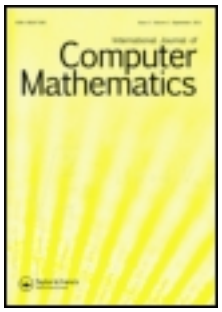

International Journal of Computer Mathematics
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gcom20

Asymptotic behaviour of a mathematical model of hematopoietic stem cell dynamics

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Accepted author version posted online: 26 Feb 2013.

To cite this article: M. Adimy , O. Angulo , J. C. López-Marcos & M. A. López-Marcos (2013): Asymptotic behaviour of a mathematical model of hematopoietic stem cell dynamics, International Journal of Computer Mathematics, DOI:10.1080/00207160.2013.778400

To link to this article: http://dx.doi.org/10.1080/00207160.2013.778400

International Journal of Computer Mathematics
Vol. 00, No. 00, January 2008, 1–11

RESEARCH ARTICLE

Asymptotic behaviour of a mathematical model of hematopoietic stem cell dynamics

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(*Received 19 Oct 2012, revised 08 Jan 2013, accepted 18 Feb 2013*)

We deeply researched into the asymptotic behaviour of a numerical method adapted for the solution of mathematical model of hematopoiesis which describes the dynamics of a stem cell population. We investigated the stationary solutions of the original model by their numerical approximation: we proved the existence of a numerical stationary solution that provides a good approximation to the nontrivial equilibrium solution of the problem. Also, we presented a numerical simulation which confirms this behaviour.

Keywords: Hematopoietic stem cell; Population dynamics; Age-structured model; Asymptotic analysis; Numerical integration

AMS Subject Classification: 35Q80; 35l50; 65M25; 92C37

1. Introduction

All blood cells arise from a common origin in the bone marrow, the hematopoietic stem cells (HSC). These stem cells are undifferentiated and have a high proliferative potential. They can proliferate and mature to form all types of blood cells: the red blood cells, white cells and platelets. Hematopoiesis is the term used to describe this process of production and regulation of blood cells. The HSC compartment is separated in two sub-compartments: proliferating and non-proliferating [16, 18] (also known as resting, quiescent or G0 phase). Resting cells represent the main part of the HSC population (90% of HSC are in a resting compartment [18]). Proliferating cells are actually in the cell cycle (G1-S-G2-M) where they are committed to divide during mitosis at the end of this phase. After division, the two newborn daughter cells enter immediately in G0-phase. A part of them remains in the HSC compartment (self-renewal) [17]. The other part can enter by differentiation into the mature cells compartment [20].

Mathematical modeling of hematopoietic stem cell dynamics has been investigated intensively since the 1970s (see, for example, Mackey [16]) and still interests a

O. Angulo, J.C. López-Marcos, M.A. López-Marcos were supported in part by the Ministerio de Ciencia e Innovación (Spain), project MTM2011-25238.
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ISSN: 0020-7160 print/ISSN 1029-0265 online

DOI: 0020716YYxxxxxxxx
http://www.informaworld.com

lot of researchers. This interest is greatly motivated, on one hand, by medical applications and, on the other hand, by the biological phenomena (such as oscillations, bifurcations, traveling waves, or chaos) observed in these models (Mackey [16], Adimy *et al.* [4–6]).

Blood cells die and must be replaced continuously. In the normal conditions, the body must maintain a constant blood volume to function properly. Then, the hematopoiesis regulates its internal environment to maintain a stable population of blood cells (homeostasis). It is believed that several hematological diseases are due to some abnormalities in the feedback loops between different compartments of hematopoietic populations [5, 6, 13, 16]. These disorders are considered as major suspects in causing destabilization of the homeostasis.

In this work, we consider a model of HSC dynamics with age-dependent coefficients which was proposed in [4]. It is comprised by a nonlinear partial differential system of equations that represents a balance law,

$$\begin{cases} r_t + r_a = -(\delta(a) + \beta(a, R(t)))\, r, & 0 < a, \quad t > 0, \\ p_t + p_a = -(\gamma(a) + g(a))\, p, & 0 < a < \tau, \quad t > 0, \end{cases} \tag{1}$$

a non local boundary condition, that means the way in which cells regenerate,

$$\begin{cases} r(0,t) = 2 \int_0^\tau g(a)\, p(a,t)\, da, & t > 0, \\ p(0,t) = \int_0^\infty \beta(a, R(t))\, r(a,t)\, da, & t > 0, \end{cases} \tag{2}$$

and a set of initial conditions

$$\begin{cases} r(a,0) = r_0(a), & 0 \le a, \\ p(a,0) = p_0(a), & 0 \le a < \tau. \end{cases} \tag{3}$$

