Local Asymptotic Stability Conditions for the Positive Equilibrium of a System Modeling Cell Dynamics in Leukemia

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Abstract. A distributed delay system with static nonlinearity has been considered in the literature to study the cell dynamics in leukemia. In this chapter local asymptotic stability conditions are derived for the positive equilibrium point of this nonlinear system. The stability conditions are expressed in terms of inequalities involving parameters of the system. These inequality conditions give guidelines for development of therapeutic actions.

1 Introduction

Starting with the early works of Mackey and his colleagues, [9, 10] there has been a growing interest in the development of mathematical models for cell dynamics in hematological processes. Over the last ten years, significant improvements have been made in this direction and, in particular, models for cell dynamics in leukemia (blood cancer) have been refined, see e.g. [1, 5, 6, 8, 11, 13, 20] and their references. In this chapter, the model of [1] will be considered. This is a cascade connection

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of a series of systems (compartments) containing distributed delays and a static nonlinear feedback. There are several possible equilibrium points for the system, the origin is being one of them. Here, local asymptotic stability conditions are studied for the "positive equilibrium" where the equilibrium states of all the compartments (sub-systems) are positive.

In [2] a global stability condition is obtained for the case where the only equilibrium is the origin. Some of the works mentioned above consider the "point delay" version of the problem; a recent one is [20], where conditions for global asymptotic stability of the origin and instability of the positive equilibrium are obtained in terms of the delay values.

Rest of the chapter is organized as follows. Details of the mathematical model are given in the next section. Then, the main results are derived and concluding remarks are made. Preliminary versions of the results of this chapter have been already presented in various meetings, [14, 15, 16, 17].

2 Mathematical Model of Cell Dynamics in Leukemia

Since the identification of leukemic stem cells (LSCs) in humans, [4], many studies have been conducted to characterize the process of formation of leukemic cells. It is now well understood that LSCs can self-renew and they can differentiate to generate leukemic progenitors which can also self-renew and differentiate. There are many stages of differentiation (compartments of progenitors between LSCs and leukemic cells) until leukemic cells are released into the blood, [7]. At each stage, there is a compartment (population) of cells of a certain biological property, characterized by specific cluster definition (CD) molecules, such as CD34, CD38, CD123, CD90, CD117, CD135 and CD33. For example, in a certain type of acute myelogenous leukemia (AML), cells with the concentration of molecules CD34+CD38-CD33- can be identified as LSCs, i.e. the first compartment, (respectively, CD34+CD38+CD33- for progenitors and CD34+CD38+CD33+ for leukemic cells, i.e., second and third compartments in a 3 compartment model), [12]. Recently, it has been shown that for mathematical modeling purposes, 4 to 8 compartment models are sufficient to diagnose chronic myelogenous leukemia in humans, [19].

At each compartment, the cells can be grouped into two: the ones in growth phase (proliferation) and the quiescent (non-proliferating) ones. At the end of growth phase, each cell is divided into two. Some of the new cells stay in the same compartment (having the same biological property as the mother cell - self renewal) and some go to the next compartment (differentiation). The dynamical behavior of cell populations in the quiescent and proliferating phases can be characterized as shown in Figure 1, where δ and γ represent the death rates of the quiescent and proliferating cells respectively, $\beta(\cdot)$ is the re-introduction function, τ is the maximal time spent in the growth phase before cell division occurs and $L = 1 - K \in (0\ ,\ 1)$ is the rate of proliferating cells that divide without differentiation. Note that each of these parameters can be different for different compartments, i.e. δ_i, γ_i, τ_i, L_i and $\beta_i(\cdot)$ are

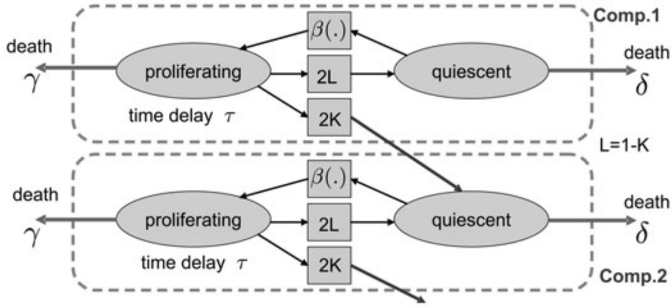

Fig. 1 Cell population dynamics in compartmental modeling.

the parameters of the ith compartment. The notation $x_i(t)$ and $y_i(t)$ will be used to denote the cell population in the quiescent and proliferation phases, respectively, in compartment i at time t.

