Computer Simulation of Haematopoietic Stem Cells Migration using COMSOL Multiphysics

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1. Motivation

Haematopoietic pluripotent stem cells (HSCs) in bone marrow give birth to the three blood cell types, because of their

- *rapid migratory activity* and ability to "home" to their niche in the bone marrow; 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;
- *high self-renewal and differentiation capacity*, responsible for the production and regulation of the three blood cell types.

Various hematological diseases (including leukaemia) are characterized by abnormal production of particular blood cells.

Main stages in the therapy of blood diseases:

TBI: Total body irradiation (TBI) and chemotherapy – kill the "tumour" cells, but also the healthy ones.

BMT: Bone marrow transplantation (BMT) – stem cells of a donor (collected under special conditions) are put in the peripheral blood.

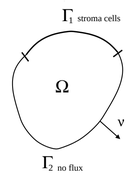
After BMT, HSCs have to:

1. find their way to the stem cell niche in the bone marrow; and
2. selfrenew and differentiate to regenerate the patient's blood system.

Adequate computer models would help medical doctors to

- understand better the HSCs migration and differentiation processes;
- design nature experiments for validation of hypotheses;
- predict the effect of various treatment options for specific blood diseases;
- shorten the period in which the patient is missing their effective immune system.

2. HSCs Migration Model



$\Omega \in R^2$, $\partial\Omega = \Gamma_1 \cup \Gamma_2$
$\Gamma_1 \cap \Gamma_2 = \emptyset$

Unknowns:

$s(t,x)$	concentration of stem cells in Ω
$a(t,x)$	concentration of chemoattractant
$b(t,x)$	concentration of stem cells bound to stroma cells at the boundary part Γ_1

$s(t,x) \geq 0,\ a(t,x) \geq 0,\ b(t,x) \geq 0$

Parameters:

ε	random motility coefficient of HSCs
$\chi(a)$	chemotactic sensitivity function
D_a	diffusion coefficient of chemoattractant
γ	consumption rate-constant for SDF-1
$c(x)$	concentration of stroma cells on Γ_1
$\beta(t,b)$	proportionality function in the production rate of chemoattractant

Chemotaxis equations:

$$\begin{cases} \partial_t s = \nabla \cdot (\varepsilon \nabla s - s \nabla \chi(a)), & \text{in } (0,T)\times\Omega \\ \partial_t a = D_a \Delta a - \gamma a s, & \text{in } (0,T)\times\Omega \end{cases}$$

Random and directional migration of HSCs

Diffusion of chemoattractant and its consumption due to binding.

Boundary conditions:

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

Attachment and detachment of HSCs at Γ_1.

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

Production of chemoattractant by the stroma cells.

$$\partial_t b = c_1 s - c_2 b, \ \text{on } (0,T)\times\Gamma_1 \qquad b = 0, \ \text{on } (0,T)\times\Gamma_2$$

Evolution of the bound stem cells due to attachment and detachment of HSCs at Γ_1.

Initial conditions:

$s(0) = s_0$, $a(0) = a_0$ in Ω, and $b(0) = b_0$ on Γ_1

Existence of unique solution

is ensured by $c \in H^{\frac{1}{2}}(\partial\Omega)$, $\beta \in C^1(R\times R, R)$, $\chi \in C^2(R)$,

$$0 \leq c(x) \leq \bar{c}, x \in \Gamma_1 \text{ and } c \equiv 0, x \in \Gamma_2, \quad \beta(0,b_0) = 0,\ 0 \leq \beta(t,b) \leq M,\ \left|\frac{\partial\beta}{\partial b}(t,b)\right| \leq M_s,\ \left|\frac{\partial\beta}{\partial t}(t,b)\right| \leq M_t$$

$$\chi \in \{\chi \in C^2(R) | 0 \leq \chi(a), 0 \leq \chi'(a) \leq C_\chi, |\chi''(a)| \leq C'_\chi, a \in R\}$$

[KNR] *A. Kettemann, M. Neuss-Radu, Derivation and analysis of a system modeling the chemotactic movement of hematopoietic stem cells, Journal of Mathematical Biology, 56, (2008), 579-610.*

3. Use of COMSOL Multiphysics

- PDE mode – system of 2 PDEs in coefficient form with an ODE in weak form on the boundary;
- Finite Element Method – nonuniform mesh for space discretization; triangular finite elements with linear quadratic shape functions
- Backward Differentiation Formula (BDF) for time integration;
- Automatic choice of nonlinear solver;
- Solution of linearized system – Implicit Euler + direct PARDISO method or iterative GMRES method with ILU preconditioner.

http://www.comsol.com and documentation distributed together with the package

4. Test Data

$$\Omega = (0,1.5)\times(0,1),\ \Gamma_1 = \{x_1 = 1.5\},\ \Delta t = 0.1$$

Parameters in chemotaxis system: $\varepsilon = 0.0015, D_a = 2, \gamma = 0.1, \quad \chi(a) = 10a,\ \chi(a) = \log(a)$

Parameters in boundary conditions: $c_1 = 0.3, c_2 = 0.5, \quad c(x_2) = 0.01(1 + 0.2\sin(5\pi x_2))$,

$$\beta(t,b) = V(t)\beta^*(b) \text{ with } V(t) = \left\{ \begin{matrix} 4t^2(3-4t) & \text{for } t \leq 0.5 \\ 1 & \text{for } t > 0.5 \end{matrix} \right\} \text{ and } \beta^*(b) = \frac{0.005}{0.005 + b^2}$$

