How Does the Type of Chemotactic Sensitivity Function Influence the Haematopoietic Stem Cells Migration?

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This work is supported in part by the Bulgarian NSF grants DO 02-214/2008, DO 02-147/2008.

Outline

- Motivation
- Model of HSCs' migration
- FEM based simulation with COMSOL Multiphysics
- Finite volume approximation
- 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).

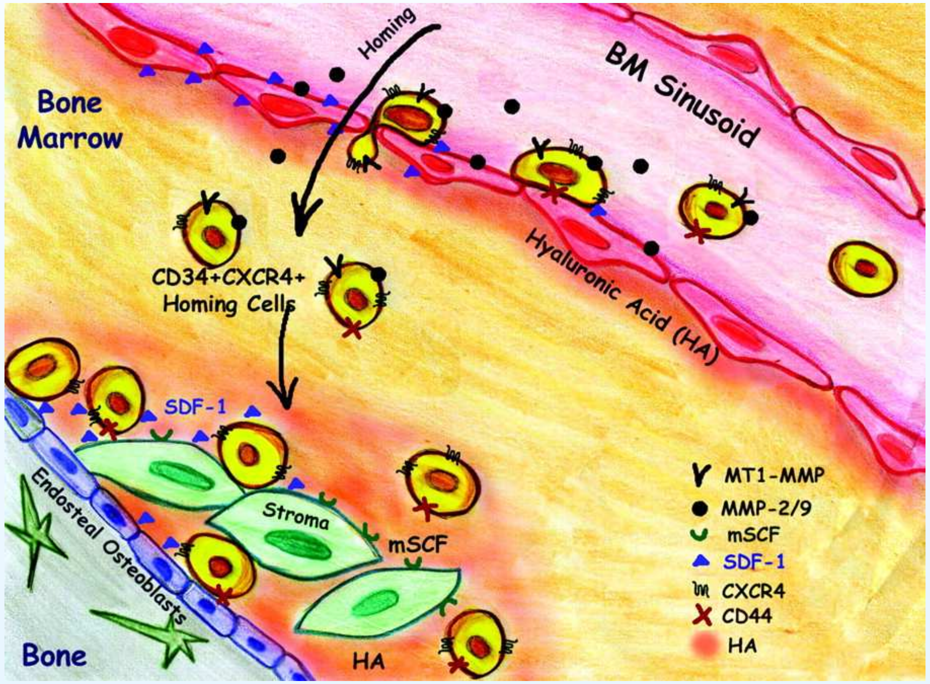
Main stages in the therapy of blood diseases:

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.

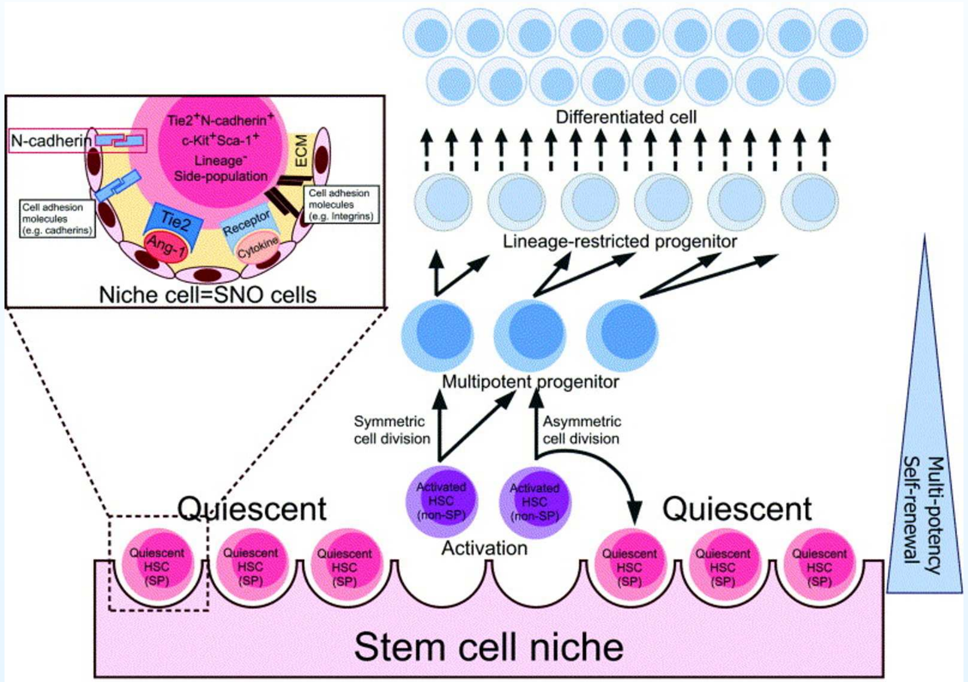
HSCs after BMT ...

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.

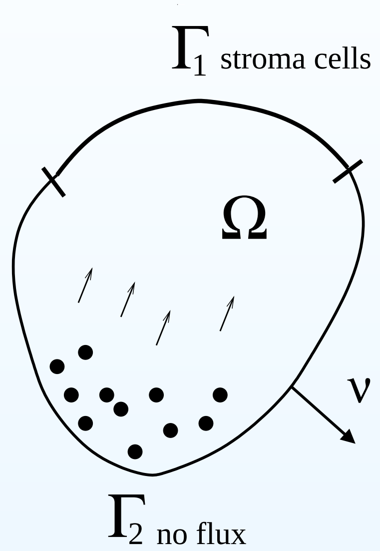
Model of HSCs' migration

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

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



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

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

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.

