Stability of a Delay System Coupled to a Differential-Difference System Describing the Coexistence of Ordinary and Mutated Hematopoietic Stem Cells

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***Abstract*— A new mathematical model that represents the coexistence between normal and leukemic populations of cells is proposed and analyzed. It is composed by a nonlinear time-delay system describing the dynamics of ordinary stem cells, coupled to a differential-difference system governing the dynamics of mutated cells. A Lyapunov-like technique is developed in order to investigate the stability properties of a steady state where healthy cells survive while leukemic ones are eradicated. Exponential stability of solutions is established, estimate of their decay rate is given and a subset of the basin of attraction of the desired steady state is provided.**

Key Words: Delay, Nonlinear, Exponential stability.

I. INTRODUCTION

Hematopoiesis is the process of blood cell formation, initiated by a population of hematopoietic stem cells (HSC) in the bone marrow. The HSC's are immature cells able to produce cells with the same maturity level or to differentiate into specialized cells. The number of cells involved in hematopoiesis should be well controlled in order to avoid some blood pathologies [15]. In one of them, namely acute myeloid leukemia (AML), a noticeable overproliferation of abnormal immature white blood cells is detected. Mathematical modeling and analysis are essential in order to understand the dynamics of healthy and unhealthy hematopoiesis. In particular, it may result in the improvement of the delivery of drugs for patients suffering from blood disorders. Not surprisingly, many authors have been interested by the modeling and the analysis of hematopoiesis, including, [19], [5], [4], [1], [2], [20], [3], [8], [13] and [24], to name but a few. In the present contribution, to obtain a coupled model of ordinary and mutated cells, we are inspired by [3] and by the new form of fast self-renewing process, recently introduced in [1], where a subpopulation of cells is considered to be always active in the proliferating phase. The present paper is a step forward the analysis of AML, by studying a coupled model that describes the cohabitation between healthy and unhealthy cells. Naturally, in our coupled model the abnormal fast self-renewal behavior of [1] will be considered only for unhealthy cells. The proportion of cells which is always proliferating will be considered as an ultimate leukemic state, as motivated in the sequel. Indeed, in recent medical research, it has been proven that cancer cells appear after an accumulation of several mutations that occur almost entirely, and in a chronological order, in the stem cell compartment [14]. A first mutation in some genes encoding enzymes in epigenetics (TET2, DNMT3A, or other [7], [25]), will increase the self-renewing activity of the affected subpopulation of cells. A more serious pathological situation arises when a second mutation, affecting pathways regulating the differentiation process such as NPM1 [16] or transcription factors will appear on some cells (already affected by the first mutation). The superposition of these two events yields a blockade in the differentiation mechanism and results in the invasion of the bone marrow by mutated cells. Finally, a subsequent mutation impairing proliferation control (e.g., of the Flt3-ITD type) will appear in a subpopulation of cells that have already encountered and accumulated one or more of the previous mutations (Figure 1). This latter mutation activates an uncontrolled overproliferation of blasts and thereby causes acute myeloid leukemia [14]. More complex successions of mutational events may occur [27], however we will in the sequel have in mind a typical TET2/DNMT3A followed by NPM1 and finally Flt3-ITD sequence of mutations.

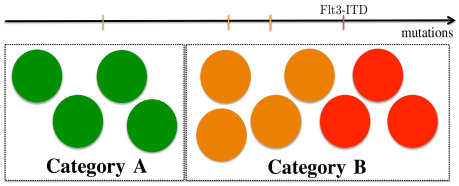

Fig. 1. In orange color are cells having some mutations. In red are those which have the Flt-3 mutation. In green are healthy cells.

In the light of the biological facts mentioned above, we consider in this paper two categories of cells:
Category A: Healthy cells, without any mutation.
Category B: Unhealthy cells. The class of cells that

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has at least two of the TET2/DNMT3A/... followed by NPM1 class gene mutations. The leukemic cells (affected by all the mutations mentioned earlier, including the Flt3 mutation) will form a subpopulation of this category.

The resulting model will be a coupled system of: i) a nonlinear delay system modeling the behavior of cells of Category A, and ii) a nonlinear differential-difference system describing cells of Category B. For the studied coupled model, we establish regional exponential stability of a biologically relevant steady state (i.e. we prove exponential stability of solutions within a determined region which is a subset of its basin of attraction).

From a mathematical point of view, the challenging problems that we have to overcome here are: i) the nonexistence of systematic methods to deal with nonlinear systems, and particularly for finding a suitable Lyapunov functional, and, ii) the analysis when the trajectories are piece-wise continuous is more difficult than in the case where they are uniformly continuous (for instance, given a weak Lyapunov function, invariance principles and Barbalat's lemma are not applicable to establish asymptotic stability of solutions).

Now, let us introduce the coupled model of ordinary and mutated cells, which is illustrated in Figure 2. As in Mackey's models ([19], [11], see also [5], [2]), we consider that a cell-cycle has two phases (resting and proliferating), each one will be described by an age-structured model (see, for instance, [18], Chapter 5).

