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Global Stability Analysis of Healthy Situation for a Coupled Model of Healthy and Cancerous Cells Dynamics in Acute Myeloid Leukemia [*]

Abdelhafid Zenati, Messaoud Chakir, Mohamed Tadjine

[*] Laboratory of Process Control **LCP** and Department of Control
Engineering, National Polytechnic School **ENP** of Algiers. 10, St
Hacen Badi El Harrach, Algiers, ALGERIA.
e-mail: abou.alielrida.zenati@gmail.com

Abstract: In this paper we aim to study the global stability of a coupled model of healthy and cancerous cells dynamics in healthy situation of Acute Myeloid Leukemia. We also clarify the effect of interconnection between healthy and cancerous cells dynamics on the global stability. The interconnected model is obtained by transforming the PDE-based model into a nonlinear distributed delay system. Using Lyapunov approach, we derive necessary and sufficient conditions for global stability for a selected equilibrium point of particular interest (healthy situation). Simulations are conducted to illustrate the obtained results.

Keywords: Leukemia, Distributed Delay, Modelling, Global stability, PDE.

1. INTRODUCTION

The mathematical formulations of biomedical problems are an important phase to understand and predict the behavior of the controlled organism. It can identify mechanisms that control the progression of a disease, or motivate and guide future experimental and clinical designs. The combination of mathematical models, experiments, and clinical trials can lead to significant improvements in the treatment of leukemia and lymphoma; see G. Clapp and D. Levy (2014).

Hematopoiesis is the process of blood cell production trough a multi-stage sytem starting in the bone marrow by hematopoiteic stem cells (HSCs). At the first level, HSCs can proliferate, self renew and differentiate into multiple lineages. The process of cell division, called proliferation or cell cycle, consists of four phases: G_1, S, G_2, and M. At the end of the M phase cell division occurs resulting two types of daughter cells: either with the same maturity as the parent or with a higher level of maturity through a differentiation process. Finally, several stages down, fully differentiated cells are released in blood circulation. One of the first mathematical models, a set of differential equations, describing haematopoietic stem cell dynamics was proposed by Mackey (1978). It considered a rest (or quiescent) phase and a proliferative phase during the cell division cycle. More recent studies of various dynamical models of hematopoiesis have been proposed and studied in the literature as in Adimy et al. (2008), Dingli and Pacheco (2010), Foley and Mackey (2009), Niculescu et al. (2010).

Acute Myeloid Leukemia (AML) combines at least two molecular events: a blockade of maturation and differentiation leading to the accumulation of immature myeloid cells, and an advantage of proliferation leading to the flooding of bone marrow by a large number of immature cells as described in Avila et al. (2014, B), where a system of delay differential equations inspired by the model of Adimy et al. (2008) with discrete maturity structure, has been proposed as a model that takes into account the differentiation blockade constantly observed in AML. From the biological and medical point of view, the healthy situation may be defined by a stable equilibrium representing the extinction of cancerous cells with positive value for healthy cells; see J. L. Avila et al. (2014, B). The aim of such a modelling is to yield conditions that make biological and medical sense ensuring a disease-free state for hematopoiesis in the bone marrow. For the equilibrium and stability analysis (linear and nonlinear system) of this model, see J. L. Avila et al.(2012) , J. L. Avila et al. (2014, A-B). and the references therein.

In J. L. Avila et al. (2014, B), a coupled model for healthy and cancerous cell dynamics in Acute Myeloid Leukemia is proposed and local stability results are obtained for the distributed delay model. Furthermore, a Lyapunov approach is used to derive sufficient conditions for boundedness of this distributed delay model in J. L. Avila et al. (2014, A).

In this paper, we address the problem of global stability analysis based on the coupled model proposed in J. L. Avila et al. (2014, B). We first derive necessary and sufficient conditions that guarantee a globally stable trivial solution for the system of cancerous cells taking into account the interconnection between healthy and cancerous cells

populations. This provides a global characterization of the stability conditions compared to J.L. Avila et al. (2014, A), where cells populations interconnection wasn't considered. Then, we manage to obtain conditions that guarantee the global stability of the healthy situation and show how it is affected by interconnection between healthy and cancerous cells. Since they give global asymptotic stability conditions and are system-parameter free, the obtained results would be of a certain importance compared to the study of the local stability presented in J. L. Avila et al. (2014, B) and the sufficient conditions for boundedness obtained in J. L. Avila et al. (2014, A). Furthermore, we try to give biological explanations to them.

