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Citation: Zenati, A., Laleg-Kirati, T-M., Chakir, M. & Tadjine, M. (2019). Dynamical Behavior of Biological Healthy Steady State in Leukemia Using a New Leukemic & Healthy Stem Cells Cohabitation Model with Distributed Delay. 2019 American Control Conference (ACC), doi: 10.23919/ACC.2019.8814334 ISSN 0743-1619 doi: 10.23919/ACC.2019.8814334

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Dynamical Behavior of Biological Healthy Steady State in Leukemia Using a New Leukemic & Healthy Stem Cells Cohabitation Model with Distributed Delay

Abdelhafid Zenati, Taous-Meriem Laleg-Kirati, Messaoud Chakir, Mohamed Tadjine

***Abstract*— Acute Myeloid Leukemia (AML) treatment protocol from clinical point of view, aims to maintain a normal amount of healthy cells and to eradicate all malignant cells. This particular objective is biologically qualified as a positive healthy situation. In this paper, we give sufficient and necessary conditions for the global stability of such a healthy situation. To this end, we first propose a new distributed delay model of AML. The latter is an improvement of an existing delayed coupled model describing the dynamics of hematopoesis stem cells in AML. We modify the PDEs equations and transform them into a set of distributed delay equations. The proposed model is more suitable for biological phenomena than constant delay models as the proliferation time differs from a cell type to another. Furthermore in the proposed model, we consider the sub-population of cells that have lost their capacity of self-renewal and became progenitors. In second, we derive sufficient and necessary conditions for the global stability of healthy steady state. For this, the positivity of the obtained model and sequences of functions theory are used to construct new Lyapunov function candidates. Finally, we conduct numerical simulations to show that the obtained results complete and generalize those published in the literature.**

Keywords: Leukemia, New Model, Distributed Delay, Healthy steady state, Global stability.

I. Introduction

The multi-stage operation of blood cell forming begins by hematopoiteic stem cells (SCs) in the bone marrow and produces different mature cell types trough the resting and the proliferating phases [1]. The resting phase G_0 contains the majority of hematopoiteic SCs [2] and the proliferating phase generates cells with different levels of maturity, by means of the cell division cycle. This latter consists of four known phases G_1, S, G_2, and M [2], [3]. Leukemia can be caused by genetic alterations or mutations the affect the control of the division of immature blood cells [4]–[6]. Mutations that corrupt proliferation control are the most interesting like the Flt3-ITD type [7], [8] which causes indefinite proliferation of immature stem cells. The mutated or cancerous cells are in the Hematopoietic tissues with healthy ones and share some aspects with them [9], [10].

Section II of this paper provides a detailed mathematical exposition of an existing leukemic and healthy stem cells coupled model presented in [11] to which we introduce two important modifications that make it more realistic and permit reaching our purpose in this work. The first modification concerns a biological observation that some cells coming from proliferation phase, may become progenitors before their complete differentiation, because of the inhibition of their self-renewal capacity [2], [3]. At the end of proliferation phase, SCs keep their proliferative capacity by generating new cells having at least the same level of maturity [12]. This difference in maturity depends on the time spent in the proliferation phase which differs from a cell type to another. This leads us to the second modification which relates to the PDEs that describe cellular dynamics in proliferation phases and consists in introducing the proliferation rates so as to obtain a distributed delay system. Compared to constant delay models, it is known that distributed delay systems are more appropriate for describing biological processes in particular the proliferation phase. Indeed, as stated in [13], events related to the delay in a real system (such as proliferation time in our case) have a distributed density that is not a delta function.

After the detailed description of the model, we mathematically characterize the global stability of the biological healthy steady state in Section III. Healthy steady state is particularly interesting because it represents theoretically the ideal situation of the organism [14]. Whilst from a practical point of view, it represents a healed status where all malignant cells are eradicated and healthy cells remain; which is the main goal of all leukemia treatment strategies. In other words, it represents an equilibrium point that may cause duplication cancerous cells and disappearance of healthy ones if it is perturbed [15]–[17]. We combine the positivity property of our model and sequences of functions theory to construct a suitable nonquadratic Lyapunov functional. Then we exploit it to derive sufficient and necessary conditions that characterize the global stability of this interesting equilibrium point. In order to validate our claims, we illustrate some results by simulation in Section IV and terminate with some concluding remarks in Section V.

