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SPATIAL DISTRIBUTION OF CELL POPULATIONS IN THE PROCESSES OF ERYTHROPOIESIS

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Abstract: We study spatial cell distribution in the bone marrow taking into account cell self-renewal, differentiation and apoptosis as well as cell motion resulting from cell proliferation. The model consists of reaction-diffusion equations in a porous medium. The existence of stationary solutions corresponding to normal erythropoiesis is proved. In the leukemic case, this stationary solution becomes unstable. Malignant cells propagate as a travelling wave filling the marrow. We study this phenomenon numerically in the 2D case. An analytical approximation for the wave speed is compared with the numerical solution of the full problem.

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Introduction

In this work we model erythropoiesis, the process which consists in production of red blood cells (RBC) in the bone marrow. Blood cell production starts with hematopoietic stem cells (HSCs) which differentiate into several cell lineages and among them erythroid lineage, see [3], [22]. Consecutive differentiation of HSCs leads to ap-

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pearance of immature erythroid progenitors, that in turn undergo several maturity stages to become mature red blood cells (erythrocytes). At each cell cycle, erythroid progenitors can self-renew, differentiate or die by apoptosis, see [19], [21].

In the previous work of some of the authors, we have studied intra-cellular regulatory networks which govern self-renewal and differentiation of erythroid progenitors and determine the RBC production and its response to anemia, see [8]. Contrary to the previous work, we will take here into account spatial cell distribution inside the bone marrow and cell motion resulting from cell proliferation. Immature erythrocytes appear and push each other through the medium formed by other cells and by porous matrix. In the process of this motion, cells increase their maturity. Mature blood cells are pushed out into blood vessels going through the marrow. Thus, normal hematopoiesis implies some spatial cell organization according to their maturity level. There are little experimental results about spatial distribution of blood cells in the bone marrow. It is known that stem cell can be localized and form a stem cell niche, see [12], [13], [17], [18], [20]. Erythroid progenitors and reticulocytes are located in erythroblastic islands, see [5]. Their interaction determine self-renewal, differentiation and apoptosis of the immature cells and, as consequence, normal functioning of erythropoiesis.

Excessive proliferation of immature cells, which can be related to certain blood diseases including leukemia, changes normal cell distribution in the marrow. If proliferation of malignant cells is sufficiently fast, then the tumor grows and can fill the whole marrow. The propagation of leukemic cells corresponds to travelling wave solutions of reaction-diffusion-convection equations. We will study in this work spatial cell distribution for both normal and leukemic hematopoiesis.

Mathematical modelling of hematopoiesis conventionally uses delay differential equations and structured population dynamics. We can cite the works by Mackey with co-authors beginning from, see [11]. A global model of hematopoietic cell dynamics is recently proposed by Colijn and Mackey, see [6], [7]. Other works on hematopoiesis modelling are carried out by Loeffler and his collaborators since the beginning of the 1980's, see [15], [16]. The works listed above do not take into account space distribution of cells in the bone marrow.

On the other hand, there is an extensive literature devoted to modelling of solid tumors. Cell proliferation results in the motion of the medium described by Darcy's law or Navier-Stokes equations, see [2], [10], [14]. The PDE models of cell motion can be justified by probabilistic methods (see [4] and the references therein). Reaction-diffusion problems in a porous medium are also studied for propagating combustion and polymerization fronts, see [1].

In this work we describe cell concentrations by reaction-diffusion equations and their motion by Darcy's law. The difference with the works cited before is related in particular to some specific features of cell production in the process of hematopoiesis. A close problem was studied in [9] in the 1D spatial case. In this work we are particularly interested by propagation of 2D waves which correspond to leukemia

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development in the bone marrow.

The paper is organized as follows. In the next section we present reaction-diffusion equations in porous media which describe evolution of cell populations. This model will be briefly discussed in the general framework and more specifically for erythroid progenitors. In Section 2 we will prove the existence of a stationary solution in the 1D case. This solution gives a stationary cell distribution in the cross-section of the bone marrow considered as a 2D rectangular domain. In the leukemic case, this 1D solution can become unstable. The region filled by malignant cells will propagate and fill the whole domain. We study this phenomenon numerically in Section 3. We will give an analytical approximation for the speed of the travelling wave and will compare it with the numerical results.

1. Models of Cell Populations

1.1. Equations of Continuous Mechanics

We consider a cell population in a porous medium. In particular, this can be blood cells in the bone marrow. Let us denote by c_i, $i = 1, ..., n$ the concentrations of different cell types, that is the mass fraction of cells of the i-th type in a unit volume. Cell population is considered as a continuous medium. The evolution of the concentrations is governed by the following equation

$$\frac{\partial c_i}{\partial t} + \nabla.(\mathbf{v}c_i) = d\Delta c_i + F_i, \tag{1.1}$$

where $\mathbf{v}$ is the velocity of the medium, d the diffusion coefficient and F_i is the production rate of the i-th type of cells. The diffusion terms describes random cell motion. Let ϕ be the total cell concentration, that is

$$\phi = c_1 + ... + c_n. \tag{1.2}$$

Taking a sum of all equations in (1.1), we obtain that ϕ satisfies the equation

$$\frac{\partial \phi}{\partial t} + \nabla.(\mathbf{v}\phi) = d\Delta\phi + \sum_{i=1}^{n} F_i. \tag{1.3}$$

Let us consider cells as spherical particles which consist of an external elastic membrane and which are filled by an incompressible fluid. Let us suppose for simplicity that all particles have the same size and denote their diameter by r and the volume by v_0. Consider next a sufficiently small cube with the side a and the volume V. Denote by p the pressure, that is the force acting from the particles on the sides of the cube. Let N be the number of particles inside the cube. If $N < N_0 = (a/r)^3$, then the particles can be distributed in such a way inside the cube that there is no

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repulsion between them and no force on the sides of the cube. The maximal number of particles can be estimated by $N_{max} = V/v_0$. In this case the cube is filled by an incompressible fluid. If the number of particles is between N_0 and N_{max}, then the pressure is a function of N.

