

Computer Simulation of Haematopoietic Stem Cells Migration using COMSOL Multiphysics

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Abstract: Two important properties of the haematopoietic stem cells are used in the therapy of various blood diseases, namely: a) rapid migratory activity and ability to "home" to their niche in the bone marrow; b) high self-renewal and differentiation capacity, responsible for the production and regulation of the three blood cell types. A mathematical model for a) consisting of a chemotaxis system of partial differential equations with nonlinear boundary conditions is implemented in COMSOL Multiphysics, using the Partial Differential Equation mode. The results from computer simulation are analyzed with respect to the quality of the obtained solution.

Keywords: haematopoietic stem cells migration, chemotaxis, computer simulation.

1. Introduction

Haematopoietic stem cells (HSCs) in bone marrow give birth to the three blood cell types, because of their a) *rapid migratory activity* and ability to "home" to 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. These two properties of HSCs play a key role in the therapy of various haematological diseases, including leukaemia, which are characterized by abnormal production of particular blood cells. The first step for such treatment is chemotherapy and a whole body irradiation to eradicate the patient's haematopoietic system. The second step is the transplantation of HSCs obtained from the mobilized peripheral blood of a donor. After transplantation, HSCs find their way to the stem cell niche in the bone marrow. Various factors are involved in the mobilization and homing processes (see, e.g. [4,7]). It has been shown that 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.

Upon homing HSCs have to multiply and differentiate rapidly (under the action of specific proteins, known as colony stimulating factors) to regenerate the blood system. The approach "trial-error" is not recommended for questions like "Is the gathered amount of HSCs enough for a successful regeneration of the blood system?" or "How to shorten the period in which the patient is missing their effective immune system?" that arise naturally in the clinical practice. To address them and many others related to understanding and predicting of human physiological processes in health and disease, the computer modelling (CM) has become a classical investigation tool. CM gained its popularity from one side because of the rapid growth in the development of high performance computer facilities, and from another side because it gives possibility, e.g., for: i) economy of expensive laboratory and nature experiments; ii) investigation of processes for which direct measurements and observations are impossible; iii) substantial acceleration of the time required to verify hypothesis for the behaviour of the considered phenomenon or process.

The attention in the current work is focused on CM of HSCs migration. The initial mathematical model for our investigations is proposed by A. Kettemann, M. Neuss-Radu in [3]. The HSCs migration in the direction of chemoattractant, produced by stroma cells is described by a chemotaxis system of nonlinear partial differential equations. The unknowns of the model are concentrations of the HSCs, of the chemoattractant SDF-1 and of the stem cells bound to stroma cells on part of the boundary. The model is implemented in COMSOL Multiphysics, using the Partial Differential Equation (PDE) mode. The chemotaxis system is represented by a system of two PDEs, where the COMSOL opportunity to add an ODE on part of the boundary is used.

The available in the PDE mode methods for time integration, as well as for direct and itera-

tive solution of the linearized system are compared on the base of test data from experiments *in vitro*. The results from computer simulation are analyzed with respect to questions like "Is the positivity of the solution ensured?", "Which solver is better for the considered problem?", "How close are the obtained solutions to the real behaviour of the populations?"

The remainder of the paper is organized as follows. The initial mathematical model for chemotactic movement of HSCs is presented in section 2. Section 3. is devoted to the COMSOL implementation of the model and on the methods used for simulation. The results from the numerical tests and their analysis are described in section 4. Concluding remarks and some notes on ongoing and future work are made in section 5.

2. The Mathematical Model

The exposition in the current section follows the one in [3], where the initial for our investigations mathematical model for the chemotactic movement of HSCs is proposed. The classical chemotaxis system is adapted there to the observations made in a specific experimental assay, involving stem cells and stroma cells placed at opposite corners of a plate called Terasaki well.

A domain $\Omega \in \mathbb{R}^2$ of class C^1 representing the Terasaki well is considered. The boundary $\partial\Omega = \Gamma_1 \cup \Gamma_2$ consists of two parts (see Figure 1), 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. The outer unit normal to the boundary $\partial\Omega$ is denoted by ν . The unknowns of the model are the concentration $s(t, x)$ of the stem cells in the domain Ω , the concentration $a(t, x)$ of the chemoattractant (SDF-1), and the concentration $b(t, x)$ of the stem cells bound to the stroma cells at the boundary part Γ_1 .

