Stability of the cell dynamics in acute myeloid leukemia

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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 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.

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, R+ denotes the set of nonnegative real numbers, Rn denotes the n-dimensional Euclidean space. For a, b ∈ Rn the inequality a < b (a ≤ b) means componentwise inequality a i < b i (a i ≤ b i) for all i = 1, ..., n. Similarly is defined the opposite vector inequality a > b (a ≥ b).
\( \mathbb{R}_+^n \) 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 \( \| \phi_i \| = \sum_{i=1}^n \max_{s \in [-\tau_i, 0]} |\phi_i(s)| \) is denoted by \( C_t^\infty, C_t^+ = \{ \phi \in C_t^\infty : \phi_i(s) \geq 0 \ s \in [-\tau_i, 0] \} \).  

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 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

\[
\begin{align*}
\dot{r}_i(t) + \alpha r_i(t) &= - (\delta_i + \beta_i(x_i(t))) r_i(t),  \\
\dot{p}_i(t) + \alpha p_i(t) &= - (\gamma_i + g_i(a)) p_i(t), \quad 0 < a < \tau_i, \ t \geq 0,
\end{align*}
\]

(1)

where \( r_i \) are resting and proliferating cell densities, \( a \) is the age of the cells, \( \tau_i \) 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

\[
r_i(t, 0) = 2(1 - K_i) \int_0^{\tau_i} g_i(a) p_i(t, a) da + 2K_{i-1} \int_0^{\tau_{i-1}} g_{i-1}(a) p_{i-1}(t, a) da,
\]

(2)

\[
p_i(t, 0) = \beta_i(x_i(t)) x_i(t), \quad t > 0, \ i = 1, \ldots, n,
\]

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 \( f_i^g_0, g_i(a) da = +\infty \). This property implies

\[
\int_0^{\tau_i} g_i(t) e^{-\int_0^t g_i(s) ds} dt = 1.
\]

- \( \lim_{a \to +\infty} r_i(t, a) = 0 \).

- The re-introduction term \( \beta_i \) 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 \( \beta_i \) is in the form of Hill function

\[
\beta_i(x) = \frac{\beta_i(0)}{1 + bx_i^N},
\]

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 \([1]\):

\[
p_i(t, a) =
\begin{cases}
  p_i(0, 0 - t e^{-\int_0^t (\gamma_i + g(a)) dt}), & t \leq a, \\
  p_i(t - a, 0) e^{-\int_a^t (\gamma_i + g(a)) ds}, & t > a,
\end{cases}
\]

(3)

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

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

(4)

where

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

is a density function with \( f_i^0, f_i(a) da = 1 \). We denote for a later use

\[
\phi_i(t, a) = \int_0^a \gamma_i(s) f_i(t, a) ds,
\]

(5)

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

\[
x_i(s) = \phi_i(s) \geq 0, \quad \forall s \in [-\tau_i, 0], \ \phi_i \in C_t^+ 
\]

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

\[
\dot{x}_i(t) = - (\delta_i + \beta_i(0)) x_i(t) + 2(1 - K_i) \int_0^{\tau_i} e^{-\gamma_i a} f_i(a) \\
\times \beta_i(x_i(t - a)) x_i(t - a) da + 2K_{i-1} \int_0^{\tau_{i-1}} e^{-\gamma_{i-1} a} f_{i-1}(a) \\
\times \beta_{i-1}(x_{i-1}(t - a)) x_{i-1}(t - a) da,
\]

(6)

This is a positive linear system that can be presented as

\[
\dot{x}(t) = Ax(t) + \sum_{i=1}^n \int_0^{\tau_i} A_i(a) x(t - a) da,
\]

(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) \( A + \sum_{i=1}^n A_i(s) ds \) is Hurwitz;
There exists a vector $0 < \lambda \in \mathbb{R}^n$ such that
\[
\lambda^T \left( A + \sum_{i=1}^n \int_0^{\tau_i} A_i(s) ds \right) x(t) < 0.
\]

Note that sufficiency of (iii) for the asymptotic stability of (7) can be derived by using the following Lyapunov functional \[6,8\]
\[
V(x_i) = \lambda^T \left[ x(t) + \sum_{i=1}^n \int_0^{\tau_i} A_i(s) \int_{t-\alpha}^t x(s) ds da \right].
\]

Due to “triangular” structure of (4), the condition (ii) for this system is equivalent to the following inequalities
\[
2(1 - K_i) \int_0^{\tau_i} e^{-\gamma a} f_i(a) da - 1 \beta_i(0) < \delta_i, \quad i = 1, \ldots, n.
\]

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

for the global asymptotic stability of (4) were derived in [2] via the linear state Lyapunov functional
\[
V(x_i) = \sum_{i=1}^n \left[ x_i(t) + 2 \int_0^{\tau_i} e^{-\gamma a} f_i(a) \int_{t-a}^t \beta_i(x_i(s)) x_i(s) ds da \right].
\]