We start by defining the following variables and functions: we consider $r(t,a)$ the density of resting healthy cells (Category A) at time $t \geq 0$ and age $a \geq 0$. The age, a, represents the time spent by a cell in the resting phase or in the proliferating phase. Respectively, $\tilde{r}(t,a)$ is the density of resting unhealthy cells. Healthy cells are mostly in the resting phase, unlike the cells of Category B that become more active in the proliferating phase. Indeed, we observe that a cell tends to start a division cycle more frequently when it accumulates mutations. Moreover, it is reasonable to assume the mutation affecting the Flt3-ITD as the ultimate unhealthy state in which the cell becomes constantly active in the proliferating phase. Moreover, a rate δ (resp. $\tilde{\delta}$) of resting cells is wasted either by differentiation or natural cell death for healthy cells (resp. unhealthy). Under the effect of some external factors, a resting cell may start a cell division cycle by entering to the proliferating phase. Denote $p(t,a)$ (resp. $\tilde{p}(t,a)$) the density of proliferating healthy cells (resp. unhealthy) at time $t \geq 0$ and age $a \geq 0$. Each proliferating healthy cell (resp. unhealthy) may die by apoptosis γ (resp. $\tilde{\gamma}$), or complete its mitosis and give birth, at the end of the proliferating phase, to two daughter cells. Denote τ (resp. $\tilde{\tau}$) the time required for mitosis in the healthy (resp. unhealthy) proliferating compartment. For Category A, daughter cells leave the proliferating compartment and join the resting compartment where they can stay until their death, differentiate, or start a new proliferating cycle. In contrast, for Category B, a rate $\tilde{K} \in (0,1)$ of daughter cells will return directly to the proliferating compartment while the other part, $1-\tilde{K}$, will join the resting unhealthy compartment. β (resp. $\tilde{\beta}$) is the reintroduction function from the healthy (resp. unhealthy) resting phase to the healthy (resp. unhealthy) proliferating phase. Furthermore, β and $\tilde{\beta}$ depend on the total density of resting healthy cells $x(t)$ and on the total density of unhealthy resting cells $\tilde{x}(t)$, defined by

$$x(t) = \int_0^\infty r(t,a)da, \quad \text{and,} \quad \tilde{x}(t) = \int_0^\infty \tilde{r}(t,a)da, \quad (1)$$

for all $t \geq 0$. Different schemes may be envisaged in order to characterize the coexistence between healthy and unhealthy cells. The simplest way is assumed in this paper, where we consider that the reintroduction functions β and $\tilde{\beta}$ depend on the total densities of resting stem cells, $C(t) = x(t) + \tilde{x}(t)$, for all $t \geq 0$.

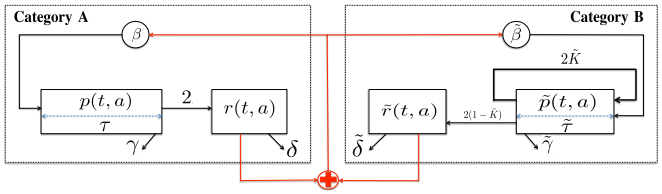

Fig. 2. Schematic representation of coupled model. The healthy part on the left and the unhealthy part on the right.

The age-structured partial differential equations describing the coupled system are given by:

$$\begin{cases} \partial_t \tilde{r}(t,a) + \partial_a \tilde{r}(t,a) = -\left(\tilde{\delta} + \tilde{\beta}(C(t))\right)\tilde{r}(t,a), \\ \text{for} \quad a > 0, t > 0, \\ \partial_t \tilde{p}(t,a) + \partial_a \tilde{p}(t,a) = -\tilde{\gamma}\tilde{p}(t,a), \\ \text{for} \quad 0 < a < \tilde{\tau}, t > 0, \\ \partial_t r(t,a) + \partial_a r(t,a) = -\left(\delta + \beta(C(t))\right) r(t,a) \\ \text{for} \quad a > 0, t > 0, \\ \partial_t p(t,a) + \partial_a p(t,a) = -\gamma p(t,a) \\ \text{for} \quad 0 < a < \tau, t > 0. \end{cases} \quad (2)$$

This is a McKendrick model ([21]) and the associated renewal conditions (new birth rates at $a = 0$) are introduced through the following boundary conditions

$$\begin{cases} \tilde{r}(t,0) = 2(1-\tilde{K})\tilde{p}(t,\tilde{\tau}), \\ \tilde{p}(t,0) = \tilde{\beta}(C(t))\tilde{x}(t) + 2\tilde{K}\tilde{p}(t,\tilde{\tau}), \\ r(t,0) = 2p(t,\tau), \\ p(t,0) = \beta(C(t))x(t), \end{cases} \quad (3)$$

for all $t > 0$. Finally, the initial age-distributions, respectively, $\tilde{r}(0,a) = \tilde{r}_0(a)$, for $a > 0$, $\tilde{p}(0,a) = \tilde{p}_0(a)$, for $0 < a < \tilde{\tau}$, $r(0,a) = r_0(a)$, for $a > 0$, and $p(0,a) = p_0(a)$, for $0 < a < \tilde{\tau}$, are assumed to be known L^1-functions.

Using the method of characteristics ([23],[11]) and following similar arguments as those in [1] (see also [2]), we reduce the system (2)-(3) to a delay differential-difference

system and we prove that its asymptotic behavior is determined by the study of the following system

$$\begin{cases} \dot{\tilde{x}}(t) = -\left[\tilde{\delta} + \tilde{\beta}(x(t)+\tilde{x}(t))\right]\tilde{x}(t) \\ \qquad +2(1-\tilde{K})e^{-\tilde{\gamma}\tilde{\tau}}\tilde{u}(t-\tilde{\tau}), \\ \tilde{u}(t) = \tilde{\beta}(x(t)+\tilde{x}(t))\tilde{x}(t) + 2\tilde{K}e^{-\tilde{\gamma}\tilde{\tau}}\tilde{u}(t-\tilde{\tau}), \\ \dot{x}(t) = -\left[\delta + \beta(x(t)+\tilde{x}(t))\right]x(t) \\ \qquad +2e^{-\gamma\tau}\beta(x(t-\tau)+\tilde{x}(t-\tau))x(t-\tau), \end{cases} \tag{4}$$

for all $t \geq 0$, where $\tilde{u}(t)$ is the density of new proliferating unhealthy cells at time $t \geq 0$. We can prove that a unique piece-wise continuous solution $(\tilde{x}(t), \tilde{u}(t), x(t))$ exists for all $t \geq 0$, when the system (4) is associated with appropriate initial conditions $(\varphi_{\tilde{x}}, \varphi_{\tilde{u}}, \varphi_x)$ such that $\varphi_{\tilde{x}} \in \mathcal{C}([-\tau, 0], \mathbb{R})$, $\varphi_x \in \mathcal{C}([-\tau, 0], \mathbb{R})$ and $\varphi_{\tilde{u}} \in \mathcal{C}([-\tilde{\tau}, 0], \mathbb{R})$.

