On the Numerical Solution of a Chemotaxis System in Haematology

Gergana Bencheva

Institute for Information and Communication Technologies, Bulgarian Academy of Sciences

Acad. G. Bontchev Str. Bl. 25A, 1113 Sofia, Bulgaria

http://www.bas.bg/clpp/

gery@parallel.bas.bg

Contents

Motivation

Blood cells production and regulation

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;
- *high self-renewal and differentiation capacity*, responsible for the production and regulation of the three blood cell types.

Growth factors or Colony Stimulating Factors (CSF) – specific proteins that stimulate the production and maturation of each blood cell type.

Blast cells – blood cells that have not yet matured.

Blood cell type	Function	Growth factors
Erythrocyte	Transport oxygen to tissues	Erythropoietin
Leukocyte	Fight infections	G-CSF, M-CSF, GM-CSF, Interleukins
Thrombocyte	Control bleeding	Thrombopoietin

Blood pathologies

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

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.

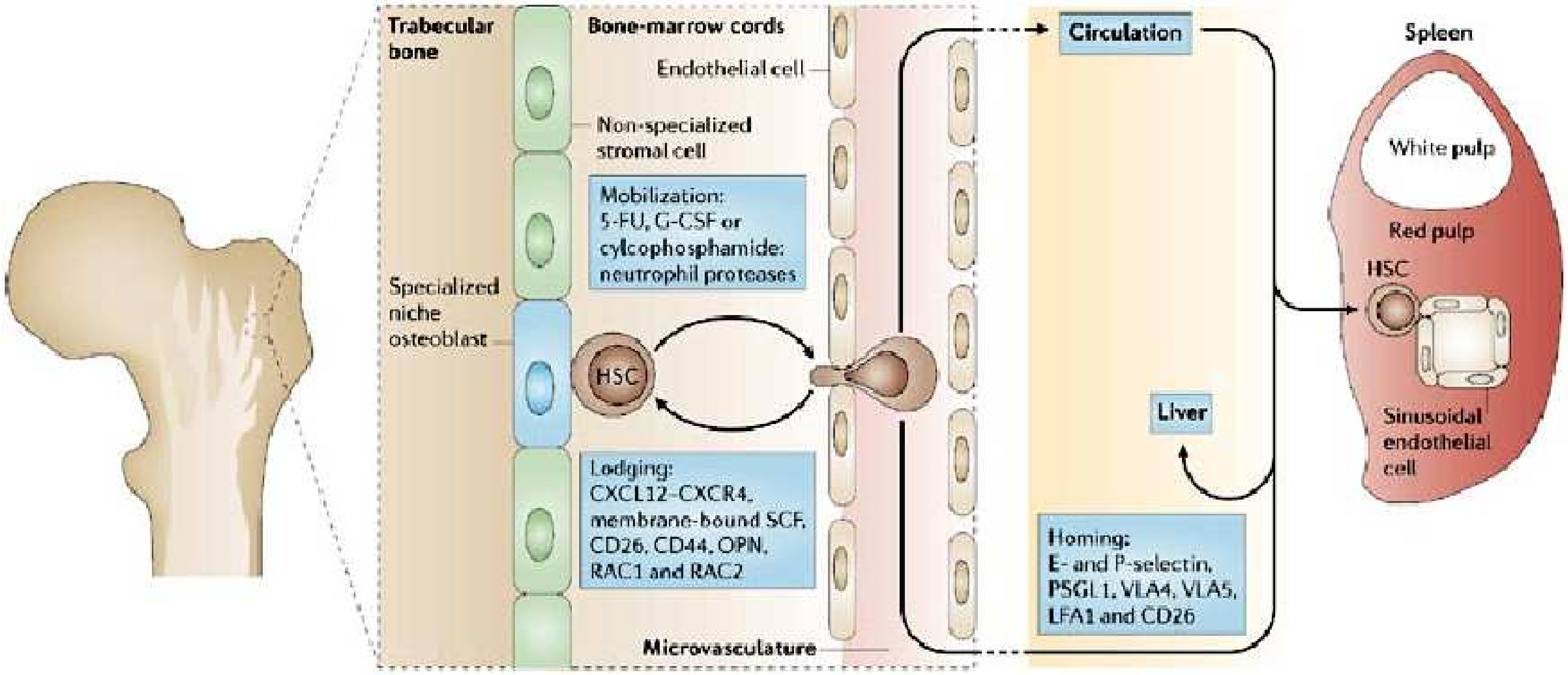
After BMT, HSCs have to:

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.

