

# Mathematical Model of Hematopoiesis Dynamics with Growth Factor-Dependent Apoptosis and Proliferation Regulations

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## Abstract

We consider a nonlinear mathematical model of hematopoietic stem cell dynamics, in which proliferation and apoptosis are controlled by growth factor concentrations. Cell proliferation is positively regulated, while apoptosis is negatively regulated. The resulting age-structured model is reduced to a system of three differential equations, with three independent delays, and existence of steady states is investigated. The stability of the trivial steady state, describing cell's dying out with a saturation of growth factor concentrations is proven to be asymptotically stable when it is the only equilibrium. The stability analysis of the unique positive steady state allows to determine a stability area, and shows that instability may occur through a Hopf bifurcation, mainly as a destabilization of the proliferative capacity control, when cell cycle durations are very short.

## 1 Introduction

Hematopoietic stem cells (HSC) are undifferentiated cells, located in the bone marrow, with unique abilities of differentiation (production of cells

committed to one blood cell lineage: white cells, red blood cells or platelets) and self-renewal (production of a cell with the same properties). These cells are at the root of the blood production process, called hematopoiesis. Through successive differentiating divisions, they produce mature blood cells, that enter the bloodstream.

Proliferation 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 / inhibitor role. Usually, a control operates between the number of circulating blood cells and the production of growth factors: the less there are circulating blood cells, the more there are growth factors produced. When the number of circulating blood cells is large enough, the release of growth factors decreases. Growth factors act at every cell compartment, not only at the HSC level.

The probably most known growth factor is erythropoietin (Epo), produced by the kidneys to trigger the production of red blood cells. Different growth factors act to help the production of red blood cells, white cells and platelets.

To our knowledge, first models of HSC dynamics have been proposed by Mackey [18], and took the form of a system of two delay differential equations describing the evolution of a stem cell population divided in two compartments, proliferating and nonproliferating cells. This model has been recently analyzed and applied to hematological diseases by Pujo-Menjouet and Mackey [21], Pujo-Menjouet et al [20], Bernard et al [11] and Colijn and Mackey [13, 14]. More general versions of Mackey's model [18] have been analyzed. We refer, for example, to Adimy et al [1, 2, 4, 5, 6, 7, 9], and the references therein.

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 phase, has been considered by Bélair et al [10] and Mahaffy et al [19]. Recently, Adimy et al. [8] dealt with a system of three delay differential equations describing the production of blood cells under the action of growth factors assumed to act on the rate of introduction in the proliferating phase, and Adimy and Crauste [3] considered, in a similar model, the influence of growth factors on HSC apoptosis.

In this work, we consider the action of growth factors on the apoptosis rate, as well as on the proliferative capacity of HSC. Some growth factors are known to decrease the apoptotic rate [23] so as to bring more cells to the division, and then increase the blood cell production [17], and others are known to increase HSC proliferation. We model the HSC dynamics with an age structured model describing the evolution of proliferating and nonproliferating cells, coupled with delay differential equations describing the production of growth factors. This is presented in the next section, where we also show that the model can be reduced to a system of delay differential equations with three different discrete delays (corresponding to the cell cycle

duration and times needed to release growth factors in the bloodstream), and a distributed delay (describing the action of growth factors on the apoptosis rate). In section 3, we investigate the existence of steady states. This leads, in Section 4, to the linearization of the system about one of its steady states, in order to perform the local asymptotic stability analysis of the trivial steady state in Section 5, and the positive steady state in Section 6.

## 2 Modelling

Let consider a HSC population, located in the bone marrow. This population is divided in proliferating and nonproliferating cells [12]. Proliferating HSC are actually performing the main stages of cell cycle (growth, DNA synthesis), in order to divide during mitosis in two daughter cells. These latter immediately enter the nonproliferating phase, also known as a resting or quiescent phase, at birth.

Nonproliferating cells are assumed to differentiate with a constant rate  $\delta > 0$ , which can also take some natural mortality into account, and they are introduced in the proliferating phase whenever during their life with a rate  $\beta$ . This latter is supposed to be dependent upon a growth factor concentration  $E_1$ , that stimulates the proliferative capacity of HSC: the more growth factor, the more proliferation of HSC. Hence the feedback induced by the growth factor is positive, and the function  $\beta$  is supposed to be increasing, with  $\beta(0) = 0$ .

As soon as a cell enters the proliferating phase, it is committed to divide a time  $\tau$  later. We assume (see [18, 20, 21]) that the duration of the proliferating phase is the same for all cells, so  $\tau$  is constant, and describes an average duration of the cell cycle.

The number of proliferating cells is controlled by apoptosis, a programmed cell death. We assume this mortality rate depends upon the concentration of growth factors [17]. Some growth factors are known to reduce the apoptosis rate, leading to a more important production of blood cells through division. This is the case for Epo: the more Epo released, the more the apoptosis rate decreases [17]. We assume, in this work, that the apoptosis rate, denoted by  $\gamma$ , is a positive function of the concentration of some growth factor, denoted by  $E_2$ . Since an increase in the growth factor concentration leads to a decrease of the apoptosis rate, we assume that  $\gamma$  is a decreasing function of  $E_2$ .

