

## ASYMPTOTIC BEHAVIOR OF A SINGULAR TRANSPORT EQUATION MODELLING CELL DIVISION

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(Communicated by Ovide Arino)

**ABSTRACT.** This paper analyses the behavior of the solutions of a model of cells that are capable of simultaneous proliferation and maturation. This model is described by a first-order singular partial differential system with a retardation of the maturation variable and a time delay. Both delays are due to cell replication. We prove that uniqueness and asymptotic behavior of solutions depend only on cells with small maturity (stem cells).

**1. Introduction.** Mathematical models of biological populations structured in age or maturity appeared in various contexts more than forty years ago. In particular, there exists a vast literature on models for progress through the cell cycle and its various phases. See for example the references given in Metz and Diekmann (1986), and in Gyllenberg and Heijmans (1987). More recently Mackey and Rudnicki (1994 and 1999) studied a particular time-and-age maturation structured model of biological process of hematological cell development in bone marrow. This model is a generalization of those that have been introduced previously both in the absence of maturation by Mackey (1978 and 1979) and presence of maturation with only one phase by Rey and Mackey (1992 and 1993). They considered a mathematical model for the dynamics of a population of cells which can be distinguished from each other according to their maturity and their position in the cell cycle phase. Mackey and Rudnicki (1994 and 1999) assumed that the cell cycle consists of two distinct phases. The cells in the first phase (resting phase) cannot divide, they mature, and provided they do not die, they eventually enter the second phase. In the second phase (proliferating phase) the cells are committed to undergo cell division a time  $\tau$  later. The position of a cell in each phase is denoted by  $a$  (cell age) which is assumed to range in the proliferating phase from  $a = 0$  (the point of commitment) to  $a = \tau$  (the point of cytokinesis), and in the resting phase from  $a = 0$ , when the cell enters, to  $a = +\infty$ . The maturity variable  $m$  represents the concentration of

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1991 *Mathematics Subject Classification.* 35F15, 35L60, 92C37, 92D25.

*Key words and phrases.* Structured Population, Cell cycle, First order partial differential equation with delays, Stem Cells, Delay, Aplastic Anemia, Instability.

what composes a cell such as proteins, or other elements one can measure experimentally. The maturity variable  $m$  can range, without loss of generality, from 0 to 1. Cells can be lost in the proliferating phase with a rate  $\gamma(m)$  and in the resting phase with a rate  $\delta(m)$ . At the point of cytokinesis, a cell with maturity  $m$  divides into two daughter cells with maturity  $g(m) \leq m$ , that enter directly the resting phase. In the resting phase, cells can return to the proliferating phase with a rate  $\beta$  and complete the cycle. The cells of both types mature with the same velocity  $V(m)$ .

In the model considered by Mackey and Rudnicki (1994 and 1999), the main results concern the global stability for the following first order partial differential equation

$$\frac{\partial}{\partial t}u(t, m) + V(m)\frac{\partial}{\partial m}u(t, m) = f(u(t, m), u(t - \tau, \Delta(m))), \quad (1)$$

where  $\Delta : [0, 1] \rightarrow [0, 1]$  is a continuous function such that  $\Delta(0) = 0$  and  $\Delta(m) < m$ , for  $m \in (0, 1]$ . These authors gave in 1999 a criterion for global stability of Equation (1). However, they considered only the case when the term  $f(u, v)$  in Equation (1) does not depend on the maturity variable. This restriction implies that the rates of mortality in the two phases, the rate of return from the resting to the proliferating phase and  $V'(m)$  are independent of the maturity variable. This allowed Mackey and Rudnicki to introduce the following delay differential equation

$$u'(t) = f(u(t), u(t - \tau)), \quad (2)$$

and to establish the connection between the global solution behavior of the equation (2) and the local and global solution behavior of the partial differential equations (1). More exactly, they proved that local stability of Equation (1) and global stability of Equation (2) yield to global stability of (1).

This model has also been analyzed by Dyson *et al.* (1996a and 1996b) in the particular case when the maturity  $X(-\tau, g^{-1}(m))$  is independent of  $\tau$  and is equal to  $\alpha m$ , with  $0 < \alpha < 1$ . In these studies, it is shown that the behavior of solutions is dependent upon the stem cells. Numerical studies performed by Rey and Mackey (1993) suggest such a result. For other recent developments concerning properties of similar equations see for example Dyson *et al.* (2000a and 2000b) and Bernard *et al.* (2001)

The model investigated in the present paper is more general than those considered by Mackey and Rudnicki in (1994 and 1999). It takes into account the maturity variable. In particular, we consider a general velocity of maturation  $V(m)$  and a general function  $g(m)$  which is the maturity of the two daughter cells if  $m$  is the maturity of their mother. Moreover, the rates of mortality and the rate of return from the resting to the proliferating phase are, in our paper, depending on the maturity variable. We prove, under local conditions on the rates of mortality and the rate of return from the resting to the proliferating phase, exponential stability of the trivial solution of our system. This result is obtained under the assumption that the proliferating phase is long enough,

$$\tau > \sup_{m \in [0, g(1)]} \left( \int_m^{g^{-1}(m)} \frac{ds}{V(s)} \right). \quad (3)$$

We also obtained under Condition (3), that if the initial population of cells  $\varphi(t, m)$  is 0 for the maturity  $m$  in  $[0, b]$ , where  $b > 0$  can be chosen as small as we want (stem cells), then the population goes to extinction at a finite time. Moreover, if

$\varphi(t, 0) = 0$  (primitive cells), then  $N(t, m) \rightarrow 0$  as  $t \rightarrow \infty$ . In the interpretation of these results the case of a sufficient supply of stem cells implies a normal blood production and the case of injury or destruction of stem cells or primitive cells corresponds to an abnormal production (the aplastic anemia).

