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A Discrete-Maturity Interconnected Model of Healthy and Cancer Cell Dynamics in Acute Myeloid Leukemia.*

J. L. Avila[1] C. Bonnet[1] H. Özbay[2] J. Clairambault[3] S. I. Niculescu[4] P. Hirsch[5] F. Delhommeau[6]

Abstract— **In this paper we propose a coupled model for healthy and cancer cell dynamics in Acute Myeloid Leukemia consisting of two stages of maturation for cancer cells and three stages of maturation for healthy cells. The cell dynamics are modeled by nonlinear partial differential equations (PDE). Applying the method of characteristics enable us to reduce the PDE model to a nonlinear distributed delay system. For an equilibrium point of interest, necessary and sufficient conditions of local asymptotic stability are given. The results are illustrated with numerical examples and simulations.**

I. INTRODUCTION

Blood cells are produced by hematopoiesis. Starting in the bone marrow by hematopoiteic stem cells (HSCs), the blood-forming system is an example of a multistage system. At the first level, HSCs can proliferate, self renew and differentiate into multiple lineages. The process of cell division, called proliferation or cell cycle, consists of four phases: G_1, S, G_2 and M. At the end of the M phase cell division occurs and two different daughter cells are produced: either with the same biological properties as the parent (self-renewal) or progenitors. The production of progenitors at cell division is called differentiation. Finally, several stages down, fully differentiated cells are released in blood circulation. One of the first mathematical models on hematopoiesis was proposed by [4]. This model consists of a system of differential equations, describing haematopoietic stem cell dynamics, considering a rest (or quiescent) phase and a proliferative phase during the cell division cycle. Several dynamical models of hematopoiesis have been proposed and studied in the literature, see e.g. [1]-[7] and their references.

Leukaemia, in common language also termed a blood cancer, is characterized by uncontrolled proliferation of blood cells. It may occur that some genetic alteration, appearing in a haematopoietic stem cell, escapes the various physiological controls and is transmitted by subsequent divisions to daughter cells to eventually yield a leukaemia. Acute Myelogenous Leukemia combines at least two molecular events : a blockade of the maturation / differentiation program (class I mutations), leading to the accumulation of immature myeloid cells, and an advantage of proliferation (class II mutations), leading to the flooding of bone marrow by immature and proliferating immature cells (blasts). A third type of mutation, reducing the rate of cell death (apoptosis), could also occur. Until now, the treatment of AML relies on heavy chemotherapy. In [8], a system of delay-differential equations, inspired by the model of [4], with discrete maturity structure has been proposed as model for AML. The model takes into account the differentiation blockade that is frequently observed in AML. For the equilibrium and stability analysis (linear and nonlinear system) of this model see [15], [4] and the references given there.

In this paper, we address the problem of modeling the interconnection of healthy and cancer cells. The model of healthy cell population dynamics is based on the mathematical model introduced in [8] but without considering the effect of leukemic cells and maintaining the philosophy of modeling the phases of the cell cycle. The dynamical behavior of the cancer cell population is based on the model studied in [8] which models the effect of AML cells as follows: the self-renewal phenomenon is written in two parts where fast and slow dynamics are separated. For both populations of healthy and cancer cells, we consider that its proliferating cells are separated into three phases: G_1, S, G_2M. We do not consider the phases G_2 and M separately since there exist technical difficulties with the identification of their parameters. The interconnection phenomenon between the healthy and cancer cells takes place on the reintroduction functions leaving the resting compartments to the proliferating compartments of both populations of cells at the first stage. Finally, we consider a second compartment of healthy and cancer cells and only a third compartment of healthy cells. The preliminary results for a single stage coupled healthy and cancer cell populations are reported in [10] where we can also find a biological and medical discussion that we do not want to repeat here. In the present

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[1]INRIA Saclay - Île-de-France, Equipe DISCO, LSS - SUPELEC, 3 rue Joliot Curie, 91192 Gif-sur-Yvette, Cedex, France. Jose.Avila@lss.supelec.fr Catherine.Bonnet@inria.fr

[2]Dept. of Electrical and Electronics Eng., Bilkent University, Ankara, 06800, Turkey. hitay@bilkent.edu.tr

[3]INRIA-Rocquencourt EPI BANG and UPMC Univ. Paris 06, CNRS UMR 7598, Lab. Jacques-Louis Lions, 4, pl. Jussieu F75252, Paris, Cedex 05, France. Jean.Clairambault@inria.fr

[4]L2S (UMR CNRS 8506), CNRS-Supélec, 3 rue Joliot Curie, 91192, Gif-sur-Yvette, France. Silviu.Niculescu@lss.supelec.fr

[5]Sorbonne Universités, UPMC Univ Paris 6, GRC n. 07, Groupe de Recherche Clinique sur les Myéloproliférations Aiguës et Chroniques MyPAC, F75012 Paris, France, AP-HP, Hôpital Saint-Antoine, Laboratoire d'Hématologie, F75012 Paris France, Sorbonne Universités, UPMC Univ Paris 6, UMR_S 938, CDR Saint-Antoine, F-75012 Paris, France and INSERM, UMR_S 938 CDR Saint-Antoine, F-75012 Paris, France pierre.hirsch@sat.aphp.fr

[6]Sorbonne Universités, UPMC Univ Paris 6, GRC n. 07, Groupe de Recherche Clinique sur les Myéloproliférations Aiguës et Chroniques MyPAC, F75012 Paris, France, AP-HP, Hôpital Saint-Antoine, Service d'hématologie et de thérapie cellulaire, F75012 Paris France, Sorbonne Universités, UPMC Univ Paris 6, UMR_S 938, CDR Saint-Antoine, F-75012 Paris, France and INSERM, UMR_S 938 CDR Saint-Antoine, F-75012 Paris, France francois.delhommeau@sat.aphp.fr

work multi-stage configurations are analyzed, with coupling in the first stage only.

The structure of this paper is as follows. Section 2 provides a detailed exposition of the partial differential equations that governs the dynamics of the healthy and cancer cells. It is also shown how to derive a nonlinear distributed delay model, by using the method of characteristics. Section 3 first deals with the study of the existence of non-negative equilibrium points of the nonlinear delay model. Then, a linearized model is obtained and a stability analysis of the linear system around a chosen equilibrium point is discussed. A detailed academic example is presented in Section 4. Finally, in Section 5, some concluding remarks are outlined.

II. Mathematical model of a coupled population of healthy and cancer cells

A. System of Partial Differential Equations

In this section, for completeness of the presentation, we perform a mathematical model derivation that is similar to the earlier works [8] and [10], where special cases of the coupled multi-compartmental model considered here are analyzed, see also [9], and its references.

Let us consider two populations of cells representing the healthy and the cancer cells. We denote by $p_i(t,a)$, $l_i(t,a)$, $n_i(t,a)$ and $r_i(t,a)$ the cell populations of the G_1, S, G_2M and G_0, respectively, of cancer immature cells at the *i-th* compartment, with age $a \geq 0$ at time $t \geq 0$. We consider only two compartments of cancerous cells, that is $i = 1, 2$. The fast-renewal effect of AML cells is represented by a new phase, located at the end of the phase M, called $\tilde{G}_0$ and its population is denoted by $\tilde{r}_i(t,a)$. The dynamical behavior of the cancer cell population is represented by the following system of transport equations dependent on age a:

$$\begin{cases} \partial_t p_i + \partial_a p_i = -\left(\gamma_i^1 + g_i^p(a)\right) p_i, & 0 < a < \tau_i^1, t > 0, \\ \partial_t l_i + \partial_a l_i = -\left(\gamma_i^2 + g_i^l(a)\right) l_i, & 0 < a < \tau_i^2, t > 0, \\ \partial_t n_i + \partial_a n_i = -\left(\gamma_i^3 + g_i^n(a)\right) n_i, & 0 < a < \tau_i^3, t > 0, \\ \partial_t r_1 + \partial_a r_1 = -\left(\delta_1 + \beta_1(z(t))\right) r_1, & a > 0, t > 0, \\ \partial_t r_2 + \partial_a r_2 = -\delta_2 r_2 & \\ \qquad + \beta_2\left(\int_0^{+\infty} r_2(t,a)\,da\right) r_2, & a > 0, t > 0, \\ \partial_t \tilde{r}_i + \partial_a \tilde{r}_i = -\tilde{\beta}_i\left(\int_0^{+\infty} \tilde{r}_i(t,a)\,da\right)\tilde{r}_i, & a > 0, t > 0. \end{cases} \quad (1)$$

