A mathematical model of multistage hematopoietic cell lineages

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Abstract. We investigate a mathematical model of blood cell production in the bone marrow (hematopoiesis). The model describes both the evolution of primitive hematopoietic stem cells and the maturation of these cells as they differentiate to form the three types of blood cells (red blood cells, white cells and platelets). The primitive hematopoietic stem cells and the first generations of each line (progenitors) are able to self-renew, and can be either in a proliferating or in a resting phase (G_0-phase). These properties are gradually lost while cells become more and more mature. The three types of progenitors and mature cells are coupled to each other via their common origin in primitive hematopoietic stem cells compartment. Peripheral control loops of primitive hematopoietic stem cells and progenitors as well as a local autoregulatory loop are considered in the model. The resulting system is composed by eleven age-structured partial differential equations. To analyze this model, we don't take into account cell age-dependence of coefficients, that prevents a usual reduction of the structured system to an unstructured delay differential system. We investigate some fundamental properties of the solutions of this system, such as boundedness and positivity. We study the existence of stationary solutions: trivial, axial and positive steady states. Then we give conditions for the local asymptotic stability of the trivial steady state and by using a Lyapunov function, we obtain a sufficient condition for its global asymptotic stability. In some particular cases, we analyze the local asymptotic stability of the positive steady state by using the characteristic equation. Finally, by numerical simulations, we illustrate our results and we show that a change in the duration of cell cycle can cause oscillations. This can be related to observations of some periodical hematological disease such as chronic myelogenous leukemia, cyclical neutropenia, cyclical thrombocytopenia, etc.

Keywords. Model of hematopoiesis, age-structured partial differential equations, delay differential system, feedback control, asymptotic stability, Lyapunov functional, numerical simulations.

1. Introduction

The process that leads to the production and regulation of blood cells is called hematopoiesis. All blood cells are derived from a common origin in the bone marrow, the primitive hematopoietic stem cells (PHSC). These multipotent stem cells are morphologically undifferentiated and

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have a high proliferative potential. Detail on PHSC dynamics can be found in Krause [37]. The PHSC have abilities to produce either similar cells with the same maturity level and same abilities (self-renewal), or cells engaged in one of different lineages of committed stem cells (differentiation), also known as progenitors, that produce in turn precursor cells. Some of these cells (especially progenitors) keep an ability to self-renew (Bauer et al. [18]). This property is gradually lost while cells become more and more mature. Finally, blood cells are produced and released in the bloodstream. As the PHSC, the progenitors are also hematopoietic stem cells (HSC). The compartments of PHSC and progenitors are separated into two sub-compartments: proliferating and quiescent. Quiescent cells represent the major part of hematopoietic stem cell (HSC) population (90% of HSC are in nonproliferating phase, also called G_0-phase). Proliferating cells are actually in the cell cycle where they are committed to divide during mitosis at the end of this phase. After division, the two newborn daughter cells enter immediately in G_0-phase. A part of them stay in the same compartment (self-renewal). The other part can enter by differentiation into one of the three lineages of progenitors: neutrophils (white blood cells), reticulocytes (red blood cells) or megakaryocytes (platelets) (see Figure 1).

Although the HSC are the source of all blood cells, the mechanisms that regulate their production and differentiation are not completely clear. However, proliferation, differentiation, self-renewal and apoptosis (programmed cell death) of HSC are mediated by growth factors. They are molecules acting like hormones in the blood production process, playing an activator or inhibitor role. Usually, a control operates between the number of circulating blood cells and the growth factors production.

The probably most known parts of hematopoiesis are erythropoiesis (the production of red blood cells) and megakaryopoiesis (the production of platelets). For the erythropoiesis, the growth factor erythropoietin (EPO) helps to regulate erythrocyte production (Adamson [1]). A decrease in numbers of mature red blood cells leads to a decrease in tissue $p0_2$ levels, which in turns increases the production of EPO by kidneys and controls erythropoiesis. For the platelets, it seems that their production are controlled by feedback mechanisms involving specific cytokines such as thrombopoietin (TPO), which is produced by the liver (and partially by kidneys and bone marrow). The quantity of circulating TPO depends on the number of circulating platelets: these latter fix TPO on their surface, so the more circulating platelets the less circulating TPO (Kaushansky [36]). Unlike the other two blood cell lines, diverse types of white blood cells exist and many growth factors help to regulate them. This makes the process of production of white blood cells (leukopoiesis) more complicated. However, under the action of mainly G-CSF (granulocyte colony stimulating factor), a growth factor acting on the leukocyte line, PHSC differentiate in progenitors, which in turn will produce precursors and after a few divisions later, white blood cells are formed (Bernard et al. [21]). It has been shown that the almost growth factors act on many cellular levels and on more than one cell lineage (Ratajczak et al. [48], Tanimukai et al. [51]).

Due to the number of growth factors and the quantity of cells involved in hematopoiesis, issues may arise at different cellular levels and sometimes result in diseases affecting one or more blood cell types. Among a wide variety of diseases affecting blood cells, periodic hematological diseases are of great interest (Foley and Mackey [27]). They are characterized by a periodic decrease in the circulating blood cells numbers, from normal to low values: chronic myelogenous leukemia (Adimy et al. [10], Colijn and Mackey [23], Fortin and Mackey [28], Fowler and Mackey [29], Pujo-Menjouet et al. [46], Pujo-Menjouet and Mackey [47]); cyclical neutropenia (Colijn and Mackey [24], Haurie et al. [33, 34]; periodic auto-immune hemolytic anemia (Bélair et al. [19], Mackey [41], Mahaffy et al. [44], Milton and Mackey [45]); and cyclical thrombocytopenia (Apostu and Mackey [16], Santillan et al. [50]). In some of these diseases, oscillations occur in all mature blood cells with the same period; in others, the oscillations appear in only one, two or three cell types. The existence of oscillations in more than one cell line seems to be due to their appearance in HSC compartment. That is why the dynamics of HSC have attracted attention of modelers (see the reviews of Batzel and Kappel [17], and Foley and Mackey [27]).

Mathematical modeling of hematopoiesis dynamics has been extensively studied in the past 40 years, with attempts to determine causes leading to a number of periodic hematological diseases. The first mathematical model has been introduced by Mackey in 1978 [40], inspired by works of Burns and Tannock [22], and Lajtha [38]. The model of Mackey is an uncoupled system of two nonlinear delay differential equations which considers HSC population divided in two compartments: proliferating and quiescent. The delay describes the average cell cycle duration. The model of Mackey stressed the influence of some factors such as the apoptotic rate, the introduction rate, the cell cycle duration playing an important role in the appearance of periodic solutions. Since then, Mackey's model has been improved by many other authors. It has been analyzed by Pujo-Menjouet et al. [46], and Pujo-Menjouet and Mackey [47] in order to prove the existence of long period oscillations, characterizing situations observed in chronic myelogenous leukemia. Bernard et al. [20] used the Mackey's model to study the existence of oscillations in cyclic neutropenia. Adimy et al. [4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14] analyzed various versions of Mackey's model and investigated the effect of perturbations of cell cycle duration, the rate of apoptosis, differentiation rate, and reintroduction rate from the quiescent compartment to the proliferating one on the behavior of the cell population. The Mackey's model has also been modified to take into account a structure in the HSC population (the structure being either age, maturity, or age-maturity) and the resulting models have been widely studied (Adimy et al. [2], Adimy and Crauste [3], Adimy and Pujo-Menjouet [15], Mackey and Rey [42, 43], Dyson et al. [25, 26]). An age-structured model of HSC dynamics, coupled with a differential equation to describe the action of growth factors on the introduction rate in the proliferating compartment, has been considered by Bélair et al. [19], Mahaffy et al. [44].

Colijn and Mackey [23, 24] developed a model that contains four compartments: the HSC and the three hematopoietic cell lines (neutrophils, erythrocytes and platelets). They applied their study to periodic chronic myelogenous leukemia [23] and cyclical neutropenia [24] in which oscillating levels of circulating leukocytes, platelets and/or reticulocytes are observed. All these three populations have the same oscillation period. In [23, 24], Colin and Mackey (see also Foley and Mackey [27], Lei and Mackey [39]) supposed that there is autonomy between the three cell lines by considering their distinct response to circulating blood cells in each line, and they assumed that the evolution of stem cell population is independent of circulating blood cells. They also simplified their model by replacing the compartments of the three progenitor lineages by amplification parameters.

In this paper, we consider a modification of Colijn and Mackey's model [23, 24], where the PHSC dynamics is described by a system similar to the one in [23, 24] (see also [27] and [39]), PHSC can differentiate in one of the three progenitor types, and progenitors can differentiate in mature cells that negatively control progenitors and PHSC proliferation through feedbacks function. Such controls continuously occur in hematopoiesis, and play a crucial role in pathological situations. For example, as a response to bleeding, or a lack of oxygen, mature blood cells trigger the release of erythropoietin that quickly induces proliferation. Contrary to the works in [23, 24], [27] and [39], we consider in each compartment of the progenitors, two sub-compartments, proliferating and resting cells (see Figure 1). We obtain a global model that contains eleven partial differential equations. To our knowledge, such a complete model has never been studied before. We are going to study the existence and stability of equilibria of the whole system in a way that we precise in the following.

In section 2, we describe the biological background leading to an age-structured model of hematopoiesis. We obtain a system of eleven age-structured partial differential equations completed by boundary and nonnegative initial conditions. In section 3, by using the characteristics method, we reduce this system to seven nonlinear delay differential equations with four delays. The delays represent the cell cycle durations. In section 4, we establish properties of the reduced system such as positivity and boundedness. In section 5, we focus on the existence of steady states: trivial, axials and positive. In section 6, we linearize the delay system about each steady state and we deduce the delay-dependent characteristic equation. Then, we obtain the local asymptotic stability. We also prove the global asymptotic stability of the trivial steady state by using a Lyapunov function. In section 7, we illustrate numerically our results and we show that a change in the parameters can cause oscillations in blood cell count.

2. Presentation of the model: Structured model of blood production

For primitive hematopoietic stem cells (PHSC), we denote by $p_0(t,a)$ (respectively, $n_0(t,a)$) the density of proliferating cells (respectively, quiescent cells) at time t which have spent a time a in their compartment. In the same way, let consider the different other hematopoietic stem cell (HSC) populations, the proliferating progenitors (neutrophils, reticulocytes and platelets) and their corresponding quiescent cells, as well as the mature cells, with densities of cells respectively denoted by $p_i(t,a)$, $n_i(t,a)$ for $0 \leq i \leq 3$, and $m_i(t,a)$ for $1 \leq i \leq 3$. In each compartment i, $0 \leq i \leq 3$, the proliferating cells can be eliminated by apoptosis $\gamma_i \geq 0$ (a programmed cell death). We denote by $\tau_i \geq 0$ the duration of the proliferating phase i. The mortality rate of quiescent cells in the compartment i is $\delta_i \geq 0$. The quiescent cells can be introduced in the proliferating phase with a rate β_i. We denote by K_i (respectively H_i) the rate of differentiation of PHSC population to progenitor population i (respectively the rate of differentiation of progenitors to mature cell population i). We suppose that $K_i, H_i \in [0,1]$. The mortality rate of mature cells is $\mu_i > 0$. The rates of reintroduction from the quiescent phases to the proliferating compartments are assumed to depend on quiescent and mature cell populations. This dependence represents the feedback control between the circulating blood cell numbers and the production of HSC (see Figure 1).