HSCs mobilization, homing and lodging



Wilson *et al. Nature Reviews Immunology* **6**, 93–106 (February 2006) | doi:10.1038/nri1779

A. Wilson, A. Trumpp, Bone-marrow haematopoietic-stem-cell niches, Nature Reviews Immunology, Vol.6, (2006), 93–106.

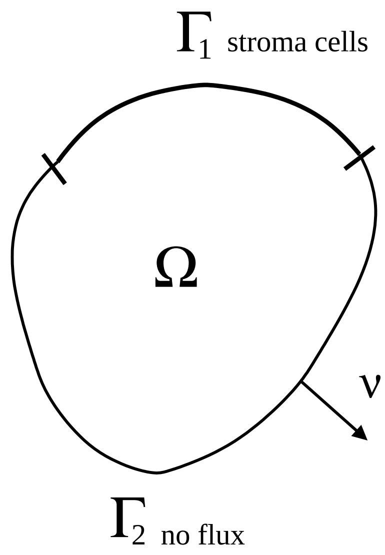
Model of HSCs’ chemotactic movement

Involved data

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

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



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

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

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.

The model

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

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

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

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

$$s(0) = s_0,\ a(0) = a_0 \text{ in } \Omega, \text{ and } b(0) = b_0 \text{ on } \Gamma_1$$

Existence of unique solution is ensured by

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

$$0 \le c(x) \le \bar{c}, x \in \Gamma_1 \text{ and } c \equiv 0, x \in \Gamma_2$$

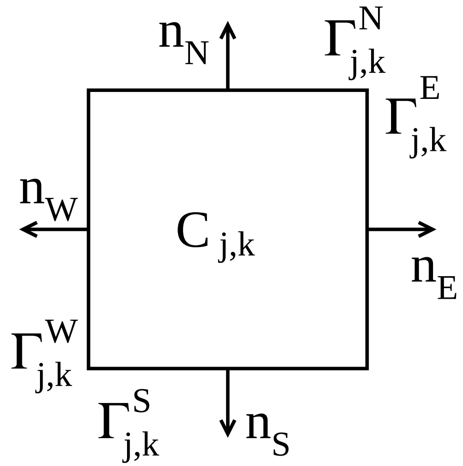
$$\beta(0, b_0) = 0,\ 0 \le \beta(t,b) \le M,\ \left|\frac{\partial\beta}{\partial b}(t,b)\right| \le M_s,\ \left|\frac{\partial\beta}{\partial t}(t,b)\right| \le M_t$$

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

Numerical solution

Finite volume method

$$\frac{d\mathbf{U}}{dt} + div\mathbf{F}(\mathbf{U}) = \mathbf{R}(\mathbf{U}),$$
$$\mathbf{U}(\mathbf{x},\mathbf{0}) = \mathbf{U_0},$$
$$\frac{\partial \mathbf{F}}{\partial \mathbf{n}} = h(U,\mathbf{x},t), \mathbf{x} \in \partial\mathbf{\Omega}$$
$$\mathbf{F}(\mathbf{U}) = \mathbf{F}_c(\mathbf{U}) + \mathbf{F}_d(\mathbf{U})$$



$$\bar{\Omega} = [0,A] \times [0,B],\ A,B > 0, \quad \Delta x = \frac{A}{N_x}, \Delta y = \frac{B}{N_y}, \ \mathbf{x} = (x,y)$$
$$\Omega = \cup C_{j,k},\ C_{j,k} := [x_{j-\frac{1}{2}}, x_{j+\frac{1}{2}}] \times [y_{k-\frac{1}{2}}, y_{k+\frac{1}{2}}]$$
$$j = 1,\ldots,N_x,\ k = 1,\ldots,N_y$$
$$x_{\frac{1}{2}} = 0,\ x_{N_x+\frac{1}{2}} = A,\ x_{j+\frac{1}{2}} = x_{j-\frac{1}{2}} + \Delta x$$
$$y_{\frac{1}{2}} = 0,\ y_{N_y+\frac{1}{2}} = B,\ y_{k+\frac{1}{2}} = y_{k-\frac{1}{2}} + \Delta y$$
$$\partial C_{j,k} = \Gamma_{j,k}^E \cup \Gamma_{j,k}^W \cup \Gamma_{j,k}^N \cup \Gamma_{j,k}^S$$

Finite volume method

$$\mathbf{U}_t + \mathbf{f}(\mathbf{U})_x + \mathbf{g}(\mathbf{U})_y = \nabla \cdot (\Lambda\, \nabla \mathbf{U}) + \mathbf{R}(\mathbf{U})$$

$$\mathbf{U} = (s, a, p, q)^T, \quad \mathbf{f}(\mathbf{U}) = (s\chi p, 0, \gamma a s, 0)^T, \quad \mathbf{g}(\mathbf{U}) = (s\chi q, 0, 0, \gamma a s)^T$$

$$p = a_x, \; q = a_y, \quad \Lambda = diag(\varepsilon, D_a, D_a, D_a), \quad \mathbf{R}(\mathbf{U}) = (0, -\gamma a s, 0, 0)^T$$

