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**Discrete maturity and delay differential-difference model of
hematopoietic cell dynamics with applications to Acute Myelogenous
Leukemia**

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In the last few years, many efforts were oriented towards describing the hematopoiesis phenomenon in normal and pathological situations. This complex biological process is organized as a hierarchical system that begins with primitive hematopoietic stem cells and ends with mature blood cells: red blood cells, white blood cells and platelets. Regarding acute myelogenous leukemia (AML), a cancer of the bone marrow and blood, characterized by a rapid proliferation of immature cells, which eventually invade the bloodstream, there is a consensus about the target cells during the hematopoietic stem cells (HSCs) development which are susceptible to leukemic transformation. We propose and analyse a mathematical model of HSC dynamics taking into account two phases in the cell cycle, a resting and a proliferating one, by allowing just after division a part of HSCs to enter the resting phase and the other part to come back to the proliferating phase to divide again. The resulting mathematical model is a system of nonlinear differential-difference equations. Due to the hierarchical organization of the hematopoiesis, we consider n stages of HSCs characterized by their maturity levels. We obtain a system of $2n$ nonlinear differential-difference equations. We study the existence, uniqueness, positivity, boundedness and unboundedness of the solutions. We then investigate the existence of positive and axial steady states for the system, and obtain conditions for their stability. Sufficient conditions for the global asymptotic stability of the trivial steady state as well as con-

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2 *Adimy, Chekroun, El Abdllaoui & Marzorati*

ditions for its instability are obtained. Using neutral differential equation associated to the differential-difference system, we also obtain results on the local asymptotic stability of the positive steady state. Numerical simulations are carried out to show the influence of variations of the differentiation rates and self-renewal coefficients of the HSCs on the behavior of the system. In particular, we show that a blocking of differentiation at an early stage of HSC development can lead in an overexpression of very immature cells. Such situation corresponds to the observation in the case of AML.

Keywords: Age-structured PDE; Delay differential-difference equation; Lyapunov function; Cell population dynamic; Acute myelogenous leukemia.

1. Introduction

The hematopoiesis is the process by which blood cells are produced and regulated. This process is sustained by a small population of cells, called hematopoietic stem cells (HSCs), which is located in the bone marrow. These cells have the ability to produce by division, either similar cells with the same maturity level (self-renewal) or cells engaged in one of different blood cell lineages (red blood cells, white cells or platelets).¹ The first differentiation of HSCs produces progenitors which are not morphologically identifiable. Progenitors form bands of cells called colony forming units (CFU) able to produce one of the three blood types. Progenitors lose their ability to self-renew gradually as differentiation progresses. CFU differentiate in precursor cells, which are not HSCs anymore, because they have lost their ability to self-renew. These cells eventually produce mature blood cells which enter the bloodstream. As it has just been explained, the hematopoiesis is organized as a hierarchy which starts by primitive hematopoietic stem cells and ends with mature blood cells. These cellular development stages correspond to more mature cells than HSCs that only proliferate. Finally, blood cells are released in the bloodstream. The life of the cell during the cell cycle is divided into two phases: resting phase and proliferating one.² In the proliferating phase, if a cell does not die by apoptosis, it passes through a series of transformations, which ends by the separation of chromosomes and the formation of two daughter cells. These cells enter either the resting phase, where they may stay their whole life, or the proliferating phase to divide again.^{1,3,4}

Acute myeloid leukemia (AML) is a cancer of blood cells that starts in the bone marrow. Its main characteristic is that chromosomal translocations in HSCs affect transcription factors involved in proliferation and differentiation.⁵ Abnormal expression of these factors leads to the rapid growth of primitive hematopoietic blast cells that accumulate in the bone marrow, then enter the bloodstream and interfere with the production of normal blood cells. For more details on the biological aspects of AML see Ref. 5.

In our knowledge, the mathematical study of hematopoiesis dates from 1970,² and most of the works dedicated to this topic are recent (see the reviews Refs. 6–8). Among the first mathematical models in the hematopoiesis phenomenon, we find that of Mackey in 1978,⁹ based on the papers Refs. 2,10. Mackey was interested in

studying the evolution of the hematopoietic cell population without distinguishing between cells according to their level of development. He considered a system of two nonlinear delay differential equations. The delay represented the cell cycle duration. Mackey and his collaborators have pointed out the existence of oscillations, which are observed during some cyclical hematological diseases.^{11–15} Then, many more sophisticated models have been developed (see Refs. 11, 12, 14–20). In Refs. 21–23, the authors considered discrete-maturity structured models with finite number of stages in blood production process, characterized by cell maturity levels. They made the difference between dividing cells that differentiate (by going to the next stage) and dividing cells that keep the same maturity level (by staying in the same stage). In Refs. 21, 22, the models consist of n nonlinear differential equations with n delays.

In all these previous works, the authors hypothesize that after each division, the daughter cells directly enter the resting phase. Such an assumption makes it possible to reduce the structured system to a delay differential system (see for instance Ref. 16). In fact, after division, cells do not always immediately enter the resting phase. They can return to the proliferating phase to divide again.^{1, 3, 4, 24, 25} In recent works,^{26, 27} models were proposed taking into account the fact that only a fraction of daughter cells enter the resting phase (long-term proliferation) and the other fraction of cells return immediately to the proliferating phase to divide again (short-term proliferation). This assumption leads to an important difference in the mathematical treatment of the model: it can no longer be posed as a system of delay differential equations. The system of equations has a different mathematical nature. An extra variable is introduced whose dynamics are ruled by a difference equation (no derivative involved).

In this paper, based on Refs. 26, 27, we consider a discrete maturity structured model to represent the evolution of HSCs. We assume that a part of dividing cells enters the resting phase while the other part returns to the proliferating phase to divide again. We obtain $2n$ nonlinear differential-difference equations with n delays. It is known that such systems (see Ref. 26) have the ability to explain the maintenance of high level production of blood cells. As a consequence, our model seems to be a good approach to study the acute myelogenous leukemia, a cancer of white blood cells, characterized by a blocking of cell differentiation leading to accumulation and overexpression of very immature HSCs that invade the circulating blood.

The paper is organized as follows. Sec. 2 is devoted to the presentation of the model. It is an age-structured system describing the dynamics of HSC population, where cells can be either proliferating or quiescent. In Sec. 3, by using the characteristics method, we reduce our system to a coupled system of differential and difference equations. Then, we prove the existence, uniqueness and positivity of the solutions. In Sec. 4, we show the existence of steady states. Among them, we find trivial, axial, and interior steady states. We then focus on properties of the system related to boundedness and unboundedness of solutions. In Sec. 5, we prove the global asymptotic stability of the trivial steady state by using a Lyapunov func-

tion, in some region when it is the only steady state. Furthermore, we prove that no nontrivial solution of the system tends to the trivial steady state when another equilibrium exists. We also obtain, using a characteristic equation, results on the local asymptotic stability of the positive steady state. In Sec. 6, numerical simulations allow us to observe the variation of the positive steady state level in terms of the main parameters of the system. We numerically show an overexpression of a primitive HSC population, which corresponds to the case of AML when blocking the cell's differentiation occurs.

2. Formulation of the model

Throughout this paper, we set

$$I_n := \{1, \dots, n\}, \quad n \in \mathbb{N}, \quad n \geq 2.$$

We denote by $q_i(t, a)$ and $p_i(t, a)$ for $i \in I_n$, the quiescent and proliferating cell population densities of the i^{th} generation of immature cells, respectively, and by $m(t, a)$ the population density of mature cells, at time $t \geq 0$ and age $a \geq 0$. The age represents the time spent by a cell in one of the two phases, quiescent or proliferating. Quiescent cells of the i^{th} generation can either be lost randomly at a constant rate $\delta_i \geq 0$, or enter into the proliferating phase of the i^{th} generation in order to ensure the population renewal, at a non-constant rate $\beta_i \geq 0$. A cell in the quiescent phase can stay its entire life there, then its age a ranges from 0 to infinity. In each i^{th} proliferating phase, cells stay a time $\tau_i \geq 0$, necessary to perform a series of processes leading to division at mitosis. They can be lost by apoptosis (programmed cell death) at a rate $\gamma_i \geq 0$. At the end of each i^{th} proliferating phase (that is when cells have spent a time $a = \tau_i$), each cell divides in two daughter cells. A part ($L_i \in [0, 1]$) of daughter cells returns immediately to the i^{th} generation of proliferating phase to go over a new cell cycle, another part ($K_i \in [0, 1]$) enters to the next generation of resting phase (differentiation), while the other part ($1 - L_i - K_i$) enters directly the i^{th} generation of resting phase ($L_i + K_i \in [0, 1]$). In the mature compartment, cells can be lost randomly at a constant rate $\delta_M \geq 0$. A schematic representation of the hematopoiesis process is given in Figure 1 to clarify the understanding of the model (we have already considered the case $n = 1$ in Ref. 26). Hence, the dynamics of the HSC population (resting and proliferating ones) is described by the following system of age-structured partial differential equations, for $t > 0$ and $i \in I_n$,

$$\begin{cases} \frac{\partial}{\partial t} q_i(t, a) + \frac{\partial}{\partial a} q_i(t, a) = -(\delta_i + \beta_i(Q_i(t))) q_i(t, a), & a > 0, \\ \frac{\partial}{\partial t} p_i(t, a) + \frac{\partial}{\partial a} p_i(t, a) = -\gamma_i p_i(t, a), & 0 < a < \tau_i, \\ \frac{\partial}{\partial t} m(t, a) + \frac{\partial}{\partial a} m(t, a) = -\delta_M m(t, a), & a > 0. \end{cases} \quad (2.2)$$

Boundary conditions describing the flux between the two phases and two successive

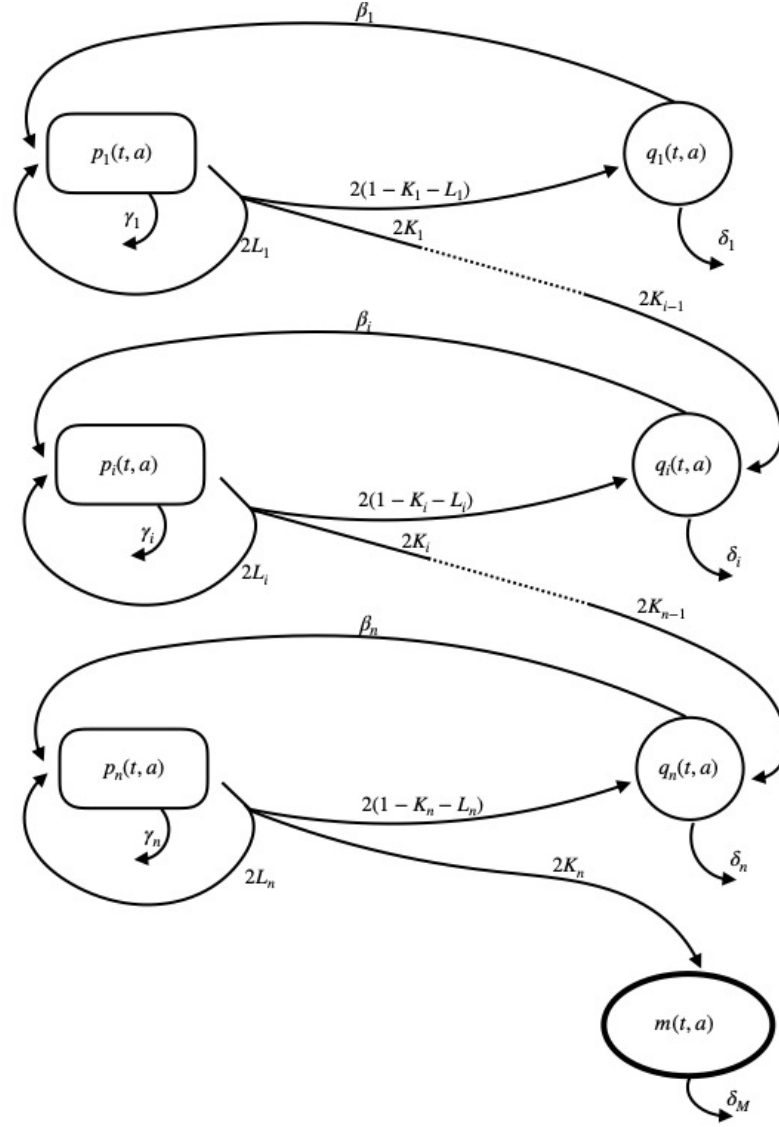


Fig. 1. Schematic representation of the hematopoiesis process. We distinguish between dividing cells that enter immediately the quiescent phase of the same stage (with a rate $1 - L_i - K_i$), dividing cells that return to the proliferating phase of the same stage (with a rate L_i) and dividing cells that go to the next stage of the quiescent phase (with a rate K_i).