On the other hand, $\bar{p}_j(t,a)$, $\bar{l}_j(t,a)$, $\bar{n}_j(t,a)$, and $\bar{r}_j(t,a)$ represent the cell populations of the G_1, S, G_2M and G_0, respectively, of healthy cells at the *j-th* compartment, with age $a \geq 0$ at time $t \geq 0$. We consider three compartments of healthy cells, this is $j = 1, 2, 3$. The dynamical behavior of the healthy cells is represented by the following system of transport equations dependent on age a:

$$\begin{cases} \partial_t \bar{p}_j + \partial_a \bar{p}_j = -\left(\bar{\gamma}_j^1 + \bar{g}_j^{\bar{p}}(a)\right) \bar{p}_j, & 0 < a < \bar{\tau}_j^1, t > 0, \\ \partial_t \bar{l}_j + \partial_a \bar{l}_j = -\left(\bar{\gamma}_j^2 + \bar{g}_j^{\bar{l}}(a)\right) \bar{l}_j, & 0 < a < \bar{\tau}_j^2, t > 0, \\ \partial_t \bar{n}_j + \partial_a \bar{n}_j = -\left(\bar{\gamma}_j^3 + \bar{g}_j^{\bar{n}}(a)\right) \bar{n}_j, & 0 < a < \bar{\tau}_j^3, t > 0, \\ \partial_t \bar{r}_1 + \partial_a \bar{r}_1 = -\left(\bar{\delta}_1 + \bar{\beta}_1(z(t))\right) \bar{r}_1, & a > 0, t > 0, \\ \partial_t \bar{r}_j + \partial_a \bar{r}_j = -\bar{\delta}_j \bar{r}_j & \\ \qquad + \bar{\beta}_j\left(\int_0^{+\infty} \bar{r}_j(t,a)\,da(t)\right) \bar{r}_j, & a > 0, t > 0. \end{cases} \quad (2)$$

The functions and variables, at the compartments i or j, needed to read (1) and (2) has the following properties and biological meaning: the death rates $\delta_i > 0$ and $\bar{\delta}_j > 0$; β_i and $\bar{\beta}_j$ are re-introduction function from the resting subpopulation into the proliferative subpopulation of cancer and healthy cells, respectively; γ_i^1, γ_i^2, γ_i^3 and $\bar{\gamma}_j^1, \bar{\gamma}_j^2, \bar{\gamma}_j^3$ are constant death rates in the G_1 , S, G_2M phases of cancer and healthy cells, respectively; the amount of time spent in the G_1, S, G_2M phases are τ_i^1, τ_i^2, τ_i^3 for the healthy cells and $\bar{\tau}_j^1$, $\bar{\tau}_j^2$, $\bar{\tau}_j^3$ for the cancer cells; and, the division rates of the phases G_1, S, G_2M are functions depending on a, denoted by g_i^p, g_i^l, g_i^n for the healthy cells and $\bar{g}_j^{\bar{p}}$, $\bar{g}_j^{\bar{l}}$, $\bar{g}_j^{\bar{n}}$ for the cancer cells.

At the compartments $i = 1, 2$, $x_i(t) := \int_0^{+\infty} r_i(t,a)\,da$ and $\tilde{x}_i(t) := \int_0^{+\infty} \tilde{r}_i(t,a)\,da$ stand for the total population of resting and fast-self renewing cells at the time t, respectively. Otherwise, at the compartments $j = 1, 2, 3$ the total population of resting healthy cells is denoted by $\bar{x}_j(t) := \int_0^{+\infty} \bar{r}_j(t,a)\,da$. The interconnection between the cancer and healthy cells occurs at their first compartments by means of the common feedback of resting cells $z(t) := x_1(t) + \bar{x}_1(t)$, which acts on the functions β_1 and $\bar{\beta}_1$.

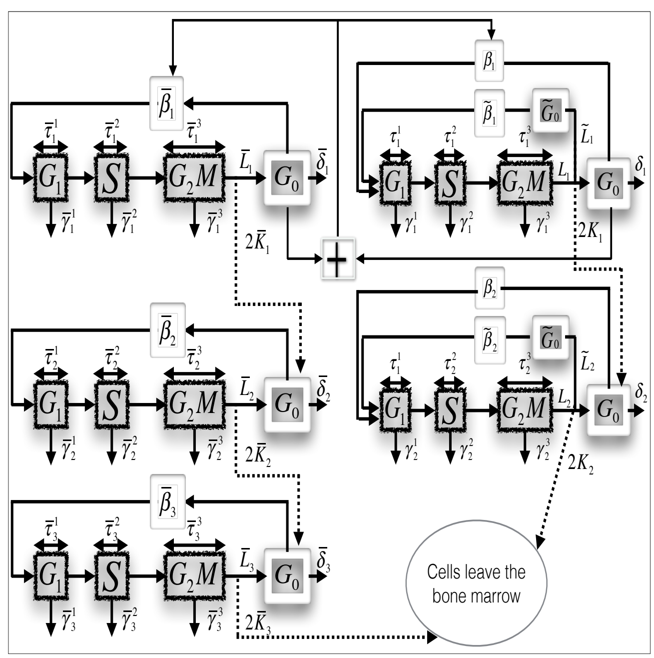

Fig. 1. Interconnected model of healthy cells (left) and cancer cells (right)

Boundary conditions associated with (1) and (2) are given by:

$$\begin{cases} p_1(t,a=0) &= \beta_1(x_1(t)+\bar{x}_1(t))\,x_1(t) \\ & \quad +\tilde{\beta}(\tilde{x}_1(t))\,\tilde{x}_1(t) \\ p_2(t,a=0) &= \beta_2(x_2(t))\,x_2(t)+\tilde{\beta}(\tilde{x}_2(t))\,\tilde{x}_2(t) \\ l_i(t,a=0) &= \int_0^{\tau_i^1} g_i^p(a)\,p_i(t,a)\,da, \\ n_i(t,a=0) &= \int_0^{\tau_i^2} g_i^l(a)\,l_i(t,a)\,da, \\ m_i(t,a=0) &= \int_0^{\tau_i^3} g_i^n(a)\,n_i(t,a)\,da, \\ r_i(t,a=0) &= L_i\int_0^{\tau^4} g_i^m(a)\,m(t,a)\,da \\ \tilde{r}_i(t,a=0) &= \tilde{L}_i\int_0^{\tau_i^4} g_i^m(a)\,m(t,a)\,da \end{cases}$$

for the cancer cells; and

$$\begin{cases} \bar{p}_1(t,a=0) &= \bar{\beta}_1(x_1(t)+\bar{x}_1(t))\,\bar{x}_1(t) \\ \bar{p}_j(t,a=0) &= \bar{\beta}_j(\bar{x}_j(t))\,\bar{x}_j(t) \\ \bar{l}_j(t,a=0) &= \int_0^{\bar{\tau}_j^1} g_j^{\bar{p}}(a)\,\bar{p}_j(t,a)\,da, \\ \bar{n}_j(t,a=0) &= \int_0^{\bar{\tau}_j^2} g_j^{\bar{l}}(a)\,\bar{l}_j(t,a)\,da, \\ \bar{m}_j(t,a=0) &= \int_0^{\bar{\tau}_j^3} g_j^{\bar{n}}(a)\,\bar{n}_j(t,a)\,da, \\ \bar{r}_j(t,a=0) &= L_j\int_0^{\bar{\tau}_j^4} g_j^{\bar{m}}(a)\,\bar{m}_j(t,a)\,da \end{cases}$$

for the healthy cells; $L_i := 2\sigma(1-K_i)$, $\tilde{L}_i := 2(1-\sigma_i)(1-K_i)$ and $\bar{L}_j = 2\left(1-\bar{K}_j\right)$. The constants K_i, and $\bar{K}_j$ represent the probability of differentiation of daughter cells so that $0 < K_i < 1$ and $0 < \bar{K}_j < 1$. The constant σ_i represents the probability of fast self-renewal $0 < \sigma_i < 1$.

