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# On the stability of a nonlinear maturity structured model of cellular proliferation\*

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## Abstract

We analyse the asymptotic behaviour of a nonlinear mathematical model of cellular proliferation which describes the production of blood cells in the bone marrow. This model takes the form of a system of two maturity structured partial differential equations, with a retardation of the maturation variable and a time delay depending on this maturity. We show that the stability of this system depends strongly on the behaviour of the immature cells population. We obtain conditions for the global stability and the instability of the trivial solution.

*Keywords:* Nonlinear partial differential equation, Maturity structured model, Blood production system, Delay depending on the maturity, Global stability, Instability.

## 1 Introduction and motivation

This paper is devoted to the analysis of a maturity structured model which involves descriptions of process of blood production in the bone marrow (hematopoiesis). Cell biologists recognize two main stages in the process of hematopoietic cells: a resting stage and a proliferating stage (see Burns and Tannock [8]).

The resting phase, or  $G_0$ -phase, is a quiescent stage in the cellular development. Resting cells mature but they can not divide. They can enter the proliferating phase, provided that they do not die. The proliferating phase is the active part of the cellular development. As soon as cells enter the proliferating phase, they are committed to divide, during mitosis. After division, each cell gives birth to two daughter cells which enter immediatly the resting phase, and complete the cycle. Proliferating cells can also die without ending the cycle.

The model considered in this paper has been previously studied by Mackey and Rudnicki in 1994 [20] and in 1999 [21], in the particular case when the proliferating phase duration is constant. That is, when

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it is supposed that all cells divide exactly at the same age. Numerically, Mackey and Rey [18, 19], in 1995, and Crabb *et al.* [9, 10], in 1996, obtained similar results as in [20]. The model in [20] has also been studied by Dyson *et al.* [11] in 1996 and Adimy and Pujo-Menjouet [3, 4] in 2001 and 2003, but only in the above-mentioned case. These authors showed that the uniqueness of the entire population depends, for a finite time, only on the population of small maturity cells.

However, it is believed that, in the most general situation in hematopoiesis, all cells do not divide at the same age (see Bradford *et al.* [7]). For example, pluripotent stem cells (the less mature cells) divide faster than committed stem cells (the more mature cells).

Mackey and Rey [17], in 1993, considered a model in which the time required for a cell to divide is not identical between cells, and, in fact, is distributed according to a density. However, the authors made only a numerical analysis of their model. Dyson *et al.* [12, 13], in 2000, also considered an equation in which all cells do not divide at the same age. But they considered only one phase (the proliferating one) which does not take into account the intermediary flux between the two phases. Adimy and Crauste [1], in 2003, studied a model in which the proliferating phase duration is distributed according to a density with compact support. The authors proved local and global stability results.

In [2], Adimy and Crauste developed a mathematical model of hematopoietic cells population in which the time spent by each cell in the proliferating phase, before mitosis, depends on its maturity at the point of commitment. More exactly, a cell entering the proliferating phase with a maturity  $m$  is supposed to divide a time  $\tau = \tau(m)$  later. This hypothesis can be found, for example, in Mitchison [22] (1971) and John [15] (1981), and, to our knowledge, it has never been used, except by Adimy and Pujo-Menjouet in [5], where the authors considered only a linear case. The model obtained in [2] is a system of nonlinear first order partial differential equations, with a time delay depending on the maturity and a retardation of the maturation variable. The basic theory of existence, uniqueness, positivity and local stability of this model was investigated.

Many cell biologists assert that the behaviour of immature cells population is an important consideration in the description of the behaviour of full cells population. The purpose of the present work is to analyse mathematically this phenomenon in our model. We show that, under the assumption that cells, in the proliferating phase, have enough time to divide, that is,  $\tau(m)$  is large enough, then the uniqueness of the entire population depends strongly, for a finite time, on the population with small maturity. This result allows us, for example, to describe the destruction of the cells population when the population of small maturity cells is affected (see Corollary 3.1).

In [21], Mackey and Rudnicki provided a criterion for global stability of their model. However, these authors considered only the case when the mortality rates and the rate of returning in the proliferating cycle are independent of the maturity variable. Thus, their criterion can not be applied directly to our situation.

This paper extends some local analysis of Adimy and Crauste [2] to global results. It proves the connection between the global behaviour of our model and the behaviour of immature cells ( $m = 0$ ).

The paper is organised as follows. In the next section, we present the equations of our model and we give an integrated formulation of the problem, by using the semigroup theory. In section 3, we show an uniqueness result which stresses the dependence of the entire population with small maturity cells population. In Section 4, we focus on the behaviour of the immature cells population, which satisfies a system of delay differential equations. We study the stability of this system by using a Lyapunov functional. In Section 5, we prove that the global stability of our model depends on its local stability and on the stability of the immature cells population. Finally, in Section 6, we give an instability result.

## 2 Equations of the model and integrated formulation

Let  $N(t, m)$  and  $P(t, m)$  denote, respectively, the population densities of resting and proliferating cells, at time  $t$  and with a maturity level  $m$ .

The maturity is a continuous variable which represents what composes a cell, such as proteins or other elements one can measure experimentally. It is supposed to range, in the two phases, from  $m = 0$  to  $m = 1$ . Cells with maturity  $m = 0$  are the most primitive stem cells, also called immature cells, whereas cells with maturity  $m = 1$  are ready to enter the bloodstream, they have reached the end of their development.

In the two phases, cells mature with a velocity  $V(m)$ , which is assumed to be continuously differentiable on  $[0, 1]$ , positive on  $(0, 1]$  and such that  $V(0) = 0$  and

$$\int_0^m \frac{ds}{V(s)} = +\infty, \quad \text{for } m \in (0, 1]. \quad (1)$$

Since  $\int_{m_1}^{m_2} \frac{ds}{V(s)}$ , with  $m_1 < m_2$ , is the time required for a cell with maturity  $m_1$  to reach the maturity  $m_2$ , then Condition (1) means that a cell with very small maturity needs a long time to become mature. For example, Condition (1) is satisfied if

$$V(m) \underset{m \rightarrow 0}{\sim} \alpha m^p, \quad \text{with } \alpha > 0 \text{ and } p \geq 1.$$

In the resting phase, cells can die at a rate  $\delta = \delta(m)$  and can also be introduced in the proliferating phase with a rate  $\beta$ . In the proliferating phase, cells can also die, by apoptosis (a programmed cell death), at a rate  $\gamma = \gamma(m)$ . The functions  $\delta$  and  $\gamma$  are supposed to be continuous and nonnegative on  $[0, 1]$ . The rate  $\beta$  of re-entry in the proliferating phase is supposed to depend on cells maturity and on the resting population density (see Sachs [23]), that is,  $\beta = \beta(m, N(t, m))$ . The mapping  $\beta$  is supposed to be continuous and positive.

Proliferating cells are committed to undergo mitosis a time  $\tau$  after their entrance in this phase. We assume that  $\tau$  depends on the maturity of the cell when it enters the proliferating phase, that means, if a cell enters the proliferating phase with a maturity  $m$ , then it will divide a time  $\tau = \tau(m)$  later. The function  $\tau$  is supposed to be positive, continuous on  $[0, 1]$ , continuously differentiable on  $(0, 1]$  and such that

$$\tau'(m) + \frac{1}{V(m)} > 0, \quad \text{for } m \in (0, 1]. \quad (2)$$

One can notice that this condition is always satisfied in a neighborhood of the origin, because  $V(0) = 0$ , and is satisfied if we assume, for example, that  $\tau$  is increasing (which describes the fact that the less mature cells divide faster than more mature cells).

Under Condition (2), if  $m \in (0, 1]$  is given, then the mapping

$$\tilde{m} \mapsto \int_{\tilde{m}}^m \frac{ds}{V(s)} - \tau(\tilde{m})$$

is continuous and strictly decreasing from  $(0, m]$  into  $[-\tau(m), +\infty)$ . Hence, we can define a function  $\Theta : (0, 1] \rightarrow (0, 1]$ , by

$$\int_{\Theta(m)}^m \frac{ds}{V(s)} = \tau(\Theta(m)), \quad \text{for } m \in (0, 1].$$

The quantity  $\Theta(m)$  represents the maturity of a cell at the point of commitment when this cell divides at a maturity level  $m$ . The function  $\Theta$  is continuously differentiable and strictly increasing on  $(0, 1]$  and satisfies

$$\lim_{m \rightarrow 0} \Theta(m) = 0 \quad \text{and} \quad 0 < \Theta(m) < m, \quad \text{for } m \in (0, 1].$$

If we consider the characteristic curves  $\chi : (-\infty, 0] \times [0, 1] \rightarrow [0, 1]$ , solutions of the ordinary differential equation

$$\begin{cases} \frac{d\chi}{ds}(s, m) = V(\chi(s, m)), & s \leq 0 \text{ and } m \in [0, 1], \\ \chi(0, m) = m, \end{cases}$$

then, it is easy to check that, for  $m \in [0, 1]$ ,  $\Theta(m)$  is the unique solution of the equation

$$x = \chi(-\tau(x), m). \quad (3)$$

The characteristic curves  $\chi(s, m)$  represent the evolution of the cell maturity to reach a maturity  $m$  at time 0 from a time  $s \leq 0$ . They satisfy  $\chi(s, 0) = 0$  and  $\chi(s, m) \in (0, 1]$  for  $s \leq 0$  and  $m \in (0, 1]$ . Moreover, we can verify that the characteristic curves are given by

$$\chi(s, m) = h^{-1}(h(m)e^s), \quad \text{for } s \leq 0 \text{ and } m \in [0, 1], \quad (4)$$

where the continuous function  $h : [0, 1] \rightarrow [0, 1]$  is defined by

$$h(m) = \begin{cases} \exp\left(-\int_m^1 \frac{ds}{V(s)}\right), & \text{for } m \in (0, 1], \\ 0, & \text{for } m = 0. \end{cases}$$

Since  $h$  is increasing, the two functions  $s \mapsto \chi(s, m)$  and  $m \mapsto \chi(s, m)$  are also increasing.