Denote by  $n(t, a)$  and  $p(t, a)$  the population densities of nonproliferating and proliferating HSC, respectively, with age  $a$  at time  $t$ . The age represents the time spent by a cell in one of the two phases, thus it ranges, in the resting phase, from 0 to infinity, and in the proliferating phase from 0 to  $\tau$ . The evolution of the HSC population is described by the following system of

age-structured partial differential equations,

$$\frac{\partial n}{\partial t}(t, a) + \frac{\partial n}{\partial a}(t, a) = -\delta n(t, a) - \beta(E_1(t))n(t, a), \quad (1)$$

$$\frac{\partial p}{\partial t}(t, a) + \frac{\partial p}{\partial a}(t, a) = -\gamma(E_2(t))p(t, a), \quad (2)$$

where  $E_i(t)$ ,  $i = 1, 2$ , is a growth factor concentration.

System (1)–(2) is completed by boundary conditions (for  $a = 0$ ), that describe the flux of cells entering each phase: new proliferating cells are non-proliferating cells introduced with a rate  $\beta$ , and new resting cells come from the division of proliferating cells that have spent a time  $\tau$  in the proliferating phase. Then the boundary conditions of (1)–(2) are

$$n(t, 0) = 2p(t, \tau), \quad (3)$$

$$p(t, 0) = \int_0^{+\infty} \beta(E_1(t))n(t, a)da = \beta(E_1(t))N(t), \quad (4)$$

where  $N(t)$  denotes the total nonproliferating cell population density at time  $t$ , defined by

$$N(t) = \int_0^{+\infty} n(t, a)da. \quad (5)$$

We also assume, for  $t \geq 0$ ,

$$\lim_{a \rightarrow +\infty} n(t, a) = 0.$$

Concentrations of growth factors  $E_i(t)$ ,  $i = 1, 2$ , follow an evolution equation given by

$$E_i'(t) = -k_i E_i(t) + f_i(N(t - T_i)). \quad (6)$$

The coefficient  $k_i$  describes the disappearance rate of the growth factor, whereas the function  $f_i$  acts as a negative feedback of the nonproliferating HSC population on the production of growth factor. A more realistic hypothesis would be that the growth factor concentration is controlled by the number of circulating blood cells. However, we make the implicit hypothesis that the number of circulating blood cells is proportional to the number of nonproliferating hematopoietic stem cells, thus not taking into account an evolution equation satisfied by the circulating blood cell population and then assuming that  $f_i$  only depends upon  $N(t)$ . The time delay  $T_i$  represents the time needed to release growth factors after the stimulation by nonproliferating cells. This time is rather short, in order of several hours.

The evolution equation (6) of growth factor concentrations  $E_i(t)$ ,  $i = 1, 2$ , has been introduced by Bélair et al [10] and Mahaffy et al [19]. However, in [10] and [19], the authors do not take into account the time needed to release growth factors, so  $T_i = 0$  in their model.

Since  $f_i$  describes a negative feedback from the HSC population on the growth factor concentration, we assume that  $f_i$  is positive and decreasing, and satisfies (see [10, 19])

$$\lim_{N \rightarrow +\infty} f_i(N) = 0.$$

The system we consider, modelling the dynamics of a HSC population under the action of two different growth factors, is then formed by equations (1) to (6). It consists of a system of age-structured differential equations, coupled with two delay differential equations. We are now going to check that system (1)–(4) reduces to a system of delay differential equations.

First, note that using the method of characteristics (see Webb [24]), the solutions  $p(t, a)$  of (2) and (4) are given, for  $0 \leq a \leq t$ , by

$$p(t, a) = \beta(E_1(t - a))N(t - a) \exp\left(-\int_{t-a}^t \gamma(E_2(s))ds\right). \quad (7)$$

Denote by  $P$  the total population of proliferating stem cells,

$$P(t) = \int_0^\tau p(t, a)da.$$

Integrating system (1)–(2) with respect to the age variable, and using (3) and (4), we obtain, for  $t \geq 0$ ,

$$\begin{aligned} N'(t) &= -\delta N(t) - \beta(E_1(t))N(t) + 2p(t, \tau), \\ P'(t) &= -\gamma(E_2(t))P(t) + \beta(E_1(t))N(t) - p(t, \tau). \end{aligned} \quad (8)$$

Using a method of steps, we obtain that the system formed by (8) and equation (6) has a unique nonnegative continuous solution defined on  $[0, \max\{\tau, T_i\}]$ . From (7), we deduce, for  $t \geq \max\{\tau, T_i\}$ ,

$$\begin{aligned} N'(t) &= -\delta N(t) - \beta(E_1(t))N(t) \\ &\quad + 2\beta(E_1(t - \tau))N(t - \tau) \exp\left(-\int_{t-\tau}^t \gamma(E_2(s))ds\right), \end{aligned} \quad (9)$$

$$\begin{aligned} P'(t) &= -\gamma(E_2(t))P(t) + \beta(E_1(t))N(t) \\ &\quad - \beta(E_1(t - \tau))N(t - \tau) \exp\left(-\int_{t-\tau}^t \gamma(E_2(s))ds\right). \end{aligned} \quad (10)$$

Then we find that the total populations  $N(t)$  and  $P(t)$  satisfy a system of differential equations with distributed delay.

