Computer Modelling and Simulation of Haematopoietic Stem Cells Migration

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Outline

- Motivation
- Model of HSCs' chemotactic movement
- Numerical solution
  - – Finite element method with COMSOL
  - – Finite volume method
- Concluding remarks

Motivation

Blood cells production and regulation

Haematopoietic pluripotent stem cells (HSCs) in bone marrow give birth to 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

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

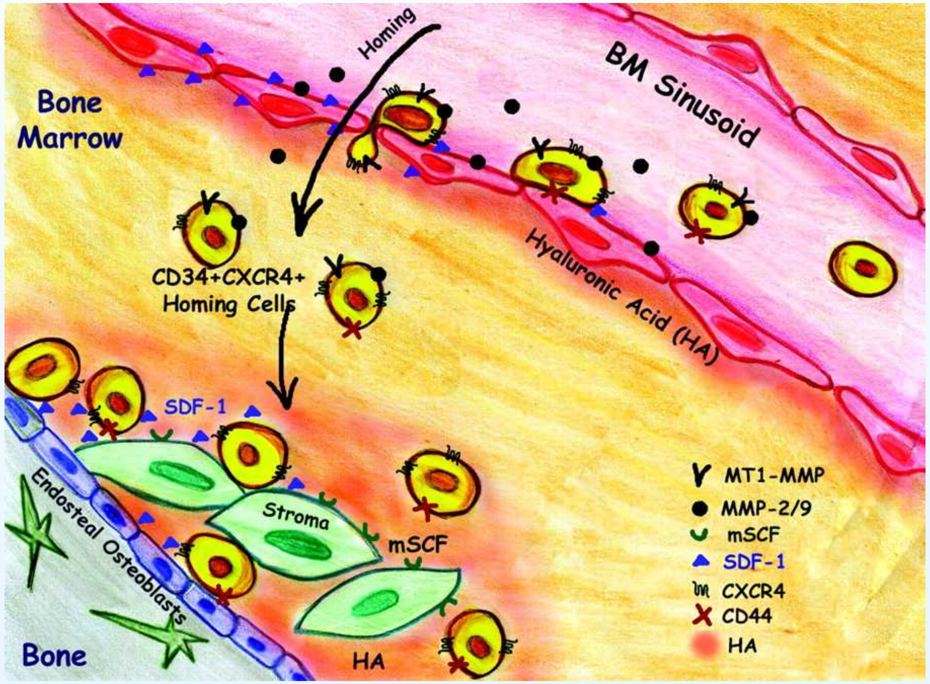
Main stages in the therapy of blood diseases:

TBI: Total Body Irradiation – kill the "tumour" cells, but also the healthy ones.

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

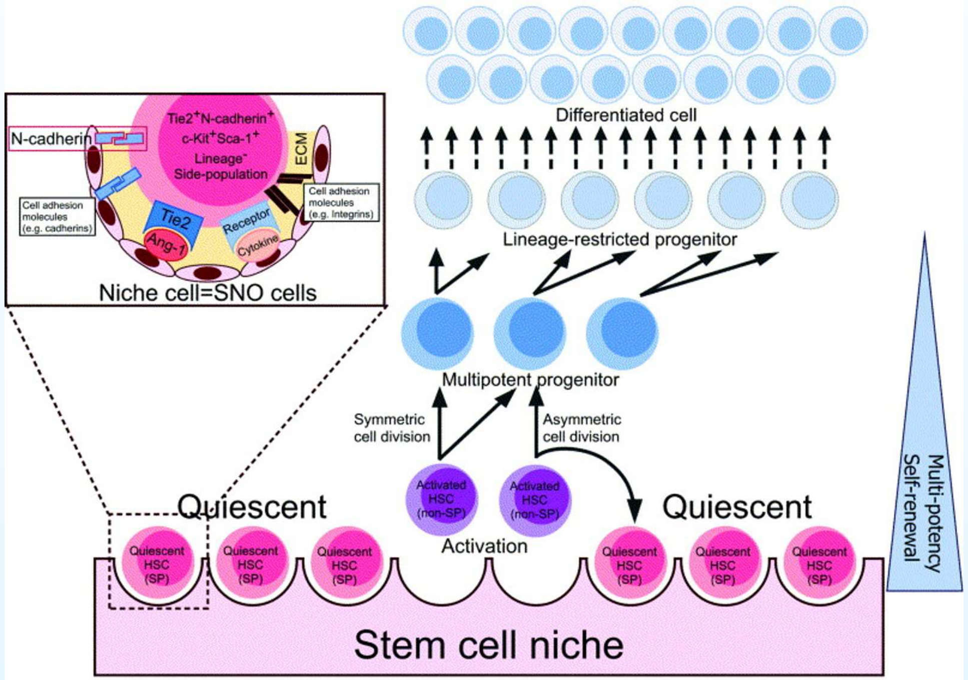
HSCs after BMT ...

