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Ordinary Differential Equations/Dynamical Systems

On the stability of hematopoietic model with feedback control

*Stabilité d'un modèle hématopoïétique avec contrôle rétroactif*Catherine Marquet^a, Mostafa Adimy^b^a Université de Pau, laboratoire de mathématiques appliquées, CNRS UMR 5142, avenue de l'université, 64000 Pau, France^b INRIA Rhône-Alpes, université Lyon 1, institut Camille Jordan, 43 boulevard du 11 novembre 1918, 69200 Villeurbanne cedex, France

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ABSTRACT

We propose and analyze a mathematical model of the production and regulation of blood cell population in the bone marrow (hematopoiesis). This model includes the primitive hematopoietic stem cells (PHSC), the three lineages of their progenitors and the corresponding mature blood cells (red blood cells, white cells and platelets). The resulting mathematical model is a nonlinear system of differential equations with several delays corresponding to the cell cycle durations for each type of cells. We investigate the local asymptotic stability of the trivial steady state by analyzing the roots of the characteristic equation. We also prove by a Lyapunov function the global asymptotic stability of this steady state. This situation illustrates the extinction of the cell population in some pathological cases.

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R É S U M É

Nous proposons et étudions un modèle mathématique de production et régulation des cellules sanguines dans la moelle osseuse (hématopoïèse). Ce modèle décrit la dynamique des cellules souches hématopoïétiques primitives (PHSC), les trois lignées de cellules souches progéniteurs qu'elles génèrent ainsi que les cellules matures correspondantes (globules rouges, globules blancs et plaquettes). Le modèle mathématique obtenu est un système non linéaire d'équations différentielles avec plusieurs retards représentant les durées de cycles cellulaires de chaque type de cellules. Nous étudions la stabilité locale du point d'équilibre trivial par l'étude de l'équation caractéristique, puis nous prouvons sa stabilité globale par la méthode de Lyapunov. Ce résultat illustre l'extinction de la population des cellules dans certains cas pathologiques.

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1. Introduction

Hematopoiesis is the term used to describe the production and regulation of blood cells (red blood cells, white cells and platelets). It consists of mechanisms triggering self-replication, differentiation and maturation of hematopoietic stem cells (HSC). This process is initiated in the bone marrow before the mature cells enter the bloodstream. It is based on a pool of primitive hematopoietic stem cells (PHSC), that have abilities to produce either cells engaged in one of the three blood cell lineages: white cells, red blood cells or platelets (differentiation), or similar cells, with the same maturity level

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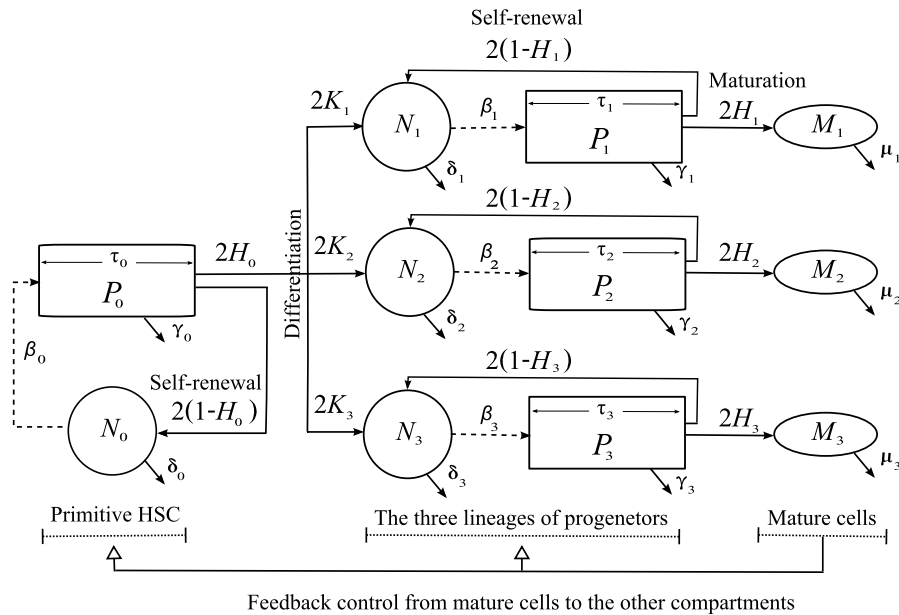


Fig. 1. Schematic representation of the hematopoiesis process. It includes the primitive hematopoietic stem cells (PHSC), the three lineages of their progenitors and the corresponding mature blood cells (red blood cells, white cells and platelets). Each compartment, except the mature cells, is divided into two sub-compartments: proliferating and nonproliferating.