Since equation (9) and the differential equation (6) do not depend on the proliferating cell population  $P$ , solution of (10), we will focus on the study of the system of delay differential equations formed by equations (6) and

(9), that is

$$\begin{cases} N'(t) = -\delta N(t) - \beta(E_1(t))N(t) \\ \quad + 2\beta(E_1(t - \tau))N(t - \tau) \exp\left(-\int_{-\tau}^0 \gamma(E_2(t + s))ds\right), \\ E'_i(t) = -k_i E_i(t) + f_i(N(t - T_i)), \quad i = 1, 2, \end{cases} \quad (11)$$

defined for  $t \geq \max\{\tau, T_i\}$ , with initial conditions given on the interval  $[0, \max\{\tau, T_i\}]$ .

For each continuous initial condition, the system (11) has a unique continuous solution, defined for  $t \geq \max\{\tau, T_i\}$  (see Hale and Verduyn Lunel [15], Theorem 2.3, page 44).

From now on, we make a translation of the initial conditions of system (11) so as to define them on the interval  $[-\max\{\tau, T_i\}, 0]$ , as it can be found in Hale and Verduyn Lunel [15].

Let us first observe that solutions of (11) associated with nonnegative initial conditions are nonnegative. Indeed, if one supposes that there exists  $t_0 \geq 0$  such that  $N(t) > 0$  for  $t < t_0$  and  $N(t_0) = 0$ , then, from (11), it follows that

$$N'(t_0) = 2\beta(E_1(t_0 - \tau))N(t_0 - \tau) \exp\left(-\int_{-\tau}^0 \gamma(E_2(t_0 + s))ds\right) > 0,$$

since  $\beta$  is strictly positive. Consequently,  $N(t)$  remains nonnegative for  $t \geq 0$ . Using a classical variation of constant formula, we obtain, for  $t \geq 0$  and  $i = 1, 2$ ,

$$E_i(t) = e^{-k_i t} E_i(0) + e^{-k_i t} \int_0^t e^{k_i \theta} f_i(N(\theta - T_i)) d\theta. \quad (12)$$

Hence, the positivity of  $E_i(t)$  follows from the fact that  $f_i$  is positive.

Next, using (12), one can show that solutions  $E_i$ ,  $i = 1, 2$ , of (11) are bounded. We state the following result, whose proof is similar to the one detailed in Adimy and Crauste [3]. We do not rewrite it.

**Proposition 1.** *The solutions  $E_i(t)$ ,  $i = 1, 2$ , of (11) are bounded and either there exists  $\bar{t}_i \geq 0$  such that  $E_i(\bar{t}_i) \leq f_i(0)/k_i$  and then  $E_i(t) \leq f_i(0)/k_i$  for all  $t > \bar{t}_i$ , or  $\lim_{t \rightarrow +\infty} E_i(t) = f_i(0)/k_i$ .*

The next section is devoted to the existence of steady states for system (11).

### 3 Existence of Steady States

We now investigate the existence of steady states of (11). Let  $(\bar{N}, \bar{E}_1, \bar{E}_2)$  be a steady state of (11). It satisfies  $d\bar{N}/dt = d\bar{E}_1/dt = d\bar{E}_2/dt = 0$ , that is

$$\begin{cases} \left[ (2e^{-\gamma(\bar{E}_2)\tau} - 1)\beta(\bar{E}_1) - \delta \right] \bar{N} = 0, \\ k_i \bar{E}_i = f_i(\bar{N}), \quad i = 1, 2. \end{cases} \quad (13)$$

One can note that  $(0, f_1(0)/k_1, f_2(0)/k_2)$  is always a steady state, describing the stem cell population's dying out with a saturation of growth factor concentrations. We will refer to this steady state as the trivial steady state.

From (13), a nontrivial steady state  $(\bar{N}, \bar{E}_1, \bar{E}_2)$ , with  $\bar{N} \neq 0, \bar{E}_i \neq f_i(0)/k_i, i = 1, 2$ , would satisfy

$$\left( 2e^{-\gamma(f_2(\bar{N})/k_2)\tau} - 1 \right) \beta \left( \frac{f_1(\bar{N})}{k_1} \right) = \delta \quad \text{and} \quad \bar{E}_i = \frac{f_i(\bar{N})}{k_i}, \quad i = 1, 2. \quad (14)$$

The next proposition deals with existence and uniqueness of steady states of system (11).