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):
\[
V(x_i) = \sum_{i=1}^n \epsilon \left[ x_i(t) + V_2(x_i) \right], \quad \epsilon > 0,
\]

\[
V_2(x_i) = 2 \left[ (1 - K_i)(1 - \epsilon) \right] \int_0^{\tau_i} e^{-\eta(t-a)} \eta a f_i(a) \beta_i(x_i(s)) x_i(s) ds da,
\]

where $\epsilon$ is small enough and where $\eta > 0$ is a decay rate for the exponential stability. We will find conditions that guarantee
\[
\dot{V}(x_i) + \eta V(x_i) \leq 0,
\]

implying the exponential stability of (4) with a decay rate $\eta > 0$ in the “norm” defined by $V$:
\[
V(x_i) \leq e^{-\eta t} V(x_0), \quad t \geq 0.
\]

**Proof.** We have along (4)
\[
\sum_{i=1}^n \epsilon \dot{x}_i(t) = \sum_{i=1}^n \epsilon \left[ - \left( \delta_i + \beta_i(x_i(t)) \right) x_i(t) + 2[1 - K_i] \int_0^{\tau_i} e^{-\gamma a} f_i(a) \beta_i(x_i(t)) x_i(t) da + 2K_i \int_0^{\tau_i} e^{-\gamma a} f_i(a) \beta_i(x_i(t)) x_i(t) da \right],
\]

\[
\leq \sum_{i=1}^n \epsilon \left[ - \left( \delta_i + \beta_i(x_i(t)) \right) x_i(t) + 2[1 - K_i(1 - \epsilon)] \int_0^{\tau_i} e^{-\gamma a} f_i(a) \beta_i(x_i(t)) x_i(t) da \right].
\]

Then differentiating $V$ of (10) along (4) we obtain
\[
\dot{V}(x_i) + \eta V(x_i) \leq \sum_{i=1}^n \epsilon \left[ - \delta_i + \eta + \left( 2(1 - K_i)(1 - \epsilon) \right) \int_0^{\tau_i} e^{-\eta(t-a)} f_i(a) da \right] \beta_i(x_i(t)) x_i(t).
\]

For each $i = 1, \ldots, n$ and for small enough $\epsilon > 0$ we have either
\[
2(1 - K_i(1 - \epsilon)) \int_0^{\tau_i} e^{-\eta(t-a)} f_i(a) da < 1
\]
or due to $0 \leq \beta_i(x_i(t)) \leq \beta_i(0)$
\[
\left( 2(1 - K_i)(1 - \epsilon) \right) \int_0^{\tau_i} e^{-\eta(t-a)} f_i(a) da \leq \left( 2(1 - K_i(1 - \epsilon)) \right) \int_0^{\tau_i} e^{-\eta(t-a)} f_i(a) da - 1 \beta_i(x_i(t))
\]

\[
\leq \left( 2(1 - K_i(1 - \epsilon)) \right) \int_0^{\tau_i} e^{-\eta(t-a)} f_i(a) da - 1 \beta_i(0) < \delta_i - \eta.
\]

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

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

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 $g_i, i = 1, \ldots, n$ were chosen as
\[
g_i(a) = \frac{m_i}{e^{m_i(a-\alpha)} - 1}, \quad 0 \leq a \leq \tau_i,
\]

where $m_i, \gamma_i$ are integers. It was found that $f_i(a) = g_i(a) e^{-\gamma_i \int_0^a g(a) da}$ has a form
\[
f_i(a) = \frac{m_i}{e^{m_i(a-\alpha)} - 1} e^{m_i a}, \quad 0 \leq a \leq \tau_i.
\]

Here the term $f_i^*$ is well-defined, although $\lim_{a \to \tau_i} g_i(a) = \infty$, and $f_i^* = \frac{m_i}{e^{m_i \tau_i} - 1} e^{m_i \tau_i}$.

**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 $\beta_1(x) = \frac{1}{1 + e^{-x}}.$

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 $\beta_2(x) = \frac{1}{1 + e^{-x/7}}.$
These parameters yield to 
\[ 2(1 - K_{1}) \int_{0}^{\tau_{1}} e^{-\gamma_{1} - \eta_{\text{max}}} f_{1}(a) da - 1 \]
\[ \beta_{1}(0) = 0.2241 < \delta_{1} \quad \text{and consequently no positive equilibrium exists.} \]

According to Proposition 1, \( \eta \in (0, \min(\delta_{1}, \delta_{2})) = (0, 0.8) \).
Numerically, we find that the largest value \( \eta_{\text{max}} \) which verifies (13) is \( \eta_{\text{max}} \approx 0.33 \).

