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A delay differential-difference system of hematopoietic stem cell dynamics

Équations différentielles et aux différences à retard pour des modèles de dynamique des cellules souches hématopoïétiques

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A R T I C L E   I N F O

A B S T R A C T

All functional blood cells are generated in the bone marrow through hematopoiesis from a small population of cells called hematopoietic stem cells (HSCs). HSCs have the capacity to self-renew and also the capacity to differentiate into any types of blood cells. We consider a system of two age-structured partial differential equations, describing the evolution of the HSC population. By integrating this system over the age and using the characteristics method, we reduce it to a system composed of a differential equation and a delay difference equation. We investigate the asymptotic stability of steady states and the existence of a Hopf bifurcation. We conclude our work by numerical simulations.

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R É S U M É

Toutes les cellules sanguines sont produites dans la moelle osseuse lors de l'hématopoïèse à partir d'une petite population de cellules appelées cellules souches hématopoïétiques (CSHs). Les CSHs ont la capacité de s'auto-renouveler et également de se différencier en tous types de cellules sanguines. Le sytème mathématique que nous considérons pour modéliser ces populations de CSHs est un système de deux équations aux dérivées partielles structurées en âge. Par intégration suivant les caractéristiques, le modèle est réduit à un système composé d'une équation différentielle et d'une équation aux différences à retard. Nous étudions le comportement asymptotique des états d'équilibre et l'existence d'une bifurcation de Hopf. Nous concluons notre travail par des simulations numériques.

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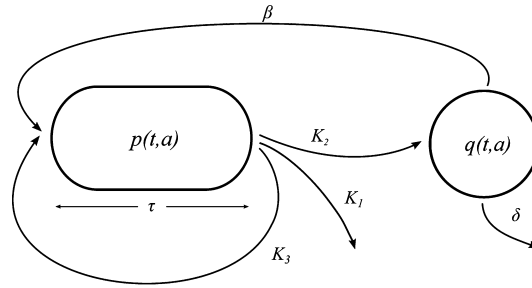
Fig. 1. Schematic representation of HSC dynamic.

1. Introduction and presentation of the model

The process that leads to the production and regulation of blood cells is called hematopoiesis. It is based on a pool of immature hematopoietic stem cells (HSCs) that have the ability to produce either cells engaged in a cell lineage (differentiation) or similar cells (self-renewal) to maintain their proliferative capacity. HSCs reside in the bone marrow and produce all blood cells (red blood cells, white cells, and platelets). The majority of HSCs is usually in a quiescent phase, even though part of them are actively proliferating. Details on HSC dynamics can be found in [11].

Many authors have been interested in modeling the dynamics of HSCs. To our knowledge, the first mathematical model was proposed by Mackey in 1978 [13], and it has been improved by many authors, including [1–7] and the references therein. In all these works, the authors assumed that all dividing HSCs enter directly the quiescent phase. This hypothesis allows the reduction of the age-structured model to a delay differential system, using the method of characteristics. In fact, it is believed that a proportion of HSCs always return immediately after division to the proliferating phase to divide again to maintain a steady-state level of HSCs and mature blood cells (see [8] and [14]).

As in [13], we take into account the fact that a cell cycle has two phases, that is, HSCs are either in a quiescent phase or actively proliferating. However, we do not suppose that all dividing HSCs enter directly the quiescent phase, a part of them enters the quiescent phase and the other part returns to the proliferating one. This assumption leads to a modification of Mackey's model, which cannot be reduced to a classical delay differential system. We obtain a system of differential and difference delayed equations.