Thus, the pressure p is a function of the total cell concentration ϕ:

$$p(\phi) = \begin{cases} 0 & , \quad \phi \leq \phi_0, \\ p_0(\phi) & , \quad \phi_0 < \phi < \phi_{max}, \end{cases}$$

where $p_0(\phi)$ is some given function, ϕ_0 and ϕ_{max} are positive parameters. If $\phi = \phi_{max}$, then from (1.3) we obtain the following equation

$$\nabla.\mathbf{v} = \frac{1}{\phi_{max}} \sum_{i=1}^{n} F_i. \tag{1.4}$$

In the case without sources ($F_i = 0, i = 1, ..., n$), we obtain an incompressible medium.

The pressure-concentration dependence is shown in Figure 1. The equation of state can be written as

$$H(p, \phi) = 0, \tag{1.5}$$

where the function H is such that $H(p(\phi), \phi) = 0$.

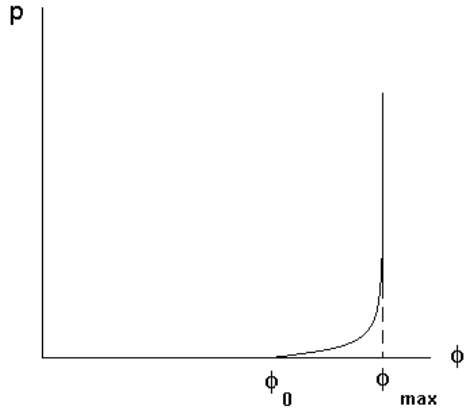

Figure 1: The pressure-concentration dependence in the equation of state.

If we consider a porous medium, then convective motion is described by Darcy's law:

$$\frac{\rho}{\epsilon}\frac{\partial \mathbf{v}}{\partial t} = -\nabla p - \frac{\mu}{K}\mathbf{v}, \tag{1.6}$$

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Here p is the pressure, ρ – the density, ϵ – the porosity of the medium, K – the permeability, and μ – the viscosity. System of equations (1.1), (1.3), (1.5), (1.6) should be considered in some domain and completed by appropriate initial and boundary conditions.

1.2. Cell Proliferation, Differentiation, Apoptosis

We will specify here the functions F_i used in the previous section. They describe the rates of production or disappearance of various cell types. Consider a single cell lineage which consists of n sub-populations with the following properties. The cells in each sub-population P_i are identical to each other. They can self-renew with the rate s_i, differentiate with the rate d_i or die by apoptosis with the rate a_i (Figure 2). By self-renewal we understand here that two daughter cells are identical to the mother cell. In the case of differentiation, daughter cells belong to the next sub-population P_{i+1}. We assume that there is an influx of cells to the first sub-population P_1 with a constant rate S. These cells can come from stem cell compartment or from other immature cell populations. Finally, the cells of the last sub-population P_n can differentiate into other cells or leave the system. This situation corresponds to the development of erythroid progenitors in the bone marrow, see [8].

Under these assumptions, homogeneous in space concentrations c_i of cell sub-populations P_i and c_D of dead cells are described by the following system of equations:

$$\frac{dc_1}{dt} = S + (s_1 - d_1 - a_1)c_1 \equiv F_1, \tag{1.7}$$

$$\frac{dc_i}{dt} = (s_i - d_i - a_i)c_i + 2d_{i-1}c_{i-1} \equiv F_i, \quad i = 2, ..., n, \tag{1.8}$$

$$\frac{dc_D}{dt} = a_1c_1 + \ldots + a_nc_n \equiv F_D. \tag{1.9}$$

The rates of cell self-renewal, differentiation and apoptosis are determined by intra-cellular regulatory networks and can be influenced by surrounding cells, by the whole cell population and by external regulatory mechanisms based on hormones and growth factors. We do not consider here intra-cellular regulatory networks (see [8] for more detailed discussion) and suppose that these rates can be only influenced by surrounding cells. This means that the coefficients s_i, d_i, a_i can depend on $c_1, ..., c_n$. In particular, we will take into account the limitation on cell proliferation. When the total cell concentration $c_\Sigma = c_1 + ... + c_n$ approaches some maximal value c_{max}, cells produce signals which reduce their proliferation rate:

$$s_i = s_i^0(c_{max} - c_\Sigma), \quad d_i = d_i^0(c_{max} - c_\Sigma). \tag{1.10}$$

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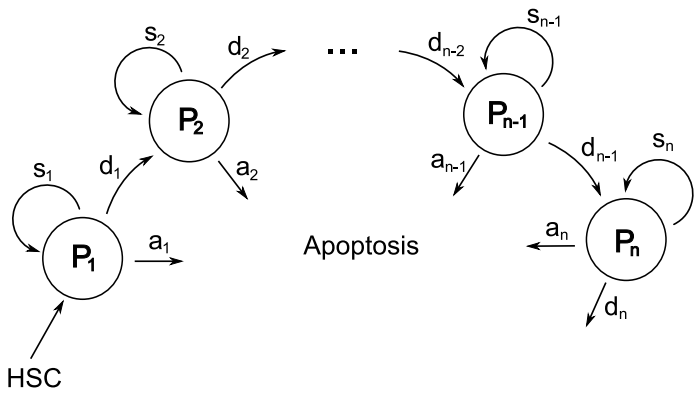

Figure 2: Schematic representation of consecutive cell sub-populations.