Throughout this paper, we set $I_0 = \{0,1,2,3\}$ and $I_1 = \{1,2,3\}$. Hence, the cell densities n_0, p_0, n_i, p_i and m_i, $i \in I_1$, satisfy the following transport system

$$\begin{cases} \dfrac{\partial n_i(t,a)}{\partial t} + \dfrac{\partial n_i(t,a)}{\partial a} = -\left(\delta_i + \beta_i\left(\chi_i(t)\right)\right) n_i(t,a), & a > 0,\ t > 0,\ i \in I_0, \\ \dfrac{\partial p_i(t,a)}{\partial t} + \dfrac{\partial p_i(t,a)}{\partial a} = -\gamma_i p_i(t,a), & 0 < a < \tau_i,\ t > 0,\ i \in I_0, \\ \dfrac{\partial m_i(t,a)}{\partial t} + \dfrac{\partial m_i(t,a)}{\partial a} = -\mu_i m_i(t,a), & a > 0,\ t > 0,\ i \in I_1. \end{cases} \tag{2.1}$$

The introduction rates β_i, $i \in I_0$, are assumed to depend on the total population in terms of weighted total density of cells as follows

$$\chi_i(t) = \rho_{i0} N_0(t) + \sum_{j=1}^{3} \left(\rho_{ij} N_j(t) + \sigma_{ij} M_j(t)\right),\ i \in I_0, \tag{2.2}$$

with ρ_{ij}, $\sigma_{ij} \geq 0$.
The population of quiescent cells and mature cells are respectively given by

$$N_i(t) = \int_0^{+\infty} n_i(t,a)da,\ M_i(t) = \int_0^{+\infty} m_i(t,a)da. \tag{2.3}$$

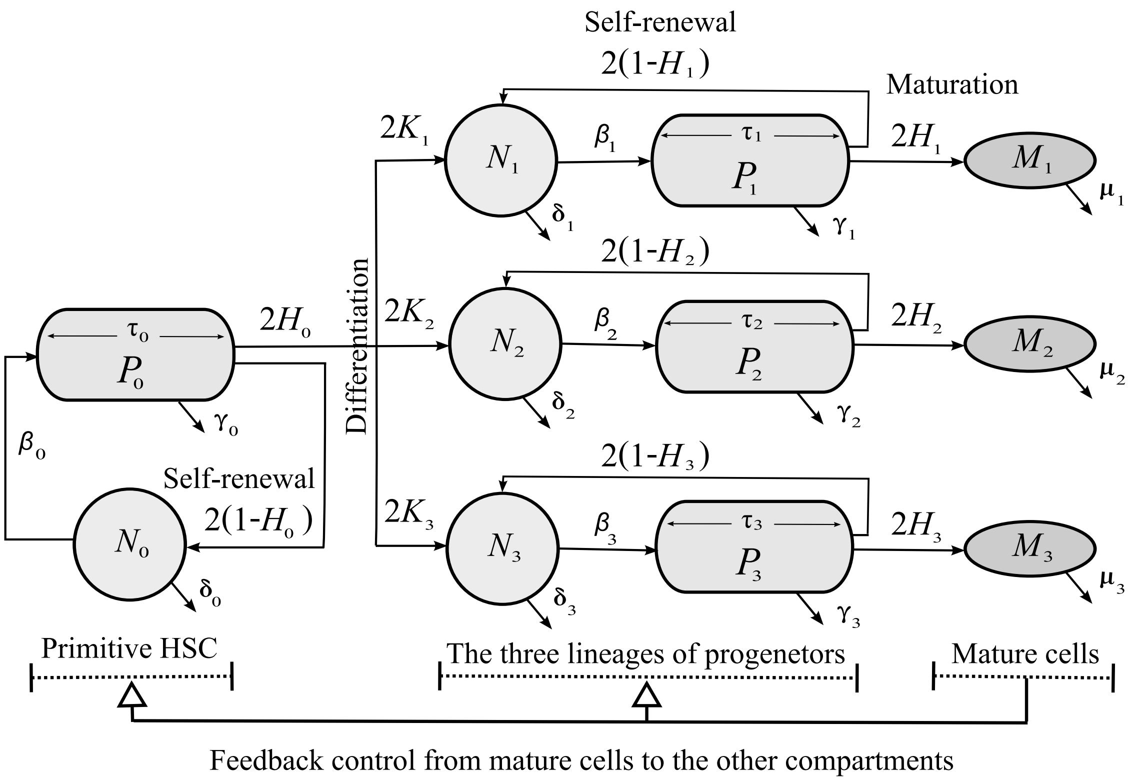

FIGURE 1. Schematic representation of the hematopoiesis process. The primitive hematopoietic stem cells (PHSC) and the first generations of each line (progenitors) are able to self-renew with a rate $1 - H_i$, and can be either in a proliferating phase (P_i) or in a resting phase (N_i). The PHSC population P_0 differentiates to progenitors N_i with a rate K_i and the progenitors P_i differentiate to mature cells M_i with a rate H_i. The Proliferating cells P_i are eliminated by apoptosis γ_i (a programmed cell death) and divide after a time τ_i in two cells, which enter immediately the resting phase. The resting cells N_i can be introduced in the proliferating phase with a rate β_i or eliminated with a rate δ_i. The mortality rate of mature cells M_i is μ_i. The feedback controls from circulating blood cells M_i to the production of HSC are given by the dependance of the introduction rates β_i on mature cells.

Usually (see Mackey [40]), the introduction rate β_i is chosen as a Hill function, that is a continuous bounded and decreasing function in terms of the total cell population χ_i, tending to zero at infinity. Hence, a general form for the introduction rate in (2.1) could be

$$\beta_i\,(x) = \beta_i^0 \frac{\theta_i^{\eta_i}}{\theta_i^{\eta_i} + x^{\eta_i}},\ x > 0,\ i \in I_0. \tag{2.4}$$

The coefficient $\beta_i^0 > 0$ is the maximum rate of reintroduction, θ_i is the quiescent population density for which the rate of re-entry β_i has its maximum rate of change with respect to the quiescent population, and $\eta_i > 1$ describes the sensitivity of β_i with respect to changes in the population.

System (2.1) is completed by boundary conditions (for $a = 0$) and initial conditions (for $t = 0$). The first ones describe the flux of cells entering each phase: new proliferating cells are quiescent cells introduced with a rate β_i, new quiescent cells come from the division of proliferating cells that have spent a time τ_i in the proliferating phase, and new mature cells come from the last three proliferating cell populations. Then, the boundary conditions of (2.1) are

$$\begin{cases} n_0(t,0) &= 2\,(1-H_0)\,p_0(t,\tau_0), \\ n_i(t,0) &= 2(1-H_i)p_i(t,\tau_i) + 2K_i p_0(t,\tau_0), & i \in I_1, \\ p_i(t,0) &= \displaystyle\int_0^{+\infty} \beta_i\left(\chi_i(t)\right) n_i(t,a)da = \beta_i\left(\chi_i(t)\right) N_i(t), & i \in I_0, \\ m_i(t,0) &= 2H_i p_i(t,\tau_i), & i \in I_1, \end{cases} \tag{2.5}$$

where $N_i(t)$ and $M_i(t)$ are given by (2.3) and

$$H_0 := K_1 + K_2 + K_3, \tag{2.6}$$

with the assumption

$$H_0 \in [0,1]\,.$$

We also assume that, for $t > 0$,

$$\begin{cases} \lim\limits_{a\to+\infty} n_i(t,a) = 0, & i \in I_0, \\ \lim\limits_{a\to+\infty} m_i(t,a) = 0, & i \in I_1. \end{cases} \tag{2.7}$$

Finally, initial conditions are given by nonnegative L^1-functions n_i^0, p_i^0 and m_i^0 such that

$$\begin{cases} n_i(0,a) = n_i^0(a), & a > 0,\, i \in I_0, \\ p_i(0,a) = p_i^0(a), & a \in (0,\tau_i)\,,\, i \in I_0, \\ m_i(0,a) = m_i^0(a), & a > 0,\, i \in I_1. \end{cases} \tag{2.8}$$

The problem (2.1), (2.5), (2.7), (2.8) can be considered as a Gurtin-MacCamy problem (Gurtin and MacCamy [30]). Similar nonlinear systems have been investigated by many researchers (we refer to Webb [52]). A classical method to study this PDE is to apply the method of characteristics to convert it to a system of Volterra integral equations. For the existence and uniqueness of solutions we refer to Webb [52].

3. Reduction to a delay differential system

We consider that β_i, γ_i, δ_i and μ_i are independent on the age a, then we can check that system (2.1), (2.5), (2.7), (2.8) reduces to a system of delay differential equations. First, let see that using the method of characteristics (see Webb [52]), the boundary conditions (2.5) and the initial conditions (2.8), the solutions $p_i(t,a)$ are given for $i \in I_0$, by

$$p_i(t,a) = \begin{cases} e^{-\gamma_i t} p_i(0,a-t) = e^{-\gamma_i t} p_i^0(a-t), & 0 \le t \le a, \\ e^{-\gamma_i a} p_i(t-a,0) = e^{-\gamma_i a} \beta_i\left(\chi_i(t-a)\right) N_i(t-a), & t > a. \end{cases} \tag{3.1}$$

Denote by P_i the total population of proliferating cells in each compartment $i \in I_0$,

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

Integrating system (2.1) over the age, remembering that $a \in [0,+\infty)$ in the quiescent and maturing phases, and $a \in [0,\tau_i]$ in the proliferating phases, and by using the boundary conditions

(2.5), (2.7), we obtain the following system

$$\begin{cases} N_0'(t) = & -\left(\delta_0 + \beta_0\left(\chi_0(t)\right)\right) N_0(t) + 2(1-H_0)p_0(t,\tau_0), \\ N_i'(t) = & -\left(\delta_i + \beta_i\left(\chi_i(t)\right)\right) N_i(t) + 2K_i p_0(t,\tau_0) \\ & +2(1-H_i)p_i(t,\tau_i), \qquad i \in I_1, \\ P_i'(t) = & -\gamma_i P_i(t) + \beta_i\left(\chi_i(t)\right) N_i(t) - p_i(t,\tau_i), \qquad i \in I_0, \\ M_i'(t) = & -\mu_i M_i(t) + 2H_i p_i(t,\tau_i), \qquad i \in I_1. \end{cases} \tag{3.2}$$

The expression (3.1) allows us to write, for $i \in I_0$,

$$p_i(t,\tau_i) = \begin{cases} e^{-\gamma_i t} p_i^0(\tau_i - t), & 0 \le t \le \tau_i, \\ e^{-\gamma_i \tau_i} \beta_i\left(\chi_i(t-\tau_i)\right) N_i(t-\tau_i), & t > \tau_i. \end{cases} \tag{3.3}$$

Because we are interested in the asymptotic behavior of solutions, we suppose for instance that

$$t \ge \tau := \max\left\{\tau_i,\ i \in I_0\right\}.$$

Then, we obtain for $i \in I_1$,

$$\begin{cases} N_0'(t) = & -\left(\delta_0 + \beta_0\left(\chi_0(t)\right)\right) N_0(t) + 2(1-H_0)e^{-\gamma_0\tau_0}\beta_0\left(\chi_0(t-\tau_0)\right) N_0(t-\tau_0), \\ P_0'(t) = & -\gamma_0 P_0(t) + \beta_0\left(\chi_0(t)\right) N_0(t) - e^{-\gamma_0\tau_0}\beta_0\left(\chi_0(t-\tau_0)\right) N_0(t-\tau_0), \\ N_i'(t) = & -\left(\delta_i + \beta_i\left(\chi_i(t)\right)\right) N_i(t) + 2K_i e^{-\gamma_0\tau_0}\beta_0\left(\chi_0(t-\tau_0)\right) N_0(t-\tau_0) \\ & +2(1-H_i)e^{-\gamma_i\tau_i}\beta_i\left(\chi_i(t-\tau_i)\right) N_i(t-\tau_i), \\ P_i'(t) = & -\gamma_i P_i(t) + \beta_i\left(\chi_i(t)\right) N_i(t) - e^{-\gamma_i\tau_i}\beta_i\left(\chi_i(t-\tau_i)\right) N_i(t-\tau_i), \\ M_i'(t) = & -\mu_i M_i(t) + 2H_i e^{-\gamma_i\tau_i}\beta_i\left(\chi_i(t-\tau_i)\right) N_i(t-\tau_i), \end{cases} \tag{3.4}$$

where χ_i is given by (2.2).

