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

W. Djema, F. Mazenc, C. Bonnet, J. Clairambault, P. Hirsch and F. Delhommeau.

Abstract—A mathematical model that represents the coexistence of normal and leukemic populations of cells is introduced and analyzed. It is a nonlinear time-delay system characterizing the dynamics of ordinary stem cells, coupled to a delay differential-difference system governing the dynamics of mutated cells. An important feature of this model is that it may explain the invasion of the bone marrow by unhealthy cells that are characterized by fast self-renewing dynamics. A Lyapunov-like technique is developed to investigate the stability properties of a steady state where the population of healthy cells will survive. Exponential stability of solutions is established, estimate on their decay rate is given and an open subset of the basin of attraction of the studied equilibrium is provided.

Key Words: Delay systems, 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. It is a complex process regulated by a series of events not fully understood. The HSC's are immature cells able to produce cells with the same maturity level or to differentiate into specialized cells. The number of divisions and the quantity of cells involved in hematopoiesis should be well controlled in order to avoid some pathologies. In the case of acute myeloid leukemia (AML), we observe an overproliferation of abnormal immature white blood cells (the blasts). 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, [1], [2], [5] [9], [14] and [18]. In the present contribution, to obtain the

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coupled model of ordinary and mutated cells, we are inspired by the new form of fast self-renewing process, recently introduced in [1], where a subpopulation of cells is considered always active in the proliferating phase. However, much remains to be done to achieve a complete representation of the cell dynamics in AML. 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 [11]. A first mutation in some genes encoding enzymes in epigenetics (TET2, DNMT3A, IDH1-2 or other [4], [19]), will increase the self-renewing activity of the affected subpopulation of cells. A more serious pathological situation arises when a second mutation, affecting transcription factors regulating the differentiation process such as NPM1 [3], 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 blasts. 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. This latter mutation activates an uncontrolled overproliferation of blasts and thereby causes acute myeloid leukemia [11]. More complex successions of mutational events may occur [20], however we will in the sequel have in mind a typical TET2/DNMT3A followed by NPM1 and finally Flt3-ITD sequence of mutations. 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 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-ITD mutation) will form a subpopulation of this category.

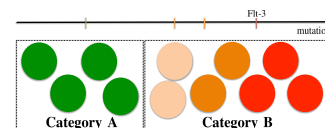


Fig. 1. In orange color are cells having some mutations. In red are those which have the Flt-3 mutation. In green are healthy cells.

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 delay differential-difference system describing cells of Category B. We investigate the stability properties of the nonlinear coupled system by establishing regional exponential stability of a biologically relevant steady state (i.e, for the studied equilibrium point, we prove exponential stability of solutions within a determined region which is an open subset of its basin of attraction). From a mathematical point of view, the challenging problems that we have to overcome here are:

*) Nonexistence of systematic methods to deal with nonlinear systems: time-domain approaches are the only way to achieve stability analysis. However, in the general case, finding a Lyapunov functional is a difficult task [12].

***) The analysis when the trajectories are piecewise continuous is more difficult than the case of uniformly continuous trajectories [17],[8]. For instance, giving a weak Lyapunov function, invariance principles (e.g, Barabrat's lemma) are not applicable to establish asymptotic stability of solutions [15].

We propose a Lyapunov-like approach by building some suitable functionals which are not usual in the sense that they take advantage from the positivity of some trajectories.

Now, let us introduce the coupled model of ordinary and mutated cells. Inspired by [14], [2] and [1], 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, [13], 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, we consider the mutation affecting the Flt-3 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 gives 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} 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 $\tilde{x}(t)$, where,

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

for all $t \geq 0$. For later use, we similarly define the total population of proliferating healthy and unhealthy cells,

$$y(t) = \int_0^\tau p(t, a) da, \quad \text{and} \quad \tilde{y}(t) = \int_0^{\tilde{\tau}} \tilde{p}(t, a) da. \quad (2)$$

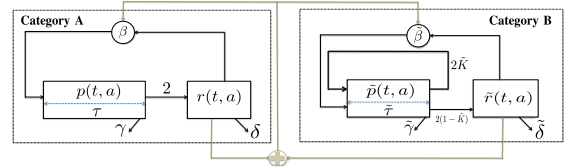


Fig. 2. Schematic representation of coupled model. The healthy part on the left and the unhealthy part on the right.

We assume that the nonlinear functions $\tilde{\beta}$ and β are continuous, decreasing and $\lim_{m \rightarrow \infty} \tilde{\beta}(m) = \beta(m) = 0$. Moreover, we consider that the nonlinearities $\tilde{\beta}$ and β are locally Lipschitz and there expressions are given by

$$\tilde{\beta}(m) = \frac{\tilde{\beta}(0)}{1 + \tilde{b}m^{\tilde{n}}}, \quad \beta(m) = \frac{\beta(0)}{1 + bm^n} \quad (3)$$

where \tilde{b} , b , \tilde{n} , n , $\tilde{\beta}(0)$ and $\beta(0)$ are strictly positive real numbers. (See, [14] for the interpretation of the Hill function in this context).

Remark 1: As a consequence of the series of mutations, we expect that: i) The maximal introduction rates verify $\tilde{\beta}(0) \gg \beta(0)$. ii) If we assume that the death rate of resting cells is the same for healthy and unhealthy cells, then the blockade in the differentiation process of unhealthy cells implies that $\delta > \tilde{\delta}$.

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

$$\left\{ \begin{array}{l} \partial_t \tilde{r}(t, a) + \partial_a \tilde{r}(t, a) = -(\tilde{\delta} + \tilde{\beta}(X(t))) \tilde{r}(t, a), \\ \text{for } a > 0, t > 0, \\ \partial_t \tilde{p}(t, a) + \partial_a \tilde{p}(t, a) = -\tilde{\gamma} \tilde{p}(t, a), \\ \text{for } 0 < a < \tilde{\tau}, t > 0, \\ \partial_t r(t, a) + \partial_a r(t, a) = -(\delta + \beta(X(t))) r(t, a) \\ \text{for } a > 0, t > 0, \\ \partial_t p(t, a) + \partial_a p(t, a) = -\gamma p(t, a) \\ \text{for } 0 < a < \tau, t > 0, \end{array} \right. \quad (4)$$

where $X(t) = x(t) + \tilde{x}(t)$. As is generally the case in Mckendrick models [21], we observe that only the death rates (δ , $\tilde{\delta}$, γ and $\tilde{\gamma}$) and the removal terms (since the reintroduction functions β and $\tilde{\beta}$ are regarded as cell loss from resting cells) appear in (4). The renewal conditions (new birth rates at $a = 0$) are introduced through the following boundary conditions,

$$\left\{ \begin{array}{l} \tilde{r}(t, 0) = 2(1 - \tilde{K})\tilde{p}(t, \tilde{\tau}), \\ \tilde{p}(t, 0) = \tilde{\beta}(x(t) + \tilde{x}(t))\tilde{x}(t) + 2\tilde{K}\tilde{p}(t, \tilde{\tau}), \\ r(t, 0) = 2p(t, \tau), \\ p(t, 0) = \beta(x(t) + \tilde{x}(t))x(t), \end{array} \right. \quad (5)$$

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 $0 < a < \tau$, are assumed to be known L^1 functions.