For $\tilde{\beta}$ and β we select the functions

$$\tilde{\beta}(m) = \frac{\tilde{\beta}(0)}{1+\tilde{b}m^{\tilde{n}}}, \quad \beta(m) = \frac{\beta(0)}{1+bm^n}, \tag{5}$$

where $\tilde{b}$, b, $\tilde{\beta}(0)$ and $\beta(0)$ are strictly positive real numbers, and $\tilde{n} \geq 2$, $n \geq 2$, (see, [19] for the interpretation of the Hill function in this context).

Moreover, system (4) is positive because $\tilde{K} \in (0, 1)$. In this paper we consider only positive solutions of (4).

Here we take $2\tilde{K}e^{-\tilde{\gamma}\tilde{\tau}} < 1$ because otherwise we have $\lim_{t\to\infty} \tilde{u}(t) = \infty$ and $\lim_{t\to\infty} \tilde{x}(t) = \infty$ (biologically, this situation may be interpreted as the invasion by blasts of the bone marrow) which is obviously an unsuitable situation. The paper is devoted to the stability analysis of the unique desired steady state, $E = (0, 0, x_e)$, where $x_e > 0$, and which represents the idealistic case where only the healthy cells survive.

II. ANALYSIS OF THE FAVOURABLE STEADY STATE E

We want to provide some realistic theoretical stability conditions (i.e. that can be satisfied under the effect of some drugs), to bring the system to the desired steady state E. First, by carefully studying the existence of nonzero steady states of system (4), one can prove that

Proposition 1: If the conditions

$$\begin{cases} \delta < [2e^{-\gamma\tau} - 1]\,\beta(0), \\ \tilde{\beta}(0) < \left[\frac{1-2\tilde{K}e^{-\tilde{\gamma}\tilde{\tau}}}{2e^{-\tilde{\gamma}\tilde{\tau}}-1}\right]\tilde{\delta}, \end{cases} \tag{6}$$

are satisfied, then $(0, 0, 0)$ and a unique point $E = (0, 0, x_e)$, where $x_e > 0$, are the only steady states that system (4) admits.

Next, we assume that (6) are satisfied and study the stability properties of E.

1) New representation of the system: We start with a simple, but useful, statement. Using Taylor's series for all $\mathfrak{z} > -\mathfrak{e}$, and $\mathfrak{e} > 0$, we get (with an abuse of notation)

$$\begin{aligned} \beta(\mathfrak{z}+\mathfrak{e}) &= \beta(\mathfrak{e}) + \theta\mathfrak{z} + R(\mathfrak{z}), \\ \tilde{\beta}(\mathfrak{z}+\mathfrak{e}) &= \tilde{\beta}(\mathfrak{e}) + \tilde{\theta}\mathfrak{z} + \tilde{R}(\mathfrak{z}), \end{aligned} \tag{7}$$

where β and $\tilde{\beta}$ are the functions defined in (5), and

$$\begin{aligned} \theta = \beta'(\mathfrak{e}), \quad R(\mathfrak{z}) &= \int_{\mathfrak{e}}^{\mathfrak{z}+\mathfrak{e}} (\mathfrak{z}+\mathfrak{e}-l)\beta^{(2)}(l)dl, \\ \tilde{\theta} = \tilde{\beta}'(\mathfrak{e}) \ \text{ and } \ \tilde{R}(\mathfrak{z}) &= \int_{\mathfrak{e}}^{\mathfrak{z}+\mathfrak{e}} (\mathfrak{z}+\mathfrak{e}-l)\tilde{\beta}^{(2)}(l)dl. \end{aligned} \tag{8}$$

Then in Appendix A we prove the following assertion:

Claim 1: For all $\mathfrak{z} > -\mathfrak{e}$ and $\mathfrak{e} > 0$, there exist strictly positive constants $\mathfrak{s}$, $\tilde{\mathfrak{s}}$, $\mathfrak{m}$ and $\tilde{\mathfrak{m}}$ such that

$$|R(\mathfrak{z})| \leq \mathfrak{s}|\mathfrak{z}|, \ \text{ and } \ |\tilde{R}(\mathfrak{z})| \leq \tilde{\mathfrak{s}}|\mathfrak{z}|, \tag{9}$$

$$|R(\mathfrak{z})| \leq \mathfrak{m}\mathfrak{z}^2, \ \text{ and } \ |\tilde{R}(\mathfrak{z})| \leq \tilde{\mathfrak{m}}\mathfrak{z}^2. \tag{10}$$

Next, by performing the change of coordinate $\mathfrak{x} = x - x_e$, and using (7) where $\mathfrak{z} = \mathfrak{x} + \tilde{x}$ and $\mathfrak{e} = x_e$, we obtain the following new representation of system (4)

$$\begin{cases} \dot{\tilde{x}}(t) = -\left[\tilde{\delta} + \tilde{\beta}(x_e)\right]\tilde{x}(t) + f(\mathfrak{x}(t), \tilde{x}(t)) \\ \qquad +2(1-\tilde{K})e^{-\tilde{\gamma}\tilde{\tau}}\tilde{u}(t-\tilde{\tau}), \\ \tilde{u}(t) = \tilde{\beta}(x_e)\tilde{x}(t) - f(\mathfrak{x}(t), \tilde{x}(t)) \\ \qquad +2\tilde{K}e^{-\tilde{\gamma}\tilde{\tau}}\tilde{u}(t-\tilde{\tau}) \\ \dot{\mathfrak{x}}(t) = -\left[\delta + \mu\right]\mathfrak{x}(t) - \theta x_e\tilde{x}(t) + g(\mathfrak{x}_t, \tilde{x}_t) \\ \qquad +2e^{-\gamma\tau}\mu\mathfrak{x}(t-\tau) + 2e^{-\gamma\tau}\theta x_e\tilde{x}(t-\tau), \end{cases} \tag{11}$$