## 2. Presentation of the model.

**2.1. Proliferating phase.** We suppose that  $V : [0, 1] \rightarrow [0, +\infty)$  is a continuously differentiable function such that  $V(m) > 0$ , for  $m \in (0, 1]$ , and  $V(0) = 0$ .

We also assume that  $\gamma : [0, 1] \rightarrow [0, +\infty)$  is a continuous function of the maturity  $m$ .

The conservation equation for the proliferating phase is

$$\frac{\partial}{\partial t} p(t, m, a) + \frac{\partial}{\partial a} p(t, m, a) + \frac{\partial}{\partial m} (V(m)p(t, m, a)) = -\gamma(m)p(t, m, a), \quad (4)$$

with the initial condition

$$p(0, m, a) = \Gamma(m, a), \quad \text{for } (m, a) \in [0, 1] \times [0, \tau],$$

where  $\Gamma \in C([0, 1] \times [0, \tau])$ .

Here,  $p(t, m, a)$  represents the density of proliferating cells at time  $t$ , maturity  $m$  and age  $a$ .

The total density of proliferating cells at a given time  $t$  and a maturity level  $m$  is defined by

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

**2.2. Resting phase.** We denote by

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

the total density of cells in the resting phase at a given time  $t$  and maturity level  $m$ , where  $n(t, m, a)$  represents the density of resting cells at time  $t$ , maturity  $m$  and age  $a$ .

We assume that the rate  $\beta(m, N(t, m))$  is a nonlinear function of  $N(t, m)$ .

The conservation equation for the resting phase is

$$\frac{\partial}{\partial t} n(t, m, a) + \frac{\partial}{\partial a} n(t, m, a) + \frac{\partial}{\partial m} (V(m)n(t, m, a)) = -[\delta(m) + \beta(N(t, m), m)] n(t, m, a), \quad (5)$$

with the initial condition

$$n(0, m, a) = \mu(m, a), \quad \text{for } (m, a) \in [0, 1] \times [0, +\infty),$$

where  $\mu \in C([0, 1] \times [0, +\infty))$  and  $\lim_{a \rightarrow +\infty} \mu(m, a) = 0$ .

We suppose that  $\delta$  and  $\beta$  are continuous functions.

**2.3. Boundary conditions.** The cellular flux between the two phases is given by the system

$$\begin{cases} n(t, m, 0) = 2(g^{-1})'(m)p(t, g^{-1}(m), \tau), & \text{for } m \leq g(1), \\ p(t, m, 0) = \int_0^{+\infty} \beta(N(t, m), m)n(t, m, a)da = \beta(N(t, m), m)N(t, m), \end{cases} \tag{6}$$

where  $g(m)$  represents the maturity of the daughter cells when  $m$  is the maturity of their mother.

The first boundary condition describes the flux of daughter cells into the resting phase just after the division of their mother. Note that the maturity  $m$  of the daughter cells just after division is smaller than  $g(1)$ . This fact is expressed by the following boundary condition

$$n(t, m, 0) = 0, \quad \text{for } m > g(1). \tag{7}$$

The second condition in (6) represents the re-entry of resting cells into the proliferating phase.

We assume that  $g : [0, 1] \rightarrow [0, 1]$  is a continuous function such that  $g \in C^1 [0, 1]$ ,  $g'(m) > 0$  and  $g(m) \leq m$ , for  $m \in [0, 1]$ .

**3. Equations for  $N$  and  $P$ .** We define the characteristic curve  $s \rightarrow X(s, m)$  through  $(0, m)$ ,  $m \in [0, 1]$ , in the two phases by the ordinary differential equation

$$\begin{cases} \frac{du}{ds}(s) = V(u(s)), & s \in \mathbb{R}, \\ u(0) = m. \end{cases} \tag{8}$$

We have  $X(0, m) = m$  and  $X(s, 0) = 0$ , for  $s \in \mathbb{R}$  and  $m \in [0, 1]$ .

Note that the expression  $X(s, m)$  appears in our model only for  $s \leq 0$ . Furthermore, one can prove that  $X(s, \cdot)$  is given explicitly, for  $s \leq 0$  and  $m \in [0, 1]$ , by

$$X(s, m) = h^{-1}(h(m)e^s), \tag{9}$$

where  $h : [0, 1] \rightarrow [0, 1]$  has the explicit form

$$h(m) = \begin{cases} \exp\left(-\int_m^1 \frac{ds}{V(s)}\right), & \text{for } m \in (0, 1], \\ 0, & \text{for } m = 0. \end{cases} \tag{10}$$

Using the method of characteristics, one can derive evolution equations for  $N(m, t)$  and  $P(m, t)$  :

(1) If  $m \in [0, g(1)]$  and  $0 \leq t \leq \tau$ ,

$$\frac{\partial}{\partial t} N(t, m) + \frac{\partial}{\partial m} (V(m)N(t, m)) = -[\delta(m) + \beta(N(t, m), m)] N(t, m) + f_1(t, m), \tag{11}$$

with

$$f_1(t, m) = 2(g^{-1})'(m)\xi(g^{-1}(m), t)\Gamma(X(-t, g^{-1}(m)), \tau - t), \tag{12}$$

and

$$\xi(m, t) = \exp \left\{ - \int_0^t (\gamma(X(-s, m)) + V'(X(-s, m))) ds \right\}. \quad (13)$$

If  $m \in [0, g(1)]$  and  $t \geq \tau$ ,

$$\begin{aligned} \frac{\partial}{\partial t} N(t, m) + \frac{\partial}{\partial m} (V(m)N(t, m)) &= - [\delta(m) + \beta(N(t, m), m)] N(t, m) \\ &+ f_2(m)\beta [N(t - \tau, X(-\tau, g^{-1}(m))), X(-\tau, g^{-1}(m))] N(t - \tau, X(-\tau, g^{-1}(m))), \end{aligned} \quad (14)$$

with

$$f_2(m) = 2(g^{-1})'(m)\xi(g^{-1}(m), \tau). \quad (15)$$

If  $m \in [g(1), 1]$  and  $t \geq 0$ ,

$$\frac{\partial}{\partial t} N(t, m) + \frac{\partial}{\partial m} (V(m)N(t, m)) = - [\delta(m) + \beta(N(t, m), m)] N(t, m). \quad (16)$$

