Electronic Journal of Differential Equations, Vol. 2003(2003), No. 107, pp. 1–14.
ISSN: 1072-6691. URL: http://ejde.math.txstate.edu or http://ejde.math.unt.edu
ftp ejde.math.txstate.edu (login: ftp)

A MATHEMATICAL MODEL DESCRIBING CELLULAR DIVISION WITH A PROLIFERATING PHASE DURATION DEPENDING ON THE MATURITY OF CELLS

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Abstract. In this paper, we investigate a linear population model of cells that are capable of simultaneous proliferation and maturation. We consider the case when the time required for a cell to divide depends on its maturity. This model is described by first order partial differential system with a retardation of the maturation variable and a time delay depending on this maturity. Both delays are due to cell replication.

1. Introduction

Time-age and time-maturity structured models have been used, for more than 40 years, to study cell replication (see for example Von Foerster in 1959 [26], Trucco in 1965 [23], [24], in 1966 [25], Oldfield in 1966 [17], Nooney in 1967 [16], Rubinow in 1968 [21], and Rubinow and Lebowitz in 1975 [22]).

More recently, in 1994 [13] and in 1999 [14], Mackey and Rudnicki considered a particular time-age-maturity structured model to study the biological process of hematological cell development in the bone marrow. This model is an extension of models that have been considered previously both in the absence of maturation (Mackey in 1978 [11] and in 1979 [12]) or with maturation and only one phase (Rey and Mackey in 1992 [19] and in 1993 [20]). It consists of a population of cells capable of both proliferating and maturating. In this model, the period of life of each cell is divided into a proliferating phase and a resting phase. In the proliferating phase the cells are committed to undergo cell division a time τ later. The position of a cell in the proliferating phase is denoted by a (cell age) which is assumed to range from $a = 0$ (the point of commitment) to $a = \tau$ (the point of cytokinesis). In addition, each cell is characterized by a maturation variable m, that is the concentration of what composes a cell such as proteins, or other elements one can measure experimentally. This maturity can be taken, without loss of generality, from $m = 0$ to $m = 1$. Cells in the proliferating phase can be lost at a rate γ. At age $a = \tau$ a cell divides and gives two daughter cells, which enter directly the resting phase. If the maturation of the mother cell at age $a = \tau$ is m,

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2000 *Mathematics Subject Classification.* 35F15, 35L60, 92C37, 92D25.
Key words and phrases. Structured population, cell cycle, stem cells,
first order partial differential equation with delays, non constant delay.

Submitted February 14, 2003. Published October 23, 2003.
L. P.-M. was partially supported by MITACS, Canada.

the maturation of a daughter cell at birth is assumed to be $g(m)$, with $g(m) \leq m$. In the resting phase, cells can either return to the proliferating phase at a rate β and complete the cycle or die at a rate δ before ending the cycle. A cell can remain in the resting phase indefinitely, and then the cell age ranges from $a = 0$, when the cell enters, to $a = +\infty$. The maturation of a cell and the total number of resting cells determine the capacity of this cell for entering the next proliferating phase. We assume that cells of both types age with unitary velocity, $da/dt = 1$, and mature with a velocity $V(m)$.

In their models, Mackey and Rudnicki [13] and [14], Dyson, Villella-Bressan and Webb [3], [4], [5], [6], [7], [8] and [9], Adimy and Pujo-Menjouet [1] and [2], and Pujo-Menjouet and Rudnicki [18], assumed that the point of cytokinesis τ is the same for all cells. This means that the time required for a cell to divide does not depend on its maturity, and in particular, the division duration of a cell with small maturity (also called stem cell) is the same as one with a higher maturity level. This assumption is not compatible with the biological reality. It is commonly believed that a stem cell proliferates more rapidly than a more mature cell. To our knowledge, the hypothesis that τ depends on the maturity variable, has been given for the first time by Mitchison in 1971 [15], and by John in 1981 [10], but never been used in recent models.

We will assume in this paper that each cell entering the proliferating phase with a maturity m divides at age $\tau(m)$, depending on this maturity, and we require that the mapping

$$m \to \int_m^1 \frac{ds}{V(s)} - \tau(m) \tag{1.1}$$

is strictly decreasing on $(0,1]$. Note that $\int_m^1 \frac{ds}{V(s)}$ represents the time required for a cell with maturity m to reach the maximal maturity 1. The assumption (1.1) is satisfied in the particular case when the mapping $m \mapsto \tau(m)$ is increasing.

Our aim in this paper is to extend and to analyze the model of Mackey and Rudnicki ([13] and [14]) taking into account the new condition. We obtain two time-age-maturity structured partial differential equations with two boundary conditions. We integrate these equations with respect to age, and we obtain two time-maturity structured partial differential equations, in which there is a delay in the time variable as well as in the maturation variable. The time delay depends on the maturity. The model takes the form of a delay-differential equation in a Banach space.

We prove in this model that if the cells have enough time in the proliferating phase,

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

to increase sufficiently their maturity, $m > \Delta(m)$, then the uniqueness of solutions depends, for a finite time, only on cells with small maturity. In particular, if the initial population of cells is 0 for small maturity then the population becomes extinct for a finite time. This result is a first step to study the asymptotic behavior of solutions. We consider here only the linear case. That is a simplification of a more general nonlinear model. We defer to a further publication the use of our approach in the nonlinear case ($\beta = \beta(N)$), to prove some results on stability of solutions.

2. Equations of the model

Denote the density of resting cells by $n(t,m,a)$ and the density of proliferating cells by $p(t,m,a)$, the governing equations of this model are

$$\frac{\partial n}{\partial t}+\frac{\partial n}{\partial a}+\frac{\partial\left(V(m)n\right)}{\partial m}=-\left(\delta(m)+\beta(m)\right)n, \tag{2.1}$$

$$\frac{\partial p}{\partial t}+\frac{\partial p}{\partial a}+\frac{\partial\left(V(m)p\right)}{\partial m}=-\gamma(m)p. \tag{2.2}$$

Throughout this paper, we shall require the following hypothesis concerning the velocity of maturation V in the two phases.

