Existence, positivity and stability for delay differential equations of cellular proliferation

Meriem Sanaa Labair

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1 Introduction

The objective of this dissertation is the mathematical analysis of a model of production and regulation of blood cells in the bone marrow called hematopoiesis. The modeling of these populations is carried out using a system of delay differential equations.
Proliferation is a physiological process of cell division that occurs in almost all tissues, resulting in an increase of the number of cells.

We assume that cells in a cycle are divided in two groups: proliferating that is and non-proliferating cells. The respective proliferating and non-proliferating cell populations are denoted by P and N.

All hematopoietic stem cells die with constant rates, namely $\gamma > 0$ for proliferating cells and $\delta > 0$ for non-proliferating cells. These latter are introduced in the proliferating phase, in order to mature and divide, with a rate β. At the end of the proliferating phase, cells divide into two daughter cells which immediately enter the non-proliferating phase.

Then the populations P and N satisfy the following evolution equations (see M. Adimy [1] or [2]),

$$\frac{dP(t)}{dt} = -\gamma P(t) + \beta N(t) - e^{-\gamma\tau}\beta N(t-\tau), \quad (1)$$

$$\frac{dN(t)}{dt} = -\delta N(t) - \beta N(t) + 2e^{-\gamma\tau}\beta N(t-\tau). \quad (2)$$

Here τ denotes the average duration of the proliferating phase. The term $e^{-\gamma\tau}$ describes the survival rate of proliferating cells. The last terms on the right-hand side of equations (1) and (2) account for cells that have performed a whole cell cycle and leave (enter, respectively) the proliferating phase (the non-proliferating phase, respectively). These cells are in fact non-proliferating cells introduced in the proliferating phase a time τ earlier. The factor 2 in equation (2) represents the division of each proliferating hematopoietic stem cell in two daughter cells.

We assume that the rate of introduction β depends upon the total population of hematopoietic stem cells, that we denote by S. With our notations, $S = P + N$. The function β is naturally assumed to be decreasing and positive with $\lim_{S\to\infty} \beta(S) = 0$.

Adding equations (1) and (2) we can then deduce an equation satisfied by the total population of hematopoietic stem cells $S(t)$. We assume, for the sake of simplicity, that proliferating and non-proliferating cells die with the same rate, that is $\delta = \gamma$. Then the populations N and S satisfy the following nonlinear system,

$$\frac{dS(t)}{dt} = -\delta S(t) + e^{-\delta\tau}\beta(S(t-\tau))N(t-\tau), \quad (3)$$

$$\frac{dN(t)}{dt} = -\delta N(t) - \beta(S(t))N(t) + 2e^{-\delta\tau}\beta(S(t-\tau))N(t-\tau). \quad (4)$$

The present work is organized as follows. In the next section we establish the existence and uniqueness of solutions of the system (3)–(4) . In section 3, we determine the equilibrium point of this model. In section 4, we linearize the system (3)–(4) about the equilibrium point, we deduce the associated characteristic equation and we focus on the asymptotic stability of the trivial equilibrium point.
Details for the analyses of delay differential equations can be found in [3] and [5].

2 Existence and uniqueness of solutions

Consider the system (3)–(4) with initial conditions

$$S(t) = \varphi(t) \quad t \in [-\tau, 0] \qquad \text{and} \qquad N(t) = \psi(t) \quad t \in [-\tau, 0]$$

2.1 Positivity of solutions

Proposition 2.1. *For all non-negative initial conditions, the unique solution $(S(t), N(t))$ of (3)–(4) is non-negative.*

Proof. First assume that there exists $\xi > 0$ such that $N(\xi) = 0$ and $N(t) > 0$ for $t < \xi$. Then, from (4) and since β is a positive function,
$\frac{dN}{dt}(\xi) = 2e^{-\delta\tau}\beta(S(\xi - \tau))N(\xi - \tau) > 0$. Consequently, $N(t) \geq 0$ for $t > 0$.
If there exists $\zeta > 0$ such that $S(\zeta) = 0$ and $S(t) > 0$ for $t < \zeta$, by the same reasoning, the use of (3) leads to $\frac{dS}{dt}(\zeta) = e^{-\delta\tau}\beta(S(\zeta - \tau))N(\zeta - \tau) > 0$, which implies $S(t) \geq 0$ for $t > 0$. □