The initial age-distribution of the populations of (1) are nonnegative age-dependent functions and they are assumed to be known: $p_i(t=0,a) = p_i^0(a)$, $l_i(t=0,a) = l_i^0(a)$, $n_i(t=0,a) = n_i^0(a)$, $m_i(t=0,a) = m_i^0(a)$, $r_i(t=0,a) = r_i^0(a)$, $\tilde{r}_i(t=0,a) = \tilde{r}_i^0(a)$, $\bar{p}_j(t=0,a) = p_j^0(a)$, $\bar{l}_j(t=0,a) = \bar{l}_j^0(a)$, $\bar{n}_j(t=0,a) = \bar{n}_j^0(a)$, $\bar{m}_j(t=0,a) = \bar{m}_j^0(a)$ and $\bar{r}_j(t=0,a) = \bar{r}_j^0(a)$.

We need the following assumptions to complete the mathematical model:

1) The division rates g_i^p, g_i^l, g_i^n,g^m, $g_j^{\bar{p}}$, $g_j^{\bar{l}}$, $g_j^{\bar{n}}$ and $g_j^{\bar{m}}$ are continuous functions such that $\int_0^{\tau_i^1} g_i^p(a)\,da = +\infty$, $\int_0^{\tau_i^2} g_i^l(a)\,da = +\infty$, $\int_0^{\tau_i^3} g_i^n(a)\,da = +\infty$, $\int_0^{\tau_i^4} g_i^m(a)\,da = +\infty$, $\int_0^{\bar{\tau}_j^1} g_j^{\bar{p}}(a)\,da = +\infty$, $\int_0^{\bar{\tau}_j^2} g_j^{\bar{l}}(a)\,da = +\infty$, $\int_0^{\bar{\tau}_j^3} g_j^{\bar{n}}(a)\,da = +\infty$, $\int_0^{\bar{\tau}_j^4} g_j^{\bar{m}}(a)\,da = +\infty$.
2) $\lim\limits_{a\to+\infty} r_i(t,a) = 0$, $\lim\limits_{a\to+\infty} \tilde{r}_i(t,a) = 0$ and $\lim\limits_{a\to+\infty} \bar{r}_j(t,a) = 0$.
3) The re-introduction terms β_i, $\tilde{\beta}_i$ and $\tilde{\beta}_j$ are differentiable, non-negative and uniformly decreasing functions.

In this paper, we are interested in functions β_i, $\tilde{\beta}_i$ and $\bar{\beta}_j$ of the form

$$\beta_i(x) = \frac{\beta_i(0)}{1+b_i x^{N_i}},\ \ \tilde{\beta}_i(\tilde{x}) = \frac{\tilde{\beta}(0)}{1+\tilde{b}_i\tilde{x}^{\tilde{N}_i}},\ \ \bar{\beta}_j(\bar{x}) = \frac{\bar{\beta}_j(0)}{1+\bar{b}_j\bar{x}^{\bar{N}_j}}$$

where N_i, $\tilde{N}_i$ and $\bar{N}_j$ are integers greater or equal to 2; $b_i > 0$, $\tilde{b}_i > 0$, $\bar{b}_j > 0$ and $\tilde{b}_i \ll 1$. These functions are known as Hill functions.

Now, we shall show how a system of ordinary differential distributed delayed equations is obtained from the PDE's (1) and (2) .

B. Distributed Delay Differential Equation Model

By using the method of characteristics and applying the same rationale as in [8] we obtain the following systems of distributed delay differential equations

$$\begin{aligned} \dot{x}_1(t) &= -(\delta_1+\beta_1(x_1(t)+\bar{x}_1(t)))\,x_1(t) && (3)\\ &\quad +L_1\left(h_1^3*h_1^2*h_1^1*\omega_1\right)(t) \\ \dot{\tilde{x}}_1(t) &= -\tilde{\beta}_1(\tilde{x}_1(t))\,\tilde{x}_1(t) && (4)\\ &\quad +\tilde{L}_1\left(h_1^3*h_1^2*h_1^1*\omega_1\right)(t) \\ \dot{\bar{x}}_1(t) &= -\left(\bar{\delta}_1+\bar{\beta}_1(x_1(t)+\bar{x}_1(t))\right)\bar{x}_1(t) && (5)\\ &\quad +\bar{L}_1\left(\bar{h}_1^3*\bar{h}_1^2*\bar{h}_1^1*\bar{\omega}_1\right)(t) \end{aligned}$$

$$\begin{aligned} \dot{x}_2(t) &= -(\delta_2+\beta_2(x_2(t)))\,x_2(t) && (6)\\ &\quad +L_2\left(h_2^3*h_2^2*h_2^1*\omega_2\right)(t) \\ &\quad +2K_1\left(h_1^3*h_1^2*h_1^1*\omega_1\right)(t) \\ \dot{\tilde{x}}_2(t) &= -\tilde{\beta}_2(\tilde{x}_2(t))\,\tilde{x}_2(t) && (7)\\ &\quad +\tilde{L}_2\left(h_2^3*h_2^2*h_2^1*\omega_2\right)(t) \\ \dot{\bar{x}}_2(t) &= -\left(\bar{\delta}_2+\bar{\beta}_2(\bar{x}_2(t))\right)\bar{x}_2(t) && (8)\\ &\quad +\bar{L}_2\left(\bar{h}_2^3*\bar{h}_2^2*\bar{h}_2^1*\bar{\omega}_2\right)(t) \\ &\quad +2\bar{K}_1\left(\bar{h}_1^3*\bar{h}_1^2*\bar{h}_1^1*\bar{\omega}_1\right)(t) \\ \dot{\bar{x}}_3(t) &= -\left(\bar{\delta}_3+\bar{\beta}_3(\bar{x}_3(t))\right)\bar{x}_3(t) && (9)\\ &\quad +\bar{L}_3\left(\bar{h}_3^3*\bar{h}_3^2*\bar{h}_3^1*\bar{\omega}_3\right)(t) \end{aligned}$$

where $\omega_1(t) := \beta_1(x_1(t)+\bar{x}_1(t))\,x_1(t) + \tilde{\beta}_1(\tilde{x}_1(t))\,\tilde{x}_1(t)$, $\bar{\omega}_1(t) := \bar{\beta}_1(x_1(t)+\bar{x}_1(t))\,\bar{x}_1(t)$, $\omega_2(t) := \beta_2(x_2(t))\,x_2(t) + \tilde{\beta}_2(\tilde{x}_2(t))\,\tilde{x}_2(t)$, $\bar{\omega}_2(t) := \bar{\beta}_2(x_2)\,\bar{x}_2(t)$, $\bar{\omega}_3(t) := \bar{\beta}_3(x_3)\,\bar{x}_3(t)$, $h_i^1(t) := f_i^p(t)\,e^{-\gamma_i^1 t}$, $h_i^2(t) := f_i^l(t)\,e^{-\gamma_i^2 t}$, $h_i^3(t) := f_i^n(t)\,e^{-\gamma_i^3 t}$, $\bar{h}_j^1(t) := f_j^{\bar{p}}(t)\,e^{-\bar{\gamma}_j^1 t}$, $\bar{h}_j^2(t) := f_j^{\bar{l}}(t)\,e^{-\bar{\gamma}_j^2 t}$, $\bar{h}_j^3(t) := f_j^{\bar{n}}(t)\,e^{-\bar{\gamma}_j^3 t}$. The functions f_i^p, f_i^l, f_i^n, $f_j^{\bar{p}}$, $f_j^{\bar{l}}$ and $f_j^{\bar{n}}$ are density functions defined on the intervals $\left[0,\tau_i^1\right]$, $\left[0,\tau_i^2\right]$, $\left[0,\tau_i^3\right]$, $\left[0,\tau_i^4\right]$,$\left[0,\bar{\tau}_j^1\right]$, $\left[0,\bar{\tau}_j^2\right]$ and $\left[0,\bar{\tau}_j^3\right]$, respectively. The symbol $*$ stands for the usual convolution operator.