The independent variables a and t are, respectively, spent age in each phase and time. The dependent variables $r(a,t)$ and $p(a,t)$ are densities of resting and proliferating HSC, respectively. The age has no limit for resting cell, whereas a maximal division age τ is used for proliferating ones. Since we assume here that τ is finite, all proliferating cells that did not die must divide before they reach it (see [14]). All the vital functions depend on age, which is the internal variable: $\delta(a)$ is the differentiation rate of resting cells (also, it could count some necrosis) and $\gamma(a)$ and $g(a)$ are the apoptosis and division rate of proliferating cells, respectively. The transition rate from resting phase to proliferating compartment, β, depends on the age and the total number of resting cells $R(t) = \int_0^\infty r(a,t)da$, $t > 0$. In our model the positive equilibrium is the homeostasis of the hematopoietic stem cell population. This age-structured model (1)–(3) was previously studied by Adimy *et al.* [4]. The authors proved the existence and uniqueness of solutions to this problem. They also investigated the existence of stationary solutions with the contribution of the conditions that a nontrivial stationary solution must satisfy. However, the stability of such equilibrium was not theoretically investigated. The authors introduced a numerical method adapted to (1)–(3) to show such stability.

Models such as the one considered above cannot be solved analytically and require numerical integration to obtain an approximation of the solutions. In [1, 2], we can find a review of the numerical schemes proposed to solve models of physiologically structured populations, which are compared with regards to accuracy, efficiency, generality, mathematical methodology and qualitative behavior depending on the compatibility conditions between initial and boundary data of the problems. On the other hand, modern numerical methods have been successfully applied to physiologically structured models to replicate available field and/or laboratory

data, for a variety of different systems [3, 7–11, 15]. All these works indicate that structured population models and numerical simulations are valid tools to investigate systems such as the one under consideration here. Besides, new techniques for the numerical solution of more general nonlocal boundary problems than (1)-(3) has been recently introduced in [12].

The numerical method used in [4] was very helpful to investigate the dynamics of the solutions of problem (1)-(3). In different numerical tests, the authors observed the existence of an asymptotically stable steady state. This represents, from a medical point of view, the situation of normal hematopoiesis (homeostasis). The unstable nontrivial steady state produces long-period oscillations which can be related to observations of some periodical hematological diseases. However, the theoretical study of this numerical procedure was not performed in our previous work [4]. This is the aim of this work.

In section 2, we introduce the theoretical results developed in [4] about system (1)–(3). In section 3, we present the numerical method. We show the existence of the nontrivial numerical steady state provided by the method, and we analyze the convergence of the numerical steady state to the theoretical one in section 4. Finally, in section 5, we numerically illustrate our results.

2. Theoretical Properties of the Model

In this section, we describe some properties of the solutions of (1)–(3). In this way, we introduce the following assumptions related to the vital rates (see [4] for more details).

(A1) For $R \in \mathbb{R}^+$, the function β satisfies $0 \leq \beta(\cdot, R) \leq \beta_+$ *a.e.*, decreasing with respect to R on $[0, +\infty)$ and $\lim_{R\to+\infty} \beta(\cdot, R) = 0$, a.e. in $[0, +\infty)$.
(A2) There is an increasing function $C : [0, +\infty) \to [0, +\infty)$ such that, if $0 \leq R_1 \leq M$ and $0 \leq R_2 \leq M$ then: $\|\beta(\cdot, R_1) - \beta(\cdot, R_2)\|_\infty \leq C(M)\,|R_1 - R_2|$.
(A3) Function δ satisfies $0 \leq \delta \leq \delta_+$ *a.e.* in $[0, +\infty)$.
(A4) Function γ satisfies $0 \leq \gamma \leq \gamma_+$ *a.e.* in $[0, \tau)$.
(A5) Function g is nonnegative, belongs to $L^1_{loc}[0, \tau)$ and $\int_0^\tau g(a)\,da = +\infty$.