$\lambda_i^{\mathbf{f}}, \lambda_i^{\mathbf{g}}$ – eigenvalues of $\dfrac{\partial \mathbf{f}}{\partial \mathbf{U}}$ and $\dfrac{\partial \mathbf{g}}{\partial \mathbf{U}}$

$\bar{\mathbf{U}}_{j,k}(t) = \dfrac{1}{\Delta x \Delta y} \displaystyle\iint\limits_{C_{j,k}} U(x, y, t)\,dxdy$ – unknowns of the discrete system

Piecewise linear reconstruction $\tilde{\mathbf{U}}$ for $\mathbf{U}$ obtained at each time step:

$$\tilde{\mathbf{U}}(x, y) := \bar{\mathbf{U}}_{j,k} + (\mathbf{U}_x)_{j,k}(x - x_j) + (\mathbf{U}_y)_{j,k}(y - y_k), \;\; (x, y) \in C_{j,k}$$

should be conservative, nonoscilatory and positivity preserving.

A. Chertock, A. Kurganov, A second-order positivity preserving central-upwind scheme for chemotaxis and haptotaxis models, Numer. Math. (2008) 111: 169-205.

Semi-discrete scheme

$$\iint\limits_{C_{j,k}} \mathbf{U}_t \, dxdy + \iint\limits_{C_{j,k}} div(\mathbf{F}_c + \mathbf{F}_d) \, dxdy = \iint\limits_{C_{j,k}} \mathbf{R} \, dxdy \, ,$$

$$\frac{d}{dt}\bar{\mathbf{U}}_{j,k}(t) + \frac{1}{\Delta x \Delta y} \int\limits_{\partial C_{j,k}} (\mathbf{F}_c + \mathbf{F}_d) \cdot \mathbf{n} \, d\gamma = \bar{\mathbf{R}}_{j,k} \, ,$$

$$I^c_{j,k} = \int\limits_{\partial C_{j,k}} \mathbf{F}_c \cdot \mathbf{n} \, d\gamma \quad \text{and} \quad I^d_{j,k} = \int\limits_{\partial C_{j,k}} \mathbf{F}_d \cdot \mathbf{n} \, d\gamma$$

$$I^c_{j,k} + I^d_{j,k} = \int\limits_{\Gamma^E_{j,k}} (\mathbf{F}_c + \mathbf{F}_d) \cdot \mathbf{n}_E \, d\gamma + \int\limits_{\Gamma^W_{j,k}} (\mathbf{F}_c + \mathbf{F}_d) \cdot \mathbf{n}_W \, d\gamma$$

$$+ \int\limits_{\Gamma^N_{j,k}} (\mathbf{F}_c + \mathbf{F}_d) \cdot \mathbf{n}_N \, d\gamma + \int\limits_{\Gamma^S_{j,k}} (\mathbf{F}_c + \mathbf{F}_d) \cdot \mathbf{n}_S \, d\gamma \, ,$$

For $\Gamma_{j,k} \in \partial\Omega$ integrals are computed from b.c. using midpoint rule

Semi-discrete scheme – cont.

$$\frac{d}{dt}\bar{\mathbf{U}}_{j,k} = -\frac{\mathbf{H}^x_{j+\frac{1}{2},k} - \mathbf{H}^x_{j-\frac{1}{2},k}}{\Delta x} - \frac{\mathbf{H}^y_{j,k+\frac{1}{2}} - \mathbf{H}^y_{j,k-\frac{1}{2}}}{\Delta y}$$

$$+ \frac{\mathbf{Q}^x_{j+\frac{1}{2},k} - \mathbf{Q}^x_{j-\frac{1}{2},k}}{\Delta x} + \frac{\mathbf{Q}^y_{j,k+\frac{1}{2}} - \mathbf{Q}^y_{j,k-\frac{1}{2}}}{\Delta y} + \bar{\mathbf{R}}_{j,k}$$

Terms with $\mathbf{H}^{x,y}$ come from approximation of $I^c_{j,k}$

Terms with $\mathbf{Q}^{x,y}$ come from approximation of $I^d_{j,k}$

$$\mathbf{Q}^x_{j+\frac{1}{2},k} = \frac{\Lambda}{\Delta x}(\bar{\mathbf{U}}_{j+1,k} - \bar{\mathbf{U}}_{j,k}),\ \mathbf{Q}^x_{j-\frac{1}{2},k} = \frac{\Lambda}{\Delta x}(\bar{\mathbf{U}}_{j,k} - \bar{\mathbf{U}}_{j-1,k})$$

$$\mathbf{Q}^y_{j,k+\frac{1}{2}} = \frac{\Lambda}{\Delta y}(\bar{\mathbf{U}}_{j,k+1} - \bar{\mathbf{U}}_{j,k}),\ \mathbf{Q}^y_{j,k-\frac{1}{2}} = \frac{\Lambda}{\Delta y}(\bar{\mathbf{U}}_{j,k} - \bar{\mathbf{U}}_{j,k-1})$$

