3$, we verify that the conditions (33) are satisfied for $\eta = 0.05$:

$$\left[(L_1 + \lambda_1^1 \tilde{L}_1) \int_0^{\tau_1} e^{-(\gamma_1-\eta)a} f_1(a) da - 1\right] \beta_1(0) = 0.7827 < 1.45 = \delta_1 - \eta$$

$$\left[(L_1 + \lambda_1^1 \tilde{L}_1) \int_0^{\tau_1} e^{-(\gamma_1-\eta)a} f_1(a) da - \lambda_1^1\right] \tilde{\beta}_1(\tilde{x}_1^*) = -0.2288 < -0.15 = -\lambda_1^1 \eta$$

$$\left[(L_2 + \lambda_2^1 \tilde{L}_2) \int_0^{\tau_2} e^{-(\gamma_2-\eta)a} f_2(a) da - 1\right] \beta_2(0) = 0.9025 < 1.95 = \delta_2 - \eta$$

$$\left[(L_2 + \lambda_2^1 \tilde{L}_2) \int_0^{\tau_2} e^{-(\gamma_2-\eta)a} f_2(a) da - \lambda_2^1\right] \tilde{\beta}_2(\tilde{x}_2^*) = -0.1951 < -0.15 = -\lambda_2^1 \eta.$$

According to (i) of Theorem 1 the origin of the system (22) is regionally exponentially stable with a decay rate η for all initial conditions $\{\phi, \tilde{\phi}\} \in \mathcal{A}(\tilde{x}^*)$. Fig. 3 illustrates this example with the previous parameters and $\phi_1 = 2 \times 10^{-3}$, (i.e., $\phi_1(s) = 2 \times 10^{-3}, \forall s \in [-\tau_1, 0]$), $\tilde{\phi}_1 = 4 \times 10^{-3}$, $\phi_2 = 10^{-3}$ and $\tilde{\phi}_2 = 3 \times 10^{-3}$. One can readily check from Lemma 3 that for these initial conditions we have $\{\phi, \tilde{\phi}\} \in \mathcal{A}(\tilde{x}^*)$; Indeed, observe that for $\epsilon = 0.1$ the inequalities (30) are satisfied

$$\left[(L_1 + 2\epsilon K_1 + \lambda_1^1 \tilde{L}_1) \int_0^{\tau_1} e^{-\gamma_1 a} f_1(a) da - 1\right] \beta_1(0) = 0.7563 < 1.5 = \delta_1$$

$$(L_1 + 2\epsilon K_1 + \lambda_1^1 \tilde{L}_1) \int_0^{\tau_1} e^{-\gamma_1 a} f_1(a) da = 2.5127 < 3 = \lambda_1^1$$

$$\left[(L_2 + 2\epsilon K_2 + \lambda_2^1 \tilde{L}_2) \int_0^{\tau_2} e^{-\gamma_2 a} f_2(a) da - 1\right] \beta_2(0) = 0.8738 < 2 = \delta_2$$

$$(L_2 + 2\epsilon K_2 + \lambda_2^1 \tilde{L}_2) \int_0^{\tau_2} e^{-\gamma_2 a} f_2(a) da = 2.7476 < 3 = \lambda_2^1.$$

Moreover,

$$K = \frac{\max\{1, \lambda_1^1, \lambda_2^1\} + \max_{i=1,2}\{\tau_i \lambda_i^1 \beta_i(0), \tau_i \lambda_i^1 \tilde{\beta}_i(0)\}}{\varepsilon \min\{1, \lambda_1^1, \lambda_2^1\}} = 270.$$

3.2. The case of uncertain or time-varying σ_i in the model

It may be of interest to consider time-varying (uncertain or known) probability rates in the model (20)–(21)

$$\sigma_{im} \le \sigma_i(t) \le \sigma_{iM}, \quad i = 1, \dots, n. \tag{37}$$

By the arguments of [14] the resulting time-delay system is given by (22). Then Theorem 1 holds, where in (25) and (33)

$$L_i = 2\sigma_i(t)(1 - K_i), \qquad \tilde{L}_i = 2(1 - \sigma_i(t))(1 - K_i).$$