Under (A1)-(A5), the existence of a unique local solution of system (1)–(3) can be proved via a fixed point argument (see [19]). On the other hand, regularity, positivity and global existence of this solution depend on the initial conditions and some criteria on the parameters of the model. With respect to stationary solutions, $r(a, t) = \varphi(a)$, $a > 0$, and $p(a, t) = \psi(a)$, $0 < a < \tau$, we observe that the trivial equilibrium (i.e. $(\varphi, \psi) \equiv (0, 0)$) always exists. On the other hand (see [4] for a more detailed discussion), we can characterize another stationary solution in the following way. We denote by Φ the total number of resting cells at the steady state, $\Phi = \int_0^\infty \varphi(a)\,da$. Then a nontrivial steady state can be written as

$$\varphi(a) = \frac{\Phi\,\Lambda(a, \Phi)}{\int_0^{+\infty} \Lambda(\sigma, \Phi)\,d\sigma}, 0 \leq a; \quad \psi(a) = \frac{\Phi\,L(a)}{2\,K\,\int_0^{+\infty} \Lambda(\sigma, \Phi)\,d\sigma}, \; 0 \leq a < \tau; \quad (4)$$

with $L(a) = \exp\left[-\int_0^a (\gamma(s) + g(s))ds\right]$, $\Lambda(a, \Phi) = \exp\left[-\int_0^a (\delta(\sigma) + \beta(\sigma, \Phi))\,d\sigma\right]$, $K = \int_0^\tau g(a) \exp\left[-\int_0^a (\gamma(\sigma) + g(\sigma))d\sigma\right]\,da$, and Φ is just a solution of the equation

$$2\,K \int_0^{+\infty} \beta(a, \Phi)\,\Lambda(a, \Phi)\,da = 1. \quad (5)$$

Therefore, if we define the net growth rate of the population at the constant size as $H(\Phi) := 2K \int_0^{+\infty} \beta(a,\Phi)\,\Lambda(a,\Phi)\,da$, from (5), the existence of such nontrivial equilibrium, is just associated to the existence of solutions of equation $H(\Phi) = 1$. So, under (A1)-(A5) we have the following result

PROPOSITION 2.1 *System (1)–(2) has exactly one nontrivial stationary solution if $H(0) > 1$. Otherwise, no nontrivial stationary solution exists.*

3. Numerical method

In this section, we describe a method which integrates numerically the nonlinear system (1)–(3) along the characteristic curves. Taking into account that the problem is defined over an unbounded age interval, for numerical purposes we introduce a maximum individual age $A_{\max}$ for resting cells ($A_{\max}$ will be considered enough large to assure that after this maximum age, the density r vanishes, and so $\tau < A_{\max}$).

The numerical method that we propose integrates the model along the characteristic curves by means of a discretization of an integral representation of the solutions of the model. We introduce an age grid in which we state τ as a node. To this end, given a positive integer J, we define the step size $k = \tau/J$ and denoting by $J^* = [A_{\max}/k]$, we introduce a uniform partition on the interval $[0, A_{\max}]$, given by $a_j = j\,k$, $0 \le j \le J^*$ (note that $a_J = \tau$). We will integrate the problem in a fixed time interval $[0,T]$, so we define the discrete time levels, $t_n = n\,k$, $0 \le n \le N$, where $N = [T/k]$.

The values U_j^n, $0 \le j \le J^*$, and V_j^n, $0 \le j \le J$, for each $0 \le n \le N$, represent numerical approximations to $r(a_j,t_n)$ and $p(a_j,t_n)$, respectively (the subscript j refers to the grid point a_j and the superscript n to the time level t_n); we also denote the discrete approximations as vectors $\mathbf{U}^n$, $\mathbf{V}^n$, $0 \le n \le N$, with components U_j^n, $0 \le j \le J^*$, and V_j^n, $0 \le j \le J$, respectively. The notations $I_k(\mathbf{W})$ and $I_k^*(\mathbf{W})$ represent the open second order quadrature rules $I_k(\mathbf{W}) = \sum_{j=1}^{J-1}{}''' k\,W_j$, for $\mathbf{W} = (W_0,\ldots,W_J)$, and $I_k^*(\mathbf{W}) = \sum_{j=1}^{J^*-1}{}''' k\,W_j$, for $\mathbf{W} = (W_0,\ldots,W_{J^*})$, that will be used to approach the nonlocal terms (the notation $\sum'''$ indicates that the first and last term are multiplied by $\frac{3}{2}$).