generations, are given by

$$\begin{cases} q_1(t, 0) = 2(1 - L_1 - K_1)p_1(t, \tau_1), \\ q_i(t, 0) = 2(1 - L_i - K_i)p_i(t, \tau_i) + 2K_{i-1}p_{i-1}(t, \tau_{i-1}), & i \in I_n \setminus \{1\}, \\ p_i(t, 0) = \beta_i(Q_i(t))Q_i(t) + 2L_i p_i(t, \tau_i), & i \in I_n, \\ m(t, 0) = 2K_n p_n(t, \tau_n). \end{cases} \quad (2.3)$$

6 *Adimy, Chekroun, El Abdllaoui & Marzorati*

The introduction rate $\beta_i := \beta_i(Q_i(t))$ is assumed to depend on the total population of the i^{th} generation of quiescent cells (see Ref. 9),

$$Q_i(t) = \int_0^{+\infty} q_i(t, a) da, \quad t \geq 0,$$

and for each $i \in I_n$, β_i is supposed to be a continuous, differentiable and strictly decreasing function with

$$\lim_{x \rightarrow +\infty} \beta_i(x) = 0. \quad (2.5)$$

Typically, the functions β_i are of the form of a Hill function (see Refs. 9, 14, 15).

In the boundary conditions (2.3), the first equation describes the dividing cells, coming from the first generation, that immediately enter to the resting phase. The second equation represents, for the next generations ($i \in I_n \setminus \{1\}$), both dividing cells coming from the $(i-1)^{\text{th}}$ generation ($2K_{i-1}p_{i-1}(t, \tau_{i-1})$) (differentiation) and dividing cells coming from the i^{th} generation ($2(1 - L_i - K_i)p_i(t, \tau_i)$) (self-renewal). The third equation describes both the introduced cells coming from the i^{th} generation of the resting phase and the dividing cells that immediately return to the proliferating phase. While the last boundary condition represents the new mature cells coming after division in the n^{th} generation of the proliferating phase. Coefficients 2 account for the division of each mother cell into two daughter cells.

The model is completed with initial conditions, that are non-negative L^1 -functions,

$$\begin{cases} q_i(0, a) = q_i^0(a), & a > 0, \quad i \in I_n, \\ p_i(0, a) = p_i^0(a), & 0 < a < \tau_i, \quad i \in I_n, \\ m(0, a) = m^0(a), & a > 0, \end{cases} \quad (2.6)$$

and the following natural conditions, for $t \geq 0$,

$$\lim_{a \rightarrow +\infty} q_i(t, a) = 0, \quad i \in I_n \quad \text{and} \quad \lim_{a \rightarrow +\infty} m(t, a) = 0.$$

We assume that the proliferating phase duration τ_i and the differentiation rates K_i as well as the mortality rates δ_i and γ_i are increasing functions with respect to the cell maturity level.^{28, 29} We suppose, for $i \in I_{n-1}$,

$$0 \leq \tau_i \leq \tau_{i+1}, \quad 0 \leq K_i \leq K_{i+1}, \quad 0 \leq \delta_i \leq \delta_{i+1} \quad \text{and} \quad 0 \leq \gamma_i \leq \gamma_{i+1}. \quad (\text{H1})$$

Furthermore, the cells loss their capacity of self-renewal when they become more and more mature. Then, we can suppose that, for $i \in I_{n-1}$,

$$0 \leq L_{i+1} \leq L_i \quad \text{and} \quad 0 \leq \beta_{i+1}(0) \leq \beta_i(0). \quad (\text{H2})$$

3. Reduction to a delay differential-difference system

The system of age-structured partial differential equations formed with (2.2)-(2.6), can be reduced to a system of delay differential-difference equations. In fact, as in

Discrete maturity and delay differential-difference model of HSCs with application to AML 7

Ref. 26, we put $u_i(t) = p_i(t, 0)$ for $i \in I_n$ (the density of new proliferating cells at the i^{th} generation). Using the method of characteristics, we obtain

$$p_i(t, a) = \begin{cases} e^{-\gamma_i t} p_i(0, a-t) = e^{-\gamma_i t} p_i^0(a-t), & 0 \leq t \leq a, \\ e^{-\gamma_i a} p_i(t-a, 0) = e^{-\gamma_i a} u_i(t-a), & t > a. \end{cases} \quad (3.1)$$

Thus, using expression (3.1) and integrating the system (2.2) over the age variable, we obtain, for $t > 0$,

$$\begin{cases} Q_1'(t) = -(\delta_1 + \beta_1(Q_1(t))) Q_1(t) \\ \quad + \begin{cases} 2(1-L_1-K_1)e^{-\gamma_1 \tau_1} u_1(t-\tau_1), & t > \tau_1, \\ 2(1-L_1-K_1)e^{-\gamma_1 t} p_1^0(\tau_1-t), & t \leq \tau_1, \end{cases} \\ u_1(t) = \beta_1(Q_1(t)) Q_1(t) + \begin{cases} 2L_1 e^{-\gamma_1 \tau_1} u_1(t-\tau_1), & t > \tau_1, \\ 2L_1 e^{-\gamma_1 t} p_1^0(\tau_1-t), & t \leq \tau_1, \end{cases} \end{cases} \quad (3.2)$$

and (recall that $\tau_{i-1} \leq \tau_i$), for $i \in I_n \setminus \{1\}$,

$$\begin{cases} Q_i'(t) = -(\delta_i + \beta_i(Q_i(t))) Q_i(t) \\ \quad + \begin{cases} 2K_{i-1} e^{-\gamma_{i-1} \tau_{i-1}} u_{i-1}(t-\tau_{i-1}), & t > \tau_{i-1}, \\ 2K_{i-1} e^{-\gamma_{i-1} t} p_{i-1}^0(\tau_{i-1}-t), & t \leq \tau_{i-1}, \end{cases} \\ \quad + \begin{cases} 2(1-L_i-K_i) e^{-\gamma_i \tau_i} u_i(t-\tau_i), & t > \tau_i, \\ 2(1-L_i-K_i) e^{-\gamma_i t} p_i^0(\tau_i-t), & t \leq \tau_i, \end{cases} \\ u_i(t) = \beta_i(Q_i(t)) Q_i(t) + \begin{cases} 2L_i e^{-\gamma_i \tau_i} u_i(t-\tau_i), & t > \tau_i, \\ 2L_i e^{-\gamma_i t} p_i^0(\tau_i-t), & t \leq \tau_i, \end{cases} \end{cases} \quad (3.3)$$

and, for $i \in I_n$,

$$P_i(t) = \begin{cases} \int_0^{\tau_i} e^{-\gamma_i a} u_i(t-a) da, & t > \tau_i, \\ \int_t^{\tau_i} e^{-\gamma_i t} p_i^0(a-t) da + \int_0^t e^{-\gamma_i a} u_i(t-a) da, & t \leq \tau_i, \end{cases} \quad (3.4)$$

where

$$P_i(t) = \int_0^{\tau_i} p_i(t, a) da,$$

is the total population of proliferating cells in the i^{th} generation. The equation of the mature cells is given by

$$M'(t) = -\delta_M M(t) + \begin{cases} 2K_n e^{-\gamma_n \tau_n} u_n(t-\tau_n), & t > \tau_n, \\ 2K_n e^{-\gamma_n t} p_n^0(\tau_n-t), & t \leq \tau_n, \end{cases} \quad (3.6)$$

where

$$M(t) = \int_0^{+\infty} m(t, a) da.$$

8 *Adimy, Chekroun, El Abdllaoui & Marzorati*

The initial conditions are, for $i \in I_n$,

$$Q_i(0) = Q_i^0 := \int_0^{+\infty} q_i^0(a) da \quad \text{and} \quad M(0) = \int_0^{+\infty} m^0(a) da.$$

Note that, the functions M and P_i , for $i \in I_n$, do not influence directly the dynamics of the system. In fact, it is easy to see, from the expressions (3.2), (3.3), (3.4) and (3.6), that the behavior of the proliferating cell density P_i as well as the density of mature cells M , are influenced by the behavior of the first n components of Q and the first n components of u . Although these are independent of P_i , $i \in I_n$, and M . Furthermore, the duration τ_i of the proliferation phase (P_i) has an impact on the behavior of the system. Consequently, our analysis will focus, in the following, only on the first n components of Q and on the first n components of u . Moreover, as we are interested in the asymptotic behavior of solutions, we suppose that t is large enough ($t > \tau_n := \max_{i \in I_n}(\tau_i)$) and we suppose that the whole past is given in $[0, \tau_n]$. We translate the initial conditions (which are given by the systems (3.2) and (3.3) for $t \leq \tau_n$) so as to define them on $[-\tau_n, 0]$. Then, we consider the following system, for $t > 0$ and $i \in I_n \setminus \{1\}$,

$$\begin{cases} Q_1'(t) = -(\delta_1 + \beta_1(Q_1(t)))Q_1(t) + 2(1 - L_1 - K_1)e^{-\gamma_1\tau_1}u_1(t - \tau_1), \\ u_1(t) = \beta_1(Q_1(t))Q_1(t) + 2L_1e^{-\gamma_1\tau_1}u_1(t - \tau_1), \\ Q_i'(t) = -(\delta_i + \beta_i(Q_i(t)))Q_i(t) + 2(1 - L_i - K_i)e^{-\gamma_i\tau_i}u_i(t - \tau_i) \\ \quad + 2K_{i-1}e^{-\gamma_{i-1}\tau_{i-1}}u_{i-1}(t - \tau_{i-1}), \\ u_i(t) = \beta_i(Q_i(t))Q_i(t) + 2L_i e^{-\gamma_i\tau_i}u_i(t - \tau_i), \end{cases} \quad (3.9)$$

with initial conditions, for $i \in I_n$,

$$Q_i(0) = Q_i^0 \quad \text{and} \quad u_i(t) = \phi_i(t) \quad \text{for } t \in [-\tau_n, 0]. \quad (3.10)$$

For the sake of simplicity, we assume that the initial conditions p_i^0 of the age-structured system (2.2) are continuous and the following compatibility conditions hold

$$\phi_i(0) = \beta_i(Q_i^0)Q_i^0 + 2L_i e^{-\gamma_i\tau_i}\phi_i(-\tau_i), \quad \text{for } i \in I_n.$$

Thereby, the initial conditions (3.10) of the system (3.9) are such that $\phi = (\phi_1, \dots, \phi_n) \in C([-\tau_n, 0], \mathbb{R}^n)$.