(2) If  $m \in [0, 1]$  and  $0 \leq t \leq \tau$ ,

$$\frac{\partial}{\partial t} P(t, m) + \frac{\partial}{\partial m} (V(m)P(t, m)) = -\gamma(m)P(t, m) + \beta(N(t, m), m)N(t, m) - f_3(t, m), \quad (17)$$

with

$$f_3(t, m) = \xi(m, t)\Gamma(X(-t, m), \tau - t). \quad (18)$$

(3) Finally, if  $m \in [0, 1]$  and  $t \geq \tau$ ,

$$\begin{aligned} \frac{\partial}{\partial t} P(t, m) + \frac{\partial}{\partial m} (V(m)P(t, m)) &= -\gamma(m)P(t, m) + \beta(N(t, m), m)N(t, m) \\ &- \xi(m, \tau)\beta [N(t - \tau, X(-\tau, m)), X(-\tau, m)] N(t - \tau, X(-\tau, m)). \end{aligned} \quad (19)$$

Since our objective in this work is to prove that uniqueness and asymptotic behavior of the solutions depend only on the cells with small maturity (stem cells), we will focus our study on the production process given by Equation (14) on the maturity interval  $[0, g(1)]$ .

The first term on the right-hand side of Equation (14) describes the loss due to death and transition to the proliferating phase. The second term describes the birth of cells with maturity  $m$  from mother cells completing their proliferating phase who entered into the proliferating phase a time  $\tau$  ago with a maturity  $X(-\tau, g^{-1}(m))$ .

**4. Existence and uniqueness.** The integrated version (variation of constants formula) of Equation (14) for  $t \geq \tau$  and  $m \in [0, g(1)]$  is given by

$$\begin{aligned}
N(t, m) = & \varphi(\tau, X(-(t-\tau), m)) K(t-\tau, m) \\
& - \int_{\tau}^t K(t-s, m) \beta[N(s, X(-(t-s), m)), X(-(t-s), m)] N(s, X(-(t-s), m)) ds \\
& + \int_{\tau}^t K(t-s, m) f_2(X(-(t-s), m)) \\
& \times \beta[N(s-\tau, X(-\tau, g^{-1}(X(-(t-s), m))))], X(-\tau, g^{-1}(X(-(t-s), m)))] \\
& \times N(s-\tau, X(-\tau, g^{-1}(X(-(t-s), m)))) ds,
\end{aligned} \tag{20}$$

and  $N(t, m) = \varphi(t, m)$ , for  $t \in [0, \tau]$ , and  $m \in [0, g(1)]$ ,  
where

$$K(t, m) = \exp \left\{ - \int_0^t (\delta(X(-\sigma, m)) + V'(X(-\sigma, m))) d\sigma \right\}, \tag{21}$$

and

$$\varphi \in C([0, \tau] \times [0, g(1)]).$$

Note that the initial datum  $\varphi$  is in fact the solution of Equation (11) for  $(t, m) \in [0, \tau] \times [0, g(1)]$ .

**PROPOSITION 4.1.** *Suppose that the function  $x \mapsto \beta(x, m)x$  is Lipschitz continuous, that is*

$$|\beta(x_1, m)x_1 - \beta(x_2, m)x_2| \leq k|x_1 - x_2|, \quad \text{for } x_1, x_2 \in \mathbb{R} \quad \text{and } m \in [0, g(1)],$$

where  $k$  is a positive constant. If  $\varphi \in C([0, \tau] \times [0, g(1)])$ , then there exists a unique solution  $N \in C([0, +\infty) \times [0, g(1)])$  of Equation (20).

*Proof.* The proof is classical. Let  $t \geq 0$ ,  $m \in [0, g(1)]$  and  $N \in C([0, +\infty) \times [0, g(1)])$ . We set

$$\begin{aligned}
G(N)(t, m) = & - \int_{\tau}^t K(t-s, m) \beta[N(s, X(-(t-s), m)), \\
& X(-(t-s), m)] N(s, X(-(t-s), m)) ds,
\end{aligned} \tag{22}$$

and

$$\begin{aligned}
H(N^\tau)(t, m) = & \int_{\tau}^t K(t-s, m) f_2(X(-(t-s), m)) \\
& \times \beta[N(s-\tau, X(-\tau, g^{-1}(X(-(t-s), m))))], X(-\tau, g^{-1}(X(-(t-s), m)))] \\
& \times N(s-\tau, X(-\tau, g^{-1}(X(-(t-s), m)))) ds.
\end{aligned} \tag{23}$$

Then, Equation (20) becomes

$$N(t, m) - G(N)(t, m) = \varphi(\tau, X(-(t - \tau), m)) K(t - \tau, m) + H(N^\tau)(t, m). \quad (24)$$

Let  $(N_n)_{n \in \mathbb{N}}$  be a sequence of continuous functions given, for  $t \in [0, 2\tau]$  and  $m \in [0, g(1)]$ , by

$$N_n(t, m) = \begin{cases} N_0(t, m) + G(N_{n-1})(t, m), & \text{for } t \in [\tau, 2\tau], \\ \varphi(t, m), & \text{for } t \in [0, \tau], \end{cases}$$

and, for  $t \in [\tau, 2\tau]$

$$\begin{aligned} N_0(t, m) &= \varphi(\tau, X(-(t - \tau), m)) K(t - \tau, m) + \int_\tau^t K(t - s, m) f_2(X(-(t - s), m)) \\ &\times \beta[\varphi(s - \tau, X(-\tau, g^{-1}(X(-(t - s), m))))], X(-\tau, g^{-1}(X(-(t - s), m)))] \\ &\times \varphi(s - \tau, X(-\tau, g^{-1}(X(-(t - s), m)))) ds. \end{aligned}$$