**Proposition 2.** *Assume*

$$\delta < \left( 2e^{-\gamma(f_2(0)/k_2)\tau} - 1 \right) \beta \left( \frac{f_1(0)}{k_1} \right). \quad (15)$$

*Then system (11) has two steady states:  $(0, f_1(0)/k_1, f_2(0)/k_2)$  and  $(N^*, E_1^*, E_2^*)$ , with  $N^* > 0$  and  $0 < E_i^* < f_i(0)/k_i, i = 1, 2$ , solutions of (14).*

*If (15) does not hold, then  $(0, f_1(0)/k_1, f_2(0)/k_2)$  is the only steady state of (11).*

*Proof.* Define, for  $N \geq 0$ , the function  $\chi$  by

$$\chi(N) = 2e^{-\gamma(f_2(N)/k_2)\tau} - 1.$$

Since  $f_2$  and  $\gamma$  are decreasing, the mapping  $N \mapsto \gamma(f_2(N)/k_2)$  is increasing. Thus  $\chi$  is decreasing. One can note that  $\chi$  is not necessarily positive, since

$$\lim_{N \rightarrow +\infty} \chi(N) = 2e^{-\gamma(0)\tau} - 1.$$

First consider the case  $2e^{-\gamma(0)\tau} - 1 \geq 0$ . Then  $\chi$  is positive and decreasing on  $[0, +\infty)$ . Since  $f_1$  is decreasing and  $\beta$  is also positive and increasing on  $[0, +\infty)$ , with  $\beta(0) = 0$ , the function  $\xi(N) := \chi(N)\beta(f_1(N)/k_1)$  is decreasing and satisfies

$$\xi(0) = \left( 2e^{-\gamma(f_2(0)/k_2)\tau} - 1 \right) \beta \left( \frac{f_1(0)}{k_1} \right) \quad \text{and} \quad \lim_{N \rightarrow +\infty} \xi(N) = 0.$$

Consequently, the equation  $\xi(N) = \delta$  (which gives the existence of a positive steady state, see (14)) has a solution if and only if (15) holds true, and the solution is unique.

Suppose now that  $2e^{-\gamma(0)\tau} - 1 < 0$ . If  $\chi(0) = 2e^{-\gamma(f_2(0)/k_2)\tau} - 1 > 0$  (which is the case when (15) holds true), then there exists a unique  $\tilde{N} > 0$  such that  $\chi(\tilde{N}) = 0$ . Since  $\chi$  is decreasing, on the interval  $(\tilde{N}, +\infty)$ , the function  $\chi$  is negative and so is the function  $\xi$ . On the interval  $[0, \tilde{N}]$ , the function  $\chi$  is positive and decreasing, so similarly to the previous case  $\xi$  is decreasing and the equation  $\xi(N) = \delta$  then has a unique solution if and only if (15) holds true. This concludes the proof.  $\square$

In the following, we analyze the asymptotic behavior of the solutions of system (11) by studying the asymptotic stability of its steady states. To that aim, we deduce the linearized system of (11) and we obtain the associated characteristic equation in the next section.

## 4 Linearized System and Characteristic Equation

Assume the functions  $\beta$ ,  $\gamma$  and  $f_i$  are continuously differentiable, and let  $(\bar{N}, \bar{E}_1, \bar{E}_2)$  be a steady state of system (11), that is, from Proposition 2, either  $(\bar{N}, \bar{E}_1, \bar{E}_2) = (0, f_1(0)/k_1, f_2(0)/k_2)$  or  $(\bar{N}, \bar{E}_1, \bar{E}_2) = (N^*, E_1^*, E_2^*)$ . We set

$$X(t) = N(t) - \bar{N} \quad \text{and} \quad Y_i(t) = E_i(t) - \bar{E}_i, \quad i = 1, 2.$$

The linearized system of (11) around  $(\bar{N}, \bar{E}_1, \bar{E}_2)$  is then

$$\left\{ \begin{array}{l} X'(t) = -(\delta + \beta(\bar{E}_1))X(t) - \bar{N}\beta'(\bar{E}_1)Y_1(t) \\ \quad + 2\beta(\bar{E}_1)e^{-\gamma(\bar{E}_2)\tau}X(t-\tau) + 2\bar{N}\beta'(\bar{E}_1)e^{-\gamma(\bar{E}_2)\tau}Y_1(t-\tau) \\ \quad - 2\bar{N}\beta(\bar{E}_1)\gamma'(\bar{E}_2)e^{-\gamma(\bar{E}_2)\tau} \int_{-\tau}^0 Y_2(t+s)ds, \\ Y_i'(t) = -k_i Y_i(t) + f_i'(\bar{N})X(t - T_i), \quad i = 1, 2. \end{array} \right. \quad (16)$$

Let set

$$\begin{aligned} a_1 &= \delta + \beta(\bar{E}_1), & a_4 &= 2\bar{N}\beta'(\bar{E}_1)e^{-\gamma(\bar{E}_2)\tau}, \\ a_2 &= 2\beta(\bar{E}_1)e^{-\gamma(\bar{E}_2)\tau}, & a_5 &= -2\bar{N}\beta(\bar{E}_1)\gamma'(\bar{E}_2)e^{-\gamma(\bar{E}_2)\tau}, \\ a_3 &= \bar{N}\beta'(\bar{E}_1), \end{aligned} \quad (17)$$

and

$$b_i = -f_i'(\bar{N}), \quad i = 1, 2. \quad (18)$$

One can note that  $a_i \geq 0$  for  $i = 1, \dots, 5$ , and  $b_i > 0$  for  $i = 1, 2$ .