(H1) V is continuously differentiable on $[0,1]$, positive on $(0,1]$ and satisfies $V(0)=0$, and

$$\int_0^m \frac{ds}{V(s)}=+\infty, \qquad \text{for } m\in(0,1]. \tag{2.3}$$

Note that the integral $\int_{m_1}^{m_2}\frac{ds}{V(s)}$, $m_1<m_2$, represents the time required for a cell to go from maturity m_1 to maturity m_2. The condition (2.3) describes the fact that the velocity of cells increases slowly for a small maturity. As example, we have

$$V(m)\underset{m\to 0}{\sim}\alpha_1 m^p, \quad \alpha_1>0,\ p\geq 1.$$

(H2) The functions δ,β and γ are continuous and nonnegative on $[0,1]$.

The total number of cells in the resting stage is given by

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

We assume that the quantity $N(t,m)$ determines the reintroduction at a rate $\beta(m)$ of cells with maturity m from the resting into the proliferating phase. This hypothesis is given by the following boundary condition

$$p(t,m,0)=\int_0^{+\infty}\beta(m)n(t,m,a)da=\beta(m)N(t,m). \tag{2.4}$$

In completing the formulation of this problem, we need a second boundary condition which determines the transfer of cells from the point of cytokinesis into the resting compartment.

We assume that a cell entering the proliferating phase with a maturity $x_0\in[0,1]$ divides at age $\tau(x_0)>0$, and we require that

(H3) τ is a continuously differentiable and positive function on $[0,1]$ such that $\tau'(m)+\frac{1}{V(m)}>0$, for $m\in(0,1]$.

Consider a cell in the proliferating phase at time t, with maturity $x\in(0,1]$, age a and initial maturity x_0, i.e. at age 0. Then, naturally we have

$$x_0\leq x \quad\text{and}\quad a=\int_{x_0}^{x}\frac{ds}{V(s)}\leq\tau(x_0).$$

If x is the maturity of the cell at the point of cytokinesis, then there exists $\Theta(x)\in(0,x)$ (the maturity at the point of commitment) such that

$$\int_{\Theta(x)}^{x}\frac{ds}{V(s)}=\tau(\Theta(x)). \tag{2.5}$$

This value $\Theta(x)$ is unique because the condition **(H3)** implies that the function

$$x_0 \to \int_{x_0}^{x} \frac{ds}{V(s)} - \tau(x_0)$$

is continuous and strictly decreasing from $(0, x]$ into $[-\tau(x), +\infty)$. Then we can define a function $\Theta : (0,1] \to (0,1]$ such that, for each $x \in (0,1]$, $\Theta(x)$ is the solution of Equation (2.5).

Remark that $0 < \Theta(x) < x$ for $x \in (0,1]$. This implies, in particular, that

$$\lim_{x\to 0} \Theta(x) = 0 \quad \text{and} \quad \lim_{x\to 0} \Big(\int_{\Theta(x)}^{x} \frac{ds}{V(s)} \Big) = \tau(0) < +\infty.$$

One can prove that Θ is continuously differentiable on $(0,1]$ and satisfies

$$\Theta'(x)V(x) = \frac{V(\Theta(x))}{1 + \tau'(\Theta(x))V(\Theta(x))}, \quad \text{for } x \in (0,1]. \tag{2.6}$$

This implies, in particular, that

$$\begin{gathered} \Theta'(x) > 0, \quad \text{for } x \in (0,1], \\ \lim_{x\to 0} \big(\Theta'(x)V(x)\big) = 0. \end{gathered}$$

From a biological point of view, $\Theta(x)$ represents the initial maturity of cells in the proliferating phase (the point of commitment) that divide at maturity x (the point of cytokinesis). We deduce that the age of a cell with maturity x at the point of cytokinesis is $\tau(\Theta(x))$. So, the total number P of proliferating cells of a given maturation level $x \in [0,1]$ is given by

$$P(t,x) = \int_0^{\tau(\Theta(x))} p(t,x,a)da. \tag{2.7}$$

At the end of the proliferating phase, a cell with a maturity x divides into two daughter cells, with maturity $g(x)$. These cells enter directly the resting phase with age $a = 0$. We assume that

(H4) $g : [0,1] \to [0,1]$ is a continuous function, continuously differentiable on $[0,1)$ and such that $g(x) \le x$, for $x \in [0,1]$ and $g'(x) > 0$, for $x \in [0,1)$.

We also assume, for technical reasons and without loss of generality, that

$$\lim_{x\to 1} g'(x) = +\infty.$$

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

$$(g^{-1})'(m) = 0, \quad \text{for } m > g(1).$$

Note that the maturity m of the daughter cells just after division is smaller than $g(1)$. Then, we can assume that

$$n(t,m,0) = 0, \quad \text{for } m > g(1). \tag{2.8}$$

The maturity of the mother cell at the point of cytokinesis was $x = g^{-1}(m)$, its age was $\tau(\Theta(g^{-1}(m)))$ and its maturity at the point of commitment was $\Theta(g^{-1}(m))$. We set,

$$\Delta(m) = \Theta\left(g^{-1}(m)\right) \quad \text{for } m \in [0,1]. \tag{2.9}$$

Then, we can give the second boundary condition

$$n(t,m,0) = 2(g^{-1})'(m)p\left(t, g^{-1}(m), \tau(\Delta(m))\right) \quad \text{for } m \in [0,1], \tag{2.10}$$

which includes also the condition (2.8). The explanation of the multiplicative term $2(g^{-1})'(m)$ in the condition (2.10) is the following. The factor 2 accounts for the division of each cell at mitosis (doubling of the cell). The term $(g^{-1})'(m)$ describes the fact that the two new born cells with maturity on an interval $(m, m+dm)$ come from a mother cell with maturity on the interval $\big(g^{-1}(m), g^{-1}(m) + (g^{-1})'(m)dm\big)$. In fact, the boundary condition (2.10) can be reformulated, by considering the total population of new born cells, as follows

$$\int_0^1 n(t,m,0)dm = 2\int_0^1 p\left(t,m,\tau(\Theta(m))\right)dm.$$

From a biological point of view, Δ gives the link between the maturity of a new born cell and the maturity of its mother at the point of commitment. This function $\Delta : [0,1] \to [0,1]$ is continuous, continuously differentiable on $(0,1]$ and satisfies the following properties:

$$\begin{gathered} \Delta(0) = 0, \\ \Theta(m) \le \Delta(m) \quad \text{and} \quad \Delta'(m) > 0, \quad \text{for } m \in (0, g(1)), \\ \Delta(m) = \Theta(1), \quad \text{for } m \in [g(1), 1]. \end{gathered}$$