Rather than applying the method of characteristics, which is generally used to solve the above transport equations. Here, we will adapt an alternative approach from [16]. Let us define $\mathbf{p}^*(a, s)$ as the density of unhealthy proliferating cells, of age a , that entered to the unhealthy proliferating phase at time s . This coincides with the density of unhealthy proliferating cells at time $t = a + s$, (we notice that in this case $t > a$). In other words,

$$\mathbf{p}^*(a, s) = \tilde{p}(a + s, a). \quad (6)$$

Therefore,

$$\begin{aligned} \frac{\partial}{\partial a} \mathbf{p}^*(a, s) &= \frac{\partial}{\partial t} \tilde{p}(t, a) \Big|_{t=a+s} + \frac{\partial}{\partial a} \tilde{p}(t, a) \Big|_{t=a+s} \\ &= -\tilde{\gamma} \tilde{p}(t, a) \Big|_{t=a+s} \\ &= -\tilde{\gamma} \mathbf{p}^*(a, s). \end{aligned} \quad (7)$$

It follows that

$$\mathbf{p}^*(a, s) = \mathbf{p}^*(0, s) e^{-\tilde{\gamma}a} \quad (8)$$

where $\mathbf{p}^*(0, s) = \tilde{p}(s, 0)$. Now, let us recover \tilde{p} from \mathbf{p}^* . Noticing that $\tilde{p}(t, a) = \mathbf{p}^*(a, t - a)$, for $t > a$, and using (8) and (5), we obtain

$$\tilde{p}(t, a) = e^{-\tilde{\gamma}a} \tilde{p}(t - a, 0), \quad t > a. \quad (9)$$

Next, by defining $\mathbf{p}^v(t, s) = \tilde{p}(t, t + s)$, which can be interpreted as the density of unhealthy proliferating cells that are in the proliferating phase at time t , and have been in the proliferating phase at time 0, with an age $a = s$ at $t = 0$, (notice that now $a \geq t$).

Similarly to (7), we find that $\frac{\partial}{\partial t} \mathbf{p}^v(t, s) = -\tilde{\gamma} \mathbf{p}^v(t, s)$. Then,

$$\mathbf{p}^v(t, s) = \mathbf{p}^v(0, s) e^{-\tilde{\gamma}t}, \quad (10)$$

where $\mathbf{p}^v(0, s) = \tilde{p}(0, s) = \tilde{p}_0(s)$. Recovering \tilde{p} from \mathbf{p}^v , for $a \geq t$, gives us

$$\tilde{p}(t, a) = e^{-\tilde{\gamma}t} \tilde{p}_0(a - t), \quad a \geq t. \quad (11)$$

We have proved the following:

$$\tilde{p}(t, a) = \begin{cases} e^{-\tilde{\gamma}t} \tilde{p}_0(a - t), & 0 \leq t \leq a \\ e^{-\tilde{\gamma}a} \tilde{p}(t - a, 0), & t > a, \end{cases} \quad (12)$$

and, by an identical procedure, we obtain,

$$p(t, a) = \begin{cases} e^{-\gamma t} p_0(a - t), & 0 \leq t \leq a \\ e^{-\gamma a} p(t - a, 0), & t > a. \end{cases} \quad (13)$$

From biological considerations, we set $\lim_{a \rightarrow \infty} \tilde{r}(t, a) = \lim_{a \rightarrow \infty} r(t, a) = 0$. Therefore, by integrating the first and the third equations in (4), with respect to the age variable a between 0 and $+\infty$, we obtain,

$$\begin{cases} \dot{\tilde{x}}(t) = \tilde{r}(t, 0) - (\tilde{\delta} + \tilde{\beta}(x(t) + \tilde{x}(t))) \tilde{x}(t) \\ \dot{x}(t) = r(t, 0) - (\delta + \beta(x(t) + \tilde{x}(t))) x(t). \end{cases} \quad (14)$$

Using (12) and (13), it follows that the first and the third equations in (5) are equivalent to:

$$\tilde{r}(t, 0) = \begin{cases} 2(1 - \tilde{K})e^{-\tilde{\gamma}t} \tilde{p}_0(\tilde{\tau} - t), & 0 \leq t \leq \tilde{\tau}, \\ 2(1 - \tilde{K})e^{-\tilde{\gamma}\tilde{\tau}} \tilde{p}(t - \tilde{\tau}, 0), & t > \tilde{\tau}, \end{cases} \quad (15)$$

and

$$r(t, 0) = \begin{cases} 2e^{-\gamma t} p_0(\tau - t), & 0 \leq t \leq \tau, \\ 2e^{-\gamma \tau} p(t - \tau, 0), & t > \tau. \end{cases} \quad (16)$$

Following [1], we ease the notation by defining,

$$\tilde{u}(t) = \begin{cases} \tilde{p}(t, 0), & \text{for all } t > 0, \\ e^{-\tilde{\gamma}t} \tilde{p}_0(-t), & \text{for all } -\tilde{\tau} \leq t \leq 0, \end{cases} \quad (17)$$

and

$$u(t) = \begin{cases} p(t, 0), & \text{for all } t > 0 \\ e^{-\gamma t} p_0(-t), & \text{for all } -\tau \leq t \leq 0. \end{cases} \quad (18)$$

By combining (14)-(18), we obtain,

$$\begin{cases} \dot{\tilde{x}}(t) = -(\tilde{\delta} + \tilde{\beta}(x(t) + \tilde{x}(t))) \tilde{x}(t) \\ \quad + 2(1 - \tilde{K})e^{-\tilde{\gamma}\tilde{\tau}} \tilde{u}(t - \tilde{\tau}), \\ \dot{x}(t) = -(\delta + \beta(x(t) + \tilde{x}(t))) x(t) \\ \quad + 2e^{-\gamma\tau} u(t - \tau). \end{cases} \quad (19)$$

Similarly, by integrating the second and the fourth equations in (4) over the age variable a , between 0 and $\tilde{\tau}$ for $\tilde{p}(t, a)$, and, between 0 and τ for $p(t, a)$, we obtain,

$$\begin{cases} \dot{\tilde{y}}(t) = -\tilde{\gamma} \tilde{y}(t) + \tilde{\beta}(x(t) + \tilde{x}(t)) \tilde{x}(t) \\ \quad - (1 - 2\tilde{K}) \tilde{p}(t, \tilde{\tau}), \\ \dot{y}(t) = -\gamma y(t) + \beta(x(t) + \tilde{x}(t)) x(t) - p(t, \tau). \end{cases} \quad (20)$$

Since $\tilde{p}(t, \tilde{\tau}) = \tilde{u}(t - \tilde{\tau})$ and $p(t, \tau) = u(t - \tau)$, we get

$$\begin{cases} \dot{\tilde{y}}(t) = -\tilde{\gamma} \tilde{y}(t) + \tilde{\beta}(x(t) + \tilde{x}(t)) \tilde{x}(t) \\ \quad - (1 - 2\tilde{K}) \tilde{u}(t - \tilde{\tau}), \\ \dot{y}(t) = -\gamma y(t) + \beta(x(t) + \tilde{x}(t)) x(t) \\ \quad - u(t - \tau). \end{cases} \quad (21)$$