1. find their way to the stem cell niche in the bone marrow; and ...



T. Lapidot, A. Dar, O. Kollet, 2005

2. self-renew and differentiate to regenerate the patient's blood system



T. Suda, F. Arai, A. Hirao, 2005

G.B. et.al., 2012

Adequate computer models would help medical doctors to shorten the period in which the patient is missing their effective immune system.

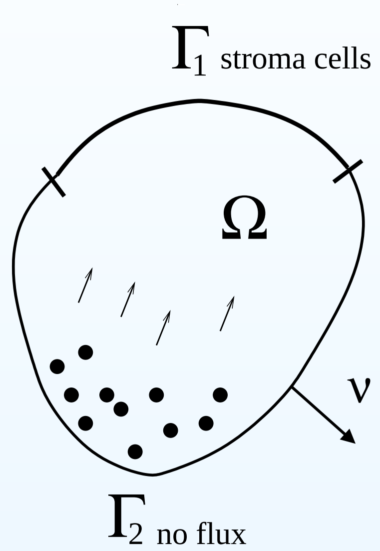
Model of HSCs' chemotactic movement

Involved data

Unknowns:

$s(t, \mathbf{x})$ – concentration of HSCs 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 Γ_1

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



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
$c(\mathbf{x})$ – concentration of stroma cells on Γ_1
$\beta(t, b)$ – proportionality function in the production rate of chemoattractant

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

The model (A. Kettemann, M. Neuss-Radu, 2008)

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

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

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

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

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

Existence of unique solution is ensured by certain conditions for the involved functions.

Numerical solution

Method of lines

Space discretizations:

- Finite Difference Method
- Finite Element Method
- Finite Volume Method
  – Formulated for systems written in conservation form;
  – Unknowns are averages on the finite volumes.

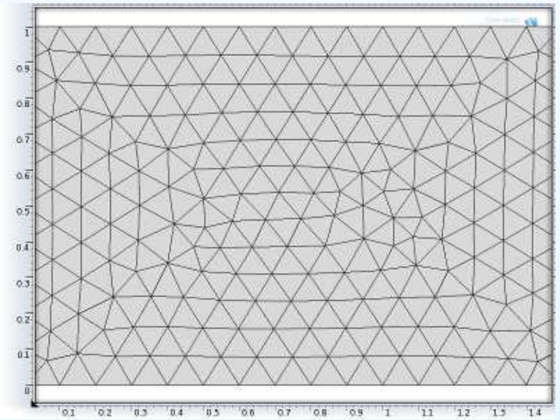
Time discretizations:

- FDM
- θ scheme
- Runge-Kutta methods
- Fractional step and Operator Splitting

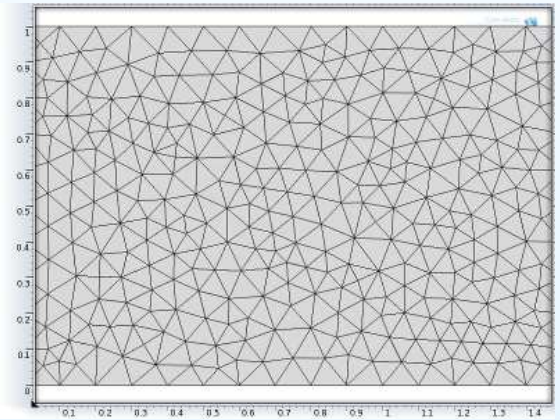
Numerical simulation with COMSOL Multiphysics (G.B., 2012)

- Linear finite elements for space discretization (nonuniform mesh);
- Implicit time integration;
- Direct or Iterative solution of linearized system.