As in [8], we will consider the following general form for the division rates h_i^k and $\bar{h}_j^k$, $k=1,2,3$:

$$h_i^k(t) = \frac{m_i^k}{e^{m_i^k\tau_i^k}-1}e^{\left(m_i^k-\gamma_i^k\right)t} \text{ for } 0 \le t \le \tau_i^k$$

and

$$\bar{h}_j^k(t) = \frac{\bar{m}_j^k}{e^{\bar{m}_j^k\bar{\tau}_j^k}-1}e^{\left(\bar{m}_j^k-\bar{\gamma}_j^k\right)t} \text{ for } 0 \le t \le \tau_j^k.$$

This gives

$$\int_0^{\tau_i^k} h_i^k(t)\,e^{-st}dt = q_i^k\left(\frac{1-e^{-\tau_i^k\left(s-r_i^k\right)}}{s-r_i^k}\right) =: H_i^k(s)$$

and

$$\int_0^{\bar{\tau}_j^k} \bar{h}_j^k(t)\,e^{-st}dt = \bar{q}_j^k\left(\frac{1-e^{-\bar{\tau}_j^k\left(s-\bar{r}_j^k\right)}}{s-\bar{r}_j^k}\right) =: \bar{H}_j^k(s)$$

with $q_i^k := \frac{m_i^k}{e^{m_i^k \tau_i^k}-1}$, $\bar{q}_j^k := \frac{\bar{m}_j^k}{e^{\bar{m}_j^k \bar{\tau}_j^k}-1}$, $r_i^k := m_i^k - \gamma_i^k$ and $\bar{r}_j^k := \bar{m}_j^k - \bar{\gamma}_j^k$.

For simplicity, we write $H_i(s) = H_i^1(s)\, H_i^2(s)\, H_i^3(s)$ and $\bar{H}_j(s) = \bar{H}_j^1(s)\, \bar{H}_j^2(s)\, \bar{H}_j^3(s)$. It is not difficult to show that $\left\|H_i^k(s)\right\|_\infty = H_i^k(0)$ and $\left\|\bar{H}_j^k(s)\right\|_\infty = \bar{H}_j^k(0)$. Thus $\|H_i(s)\|_\infty = H_i(0)$ and $\left\|\bar{H}_j(s)\right\|_\infty = \bar{H}_j(0)$.

The compartmental model is illustrated in Figure 2, and each compartment Σ_i and $\bar{\Sigma}_j$ is depicted in Figures 3 and 4, respectively.

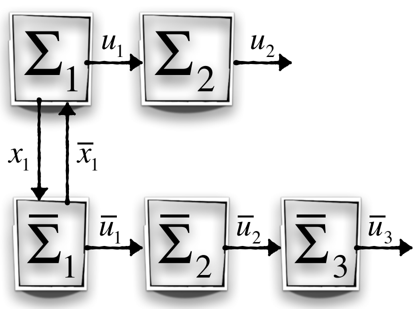

Fig. 2. Compartmental Representation of the System.

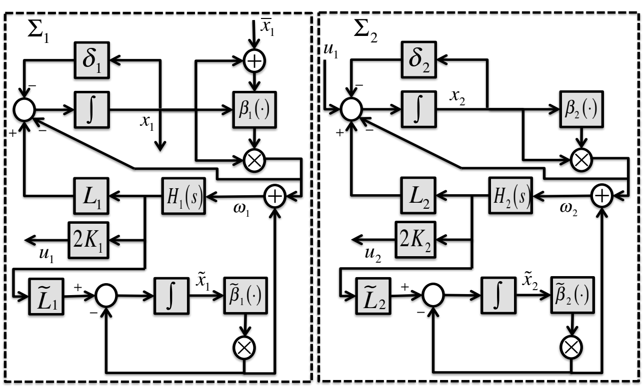

Fig. 3. Internal Structure of the Compartments Σ_1(left) and Σ_2(right).

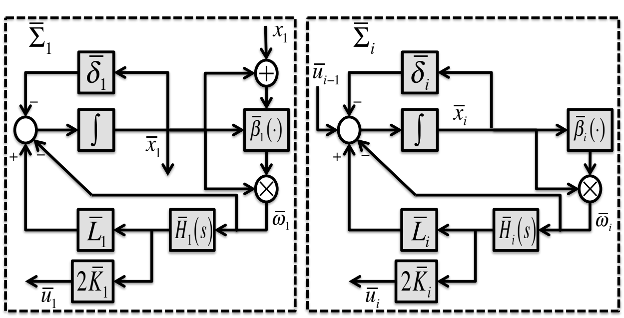

Fig. 4. Internal Structure of the Compartments $\bar{\Sigma}_1$(left) and $\bar{\Sigma}_j$, $j = 2, 3$(right).

In what follows, we will study some qualitative properties of the nonlinear system.

III. Equilibrium Existence, Model linearization and stability

A. Nonnegative equilibrium points

We call x_1^e, $\tilde{x}_1^e$, $\bar{x}_1^e$, x_2^e, $\tilde{x}_2^e$, $\bar{x}_2^e$ and $\bar{x}_3^e$ the equilibrium points of (3)-(9). It follows easily that the origin, $x_1^e = \tilde{x}_1^e = \bar{x}_1^e = x_2^e = \tilde{x}_2^e = \bar{x}_2^e = \bar{x}_3^e = 0$, is an equilibrium of the nonlinear system.

Equating to zero the right hand side of (3)-(9), it may be concluded that on the equilibrium the re-introduction functions satisfy the following relations:

$$\beta_1(x_1^e + \bar{x}_1^e) = -c_1\delta_1, \tag{10}$$

$$\tilde{\beta}_1(\tilde{x}_1^e) = -\tilde{c}_1\delta_1\left(x_1^e/\tilde{x}_1^e\right), \tag{11}$$

$$\bar{\beta}_1(x_1^e + \bar{x}_1^e) = -\frac{\bar{\delta}_1}{1-\bar{L}_1\bar{H}_1(0)}, \tag{12}$$

$$\beta_2(x_2^e) = -c_2\left(\alpha_1\delta_2 - 2K_1H_1(0)\,\delta_1\left(x_1^e/x_2^e\right)\right), \tag{13}$$

$$\tilde{\beta}_2(\tilde{x}_2^e) = -\tilde{c}_2\left(\alpha_1\delta_2 x_2 - 2K_1H_1(0)\,\delta_1 x_1^e\right)\left(1/\tilde{x}_2^e\right), \tag{14}$$

$$\bar{\beta}_2(\bar{x}_2^e) = \frac{-\bar{\delta}_2 + 2\bar{K}_1\bar{H}_1(0)\,\bar{\beta}_1(\bar{x}_1^e)\left(\bar{x}_1^e/\bar{x}_2^e\right)}{1-\bar{L}_2\bar{H}_2(0)}, \tag{15}$$

$$\bar{\beta}_3(\bar{x}_3^e)\;\frac{-\bar{\delta}_3 + 2\bar{K}_2\bar{H}_2(0)\,\bar{\beta}_2(\bar{x}_2^e)\left(\bar{x}_2^e/\bar{x}_3^e\right)}{1-\bar{L}_3\bar{H}_3(0)}, \tag{16}$$

where $\alpha_1 := 1 - \left(L_1 + \tilde{L}_1\right)$, $\alpha_2 := 1 - \left(L_2 + \tilde{L}_2\right)$, $c_1 := \left(1 - \tilde{L}_1 H_1(0)\right)\alpha_1^{-1}$, $\tilde{c}_1 := \tilde{L}_1 H_1(0)\,\alpha_1^{-1}$, $c_2 := \left(1 - \tilde{L}_2 H_2(0)\right)(\alpha_1\alpha_2)^{-1}$ and $\tilde{c}_2 := \tilde{L}_2 H_2(0)\,(\alpha_1\alpha_2)^{-1}$.