We obtain the fully reduced system, for all $t > 0$,

$$\left\{ \begin{array}{l} \dot{\tilde{x}}(t) = -[\tilde{\delta} + \tilde{\beta}(x(t) + \tilde{x}(t))] \tilde{x}(t) \\ \quad + 2(1 - \tilde{K})e^{-\tilde{\gamma}\tilde{\tau}} \tilde{u}(t - \tilde{\tau}), \\ \dot{\tilde{y}}(t) = -\tilde{\gamma}\tilde{y}(t) + \tilde{\beta}(x(t) + \tilde{x}(t))\tilde{x}(t) \\ \quad - (1 - 2\tilde{K})\tilde{u}(t - \tilde{\tau}), \\ \dot{\tilde{u}}(t) = \tilde{\beta}(x(t) + \tilde{x}(t))\tilde{x}(t) \\ \quad + 2\tilde{K}e^{-\tilde{\gamma}\tilde{\tau}} \tilde{u}(t - \tilde{\tau}), \\ \dot{x}(t) = -[\delta + \beta(x(t) + \tilde{x}(t))]x(t) \\ \quad + 2e^{-\gamma\tau}u(t - \tau), \\ \dot{y}(t) = -\gamma y(t) + \beta(x(t) + \tilde{x}(t))x(t) \\ \quad - u(t - \tau) \\ u(t) = \beta(x(t) + \tilde{x}(t))x(t). \end{array} \right. \quad (22)$$

We can prove that the asymptotic behavior of \tilde{y} and y are, respectively, related to the behavior of \tilde{u} and u . Moreover, since the first, the third, the fourth and the last equations in (22) are independent on \tilde{y} and y , we conclude that it is sufficient to study the asymptotic behavior of the following system:

$$\left\{ \begin{array}{l} \dot{\tilde{x}}(t) = -[\tilde{\delta} + \tilde{\beta}(x(t) + \tilde{x}(t))] \tilde{x}(t) \\ \quad + 2(1 - \tilde{K})e^{-\tilde{\gamma}\tilde{\tau}} \tilde{u}(t - \tilde{\tau}), \\ \dot{\tilde{u}}(t) = \tilde{\beta}(x(t) + \tilde{x}(t))\tilde{x}(t) \\ \quad + 2\tilde{K}e^{-\tilde{\gamma}\tilde{\tau}} \tilde{u}(t - \tilde{\tau}), \\ \dot{x}(t) = -[\delta + \beta(x(t) + \tilde{x}(t))]x(t) \\ \quad + 2e^{-\gamma\tau}\beta(x(t - \tau) + \tilde{x}(t - \tau))x(t - \tau), \end{array} \right. \quad (23)$$

We can prove that a unique piecewise continuous solution $(\tilde{x}(t), \tilde{u}(t), x(t))$ exists for all $t \geq 0$, when the system (23) is associated with the 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 $\varphi_{\tilde{u}} \in \mathcal{C}([-\tilde{\tau}, 0], \mathbb{R})$, (since the delay $\tilde{\tau}$ appears in the dynamics of \tilde{u} and τ in the dynamics of \tilde{x} and x). Moreover, System (23) is a positive system. In this paper we consider only the positive solutions of (23).

How to model the invasion of the bone marrow by the blasts? Let us observe the second equation in (23). Clearly, if $2\tilde{K}e^{-\tilde{\gamma}\tilde{\tau}} > 1$, then $\lim_{t \rightarrow \infty} \tilde{u}(t) = \infty$. From the first equation in (23), it follows that $\lim_{t \rightarrow \infty} \tilde{x}(t) = \infty$. Biologically, this situation may be interpreted as the invasion by blasts of the bone marrow and the circulation of blood.

Notice that the trivial equilibrium $(0, 0, 0)$ is an equilibrium point of the studied model. Biologically, it means the extinction of all the healthy and unhealthy blood cells. We will not be interested in such a situation where the healthy cells are eradicated (See, Table I).

TABLE I
EQUILIBRIUM POINTS OF THE MODEL

Steady state of \tilde{x}	0	\tilde{x}_e	0	\tilde{x}_e	∞
Steady state of \tilde{u}	0	\tilde{u}_e	0	\tilde{u}_e	∞
Steady state of x	0	0	x_e	x_e	*

We will also avoid the situation where we get unbounded solutions because it is the worst leukemic case. Theoretically, the convergence to the steady state $(\tilde{x}_e, \tilde{u}_e, x_e)$ may be investigated. This situation is beginning to attract attention in some solid cancers (known as cancer dormancy [Citer Dorban], and references therein). However, to our knowledge, it is not the case in leukemia, and particularly in AML, where the aim of Anti-AML therapy is the eradication of all malignant cells. Therefore, we are focusing on the stability analysis of the unique desired steady state, $E = (0, 0, x_e)$, which is the idealistic case where only the healthy cells survive.

We chain on a simple, but useful, statement. Using Taylor's series for all $\mathfrak{z} > -\epsilon$, and $\epsilon > 0$, we get

$$\begin{aligned} \beta(\mathfrak{z} + \epsilon) &= \beta(\epsilon) + \theta_{\mathfrak{z}} + R(\mathfrak{z}), \\ \tilde{\beta}(\mathfrak{z} + \epsilon) &= \tilde{\beta}(\epsilon) + \tilde{\theta}_{\mathfrak{z}} + \tilde{R}(\mathfrak{z}), \end{aligned} \quad (24)$$

where β and $\tilde{\beta}$ are the functions defined in (3), and

$$\begin{aligned} \theta &= \beta'(\epsilon), \quad R(\mathfrak{z}) = \int_{\epsilon}^{\mathfrak{z}} (\mathfrak{z} + \epsilon - l)\beta^{(2)}(l)dl, \\ \tilde{\theta} &= \tilde{\beta}'(\epsilon) \quad \text{and} \quad \tilde{R}(\mathfrak{z}) = \int_{\epsilon}^{\mathfrak{z}} (\mathfrak{z} + \epsilon - l)\tilde{\beta}^{(2)}(l)dl. \end{aligned} \quad (25)$$

Then we prove the following statement:

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

$$|R(\mathfrak{z})| \leq \mathfrak{s}|\mathfrak{z}|, \quad \text{and} \quad |\tilde{R}(\mathfrak{z})| \leq \tilde{\mathfrak{s}}|\mathfrak{z}| \quad (26)$$

Proof: A proof is proposed in Appendix A., where we determine the analytic expressions of \mathfrak{s} and $\tilde{\mathfrak{s}}$. ■

In the remainder of the paper, we are going to use Claim 1 by specifying (\mathfrak{z}, ϵ) differently in Sections II and III. Finally, let us define the quadratic function

$$Q(m) = \frac{1}{2}m^2. \quad (27)$$

Now, we are ready to analyze, by a Lyapunov-like technique, the stability properties of the desired steady state, $E = (0, 0, x_e)$. Clearly, when we talk about convergence to a desired state, we mean that 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.