The structure of this paper is as follows. Section 2 provides an exposition of the state space equations of the coupled model for healthy and cancerous cells dynamics in Acute Myeloid Leukemia. Section 3 is devoted to the global stability analysis of the system. Moreover, a detailed academic example is presented in Section 4. Finally, in Section 5, some concluding remarks are outlined.

Notation and preliminaries: The functions and variables needed to read the next equations (1) have the following properties and biological meaning: the death rates δ and $\bar{\delta}$ satisfy $\delta > 0$ and $\bar{\delta} > 0$, γ and $\bar{\gamma}$ are constant death rates in the proliferation phases of cancerous and healthy cells, respectively; the amount of time spent in the proliferations phases is $\bar{\tau}$ for healthy cells and τ for cancerous cells; and the division rates of the proliferation phase is a function depending on age a, denoted by $\bar{g}(a)$ for healthy cells and $g(a)$ for cancerous cells. $x_c(t)$ and $x_{cf}(t)$ stand for the total population of resting and fast-self renewing cells at time t, respectively. Moreover, the total population of resting healthy cells at time t is denoted by $x_h(t)$, The re-introduction terms β, $\bar{\beta}$ and $\tilde{\beta}$ are differentiable, non-negative and uniformly decreasing functions. Such that $\lim_{\theta \to +\infty} \beta(\theta) = 0$, $\lim_{\theta \to +\infty} \tilde{\beta}(\theta) = 0$ and $\lim_{\theta \to +\infty} \bar{\beta}(\theta) = 0$.

2. MATHEMATICAL MODEL OF A HEALTHY AND CANCEROUS CELLS COUPLED POPULATION

The total population densities $x_c(t)$, $x_{cf}(t)$ and $x_h(t)$ are described by the following time-delay system, see J. L. Avila et al. (2014),

$$\begin{cases} \dot{x}_c(t) = -(\delta + \beta(z(t)))x_c(t) + L\,(h * \omega_c)\,(t), \\ \dot{x}_{cf}(t) = -\tilde{\beta}(x_{cf}(t))x_{cf}(t) + \tilde{L}\,(h * \omega_c)\,(t), \\ \dot{x}_h(t) = -(\bar{\delta} + \bar{\beta}(z(t)))x_h(t) + \bar{L}\,(\bar{h} * \omega_h)\,(t). \end{cases} \quad (1)$$

where $\omega_c(t) = \beta(z(t))x_c(t) + \tilde{\beta}(x_{cf}(t))x_{cf}(t)$, $\omega_h(t) = \bar{\beta}(z(t))x_h(t)$, the healthy and cancerous cells are interconnected by means of the common feedback of resting cells $z(t) = x_c(t) + x_h(t)$ on the functions β and $\bar{\beta}$. The symbol $*$ stands for the usual convolution operator. Also, we define

$$L = 2\sigma(1 - K), \quad \tilde{L} = 2(1 - \sigma)(1 - K), \quad \bar{L} = 2(1 - \bar{K}).$$

The constants $\bar{K}$, and K represent the probability of differentiation of daughter cells so that $0 \le \bar{K} \le 1$ and $0 \le K \le 1$. The constant σ represents the probability of fast self-renewal with $0 < \sigma < 1$.
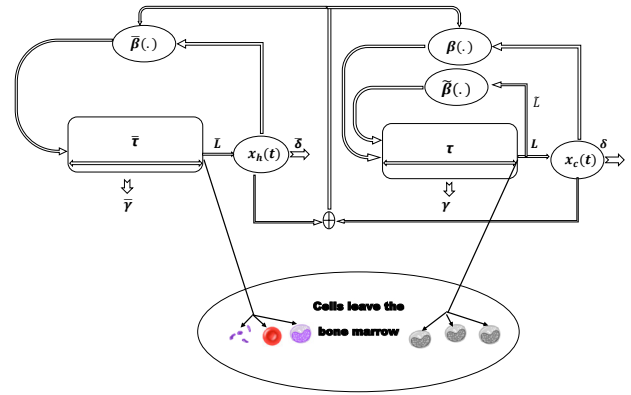

Fig. 1. Interconnected model of healthy cells (left) and cancer cells (right)

$h(t)$ and $\bar{h}(t)$ are the division rates of cancerous and healthy cells, respectively.