Types of chemotactic sensitivity function $\chi(a)$

Linear case of $\chi(a)$:

$$\chi(a) = \chi a, \quad \frac{\partial \chi}{\partial a} = \chi$$

Nonlinear forms of $\chi(a)$ (Post, 1999):

$$\chi(a) = \frac{\chi\, a}{1 + c\, a}, \quad \chi(a) = \frac{\chi\, a^2}{1 + c\, a^2}, \quad \chi(a) = \chi\, \log(a + c)$$

with constants $\chi > 0$ and $c \geq 1$.

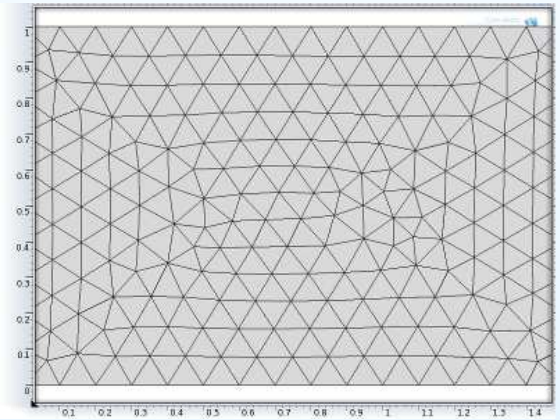
$$\frac{\partial \chi}{\partial a} = \frac{\chi}{(1 + c\, a)^2}\,, \quad \frac{\partial \chi}{\partial a} = \frac{2\, \chi\, a}{(1 + c\, a^2)^2}\,, \quad \frac{\partial \chi}{\partial a} = \frac{\chi}{(a + c)\ln 10}\,.$$

FEM based simulation with COMSOL Multiphysics

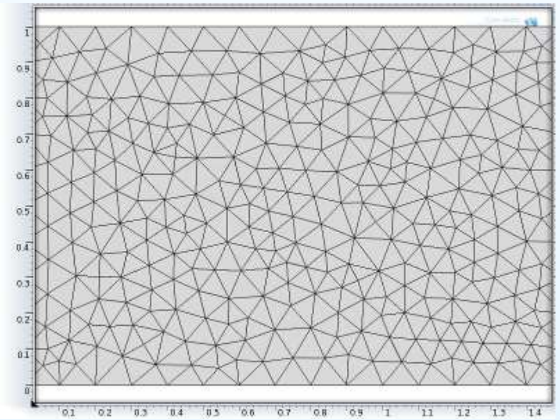
Numerical simulation with COMSOL Multiphysics (G.B., 2012)

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

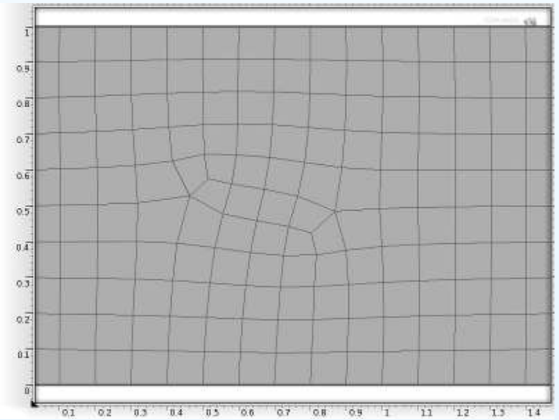
Mesh types



M1: Triangular (Advancing front)



M2: Triangular (Delaunay)



M3: Quadrilateral

Test data 1

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

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

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

$$\chi(a) = 10a,\ \chi(a) = \frac{10a}{1+a},\ \chi(a) = \frac{10a^2}{1+a^2},\ \chi(a) = 10\log(a+1)$$