The method of steps solves the system (3.9) in each interval $[k\tau_n, (k+1)\tau_n]$, for $k = 0, 1, 2, \dots$. Thus, we can check the existence and uniqueness of a piecewise function $(Q, u) := (Q_1, \dots, Q_n, u_1, \dots, u_n)$ solution of (3.9) and (3.10). Moreover, each component of Q is continuous for $t \geq 0$, has a continuous first derivative for all $t > 0$ and each component of u is continuous for all $t \geq -\tau_n$ if and only if the initial condition $(Q^0, \phi) := (Q_1^0, \dots, Q_n^0, \phi_1, \dots, \phi_n) \in \mathbb{R}^n \times C([-\tau_n, 0], \mathbb{R}^n)$ satisfies the compatibility condition

$$\phi_i(0) = \beta_i(Q_i^0)Q_i^0 + 2L_i e^{-\gamma_i\tau_i}\phi_i(-\tau_i), \quad \text{for } i \in I_n. \quad (3.12)$$

The next proposition states and proves non-negativity of the solutions of System (3.9).

Proposition 3.1 *The solutions of System (3.9) associated with non-negative initial conditions are non-negative.*

Proof. Let $(Q(t), u(t))$ be a solution of (3.9). First, we prove the non-negativity on the interval $[0, \tau_1]$.

Indeed, assume by contradiction that there exists $j \in I_n$, $T \in [0, \tau_1]$ and $\epsilon > 0$ such that $Q_j(t) > 0$ for $t < T$, $Q_j(T) = 0$ and $Q_j(t) < 0$ for $t \in (T, T + \epsilon)$. Since $T - \tau_j \in [-\tau_n, 0]$, we have $u_j(T - \tau_j) = \phi_j(T - \tau_j) > 0$ and

$$\begin{cases} Q'_j(T) \geq 2(1 - L_j - K_j)e^{-\gamma_j \tau_j} \phi_j(T - \tau_j), \\ u_j(T) = 2L_j e^{-\gamma_j \tau_j} \phi_j(T - \tau_j). \end{cases}$$

This yields $Q'_j(T) > 0$ and $u_j(T) > 0$, which give a contradiction. Thus, both functions Q and u are non-negative on $[0, \tau_1]$. Hence, applying the same reasoning on each interval $[k\tau_1, (k+1)\tau_1]$, for $k = 1, 2, \dots$, we deduce that Q and u are non-negative on $[0, +\infty)$. \square

4. Existence of steady states and properties

Now, we check the existence of steady states for the system (3.9). Let $(\bar{Q}, \bar{u}) := (\bar{Q}_1, \dots, \bar{Q}_n, \bar{u}_1, \dots, \bar{u}_n)$ be a steady state of (3.9). It satisfies, for $i \in I_n \setminus \{1\}$,

$$\begin{cases} (\delta_1 + \beta_1(\bar{Q}_1))\bar{Q}_1 = 2(1 - L_1 - K_1)e^{-\gamma_1 \tau_1} \bar{u}_1, \\ (1 - 2L_1 e^{-\gamma_1 \tau_1})\bar{u}_1 = \beta_1(\bar{Q}_1)\bar{Q}_1, \\ (\delta_i + \beta_i(\bar{Q}_i))\bar{Q}_i = 2(1 - L_i - K_i)e^{-\gamma_i \tau_i} \bar{u}_i + 2K_{i-1}e^{-\gamma_{i-1} \tau_{i-1}} \bar{u}_{i-1}, \\ (1 - 2L_i e^{-\gamma_i \tau_i})\bar{u}_i = \beta_i(\bar{Q}_i)\bar{Q}_i. \end{cases} \quad (4.1)$$

Firstly, notice that $(0, 0)$ is always a steady state of (3.9), describing the extinction of the cell population (trivial steady state). The function β_i is strictly decreasing on $[0, +\infty)$ with $\lim_{x \rightarrow +\infty} \beta_i(x) = 0$ for $i \in I_n$. Therefore, from (4.1), a positive steady state (\bar{Q}, \bar{u}) , with $\bar{Q}_i > 0$, $\bar{u}_i > 0$ for $i \in I_n$, is given by

$$\begin{cases} \bar{Q}_1 = \beta_1^{-1} \left(\delta_1 \left(\frac{1 - 2L_1 e^{-\gamma_1 \tau_1}}{2(1 - K_1)e^{-\gamma_1 \tau_1} - 1} \right) \right), \\ \bar{u}_1 = \frac{\delta_1}{2(1 - K_1)e^{-\gamma_1 \tau_1} - 1} \beta_1^{-1} \left(\delta_1 \left(\frac{1 - 2L_1 e^{-\gamma_1 \tau_1}}{2(1 - K_1)e^{-\gamma_1 \tau_1} - 1} \right) \right), \end{cases} \quad (4.2)$$

and, for $i \in I_n \setminus \{1\}$,

$$(\bar{Q}_i, \bar{u}_i) = \left(\xi_i^{-1}(\delta_i), \frac{\beta_i(\xi_i^{-1}(\delta_i))\xi_i^{-1}(\delta_i)}{1 - 2L_i e^{-\gamma_i \tau_i}} \right), \quad (4.3)$$

where ξ_i is the decreasing function given by

$$\xi_i(x) := \beta_i(x) \left(\frac{2(1 - K_i)e^{-\gamma_i \tau_i} - 1}{1 - 2L_i e^{-\gamma_i \tau_i}} \right) + 2K_{i-1}e^{-\gamma_{i-1} \tau_{i-1}} \frac{\bar{u}_{i-1}}{x}.$$

10 *Adimy, Chekroun, El Abdllaoui & Marzorati*

Straightforward calculations show that other equilibria, with some first components are zeros, may exist and that we denote by

$$(\bar{E}_{Q_j}, \bar{E}_{u_j}) := (0, \dots, \bar{Q}_j, \dots, \bar{Q}_n, 0, \dots, \bar{u}_j, \dots, \bar{u}_n),$$

$\bar{Q}_i > 0$, $\bar{u}_i > 0$, for $i = j, \dots, n$. The existence of such equilibria depends on the parameters τ_i , L_i , K_i , γ_i and $\mu_i = \beta_i(0)/\delta_i$ (see Proposition 4.1). We define for $\gamma_i > 0$, the following thresholds for the parameters τ_i , $i \in I_n$,

$$\tau_{\mu_i}^i = \begin{cases} \frac{1}{\gamma_i} \ln \left(\frac{2\mu_i(1-K_i)}{1+\mu_i} \right), & \mu_i > 1/(1-2K_i), \\ 0, & 0 \leq \mu_i \leq 1/(1-2K_i), \end{cases} \quad \tau_{\infty}^i = \frac{1}{\gamma_i} \ln(2(1-K_i)),$$

and, for $\gamma_i = 0$,

$$\tau_{\mu_i}^i = \begin{cases} +\infty, & \mu_i > 1/(1-2K_i), \\ 0, & 0 \leq \mu_i \leq 1/(1-2K_i), \end{cases} \quad \tau_{\infty}^i = +\infty.$$

In particular, for $\mu_i = 0$, which corresponds to the case $\beta_i(0) = 0$ and $\delta_i > 0$, we have $\tau_0^i = 0$. The notation $\mu_i = \infty$ corresponds to the case $\delta_i = 0$ and $\beta_i(0) > 0$.

The special case $\delta_i = \beta_i(0) = 0$ can be treated directly, and will not be considered here.

We recall that $L_i + K_i < 1$ for $i \in I_n$. So, the parameter L_i does not increase above $1 - K_i$. In order to study the existence of equilibria, we introduce thresholds for the parameter L_i . We consider the function $L_{\mu_i}^i : [0, +\infty) \rightarrow [0, 1]$, defined by

$$L_{\mu_i}^i(\tau_i) = \begin{cases} 0, & \tau_i < \tau_{\mu_i}^i, \\ (1 + \mu_i) L_0^i(\tau_i) - \mu_i(1 - K_i), & \tau_i \geq \tau_{\mu_i}^i, \end{cases}$$

where

$$L_0^i : [0, +\infty) \rightarrow [0, 1],$$

$$\tau_i \mapsto L_0^i(\tau_i) = \begin{cases} \frac{1}{2} e^{\gamma_i \tau_i}, & \tau_i < \tau_{\infty}^i, \\ 1 - K_i, & \tau_i \geq \tau_{\infty}^i, \end{cases}$$

and

$$L_{\infty}^i : [0, +\infty) \rightarrow [0, 1],$$

$$\tau_i \mapsto L_{\infty}^i(\tau_i) = \begin{cases} 0, & \tau_i < \tau_{\infty}^i, \\ 1 - K_i, & \tau_i \geq \tau_{\infty}^i. \end{cases}$$

The reader can consult Ref. 26 for a representation of such thresholds $L_{\mu_i}^i(\tau_i)$ and $L_0^i(\tau_i)$. Now, let us denote by (CD_i) , for some $i \in I_n$, the following condition

$$\begin{cases} L_{\mu_i}^i(\tau_i) < L_i < L_0^i(\tau_i), & \text{or} & \begin{cases} 0 \leq L_i < L_0^i(\tau_i), \\ 0 \leq \tau_i < \tau_{\mu_i}^i. \end{cases} \end{cases} \quad (CD_i)$$

Let us define

$$i_0 := \min\{i \in I_n \mid (CD_i) \text{ is not satisfied}\}.$$

We notice that under the hypotheses (H1), (H2) and $L_1 < L_0^1(\tau_1)$, we have, for all $i \in I_n$, if (CD_j) is not satisfied for some $j \in I_n$, then (CD_i) is not satisfied for $i = j, \dots, n$.

The next proposition deals with the existence and uniqueness of equilibria.

Proposition 4.1 *Assume that $i_0 = 1$. Then, the trivial steady state is the only equilibrium.*

Assume that $i_0 \geq 2$, that is (CD₁) holds. Under (H1)-(H2), if $L_1 < L_0^1(\tau_1)$ for $\tau_1 < \tau_\infty^1$, then System (3.9) has i_0 equilibria

$$\begin{aligned} (\bar{Q}^0, \bar{u}^0) &= (0, \dots, 0, 0, \dots, 0), \\ (\bar{Q}, \bar{u}) &= (\bar{Q}_1, \dots, \bar{Q}_n, \bar{u}_1, \dots, \bar{u}_n), \\ (\bar{E}_{Q_1}, \bar{E}_{u_1}) &= (0, \bar{Q}_2, \dots, \bar{Q}_n, 0, \bar{u}_2, \dots, \bar{u}_n), \\ &\vdots \\ (\bar{E}_{Q_{i_0-2}}, \bar{E}_{u_{i_0-2}}) &= (0, \dots, 0, \bar{Q}_{i_0-1}, \dots, \bar{Q}_n, 0, \dots, 0, \bar{u}_{i_0-1}, \dots, \bar{u}_n), \end{aligned}$$

where $\bar{Q}_i > 0$ and $\bar{u}_i > 0$ are given explicitly for $i = 1$ by (4.2), for $i \in I_n \setminus \{1, i_0 - 1\}$ by (4.3) and for $i = i_0 - 1$ by the following expression

$$\begin{cases} \bar{Q}_{i_0-1} = \beta_{i_0-1}^{-1} \left(\delta_{i_0-1} \left(\frac{1 - 2L_{i_0-1}e^{-\gamma_{i_0-1}\tau_{i_0-1}}}{2(1 - K_{i_0-1})e^{-\gamma_{i_0-1}\tau_{i_0-1}} - 1} \right) \right), \\ \bar{u}_{i_0-1} = \frac{\delta_{i_0-1}}{2(1 - K_{i_0-1})e^{-\gamma_{i_0-1}\tau_{i_0-1}} - 1} \beta_{i_0-1}^{-1} \left(\delta_{i_0-1} \left(\frac{1 - 2L_{i_0-1}e^{-\gamma_{i_0-1}\tau_{i_0-1}}}{2(1 - K_{i_0-1})e^{-\gamma_{i_0-1}\tau_{i_0-1}} - 1} \right) \right). \end{cases}$$

Proof. First, it is clear that (0, 0) is always a steady state.