We can draw the following two conclusions about non-negative steady states: 1) the right-hand side of (10)-(16) must be positive due to the non-negativeness of the re-introduction functions β_1, $\tilde{\beta}_1$, $\bar{\beta}_1$, β_2, $\tilde{\beta}_2$, $\bar{\beta}_2$ and $\bar{\beta}_3$; 2) in the first compartment, the decreasing property of the functions β_1 and $\bar{\beta}_1$ implies that $\beta_1(0) > \beta(x_1^e + \bar{x}_1^e)$ and $\bar{\beta}_1(0) > \bar{\beta}(x_1^e + \bar{x}_1^e)$. We have in this way proved that the following conditions are to be satisfied on any positive equilibrium point:

$$c_1\delta_1 < \beta_1(0), \tag{17}$$

$$-\frac{\bar{\delta}_1}{\left(1-\bar{L}_1\bar{H}_1(0)\right)} < \bar{\beta}_1(0), \tag{18}$$

$$\frac{1}{L_1+\tilde{L}_1} < H_1(0) < \frac{1}{\tilde{L}_1}, \tag{19}$$

$$\frac{1}{\bar{L}_1} < \bar{H}_1(0), \tag{20}$$

$$\frac{1}{L_2+\tilde{L}_2} < H_2(0) < \frac{1}{\tilde{L}_2}, \tag{21}$$

$$\frac{1}{\bar{L}_2} < \bar{H}_2(0), \tag{22}$$

$$\frac{1}{\bar{L}_3} < \bar{H}_3(0). \tag{23}$$

Now, we discuss under which conditions the following two cases of equilibrium points have solutions: 1) $x_1^e = 0$, $\tilde{x}_1^e = 0$, $\bar{x}_1^e > 0$, $x_2^e = 0$, $\tilde{x}_2^e = 0$, $\bar{x}_2^e > 0$ and $\bar{x}_3^e > 0$;

2) $x_1^e > 0$, $\tilde{x}_1^e > 0$, $\bar{x}_1^e > 0$, $x_2^e > 0$, $\tilde{x}_2^e > 0$, $\bar{x}_2^e > 0$ and $\bar{x}_3^e > 0$.

First, when $x_1^e = \tilde{x}_1^e = x_2^e = \tilde{x}_2^e = 0$, the conditions (17)-(23) are necessary and sufficient for the existence of a unique equilibrium point $\bar{x}_1^e > 0$, $\bar{x}_2^e > 0$ and $\bar{x}_3^e > 0$, see [4].

Finally, when we are interested in strictly positive equilibrium points at the first compartment the following relation must be fulfilled by x_1^e and $\bar{x}_1^e$ on the assumption that β_1, $\tilde{\beta}_1$ and $\bar{\beta}_1$ are Hill functions:

$$x_1^e+\bar{x}_1^e = \begin{cases} \left(\dfrac{\left(\beta_1(0) - c_1\delta_1 - 1\right)\bar{b}}{\left(\bar{\beta}_1(0) + \bar{c} - 1\right) b}\right)^{1/\left(N_1 - \bar{N}_1\right)} & , N_1 > N_1, \\ \left(\dfrac{\left(\bar{\beta}_1(0) + \bar{c} - 1\right) b_1}{\left(\beta(0) - c_1\delta_1 - 1\right)\bar{b}_1}\right)^{1/\left(\bar{N}_1 - N_1\right)} & , N_1 < N_1, \end{cases}$$

and when $N_1 = \bar{N}_1$

$$x_1^e + \bar{x}_1^e = \left(\frac{\beta_1(0) - c_1\delta_1 - 1}{b_1}\right)^{1/N_1} = \left(\frac{\bar{\beta}_1(0) + \bar{c} - 1}{\bar{b}_1}\right)^{1/\bar{N}_1}$$

where $\bar{c} = -\dfrac{\bar{\delta}}{1 - \bar{L}\bar{H}(0)}$. The remaining equilibrium points x_2^e, $\tilde{x}_2^e$, $\bar{x}_2^e$ and $\bar{x}_3^e$ are obtained uniquely from (13)-(16).

The perturbation of a healthy solution i.e. $x_1(t) = 0$, $\tilde{x}_1(t) = 0$, $\bar{x}_1(t) > 0$, $x_2(t) = 0$, $\tilde{x}_2(t) = 0$, $\bar{x}_2(t) > 0$ and $\bar{x}_3(t) > 0$ for all $t \geq 0$, may provoke the born of cancer cells and therefore we analyze its behavior in the next section.

B. Stability analysis

Consider the following perturbed trajectories: $X_1(t) := x_1(t) - x_1^e$, $\tilde{X}_1(t) := \tilde{x}_1(t) - \tilde{x}_1^e$, $\bar{X}_1(t) := \bar{x}_1(t) - \bar{x}_1^e$, $X_2(t) := x_2(t) - x_2^e$, $\tilde{X}_2(t) := \tilde{x}_2(t) - \tilde{x}_2^e$, $\bar{X}_2(t) := \bar{x}_2(t) - \bar{x}_2^e$ and $\bar{X}_3(t) := \bar{x}_3(t) - \bar{x}_3^e$. Taking the time derivative of the perturbed trajectories and setting

$$x = \begin{pmatrix} x_1 & x_1 & x_1 & x_2 & x_2 & x_2 & x_3 \end{pmatrix}^{\mathsf{T}},$$

$$x^e = \begin{pmatrix} x_1^e & x_1^e & x_1^e & x_2^e & x_2^e & x_2^e & x_3^e \end{pmatrix}^{\mathsf{T}},$$

we deduce that the linearized model around the equilibrium point $x_1^e \geq 0$, $\tilde{x}_1^e \geq 0$, $\bar{x}_1^e \geq 0$, $x_2^e \geq 0$, $\tilde{x}_2^e \geq 0$, $\bar{x}_2^e \geq 0$ and $\bar{x}_3^e \geq 0$ is represented by:

$$\begin{aligned} \dot{X}_1(t) &= -(\delta_1 + \mu_1) X_1(t) - c_{12}\bar{X}_1(t) \\ &\quad + L_1\left(h_1^3 * h_1^2 * h_1^1 * W_1\right)(t) \end{aligned} \tag{24}$$

$$\dot{\tilde{X}}_1(t) = -\tilde{\mu}_1\tilde{X}_1(t) + \tilde{L}_1\left(h_1^3 * h_1^2 * h_1^1 * W_1\right)(t) \tag{25}$$

$$\begin{aligned} \dot{\bar{X}}_1(t) &= -\left(\bar{\delta}_1 + \bar{\mu}_1\right)\bar{X}_1(t) - c_{15}X_1(t) \\ &\quad + \bar{L}_1\left(\bar{h}_1^3 * \bar{h}_1^2 * \bar{h}_1^1 * \bar{W}_1\right)(t) \end{aligned} \tag{26}$$

$$\begin{aligned} \dot{X}_2(t) &= -(\delta_2 + \mu_2) X_2(t) + L_2\left(h_2^3 * h_2^2 * h_2^1 * W_2\right)(t) \\ &\quad + 2K_1\left(h_1^3 * h_1^2 * h_1^1 * W_1\right)(t) \end{aligned} \tag{27}$$