Semi-discrete scheme – cont.

$$\frac{d}{dt}\bar{\mathbf{U}}_{j,k} = -\frac{\mathbf{H}^x_{j+\frac{1}{2},k} - \mathbf{H}^x_{j-\frac{1}{2},k}}{\Delta x} - \frac{\mathbf{H}^y_{j,k+\frac{1}{2}} - \mathbf{H}^y_{j,k-\frac{1}{2}}}{\Delta y}$$

$$+ \Lambda \left[\frac{\bar{\mathbf{U}}_{j+1,k} - 2\bar{\mathbf{U}}_{j,k} + \bar{\mathbf{U}}_{j-1,k}}{(\Delta x)^2} + \frac{\bar{\mathbf{U}}_{j,k+1} - 2\bar{\mathbf{U}}_{j,k} + \bar{\mathbf{U}}_{j,k-1}}{(\Delta y)^2} \right] + \bar{\mathbf{R}}_{j,k}$$

$$\mathbf{H}^x_{j+\frac{1}{2},k} = \frac{a^+_{j+\frac{1}{2},k}\mathbf{f}(\mathbf{U}^E_{j,k}) - a^-_{j+\frac{1}{2},k}\mathbf{f}(\mathbf{U}^W_{j+1,k})}{a^+_{j+\frac{1}{2},k} - a^-_{j+\frac{1}{2},k}} + \frac{a^+_{j+\frac{1}{2},k}\, a^-_{j+\frac{1}{2},k}}{a^+_{j+\frac{1}{2},k} - a^-_{j+\frac{1}{2},k}} \left[\mathbf{U}^W_{j+1,k} - \mathbf{U}^E_{j,k}\right]$$

$$\mathbf{H}^y_{j,k+\frac{1}{2}} = \frac{b^+_{j,k+\frac{1}{2}}\mathbf{g}(\mathbf{U}^N_{j,k}) - b^-_{j,k+\frac{1}{2}}\mathbf{g}(\mathbf{U}^S_{j,k+1})}{b^+_{j,k+\frac{1}{2}} - b^-_{j,k+\frac{1}{2}}} + \frac{b^+_{j,k+\frac{1}{2}}\, b^-_{j,k+\frac{1}{2}}}{b^+_{j,k+\frac{1}{2}} - b^-_{j,k+\frac{1}{2}}} \left[\mathbf{U}^S_{j,k+1} - \mathbf{U}^N_{j,k}\right]$$

$a^\pm_{j+\frac{1}{2},k}, b^\pm_{j,k+\frac{1}{2}}$ – computed from $\lambda^{\mathbf{f}}_i, \lambda^{\mathbf{g}}_i$ for $\mathbf{U}^E_{j,k}$, $\mathbf{U}^W_{j+1,k}$, $\mathbf{U}^N_{j,k}$, $\mathbf{U}^S_{j,k+1}$

$\bar{\mathbf{R}}_{j,k} = \dfrac{1}{\Delta x \Delta y} \displaystyle\iint_{C_{j,k}} R(U(x,y,t))dxdy$ – computed using midpoint rule

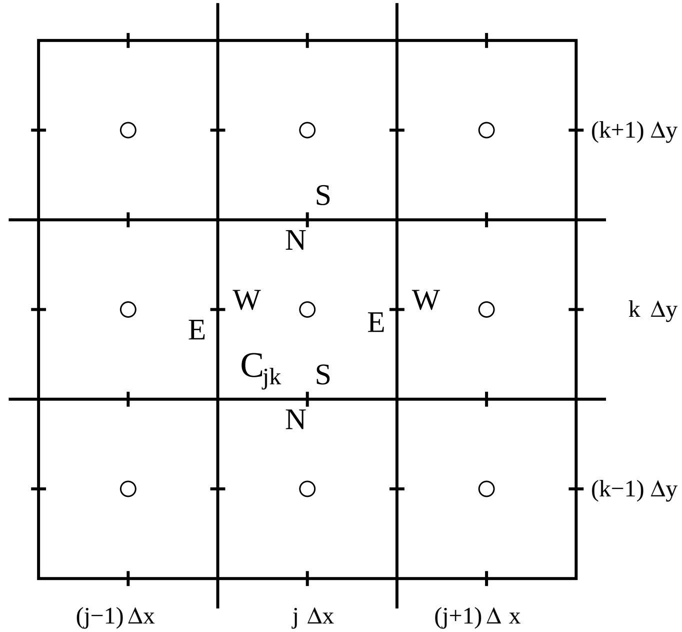
Semi-discrete scheme – cont.