Since N_i, $i \in I_0$ and M_i, $i \in I_1$, do not depend on the proliferating cell population P_i, we will focus on the study of the following system of differential equations with four delays

$$\begin{cases} N_0'(t) = & -\left(\delta_0 + \beta_0\left(\chi_0(t)\right)\right) N_0(t) + 2(1-H_0)e^{-\gamma_0\tau_0}\beta_0\left(\chi_0(t-\tau_0)\right) N_0(t-\tau_0), \\ N_i'(t) = & -\left(\delta_i + \beta_i\left(\chi_i(t)\right)\right) N_i(t) + 2K_i e^{-\gamma_0\tau_0}\beta_0\left(\chi_0(t-\tau_0)\right) N_0(t-\tau_0) \\ & +2(1-H_i)e^{-\gamma_i\tau_i}\beta_i\left(\chi_i(t-\tau_i)\right) N_i(t-\tau_i), \\ M_i'(t) = & -\mu_i M_i(t) + 2H_i e^{-\gamma_i\tau_i}\beta_i\left(\chi_i(t-\tau_i)\right) N_i(t-\tau_i). \end{cases} \tag{3.5}$$

One can notice that system (3.5) is defined for $t \ge \tau := \max\left\{\tau_i,\ i \in I_0\right\}$, with initial conditions solutions of a system of ordinary differential equations and nonautonomous delay differential equations defined on $[0,\tau]$. We assume that each initial condition of (3.5) is a given continuous function $\varphi \in C\left([0,\tau], \mathbb{R}^7\right)$. Then from Hale and Verduyn Lunel [31], system (3.5) has a unique continuous solution defined for $t \ge \tau$.

Proposition 3.1. *Let $\left((N_i)_{i\in I_0}, (M_i)_{i\in I_1}\right)^T$ be a solution of (3.5). The function P_i, $i \in I_0$, such that $\left((P_i)_{i\in I_0}, (N_i)_{i\in I_0}, (M_i)_{i\in I_1}\right)^T$ is a solution of (3.4), can be explicitly calculated in terms of N_i and M_i by*

$$P_i(t) = \int_{t-\tau_i}^{t} e^{-\gamma_i(t-s)}\beta_i\left(\chi_i(s)\right) N_i(s)ds, \ t \ge \tau. \tag{3.6}$$

Proof. Let $i \in I_0$ and $t \geq \tau$. We have

$$\frac{d}{dt}\left(e^{\gamma_i t} P_i(t)\right) = e^{\gamma_i t}\left(\frac{d}{dt} P_i(t) + \gamma_i P_i(t)\right)$$

and

$$\frac{d}{dt} P_i(t) + \gamma_i P_i(t) = \beta_i\left(\chi_i(t)\right) N_i(t) - e^{-\gamma_i \tau_i} \beta_i\left(\chi_i(t-\tau_i)\right) N_i(t-\tau_i)).$$

Then,

$$\frac{d}{dt}\left(e^{\gamma_i t} P_i(t)\right) = e^{\gamma_i t} \beta_i\left(\chi_i(t)\right) N_i(t) - e^{-\gamma_i(\tau_i - t)} \beta_i\left(\chi_i(t-\tau_i)\right) N_i(t-\tau_i)).$$

By Integrating on $[\tau_i, t]$, we get

$$e^{\gamma_i t} P_i(t) = e^{\gamma_i \tau_i} P_i(\tau_i) - \int_0^{\tau_i} e^{\gamma_i s} \beta_i\left(\chi_i(s)\right) N_i(s) ds + \int_{t-\tau_i}^{t} e^{\gamma_i s} \beta_i\left(\chi_i(s)\right) N_i(s) ds.$$

Thanks to (3.1) we have

$$e^{\gamma_i \tau_i} P_i(\tau_i) = \int_0^{\tau_i} e^{\gamma_i s} \beta_i\left(\chi_i(s)\right) N_i(s) ds.$$

Consequently, P_i is explicitly calculated in terms of N_i and M_i by (3.6). □

Lemma 3.2. *Let* $\left((P_i)_{i\in I_0}, (N_i)_{i\in I_0}, (M_i)_{i\in I_1}\right)^T$ *be a solution of (3.4). If*

$$\lim_{t\to+\infty} \left((N_i(t))_{i\in I_0}, (M_i(t))_{i\in I_1}\right)^T = \left(\left(\overline{N}_i\right)_{i\in I_0}, \left(\overline{M}_i\right)_{i\in I_1}\right)^T,$$

then

$$\lim_{t\to+\infty} P_i(t) = \begin{cases} \dfrac{1}{\gamma_i}\left(1 - e^{-\gamma_i \tau_i}\right) \overline{N}_i \beta_i \left(\rho_{i0}\overline{N}_0 + \sum\limits_{j=1}^{3}\left(\rho_{ij}\overline{N}_j + \sigma_{ij}\overline{M}_j\right)\right) & \text{if } \gamma_i > 0, \\ \tau_i \overline{N}_i \beta_i \left(\rho_{i0}\overline{N}_0 + \sum\limits_{j=1}^{3}\left(\rho_{ij}\overline{N}_j + \sigma_{ij}\overline{M}_j\right)\right) & \text{if } \gamma_i = 0. \end{cases} \tag{3.7}$$

If $\left((N_i(t))_{i\in I_0}, (M_i(t))_{i\in I_1}\right)^T$ *is* $\omega-$*periodic, then* $P_i(t)$ *is also* $\omega-$*periodic.*

Proof. From (3.6), we have

$$P_i(t) = \int_0^{\tau_i} e^{-\gamma_i s} \beta_i\left(\chi_i(t-s)\right) N_i(t-s) ds. \tag{3.8}$$

If $\lim_{t\to+\infty} \left((N_i(t))_{i\in I_0}, (M_i(t))_{i\in I_1}\right)^T = \left(\left(\overline{N}_i\right)_{i\in I_0}, \left(\overline{M}_i\right)_{i\in I_1}\right)^T$, then

$$\lim_{t\to+\infty} P_i(t) = \overline{N}_i \beta_i \left(\rho_{i0}\overline{N}_0 + \sum_{j=1}^{3}\left(\rho_{ij}\overline{N}_j + \sigma_{ij}\overline{M}_j\right)\right) \int_0^{\tau_i} e^{-\gamma_i s} ds.$$

Hence, (3.7) follows immediately.
When $\left((N_i(t))_{i\in I_0}, (M_i(t))_{i\in I_1}\right)^T$ is $\omega-$periodic, then using again (3.8) it is easy to see that $P_i(t)$ is also $\omega-$periodic. □

Lemma 3.2 shows the influence of system (3.5) on the behavior of the entire system (3.4). In the next section, we investigate positivity and boundedness properties of solutions of system (3.5).

4. Positivity and boundedness properties

Proposition 4.1. *The solutions of system (3.5) associated with nonnegative initial conditions are nonnegative.*

Proof. Let $\left((N_i(t))_{i\in I_0}, (M_i(t))_{i\in I_1}\right)^T$ be a solution of (3.5). We first check that N_0 is nonnegative. If $H_0 = 1$, it is immediate that N_0 is nonnegative. Assume that $0 \leq H_0 < 1$. By contradiction, suppose that there exists $T_0 > \tau$ such that $N_0(t) > 0$ for $t < T_0$ and $N_0(T_0) = 0$. As β_0 is a positive function and $N_0(T_0 - \tau_0) > 0$, we have

$$\begin{aligned} N_0'(T_0) &= -\left(\delta_0 + \beta_0\left(\chi_0(T_0)\right)\right) N_0(T_0) \\ &\quad +2(1-H_0)e^{-\gamma_0\tau_0}\beta_0\left(\chi_0(T_0-\tau_0)\right) N_0(T_0-\tau_0), \\ &= 2(1-H_0)e^{-\gamma_0\tau_0}\beta_0\left(\chi_0(T_0-\tau_0)\right) N_0(T_0-\tau_0). \end{aligned}$$

It follows that $N_0'(T_0) > 0$.
Consequently, $N_0(t)$ remains nonnegative for all $t > 0$. We use the same argument to prove that N_i and M_i, $i \in I_1$, are nonnegative. □

Next, we study the boundedness property of solutions of system (3.5).

Proposition 4.2. *Suppose that $\delta_i > 0$ and $\rho_{ii} > 0$, $i \in I_0$. Then the solutions of system (3.5) are bounded.*

Proof. The assumption $\rho_{ii} > 0$ means that the function β_i depends on N_i.
We define the functions f_i, $g_i : [0, +\infty) \to \mathbb{R}^+$ by

$$f_i(y) = 2(1-H_i)e^{-\gamma_i\tau_i}\beta_i(y) \quad \text{and} \quad g_i(y) = 2K_i e^{-\gamma_0\tau_0}\beta_0(y).$$

From the hypothesis of β_i, the functions f_i and g_i are decreasing and tend to zero when y tends to the infinity. As $\delta_i > 0$, $\rho_{ii} > 0$, we can find a real number $\kappa_0^i \geq 0$ such that

$$f_i(\rho_{ii}y) < \frac{\delta_i}{2} \quad \text{and} \quad g_i(\rho_{00}y) < \frac{\delta_i}{2} \quad \text{for } y > \kappa_0^i.$$

Then

$$f_i(\rho_{ii}y)y \leq \begin{cases} f_i(0)\kappa_0^i & \text{if } y \leq \kappa_0^i, \\ \dfrac{\delta_i}{2}y & \text{if } y > \kappa_0^i. \end{cases}$$

In the same way,

$$g_i(\rho_{00}z)z \leq \begin{cases} g_i(0)\kappa_0^i & \text{if } z \leq \kappa_0^i, \\ \dfrac{\delta_i}{2}z & \text{if } z > \kappa_0^i. \end{cases}$$

Let $x \geq \kappa_1^i := \dfrac{2\kappa_0^i}{\delta_i}\left(f_i(0) + g_i(0)\right)$ and $y, z \in [0, x]$. Then, we deduce

$$f_i(\rho_{ii}y)y \leq \frac{\delta_i}{2}x \quad \text{and} \quad g_i(\rho_{00}z)z \leq \frac{\delta_i}{2}x.$$

Thus for all $x \geq \kappa_1^i$, we have

$$\max_{0\leq y,z\leq x}\left(f_i(\rho_{ii}y)y + g_i(\rho_{00}z)z\right) \leq \delta_i x. \tag{4.1}$$

We assume now by contradiction that N_0 is unbounded. So, there exists $t_0 > \tau$ such that

$$N_0(t) \leq N_0(t_0) \text{ for } t \in [t_0 - \tau_0, t_0] \text{ and } N_0(t_0) > \kappa_1^0. \tag{4.2}$$

As $\rho_{00}N_0(t_0-\tau_0)\le \chi_0(t_0-\tau_0)$ and f_0 is decreasing, we deduce

$$\frac{dN_0}{dt}(t_0)\le -\left(\delta_0+\beta_0\left(\chi_0(t_0)\right)\right)N_0(t_0)+f_0\left(\rho_{00}N_0(t_0-\tau_0)\right)N_0(t_0-\tau_0).$$

Thanks to (4.1) and (4.2) we obtain

$$\begin{array}{rcl}\frac{dN_0}{dt}(t_0) & \le & -\left(\delta_0+\beta_0\left(\chi_0(t_0)\right)\right)N_0(t_0)+\delta_0 N_0(t_0),\\ & \le & -\beta_0\left(\chi_0(t_0)\right)N_0(t_0),\\ & < & 0.\end{array}$$

This leads to a contradiction. So, we can conclude that N_0 is bounded.
We show now that N_i, $i\in I_1$, is bounded. We suppose that N_i is unbounded. So we can find $t_i>\tau$ such that

$N_i(t)\le N_i(t_i)$ and $N_0(t)\le N_i(t_i)$ for $t\in[t_i-\widetilde{\tau}_i,t_i]$ and $N_i(t_i)>\kappa_1^i$, where $\widetilde{\tau}_i:=\max\left(\tau_0,\tau_i\right)$.