Now, we specify initial conditions:

$$\begin{aligned} p(0,m,a) &= \Gamma(m,a), \quad \text{for } (m,a) \in [0,1] \times [0,\overline{\tau}], \\ n(0,m,a) &= \mu(m,a), \quad \text{for } (m,a) \in [0,1] \times [0,+\infty), \end{aligned} \tag{2.11}$$

where $\overline{\tau} := \max_{x\in[0,1]} \tau(x)$, Γ and μ are assumed to be continuous and the function

$$m \mapsto \int_0^{+\infty} \mu(m,a)da$$

is continuous on $[0,1]$, (in particular, $\lim_{a\to+\infty} \mu(m,a) = 0$, for $m \in [0,1]$).

3. Equations for the total population in the resting phase

Before giving the equations for the total population in the resting phase $N(t,m)$, we define the characteristic curves $s \to \pi_s(m)$ through $(0,m)$, $m \in [0,1]$, given as follows: $s \to \pi_s(m)$ is the solution of the differential equation

$$\begin{gathered} \frac{d}{ds}u(s) = V(u(s)), \quad s \in \mathbb{R}, \\ u(0) = m. \end{gathered} \tag{3.1}$$

Note that $\pi_0(m) = m$, for $m \in [0,1]$, and $\pi_s(0) = 0$, for $s \in \mathbb{R}$. The expression $\pi_s(m)$ appears in our model, only for $s \le 0$. Furthermore, $\pi_s(m)$ is given explicitly, for $s \le 0$ and $m \in [0,1]$, by

$$\pi_s(m) = h^{-1}\left(h(m)e^s\right), \tag{3.2}$$

where $h : [0,1] \to [0,1]$ is defined as

$$h(m) = \begin{cases} \exp\big(-\int_m^1 \frac{ds}{V(s)}\big), & \text{if } m \in (0,1], \\ 0, & \text{if } m = 0. \end{cases} \tag{3.3}$$

Let $m \in [0,1]$ and $t \ge 0$. We define

$$\xi(m,t) := \exp\Big\{-\int_0^t \left(\gamma(\pi_{-s}(m)) + V'(\pi_{-s}(m))\right)ds\Big\}. \tag{3.4}$$

It is clear that

$$\xi(m,t)=\frac{V(\pi_{-t}(m))}{V(m)}\exp\Big\{-\int_{\pi_{-t}(m)}^{m}\frac{\gamma(y)}{V(y)}dy\Big\}.$$

Then we obtain the following result.

Proposition 3.1. *Let $m\in[0,1]$ and $t\geq 0$. The total population $N(t,m)$ of cells in the resting phase satisfies the following conditions:*

(1) *If $0\leq t\leq\tau(\Delta(m))$, then*

$$\frac{\partial}{\partial t}N(t,m)+\frac{\partial}{\partial m}\left(V(m)N(t,m)\right)=-\left[\delta(m)+\beta(m)\right]N(t,m)+F(t,m), \tag{3.5}$$

with

$$F(t,m)=2(g^{-1})'(m)\xi(g^{-1}(m),t)\Gamma\left(\pi_{-t}\left(g^{-1}(m)\right),\tau(\Delta(m))-t\right). \tag{3.6}$$

(2) *If $\tau(\Delta(m))\leq t$, then*

$$\begin{aligned}&\frac{\partial}{\partial t}N(t,m)+\frac{\partial}{\partial m}\left(V(m)N(t,m)\right)\\&=-\left[\delta(m)+\beta(m)\right]N(t,m)+K(m)N\left(t-\tau(\Delta(m)),\Delta(m)\right),\end{aligned} \tag{3.7}$$

with

$$K(m)=2(g^{-1})'(m)\xi\left(g^{-1}(m),\tau(\Delta(m))\right)\beta\left(\Delta(m)\right). \tag{3.8}$$

Proof. Equation (2.2) can be solved using the method of characteristics. First, we obtain the following representation of solutions of (2.2),

$$p(t,m,a)=\begin{cases}\xi(m,t)p(0,\pi_{-t}(m),a-t), & \text{for } 0\leq t<a,\\ \xi(m,a)p(t-a,\pi_{-a}(m),0), & \text{for } a\leq t.\end{cases} \tag{3.9}$$

The initial condition (2.11) and the boundary condition (2.4) give

$$p(t,m,a)=\begin{cases}\xi(m,t)\Gamma(\pi_{-t}(m),a-t), & \text{for } 0\leq t<a,\\ \xi(m,a)\beta(\pi_{-a}(m))N(t-a,\pi_{-a}(m)), & \text{for } a\leq t\,.\end{cases} \tag{3.10}$$

By integrating (2.1) with respect to the age between 0 and $+\infty$, it follows that

$$\frac{\partial}{\partial t}N(t,m)+\frac{\partial}{\partial m}\left(V(m)N(t,m)\right)=-\left[\delta(m)+\beta(m)\right]N(t,m)+n(t,m,0).$$

Because of the second boundary condition (2.10), we obtain

$$\begin{aligned}\frac{\partial}{\partial t}N(t,m)+\frac{\partial}{\partial m}\left(V(m)N(t,m)\right)=&-\left[\delta(m)+\beta(m)\right]N(t,m)\\&+2(g^{-1})'(m)p(t,g^{-1}(m),\tau(\Delta(m))).\end{aligned}$$