As in J. L. Avila et al. (2014, B), we will consider the following general form for the division rates $h(t)$ and $\bar{h}(t)$

$$\begin{cases} h(t) = f(t)e^{-\gamma t} & for \ 0 \le t \le \tau, \\ \bar{h}(t) = \bar{f}(t)e^{-\bar{\gamma} t} & for \ 0 \le t \le \bar{\tau}. \end{cases} \quad (2)$$

where

$$\begin{cases} f(t) = \dfrac{m}{e^{m\tau} - 1}e^{mt} & for \ 0 \le t \le \tau, \\ \bar{f}(t) = \dfrac{\bar{m}}{e^{\bar{m}\bar{\tau}} - 1}e^{\bar{m}t} & for \ 0 \le t \le \bar{\tau}. \end{cases}$$

$f(t)$ and $\bar{f}(t)$ are density functions describing the mitosis and are such that $\int_0^\tau f(a)\,da = 1$ and $\int_0^{\bar{\tau}} \bar{f}(t)(a)\,da = 1$. This gives

$$\begin{cases} H(s) = \displaystyle\int_0^\tau h(t)e^{-st}\,dt = \Theta\left(\dfrac{1 - e^{-\tau(s-\rho)}}{s - \rho}\right), \\ \bar{H}(s) = \displaystyle\int_0^{\bar{\tau}} \bar{h}(t)e^{-st}\,dt = \bar{\Theta}\left(\dfrac{1 - e^{-\bar{\tau}(s-\bar{\rho})}}{s - \bar{\rho}}\right). \end{cases} \quad (3)$$

with $\Theta := \frac{m}{e^{m\tau}-1}$, $\rho := m - \gamma$, $\bar{\Theta} := \frac{\bar{m}}{e^{\bar{m}\bar{\tau}}-1}$, $\bar{\rho} := \bar{m} - \bar{\gamma}$. With

$$H(s) = \int_0^\tau h(t)\exp(-st)\,dt, \bar{H}(s) = \int_0^{\bar{\tau}} \bar{h}(t)\exp(-st)\,dt.$$

Furthermore, we introduce for later use the following parameters:

$$H(0) = \int_0^\tau h(\ell)\,d\ell, \quad (4)$$

$$\bar{H}(0) = \int_0^{\bar{\tau}} \bar{h}(\ell)\,d\ell, \quad (5)$$

$$\alpha = (L + \tilde{L})H(0) - 1, \quad (6)$$

$$\bar{\alpha} = \bar{L}\bar{H}(0) - 1. \quad (7)$$

In next section, we analyze the global stability conditions of coupled healthy and cancerous cells dynamics in AML

defined by equations (1). This study brings out new results improving those presented in J. L. Avila et al. (2014, B) which covered only local stability conditions. In addition, unlike boundedness conditions proposed in J. L. Avila et al. (2014, A), it gives the exact stability conditions of equilibrium points.

3. GLOBAL STABILITY ANALYSIS OF HEALTHY SITUATION

Let us denote by x_c^e, x_{cf}^e, and x_h^e the equilibrium points of (1). Clearly, the origin is an equilibrium of this nonlinear system. Biologically, convergence to this point means the extinction of all cells. The perturbations affecting cancer cells system's origin may provoke the born of cancer cells, see J. L. Avila et al. (2014, A). On the other hand, the perturbation of the equilibrium point of the healthy situation $(0, 0, x_h^e > 0)$ may provoke the born of cancer cells and the death of healthy cells, see J. L. Avila et al. (2014, A) and J. L. Avila et al. (2014, B). This is the reason why the stability analysis is performed around these equilibrium points.

The conditions bellow are necessary for the existence of positive equilibrium points, see J. L. Avila et al. (2014, B):
For cancerous cells ($x_c^e > 0$ and $x_{cf}^e > 0$)

$$\beta(0) > \frac{(1 - \tilde{L}H(0))}{\alpha}\delta; \quad \alpha > 0; \quad 1 - \tilde{L}H(0) > 0,$$

and for healthy cells ($x_h^e > 0$)

$$\bar{\beta}(0) > \frac{\bar{\delta}}{\bar{\alpha}}; \quad \bar{\alpha} > 0,$$

where $H(0)$, $\bar{H}(0)$, α and $\bar{\alpha}$ are the constant defined in (4), (5), (6) and (7), respectively.

The following theorem has a great importance since it gives new results that have not been developed before.

