# Computer Modelling of Haematopoietic Stem Cells Migration

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# 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:

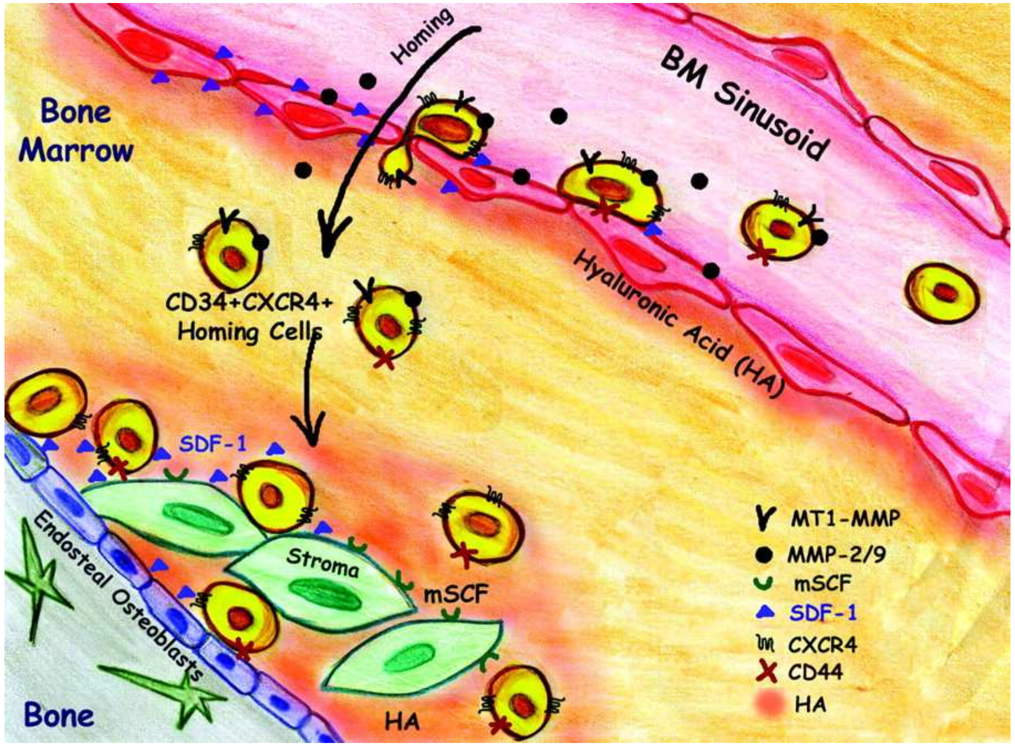
1. find their way to the stem cell niche in the bone marrow; and
2. selfrenew and differentiate to regenerate the patient's blood system.

*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.