Initial conditions:

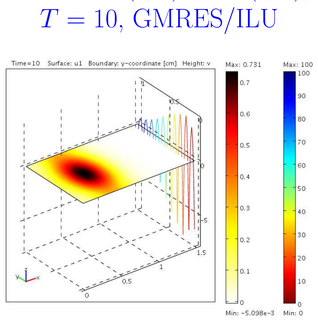
$$a_0 = 0, b_0 = 0 \text{ and } s_0(x_1,x_2) = \begin{cases} (1+\cos(5\pi(x_1 - 0.4)))sin(\pi x_2), & \text{for } 0.2 \leq x_1 \leq 0.6 \\ 0 & \text{otherwise} \end{cases}$$

5. Results from Computer Simulation

The solution is compared for $t \in [0,100]$ and

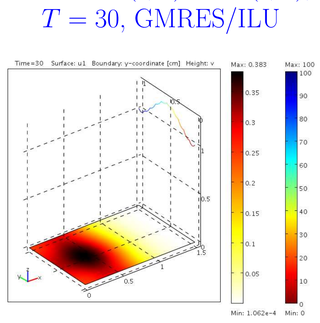
- two sizes of the mesh, which result to 1723 and 6643 degrees of freedom (dof) respectively;
- two solvers – direct PARDISO and iterative GMRES with ILU preconditioner; and
- two choices of the chemotactic sensitivity function χ: $\chi = 10a$ and $\chi = \log(a)$.

Solution $s(t,x)$ and $b(t,x)$, $T = 10$, GMRES/ILU



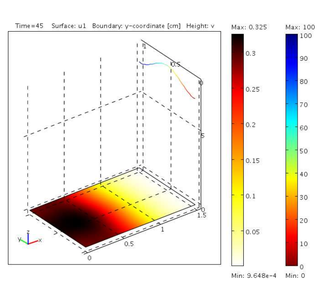
dof = 1723

Solution $s(t,x)$ and $b(t,x)$, $T = 30$, GMRES/ILU



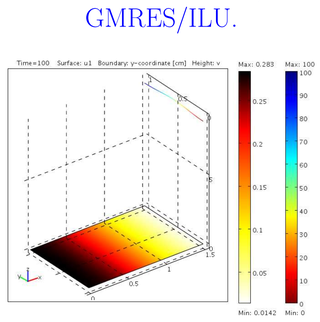
$\chi = 10a$

Solution $s(t,x)$ and $b(t,x)$, $T = 45$.

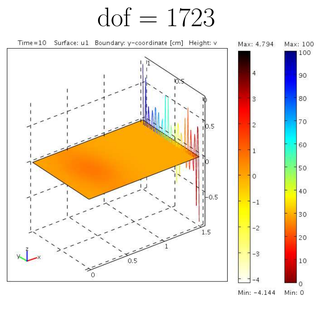


GMRES/ILU

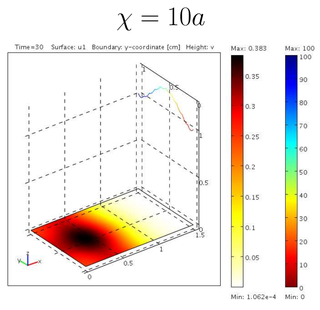
Solution $T = 100$, GMRES/ILU.



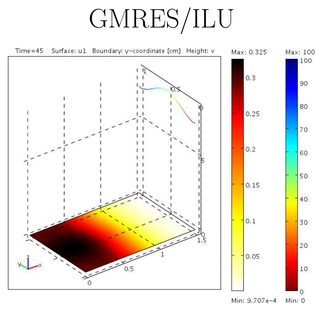
$s(t,x)$ and $b(t,x)$



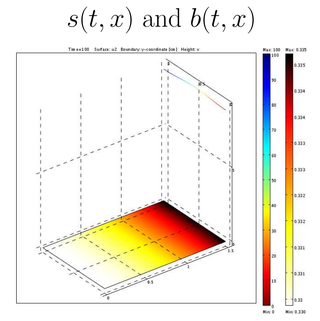
dof=6643



$\chi = log(a)$



PARDISO



$a(t,x)$ and $b(t,x)$

6. Discussion and Conclusions

Observations:

- On the finer mesh – more uniform distribution of s and larger ranges for the change of b;
- The solution with the two choices of χ does not differ quantitatively and qualitatively from each other;
- Slight differences in the lower bounds for the change of populations and their distribution with direct and iterative solvers;
- Oscillations and negative values for b for smaller times for all methods;
- Obtained solution here is different from the one presented in [KNR], and respectively from the experiment *in vitro*.

Possible reasons:

- Numerical instabilities of the used methods (stabilization techniques like artificial diffusion are not available in PDE mode);
- Different mesh sizes and solvers used by the authors of the model [KNR].

Ongoing work:

- Study the features of the modules providing stabilization techniques – Convection and Diffusion, Heat Transfer, Chemical Engineering;
- Modify in appropriate way the model implementation using them.

Further steps:

- Numerical tests with the new implementation – analysis of the properties of the solvers and of the model;
- Sensitivity analysis and parameter estimation.

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