where $\mu = \beta(x_e) + \theta x_e$, and,

$$\begin{aligned} f(\mathfrak{x}, \tilde{x}) &= -\tilde{\theta}\left[2Q(\tilde{x}) + \mathfrak{x}\tilde{x}\right] - \tilde{R}(\mathfrak{z})\tilde{x}, \\ g(\mathfrak{x}_t, \tilde{x}_t) &= -\theta\left[2Q(\mathfrak{x}(t)) + \tilde{x}(t)\mathfrak{x}(t)\right] - R(\mathfrak{z}(t))\left(\mathfrak{x}(t) + x_e\right) \\ &\quad + 2e^{-\gamma\tau}\theta\left[2Q(\mathfrak{x}(t-\tau)) + \mathfrak{x}(t-\tau)\tilde{x}(t-\tau)\right] \\ &\quad + 2e^{-\gamma\tau}R(\mathfrak{z}(t-\tau))\left(\mathfrak{x}(t-\tau) + x_e\right). \end{aligned}$$

If the trajectories of system (11) converge exponentially to the origin, then the positive trajectories of the system (4) converge exponentially to E.

2) Obtaining Decay Conditions: We study the global stability properties of the coupled system using its representation as (11). To begin, let us define the function

$$\Theta(\mathfrak{x}, \tilde{x}) = Q(\mathfrak{x}) + Q(\tilde{x}), \tag{12}$$

where, $Q(m) = \frac{1}{2}m^2$, and the following operators,

$$\mathcal{Y}(\tilde{\varphi}) = \int_{t-\tilde{\tau}}^{t} e^{\rho(m-t)}Q(\tilde{\varphi}(m))dm, \tag{13}$$

$$\mathcal{S}(\varphi) = \int_{t-\tau}^{t} e^{\rho(m-t)}Q(\varphi(m))dm, \tag{14}$$

where $\varphi \in \mathcal{C}([-\tau, 0], \mathbb{R})$, $\tilde{\varphi} \in \mathcal{C}([-\tilde{\tau}, 0], \mathbb{R})$, and ρ is a strictly positive constant to be chosen later. Finally, we introduce the following functional

$$\begin{aligned} U(\tilde{x}_t, \tilde{u}_t, \mathfrak{x}_t) =& \Theta(\mathfrak{x}(t), \tilde{x}(t)) + \lambda\mathcal{Y}(\tilde{u}_t) \\ &+ \omega\left[\mathcal{S}(\mathfrak{x}_t) + \mathcal{S}(\tilde{x}_t)\right], \end{aligned} \tag{15}$$

where λ and ω are strictly positive constants to be selected later. Now, observe that the derivative of the functional $\mathcal{Y}(\tilde{u}_t)$, satisfies

$$\dot{\mathcal{Y}}(t) = Q(\tilde{u}(t)) - e^{-\rho\tilde{\tau}}Q(\tilde{u}(t-\tilde{\tau})) - \rho\mathcal{Y}(\tilde{u}_t), \tag{16}$$

for almost all $t \geq 0$. Next, using some classical inequalities and (9), we obtain

$$\begin{aligned} Q(\tilde{u}(t)) \leq & \mathfrak{c}_1 Q(\tilde{x}(t)) + \mathfrak{c}_2 Q(\tilde{u}(t-\tilde{\tau})) \\ & + \mathfrak{c}_3 \left[Q(\mathfrak{x}(t)) + 3Q(\tilde{x}(t))\right]^2, \end{aligned} \tag{17}$$

where

$$\begin{aligned} \mathfrak{c}_1 &= \tilde{\beta}^2(x_e) + 2\tilde{\beta}(x_e)\tilde{K}e^{-\tilde{\gamma}\tilde{\tau}} + \tilde{\beta}(x_e), \\ \mathfrak{c}_2 &= \left(2\tilde{K}e^{-\tilde{\gamma}\tilde{\tau}}\right)^2 + 2\tilde{\beta}(x_e)\tilde{K}e^{-\tilde{\gamma}\tilde{\tau}} + 2\tilde{K}e^{-\tilde{\gamma}\tilde{\tau}}, \\ \mathfrak{c}_3 &= \tfrac{1}{2}\left(\tilde{\beta}(x_e) + 2\tilde{K}e^{-\tilde{\gamma}\tilde{\tau}} + 1\right)\left(|\tilde{\theta}| + \tilde{\mathfrak{s}}\right)^2. \end{aligned} \tag{18}$$

Then, (17) and (16) give,

$$\begin{aligned} \dot{\mathcal{Y}}(t) \leq & \mathfrak{c}_1 Q(\tilde{x}(t)) + \left[\mathfrak{c}_2 - e^{-\rho\tilde{\tau}}\right] Q(\tilde{u}(t-\tilde{\tau})) \\ & + \mathfrak{c}_3 \left[Q(\mathfrak{x}(t)) + 3Q(\tilde{x}(t))\right]^2 - \rho\mathcal{Y}(\tilde{u}_t). \end{aligned} \tag{19}$$