It is also possible that cells accelerate their own proliferation or proliferation of other cells. In the case of linear self-acceleration, instead of (1.8) we will have

$$s_i = s_i^0 c_i(c_{max} - c_\Sigma), \quad d_i = d_i^0 c_i(c_{max} - c_\Sigma). \tag{1.11}$$

In this case

$$F_1(c) = S + (s_1^0 - d_1^0)\, c_1^m(c_{max} - c_\Sigma) - a_1 c_1,$$

$$F_i(c) = (s_i - d_i)\, c_i^m(c_{max} - c_\Sigma) + 2d_{i-1}(c_{max} - c_\Sigma)c_{i-1} - a_i c_i, \quad i = 2, ..., n,$$

where $c = (c_1, ..., c_n)$, $m = 1, 2$. We note that the restriction on cell proliferation by the total number of cells may not take place. In particular, this can be the case for malignant cells. Similar models can be written for several cell lineages.

1.3. Summary of the Models

Depending on the value of cell concentration, we obtain the models which differ by the equations of motion. If $c_\Sigma \le \phi_0$, then $p = 0$. From (1.6) it follows that $\mathbf{v} = \mathbf{0}$ and the model is reduced to reaction-diffusion system (1.1) without convective terms. The condition on c_Σ will be verified if $c_{max} < \phi_0$.

If $c_\Sigma < \phi_{max}$, then $p = p_0(\phi)$. The model is given by equation (1.1) and

$$\frac{\rho}{\epsilon}\frac{\partial \mathbf{v}}{\partial t} = -\nabla p_0(c_\Sigma) - \frac{\mu}{K}\mathbf{v}.$$

Under the quasi-stationary approximation, the last equation is replaced by

$$\mathbf{v} = -\frac{K}{\mu}\,\nabla p_0(c_\Sigma).$$

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If we consider a linear approximation of the function p_0, we obtain $\mathbf{v} = -\kappa\nabla(c_1 + ... + c_n)$ (cf. [9]), where $\kappa = K/\mu$ is a positive parameter.

If $c_\Sigma = \phi_{max}$, then the model is given by equations (1.1), (1.4), (1.6). It is possible to have all three cases $c_\Sigma \le \phi_0$, $\phi_0 < c_\Sigma < \phi_{max}$, $c_\Sigma = \phi_{max}$ at the same time, each one in some subdomain. The boundaries between the subdomains can depend on time.

2. Incompressible Medium

In the remaining part of the paper we consider the case $c_\Sigma = \phi_{max}$. In the 1D case, we obtain the system of equations

$$\frac{\partial c_i}{\partial t} + \frac{\partial (v c_i)}{\partial x} = d\,\frac{\partial^2 c_i}{\partial x^2} + F_i(c), \quad i = 1, ..., n, \tag{2.1}$$

$$\frac{\partial v}{\partial x} = \frac{1}{\phi_{max}} \left(\sum_{i=1}^{n} F_i(c) + F_D(c) \right). \tag{2.2}$$

We consider it in the bounded interval $0 \le x \le L$ with the boundary conditions

$$x = 0 : c_1 = c_1^0, \frac{\partial c_i}{\partial x} = 0,\ i = 2, ...n, \quad x = L :\ \frac{\partial c_i}{\partial x} = 0,\ i = 1, ..., n. \tag{2.3}$$

This problem is supplemented with the condition $\frac{\partial v}{\partial x} = 0$ at $x = 0$ and is also supplemented with some suitable positive initial data. Up to a normalization of the parameters, we will assume in the sequel that $c_1^0 = 1$.

Denote

$$F_i = (s_i - d_i - a_i)c_i + 2d_{i-1}c_{i-1}, \quad c_0 = 0, \quad i = 1, \ldots, n,$$

$$F = F_1 + \ldots + F_n + F_D = \sum_{k=1}^{n-1} (s_i + d_i)c_i + (s_n - d_n)c_n.$$

Then stationary solutions of problem (2.1)-(2.3) satisfy the following system of equations:

$$d c_i'' - (c_i p')' + F_i(c) = 0, \quad i = 1, ..., n, \tag{2.4}$$

$$p'' = \nu F, \tag{2.5}$$

together with the boundary conditions

$$\begin{aligned} &c_1(0) = 1, \quad c_i'(0) = 0 \quad i = 2, ..., n, \\ &c_i'(L) = 0, \quad i = 1, ..., n, \\ &p'(0) = 0, \quad p(0) = 0. \end{aligned} \tag{2.6}$$

Here $v = p'$, $\nu = \mu/(K\phi_{max})$. We will obtain the following result.

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Theorem 2.1. *Let us suppose that*

$$d_i + a_i - s_i \geq 0, \quad i = 1, \dots n, \text{ and } s_n - d_n \geq 0.$$

Then system (2.4)-(2.6) *has a solution* $(c_{1,0}, ..., c_{n,0}, p_0) \in C^2([0, L])^{n+1}$ *such that*

$$c_{i,0} \geq 0, \ \ \forall\, i = 1, ..., n. \tag{2.7}$$

Proof. The proof of this theorem is based on the Leray-Schauder method. A similar problem but with other boundary conditions was considered in [9].

