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Équations aux dérivées partielles/*Partial Differential Equations*

A singular transport model describing cellular division

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Abstract. In this Note, we study a system of partial differential equations with a singular transport term describing blood cellular production. The population of cells considered is capable of simultaneous proliferation and maturation. We prove that uniqueness of solutions depends only on stem cells. © 2001 Académie des sciences/Éditions scientifiques et médicales Elsevier SAS

Un modèle de transport singulier décrivant une division cellulaire

Résumé. *Dans cette Note, nous étudions un système d'équations aux dérivées partielles avec un terme de transport singulier décrivant une production de cellules sanguines. La population de cellules considérée prolifère et mature simultanément. Nous prouvons que l'unicité des solutions dépend seulement des cellules souches.* © 2001 Académie des sciences/Éditions scientifiques et médicales Elsevier SAS

Version française abrégée

Dans cette Note, nous présentons un système d'équations couplées (1)–(2) issu d'un processus de division cellulaire. Ce système représente le cycle cellulaire lors de la production sanguine dans la moelle osseuse. Il a été introduit en 1978 par Mackey [2], et il a été étudié dans les années 90 par Mackey et Rey [3,4] et par Mackey et Rudnicki [5]. Il est basé sur deux hypothèses biologiques. La première est la présence d'un facteur appelé *maturation* qui gouverne la vie de chaque cellule. La deuxième est le partage du cycle de chaque cellule en deux principales phases : une phase de prolifération représentée par l'équation (1) et une phase de repos modélisée par l'équation (2). Dans la phase de prolifération, les cellules se divisent au bout d'un temps τ fixe ou meurent à un taux γ. Juste après la division, les deux cellules filles entrent dans la phase de repos. Dans cette phase, elles peuvent soit retourner dans la phase de prolifération à un taux β et compléter le cycle, soit mourir à un taux δ. Dans chacune des deux phases, les densités de cellules $p(t,m,a)$ pour la prolifération et $n(t,m,a)$ pour le repos dépendent du temps $t \geqslant 0$, de la maturation $m \in [0,1]$ et de l'âge a, où a varie de 0 à τ pour la phase de prolifération et de 0 à $+\infty$ pour la phase de repos. Nous supposons que la vitesse V de maturation des cellules est la même dans les deux phases, et que

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$V \in \mathrm{C}^1[0,1)$, $V(0)=0$, $V(1)=0$ et pour $m \in (0,1)$,

$$V(m)>0, \quad \int_0^m \frac{\mathrm{d}x}{V(x)} = +\infty \quad \text{et} \quad \int_m^1 \frac{\mathrm{d}s}{V(s)} < +\infty.$$

Les conditions de bords (3) modélisent le flux cellulaire entre les deux phases. En intégrant le système (1)–(2) par rapport à l'âge et en utilisant les conditions de bords (3) et les conditions initiales (4), nous obtenons le système d'équations aux dérivées partielles à retard (6)–(7). Nous remarquons que la solution N de l'équation (7) est indépendante de la solution P de l'équation (6). Dans [2–4] et [5], les principaux résultats concernent la stabilité globale des solutions du système (6)–(7) ce qui correspond au cas de production sanguine normale. Dans [1], les auteurs étudient le modèle dans le cas particulier où la maturité $\pi_{-\tau} \circ g^{-1}(m)$ est indépendante de τ et vaut αm, $0<\alpha<1$.

Dans cette Note, nous considérons une situation plus générale. Nous supposons que la phase de prolifération dure suffisamment longtemps de telle sorte que les cellules gardent une maturité suffisamment grande après leur division, i.e. $m > \pi_{-\tau} \circ g^{-1}(m)$. Biologiquement, il est connu que les cellules sanguines sont engendrées par des cellules souches (de petite maturité).

Dans des conditions anormales qui peuvent se caractériser par l'absence de division de cellules souches, la population de cellules sanguines peut présenter un comportement instable (cas d'anémie aplasique par exemple). Le théorème 2.2 est un premier pas pour décrire cette dernière situation biologique. Ce résultat sera étendu dans un travail ultérieur au cas non linéaire ($\beta = \beta(N)$).