Due to the continuity of  $X$ ,  $\delta$ ,  $V'$ ,  $\varphi$  and  $f_2$ , there exist  $\alpha > 0$  and  $M_0 \geq 0$  such that

$$\begin{cases} |K(t, m)| \leq \alpha, & \text{for } t \geq 0 \text{ and } m \in [0, g(1)], \\ |N_0(s, X(-(t - s), m))| \leq M_0, & \text{for } t \in [\tau, 2\tau], s \in [\tau, t] \text{ and } m \in [0, g(1)]. \end{cases}$$

Then, we obtain for  $t \in [\tau, 2\tau]$  and  $m \in [0, g(1)]$  that

$$|N_1(t, m) - N_0(t, m)| = |G(N_0)(t, m)| \leq \alpha k \int_\tau^t |N_0(s, X(-(t - s), m))| ds,$$

and thus

$$|N_1(t, m) - N_0(t, m)| \leq \alpha k M_0 (t - \tau).$$

In the general case, we have

$$N_n(t, m) - N_{n-1}(t, m) = G(N_{n-1})(t, m) - G(N_{n-2})(t, m).$$

Thus

$$\begin{aligned} |N_n(t, m) - N_{n-1}(t, m)| &\leq \alpha k \int_\tau^t |N_{n-1}(s, X(-(t - s), m)) \\ &- N_{n-2}(s, X(-(t - s), m))| ds. \end{aligned}$$

By induction, we obtain

$$|N_n(t, m) - N_{n-1}(t, m)| \leq \alpha^n k^n M_0 \frac{(t - \tau)^n}{n!}.$$

So, the limit  $N := \lim_{n \rightarrow \infty} N_n$  exists uniformly on  $[0, 2\tau]$  and  $N$  is continuous on  $[0, 2\tau]$ .

To prove that  $N$  is a solution of Equation (20), we introduce the function  $v$  defined by

$$v(t, m) = |N(t, m) - N_0(t, m) - G(N)(t, m)|.$$

Then, we have

$$\begin{aligned} v(t, m) &\leq |N(t, m) - N_{n+1}(t, m)| + |N_{n+1}(t, m) - N_0(t, m) - G(N)(t, m)|, \\ &\leq |N(t, m) - N_{n+1}(t, m)| + |G(N)(t, m) - G(N_n)(t, m)|, \\ &\leq |N(t, m) - N_{n+1}(t, m)| + \alpha k \int_{\tau}^t |N(s, X(-(t-s), m)) \\ &\quad - N_n(s, X(-(t-s), m))| ds. \end{aligned}$$

Moreover ,

$$N(t, m) - N_n(t, m) = \sum_{p=n}^{+\infty} (N_{p+1}(t, m) - N_p(t, m)).$$

This implies that,

$$|N(t, m) - N_{n+1}(t, m)| \leq M_0 \sum_{p=n+1}^{+\infty} \alpha^{p+1} k^{p+1} \frac{(t-\tau)^{p+1}}{(p+1)!}.$$

So,

$$v(t, m) \leq 2M_0 \sum_{p=n}^{+\infty} \frac{(\alpha k(t-\tau))^{p+2}}{(p+2)!}, \quad \text{for all } n \in \mathbb{N}.$$

Hence, when  $n$  tends to  $+\infty$ , we obtain

$$v(t, m) = 0, \quad \text{for } t \in [0, 2\tau] \text{ and } m \in [0, g(1)].$$

Consequently,  $N$  is a solution of Equation (20) on  $[0, 2\tau] \times [0, g(1)]$ .

To prove uniqueness, we suppose that  $Z$  is also a solution of Equation (20). Then,

$$|N(t, m) - Z(t, m)| \leq \alpha k \int_{\tau}^t |N(s, X(-(t-s), m)) - Z(s, X(-(t-s), m))| ds.$$

We suppose that  $t \in [\tau, 2\tau]$  is fixed and we consider the function  $w$  for  $\sigma \in [\tau, t]$  and  $m \in [0, g(1)]$ , defined by

$$w(\sigma) = |N(\sigma, X(-(t-\sigma), m)) - Z(\sigma, X(-(t-\sigma), m))|.$$

Remark that,

$$X(-(\sigma-s), X(-(t-\sigma), m)) = X(-(t-s), m).$$

Then, we obtain

$$w(\sigma) \leq \alpha k \int_{\tau}^{\sigma} |N(s, X(-(t-s), m)) - Z(s, X(-(t-s), m))| ds.$$

Consequently,

$$w(\sigma) \leq \alpha k \int_{\tau}^{\sigma} w(s) ds.$$

By the Gronwall's inequality, it follows that  $w = 0$ . Then,  $N = Z$  on  $[\tau, 2\tau]$ .

By the method of steps, we deduce the existence and uniqueness for all  $t \geq 0$ .  $\square$



REMARK 1. If  $x \mapsto \beta(x, m)x$  is only locally Lipschitz continuous, one can prove using Gronwall's inequality that Equation (20) has at most one solution.