Next, using some classical inequalities, we can prove that

$$\begin{aligned} \dot{\Theta}(t) \leq & -2\left[\delta - \alpha_1\right] Q(\mathfrak{x}(t)) - 2\left[\tilde{\delta} - \alpha_2\right] Q(\tilde{x}(t)) \\ & + 2e^{-\gamma\tau}\left[|\mu| Q(\mathfrak{x}(t-\tau)) + |\theta| x_e Q(\tilde{x}(t-\tau))\right] \\ & + 2(1-\tilde{K})e^{-\tilde{\gamma}\tilde{\tau}} Q(\tilde{u}(t-\tilde{\tau})) \\ & + \mathfrak{x}(t) g(\mathfrak{x}_t, \tilde{x}_t) + \tilde{x}(t) f(\mathfrak{x}(t), \tilde{x}(t)), \end{aligned} \tag{20}$$

where,

$$\begin{aligned} \alpha_1 &= -\mu + \tfrac{|\theta| x_e}{2} + \left(|\mu| + |\theta| x_e\right) e^{-\gamma\tau}, \\ \alpha_2 &= -\tilde{\beta}(x_e) + (1-\tilde{K})e^{-\tilde{\gamma}\tilde{\tau}} + \tfrac{|\theta| x_e}{2}. \end{aligned} \tag{21}$$

Now, observe that if the first decay condition $1 - \mathfrak{c}_2 > 0$, is satisfied, then for all $\rho \in \left(0, \frac{1}{\tilde{\tau}} \ln\left(\frac{2}{1+\mathfrak{c}_2}\right)\right)$, we have

$$e^{-\rho\tilde{\tau}} - \mathfrak{c}_2 > \frac{1-\mathfrak{c}_2}{2} > 0. \tag{22}$$

From the previous inequality, observe that by selecting $\lambda = \frac{8(1-\tilde{K})e^{-\tilde{\gamma}\tilde{\tau}}}{1-\mathfrak{c}_2}$, we get

$$\lambda\left(e^{-\rho\tilde{\tau}} - \mathfrak{c}_2\right) - 2(1-\tilde{K})e^{-\tilde{\gamma}\tilde{\tau}} > 2(1-\tilde{K})e^{-\tilde{\gamma}\tilde{\tau}}. \tag{23}$$

Moreover, for ρ satisfying (22), we select $\omega = 3e^{(\rho-\gamma)\tau}\max\{|\mu|, |\theta| x_e\}$. A direct consequence is that

$$\begin{aligned} w_1 &= \omega e^{-\rho\tau} - 2e^{-\gamma\tau}|\mu| > 0, \\ w_2 &= \omega e^{-\rho\tau} - 2e^{-\gamma\tau}|\theta| x_e > 0. \end{aligned} \tag{24}$$

Finally, we assume that the decay conditions

$$\delta > \alpha_1 + \frac{\omega}{2}, \quad \text{and} \quad \tilde{\delta} > \alpha_2 + \frac{\omega + \lambda\mathfrak{c}_1}{2}, \tag{25}$$

are satisfied and we conclude that for almost all $t \geq 0$,

$$\begin{aligned} \dot{U}(t) \leq & -2\mathfrak{d} U(\tilde{x}_t, \tilde{u}_t, \mathfrak{x}_t) - \varsigma_1 Q(\mathfrak{x}(t)) - \varsigma_2 Q(\tilde{x}(t)) \\ & - 2(1-\tilde{K})e^{-\tilde{\gamma}\tilde{\tau}} Q(\tilde{u}(t-\tilde{\tau})) \\ & - w_1 Q(\mathfrak{x}(t-\tau)) - w_2 Q(\tilde{x}(t-\tau)) \\ & + \mathfrak{x}(t) g(\mathfrak{x}_t, \tilde{x}_t) + \tilde{x}(t) f(\mathfrak{x}(t), \tilde{x}(t)) \\ & + \lambda\mathfrak{c}_3 \left[Q(\mathfrak{x}(t)) + 3Q(\tilde{x}(t))\right]^2, \end{aligned} \tag{26}$$

where $\mathfrak{d} = \frac{1}{2}\min\{\varsigma_1, \varsigma_2, \rho\}$, $\varsigma_1 = \delta - \alpha_1 - \frac{\omega}{2} > 0$, $\varsigma_2 = \tilde{\delta} - \alpha_2 - \frac{\omega + \lambda\mathfrak{c}_1}{2} > 0$, and w_1 and w_2 are the positive constants defined in (24). Next, let us focus on the terms $f(\mathfrak{x}(t), \tilde{x}(t))$ and $g(\mathfrak{x}_t, \tilde{x}_t)$ defined after (11). Using some classical inequalities and *Claim 1*, we check that,

$$\begin{aligned} |f(\mathfrak{x}(t), \tilde{x}(t))| &\leq \left(\tilde{\mathfrak{s}} + |\tilde{\theta}|\right) Q(\mathfrak{x}(t)) + 3\left(\tilde{\mathfrak{s}} + |\tilde{\theta}|\right) Q(\tilde{x}(t)), \\ |g(\mathfrak{x}_t, \tilde{x}_t)| &\leq \left[3\left(|\theta| + \mathfrak{s}\right) + 4\mathfrak{m} x_e\right] Q(\mathfrak{x}(t)) \\ & \quad + \left[|\theta| + \mathfrak{s} + 4\mathfrak{m} x_e\right] Q(\tilde{x}(t)) \\ & \quad + 2e^{-\gamma\tau}\left[3\left(|\theta| + \mathfrak{s}\right) + 4\mathfrak{m} x_e\right] Q(\mathfrak{x}(t-\tau)) \\ & \quad + 2e^{-\gamma\tau}\left[|\theta| + \mathfrak{s} + 4\mathfrak{m} x_e\right] Q(\tilde{x}(t-\tau)). \end{aligned}$$