Then, the characteristic equation associated with the steady state  $(\bar{N}, \bar{E}_1, \bar{E}_2)$  of (11) is

$$(\lambda + k_1)(\lambda + k_2)(\lambda + a_1 - a_2e^{-\lambda\tau}) + b_2a_5(\lambda + k_1)e^{-\lambda T_2} \int_{-\tau}^0 e^{\lambda\theta} d\theta - b_1(\lambda + k_2)(a_3 - a_4e^{-\lambda\tau})e^{-\lambda T_1} = 0. \quad (19)$$

The steady state  $(\bar{N}, \bar{E}_1, \bar{E}_2)$  of (11) is locally asymptotically stable if all roots of (19) have negative real parts, and the stability can only be lost if pure imaginary roots appear. The steady state is unstable if roots with positive real parts exist.

The next section is devoted to the asymptotic stability analysis of the trivial steady state. Then, in Section 6, we focus on the stability of the positive steady state.

## 5 Asymptotic Stability of the Trivial Steady State

We concentrate ourselves on the local asymptotic stability of the trivial steady state  $(0, f_1(0)/k_1, f_2(0)/k_2)$  of system (11).

When  $\bar{N} = 0$ , then, from (17), we have  $a_3 = a_4 = a_5 = 0$ , whereas  $a_1, a_2 > 0$ . The characteristic equation associated with  $(0, f_1(0)/k_1, f_2(0)/k_2)$  is then, from (19),

$$(\lambda + k_1)(\lambda + k_2)(\lambda + a_1 - a_2e^{-\lambda\tau}) = 0,$$

with

$$a_1 = \delta + \beta \left( \frac{f_1(0)}{k_1} \right) \quad \text{and} \quad a_2 = 2\beta \left( \frac{f_1(0)}{k_1} \right) e^{-\gamma(f_2(0)/k_2)\tau}.$$

Eigenvalues of (16) are then  $\lambda = -k_1 < 0$ ,  $\lambda = -k_2 < 0$  and roots of

$$\lambda + a_1 - a_2e^{-\lambda\tau} = 0. \quad (20)$$

Using a well-known result by Hayes [16], whose proof can be found in [15], roots of (20) have negative real parts if and only if

$$a_1 > -1, \quad a_1 - a_2 > 0 \quad \text{and} \quad a_2 < \eta \sin \eta - a_1 \cos \eta, \quad (21)$$

where  $\eta$  is the unique solution of  $\eta = -a_1 \tan(\eta)$ ,  $0 < \eta < \pi$ . One can notice that the condition  $a_1 > -1$  in (21) is always satisfied since  $a_1 > 0$ . Moreover,

$$a_1 - a_2 = \delta - \left( 2e^{-\gamma(f_2(0)/k_2)\tau} - 1 \right) \beta \left( \frac{f_1(0)}{k_1} \right).$$

The following proposition deals with the asymptotic stability of the trivial steady state.

**Proposition 3.** *The trivial steady state  $(0, f_1(0)/k_1, f_2(0)/k_2)$  of system (11) is locally asymptotically stable if and only if (15) is not fulfilled, that is if it is the only steady state of (11).*

*Proof.* First, suppose that (15) holds true. Then  $a_1 - a_2 \leq 0$  and, from (21), the characteristic equation (20) has roots with nonnegative real parts.

Assume (15) does not hold true. Then  $a_1 - a_2 > 0$ . Let us check that the condition  $a_2 < \eta \sin \eta - a_1 \cos \eta$  is fulfilled.

Suppose, by contradiction, that  $a_2 \geq \eta \sin \eta - a_1 \cos \eta$ . Then, from the definition of  $\eta$ , we get

$$a_2 \geq -a_1 \frac{1}{\cos \eta}.$$

Since  $a_1 > a_2$  and  $a_1 > 0$ , we deduce

$$1 > -\frac{1}{\cos \eta}.$$

This yields that  $\cos(\eta) > 0$ , and consequently  $\eta \in (0, \pi/2)$ . It follows that  $\tan(\eta) > 0$  and

$$\eta > 0 > -a_1 \tan(\eta).$$

This contradicts the definition of  $\eta$ , so we conclude that  $a_2 < \eta \sin \eta - a_1 \cos \eta$ . This ends the proof.  $\square$

The next section is devoted to the asymptotic stability of the positive steady state of system (11).

## 6 Asymptotic Stability of the Positive Steady State and Hopf Bifurcation

We assume, throughout this section, that condition (15) holds, to ensure the existence of the positive steady state  $(N^*, E_1^*, E_2^*)$  of system (11). From Proposition 3, the only other steady state of (11) is then unstable.

The study of the local asymptotic stability of the positive steady state  $(N^*, E_1^*, E_2^*)$  necessitates to determine the sign of real parts of roots of (19). However, (19) is a third degree exponential polynomial function, with an integral term and three different delays, so the study reveals hard to achieve, except on particular cases.

We are going to use an analytical approach, that consists in fixing one delay to zero (say,  $\tau = 0$ ), and determine the stability with respect to other delays. Then, continuity arguments allow to conclude to the stability when the first delay is nonnegative, yet rather small. This method has been used, for example, by Adimy et al [8], Adimy and Crauste [3], and Wei and Ruan [25].