$$\mathbf{U}^E_{j,k} := \tilde{\mathbf{U}}(x_{j+\frac{1}{2}} - 0, y_k) = \bar{\mathbf{U}}_{j,k} + \frac{\Delta x}{2}(\mathbf{U}_x)_{j,k}$$

$$\mathbf{U}^W_{j,k} := \tilde{\mathbf{U}}(x_{j-\frac{1}{2}} + 0, y_k) = \bar{\mathbf{U}}_{j,k} - \frac{\Delta x}{2}(\mathbf{U}_x)_{j,k}$$

$$\mathbf{U}^N_{j,k} := \tilde{\mathbf{U}}(x_j, y_{k+\frac{1}{2}} - 0) = \bar{\mathbf{U}}_{j,k} + \frac{\Delta y}{2}(\mathbf{U}_y)_{j,k}$$

$$\mathbf{U}^S_{j,k} := \tilde{\mathbf{U}}(x_j, y_{k-\frac{1}{2}} + 0) = \bar{\mathbf{U}}_{j,k} - \frac{\Delta y}{2}(\mathbf{U}_y)_{j,k}$$



$$(\mathbf{U}_x)_{j,k} = \text{minmod}\left(\Theta\frac{\bar{\mathbf{U}}_{j,k} - \bar{\mathbf{U}}_{j-1,k}}{\Delta x}, \frac{\bar{\mathbf{U}}_{j+1,k} - \bar{\mathbf{U}}_{j-1,k}}{2\Delta x}, \Theta\frac{\bar{\mathbf{U}}_{j+1,k} - \bar{\mathbf{U}}_{j,k}}{\Delta x}\right)$$

$$(\mathbf{U}_y)_{j,k} = \text{minmod}\left(\Theta\frac{\bar{\mathbf{U}}_{j,k} - \bar{\mathbf{U}}_{j,k-1}}{\Delta y}, \frac{\bar{\mathbf{U}}_{j,k+1} - \bar{\mathbf{U}}_{j,k-1}}{2\Delta y}, \Theta\frac{\bar{\mathbf{U}}_{j,k+1} - \bar{\mathbf{U}}_{j,k}}{\Delta y}\right)$$

$$\text{minmod}(z_1, z_2, \dots) := \begin{cases} \min_j\{z_j\}, & \text{if } z_j > 0 \quad \forall j, \\ \max_j\{z_j\}, & \text{if } z_j < 0 \quad \forall j, \\ 0, & \text{otherwise} \end{cases}$$

Time integration

$$\lambda := \frac{\Delta t}{\Delta x},\ \mu := \frac{\Delta t}{\Delta y},\ a := \max_{j,k}\{\max\{a^+_{j+\frac{1}{2},k}, -a^-_{j+\frac{1}{2},k}\}\},\ b := \max_{j,k}\{\max\{b^+_{j,k+\frac{1}{2}}, -b^-_{j,k+\frac{1}{2}}\}\}$$

- Explicit Euler $\Delta t \le \min(\frac{\Delta x}{8a}, \frac{\Delta y}{8b}, c)$, $c := \frac{(\Delta x)^2(\Delta y)^2}{4((\Delta x)^2+(\Delta y)^2)}$

$$\begin{aligned}\bar{\mathbf{U}}_{j,k}(t+\Delta t) = \bar{\mathbf{U}}_{j,k}(t) &- \lambda\left(H^x_{j+\frac{1}{2},k}(t) - H^x_{j-\frac{1}{2},k}(t)\right) - \mu\left(H^y_{j,k+\frac{1}{2}}(t) - H^y_{j,k-\frac{1}{2}}(t)\right) \\ &+ \Delta t \Lambda \frac{\bar{\mathbf{U}}_{j+1,k}(t) - 2\bar{\mathbf{U}}_{j,k}(t) + \bar{\mathbf{U}}_{j-1,k}(t)}{(\Delta x)^2} \\ &+ \Delta t \Lambda \frac{\bar{\mathbf{U}}_{j,k+1}(t) - 2\bar{\mathbf{U}}_{j,k}(t) + \bar{\mathbf{U}}_{j,k-1}(t)}{(\Delta y)^2} + \Delta t \bar{\mathbf{R}}_{j,k}(t)\end{aligned}$$