We denote by $q(t, a)$ (respectively, $p(t, a)$) the density of quiescent HSCs (respectively, proliferating HSCs) at time $t \geq 0$, which have spent a time $a > 0$ (respectively, $0 < a < \tau$) in their compartment. Quiescent cells can be introduced in the proliferating stage with a rate $\beta \geq 0$. We denote by $\delta \geq 0$ the rate of differentiation of HSCs to mature cells. A cell can stay in the resting phase for its entire life, then a, in this phase, ranges from 0 to infinity. As soon as a cell enters the proliferating phase, it is committed to die or divide a time $\tau \geq 0$ later. The control at some points of the cell cycle (checkpoints) can decide that a cell dies by apoptosis, enters the quiescent state, or continues the cell cycle. The decision to differentiate or to commit a new round of cell division occurs at the end of the cell cycle. We suppose that there is only one checkpoint that occurs at the end of the cell cycle with, for each cell, the choice between to leave the HSC compartment (by apoptosis or differentiation), to enter the quiescent phase, or to return to the proliferating phase. We denote by K_1 the rate at which a cell leaves the HSC compartment, K_2 the rate at which it enters the resting phase, and K_3 the rate at which it returns to the proliferating phase to divide again. Then, we have $K_1 + K_2 + K_3 = 1$ (see Fig. 1). Hence, the cell densities $q(t, a)$ and $p(t, a)$ satisfy the following age-structured partial differential equations:

$$
\begin{cases}
\dfrac{\partial q(t, a)}{\partial t} + \dfrac{\partial q(t, a)}{\partial a} = -(\delta + \beta(Q(t)))\, q(t, a), & a > 0,\ t > 0, \\[2mm]
\dfrac{\partial p(t, a)}{\partial t} + \dfrac{\partial p(t, a)}{\partial a} = 0, & 0 < a < \tau,\ t > 0, \\[2mm]
q(t, 0) = 2K_2\, p(t, \tau), & t > 0, \\[1mm]
p(t, 0) = \beta(Q(t))\, Q(t) + 2K_3\, p(t, \tau), & t > 0, \\[1mm]
\lim_{a \to +\infty} q(t, a) = 0, & t > 0.
\end{cases}
\tag{1}
$$

In addition, the model is completed by initial conditions, that are nonnegative L^1-functions, $q(0, a) = q_0(a)$, $a > 0$ and $p(0, a) = p_0(a)$, $0 < a < \tau$. We suppose that the introduction rate $\beta := \beta(Q(t))$ depends on the total resting cell population $Q(t) = \int_0^{+\infty} q(t, a)\, da$. Moreover, β is assumed to be a differentiable and decreasing function with $\lim_{Q \to +\infty} \beta(Q) = 0$ (see Mackey [13] and references therein); we set $\beta_0 := \beta(0)$.

2. Reduction to a delay differential-difference system

The method of characteristics allows us to write

$$p(t, a) = \begin{cases} p(0, a - t) = p_0(a - t), & 0 \leq t \leq a, \\ p(t - a, 0), & t > a. \end{cases} \tag{2}$$

By integrating the system (1) over the age, we obtain, for $t \geq \tau$,

$$\begin{cases} Q'(t) = -(\delta + \beta(Q(t))) Q(t) + 2K_2 u(t - \tau), \\ u(t) = \beta(Q(t)) Q(t) + 2K_3 u(t - \tau), \end{cases} \tag{3}$$

where $u(t) = p(t, 0)$, for $t \geq \tau$. We set $P(t) = \int_0^\tau p(t, a) \, da$ the total population of proliferating cells. So, thanks to (2), we have $P(t) = \int_{t-\tau}^t u(a) \, da$.

The system (3) is defined for $t \geq \tau$, with initial conditions given for $t \in [0, \tau]$ by the following system

$$\begin{cases} Q'(t) = -(\delta + \beta(Q(t))) Q(t) + 2K_2 p_0(\tau - t), \\ u(t) = \beta(Q(t)) Q(t) + 2K_3 p_0(\tau - t). \end{cases} \tag{4}$$

Our purpose is to study the asymptotic behavior of solutions to system (3)–(4). We make a translation in time so as to define system (3) on the interval $[0, \infty)$ and system (4) on the interval $[-\tau, 0]$. Then as it can be found in Hale and Verduyn Lunel [10], we consider the system (3) for $t \geq 0$ with initial conditions $Q(0) = Q_0$ and $u(t) = \phi(t)$ for $t \in [-\tau, 0]$. We suppose that $Q_0 \geq 0$ and ϕ is a nonnegative and continuous function on $[-\tau, 0]$.