We keep in mind the two previous inequalities, and the following upper bounds: $Q(\mathfrak{x}(t)) + 3Q(\tilde{x}(t)) \leq 4U(\tilde{x}_t, \tilde{u}_t, \mathfrak{x}_t)$, $|\mathfrak{x}(t)| \leq \sqrt{2U(\tilde{x}_t, \tilde{u}_t, \mathfrak{x}_t)}$, and $|\tilde{x}(t)| \leq \sqrt{2U(\tilde{x}_t, \tilde{u}_t, \mathfrak{x}_t)}$. Moreover, we define the following sublevels: $\overline{U}_1 = \frac{\mathfrak{d}}{16\lambda\mathfrak{c}_3}$, $\overline{U}_2 = \frac{1}{2}\left(\frac{\varsigma_1}{\underline{\varsigma}_1}\right)^2$, $\overline{U}_3 = \frac{1}{2}\left(\frac{\varsigma_2}{\underline{\varsigma}_2}\right)^2$, $\overline{U}_4 = \frac{1}{2}\left(\frac{w_1}{\underline{w}_1}\right)^2$, $\overline{U}_5 = \frac{1}{2}\left(\frac{w_2}{\underline{w}_2}\right)^2$, and $\overline{U} = \min\left\{\overline{U}_1, \overline{U}_2, \overline{U}_3, \overline{U}_4, \overline{U}_5\right\}$, where, $\underline{\varsigma}_1 = 3\left(|\theta| + \mathfrak{s}\right) + 4\mathfrak{m} x_e + \tilde{\mathfrak{s}} + |\tilde{\theta}|$, $\underline{\varsigma}_2 = |\theta| + \mathfrak{s} + 4\mathfrak{m} x_e + 3(\tilde{\mathfrak{s}} + |\tilde{\theta}|)$, $\underline{w}_1 = 2e^{-\gamma\tau}\left[3\left(|\theta| + \mathfrak{s}\right) + 4\mathfrak{m} x_e\right]$ and $\underline{w}_2 = 2e^{-\gamma\tau}\left[|\theta| + \mathfrak{s} + 4\mathfrak{m} x_e\right]$. Then, we deduce that for all initial conditions $(\varphi_{\tilde{x}}, \varphi_{\tilde{u}}, \varphi_{\mathfrak{x}})$ satisfying

$$U\left(\varphi_{\tilde{x}}, \varphi_{\tilde{u}}, \varphi_{\mathfrak{x}}\right) < \overline{U},$$

the time derivative of the functional U verifies,

$$\dot{U}(t) \leq -\mathfrak{d} U(\tilde{x}_t, \tilde{u}_t, \mathfrak{x}_t), \tag{27}$$

for almost all $t \geq 0$. By integrating this inequality, we get $U(\tilde{x}_t, \tilde{u}_t, \mathfrak{x}_t) \leq e^{-\mathfrak{d}t} U(\varphi_{\tilde{x}}, \varphi_{\tilde{u}}, \varphi_{\mathfrak{x}})$, for all $t \geq 0$.

Thus, $Q(\mathfrak{x}(t)) + Q(\tilde{x}(t)) \leq e^{-\mathfrak{d}t} U(\varphi_{\tilde{x}}, \varphi_{\tilde{u}}, \varphi_{\mathfrak{x}})$, for all $t \geq 0$. Therefore, we conclude that $\mathfrak{x}$ and $\tilde{x}$ converge exponentially to zero.

Now, by exploiting the linearity in the second equation in (11), it follows that $\tilde{u}$ converges exponentially to the origin, since $2\tilde{K}e^{-\tilde{\gamma}\tilde{\tau}} < 1$, as long as $\tilde{x}$ and $\mathfrak{x}$ converge exponentially to zero. To summarize, we have:

Theorem 1: Let the nonlinear system (4) be such that (6) holds true. If the conditions

i) $\frac{\omega}{2} + \alpha_1 < \delta$, ii) $\frac{w + \lambda\mathfrak{c}_1}{2} + \alpha_2 < \tilde{\delta}$, iii) $\mathfrak{c}_2 < 1$,

are satisfied then the equilibrium point $E = (0, 0, x_e)$, where $x_e > 0$, is exponentially stable, with a decay rate smaller or equal to $\frac{\mathfrak{d}}{2}$, with basin of attraction defined by

$$\begin{aligned} \mathfrak{E} = \Big\{ & \varphi_{\tilde{x}} \in \mathcal{C}\left([-\tau, 0], \mathbb{R}^+\right), \varphi_{\tilde{u}} \in \mathcal{C}\left([-\tilde{\tau}, 0], \mathbb{R}^+\right), \\ & \varphi_x \in \mathcal{C}\left([-\tau, 0], \mathbb{R}^+\right) \Big| U\left(\varphi_{\tilde{x}}, \varphi_{\tilde{u}}, \varphi_x - x_e\right) < \overline{U} \Big\}. \end{aligned}$$

A. Biological interpretation of the findings:

We are interested in evaluating the effects of drugs used in the clinic of AML, that act on cell functional targets, proliferation, differentiation and death terms. We will mention classic molecules, cytosine arabinoside, anthracyclines, G-CSF, and the family of tyrosine kinase inhibitors (TKIs, those drugs with names in "-tinib"). The condition (i) in *Theorem 1* concerns mainly ordinary stem cells. It is to be combined with the first condition in *Proposition 1* that ensures the existence of the positive value x_e. At this point, we mention that for the selected