II. ANALYSIS OF E

A. Existence of E

From the third equation in (23), we observe that if $E = (0, 0, x_e)$ exists, then it satisfies:

$$\delta x_e = (2e^{-\gamma\tau} - 1)\beta(x_e)x_e. \quad (28)$$

Since β is a continuous, decreasing function and $\lim_{m \rightarrow \infty} \beta(m) = 0$, we conclude that a unique equilibrium $(0, 0, x_e)$ exists if and only if the condition

$$(2e^{-\gamma\tau} - 1)\beta(0) > \delta, \quad (29)$$

is satisfied. Notice that the condition $2e^{-\gamma\tau} - 1 > 0$ is a necessary (but not sufficient) condition to verify (29).

B. Stability properties of E

1) *New Representation of the System:* In this section, we assume that the condition (29) is satisfied and we perform a stability analysis of $E = (0, 0, x_e)$. Let us perform the change of coordinate $\mathfrak{r} = x - x_e$. Thus, the third equation in (23) gives

$$\begin{aligned} \dot{\mathfrak{r}}(t) = & -[\delta + \beta(\mathfrak{r}(t) + x_e + \tilde{x}(t))] (\mathfrak{r}(t) + x_e) \\ & + 2e^{-\gamma\tau} \beta(\mathfrak{r}(t - \tau) + x_e + \tilde{x}(t - \tau)) \mathfrak{r}(t - \tau) \quad (30) \\ & + 2e^{-\gamma\tau} \beta(\mathfrak{r}(t - \tau) + x_e + \tilde{x}(t - \tau)) x_e. \end{aligned}$$

We are looking for a better presentation of the dynamics $\mathfrak{r}(t)$ that eases its analysis. Let us focus on the nonlinear terms. Substituting $\mathfrak{z} = \mathfrak{r} + \tilde{x}$ and $\mathfrak{e} = x_e$ in (24), we deduce that (30) gives

$$\begin{aligned} \dot{\mathfrak{r}}(t) = & -[\delta + \beta(x_e) + \theta x_e] \mathfrak{r}(t) - \theta \mathfrak{r}^2(t) - \theta \tilde{x}(t) \mathfrak{r}(t) \\ & - R(\mathfrak{z}(t)) \mathfrak{r}(t) - \theta x_e \tilde{x}(t) - R(\mathfrak{z}(t)) x_e \\ & + 2e^{-\gamma\tau} \beta(x_e) \mathfrak{r}(t - \tau) + 2e^{-\gamma\tau} \theta \mathfrak{r}^2(t - \tau) \\ & + 2e^{-\gamma\tau} \theta \mathfrak{r}(t - \tau) \tilde{x}(t - \tau) \\ & + R(\mathfrak{z}(t - \tau)) \mathfrak{r}(t - \tau) + 2e^{-\gamma\tau} \theta x_e \mathfrak{r}(t - \tau) \\ & + 2e^{-\gamma\tau} \theta x_e \tilde{x}(t - \tau) + 2e^{-\gamma\tau} x_e R(\mathfrak{z}(t - \tau)), \end{aligned}$$

where some terms were eliminated, using (28). Similarly, the first and the second equations in (23) give

$$\begin{cases} \dot{\tilde{x}}(t) = -[\tilde{\delta} + \tilde{\beta}(x_e)] \tilde{x}(t) - \tilde{\theta} \mathfrak{z}(t) \tilde{x}(t) \\ \quad - \tilde{R}(\mathfrak{z}(t)) \tilde{x}(t) + 2(1 - \tilde{K}) e^{-\tilde{\gamma}\tilde{\tau}} \tilde{u}(t - \tilde{\tau}), \\ \dot{\tilde{u}}(t) = \tilde{\beta}(x_e) \tilde{x}(t) + \tilde{\theta} \mathfrak{z}(t) \tilde{x}(t) + \tilde{R}(\mathfrak{z}(t)) \tilde{x}(t) \\ \quad + 2\tilde{K} e^{-\tilde{\gamma}\tilde{\tau}} \tilde{u}(t - \tilde{\tau}). \end{cases}$$

Using (24), it follows that,

$$\begin{cases} \dot{\tilde{x}}(t) = -[\tilde{\delta} + \tilde{\beta}(x_e)] \tilde{x}(t) - \tilde{\theta} \mathfrak{r}(t) \tilde{x}(t) - 2\tilde{\theta} Q(\tilde{x}(t)) \\ \quad - \tilde{R}(\mathfrak{z}(t)) \tilde{x}(t) + 2(1 - \tilde{K}) e^{-\tilde{\gamma}\tilde{\tau}} \tilde{u}(t - \tilde{\tau}), \\ \dot{\tilde{u}}(t) = \tilde{\beta}(x_e) \tilde{x}(t) + \tilde{\theta} \mathfrak{r}(t) \tilde{x}(t) + 2\tilde{\theta} Q(\tilde{x}(t)) \\ \quad + \tilde{R}(\mathfrak{z}(t)) \tilde{x}(t) + 2\tilde{K} e^{-\tilde{\gamma}\tilde{\tau}} \tilde{u}(t - \tilde{\tau}). \end{cases}$$

Consequently, we get the following system,

$$\begin{cases} \dot{\tilde{x}}(t) = -[\tilde{\delta} + \tilde{\beta}(x_e)] \tilde{x}(t) - \tilde{\theta} \mathfrak{r}(t) \tilde{x}(t) - 2\tilde{\theta} Q(\tilde{x}(t)) \\ \quad - \tilde{R}(\mathfrak{z}(t)) \tilde{x}(t) + 2(1 - \tilde{K}) e^{-\tilde{\gamma}\tilde{\tau}} \tilde{u}(t - \tilde{\tau}), \\ \dot{\tilde{u}}(t) = \tilde{\beta}(x_e) \tilde{x}(t) + \tilde{\theta} \mathfrak{r}(t) \tilde{x}(t) + 2\tilde{\theta} Q(\tilde{x}(t)) \\ \quad + \tilde{R}(\mathfrak{z}(t)) \tilde{x}(t) + 2\tilde{K} e^{-\tilde{\gamma}\tilde{\tau}} \tilde{u}(t - \tilde{\tau}) \\ \dot{\mathfrak{r}}(t) = -[\delta + \beta(x_e) + \theta x_e] \mathfrak{r}(t) - \theta \mathfrak{r}^2(t) - \theta \tilde{x}(t) \mathfrak{r}(t) \\ \quad - R(\mathfrak{z}(t)) \mathfrak{r}(t) - \theta x_e \tilde{x}(t) - R(\mathfrak{z}(t)) x_e \\ \quad + 2e^{-\gamma\tau} \beta(x_e) \mathfrak{r}(t - \tau) + 2e^{-\gamma\tau} \theta \mathfrak{r}^2(t - \tau) \\ \quad + 2e^{-\gamma\tau} \theta \mathfrak{r}(t - \tau) \tilde{x}(t - \tau) \\ \quad + R(\mathfrak{z}(t - \tau)) \mathfrak{r}(t - \tau) + 2e^{-\gamma\tau} \theta x_e \mathfrak{r}(t - \tau) \\ \quad + 2e^{-\gamma\tau} \theta x_e \tilde{x}(t - \tau) + 2e^{-\gamma\tau} x_e R(\mathfrak{z}(t - \tau)). \end{cases} \quad (31)$$

If the trajectories of the of the system (31) converge exponentially to the origin, then the positive trajectories of the system (23) converge exponentially to E . It is worth mentioning that the trajectories \tilde{x} and \tilde{u} are positive.