Denote $b_i = d_i + a_i - s_i$, $i = 1, \dots n$, $k_i = s_i + d_i$, $i = 1, \dots n-1$ and $k_n = s_n - d_n$ and suppose that all b_i and k_i are positive. We these notations system (2.4)-(2.5) becomes

$$dc_i'' - (c_i p')' + (2d_{i-1}c_{i-1} - b_i c_i) = 0, \ \ c_0 = 0, \ \ i = 1, ..., n,$$

$$p'' = \nu \sum_{k=1}^{n} k_i c_i.$$

Let us consider the system depending on a parameter τ:

$$dc_i'' - \tau(c_i p')' + (\tau 2d_{i-1}c_{i-1} - b_i c_i) = 0, \ \ c_0 = 0, \ \ i = 1, ..., n, \tag{2.8}$$

$$p'' = \nu |k_1 c_1 + \ldots + k_n c_n|, \tag{2.9}$$

together with boundary conditions (2.6). Here $\tau \in [0, 1]$ is the homotopy parameter. If $\tau = 1$, then we obtain the previous problem. For $\tau = 0$ we obtain a model problem with known properties.

Consider a solution of problem (2.4), (2.5) and (2.6). Show first that $c_i \geq 0$. The equation for c_1 is

$$dc_1'' - \tau c_1' p_1' - (\tau p'' + b_1)c_1 = 0, \quad c_1(0) = 1, \quad c_1'(L) = 0. \tag{2.10}$$

Since $(\tau p'' + b_1)$ is positive, then $c_1(x)$ cannot have negative minima. Indeed let x_0 be a point of a local minimum of the function $c_1(x)$. Then in this point $c_1''(x_0) > 0$ and $c_1'(x_0) = 0$. Substituting it into the equation (2.10) we obtain that $c_1(x) \geq 0$. Let us show that the case where exists $x_0 \in (0, L)$ such that $c_1(x) \geq 0$ for $x \in (0, x_0)$ and $c_1(x) < 0$ for $x \in (x_0, L)$ is not possible as well. In this case we would have $c_1''(L) > 0$ that would provide $c_1(L) > 0$. Thus, $c_1(x) \geq 0$, $\forall x \in [0, L]$. Repeating this reasoning for every $i = 2, \dots, n$ we obtain that $c_i \geq 0$. Thus the equation (2.9) is transformed into the following one:

$$p'' = \nu(k_1 c_1 + \ldots + k_n c_n).$$

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The second step is to obtain a priori estimates of these solutions. Let us multiply the equation (2.8) by c_i and integrate it over $(0, L)$. Then we obtain

$$\int_0^L dc_i'' c_i dx - \int_0^L \tau(c_i p')' c_i dx + \int_0^L (\tau 2 d_{i-1} c_{i-1} - b_i c_i) c_i dx = 0,$$

$$d\int_0^L (c_i')^2 dx + b_i \int_0^L c_i^2 dx + dc_i'(0)c_i(0) + \frac{\tau\nu}{2}\int_0^L c_i^2(k_1c_1 + \ldots + k_nc_n)dx$$
$$= -\frac{\tau}{2}c_i^2(L)p'(L) + 2\tau d_{i-1}\int_0^L c_{i-1}c_i dx.$$

Denote by C positive constants that do not depend on the solution. Since $p'(L) = \int_0^L (c_1 + \ldots + c_n)dx$, then $p'(L) \geq 0$ and

$$C\|c_i\|_{H^1}^2 \leq -dc_i'(0)c_i(0) + 2\tau d_{i-1}\int_0^L c_{i-1}c_i dx \leq -dc_i'(0)c_i(0) + 2d_{i-1}\int_0^L c_{i-1}c_i dx.$$

For $i = 1$ we have

$$C\|c_1\|_{H^1}^2 \leq -dc_1'(0), \tag{2.11}$$

while for $i \geq 2$,

$$C\|c_i\|_{H^1}^2 \leq 2d_{i-1}\int_0^L c_{i-1}c_i dx \leq 2d_{i-1}\|c_{i-1}\|_{L^2}\|c_i\|_{L^2} \leq 2d_{i-1}\|c_{i-1}\|_{L^2}\|c_i\|_{H^1},$$

and, therefore,

$$C\|c_i\|_{H^1} \leq 2d_{i-1}\|c_{i-1}\|_{L^2}.$$

By induction, we obtain that for $i \geq 2$ the following estimate holds:

$$\|c_i\|_{H^1} \leq C\|c_1\|_{H^1}. \tag{2.12}$$

In order to estimate $c_1'(0)$, let us integrate the equation for c_1 over $(0, L)$. We obtain the equality

$$-dc_1'(0) = \tau p'(L)c_1(L) + b_1\int_0^L c_1 dx.$$

We have

$$p'(L) = \nu\int_0^L (k_1c_1 + \ldots + k_nc_n)dx.$$

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The Hölder inequality provides the following estimate:

$$p'(L) \leq C(\|c_1\|_{L^2} + \ldots + \|c_n\|_{L^2}).$$

Using (2.12), we obtain

$$p'(L) \leq C\|c_1\|_{L_2}.$$

The function c_1 satisfies the problem

$$dc_1'' - \tau c_1' p_1' - (\tau p'' + b_1)c_1 = 0, \quad c_1(0) = 1, \quad c_1'(L) = 0.$$

Since $p'' \geq 0$, then from the maximum principle we obtain that $c_1 \leq 1$, and then $c_1(L) \leq 1$. This allows us to obtain the following estimate:

$$-dc_1'(0) \leq C\|c_1\|_{L^2}.$$

Finally, due to (2.11) we conclude that $\|c_i\|_{H_1}^2 \leq C$ for $i = 1, \ldots, n$. This bound provides an estimate of p in space H^3. Due to Sobolev Embedding Theorem, we obtain an estimate in $C^2[0, L]$ of the function p and due to equation (2.8) we obtain a bound in $C^1[0, L]$ for c_i.