II. Mathematical Description of Improved Model

Consider a population of healthy stem cells (HSCs) and an other population of mutated stem cells, and remember the two main phases of a cell-cycle [18] represented in Fig. 1. $\tilde{\vartheta}(t,a)$ and $\tilde{\mu}(t,a)$ are respectively the densities of proliferating and resting cancerous immature cells. The resting cells either stay waiting to enter proliferation or vanish with a rate $\tilde{\delta}$. The amount of quiescent cells (from $\tilde{G}_0$) that enter proliferation is regulated by a function $\tilde{\beta}$. They divide with a rate $\tilde{\varphi}(a)$ or die with a rate $\tilde{\gamma}$. The maximal age $\tilde{\tau}$ limits the duration of cell division in proliferation phase. An amount $\tilde{L}$ of cells exiting the proliferation phase becomes quiescent, an amount $\hat{L}$ self-renew rapidly (this is specific to cancerous cells), and an other amount $2\tilde{K}$ evolve to higher levels of maturation. $\tilde{L}$ and $\hat{L}$ depend on the occurrence of an Flt3-ITD mutation represented by the probability σ. Introduction of this fast phase is motivated by the availability of anti-proliferative agents that inhibit Flt-3 receptors with different efficiency levels [7], [15]–[17], [19] and [20].

Idem as above, $\vartheta(t,a)$ and $\mu(t,a)$ are respectively the densities of proliferating and resting healthy cells. The other parameters are death rate δ, division rate $\varphi(a)$, proliferating death rate γ and the maximum age τ; in addition to L, the amount of cells that return to resting phase and $2K$ the amount of cells that evolve to higher levels of maturation.

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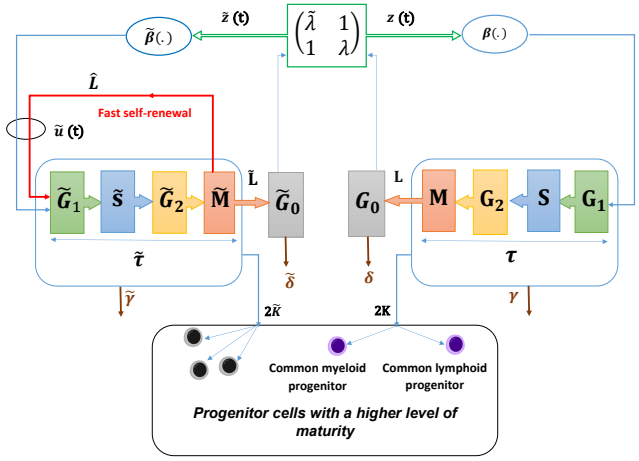

Fig. 1: Improved healthy (on the right) and cancerous (on the left) stem cells coupled model.

It is possible that some mutated cells exist in healthy organisms [21], but since this does not generate relevant neoplastic cell population [14], it is not considered in the model.

These partial differential equations describe the interconnected system : For all $0<a<\tilde{\tau},\ t>0$

$$\begin{aligned}\frac{\partial\tilde{\vartheta}(t,a)}{\partial t}+\frac{\partial\tilde{\vartheta}(t,a)}{\partial a} &= -(\tilde{\gamma}+\tilde{\varphi}(a))\tilde{\vartheta}(t,a),\\ \frac{\partial\vartheta(t,a)}{\partial t}+\frac{\partial\vartheta(t,a)}{\partial a} &= -(\gamma+\varphi(a))\vartheta(t,a).\end{aligned} \tag{1}$$

and for all $a>0,\ t>0$

$$\begin{aligned}\frac{\partial\tilde{\mu}(t,a)}{\partial t}+\frac{\partial\tilde{\mu}(t,a)}{\partial a} &= -(\tilde{\delta}+\tilde{\beta}(\tilde{z}(t)))\tilde{\mu}(t,a),\\ \frac{\partial\mu(t,a)}{\partial t}+\frac{\partial\mu(t,a)}{\partial a} &= -(\delta+\beta(z(t))\mu(t,a).\end{aligned} \tag{2}$$

where normal and cancerous cells are linked through the feedback function $\tilde{z}(t)=\tilde{\lambda}\tilde{x}(t)+x(t)$ and $z(t)=\tilde{x}(t)+\lambda x(t)$ on the functions $\tilde{\beta}$ and β, respectively. The constants $\tilde{\lambda}$ and λ are sensitivity of LSCs and HSCs, respectively.

Due to epi-genetic mutations, LSCs may become less sensitive than HSCs to the regulatory agents excreted by the body and dodging the immune system; HSCs in turn, are not sensitive to immune system action and less sensitive to the treatments, since these treatments are designed to target cancerous cells.(For the biological and medical interpretation of the sensitivity constants $\tilde{\lambda}$ and λ see [22]) . Where

$$\tilde{x}(t)=\int_0^{\infty}\tilde{\mu}(t,a)\,da,\quad x(t)=\int_0^{\infty}\mu(t,a)\,da.$$

stand for the total population of mutated and ordinary stem cells at the time t, respectively.