Second, from System (4.1), we have

$$\bar{u}_i = \frac{L_0^i(\tau_i)}{L_0^i(\tau_i) - L_i} \beta_i(\bar{Q}_i) \bar{Q}_i, \quad \text{for } 0 \leq L_i < L_0^i(\tau_i), \quad i \in I_n.$$

We substitute \bar{u}_1 in the first equation of (4.1) and we get

$$\left(\left(\frac{1 - K_1 - L_0^1(\tau_1)}{L_0^1(\tau_1) - L_1} \right) \beta_1(\bar{Q}_1) - \delta_1 \right) \bar{Q}_1 = 0, \quad \text{for } 0 \leq L_1 < L_0^1(\tau_1).$$

β_1 is a decreasing function and satisfies $\lim_{x \rightarrow +\infty} \beta_1(x) = 0$. Then, the existence of a finite $(\bar{Q}_1, \bar{u}_1) \neq (0, 0)$ is equivalent to

$$0 \leq L_1 < L_0^1(\tau) \quad \text{and} \quad L_1 > (\mu_1 + 1)L_0^1(\tau_1) - \mu_1(1 - K_1).$$

This means that, the condition (CD₁) holds. In this case, we can check the existence of $\bar{Q}_i > 0$, $\bar{u}_i > 0$ for $i \in I_n \setminus \{1\}$, where \bar{Q}_i satisfies

$$\beta_i(\bar{Q}_i) \left(\frac{2(1 - K_i)e^{-\gamma_i\tau_i} - 1}{1 - 2L_i e^{-\gamma_i\tau_i}} \right) + 2K_{i-1}e^{-\gamma_{i-1}\tau_{i-1}} \frac{\bar{u}_{i-1}}{\bar{Q}_i} = \delta_i.$$

In fact, β_i is a decreasing function and satisfies $\lim_{x \rightarrow +\infty} \beta_i(x) = 0$. Then, (\bar{Q}_i, \bar{u}_i) , $i \in I_n \setminus \{1\}$, are given by the expression (4.3). We can conclude also that if (CD₁) is not satisfied ($i_0 = 1$), then the trivial steady state is the only equilibrium.

12 *Adimy, Chekroun, El Abdllaoui & Marzorati*

The existence of other equilibria is trivial and can be done similarly as above. We omit the details. \square

Remark 4.1 (1) If $\gamma_i = 0$, the conditions (CD_i) are independent of τ_i and become

$$\begin{cases} \frac{1}{2}(1 + \mu_i) - \mu_i(1 - K_i) < L_i < \frac{1}{2}, \\ 0 \leq \mu_i \leq \frac{1}{1 - 2K_i}, \end{cases} \quad \text{or} \quad \begin{cases} 0 \leq L_i < \frac{1}{2}, \\ \mu_i > \frac{1}{1 - 2K_i}. \end{cases}$$

(2) Let $\delta_i > 0$, $\beta_i(0) > 0$, $\gamma_i \geq 0$ and $0 \leq \tau_i < \tau_\infty^i$. Then,

$$\lim_{L_i \rightarrow L_0^i(\tau_i)} \bar{Q}_i = \lim_{L_i \rightarrow L_0^i(\tau_i)} \bar{u}_i = +\infty.$$

Now, we define for $\gamma_i > 0$, the following thresholds for the parameter τ_i , $i \in I_n$,

$$\tilde{\tau}_{\mu_i}^i = \begin{cases} \frac{1}{\gamma_i} \ln \left(\frac{2\mu_i}{1 + \mu_i} \right), & \mu_i > 1, \\ 0, & 0 \leq \mu_i \leq 1, \end{cases} \quad \tilde{\tau}_\infty^i = \frac{1}{\gamma_i} \ln(2),$$

and, for $\gamma_i = 0$

$$\tilde{\tau}_{\mu_i}^i = \begin{cases} +\infty, & \mu_i > 1, \\ 0, & 0 \leq \mu_i \leq 1, \end{cases} \quad \tilde{\tau}_\infty^i = +\infty.$$

The following proposition states the boundedness and unboundedness of solutions of System (3.9).

Proposition 4.2 (1) Assume that

$$\delta_i > 0, \tau_i \geq \tilde{\tau}_{\mu_i}^i \quad \text{and} \quad 0 \leq L_i \leq (1 + \mu_i) L_0^i(\tau_i) - \mu_i, \quad \text{for all } i \in I_n.$$

Then, all solutions of the system (3.9) are bounded.

(2) Assume that $L_i > L_0^i(\tau_i)$ for some $i \in I_n$. Then, Q_i, u_i and Q_{i+1} approach infinity. Moreover, if $L_{i+1} < L_0^{i+1}(\tau_{i+1})$ and $\lim_{x \rightarrow +\infty} \beta_{i+1}(x)x = 0$, then u_{i+1} tends to zero.

(3) Assume that (H1)-(H2) and $L_n > L_0^n(\tau_n)$ hold. Then, all nontrivial solutions of the system (3.9) approach infinity.

Proof. Let $(Q(t), u(t))$ be a solution of (3.9) with initial condition $(Q^0, \phi) \in \mathbb{R}_+^n \times C([- \tau_n, 0], \mathbb{R}_+^n)$.

Consider the functional defined by

$$W(t) = \sum_{i=1}^n Q_i(t) + \sum_{i=1}^n \rho_i(\tau_i) \int_{t-\tau_i}^t u_i(\theta) d\theta, \quad t > 0,$$

where

$$\rho_i(\tau_i) = \frac{1 - L_i}{L_0^i(\tau_i) - L_i} \quad \text{and} \quad 0 \leq L_i < L_0^i(\tau_i). \quad (4.21)$$

By differentiating W on $(0, +\infty)$ and using (3.9), we obtain

$$\begin{aligned}
 W'(t) &= \sum_{i=1}^n Q_i'(t) + \sum_{i=1}^n \rho_i(\tau_i)[u_i(t) - u_i(t - \tau_i)], \\
 &= -(\delta_1 + \beta_1(Q_1(t)))Q_1(t) + 2(1 - L_1 - K_1)e^{-\gamma_1\tau_1}u_1(t - \tau_1) \\
 &\quad + \rho_1(\tau_1)\beta_1(Q_1(t))Q_1(t) + \rho_1(\tau_1)[2L_1e^{-\gamma_1\tau_1} - 1]u_1(t - \tau_1) \\
 &\quad + \sum_{i=2}^n [-(\delta_i + \beta_i(Q_i(t)))Q_i(t) + 2(1 - L_i - K_i)e^{-\gamma_i\tau_i}u_i(t - \tau_i)] \\
 &\quad + \sum_{i=2}^n [2K_{i-1}e^{-\gamma_{i-1}\tau_{i-1}}u_{i-1}(t - \tau_{i-1}) + \rho_i(\tau_i)\beta_i(Q_i(t))Q_i(t)] \\
 &\quad + \sum_{i=2}^n [2L_i\rho_i(\tau_i)e^{-\gamma_i\tau_i}u_i(t - \tau_i) - \rho_i(\tau_i)u_i(t - \tau_i)].
 \end{aligned}$$

On the other side, we have

$$\sum_{i=1}^n [2(1 - L_i)e^{-\gamma_i\tau_i} + 2L_i e^{-\gamma_i\tau_i} \rho_i(\tau_i) - \rho_i(\tau_i)] = 0.$$

Then, we get

$$\begin{aligned}
 W'(t) &= -2K_n e^{-\gamma_n\tau_n} u_n(t - \tau_n) - \sum_{i=1}^n [\delta_i - (\rho_i(\tau_i) - 1) \beta_i(Q_i(t))] Q_i(t), \\
 &\leq - \sum_{i=1}^n \left[\delta_i - \left(\frac{1 - L_0^i(\tau_i)}{L_0^i(\tau_i) - L_i} \right) \beta_i(Q_i(t)) \right] Q_i(t), \\
 &= - \sum_{i=1}^n \chi_i(Q_i(t)) Q_i(t),
 \end{aligned}$$

with

$$\chi_i(Q_i) = \delta_i - \left(\frac{1 - L_0^i(\tau_i)}{L_0^i(\tau_i) - L_i} \right) \beta_i(Q_i), \quad \text{for } Q_i \geq 0.$$

Since β_i is decreasing and $0 \leq L_i < L_0^i(\tau_i) \leq 1$, it follows that χ_i is an increasing function and

$$\chi_i(0) = \frac{\delta_i}{L_0^i(\tau_i) - L_i} [(\mu_i + 1) L_0^i(\tau_i) - \mu_i - L_i]$$

is nonnegative for $\tau_i \geq \tilde{\tau}_{\mu_i}^i$ and $0 \leq L_i \leq (1 + \mu_i) L_0^i(\tau_i) - \mu_i$. Consequently, $W'(t) \leq 0$. We conclude that $W(t) \leq W(0)$. This leads to the boundedness of the function Q on $[0, +\infty)$. Furthermore, thanks to Ref. 30, Theorem 3.5, page 275, there exist constants $C > 0$ and $\alpha > 0$ such that, for every $i \in I_n$,

$$|u_i(t)| \leq C \left[\|\phi_i\| e^{-\alpha t} + \beta_i(0) \sup_{0 \leq s \leq t} |Q_i(s)| \right], \quad t > 0,$$

14 *Adimy, Chekroun, El Abdllaoui & Marzorati*

where $\|\phi_i\| = \sup_{-\tau_i \leq \theta \leq 0} |\phi_i(\theta)|$. As a consequence, we conclude that u is also bounded on $[0, +\infty)$.

By applying the same method that we used in Ref. 26, if $L_i > L_0^i(\tau_i)$ for some $i \in I_n$, then Q_i and u_i approach infinity. Let us prove that Q_{i+1} approaches infinity. Assume by contradiction that Q_{i+1} is bounded. Then, the equation of Q_{i+1} in the system (3.9) implies that $\lim_{t \rightarrow +\infty} Q'_{i+1}(t) = +\infty$. This means that Q_{i+1} is an increasing function on some interval $[t_0, +\infty)$. Consequently, $\lim_{t \rightarrow +\infty} Q_{i+1}(t) = +\infty$ which is a contradiction with our hypothesis. We conclude that Q_{i+1} approaches infinity. Finally, the last statement is a direct consequence of Lemma 3.5 of Ref. 31 and we have that u_{i+1} tends to zero.