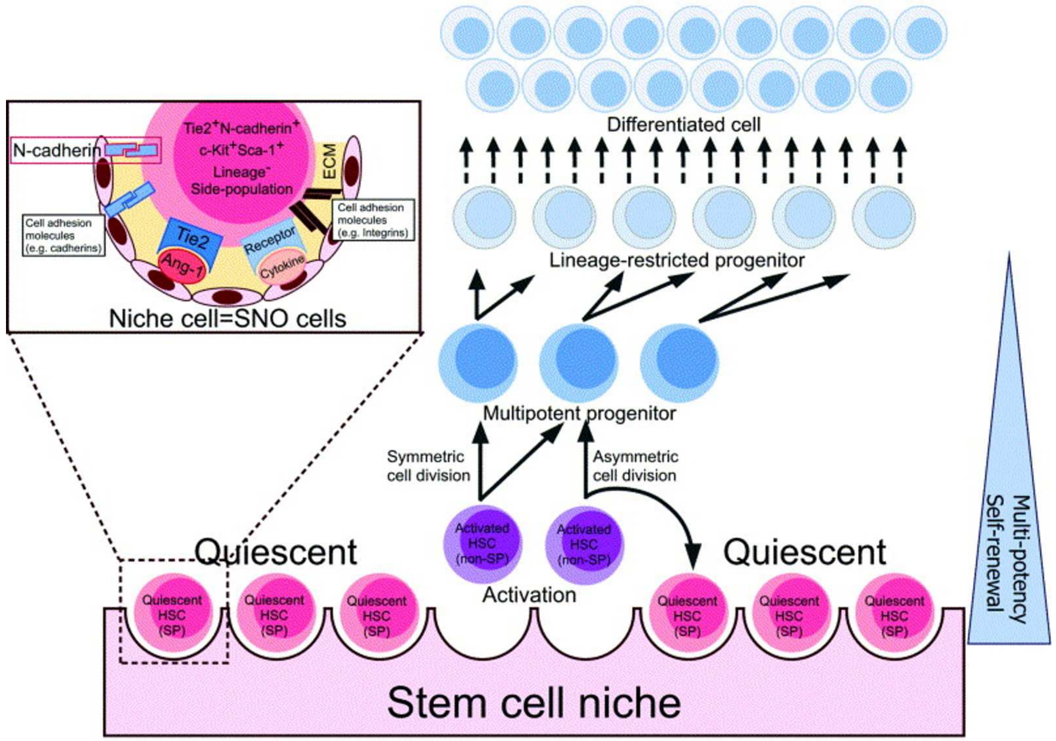
# HSCs after transplantation ...

... find the way to the niche, and ...




*T. Lapidot, A. Dar, O. Kollet, How do stem cells find their way home?, Blood, Vol. 106(6), (2005), 1901–1910.*

... self-renew and differentiate




*T. Suda, F. Arai, A. Hirao, Hematopoietic stem cells and their niche, Trends in Immunology, Vol. 26(8), (2005), 426–433.*

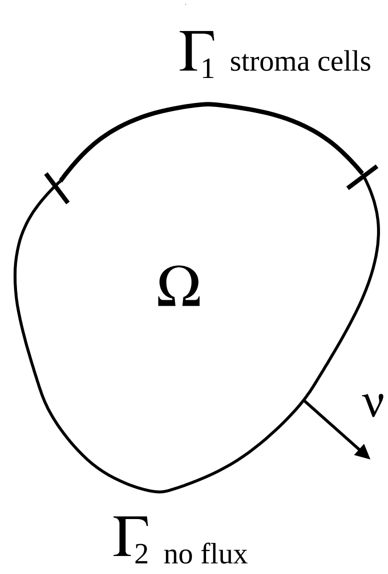
# Model of HSCs' chemotactic movement

# Involved data

## Unknowns:

$s(t,\mathbf{x})$ – concentration of stem cells in $\Omega \in R^2$
$a(t,\mathbf{x})$ – concentration of chemoattractant
$b(t,\mathbf{x})$ – concentration of stem cells bound to stroma cells at the boundary part $\Gamma_1$

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




$$\mathbf{x} = (x,y) \in \Omega$$
$$\partial\Omega = \Gamma_1 \cup \Gamma_2$$
$$\Gamma_1 \cap \Gamma_2 = \emptyset$$

## Parameters:

$\varepsilon$ – random motility coefficient of HSCs
$\chi(a)$ – chemotactic sensitivity function
$D_a$ – diffusion coefficient of chemoattractant
$\gamma$ – consumption rate-constant for SDF-1
$c(\mathbf{x})$ – concentration of stroma cells on $\Gamma_1$
$\beta(t,b)$ – 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



