Absolute Stability of a System with Distributed Delays Modeling Cell Dynamics in Leukemia

Hitay Özbay, Houda Benjelloun, Catherine Bonnet, Jean Clairambault

***Abstract*— In this paper we consider a mathematical model proposed recently by Adimy et al. (2008) for studying the cell dynamics in Acute Myelogenous Leukemia (AML). By using the circle and Popov criteria, we derive absolute stability conditions for this nonlinear system with distributed delays. Connections with the earlier results on stability of the linearized model are also made. The results are illustrated with a numerical example and simulations.**

I. Introduction

In a recent work, [1], Adimy *et al.* have proposed a mathematical model of the cell dynamics in Acute Myelogenous Leukemia (AML). This is a nonlinear system with distributed delays, consisting of several compartments connected in series. Equilibrium conditions are studied and local stability analysis for different equilibria are done in [1], where sufficient conditions for local stability are obtained using earlier results of [2]. Later, in [9] a necessary and sufficient condition is obtained for a particular choice of the distributed delay kernel for the linearized system. In the present work we study absolute stability conditions of this nonlinear system.

For delay systems with uncertain nonlinearity satisfying the sector condition, primary tools of stability analysis have been the circle criterion and the Popov criterion, [7], [12], [13], see also [3], [4], [8] and their references. Here, we show that the first compartment of the mathematical model proposed in [1] can be put within the framework of these methods. For a specific form of the distributed delay kernel (studied in [9]) we derive sufficient conditions for absolute stability using Popov criterion.

H. Özbay is with INRIA Paris-Rocquencourt, Domaine de Voluceau, B.P. 105, 78153 Le Chesnay Cedex, France; on leave from Dept. of Electrical & Electronics Engineering, Bilkent University, Ankara TR-06800, Turkey, e-mail: hitay@bilkent.edu.tr

H. Benjelloun is with INRIA Saclay - Île-de-France, 4 rue J. Monod, 91893, Orsay Cedex, France, e-mail: Houda.Benjelloun@inria.fr

C. Bonnet is with INRIA Saclay - Île-de-France, 4 rue J. Monod, 91893, Orsay Cedex, France, e-mail: Catherine.Bonnet@inria.fr

J. Clairambault is with INRIA Paris-Rocquencourt, Domaine de Voluceau, B.P. 105, 78153 Le Chesnay Cedex, France, and INSERM team U 776 "Biological Rhythms and Cancers", Hôpital Paul-Brousse, 14 Av. Paul-Vaillant-Couturier, F94807 Villejuif Cedex, e-mail: jean.clairambault@inria.fr

II. Problem Statement

In this paper we consider the first compartment of the system introduced in [1], that is described by the following equation

$$\dot{x}(t) = -\delta x(t) - w(t) + 2L \int_0^\tau e^{-\gamma a} f(a) w(t-a) da \quad (1)$$

where

$$w(t) = x(t)\ \beta(x(t)) \quad (2)$$

- x is the total density of the resting cells;
- δ is the death rate in the resting phase;
- γ is the death rate (apoptosis) in the proliferating phase;
- $\beta(\cdot)$ is the re-introduction function from the resting subpopulation into the proliferative subpopulation;
- $L := (1-K)$, with $0 \le K \le 1$, where K is the rate of proliferating cells that divide without differentiation, i.e. that remain the first compartment;
- proliferating cells can divide between the moment they enter the proliferating phase and a maximal time $\tau > 0$ (this is the distributed time delay);
- f is the mitosis (cell division) probability density; note that mitosis occurs before the age limit τ, and $f(a) \ge 0$ for all $a \in [0,\tau]$ and $\int_0^\tau f(a)da = 1$.

A block diagram representation of the system defined above is shown in Figure 1, where the subsystem represented by the transfer function $G(s)$ is a system with distributed delay, whose impulse response is $g(t) := e^{-\gamma t} f(t)$ for $t \in [0,\tau]$ and $g(t) = 0$ for $t > \tau$, i.e.,

$$G(s) = \int_0^\tau e^{-\gamma t} f(t) e^{-st} dt, \quad (3)$$

and the nonlinearity $\Psi(\cdot)$ takes $x(t)$ as the input and generates $w(t)$.