From now on, let us fix  $\tau = 0$ . Then, from (14), values  $N^*$  and  $E_1^*$  are given by

$$\beta(E_1^*) = \delta \quad \text{and} \quad f_1(N^*) = k_1 E_1^*. \quad (22)$$

The characteristic equation (19) becomes

$$(\lambda + k_2) \left[ (\lambda + k_1)(\lambda + a_1 - a_2) - b_1(a_3 - a_4)e^{-\lambda T_1} \right] = 0.$$

From (17) and (22),

$$a_1 - a_2 = \delta - \beta(E_1^*) = 0 \quad \text{and} \quad a_3 - a_4 = -N^* \beta'(E_1^*).$$

Therefore, the characteristic equation reduces to

$$(\lambda + k_2) \left[ \lambda(\lambda + k_1) + A e^{-\lambda T_1} \right] = 0,$$

where

$$A := -N^* \beta'(E_1^*) f_1'(N^*) > 0. \quad (23)$$

Characteristic roots are then either  $\lambda = -k_2 < 0$  or roots of

$$\lambda(\lambda + k_1) + A e^{-\lambda T_1} = 0. \quad (24)$$

The next proposition states and proves the asymptotic stability of  $(N^*, E_1^*, E_2^*)$  when  $\tau = 0$  and  $T_1 = 0$ .

**Proposition 4.** *Assume  $\tau = 0$  and  $T_1 = 0$ . Then the positive steady state  $(N^*, E_1^*, E_2^*)$  of system (11) is locally asymptotically stable for all  $T_2 \geq 0$ .*

*Proof.* When  $T_1 = 0$ , equation (24) becomes  $\lambda^2 + k_1 \lambda + A = 0$ , and since  $k_1 > 0$  and  $A > 0$  all roots have negative real parts. The conclusion follows.  $\square$

Assume now  $T_1 > 0$ . Since the positive steady state is locally asymptotically stable when  $T_1 = 0$  then it can only become unstable for  $T_1 > 0$  if characteristic roots cross on the imaginary axis. Hence, we look for purely imaginary roots  $\lambda = \pm i\omega$ ,  $\omega \in \mathbb{R}$ , of (24). Separating real and imaginary parts in (24), with  $\lambda = i\omega$ , we obtain

$$A \cos(\omega T_1) = \omega^2 \quad \text{and} \quad A \sin(\omega T_1) = k_1 \omega. \quad (25)$$

One can observe that if  $\omega$  is solution of (25) then so is  $-\omega$ , and  $\omega \neq 0$  since  $A > 0$ . Consequently, we only look for solutions  $\omega > 0$ . Adding the squares of both sides of equations in (25), we deduce that necessarily  $\omega$  satisfies

$$\omega^4 + k_1^2 \omega^2 - A^2 = 0.$$

It follows that

$$\omega^2 = \frac{-k_1^2 + \sqrt{k_1^4 + 4A^2}}{2}.$$

Let

$$\omega^c = \sqrt{\frac{-k_1^2 + \sqrt{k_1^4 + 4A^2}}{2}} \quad \text{and} \quad T_1^c := \frac{\arccos\left(\frac{(\omega^c)^2}{A}\right)}{\omega^c}. \quad (26)$$

Then equation (24) has a pair of purely imaginary roots if and only if  $T_1 = T_1^c$ , given by  $\pm i\omega^c$ .

The following theorem states the existence of a Hopf bifurcation that destabilizes the positive steady state of (11).

**Theorem 1.** *Assume (15) holds true, and  $\tau = 0$ . Then there exists  $T_1^c > 0$  such that the positive steady state  $(N^*, E_1^*, E_2^*)$  of system (11) is locally asymptotically stable for all  $T_2 \geq 0$  when  $0 \leq T_1 < T_1^c$ , and unstable for  $T_1 \geq T_1^c$ . Moreover, a Hopf bifurcation occurs at  $(N^*, E_1^*, E_2^*)$  when  $T_1 = T_1^c$ , and periodic solutions appear, with periods close to  $2\pi/\omega^c$ , where  $\omega^c$  is given by (26).*

*Proof.* We proved, before stating Theorem 1, that equation (24) has purely imaginary roots only when  $T_1 = T_1^c$ . Moreover, these purely imaginary roots,  $\pm i\omega^c$ , with  $\omega^c$  defined by (26), are simple. Indeed, let

$$\Delta(\lambda, T_1) := \lambda(\lambda + k_1) + Ae^{-\lambda T_1}.$$

Let  $\lambda(T_1)$  be a branch of characteristic roots such that  $\lambda(T_1^c) = i\omega^c$ . Then, from (24),  $\Delta(\lambda(T_1), T_1) = 0$ , and

$$\frac{\partial \Delta}{\partial \lambda}(\lambda(T_1), T_1) \frac{d\lambda}{dT_1} + \frac{\partial \Delta}{\partial T_1}(\lambda(T_1), T_1) = 0,$$

that is

$$\left[ 2\lambda(T_1) + k_1 - AT_1 e^{-\lambda(T_1)T_1} \right] \frac{d\lambda}{dT_1} - A\lambda(T_1) e^{-\lambda(T_1)T_1} = 0. \quad (27)$$

By contradiction, assume  $i\omega^c$  is not a simple root of (24). Then, from (27),

$$iA\omega^c e^{-i\omega^c T_1^c} = 0.$$

Since  $A > 0$  and  $\omega^c > 0$ , we obtain a contradiction. Therefore  $\pm i\omega^c$  are simple characteristic roots.