$$\dot{\tilde{X}}_2(t) = -\tilde{\mu}_2\tilde{X}_2(t) + \tilde{L}_2\left(h_2^3 * h_2^2 * h_2^1 * W_2\right)(t) \tag{28}$$

$$\begin{aligned} \dot{\bar{X}}_2(t) &= -\left(\bar{\delta}_2 + \bar{\mu}_2\right)\bar{X}_1(t) + \bar{L}_2\left(\bar{h}_2^3 * \bar{h}_2^2 * \bar{h}_2^1 * \bar{W}_2\right)(t) \\ &\quad + 2\bar{K}_1\left(\bar{h}_1^3 * \bar{h}_1^2 * \bar{h}_1^1 * \bar{W}_1\right)(t) \end{aligned} \tag{29}$$

$$\begin{aligned} \dot{\bar{X}}_3(t) &= -\left(\bar{\delta}_3 + \bar{\mu}_3\right)\bar{X}_3(t) + \bar{L}_3\left(\bar{h}_3^3 * \bar{h}_2^3 * \bar{h}_3^1 * \bar{W}_3\right)(t) \\ &\quad + 2\bar{K}_2\left(\bar{h}_2^3 * \bar{h}_2^2 * \bar{h}_2^1 * \bar{W}_2\right)(t) \end{aligned} \tag{30}$$

where $W_1(t) := \mu_1 X_1(t) + c_{12}\bar{X}_1(t) + \tilde{\mu}_1\tilde{X}_1(t)$, $\bar{W}_1(t) := \bar{\mu}_1\bar{X}_1(t) + c_{15}X_1(t)$, $W_2(t) := \mu_2 X_2(t) + \tilde{\mu}_2\tilde{X}_2(t)$, $\bar{W}_2(t) := \bar{\mu}_2\bar{X}_2(t)$, $\bar{W}_3(t) := \bar{\mu}_3\bar{X}_3(t)$, $\mu_1 = \left.\dfrac{d}{dx_1}\left(\beta_1(x_1 + \bar{x}_1)x_1\right)\right|_{x=x^e}$, $c_{12} = \left.\dfrac{d}{d\bar{x}_1}\left(\beta_1(x_1 + \bar{x}_1)x_1\right)\right|_{x=x^e}$, $\tilde{\mu}_1 = \left.\dfrac{d}{d\tilde{x}_1}\left(\tilde{\beta}_1(\tilde{x}_1)\tilde{x}_1\right)\right|_{x=x^e}$, $\bar{\mu}_1 = \left.\dfrac{d}{d\bar{x}_1}\left(\bar{\beta}_1(x_1 + \bar{x}_1)\bar{x}_1\right)\right|_{x=x^e}$, $c_{15} = \left.\dfrac{d}{dx_1}\left(\bar{\beta}_1(x_1 + \bar{x}_1)\bar{x}_1\right)\right|_{x=x^e}$, $\mu_2 = \left.\dfrac{d}{dx_2}\left(\beta_2(x_2)x_2\right)\right|_{x=x^e}$, $\tilde{\mu}_2 = \left.\dfrac{d}{d\tilde{x}_2}\left(\tilde{\beta}_2(\tilde{x}_2)\tilde{x}_2\right)\right|_{x=x^e}$, $\bar{\mu}_2 = \left.\dfrac{d}{d\bar{x}_2}\left(\bar{\beta}_2(\bar{x}_2)\bar{x}_2\right)\right|_{x=x^e}$ and $\bar{\mu}_3 = \left.\dfrac{d}{d\bar{x}_3}\left(\bar{\beta}_3(\bar{x}_3)\bar{x}_3\right)\right|_{x=x^e}$.

The linear system (24)-(30) is stable if and only if $1/\det(A(s))$ is stable, where

$$A(s) := \begin{pmatrix} & A_1(s) & & \begin{matrix} 0 & 0 \\ 0 & 0 \\ 0 & 0 \end{matrix} & \begin{matrix} 0 & 0 \\ 0 & 0 \\ 0 & 0 \end{matrix} \\ a_{41}(s) & a_{42}(s) & a_{43}(s) & & 0 \\ 0 & 0 & 0 & A_2(s) & 0 \\ a_{61}(s) & 0 & a_{63}(s) & & 0 \\ 0 & 0 & 0 & 0 \quad 0 \quad a_{76}(s) & a_{77}(s) \end{pmatrix},$$

$$A_1(s) := \begin{pmatrix} a_{11}(s) & a_{12}(s) & a_{13}(s) \\ a_{21}(s) & a_{22}(s) & a_{23}(s) \\ a_{31}(s) & 0 & a_{33}(s) \end{pmatrix},$$

$$A_2(s) := \begin{pmatrix} a_{44}(s) & a_{45}(s) & 0 \\ a_{54}(s) & a_{55}(s) & 0 \\ 0 & 0 & a_{66}(s) \end{pmatrix},$$

$a_{11}(s) := s + \delta_1 + \mu_1 - \mu_1 L_1 H_1(s)$, $a_{12}(s) := -\tilde{\mu}_1 L_1 H_1(s)$, $a_{13}(s) := c_{12} - c_{12}L_1 H_1(s)$, $a_{21}(s) := -\mu\tilde{L}_1 H_1(s)$, $a_{22}(s) := s + \tilde{\mu}_1 - \tilde{\mu}_1\tilde{L}_1 H_1(s)$, $a_{23}(s) := -c_{12}\tilde{L}_1 H_1(s)$, $a_{31}(s) := c_{15} - c_{15}\bar{L}_1\bar{H}_1(s)$, $a_{33}(s) := s + \bar{\delta}_1 + \bar{\mu}_1 - \bar{\mu}_1\bar{L}_1(s)$, $a_{41} := -2K_1\mu_1 H_1(s)$, $a_{42} := -2K_1\tilde{\mu}_1 H_1(s)$, $a_{43} := -2K_1 c_{12} H_1(s)$, $a_{44}(s) := s + \delta_2 + \mu_2 - \mu_2 L_2 H_2(s)$, $a_{45}(s) := -\tilde{\mu}_2 L_2 H_2(s)$, $a_{54}(s) := -\mu\tilde{L}_2 H_2(s)$, $a_{55}(s) := s + \tilde{\mu}_2 - \tilde{\mu}_2\tilde{L}_2 H_2(s)$, $a_{61} := -2\bar{K}_1\bar{\mu}_1\bar{H}_1(s)$, $a_{61} := -2\bar{K}_1 c_{15}\bar{H}_1(s)$, $a_{66}(s) := s + \bar{\delta}_2 + \bar{\mu}_2 - \bar{\mu}_2\bar{L}_2(s)$, $a_{76} := -2\bar{K}_2\bar{\mu}_{15}\bar{H}_2(s)$, $a_{77}(s) := s + \bar{\delta}_3 + \bar{\mu}_3 - \bar{\mu}_3\bar{L}_3(s)$.

Consequently, since the matrix $A(s)$ has a block lower triangular form with diagonal blocks $A_1(s)$, $A_2(s)$ and $a_{77}(s)$ we have

$$\det(A(s)) = \det(A_1(s))\det(A_2(s))a_{77}(s) \tag{31}$$

and the stability of the linearized model is determined by the roots of

$$\begin{aligned} \det(A_1(s)) &= a_{33}(s)\left(a_{11}(s)a_{22}(s) - a_{12}(s)a_{21}(s)\right) \\ &\quad - a_{31}(s)\left(a_{12}(s)a_{23}(s) - a_{13}(s)a_{22}(s)\right), \\ \det(A_2(s)) &= a_{66}(s)\left(a_{44}(s)a_{55}(s) - a_{45}(s)a_{54}(s)\right) \end{aligned}$$

and $a_{77}(s)$.