- IMEX Scheme $\Delta t \le \min(\frac{\Delta x}{4a}, \frac{\Delta y}{4b})$

$$\begin{aligned}\bar{\mathbf{U}}_{j,k}(t+\Delta t) = \bar{\mathbf{U}}_{j,k}(t) &- \lambda\left(H^x_{j+\frac{1}{2},k}(t) - H^x_{j-\frac{1}{2},k}(t)\right) - \mu\left(H^y_{j,k+\frac{1}{2}}(t) - H^y_{j,k-\frac{1}{2}}(t)\right) \\ &+ \Delta t \Lambda \frac{\bar{\mathbf{U}}_{j+1,k}(t+\Delta t) - 2\bar{\mathbf{U}}_{j,k}(t+\Delta t) + \bar{\mathbf{U}}_{j-1,k}(t+\Delta t)}{(\Delta x)^2} \\ &+ \Delta t \Lambda \frac{\bar{\mathbf{U}}_{j,k+1}(t+\Delta t) - 2\bar{\mathbf{U}}_{j,k}(t+\Delta t) + \bar{\mathbf{U}}_{j,k-1}(t+\Delta t)}{(\Delta y)^2} + \Delta t \bar{\mathbf{R}}_{j,k}(t+\Delta t)\end{aligned}$$

Numerical tests

Test data: $\Omega = (0, 1.5) \times (0, 1),\ \Gamma_1 = \{x_1 = 1.5\},\ \Delta t = 0.1$
$c(x_2) = 0.01(1 + 0.2\sin(5\pi x_2)),\ \beta(t, b) = V(t)\beta^*(b)$ with

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

$$\chi(a) = 10a \qquad \chi(a) = \log(a)$$

$$\varepsilon = 0.0015, D_a = 2, \gamma = 0.1, c_1 = 0.3, c_2 = 0.5$$

$$a_0 = 0, b_0 = 0 \text{ and}$$

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

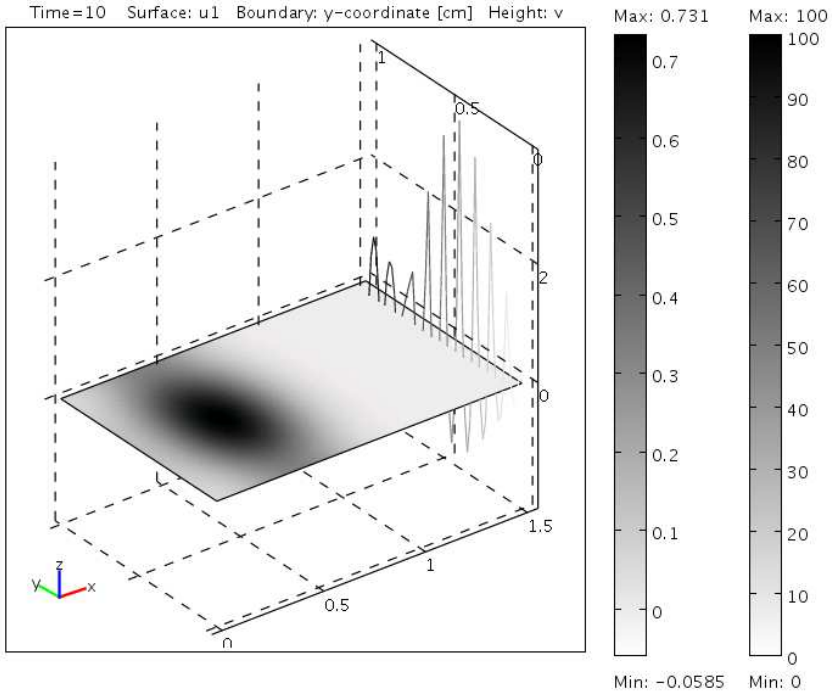
Classical approach

COMSOL Multiphysics (`http://www.comsol.com`)

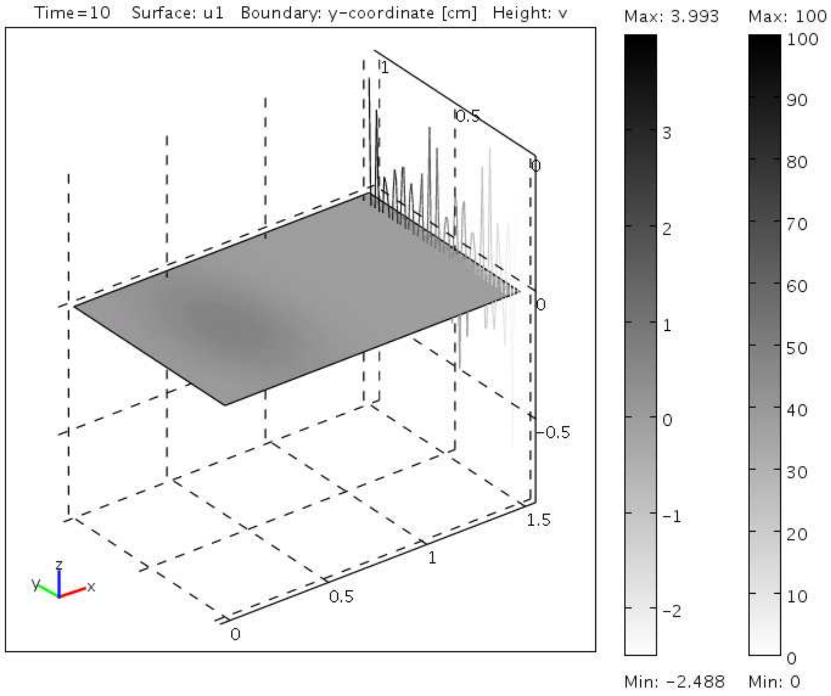
- PDE mode – system of 2 PDEs + ODE on the boundary;
- Finite Element Method – nonuniform mesh for space discretizetion;
- BDF for time integration;
- Automatic choice of nonlinear solver;
- Implicit Euler + PARDISO or GMRES/ILU for solution of linearised system.