With the above definitions, dynamical equations for x_i and y_i can be given as follows, see e.g. [1],

$$\dot{x}_i(t) = -\delta_i x_i(t) - w_i(t) + 2L_i \int_0^{\tau_i} e^{-\gamma_i a} f_i(a) w_i(t-a)da + u_{i-1}(t) \tag{1}$$

$$\dot{y}_i(t) = -\gamma_i\, y_i(t) + w_i(t) - 2\int_0^{\tau_i} e^{-\gamma_i a} f_i(a) w_i(t-a)da \tag{2}$$

$$u_i(t) = 2K_i \int_0^{\tau_i} e^{-\gamma_i a} f_i(a) w_i(t-a)da \tag{3}$$

$$w_i(t) := \beta_i(x_i(t))x_i(t)\ , \tag{4}$$

$$f_i(a) \geq 0 \quad \text{for all } \ a \in [0, \tau_i] \ \text{ and } \int_0^{\tau_i} f_i(a)da = 1 \tag{5}$$

with $K_0 = 0$. Here f_i is the cell division probability and we consider the form

$$f_i(a) = \frac{m_i}{e^{m_i \tau_i} - 1}\, e^{m_i a}, \quad a \in [0\ ,\ \tau_i] \quad m_i > \gamma_i \tag{6}$$

which is originally proposed in [14]. Define $g_i(a) := e^{-\gamma_i a} f_i(a)$ for $0 \leq a \leq \tau_i$ and $g_i(a) = 0$ otherwise. Then, the Laplace transform $G_i(s)$ of $g_i(t)$ is

$$G_i(s) = q_i\, \frac{1 - e^{-\tau_i(s - r_i)}}{(s - r_i)} \tag{7}$$

where $q_i = m_i/(e^{m_i \tau_i} - 1) > 0$ and $r_i = m_i - \gamma_i > 0$.

In [1], the above system is analyzed for the choice of $G_i(s) = e^{-\tau_i(s+\gamma_i)}$, which is a system with "point delay". We feel that the choice (7) is more natural, it corresponds to a distributed delay system, [14].

Dynamical equations given above for the ith compartment can be combined into a single block diagram as shown in Figure 2. Note that the sub-system Σ_{yi} is a stable system, i.e. when its input $(I-2G_i)w_i$ is bounded we get a bounded y_i. Therefore, we will be interested in the analysis of the system represented by the equations (1), (3) and (4), with the distributed delay term (7) and nonlinearity β_i specified as

$$\beta_i(x) = \frac{\beta_i(0)}{1+b_i x^{N_i}} \tag{8}$$

where $\beta_i(0) > 0$, $b_i > 0$ and N_i is an integer greater or equal to 2, see [5, 6, 9] for biological justifications of this selection.

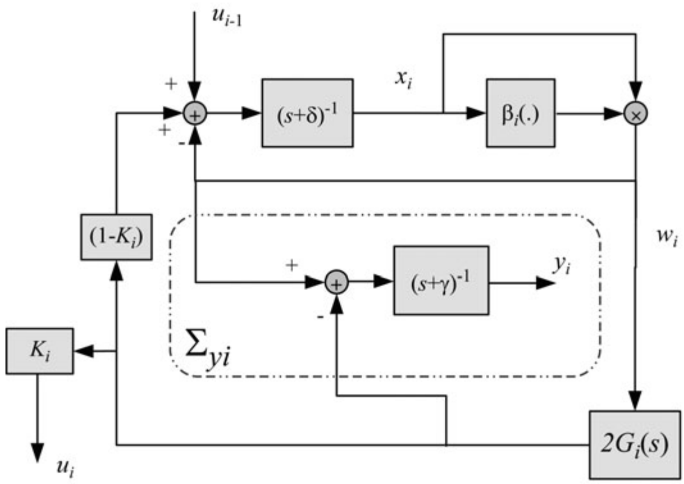

Fig. 2 Block diagram representation of the ith compartment cell dynamics.