Now, we will prove the unboundedness of the solutions $(Q(t), u(t))$ of System (3.9) for $L_n > L_0^n(\tau_n)$. The last condition implies that $L_i > L_0^i(\tau_i)$ for each $i \in I_n$ (see Hypotheses (H1) and (H2)). So, the result is immediate by applying the same argument as above (see Ref. 26). \square

Let $\delta_i > 0$ and $L_i = 0$ for all $i \in I_n$ (see Ref. 21). All nontrivial solutions are bounded. But, in our model when L_i approaches $L_0^i(\tau_i)$ the positive equilibrium \bar{Q}_i (then, the solutions Q_i of (3.9)) approaches infinity. So in our model, the introduction of the parameters L_i can explain the maintenance of high level of production of blood cells.

The goal of the next proposition is to prove the existence of unbounded solutions when $\delta_i = 0$ for some $i \in I_n$.

Proposition 4.3 *Assume that $\delta_i = 0$ for some $i \in I_n$ and $0 \leq L_i < 1 - K_i - L_0^i(\tau_i)$. Let (Q, u) be a solution of (3.9). Suppose that there exists $\bar{x} \geq 0$ such that the function $\beta_i(x)x$ is decreasing for $x \geq \bar{x}$. If there exists $\bar{t} \geq 0$ such that $Q_i(\bar{t}) > \bar{x}$ and Q_i is increasing on $[\bar{t}, \bar{t} + \tau_i]$. Then, Q_i is increasing for all $t \geq \bar{t}$ and $\lim_{t \rightarrow +\infty} Q_i(t) = +\infty$.*

Proof. The hypothesis of the proposition implies that $Q_i(\bar{t} + \tau_i) \geq Q_i(\bar{t}) > \bar{x}$. It follows that $\beta_i(Q_i(\bar{t} + \tau_i))Q_i(\bar{t} + \tau_i) \leq \beta_i(Q_i(\bar{t}))Q_i(\bar{t})$. Then

$$\begin{aligned} Q'_i(\bar{t} + \tau_i) &\geq -\beta_i(Q_i(\bar{t} + \tau_i))Q_i(\bar{t} + \tau_i) + 2(1 - L_i - K_i)e^{-\gamma_i\tau_i}u_i(\bar{t}), \\ &= -\beta_i(Q_i(\bar{t} + \tau_i))Q_i(\bar{t} + \tau_i) + 2(1 - L_i - K_i)e^{-\gamma_i\tau_i}\beta_i(Q_i(\bar{t}))Q_i(\bar{t}) \\ &\quad + 4L_i(1 - L_i - K_i)e^{-2\gamma_i\tau_i}u_i(\bar{t} - \tau_i), \\ &\geq \beta_i(Q_i(\bar{t} + \tau_i))Q_i(\bar{t} + \tau_i) \left(\frac{1 - L_i - K_i - L_0^i(\tau_i)}{L_0^i(\tau_i)} \right), \\ &> 0. \end{aligned}$$

Hence Q_i is increasing on $[\bar{t}, \bar{t} + \tau_i + \varepsilon]$ for some $\varepsilon > 0$. We repeat the same reasoning and we get $Q'_i(\bar{t} + \tau_i + \varepsilon) \geq 0$. Then, we obtain that Q_i is increasing on $[\bar{t}, +\infty)$.

Now, We show that $\lim_{t \rightarrow +\infty} Q_i(t) = +\infty$. Suppose by contradiction that Q_i is bounded. Hence, the limit $B := \lim_{t \rightarrow +\infty} Q_i(t)$ exists and $\lim_{t \rightarrow +\infty} Q'_i(t) = 0$. Then, we

obtain from (3.9) that $0 \geq \beta_i(B)B(2(1 - L_i - K_i)e^{-\gamma_i\tau_i} - 1)$. Consequently, $B = 0$. This leads to a contradiction. \square

The condition $L_i < 1 - K_i - L_0^i(\tau_i)$ in Proposition 4.3 is in fact equivalent to $2(1 - L_i - K_i)e^{-\gamma_i\tau_i} > 1$ and this means that the proportion of proliferating cells entering the resting phase in the i^{th} generation is greater than one. So, it is no surprising that $\lim_{t \rightarrow +\infty} Q_i(t) = +\infty$.

Remark 4.2 One can notice that if β is given by a Hill function (we drop the index for the simplicity), see Refs. 9, 14, 15,

$$\beta(Q) = \frac{\tilde{\beta}_0\theta^\alpha}{\theta^\alpha + Q^\alpha}, \quad \alpha > 1, \quad (4.29)$$

then, the function $Q \mapsto \beta(Q)Q$ is decreasing on $[\bar{x}, +\infty)$, with

$$\bar{x} := \frac{\theta}{(\alpha - 1)^{1/\alpha}}.$$

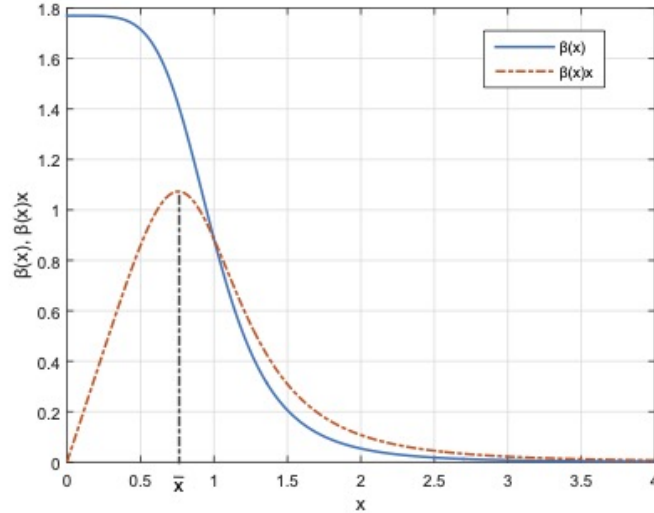


Fig. 2. A Hill function $x \mapsto \beta(x)$ and the function $x \mapsto \beta(x)x$ are plotted with the parameters $\alpha = 5$, $\theta = 1$ and $\tilde{\beta}_0 = 1.77 \text{ d}^{-1}$.

5. Stability of the steady states

5.1. Global asymptotic stability of the trivial steady state

In this section, we study the global asymptotic stability of the trivial steady state. We start by establishing the following lemma, which is helpful to obtain the stability of u .

Lemma 5.1 *If $0 \leq L_i < L_0^i(\tau_i)$ for some $i \in I_n$, then there exist constants $C > 0$ and $\alpha > 0$ such that the component (Q_i, u_i) of (3.9) satisfies*

$$|u_i(t)| \leq C \left[\|\phi_i\| e^{-\alpha t} + \beta_i(0) \sup_{0 \leq s \leq t} |Q_i(s)| \right],$$

where ϕ_i is the initial condition for u_i on the interval $[-\tau_i, 0]$.

Proof. This is an immediate consequence of Ref. 30, Theorem 3.5, page 275. \square

Suppose that $\delta_i > 0$ for $i \in I_n$. The following theorem gives a sufficient condition for the trivial steady state of (3.9) to be globally asymptotically stable.

Theorem 5.1 (1) *Assume that, for all $i \in I_n$ (or under the conditions (H1)-(H2) that we assume only for $i = 1$),*

$$\tau_i \geq \tilde{\tau}_{\mu_i}^i \quad \text{and} \quad 0 \leq L_i \leq (1 + \mu_i) L_0^i(\tau_i) - \mu_i. \quad (5.2)$$

Then, the trivial steady state of System (3.9) is globally asymptotically stable.

(2) *Assume that $L_1 < L_0^1(\tau_1)$ and suppose that either*

$$\tau_1 \geq \tau_{\mu_1}^1 \quad \text{and} \quad L_1 > L_{\mu_1}^1(\tau_1) \quad \text{or} \quad \tau_1 < \tau_{\mu_1}^1. \quad (5.3)$$

Then, no nontrivial solution of System (3.9) tends to the trivial steady state.

Proof. 1. Assume that (5.2) is satisfied. Then, the estimation in Lemma 5.1 holds for all $i \in I_n$. On the other hand, consider the following continuous function

$$V: \mathbb{R}_+^n \times C([- \tau, 0], \mathbb{R}_+^n) \rightarrow \mathbb{R}^+, \\ (Q^0, \psi) \mapsto V(Q^0, \psi),$$

defined by

$$V(Q^0, \psi) = \sum_{i=1}^n Q_i^0 + \sum_{i=1}^n \rho_i(\tau_i) \int_{-\tau_i}^0 \psi_i(\theta) d\theta,$$

where $\rho_i(\tau_i)$ is given by (4.21). Remark that V is the same function as the one used in the proof of Proposition 4.2. It is not difficult to see that

$$|Q^0| \leq V(Q^0, \psi) \leq 2 \max\{1, \max_{i \in I_n} \{\tau_i \rho_i(\tau_i)\}\} \max\{|Q^0|, \|\psi\|\},$$

where

$$|Q^0| = \sum_{i=1}^n |Q_i^0| \quad \text{and} \quad \|\psi\| = \sum_{i=1}^n \|\psi_i\|.$$

Furthermore, by differentiating the function $t \mapsto V(Q(t), u_t)$ along the solution (Q, u) of System (3.9), we obtain, for $t > 0$,

$$\begin{aligned} \frac{d}{dt}V(Q(t), u_t) &= - \sum_{i=1}^n \left[\delta_i - \left(\frac{1 - L_0^i(\tau_i)}{L_0^i(\tau_i) - L_i} \right) \beta_i(Q_i(t)) \right] Q_i(t), \\ &= - \sum_{i=1}^n \chi_i(Q_i(t)) Q_i(t), \end{aligned}$$

with

$$\chi_i(Q_i) = \delta_i - \left(\frac{1 - L_0^i(\tau_i)}{L_0^i(\tau_i) - L_i} \right) \beta_i(Q_i), \quad \text{for } Q_i \geq 0.$$

The function χ_i is strictly increasing and

$$\chi_i(0) = \frac{\delta_i}{L_0^i(\tau_i) - L_i} [(1 + \mu_i)L_0^i(\tau_i) - \mu_i - L_i].$$

Moreover, (5.2) is equivalent to $\chi_i(0) > 0$ for all $i \in I_n$. Consequently,

$$\frac{d}{dt}V(Q(t), u_t) \leq - \min_{i \in I_n} [\chi_i(0)] |Q(t)| = -w(|Q(t)|), \quad t > 0.$$

Then, we conclude by Theorem 3 of Ref. 32, that the trivial steady state is globally asymptotically stable.