Given approximations $\mathbf{U}^0 \in \mathbb{R}^{J^*+1}$, $\mathbf{V}^0 \in \mathbb{R}^{J+1}$ of the initial conditions in (3), the numerical method is defined from the following general recursion that provides the numerical approximation at the time level $n+1$, $(\mathbf{U}^{n+1},\mathbf{V}^{n+1})$, from the approximations at the time level n, $(\mathbf{U}^n,\mathbf{V}^n)$:

$$U_{j+1}^{n+1} = U_j^n \exp\left(-\frac{k}{2}\left(\boldsymbol{\beta}_j^n + \boldsymbol{\beta}_{j+1}^{n+1}\right) - \int_0^k \delta(a_j+\sigma)\,d\sigma\right),\ 0 \le j \le J^*-1, \quad (6)$$

$$V_{j+1}^{n+1} = V_j^n \exp\left(-\int_0^k \left(\gamma(a_j+\sigma) + g(a_j+\sigma)\right)d\sigma\right), \quad 0 \le j \le J-1. \quad (7)$$

The discretization of the boundary conditions provides the numerical boundary values that complete the description of this time step,

$$U_0^{n+1} = 2\,I_k(\mathbf{g}\cdot\mathbf{V}^{n+1}), \quad (8)$$

$$V_0^{n+1} = I_k^*(\boldsymbol{\beta}^{n+1}\cdot\mathbf{U}^{n+1}), \quad (9)$$

$0 \le n \le N-1$. We denote as $\mathbf{g}$ and $\boldsymbol{\beta}^n$, $1 \le n \le N$, vectors with components

$g(a_j)$, $0 \le j \le J$, and $\beta(a_j, I_k^*(\mathbf{U}^n))$, $0 \le j \le J^*$, respectively. The products $\mathbf{g} \cdot \mathbf{V}^n$ and $\boldsymbol{\beta}^n \cdot \mathbf{U}^n$, in (8)-(9), represent the componentwise product of the vectors $\mathbf{g}$, $\mathbf{V}^n$, and $\boldsymbol{\beta}^n$, $\mathbf{U}^n$, respectively. Note, that for sake of simplicity only the nonlocal dependent function β has been discretized. Depending on the expressions of the other age-dependent functions, the required integrals may be exactly obtained or numerically computed. In any case, taking into account that these values do not change with time, they can be obtained before the numerical method starts. An analysis of convergence as in [11] can be applicable for this numerical procedure.

4. Asymptotic Behavior of the Numerical Scheme

As in the model, the trivial solution is a steady state of the numerical method. Now, if we look for a nontrivial equilibrium solution of (6)-(9), it is easy to see that such solution $(\mathbf{U}, \mathbf{V})$ satisfies

$$
\begin{aligned}
U_{j+1} &= U_j \, \exp\left(-\frac{k}{2}\left(\boldsymbol{\beta}_j + \boldsymbol{\beta}_{j+1}\right) - \int_0^k \delta\left(a_j + \sigma\right) d\sigma\right), \quad 0 \le j \le J^* - 1, \\
V_{j+1} &= V_j \, \exp\left(-\int_0^k \left(\gamma\left(a_j + \sigma\right) + g\left(a_j + \sigma\right)\right) d\sigma\right), \quad 0 \le j \le J - 1, \\
U_0 &= 2\, I_k(\mathbf{g} \cdot \mathbf{V}), \\
V_0 &= I_k^*(\boldsymbol{\beta} \cdot \mathbf{U}).
\end{aligned}
$$

Now $\boldsymbol{\beta}$ represents the vector with components $\boldsymbol{\beta}_j = \beta\left(a_j, I_k^*\left(\mathbf{U}\right)\right)$, $0 \le j \le J^* - 1$. Next, we can describe the equilibrium solution of the numerical method in terms of the numerical total population of resting cells, and such total population as a solution of a transcendental equation only involving the parameters of the problem. So, denoting by $S_k = I_k^*\left(\mathbf{U}\right)$, then a nontrivial numerical steady state can be written as

$$
U_j = \frac{S_k \, \Lambda_k(a_j, S_k)}{\Theta_k^*(S_k)}, \; 0 \le j \le J^*; \quad V_j = \frac{S_k \, L(a_j)}{2\, K_k \, \Theta_k^*(S_k)}, \; 0 \le j \le J, \tag{10}
$$

with $\Lambda_k(a_j, S_k) = \exp\left(-\sum_{i=0}^{j}{}'' k\, \boldsymbol{\beta}_i - \int_0^{a_j} \delta\left(\sigma\right) d\sigma\right)$, $K_k = \sum_{j=1}^{J-1}{}''' k\, g(a_j) \exp\left(-\int_0^{a_j} \left(\gamma\left(\sigma\right) + g\left(\sigma\right)\right) d\sigma\right)$, $\Theta_k(S_k) = \sum_{j=1}^{J^*-1}{}''' k\, \boldsymbol{\beta}_j \, \Lambda_k(a_j, S_k)$, $\Theta_k^*(S_k) = \sum_{j=1}^{J^*-1}{}''' k\, \Lambda_k(a_j, S_k)$, (where the notation $\sum''$ indicates that the first and the last term are multiplied by $\frac{1}{2}$). Now S_k is just a solution of the equation

$$
2\, K_k \, \Theta_k(S_k) = 1, \tag{11}
$$

discrete counterpart of (5). Associated to this equation we define the numerical growth rate of the population at the constant size as $H_k(S_k) := 2\, K_k \, \Theta_k(S_k)$.