1. Introduction

The objective of this Note is to study a mathematical model of a blood production system introduced and studied by Mackey et al. in [2–4] and in [5]. In this model, the blood production system is based on two biological hypotheses. We first assume that a factor called maturation, or biological age, governs the life history of any cell. The second assumption is that the period of life of a cell is divided into a resting phase and a proliferating phase. In the proliferating phase cells are committed to undergo cell division a fixed time τ later. Cells in this phase can also be lost at a rate γ. Just after division, both daughter cells enter the resting phase. In this phase, they 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. In [2–4] and [5] the main results concern the global stability. It corresponds to the case of a normal production of blood. In [1], the authors investigate this model in the particular case when the maturity $\pi_{-\tau} \circ g^{-1}(m)$ is independent of τ and equal to αm, $0<\alpha<1$ (we are unable to find examples of this particular case). They obtain a behavior of solutions depending on the initial condition. Our main goal is to investigate a more general situation. We consider here only the linear case. We defer to a further publication the use of our result in the nonlinear case ($\beta = \beta(N)$). It is believed that the production of blood cells has two types of behavior. The first case is a normal production. It corresponds to a density of stem cells strictly positive. The second type of behavior is an abnormal production corresponding to an aplastic anemia. The pathology of aplastic anemia is due to destruction of stem cells. Theorem 2.2 is a first step to describe this biological situation. We will assume in this paper that the proliferating phase is long enough, $\tau > \tau_0$, so that cells can increase sufficiently their maturity, $m > \pi_{-\tau} \circ g^{-1}(m)$. Thus, we will prove that uniqueness of solutions depends only on stem cells.

We assume that γ, δ, and β are continuous functions depending on the maturity. The conservation equations describing the two phases are

$$\frac{\partial}{\partial t}p(t,m,a) + \frac{\partial}{\partial a}p(t,m,a) + \frac{\partial}{\partial m}\big(V(m)p(t,m,a)\big) = -\gamma(m)\,p(t,m,a), \tag{1}$$

$$\frac{\partial}{\partial t}n(t,m,a) + \frac{\partial}{\partial a}n(t,m,a) + \frac{\partial}{\partial m}\big(V(m)n(t,m,a)\big) = -\big(\delta(m)+\beta(m)\big)n(t,m,a). \tag{2}$$

Here, $p(t,m,a)$ and $n(t,m,a)$ represent respectively the density of proliferating and resting cells at time t, maturity m and age a. All cells mature with the same velocity $V(m)$. We assume that V satisfies: $V \in \mathrm{C}^1[0,1)$, $V(0)=0$, $V(1)=0$, which give the singularity of the system. We assume also that, for $m \in (0,1)$,

$$V(m)>0, \quad \int_0^m \frac{\mathrm{d}x}{V(x)} = +\infty \quad \text{and} \quad \int_m^1 \frac{\mathrm{d}s}{V(s)} < +\infty,$$

which describes the fact that the velocity of a cell increases slowly for a small maturity and decreases rapidly for a maturity close to 1. As example:

$$V(m) \underset{m\to 0}{\sim} \alpha_1 m^p, \quad \alpha_1>0,\ p\geqslant 1, \quad \text{and} \quad V(m) \underset{m\to 1}{\sim} \alpha_2(1-m)^q, \quad \alpha_2>0,\ 0<q<1.$$

Note that $\int_{m_1}^{m_2} \frac{\mathrm{d}x}{V(x)}$ represents the time for a cell to mature from m_1 to m_2. We denote $g(m)$ the maturity of the two daughter cells at birth when m is the maturity of the mother cell. Then, it is natural to assume that $g:[0,1]\to[0,1]$ is a continuous function such that $g\in \mathrm{C}^1[0,1)$, $g'(m)>0$ and $g(m)\leqslant m$ for $m\in(0,1)$. We also assume, for technical reasons, that $\lim_{m\to 1} g'(m)=+\infty$ and $g^{-1}(m)=1$ for $m>g(1)$. The cellular flux between the phases is

$$\begin{cases} n(t,m,0) = 2p(t,g^{-1}(m),\tau)(g^{-1})'(m), & \text{for } m\leqslant g(1),\\ p(t,m,0) = \int_0^{+\infty} \beta(m) n(t,m,a)\,\mathrm{d}a = \beta(m)N(t,m), \end{cases} \tag{3}$$

where $N(t,m)=\int_0^{+\infty} n(t,m,a)\,\mathrm{d}a$. The first condition of (3) describes the cellular division and the second condition represents the re-entry of resting cells into the proliferating phase. The initial conditions are