Furthermore, (3.10) implies

$$\begin{aligned}&p(t,g^{-1}(m),\tau(\Delta(m)))\\&=\begin{cases}\xi(g^{-1}(m),t)\Gamma\left(\pi_{-t}\left(g^{-1}(m)\right),\tau(\Delta(m))-t\right), & \text{for } 0\leq t<\tau(\Delta(m)),\\ \xi(g^{-1}(m),\tau(\Delta(m)))\beta\left(\pi_{-\tau(\Delta(m))}\left(g^{-1}(m)\right)\right) & \\ \times N\left(t-\tau(\Delta(m)),\pi_{-\tau(\Delta(m))}\left(g^{-1}(m)\right)\right), & \text{for } \tau(\Delta(m))\leq t\,.\end{cases}\end{aligned} \tag{3.11}$$

Set $x=\pi_{-\tau(\Delta(m))}\left(g^{-1}(m)\right)$ and remark that

$$\frac{h(x)}{h(g^{-1}(m))}=e^{-\tau(\Theta(g^{-1}(m)))}.$$

Then

$$\int_x^{g^{-1}(m)} \frac{ds}{V(s)} = \tau(\Theta(g^{-1}(m))).$$

According to the definition of Θ, we deduce that

$$x = \Theta(g^{-1}(m)) = \Delta(m).$$

Then, the equations (3.5) and (3.7) follow immediately from Equation (3.11). $\square$

We remark that the solutions of System (3.5)-(3.7) are independent of the proliferating cells, and it is easy to prove (by steps) the existence, uniqueness and regularity of these solutions. We focus our study on Equation (3.7) for $t \geq \overline{\tau}$, with an initial condition φ, which is a solution of the system (3.5)-(3.7) on the set $[0,\overline{\tau}] \times [0,1]$. We assume that this function φ is continuous ($\varphi \in C([0,\overline{\tau}],X)$, with $X = C[0,1]$). We shall look for integrated solutions of Problem (3.7), for $t \geq \overline{\tau}$, which are continuous functions on t with values in X. Therefore, we rewrite Problem (3.7) as the following abstract delay differential equation

$$\begin{aligned} \frac{d}{dt}u(t) &= Au(t) + L(u_t^{\overline{\tau}}), \quad t \geq \overline{\tau}, \\ u(t) &= \varphi(t,.), \quad t \in [0,\overline{\tau}], \end{aligned} \tag{3.12}$$

where $u_t^{\overline{\tau}} : [0,\overline{\tau}] \mapsto X$ is the function defined for $t \geq \overline{\tau}$ by $u_t^{\overline{\tau}}(s) = u(t+s-\overline{\tau})$, $A : D(A) \subseteq C[0,1] \to C[0,1]$ is the unbounded closed linear operator defined by:

$$\begin{aligned} D(A) = \big\{ & u \in C[0,1], u \text{ differentiable on } (0,1], u' \in C(0,1], \\ & \text{and } \lim_{m\to 0} V(m)u'(m) = 0 \big\}, \end{aligned}$$

and

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

and $L : C([0,\overline{\tau}],X) \to X$ is the linear operator defined for all ψ in $C([0,\overline{\tau}],X)$ by

$$L(\psi)(m) = K(m)\psi\left(\overline{\tau} - \tau(\Delta(m)), \Delta(m)\right), \quad m \in [0,1].$$

We establish now the C_0-semigroup generated by the operator A.

Proposition 3.2. *Operator A is the infinitesimal generator of the C_0-semigroup $(S(t))_{t\geq 0}$ defined on $C[0,1]$ by*

$$\left(S(t)y\right)(m) = \overline{\xi}(m,t)y\left(\pi_{-t}(m)\right), \quad \textit{for } y \in C[0,1] \quad \textit{and} \quad m \in [0,1],$$

where

$$\overline{\xi}(m,t) = \frac{V\left(\pi_{-t}(m)\right)}{V(m)} \exp\Big\{ -\int_{\pi_{-t}(m)}^{m} \frac{\delta(s)+\beta(s)}{V(s)} ds \Big\}.$$

The proof of this proposition is similar to the proof of Proposition 1, in [3]; therefore we omit it.

Let $\varphi \in C\left([0,\overline{\tau}],X\right)$ and $t_0 \in [0,\overline{\tau}]$. The following variation of constants formula gives an integrated version of (3.12),

$$u(t) = \begin{cases} S(t-t_0)\varphi(t_0,.) + \int_{t_0}^{t} S(t-s)L(u_s^{t_0})ds, & t \geq t_0, \\ \varphi(t,.), & t \in [0,t_0]. \end{cases} \tag{3.13}$$

Then, for $m \in [0,1]$ and $t \geq t_0$

$$u(t)(m) = \overline{\xi}(m, t-t_0)\varphi\left(t_0, \pi_{-(t-t_0)}(m)\right) + \int_{t_0}^{t} \overline{\xi}(m, t-s) L(u_s^{t_0})(\pi_{-(t-s)}(m))\, ds. \tag{3.14}$$

Consequently, the integrated solutions of Equation (3.7) for $m \in [0,1]$ and $t \geq \overline{\tau}$ are given by

$$\begin{aligned} &N(t,m) \\ &= \overline{\xi}(m, t-\overline{\tau})\varphi\left(\overline{\tau}, \pi_{-(t-\overline{\tau})}(m)\right) \\ &\quad + \int_{\overline{\tau}}^{t} \overline{\xi}(m, t-s) K(\pi_{-(t-s)}(m)) N\left(s - \tau\left(\Delta(\pi_{-(t-s)}(m))\right), \Delta(\pi_{-(t-s)}(m))\right) ds, \end{aligned} \tag{3.15}$$

and $N(t,m) = \varphi(t,m)$, for $(t,m) \in [0,\overline{\tau}] \times [0,1]$.

Proposition 3.3. *There exists a unique continuous solution N of (3.15) with initial condition $\varphi \in C([0,\overline{\tau}] \times [0,1])$.*

The proof of this proposition follows immediately using standard techniques.

The maturity of the daughter cells just after division is smaller than $g(1)$. Then, we can first focus our study on the resting phase for the maturity interval $[0, g(1)]$, which is the source of the cells production. Suppose that

(H5) the mapping

$$m \mapsto \int_{m}^{g^{-1}(m)} \frac{ds}{V(s)}, \quad m \in [0, g(1)],$$

is bounded on a neighborhood of 0.