We have

$$\frac{dN_i}{dt}(t_i)=-\left(\delta_i+\beta_i\left(\chi_i(t_i)\right)\right)N_i(t_i)+f_i\left(\chi_i(t_i-\tau_i)\right)N_i(t_i-\tau_i)+g_i\left(\chi_0(t_i-\tau_0)\right)N_0(t_i-\tau_0),$$

with $\rho_{ii}N_i(t_i-\tau_i)\le \chi_i(t_i-\tau_i)$, $\rho_{00}N_0(t_i-\tau_0)\le \chi_0(t_i-\tau_0)$, $N_i(t_i-\tau_i)\le N_i(t_i)$ and $N_0(t_i-\tau_0)\le N_i(t_i)$. Then

$$\begin{array}{rcl}\frac{dN_i}{dt}(t_i) & \le & -\left(\delta_i+\beta_i\left(\chi_i(t_i)\right)\right)N_i(t_i)+f_i\left(\rho_{ii}N_i(t_i-\tau_i)\right)N_i(t_i-\tau_i)\\ & & +g_i\left(\rho_{00}N_0(t_i-\tau_0)\right)N_0(t_i-\tau_0),\\ & \le & -\left(\delta_i+\beta_i\left(\chi_i(t_i)\right)\right)N_i(t_i)+\max\limits_{0\le y,z\le N_i(t_i)}\left(f_i(\rho_{ii}y)y+g_i(\rho_{00}z)z\right).\end{array}$$

Using (4.1), we obtain

$$\begin{array}{rcl}\frac{dN_i}{dt}(t_i) & \le & -\left(\delta_i+\beta_i\left(\chi_i(t_i)\right)\right)N_i(t_i)+\delta_i N_i(t_i),\\ & < & -\beta_i\left(\chi_i(t_i)\right)N_i(t_i).\end{array}$$

This leads to a contradiction. So, we deduce that N_i is bounded. This implies that M_i is also bounded. ☐

When there exits $i\in I_0$ such that $\delta_i=0$ or $\rho_{ii}=0$, the method used in the proof of the last proposition is no longer valid. We need in addition the assumptions (4.3) or (4.4).

Proposition 4.3. *Suppose that* $\delta_0=0$ *and*

$$\tau_0\ge \frac{1}{\gamma_0}\ln\left(2\left(1-H_0\right)\right). \tag{4.3}$$

Then, for all solutions $\left((N_i(t))_{i\in I_0},(M_i(t))_{i\in I_1}\right)^T$ *of system (3.5),* N_0 *is bounded.*

Proof. We consider the function $W:[\tau,+\infty)\to\mathbb{R}^+$ defined by

$$W(t)=N_0(t)+2(1-H_0)e^{-\gamma_0\tau_0}\int_{t-\tau_0}^{t}\beta_0(\chi_0(s))N_0(s)ds.$$

We have

$$\begin{array}{rcl}W'(t) & = & N_0'(t)+2(1-H_0)e^{-\gamma_0\tau_0}\left[\beta_0(\chi_0(t))N_0(t)-\beta_0(\chi_0(t-\tau_0))N_0(t-\tau_0)\right],\\ & = & \left(2\left(1-H_0\right)e^{-\gamma_0\tau_0}-1\right)\beta_0(\chi_0(t))N_0(t).\end{array}$$

Thanks to (4.3), we have

$$2\,(1-H_0)\,e^{-\gamma_0\tau_0}-1\leq 0.$$

Then $W'(t)\leq 0$.
Therefore

$$0\leq N_0(t)\leq W(t)\leq W(\tau),\ t\geq\tau.$$

We conclude that N_0 *is* bounded. □

When $\delta_i=0$, for all $i\in I_0$, the assumption (4.3) implies that N_0 is bounded, but this hypothesis is not enough to prove the boundedness of $N_i,\ i\in I_1$. We need in addition the assumption (4.4).

Proposition 4.4. *Suppose that $\delta_i=0$, for $i\in I_0$,*

$$\tau_0\geq\frac{1}{\gamma_0}\ln(2)\quad and\quad \tau_i\geq\frac{1}{\gamma_i}\ln\left(2(1-H_i)\right),\quad for\ i\in I_1. \tag{4.4}$$

Then the solutions $\left((N_i(t))_{i\in I_0},(M_i(t))_{i\in I_1}\right)^T$ of system (3.5) are bounded.

Proof. Consider the function $Z:[\tau,+\infty)\to\mathbb{R}^+$ defined by

$$Z(t)=\sum_{i=0}^{3}N_i(t)+2\sum_{i=1}^{3}(1-H_i)e^{-\gamma_i\tau_i}\int_{t-\tau_i}^{t}\beta_i\left(\chi_i(s)\right)N_i(s)ds+2e^{-\gamma_0\tau_0}\int_{t-\tau_0}^{t}\beta_0\left(\chi_0(s)\right)N_0(s)ds,$$

where $\left((N_i(t))_{i\in I_0},(M_i(t))_{i\in I_1}\right)^T$ is a solution of (3.5). Then differentiating Z gives

$$\begin{aligned}Z'(t)=\ &(2e^{-\gamma_0\tau_0}-1)\,\beta_0\left(\chi_0(t)\right)N_0(t)-2H_0e^{-\gamma_0\tau_0}\beta_0\left(\chi_0(t-\tau_0)\right)N_0(t-\tau_0)\\&+\sum_{i=1}^{3}\left(2(1-H_i)e^{-\gamma_i\tau_i}-1\right)\beta_i\left(\chi_i(t)\right)N_i(t)+2\sum_{i=1}^{3}K_ie^{-\gamma_0\tau_0}\beta_0\left(\chi_0(t-\tau_0)\right)N_0(t-\tau_0).\end{aligned}$$

Using (2.6), the expression of $Z'(t)$ becomes

$$Z'(t)=(2e^{-\gamma_0\tau_0}-1)\,\beta_0\left(\chi_0(t)\right)N_0(t)+\sum_{i=1}^{3}\left(2(1-H_i)e^{-\gamma_i\tau_i}-1\right)\beta_i\left(\chi_i(t)\right)N_i(t).$$

From (4.4), we deduce that $Z'(t)\leq 0$. As $Z(t)$ is a nonnegative function, we conclude that $Z:[\tau,+\infty)\to\mathbb{R}^+$ is bounded. Then $\left((N_i(t))_{i\in I_0},(M_i(t))_{i\in I_1}\right)^T$ is bounded. □

When $\delta_0=0$ and

$$\tau_0<\frac{1}{\gamma_0}\ln\left(2\left(1-H_0\right)\right), \tag{4.5}$$

we will show in the next proposition, that the solutions of (3.5) are may not be bounded.

Proposition 4.5. *Assume that $\delta_0=0$, $\chi_0(t)=N_0(t)$ and (4.5) is satisfied. In addition, assume that there exists $\overline{x}\geq 0$ such that the function $x\to\beta_0(x)x$ is decreasing for $x\geq\overline{x}$. Let $\left((N_i(t))_{i\in I_0},(M_i(t))_{i\in I_1}\right)^T$ be a solution of system (3.5). Suppose that there exists $t_0\geq\tau$ such that $N_0(t_0)\geq\overline{x}$ and N_0 is increasing on $[t_0,t_0+\tau_0]$. Then N_0 is increasing on $[t_0,+\infty)$ and $\lim\limits_{t\to+\infty}N_0(t)=+\infty$.*

Proof. One can notice that, if $\lim\limits_{t\to+\infty} N_0(t) = \overline{N}_0$ exists, then the first equation of (3.5) leads to $(2(1-H_0)e^{-\gamma_0\tau_0}-1)\,\beta_0\left(\overline{N}_0\right)\overline{N}_0 = 0$. We deduce from (4.5) that $(2(1-H_0)e^{-\gamma_0\tau_0}-1)\,\beta_0\left(\overline{N}_0\right) > 0$. Then $\overline{N}_0 = 0$. Suppose that there exists $t_0 \geq \tau$ such that $N_0(t_0) \geq \overline{x}$ and N_0 is an increasing function on $[t_0, t_0+\tau_0]$. Since we have $N_0(t_0+\tau_0) \geq N_0(t_0) \geq \overline{x}$ and the function $x \to \beta_0(x)x$ is decreasing for $x \geq \overline{x}$, it follows that $\beta_0\left(N_0(t_0+\tau_0)\right)N_0(t_0+\tau_0) \leq \beta_0\left(N_0(t_0)\right)N_0(t_0)$. Consequently,

$$
\begin{array}{rcl}
N_0'(t_0+\tau_0) & = & -\beta_0\left(N_0(t_0+\tau_0)\right)N_0(t_0+\tau_0) + 2(1-H_0)e^{-\gamma_0\tau_0}\beta_0\left(N_0(t_0)\right)N_0(t_0), \\
& \geq & -\beta_0\left(N_0(t_0+\tau_0)\right)N_0(t_0+\tau_0) + 2(1-H_0)e^{-\gamma_0\tau_0}\beta_0\left(N_0(t_0+\tau_0)\right)N_0(t_0+\tau_0), \\
& \geq & (2(1-H_0)e^{-\gamma_0\tau_0}-1)\,\beta_0\left(N_0(t_0+\tau_0)\right)N_0(t_0+\tau_0), \\
& > & 0.
\end{array}
$$

So, there exists $\varepsilon > 0$ such that N_0 is increasing on $[t_0, t_0+\tau_0+\varepsilon]$. Using a similar technique, we prove that $N_0'(t_0+\tau_0+\varepsilon) > 0$. Then, N_0 is increasing on $[t_0, +\infty)$. Suppose that $N_0(t)$ is bounded. Then $\lim\limits_{t\to+\infty} N_0(t) = \overline{N}_0$ exists. So $\overline{N}_0 = 0$, which gives a contradiction. We conclude that $\lim\limits_{t\to+\infty} N_0(t) = +\infty$. □

Our next objective is to construct an initial condition on $[0, \tau_0]$ such that the solution N_0 satisfies the assumptions of proposition 4.5 on an interval $[t_0, t_0+\tau_0]$.