By the method of steps, we can solve the system (3) in each interval $[k\tau, (k + 1)\tau]$, $k = 0, 1, \dots$. Then it is easy to check the positivity of the solutions. On the other hand, the unique piecewise function Q obtained above has a continuous first derivative for all $t > 0$ and the unique function u is continuous for all $t \geq -\tau$ if and only if the initial condition $(Q_0, \phi) \in \mathbb{R}^+ \times C([-\tau, 0], \mathbb{R}^+)$ satisfies the compatibility assumption:

$$\phi(0) = \beta(Q_0) Q_0 + 2K_3 \phi(-\tau). \tag{5}$$

We now consider the steady states (stationary solutions) to system (3). First, notice that $(0, 0)$ is always a steady state. It describes the extinction of the cell populations. A unique positive steady state $(\overline{Q}, \overline{u})$ of (3) satisfies

$$(\delta + \beta(\overline{Q})) \overline{Q} = 2K_2 \overline{u} \quad \text{and} \quad (1 - 2K_3) \overline{u} = \beta(\overline{Q}) \overline{Q}. \tag{6}$$

$(\overline{Q}, \overline{u})$ exists if and only if

$$0 < \delta (1 - 2K_3) < \beta_0 (1 - 2K_1). \tag{7}$$

In fact, (6) and (7) imply that $\delta > 0$, $K_1 < 1/2$, $K_3 < 1/2$ and

$$(\overline{Q}, \overline{u}) = \left(\beta^{-1} \left(\frac{\delta(1 - 2K_3)}{1 - 2K_1} \right), \frac{\delta}{1 - 2K_1} \beta^{-1} \left(\frac{\delta(1 - 2K_3)}{1 - 2K_1} \right) \right). \tag{8}$$

We also have $\overline{P} = \tau \overline{u}$. If (7) does not hold, then $(0, 0)$ is the only steady state of (3).

3. Global asymptotic stability of the trivial steady state

In this section, we deal with the global asymptotic stability of the trivial steady state of (3) using the Lyapunov–Krasovskii functional approach. Assume that $\delta > 0$.

Theorem 3.1. *Suppose that $K_3 < 1/2$ and that (7) does not hold. Then, the trivial steady state is the only equilibrium and it is globally asymptotically stable.*

Proof. We consider the continuous functional $V : \mathbb{R}^+ \times C([-\tau, 0], \mathbb{R}^+) \longrightarrow \mathbb{R}$, defined along the solutions (Q, u) to (3) by

$$V(Q_0, \phi) = Q_0 + \rho \int_{-\tau}^0 \phi(\theta) \, d\theta, \quad \text{with } \rho = 2K_2/(1 - 2K_3).$$

Then,

$$V(Q(t), u_t) = Q(t) + \rho \int_{t-\tau}^t u(s) \, ds, \quad \text{where } u_t(\theta) = u(t + \theta), \quad \text{for } t \geq 0 \text{ and } \theta \in [-\tau, 0].$$

Recall that $K_1 + K_2 + K_3 = 1$, then

$$\frac{\mathrm{d}}{\mathrm{d}t} V(Q(t), u_t) = -\left(\delta - \beta(Q(t))\frac{1 - 2K_1}{1 - 2K_3}\right) Q(t).$$

If $K_1 < \frac{1}{2}$

$$\frac{\mathrm{d}}{\mathrm{d}t} V(Q(t), u_t) \leq -\left(\delta - \frac{\beta_0(1 - 2K_1)}{1 - 2K_3}\right) Q(t),$$

and if $K_1 \geq \frac{1}{2}$

$$\frac{\mathrm{d}}{\mathrm{d}t} V(Q(t), u_t) \leq -\delta \, Q(t).$$

On the other hand, the second equation of (3) and the fact that $K_3 < 1/2$ imply that there exist constants $C > 0$ and $\alpha > 0$ such that

$$|u(t)| \leq C\left[\|\phi\|e^{-\alpha t} + \beta_0 \sup_{0 \leq s \leq t} |Q(s)|\right], \quad t > 0,$$

where $\|\phi\| = \sup_{-\tau \leq \theta \leq 0} |\phi(\theta)|$ (see [10], Theorem 3.5, page 275).