Theorem 1. Lets consider a positive equilibrium point in healthy situation i.e. $x_c^e = 0$, $x_{cf}^e = 0$ and $x_h^e > 0$ for system (1), then the system is globally stable around the equilibrium point. if and only if:
We have $\tilde{L}H(0) - 1 < 0$ and exculsively one of the following

$$\alpha \leq 0 \qquad (8)$$

or

$$\beta(0) \leq \frac{1 - \tilde{L}H(0)}{\alpha}\delta \qquad (9)$$

or

$$\bar{\beta}^{-1}(\frac{\bar{\delta}}{\bar{\alpha}}) > \beta^{-1}(\frac{(1 - \tilde{L}H(0))\delta}{\alpha}) \qquad (10)$$

with $\bar{\beta}^{-1}(.)$ and $\beta^{-1}(.)$ are inverse functions of $\bar{\beta}(.)$ and $\beta(.)$, respectively.

Proof. case 1: If $\tilde{L}H(0) - 1 < 0$ and $\alpha \leq 0$ then $x_c(t)$ and $x_{cf}(t)$ converge to zero.
Let us introduce for all $x_h(t)$ the functional

$$\Phi(t) = \int_{t-\tau}^{t} \int_{\theta}^{t} h(\theta - a + \tau)\omega_c(a) \, da \, d\theta. \qquad (11)$$

with

$$\omega_c(t)) = \beta(x_c(t) + x_h(t))x_c(t) + \tilde{\beta}(x_{cf}(t))x_{cf}(t). \qquad (12)$$

Simple calculations give:

$$\dot{\Phi}(t) = \int_{t-\tau}^{t} h(\theta - t + \tau)\omega_c(t) \, d\theta - \int_{t-\tau}^{t} h(t - a)\omega_c(a) \, da.$$

Now, Let us introduce a lypunov fonction:

$$V(t) = x_c(t) + x_{cf}(t) + (L + \tilde{L})\Phi(t). \qquad (13)$$

Then its derivative along the trajectories of $x_c(t)$ and $x_{cf}(t)$ satisfies

$$\dot{V}(t) = \dot{x}_c(t) + \dot{x}_{cf}(t) + (L + \tilde{L})H(0)\omega_c(t)$$
$$- (L + \tilde{L}) \int_{t-\tau}^{t} h(t - a)\omega_c(a) \, da. \qquad (14)$$

By replacing $\dot{x}_c(t)$ and $\dot{x}_{cf}(t)$ with their expressions, we find:

$$\dot{V}(t) = -\omega_c(t) - \delta x_c(t) + (L + \tilde{L})H(0)\omega_c(t). \qquad (15)$$

Next, we consider the case where $\alpha < 0$ and we show that $x_c(t)$ and $x_{cf}(t)$ are globally asymptotically stable. We consider a positive solution of $x_c(t)$ and $x_{cf}(t)$ and since $\delta x(t) \geq 0$ we get

$$\dot{V}(t) \leq \alpha \omega_c(t). \qquad (16)$$

By integrating this inequality, we get, for all $t \geq 0$;

$$V(t) - V(0) \leq \alpha \int_{0}^{t} \omega_c(\ell) \, d\ell. \qquad (17)$$

Since $V(t) > 0$ for all $t \geq 0$ and $\alpha \neq 0$, it follows that

$$\int_{0}^{t} \omega_c(\ell) \, d\ell \leq \frac{V(0)}{\alpha}. \qquad (18)$$

Moroever, the inequality $V(t) \geq x_c(t) + x_{cf}(t)$ and (16) imply that $x_c(t)$, $x_{cf}(t)$ and $\omega_c(t)$ are bounded. Then from (18) and *Barbalat's* lemma (see F.Mazenc and M.Malisoff (2009)), we deduce that:

$$\lim_{t \to +\infty} \omega_c(t) = 0. \qquad (19)$$

This implies that:

$$\lim_{t \to +\infty} x_c(t) = 0. \quad and \quad \lim_{t \to +\infty} x_{cf}(t) = 0. \qquad (20)$$

.