The proliferation phases of cancerous and healthy cells are represented by $\tilde{\omega}(t)$ and $\omega(t)$ transfer functions respectively. And the associated renewal conditions (new birth rates at a = 0) are introduced through the following boundary conditions:

$$\begin{cases}\tilde{\vartheta}(t,a=0) &= \tilde{\beta}(\tilde{z}(t))\tilde{x}(t)+2(1-\tilde{\sigma})(1-\tilde{K})\\ &\quad\times\int_0^{\tau}\tilde{\omega}(a)\tilde{u}(t-a)\,da=\tilde{u}(t),\\ \vartheta(t,a=0) &= \beta(z(t))x(t)=u(t),\\ \tilde{\mu}(t,a=0) &= 2\tilde{\sigma}(1-\tilde{K})\int_0^{\tilde{\tau}}\tilde{\omega}(a)\tilde{u}(t-a)\,da,\\ \mu(t,a=0) &= 2(1-K)\int_0^{\tau}\omega(a)u(t-a)\,da.\end{cases} \tag{3}$$

Also, we define

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

$\tilde{K}$ and respectively K (such that $0\le\tilde{K}\le 1$ and $0\le K\le 1$) are probability that daughter cancerous and healthy cells differentiate. Also, $\tilde{\sigma}$ $(0<\tilde{\sigma}<1)$ is the probability of fast self-renewal. The method of characteristics gives the following [16], [17],

$$\begin{cases}\tilde{\omega}(t)=e^{-\tilde{\gamma}t}\tilde{\varphi}(t)exp(-\int_0^t\tilde{\varphi}(a)\,da),\\ \omega(t)=e^{-\gamma t}\varphi(t)exp(-\int_0^t\varphi(a)\,da).\end{cases} \tag{4}$$

We complete the mathematical model by the following assumptions [15]–[17]

1) Biological death (aging) is written as:

$$\lim_{a\to+\infty}\tilde{\mu}(t,a)=0,\quad \lim_{a\to+\infty}\mu(t,a)=0,\quad \forall t>0. \tag{5}$$

2) $\tilde{\beta}$ and β or re-introduction terms, in addition to be uniformly decreasing, they are differentiable and non-negative functions of the form

$$\tilde{\beta}(\tilde{z}(t))=\frac{\tilde{\beta}(0)}{1+\tilde{b}[\tilde{z}(t)]^{\tilde{N}}},\ \beta(z(t))=\frac{\beta(0)}{1+b[z(t)]^{N}}.$$

where $\tilde{N}$ and N are integers greater or equal to 2; $\tilde{b}>0$ and $b>0$. These functions are known as Hill functions, [15], [16], [23].

Using characteristic method, we obtain the following nonlinear positive system with distributed delay :

$$\begin{cases}\dot{\tilde{x}}(t) &= -(\tilde{\delta}+\tilde{\beta}(\tilde{z}(t)))\tilde{x}(t)+\tilde{L}\int_0^{\tilde{\tau}}\tilde{\omega}(a)\tilde{u}(t-a)\,da,\\ \tilde{u}(t) &= \tilde{\beta}(\tilde{z}(t))\tilde{x}(t)+\hat{L}\int_0^{\tau}\tilde{\omega}(a)\tilde{u}(t-a)\,da.\\ \dot{x}(t) &= -(\delta+\beta(z(t)))x(t)+L\int_0^{\tau}\omega(a)u(t-a)\,da.\end{cases} \tag{6}$$

where $u(t)=\beta(z(t))x(t)$ and $\tilde{u}(t)$ represent respectively the densities of new proliferating normal and leukemic cells at time $t>0$. As we stated in the introduction, system (6) that we have built is a distributed delay model because the function $\omega(t)$ related to proliferation phase is a distributed density (not a delta function). This would make the model more realistic in representing this particular biological phenomenon of cell proliferation (see [13] for instance) compared to the model we started from.

For later use, we introduce the following parameters:

$$\tilde{\Omega}=\int_0^{\tilde{\tau}}\tilde{\omega}(\ell)\,d\ell, \tag{7}$$

$$\Omega=\int_0^{\tau}\omega(\ell)\,d\ell,, \tag{8}$$

$$\tilde{\alpha}=(\hat{L}+\tilde{L})\tilde{\Omega}-1, \tag{9}$$

$$\bar{\alpha}=L\Omega-1, \tag{10}$$

$$\hat{\alpha}=\hat{L}\tilde{\Omega}-1. \tag{11}$$

Next, we analyze the global stability of the biological healthy steady state based on the improved distributed delay system (6). It was shown as in [16], [17], [24], [25] that a unique piece-wise continuous positive solution $(\tilde{x}(t),\ \tilde{u}(t),\ x(t))$ exists for all $t>0$, when the system (6) is associated with appropriate initial conditions $(\phi_{\tilde{x}},\ \phi_{\tilde{u}},\ \phi_x)$ such that $\phi_{\tilde{x}}\in\mathscr{C}([-\tilde{\tau},\ 0],\mathbb{R}_+)$, $\phi_{\tilde{u}}\in\mathscr{C}([-\tilde{\tau},\ 0])$ and $\phi_x\in\mathscr{C}([-\tau,\ 0],\mathbb{R}_+)$ (i.e. it is a positive system [26]). We use this property to build linear Lyapunov functions and derive the sufficient and necessary conditions which grant global stability for this healthy positive equilibrium point (i.e. the conditions that lead to eradication of all cancerous stem cells and subsistence of normal stem cells when they are satisfied).