Consider now the Banach space Y defined by

$$Y = \left(C^1([0, L])\right)^n \times C^2([0, L]),$$

endowed with the norm

$$\|(c_1, \ldots, c_n, p)\|_Y = \|c_1\|_{C^1([0,L])} + \ldots + \|c_n\|_{C^1([0,L])} + \|p\|_{C^2([0,L])}.$$

Consider the mapping $T_\tau : Y \to Y$ defined by $T_\tau((\widetilde{c}_1, \ldots, \widetilde{c}_n), q) = ((c_1, \ldots, c_n), p)$, where $(c_1, \ldots, c_n, p)$ is the solution of the linear system

$$dc_i'' - b_i c_i = \tau((\widetilde{c}_i q')' - 2d_{i-1}\widetilde{c}_{i-1}), \quad c_0 = 0, \quad i = 1, ..., n, \tag{2.13}$$

$$p'' = \nu(k_1 c_1 + \ldots + k_n c_n), \tag{2.14}$$

together with boundary conditions (2.6). From the elliptic regularity it follows that the mapping T_τ is a compact operator.

Next, from the above a priori estimates it follows that there exists such constant $M > 0$ that for any $\tau \in [0, 1]$, (C, p) is a fixed point of the operator T_τ implies that $\|C, p\|_Y < M$. If we consider $B = B_Y(0, M)$, then the topological degree $\deg(I - T_\tau, B, 0)$ is well defined and from the homotopy invariance we have

$$\deg(I - T_0, B, 0) = \deg(I - T_1, B, 0). \tag{2.15}$$

The operator T_0 corresponds to the constant operator

$$T(\widetilde{C}, q) = (c_1^0, \ldots, c_n^0, p^0),$$

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where $c_i^0 \equiv 0$, $i \geq 2$, the function c_1^0 is given by resolution of the equation

$$dc_1'' - b_1 c_1 = 0, \quad c_1(0) = 1, \quad c_1'(L) = 0,$$

and $p^0(x) = \int_x^L \int_0^s (c_1^0(t))dtds$. Thus we obtain that $\deg(I - T_0, B, 0) = 1$ and, due to (2.15), system (2.4)-(2.6) has a solution. This completes the proof of the theorem. □

3. Numerical Simulations

In this section we present numerical simulations of the system considered in the previous section but in the 2D space. We suppose for simplicity that all parameters k_i defined in the proof of Theorem 1 are equal to each other. We denote them by k. The system of equations

$$\frac{\partial c_i}{\partial t} + \nabla.(c_i v) = d\Delta c_i + k(c_{i-1} - c_i), \quad i = 1, \ldots, n, \quad c_0 = 0,$$
$$\Delta P = k(c_1 + \ldots + c_n), \quad \nabla P = \nu v$$

is considered in the domain

$$\Omega = (0, L_x) \times (0, L_y)$$

with the boundary conditions

$$\frac{\partial P}{\partial x}(0, y) = 0, \quad \frac{\partial P}{\partial y}(x, 0) = 0, \quad \frac{\partial P}{\partial y}(x, L_y) = 0, \quad P(L_x, y) = 0,$$
$$c_1(0, y) = 1, \quad \frac{\partial c_1}{\partial y}(x, 0) = 0, \quad \frac{\partial c_1}{\partial y}(x, L_y) = 0, \quad \frac{\partial c_1}{\partial x}(L_x, y) = 0,$$
$$\frac{\partial c_i}{\partial x}(0, y) = 0, \quad \frac{\partial c_i}{\partial y}(x, 0) = 0, \quad \frac{\partial c_i}{\partial y}(x, L_y) = 0, \quad \frac{\partial c_i}{\partial x}(L_x, y) = 0,$$
$$i = 2, \ldots, n.$$

The boundary conditions for the pressure mean that the vertical component v_y of the velocity vanishes at the top and at the bottom of the rectangular domain. The horizontal component of the velocity v_x equals zero at the left boundary because there is no convective flux. This means that stem cells are attached to the left boundary and provide a constant concentration of immature cells c_1. Cell proliferation inside the domain results in cell flow outside the domain through the right boundary where the pressure is zero.

Computer simulations are carried out using *COMSOL Multiphysics 3.4* software. This software uses finite element methods. We do not list technical parameters of

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the calculations for the sake of brevity. The simulations are carried out for three cell populations c_1, c_2 and c_3, $L_x = 10$, $L_y = 20$, $d = 0.1$, $k = 15$.

Hereafter we present simulations of the stationary solution the existence of which was proved in the previous section, simulations of wave propagation and the calculation of the wave speed.

3.1. Stationary Solution

We first present simulations of the stationary problem. Note that the stationary solution does not depend on the variable y. Hence, the solution of the 2D problem considered as a function of x coincides with the 1D stationary solution. Its existence is proved in Section 2. The left image of Figure 3 represents cell population distributions, the right image shows the pressure distribution.

Recall that the domain Ω represents a bone marrow in which the wall $x = 0$ is the wall with stem cells fixed on it, the boundary $x = L_x$ is the boundary between the bone marrow and the blood stream. Mature cells pass it and leave the bone marrow into the blood stream. Cells of population c_i are considered to be more mature than those of population c_{i-1}. As we can see from the left image of Figure 3, the majority of cells located on the left boundary $x = 0$ are immature cells of population c_1, whereas among cells leaving the bone marrow mature cells are present in bigger quantity.