Now, if $\alpha = 0$, we have $V(t) \geq 0$ is Lyapunov functional positive definite and $\dot{V}(t) = -\delta x_c(t)$ is negative semidefinite. To find

$$S = \{(x_c, x_{cf}) \in \mathbf{R}_+^2 \mid \dot{V}(t) = 0 \} \qquad (21)$$

notice that

$$\dot{V}(t) = 0 \Longrightarrow \delta x_c(t) = 0 \Longrightarrow x_c(t) = 0. \tag{22}$$

Hence,

$$S = \{(x_c, x_{cf}) \in \mathbf{R}_+^2 \quad | \quad x_c(t) = 0 \quad\} \tag{23}$$

Let x_{cf} be a solution that belongs identically to S:

$$x_c(t) = 0 \Longrightarrow \dot{x}_c(t) = 0 \Longrightarrow x_{cf}(t) = 0. \tag{24}$$

Therefore, the only solution that can stay identically in S is the trivial solution $x_{cf}(t) = 0$. Thus, from LaSalle's invariance principle theorem (see Jinhuan Wang et al. (2008)), we conclude that:

$$\lim_{t \to +\infty} (x_c(t), \ x_{cf}(t)) = (0, 0) \tag{25}$$

case 2: If $\alpha > 0$, $\tilde{L}H(0) - 1 < 0$ and $\beta(0) \le \frac{1 - \tilde{L}H(0)}{\alpha}\delta$ then $x_c(t)$ and $x_{c,f}(t)$ converge to zero.

Now, we consider the case where $\alpha > 0$ and $\tilde{L}H(0) - 1 < 0$. Then we define the Lyapunov functional $\Lambda(t) \in \mathbb{R}_+$:

$$\Lambda(t) = \frac{1 - \tilde{L}H(0)}{\alpha}V(t) + x_{cf}(t) + \tilde{L}\Phi(t) \tag{26}$$

Simple calculations give:

$$\dot{\Lambda}(t) = (\beta(z(t)) - \frac{1 - \tilde{L}H(0)}{\alpha}\delta)x_c(t) \tag{27}$$

Thus, if

$$\beta(0) \le \frac{1 - \tilde{L}H(0)}{\alpha}\delta \tag{28}$$

By using the decreasing property of the function β, we deduce that $\dot{\Lambda}(t) < 0$. Thus, $x_c(t)$ and $x_{cf}(t)$ admit the origin as a globally asymptotically stable equilibrium point.

If we have $\alpha > 0$ and $\tilde{L}H(0) - 1 \ge 0$ then we define the Lyapunov functional $\Upsilon(t) \in \mathbb{R}_+$:

$$\Upsilon(t) = x_{cf}(t) + \tilde{L}\Phi(t) \tag{29}$$

Simple calculations give:

$$\dot{\Upsilon}(t) = \tilde{L}H(0)\omega_c(t) - \tilde{\beta}(x_{c,f}(t)) \ge (\tilde{L}H(0) - 1)\omega_c(t).$$

we have

(1) $\Upsilon(t) = 0 \Longleftrightarrow x_c(t) = 0$ and $x_{cf}(t) = 0$;

(2) $\Upsilon(t) > 0$ and $\dot{\Upsilon}(t) > 0$ for all $x_c(t) > 0$ and $x_{cf}(t) > 0$;

This allows us to conclude from Lyapunov Instability Theorem (see H. Khalil (1996) and Cristian Carcamo and Claudio Vidal (2009)) , that The system of the cancerous cells has the origin unstable if $\tilde{L}H(0) - 1 \ge 0$.

Next, Let us introduce for all $x_c(t)$ the functional

$$\bar{\xi}(t) = \int_{t-\bar{\tau}}^{t} \int_{\theta}^{t} \bar{h}(\theta - a + \bar{\tau})\bar{\beta}(z(a))x_h(a) \, da \, d\theta. \tag{30}$$

Simple calculations give:

$$\dot{\bar{\xi}}(t) = \int_{t-\bar{\tau}}^{t} \bar{h}(\theta - t + \bar{\tau})\bar{\beta}(x_h(t) + x_c(t))x_h(t) \, d\theta$$
$$- \int_{t-\bar{\tau}}^{t} \bar{h}(t - a)\bar{\beta}(x_h(a) + x_c(a))x_h(a) \, da.$$

Now, Let us introduce a lyapunov functional:

$$\bar{\varsigma}(t) = x_h(t) + \bar{L}\bar{\xi}(t). \tag{31}$$

Then its derivative along the trajectories of $x_h(t)$ satisfies

$$\dot{\bar{\varsigma}}(t) = (-\bar{\delta} + \bar{\alpha}\bar{\beta}(x_h(t) + x_c(t)))x_h(t). \tag{32}$$

where $\bar{\alpha}$ is the constant defined in (7).