At the end of the proliferating phase, a cell with a maturity  $m$  divides into two daughter cells with maturity  $g(m)$ . We assume that  $g : [0, 1] \rightarrow [0, 1]$  is a continuous and strictly increasing function, continuously differentiable on  $[0, 1)$  and such that  $g(m) \leq m$  for  $m \in [0, 1]$ . We also assume, for technical reason and without loss of generality, that

$$\lim_{m \rightarrow 1} g'(m) = +\infty.$$

Then we can set

$$g^{-1}(m) = 1, \quad \text{for } m > g(1).$$

This means that the function  $g^{-1} : [0, 1] \rightarrow [0, 1]$  is continuously differentiable and satisfies  $(g^{-1})'(m) = 0$ , for  $m > g(1)$ . We set

$$\Delta(m) = \Theta(g^{-1}(m)), \quad \text{for } m \in [0, 1].$$

The quantity  $\Delta(m)$  is the maturity of a mother cell at the point of commitment, when the daughter cells have a maturity  $m$  at birth. The function  $\Delta : [0, 1] \rightarrow [0, 1]$  is continuous and continuously differentiable on  $(0, 1]$ . It satisfies  $\Delta(0) = 0$ ,  $\Delta$  is strictly increasing on  $(0, g(1))$ , with  $\Theta(m) \leq \Delta(m)$ , and  $\Delta(m) = \Theta(1)$  for  $m \in [g(1), 1]$ .

At time  $t = 0$ , the resting and proliferating populations are given by

$$N(0, m) = \bar{\mu}(m), \quad (5)$$

and

$$P(0, m) = \bar{\Gamma}(m) := \int_0^{\tau(\Theta(m))} \Gamma(m, a) da, \quad (6)$$

where  $\Gamma(m, a)$  is the density of cells with maturity  $m$ , at time  $t = 0$ , which have spent a time  $a$  in the proliferating phase, or, equivalently, with age  $a$ . The functions  $\bar{\mu}$  and  $\bar{\Gamma}$  are supposed to be continuous on their domains.

We define the sets

$$\Omega := [0, 1] \times [0, \tau_{max}],$$

where  $\tau_{max} := \max_{m \in [0, 1]} \tau(m) > 0$ ,

$$\Omega_{\Delta} := \left\{ (m, t) \in \Omega ; 0 \leq t \leq \tau(\Delta(m)) \right\},$$

and

$$\Omega_{\Theta} := \left\{ (m, t) \in \Omega ; 0 \leq t \leq \tau(\Theta(m)) \right\}.$$

Then, the population densities  $N(t, m)$  and  $P(t, m)$  satisfy, for  $m \in [0, 1]$  and  $t \geq 0$ , the following equations,

$$\begin{aligned} \frac{\partial}{\partial t} N(t, m) + \frac{\partial}{\partial m} (V(m)N(t, m)) &= -\left(\delta(m) + \beta(m, N(t, m))\right)N(t, m) \\ + \begin{cases} 2\xi(t, m)\Gamma\left(\chi(-t, g^{-1}(m)), \tau(\Delta(m)) - t\right), & \text{if } (m, t) \in \Omega_{\Delta}, \\ 2\xi(\tau(\Delta(m)), m)\beta\left(\Delta(m), N(t - \tau(\Delta(m)), \Delta(m))\right) \times \\ N(t - \tau(\Delta(m)), \Delta(m)), & \text{if } (m, t) \notin \Omega_{\Delta}, \end{cases} \end{aligned} \quad (7)$$

and

$$\begin{aligned} \frac{\partial}{\partial t} P(t, m) + \frac{\partial}{\partial m} (V(m)P(t, m)) &= -\gamma(m)P(t, m) + \beta(m, N(t, m))N(t, m) \\ - \begin{cases} \pi(t, m)\Gamma\left(\chi(-t, m), \tau(\Theta(m)) - t\right), & \text{if } (m, t) \in \Omega_{\Theta}, \\ \pi(\tau(\Theta(m)), m)\beta\left(\Theta(m), N(t - \tau(\Theta(m)), \Theta(m))\right) \times \\ N(t - \tau(\Theta(m)), \Theta(m)), & \text{if } (m, t) \notin \Omega_{\Theta}, \end{cases} \end{aligned} \quad (8)$$

where the mappings  $\xi : \Omega_{\Delta} \rightarrow [0, +\infty)$  and  $\pi : \Omega_{\Theta} \rightarrow [0, +\infty)$  are continuous and satisfy

$$\xi(\cdot, m) = 0 \quad \text{if } m > g(1),$$

because, from the definition of  $g$ , a daughter cell can not have a maturity greater than  $g(1)$ .

In Equation (7), the first term in the right hand side accounts for cellular loss, through cells death ( $\delta$ ) and introduction in the proliferating phase ( $\beta$ ). The second term describes the contribution of proliferating cells, one generation time ago. In a first time, cells can only proceed from cells initially in the proliferating phase ( $\Gamma$ ). Then, after one generation time, all cells have divided and the contribution can only comes from resting cells which have been introduced in the proliferating phase one generation time ago.

The factor 2 always accounts for mitosis. The quantity  $\xi(t, m)$  is for the rate of surviving cells.

In Equation (8), the first term in the right hand side also accounts for cellular loss, whereas the second term is for the contribution of the resting phase. The third term describes the same situation as in Equation (7), however, in this case, cells leave the proliferating phase to the resting one. The quantity  $\pi(t, m)$  is also for the rate of surviving cells.

We can observe two different behaviours of the rates of surviving cells, in the two phases. In a first time, they depend on time and maturity, and after a certain time, they only depend on the maturity variable. When the process of production of blood cells has just begun, the only cells which divide come from the initial proliferating phase population. But after one cellular cycle, that means when  $t > \tau(\Delta(m))$  (respectively,  $t > \tau(\Theta(m))$ ), the amount of cells only comes from resting cells (respectively, proliferating cells) which have been introduced in the proliferating phase (respectively, resting phase) one generation time ago. Consequently, we take into account the duration of the cell cycle, and not the present time.

Equations (7) and (8) are derived, after integration, from an age-maturity structured model, presented by the authors in [2]. In fact, the rates  $\xi$  and  $\pi$  are explicitly given (see [2]) by

$$\xi(t, m) = (g^{-1})'(m) \exp \left\{ - \int_0^t \left( \gamma(\chi(-s, g^{-1}(m))) + V'(\chi(-s, g^{-1}(m))) \right) ds \right\},$$

and

$$\pi(t, m) = \alpha(m) \exp \left\{ - \int_0^t \left( \gamma(\chi(-s, m)) + V'(\chi(-s, m)) \right) ds \right\},$$

with  $\alpha : [0, 1] \rightarrow [0, +\infty)$  a positive and continuous function, such that  $\alpha(0) = 1$ .

In the following, to simplify the notations, we will denote by  $\bar{\xi}$  and  $\bar{\pi}$  the quantities

$$\bar{\xi}(m) = \xi(\tau(\Delta(m)), m),$$

and

$$\bar{\pi}(m) = \pi(\tau(\Theta(m)), m).$$

One can remark that the solutions of Equation (7) do not depend on the solutions of Equation (8), whereas the converse is not true.

Before we study the asymptotic behaviour of the solutions of Problem (5)-(8), we establish an integrated formulation of this problem. We first extend  $N$  by setting

$$N(t, m) = \bar{\mu}(m), \quad \text{for } t \in [-\tau_{max}, 0] \text{ and } m \in [0, 1]. \quad (9)$$

One can remark that this extension does not influence the system.

We also define two mappings,  $F : [0, +\infty) \times [0, 1] \times \mathbb{R} \rightarrow \mathbb{R}$  and  $G : [0, +\infty) \times [0, 1] \times \mathbb{R} \rightarrow \mathbb{R}$ , by

$$F(t, m, x) = \begin{cases} 2\xi(t, m)\Gamma(\chi(-t, g^{-1}(m)), \tau(\Delta(m)) - t), & \text{if } (m, t) \in \Omega_\Delta, \\ 2\bar{\xi}(m)\beta(\Delta(m), x)x, & \text{if } (m, t) \notin \Omega_\Delta, \end{cases} \quad (10)$$

and

$$G(t, m, x) = \begin{cases} \pi(t, m)\Gamma(\chi(-t, m), \tau(\Theta(m)) - t), & \text{if } (m, t) \in \Omega_\Theta, \\ \bar{\pi}(m)\beta(\Theta(m), x)x, & \text{if } (m, t) \notin \Omega_\Theta. \end{cases} \quad (11)$$

We denote by  $C[0, 1]$  the space of continuous functions on  $[0, 1]$ , endowed with the supremum norm  $\|\cdot\|$ , defined by

$$\|v\| = \sup_{m \in [0, 1]} |v(m)|, \quad \text{for } v \in C[0, 1],$$

and we consider the unbounded closed linear operator  $A : D(A) \subset C[0, 1] \rightarrow C[0, 1]$  defined by

$$D(A) = \left\{ u \in C[0, 1] ; u \text{ differentiable on } (0, 1], u' \in C(0, 1], \lim_{x \rightarrow 0} V(x)u'(x) = 0 \right\}$$

and

$$Au(x) = \begin{cases} -(\delta(x) + V'(x))u(x) - V(x)u'(x), & \text{if } x \in (0, 1], \\ -(\delta(0) + V'(0))u(0), & \text{if } x = 0. \end{cases}$$

**Proposition 2.1.** *The operator  $A$  is the infinitesimal generator of the strongly continuous semigroup  $(T(t))_{t \geq 0}$  defined on  $C[0, 1]$  by*

$$(T(t)\psi)(x) = K(t, x)\psi(\chi(-t, x)), \quad \text{for } \psi \in C[0, 1], t \geq 0 \text{ and } x \in [0, 1],$$

where

$$K(t, x) = \exp \left\{ - \int_0^t \left( \delta(\chi(-s, x)) + V'(\chi(-s, x)) \right) ds \right\}.$$

*Proof.* The proof is similar to the proof of Proposition 2.4 in Dyson *et al.* [11]. □

Now, by using the variation of constants formula associated to the  $C_0$ -semigroup  $(T(t))_{t \geq 0}$ , we can write an integrated formulation of Problem (5)-(8).