III. Global Stability for Biological Healthy Steady State

$\tilde{x}_e$, $\tilde{u}_e$ and x_e denote the equilibrium points of (6). By analogy with [11] the conditions bellow are necessary for the existence of the desired equilibrium points:

For cancerous stem cells (i.e. to have $\tilde{x}_e>0$ and $\tilde{u}_e>0$)

$$\tilde{\beta}(0)>-\frac{\hat{\alpha}}{\tilde{\alpha}}\tilde{\delta};\quad \tilde{\alpha}>0;\quad \hat{\alpha}<0.$$

and for healthy stem cells (i.e. to have $x_e>0$)

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

Clearly, the origin $(\tilde{x}_e=0,\ \tilde{u}_e=0,\ x_e=0)$ is an equilibrium point, but biologically it represents the extinction of all leukemic and non-leukemic SCs. The ideal healthy situation (see [14],zenati-jtb, zenatiiet) is characterized by $(\tilde{x}_e=0,\ \tilde{u}_e=0,\ x_e>0)$. However the perturbations that affect the parameters of (6) may decal this ideal equilibrium point. Biologically this leads to the appearance of LSCs and the death of HSCs [15]–[17]. For this reason we study the stability around this equilibrium point and provide in in Theorem 1 the necessary and sufficient conditions for (6) to converge to it.

From equation of $\tilde{u}(t)$ in (6), we observe that $\lim_{t\to+\infty}\tilde{u}(t)=+\infty$ if $\hat{L}\tilde{\Omega}\geq 1$. This permit us to conclude from the first equation of (6) that $\lim_{t\to+\infty}\tilde{x}(t)=+\infty$. *Biologically, this represents the uncontrollably tumor growing. To avoid this undesirable situation, we use the inverse case (i.e. $\hat{L}\tilde{\Omega}<1$) in the next mathematical analysis.*

A. Building a Lyapunov Functional Candidate

Due to the complex mathematical form of model (6), we need to use adequate Lyapunov function candidates to solve stability issues, especially if we need to generate sufficient and necessary conditions for global stability. The following lemmas are related to the construction and time derivation of a positive function that permits to characterize the dynamics of Leukemic stem cells.

Lemma 1 *Let be a positive sequence $\tilde{\zeta}_n(t)$ of time function given by*

$$\tilde{\zeta}_n(t)=\tilde{x}(t)+\tilde{L}\left[\sum_{k=0}^{n-1}(\hat{L}\tilde{\Omega})^k\right]\tilde{\xi}(t). \tag{12}$$

where

$$\tilde{\xi}(t)=\int_{t-\tilde{\tau}}^{t}\int_{\theta}^{t}\tilde{\omega}(\theta-a+\tilde{\tau})\tilde{u}(a)\,da\,d\theta. \tag{13}$$

For all $n\in\mathbb{N}$, the derivative of (12) along (6) is given by

$$\dot{\tilde{\zeta}}_n(t)=-[\tilde{\delta}+\tilde{\beta}(\tilde{z}(t))]\tilde{x}(t)+\tilde{L}\tilde{\Omega}\left[\sum_{k=0}^{n-1}(\hat{L}\tilde{\Omega})^k\right]\tilde{\beta}(\tilde{z}(t))\tilde{x}(t)$$
$$+\tilde{L}(\hat{L}\tilde{\Omega})^n\int_0^{\tilde{\tau}}\tilde{\omega}(a)\tilde{u}(t-a)\,da. \tag{14}$$

Proof: This lemma is proved in [27]. ■

Lemma 2 *Let $\hat{\alpha}<0$, the sequences $\tilde{\zeta}_n(t)$ and $\dot{\tilde{\zeta}}_n(t)$ of time functions satisfy:*

$$\begin{cases}\tilde{\zeta}(t) &= \lim_{n\to+\infty}\tilde{\zeta}_n(t)=\tilde{x}(t)-\dfrac{\tilde{L}}{\hat{\alpha}}\tilde{\xi}(t),\\ \dot{\tilde{\zeta}}(t) &= \lim_{n\to+\infty}\dot{\tilde{\zeta}}_n(t)=-\left[\tilde{\delta}+\dfrac{\tilde{\alpha}}{\hat{\alpha}}\tilde{\beta}(\tilde{z}(t))\right]\tilde{x}(t).\end{cases} \tag{15}$$

where $\tilde{\alpha}$ and $\hat{\alpha}$ are constants defined in (9) and (11), respectively.