This condition means that the time required for a cell to reach the maturity of its mother is bounded. As a simple mathematical example we have

$$V(m) \underset{m \to 0}{\sim} \alpha_1 m, \quad \alpha_1 > 0.$$

Then, Condition (H5) is satisfied if and only if $g'(0) > 0$. We also assume that

(H6) $\tau(m) > \int_{m}^{g^{-1}(m)} \frac{ds}{V(s)}$, for all $m \in (0, g(1)]$.

This assumption means that, in the proliferating phase, cells have enough time to reach the maturity of their mother. With the conditions **(H5)** and **(H6)**, we obtain more than uniqueness. Before reformulating this result, we need the following lemmas.

Lemma 3.4. *Let $m \in [0,1]$. Then $\Theta(m)$ is the unique solution of the equation*

$$x = \pi_{-\tau(x)}(m) \quad \text{and} \quad x \leq m.$$

Proof. The equation

$$\int_{x}^{m} \frac{ds}{V(s)} = \tau(x) \quad \text{with } x \leq m$$

is equivalent to $x = \pi_{-\tau(x)}(m)$ and $x \leq m$, which completes the proof. □

Lemma 3.5. *If the conditions (H5) and (H6) are satisfied, then for all $m \in (0, g(1)]$, we have $\Delta(m) < m$.*

Proof. First, recall that for all $m \in (0, g(1)]$,

$$\int_{\Delta(m)}^{g^{-1}(m)} \frac{ds}{V(s)} = \tau(\Delta(m)) .$$

Then, from Condition (H6), it follows that

$$\tau(m) - \int_m^1 \frac{ds}{V(s)} > \tau(\Delta(m)) - \int_{\Delta(m)}^1 \frac{ds}{V(s)}.$$

On the other hand, Condition (H3) implies that the mapping

$$m \mapsto \tau(m) - \int_m^1 \frac{ds}{V(s)}$$

is continuous and strictly increasing on $(0, g(1)]$. Then $m > \Delta(m)$ which completes the proof. $\square$

We remark that Lemma 3.5 implies, in particular, that

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

Let $0 < b < \Theta(1)$ be fixed. The transmission of the maturity from a generation n to the generation $(n + 1)$ can be defined by the sequence

$$b_{n+1} = \begin{cases} \Delta^{-1}(b_n), & \text{if } b_n \in [0, \Theta(1)], \\ g(1), & \text{if } b_n \in [\Theta(1), g(1)], \end{cases} \tag{3.16}$$

and $b_0 = b$. Note that the sequence $(b_n)_{n\in\mathbb{N}}$ is increasing. The following result is immediate.

Lemma 3.6. *There exists* $N \in \mathbb{N}$ *such that* $b_N < \Theta(1) \le b_{N+1} \le g(1)$.

We give now our main result, which emphasizes the strong link between the process of production of cells and the population of stem cells.

Theorem 3.7. *Let* $N(t, m)$ *be a solution of (3.15) with an initial condition* $\varphi \in C([0, \overline{\tau}] \times [0, 1])$. *Suppose that there exists* $0 < b < \Theta(1)$ *such that* $\varphi(t, m) = 0$, *for* $t \in [0, \overline{\tau}]$ *and* $m \in [0, b]$. *Then, there exists* $\overline{t} \ge \overline{\tau}$ *such that* $N(t, m) = 0$, *for* $m \in [0, g(1)]$ *and* $t \ge \overline{t}$, *where* $\overline{t}$ *can be chosen to be*

$$\overline{t} = \ln\left[\frac{h(g(1))}{h(b)}\right] + (N + 2)\overline{\tau},$$

$N \in \mathbb{N}$ *is given by Lemma 3.6, and* $N(t, m) = 0$, *for* $m \in [g(1), 1]$ *and*
$t \ge \overline{t} + \overline{\tau} - \ln(h(g(1))) = (N + 3)\overline{\tau} - \ln(h(b))$.

Proof. First, we prove by induction that $N(t, m) = 0$, for $m \in [0, b]$ and $t \ge 0$. We know that $N(t, m) = 0$ for $(t, m) \in [0, \overline{\tau}] \times [0, b]$. Let $m \in [0, b]$ and $t \ge \overline{\tau}$. We have

$$\pi_{-(t-\overline{\tau})}(m) \le m \le b.$$

So $\varphi\left(\overline{\tau}, \pi_{-(t-\overline{\tau})}(m)\right) = 0$. We suppose that $t \in [\overline{\tau}, \overline{\tau} + \underline{\tau}]$, with $\underline{\tau} := \min_{x\in[0,1]} \tau(x) > 0$, and $s \in [\overline{\tau}, t]$. Then $s - \tau\left(\Delta(\pi_{-(t-s)}(m))\right) \in [0, \overline{\tau}]$. Because Δ is an increasing function and $\pi_{-(t-s)}(m) \le m$, then

$$\Delta(\pi_{-(t-s)}(m)) \le \Delta(m).$$

From lemma 3.5, we deduce that $\Delta(\pi_{-(t-s)}(m)) < m \leq b$. Consequently,

$$N\left(s - \tau\left(\Delta(\pi_{-(t-s)}(m))\right), \Delta(\pi_{-(t-s)}(m))\right) = 0.$$

Then, (3.15) implies that $N(t,m) = 0$ for $m \in [0,b]$ and $t \in [0, \overline{\tau} + \underline{\tau}]$. By steps on the intervals $[0, \overline{\tau} + n\underline{\tau}]$, $n = 1, 2, \dots$, we conclude that

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

Let us now reconsider the sequence $(b_n)_{n\geq 0}$ given by (3.16), and the sequence $(t_n)_{n\in\mathbb{N}}$ defined by

$$\begin{gathered} t_0 = 0, \\ t_{n+1} = t_n + \ln[h(b_{n+1})/h(b_n)] + \overline{\tau}. \end{gathered} \tag{3.17}$$

Then,

$$t_n = \ln\big[\frac{h(b_n)}{h(b)}\big] + n\overline{\tau}. \tag{3.18}$$

We recall that the sequence $(b_n)_{n\in\mathbb{N}}$ is increasing. Then, the sequence $(t_n)_{n\in\mathbb{N}}$ is also increasing.