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

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

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

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

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

Existence of unique solution is ensured by

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

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

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

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

# Numerical solution

# Initial system in conservation form

$$
\begin{aligned}
s_t &+ \left(s\frac{\partial\chi}{\partial a}p\right)_x + \left(s\frac{\partial\chi}{\partial a}q\right)_y = \nabla\cdot(\varepsilon\nabla s)\\
a_t &= D_a\Delta a - \gamma a s\\
p_t &+ (\gamma a s)_x = D_a\Delta p\\
q_t &+ (\gamma a s)_y = D_a\Delta q
\end{aligned}
$$

$$\mathbf{x} = (x,y)\in\Omega$$

$$p(t,\mathbf{x}) := \Big(a(t,\mathbf{x})\Big)_x$$

$$q(t,\mathbf{x}) := \Big(a(t,\mathbf{x})\Big)_y$$

## Boundary conditions:

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

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

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

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

## Initial conditions:

$$s(0,\mathbf{x}) = s_0(\mathbf{x}),$$
$$a(0,\mathbf{x}) = a_0(\mathbf{x}),$$
$$p(0,\mathbf{x}) = p_0(\mathbf{x}) \equiv \Big(a_0(\mathbf{x})\Big)_x$$
$$q(0,\mathbf{x}) = q_0(\mathbf{x}) \equiv \Big(a_0(\mathbf{x})\Big)_y$$

## Evolution of $b(t,\mathbf{x})$:

$$\partial_t b = c_1 s - c_2 b\,, \text{ on } (0,T)\times\Gamma_1$$
$$b = 0, \text{ on } (0,T)\times\Gamma_2$$
$$b(0,\mathbf{x}) = b_0(\mathbf{x}), \text{ on } \Gamma_1$$

# Initial system in conservation form – cont.

PDE

$$\frac{d\mathbf{U}}{dt} + div\mathbf{F}(\mathbf{U}) = \mathbf{R}(\mathbf{U}), \quad t \in (0,T),\ \mathbf{x} \in \Omega$$

$$\frac{\partial \mathbf{F}}{\partial \mathbf{n}} = h(U, b, \mathbf{x}, t), \quad t \in (0,T),\ \mathbf{x} \in \partial\Omega$$

$$\mathbf{U}(\mathbf{x}, \mathbf{0}) = \mathbf{U_0}, \quad \mathbf{x} \in \Omega$$

ODE

$$\frac{db}{dt} = B(U, b),\ t \in (0,T),\ \mathbf{x} \in \Gamma_1$$

$$b(0, \mathbf{x}) = b_0(\mathbf{x}),\ \mathbf{x} \in \Gamma_1$$

$$b = 0,\ t \in (0,T),\ \mathbf{x} \in \Gamma_2$$

$\mathbf{F}(\mathbf{U}) = \mathbf{F}_c(\mathbf{U}) + F_d(\mathbf{U})$, where $\mathbf{F}_c(\mathbf{U}) = (\mathbf{f}, \mathbf{g})$, $\mathbf{F}_d(\mathbf{U}) = -\Lambda\, \nabla \mathbf{U}$

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

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

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

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

# Finite volume method



$$\bar{\Omega} = [0, A] \times [0, B],\ \ A, B > 0, \qquad \Delta x = \frac{A}{N_x},\ \Delta y = \frac{B}{N_y}$$

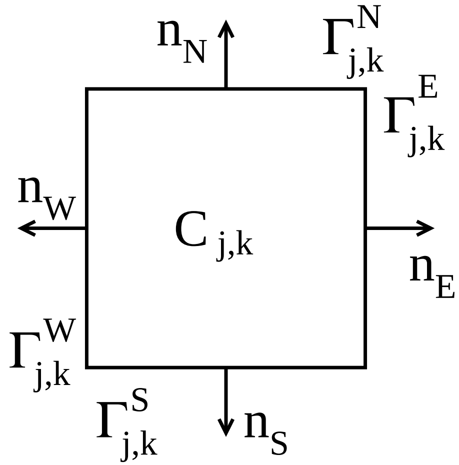
$$\Omega = \cup C_{j,k},\ j = 1, \ldots, N_x,\ k = 1, \ldots, N_y,\quad \partial\Omega = \Gamma^E \cup \Gamma^W \cup \Gamma^N \cup \Gamma^S$$

$$C_{j,k} := [x_{j-\frac{1}{2}}, x_{j+\frac{1}{2}}] \times [y_{k-\frac{1}{2}}, y_{k+\frac{1}{2}}]$$