Proof: For instance, see [27]. ■

B. Main Results

Theorem 1 *The biological healthy steady state of system (6) is globally stable if and only if we have $\hat{\alpha}<0$ and exclusively one of the following a, b or c_η (c_η depends on sign of the constant $\eta=\lambda.\tilde{\lambda}-1$)*

a)
$$\tilde{\alpha}<0. \tag{16}$$

b)
$$\tilde{\beta}(0)\leq-\frac{\hat{\alpha}}{\tilde{\alpha}}\tilde{\delta}. \tag{17}$$

c_η) *i)* $\eta=0$
$$\lambda\tilde{\beta}^{-1}\left(-\frac{\hat{\alpha}}{\tilde{\alpha}}\tilde{\delta}\right)<\beta^{-1}\left(\frac{\delta}{\alpha}\right). \tag{18}$$

ii) $\eta>0$
$$\lambda\tilde{\beta}^{-1}\left(-\frac{\hat{\alpha}}{\tilde{\alpha}}\tilde{\delta}\right)\leq\beta^{-1}\left(\frac{\delta}{\alpha}\right). \tag{19}$$

iii) $\eta<0$
$$\tilde{\beta}^{-1}\left(-\frac{\hat{\alpha}}{\tilde{\alpha}}\tilde{\delta}\right)<\tilde{\lambda}\beta^{-1}\left(\frac{\delta}{\alpha}\right). \tag{20}$$

Proof:

We study the system (6) according to the definition of the healthy situation where all LSCs vanish and HSCs have a positive value [3]. We start by finding conditions granting the eradication of LSCs which mathematically is modeled by convergence of $\tilde{x}(t)$ to the origin.

Cases (a) and (b): Having $\hat{\alpha}<0$, if exclusively (16) or (17) is

satisfied then $\tilde{x}(t)$ converges to zero.

From Lemma 2, we have

$$\begin{cases} \tilde{\zeta}(t) &= \lim\limits_{n\to+\infty} \tilde{\zeta}_n(t) = \tilde{x}(t) - \dfrac{\tilde{L}}{\tilde{\alpha}}\tilde{\xi}(t), \\ \dot{\tilde{\zeta}}(t) &= \lim\limits_{n\to+\infty} \dot{\tilde{\zeta}}_n(t) = -\left[\tilde{\delta} + \dfrac{\tilde{\alpha}}{\hat{\alpha}}\tilde{\beta}(\tilde{z}(t))\right]\tilde{x}(t). \end{cases} \tag{21}$$

It follows from the conditions of cases (a) and (b), that $\tilde{\zeta}(t)$ is positive define and $\dot{\tilde{\zeta}}(t)$ negative define. Therefore, according to Lyapunov theorem [28], the origin of cancerous sub-system $\tilde{x}(t)$ is globally asymptotically stable.

Case (c_η): Having $\hat{\alpha} < 0$, Consider that $\tilde{\alpha} > 0$ and $\tilde{\beta}(0) > -\dfrac{\hat{\alpha}}{\tilde{\alpha}}\tilde{\delta}$ are satisfied (these are necessary conditions for existence of cancerous positive equilibrium points). In order to demonstrate the case (c_η), we first introduce another positive functional :

$$\zeta(t) = x(t) + L\xi(t). \tag{22}$$

where

$$\xi(t) = \int_{t-\tau}^{t}\int_{\theta}^{t} \omega(\theta - a + \tau)\beta(z(a))x(a)\,da\,d\theta. \tag{23}$$

by simple calculations, we obtain its derivative

$$\dot{\zeta}(t) = -[\delta - \alpha\beta(z(t))]x(t). \tag{24}$$

then we gather the previously defined functions and their derivatives in the following time function systems:

$$\begin{cases} \tilde{\zeta}(t) &= \tilde{x}(t) - \dfrac{\tilde{L}}{\tilde{\alpha}}\tilde{\xi}(t), \\ \zeta(t) &= x(t) + L\xi(t), \\ \psi(t) &= \zeta(t) + \tilde{\zeta}(t). \end{cases} \tag{25}$$

$$\begin{cases} \dot{\tilde{\zeta}}(t) &= -\left[\tilde{\delta} + \dfrac{\tilde{\alpha}}{\hat{\alpha}}\tilde{\beta}(\tilde{z}(t))\right]\tilde{x}(t), \\ \dot{\zeta}(t) &= -[\delta - \alpha\beta(z(t))]x(t), \\ \dot{\psi}(t) &= \dot{\zeta}(t) + \dot{\tilde{\zeta}}(t). \end{cases} \tag{26}$$

we see that the sign of $\dot{\tilde{\zeta}}(t)$, $\dot{\zeta}(t)$ and $\dot{\psi}(t)$ depends on $\tilde{z}(t)$ and $z(t)$.

Also, $\psi(t)$ and $\dot{\psi}(t)$ inform about steady state values of $\tilde{z}(t)$ and $z(t)$. Then, based on these values, it is possible to evaluate the signs of $\dot{\tilde{\zeta}}(t)$ and $\dot{\zeta}(t)$ and know when the system (6) converges.