We will prove, by induction, the following result

($\mathbf{H_n}$) $N(t,m) = 0$ for $m \in [0, b_n]$ and $t \geq t_n$.

We remark that for $m \in (0, g(1)]$,

$$\int_m^{g^{-1}(m)} \frac{ds}{V(s)} = \ln\Big(\frac{h\left(g^{-1}(m)\right)}{h(m)}\Big).$$

First, (H_0) is true. Let us suppose that (H_n) is true. Let $m \in [0, b_{n+1}]$ and $t \geq t_{n+1}$. Then, because of (3.17),

$$t_{n+1} \geq t_n + \overline{\tau}.$$

Using the variation of constant formula (3.14), the solutions of (3.15) can be reformulated, for $t \geq t_{n+1}$, as

$$\begin{aligned} N(t,m) &= \overline{\xi}(m, t - t_n - \overline{\tau}) N\big(t_n + \overline{\tau}, \pi_{-(t-t_n-\overline{\tau})}(m))\big) \\ &\quad + \int_{t_n+\overline{\tau}}^{t} \overline{\xi}(m, t-s) K(\pi_{-(t-s)}(m)) \\ &\quad \times N\left(s - \tau(\Delta(\pi_{-(t-s)}(m))), \Delta(\pi_{-(t-s)}(m))\right) ds. \end{aligned}$$

We remark that $\pi_{-(t-t_n-\overline{\tau})}(m)) = h^{-1}\big(h(m)e^{-(t-t_n-\overline{\tau})}\big)$ and

$$e^{-(t-t_n-\overline{\tau})} = \frac{h(b_n)}{h(b_{n+1})} e^{-(t-t_{n+1})} \leq \frac{h(b_n)}{h(b_{n+1})}.$$

Then, we deduce that

$$\pi_{-(t-t_n-\overline{\tau})}(m)) \leq h^{-1}\big(h(m)\frac{h(b_n)}{h(b_{n+1})}\big) \leq h^{-1}\big(h(b_{n+1})\frac{h(b_n)}{h(b_{n+1})}\big) = b_n.$$

Hence, (H_n) implies

$$N\left(t_n + \overline{\tau}, \pi_{-(t-t_n-\overline{\tau})}(m))\right) = 0.$$

Furthermore, for $t_n + \overline{\tau} \leq s \leq t$, we have

$$s - \tau(\Delta(\pi_{-(t-s)}(m))) \geq (t_n + \overline{\tau}) - \tau(\Delta(\pi_{-(t-s)}(m)) \geq t_n,$$

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

$$N\left(s - \tau(\Delta(\pi_{-(t-s)}(m))) \,,\, \Delta(\pi_{-(t-s)}(m)\right) = 0.$$

Then, we deduce that (H_{n+1}): $N(t,m)=0$ for $m\in[0,b_{n+1}]$ and $t\geq t_{n+1}$. Thanks to Lemma 3.6, we have $b_N<\Theta(1)\leq b_{N+1}\leq g(1)$, which implies

$$N(t,m)=0, \quad \text{for } m\in[0,\Theta(1)], \quad t\geq t_{N+1}=\ln\big[\frac{h(b_{n+1})}{h(b)}\big]+(N+1)\overline{\tau}.$$

Suppose now that $m\in[\Theta(1),g(1)]$ and $t\geq t_{N+1}+\ln[\frac{h(g(1))}{h(b_{n+1})}]+\overline{\tau}=\overline{t}$. Since $\Delta^{-1}(g(1))=\Theta(1)$, using the same technique as in the first part of this proof, we obtain $N(t,m)=0$ for $m\in[0,g(1)]$ and $t\geq\overline{t}$. Finally, take $m\in[g(1),1]$ and $t\geq\overline{t}+\overline{\tau}$. We can write

$$\begin{aligned} N(t,m)=&\;\overline{\xi}(m,t-\overline{t}-\overline{\tau})N\left(\overline{t}+\overline{\tau},\pi_{-(t-\overline{t}-\overline{\tau})}(m))\right)\\ &+\int_{\overline{t}+\overline{\tau}}^{t}\overline{\xi}(m,t-s)K(\,\pi_{-(t-s)}(m))\\ &\times N\left(s-\tau(\Delta(\pi_{-(t-s)}(m))),\Delta(\pi_{-(t-s)}(m))\right)ds. \end{aligned}$$

Let $\overline{t}+\overline{\tau}\leq s\leq t$. Then

$$s-\tau(\Delta(\pi_{-(t-s)}(m)))\geq\left(\overline{t}+\overline{\tau}\right)-\tau(\Delta(\pi_{-(t-s)}(m))\geq\overline{t}.$$

Consequently, if $\pi_{-(t-s)}(m)\leq g(1)$, then, $\Delta(\pi_{-(t-s)}(m))\leq g(1)$. This implies that

$$N\left(s-\tau(\Delta(\pi_{-(t-s)}(m))),\Delta(\pi_{-(t-s)}(m))\right)=0.$$

On the other hand, if $\pi_{-(t-s)}(m)>g(1)$, then, by the definition of K, we have $K(\pi_{-(t-s)}(m))=0$. We conclude that, for $m\in[g(1),1]$ and $t\geq\overline{t}+\overline{\tau}$,

$$N(t,m)=\overline{\xi}(m,t-\overline{t}-\overline{\tau})N\left(\overline{t}+\overline{\tau},\pi_{-(t-\overline{t}-\overline{\tau})}(m))\right).$$

We remark that $\ln(h(m))<0$, for all $m\in(0,g(1)]$. Then, for $m\in[g(1),1]$ and $t\geq(N+3)\overline{\tau}-\ln\left(h(b)\right)=\overline{t}+\overline{\tau}-\ln(h(g(1)))$, we have

$$\pi_{-(t-\overline{t}-\overline{\tau})}(m)=h^{-1}\left(h(m)e^{-(t-\overline{t}-\overline{\tau})}\right)\leq h^{-1}\left(h(m)h(g(1))\right)\leq h^{-1}(h(g(1)))=g(1).$$

Hence,

$$N\left(\overline{t}+\overline{\tau},\pi_{-(t-\overline{t}-\overline{\tau})}(m))\right)=0.$$

This completes the proof of the theorem. ☐

This result proves that the production of cells depends strongly on the state of the population of stem cells. It describes, in particular, the destruction of the cell population in the resting phase when its starting value is defective. It is believed that the pathology of aplastic anemia is due to injury or destruction of a common pluripotential stem cell. This result is a first step to prove stability or instability results in the nonlinear case $\beta=\beta(N)$ (see further publication). In the next section, we prove that the proliferating cells also depends strongly on the state of the population of stem cells.

