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Computer modelling of haematopoietic stem cells migration

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ABSTRACT

A mathematical model for migration of haematopoietic stem cells towards their niche in the bone marrow has been proposed in the literature. It consists of a chemotaxis system of partial differential equations with nonhomogeneous boundary conditions and an additional ordinary differential equation on a part of the computational boundary. The aim of the current work is to extend appropriately a second order positivity preserving central upwind scheme, originally proposed for a chemotaxis system with zero-flux boundary conditions and to apply it for the numerical solution of the considered problem. This paper introduces a first glance of such modification and outlines open questions in the handling of the nonlinear boundary conditions in a way that preserves the positivity of the solution. The presented numerical tests illustrate the need of the development of new specialized schemes for more complex chemotaxis systems.

1. Motivation

Computer modelling (CM) has become a classical investigation tool in various real life areas, where the trial–error approach is not applicable. In particular, CM can be very useful in every day clinical practice, where questions related to understanding and predicting of human physiological processes in health and disease have to be answered. Current work is related to haematology when tumours and blood diseases (including leukaemia) are treated by an autologous haematopoietic stem cells (HSCs) transplantation. The latter means that: first the HSCs are mobilized from their niche in the bone marrow to the patient's peripheral blood and extracted out of the body; then the HSCs are stored under special conditions, while the patient is treated (by chemotherapy or total body irradiation) to eradicate his/her malignant cell population; and finally the patient's own HSCs are reinfused to his/her peripheral blood, from where they find the bone marrow niche and resume the normal haematopoiesis (i.e. the production and regulation of all types of blood cells under the action of specific proteins, known as cytokines and growth factors). This therapeutic procedure is possible because of the two main properties of the HSCs, illustrated schematically in Fig. 1: (a) *rapid migratory activity* and ability to enter and exit their niche in the bone marrow and (b) *high self-renewal and differentiation capacity*, responsible for the production and regulation of the three blood cell types. Adequate computer models for the processes after transplantation would be helpful for issues like: understanding better the HSCs migration and differentiation processes; predicting the effect of various treatment options for specific blood diseases; shortening the period in which the patient is missing their effective immune system.

During the CM procedure, the starting model of the considered real (physical, biochemical, etc.) process is transformed to a mathematical model adequate to the results of planned and/or performed experiments. Various factors are involved in the mobilization and homing processes (see, e.g. [1–3]). It has been shown that the human HSCs migrate *in vitro* and *in vivo* following the gradient of a chemotactic factor SDF-1 (stromal cell-derived factor-1) produced by stroma cells. This fact is taken into account in the mathematical model for the chemotactic movement of HSCs towards their niche, proposed

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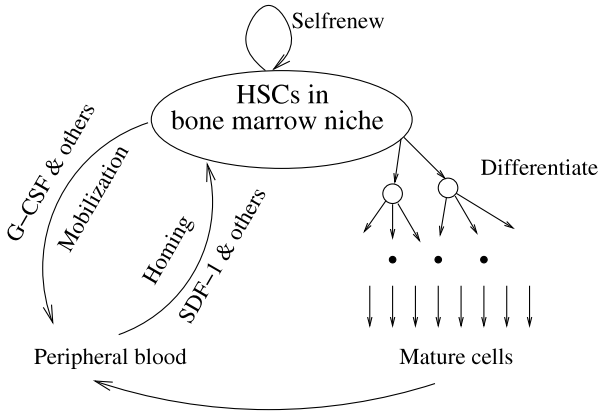

Fig. 1. Main properties of haematopoietic stem cells.

in [4]. It consists of a nonlinear system of chemotaxis equations coupled with an ordinary differential equation (ODE) on the boundary of the domain in the presence of nonhomogeneous boundary conditions. The unknowns of the system are the concentrations of HSCs, of SDF-1, and of the stem cells bound to the stroma cells.

The next two steps in CM are first to apply an appropriate numerical method for discretization of the mathematical model and then to develop (or to choose among already existing) efficient methods and algorithms for a solution of the resulting large systems of algebraic equations and high-performance computer programs for their implementation. Our attention is focused on the numerical solution of the model from [4]. Various classical numerical methods applied directly to a general chemotaxis system and in particular to the HSCs migration model may lead to numerical instabilities and loss of the positivity property of the solution. Such an example is shown in [5], where the model from [4] is implemented using commercial software COMSOL Multiphysics [6]. A finite-volume method, based on a second-order positivity preserving central-upwind scheme is proposed by Chertock and Kurganov in [7] for a class of chemotaxis and haptotaxis models with homogeneous Neumann conditions. Other authors [8,9] have also developed special methods for taxis-diffusion-reaction problems. All of them consider chemotaxis equations with zero-flux boundary conditions and therefore their methods are not directly applicable in our case. The goal in the current work is to modify appropriately the approach of Chertock and Kurganov for numerical solution of the HSCs migration model in [4]. This paper introduces a first glance of such modification and outlines open questions for the approximation of the nonhomogeneous boundary conditions preserving the positivity property.

The last stage of CM consists of numerical experiments, visualization and an analysis of the obtained results. The aim is to verify the created computer model and to evaluate its reliability for the study of the original process. If an improvement of the model is needed, then a part (or all) of the described steps are performed again. The numerical tests presented in the paper illustrate the need of the development of new specialized schemes for more complex chemotaxis systems.

2. Mathematical model

For the sake of completeness, we present in the current section the investigated mathematical model, as it is proposed in [4]. The following system of equations have to be solved to simulate the *in vitro* HSCs migration towards the gradient of SDF-1, produced by stroma cells:

$$s_t = \nabla \cdot (\varepsilon \nabla s - s \nabla \chi(a)), \quad \text{in } (0,T) \times \Omega, \tag{1}$$

$$a_t = D_a \Delta a - \gamma a s, \quad \text{in } (0,T) \times \Omega, \tag{2}$$

$$b_t = c_1 s - c_2 b, \quad \text{on } (0,T) \times \Gamma_1, \tag{3}$$

$$-(\varepsilon \partial_\nu s - s \chi'(a) \partial_\nu a) = \begin{cases} c_1 s - c_2 b, & \text{on } (0,T) \times \Gamma_1, \\ 0, & \text{on } (0,T) \times \Gamma_2, \end{cases} \tag{4}$$

$$D_a \partial_\nu a = \begin{cases} \beta(t,b) c(\mathbf{x}), & \text{on } (0,T) \times \Gamma_1, \\ 0, & \text{on } (0,T) \times \Gamma_2, \end{cases} \tag{5}$$

$$s(0,\mathbf{x}) = s_0(\mathbf{x}), \qquad a(0,\mathbf{x}) = a_0(\mathbf{x}) \quad \text{in } \Omega, \quad \text{and} \quad b(0,\mathbf{x}) = b_0(\mathbf{x}) \quad \text{on } \Gamma_1. \tag{6}$$

The computational domain $\Omega \in \mathbb{R}^2$ of class C^1 represents the Terasaki well, where the experiment *in vitro* has been performed. Its boundary $\partial\Omega = \Gamma_1 \cup \Gamma_2$ consists of two parts, where $\Gamma_1 \cap \Gamma_2 = \emptyset$ and Γ_2 is a closed set. The stroma cells are cultivated in the part Γ_1 of the boundary and the stem cells are placed at the opposite part of the domain. The time variable, the space variable and the outer unit normal to the boundary $\partial\Omega$ are denoted respectively by t, $\mathbf{x} = (x, y)$ and ν. The unknowns of the model are the concentration $s(t, \mathbf{x}) \geq 0$ of the stem cells in the domain Ω, the concentration