3 Stability Analysis for the Positive Equilibrium

In this section local asymptotic stability conditions are obtained for the "positive equilibrium" point $\bar{\mathbf{x}} = [\bar{x}_1,\ldots,\bar{x}_n]^{\mathrm{T}}$ where all $\bar{x}_i$ are strictly positive. Existence of such an equilibrium point depends on certain conditions derived as follows. First define

$$\alpha_i := 2L\int_0^{\tau_i} g_i(t)dt - 1 = 2L_i G_i(0) - 1 \tag{9}$$

and make the following assumption.

Assumption. We have $\alpha_i > 0$ for all $i = 1,\ldots,n$, and $\beta_1(0) > \delta_1/\alpha_1$. □

Then, a unique positive equilibrium exists, see e.g. [1]. It can be computed from the following equations: $\bar{x}_1$ is such that

$$\beta(\bar{x}_1) = \delta_1/\alpha_1 \; ; \tag{10}$$

and for $i \geq 2$, the equilibrium points $\bar{x}_i$ are the unique solutions of

$$\beta_i(\bar{x}_i) = \frac{1}{\alpha_i}\left(\delta_i \;-\; \frac{1}{\bar{x}_i}\;\left(\frac{\bar{x}_{i-1}K_{i-1}(\beta(\bar{x}_{i-1}) + \delta_{i-1})}{L_{i-1}}\right)\;\right). \tag{11}$$

Since $G_i(s)$ is strictly proper, the system is locally asymptotically stable around the positive equilibrium if and only if all the roots of

$$s + \delta_i + \mu_i - 2L_i\mu_i G_i(s) = 0 \tag{12}$$

are in $\mathbb{C}_-$ for all i, where

$$\mu_i := \frac{\mathrm{d}}{\mathrm{d}x} x\,\beta_i(x)\;|_{\bar{x}_i}\;. \tag{13}$$

As noted in [3] depending on the parameters of the system, μ_i can be positive, negative or zero. Clearly, when $\mu_i = 0$ the the equation (12) has its roots at $-\delta_i < 0$. Therefore, the most interesting case is $\mu_i \neq 0$.

Since the analysis has to be done individually for each compartment, in the rest of the paper the subscript i is dropped whenever it is clear from the context that ith characteristic equation (12) is considered.

3.1 Local Asymptotic Stability for $\mu > 0$

Consider the characteristic equation (12) with $\mu > 0$. Figure 3 shows that under different parameter selections one may have a common equilibrium point with different positive μ values.

When $\mu > 0$, the system is locally asymptotically stable if and only if

$$\mu < \frac{\delta}{\alpha} \quad \text{which is equivalent to} \quad 2LG(0) < \frac{\delta + \mu}{\mu}. \tag{14}$$

For the proof, see [1, 14]. Also, it has been recently shown, [18], that he condition (14) holds true for all β in the form (8). So, whenever we have a unique positive equilibrium with $\mu_i > 0$ for all i, we have local asymptotic stability.

3.2 Local Asymptotic Stability for $\mu < 0$

Consider the system whose characteristic equation is in the form (12) with $\mu < 0$. In this case (12) can be re-written as