Now, we want to show that the equilibrium solution of (6)-(9) is just an appropriate approximation of the equilibrium solution of (1)-(2) as the step size k tends to zero. In order to obtain this convergence result, we consider the following steps. First, note that the inclusion of $A_{\max}$ for the numerical method could be interpreted as a modification of the original model by truncation of the age interval. Therefore, we will show the convergence of the steady state solution of this truncated model to the steady state of (1)-(2) as $A_{\max}$ goes to infinity. Then we

conclude the convergence of the numerical equilibrium solution to the equilibrium of the truncated system as k goes to zero.

Therefore, we consider the introduction of $A_{\max}$ for resting cells as a change of the original model by means of a truncation version of the system over $[0, A_{\max}]$. So we introduce

$$\begin{cases} r_t + r_a = -(\delta(a) + \beta(a, R(t)))\, r, & 0 < a < A_{\max}, \quad t > 0, \\ p_t + p_a = -(\gamma(a) + g(a))\, p, & 0 < a < \tau, \quad t > 0, \end{cases} \tag{12}$$

$$\begin{cases} r(0,t) = 2 \int_0^{\tau} g(a)\, p(a,t)\, da, & t > 0, \\ p(0,t) = \int_0^{A_{\max}} \beta(a, R(t))\, r(a,t)\, da, & t > 0, \end{cases} \tag{13}$$

$$\begin{cases} r(a,t) = r_0(a), & 0 \le a \le A_{\max}, \\ p(a,t) = p_0(a), & 0 \le a \le \tau. \end{cases} \tag{14}$$

Now, the total number of resting cells is defined by $R(t) = \int_0^{A_{\max}} r(a,t)\, da$, $t > 0$.

By means of the same procedure than the one used to obtain the equilibrium solution of (1)-(2), we can characterize the equilibrium solution of (12)-(13) in terms of the total number of resting cells at the steady state. So, denoting by $(\bar{\varphi}(a), \bar{\psi}(a))$ a nontrivial steady state of the truncated model, and $\bar{\Phi} = \int_0^{A_{\max}} \bar{\varphi}(a)\, da$, its total number of resting cells, we can write

$$\bar{\varphi}(a) = \frac{\bar{\Phi}\, \Lambda\left(a, \bar{\Phi}\right)}{\int_0^{A_{\max}} \Lambda\left(\sigma, \bar{\Phi}\right) d\sigma},\ 0 \le a < A_{\max};\ \bar{\psi}(a) = \frac{\bar{\Phi}\, L(a)}{2\, K \int_0^{A_{\max}} \Lambda\left(\sigma, \bar{\Phi}\right) d\sigma},\ 0 \le a < \tau, \tag{15}$$

where $\bar{\Phi}$ is just a solution of the equation

$$2K \int_0^{A_{\max}} \beta\left(a, \bar{\Phi}\right) \Lambda\left(a, \bar{\Phi}\right) da = 1, \tag{16}$$

truncated version of (5). Again, we define the net growth rate of the population at the constant size $\bar{\Phi}$ as $H_{\max}\left(\bar{\Phi}\right) := 2K \int_0^{A_{\max}} \beta\left(a, \bar{\Phi}\right) \Lambda\left(a, \bar{\Phi}\right) da$. The following result states that the equilibrium solution of (12)-(13) converges to the nontrivial stationary solution of (1)-(2) exponentially with $A_{\max}$, by assuming the following regularity condition

(A6) The function $x \to \beta(a,x)$ is continously differentiable on $[0,\infty)$, for $a \ge 0$, and $\beta_x(\cdot, x)$ belongs to L^1 for $x \ge 0$. Where β_x describes the derivative with respect to the second argument,

THEOREM 4.1 *Let (A1)-(A6) be satisfied. If $H(0) > 1$, there exists $A^*_{\max}$ such that if $A_{\max} > A^*_{\max}$, (12)-(13) has exactly one nontrivial stationary solution. In such case, let Φ and $\bar{\Phi}$ denote the unique positive solutions of (5) and (16), respectively, and let be defined φ and ψ by (4) and $\bar{\varphi}$ and $\bar{\psi}$ by (15).Then, there exist positive constants α_i, $i = 1, 2, 3$, such that,*

$$|\Phi - \bar{\Phi}| = \mathcal{O}(\mathrm{e}^{-\alpha_1 A_{\max}}), \tag{17}$$

$$|\varphi(a) - \bar{\varphi}(a)| = \mathcal{O}(\mathrm{e}^{-\alpha_2 A_{\max}}), \quad a \in [0, A_{\max}], \tag{18}$$

$$|\psi(a) - \bar{\psi}(a)| = \mathcal{O}(\mathrm{e}^{-\alpha_3 A_{\max}}), \quad a \in [0, A_{\max}]. \tag{19}$$

Otherwise, no nontrivial stationary solution of (12)-(13) exists.