However, due to the shifting, the trajectories \mathfrak{r} , in the representation as (31), may be positive or negative. We will consider these facts when constructing the suitable Lyapunov functional.

2) *Obtaining Decay Conditions:* We study the global stability properties of the coupled system using its representation as (31). To begin, using (26), we notice that the derivative of $Q(\mathfrak{r}(t))$ along the trajectories of (31), satisfies:

$$\begin{aligned} \dot{Q}(t) \leq & -c_1 Q(\mathfrak{r}(t)) + c_2 |\mathfrak{r}(t)| Q(\mathfrak{r}(t)) \\ & + c_3 \tilde{x}(t) Q(\mathfrak{r}(t)) + c_4 \tilde{x}(t) |\mathfrak{r}(t)| \\ & + c_5 |\mathfrak{r}(t)| |\mathfrak{r}(t - \tau)| + c_6 |\mathfrak{r}(t)| Q(\mathfrak{r}(t - \tau)) \quad (32) \\ & + c_7 \tilde{x}(t - \tau) |\mathfrak{r}(t)| |\mathfrak{r}(t - \tau)| \\ & + c_8 \tilde{x}(t - \tau) |\mathfrak{r}(t)|, \end{aligned}$$

where,

$$\begin{aligned} c_1 &= 2[\delta + \beta(x_e)] - \omega, \\ \omega &= 2[(1 - x_e)\mathfrak{s} - \theta x_e], \\ c_2 &= 2(|\theta| + \mathfrak{s}), \quad c_3 = 2|\theta|, \\ c_4 &= (|\theta| + \mathfrak{s})x_e, \\ c_5 &= 2e^{-\gamma\tau} [\beta(x_e) + (|\theta| + \mathfrak{s})x_e], \\ c_6 &= 4e^{-\gamma\tau} + 2\mathfrak{s}, \\ c_7 &= \frac{1}{2}c_6, \quad \text{and,} \quad c_8 = x_e e^{-\gamma\tau} c_2. \end{aligned} \quad (33)$$

Notice that c_1 may be positive or negative while, for all $i \in \{2, \dots, 8\}$, $c_i > 0$. Next, let us introduce the operators,

$$\begin{aligned} \mathcal{Y}(\tilde{u}_t) &= \int_{t-\tilde{\tau}}^t (m - t + 2\tilde{\tau}) \tilde{u}(m) dm, \\ \mathcal{S}(\phi_t) &= \int_{t-\tau}^t (m - t + 2\tau) Q(\phi(m)) dm. \end{aligned} \quad (34)$$

Therefore, for all $t \geq 0$, we have

$$\begin{aligned} \dot{\mathcal{Y}}(t) &\leq 2\tilde{\tau} \tilde{u}(t) - \tilde{\tau} \tilde{u}(t - \tilde{\tau}) - \int_{t-\tilde{\tau}}^t \tilde{u}(m) dm, \\ \dot{\mathcal{S}}(t) &\leq 2\tau Q(\phi(t)) - \tau Q(\phi(t - \tau)) \\ &\quad - \int_{t-\tau}^t Q(\phi(m)) dm. \end{aligned} \quad (35)$$

For later use, let us notice that:

$$\begin{aligned} \mathcal{Y}(\tilde{u}_t) &\leq 2\tilde{\tau} \int_{t-\tilde{\tau}}^t \tilde{u}(m) dm, \quad \text{and} \\ \mathcal{S}(\phi_t) &\leq 2\tau \int_{t-\tau}^t Q(\phi(m)) dm, \end{aligned} \quad (36)$$

Now, we introduce the functional,

$$\begin{aligned} V(\tilde{x}_t, \tilde{u}_t, \mathfrak{r}_t) &= Q(\mathfrak{r}(t)) + A\tilde{x}(t) + \frac{B}{2\tilde{\tau}} \mathcal{Y}(\tilde{u}_t) \\ &\quad + \frac{C}{2\tau} [\mathcal{S}(\mathfrak{r}_t) + \mathcal{S}(\tilde{x}_t)], \end{aligned} \quad (37)$$

where A , B and C are strictly positive constants that we select later. Using (32) and (35), we prove that the

derivative of V , along the trajectories of (31), satisfies

$$\begin{aligned}
\dot{V}(t) \leq & -c_1 Q(\mathbf{x}(t)) + c_2 |\mathbf{x}(t)| Q(\mathbf{x}(t)) + c_3 \tilde{x}(t) Q(\mathbf{x}(t)) \\
& + c_4 \tilde{x}(t) |\mathbf{x}(t)| + c_5 |\mathbf{x}(t)| |\mathbf{x}(t-\tau)| \\
& + c_6 |\mathbf{x}(t)| Q(\mathbf{x}(t-\tau)) + c_7 \tilde{x}(t-\tau) |\mathbf{x}(t)| |\mathbf{x}(t-\tau)| \\
& + c_8 \tilde{x}(t-\tau) |\mathbf{x}(t)| - A [\tilde{\delta} + \tilde{\beta}(x_e)] \tilde{x}(t) \\
& - A \tilde{\theta} \mathbf{x}(t) \tilde{x}(t) - 2A \tilde{\theta} Q(\tilde{x}(t)) - A \tilde{R}(\mathfrak{z}(t)) \tilde{x}(t) \\
& + 2A(1 - \tilde{K}) e^{-\tilde{\gamma}\tilde{\tau}} \tilde{u}(t - \tilde{\tau}) + B \tilde{\beta}(x_e) \tilde{x}(t) \\
& + B \tilde{\theta} \mathbf{x}(t) \tilde{x}(t) + 2B \tilde{\theta} Q(\tilde{x}(t)) + B \tilde{R}(\mathfrak{z}(t)) \tilde{x}(t) \\
& + 2B \tilde{K} e^{-\tilde{\gamma}\tilde{\tau}} \tilde{u}(t - \tilde{\tau}) - \frac{B}{2} \tilde{u}(t - \tilde{\tau}) \\
& - \frac{B}{2\tilde{\tau}} \int_{t-\tilde{\tau}}^t \tilde{u}(m) dm + C (Q(\mathbf{x}(t)) + Q(\tilde{x}(t))) \\
& - \frac{C}{2} [Q(\mathbf{x}(t-\tau)) + Q(\tilde{x}(t-\tau))] \\
& - \frac{C}{2\tau} \int_{t-\tau}^t [Q(\mathbf{x}(m)) + Q(\tilde{x}(m))] dm.
\end{aligned}$$