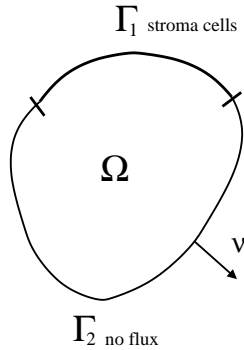


Figure 1: Computational domain

The evolution of the concentrations $s(t, x)$ and $a(t, x)$ is described by the following chemotaxis system

$$(1) \quad \partial_t s = \nabla \cdot (\varepsilon \nabla s - s \nabla \chi(a)), \quad (0, T) \times \Omega$$

$$(2) \quad \partial_t a = D_a \Delta a - \gamma a s, \quad (0, T) \times \Omega$$

together with the boundary conditions

$$(3) \quad -(\varepsilon \partial_\nu s - s \chi'(a) \partial_\nu a) = \begin{cases} c_1 s - c_2 b, & \text{on } (0, T) \times \Gamma_1 \\ 0, & \text{on } (0, T) \times \Gamma_2 \end{cases}$$

$$(4) \quad D_a \partial_\nu a = \begin{cases} \beta(t, b) c(x), & \text{on } (0, T) \times \Gamma_1 \\ 0, & \text{on } (0, T) \times \Gamma_2 \end{cases}$$

The evolution of the concentration $b(t, x)$ is described by the ODE

$$(5) \quad \partial_t b = c_1 s - c_2 b, \quad \text{on } (0, T) \times \Gamma_1$$

and $b = 0$, on $(0, T) \times \Gamma_2$. The following initial conditions are also imposed

$$(6) \quad \begin{aligned} s(0) &= s_0, \quad a(0) = a_0 \text{ in } \Omega, \\ b(0) &= b_0 \text{ on } \Gamma_1. \end{aligned}$$

Equation (1) describes the random migration of the HSCs, with random motility coefficient ε , as well as the directional migration in response to the spatial gradient of the chemoattractant. The chemotactic sensitivity function $\chi(a)$ specifies the ability of the HSCs to sense the attractant gradient. Equation (2) describes the diffusion (with coefficient D_a) of the chemoattractant and its consumption due to binding to the receptors expressed on the stem cell membranes. The consumption rate is proportional to the product of the concentrations of stem cells and of the chemoattractant, with a rate-constant γ .

The boundary condition (3) describes the attachment and detachment of stem cells at the part of the boundary coated with stroma cells. The boundary condition (4) models the production of the chemoattractant by the stroma cells. The production rate is proportional to the concentration $c(x)$ of stroma cells, which is assumed to be fixed for the investigations in the paper [3]. The proportionality function $\beta(t, b)$ is a nonlinear function of the time and of the concentration b of the bound haematopoietic stem cells. At the beginning of the experiment the stroma cells need some time for adaptation to their environment. The dependence of β on time is used to model this fact. The ODE (5) describes the evolution of the bound stem cells due to the attachment and detachment of stem cells at the part Γ_1 of the boundary.

Using the standard notations for Sobolev spaces (see, e.g., [2,6]), the following assumptions are made on the data:

(7)

$$\begin{aligned}
& c \in H^{\frac{1}{2}}(\partial\Omega), \\
& 0 \leq c(x) \leq \bar{c}, \quad x \in \Gamma_1 \quad \text{and} \quad c \equiv 0, \quad x \in \Gamma_2; \\
& \beta \in C^1(\mathbb{R} \times \mathbb{R}, \mathbb{R}), \quad \beta(0, b_0) = 0, \\
& 0 \leq \beta(t, b) \leq M, \\
& \left| \frac{\partial\beta}{\partial b}(t, b) \right| \leq M_s, \quad \left| \frac{\partial\beta}{\partial t}(t, b) \right| \leq M_t; \\
& \chi \in \mathcal{S}_\chi, \\
& \mathcal{S}_\chi = \left\{ \chi \in C^2(\mathbb{R}) \mid \begin{array}{l} 0 \leq \chi(a), \\ 0 \leq \chi'(a) \leq C_\chi, \\ |\chi''(a)| \leq C'_\chi, \\ a \in \mathbb{R} \end{array} \right\}; \\
& s_0 \in L_+^\infty(\Omega), \quad a_0 \in L_+^\infty(\Omega) \cap H^2(\Omega), \\
& b_0 \in \mathcal{S}_{b_0} \cap H^{\frac{1}{2}}(\Gamma_1), \\
& \mathcal{S}_{b_0} = \{b \in L_+^\infty(\partial\Omega) \mid b(x) = 0 \text{ for } x \in \Gamma_2\}.
\end{aligned}$$