$$1 + |\mu|\frac{(2LG(s) - 1)}{(s + \delta)} = 0 \;\;. \tag{15}$$

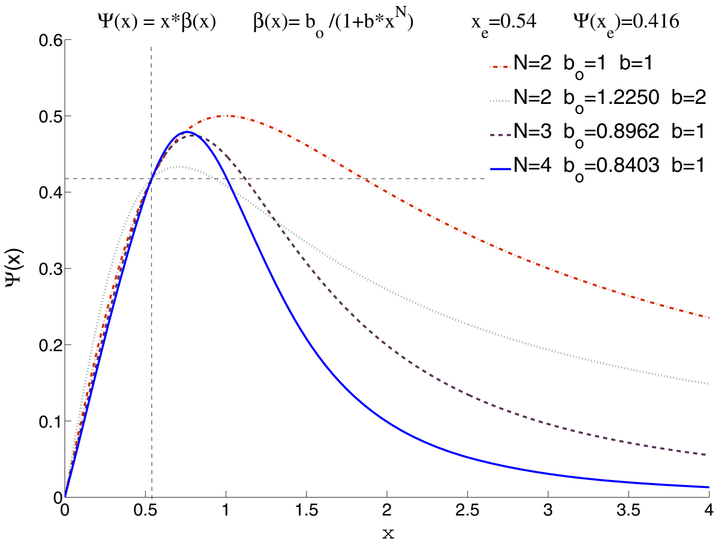

Fig. 3 Different parameters resulting in a same equilibrium with different positive μ.

The equation (15) can be seen as a characteristic equation of a feedback system composed of stable open loop transfer functions $(2LG(s)-1)$ and $|\mu|/(s+\delta)$. Hence the small gain condition

$$|\mu| \; \|(s+\delta)^{-1}\|_\infty \; \|2LG(s)-1\|_\infty < 1 \tag{16}$$

implies stability.

Clearly, a sufficient condition for (16) is $|\mu| \; (2LG(0)+1) < \delta$ (see also [1, 3]), i.e.,

$$2LG(0) < \frac{\delta - |\mu|}{|\mu|}, \tag{17}$$

which is valid only when $\delta > |\mu|$.

A weaker condition for stability, again by the small gain on (15), is

$$|\mu| < 1/\|H\|_\infty \tag{18}$$

where

$$H(s) = \frac{2LG(s)-1}{(s+\delta)}. \tag{19}$$

Note that $H(0) = \alpha/\delta$. Thus (18) is equivalent to

$$|\mu| < \frac{1}{K_H} \; \frac{\delta}{\alpha} \tag{20}$$

where

$$K_H := \| \frac{1}{H(0)} H(s) \|_\infty . \tag{21}$$

We now investigate K_H for G in the form (7).

Proposition 1. *Consider the function $G(s)$ in the form* (7) *and define*

$$\kappa := \frac{(\alpha+1)(\tau r+1)+0.28}{\alpha\sqrt{1+r^2/\delta^2}} . \tag{22}$$

The feedback system represented by the characteristic equation (15) *is stable if one of the following two conditions are satisfied:*

(i) $\kappa \le 1$ *and* $|\mu| < (\delta/\alpha)$*;*
(ii) $\kappa > 1$ *and* $|\mu| < \kappa^{-1}(\delta/\alpha)$.

Proof. We claim that (i) when $\kappa \le 1$ we have $K_H = 1$, and (ii) when $\kappa > 1$ we have $K_H \le \kappa$. Recall that

$$H(s) = \left(\frac{1}{s+\delta}\right)\left(q\left(\frac{1-e^{-\tau(s-r)}}{(s-r)}\right)-1\right) \; ; \quad H(0) = \frac{\alpha}{\delta}.$$

Then, scaling the frequency by r and using simple algebra it can be shown that

$$K_H = \max_{\omega\in\mathbb{R}} \left| \frac{1+j\omega\frac{\delta}{r\alpha}+j\omega\frac{qe^{\tau r}\delta\tau}{r\alpha}\left(\frac{e^{-j\tau r\omega}-1}{j\tau r\omega}\right)}{(1+j\omega)(1-j\omega\frac{\delta}{r})} \right| .$$

Expanding the numerator of the above expression into its real and imaginary parts, we get

$$1 \;\le\; K_H^2 \;\le\; \max_{\omega\in\mathbb{R}} \frac{1+\omega^2\frac{\delta^2}{r^2\alpha^2}\left((1-q\tau e^{\tau r}\frac{\sin(\tau r\omega)}{\tau r\omega})^2+(q\tau e^{\tau r}(\frac{1-\cos(\tau r\omega)}{\tau r\omega}))^2\right)}{(1+\omega^2)(1+\omega^2\frac{\delta^2}{r^2})}$$