Since $\tilde{\beta}(\tilde{z}(t))$ and $\beta(z(t))$ are decreasing, we have:

$$\begin{cases} \tilde{z}(t) &= \tilde{\beta}^{-1}\left(-\dfrac{\hat{\alpha}}{\tilde{\alpha}}\tilde{\delta}\right) \Longrightarrow \dot{\tilde{\zeta}}(t) = 0, \\ \tilde{z}(t) &> \tilde{\beta}^{-1}\left(-\dfrac{\hat{\alpha}}{\tilde{\alpha}}\tilde{\delta}\right) \Longrightarrow \dot{\tilde{\zeta}}(t) < 0, \\ \tilde{z}(t) &< \tilde{\beta}^{-1}\left(-\dfrac{\hat{\alpha}}{\tilde{\alpha}}\tilde{\delta}\right) \Longrightarrow \dot{\tilde{\zeta}}(t) > 0. \end{cases} \tag{27}$$

And

$$\begin{cases} z(t) &= \beta^{-1}\left(\dfrac{\delta}{\alpha}\right) \Longrightarrow \dot{\zeta}(t) = 0, \\ z(t) &> \beta^{-1}\left(\dfrac{\delta}{\alpha}\right) \Longrightarrow \dot{\zeta}(t) < 0, \\ z(t) &< \beta^{-1}\left(\dfrac{\delta}{\alpha}\right) \Longrightarrow \dot{\zeta}(t) > 0. \end{cases} \tag{28}$$

According to (27) and (28), we determine how the signs of both functions $\dot{\tilde{\zeta}}(t)$ and $\dot{\zeta}(t)$ will change by the study of the following system

$$\begin{pmatrix} \tilde{z}(t) \\ z(t) \end{pmatrix} = \begin{pmatrix} \tilde{\lambda}\tilde{x}(t) + x(t) \\ \tilde{x}(t) + \lambda x(t) \end{pmatrix} = \begin{pmatrix} \tilde{\Theta} \\ \Theta \end{pmatrix} \tag{29}$$

where $\tilde{\Theta} = \tilde{\beta}^{-1}\left(-\dfrac{\hat{\alpha}}{\tilde{\alpha}}\tilde{\delta}\right)$ and $\Theta = \beta^{-1}\left(\dfrac{\delta}{\alpha}\right)$.

We define two equation lines $\tilde{\Delta}$ and Δ

$$\begin{cases} \tilde{\Delta} &\triangleq: x(t) = \tilde{\Theta} - \tilde{\lambda}\tilde{x}(t), \\ \Delta &\triangleq: x(t) = \dfrac{1}{\lambda}\Theta - \dfrac{1}{\lambda}\tilde{x}(t). \end{cases} \tag{30}$$

Which implies

$$\begin{cases} x(t) &= \tilde{\Theta} - \tilde{\lambda}\tilde{x}(t) \Longrightarrow \dot{\tilde{\zeta}}(t) = 0, \\ x(t) &> \tilde{\Theta} - \tilde{\lambda}\tilde{x}(t) \Longrightarrow \dot{\tilde{\zeta}}(t) < 0, \\ x(t) &< \tilde{\Theta} - \tilde{\lambda}\tilde{x}(t) \Longrightarrow \dot{\tilde{\zeta}}(t) > 0. \end{cases} \tag{31}$$

And

$$\begin{cases} x(t) &= \dfrac{1}{\lambda}\Theta - \dfrac{1}{\lambda}\tilde{x}(t) \Longrightarrow \dot{\zeta}(t) = 0, \\ x(t) &> \dfrac{1}{\lambda}\Theta - \dfrac{1}{\lambda}\tilde{x}(t) \Longrightarrow \dot{\zeta}(t) < 0, \\ x(t) &< \dfrac{1}{\lambda}\Theta - \dfrac{1}{\lambda}\tilde{x}(t) \Longrightarrow \dot{\zeta}(t) > 0. \end{cases} \tag{32}$$

According to (31) and (32), we easily deduce that there exists a trajectory $x(t) = \phi(\tilde{x}(t))$ between $\tilde{\Delta}$ and Δ so as $\dot{\psi}(t) = 0$. This allows us to conclude that in order to ensure the convergence of $\tilde{x}(t)$ to the origin, Δ must always be above $\tilde{\Delta}$; which yields other conditions in terms of different parameters as discussed bellow.

We start by determining the intersection between $\tilde{\Delta}$ and Δ which is the solution of the flowing system:

$$\begin{pmatrix} \tilde{\lambda}\tilde{x}(t) + x(t) \\ \tilde{x}(t) + \lambda x(t) \end{pmatrix} = \begin{pmatrix} \tilde{\lambda} & 1 \\ 1 & \lambda \end{pmatrix}\begin{pmatrix} \tilde{x}(t) \\ x(t) \end{pmatrix} = \begin{pmatrix} \tilde{\Theta} \\ \Theta \end{pmatrix} \tag{33}$$

Therefore

$$det\begin{pmatrix} \tilde{\lambda} & 1 \\ 1 & \lambda \end{pmatrix} = \tilde{\lambda}.\lambda - 1 = \eta. \tag{34}$$