Typical choice for β is (see [1], [2])

$$\beta(x) = \beta_o/(1+x^N) \quad \text{where} \quad \beta(0) = \beta_o > 0 \quad (4)$$

and $N \ge 2$ is an integer.

ISBN 978-963-311-370-7

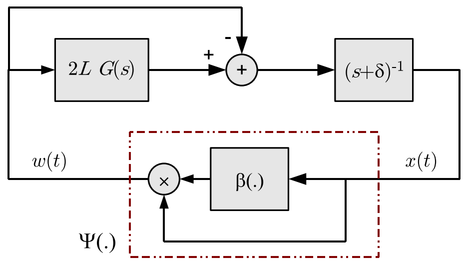

Fig. 1. The Nonlinear System with Distributed Delay.

In this paper we are interested in the form of G given by

$$G(s) = q\,\frac{1-e^{-\tau(s-r)}}{(s-r)}\ , \qquad r>0 \tag{5}$$

where $q = m/(e^{m\tau}-1) > 0$ and $m = r-\gamma > 0$. Note that $G \in \mathcal{H}_\infty$ and it does not have a pole, in fact $G(r) = q\tau$. See [9] for the motivation of the selection of this form of G.

Clearly, the origin is an equilibrium point, which corresponds to death of cells. Under the assumptions stated below there is a unique non-trivial equilibrium point x_e which is positive, see e.g. [1].

Assumption 1. $\alpha := (2LG(0)-1) > 0$.

Assumption 2. $\beta_o := \beta(0) > \delta/\alpha$.

III. Main Results

In [1], [9], [10] conditions for local asymptotic stability of the origin and the positive equilibrium are derived for various cases. In the next section we discuss absolute stability conditions when $x_e > 0$.

Let Assumptions 1 and 2 hold. Then, x_e is such that

$$\beta(x_e) = \frac{\delta}{\alpha}.$$

In particular, when $\beta(\cdot)$ is in the form (4), we have

$$x_e = \left(\frac{\beta_o}{\delta/\alpha} - 1\right)^{1/N}.$$

Define

$$\mu := \frac{\partial}{\partial x}\Psi(x)|_{x_e}$$

We will discuss two different cases: $\mu > 0$ and $\mu < 0$. It can be shown that when $\mu > 0$, local asymptotic stability of this system is equivalent to having (see [9], [10])

$$\mu < \frac{\delta}{\alpha}. \tag{6}$$

For the special choice (4) we have

$$\mu = \frac{\delta}{\alpha}\ \left(1 - N + N\frac{(\delta/\alpha)}{\beta_o}\right).$$

So, in this case, $\mu > 0$ if and only if

$$\frac{(\delta/\alpha)}{\beta_o} > \frac{N-1}{N}.$$

Moreover, under this condition, (6) is always satisfied, see [10] for the details.

For the nonlinear system analysis let us define

$$\widetilde{x}(t) := x(t) - x_e \qquad \text{and} \qquad \widetilde{w}(t) := w(t) - w_e \tag{7}$$

where $w_e := \beta(x_e)x_e$. Under the above equilibrium conditions the system (1) can be transformed to

$$\frac{d}{dt}\widetilde{x}(t) = -\delta\widetilde{x}(t) - \widetilde{w}(t) + 2L\int_0^\tau e^{-\gamma a} f(a)\widetilde{w}(t-a)da. \tag{8}$$

Using the new coordinates (7), the origin (i.e. $\widetilde{x} = 0$) is the equilibrium of the system (8), whose feedback diagram is shown in Figure 2, where ψ is the static nonlinearity defined by $\psi(\widetilde{x}) = \widetilde{w}$.

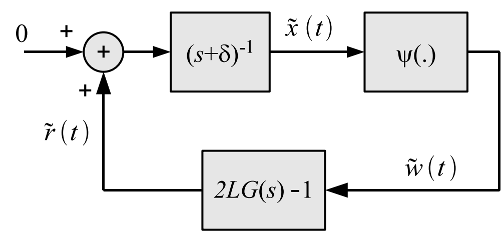

Fig. 2. Feedback system with equilibrium at the origin.