Moreover, from (27),

$$\left( \frac{d\lambda}{dT_1} \right)^{-1} = \frac{[2\lambda(T_1) + k_1]e^{\lambda(T_1)T_1} - AT_1}{A\lambda(T_1)}.$$

Using (24), one deduces that

$$\left( \frac{d\lambda}{dT_1} \right)^{-1} = -\frac{2\lambda(T_1) + k_1}{\lambda(T_1)^2(\lambda(T_1) + k_1)} - \frac{T_1}{\lambda(T_1)}.$$

Hence,

$$\operatorname{Re} \left( \frac{d\lambda}{dT_1} \right)_{T_1=T_1^c}^{-1} = \operatorname{Re} \left( \frac{2i\omega^c + k_1}{(\omega^c)^2(i\omega^c + k_1)} \right) = \frac{2(\omega^c)^2 + k_1^2}{(\omega^c)^2[(\omega^c)^2 + k_1^2]} > 0.$$

It follows that

$$\frac{d\operatorname{Re}(\lambda)}{dT_1}(T_1 = T_1^c) > 0. \quad (28)$$

Consequently,  $\operatorname{Re}(\lambda(T_1)) < 0$  for  $T_1 < T_1^c$ , and the stability of the positive steady state follows, and  $\operatorname{Re}(\lambda(T_1)) > 0$  for  $T_1 > T_1^c$ , so we conclude to the instability in this case. Since  $\pm i\omega^c$  are simple characteristic roots satisfying (28), we also conclude to the existence of the Hopf bifurcation when  $T_1 = T_1^c$ . This ends the proof.  $\square$

We now return to the case  $\tau \neq 0$ . The next lemma, whose proof is similar to the one in Adimy et al [8] and then is not given here, deals with the sign of the real parts of characteristic roots of (19). It will allow to conclude to the stability of the positive steady state in Theorem 2.

**Lemma 1.** *If all roots of equation (19) have negative real parts for given  $T_1 > 0$  and  $T_2 \geq 0$ , then there exists  $\bar{\tau}(T_1, T_2) > 0$  such that all roots of equation (19) have negative real parts when  $\tau < \bar{\tau}(T_1, T_2)$ .*

Using Theorem 1 and Lemma 1, we state the next theorem dealing with the asymptotic stability of the steady state  $(N^*, E_1^*, E_2^*)$  of (11) when time delays  $\tau$ ,  $T_1$  and  $T_2$  are nonzero.

**Theorem 2.** *Assume that condition (15) holds true, and  $T_1 < T_1^c$ , defined in (26). Then, for all  $T_2 \geq 0$  there exists  $\bar{\tau} = \bar{\tau}(T_1, T_2) > 0$  such that the positive steady state  $(N^*, E_1^*, E_2^*)$  of system (11) is locally asymptotically stable for  $0 \leq \tau < \bar{\tau}$ .*

This theorem establishes the asymptotic stability of  $(N^*, E_1^*, E_2^*)$  for small values of the time delay  $\tau$ . However, one may expect a destabilization of the steady state when  $\tau$ , or  $T_1$ , pass through a threshold value (as demonstrated in Theorem 1 when  $\tau = 0$ ), or even several stability switch. Yet, it appears almost impossible, at this time, to analytically determine such a stability switch. The complexity introduced in the model by two feedbacks and three different delays prevents such an analysis. A numerical tool shows then its importance to obtain an insight in the asymptotic behavior of the steady state.

Using the MATLAB solver dde23 [22], one can numerically solve system (11). Let us take

$$\beta(E_1) = \frac{\beta_0 E_1}{1 + E_1}, \quad \gamma(E_2) = \frac{\gamma_0}{1 + E_2^3} \quad \text{and} \quad f_1(N) = f_2(N) = \frac{a}{1 + N^q},$$

where  $\beta_0$  is the maximum rate of introduction,  $\gamma_0$  is the maximum apoptosis rate, and functions  $f_1$  and  $f_2$  are usual functions, obtained from [3, 10, 19]. We suppose that  $k_1 = k_2 = 2.5 \text{ d}^{-1}$ , and we investigate the roles of time delays  $T_1$  and  $T_2$  in the stability of system (11), when  $\tau$  is fixed. We consider  $\tau = 0.5$  day, which is a short but still reasonable duration for HSC cell cycle duration.

According to [3, 7, 8, 18], we choose

$$\delta = 0.05 \text{ d}^{-1}, \beta_0 = 1 \text{ d}^{-1}, \gamma_0 = 0.2 \text{ d}^{-1}, a = 10 \text{ mol.d}^{-1}, q = 7.$$

Figure 1 presents the stability diagram with respect to  $T_1$  and  $T_2$ . It appears clearly that  $T_2$  has almost no effect on the destabilization of the system, whereas  $T_1$  actively plays a role in its destabilization. This indicates that modifications in the feedback loop controlling the proliferative capacity of HSC are more likely to be responsible for a destabilization of the entire system, that is often associated with pathological situations, such as leukemias [7, 20] or anemias [18].