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

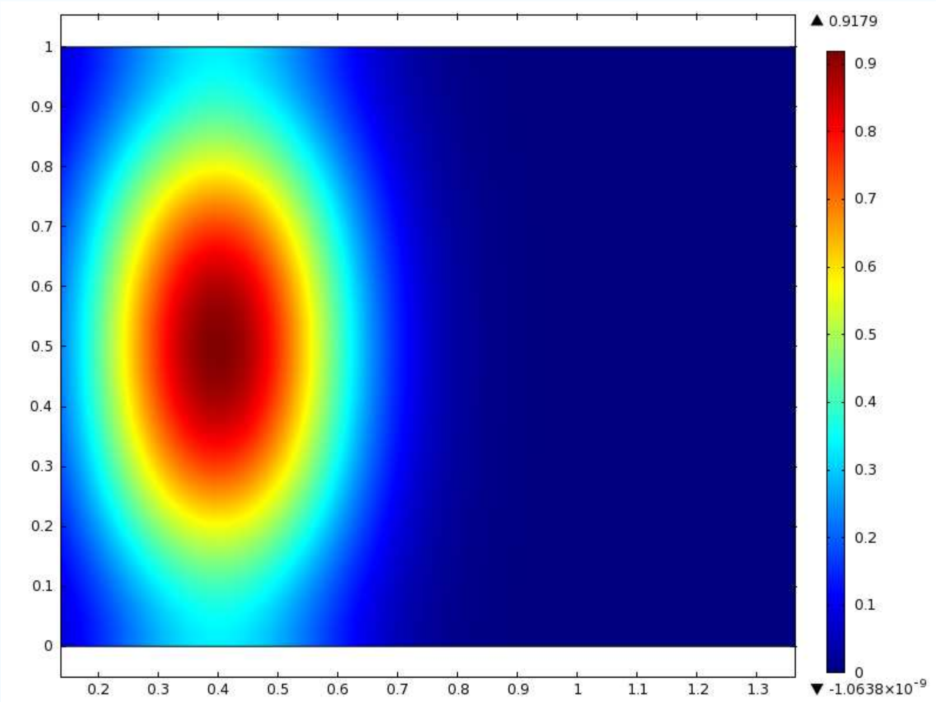
$$a_0 = 0, b_0 = 0 \text{ and}$$

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

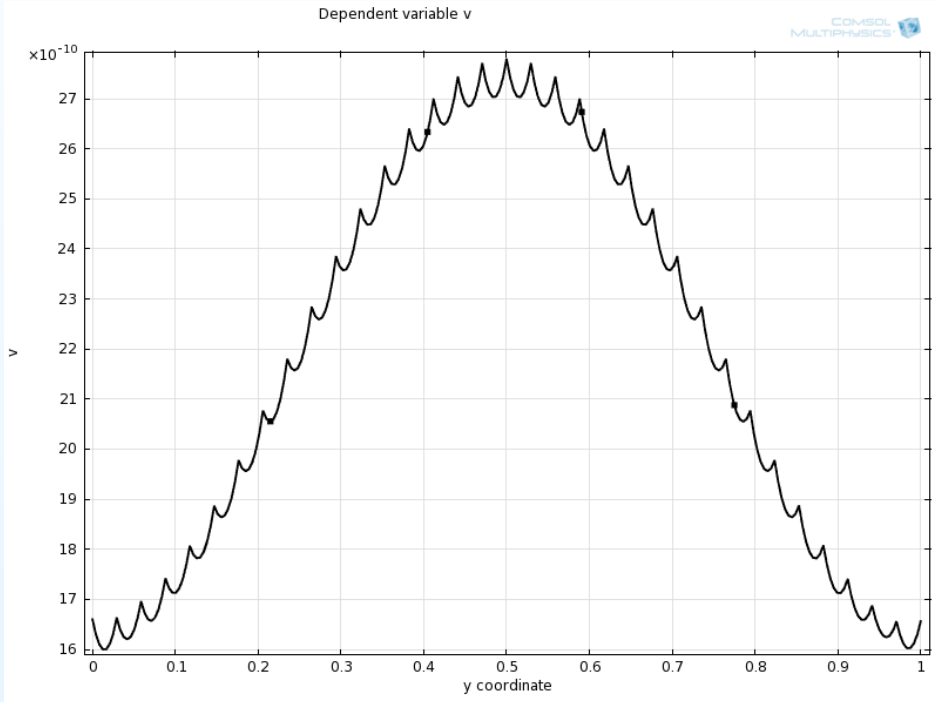
Solution $s(t,x)$ and $b(t,x)$ with for M1ef