It is clear that if $\bar{\alpha} \le 0$ or $\bar{\alpha} > 0$ and $\bar{\beta}(0) \le \frac{\bar{\delta}}{\bar{\alpha}}$ we have $\dot{\bar{\varsigma}}(t) \le 0$

We deduce easily from *Barbalat's* lamma that

$$\lim_{t \to +\infty} x_h(t) = 0. \tag{33}$$

Now, consider **case 1** or **case 2** where $(x_c(t), \ x_{cf}(t))$ converges to zero $(0, \ 0)$ and the necessary conditions for the existence of positive equilibrium points for healthy cells $\bar{\alpha} > 0$ and $\bar{\beta}(0) > \frac{\bar{\delta}}{\bar{\alpha}}$. Then, let $t_c > 0$ be the necessary time for $x_c(t)$ to converges to zero.
It is clear that for all $t \ge t_c$

$$\dot{\bar{\varsigma}}(t) = [-\bar{\delta} + \bar{\alpha}\bar{\beta}(x_h(t))]x_h(t). \tag{34}$$

This implies that:

- If $x_h(t) > x_h^e$ then $\dot{\bar{\varsigma}}(t) < 0$.

- If $x_h(t) < x_h^e$ then $\dot{\bar{\varsigma}}(t) > 0$

- If $x_h(t) = x_h^e$ then $\dot{\bar{\varsigma}}(t) = 0$

And allows us to deduce

$$\lim_{t \to +\infty} (x_c(t), x_{c,f}(t), x_h(t)) = (0, 0, x_h(t) > 0) \tag{35}$$

case 3: If $\alpha > 0$, $\tilde{L}H(0) - 1 < 0$, $\beta(0) > \frac{1 - \tilde{L}H(0)}{\alpha}\delta$ and $\bar{\beta}^{-1}(\frac{\bar{\delta}}{\bar{\alpha}}) > \beta^{-1}(\frac{1 - \tilde{L}H(0)}{\alpha}\delta)$ then $(x_c(t), x_{c,f}(t), x_h(t))$ converge to $(0, 0, x_h(t) > 0)$

To illustrate the effect of the interconnection between healthy and cancerous populations on cellular dynamics, let us introduce the functional

$$\chi(t) = \bar{\varsigma}(t) + \Lambda(t) \tag{36}$$

where $\Lambda(t)$ and $\bar{\zeta}(t)$ are the functionals defined in (25) and (31), respectively.
Using (26) and (32), we obtain

$$\begin{cases} \dot{\chi}(t) = \dot{\bar{\varsigma}}(t) + \dot{\Lambda}(t) \\ \dot{\bar{\varsigma}}(t) = (-\bar{\delta} + \bar{\alpha}\bar{\beta}(z(t)))x_h(t) \\ \dot{\Lambda}(t) = (\beta(z(t)) - \frac{1 - \tilde{L}H(0)}{\alpha}\delta)x_c(t) \end{cases} \tag{37}$$

It is clear that the signs of $\dot{\bar{\varsigma}}(t)$ and $\dot{\Lambda}(t)$ depend on $z(t)$. Now, we consider the case where necessary conditions for

the existence of positive equilibrium points are satisfied. Since the functions β and $\bar{\beta}$ are decreasing, we have:

$$\begin{cases} z(t) = \bar{\beta}^{-1}(\dfrac{\bar{\delta}}{\bar{\alpha}}) \Longrightarrow \dot{\varsigma}(t) = 0 \\ z(t) > \bar{\beta}^{-1}(\dfrac{\bar{\delta}}{\bar{\alpha}}) \Longrightarrow \dot{\varsigma}(t) < 0 \\ z(t) < \bar{\beta}^{-1}(\dfrac{\bar{\delta}}{\bar{\alpha}}) \Longrightarrow \dot{\varsigma}(t) > 0 \end{cases} \qquad (38)$$

Also,

$$\begin{cases} z(t) = \beta^{-1}(\dfrac{1 - \tilde{L}H(0)}{\alpha}\delta) \Longrightarrow \dot{\Lambda}(t) = 0 \\ z(t) > \beta^{-1}(\dfrac{1 - \tilde{L}H(0)}{\alpha}\delta) \Longrightarrow \dot{\Lambda}(t) < 0 \\ z(t) < \beta^{-1}(\dfrac{1 - \tilde{L}H(0)}{\alpha}\delta) \Longrightarrow \dot{\Lambda}(t) > 0 \end{cases} \qquad (39)$$

We deduce easily that, $\exists \eta \in \mathbb{R}_+^*$, such that:

$$\begin{cases} z(t) = \eta \Longrightarrow \dot{\chi}(t) = 0 \\ z(t) > \eta \Longrightarrow \dot{\chi}(t) < 0 \\ z(t) < \eta \Longrightarrow \dot{\chi}(t) > 0 \end{cases} \qquad (40)$$