- Choosing \( \eta = \eta_{\text{max}} \):
\[
\left[ 2(1 - K_{1}) \int_{0}^{\tau_{1}} e^{-\gamma_{1} - \eta_{\text{max}}} f_{1}(a) da - 1 \right] \beta_{1}(0) - \delta_{1} + \eta_{\text{max}}
= -0.2118 < 0
\]
and
\[
\left[ 2(1 - K_{2}) \int_{0}^{\tau_{2}} e^{-\gamma_{2} - \eta_{\text{max}}} f_{2}(a) da - 1 \right] \beta_{2}(0) - \delta_{2} + \eta_{\text{max}}
= -0.0015 < 0.
\]

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
\[
V(t) = \sum_{i=1}^{n} e^{\eta} \left[ x_{i}(t) + V_{2i}(t) \right], \quad \varepsilon > 0,
\]
\[
V_{2i}(t) = \frac{1}{q_{i}} \int_{0}^{\tau_{i}} e^{\int_{s}^{t} g_{i}(s) ds} g_{i}(s) p_{i}(s, t) da,
\]
\[ i = 1, \ldots, n; \quad q_{i} > 0. \]

Differentiating \( x_{i}(t) \) along (1) and taking into account the boundary conditions we have
\[
\dot{x}_{i}(t) = \int_{0}^{\tau_{i}} \left( -\partial_{t} r_{i}(t, a) - (\delta_{i} + \beta_{i}(x_{i}(t))) r_{i}(t, a) \right) da
= -[\delta_{i} + \beta_{i}(x_{i}(t))] x_{i}(t) + 2(1 - K_{i}) \int_{0}^{\tau_{i}} g_{i}(a) p_{i}(t, a) da
+ 2K_{i-1} \int_{0}^{\tau_{i}} g_{i-1}(a) p_{i-1}(t, a) da.
\]
Then
\[
\int_{0}^{\tau_{i}} g_{i}(a) p_{i}(t, a) da
= \int_{0}^{\tau_{i}} g_{i}(a) e^{-\int_{0}^{\tau_{i}} g_{i}(s) ds} e^{\int_{s}^{t} g_{i}(s) ds} p_{i}(t, a) da
\leq q e^{\int_{1}^{t} g_{i}(s) ds} p_{i}(s, t) ds da,
\]
\[ \varepsilon > 0. \]

implying
\[
\sum_{i=1}^{n} e^{\eta} \dot{x}_{i}(t) \leq - \sum_{i=1}^{n} e^{\eta} \left[ \delta_{i} + \beta_{i}(x_{i}(t)) \right] x_{i}(t)
+ 2 \sum_{i=1}^{n} e^{\eta} q_{i} (1 - K_{i} (1 - \varepsilon)) f_{i}^{*} V_{2i}(t).
\]

Differentiating \( V_{2i}(t) \) along (1) and taking into account the boundary conditions we obtain
\[
\dot{V}_{2i}(t) = \frac{1}{q_{i}} \int_{0}^{\tau_{i}} [- \partial_{t} p_{i}(t, a)] \cdot d_{i} \cdot \int_{0}^{\tau_{i}} p_{i}(t, a) e^{\int_{s}^{t} g_{i}(s) ds} da
= -\gamma_{i} V_{2i}(t) - \frac{1}{q_{i}} \int_{0}^{\tau_{i}} p_{i}(t, a) e^{\int_{s}^{t} g_{i}(s) ds} \frac{d_{i}}{q_{i}} \int_{0}^{\tau_{i}} p_{i}(t, a) e^{\int_{s}^{t} g_{i}(s) ds} da
\leq -\gamma_{i} V_{2i}(t) + \frac{\beta_{i}(x_{i})}{q_{i}} x_{i}(t).
\]

Therefore,
\[
\dot{V}(t) + \gamma_{i} V(t) \leq - \sum_{i=1}^{n} e^{\eta} \left[ \delta_{i} + (1 - 1/q_{i}) \beta_{i}(x_{i}) \right] x_{i}(t)
+ [\gamma_{i} - 2q_{i}(1 - K_{i} (1 - \varepsilon)) f_{i}^{*}] V_{2i}(t) \leq 0
\]
if
\[
\delta_{i} + (1 - 1/q_{i}) \beta_{i}(x_{i}) \geq 0, 
\gamma_{i} - 2q_{i}(1 - K_{i} (1 - \varepsilon)) f_{i}^{*} \geq 0.
\]

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
\[
\delta_{i} - \eta + \left[ 1 - \frac{2(1 - K_{i} (1 - \varepsilon)) f_{i}^{*}}{\gamma_{i} - \eta} \right] \beta_{i}(x_{i}) \geq 0.
\]

For small enough \( \varepsilon \) the latter inequality is feasible if
\[
\frac{2(1 - K_{i}) f_{i}^{*}}{\gamma_{i} - \eta} - 1 \beta_{i}(0) < \delta_{i} - \eta, \quad \eta < \delta_{i}, \quad i = 1, \ldots, n.
\]

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 \( \eta \in (0, \min(\delta_{1}, \ldots, \delta_{n})) \) such that the inequalities (18) are satisfied. Then the system (1), (2) is globally exponentially stable with a decay rate \( \eta \). 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:
\[
V(t) = \sum_{i=1}^{n} e^{\eta} \left[ x_{i}(t) + 2(1 - K_{i} (1 - \varepsilon)) \int_{0}^{\tau_{i}} g_{i}(a) \right.
\times \int_{t}^{t+\sigma} e^{-\eta(t-s)} p_{i}(s, a) ds da, \quad \varepsilon > 0.
\]

