Systems & Control Letters 88 (2016) 91–100

Contents lists available at ScienceDirect

Systems & Control Letters

journal homepage: www.elsevier.com/locate/sysconle

Stability of the cell dynamics in acute myeloid leukemia ☆

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ARTICLE INFO

Article history:
Received 5 March 2015
Received in revised form
23 July 2015
Accepted 9 September 2015
Available online 17 December 2015

Keywords:
Leukemia model
Time-delay systems
Positive systems
Transport equations
Lyapunov method

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 $a < b$ ($a \leq b$) means componentwise inequality $a_i < b_i$ ($a_i \leq b_i$) for all $i = 1, \dots, n$. Similarly is defined the opposite vector inequality $a > b$ ($a \geq b$).

☆ This work was partially supported by Israel Science Foundation (Grant No. 1128/14), by iCODE institute and the research project of the Idex Paris-Saclaand Digiteo project ALMA3.

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http://dx.doi.org/10.1016/j.sysconle.2015.09.006
0167-6911/

$\mathbb{R}^n_+$ 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;*