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

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



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

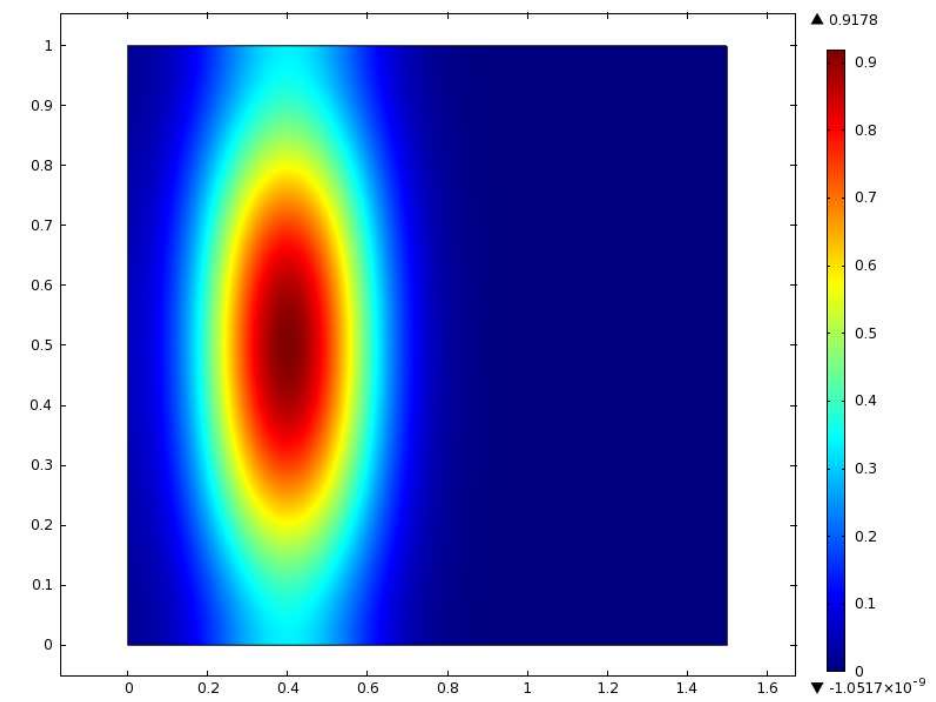


$b(t,\mathbf{x})$

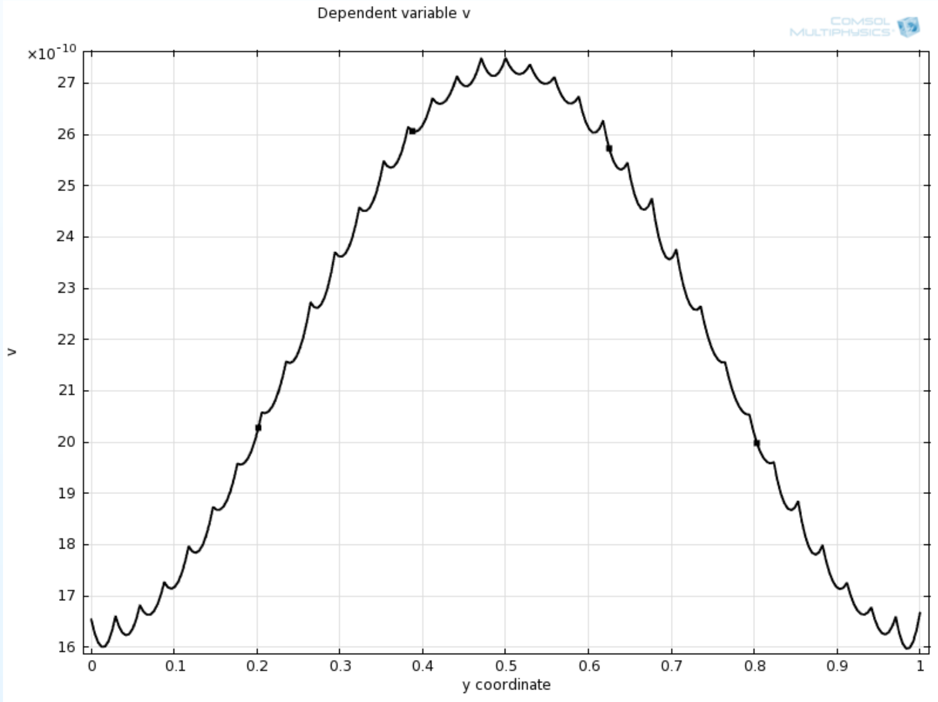
Solution $s(t, x)$ and $b(t, x)$ with for M2ef