Let  $C(\Omega)$  be the space of continuous functions on  $\Omega$ , endowed with the norm

$$\|\Upsilon\|_{\Omega} := \sup_{(m,a) \in \Omega} |\Upsilon(m,a)|, \quad \text{for } \Upsilon \in C(\Omega).$$

Let  $\bar{\mu} \in C[0,1]$  and  $\Gamma \in C(\Omega)$ . An *integrated solution* of Problem (5)-(8) is a continuous solution of the system

$$\begin{aligned} N(t,m) &= K(t,m)\bar{\mu}(\chi(-t,m)) \\ &- \int_0^t K(t-s,m)\beta\left(\chi(-(t-s),m), N(s,\chi(-(t-s),m))\right)N(s,\chi(-(t-s),m))ds \\ &+ \int_0^t K(t-s,m)F\left(s,\chi(-(t-s),m), N(s-\tau(\Delta(\chi(-(t-s),m))), \Delta(\chi(-(t-s),m)))\right)ds, \end{aligned} \quad (12)$$

and

$$\begin{aligned} P(t,m) &= H(t,m)\bar{\Gamma}(\chi(-t,m)) \\ &+ \int_0^t H(t-s,m)\beta\left(\chi(-(t-s),m), N(s,\chi(-(t-s),m))\right)N(s,\chi(-(t-s),m))ds \\ &- \int_0^t H(t-s,m)G\left(s,\chi(-(t-s),m), N(s-\tau(\Theta(\chi(-(t-s),m))), \Theta(\chi(-(t-s),m)))\right)ds, \end{aligned} \quad (13)$$

for  $t \geq 0$  and  $m \in [0,1]$ , where  $F$  and  $G$  are given by (10) and (11),  $\bar{\Gamma}$  is given by (6) and

$$H(t,m) := \exp\left\{-\int_0^t \left(\gamma(\chi(-s,m)) + V'(\chi(-s,m))\right)ds\right\}, \quad \text{for } t \geq 0 \text{ and } m \in [0,1].$$

We can easily prove (see [2]), under the assumptions that the function  $x \mapsto \beta(m,x)$  is uniformly bounded and the function  $x \mapsto x\beta(m,x)$  is locally Lipschitz continuous for all  $m \in [0,1]$ , that Problem (12)-(13) has a unique continuous global solution  $(N^{\bar{\mu},\Gamma}, P^{\bar{\mu},\Gamma})$ , for initial conditions  $(\bar{\mu}, \Gamma) \in C[0,1] \times C(\Omega)$ .

### 3 A uniqueness result

In this section, we establish more than uniqueness. Indeed, we show a result which stresses, for a finite time, the dependence of the entire population with the small maturity cells population. It has been shown for the first time by Dyson *et al.* [11], for a model with a constant delay. We will see that this result is important in order to obtain the asymptotic behaviour of the solutions of (12)-(13).

We first assume that

$$\Delta(m) < m, \quad \text{for all } m \in (0,1]. \quad (14)$$

This condition is equivalent to

$$\tau(\Delta(m)) > \int_m^{g^{-1}(m)} \frac{ds}{V(s)}, \quad \text{for } m \in (0,1]. \quad (15)$$

This equivalence is immediate when one notices that, from (3),

$$\Delta(m) = \chi(-\tau(\Delta(m)), g^{-1}(m)) = h^{-1}(h(g^{-1}(m))e^{-\tau(\Delta(m))}).$$



Since the quantity  $\int_m^{g^{-1}(m)} \frac{ds}{V(s)}$  represents the time required for a cell with maturity  $m$ , at birth, to reach the maturity of its mother at the cytokinesis point (the point of division), Condition (15) means that, in the proliferating phase, cells have enough time to reach the maturity of their mother. Condition (14) implies in particular that

$$\Theta(1) := \Delta(g(1)) < g(1).$$

From now on, and throughout this section, we assume that the function  $x \mapsto \beta(m, x)$  is uniformly bounded, the function  $x \mapsto x\beta(m, x)$  is locally Lipschitz continuous for all  $m \in [0, 1]$ , and that Condition (14) holds. For  $b \in (0, 1]$  and  $\psi \in C[0, 1]$ , we define  $\|\cdot\|_b$  as follows

$$\|\psi\|_b := \sup_{m \in [0, b]} |\psi(m)|.$$

We first show the following proposition.

**Proposition 3.1.** *Let  $\bar{\mu}_1, \bar{\mu}_2 \in C[0, 1]$  and  $\Gamma_1, \Gamma_2 \in C(\Omega)$ . If there exists  $0 < b < 1$  such that*

$$\bar{\mu}_1(m) = \bar{\mu}_2(m) \quad \text{and} \quad \Gamma_1(m, a) = \Gamma_2(m, a), \quad (16)$$

for  $m \in [0, b]$  and  $a \in [0, \tau_{max}]$ , then,

$$N^{\bar{\mu}_1, \Gamma_1}(t, m) = N^{\bar{\mu}_2, \Gamma_2}(t, m), \quad \text{for } t \geq 0 \text{ and } m \in [0, g(b)]. \quad (17)$$

*Proof.* We suppose that there exists  $b \in (0, 1)$  such that (16) holds. Let  $T > 0$  be given, and let  $t \in (0, T]$  and  $m \in [0, g(b)]$  be fixed. Since  $h$  is increasing, it follows from (4) that

$$\chi(-t, m) \leq m \leq g(b) \leq b.$$

Then

$$\bar{\mu}_1(\chi(-t, m)) = \bar{\mu}_2(\chi(-t, m)).$$

Let  $s \in [0, t]$ . Since  $g^{-1}$  is increasing, then

$$\chi(-s, g^{-1}(\chi(-(t-s), m))) \leq g^{-1}(\chi(-(t-s), m)) \leq g^{-1}(m) \leq b.$$

Moreover, if  $0 \leq s \leq \tau(\Delta(\chi(-(t-s), m)))$ , then

$$\tau(\Delta(\chi(-(t-s), m))) - s \in [0, \tau_{max}].$$

Thus, we have

$$\begin{aligned} & \Gamma_1\left(\chi(-s, g^{-1}(\chi(-(t-s), m))), \tau(\Delta(\chi(-(t-s), m))) - s\right) \\ &= \Gamma_2\left(\chi(-s, g^{-1}(\chi(-(t-s), m))), \tau(\Delta(\chi(-(t-s), m))) - s\right). \end{aligned}$$

Since the solutions  $N^{\bar{\mu}_1, \Gamma_1}(t, m)$  and  $N^{\bar{\mu}_2, \Gamma_2}(t, m)$  of Equation (12) are continuous and satisfy

$$N^{\bar{\mu}_1, \Gamma_1}(0, m) = N^{\bar{\mu}_2, \Gamma_2}(0, m), \quad \text{for } m \in [0, b],$$

then, by using the locally Lipschitz continuous property of the function  $x \mapsto x\beta(m, x)$ , we can write

$$\begin{aligned}
 & |N^{\bar{\mu}_1, \Gamma_1}(t, m) - N^{\bar{\mu}_2, \Gamma_2}(t, m)| \\
 & \leq \tilde{K}L \int_0^t |N^{\bar{\mu}_1, \Gamma_1}(s, \chi(-(t-s), m)) - N^{\bar{\mu}_2, \Gamma_2}(s, \chi(-(t-s), m))| ds \\
 & + 2\tilde{K}L\|\bar{\xi}\| \int_0^t |N^{\bar{\mu}_1, \Gamma_1}(s - \tau(\Delta(\chi(-(t-s), m))), \Delta(\chi(-(t-s), m))) \\
 & \quad - N^{\bar{\mu}_2, \Gamma_2}(s - \tau(\Delta(\chi(-(t-s), m))), \Delta(\chi(-(t-s), m)))| ds, \\
 & \leq \tilde{K}L \int_0^t \|N^{\bar{\mu}_1, \Gamma_1}(s, \cdot) - N^{\bar{\mu}_2, \Gamma_2}(s, \cdot)\|_{g(b)} ds \\
 & + 2\tilde{K}L\|\bar{\xi}\| \int_0^t \|N^{\bar{\mu}_1, \Gamma_1}(s - \tau(\Delta(\chi(-(t-s), m))), \cdot) - N^{\bar{\mu}_2, \Gamma_2}(s - \tau(\Delta(\chi(-(t-s), m))), \cdot)\|_{g(b)} ds,
 \end{aligned}$$

for  $T > 0$  small enough, where  $L$  is a Lipschitz constant of the function  $x \mapsto x\beta(m, x)$  and  $\tilde{K}$  is defined by

$$K(s, m) \leq \tilde{K}, \quad \text{for } s \in [0, T] \text{ and } m \in [0, 1].$$

The extension given by (9) allows to give sense to the integral terms in the above inequality.