Regarding the existence of unique solution of the system (1)–(6) it is proved in [3], that the theorem given below holds true.

Theorem 2.1 *Let the data of the model satisfy the assumptions (7). Then there exists $T > 0$ and a unique weak solution (s, a, b) of the system (1)–(6). This solution is positive and has the additional regularity properties $a \in L^2(0, T; H^2(\Omega)) \cap C([0, T]; H^1(\Omega)) \cap L^\infty(0, T; L^\infty(\Omega))$ and $b \in C([0, T]; L^2(\partial\Omega))$.*

3. Use of COMSOL Multiphysics

COMSOL Multiphysics provides various application modules for implementation, solution and postprocessing of a particular mathematical model. Results in the current paper represent our first experience with COMSOL Multiphysics. The features used upto now are described in this section. Possible application modes for further investigations on the topic are mentioned in section 5.

To implement a particular model in COMSOL Multiphysics, we have first to decide which mode(s) to use, and then to define the geometries, physics, local and global expressions and equations, initial and boundary conditions. Afterwards solution method should be chosen.

HSCs migration is modelled by a coupled system of two nonlinear advection-diffusion-reaction equations defined on the whole domain Ω and one nonlinear ordinary differential equa-

tion defined on part of the boundary in the presence of nonhomogeneous Neumann boundary conditions. As a starting point for our simulations with COMSOL, we have chosen the Partial Differential Equation (PDE) application mode, since it gives the opportunity to directly represent the chemotaxis system (1)–(6) in coefficient form. The equation (5) is modelled by the feature of COMSOL to add an ODE in a weak form on part of the boundary. The computational domain is defined according to the test example described in the next section. The parameters and functions involved in the model are defined in the appropriate sections of the model tree – functions, constants, global and subdomain expressions. Triangular finite elements with the default Lagrange Quadratic shape functions are used to generate the mesh and to obtain the discrete problem.

There are two possibilities in COMSOL Multiphysics for time integration, namely backward differentiation formula (BDF) or generalized α method. We have presented below results with the BDF, since it is robust method that is commonly used for a wide range of problems. The general behaviour of the solution obtained using the generalized α method does not differ from the one with BDF. The system is solved with the default values for time dependent solver, with automatic choice of the nonlinear solver. COMSOL provides five direct and five iterative solvers for the linearized system. And for each of the iterative solvers there is a choice among six preconditioners depending on the properties of the problem. At the current stage of our investigations the PARDISO direct solver is used and the GMRES iterative one, with Incomplete LU preconditioner. We should note here that GMRES was tested with the other preconditioners, but the method was not convergent with them.

4. Experimental Results

At the beginning of this section the values of the coefficients and functions involved in the model are given, followed by the results from the numerical simulation and their analysis.

4.1. Test Data

We use the test data from [3], where rectangular domain $\Omega = (0, 1.5) \times (0, 1)$ is considered. The size of the time step is $\Delta t = 0.1$. The stroma cells are concentrated on the right boundary $\Gamma_1 = \{x_1 = 1.5\}$, where they are mainly distributed in three clusters described by $c(x_2) = 0.01(1 + 0.2 \sin(5\pi x_2))$. The function

$\beta(t, b)$ in the production rate of the chemoattractant is chosen as

$$\beta(t, b) = V(t)\beta^*(b) \text{ with}$$

$$V(t) = \begin{cases} 4t^2(3 - 4t) & \text{for } t \leq 0.5 \\ 1 & \text{for } t > 0.5 \end{cases}$$

$$\text{and } \beta^*(b) = \frac{0.005}{0.005 + b^2}.$$

Here $V(t)$ describes the adaptation of the stroma cells to their environment and β^* models the inhibition in the production of chemoattractant for high concentrations of attached stem cells.