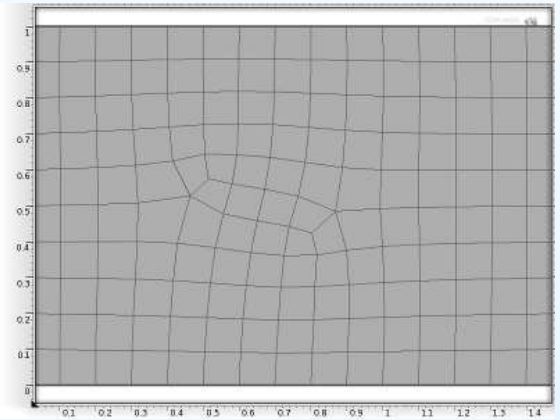
Mesh types



M1: Triangular (Advancing front)



M2: Triangular (Delaunay)



M3: Quadrilateral

Test data

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

$$c(x_2) = 0.01(1 + 0.2\sin(5\pi x_2)),\ \beta(t, b) = V(t)\beta^*(b) \text{ with}$$

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

$$\chi(a) = 10a \quad \chi(a) = \log(a+1)$$

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

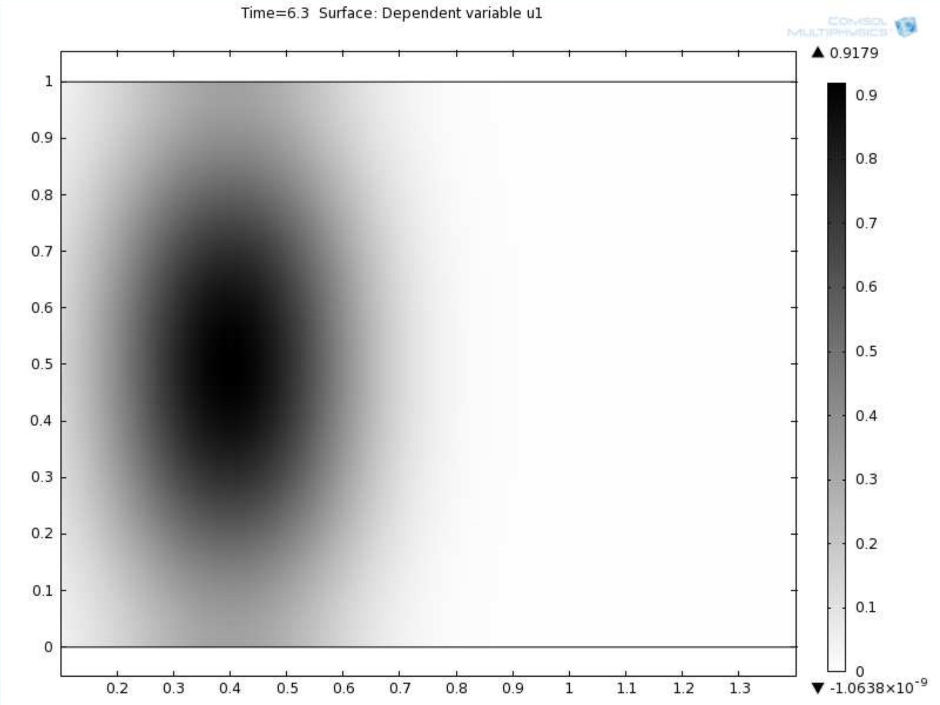
$$a_0 = 0, b_0 = 0 \text{ and}$$

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

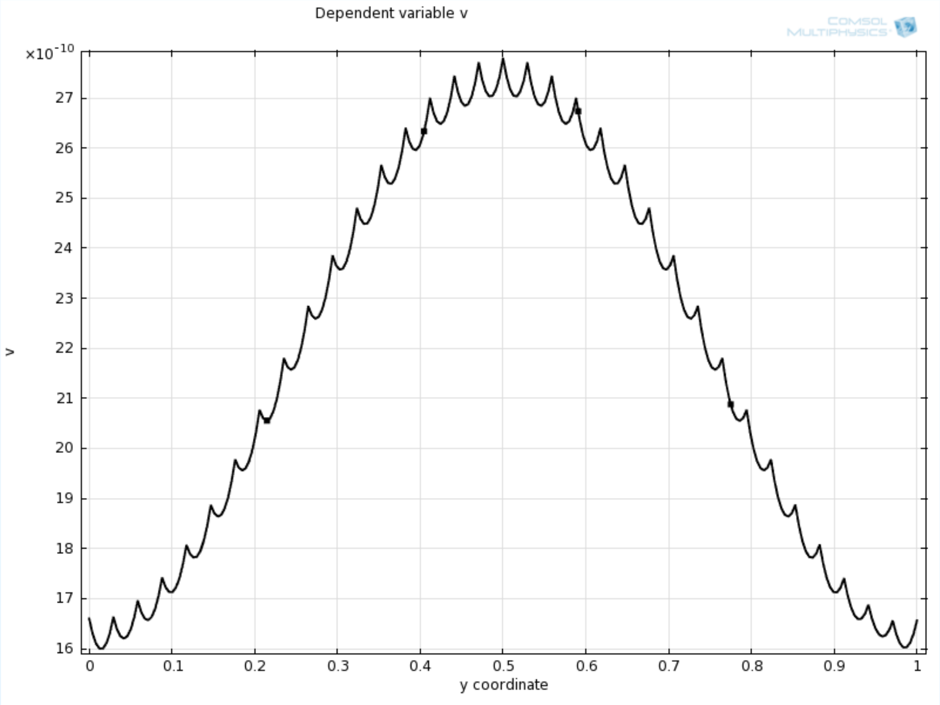
Solution $s(t,x)$ and $b(t,x)$ with for M1ef

Solution time: 21 s, 30 iterations, $T = 6.3$.