By grouping the terms we obtain,

$$\begin{aligned}
\dot{V}(t) \leq & -[c_1 - C] Q(\mathbf{x}(t)) + [c_2 |\mathbf{x}(t)| + c_3 \tilde{x}(t)] Q(\mathbf{x}(t)) \\
& - [A (\tilde{\delta} + \tilde{\beta}(x_e)) - B \tilde{\beta}(x_e)] \tilde{x}(t) \\
& - [2(A - B) \tilde{\theta} - C] Q(\tilde{x}(t)) \\
& - \left[\left(\frac{1}{2} - 2\tilde{K} e^{-\tilde{\gamma}\tilde{\tau}} \right) B - 2A(1 - \tilde{K}) e^{-\tilde{\gamma}\tilde{\tau}} \right] \tilde{u}(t - \tilde{\tau}) \\
& - \frac{B}{2\tilde{\tau}} \int_{t-\tilde{\tau}}^t \tilde{u}(m) dm - \frac{C}{2} (Q(\mathbf{x}(t-\tau)) + Q(\tilde{x}(t-\tau))) \\
& - \frac{C}{2\tau} \int_{t-\tau}^t (Q(\mathbf{x}(m)) + Q(\tilde{x}(m))) dm \\
& + [c_4 + |\tilde{\theta}(B - A)|] \tilde{x}(t) |\mathbf{x}(t)| + c_5 |\mathbf{x}(t)| |\mathbf{x}(t-\tau)| \\
& + c_6 |\mathbf{x}(t)| Q(\mathbf{x}(t-\tau)) + c_7 \tilde{x}(t-\tau) |\mathbf{x}(t)| |\mathbf{x}(t-\tau)| \\
& + c_8 \tilde{x}(t-\tau) |\mathbf{x}(t)| - (A - B) \tilde{R}(\mathfrak{z}(t)) \tilde{x}(t).
\end{aligned}$$

Thanks to Claim 1, we get

$$\begin{aligned}
\dot{V}(t) \leq & -[c_1 - C] Q(\mathbf{x}(t)) + [c_2 |\mathbf{x}(t)| + c_3 \tilde{x}(t)] Q(\mathbf{x}(t)) \\
& - [A (\tilde{\delta} + \tilde{\beta}(x_e)) - B \tilde{\beta}(x_e)] \tilde{x}(t) \\
& - [2(A - B) \tilde{\theta} - C - 2\tilde{\mathfrak{s}} |A - B|] Q(\tilde{x}(t)) \\
& - \left[\left(\frac{1}{2} - 2\tilde{K} e^{-\tilde{\gamma}\tilde{\tau}} \right) B - 2A(1 - \tilde{K}) e^{-\tilde{\gamma}\tilde{\tau}} \right] \tilde{u}(t - \tilde{\tau}) \\
& - \frac{B}{2\tilde{\tau}} \int_{t-\tilde{\tau}}^t \tilde{u}(m) dm - \frac{C}{2} (Q(\mathbf{x}(t-\tau)) + Q(\tilde{x}(t-\tau))) \\
& - \frac{C}{2\tau} \int_{t-\tau}^t (Q(\mathbf{x}(m)) + Q(\tilde{x}(m))) dm \\
& + [c_4 + |A - B|(|\tilde{\theta}| + \tilde{\mathfrak{s}})] \tilde{x}(t) |\mathbf{x}(t)| \\
& + c_5 |\mathbf{x}(t)| |\mathbf{x}(t-\tau)| + c_6 |\mathbf{x}(t)| Q(\mathbf{x}(t-\tau)) \\
& + c_7 \tilde{x}(t-\tau) |\mathbf{x}(t)| |\mathbf{x}(t-\tau)| + c_8 \tilde{x}(t-\tau) |\mathbf{x}(t)|.
\end{aligned}$$

Next, using the inequalities:

$$\begin{aligned}
\tilde{x}(t) |\mathbf{x}(t)| & \leq Q(\tilde{x}(t)) + Q(\mathbf{x}(t)), \\
|\mathbf{x}(t)| |\mathbf{x}(t-\tau)| & \leq Q(\mathbf{x}(t)) + Q(\mathbf{x}(t-\tau)),
\end{aligned}$$

$$\tilde{x}(t-\tau) |\mathbf{x}(t)| \leq Q(\tilde{x}(t-\tau)) + Q(\mathbf{x}(t)),$$

$$\tilde{x}(t-\tau) |\mathbf{x}(t)| |\mathbf{x}(t-\tau)| \leq Q(\tilde{x}(t-\tau)) + 2Q(\mathbf{x}(t-\tau)) Q(\mathbf{x}(t)),$$

we deduce that,

$$\begin{aligned}
\dot{V}(t) \leq & -[c_1 - C - c_4 - c_5 - c_8 - |A - B|(|\tilde{\theta}| + \tilde{\mathfrak{s}})] Q(\mathbf{x}(t)) \\
& + [c_2 |\mathbf{x}(t)| + c_3 \tilde{x}(t)] Q(\mathbf{x}(t)) \\
& - [A (\tilde{\delta} + \tilde{\beta}(x_e)) - B \tilde{\beta}(x_e)] \tilde{x}(t) \\
& - [2(A - B) \tilde{\theta} - C - c_4 - |A - B|(|\tilde{\theta}| + 3\tilde{\mathfrak{s}})] Q(\tilde{x}(t)) \\
& - \left[\left(\frac{1}{2} - 2\tilde{K} e^{-\tilde{\gamma}\tilde{\tau}} \right) B - 2A(1 - \tilde{K}) e^{-\tilde{\gamma}\tilde{\tau}} \right] \tilde{u}(t - \tilde{\tau}) \\
& - \frac{B}{2\tilde{\tau}} \int_{t-\tilde{\tau}}^t \tilde{u}(m) dm - \left[\frac{C}{2} - c_5 \right] Q(\mathbf{x}(t-\tau)) \\
& - \left[\frac{C}{2} - c_8 - c_7 \right] Q(\tilde{x}(t-\tau)) \\
& + c_6 [|\mathbf{x}(t)| + Q(\mathbf{x}(t))] Q(\mathbf{x}(t-\tau)) \\
& - \frac{C}{2\tau} \int_{t-\tau}^t [Q(\mathbf{x}(m)) + Q(\tilde{x}(m))] dm,
\end{aligned}$$

Now, let us select

$$C = 3 \max\{c_8 + c_7, c_5\}. \quad (38)$$

If the following decay conditions are satisfied,

$$\begin{aligned}
1 - 4\tilde{K} e^{-\tilde{\gamma}\tilde{\tau}} & > 0, \\
\delta + \beta(x_e) & > \bar{\omega}, \\
\tilde{\delta} & > 4\tilde{\beta}(x_e),
\end{aligned} \quad (39)$$

where $\bar{\omega} = \frac{1}{2} [\omega + c_4 + c_5 + c_8 + |A - B|(|\tilde{\theta}| + \tilde{\mathfrak{s}}) + C]$. Moreover, we choose

$$\begin{aligned}
A & = 1 - 4\tilde{K} e^{-\tilde{\gamma}\tilde{\tau}}, \\
B & = 5A.
\end{aligned} \quad (40)$$

A direct consequence of (38), (39) and (40), is that the following inequalities are fulfilled:

$$\begin{aligned}
c_1 & > C + c_4 + c_5 + c_8 + |A - B|(|\tilde{\theta}| + \tilde{\mathfrak{s}}), \\
A\tilde{\delta} & > (B - A)\tilde{\beta}(x_e) \\
\frac{1 - 4\tilde{K} e^{-\tilde{\gamma}\tilde{\tau}}}{4(1 - \tilde{K}) e^{-\tilde{\gamma}\tilde{\tau}}} & > \frac{A}{B}, \\
C & > 2 \max\{c_8 + c_7, c_5\}.
\end{aligned} \quad (41)$$