Proof: First we prove the existence and uniqueness of solutions of the equa-

tion (16). As $H(0) > 1$ and $\lim_{A_{\max}\to\infty} H_{\max}(0) = H(0)$, we can find $A^*_{\max}$ such that if $A_{\max} > A^*_{\max}$ then $H_{\max}(0) > 1$. Now, we consider the function $\xi(x) = 1 - H_{\max}(x)$, related to the transcendental equation (16) that defines $\bar{\Phi}$ (i.e., $\xi(\bar{\Phi}) = 0$). Note that for $A_{\max} > A^*_{\max}$, $\xi(0) < 0$ and $\xi'(x) > 0$ (because function $H_{\max}(x)$ is decreasing in $(0, +\infty)$). Now, from the assumptions imposed to the vital functions, and using similar arguments used in the proof of Proposition 2.1 (see [4]) for the original model, we can conclude that, $\lim_{x\to+\infty} \xi(x) = 1$. So, $\bar{\Phi}$ is the unique positive root of ξ, and $\bar{\Phi} < \Phi$ because $\xi(\Phi) > 0$.

By means of the mean value theorem, (A1) and (A6) and the smoothness properties of vital functions, there exists $\widetilde{\Phi} \in (\bar{\Phi}, \Phi)$ such that

$$|\bar{\Phi} - \Phi| \leq C \frac{\int_{A_{\max}}^{+\infty} \beta(a,\Phi)\,\Lambda(a,\Phi)\,da}{\Lambda\left(A_{\max}, \widetilde{\Phi}\right) \int_0^{A_{\max}} \left(-\beta_x\left(a, \widetilde{\Phi}\right)\right) da} \leq C\, e^{-\int_0^{A_{\max}} \beta(a,\Phi) da} \leq C\, e^{-\alpha_1 A_{\max}},$$

so (17) holds. On the other hand, if $a \in [0, A_{\max}]$, then, (4) and (15), the mean value theorem, (A3), (A1) and (A6), allow us to arrive at

$$\begin{aligned} |\varphi(a) - \bar{\varphi}(a)| &\leq |\varphi(0) - \bar{\varphi}(0)| + C \left| \int_0^a \beta(s,\Phi)\,ds - \int_0^a \beta\left(s, \bar{\Phi}\right) ds \right| \\ &\leq |\varphi(0) - \bar{\varphi}(0)| + C \left|\Phi - \bar{\Phi}\right|. \end{aligned} \tag{20}$$

Now, after some computations we arrive at

$$|\varphi(0) - \bar{\varphi}(0)| \leq C\,|\bar{\Phi} - \Phi| + C \int_{A_{\max}}^{+\infty} \Lambda(a,\Phi)\,da + C \left| \int_0^{A_{\max}} \Lambda\left(a, \bar{\Phi}\right) da - \int_0^{+\infty} \Lambda(a,\Phi)\,da \right|, \tag{21}$$

Therefore, by means of (A3), (A1) and (A6), and using (21) in (20) we can conclude (18). Finally, if $a \in [0, A_{\max}]$, (4) and (15) and properties (A4)-(A5) produce

$$|\psi(a) - \bar{\psi}(a)| \leq |\psi(0) - \bar{\psi}(0)| = \frac{1}{2\,K} |\varphi(0) - \bar{\psi}(0)|$$

that, by means of (18) and properties (A3), (A1) allows us to obtain (19). ∎

By means of similar arguments than in Theorem 4.1, and using the convergence properties of the quadrature rules that are included in the description of the numerical scheme, we can arrive to the following result which shows that the equilibrium solution of the numerical method (6)-(9) converges to the equilibrium solution of the truncated problem as k tends to zero. More precisely, the convergence is of second order.