4. Equations for the total population in the proliferating phase

To complete the formulation of our model, we give the equations satisfied by the total population

$$P(t,m)=\int_0^{\tau(\Theta(m))}p(t,m,a)da$$

of proliferating cells for a given maturation level $m\in[0,1]$.

Proposition 4.1. *Let $m \in [0,1]$ and $t \geq 0$. Then $P(t,m)$ satisfies the following equations:*

(1) *If $0 \leq t \leq \tau(\Theta(m))$, then*

$$\begin{aligned}&\frac{\partial}{\partial t}P(t,m) + \frac{\partial}{\partial m}\left(V(m)P(t,m)\right)\\&= -\gamma(m)P(t,m) + \beta(m)N(t,m) - G(t,m),\end{aligned} \tag{4.1}$$

with

$$G(t,m) = \frac{1}{1+\tau'(\Theta(m))V(\Theta(m))}\xi(m,t)\Gamma\left(\pi_{-t}(m), \tau(\Theta(m)) - t\right), \tag{4.2}$$

where ξ is given by (3.4) and Γ is the initial data given by (2.11).

(2) *If $t \geq \tau(\Theta(m))$, then*

$$\begin{aligned}&\frac{\partial}{\partial t}P(t,m) + \frac{\partial}{\partial m}\left(V(m)P(t,m)\right)\\&= -\gamma(m)P(t,m) + \beta(m)N(t,m) - H(m)N\left(t - \tau(\Theta(m)), \Theta(m)\right),\end{aligned} \tag{4.3}$$

where

$$H(m) = \frac{\xi\left(m, \tau(\Theta(m))\right)\beta\left(\Theta(m)\right)}{1+\tau'(\Theta(m))V(\Theta(m))}. \tag{4.4}$$

Proof. Taking $a = \tau(\Theta(m))$ in (3.10), we obtain

$$p(t,m,\tau(\Theta(m))) = \begin{cases}\xi(m,t)\Gamma(\pi_{-t}(m), \tau(\Theta(m)) - t), & \text{for } 0 \leq t < \tau(\Theta(m)),\\ \xi(m,\tau(\Theta(m)))\beta\left(\pi_{-\tau(\Theta(m))}(m)\right) & \\ \times N(t-\tau(\Theta(m)), \pi_{-\tau(\Theta(m))}(m)), & \text{for } \tau(\Theta(m)) \leq t.\end{cases} \tag{4.5}$$

According to Lemma 3.4, we deduce that $\pi_{-\tau(\Theta(m))}(m) = \Theta(m)$ for all $m \in [0,1]$. On the other hand, we have

$$\begin{aligned}&\frac{\partial}{\partial m}\left(V(m)P(t,m)\right)\\&= \frac{\partial}{\partial m}\Big(\int_0^{\tau(\Theta(m))} V(m)p(t,m,a)da\Big),\\&= \int_0^{\tau(\Theta(m))}\frac{\partial}{\partial m}\left(V(m)p(t,m,a)\right)da + \tau'(\Theta(m))\Theta'(m)V(m)p(t,m,\tau(\Theta(m))).\end{aligned}$$

Consequently, by integrating (2.2) with respect to the age between 0 and $\tau(\Theta(m))$, we obtain the following time-maturation structured equation,

$$\begin{aligned}&\frac{\partial}{\partial t}P(t,m) + \frac{\partial}{\partial m}\left(V(m)P(t,m)\right)\\&= -\gamma(m)P(t,m) + p(t,m,0) - p(t,m,\tau(\Theta(m)))\\&\quad + \tau'(\Theta(m))\Theta'(m)V(m)p(t,m,\tau(\Theta(m))),\\&= -\gamma(m)P(t,m) + p(t,m,0) - \left[1 - \tau'(\Theta(m))\Theta'(m)V(m)\right]p(t,m,\tau(\Theta(m))).\end{aligned}$$

Using (2.4), (2.6) and (4.5) in this last equation, we obtain (4.1) and (4.3). □

It is not difficult to prove, by steps, the existence, uniqueness and regularity of solutions of System (4.1)–(4.3). Let $\psi \in C\left([0,\overline{\tau}] \times [0,1]\right)$ be an integrated solution of this system on the set $[0,\overline{\tau}]\times[0,1]$. As for the resting phase, an integrated expression of Equation (4.3), for $t\geq\overline{\tau}$ and $m\in[0,1]$, is given by

$$\begin{aligned} &P(t,m)\\ &=\xi(m,t-\overline{\tau})\psi\left(\overline{\tau},\pi_{-(t-\overline{\tau})}(m)\right)\\ &\quad+\int_{\overline{\tau}}^{t}\xi(m,t-s)\beta(\pi_{-(t-s)}(m))N\left(s,\pi_{-(t-s)}(m)\right)ds\\ &\quad+\int_{\overline{\tau}}^{t}\xi(m,t-s)H(\pi_{-(t-s)}(m))N\left(s-\tau\left(\Theta\left(\pi_{-(t-s)}(m)\right)\right),\Theta\left(\pi_{-(t-s)}(m)\right)\right)ds, \end{aligned} \tag{4.6}$$

and $P(t,m)=\psi\left(t,m\right)$, for $(t,m)\in[0,\overline{\tau}]\times[0,1]$. Then we have the following result.

Proposition 4.2. *Under the assumptions in Theorem 3.7 and* $\psi(t,m)=0$ *for* $t\in[0,\overline{\tau}]$, $m\in[0,b]$, *the solution* P *of* (4.6) *is equal to* 0, *for* $t\geq\overline{t}$, $m\in[0,g(1)]$, *and for* $t\geq\overline{t}+\overline{\tau}-\ln(h(g(1)))$, $m\in[g(1),1]$.