Since

$$q = 2LG(0)\frac{r}{e^{\tau r}-1} = \frac{r\,(\alpha+1)}{e^{\tau r}-1}$$

we have

$$1 \le q\tau e^{\tau r} = \frac{(\alpha+1)\,\tau r}{1-e^{-\tau r}} \le (\alpha+1)(\tau r+1). \tag{23}$$

Also note that for all $q\tau e^{\tau r} \ge 1$ we have

$$\max_{\omega\in\mathbb{R}} \sqrt{(1-q\tau e^{\tau r}\frac{\sin(\tau r\omega)}{\tau r\omega})^2+(q\tau e^{\tau r}\frac{1-\cos(\tau r\omega)}{\tau r\omega})^2} \le q\tau e^{\tau r}+0.28.$$

Thus

$$1 \leq K_H^2 \leq \max_{\omega\in\mathbb{R}} \frac{1+\omega^2 A^2\delta^2/r^2}{1+(1+\delta^2/r^2)\omega^2+(\delta^2/r^2)\omega^4} \tag{24}$$

where

$$A := \alpha^{-1}\left((\alpha+1)(\tau r+1)+0.28\right).$$

By studying the maximum condition on the right hand side of (24) we see that $K_H = 1$ if $A^2 \leq (1+\frac{r^2}{\delta^2})$. Note that $\kappa = A/\sqrt{1+(r^2/\delta^2)}$. Hence part (i) of the proposition is proven. For the second part, when $\kappa > 1$, it can be shown that the maximum on the right hand side of (24) gives

$$K_H^2 \leq \left(1-\frac{r^2}{A^4\delta^2}(\sqrt{1+\varpi^2}-1)^2\right)^{-1} \text{ where } \varpi^2 = \frac{A^4\delta^2}{r^2}\left(1-\frac{1}{\kappa^2}\right). \tag{25}$$

Now using the fact

$$\sqrt{1+\varpi^2}-1 = \frac{\varpi^2}{\sqrt{1+\varpi^2}+1} \leq \varpi$$

a new bound can be found from (25)

$$K_H^2 \leq \left(1-\frac{r^2}{A^4\delta^2}\varpi^2\right)^{-1} = (1-(1-\frac{1}{\kappa^2}))^{-1} = \kappa^2.$$

In conclusion, if $\kappa > 1$ then $K_H \leq \kappa$. □

The inequality conditions expressed in Proposition 1 can be easily checked once the parameters of the system are given. The first stability condition is equivalent to

$$2LG(0) < \frac{\delta+|\mu|}{|\mu|} \tag{26}$$

when $\kappa \leq 1$, and the second condition means

$$2LG(0) < \kappa^{-1}\,\frac{\delta+|\mu|}{|\mu|} \tag{27}$$

when $\kappa > 1$. In both cases there is a lower bound for $2LG(0)$ given by

$$\frac{(1-e^{-\tau r})}{(\tau r+1)} < 2LG(0), \tag{28}$$

which is derived from (23) by recalling that $2LG(0) = \alpha+1$.

Proposition 1 gives the above sufficient conditions, (26) and (27), which are valid for $\delta > |\mu|$ as well as $\delta < |\mu|$. Necessary and sufficient conditions for these two

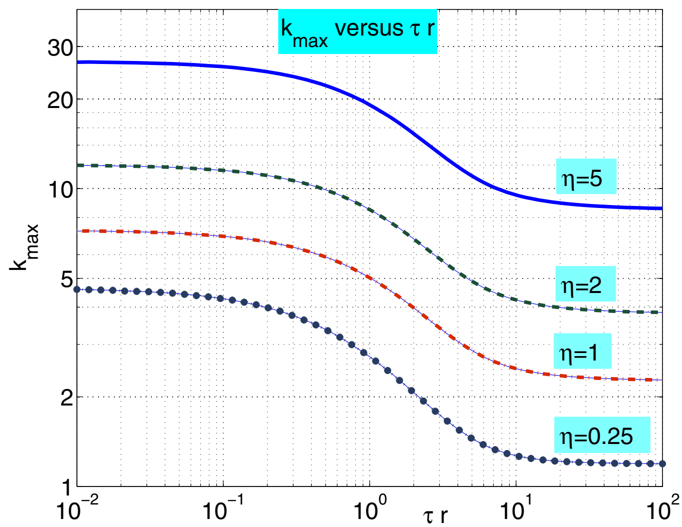

Fig. 4 Gain $k_{\max}$ versus τr for different values of η.