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Then
\[
\dot{V}(t) = \sum_{i=1}^{n} \varepsilon_i x_i(t) + \sum_{i=1}^{n} 2\varepsilon \left[1 - K_i(1 - \varepsilon)\right] \\
\times \int_0^t e^{\varepsilon \tau} g_i(a) p_i(t + a, a) da \\
- \sum_{i=1}^{n} 2\varepsilon [1 - K_i(1 - \varepsilon)] \int_0^t g_i(a) p_i(t, a) da.
\]

Taking into account (4) and the boundary conditions we have
\[
p_i(t + a, a) = p_i(t, 0) e^{-\int_0^t (\gamma_i + g_i(a)) da} = \beta_i(x(t)) x(t) e^{-\int_0^t (\gamma_i + g_i(a)) da}.
\]

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 \( \eta \) 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 \( r_i(t, a) \). The dynamics of the cell populations are governed by the following system of PDEs:

- \( \partial_t p_i + \partial_a p_i = (\gamma_i + g_i(a)) p_i \) for \( 0 < a < r_i, t > 0, i = 1, \ldots, n \),
- \( \partial_t r_i + \partial_a r_i = (\delta_i + \beta_i(x(t))) r_i \) for \( a > 0, t > 0, i = 0, 1, \ldots, n \),

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 \( \beta_i \), the death rate in the proliferating phase is \( \gamma_i > 0 \); the time elapsed in the proliferating phase is \( r_i > 0 \); and the division rate of the proliferating phases is \( g_i(a) \).

Finally, we complete the model by defining
\[
x_i(t) = \int_0^{+\infty} r_i(t, a) da, \quad \tilde{x}_i(t) = \int_0^{+\infty} \tilde{r}_i(t, a) da
\]

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

\[
p_i(t, 0) = \beta_i(x(t)) x_i(t) + \tilde{\beta}(\tilde{x}(t)) \tilde{x}_i(t)
\]

\[
r_i(t, 0) = \tilde{L}_i \int_0^t g_i(a) p_i(t, a) da \\
+ 2K_{i-1} \int_0^{t-1} g_i(a) p_i(t, a) da \\
\tilde{r}_i(t, 0) = \tilde{L}_i \int_0^t g_i(a) p_i(t, a) da,
\]

where \( K_i \) and \( \sigma_i \) are probability rates such that \( 0 < K_i < 1 \) and \( 0 < \sigma_i < 1 \) (i = 1, \ldots, 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 \( \int_0^t g_i(a) da = +\infty \).
- For any fixed \( t \geq 0 \)
  \[ \lim_{a \to +\infty} r_i(t, a) = 0, \quad \lim_{a \to +\infty} \tilde{r}(t, a) = 0, \]
  \[ \lim_{a \to +\infty} \tilde{r}_i(t, a) = 0. \]
- The re-introduction terms \( \tilde{\beta}_i \geq 0 \) and \( \tilde{\beta}_i > 0 \) (for \( x_i < \infty \)) are differentiable and decreasing functions.

Note that in the literature the functions \( \beta_i \) and \( \tilde{\beta}_i \) are usually Hill functions with \( \tilde{\beta}_i(0) \gg \beta_i(0) \).

By the 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
\[
x_i(t) = (\delta_i + \beta_i(0)) x_i(t) + \int_0^t e^{-\gamma_i \sigma_i f_i(a)} [\beta_i(0) x_i(t - a) \\
\times x_i(t - a) + \tilde{\beta}_i(\tilde{x}_i(t) - a) \tilde{x}_i(t - a)] da \\
+ 2K_{i-1} \int_0^{t-1} e^{-\gamma_i \sigma_i f_i(a)} [\beta_i(0) x_i(t - a) \\
\times x_i(t - a) + \tilde{\beta}_i(\tilde{x}_i(t) - a) \tilde{x}_i(t - a)] da.
\]

\[
\tilde{x}_i(t) = (\delta_i + \tilde{\beta}_i(0)) \tilde{x}_i(t) + \tilde{L}_i \int_0^t e^{-\gamma_i \sigma_i f_i(a)} [\beta_i(\tilde{x}_i(t) - a) \\
\times \tilde{x}_i(t - a) + \tilde{\beta}_i(\tilde{x}_i(t) - a) \tilde{x}_i(t - a)] da.
\]

This is a positive linear system that can be presented as (7), where \( x = [x_1, \ldots, x_n, \tilde{x}_1, \ldots, \tilde{x}_n] \). Due to “block-triangular” structure of (23), the condition (ii) of Lemma 1 for this system is equivalent to the fact that the matrices
\[
H_i = \begin{bmatrix}
-\delta_i - \beta_i(0) & \int_0^t e^{-\gamma_i \sigma_i f_i(a) da} & \tilde{\beta}_i(0) \tilde{L}_i \int_0^t e^{-\gamma_i \sigma_i f_i(a) da} \\
\beta_i(0) L_i \int_0^t e^{-\gamma_i \sigma_i f_i(a) da} & -\tilde{\beta}_i(0) & \int_0^t e^{-\gamma_i \sigma_i f_i(a) da}
\end{bmatrix},
\]

where \( i = 1, \ldots, n \).