Therefore, there exist strictly positive constants a_1, a_2, a_3, a_4, a_5 and α , such that

$$\begin{aligned}
\dot{V}(t) \leq & -a_1 Q(\mathbf{x}(t)) + [c_2 |\mathbf{x}(t)| + c_3 \tilde{x}(t)] Q(\mathbf{x}(t)) \\
& - a_2 \tilde{x}(t) + \alpha Q(\tilde{x}(t)) - a_3 Q(\tilde{x}(t-\tau)) \\
& - a_4 \tilde{u}(t - \tilde{\tau}) - a_5 Q(\mathbf{x}(t-\tau)) \\
& + c_6 [|\mathbf{x}(t)| + Q(\mathbf{x}(t))] Q(\mathbf{x}(t-\tau)) \\
& - \frac{B}{2\tilde{\tau}} \int_{t-\tilde{\tau}}^t \tilde{u}(m) dm \\
& - \frac{C}{2\tau} \int_{t-\tau}^t [Q(\mathbf{x}(m)) + Q(\tilde{x}(m))] dm,
\end{aligned} \quad (42)$$

From (36), we find suitable upper bounds to the integral terms in (42), and we straightforwardly determine a strictly positive constant \mathfrak{d} , such that

$$\begin{aligned} \dot{V}(t) &\leq -\mathfrak{d}V(\tilde{x}_t, \tilde{u}_t, \mathfrak{r}_t) \\ &\quad - \left[\frac{a_1}{2} + c_2|\mathfrak{r}(t)| + c_3\tilde{x}(t) \right] Q(\mathfrak{r}(t)) \\ &\quad - [a_4 - c_6(|\mathfrak{r}(t)| + Q(\mathfrak{r}(t)))] Q(\mathfrak{r}(t - \tau)) \\ &\quad - \frac{1}{2} [a_2 + \alpha\tilde{x}(t)] \tilde{x}(t). \end{aligned} \quad (43)$$

On the other hand, observe that

$$\begin{aligned} |\mathfrak{r}(t)| &\leq \sqrt{2V(\tilde{x}_t, \tilde{u}_t, \mathfrak{r}_t)}, \\ \tilde{x}(t) &\leq \frac{1}{A}V(\tilde{x}_t, \tilde{u}_t, \mathfrak{r}_t), \\ Q(\mathfrak{r}(t)) &\leq V(\tilde{x}_t, \tilde{u}_t, \mathfrak{r}_t). \end{aligned} \quad (44)$$

Therefore, by defining the sublevels

$$\begin{aligned} \bar{V}_1 &= \frac{1}{2} \left(\frac{a_1}{4c_2} \right)^2, \quad \bar{V}_2 = \frac{a_1 A}{4c_3} \\ \bar{V}_3 &= \frac{1}{2} \left(\frac{a_4}{2c_6} \right)^2, \quad \bar{V}_4 = \frac{a_4}{2c_6}, \quad \bar{V}_5 = \frac{a_2}{\alpha A} \\ \bar{V} &= \min \{ \bar{V}_1, \bar{V}_2, \bar{V}_3, \bar{V}_4, \bar{V}_5 \}, \end{aligned} \quad (45)$$

we deduce that for all adequate initial conditions satisfying $V(\varphi_{\tilde{x}}, \varphi_{\tilde{u}}, \varphi_{\mathfrak{r}}) \leq \bar{V}$, the time derivative of the functional V verifies

$$\dot{V}(t) \leq -\mathfrak{d}V(\tilde{x}_t, \tilde{u}_t, \mathfrak{r}_t). \quad (46)$$

We conclude that

$$V(\tilde{x}_t, \tilde{u}_t, \mathfrak{r}_t) \leq e^{-\mathfrak{d}t} V(\varphi_{\tilde{x}}, \varphi_{\tilde{u}}, \varphi_{\mathfrak{r}}). \quad (47)$$

Thus,

$$Q(\mathfrak{r}(t)) + A\tilde{x}(t) \leq e^{-\mathfrak{d}t} V(\varphi_{\tilde{x}}, \varphi_{\tilde{u}}, \varphi_{\mathfrak{r}}). \quad (48)$$

Therefore, \mathfrak{r} and \tilde{x} converge exponentially to zero. Consequently, from the second equation in (31), (we recall that $2(1 - \tilde{K})e^{-\tilde{\gamma}\tilde{\tau}} < 1$), it follows that \tilde{u} converges to the origin. To summarize, we proved the following:

Theorem 1: Let the nonlinear system (23) be such that

- i) $\bar{\omega} - \beta(x_e) < \delta < (2e^{-\gamma\tau} - 1)\beta(0)$,
- ii) $4\tilde{\beta}(x_e) < \tilde{\delta}$,
- iii) $4\tilde{K}e^{-\tilde{\gamma}\tilde{\tau}} < 1$.

Therefore, the equilibrium point $E = (0, 0, x_e)$ exists, it is unique, and it is exponentially stable for all initial conditions satisfying

$$\begin{aligned} \mathfrak{E} &= \left\{ (\varphi_{\tilde{x}}, \varphi_{\tilde{u}}, \varphi_x), \varphi_{\tilde{x}} \in \mathcal{C}([-\tau, 0], \mathbb{R}^+), \right. \\ &\quad \varphi_{\tilde{u}} \in \mathcal{C}([-\tilde{\tau}, 0], \mathbb{R}^+), \varphi_x \in \mathcal{C}([-\tau, 0], \mathbb{R}^+), \\ &\quad \left. V(\varphi_{\tilde{x}}, \varphi_{\tilde{u}}, \varphi_x - x_e) \leq \bar{V} \right\}. \end{aligned} \quad (49)$$

C. Biological Interpretation of the findings:

The condition i), in Theorem 1, concerns mainly the ordinary (healthy) stem cells, even if the lower bound is impacted by some unhealthy parameters. Indeed, the

inequality on the right gives a necessary and sufficient condition for the existence of the positive equilibrium point x_e . Moreover, the upper bound on δ means that daughter cells, which join the healthy resting phase, must be larger than the lost by differentiation and natural death in the healthy resting compartment. 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 small population of healthy resting cells will tend to enter into proliferation more frequently, in order to regenerate and create new daughter cells.

The condition ii), in Theorem 1, seems to correspond more to the mutated cells which are not severely affected (i.e, without the FLT3 mutation, since it involves parameters that characterize only the resting unhealthy cells). It may be achieved under the therapeutic effect of drugs that act to promote the differentiation or death of mutated cells (i.e, making $\tilde{\delta}$ sufficiently high, exceeding a threshold which depends on $\beta(x_e)$).

Now, observe that the condition iii), in Theorem 1, concerns the unhealthy cells which are always active in the proliferating phase (i.e, leukemic cells with the FLT3 mutation). Unsurprisingly, the therapeutic action must focus on the rate of fast-self renewing, \tilde{K} , to decrease it. Simultaneously, we may 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 apoptosis of proliferating cells).