This allows us to conclude that:

$$\lim_{t \to +\infty} z(t) = \eta. \qquad (41)$$

Thus, we distinguish three different cases:

- If $\bar{\beta}^{-1}(\frac{\bar{\delta}}{\bar{\alpha}}) > \beta^{-1}(\frac{1-\tilde{L}H(0)}{\alpha}\delta)$ then

$$\bar{\beta}^{-1}(\dfrac{\bar{\delta}}{\bar{\alpha}}) > \eta > \beta^{-1}(\dfrac{1 - \tilde{L}H(0)}{\alpha}\delta) \qquad (42)$$

also,

$$\begin{cases} z(t) = \eta \Longrightarrow \dot{\Lambda}(t) < 0, \quad \dot{\varsigma}(t) > 0 \\ \bar{\beta}^{-1}(\dfrac{\bar{\delta}}{\bar{\alpha}}) > z(t) > \eta \Longrightarrow \dot{\Lambda}(t) < 0, \quad \dot{\varsigma}(t) > 0 \\ \beta^{-1}(\dfrac{1 - \tilde{L}H(0)}{\alpha}\delta) < z(t) < \eta \Longrightarrow \dot{\Lambda}(t) < 0, \quad \dot{\varsigma}(t) > 0 \\ \beta^{-1}(\dfrac{1 - \tilde{L}H(0)}{\alpha}\delta) > z(t) \Longrightarrow \dot{\Lambda}(t) > 0, \quad \dot{\varsigma}(t) > 0 \\ \bar{\beta}^{-1}(\dfrac{\bar{\delta}}{\bar{\alpha}}) < z(t) \Longrightarrow \dot{\Lambda}(t) < 0, \quad \dot{\varsigma}(t) < 0 \end{cases}$$

This allows us to conclude for this case that:

$$\lim_{t \to +\infty} (x_c(t), \ x_{cf}(t), \ x_h(t)) = (0, 0, \ x_h(t) > 0). \qquad (43)$$

By using the same above development, we can prove that: the healthy situation is not stable for the cases :
- $\bar{\beta}^{-1}(\frac{\bar{\delta}}{\bar{\alpha}}) < \beta^{-1}(\frac{1-\tilde{L}H(0)}{\alpha}\delta)$,
- $\bar{\beta}^{-1}(\frac{\bar{\delta}}{\bar{\alpha}}) = \beta^{-1}(\frac{1-\tilde{L}H(0)}{\alpha}\delta)$.

Remarks:

- This result would be of a certain importance in the treatment of this type of cancer. Let us now interpret this result relative to therapy of AML. The coefficient $\tilde{L}$ models the effect of a new anti-proliferative drug (an inhibitor of Flt-3 receptors) that specifically acts on fast cell renewal dynamics, see B. Douglas Smith et al. (2004)and J. L. Avila et al. (2014, A).

- The obtained result brings some suggestions in the treatment of AML and has not been developed in previous researches. It allows us to propose a new treatment approach for this type of cancer interpreted as follows: According to relation (10) that represents the effect of interconnection between healthy and cancerous cell dynamics, and in order to eliminate cancerous cells, we can develop a new drug which acts specifically on the interconnection between healthy and cancerous cells.
- Biologically, this result clearly explains the hematopoiesis phenomenon and how the biological system makes the number of cells in a biologically acceptable range, see Eric M. Pietras and Matthew R. Warr (2011). Thus, if the number of cells is more or less than the equilibrium point, the system will work to return it to a *positive steady state*.

4. NUMERICAL EXAMPLES AND SIMULATION RESULTS

Consider a system with $H(0) = 1$, $\bar{H}(0) = 1$, $\beta(z(t)) = \frac{\beta(0)}{1 + z(t)^3}$, $\bar{\beta}(z(t)) = \frac{\bar{\beta}(0)}{1 + z(t)^3}$ and the parameters indicated in the tables bellow.

Example 1. see **Table 1**. It can be verified that with the

Table 1. Simulation parameters.