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

$$
\left( L_i + \lambda_i^1 \tilde{L}_i \right) \int_0^{\tau_i} e^{-\gamma_0 t} f_i(a) da - 1 \beta_i(0) < \delta_i,
$$

$$
(L_i + \lambda_i^1 \tilde{L}_i) \int_0^{\tau_i} e^{-\gamma_0 t} f_i(a) da - \lambda_i^1 < 0, \quad i = 1, \ldots, n. \tag{25}
$$

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 $\lambda_i^1 > 0$, $i = 1, \ldots, n$ that satisfy the inequalities (25), or, equivalently, if the Metzler matrices $H^0$ 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

$$
2(1 - K_i) \int_0^{\tau_i} e^{-\gamma_0 t} f_i(a) da < 1, \quad i = 1, \ldots, n. \tag{26}
$$

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

$$
1 < 2(1 - K_i) \int_0^{\tau_i} e^{-\gamma_0 t} f_i(a) da < \frac{1}{1 - \sigma_i}, \quad i = 1, \ldots, n \tag{27}
$$

and

$$
\beta_i(0) > \frac{1}{1 - \sigma_i} - 1 - \frac{1}{1 - \sigma_i}(1 - K_i) \int_0^{\tau_i} e^{-\gamma_0 t} f_i(a) da.
$$

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

$$
\dot{V}_2(x_i) + \eta V_2(x_i) = \int_0^{\tau_i} e^{-(\gamma_0 - \eta) t} f_i(a) da \beta_i(x_i(t)) \xi_i(t) - \int_0^{\tau_i} e^{-\gamma_0 t} f_i(a) \beta_i(x_i(t-a)) \lambda_i^1 \tilde{L}_i \tilde{x}_i(t-a) da,
$$

$$
\dot{V}_3(x_i) + \eta V_3(x_i) = \int_0^{\tau_i} e^{-(\gamma_0 - \eta) t} f_i(a) da \beta_i(x_i(t-a)) \tilde{L}_i \tilde{x}_i(t-a) da - \int_0^{\tau_i} e^{-\gamma_0 t} \tilde{L}_i \tilde{x}_i(t-a) \xi_i(t-a) da,
$$

we obtain

$$
\dot{V}(x_i, \tilde{x}_i) + \eta V(x_i, \tilde{x}_i) \leq \sum_{i=1}^n \varepsilon_i \eta_i + \left[ L_i + 2\varepsilon K_i + \lambda_i^1 \tilde{L}_i \right] + \frac{\varepsilon}{2} \eta_i \lambda_i^1 \tilde{L}_i \tilde{x}_i(t-a) \tilde{x}_i(t-a)
$$

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

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

$$
\left[ L_i + 2\varepsilon K_i + \lambda_i^1 \tilde{L}_i \right] \int_0^{\tau_i} e^{-\gamma_0 t} f_i(a) da - 1 \beta_i(0) \leq \delta_i,
$$

$$
(L_i + 2\varepsilon K_i + \lambda_i^1 \tilde{L}_i) \int_0^{\tau_i} e^{-\gamma_0 t} f_i(a) da \leq \lambda_i^1, \quad i = 1, \ldots, n. \tag{30}
$$

Moreover, given $\varepsilon \in (0, 1)$ that satisfies (30), the following bound holds for solutions of (22) starting from the initial functions $\phi \in$
Given $\mathcal{X} \in \mathbb{R}^n$, denote by

$\mathcal{A}(\mathcal{X}) = \{ \phi \in C^n_{\tau_+} : \tilde{\phi}(t), \tilde{\phi}(\mathcal{X}) \leq \mathcal{X} \quad \forall t \geq 0 \}$

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

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 $\eta \in (0, \min(\delta_1, \ldots, \delta_n))$, $\lambda_1 > 0$, $\ldots$, $\lambda_n > 0$, and $\bar{x}_1 > 0$, $\ldots$, $\bar{x}_n > 0$ such that the following inequalities are satisfied:

$$
\left[ (L_1 + \lambda_1 \bar{L}_1) \int_0^{\tau_i} e^{-(\gamma_1 - \eta) t} f_i(a) da - \lambda_i \right] \beta_i(0) < \delta_i - \eta,
$$

$$
\left[ (L_1 + \lambda_1 \bar{L}_1) \int_0^{\tau_i} e^{-(\gamma_1 - \eta) t} f_i(a) da - \lambda_i \right] \tilde{\beta}_i(\bar{x}_1) < -\lambda_1 \eta,
$$

or, equivalently, let the Metzler matrices

$$
H_i = \left[ -\beta_i(0) (1 - \bar{L}_i) \int_0^{\tau_i} e^{-(\gamma_1 - \eta) t} f_i(a) da - \bar{L}_i(0) \int_0^{\tau_i} e^{-(\gamma_1 - \eta) t} f_i(a) da \right] - \tilde{\beta}_i(\bar{x}_1) \left[ 1 - \bar{L}_i \int_0^{\tau_i} e^{-(\gamma_1 - \eta) t} f_i(a) da \right]
$$

+ $\text{diag}(\eta, \ldots, \eta, \ldots, \eta)$

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

Moreover, if the above conditions hold with $\bar{x}_1 = \ldots = \bar{x}_n = 0$, then the zero solution of the system (22) is exponentially stable with a decay rate $\eta$ 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 $\eta$).