M1ef (triangular): Number of elements 4 268, Degrees of freedom 17 479



$s(t, \mathbf{x})$

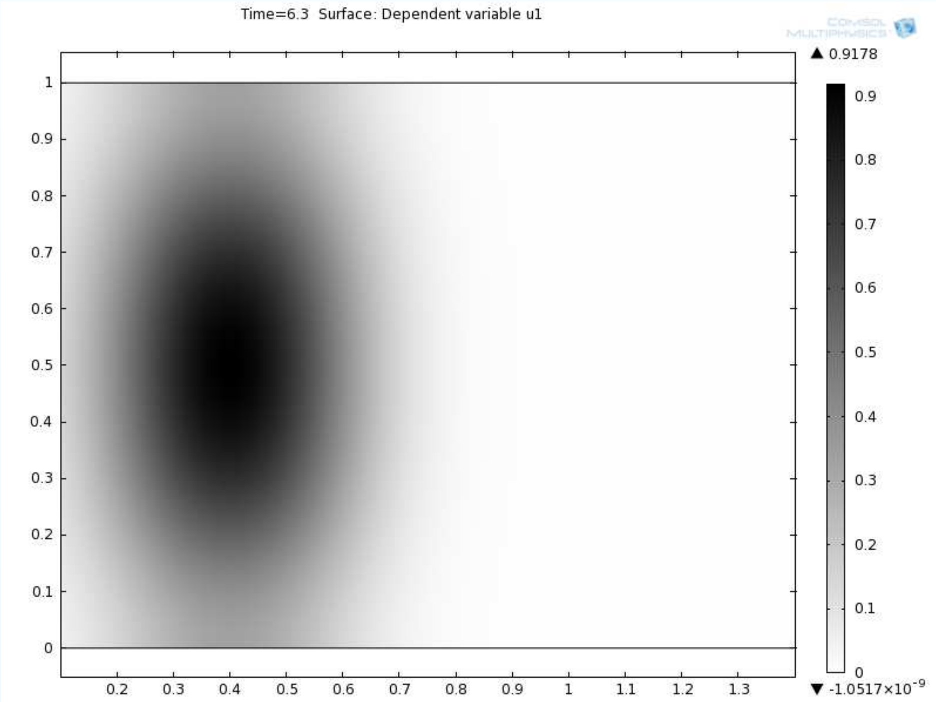


$b(t, \mathbf{x})$

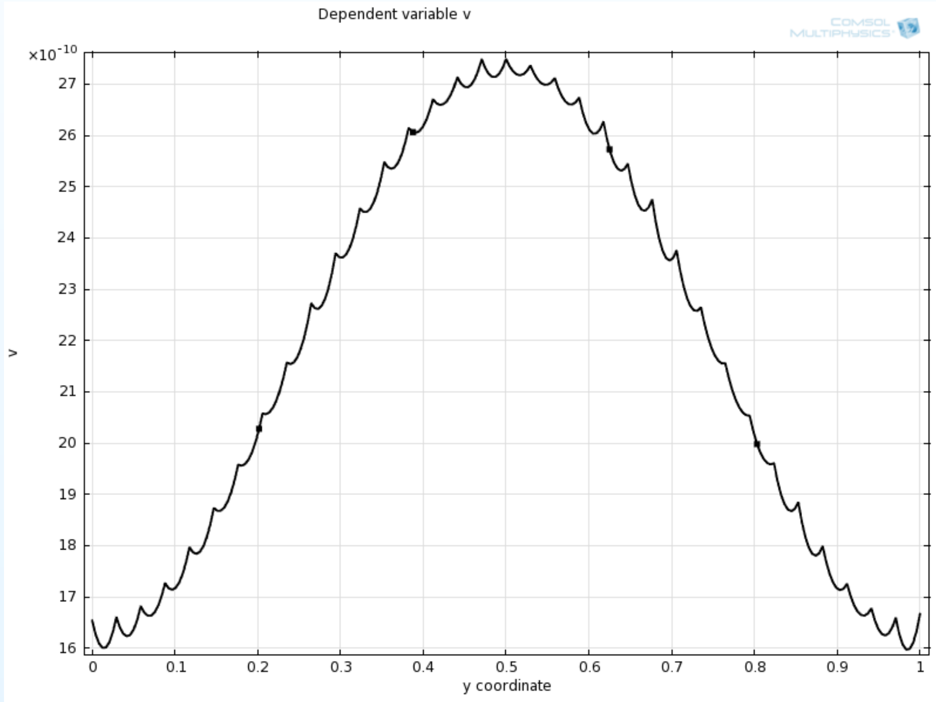
Solution $s(t, x)$ and $b(t, x)$ with for M2ef

Solution time: 34 s, 30 iterations, $T = 6.3$.