Model data – solution $s(t,x)$ and $b(t,x)$, $T = 10$.

GMRES/ILU



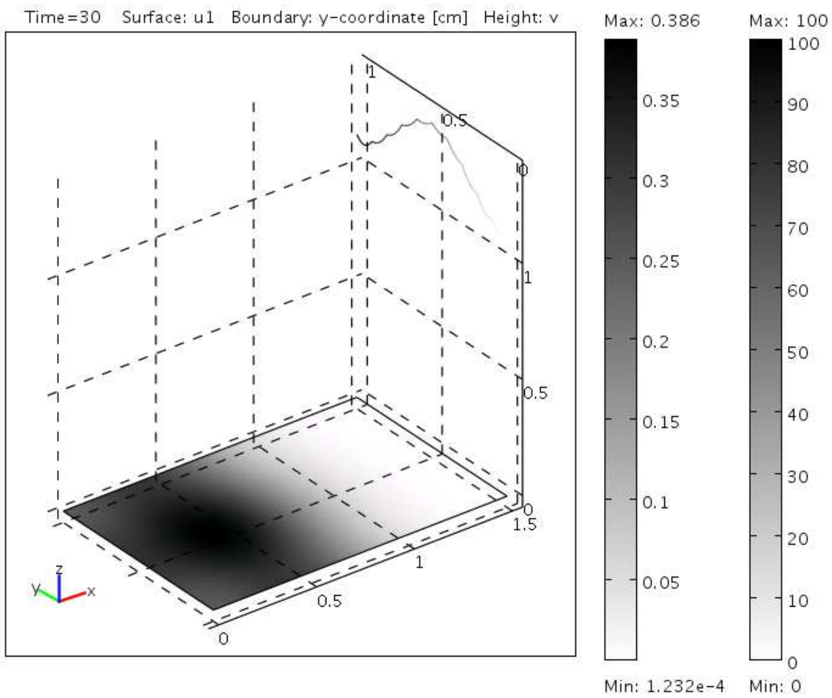
dof = 1723



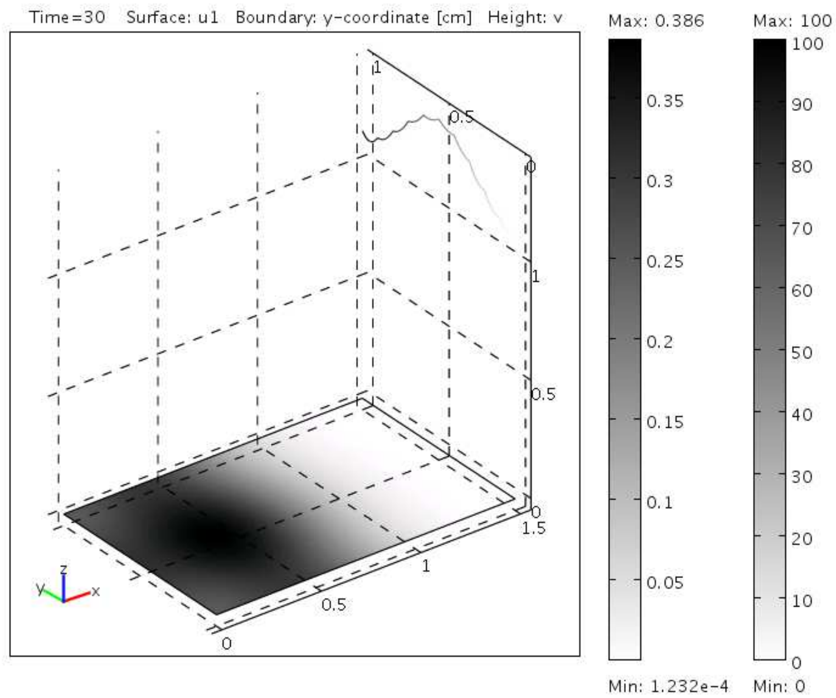
dof=6643

Model data – solution $s(t,x)$ and $b(t,x)$, $T = 30$.