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

**Proof.**

(i) For each $i = 1, \ldots, n$ we have either

$$
[\lambda_i + 2eK_i + \lambda_1 \bar{L}_1] \int_0^{\tau_i} e^{-(\gamma_1 - \eta) t} f_i(a) da - \lambda_i < 0
$$

or, due to $0 \leq \beta_i(x_0) = \beta_i(0)$,

$$
[\lambda_i + 2eK_i + \lambda_1 \bar{L}_1] \int_0^{\tau_i} e^{-(\gamma_1 - \eta) t} f_i(a) da - \lambda_i < 0,
$$

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

$$
\eta \left[ \lambda_i + 2eK_i + \lambda_1 \bar{L}_1 \int_0^{\tau_i} e^{-(\gamma_1 - \eta) t} f_i(a) da - \lambda_i \right]
$$

$$
\times \beta_i(x(t)) - \delta_i < 0.
$$

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

$$
\lambda_i \eta + [\lambda_i + 2eK_i + \lambda_1 \bar{L}_1 \int_0^{\tau_i} e^{-(\gamma_1 - \eta) t} f_i(a) da - \lambda_i]
$$

$$
\times \tilde{\beta}(\bar{x}(t)) < 0.
$$

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

(ii) If the inequalities (25) are satisfied, then for all $x_0 \in \mathbb{R}^n$, there exists $\eta = \eta(x_0)$ such that (33) holds. The latter guarantees due to (i) that for all $(\phi, \tilde{\phi}) \in \mathcal{A}(\mathcal{X})$ the corresponding solutions $x(t)$ and $\tilde{x}(t)$ of (22) approach zero as $t \to \infty$. For $\bar{x}_i \to \infty$ $(i = 1, \ldots, n)$ by employing Lemma 3 we have $\|x(t)\| \leq \|x_0\| + \|\phi\|_c \to \infty$ (cf. the inequality (31)) meaning that $\mathcal{A}(\mathcal{X}) = \{C^n_{\tau_+}, C^n_{\tau_+}\}$. Therefore, the zero solution of (22) is globally asymptotically stable. □

**Example 2.**

Choosing $f_i(a) = \frac{m_i}{e^{a(\gamma_1 - \eta)} - 1}$, with $m_i > 0$ for all $i \in [1, n]$, the following parameters satisfy (25).

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

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

Choosing $\lambda_1 = 3$: $\left( (L_1 + \lambda_1 \bar{L}_1) \int_0^{\tau_1} e^{-(\gamma_1 - \eta) t} f_i(a) da - \lambda_i \right) \beta_1(0) = 1.5030 < 2 = \delta_1$.
and
\[
(L_1 + \lambda_1^1 L_1) \int_0^{\tau_1} e^{-\gamma_1 \sigma f_1(a) da} - \lambda_1^1 = -0.4970 < 0.
\]

- Choosing \( \lambda_1^1 = 5: \)
\[
\left[ (L_1 + \lambda_1^1 L_1) \int_0^{\tau_2} e^{-\gamma_2 \sigma f_2(a) da} - 1 \right] \beta_2(0) = 2.6629 < 4.2 = \delta_2
\]
and
\[
(L_2 + \lambda_2^1 L_2) \int_0^{\tau_2} e^{-\gamma_2 \sigma f_2(a) da} - \lambda_2^1 = -0.1959 < 0.
\]

- We can also verify that the positive steady state does not exist:
\[
\beta_1(0) = 0.7 < 1.6309
\]
\[
= \delta_1 \frac{1 - 2(1 - \sigma_1)(1 - K_1) \int_0^{\tau_1} e^{-\gamma_1 \sigma f_1(a) da}}{2(1 - K_1) \int_0^{\tau_1} e^{-\gamma_1 \sigma f_1(a) da}}.
\]

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 \( x^* = \text{col}[3, 3]. \)

For \( i = 1: \quad \delta_1 = 1.5, \quad \sigma_1 = 0.8, \quad K_1 = 0.02, \quad L_1 = 2 \sigma_1(1 - K_1) = 1.5680, \quad L_1 = 2(1 - \sigma_1)(1 - K_1) = 0.3920, \quad m_1 = 1, \quad \tau_1 = 0.8, \quad \gamma_1 = 0.2, \quad \beta_1(\bar{x}_1) = \frac{0.5 \sigma_1}{1 + \lambda_1^1} \) and \( \beta_1(\bar{x}_1) = \frac{10}{1 + \lambda_1^1}. \)