The numerical tests in [3] are made for the linear case of chemotactic sensitivity function: $\chi(a) = \chi a$ with $\chi = 10$. According to the overview in [5], $\chi(a)$ may be found in the biological literature in three more forms, namely

$$(8) \quad \chi(a) = \chi \log(a + c),$$

$$\chi(a) = \frac{\chi a}{1 + ca}, \chi(a) = \frac{\chi a^2}{1 + ca^2}$$

with constants $\chi > 0$ and $c \geq 1$. We have performed additional numerical tests with $\chi(a) = \log(a)$. The values for the rest of the parameters are $\varepsilon = 0.0015$, $D_a = 2$, $\gamma = 0.1$, $c_1 = 0.3$ and $c_2 = 0.5$. The initial conditions are $a_0 = 0$, $b_0 = 0$, $s_0(x_1, x_2) = (1 + \cos(5\pi(x_1 - 0.4)))\sin(\pi x_2)$ for $0.2 \leq x_1 \leq 0.6$ and $s_0(x_1, x_2) = 0$ otherwise.

4.2. Results from Computer Simulation

We focus our attention on the question "How does the choice of the numerical method influence the solution of the problem?". We have compared the solution with

- two sizes of the mesh, which result to 1723 and 6643 degrees of freedom (dof) respectively;
- two solvers – direct PARDISO and iterative GMRES with ILU preconditioner; and
- two choices of the chemotactic sensitivity function χ : $\chi = 10a$ and $\chi = \log(a)$.

The obtained results are illustrated with the eight plots in Figures 2, 3, 4 and 5, for values 10, 30, 45 and 100 of T , respectively. The upper plot in all of them is for the populations $s(t, x)$ and $b(t, x)$ obtained with GMRES/ILU on the coarser mesh with 1723 dof, and one can observe how s and b are changed with the time. The bottom plot in Figure 2 is for the higher number of dof, namely 6643, for $T = 10$ and in both cases the system is solved with GMRES/ILU. It is seen

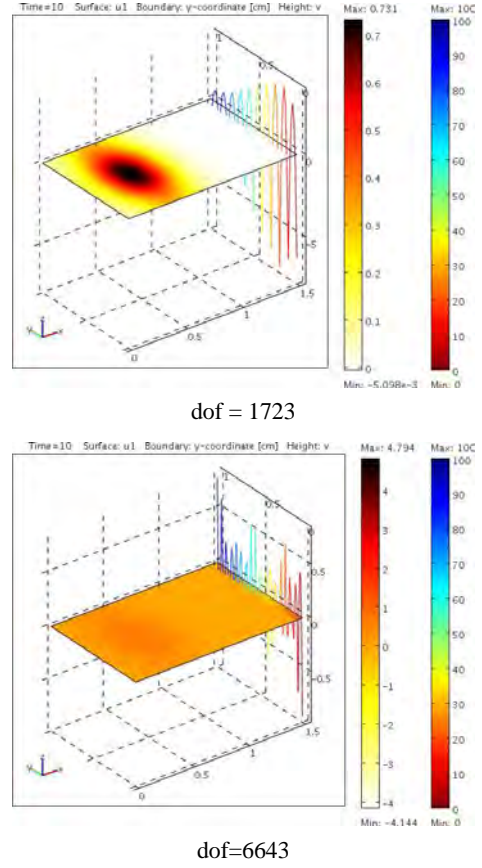


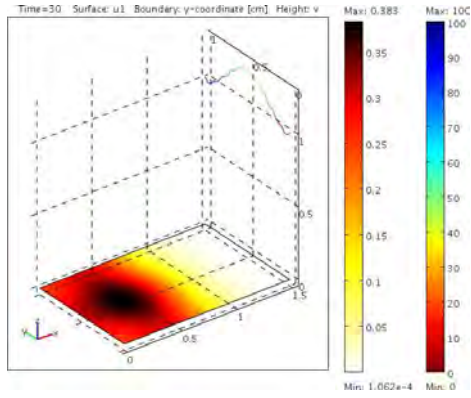
Figure 2: Model data – solution $s(t, x)$ and $b(t, x)$, $T = 10$, GMRES/ILU.

there that on the finer mesh the distribution of s is more uniform, and the ranges for the change of b are larger than those on coarser mesh, with negative values of b for both mesh sizes. One possible reason for the latter effect is that the used discretization and solution methods and/or software parameters lead to numerical instabilities and loss of the positivity property of the solution.