Let  $\theta \in [-\tau_{max}, 0]$  be given. If  $t + \theta < 0$ , then  $N^{\bar{\mu}_1, \Gamma_1}(t + \theta, m) = N^{\bar{\mu}_2, \Gamma_2}(t + \theta, m)$ . If  $t + \theta \geq 0$ , then

$$\begin{aligned}
 & |N^{\bar{\mu}_1, \Gamma_1}(t + \theta, m) - N^{\bar{\mu}_2, \Gamma_2}(t + \theta, m)| \\
 & \leq \tilde{K}L \int_0^{t+\theta} \|N^{\bar{\mu}_1, \Gamma_1}(s, \cdot) - N^{\bar{\mu}_2, \Gamma_2}(s, \cdot)\|_{g(b)} ds \\
 & + 2\tilde{K}L\|\bar{\xi}\| \int_0^{t+\theta} \|N^{\bar{\mu}_1, \Gamma_1}(s - \tau(\Delta(\chi(-(t+\theta-s), m))), \cdot) - N^{\bar{\mu}_2, \Gamma_2}(s - \tau(\Delta(\chi(-(t+\theta-s), m))), \cdot)\|_{g(b)} ds, \\
 & \leq \tilde{K}L(1 + 2\|\bar{\xi}\|) \int_0^t \sup_{\bar{\theta} \in [-\tau_{max}, 0]} \|N^{\bar{\mu}_1, \Gamma_1}(s + \bar{\theta}, \cdot) - N^{\bar{\mu}_2, \Gamma_2}(s + \bar{\theta}, \cdot)\|_{g(b)} ds.
 \end{aligned}$$

It follows that

$$\begin{aligned}
 & \sup_{\theta \in [-\tau_{max}, 0]} \|N^{\bar{\mu}_1, \Gamma_1}(t + \theta, \cdot) - N^{\bar{\mu}_2, \Gamma_2}(t + \theta, \cdot)\|_{g(b)} \\
 & \leq \tilde{K}L(1 + 2\|\bar{\xi}\|) \int_0^t \sup_{\theta \in [-\tau_{max}, 0]} \|N^{\bar{\mu}_1, \Gamma_1}(s + \theta, \cdot) - N^{\bar{\mu}_2, \Gamma_2}(s + \theta, \cdot)\|_{g(b)} ds.
 \end{aligned}$$

By using the Gronwall's Inequality, we obtain

$$\sup_{\theta \in [-\tau_{max}, 0]} \|N^{\bar{\mu}_1, \Gamma_1}(t + \theta, \cdot) - N^{\bar{\mu}_2, \Gamma_2}(t + \theta, \cdot)\|_{g(b)} = 0.$$

In particular,

$$\|N^{\bar{\mu}_1, \Gamma_1}(t, \cdot) - N^{\bar{\mu}_2, \Gamma_2}(t, \cdot)\|_{g(b)} = 0, \quad \text{for } t \in (0, T].$$

By steps, this result holds for all  $T > 0$ , therefore (17) is satisfied and the proof is complete.  $\square$

Now, let  $0 < \bar{b} < g(1)$  be fixed and consider the sequence  $(b_n)_{n \in \mathbb{N}}$  defined by

$$b_0 = \bar{b} \quad \text{and} \quad b_{n+1} = \begin{cases} \Delta^{-1}(b_n), & \text{if } b_n \in [0, \Theta(1)), \\ g(1), & \text{if } b_n \in [\Theta(1), g(1)]. \end{cases} \quad (18)$$

The sequence  $(b_n)_{n \in \mathbb{N}}$  represents the transmission of the maturity between two successive generations,  $n$  and  $n + 1$ . The following result is immediate.

**Lemma 3.1.** *If  $0 < \bar{b} < \Theta(1) := \Delta(g(1))$ , then there exists  $N \in \mathbb{N}$  such that  $b_N < \Theta(1) \leq b_{N+1} \leq g(1)$ .*

We give now a first result, which emphasizes the strong link between the process of production of cells and the population of stem cells. A similar result has been proved by Adimy and Pujo-Menjouet [5] in the linear case.

**Theorem 3.1.** *Let  $\bar{\mu}_1, \bar{\mu}_2 \in C[0, 1]$  and  $\Gamma_1, \Gamma_2 \in C(\Omega)$ . If there exists  $0 < b < 1$  such that (16) holds, then, there exists  $\bar{t} > 0$  such that*

$$N^{\bar{\mu}_1, \Gamma_1}(t, m) = N^{\bar{\mu}_2, \Gamma_2}(t, m),$$

for  $m \in [0, g(1)]$  and  $t \geq \bar{t}$ , where  $\bar{t}$  can be chosen to be

$$\bar{t} = \ln \left[ \frac{h(g(1))}{h(g(b))} \right] + (N + 2)\tau_{max}, \quad (19)$$

and  $N \in \mathbb{N}$  is given by Lemma 3.1, for  $\bar{b} = g(b)$ . Furthermore,

$$N^{\bar{\mu}_1, \Gamma_1}(t, m) = N^{\bar{\mu}_2, \Gamma_2}(t, m),$$

for  $m \in [g(1), 1]$  and  $t \geq \bar{t} + \tau_{max} - \ln(h(g(1))) = (N + 3)\tau_{max} - \ln(h(g(b)))$ .

*Proof.* Let  $\bar{b} = g(b)$ . Since  $g$  is increasing, then  $\bar{b} < g(1)$ . Proposition 3.1 implies that

$$N^{\bar{\mu}_1, \Gamma_1}(t, m) = N^{\bar{\mu}_2, \Gamma_2}(t, m), \quad \text{for } t \geq 0 \text{ and } m \in [0, \bar{b}].$$

Let us reconsider the sequence  $(b_n)_{n \in \mathbb{N}}$ , given by (18), and let us consider the sequence  $(t_n)_{n \in \mathbb{N}}$  defined by

$$\begin{cases} t_{n+1} = t_n + \ln \left[ \frac{h(b_{n+1})}{h(b_n)} \right] + \tau_{max}, \\ t_0 = 0. \end{cases} \quad (20)$$

Then,

$$t_n = \ln \left[ \frac{h(b_n)}{h(g(b))} \right] + n\tau_{max}.$$

The sequence  $(b_n)_{n \in \mathbb{N}}$  is increasing. Then, the sequence  $(t_n)_{n \in \mathbb{N}}$  is also increasing. We are going to prove, by induction, the following result

$$(H_n) : \quad N^{\bar{\mu}_1, \Gamma_1}(t, m) = N^{\bar{\mu}_2, \Gamma_2}(t, m), \quad \text{for } t \geq t_n \text{ and } m \in [0, b_n].$$

First,  $(H_0)$  is true, from Proposition 3.1.

Let suppose that  $(H_n)$  is true for  $n \in \mathbb{N}$ . Let  $t \geq t_{n+1}$  and  $m \in [0, b_{n+1}]$ . Then, from (20),

$$t_{n+1} \geq t_n + \tau_{max} \geq \tau_{max}.$$

Since Equation (12) is autonomous, its solutions can be reformulated, for  $t \geq t_{n+1}$ , as follows

$$\begin{aligned} N^{\bar{\mu}_i, \Gamma_i}(t, m) &= K(t - t_n - \tau_{max}, m) N^{\bar{\mu}_i, \Gamma_i}(t_n + \tau_{max}, \chi(-(t - t_n - \tau_{max}), m)) \\ &- \int_{t_n + \tau_{max}}^t K(t - s, m) \beta \left( \chi(-(t - s), m), N^{\bar{\mu}_i, \Gamma_i}(s, \chi(-(t - s), m)) \right) N^{\bar{\mu}_i, \Gamma_i}(s, \chi(-(t - s), m)) ds \\ &+ 2 \int_{t_n + \tau_{max}}^t K(t - s, m) \bar{\xi} \left( \chi(-(t - s), m) \right) N^{\bar{\mu}_i, \Gamma_i} \left( s - \tau(\Delta(\chi(-(t - s), m))), \Delta(\chi(-(t - s), m)) \right) \times \\ &\quad \beta \left( \Delta(\chi(-(t - s), m)), N^{\bar{\mu}_i, \Gamma_i} \left( s - \tau(\Delta(\chi(-(t - s), m))), \Delta(\chi(-(t - s), m)) \right) \right) ds, \end{aligned}$$

for  $i = 1, 2$ . Remark that, from (4),

$$\chi(-(t - t_n - \tau_{max}), m) = h^{-1} \left( h(m) e^{-(t - t_n - \tau_{max})} \right),$$

and from (20),

$$\begin{aligned} e^{-(t - t_n - \tau_{max})} &= \frac{h(b_n)}{h(b_{n+1})} e^{-(t - t_{n+1})}, \\ &\leq \frac{h(b_n)}{h(b_{n+1})}. \end{aligned}$$

Then, we deduce that

$$\begin{aligned} \chi(-(t - t_n - \tau_{max}), m) &\leq h^{-1} \left( h(m) \frac{h(b_n)}{h(b_{n+1})} \right), \\ &\leq h^{-1} \left( h(b_{n+1}) \frac{h(b_n)}{h(b_{n+1})} \right) = b_n. \end{aligned}$$

Hence,  $(H_n)$  implies

$$N^{\bar{\mu}_1, \Gamma_1}(t_n + \tau_{max}, \chi(-(t - t_n - \tau_{max}), m)) = N^{\bar{\mu}_2, \Gamma_2}(t_n + \tau_{max}, \chi(-(t - t_n - \tau_{max}), m)).$$