(self-renewal) (see Fig. 1). Usually, an indirect control operates between the number of the mature cells and the production of HSC. This control is mediated by molecules acting like hormones in the production process. It acts in particular at the PHSC level.

To our knowledge, the first mathematical model of HSC dynamics has been introduced by Mackey [8], in 1978, inspired by work of Burns and Tannock [3]. The model of Mackey is an uncoupled system of two nonlinear delay differential equations, which considers an HSC population divided in two compartments: proliferating and nonproliferating. The delay describes the average cell cycle duration. This model stressed the influence of some factors (such as the apoptotic rate, the introduction rate, the cell cycle duration) playing an important role in the appearance of periodic solutions. Since then, the model of Mackey has been improved and analyzed by many authors, in particular with applications to periodic hematological diseases, such as autoimmune hemolytic anemia (Mahaffy, Bélair, and Mackey [9]), cyclical neutropenia (Haurie, Dale and Mackey [6]), and chronic myelogenous leukemia (Fowler and Mackey [4], Pujo-Menjouet, Bernard and Mackey [10], and Adimy, Crauste and Ruan [2]).

Each HSC compartment (the PHSC and the three progenitor compartments) is separated in two sub-compartments: proliferating and nonproliferating. Proliferating cells are actually in the cell cycle where they are committed to divide during mitosis at the end of this compartment. After division, the two newborn daughter cells enter immediately in the nonproliferating compartment. A part of them stay in the same compartment (self-renewal). For PHSC, the other part can enter into one of the progenitor compartments corresponding to the three blood cell lineages. We assume that the progenitors can also self-renew. On the other hand, they can differentiate into their corresponding mature cells (see Fig. 1). Delays appear in the model, describing the cell cycle durations in each proliferating compartment. Then we obtain a system of eleven delay differential equations.

2. Presentation of the model

For PHSC compartment, let denote by $P_0(t)$ (respectively, $N_0(t)$) the population of proliferating cells (respectively, nonproliferating cells) at time t . In the same way, let consider the different other cell populations: the three compartments of proliferating progenitors, and their corresponding nonproliferating cells, and mature cells, respectively denoted by $P_i(t)$, $N_i(t)$, and $M_i(t)$, $1 \leq i \leq 3$. In each compartment i ($0 \leq i \leq 3$) of the four proliferating compartments, cells can be eliminated by apoptosis γ_i , a specific process aimed to kill deficient cells (a programmed cell death). We denote by τ_i the duration of the proliferating compartment i . The mortality rate of nonproliferating cells in the compartment i is δ_i . Cells in the nonproliferating compartment i can be introduced in the proliferating compartment i with a rate β_i . We denote by K_i (respectively H_i), $1 \leq i \leq 3$, the rate of differentiation of PHSC to a progenitor of compartment i (respectively the rate of differentiation of progenitor of compartment i to a mature cell). We put $H_0 = K_1 + K_2 + K_3$ and we suppose that $K_i, H_i \in (0, 1)$. The rates of reintroduction from the nonproliferating compartments to the proliferating ones are assumed to depend (in terms of weighted total populations) of nonproliferating HSC and mature cells (see Mackey [8] and Adimy,

Crauste and Marquet [1]). This dependence represents the feedback control between the total population of cells and the production in each proliferating compartment (see Fig. 1).