Then, V is a generalized Lyapunov–Krasovskii functional (see [9]). We conclude the global asymptotic stability of the trivial steady state by using Theorem 3 in [9]. $\quad\square$

In the next section, we linearize system (3) about steady states, and we determine the characteristic equation.

4. Local asymptotic stability and Hopf bifurcation for the positive steady state

Our approach is to write system (3) as a neutral differential system

$$\begin{cases} Q'(t) = -(\delta + \beta(Q(t))) \, Q(t) + 2K_2 u(t - \tau), \\ \dfrac{\mathrm{d}}{\mathrm{d}t}[u(t) - 2K_3 u(t - \tau) - \beta(Q(t))Q(t)] = 0. \end{cases} \tag{9}$$

By restricting the set of initial conditions to the manifold $\{(Q_0, \phi) \in \mathbb{R}^+ \times C([-\tau, 0], \mathbb{R}^+) : \phi(0) = \beta(Q_0)Q_0 + 2K_3\phi(-\tau)\}$, systems (3) and (9) are equivalent. The linearization of (9) about $(\overline{Q}, \overline{u})$ leads to

$$\begin{cases} Q'(t) = -(\delta + \overline{\beta}) \, Q(t) + 2K_2 u(t - \tau), \\ \dfrac{\mathrm{d}}{\mathrm{d}t}[u(t) - 2K_3 u(t - \tau) - \overline{\beta} Q(t)] = 0, \end{cases} \tag{10}$$

restricted to the set of initial conditions $\{(Q_0, \phi) \in \mathbb{R}^+ \times C([-\tau, 0], \mathbb{R}^+) : \phi(0) = \overline{\beta} Q_0 + 2K_3\phi(-\tau)\}$, with $\overline{\beta} = \frac{\mathrm{d}}{\mathrm{d}Q}[\beta(Q)Q]_{Q=\overline{Q}}$. Then, the characteristic equation of this system (see [10]) is given by

$$\Delta_\tau(\lambda) := \lambda + \delta + \overline{\beta} + (\overline{\alpha}\lambda + \overline{\gamma})\,e^{-\lambda\tau} = 0, \tag{11}$$

with

$$\overline{\alpha} = -2K_3 \quad \text{and} \quad \overline{\gamma} = -2(\delta K_3 + \overline{\beta}(1 - K_1)). \tag{12}$$

We recall from [10] that the steady state $(\overline{Q}, \overline{u})$ of (3) is locally asymptotically stable if all roots of the characteristic equation have negative real parts, and unstable if roots with positive real parts exist.

Theorem 4.1. 1) *Assume that $K_3 > 1/2$. Then, $(0, 0)$ is unstable for all $\tau \geq 0$.*
2) *Assume that (7) holds true. Then, $(0, 0)$ is unstable for all $\tau \geq 0$. Moreover,*
(i) *if $\delta + \overline{\beta} \geq \overline{\gamma}$, then $(\overline{Q}, \overline{u})$ is locally asymptotically stable for all $\tau \geq 0$,*
(ii) *if $\delta + \overline{\beta} < \overline{\gamma}$, then there exists $\tau_0 := \Theta/\varpi$ with*

$$\Theta = \operatorname{arccot}\left(-\frac{\overline{\alpha}\varpi^2 + (\delta + \overline{\beta})\overline{\gamma}}{\varpi(\overline{\gamma} - (\delta + \overline{\beta})\overline{\alpha})}\right) \quad \text{and} \quad \varpi = \sqrt{(\overline{\gamma}^2 - (\overline{\beta} + \delta)^2)(1 - \overline{\alpha}^2)^{-1}},$$