For $t \in [0, \tau_0]$, the system (3.2), (3.3) becomes

$$
N_0'(t) = -\beta_0\left(N_0(t)\right)N_0(t) + 2(1-H_0)e^{-\gamma_0 t}p_0^0(\tau_0 - t),
$$

with

$$
N_0(0) = \int_0^{+\infty} n_0^0(a)da \quad \text{and} \quad p_0^0(0) = \beta_0\left(\int_0^{+\infty} n_0^0(a)da\right)\int_0^{+\infty} n_0^0(a)da.
$$

Let $\upsilon \in \mathbb{R}^+$ such that $\upsilon \geq \overline{x}$. We put

$$
\left\{\begin{array}{ll}
n_0^0(a) = \exp\left(-\dfrac{a}{\upsilon}\right), & a \geq 0, \\
p_0^0(a) = \beta_0\left(\upsilon\right)\upsilon, & 0 \leq a \leq \tau_0.
\end{array}\right.
$$

Then we obtain

$$
\left\{\begin{array}{l}
N_0'(t) = -\beta_0\left(N_0(t)\right)N_0(t) + 2(1-H_0)e^{-\gamma_0 t}\beta_0\left(\upsilon\right)\upsilon, \quad 0 \leq t \leq \tau_0, \\
N_0(0) = \upsilon.
\end{array}\right.
$$

Let $t \in [0, \tau_0]$. We have

$$
N_0'(t) \geq -\beta_0\left(N_0(t)\right)N_0(t) + 2(1-H_0)e^{-\gamma_0\tau_0}\beta_0\left(\upsilon\right)\upsilon,
$$

and

$$
N_0'(0) \geq \left(2(1-H_0)e^{-\gamma_0\tau_0} - 1\right)\beta_0\left(\upsilon\right)\upsilon > 0.
$$

So, there exists $\varepsilon \in (0, \tau_0]$ such that N_0 is increasing on $[0, \varepsilon]$ and $N_0(\varepsilon) > \upsilon \geq \overline{x}$. Consequently,

$$
\begin{array}{rcl}
N_0'(\varepsilon) & \geq & -\beta_0\left(N_0(\varepsilon)\right)N_0(\varepsilon) + 2(1-H_0)e^{-\gamma_0\tau_0}\beta_0\left(\upsilon\right)\upsilon, \\
& \geq & (2(1-H_0)e^{-\gamma_0\tau_0} - 1)\,\beta_0\left(\upsilon\right)\upsilon, \\
& > & 0.
\end{array}
$$

We conclude that N_0 is an increasing function on $[0, \tau_0]$ with $N_0(t) > \upsilon \geq \overline{x}$ for all $t \in [0, \tau_0]$. We use the same argument as in the proof of the last proposition to prove that N_0 is an increasing function on $[\tau_0, 2\tau_0]$ with $N_0(t) > \upsilon \geq \overline{x}$ for all $t \in [\tau_0, 2\tau_0]$. Then, N_0 is an increasing function on $[0, +\infty)$ and $\lim\limits_{t\to+\infty} N_0(t) = +\infty$.

The assumption on the function $x \to \beta_0(x)x$ is satisfied for example when β_0 is given by (2.4), with $\eta_0 > 1$. We can take

$$\overline{x} = \frac{\theta_0}{(\eta_0 - 1)^{1/\eta_0}}.$$

5. Existence of steady states

This section is devoted to the existence of steady states of system (3.5). That is a time-independent solution $\overline{E} = \left((\overline{N}_i)_{i\in I_0}, (\overline{M}_i)_{i\in I_1} \right)^T \in \mathbb{R}^7_+$ of (3.5). We put

$$\overline{\chi}_i := \overline{\chi}_i(\overline{E}) = \rho_{i0}\overline{N}_0 + \sum_{j=1}^{3} \left(\rho_{ij}\overline{N}_j + \sigma_{ij}\overline{M}_j \right),\ i \in I_0.$$

Then, $\overline{E}$ satisfies

$$\begin{cases} -\left[\delta_0 - (2(1-H_0)e^{-\gamma_0\tau_0} - 1)\,\beta_0(\overline{\chi}_0)\right]\overline{N}_0 = 0, & \\ 2K_i e^{-\gamma_0\tau_0}\beta_0(\overline{\chi}_0)\overline{N}_0 - \left[\delta_i - (2(1-H_i)e^{-\gamma_i\tau_i} - 1)\,\beta_i(\overline{\chi}_i)\right]\overline{N}_i = 0, & i \in I_1, \\ 2H_i e^{-\gamma_i\tau_i}\beta_i(\overline{\chi}_i)\overline{N}_i - \mu_i\overline{M}_i = 0. & i \in I_1. \end{cases} \tag{5.1}$$

This system can be represented in the following form

$$A\left(\overline{E}\right)\overline{E} = 0,$$

where

$$A\left(\overline{E}\right) = \begin{pmatrix} -F_0\left(\overline{E}\right) & 0 & 0 & 0 & 0 & 0 & 0 \\ K_1G_0\left(\overline{E}\right) & -F_1\left(\overline{E}\right) & 0 & 0 & 0 & 0 & 0 \\ K_2G_0\left(\overline{E}\right) & 0 & -F_2\left(\overline{E}\right) & 0 & 0 & 0 & 0 \\ K_3G_0\left(\overline{E}\right) & 0 & 0 & -F_3\left(\overline{E}\right) & 0 & 0 & 0 \\ 0 & H_1G_1\left(\overline{E}\right) & 0 & 0 & -\mu_1 & 0 & 0 \\ 0 & 0 & H_2G_2\left(\overline{E}\right) & 0 & 0 & -\mu_2 & 0 \\ 0 & 0 & 0 & H_3G_3\left(\overline{E}\right) & 0 & 0 & -\mu_3 \end{pmatrix}$$

and $F_i\left(\overline{E}\right)$ and $G_i\left(\overline{E}\right)$ are given, for $i \in I_0$, by

$$\begin{cases} F_i\left(\overline{E}\right) = \delta_i - \left(2\left(1-H_i\right)e^{-\gamma_i\tau_i} - 1\right)\beta_i\left(\overline{\chi}_i\right), \\ G_i\left(\overline{E}\right) = 2e^{-\gamma_i\tau_i}\beta_i\left(\overline{\chi}_i\right). \end{cases}$$

It is easy to see that $0_{\mathbb{R}^7} = (0, ..., 0)^T$ is always a steady state of (3.5). It is the trivial equilibrium, describing the extinction of all cell population, either mature or stem cells. The other steady states can be of different kinds. They can have some components equal to zero and others positive. They are called axial steady states, and describe extinction of some cell types together with persistence of others. On the opposite, they can be a positive steady states. These correspond to all cell generations' persistence.

Assume that

$$\tau_i > \frac{1}{\gamma_i}\ln\left(\frac{2(1-H_i)\beta_i(0)}{\beta_i(0)+\delta_i}\right),\ \text{for all } i \in I_0. \tag{5.2}$$

One can note that $F_i\left(0_{\mathbb{R}^7}\right) = \delta_i - \left(2\left(1-H_i\right)e^{-\gamma_i\tau_i} - 1\right)\beta_i\left(0\right)$. Then, assumption (5.2) is equivalent to $F_i\left(0_{\mathbb{R}^7}\right) > 0$. From the monotonicity of β_i, we deduce that $F_i\left(\overline{E}\right) > 0$ for all $\overline{E} \in \mathbb{R}^7$. Then

$$\det A(\overline{E}) = -\mu_1\mu_2\mu_3\prod_{j=0}^{3} F_j(\overline{E}) \neq 0,\ \text{for all } \overline{E} \in \mathbb{R}^7.$$

Consequently, under condition (5.2), $0_{\mathbb{R}^7}$ is the unique steady state.

Inequality (5.2), which is equivalent to

$$\delta_i > \left(2\left(1-H_i\right)e^{-\gamma_i\tau_i}-1\right)\beta_i\left(0\right),$$

characterizes cell population of the compartment i with large death rate δ_i compared to the "birth" rate: $\beta_i(0)$ is the maximum introduction rate in proliferating phase i and, since one mother cell produces $2\left(1-H_i\right)e^{-\gamma_i\tau_i}$ self-renewing daughter cells, $\left(2\left(1-H_i\right)e^{-\gamma_i\tau_i}-1\right)$ measures the difference (either positive or negative) between surviving self-renewing daughter cells and pre-existing mother cells in the compartment i. Hence, cells satisfying (5.2) are expected to not survive, and they have only one steady state value $0_{\mathbb{R}^7}$.

We assume now that there exists $i_0 \in I_1$, such that

$$\tau_{i_0} < \frac{1}{\gamma_{i_0}}\ln\left(\frac{2(1-H_{i_0})\beta_{i_0}(0)}{\beta_{i_0}(0)+\delta_{i_0}}\right)$$

and for $i \in I_0 - \{i_0\}$ the assumption (5.2) is satisfied.
Let $\overline{E}^{i_0} = (\overline{N}_0, \overline{N}_1, \overline{N}_2, \overline{N}_3, \overline{M}_1, \overline{M}_2, \overline{M}_3)^T \neq 0_{\mathbb{R}^7}$ be a steady state. As $F_i\left(\overline{E}\right) > 0$, for $i \in I_0 - \{i_0\}$ and $\overline{E} \in \mathbb{R}^7$, we deduce that $\overline{N}_0 = \overline{N}_i = \overline{M}_i = 0$, for $i \in I_1 - \{i_0\}$. Then, $\overline{E}^{i_0}$ is a steady state if and only if

$$\begin{cases} \overline{N}_0 = \overline{N}_i = \overline{M}_i = 0, \text{ for } i \in I_1 - \{i_0\}, \\ \rho_{i_0 i_0}\overline{N}_{i_0} + \sigma_{i_0 i_0}\overline{M}_{i_0} = \beta_{i_0}^{-1}\left(\dfrac{\delta_{i_0}}{2\left(1-H_{i_0}\right)e^{-\gamma_{i_0}\tau_{i_0}}-1}\right), \\ \alpha_{i_0}\overline{N}_{i_0} - \mu_{i_0}\overline{M}_{i_0} = 0, \end{cases}$$

with

$$\alpha_{i_0} := \frac{2H_{i_0}e^{-\gamma_{i_0}\tau_{i_0}}\delta_{i_0}}{2\left(1-H_{i_0}\right)e^{-\gamma_{i_0}\tau_{i_0}}-1} \geq 0.$$

It is not difficult to see that if

$$\mu_{i_0}\rho_{i_0 i_0} + \alpha_{i_0}\sigma_{i_0 i_0} \neq 0,$$

system (3.5) has a unique axial steady state $\overline{E}^{i_0}$ given by

$$\overline{E}^{i_0} = \begin{cases} (0, \overline{N}_1, 0, 0, \overline{M}_1, 0, 0)^T & \text{if } i_0 = 1, \\ (0, 0, \overline{N}_2, 0, 0, \overline{M}_2, 0)^T & \text{if } i_0 = 2, \\ (0, 0, 0, \overline{N}_3, 0, 0, \overline{M}_3)^T & \text{if } i_0 = 3. \end{cases}$$

Assume now that there exists $\{i_0, i_1\} \subset I_1,\ i_0 < i_1$, such that

$$\tau_i < \frac{1}{\gamma_i}\ln\left(\frac{2(1-H_i)\beta_i(0)}{\beta_i(0)+\delta_i}\right),\ i \in \{i_0, i_1\},$$

and for $i \in I_0 - \{i_0, i_1\}$ the assumption (5.2) is satisfied. Then
$\overline{E}^{i_0,i_1} = (\overline{N}_0, \overline{N}_1, \overline{N}_2, \overline{N}_3, \overline{M}_1, \overline{M}_2, \overline{M}_3)^T \neq 0_{\mathbb{R}^7}$ is a steady state of system (3.5) if and only if

$$\begin{cases} \overline{N}_0 = \overline{N}_i = \overline{M}_i = 0, \text{ for } i \in I_1 - \{i_0, i_1\}, \\ \rho_{i_0 i_0}\overline{N}_{i_0} + \rho_{i_0 i_1}\overline{N}_{i_1} + \sigma_{i_0 i_0}\overline{M}_{i_0} + \sigma_{i_0 i_1}\overline{M}_{i_1} = \beta_{i_0}^{-1}\left(\dfrac{\delta_{i_0}}{2\left(1-H_{i_0}\right)e^{-\gamma_{i_0}\tau_{i_0}}-1}\right), \\ \rho_{i_1 i_0}\overline{N}_{i_0} + \rho_{i_1 i_1}\overline{N}_{i_1} + \sigma_{i_1 i_0}\overline{M}_{i_0} + \sigma_{i_1 i_1}\overline{M}_{i_1} = \beta_{i_1}^{-1}\left(\dfrac{\delta_{i_1}}{2\left(1-H_{i_1}\right)e^{-\gamma_{i_1}\tau_{i_1}}-1}\right), \\ \alpha_{i_0}\overline{N}_{i_0} - \mu_{i_0}\overline{M}_{i_0} = 0, \\ \alpha_{i_1}\overline{N}_{i_1} - \mu_{i_1}\overline{M}_{i_1} = 0, \end{cases}$$

with

$$\alpha_i := \frac{2H_i e^{-\gamma_i \tau_i}\delta_i}{2\left(1-H_i\right)e^{-\gamma_i\tau_i}-1},\ i\in\{i_0,i_1\}.$$