Furthermore, for  $t_n + \tau_{max} \leq s \leq t$ , we have

$$s - \tau(\Delta(\chi(-(t - s), m))) \geq (t_n + \tau_{max}) - \tau(\Delta(\chi(-(t - s), m))) \geq t_n,$$

and

$$\Delta(\chi(-(t - s), m)) \leq \Delta(m) \leq \Delta(b_{n+1}) = b_n.$$

Consequently,

$$N^{\bar{\mu}_1, \Gamma_1}(s - \tau(\Delta(\chi(-(t - s), m))), \Delta(\chi(-(t - s), m))) = N^{\bar{\mu}_2, \Gamma_2}(s - \tau(\Delta(\chi(-(t - s), m))), \Delta(\chi(-(t - s), m))).$$

Then, we obtain that

$$\begin{aligned} &|N^{\bar{\mu}_1, \Gamma_1}(t, m) - N^{\bar{\mu}_2, \Gamma_2}(t, m)| \leq \\ &\int_{t_n + \tau_{max}}^t K(t - s, m) \left| \beta \left( \chi(-(t - s), m), N^{\bar{\mu}_1, \Gamma_1}(s, \chi(-(t - s), m)) \right) N^{\bar{\mu}_1, \Gamma_1}(s, \chi(-(t - s), m)) \right. \\ &\quad \left. - \beta \left( \chi(-(t - s), m), N^{\bar{\mu}_2, \Gamma_2}(s, \chi(-(t - s), m)) \right) N^{\bar{\mu}_2, \Gamma_2}(s, \chi(-(t - s), m)) \right| ds, \end{aligned}$$

and, by using the Gronwall's inequality, we deduce that  $(H_{n+1})$  is true. Consequently,  $(H_n)$  is true for  $n \in \mathbb{N}$ .

In particular,  $(H_n)$  holds for  $n = N + 2$ , where  $N$  is given by Lemma 3.1, with  $\bar{b} = g(b)$ . Since  $b_{N+1} \in [\Theta(1), g(1)]$ , then  $b_{N+2} = g(1)$ . We deduce that

$$N^{\bar{\mu}_1, \Gamma_1}(t, m) = N^{\bar{\mu}_2, \Gamma_2}(t, m) \quad \text{for } m \in [0, g(1)] \text{ and } t \geq \bar{t}, \quad (21)$$

where  $\bar{t} = t_{N+2}$  is given by (19).

Finally, take  $m \in [g(1), 1]$  and  $t \geq \bar{t} + \tau_{max}$ . We can write, for  $i = 1, 2$ ,

$$\begin{aligned} N^{\bar{\mu}_i, \Gamma_i}(t, m) &= K(t - \bar{t} - \tau_{max}, m) N^{\bar{\mu}_i, \Gamma_i}(\bar{t} + \tau_{max}, \chi(-(t - \bar{t} - \tau_{max}), m)) \\ &\quad - \int_{\bar{t} + \tau_{max}}^t K(t - s, m) \beta \left( \chi(-(t - s), m), N^{\bar{\mu}_i, \Gamma_i}(s, \chi(-(t - s), m)) \right) N^{\bar{\mu}_i, \Gamma_i}(s, \chi(-(t - s), m)) ds \\ &\quad + 2 \int_{\bar{t} + \tau_{max}}^t K(t - s, m) \bar{\xi} \left( \chi(-(t - s), m) \right) N^{\bar{\mu}_i, \Gamma_i} \left( s - \tau(\Delta(\chi(-(t - s), m))), \Delta(\chi(-(t - s), m)) \right) \times \\ &\quad \quad \beta \left( \Delta(\chi(-(t - s), m)), N^{\bar{\mu}_i, \Gamma_i} \left( s - \tau(\Delta(\chi(-(t - s), m))), \Delta(\chi(-(t - s), m)) \right) \right) ds. \end{aligned}$$

Let  $\bar{t} + \tau_{max} \leq s \leq t$ . Then,

$$s - \tau(\Delta(\chi(-(t - s), m))) \geq (\bar{t} + \tau_{max}) - \tau(\Delta(\chi(-(t - s), m))) \geq \bar{t}.$$

Consequently, if

$$\chi(-(t - s), m) \leq g(1),$$

then,

$$\Delta(\chi(-(t - s), m)) \leq \Delta(g(1)) < g(1),$$

and (21) implies that

$$N^{\bar{\mu}_1, \Gamma_1} \left( s - \tau(\Delta(\chi(-(t - s), m))), \Delta(\chi(-(t - s), m)) \right) = N^{\bar{\mu}_2, \Gamma_2} \left( s - \tau(\Delta(\chi(-(t - s), m))), \Delta(\chi(-(t - s), m)) \right).$$

On the other hand, if

$$\chi(-(t - s), m) > g(1),$$

then, from the definition of  $\bar{\xi}$ , we have

$$\bar{\xi}(\chi(-(t - s), m)) = 0.$$

Furthermore, by remarking that  $\ln(h(m)) \leq 0$ , for all  $m \in (0, 1]$ , then we deduce, for  $m \in [g(1), 1]$  and  $t \geq \bar{t} + \tau_{max} - \ln(h(g(1)))$ , that

$$\begin{aligned} \chi(-(t - \bar{t} - \tau_{max}), m) &= h^{-1} \left( h(m) e^{-(t - \bar{t} - \tau_{max})} \right), \\ &\leq h^{-1} (h(m) h(g(1))), \\ &\leq h^{-1} (h(g(1))) = g(1). \end{aligned}$$

Hence,

$$N^{\bar{\mu}_1, \Gamma_1} \left( \bar{t} + \tau_{max}, \chi(-(t - \bar{t} - \tau_{max}), m) \right) = N^{\bar{\mu}_2, \Gamma_2} \left( \bar{t} + \tau_{max}, \chi(-(t - \bar{t} - \tau_{max}), m) \right).$$

Using once again the Gronwall's inequality, we conclude that

$$N^{\bar{\mu}_1, \Gamma_1}(t, m) = N^{\bar{\mu}_2, \Gamma_2}(t, m), \quad \text{for } m \in [g(1), 1] \text{ and } t \geq \bar{t} + \tau_{max} - \ln(h(g(1))).$$

This completes the proof.  $\square$

**Corollary 3.1.** *Let  $\bar{\mu} \in C[0, 1]$  and  $\Gamma \in C(\Omega)$ . If there exists  $0 < b < 1$  such that*

$$\bar{\mu}(m) = 0 \quad \text{and} \quad \Gamma(m, a) = 0, \quad \text{for } m \in [0, b] \text{ and } a \in [0, \tau_{max}],$$

then,

$$N^{\bar{\mu}, \Gamma}(t, m) = 0, \quad \text{for } m \in [0, 1] \text{ and } t \geq (N + 3)\tau_{max} - \ln(h(g(b))),$$

where  $N \in \mathbb{N}$  is given by Lemma 3.1, for  $\bar{b} = g(b)$ .

This result stresses the dependence of the production of cells with the population of stem cells. In particular, if the stem cells population is defective in the initial stage, then the entire population is doomed to extinction in a finite time. This situation describes what usually happens with the aplastic anemia, a disease which yields to injury or destruction of pluripotential stem cells.

In the next corollary, we show that the proliferating population depends also strongly on the stem cells population.

**Corollary 3.2.** *Let  $\bar{\mu}_1, \bar{\mu}_2 \in C[0, 1]$  and  $\Gamma_1, \Gamma_2 \in C(\Omega)$ . If there exists  $0 < b < 1$  such that (16) holds, then*

$$P^{\bar{\mu}_1, \Gamma_1}(t, m) = P^{\bar{\mu}_2, \Gamma_2}(t, m), \quad \text{for } m \in [0, 1] \text{ and } t \geq (N + 3)\tau_{max} - \ln(h(g(b))),$$

where  $N \in \mathbb{N}$  is given by Lemma 3.1, for  $\bar{b} = g(b)$ .

*Proof.* The proof is immediate by using Theorem 3.1, Equation (13) and a method of steps.  $\square$

## 4 Behaviour of the immature cells population

In this section, we investigate the behaviour of the immature cells population, that means, the population of cells with maturity  $m = 0$ .

Let  $\bar{\mu} \in C[0, 1]$  and  $\Gamma \in C(\Omega)$  be fixed. Let us consider the continuous solutions  $N^{\bar{\mu}, \Gamma}(t, m)$  and  $P^{\bar{\mu}, \Gamma}(t, m)$  of Problem (12)-(13). We set  $x(t) = N^{\bar{\mu}, \Gamma}(t, 0)$  and  $y(t) = P^{\bar{\mu}, \Gamma}(t, 0)$ , for all  $t \geq 0$ . Then,  $(x(t), y(t))$  is solution of the system

$$\begin{aligned} x(t) &= e^{-\rho t} \bar{\mu}(0) - \int_0^t e^{-\rho(t-s)} \beta(0, x(s)) x(s) ds \\ &+ \begin{cases} 2 \int_0^t e^{-\rho(t-s)} \xi(s, 0) \Gamma(0, r-s) ds, & \text{for } t \in [0, r], \\ 2 \int_0^r e^{-\rho(t-s)} \xi(s, 0) \Gamma(0, r-s) ds + 2\bar{\xi}(0) \int_r^t e^{-\rho(t-s)} \beta(0, x(s-r)) x(s-r) ds, & \text{for } r \leq t, \end{cases} \end{aligned} \quad (22)$$