M2ef (triangular, Delaunay): Number of elements 7 160, Degrees of freedom 29 047



$s(t, \mathbf{x})$

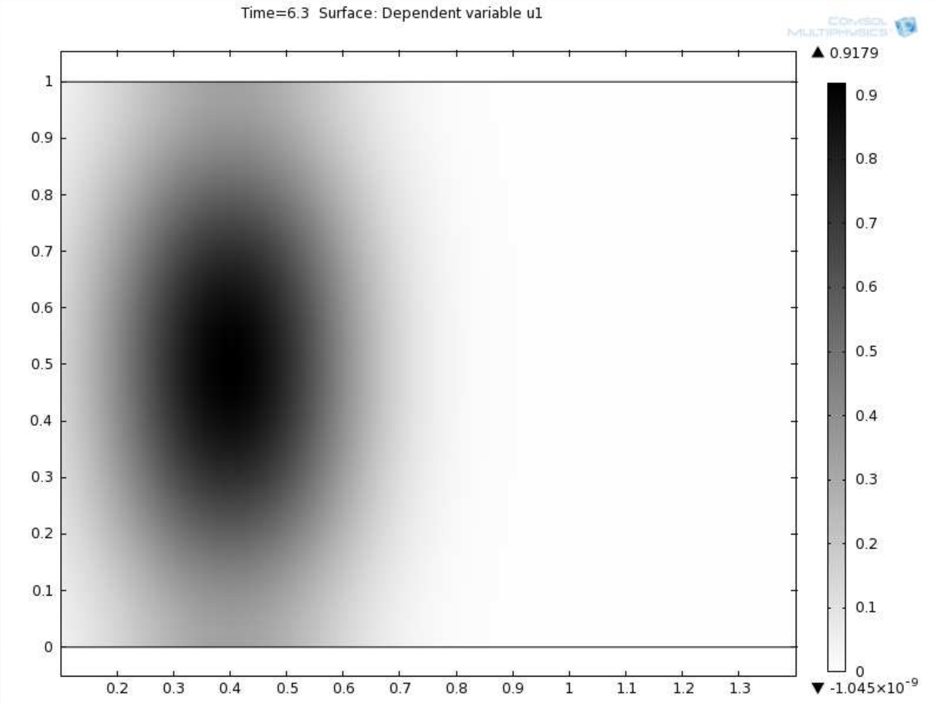


$b(t, \mathbf{x})$

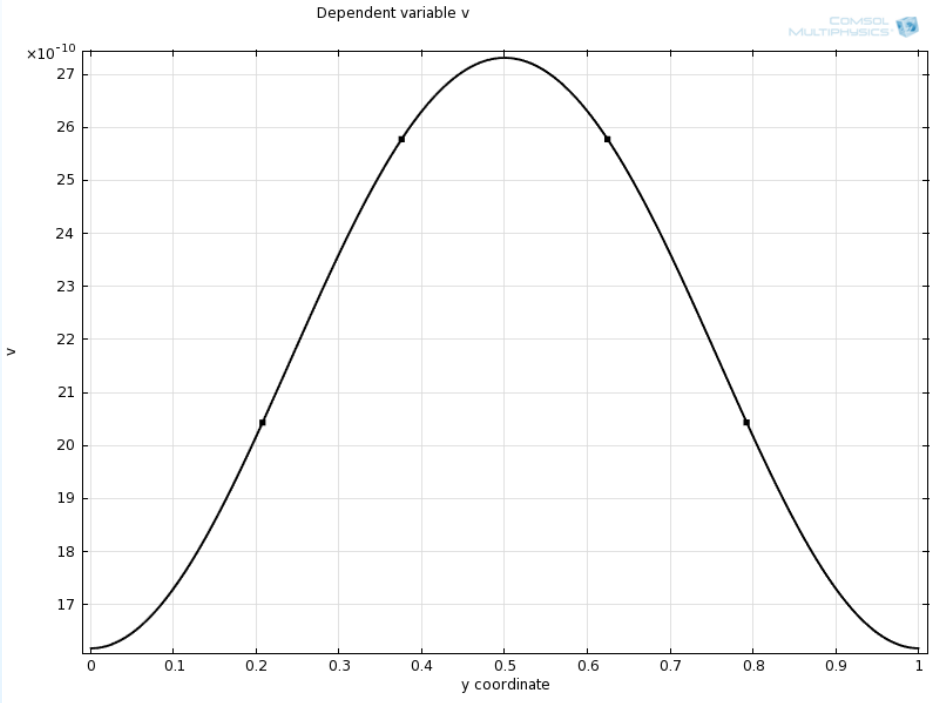
Solution $s(t, x)$ and $b(t, x)$ with for M3ef

Solution time: 18 s, 30 iterations, $T = 6.3$.

M3ef (quadrangular): Number of elements 1 777, Degrees of freedom 14 623



$s(t, \mathbf{x})$



$b(t, \mathbf{x})$

Remarks

- Observations:
  - Not always convergent
  - Negative values and oscillations for the solution
- We need nonoscillatory and positivity preserving numerical scheme and software to
  - ”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?”
- Possible improvements in the direction of:
  - space discretization – FVM
  - discretization of nonlinear boundary conditions
  - time discretization

Initial system in conservation form (Chertock, Kurganov, 2008)

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

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

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

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

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

$\partial_t b = c_1 s - c_2 b\,,$ on $(0,T)\times\Gamma_1$

$b = 0,$ on $(0,T)\times\Gamma_2$

$b(0,\mathbf{x}) = b_0(\mathbf{x})$, on Γ_1

Initial system in conservation form – cont.