THEOREM 4.2 *Let be the vital functions δ, β, g and γ sufficiently smooth. If $H_{\max}(0) > 1$ then, for $k > 0$ enough small, (11) has a unique solution. In such case, let $\bar{\Phi}$ and S_k denote the unique positive solutions of (16) and (11), respectively, and let be defined $\bar{\varphi}$ and $\bar{\psi}$ by (15) and $\mathbf{U}$ and $\mathbf{V}$ by (10). Then, as $k \to 0$*

$$|\bar{\Phi} - S_k| = \mathcal{O}(k^2), \tag{22}$$

$$|\bar{\varphi}(a_j) - U_j| = \mathcal{O}(k^2), \quad 0 \leq j \leq J^*, \tag{23}$$

$$|\bar{\psi}(a_j) - V_j| = \mathcal{O}(k^2), \quad 0 \leq j \leq J. \tag{24}$$

Proof: Consider the function $\xi_k(x) = 1 - H_k(x)$, related to the transcendental equation (11) that defines S_k (i.e. $\xi_k(S_k) = 0$). Note that, for k sufficiently small,

due to the regularity properties of function β and the error bound of the quadrature rule, $(\xi_k)'(x) = -2\,K_k\,\Theta_k'(x) > 0$ on $(0,+\infty)$; $\lim_{x\to\infty}\xi_k(x) = 0$ and $H_k(0) = H_{\max}(0) + O(k^2)$, so S_k is the unique positive root of ξ_k.

By means of the mean value theorem applied to the function ξ_k^{-1} on the interval defined by $\xi_k(\bar{\Phi})$ and $\xi_k(S_k)$, there exists $\widetilde{\Phi}$ in this interval such that

$$|\bar{\Phi} - S_k| = \left|\left(\xi_k^{-1}\right)'\left(\xi_k(\widetilde{\Phi})\right)\right| \left|\xi_k(\bar{\Phi}) - \xi_k(S_k)\right|$$

$$= \left| \frac{2\,(K - K_k)\,\displaystyle\int_0^{A_{\max}} \beta(a,\bar{\Phi})\Lambda\left(a,\bar{\Phi}\right) da - 2\,K_k\,\left(\displaystyle\int_0^{A_{\max}} \beta(a,\bar{\Phi})\Lambda\left(a,\bar{\Phi}\right) da - \Theta_k(\bar{\Phi})\right)}{2\,K_k\,\Theta_k'(\widetilde{\Phi})} \right|.$$

The regularity properties of the vital functions, and the error bounds of the quadrature rule allow us to obtain that

$$|K - K_k| \le C\,k^2,$$
$$\left|\int_0^{A_{\max}} \beta(a,\bar{\Phi})\Lambda\left(a,\bar{\Phi}\right) da - \Theta_k(\bar{\Phi})\right| \le C\,k^2.$$

By means of these inequalities, and that $K > 0$ and bounded, we conclude (22). Next, if $0 \le j \le J^*$, (15) and (10) allows us to have

$$|\bar{\varphi}(a_j) - U_j| \le |\bar{\varphi}(a_0) - U_0|\,\Lambda\left(a_j,\bar{\Phi}\right) + U_0\,\left|\Lambda\left(a_j,\bar{\Phi}\right) - \Lambda_k\left(a_j,S_k\right)\right|, \tag{25}$$

the smoothness properties of the vital functions and the error bounds of the quadrature rules allow us to get

$$\left|\Lambda\left(a_j,\bar{\Phi}\right) - \Lambda_k\left(a_j,S_k\right)\right| \le C\,k^2. \tag{26}$$

On the other hand, due to the boundedness and regularity properties of the vital functions, (22) and the error bounds of the quadrature rules, we arrive at

$$|\bar{\varphi}(a_0) - U_0| \le C\,\left|\bar{\Phi} - S_k\right| + C\,\left|\int_0^{A_{\max}} \Lambda\left(a,\bar{\Phi}\right) da - \Theta_k^*(S_k)\right| \le C\,k^2. \tag{27}$$

Then, we obtain (23) by using (26)-(27) in (25). Finally, using (15) and (10), and the positivity of the vital functions, we have

$$|\bar{\psi}(a_j) - V_j| \le |\bar{\psi}(a_0) - V_0|. \tag{28}$$

And, with the boundedness of data functions, we get

$$|\bar{\psi}(a_0) - V_0| \le C\,\left|\bar{\Phi} - S_k\right| + C\,\left|\int_0^{A_{\max}} \Lambda\left(a,\bar{\Phi}\right) da - \Theta_k^*(S_k)\right|$$
$$+ \left|\int_0^{A_{\max}} \beta\left(a,\bar{\Phi}\right)\Lambda\left(a,\bar{\Phi}\right) da - \Theta_k(S_k)\right| \tag{29}$$

and by means of the same smoothness arguments applied to (29) we arrive at

$$|\bar{\psi}(a_0) - V_0| \le C\,k^2,$$

which substituted in (28) allow us to have (24). ■

From Theorem 4.1 and Theorem 4.2, we can conclude that the equilibrium solution of the numerical method, given by (10), is close to the theoretical equilibrium solution, given by (4), by taking $A_{\max}$ large enough and k sufficiently small. On the other hand, we can conclude the same convergence result for the total populations.