2. We focus now on the instability of the trivial steady state. Let (Q, u) be a solution of (3.9). Assume by contradiction that $(Q_1(t), u_1(t)) \rightarrow 0$ as $t \rightarrow +\infty$. By the continuity of the function β_1 , we have $\beta_1(Q_1(t)) \rightarrow \beta_1(0)$ as $t \rightarrow +\infty$. Consequently, for all $\epsilon > 0$ there exists $A(\epsilon)$ such that, for all $t \geq A(\epsilon)$,

$$\beta_1(0) - \epsilon < \beta_1(Q_1(t)) \leq \beta_1(0). \quad (5.12)$$

We fix $0 < \epsilon < \beta_1(0)$. By integration the system (3.9) over $t \in (A(\epsilon), T)$ for an arbitrary large $T > 0$, we get

$$\left\{ \begin{aligned} Q_1(A(\epsilon)) - Q_1(T) &= \int_{A(\epsilon)}^T [\delta_1 + \beta_1(Q_1(t))] Q_1(t) dt \\ &\quad - 2(1 - L_1 - K_1) e^{-\gamma_1 \tau_1} \int_{A(\epsilon)}^T u_1(t - \tau_1) dt, \\ \int_{A(\epsilon)}^T u_1(t) dt &= \int_{A(\epsilon)}^T \beta_1(Q_1(t)) Q_1(t) dt + 2L_1 e^{-\gamma_1 \tau_1} \int_{A(\epsilon)}^T u_1(t - \tau_1) dt. \end{aligned} \right. \quad (5.13)$$

By a change of variable, we obtain

$$\begin{aligned} \int_{A(\epsilon)}^T u_1(t - \tau_1) dt &= \int_{A(\epsilon) - \tau_1}^{T - \tau_1} u_1(t) dt, \\ &\geq \int_{A(\epsilon)}^{T - \tau_1} u_1(t) dt, \\ &= \int_{A(\epsilon)}^T u_1(t) dt - \int_{T - \tau_1}^T u_1(t) dt. \end{aligned} \quad (5.14)$$

18 *Adimy, Chekroun, El Abdllaoui & Marzorati*

From (5.12) and the second equation of (5.13), it follows

$$\int_{A(\epsilon)}^T u_1(t)dt \geq (\beta_1(0) - \epsilon) \int_{A(\epsilon)}^T Q_1(t)dt + 2L_1 e^{-\gamma_1 \tau_1} \left(\int_{A(\epsilon)}^T u_1(t)dt - \int_{T-\tau_1}^T u_1(t)dt \right).$$

Since $L_1 < \frac{1}{2}e^{\gamma_1 \tau_1}$, we obtain

$$\int_{A(\epsilon)}^T u_1(t)dt \geq \frac{\beta_1(0) - \epsilon}{1 - 2L_1 e^{-\gamma_1 \tau_1}} \int_{A(\epsilon)}^T Q_1(t)dt - \frac{2L_1 e^{-\gamma_1 \tau_1}}{1 - 2L_1 e^{-\gamma_1 \tau_1}} \int_{T-\tau_1}^T u_1(t)dt. \quad (5.16)$$

We deduce from the first equation of (5.13) and (5.14), that

$$\begin{aligned} Q_1(A(\epsilon)) &\leq Q_1(T) + (\delta_1 + \beta_1(0)) \int_{A(\epsilon)}^T Q_1(t)dt \\ &\quad - 2(1 - L_1 - K_1)e^{-\gamma_1 \tau_1} \left(\int_{A(\epsilon)}^T u_1(t)dt - \int_{T-\tau_1}^T u_1(t)dt \right), \\ &\leq Q_1(T) + (\delta_1 + \beta_1(0)) \int_{A(\epsilon)}^T Q_1(t)dt \\ &\quad + 2(1 - L_1 - K_1)e^{-\gamma_1 \tau_1} \int_{T-\tau_1}^T u_1(t)dt \\ &\quad - \frac{2(1 - L_1 - K_1)e^{-\gamma_1 \tau_1}(\beta_1(0) - \epsilon)}{1 - 2L_1 e^{-\gamma_1 \tau_1}} \int_{A(\epsilon)}^T Q_1(t)dt \\ &\quad + \frac{2L_1 e^{-\gamma_1 \tau_1} 2(1 - L_1 - K_1)e^{-\gamma_1 \tau_1}}{1 - 2L_1 e^{-\gamma_1 \tau_1}} \int_{T-\tau_1}^T u_1(t)dt, \\ &= Q_1(T) + \kappa_\epsilon \int_{A(\epsilon)}^T Q_1(t)dt + 2(1 - L_1 - K_1)e^{-\gamma_1 \tau_1} \int_{T-\tau_1}^T u_1(t)dt \\ &\quad + \frac{2L_1 e^{-\gamma_1 \tau_1} 2(1 - L_1 - K_1)e^{-\gamma_1 \tau_1}}{1 - 2L_1 e^{-\gamma_1 \tau_1}} \int_{T-\tau_1}^T u_1(t)dt, \\ &= Q_1(T) + \kappa_\epsilon \int_{A(\epsilon)}^T Q_1(t)dt + \frac{2(1 - L_1 - K_1)e^{-\gamma_1 \tau_1}}{1 - 2L_1 e^{-\gamma_1 \tau_1}} \int_{T-\tau_1}^T u_1(t)dt, \end{aligned}$$

with

$$\kappa_\epsilon := \delta_1 - \beta_1(0) \frac{2(1 - K_1)e^{-\gamma_1 \tau_1} - 1}{1 - 2L_1 e^{-\gamma_1 \tau_1}} + \epsilon \frac{2(1 - L_1 - K_1)e^{-\gamma_1 \tau_1}}{1 - 2L_1 e^{-\gamma_1 \tau_1}}.$$

So, by (5.3) one can fix $\epsilon \in (0, \beta_1(0))$ small enough such that $\kappa_\epsilon < 0$. As we assumed that (Q_1, u_1) tend to $(0, 0)$ when $t \rightarrow +\infty$, we obtain for a large T

$$Q_1(T) < \epsilon \quad \text{and} \quad \frac{1}{\tau_1} \int_{T-\tau_1}^T u_1(t)dt < \epsilon.$$

Then, we obtain a contradiction with the positivity of the solutions. Then, $(Q_1(t), u_1(t))$ does not tend to zero as $t \rightarrow +\infty$. \square

The condition (5.2) is sufficient to ensure that the trivial steady state is the only equilibrium. However, the condition (5.3) is a necessary and sufficient one for which the trivial steady state is not the only equilibrium. The assumption (5.2) is satisfied when δ_i and γ_i (the mortality rates) or τ_i (the duration of the cell cycle) are large enough, or when $\beta_i(0)$ (the maximum rate of introduction from resting phase to proliferating phase) or L_i (the introduction rate after division into the proliferating phase) are small. In fact, the condition (5.2) corresponds to a population which cannot survive for a long term. From a biological point of view, if the mortality rates are too large and/or the cell cycle duration is too long and/or there is not enough cells introduced in the proliferating phase, then the cell population will die out.

5.2. Local asymptotic stability around a steady state

We notice that the local asymptotic stability of a steady state and even its instability is obtained by linearization around the steady state of the neutral differential equation associated to the system (3.9). This leads to a characteristic equation (see Ref. 26).

Let us consider the delay differential-difference system (3.9) as a special case of the following neutral differential system

$$\begin{cases} \frac{d}{dt}G(Q(t), u_t) = F(Q(t), u_t), & t > 0, \\ Q(0) = Q^0 \quad \text{and} \quad u_0 = \phi, \end{cases} \quad (5.20)$$

where $Q^0 \in \mathbb{R}_+^n$ and $\phi \in C([- \tau_n, 0], \mathbb{R}_+^n)$. The functions $G(Q, \phi) = (G_1(Q, \phi), \dots, G_n(Q, \phi))$ and $F(Q, \phi) = (F_1(Q, \phi), \dots, F_n(Q, \phi))$ are defined, for $(Q, \phi) \in \mathbb{R}_+^n \times C([- \tau_n, 0], \mathbb{R}_+^n)$, by

$$\begin{cases} G_i(Q, \phi) = (Q_i, \phi_i(0) - \beta_i(Q_i)Q_i - 2L_i e^{-\gamma_i \tau_i} \phi_i(-\tau_i)), & i \in I_n, \\ F_1(Q, \phi) = (-(\delta_1 + \beta_1(Q_1))Q_1 + 2(1 - L_1 - K_1)e^{-\gamma_1 \tau_1} \phi_1(-\tau_1), 0), \\ F_i(Q, \phi) = (-(\delta_i + \beta_i(Q_i))Q_i + 2(1 - L_i - K_i)e^{-\gamma_i \tau_i} \phi_i(-\tau_i) \\ \quad + 2K_{i-1}e^{-\gamma_{i-1} \tau_{i-1}} \phi_{i-1}(-\tau_{i-1}), 0), & i \in I_n \setminus \{1\}. \end{cases} \quad (5.21)$$

The linearization of the system (5.20) around a steady state (\bar{Q}, \bar{u}) gives, for $t > 0$,

$$\begin{cases} \frac{d}{dt}D_1(Q(t), u_t) = R_1(Q(t), u_t), \\ \frac{d}{dt}D_i(Q(t), u_t) = R_i(Q(t), u_t), & i \in I_n \setminus \{1\}, \\ Q(0) = Q^0 \quad \text{and} \quad u_0 = \phi, \end{cases} \quad (5.22)$$

with

$$\begin{cases} D_i(Q, \phi) = (Q_i, \phi_i(0) - \bar{\beta}_i Q_i - 2L_i e^{-\gamma_i \tau_i} \phi_i(-\tau_i)), & i \in I_n, \\ R_1(Q, \phi) = (-(\delta_1 + \bar{\beta}_1)Q_1 + 2(1 - L_1 - K_1)e^{-\gamma_1 \tau_1} \phi_1(-\tau_1), 0), \\ R_i(Q, \phi) = (-(\delta_i + \bar{\beta}_i)Q_i + 2(1 - L_i - K_i)e^{-\gamma_i \tau_i} \phi_i(-\tau_i) \\ \quad + 2K_{i-1}e^{-\gamma_{i-1} \tau_{i-1}} \phi_{i-1}(-\tau_{i-1}), 0), & i \in I_n \setminus \{1\}, \end{cases}$$

20 *Adimy, Chekroun, El Abdllaoui & Marzorati*

and

$$\bar{\beta}_i := \beta_i(\bar{Q}_i) + \beta'_i(\bar{Q}_i)\bar{Q}_i, \quad i \in I_n.$$

The system (5.22) is restricted to the set of initial conditions $Q(0) = Q^0 \in \mathbb{R}_+^n$ and $u_0 = \phi \in C([-\tau_n, 0], \mathbb{R}_+^n)$ such that

$$\phi_i(0) - \bar{\beta}_i Q_i^0 - 2L_i e^{-\gamma_i \tau_i} \phi_i(-\tau_i) = 0, \quad i \in I_n.$$

Straightforward calculations lead to the following characteristic equation

$$\prod_{i=1}^n \left[(\lambda + \delta_i + \bar{\beta}_i)(2L_i e^{-(\lambda + \gamma_i)\tau_i} - 1) + 2\bar{\beta}_i \lambda (1 - L_i - K_i) e^{-(\lambda + \gamma_i)\tau_i} \right] = 0.$$

Remark that the characteristic equation can be written as

$$\prod_{i=1}^n \left[\lambda + \delta_i + \bar{\beta}_i + (\bar{\alpha}_i(\tau_i)\lambda + \bar{\gamma}_i(\tau_i))e^{-\lambda\tau_i} \right] = 0,$$

with

$$\bar{\alpha}_i(\tau_i) = -2(L_i + \bar{\beta}_i(1 - L_i - K_i))e^{-\gamma_i\tau_i} \quad \text{and} \quad \bar{\gamma}_i(\tau_i) = -2L_i(\delta_i + \bar{\beta}_i)e^{-\gamma_i\tau_i}.$$

This equation can be spread into n equations of the same form

$$\lambda + \delta_i + \bar{\beta}_i + (\bar{\alpha}_i(\tau_i)\lambda + \bar{\gamma}_i(\tau_i))e^{-\lambda\tau_i} = 0, \quad i \in I_n.$$

We refer the reader to our paper²⁶ for a complete study of this type of equation. We only want to emphasize here that if we start the system from $\tau_i = 0$, for all $i \in I_n$, with the positive equilibrium locally asymptotically stable, by increasing each delay shows the existence of periodic oscillations through Hopf bifurcations (see²⁶). Indeed, if we suppose that $\tau_i = 0$, for all $i \in I_n$, then we have n real eigenvalues

$$\lambda_i = -\frac{\delta_i + \bar{\beta}_i + \bar{\gamma}_i(0)}{1 + \alpha_i(0)}.$$

The condition

$$\frac{\delta_i + \bar{\beta}_i + \bar{\gamma}_i(0)}{1 + \alpha_i(0)} > 0$$

guarantees the local asymptotically stably of the positive equilibrium for $\tau_i = 0$. Then, the local asymptotic stability persists in a region where $\tau_i > 0$ are small enough. The purpose of this paper is to apply the model (2.2)-(2.3) to acute myelogenous leukemia. However, this model can also be adapted to other blood diseases such as chronic myelogenous leukemia which is characterized by the existence of long periodic oscillations (see Refs. 13, 14, 20).