2.2 Uniqueness and boundedness of solutions

Proposition 2.2. *For any initial condition $(\varphi, \psi) \in (C([-\tau, 0], \mathbb{R}_+^*))^2$ the system (3)-(4) has only one positive solution on $[0, +\infty[$,denoted by (S(t),N(t)),and this solution is bounded.*

Proof. From Hale and Verduyn Lunel [4], for each continuous initial condition, system (3)-(4) has a continuous maximal solution $(S(t), P(t))$, well-defined for $t \in [0, \mathrm{T})$. We can prove that this solution is bounded.
In fact, for $t \in [0, \mathrm{T}[$ we have by using a classical variation of constant formula [5],

$$N(t) = e^{-\delta t}N(0) - \int_0^t e^{-\delta(t-\theta)}\beta(S(\theta))N(\theta)d\theta + 2e^{-\delta\tau}\int_0^t e^{-\delta(t-\theta)}\beta(S(\theta-\tau))N(\theta-\tau)d\theta.$$

Thus $N(t) \leq e^{-\delta t}N(0) + 2e^{-\delta\tau}\int_0^t e^{-\delta(t-\theta)}\beta(S(\theta - \tau))N(\theta - \tau)d\theta.$

Let $\sigma = \theta - \tau$, then

$$N(t) \leq e^{-\delta t}N(0) + 2e^{-\delta\tau}\int_{-\tau}^{t-\tau} e^{-\delta(t-\sigma-\tau)}\beta(S(\sigma))N(\sigma)d\sigma,$$

thus

$$N(t) \leq e^{-\delta t}N(0) + 2\beta(0)e^{-\delta t}\int_{-\tau}^{t-\tau} e^{\delta\sigma}N(\sigma)d\sigma,$$

then

$$N(t) \leq N(0) + 2\beta(0)\int_{-\tau}^{T} e^{\delta\sigma}N(\sigma)d\sigma,$$

since $e^{-\delta t} < 1, \quad t < T, \quad$ i.e $\quad t - \tau < T - \tau < T.$

From the Gronwall lemma [5], we have,

$$N(t) \leq N(0)e^{\int_{-\tau}^{T} 2\beta(0)e^{\delta\sigma}d\sigma},$$

this implies

$$N(t) \leq N(0)e^{\frac{2\beta(0)}{\delta}\left[e^{\delta T} - e^{-\delta\tau}\right]} = M.$$

and N is bounded .
By using a classical variation of constant formula,

$$S(t) = e^{-\delta t}S(0) + e^{-\delta\tau}\int_0^t e^{-\delta(t-\theta)}\beta(S(\theta - \tau))N(\theta - \tau)d\theta$$

Let $\sigma = \theta - \tau$, this expression becomes

$$S(t) = e^{-\delta t} S(0) + e^{-\delta\tau} \int_{-\tau}^{t-\tau} e^{-\delta(t-\sigma-\tau)} \beta(S(\sigma)) N(\sigma) d\sigma$$

Then $S(t) \leq e^{-\delta t} S(0) + \beta(0) e^{-\delta t} \int_{-\tau}^{t-\tau} e^{\delta\sigma} N(\sigma) d\sigma$
and since N is bounded and $e^{-\delta t} < 1$, $t < T$ i.e $t - \tau < T - \tau < T$ then
$S(t) \leq S(0) + \beta(0) M \int_{-\tau}^{T} e^{\delta\sigma} d\sigma$ implies $S(t) \leq S(0) + \beta(0) M \left[\frac{e^{\delta T} - e^{-\delta\tau}}{\delta} \right] = M'$.
Then S is bounded. Therefore (S(t),N(t)) defined on $[0, +\infty[$. □

3 Existence of equilibrium point

let

$$\beta(S) = \beta_0 \frac{\theta^n}{\theta^n + S^n} \qquad \theta > 0, \quad \beta_0 > 0$$

The equilibrium point of (3)-(4) is a solution (S^*, N^*) satisfying

$$\frac{dS^*}{dt} = \frac{dN^*}{dt} = 0.$$

Then $\delta S^* = e^{-\delta\tau} \beta(S^*) N^*$ and $(\delta + \beta(S^*)) N^* = 2e^{-\delta\tau} \beta(S^*) N^*$.
Therefore the trivial equilibrium $X_0 = (0, 0)$ of system (3)-(4) exists for all $\tau \geq 0$.
Suppose that (S^*, N^*) is a nontrivial equilibrium of (3)-(4) . Thus,

$$\begin{cases} (2e^{-\delta\tau} - 1)\beta(S^*) = \delta \\ N^* = \dfrac{\delta S^*}{e^{-\delta\tau} \beta(S^*)} \end{cases} .$$

A necessary condition to obtain a non trivial equilibrium point is then $\tau < \frac{\ln(2)}{\delta}$.