GMRES/ILU

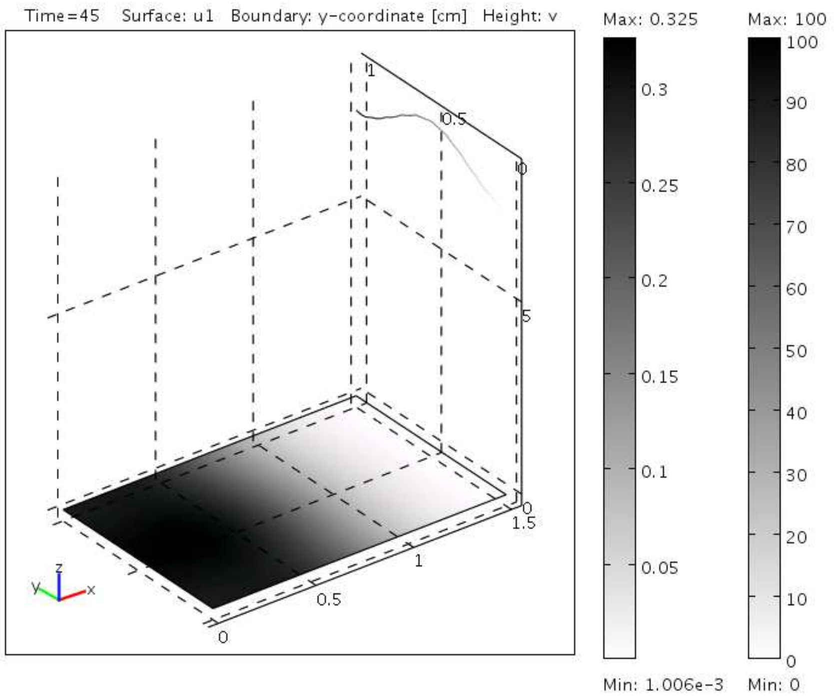


$\chi = 10a$

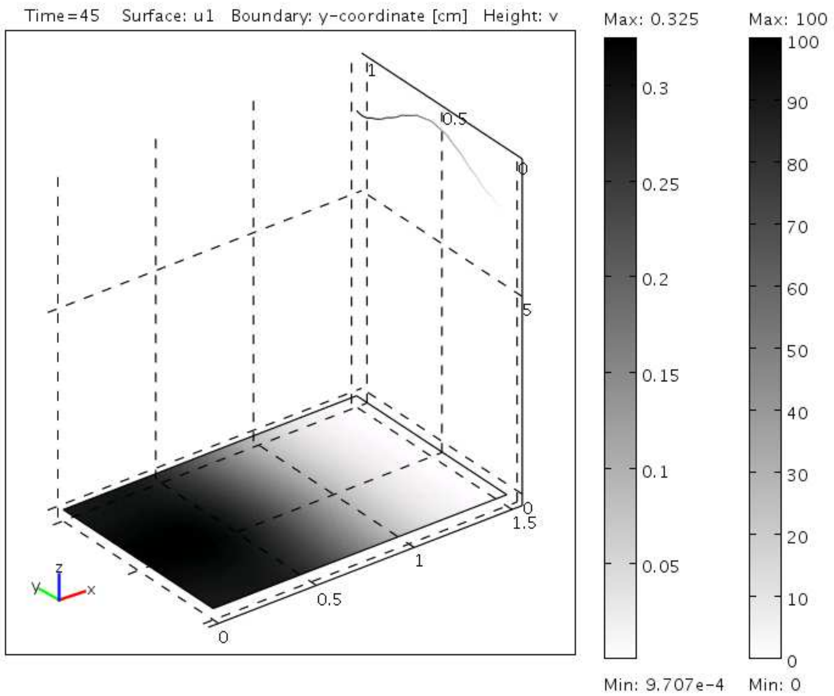


$\chi = log(a)$

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



GMRES/ILU



PARDISO

Concluding remarks

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- Ongoing work – development and debugging of own software
- Further steps
  - Chemotactic movement:
    - Ranges for parameters where the model works or fails?
    - Experimental/clinical data for calibration of the model?
    - Sensitivity analysis and parameter estimation.
  - Parallel algorithms
    - Comparative analysis of two approaches for parallel mplementation;
    - Modifications for non-linear diffusion case.
- Acknowledgements

  - The study is motivated by recently initiated cooperation between DSC at IPP-BAS and the group of Dr. M. Guenova from Laboratory of Haematopathology and Immunology, National Specialized Hospital for Active Treatment of Haematological Diseases, Bulgaria.
  - Discussion with Dr. Maria Neuss-Radu was held during my HPC-EUROPA++ funded visit in HLRS and IANS, Stuttgart.
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Thank you for your attention!