6. Simulations and application to acute myelogenous leukemia

6.1. Influence of the parameters K_i and L_i

In this part, we focus on the influence of the parameters K_i and L_i , which represent the rate of cells that leave the proliferating stage i and the rate of cells that remain in the same proliferating stage i , respectively. We compare the following situations.

- The influence of the differentiation parameters K_{i-1} and K_i on the i^{th} generation (here the third and the fourth generations on the fourth generation).
- The influence of the two parameters K_i and L_i on the same generation i (here K_4 and L_4 on the fourth generation).
- The influence of the parameters K_{i-1} and L_i on the i^{th} generation (here K_3 and L_4 on the fourth generation).

Let us first state the different quantities used in this paper. In our case, the functions $\beta_i := \beta$, for $i \in I_n$, take the form of a Hill function (see Refs. 9, 14, 15) given by

$$\beta(x) = \frac{\tilde{\beta}_0 \theta^\alpha}{\theta^\alpha + x^\alpha}, \quad \alpha > 1.$$

The coefficient $\tilde{\beta}_0 > 0$ is the maximum rate of reintroduction, θ is a threshold value for which β reaches half of its maximum, and α is the so-called sensitivity of the introduction rate, it describes the reaction of β due to external stimuli, the action of a growth factor for example.

In most of the following situations, the fixed parameters take the following values, for $i \in I_n$,

$$\begin{cases} \tau_i = 1 \text{ d}, & \gamma_i = 0.2 \text{ d}^{-1}, & \delta_i = 0.01 \text{ d}^{-1}, \\ \theta = 1 \text{ cell.kg}^{-1}, & \tilde{\beta}_0 = 1 \text{ d}^{-1}, & \alpha = 3 \text{ d}^{-1}. \end{cases} \quad (6.2)$$

If necessary, some values of these parameters can be modified to suit particular situations.

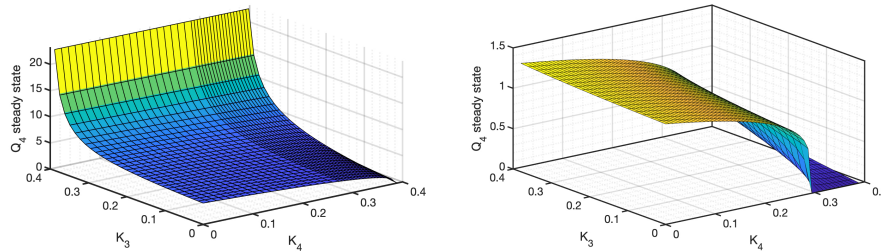


Fig. 3. Representation of the 4th generation of the positive steady state by varying K_3 and K_4 . Parameters are given by: In the left, $K_1 = K_2 = 0.22 \text{ d}^{-1}$ and $L_i = 0.05 \text{ d}^{-1}$. In the right, $\tilde{\beta}_0 = 0.5 \text{ d}^{-1}$, $\alpha = 5 \text{ d}^{-1}$, $\delta_i = 0.2 \text{ d}^{-1}$, $K_1 = 0.1 \text{ d}^{-1}$, $K_2 = 0.381 \text{ d}^{-1}$ and L_i are linearly distributed between 0.05 d^{-1} and 0 d^{-1}

In Figure 3, we illustrate the behavior of \bar{Q}_4 by varying K_3 and K_4 . It is decreasing with respect to K_4 . However, it increases with respect to K_3 , which can be seen directly from the expressions (4.2) and (4.3). The influence of K_3 becomes more important when the parameter tends towards a specific maximum value. In fact, the level of the equilibrium increases more and more (we stopped the simulation before reaching the maximum of K_3 because the more we increase it the less the figure is readable). So, it seems that an increase of the differentiation rate K_{i-1} of the previous generation, tends to increase the value of the i^{th} generation \bar{Q}_i of the steady state. In addition, the variation of the parameters as in the right of Figure 3, shows large sensitivity. In the case we have plotted, the sensitivity to K_{i-1} in the right of Figure 3 seems to be less important than that of the left of Figure 3.

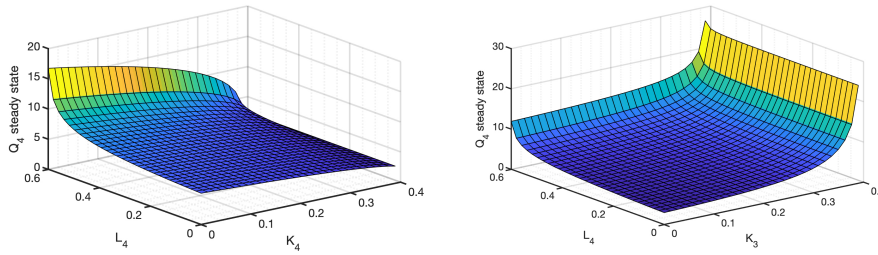


Fig. 4. Representation of the 4th generation of the positive steady state by varying, respectively, K_4 and L_4 in the left and K_3 and L_4 in the right. Parameters are given by $L_j = 0.05 \text{ d}^{-1}$ and $K_j = 0.22 \text{ d}^{-1}$ for $j \neq 4$ (left) and $K_j = 0.22 \text{ d}^{-1}$ for $j \neq 3$ (right).

In Figure 4 (left), we compare the influence of the two parameters K_i and L_i on the i^{th} generation. We also notice the negative impact of the parameter K_i on the current generation i by reducing the level of this generation at the equilibrium. On the other hand, the parameter L_i seems to be relevant for maintaining a high level of blood cell production (by increasing the value of the i^{th} generation at the equilibrium). However, according to the left of Figure 4, it seems that the influence of L_i is less important than that of K_i .

Finally, we compare (see the right of Figure 4) the impact of the two parameters K_{i-1} and L_i on the level of the current generation i at the equilibrium. The influence of K_{i-1} seems to be more important than that of L_i . In fact, K_{i-1} represents the cells of the $(i-1)^{\text{th}}$ generation that enter in the current i^{th} resting generation. The higher it is, the more cells supply the current generation. However, as we have seen in the left of Figure 3, if K_{i-1} is too high then the previous equilibrium could be reduced and this could have a negative impact on the current generation. In conclusion and from a biological point of view, Figures 3 and 4 underline the importance of the combination of the two phenomena, the differentiation of the $(i-1)^{\text{th}}$ previous generation and the self-renewal of the current i^{th} generation in

the overproduction of the i^{th} generation.

6.2. Influence of the parameters L_i on the positive steady state

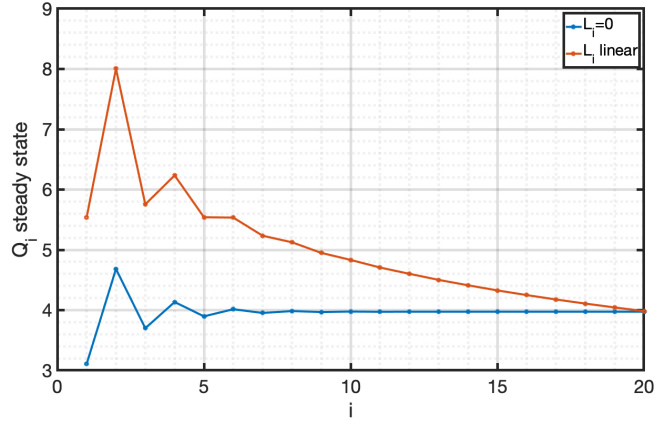


Fig. 5. Distribution of the equilibrium of 20 generations, with $K_i = 0.2 \text{ d}^{-1}$ fixed. (a) Blue: $L_i = 0$ and (b) Red: L_i are linearly distributed between 0.5 d^{-1} and 0.

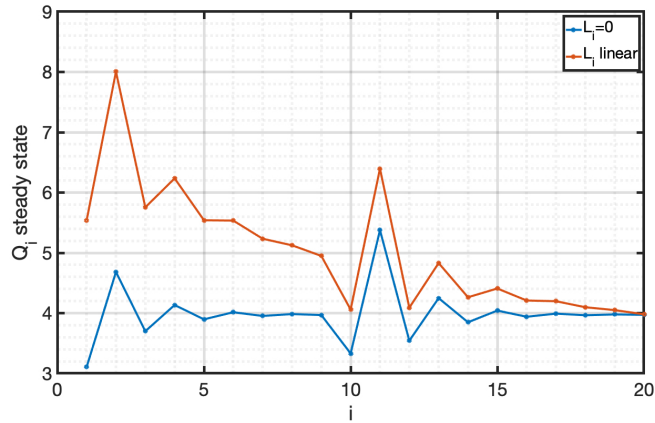


Fig. 6. Distribution of the equilibrium of 20 generations, with $K_i = 0.2 \text{ d}^{-1}$ for all $i \in I_{20} \setminus \{10\}$ and $K_{10} = 0.3 \text{ d}^{-1}$. (a) Blue: $L_i = 0$ and (b) Red: L_i are linearly distributed between 0.5 d^{-1} and 0.

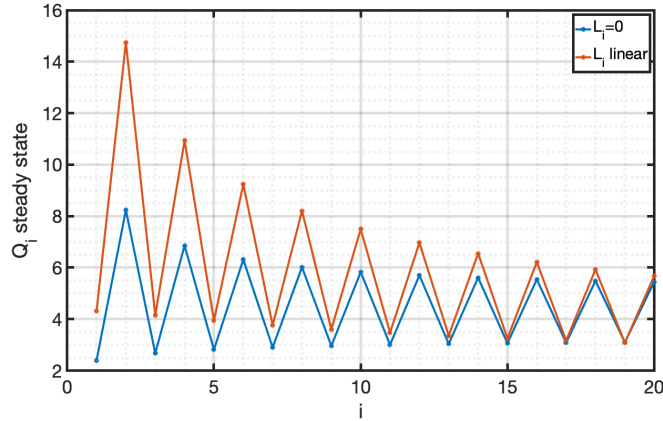


Fig. 7. Distribution of the equilibrium of 20 generations with $K_i = 0.3 \text{ d}^{-1}$ for all $i \in I_{20}$. (a) Blue: $L_i = 0$ and (b) Red: L_i are linearly distributed between 0.5 d^{-1} and 0.

In this part, we study numerically the influence of the parameters $(L_i)_{1 \leq i \leq n}$ on the behavior of the steady state components. In the hematopoietic system, HSCs give rise to at least 9 distinct cell types that can be observed during successive processes of differentiation and maturation of increasingly committed cells.³³ However, this number is underestimated because primitive HSCs, which are difficult to differentiate, must also be considered. We chose 20 generations which seems reasonable to observe the behavior of the different cell populations. In all the figures 5, 6 and 7, we consider $n = 20$.