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

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



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

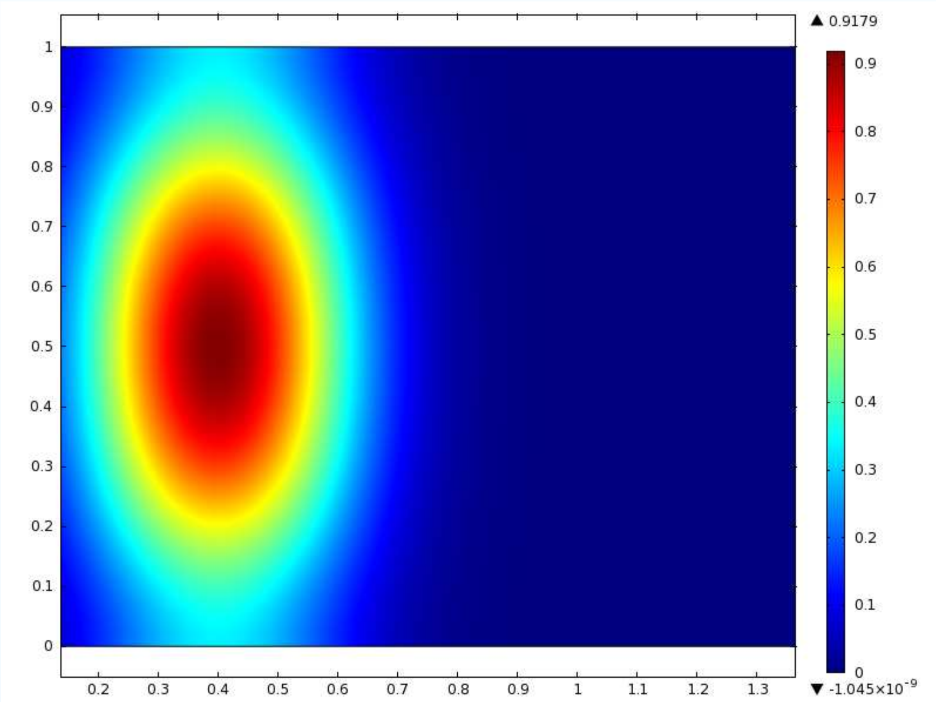


$b(t, \mathbf{x})$

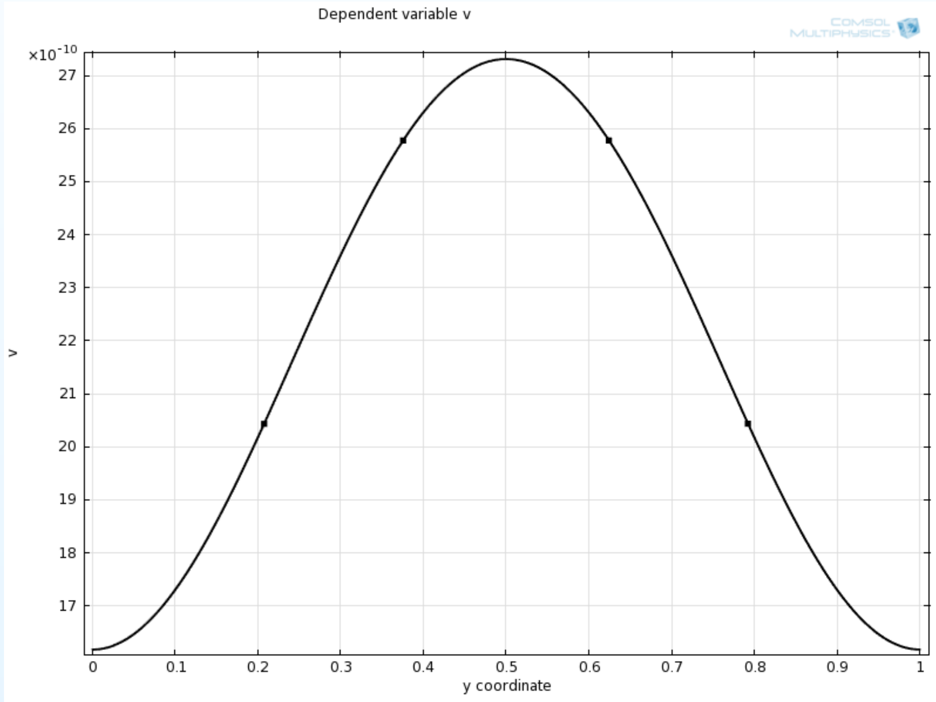
Solution $s(t,x)$ and $b(t,x)$ with for M3ef

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

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



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

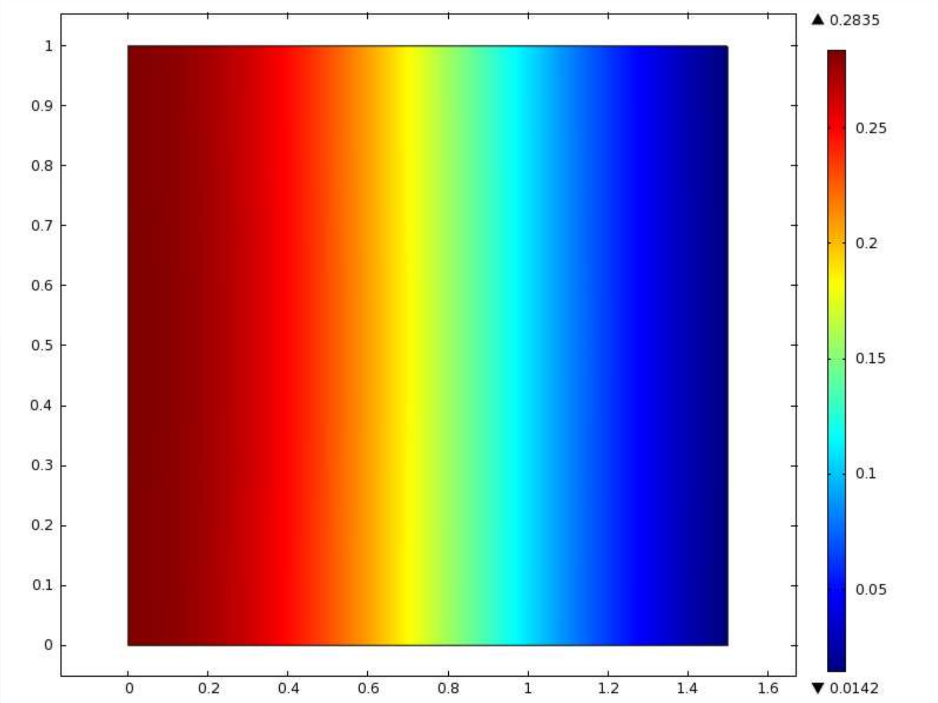


$b(t, \mathbf{x})$

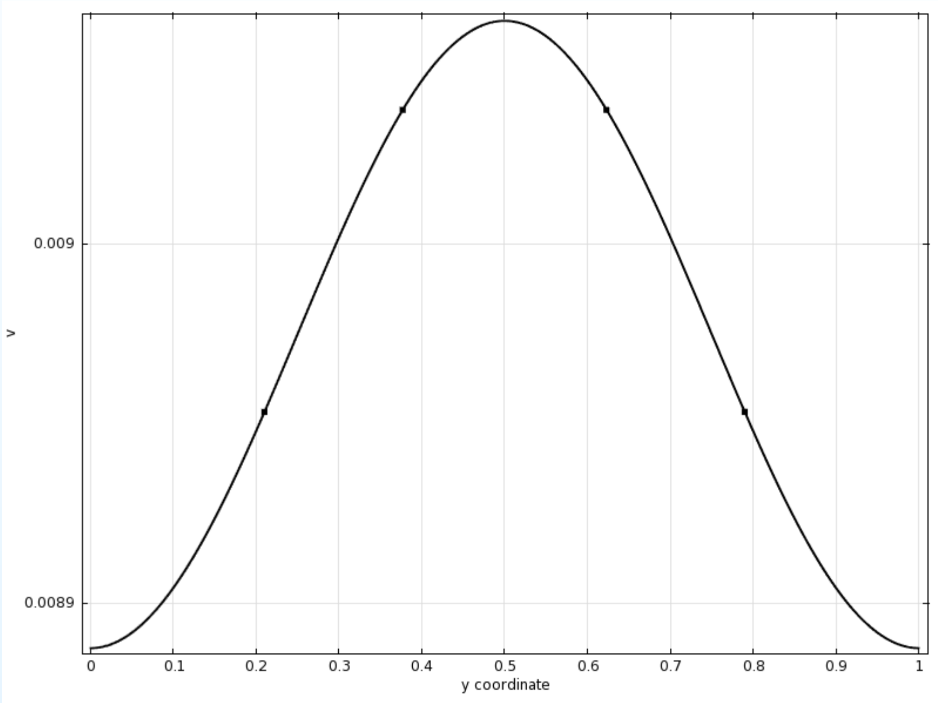
Solution $s(t,x)$ and $b(t,x)$ with for M3ef

Solution time: 18 s, 30 iterations, $T = 100$.