$$\begin{cases} p(0,m,a)=\Gamma(m,a) & \text{for } (m,a)\in[0,1]\times[0,\tau],\\ n(0,m,a)=\mu(m,a) & \text{for } (m,a)\in[0,1]\times[0,+\infty), \end{cases} \tag{4}$$

with $\Gamma\in \mathrm{C}([0,1]\times[0,\tau])$, $\mu\in\mathrm{C}([0,1]\times[0,+\infty))$ and $\lim_{a\to+\infty}\mu(m,a)=0$. We denote by $\pi_s:[0,1)\to[0,1)$, $s\in\mathbb{R}$, the flow, solution of the equation

$$\begin{cases} \dfrac{\mathrm{d}u}{\mathrm{d}s}(s) = V\big(u(s)\big), \quad s\in\mathbb{R},\\ u(0)=m. \end{cases} \tag{5}$$

We have $\pi_0(m)=m$, $\pi_s(0)=0$, $\pi_s(m)\in(0,1)$ for $s\in\mathbb{R}$ and $m\in(0,1)$. Actually, we have

$$\pi_s(m) = h^{-1}\big(h(m)\,\mathrm{e}^s\big), \quad \text{for } s\in(-\infty,0], \text{ and } m\in[0,1),$$

where $h(m)=\exp\big(-\int_m^1 \frac{\mathrm{d}s}{V(s)}\big)$, for $m\in(0,1)$, and $h(0)=0$.

Let $\omega:\mathbb{R}\to\mathbb{R}^+$ be the function defined by $\omega(s)=h^{-1}\big(\mathrm{e}^s\big)$ if $s\leqslant 0$, and $\omega(s)=1$ if $s\geqslant 0$. Remark that ω is a solution of (5) and $\pi_s(m)<\omega(s)$, for $s\in\mathbb{R}$ and $m\in[0,1)$. We set $P(t,m)=\int_0^\tau p(t,m,a)\,\mathrm{d}a$. Integrating (1) and (2) over the age variable and using condition (3) we obtain, for $t>0$ and $m\in(0,1)$,

$$\frac{\partial}{\partial t}P(t,m) + \frac{\partial}{\partial m}\big(V(m)P(t,m)\big) = -\gamma(m)P(t,m) + L_1\big(t,m,N(t,m),N_\tau(t,m)\big), \tag{6}$$

$$\frac{\partial}{\partial t}N(t,m) + \frac{\partial}{\partial m}\big(V(m)N(t,m)\big) = -\big[\delta(m)+\beta(m)\big]N(t,m) + L_2\big(t,m,N^\tau(t,m)\big), \tag{7}$$

where

$$\begin{cases} N_\tau(t,m) = N\big(t-\tau, \pi_{-\tau}(m)\big), \\ N^\tau(t,m) = N\big(t-\tau, \pi_{-\tau}\circ g^{-1}(m)\big) = N_\tau\big(t, g^{-1}(m)\big), \end{cases}$$

$$L_1\big(t,m,N(t,m),N_\tau(t,m)\big) = \beta(m)N(t,m) - \begin{cases} \xi(m,t)\,\Gamma\big(\pi_{-t}(m),\tau-t\big), & t\in[0,\tau), \\ \beta\big(\pi_{-\tau}(m)\big)\,\xi(m,\tau)N_\tau(t,m), & t\geqslant\tau, \end{cases}$$

$$L_2\big(t,m,N^\tau(t,m)\big) = \begin{cases} 2\big(g^{-1}\big)'(m)\,\xi\big(g^{-1}(m),t\big)\,\Gamma\big(\pi_{-t}\circ g^{-1}(m),\tau-t\big), & t\in[0,\tau), \\ 2\big(g^{-1}\big)'(m)\,\beta\big(\pi_{-\tau}\circ g^{-1}(m)\big)\,\xi\big(g^{-1}(m),\tau\big)N^\tau(t,m), & t\geqslant\tau, \end{cases}$$

and

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

Notice that, for $t\in[0,\tau]$, both equations (6) and (7) contain the initial condition Γ, and their solutions become initial conditions respectively for (6) and (7) when $t\geqslant\tau$. Moreover, the solution of (7) is independent of the solution of (6), and the solution of (7) is a forcing term of (6). Also, remark that $L_2(t,m,N^\tau(t,m))=0$, for $m\geqslant g(1)$. Our objective is to prove that uniqueness of solutions depends only on stem cells. Then, we will focus our study on the maturity interval $[0,g(1)]$.