and

$$\begin{aligned} y(t) &= e^{-\eta t} \bar{\Gamma}(0) + \int_0^t e^{-\eta(t-s)} \beta(0, x(s)) x(s) ds \\ &- \begin{cases} \int_0^t e^{-\eta(t-s)} \pi(s, 0) \Gamma(0, r-s) ds, & \text{for } t \in [0, r], \\ \int_0^r e^{-\eta(t-s)} \pi(s, 0) \Gamma(0, r-s) ds + \bar{\pi}(0) \int_r^t e^{-\eta(t-s)} \beta(0, x(s-r)) x(s-r) ds, & \text{for } r \leq t, \end{cases} \end{aligned} \quad (23)$$

where  $\rho := \delta(0) + V'(0)$ ,  $\eta := \gamma(0) + V'(0)$  and  $r := \tau(0) > 0$ .  
 Let us recall that  $\bar{\xi}(0) = \xi(r, 0)$ ,  $\bar{\pi}(0) = \pi(r, 0)$  and

$$\bar{\Gamma}(0) = \int_0^r \Gamma(0, a) da.$$

Then, we easily deduce that System (22)-(23) is equivalent to the system

$$\begin{cases} \frac{dx}{dt}(t) = -(\rho + \beta(0, x(t)))x(t) + \begin{cases} 2\xi(t, 0)\Gamma(0, r-t), & \text{for } 0 \leq t \leq r, \\ 2\bar{\xi}(0)\beta(0, x(t-r))x(t-r), & \text{for } r \leq t, \end{cases} \\ x(0) = \bar{\mu}(0), \end{cases} \quad (24)$$

$$\begin{cases} \frac{dy}{dt}(t) = -\eta y(t) + \beta(0, x(t))x(t) - \begin{cases} \pi(t, 0)\Gamma(0, r-t), & \text{for } 0 \leq t \leq r, \\ \bar{\pi}(0)\beta(0, x(t-r))x(t-r), & \text{for } r \leq t, \end{cases} \\ y(0) = \bar{\Gamma}(0). \end{cases} \quad (25)$$

Of course, at  $t = r$ , the derivatives in (24) and (25) represent the right-hand side and the left-hand side derivatives.

First, consider the system, for  $t \in [0, r]$ ,

$$\begin{cases} \frac{d\phi}{dt}(t) = -(\rho + \beta(0, \phi(t)))\phi(t) + 2\xi(t, 0)\Gamma(0, r-t), \\ \frac{d\psi}{dt}(t) = -\eta\psi(t) + \beta(0, \phi(t))\phi(t) - \pi(t, 0)\Gamma(0, r-t), \end{cases} \quad (26)$$

with

$$\begin{cases} \phi(0) = \bar{\mu}(0), \\ \psi(0) = \bar{\Gamma}(0). \end{cases} \quad (27)$$

It is obvious that, under the assumptions that the function  $x \mapsto \beta(0, x)$  is bounded and the function  $x \mapsto x\beta(0, x)$  is locally Lipschitz continuous, Problem (26)-(27) has a unique solution  $(\phi(t), \psi(t))$ , for  $t \in [0, r]$ . Remark that  $\psi(t)$  is explicitly given by

$$\psi(t) = e^{-\eta t} \int_0^{r-t} \Gamma(0, a) da + \int_0^t e^{-\eta(t-s)} \beta(0, \phi(s))\phi(s) ds, \quad \text{for } t \in [0, r]. \quad (28)$$

Moreover, if  $\bar{\mu}(0) \geq 0$  and  $\Gamma(0, \cdot) \geq 0$ , then  $\phi(t)$  and  $\psi(t)$  are nonnegative.

Hence, for  $t \geq r$ , Problem (24)-(25) reduces to the delay differential system

$$\frac{dx}{dt}(t) = -(\rho + \beta(0, x(t)))x(t) + 2\bar{\xi}(0)\beta(0, x(t-r))x(t-r), \quad (29)$$

$$\frac{dy}{dt}(t) = -\eta y(t) + \beta(0, x(t))x(t) - \bar{\pi}(0)\beta(0, x(t-r))x(t-r), \quad (30)$$

with, for  $t \in [0, r]$ ,

$$\begin{cases} x(t) = \phi(t), \\ y(t) = \psi(t). \end{cases} \quad (31)$$

As  $\psi(t)$ , for  $t \in [0, r]$ ,  $y(t)$  is explicitly given, for  $t \geq r$ , by

$$y(t) = \int_{t-r}^t e^{-\eta(t-s)} \beta(0, x(s))x(s) ds. \quad (32)$$

**Proposition 4.1.** *Assume that the function  $x \mapsto \beta(0, x)$  is bounded and the function  $x \mapsto x\beta(0, x)$  is locally Lipschitz continuous. Let  $\bar{\mu} \in C[0, 1]$  and  $\Gamma \in C(\Omega)$  be given. Then, Problem (29)-(31) has a unique solution  $(x^\phi(t), y^\psi(t))$ , defined for  $t \geq 0$ , where  $(\phi(t), \psi(t))$  is the unique solution of (26)-(27). Moreover,  $(x^\phi(t), y^\psi(t))$  has a continuous derivative at  $t = r$  if and only if*

$$\Gamma(0, 0) = \beta(0, \bar{\mu}(0))\bar{\mu}(0). \quad (33)$$

Furthermore, if  $\bar{\mu}(0) \geq 0$  and  $\Gamma(0, \cdot) \geq 0$ , then  $x^\phi(t)$  and  $y^\psi(t)$  are nonnegative.

*Proof.* Existence, uniqueness and regularity of solutions of Problem (29)-(31) come from Hale and Verduyn Lunel [14]. The positivity of  $x^\phi(t)$  is easily obtained by steps. Moreover, by using (32), we deduce immediately the positivity of  $y^\psi(t)$ .  $\square$

In the sequel, we will consider, for a biological reason, only nonnegative solutions of Problem (29)-(30).

**Lemma 4.1.** *If  $\lim_{t \rightarrow +\infty} x^\phi(t) = C$  exists, then  $\lim_{t \rightarrow +\infty} y^\psi(t)$  exists and is equal to*

$$\begin{cases} \frac{1}{\eta}(1 - e^{-\eta r})\beta(0, C)C, & \text{if } \eta > 0, \\ r\beta(0, C)C, & \text{if } \eta = 0. \end{cases}$$

*Proof.* We assume that

$$\lim_{t \rightarrow +\infty} x^\phi(t) = C.$$

By using (32), we obtain that

$$y^\psi(t) = \int_0^r e^{-\eta s} \beta(0, x^\phi(t-s)) x^\phi(t-s) ds, \quad \text{for } t \geq r.$$

Then, we easily conclude that

$$\lim_{t \rightarrow +\infty} y^\psi(t) = \left( \int_0^r e^{-\eta s} ds \right) \beta(0, C)C.$$

This ends the proof.  $\square$

Lemma 4.1 implies that, in order to study the stability of the solutions of Problem (29)-(30), we only need to concentrate on the stability of the solutions of the delay differential equation (29).

In [16], Mackey has proposed that the function  $\beta(0, \cdot)$  is a Hill function, defined by

$$\beta(0, x) = \beta_0 \frac{\theta^n}{\theta^n + x^n}, \quad (34)$$

where  $\beta_0$  and  $\theta$  are two positive constants and  $n \geq 1$ . This function is used to describe, from a reasonable biological point of view, the fact that the rate of re-entry in the proliferating compartment is a decreasing function of the total number of resting cells.

We recall that the function  $x \mapsto \beta(0, x)$  is supposed to be continuous and positive. From now on, we also suppose that  $x \mapsto \beta(0, x)$  is decreasing on  $[0, +\infty)$  and satisfies

$$\lim_{x \rightarrow +\infty} \beta(0, x) = 0. \quad (35)$$

These assumptions have been done, for the first time, by Mackey [16] in 1978 and have been used by Mackey and Rudnicki [20] in 1994.

Before studying the stability of Problem (29)-(30), we recall a non-trivial property of the solutions of (29). The result in Proposition 4.2 has been proved for a similar equation by Mackey and Rudnicki [20], in 1994.



**Proposition 4.2.** *Assume that  $\rho > 0$ . Then, every solution of Equation (29) is bounded.*

One can notice that, if  $\rho = 0$ , then Equation (29) may have unbounded solutions. A counter example is given in the next proposition.

**Proposition 4.3.** *Assume that  $\rho = 0$  and that there exists  $\bar{x} > 0$  such that the function  $x \mapsto x\beta(0, x)$  is decreasing on  $[\bar{x}, +\infty)$ . Let  $\bar{\mu} \in C[0, 1]$  and  $\Gamma \in C(\Omega)$  be such that (33) holds,  $\bar{\mu}(0) > \bar{x}$  and*

$$2\xi(t, 0)\Gamma(0, r - t) > \Gamma(0, 0), \quad \text{for } t \in [0, r]. \quad (36)$$

*Then, the solution of Equation (29) is unbounded.*

*Proof.* Let consider the solution  $x(t)$  of the problem

$$\begin{cases} x'(t) &= 2\bar{\xi}(0)\beta(0, x(t-r))x(t-r) - \beta(0, x(t))x(t), & \text{for } t \geq r, \\ x(t) &= \phi(t), & \text{for } 0 \leq t \leq r. \end{cases}$$

First, one can notice that, if  $\lim_{t \rightarrow +\infty} x(t)$  exists and is equal to  $C$ , then  $C = 0$ .