$$x_{\frac{1}{2}} = 0,\ x_{N_x+\frac{1}{2}} = A,\ x_{j+\frac{1}{2}} = x_{j-\frac{1}{2}} + \Delta x$$

$$y_{\frac{1}{2}} = 0,\ y_{N_y+\frac{1}{2}} = B,\ y_{k+\frac{1}{2}} = y_{k-\frac{1}{2}} + \Delta y$$

$$\partial C_{j,k} = \Gamma^E_{j,k} \cup \Gamma^W_{j,k} \cup \Gamma^N_{j,k} \cup \Gamma^S_{j,k}$$




$$\bar{\mathbf{U}}_{j,k}(t) = \frac{1}{\Delta x \Delta y} \iint\limits_{C_{j,k}} U(x, y, t)\,dx\,dy$$ – 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.

# Semi-discrete scheme



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

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

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

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

Integrals on $\Gamma^W_{1,k}$, $\Gamma^E_{N_x,k}$, $\Gamma^S_{j,1}$ and $\Gamma^N_{j,N_y}$ are computed from b.c.

# 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 $I^d_{j,k}$

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

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

$$\bar{h}^E_k = \frac{1}{\Delta x}(\mathbf{Q}^x_{j+\frac{1}{2},k} - \mathbf{H}^x_{j+\frac{1}{2},k}),\ \bar{h}^W_k = -\frac{1}{\Delta x}(\mathbf{Q}^x_{j-\frac{1}{2},k} - \mathbf{H}^x_{j-\frac{1}{2},k})$$

$$\bar{h}^N_j = \frac{1}{\Delta y}(\mathbf{Q}^y_{j,k+\frac{1}{2}} - \mathbf{H}^y_{j,k+\frac{1}{2}}),\ \bar{h}^S_j = -\frac{1}{\Delta y}(\mathbf{Q}^y_{j,k-\frac{1}{2}} - \mathbf{H}^y_{j,k-\frac{1}{2}})$$

# 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 $\mathbf{U}^E_{j,k}$, $\mathbf{U}^W_{j+1,k}$, $\mathbf{U}^N_{j,k}$, $\mathbf{U}^S_{j,k+1}$

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

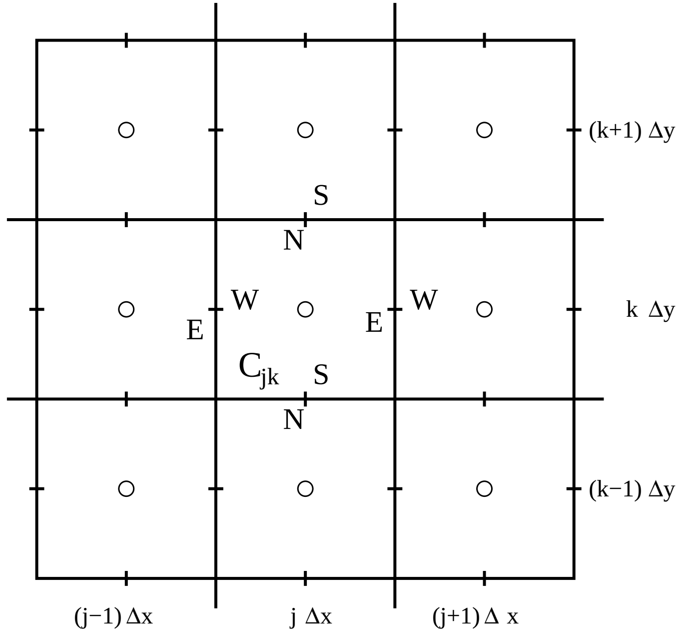
# Semi-discrete scheme – cont.