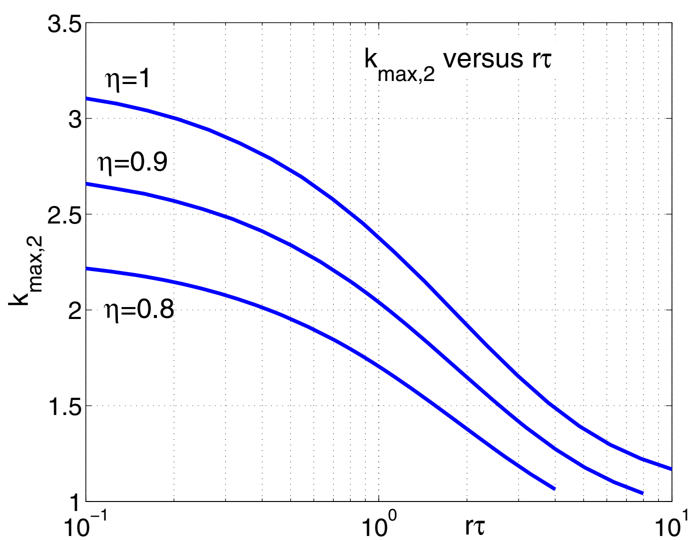

Fig. 5 Gain $k_{\max,2}$ versus τr for different values of η and τr pairs satisfying (30).

different cases are obtained in [15] as inequalities in the following forms. For $\delta > |\mu|$, the system is locally asymptotically stable if and only if

$$2LG(0) < \frac{\delta - |\mu|}{|\mu|}\, k_{\max} \tag{29}$$

where $k_{\max} > 1$ depends on τr, and $\eta := \tau^{-1}(\delta - |\mu|)^{-1}$, as shown in Figure 4.

Similarly, for $\delta < |\mu|$, the system is locally asymptotically stable if and only if

$$\eta > (1 - e^{-\tau r})^{-1} - (\tau r)^{-1} \tag{30}$$

and

$$\frac{|\mu| - \delta}{|\mu|} < 2LG(0) < \frac{|\mu| - \delta}{|\mu|}\, k_{\max,2}, \tag{31}$$

where $k_{\max,2} > 1$ depends on τr, and η, as shown in Figure 5.

4 Conclusions

In this chapter, local asymptotic stability conditions are studied for a distributed delay system modeling cell dynamics in leukemia. Proposition 1 gives a simple sufficient condition which is valid for the case $\mu < 0$, independent of the relative size of δ with respect to $|\mu|$. Necessary and sufficient conditions for local asymptotic stability are obtained in [15, 18] and they can be checked graphically (there are no analytic expressions for the functions $k_{\max}$ and $k_{\max,2}$). The conditions derived here can be easily checked in terms of the parameters of the dynamical equation δ, τ, μ and the product $2LG(0) = (\alpha + 1)$ which depend on the mitosis function f, the death rate γ as well as the gain L. Some of these parameters can be adjusted by therapeutic actions, that may be useful in achieving stability.

For global asymptotic stability, a nonlinear small gain argument is used in [18] and an inequality condition is obtained. However the level of conservatism in this inequality has not been established yet. In particular, checking whether the following conjecture holds is an interesting open problem: if the positive equilibrium of the system represented by the equations (1)–(4) is locally asymptotically stable, then it is globally asymptotically stable. Recently, for the case where the origin is the only equilibrium point for the point delay version of the system, the conjecture has been proven to hold [20], see also for a related result [2].

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