For \( i = 2: \quad \delta_2 = 2, \quad \sigma_2 = 0.7, \quad K_2 = 0.02, \quad L_2 = 2 \sigma_2(1 - K_2) = 1.3720, \quad L_2 = 2(1 - \sigma_2)(1 - K_2) = 0.5880, \quad m_2 = 1, \quad \tau_2 = 0.8, \quad \gamma_2 = 0.3, \quad \beta_2(\bar{x}_1) = \frac{0.5 \sigma_2}{1 + \lambda_2^1} \) and \( \beta_2(\bar{x}_1) = \frac{10}{1 + \lambda_2^1}. \)

- Choosing \( \lambda_1^1 = \lambda_2^1 = 3, \) we verify that the conditions (33) are satisfied for \( \eta = 0.05: \)
\[
\left[ (L_1 + \lambda_1^1 L_1) \int_0^{\tau_1} e^{-\gamma_1 \sigma f_1(a) da} - 1 \right] \beta_1(0) \]
\[
= 0.7827 < 1.45 = \delta_1 - \eta
\]
\[
\left[ (L_1 + \lambda_1^1 L_1) \int_0^{\tau_1} e^{-\gamma_1 \sigma f_1(a) da} - 1 \right] \tilde{\beta}_1(\bar{x}_1^1) \]
\[
= -0.2288 < -0.15 = -\lambda_1^1 \eta
\]
\[
\left[ (L_2 + \lambda_2^1 L_2) \int_0^{\tau_2} e^{-\gamma_2 \sigma f_2(a) da} - 1 \right] \beta_2(0) \]
\[
= 0.9025 < 1.95 = \delta_2 - \eta
\]
\[
\left[ (L_2 + \lambda_2^1 L_2) \int_0^{\tau_2} e^{-\gamma_2 \sigma f_2(a) da} - 1 \right] \tilde{\beta}_2(\bar{x}_2^1) \]
\[
= -0.1951 < -0.15 = -\lambda_2^1 \eta.
\]

According to (i) of Theorem 1 the origin of the system (22) is regionally exponentially stable with a decay rate \( \eta \) for all initial conditions \( (\phi, \phi) \in A(x^*) \). Fig. 3 illustrates this example with the previous parameters and \( \phi_1 = 2 \times 10^{-3}, \) (i.e., \( \phi_1(s) = 2 \times 10^{-3}, vs \in [-\tau_1, 0], \phi_1 = 4 \times 10^{-3}, \phi_2 = 3 \times 10^{-3} \) and \( \phi_3 = 3 \times 10^{-3}. \) One can readily check from Lemma 3 that for these initial conditions we have \( (\phi, \phi) \in A(x^*) \); Indeed, observe that for \( \epsilon = 0.1 \) the inequalities (30) are satisfied
\[
\left[ (L_1 + 2 \epsilon K_1 + \lambda_1^1 L_1) \int_0^{\tau_1} e^{-\gamma_1 \sigma f_1(a) da} - 1 \right] \beta_1(0) \]
\[
= 0.7563 < 1.55 = \delta_1
\]
\[
(L_1 + 2 \epsilon K_1 + \lambda_1^1 L_1) \int_0^{\tau_1} e^{-\gamma_1 \sigma f_1(a) da} - 1 = 2.5127 < 3 = \lambda_1^1
\]
\[
\left[ (L_2 + 2 \epsilon K_2 + \lambda_2^1 L_2) \int_0^{\tau_2} e^{-\gamma_2 \sigma f_2(a) da} - 1 \right] \beta_2(0) \]
\[
= 0.8738 < 2 = \delta_2
\]
\[
(L_2 + 2 \epsilon K_2 + \lambda_2^1 L_2) \int_0^{\tau_2} e^{-\gamma_2 \sigma f_2(a) da} - 1 = 2.7476 < 3 = \lambda_2^1.
\]

Moreover,
\[
\frac{\max\{1, \lambda_1^1, \lambda_2^1\}}{\epsilon \min\{1, \lambda_1^1, \lambda_2^1\}} = 270.
\]

**3.2. The case of uncertain or time-varying \( \sigma_i \) in the model**

It may be of interest to consider time-varying (uncertain or known) probability rates in the model (20)–(21)
\[
\sigma_{im} \leq \sigma_i(t) \leq \sigma_{IM}, \quad i = 1, \ldots, n.
\]

By the arguments of [14] the resulting time-delay system is given by (22). Then Theorem 1 holds, where in (25) and (33)
\[
L_i = 2\sigma_i(t)(1 - K_i), \quad \tilde{L}_i = 2(1 - \sigma_i(t)) - 1.
\]