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

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

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

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




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

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

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

# 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

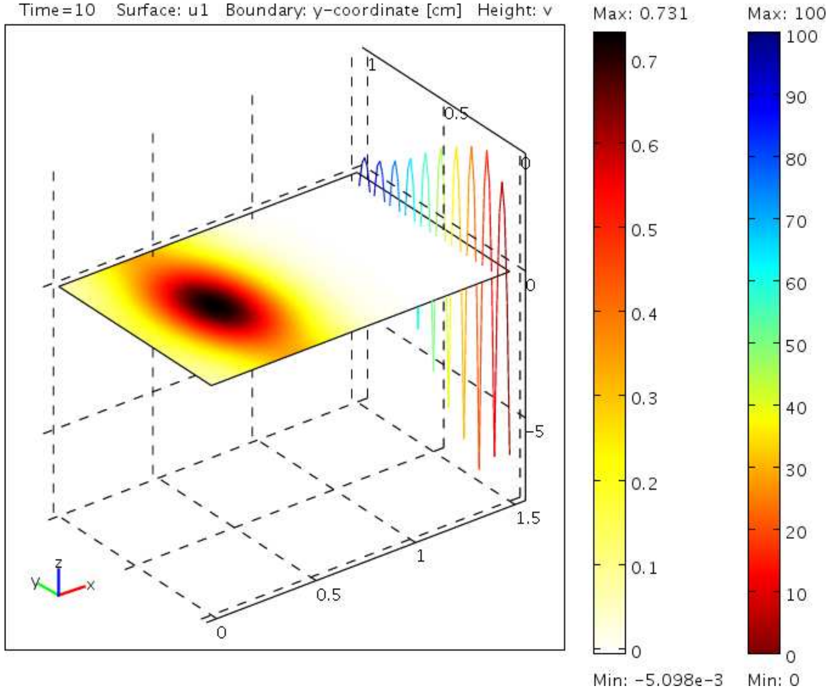


COMSOL Multiphysics (http://www.comsol.com)

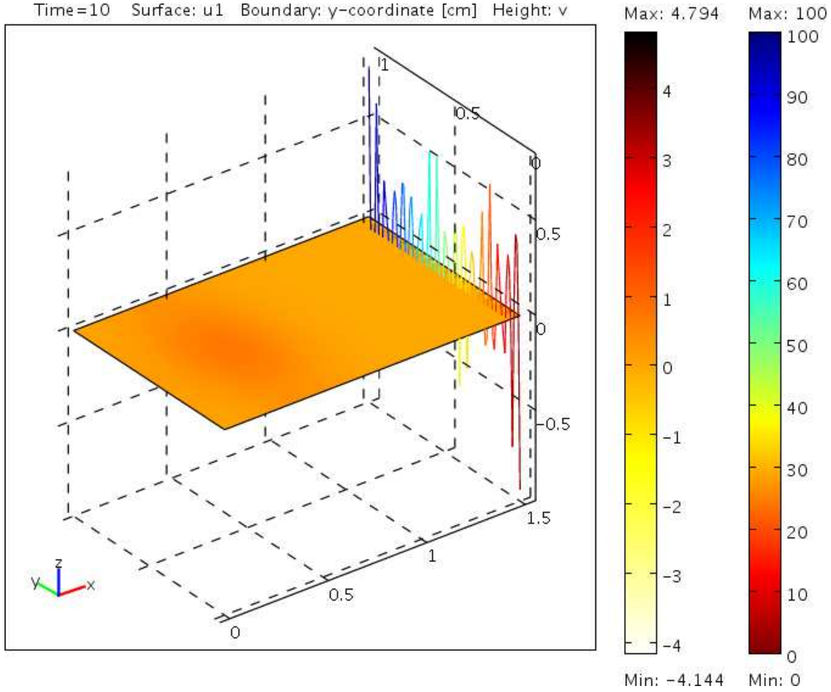
- PDE mode – system of 2 PDEs + ODE on the boundary;
- Finite Element Method – nonuniform mesh for space discretization;
- BDF for time integration;
- Automatic choice of nonlinear solver;
- Implicit Euler + PARDISO or GMRES/ILU for solution of linearized system.