Since $\beta(S^*) = \beta_0 \dfrac{\theta^n}{\theta^n + (S^*)^n}$,

$$S^* = \theta \left(\frac{\beta_0 (2e^{-\delta\tau} - 1)}{\delta} - 1 \right)^{\frac{1}{n}}, \quad N^* = \left(\frac{(2e^{-\delta\tau} - 1)\beta_0}{\delta} - 1 \right)^{\frac{1}{n}} \theta \left(\frac{(2e^{-\delta\tau} - 1)}{e^{-\delta\tau}} \right).$$

$S^* \geq 0, N^* \geq 0$ implies $\left(\frac{\beta_0 (2e^{-\delta\tau} - 1)}{\delta} - 1 \right) \geq 0$, then $\tau \leq \frac{1}{\delta} \ln \left(\frac{2\beta_0}{\delta + \beta_0} \right) = \overline{\tau}$.

Remark 1. *$\overline{\tau} > 0$ if and only if $\beta_0 > \delta$.*

We have the following result.

Theorem 3.1.

1. *If $\beta_0 \leq \delta$, then (3)-(4) has a unique equilibrium point X_0 exists for all $\tau \geq 0$.*
2. *If $\beta_0 > \delta$, then (3)-(4) has two equilibrium points X_0 and $X_1 = (S^*, N^*)$ and they exist for all τ on $[0, \overline{\tau}[$ where*

$$S^* = \theta \left(\frac{(2e^{-\delta\tau} - 1)\beta_0}{\delta} - 1 \right)^{1/n} \quad \text{and} \quad N^* = \theta \frac{2e^{-\delta\tau} - 1}{e^{-\delta\tau}} \left(\frac{(2e^{-\delta\tau} - 1)\beta_0}{\delta} - 1 \right)^{1/n}$$

Furthermore $X_1 \to X_0$ when $\tau \to \overline{\tau}$.

4 Characteristic Equation and Stability

Let $(\overline{S}, \overline{N})$ be the equilibrium point of system (3)–(4). The linearization of system (3)–(4) around $(\overline{S}, \overline{N})$ is

$$\begin{pmatrix} \frac{dS}{dt}(t) \\ \frac{dN}{dt}(t) \end{pmatrix} = A_1 \begin{pmatrix} S(t) \\ N(t) \end{pmatrix} + A_2 \begin{pmatrix} S(t-\tau) \\ N(t-\tau) \end{pmatrix}.$$

Let $f(S,N) = \frac{dS}{dt}(t)$ and $g(S,N) = \frac{dN}{dt}(t)$ such that :

$$A_1 = \begin{pmatrix} \frac{\partial f}{\partial \overline{S}}(t) & \frac{\partial f}{\partial \overline{N}}(t) \\ \frac{\partial g}{\partial \overline{S}}(t) & \frac{\partial g}{\partial \overline{N}}(t) \end{pmatrix} = \begin{pmatrix} -\delta & 0 \\ -\beta'(\overline{S})\overline{N} & -\delta - \beta(\overline{S}) \end{pmatrix}$$

and

$$A_2 = \begin{pmatrix} \frac{\partial f}{\partial \overline{S}}(t-\tau) & \frac{\partial f}{\partial \overline{N}}(t-\tau) \\ \frac{\partial g}{\partial \overline{S}}(t-\tau) & \frac{\partial g}{\partial \overline{N}}(t-\tau) \end{pmatrix} = \begin{pmatrix} e^{-\delta\tau}\beta'(\overline{S})\overline{N} & e^{-\delta\tau}\beta(\overline{S}) \\ 2e^{-\delta\tau}\beta'(\overline{S})\overline{N} & 2e^{-\delta\tau}\beta(\overline{S}) \end{pmatrix}$$

The characteristic equation of system (3)-(4) is defined by $\det(\lambda I - A_1 - e^{-\lambda\tau}A_2) = 0$
After calculation,and since $\delta > 0$, this equation reduces to

$$\lambda + \delta + \beta(\overline{S}) - (2\beta(\overline{S}) + \overline{N}\beta'(\overline{S})e^{-\delta\tau})e^{-\lambda\tau} = 0 \tag{5}$$