Since the linear with respect to decision variables λ_i^1 inequalities (25) and (33) are affine in σ_i, they are feasible for all σ_i subject to (37) if they are satisfied for $\sigma_i = \sigma_{im}$ and $\sigma_i = \sigma_{iM}$ [15]. We arrive at the following result on global asymptotic stability:

Corollary 1. *Let there exist $\lambda_1^1 > 0, \dots, \lambda_n^1 > 0$ such that the following 4n linear inequalities are satisfied:*

$$\begin{aligned}
&\left[(L_i + \lambda_i^1 \tilde{L}_i) \int_0^{\tau_i} e^{-\gamma_i a} f_i(a) da - 1\right] \beta_i(0)_{\sigma_i=\sigma_{im}} < \delta_i, \\
&\left[(L_i + \lambda_i^1 \tilde{L}_i) \int_0^{\tau_i} e^{-\gamma_i a} f_i(a) da - 1\right] \beta_i(0)_{|\sigma_i=\sigma_{iM}} < \delta_i, \\
&(L_i + \lambda_i^1 \tilde{L}_i) \int_0^{\tau_i} e^{-\gamma_i a} f_i(a) da_{|\sigma_i=\sigma_{im}} < \lambda_i^1, \\
&(L_i + \lambda_i^1 \tilde{L}_i) \int_0^{\tau_i} e^{-\gamma_i a} f_i(a) da_{|\sigma_i=\sigma_{iM}} < \lambda_i^1, \\
&i = 1, \dots, n.
\end{aligned} \tag{38}$$

Then the zero solution of the system (22), (37) is globally asymptotically stable.

Consider now the case, where $\sigma_{im} = 0$ and $\sigma_{iM} = 1$, i.e.

$$0 \le \sigma_i(t) \le 1, \; i = 1, \dots, n. \tag{39}$$

Here

$$(L_i + \lambda_i^1 \tilde{L}_i)_{|\sigma_i=0} = 2\lambda_i^1(1 - K_i), \qquad (L_i + \lambda_i^1 \tilde{L}_i)_{|\sigma_i=1} = 2(1 - K_i).$$

It is easy to see that the inequalities (38) are feasible with some $\lambda_i^1 > 0$ if and only if they are feasible with $\lambda_i^1 = 1$, i.e. if the following holds

$$\left[2(1 - K_i) \int_0^{\tau_i} e^{-\gamma_i a} f_i(a) da - 1\right] \beta_i(0) < \delta_i, \quad i = 1, \dots, n \tag{40}$$

and

$$2(1 - K_i) \int_0^{\tau_i} e^{-\gamma_i a} f_i(a) da < 1, \quad i = 1, \dots, n. \tag{41}$$

Clearly the inequalities (41) imply (40). Note that the conditions (41) are β_i-independent.

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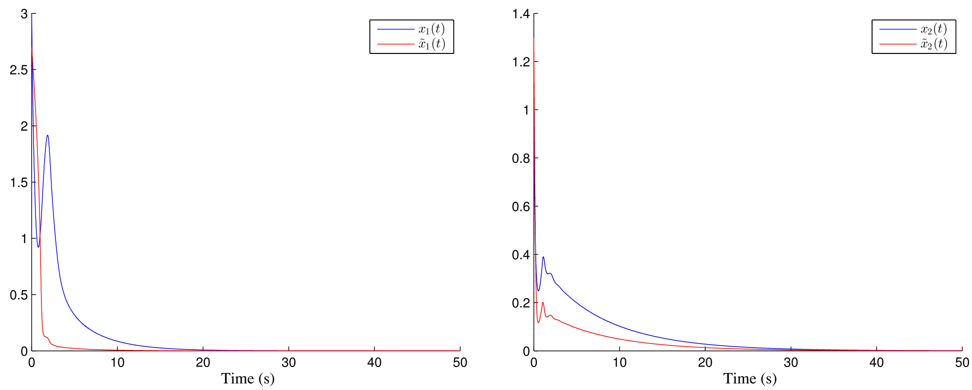

Fig. 2. Trajectories of the states x and $\tilde{x}$ for the parameters of Example 2.