PDE

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

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

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

ODE

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

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

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

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

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

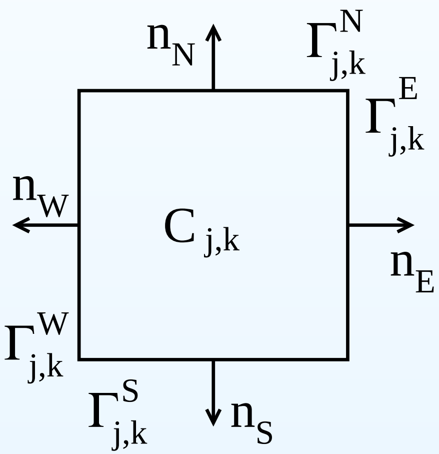
$$\Lambda = diag(\varepsilon, D_a, D_a, D_a),\ \mathbf{R}(\mathbf{U}) = (0, -\gamma as, 0, 0)^T$$

Finite volume method

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

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

$$C_{j,k} := [x_{j-\frac{1}{2}}, x_{j+\frac{1}{2}}] \times [y_{k-\frac{1}{2}}, y_{k+\frac{1}{2}}]$$
$$x_{\frac{1}{2}} = 0, x_{N_x+\frac{1}{2}} = A, x_{j+\frac{1}{2}} = x_{j-\frac{1}{2}} + \Delta x$$
$$y_{\frac{1}{2}} = 0, y_{N_y+\frac{1}{2}} = B, y_{k+\frac{1}{2}} = y_{k-\frac{1}{2}} + \Delta y$$
$$\partial C_{j,k} = \Gamma^E_{j,k} \cup \Gamma^W_{j,k} \cup \Gamma^N_{j,k} \cup \Gamma^S_{j,k}$$



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

Semi-discrete scheme

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

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

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

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

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

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

Semi-discrete scheme – interior cells $j = 2, \dots N_x - 1, k = 2, \dots N_y - 1$

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

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

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

Semi-discrete scheme – interior cells $j = 2, \dots N_x - 1, k = 2, \dots N_y - 1$

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

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

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

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

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

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

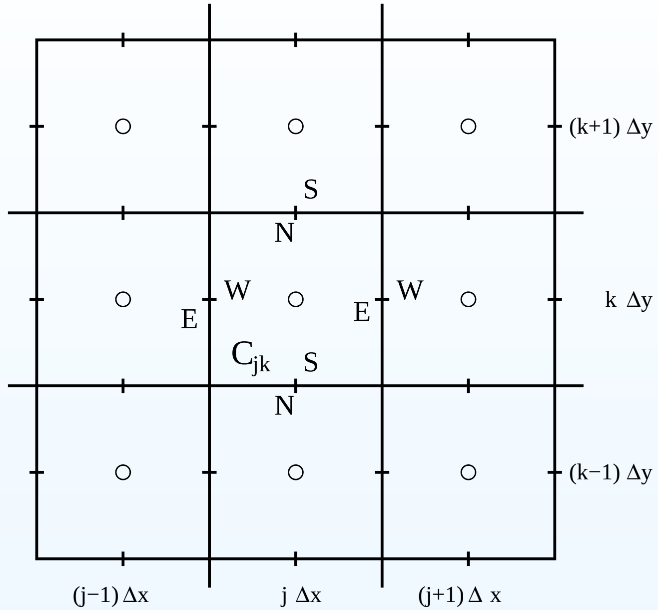
Semi-discrete scheme – cont.