We will now study the transformation of maturity from one generation of cells to another. We put

$$\Delta(m) = X(-\tau, g^{-1}(m)), \quad \text{for } m \leq g(1). \quad (25)$$

Recall that  $\Delta(m)$  represents the maturity of a mother cell at commitment when  $m$  is the maturity of its two daughter cells. The function  $\Delta : [0, g(1)] \rightarrow [0, g(1)]$  is continuously differentiable and satisfies

$$\begin{cases} \Delta(0) = 0, & \Delta(g(1)) = h^{-1}(e^{-\tau}), \\ \Delta'(m) > 0, & \text{for } m \in [0, g(1)]. \end{cases}$$

Note that for  $s \leq 0$

$$\max_{m \in [0, 1]} (X(s, m)) = X(s, 1) = h^{-1}(e^s).$$

Let  $0 < m_0 \leq g(1)$  be fixed. We set

$$\begin{cases} \tau_0 = \sup_{m \in [m_0, g(1)]} \left( \int_m^{g^{-1}(m)} \frac{ds}{V(s)} \right), \\ \tau_1 = \int_{m_0}^1 \frac{ds}{V(s)}. \end{cases}$$

Remark that, if

$$\lim_{m \rightarrow 0} \left( \int_m^{g^{-1}(m)} \frac{ds}{V(s)} \right) < +\infty$$

then  $m_0$  can be chosen equal to zero, and which in this case means that  $\tau_1 = +\infty$ . As in the linear case, to prove our main results, we need the following lemma.

- LEMMA 4.1. (i)  $\tau_0 < \tau_1$ ,  
(ii)  $m_0 < h^{-1}(e^{-\tau})$  if and only if  $\tau < \tau_1$ ,  
(iii) if  $\tau > \tau_0$  then  $h^{-1}(e^{-\tau}) < g(1)$ ,  
(iv)  $\tau > \tau_0$  if and only if  $\Delta(m) < m$ , for all  $m \in [m_0, g(1)]$ .

The condition  $\tau > \tau_0$  means that the duration of the proliferating phase is sufficiently long to let a future mother cell, whose maturity at the point of commitment was  $\Delta(m)$ , increase sufficiently its maturity during this phase such that, just after its division the maturity  $m$  of its daughter cells will be greater than the maturity  $\Delta(m)$ .

We assume in the sequel of this paper that

$$\lim_{m \rightarrow 0} \left( \int_m^{g^{-1}(m)} \frac{ds}{V(s)} \right) < +\infty, \quad (26)$$

and

$$\tau > \tau_0, \quad \text{with } m_0 = 0.$$

The results hold with obvious modifications, for any  $m_0 \in (0, g(1)]$ .

We give now an example for which the condition (26) is satisfied.

EXAMPLE 4.1. *Suppose that  $V(s) \underset{s \rightarrow 0}{\sim} \alpha s$ , with  $\alpha > 0$ .*

Then,

$$\lim_{m \rightarrow 0} \left( \int_m^{g^{-1}(m)} \frac{ds}{V(s)} \right) < +\infty \quad \text{if and only if} \quad g'(0) > 0.$$

Note that a cell in the proliferating phase whose maturity at the point of commitment is  $h^{-1}(e^{-\tau})$  will give birth to two daughter cells with maturity  $g(1)$ , which is the maximal maturity of cells just after division. So, we can consider the function  $\Lambda : [0, g(1)] \rightarrow [0, 1]$  defined by

$$\Lambda(m) = \begin{cases} \Delta^{-1}(m), & \text{for } m \in [0, h^{-1}(e^{-\tau})], \\ g(1), & \text{for } m \in [h^{-1}(e^{-\tau}), g(1)]. \end{cases}$$

Note that the function  $\Lambda$  is continuously differentiable on  $[0, h^{-1}(e^{-\tau})]$  and satisfies

$$\begin{cases} \Lambda(0) = 0, & \Lambda(h^{-1}(e^{-\tau})) = g(1), \\ \Lambda(m) > m, & \text{for } m \in (0, h^{-1}(e^{-\tau})], \\ \Lambda'(m) > 0, & \text{for } m \in [0, h^{-1}(e^{-\tau})]. \end{cases}$$

Let  $b \in (0, h^{-1}(e^{-\tau}))$  be fixed. Consider the following sequence

$$\begin{cases} b_{n+1} = \Lambda(b_n), \\ b_0 = b. \end{cases} \tag{27}$$

The condition  $\tau > \tau_0$  implies that the sequence  $(b_n)_{n \in \mathbb{N}}$  is increasing and that there exists  $N \in \mathbb{N}^*$  such that

$$b_0 < b_1 < \dots < b_N < h^{-1}(e^{-\tau}) \leq b_{N+1} < b_{N+2} = \dots = g(1). \tag{28}$$

Now we give the first of our main results, which emphasizes the strong link between the process of production of cells and cells with small maturity (stem cells).

The following result has been proved by Adimy and Pujon-Menjouet (2001) in the linear case (i.e.  $\beta = \beta(m)$ ). It has also been proved by Dyson, Villella-Bressan and Webb (1996b) in the special case when the maturity  $X(-\tau, g^{-1}(m))$  is independent of  $\tau$  and equal to  $\alpha m$ ,  $0 < \alpha < 1$ . It is also a first step to study the asymptotic behavior and instability of our model.

THEOREM 4.1. *Assume that the function  $x \mapsto \beta(x, m)x$  is locally Lipschitz continuous and  $N^1(t, m)$ ,  $N^2(t, m)$  are solutions of Equation (20) with initial conditions  $\varphi^1, \varphi^2 \in C([0, \tau] \times [0, g(1)])$  respectively. Suppose that there exist  $\tau > \tau_0$  and  $b \in (0, h^{-1}(e^{-\tau}))$  such that  $\varphi^1(t, m) = \varphi^2(t, m)$  for  $m \in [0, b]$  and  $t \in [0, \tau]$ . Then, there exists  $\bar{t} > \tau$  such that  $N^1(t, m) = N^2(t, m)$ , for all  $m \in [0, g(1)]$  and  $t \geq \bar{t}$ , where  $\bar{t}$  can be chosen equal to  $t_{N+2} = \ln \left[ \frac{h(b_{N+2})}{h(b)} \right] + (N + 2)\tau$ .*

*Proof.* Recall that  $h^{-1}(e^{-\tau}) < g(1)$ .