The system (33) has solution if and only if $\eta = \tilde{\lambda}.\lambda - 1 \neq 0$ and its solution is given by

$$\begin{pmatrix} \tilde{x}(t) \\ x(t) \end{pmatrix} = \frac{1}{\tilde{\lambda}.\lambda - 1}\begin{pmatrix} \lambda & -1 \\ -1 & \tilde{\lambda} \end{pmatrix}\begin{pmatrix} \tilde{\Theta} \\ \Theta \end{pmatrix} = \begin{pmatrix} \dfrac{\lambda\tilde{\Theta} - \Theta}{\tilde{\lambda}.\lambda - 1} \\ \dfrac{\tilde{\lambda}\Theta - \tilde{\Theta}}{\tilde{\lambda}.\lambda - 1} \end{pmatrix} \tag{35}$$

When Δ is above $\tilde{\Delta}$, We have three situations:

First situation $(c_\eta - i)$**:** $\eta = 0$.

In this situation Δ and $\tilde{\Delta}$ are parallel. Thus, for Δ to be above $\tilde{\Delta}$, we must have $\dfrac{\Theta}{\lambda} > \tilde{\Theta}$.

Second situation $(c_\eta - ii)$**:** $\eta > 0$.

In this situation the decreasing velocity of $\tilde{\Delta}$ is greater than the decreasing velocity of Δ. Then, fro Δ to be above $\tilde{\Delta}$, we must have $\dfrac{\Theta}{\lambda} \geq \tilde{\Theta}$.

Third situation $(c_\eta - iii)$**:** $\eta < 0$.

In this situation the decreasing velocity of $\tilde{\Delta}$ is less than the decreasing velocity of Δ. Then, for Δ to be above $\tilde{\Delta}$, we must have $\dfrac{\Theta}{\lambda} > \tilde{\Theta}$ and the intersection must not exist where $\tilde{x}(t) > 0$ and $x(t) > 0$. This is equivalent to $\tilde{\lambda}\Theta > \tilde{\Theta}$.

Let t_ε necessary time for $\tilde{x}(t)$ converges to the origin then $\dot{\zeta}(t)$ become

$$\dot{\zeta}(t) = -\left[\delta - \alpha\beta\left(\lambda x(t)\right)\right]x(t). \tag{36}$$

If $\alpha \leq 0$ or $\delta \geq \alpha\beta\left(0\right)$ then $\zeta(t)$ is positive define and $\dot{\zeta}(t)$ negative define. Therefore, according to Lyapunov theorem, the origin of cancerous sub-system $x(t)$ is globally asymptotically stable.

Now, we show by contradiction that instability of the healthy origin occurs if and only if $\alpha > 0$ and $\delta < \alpha\beta\left(0\right)$. Having a positive solution that converges to the origin, the continuity of β imply that there exists $t_h > 0$ such that, for all $t > t_h$,

$$\dot{\zeta}(t) = -\left[\delta - \alpha\beta\left(\lambda x(t)\right)\right] \geq \frac{\left(-\delta + \alpha\beta(0)\right)}{2}. \tag{37}$$

It follows from (24) that, for all $t > t_h$

$$\dot{\zeta}(t) \geq \frac{\left(-\delta + \alpha\beta(0)\right)}{2}x(t). \tag{38}$$

Since $\dfrac{\left(-\delta + \alpha\beta(0)\right)}{2}x(t)$ for all $t > t_h$,

$$\zeta(t) \geq \zeta(t_h) > 0. \tag{39}$$

It follows that $\zeta(t)$ does not converge to zero, and in the same time $\zeta(t)$ converges to zero, because $x(t)$ converges to the origin. This is contradictory .

■

IV. Simulations Results

Bellow, some of the obtained results are illustrated through numerical examples. To simulate the several cases, we used the parameters published in [18], [29] because a cancer state is characterized by abnormal biological values different from healthy ones [24].

a) Situation $\eta = 0$: Choosing $\tilde{\Omega} = \Omega = 1$, $\beta(z(t)) = \dfrac{\beta(0)}{1+z(t)^2}$, $\tilde{\beta}(\tilde{z}(t)) = \dfrac{\tilde{\beta}(0)}{1+\tilde{z}(t)^2}$ and the parameters of table I. We verify that

TABLE I: Simulation parameters.

$\tilde{\tau}$	τ	$\tilde{L}$	$\hat{L}$	L	$\tilde{\beta}$	$\beta(0)$	$\tilde{\delta}(0)$	δ	$\tilde{\lambda}$	λ
2.9	2.5	1	0.5	1.5	9	8	0.6	0.2	1	1

$\eta = 0$ and the the condition (18) holds. Which gives the global stability of the biological healthy steady state.

b) Situation $\eta > 0$: By decreasing $\tilde{\beta}(0) = 8$, $\tilde{\delta} = 0.4$, and increasing $\tilde{\lambda} = 1.1$ and by maintaining the previous values of the other parameters, we verify that $\eta = \tilde{\lambda}\lambda - 1 = 0.1 > 0$ and that the condition (19) is satisfied. According the theorem 1, this leads to the global stability of the healthy steady state.

c) Situation $\eta < 0$: For this situation, we decrease $\lambda = 0.9$ and maintain the previous values for the other parameters. We verify that $\eta = \tilde{\lambda}\lambda - 1 = -0.01 > 0$ and that the condition (20) is satisfied. Thus, according the theorem 1, the biological healthy steady state is globally stable.