Since the linear with respect to decision variables \( \lambda_i^1 \) inequalities (25) and (33) are affine in \( \lambda_i^1 \), they are feasible for all \( \lambda_i^1 \) 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 \( \lambda_i^1 > 0, \ldots, \lambda_n^1 > 0 \) such that the following 4n linear inequalities are satisfied:

\[
\left[ (L_i + \lambda_i^1 L_i) \int_0^{\tau_i} e^{-\gamma_i \sigma f_i(a) da} - 1 \right] \beta_i(0)_{\eta = \sigma_{im}} < \delta_i,
\]
\[
\left[ (L_i + \lambda_i^1 L_i) \int_0^{\tau_i} e^{-\gamma_i \sigma f_i(a) da} - 1 \right] \beta_i(0)_{\eta = \sigma_{IM}} < \delta_i,
\]
\[
(L_i + \lambda_i^1 L_i) \int_0^{\tau_i} e^{-\gamma_i \sigma f_i(a) da} < \lambda_i^1,
\]
\[
(L_i + \lambda_i^1 L_i) \int_0^{\tau_i} e^{-\gamma_i \sigma f_i(a) da} < \lambda_i^1,
\]
\[
(1, \ldots, n).
\]

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.
\[
0 \leq \sigma_i(t) \leq 1, \quad i = 1, \ldots, n.
\]

Here
\[
(L_i + \lambda_i^1 L_i)_{\eta = 0} = 2 \lambda_i^1 (1 - K_i), \quad (L_i + \lambda_i^1 L_i)_{\eta = 1} = 2(1 - K_i).
\]

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
\[
2(1 - K_i) \int_0^{\tau_i} e^{-\gamma_i \sigma f_i(a) da} - 1 < \delta_i, \quad i = 1, \ldots, n
\]
and
\[
2(1 - K_i) \int_0^{\tau_i} e^{-\gamma_i \sigma f_i(a) da} - 1 < \delta_i, \quad i = 1, \ldots, n.
\]

Clearly the inequalities (41) imply (40). Note that the conditions (41) are \( \beta_i \)-independent.
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) was derived

\[ 2(1 - K_i)f_i^* < γ_1, \quad f_i^* = \sup_{a \in [0, r_1]} f_i(a). \]

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

Example 4. Let us consider the following parameters:

For i = 1: δ_1 = 3.3, K_1 = 0.1, m_1 = 1, r_1 = 0.8, γ_1 = 0.2, β_1(x_1) = \frac{0.8}{1 + x_1^2} and \tilde{β}_1(x_1) = \frac{10}{1 + x_1^2}.

For i = 2: δ_2 = 4, K_2 = 0.08, m_2 = 1, r_2 = 0.8, γ_2 = 0.3, β_2(x_2) = \frac{1}{1 + x_2^2} and \tilde{β}_2(x_2) = \frac{10}{1 + x_2^2}.

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

\[ 0.5 = \sigma_{im} \leq \sigma_i(t) \leq \sigma_{im} = 0.9, \quad \text{for } i = 1, 2 \] (42)

and

\[ σ_i(t) = \frac{σ_{im} + σ_{im}}{2} + \frac{σ_{im} - σ_{im}}{2} \cos(t). \] (43)

The condition (39) is satisfied with λ_1 = λ_2 = 5:

\[ (L_1 + λ_1I_1) \int_0^{t_1} e^{-γ_i f_i(a) da} - \int_0^{t_1} e^{-γ_i f_i(a) da} \big|_{σ_1=σ_{im}} = 3.1501 < 3.3 = δ_1 \]

\[ (L_1 + λ_1I_1) \int_0^{t_1} e^{-γ_i f_i(a) da} - \int_0^{t_1} e^{-γ_i f_i(a) da} \big|_{σ_1=σ_{im}} = 1.0434 < 3.3 = δ_1. \]

\[ (L_1 + λ_1I_1) \int_0^{t_1} e^{-γ_i f_i(a) da} - \int_0^{t_1} e^{-γ_i f_i(a) da} \big|_{σ_1=σ_{im}} = 4.9376 < 5 = λ_1 \]

\[ (L_1 + λ_1I_1) \int_0^{t_1} e^{-γ_i f_i(a) da} - \int_0^{t_1} e^{-γ_i f_i(a) da} \big|_{σ_1=σ_{im}} = 2.3042 < 5 = λ_1 \]

\[ (L_2 + λ_2I_2) \int_0^{t_2} e^{-γ_i f_i(a) da} - \int_0^{t_2} e^{-γ_i f_i(a) da} \big|_{σ_1=σ_{im}} = 3.8302 < 4 = δ_2 \]

\[ (L_2 + λ_2I_2) \int_0^{t_2} e^{-γ_i f_i(a) da} - \int_0^{t_2} e^{-γ_i f_i(a) da} \big|_{σ_1=σ_{im}} = 1.2541 < 4 = δ_2 \]

\[ (L_2 + λ_2I_2) \int_0^{t_2} e^{-γ_i f_i(a) da} - \int_0^{t_2} e^{-γ_i f_i(a) da} \big|_{σ_1=σ_{im}} = 4.8302 < 5 = λ_2 \]

\[ (L_2 + λ_2I_2) \int_0^{t_2} e^{-γ_i f_i(a) da} - \int_0^{t_2} e^{-γ_i f_i(a) da} \big|_{σ_1=σ_{im}} = 2.2541 < 5 = λ_2. \]

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

References