5. Numerical experiments

In this section, we will integrate numerically (1)–(3) by means of the numerical method introduced in Section 3. We are going to show how much the numerical stationary state approaches the theoretical one. The initial conditions are given by functions $r_0(a) = \nu\,(A_{\max} - a)$ and $p_0(a) = \Gamma(\tau - a)$, where ν and Γ are fixed constants, chosen in a suitable form in order to satisfy the compatibility condition between the initial and boundary conditions. We also use the following values (see Adimy et al. [4]) $\tau = 7$, $\delta(a) = 0.05$, $\gamma(a) = 0.2$, $g(a) = \frac{1}{\tau - a}$. The transition rate function β is taken as

$$\beta(a, R) = \widetilde{\beta}_0(a)\,\frac{\theta^n}{\theta^n + R^n},$$

with $\theta = 1.62 \times 10^8$. We have considered two kinds of functions $\widetilde{\beta}_0(a)$ but, in all the cases, the maximum of $\widetilde{\beta}_0(a)$ is $\beta_0 = 1.77$. In the first test problem, we use $\widetilde{\beta}_0(a) = \beta_0\,(1 - e^{-\alpha\, a})$, with $\alpha = 1$ and $n = 6$, which satisfies $H(0) > 1$. In this case, the theoretical study of the model (1)–(3) (see [4]) predicts a positive steady state. It describes, from a medical point of view, a normal hematopoiesis (homeostasis). We show in Fig. 1 the results obtained with our numerical method. We present the evolution with time of total populations of resting and proliferating cells. We observe that the numerical solution is attracted towards a positive stable equilibrium. Due to the convergence results (Theorem 4.1 and Theorem 4.2), such asymptotically stable equilibrium provides an accurate numerical approximation of the theoretical steady state predicted in the analysis of the model. So, the numerical observations carried out provide relevant information about the dynamics of the solutions of the model.

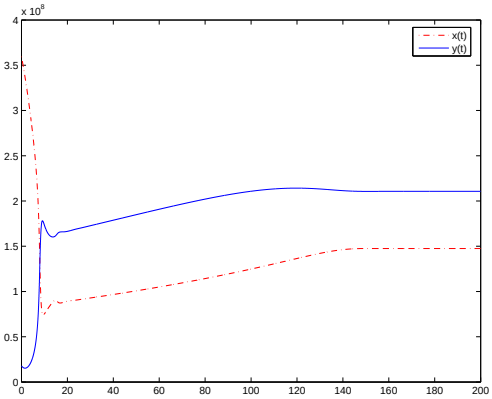

Figure 1. Evolution with time of resting population (straight line) and proliferating population (dashed line), for $\alpha = 1$ and $n = 6$.

In the second test problem we have taken $n = 2$ and $\widetilde{\beta}_0(a) = \beta_0$, because we are able to obtain the exact value of the theoretical steady state Φ. So we compare this value with the numerical results in order to show its convergence. We have

used $A_{\max} = 400$, and we have computed the difference between the theoretical and numerical steady states for different values of the step size. Then, the quantity $r_k = \log\left(|\Phi - S_k|/|\Phi - S_{\frac{k}{2}}|\right)/\log 2$, provides numerically the order of convergence to the theoretical steady state. The results in table 1 shows the predicted second order of convergence.

k	r_k
1e-2	2.045
5e-3	2.003
2.5e-3	1.997
1.25e-3	1.997

Table 1. Numerical order of convergence of the numerical steady state to the theoretical one.

6. Conclusions

We considered a problem that describes the evolution of an hematopoietic stem cell population. We took into account cell age dependence of coefficients. We analyzed the asymptotic behaviour of a new numerical method proposed *ad hoc* to solve the model. We obtained that when the model presents a nontrivial stationary solution, the numerical method also does, and the numerical stationary solution converges to the original one. We presented numerical experiments which corroborate the theoretical results. First, the numerical method was able to approach the nontrivial steady state in a case in which it is not possible to obtain theoretically such equilibrium. On the other hand, we showed that this convergence is of second order.

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