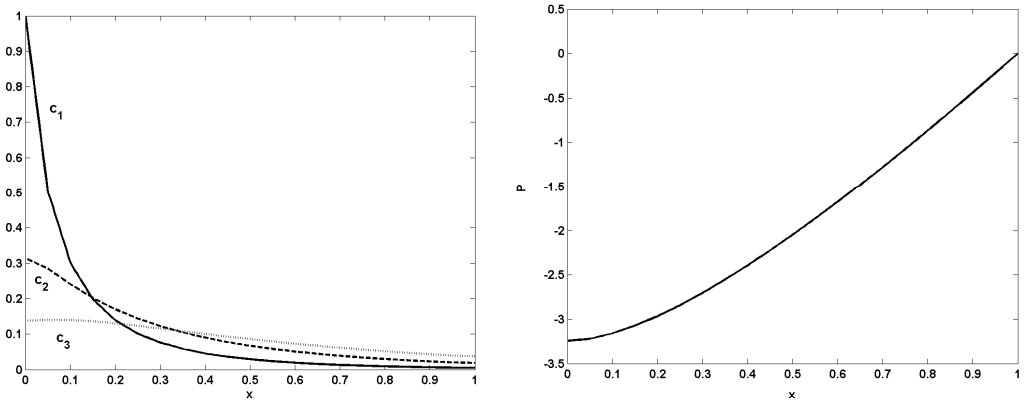

Figure 3: Stationary solution as a function of the variable x (it does not depend on y). Simulations are carried out for three cell populations. Left: cell population distributions. Right: pressure distribution.

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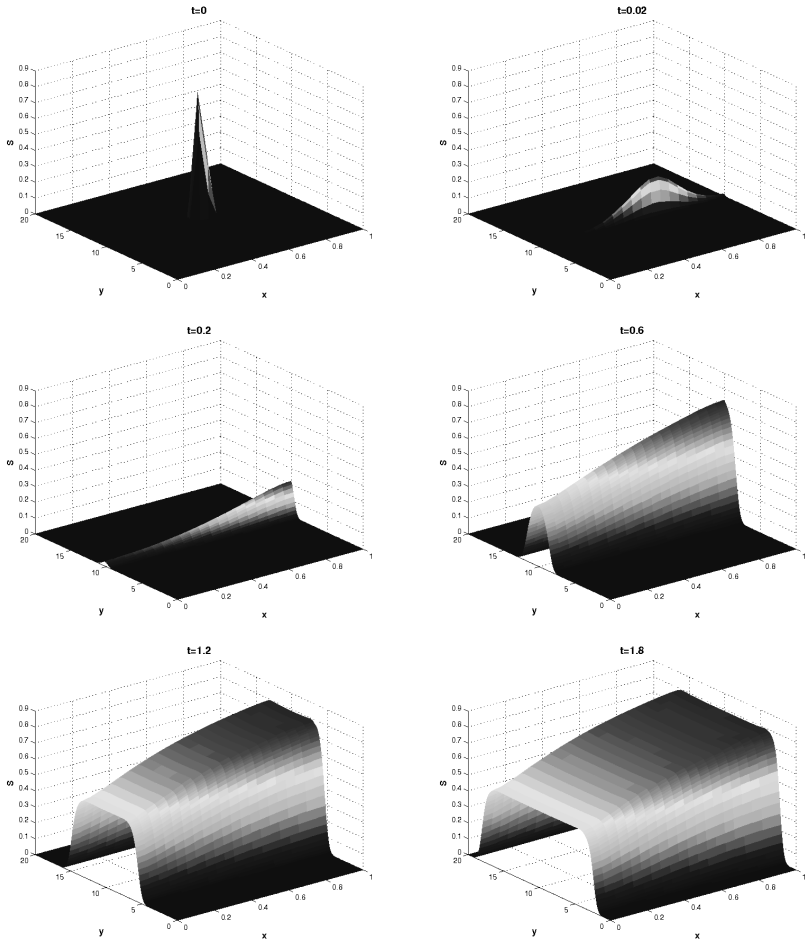

Figure 4: Propagation of malignant cells in the bone marrow. Their concentration at times $t = 0, 0.02, 0.2, 0.6, 1.2$ and 1.8. Malignant cells propagate and finally occupy the whole bone marrow.

3.2. 2D Waves

Suppose that malignant cells appear at some moment of time. These cells lose (or decrease) their ability to differentiate and excessively self-renew. Their distribution in the bone marrow can be described by the following equation:

$$\frac{\partial s}{\partial t} + \nabla.(sv) = d_s \Delta s + k_s s,$$

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with the same boundary conditions as for other cells:

$$\frac{\partial s}{\partial x}(0,y)=0, \quad \frac{\partial s}{\partial y}(x,0)=0, \quad \frac{\partial s}{\partial y}(x,L_y)=0, \quad \frac{\partial s}{\partial x}(L_x,y)=0.$$

In this section, we present simulations of propagations of the region filled by malignant cells. As initial condition for malignant cell population we consider a function that is zero everywhere in the domain except for a small area inside the domain, the nidus from where malignant cells start developing. Example of numerical simulations is given in Figure 4. The values of the parameters are the same as above. We can see that the concentration of malignant cells gradually grows and propagates along the bone marrow as a travelling wave. At the first stage of the development the tumor propagates along the x-direction (along the flow), at the second stage along the y-direction (perpendicular to the flow).

