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Dynamics and numerical simulations in a production and development of red blood cells model with one delay

Radouane Yafia

Université Ibn Zohr, Faculté Polydisciplinaire, B.P:638 Ouarzazate, Morocco

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Abstract

In this paper, we study an unstructured model of a cellular population in the spirit of Grabosch and Heijmans [Grabosch A, Heijmans HJAM. Production, development and maturation of red blood cells, A mathematical model. AM-R 8919, ISSN 0924-2953, 1989.] model. The cellular population is described by a system of differential equations with one delay. The basic assumption is that the cell population responsible for the production of blood cells consists of three compartments: the stem cells, the precursor cells, and the blood cells. We prove that the model has two possible steady states and their dynamics (depending on time delay) are studied in term of the local stability, we illustrate these results with numerical simulations for some different values of the time delay.

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Keywords: Red blood cells; Delayed differential equations; Equilibrium point; Stability; Oscillating solutions

1. Introduction

The main processes that have to be accomplished by the blood production system are basic production, differentiation, amplification, and maturation. The human blood production system can be split up in three compartments where these physiological processes take place. One can distinguish (1) the self maintained stem cell compartment (located in the bone morrow), (2) the precursor cell compartment (located partly in the bone morrow and partly in the blood fluid), and (3) the blood cell compartment (located in the blood fluid). The only compartment capable of self maintenance is the stem cell compartment. Here the production of new cells takes place. Already at this early stage of the development a first commitment toward a special cell line. Cells entering the precursor stage are still morphologically indistinguishable from each other. In the precursor or transition stage, differentiation takes place. Cells passes through several successive stages. The total number of cells increases during the precursor stage by a factor 3, since cells undergo division independent of their morphological type. In average 2 days for a cell to transit through the precursor cell stage. Mitosis occurs only

E-mail address: yafia1@yahoo.fr

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in the precursor cell stage. In the last stage of the subdivision, the blood cell compartment or blood fluid, the newly formed red blood cells are completely developed (see [16]).

In Grabosh and Heijmans [4], the proteins play an important role in the regulation of this complex production system. For red blood cell production, the protein seems to be of some importance. This influence has an obvious explanation from the following observation. A decreased number of red blood cells leads to a decreased amount hemoglobin, thus to a decrease in the arterial oxygen tension. Finally, this protein causes an increased influx of red blood cells into the blood. Nevertheless, it seems not to be clear precisely what leads to the increased influx flow: a sudden release of nearly mature precursor cells, a higher division rate of stem cells, an increased flow from the stem cell compartment to the precursor cell compartment. For more details see [8,4].

2. Mathematical model

In the first, we recall the structured model of Grabosh and Heijmans [4]:

$$\frac{\partial}{\partial t}p(t,x)+\tilde{\psi}(E(t))\frac{\partial}{\partial x}(g(x)p(t,x))=b(x)p(t,x)-\tilde{\psi}(E(t))a(x)p(t,x)-\mu_p p(t,x) \tag{2.1}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}Z(t)=-\mu_Z Z(t)+\tilde{\psi}(E(t))\int_0^{+\infty}a(x)p(t,x) \tag{2.2}$$

where $p(t,x)$ is the density of the precursor cells at time t and maturation x (x is the level of maturation). $Z(t)$ is the number of blood cells at time t, $E(t)$ is the number of proteins acting between the red blood cell compartment $Z(t)$ and the precursor cell stage $P(t)$ at time t, where $P(t)=\int_0^{+\infty}p(t,x)$ is the total number of precursor cells at time t. In [4], it is considered that a lot of proteins slows down the maturation velocity of the precursor cells. Mathematically, this process can be described by an ordinary differential equation for the maturation $x(t)$ of an individual precursor cell:

$$\frac{\mathrm{d}x}{\mathrm{d}t}(t)=\tilde{\psi}(E(t))g(x(t))$$

where $\tilde{\psi}(E(t))$ is a real valued decreasing function in E.

$b(x)$ is the division rate of cells with maturation level x and μ_p and μ_Z are the death rates of precursor cells and blood cells, respectively.

Concerning the protein, it is assumed that it is produced by the red blood cells at a rate $h(Z(t))$, and that it disintegrates at a rate σ. The function h is supposed decreasing (i.e. if there is a few red blood cells there are a lot of protein see [4]). This amounts to the following equation for $E(t)$:

$$\frac{\mathrm{d}}{\mathrm{d}t}E(t)=-\sigma E(t)+h(Z(t)) \tag{2.3}$$

Concerning the dynamics of S, one could follows the models of Mackey (see [9–14]). Depending on the number of cells in the precursor cell compartment (via the function q), cells leave a quiescent stage after division. A fraction $1-d$ goes through the cell division process, whereas the other fraction d enters the precursor cell stage with a maturity level zero. One knows that hardly any quiescent cells die; thus a death rate μ_S is included only for the active part of the cell cycle of stem cells. If τ is the time duration of the cell division process, then $\mathrm{e}^{-\mu_S\tau}$ is the fraction of cells that survive the mitotic phase, and the number of daughter cells at time t is $2(1-d)q(P_\tau(t))S_\tau(t)\mathrm{e}^{-\mu_S\tau}$. Here $P_\tau(t)=P(t-\tau)$ and the same for S_τ. This assumptions would lead to the following delay differential equation for S:

$$\frac{\mathrm{d}}{\mathrm{d}t}S(t)=2(1-d)q(P_\tau(t))S_\tau(t)\mathrm{e}^{-\mu_S\tau}-dq(P(t))S(t) \tag{2.4}$$

and the following boundary condition for p:

$$\tilde{\psi}(E(t))g(0)p(t,0)=dq(P(t))S(t) \tag{2.5}$$

and the function q takes the form of hill (see [9–12]):