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

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

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

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



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

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

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

Semi-discrete scheme – boundary cells

$$\int_{\Gamma^l_{j,k}} (\mathbf{F}_c + \mathbf{F}_d) \cdot \mathbf{n}_l \, d\bar{\gamma} = \int_{\Gamma^l_{j,k}} \mathbf{h}^l \, d\bar{\gamma}, \; l \in \{E, W, N, S\}, \; \bar{\mathbf{h}}^l_{j,k} := \frac{1}{|\Gamma^l_{j,k}|} \int_{\Gamma^l_{j,k}} \mathbf{h}^l \, d\bar{\gamma} \,,$$

$$\left(\bar{\mathbf{U}}_{1,k}\right)_t = \frac{\mathbf{Q}^x_{\frac{3}{2},k} - \mathbf{H}^x_{\frac{3}{2},k} - \bar{\mathbf{h}}^W_{1,k}}{\Delta x} - \frac{\mathbf{H}^y_{1,k+\frac{1}{2}} - \mathbf{H}^y_{1,k-\frac{1}{2}}}{\Delta y} + \frac{\mathbf{Q}^y_{1,k+\frac{1}{2}} - \mathbf{Q}^y_{1,k-\frac{1}{2}}}{\Delta y} + \bar{\mathbf{R}}_{1,k} \,,$$

$$\left(\bar{\mathbf{U}}_{N_x,k}\right)_t = \frac{\mathbf{H}^x_{N_x-\frac{1}{2},k} - \mathbf{Q}^x_{N_x-\frac{1}{2},k} - \bar{\mathbf{h}}^E_{N_x,k}}{\Delta x} - \frac{\mathbf{H}^y_{N_x,k+\frac{1}{2}} - \mathbf{H}^y_{N_x,k-\frac{1}{2}}}{\Delta y} + \frac{\mathbf{Q}^y_{N_x,k+\frac{1}{2}} - \mathbf{Q}^y_{N_x,k-\frac{1}{2}}}{\Delta y} + \bar{\mathbf{R}}_{N_x,k} \,,$$

$$\left(\bar{\mathbf{U}}_{j,1}\right)_t = -\frac{\mathbf{H}^x_{j+\frac{1}{2},1} - \mathbf{H}^x_{j-\frac{1}{2},1}}{\Delta x} + \frac{\mathbf{Q}^y_{j,\frac{3}{2}} - \mathbf{H}^y_{j,\frac{3}{2}} - \bar{\mathbf{h}}^S_{j,1}}{\Delta y} + \frac{\mathbf{Q}^x_{j+\frac{1}{2},1} - \mathbf{Q}^x_{j-\frac{1}{2},1}}{\Delta x} + \bar{\mathbf{R}}_{j,1} \,,$$

$$\left(\bar{\mathbf{U}}_{j,N_y}\right)_t = -\frac{\mathbf{H}^x_{j+\frac{1}{2},N_y} - \mathbf{H}^x_{j-\frac{1}{2},N_y}}{\Delta x} + \frac{\mathbf{H}^y_{j,N_y-\frac{1}{2}} - \mathbf{Q}^y_{j,N_y-\frac{1}{2}} - \bar{\mathbf{h}}^N_{j,N_y}}{\Delta y} + \frac{\mathbf{Q}^x_{j+\frac{1}{2},N_y} - \mathbf{Q}^x_{j-\frac{1}{2},N_y}}{\Delta x} + \bar{\mathbf{R}}_{j,N_y} \,.$$

Possible time integration schemes

- Implicit schemes – introduce negative values of the solution; high computational cost
- Approach by A. Chertock, A. Kurganov, 2008:
  - Explicit Euler $\Delta t \le \min(\frac{\Delta x}{8a}, \frac{\Delta y}{8b}, c)$

$$a := \max_{j,k}\{\max\{a^+_{j+\frac{1}{2},k}, -a^-_{j+\frac{1}{2},k}\}\},$$
$$b := \max_{j,k}\{\max\{b^+_{j,k+\frac{1}{2}}, -b^-_{j,k+\frac{1}{2}}\}\}$$

$$c := \frac{(\Delta x)^2(\Delta y)^2}{4((\Delta x)^2 + (\Delta y)^2)}$$

  - IMEX Scheme $\Delta t \le \min(\frac{\Delta x}{4a}, \frac{\Delta y}{4b})$
  - First order methods, additional stability restrictions on Δt
- Explicit second order Runge-Kutta based local time-stepping (joint work with T. Mitkova)

Concluding remarks

Concluding remarks

- Ongoing work
  - Development of own simulation package
  - Robust discretization of the nonlinear boundary conditions
  - Second order local time stepping time integration
- 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.

Thank you for your attention!