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



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



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

Test data 2 – simplified model

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

Zero flux conditions, unknowns $s(t, x)$ and $a(t, x)$.

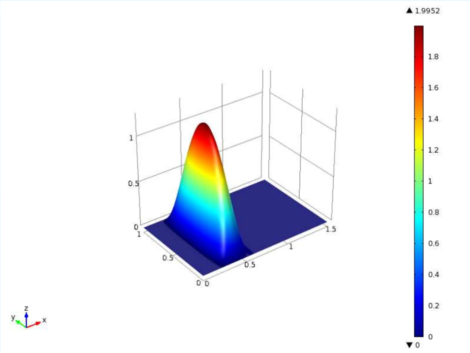
$$\chi_1(a) = \chi a,\ \chi_2(a) = \frac{\chi a}{1+a},\ \chi_3(a) = \frac{\chi a^2}{1+a^2},\ \chi_4(a) = \chi \log(a+1)$$

Parameter case 1: $\varepsilon = 0.0015, D_a = 2, \gamma = 0.1, \chi = 10$

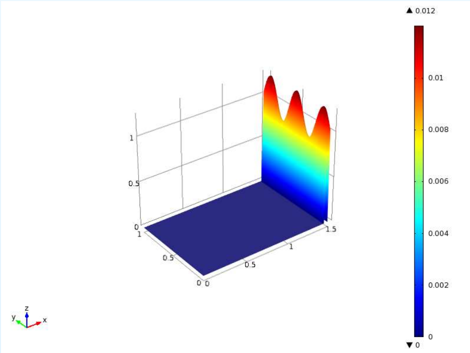
Parameter case 2: $\varepsilon = 0.015, D_a = 1.3, \gamma = 0.1, \chi = 100$

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

$$a_0(x_1, x_2) = \begin{cases} 0.01(1 + 0.2\sin(5\pi x_2)), & \text{for } 1.455 \le x_1 \le 1.5 \\ 0 & \text{otherwise} \end{cases}$$