Now, we will show how to obtain bounds on $H_1(0)$, $\bar{H}_1(0)$, $H_2(0)$, $\bar{H}_2(0)$ and $\bar{H}_3(0)$ such that the stability of the equilibrium point $x_1^e = 0$, $\tilde{x}_1^e = 0$, $\bar{x}_1^e \geq 0$, $x_2^e = 0$, $\tilde{x}_2^e = 0$, $\bar{x}_2^e \geq 0$ and $\bar{x}_3^e \geq 0$ is guaranteed.

Proposition 1: Suppose that $\bar{\delta}_1 + \bar{\mu}_1 > 0$, $\delta_1 + \mu_1 > 0$, $\tilde{\mu}_1 > 0$, $\bar{\delta}_2 + \bar{\mu}_2 > 0$, $\delta_2 + \mu_2 > 0$, $\tilde{\mu}_2 > 0$, $\bar{\delta}_3 + \bar{\mu}_3 > 0$,

$$H_1(0) < \frac{\delta_1 + \mu_1}{2(1-K_1)(|\mu_1| + (1-\sigma_1)\delta_1)} \tag{32}$$

$$\bar{H}_1(0) < \frac{\bar{\delta}_1 + \bar{\mu}_1}{2\left(1-\bar{K}_1\right)|\bar{\mu}_1|} \tag{33}$$

$$H_2(0) < \frac{\delta_2 + \mu_2}{2(1-K_2)(|\mu_2| + (1-\sigma_2)\delta_2)} \tag{34}$$

$$\bar{H}_2(0) < \frac{\bar{\delta}_2 + \bar{\mu}_2}{2\left(1-\bar{K}_2\right)|\bar{\mu}_2|} \tag{35}$$

$$\bar{H}_3(0) < \frac{\bar{\delta}_3 + \bar{\mu}_3}{2\left(1-\bar{K}_3\right)|\bar{\mu}_3|} \tag{36}$$

Then the system (24)-(30) linearized at the equilibrium point $x_1^e = 0$, $\tilde{x}_1^e = 0$, $\bar{x}_1^e \geq 0$, $x_2^e = 0$, $\tilde{x}_2^e = 0$, $\bar{x}_2^e \geq 0$ and $\bar{x}_3^e \geq 0$ is $\mathcal{H}_\infty$ stable. In particular, the nonlinear system (3)-(9) is locally asymptotically stable.

Proof: At the equilibrium point of interest, we can see that $c_{12} = 0$ evaluated at this point. This gives $a_{13}(s) = 0$ and $a_{23}(s) = 0$. Thus, the stability depends on the location of the roots of $a_{77}(s)$,

$$a_{33}(s)\left(a_{11}(s)\,a_{22}(s) - a_{12}(s)\,a_{21}(s)\right)$$

and

$$a_{66}(s)\left(a_{44}(s)\,a_{55}(s) - a_{45}(s)\,a_{54}(s)\right).$$

Note that $a_{33}(s)$, $a_{66}(s)$ and $a_{77}(s)$ are of the form

$$s + \bar{\delta} + \bar{\mu} - \bar{\mu}\bar{L}\bar{H}(s); \tag{37}$$

on the other hand, $a_{11}(s)\,a_{22}(s) - a_{12}(s)\,a_{21}(s)$ and $a_{44}(s)\,a_{55}(s) - a_{45}(s)\,a_{54}(s)$ are of the form

$$(s + \delta + \mu)(s + \tilde{\mu}) - \left(\delta\tilde{L} + \left(L + \tilde{L}\right)\mu\right)\tilde{\mu}H(s). \tag{38}$$

We can rewrite (37) and (38) as

$$(s + \bar{\delta} + \bar{\mu})\left(1 - \frac{\bar{\mu}\bar{L}\bar{H}(s)}{s + \bar{\delta} + \bar{\mu}}\right)$$

and

$$(s + \delta + \mu)(s + \tilde{\mu})\left(1 - \left(\frac{L\mu}{s + \delta + \mu} + \frac{\tilde{L}\tilde{\mu}}{s + \tilde{mu}}\right)H(s)\right).$$

From the fact that $\|H\|_\infty = H(0)$, $\|\bar{H}\|_\infty = \bar{H}(0)$ and that $\frac{\bar{\mu}\bar{L}\bar{H}(s)}{s + \bar{\delta} + \bar{\mu}}$ and $\frac{L\mu}{s + \delta + \mu} + \frac{\tilde{L}\tilde{\mu}}{s + \tilde{\mu}}$ are low pass filters whose H_∞ norms are attained at $s = 0$. Then, by the Nyquist stability criterion (due to positive feedback, i.e. $-$ sign in the characteristic equation) and substituting the corresponding values, we see that the roots of $\det(A_1(s))\det(A_1(s))a_{77}(s)$ are in the open left half plane if and only if (32)-(36) hold. ■

IV. NUMERICAL EXAMPLES AND SIMULATION RESULTS

Let us study a system with $\delta_1 = 2$, $\bar{\delta}_1 = 7$, $\delta_2 = 1.5$, $\bar{\delta}_2 = 0.85$, $\bar{\delta}_3 = 1.4$, $K_1 = 0.1$, $\bar{K}_1 = 0.2$, $K_2 = 0.1$, $\bar{K}_2 = 0.2$, $\bar{K}_3 = 0.4$, $\sigma_1 = 0.9$, $\sigma_2 = 0.8$ and the other parameters as indicated in Table 1. The resulting equilibrium point is $\bar{x}_1^e = 0.5608$, $\bar{x}_2^e = 3.3188$, $\bar{x}_3^e = 0.1295$, $x_1^e = \tilde{x}_1^e = x_2^e = \tilde{x}_2^e = 0$ with the parameters $\mu_1 = 1.5215$, $\tilde{\mu}_1 = 1$, $\bar{\mu}_1 = 7.0159$, $\mu_2 = 1$, $\tilde{\mu}_2 = 1$, $\bar{\mu}_2 = -0.0511$ and $\bar{\mu}_3 = 0.9913$.

TABLE I

SIMULATION PARAMETERS.

i	$\beta_i(0)$	$\tilde{\beta}_i(0)$	$\bar{\beta}_i(0)$	b_i	$\tilde{b}_i$	$\bar{b}_i$	N_i	$\tilde{N}_i$	$\bar{N}_i$
1	2	1	15	1	0.1	1	2	2	3
2	1	1	1	1	0.3	1	4	4	3
3	-	-	6	-	-	1	-	-	4

i	m_i^1	m_i^2	m_i^3	τ_i^1	τ_i^2	τ_i^3	γ_i^1	γ_i^2	γ_i^3
1	3	1	2	0.3	0.1	0.2	0.03	0.01	0.02
2	3	1	2	0.3	0.1	0.2	0.05	0.01	0.08

i	$\bar{m}_i^1$	$\bar{m}_i^2$	$\bar{m}_i^3$	$\bar{\tau}_i^1$	$\bar{\tau}_i^2$	$\bar{\tau}_i^3$	$\bar{\gamma}_i^1$	$\bar{\gamma}_i^2$	$\bar{\gamma}_i^3$
1	3	1	2	1.3	0.1	0.2	0.03	0.01	0.02
2	3	1	2	0.3	0.1	0.2	0.03	0.01	0.02
3	3	4	2	0.3	0.5	0.2	0.03	0.01	0.02

Time domain simulation, performed in Matlab Simulink, shows that with the initial conditions

$$\begin{aligned}
x_1(\tau) &= 0.5 \quad \text{for all} \quad -0.6 \leq \tau < 0; \\
\bar{x}_1(\tau) &= 0.2 \quad \text{for all} \quad -1.6 \leq \tau < 0; \\
x_2(\tau) &= 0.5 \quad \text{for all} \quad -0.6 \leq \tau < 0; \\
\bar{x}_2(\tau) &= 0.2 \quad \text{for all} \quad -1.6 \leq \tau < 0; \\
\bar{x}_3(\tau) &= 0.1 \quad \text{for all} \quad -1.0 \leq \tau < 0;
\end{aligned}$$