Throughout this Note, we set $I_0 = \{0, 1, 2, 3\}$ and $I_1 = \{1, 2, 3\}$. Hence, N_0, P_0, N_i, P_i and M_i satisfy the following equations for $t \geq 0$ and $i \in I_1$

$$\begin{cases} N'_0(t) = -(\delta_0 + \beta_0(\chi_0(t)))N_0(t) + 2(1 - H_0)e^{-\gamma_0\tau_0}\beta_0(\chi_0(t - \tau_0))N_0(t - \tau_0), \\ P'_0(t) = -\gamma_0P_0(t) + \beta_0(\chi_0(t))N_0(t) - e^{-\gamma_0\tau_0}\beta_0(\chi_0(t - \tau_0))N_0(t - \tau_0), \\ N'_i(t) = -(\delta_i + \beta_i(\chi_i(t)))N_i(t) + 2(1 - H_i)e^{-\gamma_i\tau_i}\beta_i(\chi_i(t - \tau_i))N_i(t - \tau_i) + 2K_i e^{-\gamma_0\tau_0}\beta_0(\chi_0(t - \tau_0))N_0(t - \tau_0), \\ P'_i(t) = -\gamma_iP_i(t) + \beta_i(\chi_i(t))N_i(t) - e^{-\gamma_i\tau_i}\beta_i(\chi_i(t - \tau_i))N_i(t - \tau_i), \\ M'_i(t) = -\mu_iM_i(t) + 2H_i e^{-\gamma_i\tau_i}\beta_i(\chi_i(t - \tau_i))N_i(t - \tau_i), \end{cases}$$

where

$$\chi_i(t) = \rho_{i0}N_0(t) + \sum_{j=1}^3(\rho_{ij}N_j(t) + \sigma_{ij}M_j(t)), \quad \rho_{ij}, \sigma_{ij} \geq 0. \tag{1}$$

The initial condition is given by $(N_0(t), P_0(t), (N_i(t))_{i \in I_1}, (P_i(t))_{i \in I_1}, (M_i(t))_{i \in I_1}) = \phi(t)$, for $t \in [-\tau, 0]$, with $\phi \in C([-\tau, 0], \mathbb{R}_+^{11})$ and $\tau = \max\{\tau_i, i \in I_0\}$.

In the equation for $N_i(t)$, $i \in I_0$, the first term in the right-hand side accounts for cell loss due to either mortality ($\delta_i > 0$) and re-introduction in the proliferating compartment (β_i). The second term represents a cellular gain due to self-renewal at division. The third term, for $i \in I_1$, is a cellular gain due to differentiation at division of PHSC. In the equation of $P_i(t)$, $i \in I_0$, the first term in the right-hand side accounts for cellular loss by apoptosis ($\gamma_i > 0$) and the second term is for cellular entry from the nonproliferating compartment (β_i). The last term accounts for the flux of proliferating cells to the nonproliferating compartment. In the equation of $M_i(t)$, $i \in I_1$, the first term accounts for cell loss due to mortality ($\mu_i > 0$). The second term is due to differentiation at division of progenitors.

The introduction rates β_i are assumed to depend, in terms of weighted total populations, of nonproliferating PHSC and progenitors, and mature cells $\chi_i(t)$.

Usually (see Mackey [8]), the introduction rate β_i is chosen as a continuously differentiable Hill function, that is a continuous bounded and decreasing function tending to zero at infinity.

Since N_i and M_i do not depend on the proliferating cell population P_i , we will focus on the study of the reduced system of delay differential equations for $t \geq 0$ and $i \in I_1$

$$\begin{cases} N'_0(t) = -(\delta_0 + \beta_0(\chi_0(t)))N_0(t) + 2(1 - H_0)e^{-\gamma_0\tau_0}\beta_0(\chi_0(t - \tau_0))N_0(t - \tau_0), \\ N'_i(t) = -(\delta_i + \beta_i(\chi_i(t)))N_i(t) + 2(1 - H_i)e^{-\gamma_i\tau_i}\beta_i(\chi_i(t - \tau_i))N_i(t - \tau_i) \\ \quad + 2K_i e^{-\gamma_0\tau_0}\beta_0(\chi_0(t - \tau_0))N_0(t - \tau_0), \\ M'_i(t) = -\mu_iM_i(t) + 2H_i e^{-\gamma_i\tau_i}\beta_i(\chi_i(t - \tau_i))N_i(t - \tau_i). \end{cases} \tag{2}$$

First, one can note that 0 is always a steady state, describing the cell population's dying out, and all solutions of system (2) associated with nonnegative initial conditions are nonnegative and bounded (the proof use the same argument as in [1]).

