1. Motivation

Haematopoietic pluripotent stem cells (HSCs) in bone marrow give birth to the three blood cell types, because of their:
- rapid mitogenic 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 leukemia) 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;
- 2. self-renew and differentiate to regenerate the patient's blood system.

Adequate computer models would help medical doctors to:
- understand better the HSC migration and differentiation process;
- 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

• Unknowns:
  - \( s(t, x) \) concentration of stem cells in \( \Omega \)
  - \( b(t, x) \) concentration of chemotaxant in \( \Omega \)

\( \Omega \subseteq \mathbb{R}^2, \partial \Omega = \Gamma_1 \cup \Gamma_2, \Gamma_1 \cap \Gamma_2 = \emptyset \)

Chemotaxis equations:
- \( \partial_t s - \nabla \cdot (s \nabla s) + \chi \nabla \cdot (s \nabla \chi) \in (0, T) \times \Omega \) Random and directional migration of HSCs
- \( \partial_t b - D_b \Delta b - \beta b \in (0, T) \times \Omega \) Diffusion of chemotaxant and its consumption due to binding.

Boundary conditions:
- \( -\rho \partial_t s = \chi s \sigma(b) b \in (0, T) \times \Gamma_1 \) Attachment and detachment of HSCs at \( \Gamma_1 \)
- \( D_b \partial_n b = \beta b \in (0, T) \times \Gamma_1 \) Production of chemotaxant by the stroma cells
- \( \rho \partial_t b = \rho \sigma(b) \chi s b \in (0, T) \times \Gamma_2 \) Evolution of the bound stem cells due to attachment and detachment of HSCs at \( \Gamma_2 \)

Initial conditions:
- \( s(0) = a_0, b(0) = 0 \) in \( \Omega \), and \( b(0) = 0 \) on \( \Gamma_1 \)

Existence of unique solution is ensured by \( \epsilon \in \mathbb{R}; \beta \in C^2(\Omega \times \mathbb{R}), \chi \in C^2(\mathbb{R}) \)

\( \frac{\partial s}{\partial t} + \chi \frac{\partial s}{\partial x} = 0 \) on \( \partial \Omega \)

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.

4. Test Data

\( \Omega \subseteq \mathbb{R}^2, \partial \Omega = \Gamma_1 \cup \Gamma_2, \Gamma_1 \cap \Gamma_2 = \emptyset \)

Parameters in chemotaxis system:
- \( \epsilon = 0.0015, \Omega_2 = 2, \gamma = 0.1, \chi(a) = \ln(a) \)
- Parameters in boundary conditions:
  - \( \epsilon = 0.0015, \chi(a) = \ln(a) \)
  - \( \frac{\partial s}{\partial t} + \chi \frac{\partial s}{\partial x} = 0 \) on \( \partial \Omega \)

Initial conditions:
- \( s(x, 0) = 0, b(x, 0) = 0 \) on \( \partial \Omega \)

5. Results from Computer Simulation

The solution is compared for \( t \in [0, 100] \) and
- two sizes of the mesh, which result to 3723 and 6643 degrees of freedom (dfd) respectively;
- two solvers – direct PARDISO and iterative GMRES with ILU preconditioner; and
- two choices of the chemotactic sensitivity function \( \chi = 10a \) and \( \chi = \ln(a) \).

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 \( \chi \) 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 [KNN], 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 [KNN].

Ongoing work:
- Study the features of the meshes providing stabilization techniques – Convexion 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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