The proof is based on our proof in the linear case and the use of the Gronwall's lemma.

First, we establish by induction that  $N^1(t, m) = N^2(t, m)$ , for  $m \in [0, b]$  and  $t \geq 0$ . That is, for  $t \in [\tau, 2\tau]$  and  $\tau \leq \sigma \leq t$ , we obtain

$$\Delta(X(-(t-\sigma), m)) \leq \Delta(m) \leq m \leq b.$$

Hence,

$$N^1(\sigma - \tau, \Delta(X(-(t-\sigma), m))) = N^2(\sigma - \tau, \Delta(X(-(t-\sigma), m))).$$

Consequently,

$$N^1(t, m) - N^2(t, m) = G(N^1)(t, m) - G(N^2)(t, m).$$

By the Gronwall's inequality, it follows that

$$N^1(t, m) = N^2(t, m), \quad \text{for } m \in [0, b] \quad \text{and } t \in [\tau, 2\tau].$$

By a method of steps, we deduce that

$$N^1(t, m) = N^2(t, m), \quad \text{for } m \in [0, b] \quad \text{and } t \geq 0.$$

Secondly, we reconsider the sequence  $(b_n)_{n \geq 0}$  given by (27), and the sequence  $(t_n)_{n \in \mathbb{N}}$  defined by

$$t_n = \ln \left[ \frac{h(b_n)}{h(b)} \right] + n\tau. \quad (29)$$

This sequence  $(t_n)_{n \in \mathbb{N}}$  is increasing. Thus, we prove by induction the following result

$$N^1(t, m) = N^2(t, m), \quad \text{for } m \in [0, b_n] \quad \text{and } t \geq t_n.$$

So, by induction and using (28), we obtain

$$N^1(t, m) = N^2(t, m), \quad \text{for } m \in [0, g(1)] \quad \text{and } t \geq \bar{t} = t_{N+2},$$

with

$$t_{N+2} = \ln \left[ \frac{h(b_{N+2})}{h(b)} \right] + (N+2)\tau.$$

□

According to the proof above, we also have the following existence result.

**COROLLARY 4.1.** *Let  $\tau > \tau_0$  and  $b \in (0, h^{-1}(e^{-\tau}))$ . Suppose that the function  $x \mapsto \beta(x, m)x$  is Lipschitz continuous and  $\varphi \in C([0, \tau] \times [0, b])$ . Equation (20) has a unique solution  $N^\varphi(t, m)$ , for  $m \in [0, b]$  and  $t \geq 0$ .*

It is believed that the pathology of aplastic anemia is due to injury or destruction of a common pluripotential stem cell. Theorem 4.1 proves that the production of cells depends strongly on the state of cells with small maturity. In particular, it describes the destruction of a cell population when its starting value is defective. This is the first step to study the asymptotic behavior of our model that we present in the following section.

**5. Invariance and asymptotic behavior.** Let  $\tau > \tau_0$ ,  $b \in (0, h^{-1}(e^{-\tau}))$  and  $\varphi \in C([0, \tau] \times [0, b])$ .

We set

$$\|\varphi\|_b = \sup_{0 \leq t \leq \tau, 0 \leq m \leq b} |\varphi(t, m)|.$$

We define the sequence of continuous functions  $(N_n)_{n \in \mathbb{N}}$ , for  $t \geq 0$  and  $m \in [0, b]$ , by

$$N_0(t, m) = \begin{cases} \varphi(\tau, X(-(t - \tau), m)) K(t - \tau, m), & \text{for } t \geq \tau, \\ \varphi(t, m), & \text{for } t \in [0, \tau], \end{cases}$$

and

$$N_n(t, m) = \begin{cases} N_0(t, m) - G(N_{n-1})(t, m) + H(N_{n-1}^\tau)(t, m), & \text{for } t \geq \tau, \\ \varphi(t, m), & \text{for } t \in [0, \tau]. \end{cases} \tag{30}$$

PROPOSITION 5.1. *Let  $\epsilon > 0$ . Suppose that*

$$\delta(m) + V'(m) > 0, \quad \text{for } m \in [0, b],$$

*and that the function  $x \rightarrow \beta(x, m)x$  satisfies the following Lipschitz condition*

$$|\beta(x_1, m)x_1 - \beta(x_2, m)x_2| \leq k|x_1 - x_2|, \text{ for } |x_1| \leq \epsilon, |x_2| \leq \epsilon \text{ and } m \in [0, b],$$

*where  $k := k(\epsilon)$  is a positive constant such that*

$$k < \frac{I_b}{1 + \tilde{\xi}_b},$$

*with  $I_b = \inf_{m \in [0, b]} (\delta(m) + V'(m))$  and  $\tilde{\xi}_b := \sup_{m \in [0, b]} |f_2(m)|$ . If the initial condition  $\varphi \in C([0, \tau] \times [0, b])$  satisfies*

$$\|\varphi\|_b \leq \epsilon,$$

*then, the unique solution  $N^\varphi$  of Equation (20) satisfies*

$$|N^\varphi(t, \cdot)|_b := \sup_{m \in [0, b]} |N^\varphi(t, m)| \leq \epsilon, \quad \text{for all } t \geq 0, \tag{31}$$

*and*

$$|N^\varphi(t, \cdot)|_\infty := \sup_{m \in [0, g(1)]} |N^\varphi(t, m)| \leq \epsilon, \quad \text{for all } t \geq t_{N+2}. \tag{32}$$

*Furthermore,*

$$\sup_{m \in [0, g(1)]} |N^\varphi(t, m)| \rightarrow 0 \quad \text{exponentially as } t \rightarrow +\infty.$$

*Proof.* Let  $T \geq \tau$ . We consider the sequence  $(N_n)_{n \in \mathbb{N}}$  given by (30) for  $t \in [0, T]$  and  $m \in [0, b]$ .