By contradiction, if we suppose that  $C > 0$ , then we obtain that

$$\lim_{t \rightarrow +\infty} x'(t) = (2\bar{\xi}(0) - 1)\beta(0, C)C > 0,$$

because Condition (36) implies that  $2\bar{\xi}(0) > 1$ . This contradicts the fact that  $x(t)$  converges. Then  $C = 0$ . Secondly, let  $\bar{\mu} \in C[0, 1]$  and  $\Gamma \in C(\Omega)$  be such that (33) and (36) hold, and  $\bar{\mu}(0) > \bar{x}$ . The solution  $\phi(t)$  of the problem

$$\begin{cases} \phi'(t) &= 2\xi(t, 0)\Gamma(0, r - t) - \beta(0, \phi(t))\phi(t), & \text{for } t \geq r, \\ \phi(0) &= \bar{\mu}(0), \end{cases}$$

satisfies

$$\phi'(0) = 2\xi(0, 0)\Gamma(0, r) - \Gamma(0, 0) > 0.$$

Consequently, there exists  $\epsilon \in (0, r]$  such that  $\phi'(t) > 0$ , for  $t \in [0, \epsilon)$ .

Hence,  $\phi(0) < \phi(\epsilon)$ . Then,

$$\begin{aligned} \phi'(\epsilon) &> \Gamma(0, 0) - \beta(0, \phi(\epsilon))\phi(\epsilon), \\ &\geq \beta(0, \bar{\mu}(0))\bar{\mu}(0) - \beta(0, \phi(\epsilon))\phi(\epsilon), \\ &\geq 0. \end{aligned}$$

By steps, we conclude that  $\phi'(t) > 0$ , for  $t \in [0, r]$ .

By the same way, we obtain that

$$x'(r) > \beta(0, \phi(0))\phi(0) - \beta(0, \phi(r))\phi(r) \geq 0.$$

By using the same reasoning, we show that  $x'(t) > 0$ , for  $t \geq r$ . Hence,  $x$  is unbounded and the proof is complete.  $\square$

**Remark 1.** *Even if the trivial solution of (29) is unstable, the trivial solution of (30) may be stable. For example, if  $\lim_{t \rightarrow +\infty} x^\phi(t) = +\infty$ , then, by using (32) and (35), we easily obtain that  $\lim_{t \rightarrow +\infty} y^\psi(t) = 0$ .*

The assumption on the function  $x \mapsto x\beta(0, x)$ , in Proposition 4.3, holds, for example, if  $\beta$  is given by (34) with  $n > 1$ . In this case, the function  $x \mapsto x\beta(0, x)$  is decreasing for  $x \geq \bar{x} = \theta/(n-1)^{1/n}$ .

We determine, in the next theorem, the global stability area of the trivial solution of Equation (29).

**Theorem 4.1.** *The trivial solution of Equation (29) is globally stable if and only if*

$$(2\bar{\xi}(0) - 1)\beta(0, 0) < \rho.$$

*Proof.* First, we assume that  $(2\bar{\xi}(0) - 1)\beta(0, 0) < \rho$ . We are going to show the global stability by using a Lyapunov functional.

We denote by  $C^+$  the subset of  $C[0, r]$  containing nonnegative functions. We set

$$f(x) = x\beta(0, x)$$

and

$$\mathcal{F}(x) = \int_0^x f(s)ds, \quad \text{for } x \geq 0.$$

We define the mapping  $J : C^+ \rightarrow \mathbb{R}$  by

$$J(\phi) = \mathcal{F}(\phi(r)) + \bar{\xi}(0) \int_0^r f^2(\phi(\sigma))d\sigma, \quad \text{for } \phi \in C^+.$$

Then

$$\dot{J}(\phi) = \frac{d\phi}{dt}(r)f(\phi(r)) + \bar{\xi}(0)(f^2(\phi(r)) - f^2(\phi(0))).$$

Since

$$\frac{d\phi}{dt}(r) = -\rho\phi(r) - f(\phi(r)) + 2\bar{\xi}(0)f(\phi(0)),$$

then

$$\begin{aligned} \dot{J}(\phi) &= -\rho\beta(0, \phi(r))\phi^2(r) - f^2(\phi(r)) + \bar{\xi}(0)\left(f^2(\phi(r)) + 2f(\phi(r))f(\phi(0)) - f^2(\phi(0))\right), \\ &= -\left(\rho + \beta(0, \phi(r))\right)\beta(0, \phi(r))\phi^2(r) + 2\bar{\xi}(0)f^2(\phi(r)) - \bar{\xi}(0)\left(f(\phi(r)) - f(\phi(0))\right)^2. \end{aligned}$$

Hence,

$$\dot{J}(\phi) \leq -\left(\rho - (2\bar{\xi}(0) - 1)\beta(0, \phi(r))\right)\beta(0, \phi(r))\phi^2(r).$$

Since  $(2\bar{\xi}(0) - 1)\beta(0, 0) < \rho$  and the function  $x \mapsto \beta(0, x)$  is decreasing and positive on  $\mathbb{R}^+$ , then the function

$$\lambda(u) = \left(\rho - (2\bar{\xi}(0) - 1)\beta(0, u)\right)\beta(0, u)u^2$$

is nonnegative on  $\mathbb{R}^+$  and  $\lambda(u) = 0$  if and only if  $u = 0$ . Consequently, every solution of Equation (29) with  $\phi \in C^+$  tends to zero as  $t$  tends to  $+\infty$ .

Now, if we assume that  $\rho \leq (2\bar{\xi}(0) - 1)\beta(0, 0)$ , then, immediatly,

$$-(\rho + \beta(0, 0)) \geq -2\bar{\xi}(0)\beta(0, 0).$$

Hence, by using Bellman and Cooke ([6], Theorem 13.8), we obtain that the trivial solution of (29) is unstable.  $\square$

Remark that, by using Lemma 4.1, if  $(2\bar{\xi}(0) - 1)\beta(0, 0) < \rho$ , then the trivial solution of (30) is also globally stable.

We are going to use the results of Theorem 4.1 in the next sections to obtain global stability and instability for the solutions of Problem (12)-(13).

## 5 Global stability for the maturity structured model

In this section, we establish a result of global stability for Problem (12)-(13) which stresses the influence of immature cells on the total population. First, we recall some definitions.

**Definition 5.1.** *The trivial solution of Problem (12)-(13) is locally stable if, for all  $\varepsilon > 0$ , there exist  $\nu > 0$  and  $T > 0$  such that, if  $\bar{\mu} \in C[0, 1]$  and  $\Gamma \in C(\Omega)$  satisfy*

$$\|\bar{\mu}\| < \nu \quad \text{and} \quad \|\Gamma\|_{\Omega} < \nu,$$

then

$$\|N^{\bar{\mu}, \Gamma}(t, \cdot)\| < \varepsilon \quad \text{and} \quad \|P^{\bar{\mu}, \Gamma}(t, \cdot)\| < \varepsilon, \quad \text{for } t \geq T. \quad (37)$$

The trivial solution of Problem (12)-(13) is globally stable if, for all  $\varepsilon > 0$ , there exists  $T > 0$  such that (37) holds.

Throughout this section, we assume that the function  $x \mapsto \beta(m, x)$  is uniformly bounded and that the function  $x \mapsto x\beta(m, x)$  is locally Lipschitz continuous for all  $m \in [0, 1]$ . In the next theorem, we show our main result, which makes the link between the global stability of the trivial solution of Problem (12)-(13) and the stability of the immature cells population.

**Theorem 5.1.** *Assume that Condition (14) holds. Let us suppose that the trivial solution of Problem (12)-(13) is locally stable. Then this solution is globally stable on the set*

$$\Omega_{GS} = \left\{ (\bar{\mu}, \Gamma) \in C[0, 1] \times C(\Omega) \quad : \quad \lim_{t \rightarrow +\infty} N^{\bar{\mu}, \Gamma}(t, 0) = \lim_{t \rightarrow +\infty} P^{\bar{\mu}, \Gamma}(t, 0) = 0 \right\}.$$

*Proof.* We first show that, if the trivial solution of Equation (12) is locally stable, then it is globally stable on the set

$$\Omega_N = \left\{ (\bar{\mu}, \Gamma) \in C[0, 1] \times C(\Omega) \quad : \quad \lim_{t \rightarrow +\infty} N^{\bar{\mu}, \Gamma}(t, 0) = 0 \right\}.$$

Let us suppose that the trivial solution of (12) is locally stable. Then, for all  $\bar{\mu} \in C[0, 1]$ ,  $\Gamma \in C(\Omega)$  and  $\varepsilon > 0$ , there exist  $\nu > 0$  and  $T > 0$ , such that, if

$$\|\bar{\mu}\| < \nu \quad \text{and} \quad \|\Gamma\|_{\Omega} < \nu,$$

then,

$$|N^{\bar{\mu}, \Gamma}(t, m)| < \varepsilon, \quad \text{for } t \geq T \text{ and } m \in [0, 1]. \quad (38)$$

Let  $\varepsilon > 0$  be given and let  $(\bar{\mu}, \Gamma) \in \Omega_N$ . Then  $\lim_{t \rightarrow +\infty} N^{\bar{\mu}, \Gamma}(t, 0) = 0$ , so there exists  $t_0 > 0$  such that

$$|N^{\bar{\mu}, \Gamma}(t, 0)| < \frac{\nu}{2}, \quad \text{for } t \geq t_0.$$

Let  $\zeta \in C[0, 1]$  and  $\Upsilon \in C(\Omega)$  be given. Since the solutions of Equation (12) are continuous, then there exists  $\delta > 0$  such that, if

$$|\zeta(m) - \bar{\mu}(0)| < \delta \quad \text{and} \quad |\Upsilon(m, a) - \Gamma(0, a)| < \delta,$$

for  $m \in [0, 1]$  and  $a \in [0, \tau_{max}]$ , then

$$|N^{\zeta, \Upsilon}(t, m) - N^{\bar{\mu}, \Gamma}(t, 0)| < \frac{\nu}{2},$$

for  $t \in [t_0, t_0 + \tau_{max}]$  and  $m \in [0, 1]$ .