First, we consider the system by setting $L_i = 0$ for all generations. Then, we increase the values of L_i , by using a linear distribution between the values of L_i (this conforms to the assumption (H2)), to see the influence of these parameters on the behavior of the components of the steady state of the system. Three scenarios were studied by varying the values of the parameters K_i .

In the first scenario, Figure 5, we vary the values of K_i by taking them equal to each other, up to a threshold $K_i = 0.3 \text{ d}^{-1}$. As long as the values of K_i are below this threshold (in Figure 5, we choose $K_i = 0.2 \text{ d}^{-1}$), the equilibrium components seem to be stable and they always return after damped oscillations to their starting value at the 20th generation.

In the second scenario, Figure 6, we have disturbed only one value of the parameters K_i , let say for example K_{10} . The equilibrium components seem also to be stable and they return after damped oscillations to their starting value at the 20th generation. The perturbation of K_i for one intermediate generation (even if it reaches the threshold) does not affect too much the behavior of the equilibrium components.

In the last scenario, Figure 7, we take all the values of K_i equal to the threshold

0.3 d^{-1} . We observe that the oscillations observed in the two other scenarios become periodic (unstable).

As we have already seen previously, an increase of the parameter L_i increases the level of the component of the equilibrium at the same i^{th} generation. This is confirmed by the fact that the blue curve is always located below the red one (see Figures 5, 6 and 7). Furthermore, the parameters L_i do not influence the behavior of the components of the equilibrium.

HSCs are very sensitive to their environment and their production can be disrupted by external factors such as certain treatments. The HSC population at a certain level of maturity can sometimes decrease or increase due to external factors. However, the hematopoietic system adapts quickly to these perturbations and is able to mitigate them and eventually maintain a constant production of the most mature cells, which are the most important for the system. We tested our model to see if it is able to reproduce this phenomenon. We showed that there is a threshold in the rate of differentiation K_i below which the system is still able to absorb perturbations induced at lower levels of maturity. On the other hand, the system is no longer able to absorb these perturbations when the differentiation rate K_i exceeds this threshold.

6.3. Application to acute myelogenous leukemia

In this part, we are interested in the behavior of the system in case of Acute Myelogenous Leukemia (AML). This blood cancer is characterized by an uncontrolled proliferation of blasts (immature white blood cells), accompanied by a blockage of differentiation at the immature stages of white blood cells. The result is that the blasts accumulate in the bone marrow and eventually invade the entire bloodstream, preventing mature cells from performing their functions. Our model is able to describe these behaviors in the event of blocking the differentiation at a given generation and/or of overproduction at other generations. In other words, it can be observed that the population of immature cells becomes larger than the population of more mature cells.

We numerically simulate four cases of blocking the differentiation at an immature stage. All the values of the parameters are given by (6.2). The others will be specified below. At the beginning, the twenty generations ($n = 20$) are taken at their equilibrium (initial conditions at equilibrium). Then, after a certain arbitrary time (in the figures, $t = 20$ days), we simulate four scenarios of blocking the differentiation.

In Figure 8, we start from the equilibrium with the parameters $K_i = 0.2 \text{ d}^{-1}$ equal to each other, then at time $t = 20$, we put the value of the parameter $K_{10} = 0$. This is a simple case of blocking the differentiation at a single generation, here the 10th generation. On the left of Figure 8, we can observe the evolution of some generations. For example, generations 9 (blue) and 20 (green) do not seem to be influenced by this change. However, the 10th generation (red) increases significantly

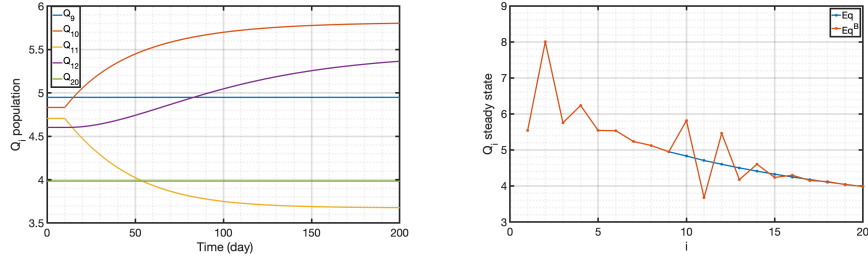


Fig. 8. Blocking of cell differentiation. The parameters are given by (6.2), L_i are linearly distributed between 0.5 d^{-1} and 0. In the beginning, we take $K_i = 0.2 \text{ d}^{-1}$ and at $t = 20 \text{ d}$, we set $K_{10} = 0$. The left figure shows the evolution of five generations. The right figure shows the components of the equilibrium of the 20 generations before (blue) and after (red) the blocking of cell differentiation.

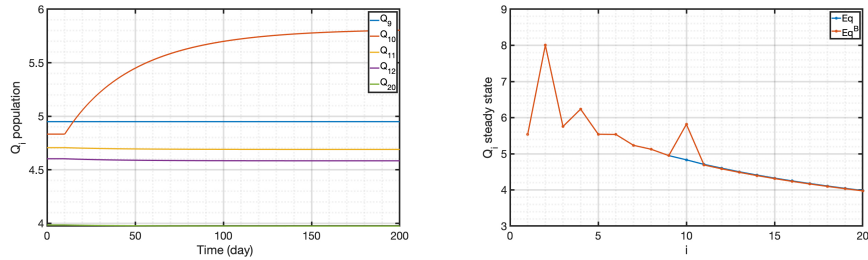


Fig. 9. Blocking of cell differentiation. The parameters are given by (6.2), L_i are linearly distributed between 0.5 d^{-1} and 0. In the beginning, we take $K_i = 0.2 \text{ d}^{-1}$ and at $t = 20 \text{ d}$, we set $K_i = 0$, for $i = 10, \dots, 20$. The left figure shows the evolution of five generations. The right figure shows the equilibria of the 20 generations before (blue) and after (red) the blocking of cell differentiation.

while the following generation (the 11th) (yellow), decreases. The behavior of generation 12 (purple) is an interesting case because it is increasing which was not expected.

In Figure 9, we consider the same situation as in Figure 8, except that at time $t = 20 \text{ d}$ we put all the parameters $K_i = 0$, for $i = 10, \dots, 20$. We observe a change only for the 10th generation which increases significantly. All other generations remain almost unchanged. The explanation comes from the figure on the right, the blue and red curves coincide before and after the 10th generation, unlike the previous figure where we observe oscillations before a return to a normal situation.

In Figure 10, we simulate the same blocking of differentiation at the 10th generation, except that we consider the limit situation for the parameters $K_i = 0.3 \text{ d}^{-1}$. The variations between the components of the equilibrium before and after the blocking of differentiation are not very large compared to the previous situations.

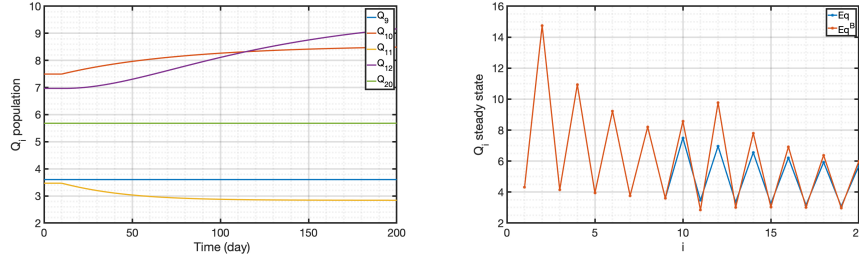


Fig. 10. Blocking of cell differentiation. The parameters are given by (6.2), L_i are linearly distributed between 0.5 d^{-1} and 0. In the beginning, we take $K_i = 0.3 \text{ d}^{-1}$ and at $t = 20 \text{ d}$, we set $K_{10} = 0$. The left figure shows the evolution of five generations. The right figure shows the equilibria of the 20 generations before (blue) and after (red) the blocking of cell differentiation.

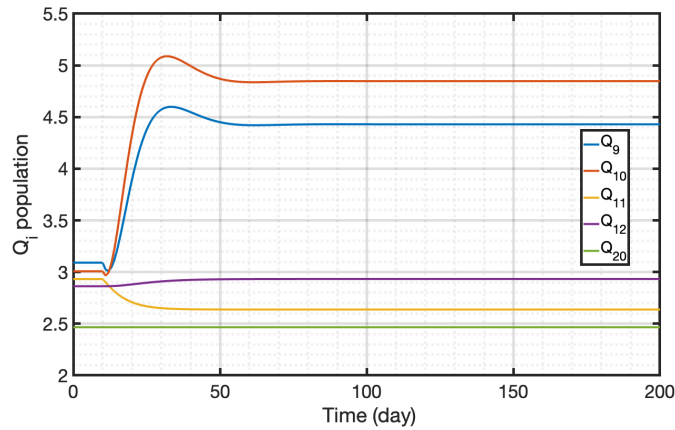


Fig. 11. Blocking of cell differentiation. The parameters are given by (6.2), $\delta_i = 0.04 \text{ d}^{-1}$, $K_i = 0.1 \text{ d}^{-1}$, L_i are linearly distributed between 0.5 d^{-1} and 0. For $t \geq 20 \text{ d}$, we set $K_{10} = 0$ and $L_i = 0.5 \text{ d}^{-1}$ for $i = 1, \dots, 10$.

In Figure 11, we also simulate the blocking of differentiation at the 10th generation. The main change in this simulation is that we increase, at time $t = 20 \text{ d}$, all the values of L_i , for $i = 1, \dots, 10$, to 0.5 d^{-1} . Then, we can observe a significant increase of the 9th (blue) and 10th (red) generations with some fluctuations before reaching their levels at the equilibrium.

7. Discussion

A new mathematical model based on differential-difference equations, structured in discrete maturity, was proposed to describe the hierarchical organization of

hematopoietic cells. This system was obtained after reduction by the method of the characteristics of a more general age-structured system. To our knowledge, this model is more general than the previous hematopoietic models (see Refs. 21–23). We studied the existence, uniqueness, positivity, boundedness and unboundedness of the solutions. We then investigated the existence of positive and axial steady states and obtained conditions for their stability. By constructing a Lyapunov function, we proved under sufficient conditions (when the trivial steady state is the only equilibrium), the global asymptotic stability of the trivial steady state. This extreme situation describes the cell population's dying out. We also proved that if the trivial steady state is not the only equilibrium, then it is unstable (persistence of cell population). Using neutral differential equation associated to our differential-difference system, we linearized the system around the positive steady state and obtained a characteristic equation. This allowed us to obtain results on the local asymptotic stability of the positive steady state. At the end of this paper, we focused, using numerical simulations, on the influence of the differentiation rates K_i and the self-renewal coefficients L_i of some generations on the behavior of cell population. Our system presents an interesting feature coming from the introduction of the difference equations in the model, and which is due to the parameters L_i , describing a rapid proliferation of the cell population. Increasing L_i could lead to overproduction of blood cells. Such a situation is of great interest to describe certain hematological diseases (Myeloproliferative Disorders), in which high cell production is observed. In this paper, we focused on applying our model to Acute Myelogenous Leukemia (AML) in which hematopoietic cells are arrested in an early stage of their development. The consequence is an overproduction of immature cells which invade the bone marrow and then the bloodstream. We have underlined this phenomenon using our model. We showed that a blocking of differentiation could lead to an overproduction of immature cells and to the predominance of the latter population over all the others. We believe that our model could also be used for other hematological diseases in which differentiation and self-renewal play an important role at different stages of maturity of hematopoietic cells, to explain certain phenomena observed in the blood. This will be the subject of future study.

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30 Adimy, Chekroun, El Abdllaoui & Marzorati

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