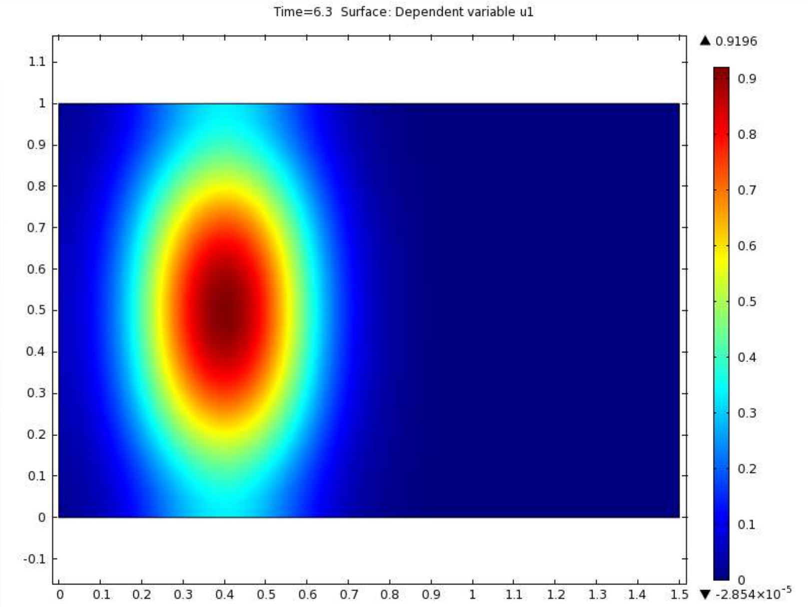


$s_0(x_1, x_2)$

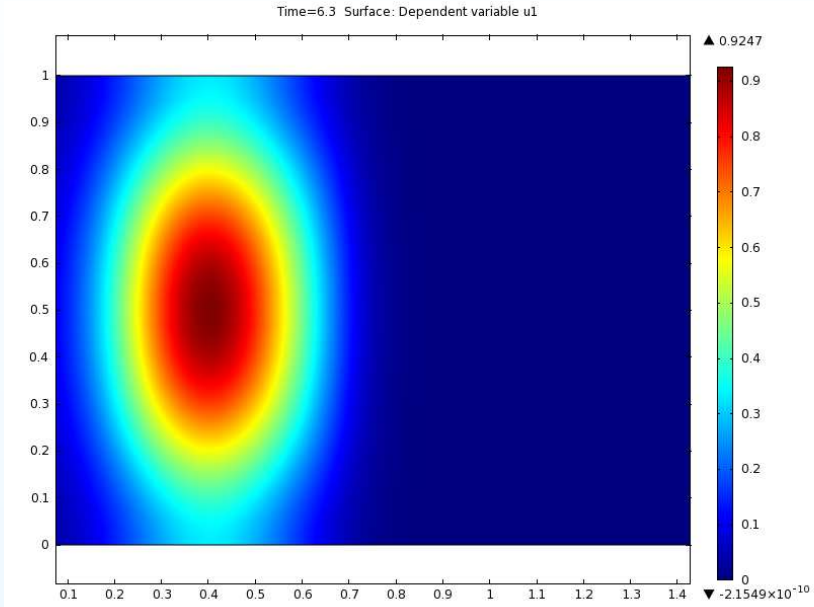


$a_0(x_1, x_2)$

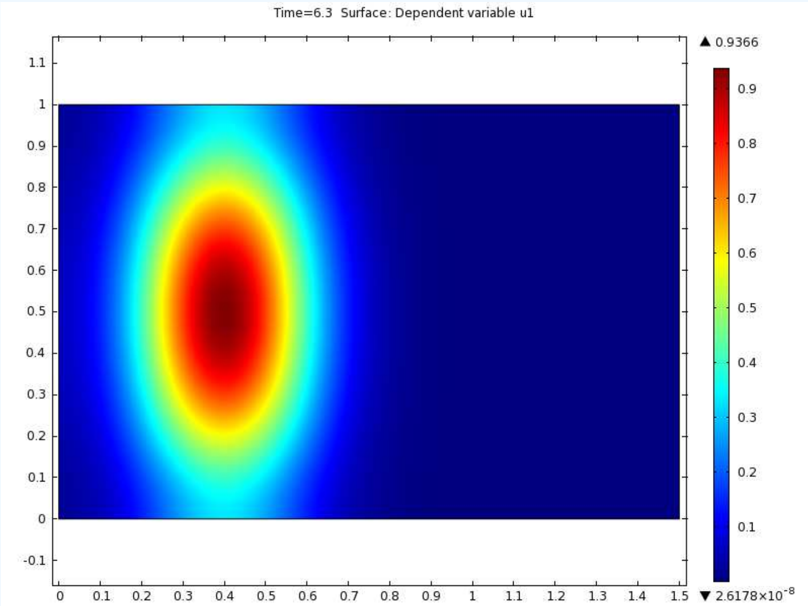
Solution $s(t, x)$ for M3ef, Parameter case 1, $T = 6.3$