Wave propagation occurs if the stationary solution discussed above becomes unstable. The stability of the stationary solution for a similar problem is studied in [9].

The speed of the propagation depends on the diffusion coefficients d and d_s of normal and malignant cells, and on the parameters k and k_s. We study the speed of propagation in the section.

3.3. Wave Speed

From the mathematical point of view, wave propagation should be studied in the infinite strip $\Omega=(0,L)\times\mathbb{R}$. We consider the system of equations

$$\frac{\partial c_i}{\partial t}+\nabla.(c_i\mathbf{v})=d\Delta c_i+k(c_{i-1}-c_i), \quad i=1,...,n, \quad c_0=0, \tag{3.1}$$

$$\frac{\partial s}{\partial t}+\nabla.(s\mathbf{v})=d_s\Delta s+k_s s, \tag{3.2}$$

$$\nabla.\mathbf{v}=k(c_1+...+c_n)+k_s s, \quad \nabla p=\nu\mathbf{v}, \tag{3.3}$$

in this domain together with boundary conditions

$$c_1(0,y)=1, \quad \partial_x s(0,y)=\partial_x c_i(0,y)=0 \text{ for } y\in\mathbb{R} \text{ and } i=2,...,n, \tag{3.4}$$

$$\partial_x s(L,y)=\partial_x c_i(L,y)=0 \text{ for } y\in\mathbb{R} \text{ and } i=1,...,n, \tag{3.5}$$

$$\frac{\partial p}{\partial x}(0,y)=0, \quad p(L,y)=0 \text{ for } y\in\mathbb{R}. \tag{3.6}$$

In order to find an analytical approximation of the wave front speed we suppose first that there exists a one-dimensional disease free stationary solution

$$(c_{i,0},s_0,p_0,v_0)=(c_{i,0}(x),0,p_0(x),v_0(x)).$$

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It corresponds to solutions of the stationary problem in the interval $(0, L)$:

$$\begin{aligned}
&(c_{i,0}v_0)' = dc''_{i,0} + k(c_{i-1,0} - c_{i,0}), \quad i = 1, ..., n, \quad c_0 = 0,\\
&v'_0 = k(c_{1,0} + ... + c_{n,0}), \quad p'_0 = \nu v_0,\\
&c_{1,0}(0) = 1, \quad c'_{i,0} = 0 \text{ for } i = 2, ..., n,\\
&c'_{i,0}(L) = 0, \quad p'_0(0) = 0, \quad p_0(L) = 0.
\end{aligned}$$

This stationary solution is supposed to be stable with respect to the system without malignant cells. This means that the eigenvalue problem: find $\lambda \in \mathbb{C}$, $c_1, ..., c_n$ and v satisfying

$$\begin{aligned}
&\lambda c_i + (c_{i,0}v)' + (c_i v_0)' = dc''_i + k(c_{i-1} - c_i), \quad i = 1, ..., n, \quad c_0 = 0,\\
&v' = k(c_1 + ... + c_n), \quad p' = \nu v,\\
&c_1(0) = 0, \quad c'_i(0) = 0 \text{ for } i = 2, ..., n,\\
&c'_i(L) = 0, \quad p'(0) = 0, \quad p(L) = 0,
\end{aligned} \tag{3.7}$$

only has solution with $\Re\lambda < 0$.

We now consider travelling wave solutions for problem (3.1)-(3.6), that are solutions of the form

$$(c_1, ..., c_n, s, p, \mathbf{v})\,(t, x, y) = (\widetilde{c_1}, ..., \widetilde{c_n}, \widetilde{s}, \widetilde{p}, \widetilde{\mathbf{v}})\,(x, y - ct),$$

where $c > 0$ is the wave speed. In order to simplify the notations, we omit the tilde. Setting $z = y - ct$, we obtain that the travelling wave solution satisfies the following problem in the moving frame:

$$\begin{aligned}
&d\Delta c_i + c\frac{\partial c_i}{\partial z} - \nabla.(c_i\mathbf{v}) + k(c_{i-1} - c_i) = 0, \quad i = 1, ..., n, \quad c_0 = 0,\\
&d_s\Delta s + c\frac{\partial s}{\partial z} - \nabla.(s\mathbf{v}) + k_s s = 0,\\
&\nabla.\mathbf{v} = k(c_1 + ..c_n) + k_s s, \quad \nabla p = \nu\mathbf{v},
\end{aligned} \tag{3.8}$$

together with the boundary conditions

$$\begin{aligned}
&c_1(0, z) = 1, \quad \partial_x s(0, z) = \partial_x c_i(0, z) = 0 \text{ for } z \in \mathbb{R} \text{ and } i = 2, ..., n,\\
&\partial_x s(L, z) = \partial_x c_i(L, z) = 0 \text{ for } z \in \mathbb{R} \text{ and } i = 1, ..., n,\\
&\frac{\partial p}{\partial x}(0, z) = 0, \quad p(L, z) = 0 \text{ for } z \in \mathbb{R}.
\end{aligned}$$

We are looking for travelling wave that connects the disease free stationary state when unstable (with respect to the complete model) to what we expect to be a stationary solution, which corresponds to the disease, that is

$$\lim_{z \to +\infty} (c_1, ..., c_n, s, p, \mathbf{v})(x, z) = (c_{1,0}(x), ..., c_{n,0}(x), 0, p_0(x), v_0(x)), \tag{3.9}$$