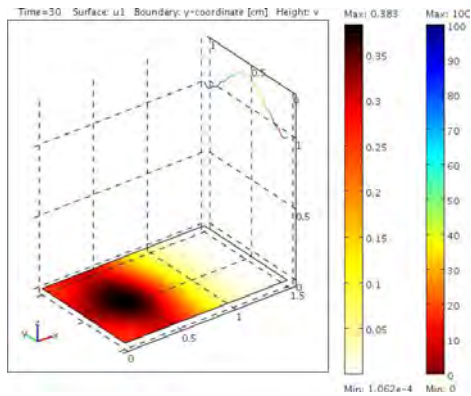
The bottom plot in Figure 3 is for the smaller mesh, but changed χ . The solution for $T = 30$ obtained with GMRES/ILU is presented. This figure illustrates the general behaviour for the considered mesh sizes, solvers and values of T , namely that the solution with the two choices of χ does not differ qualitatively and quantitatively from each other.

The direct and iterative solvers are compared in Figure 4. Slight differences in the lower bounds for the change of the populations and in their distribution are observed in all compared values of T , not only for the presented here $T = 45$.

In the last Figure 5 the solution for a and b , obtained with GMRES/ILU is given on the bot-

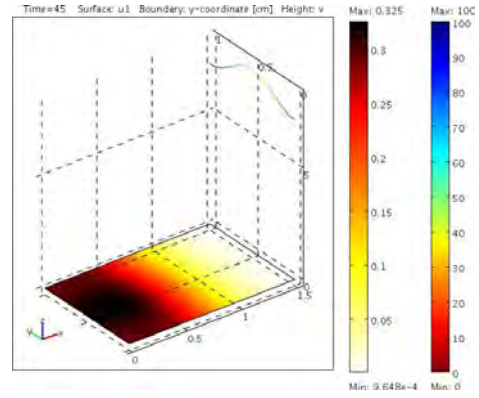


$$\chi = 10a$$

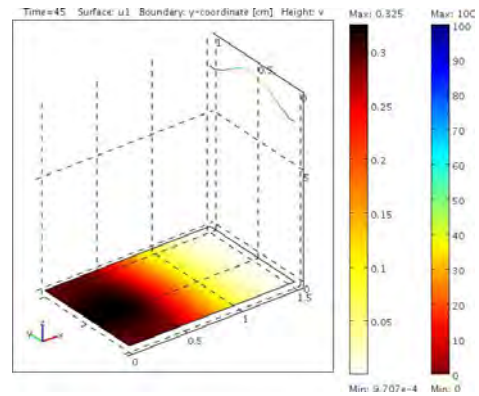


$$\chi = \log(a)$$

Figure 3: Model data – solution $s(t, x)$ and $b(t, x)$, $T = 30$, GMRES/ILU.



GMRES/ILU



PARDISO

Figure 4: Model data – solution $s(t, x)$ and $b(t, x)$, $T = 45$.

tom plot. It is seen that with the time ($T = 100$), the distribution of all three populations becomes uniform.

4.3. Discussion

The plots presented in this paper differ from those in [3] for $T = 45$ and $T = 100$ and, respectively, from the observations made in the experiment *in vitro*. Namely, the migration of the HSCs towards stromal cells is not clearly seen, but only the flatter due to diffusion. Possible reasons for this behaviour are the different mesh sizes and the different solvers used by the authors of the model. The numerical tests in [3] are performed with finite element tool Gascoigne (www.gascoigne.de) for solving partial differential equations, developed in the Numerical Methods group of Prof. Dr. Rolf Rannacher, University of Heidelberg. Their solution method for parabolic equations is based on the Rothe method with explicit Euler scheme with constant time steps.