We have

$$K(t, m) \leq e^{-I_b t}. \quad (33)$$

On the other hand, we have for all  $t \in [\tau, T]$  and  $m \in [0, b]$

$$X(-(t - \tau), m) \leq m \leq b.$$

Then,

$$|\varphi(\tau, X(-(t - \tau), m))| \leq \epsilon.$$

Consequently,

$$|N_0(t, m)| \leq \epsilon e^{-I_b(t-\tau)} \leq \epsilon.$$

Similarly, we have

$$\begin{aligned} |G(N_0)(t, m)| &\leq k \int_{\tau}^t e^{-I_b(t-s)} |N_0(s, X(-(t-s), m))| ds, \\ &\leq k\epsilon \int_{\tau}^t e^{-I_b(t-s)} ds, \end{aligned}$$

and

$$\begin{aligned} |H(N_0^\tau)(t, m)| &= \\ &k \int_{\tau}^t e^{-I_b(t-s)} |f_2(X(-(t-s), m))| |N_0(s - \tau, X(-\tau, g^{-1}(X(-(t-s), m))))| ds. \end{aligned}$$

As  $g'(m) > 0$  for  $m \in [0, 1]$ , we have

$$\tilde{\xi}_b := \sup_{m \in [0, b]} |f_2(m)| < +\infty. \quad (34)$$

On the other hand,

$$\begin{aligned} X(-\tau, g^{-1}(X(-(t-s), m))) &= \Delta(X(-(t-s), m)), \\ &\leq X(-(t-s), m), \\ &\leq m \leq b. \end{aligned}$$

Then,

$$|H(N_0^\tau)(t, m)| \leq \tilde{\xi}_b k \epsilon \int_{\tau}^t e^{-I_b(t-s)} ds.$$

Consequently,

$$|N_1(t, m)| \leq \epsilon \left( e^{-I_b(t-\tau)} + \mu_0 \left( 1 - e^{-I_b(t-\tau)} \right) \right),$$

where

$$\mu_0 = \frac{k(1 + \tilde{\xi}_b)}{I_b} < 1.$$

Hence,

$$|N_1(t, m)| \leq \epsilon \left( e^{-I_b(t-\tau)} [1 - \mu_0] + \mu_0 \right) \leq \epsilon.$$

By induction we show that for  $n \in \mathbb{N}^*$ ,  $t \in [0, T]$  and  $m \in [0, b]$

$$|N_n(t, m)| \leq |N_0(t, m)| + |G(N_{n-1})(t, m)| + |H(N_{n-1}^\tau)(t, m)| \leq \epsilon.$$

On the other hand, using the same technique as in the proof of Proposition 5.1, we can see that the sequence  $(N_n)_{n \in \mathbb{N}}$  converges to the solution  $N^\varphi \in C([0, +\infty) \times [0, b])$  of Equation (20). When  $n \rightarrow +\infty$ , we obtain

$$|N^\varphi(t, \cdot)|_b \leq \epsilon, \quad \text{for all } t \in [0, T].$$

Then, the inequality (31) holds for  $t \geq 0$ .

Moreover, as in Theorem 4.1, we can prove that

$$|N^\varphi(t, \cdot)|_{b_n} \leq \epsilon, \quad \text{for all } t \geq t_n.$$

In particular,

$$|N^\varphi(t, \cdot)|_\infty \leq \epsilon, \quad \text{for all } t \geq t_{N+2}.$$

Let  $\lambda_0 \in (0, I_b)$  such that

$$k < \frac{I_b - \lambda_0}{1 + \tilde{\xi}_b e^{\lambda_0 \tau}} < \frac{I_b}{1 + \tilde{\xi}_b},$$

and set

$$\lambda_1 = \frac{(1 + \tilde{\xi}_b e^{\lambda_0 \tau})k}{I_b - \lambda_0}.$$

Then, by induction we obtain

$$|N_n(t, m)| \leq \epsilon \frac{1 - \lambda_1^{n+1}}{1 - \lambda_1} e^{-\lambda_0(t-\tau)},$$

for  $n \in \mathbb{N}$ ,  $t$  large enough and  $m \in [0, g(1)]$ . Remark that

$$0 < \lambda_1 < 1.$$

When  $n \rightarrow +\infty$ , we obtain exponential decay. This completes the proof. □

**COROLLARY 5.1.** *Assume that the assumptions of Proposition 5.1 are satisfied. If the initial condition  $\varphi \in C([0, \tau] \times [0, b])$  is such that*

$$\varphi(t, 0) = 0, \quad \text{for all } t \in [0, \tau], \tag{35}$$

*then, the unique solution  $N^\varphi$  of Equation (20) satisfies*

$$\sup_{m \in [0, g(1)]} |N^\varphi(t, m)| \rightarrow 0 \quad \text{exponentially as } t \rightarrow +\infty.$$

*Proof.* Condition (35) and the continuous property of  $\varphi$  imply that there exists  $\bar{b}$  such that

$$\|\varphi\|_{\bar{b}} \leq \epsilon.$$

Let  $b_0 = \min(b, \bar{b})$ . Then,

$$\|\varphi\|_{b_0} \leq \epsilon \quad \text{and} \quad k < \frac{I_b}{1 + \xi_b} \leq \frac{I_{b_0}}{1 + \xi_{b_0}}.$$

Consequently, Proposition 5.1 gives the result.  $\square$

We also obtain the following global stability result.