V. Conclusion & Discusion

This work highlights major aspects of modeling and studying the stability of AML. We started from an existing model that we improved by transforming the constant delay to a distributed one to give a more realistic description of the biological proliferation phenomenon. This modification yielded a bit increase in model

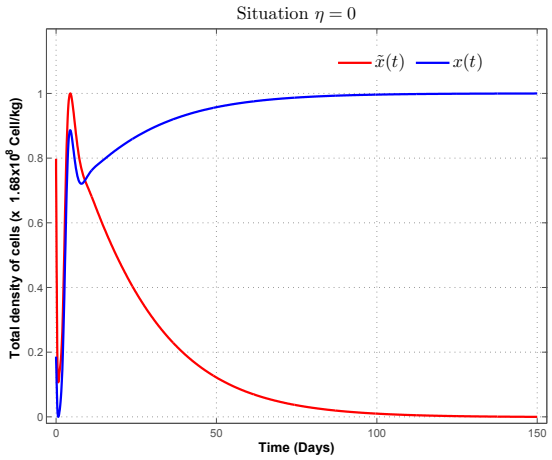

Fig. 2: Evolution of cancerous and healthy stem cells, **Situation** $\eta = 0$.

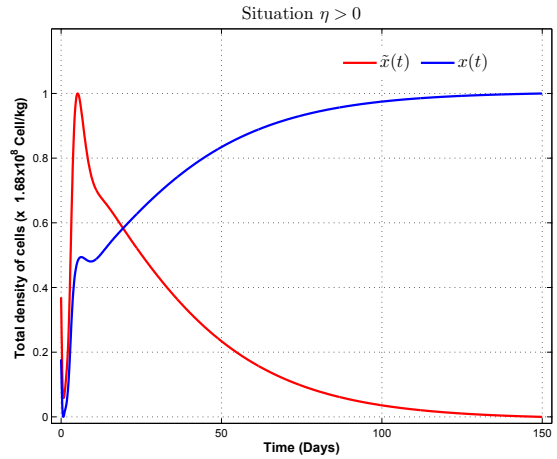

Fig. 3: Evolution of cancerous and healthy stem cells, **Situation** $\eta > 0$.

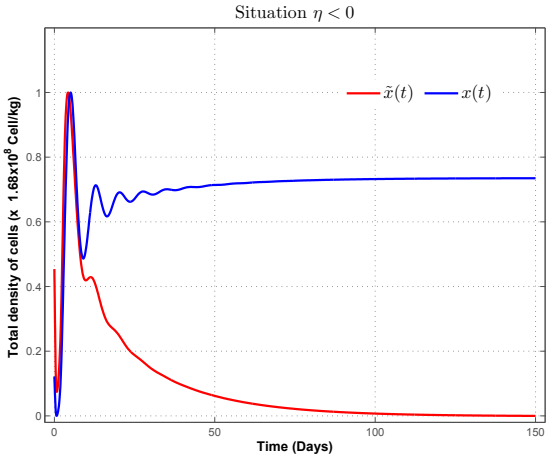

Fig. 4: Evolution of cancerous and healthy stem cells, **Situation** $\eta < 0$.

complexity reflected in the choice of the Lyapunov function candidate which was built by using sequences of functions theory. We then used it to elaborate the conditions that are sufficient and necessary for the global asymptotic stability of the positive healthy steady state; knowing its significant meaning from clinical point of view.

This result confirms our previous researches [30], [31] and is explained as follows: if we act on the interconnection mechanism modeled by (18), (19) and (20) in a specific way, we may be able to eradicate LSCs and hence reinforce HSCs. The HSCs reinforcement stabilizes pre-leukemic states as introduced in [14]. Based on this interpretation, we underling the importance of understanding the interconnection mechanism [10] and the necessity to work on it in order to establish a new treatment approach. Besides, separation of residual HSCs from LSCs is also a very critical problem [32], and our results highlight the the effect of interconnection on this aspect (separation between normal and leukemic cells). This results would be confirmed by the dependence of (18), (19) and (20) on the sensitivity of HSCs and LSCs. As it is known, the drugs target cancerous cells. Therefore, HSCs are less sensitive to the drugs and are insensitive to the immune system effect. On the other hand, LSCs are more sensitive to the drugs and may become less sensitive to the regulatory molecules than healthy ones. They may also avoid the immune system due to epigenetic mutations. This demonstrates the importance of sensitivity which appears only in the interconnection terms.

The obtained results are more general compared to those given in the references we mentioned across the manuscript and are validated by simulation.

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