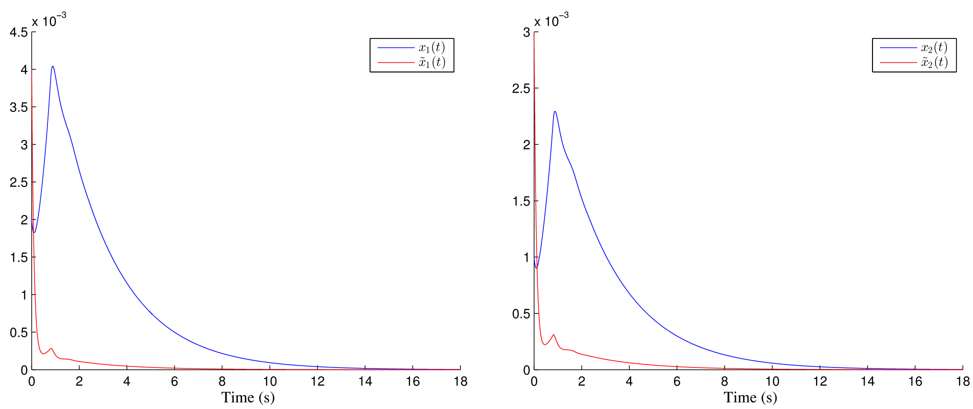

Fig. 3. Trajectories of the states x and $\tilde{x}$ for the parameters of Example 3.

Corollary 2. *If the inequalities (41) are satisfied, then the zero solution of the system (22), (39) is globally asymptotically stable.*

Remark 3. In [14] for $n = 1$ the following sufficient condition for the global asymptotic stability of (22) (with a constant given σ_1) was derived

$$2(1 - K_1)f_1^* < \gamma_1, \quad f_1^* = \sup_{a\in[0,\tau_1]} f_1(a).$$

Clearly if the latter inequality holds, then (41) is satisfied. However, Corollary 2 shows that the stability is guaranteed for all $\sigma_1(t)$ subject to (39).

Example 4. Let us consider the following parameters:

For $i = 1$: $\delta_1 = 3.3$, $K_1 = 0.1$, $m_1 = 1$, $\tau_1 = 0.8$, $\gamma_1 = 0.2$, $\beta_1(x_1) = \frac{0.8}{1+x_1^3}$ and $\tilde{\beta}_1(\tilde{x}_1) = \frac{10}{1+2\tilde{x}_1^2}$.

For $i = 2$: $\delta_2 = 4$, $K_2 = 0.08$, $m_2 = 1$, $\tau_2 = 0.8$, $\gamma_2 = 0.3$, $\beta_2(x_2) = \frac{1}{1+x_2^3}$ and $\tilde{\beta}_2(\tilde{x}_2) = \frac{10}{1+\tilde{x}_2^2}$.

We assume that σ_i is uncertain for $i \in \{1, 2\}$. For example

$$0.5 = \sigma_{im} \le \sigma_i(t) \le \sigma_{iM} = 0.9, \quad \text{for } i = 1, 2 \tag{42}$$

and

$$\sigma_i(t) = \frac{\sigma_{iM} + \sigma_{im}}{2} + \frac{\sigma_{iM} - \sigma_{im}}{2}\cos(t). \tag{43}$$

The condition (39) is satisfied with $\lambda_1^1 = \lambda_2^1 = 5$:

- $\left[(L_1 + \lambda_1^1\tilde{L}_1)\int_0^{\tau_1} e^{-\gamma_1 a} f_1(a)da - 1\right]\beta_1(0)|_{\sigma_1=\sigma_{1m}} = 3.1501 < 3.3 = \delta_1$
  $\left[(L_1 + \lambda_1^1\tilde{L}_1)\int_0^{\tau_1} e^{-\gamma_1 a} f_1(a)da - 1\right]\beta_1(0)|_{\sigma_1=\sigma_{1M}} = 1.0434 < 3.3 = \delta_1$
  $(L_1 + \lambda_1^1\tilde{L}_1)\int_0^{\tau_1} e^{-\gamma_1 a} f_1(a)da|_{\sigma_1=\sigma_{1m}} = 4.9376 < 5 = \lambda_1^1$
  $(L_1 + \lambda_1^1\tilde{L}_1)\int_0^{\tau_1} e^{-\gamma_1 a} f_1(a)da|_{\sigma_1=\sigma_{1M}} = 2.3042 < 5 = \lambda_1^1$
- $\left[(L_2 + \lambda_2^1\tilde{L}_2)\int_0^{\tau_2} e^{-\gamma_2 a} f_2(a)da - 1\right]\beta_2(0)|_{\sigma_2=\sigma_{2m}} = 3.8302 < 4 = \delta_2$
  $\left[(L_2 + \lambda_2^1\tilde{L}_2)\int_0^{\tau_2} e^{-\gamma_2 a} f_2(a)da - 1\right]\beta_2(0)|_{\sigma_2=\sigma_{2M}} = 1.2541 < 4 = \delta_2$
  $(L_2 + \lambda_2^1\tilde{L}_2)\int_0^{\tau_2} e^{-\gamma_2 a} f_2(a)da|_{\sigma_2=\sigma_{2m}} = 4.8302 < 5 = \lambda_2^1$
  $(L_2 + \lambda_2^1\tilde{L}_2)\int_0^{\tau_2} e^{-\gamma_2 a} f_2(a)da|_{\sigma_2=\sigma_{2M}} = 2.2541 < 5 = \lambda_2^1$.

According to Corollary 1 the origin is globally asymptotically stable (see Fig. 4).

Remark 4. As in the case without fast self-renewal, the Lyapunov approach can be developed directly for the PDE model (20). We do not present these results here since the resulting conditions either recover the results of Theorem 1 (that are necessary and sufficient for the local exponential stability) or give some sufficient conditions for the stability.

4. Conclusion

In this paper we have presented global asymptotic stability analysis of the trivial solution for the multi-stage acute myeloid leukemia model. The same conditions are necessary for the local exponential stability. This was done by employing the positivity of the resulting nonlinear time-delay model via a novel for multi-stage case construction of linear Lyapunov functionals. In a simpler model of hematopoiesis (without fast self-renewal) our conditions guarantee also global exponential stability with a given decay rate. Moreover, in this simpler case the analysis of the PDE model is presented via novel Lyapunov functionals for the

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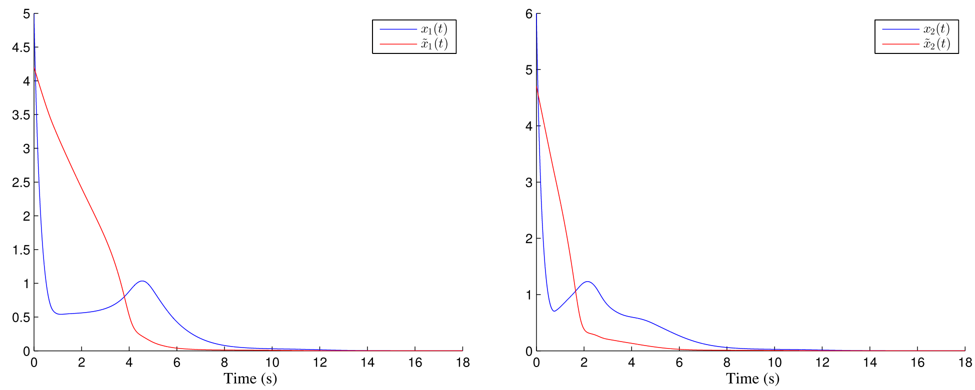

Fig. 4. Trajectories of the states x and $\tilde{x}$ for the parameters of Example 4.

transport equations. Future work will include the stability analysis of the positive equilibrium points of the acute myeloid leukemia model.

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