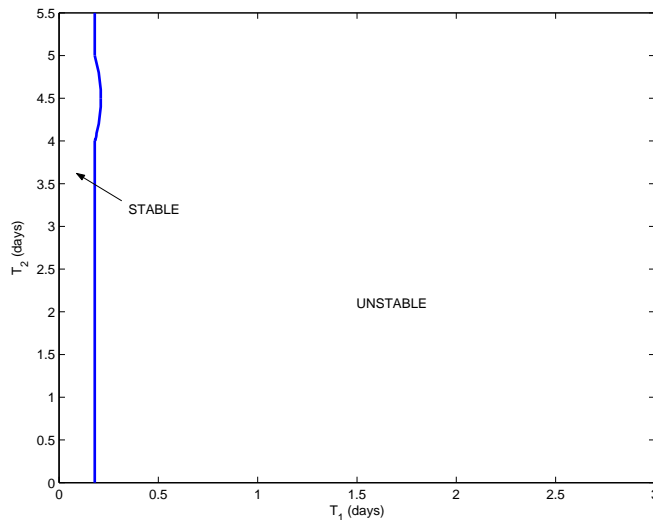


Figure 1: Stability Diagram. The positive steady state  $(N^*, E_1^*, E_2^*)$  of system (11) is stable for small values of  $T_1$  ( $T_1 < 0.18$  days), and the value of  $T_2$  plays almost no role in its stability.

Yet, one may notice that this stability diagram holds when the controls by HSC of growth factor concentrations are assumed to be similar ( $f_1 = f_2$ ), and in the absence of a deregulation of cell cycle durations ( $\tau$  is fixed). The works in [7, 20], for example, indicate clearly that a destabilization of cell cycle durations can lead to pathological situations. This is not investigated in this work, but could lead to stability switch [3, 7].

One may observe, in Figure 2, that destabilization of system (11) can result in long period oscillations, when compared to time delays, of both the HSC population and growth factor concentrations. This has been previously observed in mathematical models of HSC dynamics, but usually due to a destabilization of cell cycle durations [7, 8, 20]. Here, this is due to a destabilization of the feedback loop controlling the proliferative capacity of HSC.

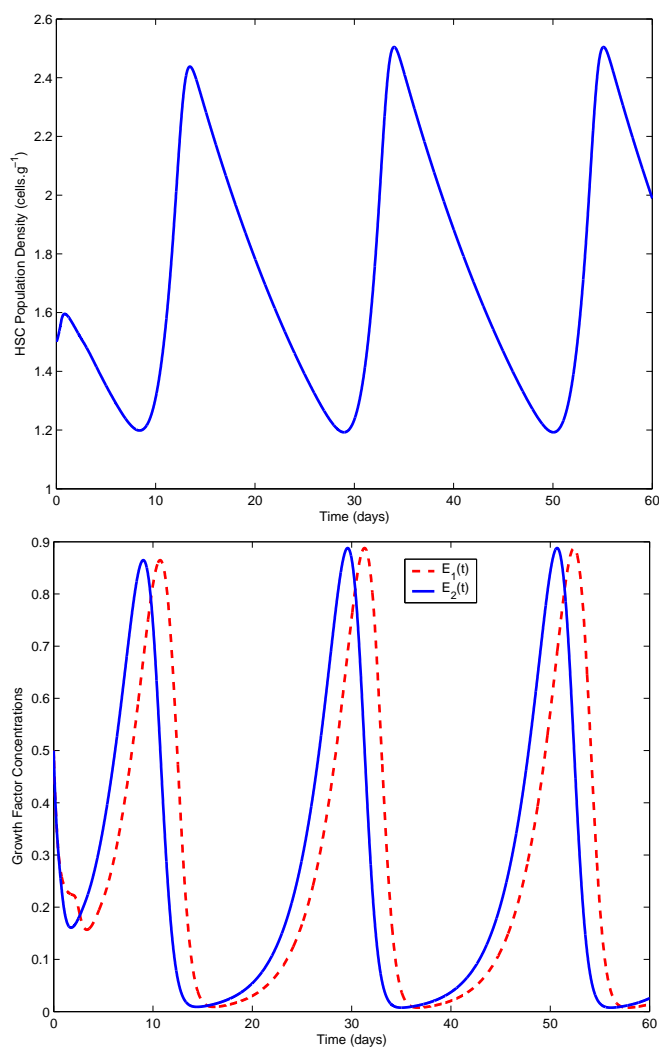


Figure 2: Long Period Oscillations. The HSC population density  $N(t)$  (top) and growth factor concentrations  $E_1(t)$  and  $E_2(t)$  (bottom), solutions of (11), are simulated for  $T_1 = 2$  days and  $T_2 = 0.4$  days, with  $\tau = 0.5$  day. Periods of the oscillations are in the order of 20 days.

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