form of the functions β and $\tilde{\beta}$, x_e has a normalized value of same order as the other biological parameters involved in the model (more precisely, taking $x_e = 1$ corresponds to $x_e = 1.62 \times 10^8$ cells/kg [1]). We suggest that the therapeutic action should target the parameter $\beta(0)$. Practically, increasing $\beta(0)$ means that when the total density of resting cells becomes very low, the population of healthy resting cells will enter into proliferation more frequently, in order to regenerate and create new daughter cells. This may be achieved clinically by infusing G-CSF ([12], [6]). The condition (ii) in *Theorem 1* is more difficult to understand. The simplest way to enforce it is to increase $\tilde{\delta}$ (which also goes in the direction of *Proposition 1*), by increasing differentiation (rather than cell death) in nonproliferating unhealthy cells. This has been shown to be possible using molecules such as dasatinib [17]. Now, observe that the last condition (iii) concerns the unhealthy cells which are always active in the proliferating phase (i.e. leukemic cells with the FLT3 mutation). We may simultaneously carry out a joint therapeutic action that aims to increase the product $\tilde{\tau}\tilde{\gamma}$ (i.e., extending the duration of the cell cycle and increasing the death rate in proliferating cells). Decreasing the fast self-renewal rate $\tilde{K}$ is not easily obtained, due to preexisting mutations of epigenetic enzymes such as TET2 [25], [26], but quizartinib (AC220) [28], a selective inhibitor of Flt-3 may at least partly achieve this goal. Increasing the duration of the cell division cycle $\tilde{\tau}$ may be obtained by TKIs, such as quizartinib again, and others that are also primarily cytostatics, but less selective (such as erlotinib [17]), i.e., at moderate doses slowing down the cell cycle rather than arresting it. Increasing the death rate $\tilde{\gamma}$ in the population of proliferating leukemic cells may be obtained better by cytosine arabinoside or anthracyclines, such as idarubicin or daunorubicin.

III. Conclusion

We have taken into account some recent biological observations to develop a new model that describes the coexistence of healthy and unhealthy hematopoietic stem cells. The biological phenomenon is described by some transport equations, that we reduced to a nonlinear time-delay system, coupled to a nonlinear differential-difference equation. We developed a Lyapunov-based technique to investigate the exponential convergence of the trajectories to a biologically relevant steady state. Based on our theoretical study, we suggest innovative combined therapeutic tracks towards possible improvements of current treatments of AML.

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Appendix

A. Proof of Claim 1

Since R and $\tilde{R}$ are of identical form we prove *Claim 1* only for R. Using the expression of β, which is given in (5), we observe that for all $x_e > 0$ and $\mathfrak{z} > -x_e$,

$$R(\mathfrak{z}) = \beta(0)\left(\frac{1}{1+b(\mathfrak{z}+x_e)^n} - \frac{1}{1+bx_e^n}\right) - \theta\mathfrak{z}. \quad (28)$$

Obviously, when $|\mathfrak{z}| > 1$, we have

$$\frac{|R(\mathfrak{z}|}{|\mathfrak{z}|} \leq \frac{2\beta(0)+|\theta|}{|\mathfrak{z}|} \leq 2\beta(0)+|\theta|. \quad (29)$$

To study the case where $|\mathfrak{z}| \leq 1$, for all $\mathfrak{z} > -x_e$, $x_e > 0$, we introduce the function,

$$\rho(\mathfrak{z}) = \frac{1}{1+b(\mathfrak{z}+x_e)^n} - \frac{1}{1+bx_e^n} = \frac{b\left[x_e^n - (\mathfrak{z}+x_e)^n\right]}{q(\mathfrak{z})},$$

where $q(\mathfrak{z}) = \left[1+b(\mathfrak{z}+x_e)^n\right](1+bx_e^n)$. Using,

$$(\mathfrak{z}+a)^n - a^n = na^{n-1}\mathfrak{z} + n(n-1)\int_0^{\mathfrak{z}}\int_a^{a+l} m^{n-2}dmdl,$$

we deduce that,

$$\rho(\mathfrak{z}) = -nbx_e^{n-1}\frac{\mathfrak{z}}{q(\mathfrak{z})} + \mathfrak{C}(\mathfrak{z}). \quad (30)$$

where $\mathfrak{C}(\mathfrak{z}) = -nb(n-1)\frac{1}{q(\mathfrak{z})}\int_0^{\mathfrak{z}}\int_0^{l}(m+x_e)^{n-2}dmdl$. To ease the notation, we put $h = 1+bx_e^n$. Noticing that, $\frac{1}{q(\mathfrak{z})} = \frac{1}{h}\left(\rho(\mathfrak{z})+\frac{1}{h}\right)$, it follows that $\rho(\mathfrak{z}) = -nbx_e^{n-1}\left(\frac{\rho(\mathfrak{z})}{h}+\frac{1}{h^2}\right)\mathfrak{z} + \mathfrak{C}(\mathfrak{z})$. Consequently,

$$\rho(\mathfrak{z}) = -\frac{nbx_e^{n-1}}{h^2}\mathfrak{z} + \mathfrak{C}(\mathfrak{z}) - \frac{nbx_e^{n-1}}{h}\rho(\mathfrak{z})\mathfrak{z}. \quad (31)$$

We should point out that $\theta := \beta'(x_e) = \beta(0)\frac{nbx_e^{n-1}}{h^2}$. Therefore,

$$\rho(\mathfrak{z}) + \frac{\theta}{\beta(0)}\mathfrak{z} = \mathfrak{C}(\mathfrak{z}) - \frac{nbx_e^{n-1}}{h}\rho(\mathfrak{z})\mathfrak{z}. \quad (32)$$

On the other hand, observe that (28) is equivalent to $R(\mathfrak{z}) = \beta(0)\left[\rho(\mathfrak{z}) - \frac{\theta}{\beta(0)}\mathfrak{z}\right]$. By combining the last equality with (32), we obtain the intermediate consequence,

$$\frac{R(\mathfrak{z})}{\beta(0)} = \mathfrak{C}(\mathfrak{z}) - \frac{nbx_e^{n-1}}{h}\rho(\mathfrak{z})\mathfrak{z}. \quad (33)$$

Now, we readily check that

$$|\mathfrak{C}(\mathfrak{z})| \leq \frac{nb(n-1)}{q(\mathfrak{z})}\left(|\mathfrak{z}|+x_e\right)^{n-2}\frac{\mathfrak{z}^2}{2}. \quad (34)$$