$\tilde{x}_1(\tau) = \tilde{x}_2(\tau) = 0$, for all $\tau < 0$, $x_1(0) = 1$, $\tilde{x}_1(0) = 0.38$, $\bar{x}_1(0) = 1.05$, $x_2(0) = 1$, $\tilde{x}_2(0) = 0.38$, $\bar{x}_2(0) = 1.05$ and $\bar{x}_3(0) = 1.05$ the states converge to the equilibrium points $\bar{x}_1^e = 0.5608$, $\bar{x}_2^e = 3.3188$, $\bar{x}_3^e = 0.1295$, $x_1^e = \tilde{x}_1^e = x_2^e = \tilde{x}_2^e = 0$, see Figures 5-7. Indeed it can be verified that with the parameters in Table 1 the local stability conditions stated in 32-36 are satisfied:

$$H_1(0) = 0.992 < \frac{\delta_1 + \mu_1}{2(1-K_1)(|\mu_1| + (1-\sigma_1)\delta_1)} = 1.136,$$

$$\bar{H}_1(0) = 0.968 < \frac{\bar{\delta}_1 + \bar{\mu}_1}{2\left(1-\bar{K}_1\right)|\bar{\mu}_1|} = 1.246,$$

$$H_2(0) = 0.981 < \frac{\delta_2 + \mu_2}{2(1-K_2)(|\mu_2| + (1-\sigma_2)\delta_2)} = 1.068,$$

$$\bar{H}_2(0) = 0.922 < \frac{\bar{\delta}_2 + \bar{\mu}_2}{2\left(1-\bar{K}_2\right)|\bar{\mu}_1|} = 9.7659,$$

$$\bar{H}_3(0) = 0.989 < \frac{\bar{\delta}_3 + \bar{\mu}_3}{2\left(1-\bar{K}_3\right)|\bar{\mu}_3|} = 1.028.$$

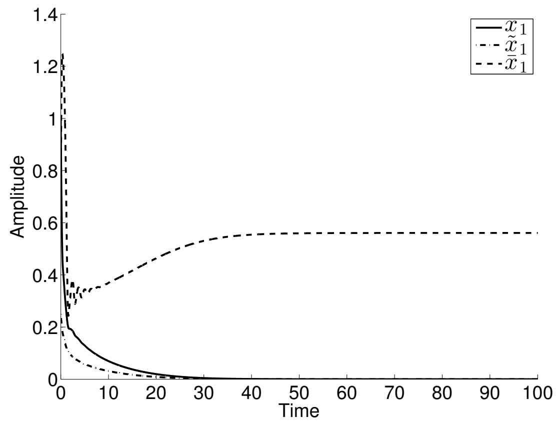

Fig. 5. Trajectories of the states x_1, $\tilde{x}_1$ and $\bar{x}_1$.

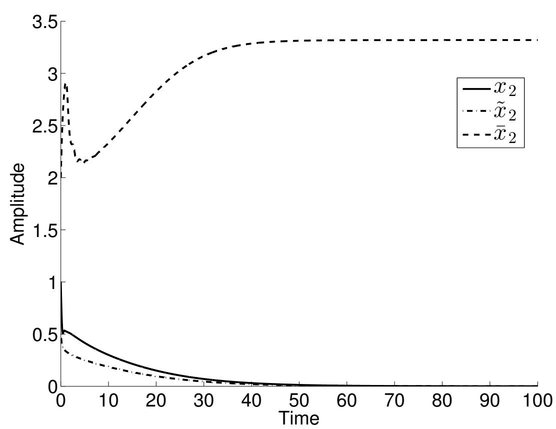

Fig. 6. Trajectories of the states x_2, $\tilde{x}_2$ and $\bar{x}_2$.

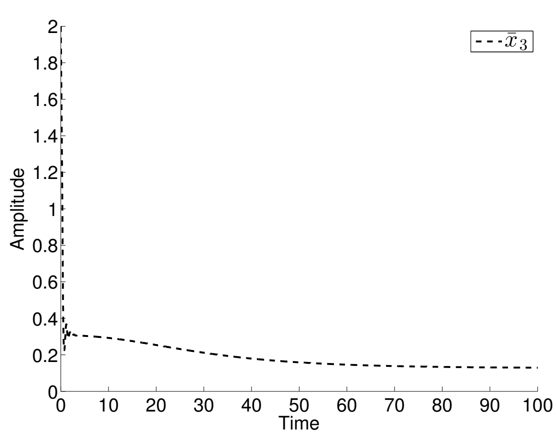

Fig. 7. Trajectory of the state $\bar{x}_3$.

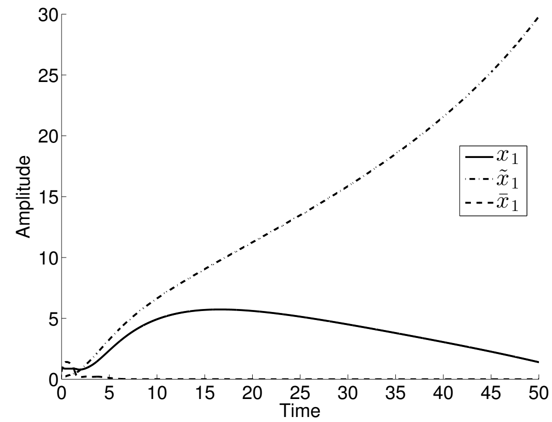

Fig. 8. Trajectories of the states x_1, $\tilde{x}_1$ and $\bar{x}_1$.

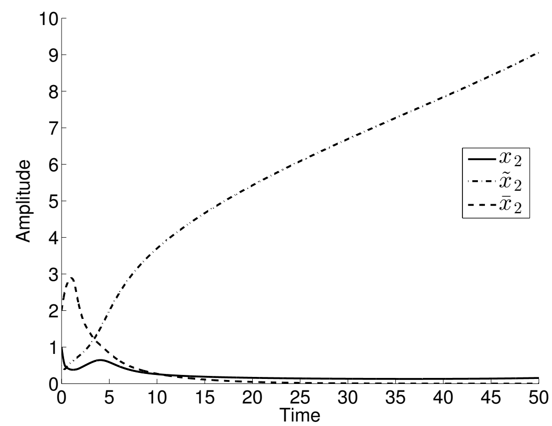

Fig. 9. Trajectories of the states x_2, $\tilde{x}_2$ and $\bar{x}_2$.

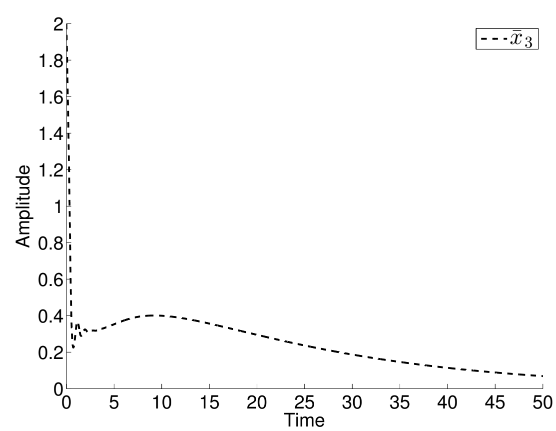

Fig. 10. Trajectory of the state $\bar{x}_3$.

Further simulations showed that decreasing σ_1 and σ_2, and fixing the remaining parameters as in the previous example the local stability condition is no longer satisfied. For example, when $\sigma_1 = 0.4$ and $\sigma_2 = 0.5$ the states $\tilde{x}_1$ and $\tilde{x}_2$ are far from its equilibrium value, see Figures 8-10.

V. CONCLUSION

In this paper, we have proposed a multi-stage interconnected model of healthy cells and cancer cells of AML. The PDE's governing the dynamics of the cells are based on [8], for both populations of cells.

Local stability conditions for a particular equilibrium point, corresponding to a positive number of healthy cells, are derived in terms of a set of inequalities involving the parameters of the mathematical model.

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