3. Local asymptotic stability of the trivial steady state

We investigate the local stability of the trivial steady state of system (2). It describes cell's dying out.

Proposition 3.1. *Suppose that*

$$\tau_i > \frac{1}{\gamma_i} \ln\left(\frac{2(1 - H_i)\beta_i(0)}{\beta_i(0) + \delta_i}\right), \quad i \in I_0. \tag{3}$$

Then 0 is the only steady state, and it is locally asymptotically stable.

If (3) does not hold, 0 is unstable.

Proof. The characteristic equation of the linearized system about the trivial steady state is given by

$$\Delta(\lambda) = \Delta_0(\lambda) \prod_{i=1}^3(\lambda + \mu_i)\Delta_i(\lambda) = 0, \tag{4}$$

where $\Delta_i(\lambda) = \lambda + \delta_i + \beta_i(0) - 2\beta_i(0)(1 - H_i)e^{-(\lambda + \gamma_i)\tau_i}$, $i \in I_0$. Eigenvalues of the linearized equation of (2) are then $\lambda = -\mu_i < 0$, $i \in I_1$, and roots of

$$\lambda + \delta_i + \beta_i(0) - 2\beta_i(0)(1 - H_i)e^{-(\lambda+\gamma_i)\tau_i} = 0, \quad i \in I_0. \tag{5}$$

It is easy to check that this equation has the following form

$$(z + a_i)e^z + b_i = 0, \tag{6}$$

with $a_i = \tau_i(\delta_i + \beta_i(0))$, $b_i = -2\tau_i\beta_i(0)(1 - H_i)e^{-\gamma_i\tau_i}$ and $z = \lambda\tau_i$. Using a result by Hayes (see [7] or the book by Hale [5], p. 416), roots of (6) have negative real parts if and only if (3) is satisfied. \square

4. Global stability of the trivial steady state

We are interested, in this section, in the global stability of the trivial steady state of (2) under a stronger condition than (3).

Theorem 4.1. *Suppose that*

$$\tau_i > \frac{1}{\gamma_i} \ln\left(\frac{2\beta_i(0)}{\beta_i(0) + \delta_i}\right), \quad i \in I_0. \tag{7}$$

Then the trivial steady state is globally asymptotically stable.

Proof. We consider the functional

$$V : \prod_{i=0}^3 C([- \tau_i, 0], \mathbb{R}_+) \times \prod_{i=1}^3 C([- \tau_i, 0], \mathbb{R}_+) \rightarrow \mathbb{R}_+,$$

$$\Phi = (\varphi_0, \varphi_1, \varphi_2, \varphi_3, \psi_1, \psi_2, \psi_3) \rightarrow V(\Phi)$$

defined by

$$V(\Phi) = \varphi_0(0) + \sum_{i=1}^3 (\varphi_i(0) + \psi_i(0)) + 2 \sum_{i=0}^3 e^{-\gamma_i\tau_i} \int_{-\tau_i}^0 \beta_i(L_i(\Phi(s)))\varphi_i(s) \, ds,$$

where $L_i(\Phi(s)) = \rho_{i0}\varphi_0(s) + \sum_{j=1}^3 (\rho_{ij}\varphi_j(s) + \sigma_{ij}\psi_j(s))$.

Let $a(s) = s$, for $s \in \mathbb{R}_+$. We have

$$a(|\Phi(0)|) = |\Phi(0)| := \varphi_0(0) + \sum_{i=1}^3 (\varphi_i(0) + \psi_i(0)) \leq V(\Phi).$$

Along the solution of Eq. (2), we have

$$\dot{V}(\Phi) = - \left[\sum_{i=0}^3 [\delta_i - (2e^{-\gamma_i\tau_i} - 1)\beta_i(L_i(\Phi(s)))]\varphi_i(0) + \sum_{i=1}^3 \mu_i\psi_i(0) \right] \leq -k|\Phi(0)|,$$

where

$$k = \min_{j \in I_0} [\delta_j - (2e^{-\gamma_j\tau_j} - 1)\beta_j(0)], \min_{j \in I_1} (\mu_j).$$

The assumption (7) implies that $k > 0$. Then, thanks to Hale [5], Corollary 3.1, p. 143, every solution approaches zero as $t \rightarrow +\infty$. \square

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