From (30) we deduce that $|\rho(\mathfrak{z})| \leq \frac{nbx_e^{n-1}}{q(\mathfrak{z})}|\mathfrak{z}| + |\mathfrak{C}(\mathfrak{z})|$. Using (34), it follows that

$$|\mathfrak{z}\rho(\mathfrak{z})| \leq \frac{nbx_e^{n-1}}{q(\mathfrak{z})}\mathfrak{z}^2 + \frac{nb(n-1)}{2q(\mathfrak{z})}\left(|\mathfrak{z}|+x_e\right)^{n-2}|\mathfrak{z}|^3. \quad (35)$$

Consequently, from (33), and using (34) and (35), we obtain the upper bound,

$$\begin{aligned}\frac{|R(\mathfrak{z})|}{\beta(0)} &\leq \frac{(nb)^2(n-1)x_e^{n-1}}{2hq(\mathfrak{z})}\left(|\mathfrak{z}|+x_e\right)^{n-2}|\mathfrak{z}|^3 \\ &+ \left[\frac{nb(n-1)}{2q(\mathfrak{z})}\left(|\mathfrak{z}|+x_e\right)^{n-2} + \frac{\left(nbx_e^{n-1}\right)^2}{hq(\mathfrak{z})}\right]\mathfrak{z}^2.\end{aligned} \quad (36)$$

On the other hand, we observe that $\frac{1}{q(\mathfrak{z})} = \frac{1}{[1+b(\mathfrak{z}+x_e)^n]h}$. Therefore, when $\mathfrak{z} \geq 0$, we have $\frac{1}{q(\mathfrak{z})} = \frac{1}{[1+b(|\mathfrak{z}|+x_e)^n]h}$, and when $\mathfrak{z} \leq 0$, then $\mathfrak{z} \in (-x_e, 0]$. Thus $\frac{1}{q(\mathfrak{z})} \leq \frac{1}{h} \leq \frac{1+b(2x_e)^n}{[1+b(|\mathfrak{z}|+x_e)^n]h}$. Consequently, for all $\mathfrak{z} > -x_e$, we have

$$\frac{1}{q(\mathfrak{z})} \leq \frac{1+b(2x_e)^n}{\left[1+b(|\mathfrak{z}|+x_e)^n\right]h}. \quad (37)$$

From (37) and (36), we deduce that

$$\begin{aligned}\frac{|R(\mathfrak{z})|}{\beta(0)} &\leq \left[\mathfrak{a}_1\frac{1+(|\mathfrak{z}|+x_e)^{n-2}}{1+b\left(|\mathfrak{z}|+x_e\right)^n} + \mathfrak{a}_2\frac{(|\mathfrak{z}|+x_e)^{n-2}|\mathfrak{z}|}{1+b\left(|\mathfrak{z}+x_e\right)^n}\right]\mathfrak{z}^2 \\ &\leq \left[\mathfrak{a}_1\frac{1+(|\mathfrak{z}|+x_e)^{n-2}}{1+b\left(|\mathfrak{z}|+x_e\right)^n} + \mathfrak{a}_2\frac{(|\mathfrak{z}|+x_e)^{n-1}}{1+b\left(|\mathfrak{z}+x_e\right)^n}\right]\mathfrak{z}^2,\end{aligned}$$

where the positive constants $\mathfrak{a}_1$ and $\mathfrak{a}_2$ are given by $\mathfrak{a}_1 = \left[1+b(2x_e)^2\right]^n \max\left\{\frac{nb(n-1)}{2h}, \frac{\left(nbx_e^{n-1}\right)^2}{h^2}\right\}$, and $\mathfrak{a}_2 = \frac{\left((nb)^2(n-1)x_e^{n-1}\right)(1+b(2x_e)^n)}{2h^2}$. Next, observe that:

case 1: if $|\mathfrak{z}|+x_e \leq 1$, then

$$,\ \frac{1+(|\mathfrak{z}|+x_e)^{n-2}}{1+b\left(|\mathfrak{z}|+x_e\right)^n} \leq 2,\ \ \frac{(|\mathfrak{z}|+x_e)^{n-1}}{1+b\left(|\mathfrak{z}+x_e\right)^n} \leq 1.$$

case 2: if $|\mathfrak{z}|+x_e > 1$, then

$$\frac{1+(|\mathfrak{z}|+x_e)^{n-2}}{1+b\left(|\mathfrak{z}|+x_e\right)^n} \leq \bar{b},\ \ \frac{(|\mathfrak{z}|+x_e)^{n-1}}{1+b\left(|\mathfrak{z}+x_e\right)^n} \leq \bar{b}.$$

where $\bar{b} = \max\left\{1, \frac{1}{b}\right\}$ Therefore, in both cases, we proved that

$$|R(\mathfrak{z})| \leq \mathfrak{m}\mathfrak{z}^2, \quad (38)$$

where $\mathfrak{m} = \beta(0)\max\left\{\mathfrak{a}_1\max\left\{2, b^{-1}\right\}, \mathfrak{a}_2\bar{b}\right\}$. Now, recall that $R(\mathfrak{z}) = \beta(0)\left[\rho(\mathfrak{z}) - \frac{\theta}{\beta(0)}\mathfrak{z}\right]$. From (38), we get,

$$\frac{|\beta(0)\rho(\mathfrak{z}) - \theta\mathfrak{z}|}{|\mathfrak{z}|} \leq \mathfrak{m}|\mathfrak{z}|.$$

Therefore, we observe that if $|\mathfrak{z}| \leq 1$, the inequality (A) implies that

$$|\beta(0)\rho(\mathfrak{z}) - \theta\mathfrak{z}| \leq \mathfrak{m}|\mathfrak{z}|. \quad (39)$$

From (29) and (39), we conclude that, for all $\mathfrak{z} > -x_e$ and $x_e > 0$, we have

$$|R(\mathfrak{z})| \leq \mathfrak{s}|\mathfrak{z}|,$$

where $\mathfrak{s} = \max\{\mathfrak{m}, 2\beta(0)+|\theta|\}$.