Let $m_0\in(0,g(1))$ and $\tau_0=\sup_{m>m_0}\big(\int_m^{g^{-1}(m)}\frac{\mathrm{d}s}{V(s)}\big)$.

If $\lim_{m\to0}\big(\int_m^{g^{-1}(m)}\frac{\mathrm{d}s}{V(s)}\big)<+\infty$; then m_0 can be chosen equal to zero. We suppose that

$$\tau>\tau_0.$$

Then, the non-local dependence $\big(\pi_{-\tau}\circ g^{-1}(m)\big)$ in the maturation variable satisfies

$$\begin{cases} \pi_{-\tau}\circ g^{-1}(m) < m, & \text{for } m\in[m_0,g(1)], \\ \pi_{-\tau}\circ g^{-1}(m) \leqslant \omega(-\tau) < g(1), & \text{for } m\in[0,g(1)]. \end{cases}$$

It means that the equations (6) and (7) can be solved for $m\in[0,g(1)]$ separately. The non-local dependence $\big(\pi_{-\tau}\circ g^{-1}(m)\big)$ represents the maturity of the mother cell before starting the proliferation phase when its daughter cells have the maturity m.

2. Main result

We consider the following integrated version of equation (7)

$$\begin{aligned} N(t,m) = {} & \varphi\big(\tau,\pi_{-(t-\tau)}(m)\big)\exp\Big\{-\int_0^{t-\tau}\delta\big(\pi_{-s}(m)\big)+\beta\big(\pi_{-s}(m)\big)+V'\big(\pi_{-s}(m)\big)\,\mathrm{d}s\Big\} \\ & + \int_\tau^t L_2\big(s,\pi_{-(t-s)}(m),N^\tau\big(s,\pi_{-(t-s)}(m)\big)\big) \\ & \times\exp\Big\{-\int_0^{t-s}\delta\big(\pi_{-\sigma}(m)\big)+\beta\big(\pi_{-\sigma}(m)\big)+V'\big(\pi_{-\sigma}(m)\big)\,\mathrm{d}\sigma\Big\}\,\mathrm{d}s, \end{aligned} \tag{8}$$

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

The integrated form of equation (6) has the same form and will be omitted. Using the method of steps, it is easy to prove the following proposition.

PROPOSITION 2.1. – *There exists a unique solution of* (8) *with initial condition* $\varphi\in\mathrm{C}\big([0,\tau]\times[0,g(1)]\big)$.

We obtain the same result for the integrated form of equation (6). We need the following lemma.

LEMMA 2.1. – *Let*

$$m_0 \in \big(0, g(1)\big), \quad \tau_0 = \sup_{m>m_0} \left(\int_m^{g^{-1}(m)} \frac{\mathrm{d}s}{V(s)} \right) \quad \textit{and} \quad \tau_1 = \int_{m_0}^{1} \frac{\mathrm{d}s}{V(s)}.$$

Then, we have:
(i) $\tau_0 < \tau_1$,
(ii) $m_0 < \omega(-\tau)$ *if and only if* $\tau < \tau_1$.

Our main result says more about uniqueness.

THEOREM 2.2. – *Let* $m_0 \in (0, g(1))$. *Suppose that* $N_1(t,m)$ *and* $N_2(t,m)$ *are solutions of equation* (7) *with initial functions* φ_1 *and* φ_2 *respectively. Suppose that there exist* $\tau \in (\tau_0, \tau_1)$ *and* $b \in (m_0, \omega(-\tau))$ *such that* $\varphi_1(t,m) = \varphi_2(t,m)$ *for* $m \in [0,b]$ *and* $t \in [0,\tau]$. *Then, there exists* $\overline{t} > \tau$ *such that* $N_1(t,m) = N_2(t,m)$ *for all* $m \in [0, g(1)]$ *and* $t \geqslant \overline{t}$.

We obtain the same result for equation (6).