Proof. In the proof of Theorem 3.7, we obtained that $N(t,m)=0$ for $m\in[0,b_n]$ and $t\geq t_n$. Then (4.6) becomes

$$P(t,m)=\xi(m,t-t_n)P\left(t_n,\pi_{-(t-t_n)}(m)\right)\quad\text{for } t\geq t_n\ m\in[0,b_n].$$

Then, by steps, we prove that $P(t,m)=0$ for $t\geq t_n$ and $m\in[0,b_n]$. This leadds to

$$P(t,m)=0,\quad\text{for } t\geq\overline{t},\ m\in[0,g(1)].$$

Using the same argument as in the proof of Theorem 3.7, we also obtain, for $m\in[0,1]$ and $t\geq\overline{t}+\overline{\tau}-\ln(h(g(1)))$,

$$P(t,m)=\xi(m,t-\overline{t}-\overline{\tau})P\left(\overline{t}+\overline{\tau},\pi_{-(t-\overline{t}-\overline{\tau})}(m)\right).$$

Then $P(t,m)=0$ for $m\in[g(1),1]$ and $t\geq\overline{t}+\overline{\tau}-\ln(h(g(1)))$, which completes the proof. ☐

References

[1] M. Adimy and L. Pujo-Menjouet, *A singular transport model describing cellular division*, C. R. Acad. Sci. Paris, t. **332**, Série I, (2001), 1071-1076.

[2] M. Adimy and L. Pujo-Menjouet, *Asymptotic behavior of a singular transport equation modelling cell division*, Disc. Cont. Dyn. Sys., **3**, Series B, (2003), 439-456.

[3] J. Dyson, R. Villella-Bressan and G.F. Webb, *A singular transport equation modelling a proliferating maturity structured cell population,* Can. Appl. Math. Quart., **4**, (1996), 65-95.

[4] J. Dyson, R. Villella-Bressan and G.F. Webb, *Hypercyclicity of solutions of a transport equation with delays*, J. Nonlinear Anal. : Theory, Methods and Appl., **29**, (1997), 1343-1351.

[5] J. Dyson, R. Villella-Bressan and G.F. Webb, *An age and maturity structured model of cell population dynamics*, in "Mathematical Models in Medical and Health Science", (M. Horn, G. Simonnett, and G.F. Webb, Eds.), p. 99-116, Vanderbilt University Press, Nashville, TN, 1998.

[6] J. Dyson, R. Villella-Bressan and G.F. Webb, *A nonlinear age and maturity structured model of population dynamics. I. Basic Theory,* J. Math. Anal. Appl., **242**, (2000), 93-104.

[7] J. Dyson, R. Villella-Bressan and G.F. Webb, *A nonlinear age and maturity structured model of population dynamics. II. Chaos,* J. Math. Anal. Appl., **242**, (2000), 255-270.

[8] J. Dyson, R. Villella-Bressan and G.F. Webb, *A maturity structured model of a population of proliferating and quiescent cells,* in "Special Issue on Control and Estimation in Biological and Medicine Sciences", (M. Kimmel and A. Swierniak, Eds), Silesian University of Technology, Gliwice, Poland, 1999.

[9] J. Dyson, R. Villella-Bressan and G.F. Webb, *A singular transport equation with delays*, International Journal of Mathematics and Mathematical Sciences, **32**, (2003), 65-95.

[10] P. C. L. John, *The cell cycle, London*, Cambridge University Press, 1981.

[11] M. C. Mackey, *Unified hypothesis of the origin of aplastic anemia and periodic hematopoiesis*, Blood, **51**, (1978), 941-956.

[12] M. C. Mackey, *Dynamic hematological disorders of stem cell origin, Biophysical and biochemical Information Transfer in recognition*, 373-409, Eds. Vassileva-Popova J. G., Jensen E. V. New-york: Plenum Press, 1979.

[13] M. C. Mackey and R. Rudnicki, *Global stability in a delayed partial differential equation describing cellular replication*, J. Math. Biol., **33**, (1994), 89–109.

[14] M. C. Mackey and R. Rudnicki, *A new criterion for the global stability of simultaneous cell replication and maturation processes*, J. Math. Biol., **38**, (1999), 195–219.

[15] J. M. Mitchison, *The biology of the cell cycle*, Cambridge University Press, London, 1971.

[16] G. C. Nooney, *Age distributions in dividing populations*, Biophy. J., **7**, (1967), 69–76.

[17] D. G. Oldfield, *A continuity equation for cell populations*, Bull. Math. Biophys, **28**, (1966), 545–554.

[18] L. Pujo-Menjouet and R. Rudnicki, *Global stability of cellular populations with unequal division*, Can. Applied Math. Quart., **8**, (2000), 185-203.

[19] A. Rey and M.C. Mackey, *Bifurcations and traveling waves in a delayed partial differential equation*, Chaos, **2**, (1992), 231-244.

[20] A. Rey and M. C. Mackey, *Multistability and boundary layer development in a transport equation with retarded arguments*, Can. Appl. Math. Quart., **1**, (1993), 61-81.

[21] S. I. Rubinow, *A maturity time representation for cell populations*, Biophy. J., **8**, (1968), 1055–1073.

[22] S. Rubinow and J.L. Lebowitz, *A mathematical model of neutrophil production and control in normal man,* J. Math. Biology, **1**, (1975), 187-225.

[23] E. Trucco, *Mathematical models for cellular systems: The Von Foerster equation. Parts I* , Bull. Math. Biophys.,**27**, (1965), 285–304.

[24] E. Trucco, *Mathematical models for cellular systems: The Von Foerster equation. Part II*, Bull. Math. Biophys., **27**, (1965), 449–470.

[25] E. Trucco, *Some remarks on changing populations*, J. Ferm. Technol.,**44**, (1966), 218-226.

[26] H. Von Foerster, *Some remarks on changing populations*, The Kinetics of Cellular Proliferation (F. Stohlman eds.), Grune et Stratton, New York, p. 382–407, 1959.

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