The observed here oscillations and negative values of the unknowns for smaller times, are

possibly due to numerical instabilities of the used methods. Explicit Euler method, which avoids them is not included (to our knowledge) in the COMSOL solution methods. As it is written in the Modelling Guide, Comsol Multiphysics provides a set of stabilization techniques to restore the numerical stability. These techniques are available only in part of the modules and PDE mode is not among them. Therefore in order to use them we should study the features of the modes providing stabilization techniques, like e.g. Convection and Diffusion, Heat Transfer or Chemical engineering modules, and to modify in appropriate way the implementation of the model for HSCs movement using (one or more of) them.

5. Concluding Remarks

The numerical results discussed in section 4. represent our first experience with COMSOL Multiphysics for the numerical solution of a chemotaxis system of PDEs. Our ongoing work is focused on the question "How to modify the model

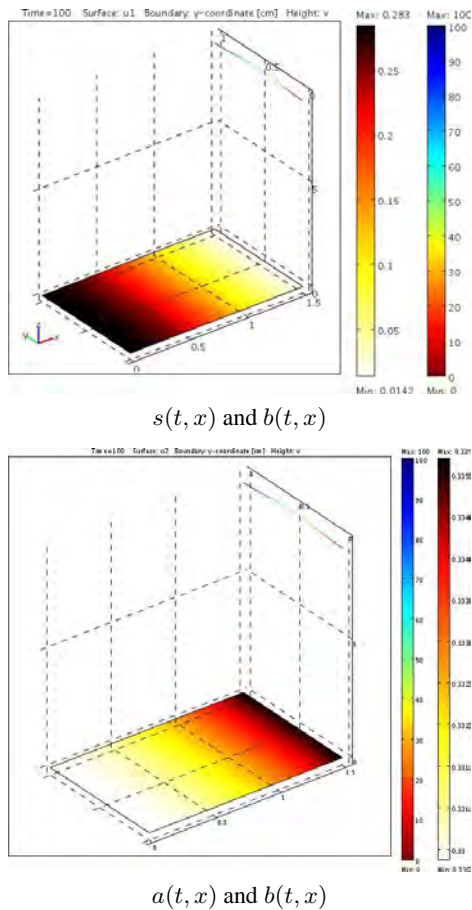


Figure 5: Model data – solution $T = 100$, GMRES/ILU.

implementation and which modules should be included to overcome the numerical instabilities problem?” Afterwards, more numerical tests and detailed analysis of the results as well as of the properties of the solvers are to be performed in order to answer questions like “Which solver is better for the considered problem?”, “How close are the obtained solutions to the real behaviour of the populations?” Comparison with other solvers and positivity preserving schemes is also advisable before we start with the analysis of issues like “What are the ranges for parameters where the model works or fails?”, “How the velocity of HSCs depends on different parameters of the model?”, “How does the type of χ influences the solution?” arisen in a discussion with Dr. M. Neuss-Radu – one of the authors of the

HSCs migration model. Further steps towards calibration of this model include sensitivity analysis (with the related tool of COMSOL Multiphysics) and parameter estimation with the help of experimental/patient specific clinical data.

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7. References

1. <http://www.comsol.com>
2. L. Evans, *Partial Differential Equations*, 662 pages, American Mathematical Society, Providence (1998)
3. A. Kettemann, M. Neuss-Radu, Derivation and analysis of a system modeling the chemotactic movement of hematopoietic stem cells, *Journal of Mathematical Biology*, **56**, pp. 579–610, (2008).
4. T. Lapidot, A. Dar, O. Kollet, “How do stem cells find their way home?”, *Blood*, **106** (6), pp. 1901–1910, (2005).
5. K. Post, *A system of non-linear partial differential equations modeling chemotaxis with sensitivity functions*, Humboldt Universität zu Berlin, Mathematisch-Naturwissenschaftliche Fakultät II, electronic, (1999).
6. A. Quarteroni, *Numerical Models of Differential Problems*, Springer Series MS&A, Vol. 2, 602 pages, Springer, Italy (2009)
7. A. Wilson and A. Trumpp, Bone marrow haematopoietic stem cell niches, *Nat. Rev. Immunol.*, **6**, pp. 93–106, (2006).