Finally, the estimates of the basin of attraction as well as the decay rates, may assist for prescribing adequate concentrations of drug and define the minimum duration of therapy.

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 phenomena is described by some transport equations, that we reduced to a nonlinear time-delay system, coupled to a nonlinear differential-difference system. 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 a treatment regimen to promote the survival of healthy cells and completely eradicate the mutated cells.

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APPENDIX

A. Proof of Claim 1

Since R and \tilde{R} are of identical form we will prove Claim 3 only for the function R .

Using the expression of β , which is given in (3), we observe that for all $x_e > 0$ and $\mathfrak{z} > -x_e$,

$$R(\mathfrak{z}) = \beta(0) \left(\frac{1}{1 + b(\mathfrak{z} + x_e)^n} - \frac{1}{1 + bx_e^n} \right) - \theta \mathfrak{z}. \quad (50)$$

Obviously, when $|z| > 1$, we have

$$\frac{|R(\mathfrak{z})|}{|\mathfrak{z}|} \leq \frac{2\beta(0) + |\theta|}{|\mathfrak{z}|} \leq 2\beta(0) + |\theta| = \mathfrak{s}. \quad (51)$$

For the case $|\mathfrak{z}| \leq 1$, let us study the function

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

where $q(\mathfrak{z}) = [1 + b(\mathfrak{z} + x_e)^n](1 + bx_e^n)$. Furthermore, using the equality,

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

we deduce that,

$$\rho(\mathfrak{z}) = -nbx_e^{n-1} \frac{\mathfrak{z}}{q(\mathfrak{z})} + \mathfrak{C}(\mathfrak{z}). \quad (52)$$

where

$$\mathfrak{C}(\mathfrak{z}) = -nb(n-1) \frac{1}{q(\mathfrak{z})} \int_0^{\mathfrak{z}} \int_0^l (m + x_e)^{n-2} dm dl.$$

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,

$$\rho(\mathfrak{z}) = -\frac{nbx_e^{n-1}}{h^2} \mathfrak{z} + \mathfrak{C}(\mathfrak{z}) - \frac{nbx_e^{n-1}}{h} \rho(\mathfrak{z}) \mathfrak{z}. \quad (53)$$

We should point out that

$$\theta := \beta'(x_e) = \beta(0) \frac{nbx_e^{n-1}}{h^2}.$$

Therefore,

$$\rho(\mathfrak{z}) + \frac{\theta}{\beta(0)} \mathfrak{z} = \mathfrak{C}(\mathfrak{z}) - \frac{nbx_e^{n-1}}{h} \rho(\mathfrak{z}) \mathfrak{z}. \quad (54)$$

On the other hand, observe that (50) is equivalent to $R(\mathfrak{z}) = \beta(0) \left[\rho(\mathfrak{z}) - \frac{\theta}{\beta(0)} \mathfrak{z} \right]$. By combining the last inequality with (54), we obtain the intermediate consequence,

$$\frac{R(\mathfrak{z})}{\beta(0)} = \mathfrak{C}(\mathfrak{z}) - \frac{nbx_e^{n-1}}{h} \rho(\mathfrak{z}) \mathfrak{z} \quad (55)$$

Now, we readily check that

$$|\mathfrak{C}(\mathfrak{z})| \leq \frac{nb(n-1)}{q(\mathfrak{z})} (|\mathfrak{z}| + x_e)^{n-2} \frac{\mathfrak{z}^2}{2}. \quad (56)$$

From (52) we deduce that $|\rho(\mathfrak{z})| \leq \frac{nbx_e^{n-1}}{q(\mathfrak{z})} |\mathfrak{z}| + |\mathfrak{C}(\mathfrak{z})|$.

Using (56), it follows that

$$|\mathfrak{z}\rho(\mathfrak{z})| \leq \frac{nbx_e^{n-1}}{q(\mathfrak{z})}\mathfrak{z}^2 + \frac{nb(n-1)}{2q(\mathfrak{z})}(|\mathfrak{z}| + x_e)^{n-2}|\mathfrak{z}|^3. \quad (57)$$

Consequently, from (55), and using (56) and (57), we attain the upper bound,

$$\begin{aligned} \frac{|R(\mathfrak{z})|}{\beta(0)} &\leq \left[\frac{nb(n-1)}{2q(\mathfrak{z})}(|\mathfrak{z}| + x_e)^{n-2} + \frac{(nbx_e^{n-1})^2}{hq(\mathfrak{z})} \right] \mathfrak{z}^2 \\ &\quad + \frac{(nb)^2(n-1)x_e^{n-1}}{2hq(\mathfrak{z})}(|\mathfrak{z}| + x_e)^{n-2}|\mathfrak{z}|^3. \end{aligned} \quad (58)$$

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

$$\frac{1}{q(\mathfrak{z})} \leq \frac{1+b(2x_e)^n}{[1+b(|\mathfrak{z}|+x_e)^n]h}. \quad (59)$$

From (59) and (58), we deduce that

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

where the positive constants \mathfrak{a}_1 and \mathfrak{a}_2 are given by

$$\mathfrak{a}_1 = [1 + b(2x_e)^2]^n \max \left\{ \frac{nb(n-1)}{2h}, \frac{(nbx_e^{n-1})^2}{h^2} \right\},$$

and

$$\mathfrak{a}_2 = \frac{((nb)^2(n-1)x_e^{n-1})(1+b(2x_e)^n)}{2h^2}.$$

Next, observe that:

case 1: if $|\mathfrak{z}| + x_e \leq 1$, then $\forall b > 0$,

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

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

*) if $b \geq 1$

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

*) if $b < 1$

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

Therefore, in both cases, we proved that

$$|R(\mathfrak{z})| \leq \mathfrak{a}_3 \mathfrak{z}^2, \quad (60)$$

where

$$\mathfrak{a}_3 = \beta(0) \max \{ \mathfrak{a}_1 \max \{ 2, b^{-1} \}, \mathfrak{a}_2 \max \{ 1, b^{-1} \} \}.$$

Now, recall that $R(\mathfrak{z}) = \beta(0) \left[\rho(\mathfrak{z}) - \frac{\theta}{\beta(0)} \mathfrak{z} \right]$. From (60), it follows that,

$$\frac{|\beta(0)\rho(\mathfrak{z}) - \theta\mathfrak{z}|}{|\mathfrak{z}|} \leq \mathfrak{a}_3 |\mathfrak{z}|. \quad (61)$$

Therefore, we observe that if $|\mathfrak{z}| \leq 1$, the inequality (61) implies that

$$\frac{|\beta(0)\rho(\mathfrak{z}) - \theta\mathfrak{z}|}{|\mathfrak{z}|} \leq \mathfrak{a}_3. \quad (62)$$

From (51) and (62), we conclude that, for all $\mathfrak{z} > -x_e$ and $x_e > 0$, we have

$$|R(\mathfrak{z})| \leq \mathfrak{s} |\mathfrak{z}|, \quad (63)$$

where

$$\mathfrak{s} = \max \{ \mathfrak{a}_3, 2\beta(0) + |\theta| \}. \quad (64)$$