It is not difficult (we let the reader check it) to find necessary and sufficient conditions on the parameters such that system (3.5) has a unique axial steady state of the form

$$\overline{E}^{i_0,i_1} = \begin{cases} (0,\overline{N}_1,\overline{N}_2,0,\overline{M}_1,\overline{M}_2,0)^T & \text{if } i_0=1 \text{ and } i_1=2,\\ (0,\overline{N}_1,0,\overline{N}_3,\overline{M}_1,0,\overline{M}_3)^T & \text{if } i_0=1 \text{ and } i_1=3,\\ (0,0,\overline{N}_2,\overline{N}_3,0,\overline{M}_2,\overline{M}_3)^T & \text{if } i_0=2 \text{ and } i_1=3.\end{cases}$$

Assume

$$\tau_i < \frac{1}{\gamma_i}\ln\left(\frac{2(1-H_i)\beta_i(0)}{\beta_i(0)+\delta_i}\right),\ i\in I_1 \ \text{ and } \tau_0 > \frac{1}{\gamma_0}\ln\left(\frac{2(1-H_0)\beta_0(0)}{\beta_0(0)+\delta_0}\right).$$

One can use the same technique as above to prove, under some conditions on the parameters, the existence of unique axial steady state $\overline{E}^{1,2,3}\neq 0_{\mathbb{R}^7}$ of the form

$$\overline{E}^{1,2,3} = (0,\overline{N}_1,\overline{N}_2,\overline{N}_3,\overline{M}_1,\overline{M}_2,\overline{M}_3)^T.$$

We now investigate the existence of positive steady state $\overline{E}$. Assume that

$$0\le \tau_0 < \tau_0^{\max} := \frac{1}{\gamma_0}\ln\left(\frac{2(1-H_0)\beta_0(0)}{\beta_0(0)+\delta_0}\right). \tag{5.3}$$

This assumption implies in particular that

$$\beta_0(0)>\delta_0 \ \text{ and } \ H_0 < \frac{\beta_0(0)-\delta_0}{2\beta_0(0)}.$$

We focus on the particular case

$$\chi_0(t) = \rho_{00}N_0(t) + \sum_{j=1}^{3}\sigma_{0j}M_j(t) \text{ and } \chi_i(t) = M_i(t) \text{ for } i\in I_1. \tag{5.4}$$

Proposition 5.1. *Suppose that (5.3) and (5.4) are satisfied. Then, system (3.5) has a unique positive steady state* $\overline{E} = \left(\left(\overline{N}_i\right)_{i\in I_0},\left(\overline{M}_i\right)_{i\in I_1}\right)^T$.

Proof. Under the condition (5.3), the first equation of system (5.1) gives a unique

$$\overline{\chi}_0 = \rho_{00}\overline{N}_0 + \sum_{j=1}^{3}\sigma_{0j}\overline{M}_j = \beta_0^{-1}\left(\frac{\delta_0}{2\left(1-H_0\right)e^{-\gamma_0\tau_0}-1}\right).$$

From the last equation of (5.1), we obtain

$$\overline{N}_i = \frac{\mu_i}{2H_i e^{-\gamma_i\tau_i}}\frac{\overline{M}_i}{\beta_i(\overline{M}_i)},\ i\in I_1.$$

Let $\Lambda_i:\mathbb{R}_+\to\mathbb{R}_+,\ i\in I_1$, be the function defined by

$$\Lambda_i(x) = \frac{\mu_i}{2H_i e^{-\gamma_i\tau_i}}\frac{x}{\beta_i(x)}.$$

Λ_i is an increasing function with $\Lambda_i(0)=0$ and $\lim_{x\to+\infty}\Lambda_i(x)=+\infty$.

The second equation of (5.1) implies that

$$\frac{2\left(1-H_0\right)-e^{\gamma_0\tau_0}}{2K_i\delta_0}\left[\delta_i - \left(2(1-H_i)e^{-\gamma_i\tau_i}-1\right)\beta_i(\overline{M}_i)\right]\Lambda_i(\overline{M}_i) = \overline{N}_0.$$

Let $\Omega_i : \mathbb{R}_+ \to \mathbb{R}_+,\ i \in I_1$, be the function defined by

$$\Omega_i(x) = \frac{2\,(1-H_0) - e^{\gamma_0\tau_0}}{2K_i\delta_0}\left[\delta_i - \left(2(1-H_i)e^{-\gamma_i\tau_i} - 1\right)\beta_i(x)\right]\Lambda_i(x).$$

Ω_i is an increasing function with $\Omega_i(0) = 0$ and $\lim_{x\to+\infty} \Omega_i(x) = +\infty$. Then,

$$\overline{M}_i = \Omega_i^{-1}(\overline{N}_0),\ i \in I_1.$$

Then the system (5.1) is reduced to find $\overline{N}_0 > 0$ solution of

$$\rho_{00}\overline{N}_0 + \sum_{j=1}^{3}\sigma_{0j}\Omega_j^{-1}(\overline{N}_0) = \beta_0^{-1}\left(\frac{\delta_0}{2\,(1-H_0)\,e^{-\gamma_0\tau_0} - 1}\right).$$

Let $h : \mathbb{R}_+ \to \mathbb{R}_+$ be the function defined by

$$h(x) = \rho_{00}x + \sum_{j=1}^{3}\sigma_{0j}\Omega_j^{-1}(x).$$

h is an increasing function with $h(0) = 0$ and $\lim_{x\to+\infty} h(x) = +\infty$. Consequently, there exists a unique positive steady state $\overline{E} = \left(\left(\overline{N}_i\right)_{i\in I_0}, \left(\overline{M}_i\right)_{i\in I_1}\right)$ given by

$$\begin{cases} \overline{N}_0 = h^{-1}\left(\beta_0^{-1}\left(\dfrac{\delta_0}{2\,(1-H_0)\,e^{-\gamma_0\tau_0} - 1}\right)\right), & \\ \overline{M}_i = \Omega_i^{-1}(\overline{N}_0), & i \in I_1, \\ \overline{N}_i = \dfrac{\mu_i}{2H_ie^{-\gamma_i\tau_i}}\dfrac{\Omega_i^{-1}(\overline{N}_0)}{\beta_i(\Omega_i^{-1}(\overline{N}_0))}, & i \in I_1. \end{cases}$$

□

Remark 5.2. Let consider the function $\overline{N}_0 : [0, \tau_0^{\max}) \mapsto \mathbb{R}^+$ defined by

$$\overline{N}_0(\tau_0) = h^{-1}\left(\beta_0^{-1}\left(\frac{\delta_0}{2\,(1-H_0)\,e^{-\gamma_0\tau_0} - 1}\right)\right).$$

Then $\overline{N}_0$ is decreasing with

$$\overline{N}_0(0) = h^{-1}\left(\beta_0^{-1}\left(\frac{\delta_0}{1-2H_0}\right)\right) \quad \text{and} \quad \lim_{\tau_0\to\tau_0^{\max}} \overline{N}_0(\tau_0) = 0.$$

One can deduce similar properties for the functions

$$\begin{cases} \tau_0 \in [0, \tau_0^{\max}) \mapsto \overline{M}_i(\tau_0) = \Omega_i^{-1}(\overline{N}_0(\tau_0)), \\ \tau_0 \in [0, \tau_0^{\max}) \mapsto \overline{N}_i(\tau_0) = \dfrac{\mu_i}{2H_ie^{-\gamma_i\tau_i}}\dfrac{\Omega_i^{-1}(\overline{N}_0(\tau_0))}{\beta_i(\Omega_i^{-1}(\overline{N}_0(\tau_0)))}. \end{cases}$$

6. Asymptotic stability of steady states

6.1. **Local and global asymptotic stability of the trivial steady state .** We first concentrate on the local asymptotic stability of the trivial steady state $0_{\mathbb{R}^7}$ of (3.5). In the next proposition, we give a necessary and sufficient condition for $0_{\mathbb{R}^7}$ when it is unique, to be locally asymptotically stable.

Proposition 6.1. *Suppose that the assumption (5.2) is satisfied. Then, $0_{\mathbb{R}^7}$ is locally asymptotically stable. If (5.2) does not hold, $0_{\mathbb{R}^7}$ is unstable.*

Proof. The linearized equation about the trivial steady state gives the following system

$$\begin{cases} N_0'(t) = & -\left(\delta_0+\beta_0\left(0\right)\right)N_0(t)+2(1-H_0)e^{-\gamma_0\tau_0}\beta_0\left(0\right)N_0(t-\tau_0), \\ N_i'(t) = & -\left(\delta_i+\beta_i\left(0\right)\right)N_i(t)+2K_ie^{-\gamma_0\tau_0}\beta_0(0)N_0(t-\tau_0) \\ & +2(1-H_i)e^{-\gamma_i\tau_i}\beta_i\left(0\right)N_i(t-\tau_i), \qquad i\in I_1, \\ M_i'(t) = & -\mu_iM_i(t)+2H_ie^{-\gamma_i\tau_i}\beta_i\left(0\right)N_i(t-\tau_i), \qquad i\in I_1. \end{cases} \tag{6.1}$$

Let $B=(b_{ij})_{1\leq i,j\leq 7}$ and $C_k=\left(c_{ij}^k\right)_{1\leq i,j\leq 7}$, $k\in I_0$, be the $7\times 7-$matrices, with

$$b_{ij}=\begin{cases} -\left(\delta_{i-1}+\beta_{i-1}\left(0\right)\right), & \text{if } i=j\in\{1,2,3,4\}, \\ -\mu_{i-4}, & \text{if } i=j\in\{5,6,7\}, \\ 0, & \text{else}, \end{cases}$$

$$c_{ij}^0=\begin{cases} 2(1-H_0)e^{-\gamma_0\tau_0}\beta_0\left(0\right), & \text{if } i=j=1, \\ 2K_{i-1}e^{-\gamma_0\tau_0}\beta_0(0), & \text{if } i\in\{2,3,4\},\ j=1, \\ 0, & \text{else}, \end{cases}$$

and for $k\in I_1$

$$c_{ij}^k=\begin{cases} 2(1-H_{i-1})e^{-\gamma_{i-1}\tau_{i-1}}\beta_{i-1}\left(0\right), & \text{if } i=j=k+1, \\ 2H_{i-4}e^{-\gamma_{i-4}\tau_{i-4}}\beta_{i-4}\left(0\right), & \text{if } i=k+4,\ j=k+1, \\ 0, & \text{else}. \end{cases}$$

Equation (6.1) has the following form

$$X'(t)=BX(t)+\sum_{k=0}^{3}C_kX(t-\tau_k),$$

with $X(t)=\left((N_i(t))_{i\in I_0},(M_i(t))_{i\in I_1}\right)^T\in\mathbb{R}^7$. The characteristic equation of system (6.1) is

$$\det\left(\lambda I-B-\sum_{k=0}^{3}e^{-\lambda\tau_k}C_k\right)=0,\ \lambda\in\mathbb{C}.$$

One can see that the matrix

$$\lambda I-B-\sum_{k=0}^{3}e^{-\lambda\tau_k}C_k$$

is lower triangular with along the diagonal the following seven elements

$$\Delta_0\left(\lambda\right),\ \Delta_1\left(\lambda\right),\ \Delta_2\left(\lambda\right),\ \Delta_3\left(\lambda\right),\ \lambda+\mu_1,\ \lambda+\mu_2 \text{ and } \lambda+\mu_3,$$

where

$$\Delta_i\left(\lambda\right)=\lambda+\delta_i+\beta_i(0)-2\beta_i(0)\left(1-H_i\right)e^{-(\lambda+\gamma_i)\tau_i},\ i\in I_0.$$