Now a stability condition can be derived by putting the system of Figure 2 into the framework of the circle (or Popov) criterion. For this purpose, let us assume that there exists $\widetilde{\rho} > 0$ satisfying the sector condition (i) if $\mu > 0$

$$0 < \psi(\widetilde{x})\widetilde{x} < \widetilde{\rho}\widetilde{x}^2 \quad \forall\ \widetilde{x} \neq 0, \quad \text{and} \quad \widetilde{x} \in (-\bar{x}\ ,\ x^r) =: X_+ \tag{9}$$

where x^r is the unique point which makes $\bar{w} > w$ for all $x > x^r$; and (ii) if $\mu < 0$

$$0 < (-\psi(\widetilde{x}))\widetilde{x} < \widetilde{\rho}\widetilde{x}^2 \quad \forall\ \widetilde{x} \neq 0,\ \widetilde{x} \in (-\bar{x}+x^\ell\ ,\ \infty) =: X_- \tag{10}$$

where x^ℓ is the unique point which satisfies the condition $\bar{w} > w$ for all $0 < x < x^\ell$. In general, $\rho \geq \widetilde{\rho} \geq |\mu|$ for both cases $\mu > 0$ and $\mu < 0$.

Applying the circle criterion, see e.g. [5], for the case $\mu > 0$, we see that with $\widetilde{x}(\theta) \in X_+$ for all $\theta \in [-\tau\ ,\ 0]$, the feedback system is absolutely stable if $(1 - \widetilde{\rho}H(s))$ is strictly positive real, which is equivalent to having

$$\Re\{H(j\omega)\} < 1/\widetilde{\rho} \qquad \forall\ \ \omega \in \mathbb{R} \tag{11}$$

where

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

Although the condition (11) is in general less restrictive than the small gain condition

$$\|H\|_\infty < 1/\widetilde{\rho}\ , \tag{12}$$

for the case when $H(0) = \|H\|_\infty$ they are equivalent. For $G(s)$ in the form (5), when $\kappa \le 1$, where

$$\kappa := \frac{(\alpha+1)(\tau r+1)+0.28}{\alpha\ \sqrt{1+r^2/\delta^2}}\ . \tag{13}$$

absolute stability condition (11) becomes equivalent to (12), which reduces to

$$\frac{\alpha}{\delta} < 1/\widetilde{\rho}. \tag{14}$$

Clearly, this is a stronger condition than the local asymptotic stability condition; but if $\widetilde{\rho} = \mu$, then these conditions are identical.

Now consider the case for $\mu < 0$ and assume $|\mu| < \delta$. Then, apply the Popov criterion, [5], [6], [12], [13] on the system shown in Figure 2 with ψ replaced by $-\psi$ satisfying the sector condition (10). In this case, with the initial condition $\widetilde{x}(\theta) \in X_-$ for $\theta \in [-\tau\ ,\ 0]$, the system is absolutely stable if there exists $\widetilde{\eta} \ge 0$ such that $\widetilde{\eta}$ is not a pole of $H(s)$ and

$$\Re\{\widetilde{\rho}^{-1} + (1+j\omega\widetilde{\eta})H(j\omega)\} > 0 \qquad \forall\ \ \omega \in \mathbb{R}\ \ . \tag{15}$$

Choosing $\widetilde{\eta} = \delta^{-1} + \epsilon$ for $\epsilon > 0$ and letting $\epsilon \to 0$ we see that (15) becomes

$$\min_{\omega\in\mathbb{R}} \Re\{G(j\omega)\} > -\frac{\delta-\widetilde{\rho}}{2L\widetilde{\rho}}. \tag{16}$$

Note that, typically the left hand side of (16) is negative in the form

$$\min_{\omega\in\mathbb{R}} \Re\{G(j\omega)\} = -\widetilde{K}_G^{-1}G(0) \tag{17}$$

where $\widetilde{K}_G > 0$ depends on the parameters of $G(s)$. Therefore, (16) can be satisfied only if $\delta > \widetilde{\rho}$. In conclusion, for the case $\mu < 0$, with $|\mu| < \delta$, and $\delta > \widetilde{\rho}$, absolute stability condition obtained from the Popov criterion is

$$2LG(0) < \frac{\delta-\widetilde{\rho}}{\widetilde{\rho}}\ \widetilde{K}_G \tag{18}$$

where

$$\widetilde{K}_G = \left|\min_{\omega\in\mathbb{R}} \frac{\Re\{G(j\omega)\}}{G(0)}\right|^{-1}. \tag{19}$$