Now, since  $\bar{\mu}$  and  $\Gamma$  are continuous, then there exists  $b \in (0, 1)$  such that

$$|\bar{\mu}(m) - \bar{\mu}(0)| < \delta \quad \text{and} \quad |\Gamma(m, a) - \Gamma(0, a)| < \delta,$$

for  $m \in [0, b]$  and  $a \in [0, \tau_{max}]$ . We define the following functions,

$$\bar{\mu}_b(m) = \begin{cases} \bar{\mu}(m), & \text{if } m \in [0, b], \\ \bar{\mu}(b), & \text{if } m \in [b, 1], \end{cases} \quad \text{and} \quad \Gamma_b(m, \cdot) = \begin{cases} \Gamma(m, \cdot), & \text{if } m \in [0, b], \\ \Gamma(b, \cdot), & \text{if } m \in [b, 1]. \end{cases}$$

Then, for  $m \in [0, 1]$  and  $a \in [0, \tau_{max}]$ , we get

$$|\bar{\mu}_b(m) - \bar{\mu}(0)| < \delta \quad \text{and} \quad |\Gamma_b(m, a) - \Gamma(0, a)| < \delta.$$

Consequently,

$$|N^{\bar{\mu}_b, \Gamma_b}(t, m) - N^{\bar{\mu}, \Gamma}(t, 0)| < \frac{\nu}{2},$$

for  $t \in [t_0, t_0 + \tau_{max}]$  and  $m \in [0, 1]$ . It follows that

$$|N^{\bar{\mu}_b, \Gamma_b}(t, m)| < \nu, \quad \text{for } t \in [t_0, t_0 + \tau_{max}] \text{ and } m \in [0, 1].$$

Since  $N^{\bar{\mu}_b, \Gamma_b}(t, m)$  is a solution of Equation (12) and since this equation is autonomous for  $t$  large enough, then  $N^{\bar{\mu}_b, \Gamma_b}(t, m)$  becomes an initial condition of (12) on  $[t_0, t_0 + \tau_{max}] \times [0, 1]$ . We deduce, from (38), that there exists  $\tilde{T} \geq t_0 + \tau_{max}$  such that

$$|N^{\bar{\mu}_b, \Gamma_b}(t, m)| < \varepsilon, \quad \text{for } t \geq \tilde{T} \text{ and } m \in [0, 1].$$

From Theorem 3.1, there exists  $\bar{t} > 0$  such that

$$N^{\bar{\mu}_b, \Gamma_b}(t, m) = N^{\bar{\mu}, \Gamma}(t, m), \quad \text{for } t \geq \bar{t} + \tau_{max} - \ln(h(g(1))) \text{ and } m \in [0, 1].$$

Hence,

$$\|N^{\bar{\mu}, \Gamma}(t, \cdot)\| < \varepsilon, \quad \text{for } t \geq \max\{\tilde{T}, \bar{t} + \tau_{max} - \ln(h(g(1)))\}.$$

Then, the trivial solution of Equation (12) is globally stable.

By the same way and using Corollary 3.2, we show that, if  $\bar{\mu}$  and  $\Gamma$  are such that

$$\lim_{t \rightarrow +\infty} P^{\bar{\mu}, \Gamma}(t, 0) = 0,$$

then, the trivial solution of Equation (13) is globally stable. This completes the proof.  $\square$

**Remark 2.** One has to notice that the result in Theorem 5.1 allows us to obtain the global exponential stability of the trivial solution of Problem (12)-(13) on the set  $\Omega_{GS}$ , when this solution is locally exponentially stable. The proof, in this case, is identical to the previous one.

The behaviour of the immature cells population has been studied in Section 4. The local stability of System (12)-(13) has been studied by Adimy and Crauste [2]. The author proved that, under the assumptions that the function  $x \mapsto \beta(m, x)$  is uniformly bounded and the function  $x \mapsto x\beta(m, x)$  is locally Lipschitz continuous for all  $m \in [0, 1]$ , then the trivial solution of (12)-(13) is locally exponentially stable if

$$\left(1 + 2 \sup_{(m,t) \in \Omega_\Delta} \xi(t, m)\right) \sup_{m \in [0,1]} \left(\beta(m, 0)\right) < \min \left\{ \inf_{m \in [0,1]} \left(\delta(m) + V'(m)\right), \inf_{m \in [0,1]} \left(\gamma(m) + V'(m)\right) \right\}. \quad (39)$$

The proof is based on an induction reasoning.

Then, we can deduce the following corollary, which deals with the global stability of the system.

**Corollary 5.1.** *Assume that Condition (14) and Inequality (39) hold. Then the trivial solution of System (12)-(13) is globally exponentially stable.*

*Proof.* From Inequality (39), we obtain the local exponential stability of the trivial solution of (12)-(13). From the definition of  $\rho$ , we get

$$\inf_{m \in [0,1]} \left( \delta(m) + V'(m) \right) \leq \rho.$$

Moreover,

$$\bar{\xi}(0) \leq \sup_{(m,t) \in \Omega_\Delta} \xi(t, m) \quad \text{and} \quad \beta(0,0) \leq \sup_{m \in [0,1]} \beta(m,0).$$

Hence, we obtain

$$(2\bar{\xi}(0) - 1)\beta(0,0) < \rho.$$

Then, Theorem 4.1 yields to the global stability of the trivial solution of (29)-(30)

By using Theorem 5.1 and Remark 2, we conclude.  $\square$

As an example, let us suppose that  $\delta \geq 0$  and  $\gamma \geq 0$  are constant,  $V$  and  $g$  are linear functions of the maturity  $m$ , given, for  $m \in [0, 1]$ , by

$$V(m) = m, \quad \text{and} \quad g(m) = \frac{1}{\kappa}m, \quad \text{with } \kappa > 1,$$

and the function  $\beta$  is a Hill function (see Mackey [16]), defined by

$$\beta(m, x) = \beta_0(m) \frac{\theta^n(m)}{\theta^n(m) + x^n},$$

with  $\beta_0$  and  $\theta$  two continuous and positive functions on  $[0, 1]$ , and  $n > 1$ . One can remark that, in this case, the function  $V$  satisfies Condition (1).

Furthermore, we assume that the function  $\tau$  is given, for  $m \in [0, 1]$ , by

$$\tau(m) = \ln(m + \alpha), \quad \text{with } \alpha > 1.$$

In this case,  $\tau$  is increasing. Therefore, Condition (2) is satisfied. We obtain that

$$\Delta(m) = \frac{1}{2} \left( \sqrt{4\kappa m + \alpha^2} - \alpha \right), \quad \text{for } m \in [0, 1],$$

and the characteristic curves are given by

$$\chi(s, m) = me^s, \quad \text{for } s \leq 0 \text{ and } m \in [0, 1].$$

By remarking that  $\Delta(m) < m$  for  $m \in (0, 1]$  if and only if  $\alpha > \kappa$ , then we obtain that the trivial solution of (12)-(13) is globally exponentially stable if

$$(1 + 2\kappa) \sup_{m \in [0,1]} \beta_0(m) < \min\{\delta, \gamma\} \quad \text{and} \quad \alpha > \kappa.$$

In the next section, we conclude our asymptotic study by giving a result of instability, based on the results of Section 4.

## 6 Instability

The trivial solution of (12) is *unstable* if it is not stable, this means, if there exists  $\varepsilon > 0$  such that, for all  $\nu > 0$ , there exists  $(\bar{\mu}, \Gamma) \in C[0, 1] \times C(\Omega)$  which satisfies

$$\|\bar{\mu}\| < \nu \quad \text{and} \quad \|\Gamma\|_{\Omega} < \nu,$$

and

$$\|N^{\bar{\mu}, \Gamma}(t, \cdot)\| > \varepsilon, \quad \text{for } t \geq 0.$$

In the next theorem, we show that the instability of the immature cells population leads to the instability of the entire population.

**Theorem 6.1.** *Assume that*

$$\rho \leq (2\bar{\xi}(0) - 1)\beta(0, 0). \quad (40)$$

*Then, the trivial solution of Problem (12) is unstable.*

*Proof.* From Theorem 4.1 and (40), we obtain that the trivial solution of Equation (29) is unstable. That is there exist  $\varepsilon > 0$ ,  $\bar{\mu} \in C[0, 1]$  and  $\Gamma \in C(\Omega)$  such that  $N^{\bar{\mu}, \Gamma}(t, 0)$  does not tend to zero when  $t$  goes to infinity. Then, there exist  $\varepsilon > 0$  and  $(t_n)_{n \in \mathbb{N}}$ , with  $t_n \rightarrow +\infty$ , such that

$$N^{\bar{\mu}, \Gamma}(t_n, 0) > \varepsilon, \quad \text{for } n \in \mathbb{N}.$$

Let us suppose, by contradiction, that the trivial solution of (12) is stable. Then, in particular, there exist  $\nu > 0$  and  $T > 0$  such that, if

$$\|\bar{\mu}\| < \nu \quad \text{and} \quad \|\Gamma\|_{\Omega} < \nu,$$

then

$$\|N^{\bar{\mu}, \Gamma}(t, \cdot)\| < \varepsilon, \quad \text{for } t \geq T.$$

Consequently,

$$|N^{\bar{\mu}, \Gamma}(t_n, 0)| < \varepsilon, \quad \text{for } n \in \mathbb{N} \text{ such that } t_n \geq T.$$

Since we can choose  $\bar{\mu}$  and  $\Gamma$  as small as necessary, this yields a contradiction. We deduce the instability of the trivial solution of (12).  $\square$

One can remark that, even if the trivial solution of (12) is unstable, the trivial solution of (13) may be stable.

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