Then, the associated characteristic equation is given by

$$\Delta\left(\lambda\right)=\Delta_0\left(\lambda\right)\prod_{i=1}^{3}\left(\lambda+\mu_i\right)\Delta_i\left(\lambda\right)=0.$$

Eigenvalues of (6.1) are then $\lambda=-\mu_i<0,\ i\in I_1$, and roots of

$$\lambda+\delta_i+\beta_i(0)-2\beta_i(0)\left(1-H_i\right)e^{-(\lambda+\gamma_i)\tau_i}=0,\ i\in I_0.$$

These last equations have the following form

$$(z + a_i) e^z + b_i = 0, \tag{6.2}$$

with

$$a_i = \tau_i (\delta_i + \beta_i(0)), \; b_i = -2\tau_i \beta_i(0) (1 - H_i) e^{-\gamma_i \tau_i} \;\text{ and } z = \lambda \tau_i.$$

Using a result by Hayes [32] (see the book by Hale and Verduyn Lunel [31], page 416), roots of (6.2) have negative real parts if and only if

$$a_i > -1, \; a_i + b_i > 0 \;\text{ and }\; b_i < \xi \sin(\xi) - a_i \cos(\xi), \tag{6.3}$$

where ξ is the unique solution of

$$\xi = -a_i \tan(\xi), \; 0 < \xi < \pi.$$

The condition $a_i > -1$ is always satisfied. Moreover,

$$a_i + b_i = \tau_i \left[\delta_i - \left(2 (1 - H_i) e^{-\gamma_i \tau_i} - 1\right) \beta_i(0)\right] = \tau_i F_i (0_{\mathbb{R}^7}).$$

Thanks to (5.2), $a_i + b_i > 0$.
We have now to verify the last condition of (6.3). We suppose by contradiction, that

$$b_i \geq \xi \sin(\xi) - a_i \cos(\xi) \quad\text{and}\quad \xi = -a_i \tan(\xi), \; 0 < \xi < \pi.$$

So $\xi \sin(\xi) - a_i \cos(\xi) = -a_i (\sin(\xi) \tan(\xi) + \cos(\xi))$ and $b_i \geq -\dfrac{a_i}{\cos(\xi)}$.
Since $b_i < 0$, then $a_i \geq -\dfrac{a_i}{\cos(\xi)}$. As $a_i > 0$, we deduce that $1 > -\dfrac{1}{\cos(\xi)}$. Hence $\cos(\xi) > 0$ and $0 < \xi < \dfrac{\pi}{2}$. Consequently $\tan(\xi) > 0$, which contradicts $\xi = -a_i \tan(\xi)$. It follows that all eigenvalues have negative real parts. Then, the trivial steady state $0_{\mathbb{R}^7}$ is locally asymptotically stable if and only if (5.2) is satisfied. □

We are interested now, in the global asymptotic stability of the trivial steady state $0_{\mathbb{R}^7}$ of (3.5) under a stronger condition than (5.2).

Theorem 6.2. *Suppose that*

$$\tau_i > \frac{1}{\gamma_i} \ln\left(\frac{2\beta_i(0)}{\beta_i(0) + \delta_i}\right), \; i \in I_0. \tag{6.4}$$

Then the trivial steady state $0_{\mathbb{R}^7}$ is globally asymptotically stable.

Proof. First we make a translation of the initial conditions of system (3.5) so as to define them on the interval $[-\tau, 0]$, $\tau := \max\{\tau_i, \, i \in I_0\}$, as it can be found in Hale and Verduyn Lunel [31]. Then, we consider the functional

$$\begin{array}{llll} V: & (C([-\tau, 0], \mathbb{R}_+))^7 & \to & \mathbb{R}_+ \\ & \Phi = (\varphi_0, \varphi_1, \varphi_2, \varphi_3, \psi_1, \psi_2, \psi_3) & \to & V(\Phi), \end{array}$$

defined by

$$V(\Phi) = \varphi_0(0) + \sum_{i=1}^{3} (\varphi_i(0) + \psi_i(0)) + 2 \sum_{i=0}^{3} e^{-\gamma_i \tau_i} \int_{-\tau_i}^{0} \beta_i (L_i (\Phi(s))) \varphi_i(s) ds,$$

where

$$L_i(\Phi(s)) = \rho_{i0} \varphi_0(s) + \sum_{j=1}^{3} \left(\rho_{ij} \varphi_j(s) + \sigma_{ij} \psi_j(s)\right), \; s \in [-\tau, 0].$$

Let $a(x) = x$, for $x \in \mathbb{R}_+$. We have for $\Phi \in (C([-\tau, 0], \mathbb{R}_+))^7$

$$a(\|\Phi(0)\|) = \|\Phi(0)\| := \varphi_0(0) + \sum_{i=1}^{3} (\varphi_i(0) + \psi_i(0)) \leq V(\Phi).$$

The composition with the solution $X = \left((N_i)_{i \in I_0}, (M_i)_{i \in I_1}\right)^T$ of equation (3.5) leads the following function

$$\begin{aligned} t \to V(X_t) &= N_0(t) + \sum_{i=1}^{3} (N_i(t) + M_i(t)) + 2\sum_{i=0}^{3} e^{-\gamma_i \tau_i} \int_{-\tau_i}^{0} \beta_i(L_i(X(t+s))) N_i(t+s) ds, \\ &= N_0(t) + \sum_{i=1}^{3} (N_i(t) + M_i(t)) + 2\sum_{i=0}^{3} e^{-\gamma_i \tau_i} \int_{t-\tau_i}^{t} \beta_i(\chi_i(s)) N_i(s) ds, \end{aligned}$$

where $\chi_i(s)$ is given by (2.2). The derivative of V along the solutions leads to

$$\begin{aligned} \frac{d}{dt} V(X_t) &= N_0'(t) + \sum_{i=1}^{3} (N_i'(t) + M_i'(t)) \\ &\quad + 2\sum_{i=0}^{3} e^{-\gamma_i \tau_i} \left[\beta_i(\chi_i(t)) N_i(t) - \beta_i(\chi_i(t-\tau_i)) N_i(t-\tau_i)\right], \\ &= -\left(\sum_{i=0}^{3} \left[\delta_i - (2e^{-\gamma_i \tau_i} - 1)\beta_i(\chi_i(t))\right] N_i(t) + \sum_{i=1}^{3} \mu_i M_i(t)\right). \end{aligned}$$

Along the solutions of equation (3.5), we obtain

$$\dot{V}(\Phi) = -\left(\sum_{i=0}^{3} \left[\delta_i - \left(2e^{-\gamma_i \tau_i} - 1\right)\beta_i(L_i(\Phi(0)))\right] \varphi_i(0) + \sum_{i=1}^{3} \mu_i \psi_i(0)\right).$$

The monotonicity of β_i gives that

$$\dot{V}(\Phi) \leq -k\|\Phi(0)\|, \quad \text{where } k = \min\left[\min_{j \in I_0} \left[\delta_j - \left(2e^{-\gamma_j \tau_j} - 1\right)\beta_j(0)\right], \ \min_{j \in I_1} (\mu_j)\right].$$

So, the assumption (6.4) implies that $k > 0$. Then, thanks to Hale and Verduyn Lunel ([31], corollary 3.1, page 143), every solution approaches zero as $t \to +\infty$. □

6.2. **Local asymptotic stability of the positive steady state.** Suppose that the assumptions (5.3) and (5.4) are satisfied. Then, system (3.5) has a unique positive steady state $\overline{E}$ (see proposition 5.1). Stability of $\overline{E}$ cannot be handled as easily as the one of trivial steady state, because of the nature of the characteristic equation that induces technical difficulties. However, sufficient conditions for the stability of $\overline{E}$ can be obtained.

Assume that

$$H_i = \frac{1}{2}, \text{ for } i \in I_1, \tag{6.5}$$

and remember that (5.3) implies in particular that

$$\beta_0(0) > \delta_0 \quad \text{and} \quad H_0 < \frac{\beta_0(0) - \delta_0}{2\beta_0(0)} < \frac{1}{2}. \tag{6.6}$$

We have the following theorem about the asymptotic stability of the positive steady state $\overline{E}$ of system (3.5).

Theorem 6.3. *Assume that (5.3), (5.4) and (6.5) hold true. Then there exists $\sigma^* > 0$ such that for any $\sigma_{0i} \in [0, \sigma^*)$, $i \in I_1$, there exists $\tau^* := \tau^*\left((\sigma_{0i})_{i \in I_1}\right) \in (0, \tau_0^{\max})$ such that the positive steady state $\overline{E}$ is locally asymptotically stable for $\tau_i \in [0, \tau^*)$, $i \in I_0$.*

Proof. In order to study the local asymptotic stability of the positive steady state, we study the sign of the real parts of the characteristic roots of the following linearized system of (3.5) around $\overline{E}$

$$Y'(t) = AY(t) + 2\sum_{k=0}^{3} e^{-\gamma_k \tau_k} B_k Y(t-\tau_k), \tag{6.7}$$

where the matrices A and B_k are defined by

$$A = \begin{pmatrix} -\delta_0 - \overline{a}_0 & 0 & 0 & 0 & \sigma_{01}\overline{b}_0 & \sigma_{02}\overline{b}_0 & \sigma_{03}\overline{b}_0 \\ 0 & -\delta_1 - \overline{a}_1 & 0 & 0 & \overline{b}_1 & 0 & 0 \\ 0 & 0 & -\delta_2 - \overline{a}_2 & 0 & 0 & \overline{b}_2 & 0 \\ 0 & 0 & 0 & -\delta_3 - \overline{a}_3 & 0 & 0 & \overline{b}_3 \\ 0 & 0 & 0 & 0 & -\mu_1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -\mu_2 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -\mu_3 \end{pmatrix},$$

with

$$\begin{cases} \overline{a}_0 = \rho_{00}\beta_0'(\overline{\chi}_0)\overline{N}_0 + \beta_0\left(\overline{\chi}_0\right), & \\ \overline{a}_i = \beta_i\left(\overline{M}_i\right) > 0, & \text{for } i \in I_1, \\ \overline{b}_0 = -\beta_0'(\overline{\chi}_0)\overline{N}_0 > 0, & \\ \overline{b}_i = -\beta_i'(\overline{M}_i)\overline{N}_i > 0, & \text{for } i \in I_1, \end{cases} \tag{6.8}$$

and, the $7\times 7-$matrices $B_k,\ k \in I_0$, are given by

$$B_0 = \begin{pmatrix} (1-H_0)\overline{a}_0 & 0 & 0 & 0 & -(1-H_0)\sigma_{01}\overline{b}_0 & -(1-H_0)\sigma_{02}\overline{b}_0 & -(1-H_0)\sigma_{03}\overline{b}_0 \\ K_1\overline{a}_0 & 0 & 0 & 0 & -K_1\sigma_{01}\overline{b}_0 & -K_2\sigma_{02}\overline{b}_0 & -K_3\sigma_{03}\overline{b}_0 \\ K_2\overline{a}_0 & 0 & 0 & 0 & 0 & 0 & 0 \\ K_3\overline{a}_0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

$$B_1 = \begin{pmatrix} 0_{1\times1} & 0_{1\times4} & 0_{1\times2} \\ 0_{4\times1} & D_1 & 0_{4\times2} \\ 0_{2\times1} & 0_{2\times4} & 0_{2\times2} \end{pmatrix},\ B_2 = \begin{pmatrix} 0_{2\times2} & 0_{2\times4} & 0_{2\times1} \\ 0_{4\times2} & D_2 & 0_{4\times1} \\ 0_{1\times2} & 0_{1\times4} & 0_{1\times1} \end{pmatrix} \text{ and } B_3 = \begin{pmatrix} 0_{3\times3} & 0_{3\times4} \\ 0_{4\times3} & D_3 \end{pmatrix},$$

where $0_{n\times p}$ is the $n\times p-$zero matrix and

$$D_i = \begin{pmatrix} \overline{a}_i & 0 & 0 & -\overline{b}_i \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ \overline{a}_i & 0 & 0 & -\overline{b}_i \end{pmatrix},\ i \in I_1.$$