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

GMRES/ILU



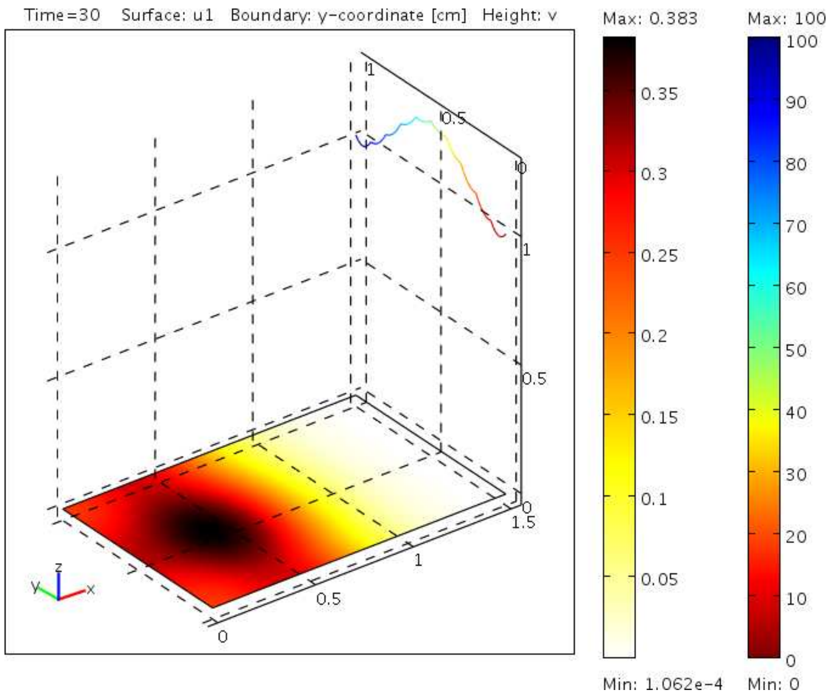

dof = 1723



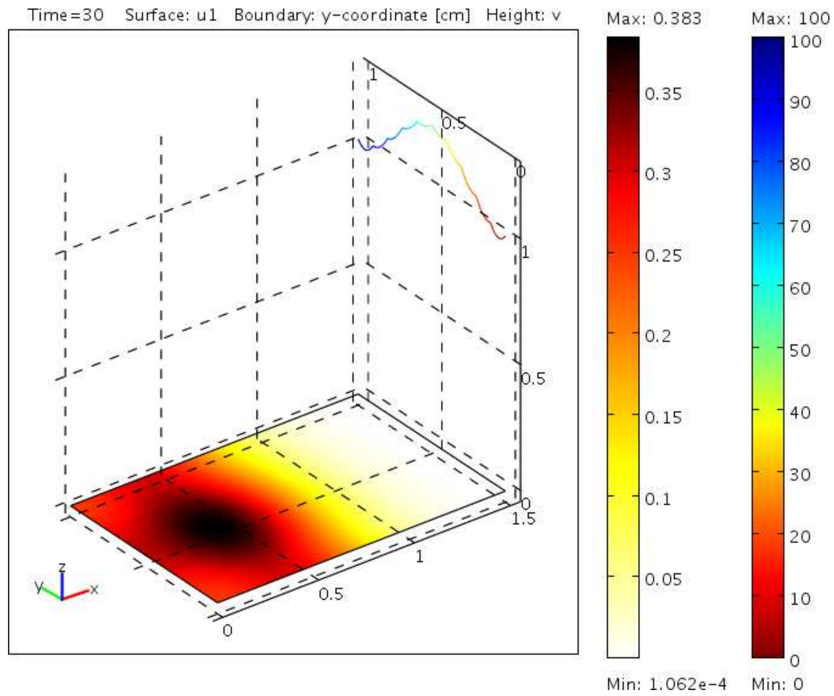

dof=6643

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

GMRES/ILU

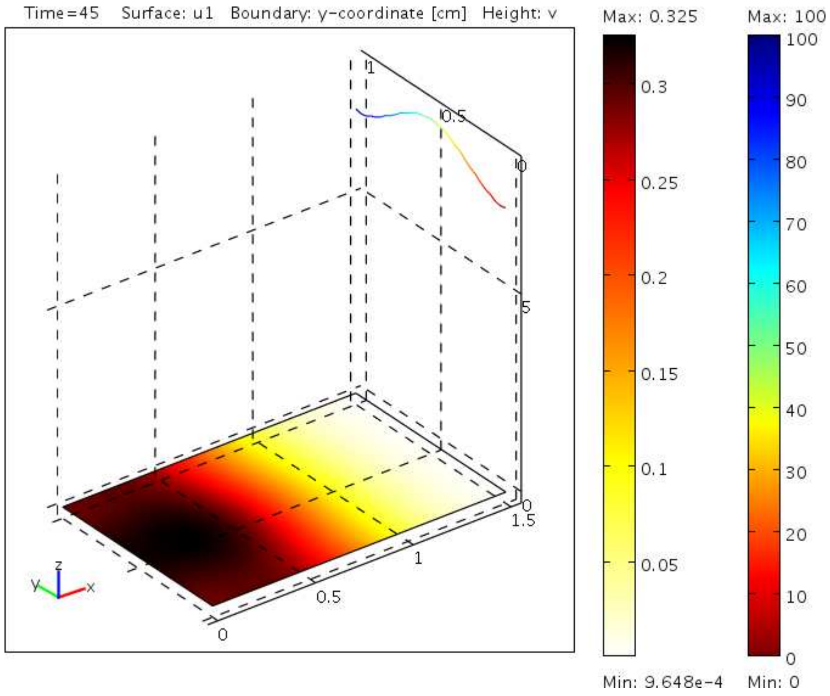



$\chi = 10a$

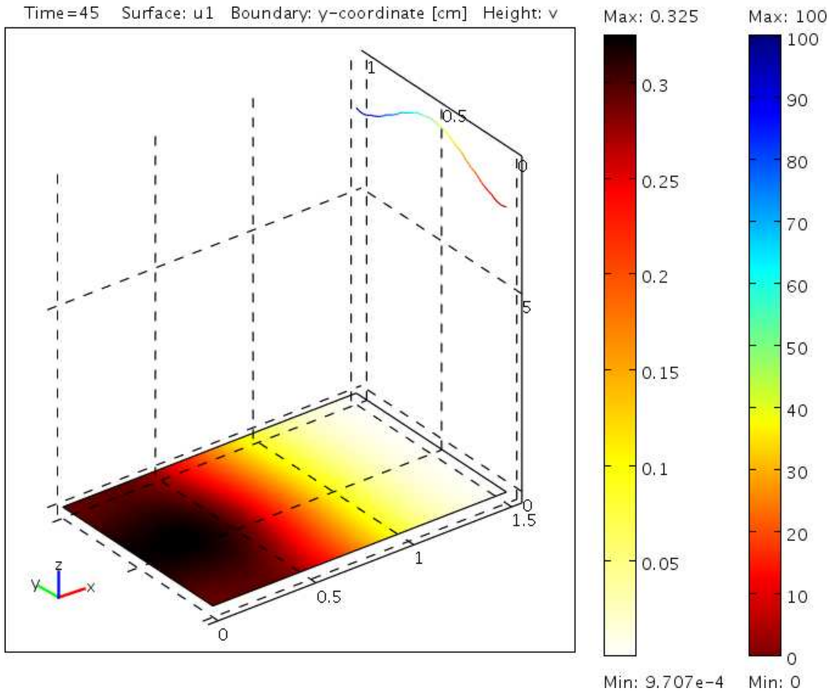



$\chi = log(a)$

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




GMRES/ILU

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# 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 implementation;
    - Modifications for non-linear diffusion case.
- Acknowledgements

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Thank you for your attention!