δ	$\beta(0)$	L	$\tilde{\beta}(0)$	$\tilde{L}$	$\bar{\delta}$	$\bar{\beta}(0)$	$\bar{L}$
0.2	1	0.35	12	0.6	0.02	1	1.2

parameters in Table 1 the global stability conditions (9) are satisfied,

$$\alpha = 0.01 > 0; \quad \bar{\alpha} = 0.002 > 0; \quad \bar{\beta}(0) = 1 > \frac{\bar{\delta}}{\bar{\alpha}} = 0.1;$$

$$\beta(0) = 1 < \frac{1 - \tilde{L}H(0)}{\alpha}\delta = 10.$$

For this example, time domain simulation, showed that the states $x_c(t)$ and $x_{cf}(t)$ converge to the origin, and the state $x_h(t)$ converges to $x_{h^e} > 0$, see Figure 2.

To complete the above numerical study we also illustrate the effect of the interconnection between healthy and cancerous cells on the cellular population dynamics. The other parameters as indicated in **Example 2**.

Example 2. see **Table 2**.
Indeed, it can be verified that with the parameters in

Table 2. Simulation parameters.

δ	$\beta(0)$	L	$\tilde{\beta}(0)$	$\tilde{L}$	$\bar{\delta}$	$\bar{\beta}(0)$	$\bar{L}$
0.1	1	0.8	12	0.6	0.2	1	1.2

Table 2 that the global stability conditions (10) hold.

$$\bar{\beta}^{-1}(\frac{\bar{\delta}}{\bar{\alpha}}) > \beta^{-1}(\frac{(1 - \tilde{L}H(0))\delta}{\alpha}).$$
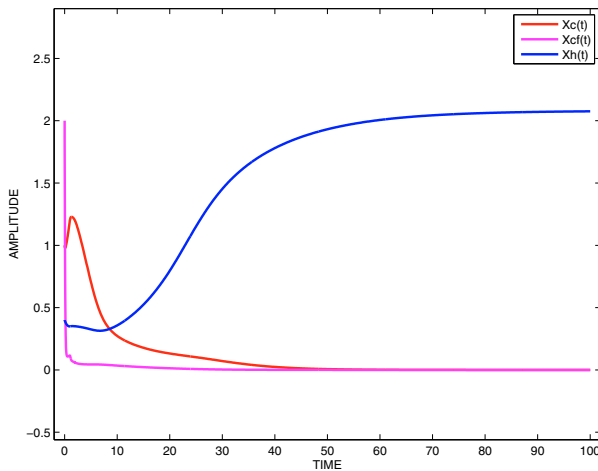
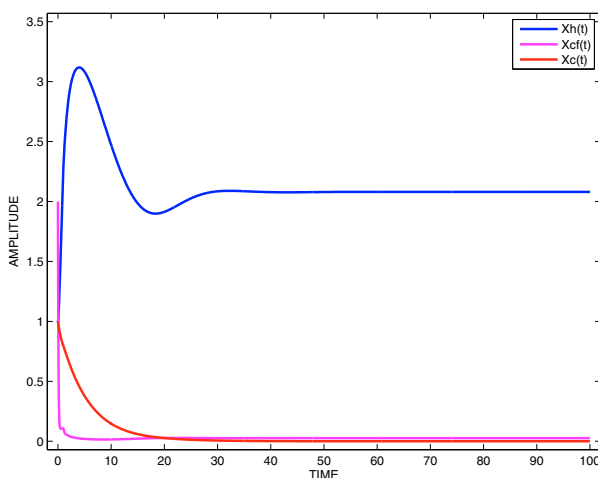Fig. 2. Trajectories of the states $x_c(t)$, $x_{cf}(t)$ and $x_h(t)$ (case 1 of the healthy situation)

Fig. 3. Trajectories of the states $x_c(t)$, $x_{cf}(t)$ and $x_h(t)$ (case 2 of the healthy situation)

For this example, time domain simulation, showed that the states $(x_c(t);\ x_{cf}(t);\ x_h(t))$ converge to $(x_c^e = 0;\ x_{cf}^e = 0;\ x_h^e > 0)$, see Figure 3.

5. CONCLUSION

We have presented global stability analysis of a coupled healthy and cancerous dynamics model, in healthy situation of Acute Myeloid Leukemia. The first problem we addressed was to establish necessary and sufficient conditions that guarantee a globally stable trivial solution of cancerous cells system. We obtained conditions in terms of biological parameters that ensure global stability, taking into account the interconnection between healthy and cancerous cell dynamics. We conducted simulations to illustrate the effect of such an interconnection on cells dynamics, and to verify that the obtained results have biological explanations, and medically make sense. Lastly, we would like to say that novel results presented in this work, could be an important step forward in studying Acute Leukemia dynamic.

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