Proof. – Lemma 2.1 says that $\tau_0 < \tau_1$ and $m_0 < \omega(-\tau)$; $N_1(t,m)$ and $N_2(t,m)$ are solutions of (8). Then, they can be reformulated as

$$\begin{aligned} N(t,m) = {} & N\big(s+\tau, \pi_{-(t-s-\tau)}(m)\big) \exp\left\{ -\int_0^{t-s-\tau} \big(\delta\big(\pi_{-\sigma}(m)\big) + \beta\big(\pi_{-\sigma}(m)\big) + V'\big(\pi_{-\sigma}(m)\big)\big)\mathrm{d}\sigma \right\} \\ & + \int_{s+\tau}^{t} L_2\big(\sigma, \pi_{-(t-\sigma)}(m), N^\tau\big(\sigma, \pi_{-(t-\sigma)}(m)\big)\big) \\ & \times \exp\left\{ -\int_0^{t-\sigma} \big(\delta\big(\pi_{-\varsigma}(m)\big) + \beta\big(\pi_{-\varsigma}(m)\big) + V'\big(\pi_{-\varsigma}(m)\big)\big)\mathrm{d}\varsigma \right\} \mathrm{d}\sigma, \end{aligned}$$

for $m \in [0, g(1)]$, $s \geqslant 0$ and $t \geqslant s + \tau$. Then, by induction it is not difficult to prove that $N_1(t,m) = N_2(t,m)$ for $m \in [0,b]$ and $t \geqslant 0$. Remark that

$$\int_m^{g^{-1}(m)} \frac{\mathrm{d}s}{V(s)} = \ln \frac{h(g^{-1}(m))}{h(m)}, \quad \text{for } m > 0.$$

Consider the sequence $(t_n)_{n\in\mathbb{N}}$ defined by:

$$t_0 = \tau \quad \text{and} \quad t_{n+1} = t_n + \ln\left[\frac{h\big((\pi_{-\tau} \circ g^{-1})^{-(n+1)}(b)\big)}{h\big((\pi_{-\tau} \circ g^{-1})^{-n}(b)\big)} \right] + 2\tau.$$

Then,

$$t_{n+1} = -\ln\left[\frac{h(b)}{h\big((\pi_{-\tau} \circ g^{-1})^{-(n+1)}(b)\big)} \right] + (n+3)\tau.$$

Note that the sequence $\big((\pi_{-\tau} \circ g^{-1})^{-n}(b)\big)_{n\in\mathbb{N}}$ is increasing because $\tau > \tau_0$. Then, $(t_n)_{n\in\mathbb{N}}$ is also increasing. By induction, we obtain the following assertion:

(H$_n$): $\big(\pi_{-\tau} \circ g^{-1}\big)^{-n}(b) \leqslant \omega(-\tau) \implies N_1(t,m) = N_2(t,m)$ for $m \in \big[0, (\pi_{-\tau} \circ g^{-1})^{-n}(b)\big]$ and $t \geqslant t_n - \tau$.

It is not difficult to check that there exists $M \in \mathbb{N}$ such that

$$\left(\pi_{-\tau} \circ g^{-1}\right)^{-M}(b) < \omega(-\tau) \leqslant \left(\pi_{-\tau} \circ g^{-1}\right)^{-(M+1)}(b).$$

Then,

$$N_1(t,m) = N_2(t,m) \quad \text{for } m \in [0, \omega(-\tau)] \quad \text{and } t \geqslant t_M + \tau - \ln\left[h\left(\left(\pi_{-\tau} \circ g^{-1}\right)^{-M}(b)\right)\right].$$

To end the proof, it suffices to remark that if we take $m \in [0, g(1)]$, then

$$\left(\pi_{-\tau} \circ g^{-1}\right)\left(\pi_{-(t-\sigma)}(m)\right) \in \left[0, \omega(-\tau)\right] \quad \text{and} \quad \pi_{-(t-\sigma)}(m) \in \left[0, \omega(-\tau)\right].$$

Then, we can proceed in same manner as above. Consequently, there exists $\overline{t} > \tau$ such that $N_1(t,m) = N_2(t,m)$ for all $m \in [0, g(1)]$ and $t \geqslant \overline{t}$. □

Remark 1. – If $\lim_{m\to 0}\left(\int_m^{g^{-1}(m)} \frac{\mathrm{d}s}{V(s)}\right) < +\infty$, then the result of the theorem is true with $m_0 = 0$ and $\tau > \tau_0$. In this case, the behavior of solutions depend upon the density of stem cells at the maturity value $m = 0$.

We give now some examples of this last important situation.

Example 1. – Suppose that $V(s) \underset{s\to 0}{\sim} \alpha s^p$, where $\alpha > 0$ and $p \geqslant 1$.

If $p = 1$, then

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

If $p > 1$, then

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

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