With other choices of $\widetilde{\eta}$ in (15) one may obtain a less conservative result, but the above particular selection give a simple result (18) which allows easy comparison with local stability condition: For the case where x_e is such that $-\delta < \mu < 0$, the system is locally asymptotically stable if and only if (see [10])

$$2LG(0) < \frac{\delta-|\mu|}{|\mu|}\ k_{\max} \tag{20}$$

where $k_{\max}$ depends on $\eta := \tau^{-1}(\delta-|\mu|)^{-1}$ and it is given explicitly in Figure 3. In general

$$\widetilde{K}_G \le k^o_{\max} \tag{21}$$

where $k^o_{\max}$ is the value of $k_{\max}$ for $\eta \to 0$. For G in the special form (5), for small values of $r\tau$, we have equality in (21) as illustrated in Figure 3.

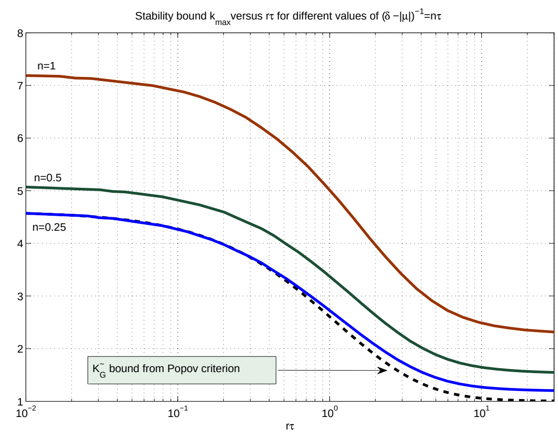

Fig. 3. $k_{\max}$ versus $r\tau$ for various $(\delta - |\mu|)$; and $\widetilde{K}_G$ versus $r\tau$.

IV. Examples

A. Example 1

Let us consider a system with $L = 0.9$ and $\beta_o = 1$, $N = 2$, $\delta = 0.5$, $\tau = 1.0$, $\gamma = 0.04$, $m = 10$. For these parameters we compute that $\alpha = 0.7364$, $x_e = 0.6876$, $\mu = 0.2431$, $x_r = 1.4544$, $\widetilde{\rho} = 0.6790$. So, the system is locally asymptotically stable (i.e. it satisfies $\mu < \delta/\alpha$). It is interesting that in this particular example we have $\widetilde{\rho} = \delta/\alpha$, so the absolute stability condition is not satisfied (but $\widetilde{\rho} < \delta/\alpha$ is just a sufficient condition for stability). Nevertheless, starting from initial conditions $x(\theta) = 1$ for all $\theta \in [-1\ ,\ 0]$, the simulations show convergence to the positive equilibrium, see Figure 4.

B. Example 2

In this example we have $L = 0.985$ and $\beta_o = 7$, $N = 3$, $\delta = 2.1$, $\tau = 2.812$, $\gamma = 0.095$, $m = 1$. For these parameters we compute that $\alpha = 0.6339$, $x_e = 1.0363$, $\mu = -1.9222$,

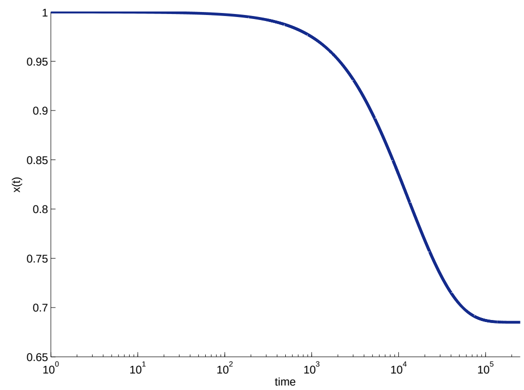

Fig. 4. Simulation results for Example 1.

$x_\ell = 0.5924$, $\widetilde{\rho} = 2.2429$, $k_{\max} = 6.194$, $\widetilde{K}_G = 1.6607$. In this case local stability condition is not satisfied. As shown in the time response Figure 5, $x(t)$ does not converge.