**COROLLARY 5.2.** *Suppose that*

$$\delta(m) + V'(m) > 0, \quad \text{for } m \in [0, g(1)],$$

*and that the function  $x \rightarrow \beta(x, m)x$  is Lipschitz continuous for all  $m \in [0, g(1)]$  with a Lipschitz constant  $k$  such that*

$$k < \frac{I_{g(1)}}{1 + \xi_{g(1)}}.$$

*Then, for all initial condition  $\varphi \in C([0, \tau] \times [0, g(1)])$ , the solution  $N^\varphi$  of Equation (20) satisfies*

$$\sup_{m \in [0, g(1)]} |N^\varphi(t, m)| \rightarrow 0 \quad \text{exponentially as } t \rightarrow +\infty.$$

*Proof.* As in the proof of Proposition 5.1, we have

$$|N^\varphi(t, m)| \leq \|\varphi\|, \quad \text{for } m \in [0, g(1)] \text{ and } t \geq 0.$$

Then,  $\sup_{m \in [0, g(1)]} |N^\varphi(t, m)| \rightarrow 0$  exponentially as  $t \rightarrow +\infty$ .  $\square$

We now give an example.

**EXAMPLE 5.1.** *Let*

$$V(x) = rx \quad \text{and} \quad g(x) = \alpha x, \quad \text{with } r > 0 \text{ and } 0 < \alpha < 1.$$

*Equation (14) reduces to*

$$\begin{aligned} \frac{\partial}{\partial t} N(t, m) + rm \frac{\partial}{\partial m} N(t, m) &= -[\delta + r + \beta[N(t, m), m]] N(t, m) \\ &+ 2\alpha^{-1} e^{-(\gamma+r)\tau} \beta[N(t-\tau, \Delta(m)), \Delta(m)] N(t-\tau, \Delta(m)). \end{aligned} \quad (36)$$

*This particular model has been considered by Rey and Mackey (1995b) and Mackey and Rudnicki (1999).*

*We have in this case*

$$\begin{cases} \tau_0 & := \sup_{m \in [0, \alpha]} \left( \int_m^{g^{-1}(m)} \frac{ds}{V(s)} \right) = -\frac{1}{r} \ln \alpha, \\ \tau_1 & := \int_0^1 \frac{ds}{V(s)} = +\infty, \end{cases}$$

and

$$\Delta(m) = X(-\tau, g^{-1}(m)) = \alpha^{-1} e^{-r\tau} m.$$

So,

$$\tau > \tau_0 \quad \text{if and only if} \quad \Delta(m) < m, \quad \text{for } m \neq 0.$$

We also have

$$\begin{cases} h^{-1}(e^{-\tau}) & = e^{-r\tau}, \\ I_b & = r + \delta, \\ \tilde{\xi}_b & = 2\alpha^{-1} e^{-(\gamma+r)\tau}. \end{cases}$$

Consequently,

$$\frac{I_b}{1 + \tilde{\xi}_b} = \frac{r + \delta}{2\alpha^{-1} e^{-(\gamma+r)\tau} + 1}.$$

Then, we have the following result.

PROPOSITION 5.2. *Let  $\epsilon > 0$ ,  $\tau > -\frac{1}{r} \ln \alpha$  and  $0 < b < e^{-r\tau}$ . Suppose that the function  $x \rightarrow \beta(x, m)x$  satisfies*

$$|\beta(x_1, m)x_1 - \beta(x_2, m)x_2| \leq k |x_1 - x_2|, \quad \text{for } |x_1| \leq \epsilon, |x_2| \leq \epsilon \text{ and } m \in [0, b].$$

where  $k$  is a positive constant such that

$$k < \frac{r + \delta}{2\alpha^{-1} e^{-(\gamma+r)\tau} + 1}.$$

If the initial datum  $\varphi \in C([0, \tau] \times [0, b])$  is such that,

$$\|\varphi\|_b \leq \epsilon.$$

Then, the unique solution  $N^\varphi$  of Equation (36) satisfies

$$\sup_{m \in [0, b]} |N^\varphi(t, m)| \leq \epsilon, \quad \text{for } t \geq 0,$$

and

$$\sup_{m \in [0, \alpha]} |N^\varphi(t, m)| \rightarrow 0 \quad \text{exponentially as } t \rightarrow +\infty.$$



**6. Instability.** Consider the space

$$C_0 = \{\varphi \in C([0, \tau] \times [0, g(1)]) : \varphi(t, 0) = 0, \text{ for } t \in [0, \tau]\}.$$

DEFINITION 6.1. *We say that a solution  $N^\varphi$  of Equation (20) with initial datum  $\varphi \in C([0, \tau] \times [0, g(1)])$  is stable if for given  $\varepsilon > 0$  there exists  $\rho > 0$  such that*

$$\|\varphi - \psi\| < \rho,$$

*implies*

$$\|N^\varphi(t, \cdot) - N^\psi(t, \cdot)\|_\infty < \varepsilon, \quad \text{for all } t \geq T.$$

*We say that  $N^\varphi$  is unstable if it is not stable.*

To prove the instability of solutions of Equation (20) we need the following hypothesis.

**(H)** There exists a solution of Equation (20) that does not converge to 0, as  $t \rightarrow +\infty$ .

Dyson *et al.* (1996b) showed, for a particular model, that if **(H)** is satisfied for an initial datum  $\varphi_0 \in C_0$ , then for every  $\varphi \in C_0$ ,  $N^{\varphi_0}$  is unstable. They also give an example for which **(H)** is satisfied.

We obtain the same instability property for the more general model (20), that is

THEOREM 6.1. *Suppose that Hypothesis (H) holds for an initial datum  $\varphi_0$  in  $C_0$ . Then, for all  $\varphi \in X_0$ ,  $N^\varphi$  is unstable.*

*Proof.* The proof is similar to the ones given by Dyson *et al.* (1996a and 1996b). It suffices to suppose that there exists  $N^\varphi$  that is stable and the contradiction comes from Theorem 4.1.  $\square$

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Received May 2002; revised October 2002; final version January 2003.

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