such that $(\overline{Q}, \overline{u})$ is locally asymptotically stable for $\tau < \tau_0$ and unstable for $\tau > \tau_0$. Moreover, a Hopf bifurcation occurs when $\tau = \tau_0$ and periodic solutions appear, with periods close to $2\pi/\varpi$.
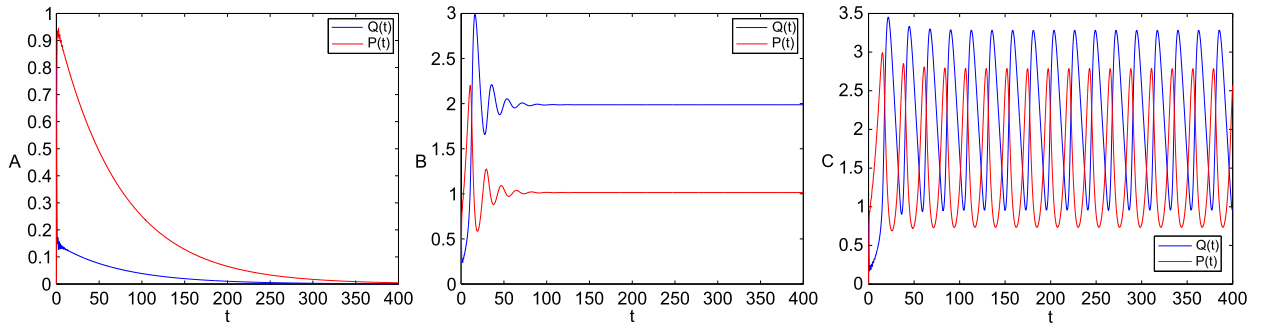
Fig. 2. (Color online.) Asymptotic behavior of the steady states. A) $(0,0)$ is globally asymptotically stable (Theorem 3.1). B) $(\overline{Q}, \overline{P})$ is local asymptotic stability when $\tau < \tau_0$ (Theorem 4.1, **2**)-(**ii**)). C) $(\overline{Q}, \overline{P})$ is unstable, and solutions periodically oscillate about $(\overline{Q}, \overline{P})$ when $\tau = \tau_0$ (Theorem 4.1, **2**)-(**ii**)).

Remark 1.

– When $\overline{\beta} \geq 0$, then $\delta + \overline{\beta} \geq \overline{\gamma}$ is always satisfied.
– The fact that periodic solutions appear with a period close to $2\pi/\varpi$, with ϖ an angular frequency, is a direct consequence of the Hopf bifurcation theorem (see [10], page 332).

Proof. The proof of this theorem is based on some ideas taken from ([12], page 68).

For the trivial steady state $(0,0)$, we have $\overline{\beta} = \beta_0$. Consider Δ_τ as a real function. Then, we have $\lim_{\lambda \to +\infty} \Delta_\tau(\lambda) = +\infty$ and $\Delta_\tau(0) = \delta(1 - 2K_3) - \beta_0(1 - 2K_1)$. The assumptions **1**) or **2**) imply that $\Delta_\tau(0) < 0$. Then, $\Delta_\tau(\lambda) = 0$ has a positive real root. Consequently, the steady state $(0,0)$ is unstable.

For the asymptotic stability of the positive steady state $(\overline{Q}, \overline{u})$, we will think of the roots $\lambda(\tau)$ of (11) as a continuously differentiable function in terms of the delay. First, remark that $\delta + \overline{\beta} + \overline{\gamma} = -(1 - 2K_1)\beta'(\overline{Q})\overline{Q} > 0$. Then, when $\tau = 0$, (11) has one root $\lambda(0) = -(\delta + \overline{\beta} + \overline{\gamma})(1 + \overline{\alpha})^{-1} < 0$. So, $(\overline{Q}, \overline{u})$ is locally asymptotically stable for $\tau = 0$. If $\delta + \overline{\beta} \geq \overline{\gamma}$, then $\lambda(\tau)$ does not cross the imaginary axis. Consequently, $(\overline{Q}, \overline{u})$ is locally asymptotically stable for all $\tau \geq 0$. If $\delta + \overline{\beta} < \overline{\gamma}$, we can prove that $\lambda(\tau)$ crosses the imaginary axis for $\tau = \tau_0$, with $\lambda(\tau_0) = i\varpi$ and $sign\{Re(\lambda'(\tau_0))\} = sign\{1 - \overline{\alpha}^2\} > 0$. Then, a Hopf bifurcation occurs when $\tau = \tau_0$. □

5. Numerical simulations

In this section, we carry out simulations with β taken as a Hill function ([13]) to confirm the theoretical results; all parameters are chosen to place ourselves in each situation (see Fig. 2).

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