The characteristic equation of system (6.7) is

$$\Delta\left(\lambda, (\sigma_{0i})_{i\in I_1}, (\tau_i)_{i\in I_0}\right) := \det\left(\lambda I - A - 2\sum_{k=0}^{3} e^{-\lambda\tau_k} B_k\right) = 0. \tag{6.9}$$

Let suppose that $\tau_i = 0,\ i \in I_0$. Then the equation (6.9) becomes

$$\det\left(\lambda I - A - 2\sum_{k=0}^{3} B_k\right) = 0,$$

where the matrix $A+2\sum_{k=0}^{3}B_k$ is given by

$$\begin{pmatrix} -\delta_0+(1-2H_0)\,\overline{a}_0 & 0 & 0 & 0 & -(1-2H_0)\sigma_{01}\overline{b}_0 & -(1-2H_0)\sigma_{02}\overline{b}_0 & -(1-2H_0)\sigma_{03}\overline{b}_0 \\ 2K_1\overline{a}_0 & -\delta_1 & 0 & 0 & -K_1\sigma_{01}\overline{b}_0 & -K_2\sigma_{02}\overline{b}_0 & -K_3\sigma_{03}\overline{b}_0 \\ 2K_2\overline{a}_0 & 0 & -\delta_2 & 0 & 0 & 0 & 0 \\ 2K_3\overline{a}_0 & 0 & 0 & -\delta_3 & 0 & 0 & 0 \\ 0 & \overline{a}_1 & 0 & 0 & -\mu_1-\overline{b}_1 & 0 & 0 \\ 0 & 0 & \overline{a}_2 & 0 & 0 & -\mu_2-\overline{b}_2 & 0 \\ 0 & 0 & 0 & \overline{a}_3 & 0 & 0 & -\mu_3-\overline{b}_3 \end{pmatrix}.$$

Let us regard $(\sigma_{0i})_{i\in I_1}\geq 0$ as parameters. For $\sigma_{0i}=0,\ i\in I_1$, the roots of (6.9) are

$$-\delta_0+\overline{a}\,(1-2H_0)\,,\ -\overline{a}_1+\overline{\beta}_1,\ -\overline{a}_2+\overline{\beta}_2,\ -\overline{a}_3+\overline{\beta}_3,\ -\mu_1+\overline{b}_1,\ -\mu_2+\overline{b}_2 \text{ and } -\mu_3+\overline{b}_3.$$

From (6.8), we deduce that $-\overline{a}_i+\overline{\beta}_i=-\delta_i<0$ and $-\mu_i+\overline{b}_i=-\mu_i+\overline{N}_i\beta_i'(\overline{M}_i)<0$ for $i\in I_1$. On the other hand, we have

$$-\delta_0+\overline{a}\,(1-2H_0)=-\delta_0+\left(\beta_0'(\overline{N}_0)\overline{N}_0+\beta_0\left(\overline{N}_0\right)\right)(1-2H_0)$$

and from the first equation of (5.1), we deduce that

$$(1-2H_0)\,\beta_0(\overline{N_0})=\delta_0 \quad \text{with } 0\leq H_0<\frac{1}{2}.$$

Then

$$-\delta_0+\overline{a}\,(1-2H_0)=\beta_0'(\overline{N}_0)\overline{N}_0<0.$$

Clearly, $\Delta\left(\lambda,(\sigma_{0i})_{i\in I_1},0\right)$ is a polynomial function in λ and $(\sigma_{0i})_{i\in I_1}$. Then, by a simple argument of continuity, we conclude that as σ_{0i} vary slightly, zeros of $\lambda\to\Delta\left(\lambda,(\sigma_{0i})_{i\in I_1},0\right)$ stay in the open right half-plane. Then, there exists $\sigma^*>0$ such that for $\sigma_{0i}\in[0,\sigma^*)\,,\ i\in I_1$, the roots of the characteristic equation (6.9) have negative real parts. We fix now $\sigma_{0i}\in[0,\sigma^*)\,,\ i\in I_1$, and regard τ_i as parameters. As $\Delta\left(\lambda,(\sigma_{0i})_{i\in I_1},(\tau_i)_{i\in I_0}\right)$ is analytic in λ and τ_i. Following Theorem 2.1 of Ruan and Wei [49], as τ_i vary, the sum of the multiplicity of zeros of $\lambda\to\Delta\left(\lambda,(\sigma_{0i})_{i\in I_1},(\tau_i)_{i\in I_0}\right)$ in the open right half-plane can only change if a zero appears on or crosses the imaginary axis. Then there exists $\tau^*:=\tau^*\left((\sigma_{0i})_{i\in I_1}\right)\in(0,\tau_0^{\max})$ such that for $\tau_i\in[0,\tau^*)\,,\ i\in I_0$, all roots of (6.9) have negative real parts. □

7. Numerical illustrations and conclusion

We numerically illustrate the behavior of the positive steady state (stable or unstable), as well as the existence of oscillations. Inspired by Mackey [40], Pujo-Menjouet and Mackey [47], and Adimy, Crauste and Ruan [10], we take β_i as Hill functions, given by (2.4). Suppose that the assumptions (5.3) and (5.4) are satisfied and consider the following values of parameters

$$\begin{aligned} &\delta_i=\gamma_i=0.05\ d^{-1},\ \mu_i=0.2\ d^{-1},\ \beta_i(x)=\frac{1.77}{1+x^3}\ d^{-1},\ \text{for all } i\in I_0,\\ &\rho_{00}=1,\ \sigma_{0j}=0.01,\ \text{for all } j\in I_1,\\ &H_0=0.25,\ H_j=0.5 \text{ and } K_j=\frac{1}{3}H_0,\ \text{for all } j\in I_1. \end{aligned}$$

In fact, the real biological values of the above parameters are unknown. Therefore, we ask the question: is there any set of parameter values for which the model exhibits the desired qualitative behavior (stable and unstable steady state)? It should be helpful in understanding the effect of the duration of cell cycle (the delay) on the stability of the positive steady state.

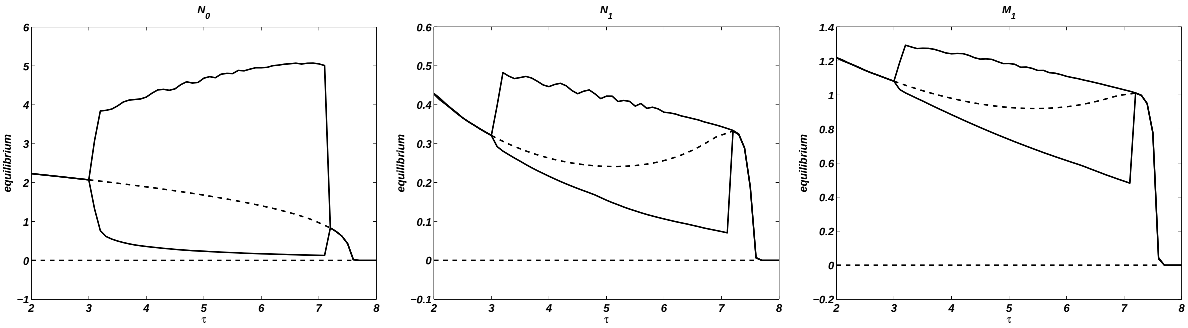

FIGURE 2. Steady states bifurcation diagram. The values of the steady states $\overline{N}_0$, $\overline{N}_1$ and $\overline{M}_1$ are drawn as functions of $\tau := \tau_1 = \tau_2 = \tau_3 \geq 0$ (the *solid curve* is for stable steady states and the *dashed curve* is for unstable steady states). When τ is close to zero, the positive steady states are stable, and they become unstable for $\tau \approx 3.04$ days (a Hopf bifurcation occurs for this critical value). A stability switch stabilizes the steady states for τ between 7.18 and 7.55 ($\tau_0^{\max}$) days. Oscillations are observed for τ between 3.04 and 7.18 days. The low and the high values of the amplitudes of these oscillations are drawn. They correspond to *solid curves* up and down of the unstable positive steady states. One can consider that amplitudes of oscillations do not vary: they quickly reach some plateau and finally decrease rapidly before the stability switch. When τ is greater than 7.55 days, zero is the only steady state and it is asymptotically stable. Similar behaviors can be observed for the other steady states $\overline{N}_2$, $\overline{M}_2$, $\overline{N}_3$ and $\overline{M}_3$.

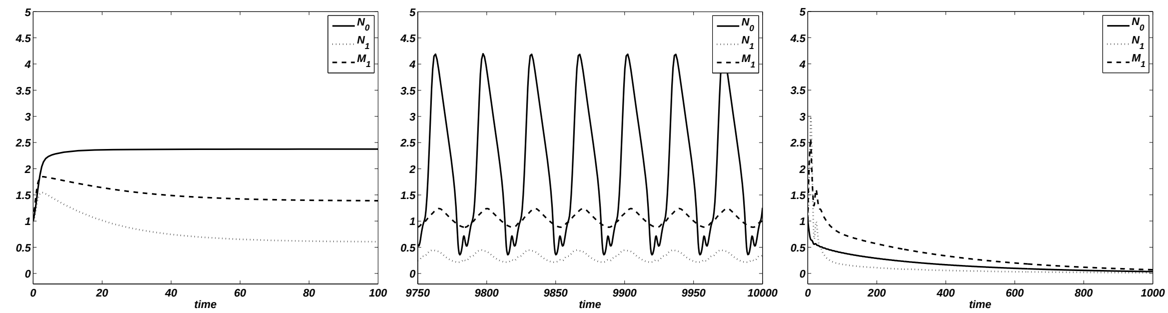

FIGURE 3. (a) Asymptotic stability of the positive steady states for τ between 3.04 and 7.18 days. Parameters are the same as in Figure 2, with $\tau = 1$. The solutions N_0, N_1, M_1 converge to the positive steady states $\overline{N}_0$, $\overline{N}_1$, $\overline{M}_1$.
(b) Oscillating solutions for τ between 3.04 and 7.18 days. Parameters are the same as in Figure (a) except that $\tau = 4$. The solutions N_0, N_1, M_1 converge to periodic solutions with period about 50 days.
(c) Asymptotic stability of the trivial steady state for τ greater than 7.55 days. For $\tau = 8$, the solutions N_0, N_1, M_1 converge to zero.

Many hematological diseases involve oscillations about a steady state. These oscillations give rise to instability in a part or all types of blood cell count. Experimental observations have led to the conclusion that this dynamics instability is located in the hematopoietic stem cells compartment. In order to understand this phenomenon, Colijn and Mackey [23, 24] (see also Foley and Mackey [27], Lei and Mackey [39]) proposed for the first time a complete model of hematopoietic stem cell dynamics that contains the three blood cell lines. They applied their study to prove the existence of oscillations in chronic myelogenous leukemia [23] and cyclical neutropenia [24]. Colijn and Mackey simplified their model by assuming, on one hand that the stem cell populations is independent of circulating blood cells, and on the other hand that there is autonomy between the three cell lines. The model we consider in this paper incorporates features that were not taken into account in previous models: the dynamics of the three types of blood cells and the feedback controls from circulating blood cells to the production of each type of hematopoietic stem cells. The situation described in Figure 2 gives some information that can be related to periodic hematological diseases. It also indicate that our model may have rich dynamics, with very long oscillations, as noticed for a simpler model by Colijn and Mackey [23, 24], Foley and Mackey [27] and, Lei and Mackey [39]. A further analysis could help in understanding the complicated dynamics of the blood cell production system and leave it to future consideration.

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