4.1 Stability of trivial equilibrium point

In this subsection we concentrate on the stability of the trivial equilibrium $X_0 = (0,0)$. For $\overline{S} = \overline{N} = 0$, the equation (5) becomes

$$\lambda + \delta + \beta_0 - 2\beta_0 e^{-\delta\tau}e^{-\lambda\tau} = 0. \tag{6}$$

Let us consider the mapping f such that $f(\lambda) = \lambda+\delta+\beta_0-2\beta_0 e^{-\delta\tau}e^{-\lambda\tau}$ as a function of the real variable λ .then it is increasing function from $-\infty$ to $+\infty$ yielding the existence and uniqueness of λ_0. Assume that $\lambda = \mu + i\omega \neq \lambda_0$ such that $\omega \neq 0$ a solution of (6). Then

$$\begin{cases} \mu + \delta + \beta_0 - 2\beta_0 e^{-\delta\tau}e^{-\mu\tau}\cos(\omega\tau) &= 0 \\ \omega + 2\beta_0 e^{-\delta\tau}e^{-\mu\tau}\sin(\omega\tau) &= 0. \end{cases}$$

and since λ_0 is a unique real solution, then $\lambda_0 + \delta + \beta_0 - 2\beta_0 e^{-\delta\tau}e^{-\lambda_0\tau} = 0$, and then we obtain $\lambda_0 = -\delta - \beta_0 + 2\beta_0 e^{-\delta\tau}e^{-\lambda_0\tau}$ then we obtain

$$\mu - \lambda_0 = 2\beta_0 e^{-\delta\tau}\left[e^{-\mu\tau}\cos(\omega\tau) - e^{-\lambda_0\tau}\right] \tag{7}$$

Suppose that $\mu > \lambda_0$ then $-\mu\tau < -\lambda_0\tau$ thus $e^{-\mu\tau} < e^{-\lambda_0\tau}$, therefore $e^{-\mu\tau} - e^{-\lambda_0\tau} < 0$. We have

$$\mu - \lambda_0 = 2\beta_0 e^{-\delta\tau}\left[e^{-\mu\tau}\cos(\omega\tau) - e^{-\lambda_0\tau}\right].$$

since $\cos(\omega\tau) \leq 1$, then $e^{-\mu\tau}\cos(\omega\tau) \leq e^{-\mu\tau}$. So $e^{-\mu\tau}\cos(\omega\tau) - e^{-\lambda_0\tau} \leq e^{-\mu\tau} - e^{-\lambda_0\tau}$. Therefore

$$\mu - \lambda_0 \leq 2\beta_0 e^{-\delta\tau}\left(e^{-\mu\tau} - e^{-\lambda_0\tau}\right)$$

since $e^{-\mu\tau} - e^{-\lambda_0\tau} < 0$, then $2\beta_0 e^{-\delta\tau}\left(e^{-\mu\tau} - e^{-\lambda_0\tau}\right) \leq 0$.
Thus $\mu - \lambda_0 \leq 0$. Then $\mu \leq \lambda_0$, and we have the contradiction. Therefore $\mu \leq \lambda_0$.
If $\mu = \lambda_0$, then from (7), $\cos(\omega\tau) = 1$. Therefore $\sin(\omega\tau) = 0$.
For the imaginary part of (5), we have $\omega = 0$, which gives a contradiction. Therefore, $\mu < \lambda_0$.
Then, for all eventual solution $\lambda \neq \lambda_0$ of (5) satisfy $\mathrm{Re}(\lambda) < \lambda_0$.
Since $f(0) = \delta + \beta_0 - 2\beta_0 e^{-\delta\tau}$, $f(\lambda_0) = 0$ and f is an increasing function, then $\lambda_0 < 0$ for $\delta + \beta_0 - 2\beta_0 e^{-\delta\tau} > 0$, i.e $\tau > \bar{\tau}$.
In this case all eigenvalues of (5) have negative real parts ,and for $\tau < \bar{\tau}$ we have $\lambda_0 > 0$.
We obtain the following result.

Theorem 4.1. *1. If $\beta_0 \leq \delta$ the unique equilibrium X_0 is locally asymptotically stable for all $\tau \geq 0$.*

2. If $\beta_0 > \delta$ the equilibrium X_0 is locally asymptotically stable for all $\tau > \bar{\tau}$ and unstable for all $\tau < \bar{\tau}$.

References

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