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$$\partial_y p(x, \pm\infty) = 0 \text{ for } x \in (0, L),$$

and we assume that

$$\partial_y (c_1, ..., c_n)(x, \pm\infty) = 0 \text{ for } x \in (0, L).$$

To find the wave speed, we assume that the solution has an exponential behavior as $z \to +\infty$. More precisely we suppose that

$$s(z, x) \approx e^{-\mu z} \overline{s}(x) \;\; z \to +\infty.$$

Since the function $s(z, x)$ is assumed to be positive, one obtains the conditions

$$\mu \in (0, \infty), \;\; \overline{s} \geq 0.$$

We substitute the solution in this form into (3.8) and using condition (3.9), we obtain that

$$\begin{aligned} &(d_s \mu^2 - c\mu)\overline{s} + d_s \partial_y^2 \overline{s} - (\overline{s} v_0(x))' + k_s \overline{s} = 0, \\ &\overline{s}'(0) = 0, \;\; \overline{s}'(L) = 0. \end{aligned}$$

Consider the operator

$$\mathcal{L}s = d_s \partial_y^2 s - (s v_0(x))' + k_s s, \;\; s'(0) = 0, \;\; s'(L) = 0. \tag{3.10}$$

Then $\overline{s}$ is its eigenvector and $c\mu - d_s\mu^2$ is an associated eigenvalue. Since $\overline{s} \geq 0$, then we conclude that it is an eigenvector associated to the principal eigenvalue $\lambda_p > 0$ of the operator $\mathcal{L}$, i.e., $\mathcal{L}\overline{s} = \lambda_p \overline{s}$, and μ satisfies

$$c\mu - d_s\mu^2 = \lambda_p, \;\; \mu > 0.$$

This equation has a real and positive solution if and only if $c^2 - 4 d_s \lambda_p \geq 0$, that is for any c such that

$$c \geq c^* \text{ with } c^* = 2\sqrt{d_s \lambda_p}. \tag{3.11}$$

Finally we expect that c^* corresponds to the spreading rate of the malignant cells.

Numerical computations of c^* for $n = 3$ and $L_x = 1$ and direct numerical computations of the speed of front propagation of malignant cells c_{num} are presented in Table 1. The wave speed obtained by the analytical approximation is in a good agreement with the wave speed found by direct numerical simulations.

Since λ_p is the principal eigenvalue of the operator $\mathcal{L}$ defined by (3.10), then one can conclude that λ_p depends linearly on k_s. Then from (3.11) we obtain that $(c^*)^2$ linearly depends on k_s. We verify this dependence for the theoretical and numerical computations. For the values given in Table 1, we test this linear dependence between k_s and c_{num}^2. The results are presented in Figure 5.

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k_s	8	10	12	14	16	18	20
c^*	2.06	3.26	4.13	4.84	5.46	6.02	6.53
c_{num}	1.98	3.20	4.06	4.80	5.49	6.15	6.83

Table 1: Comparison between theoretical approximation of the wave speed and numerical simulations. The values of the parameters are $d = 0.1$, $k = 15$ and $d_s = 0.8$. Theoretical approximation is done by linearization of the equation.

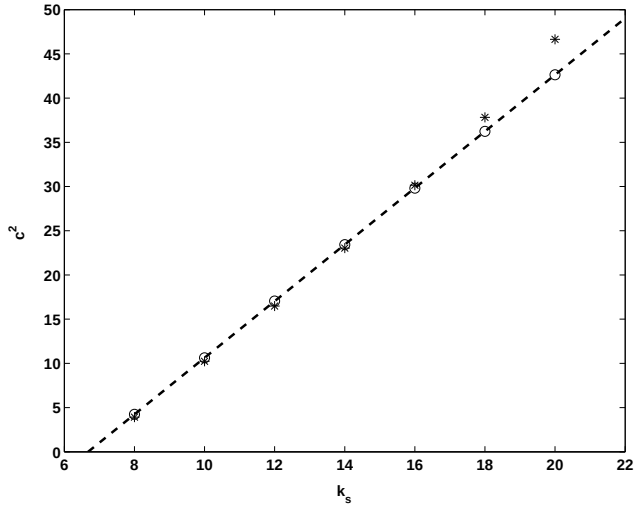

Figure 5: Dependence of c^2 on k_s. Circles: analytical approximation, asterisks: direct numerical simulations.

4. Discussion

In this paper we considered a simple spatial model of erythropoiesis. The model was described by a system of reaction-diffution-convection equations. We proved a theorem of existence of a solution for 1D case but we did not consider the uniqueness of the solution. For non-linear elliptic problems the solution is not necessarily unique. We considered the appearence of malignant cells in the bone marrow and we carried out simulations of malignant cell propagation in 2D case. This propagation had a form of a travelling wave. Leukemic cells propagated and finally occupied all the bone marrow with a certain final distribution.

The speed of malignant cells propagation was calculated in two ways. Firstly, we used theoretical approach, we linearized the system and obtained an eigenvalue

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problem solution of which allowed us to find the minimal wave speed and we supposed that the wave propagates with this minimal speed. It should be noted that we did not provide a strict proof of this formula. Secondly, we calculated the wave speed directly in simulations. The obtained numerical calculations approximated quite well the theoretical computations, see Table 1. Thus we can suppose that the applied algorythm is correct.

In Section 1.2 we discussed possible feedbacks on self-renewal and on differentiation rates. We said that the two rates decrease when the number of cells increases. However we did not take it into account for our simulations where we supposed that these rates are constant. This could be a let for a future work.

Now we are working on a model of cell dynamics. In this model we observe the propagation of malignant cells as a travelling wave that is similar to the modelling presented in this paper.

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