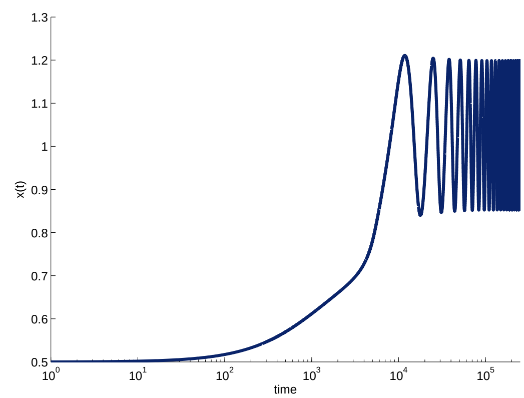

Fig. 5. Simulation results for Example 2.

V. Concluding Remarks

For the compartmental model of [1], local stability conditions were derived in earlier papers, [9], [10]. In this paper we considered the first compartment and applied the circle and Popov criteria for absolute stability. An extension of these results to the full compartmental system is possible: in this case one needs to use the present results on the first compartment along with the results of [6] where non-zero external input is allowed in the stability criterion.

A global stability result can also be obtained using the nonlinear small-gain arguments. We will report our results on this approach elsewhere, see [11].

Acknowledgments

The authors would like to thank Prof. V. Rasvan for pointing out important early references on the subject. They would also acknowledge fruitful discussions with Prof. J. P. Marie on justifications of the mathematical model considered.

References

[1] Adimy, M., Crauste, F., El Abdllaoui, A., "Discrete maturity-structured model of cell differentiation with applications to acute myelogenous leukemia", *J. Biological Systems*, vol. 16 No. 3 (2008), pp. 395–424.

[2] Adimy, M., Crauste, F., Ruan, S., "A Mathematical Study of the Hematopoiesis Process with Applications to Chronic Myelogenous Leukemia," *SIAM J. Appl. Math.*, vol. 65 (2005), pp. 1328–1352.

[3] Bliman, P-A., "Extension of Popov Absolute Stability Criterion to Nonautonomous Systems with Delays", INRIA Technical Report No. 3625, February 1999.

[4] Bliman, P-A., "Robust Absolute Stability of Delay Systems," in *Nonlinear Control in the Year 2000*, A. Isidori, F. Lamnabhi-Lagarrigue, W. Respondek, eds., LNCIS vol. 258, Springer Verlag, 2000, pp. 207–237.

[5] Corduneanu, C., *Integral Equations and Stability of Feedback Systems*, Academic Press, New York, 1973.

[6] Curtain, R.F., Logemann, H., Staffans, O., "Stability Results of Popov-Type for Infinite-Dimensional Systems with Applications to Integral Control," *Proc. London Math. Soc.*, (3) 86 (2003), pp. 779–816.

[7] Halanay, A., *Differential Equations, Stability, Oscillations, Time Lags*, (in Romanian), Editura Academiei R.P.R., Bucharest, 1963 (English version by Academic Press, 1966).

[8] Niculescu, S-I., Ionescu, V., Ivanescu, D., Dugard, L., Dion, J-M., "On Generalized Popov Theory for Delay Systems," *Kybernetica* vol. 36 (2000), pp. 2–20.

[9] Özbay, H., Bonnet, C., Clairambault, J., "Stability Analysis of Systems with Distributed Delays and Application to Hematopoietic Cell Maturation Dynamics," in *Proc. of the 47th IEEE Conference on Decision and Control*, Cancun, Mexico, December 2008, pp. 2050-2055.

[10] Özbay, H., Benjelloun, H., Bonnet, C., Clairambault, J., "Stability Conditions for a System Modeling Cell Dynamics in Leukemia," to appear in the *Proc. of the 9th IFAC Workshop on Time Delay Systems, TDS2010*, Prague, Czech Republic, June 2010.

[11] Özbay, H., Bonnet, C., Benjelloun, H., Clairambault, J., "Global Stability Analysis of a System Modelling Cell Dynamics in AML" to be presented at *the Thirds Conference on Computational and Mathematical Population Dynamics, CMPD-3*, Bordeaux, France, May-June 2010.

[12] Popov, V.M., Halanay, A., "On stability for nonlinear systems with time delay," (in Russian), *Automat. i Telemekhanika*, vol. 23, no. 7, pp. 849-851, 1962.

[13] Răsvan, V., *Absolute Stability of Time Lag Control Systems*, (in Romanian) Editura Academiei, R.S.R., Bucharest, 1975 (Russian version by Nauka, Moscow, 1983).