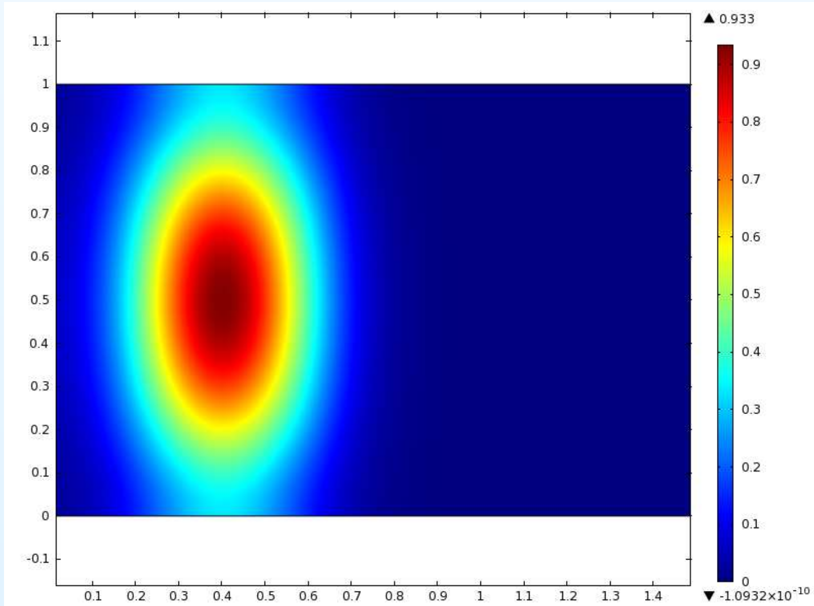
$\chi 1$



$\chi 2$

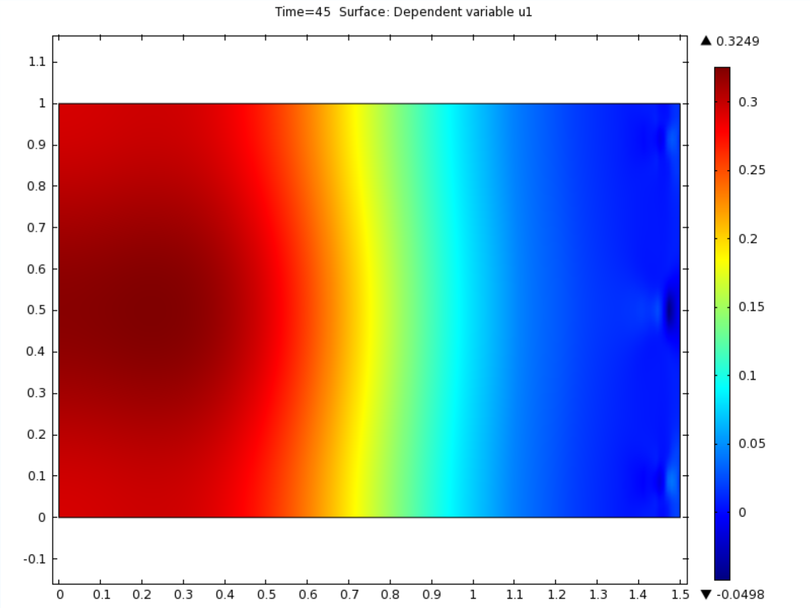


$\chi 3$

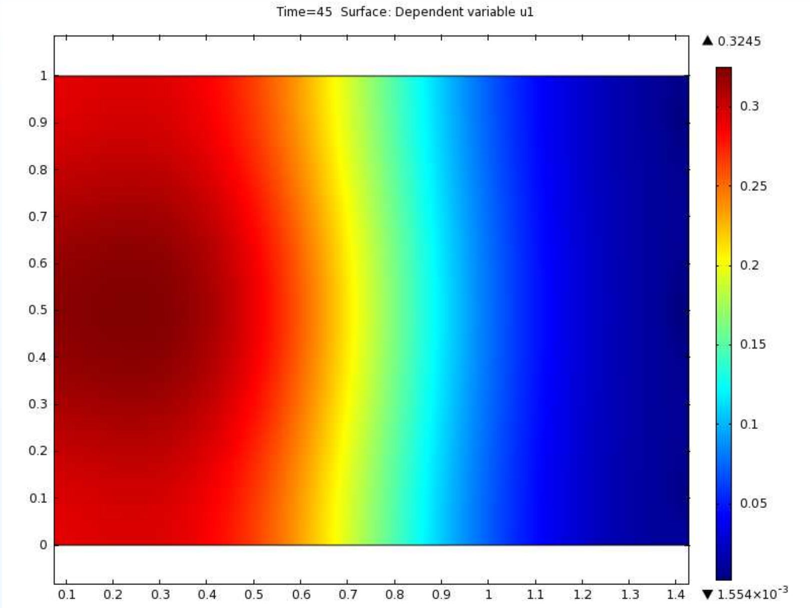


$\chi 4$

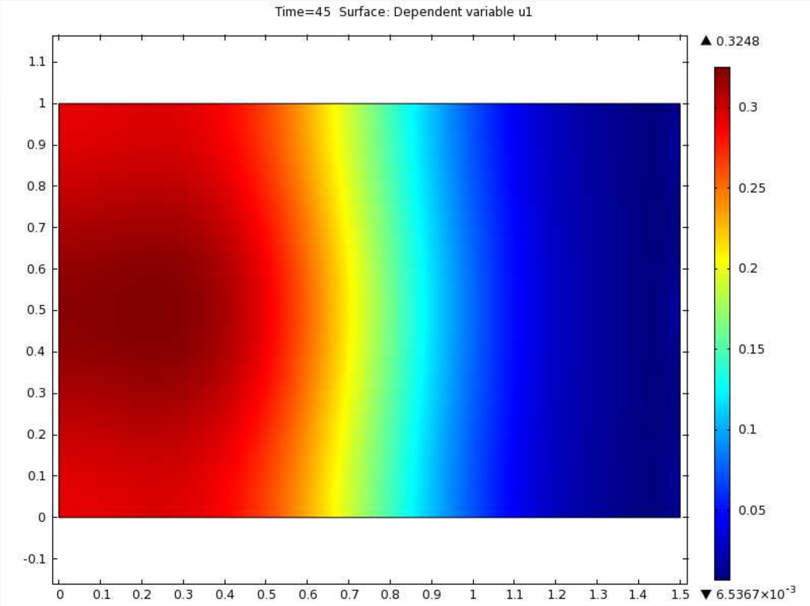
Solution $s(t, x)$ for M3ef, Parameter case 1, $T = 45$



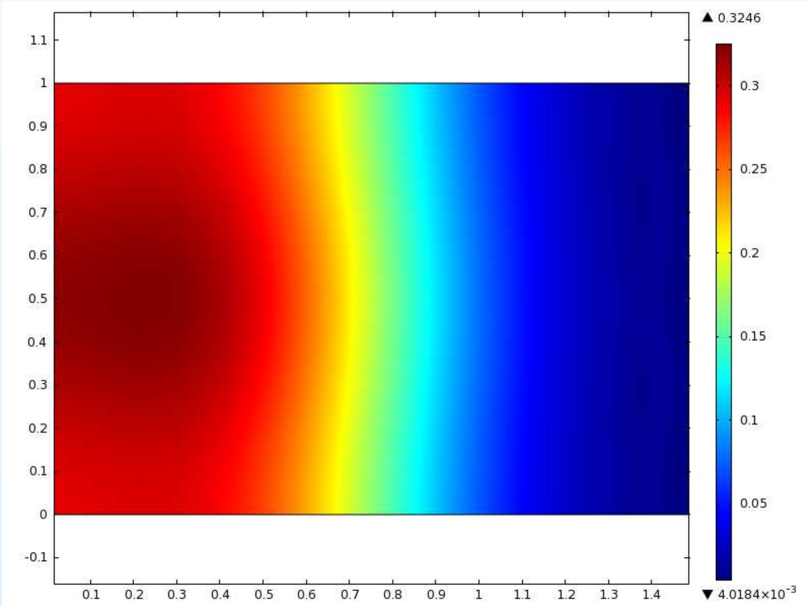
$\chi 1$



$\chi 2$

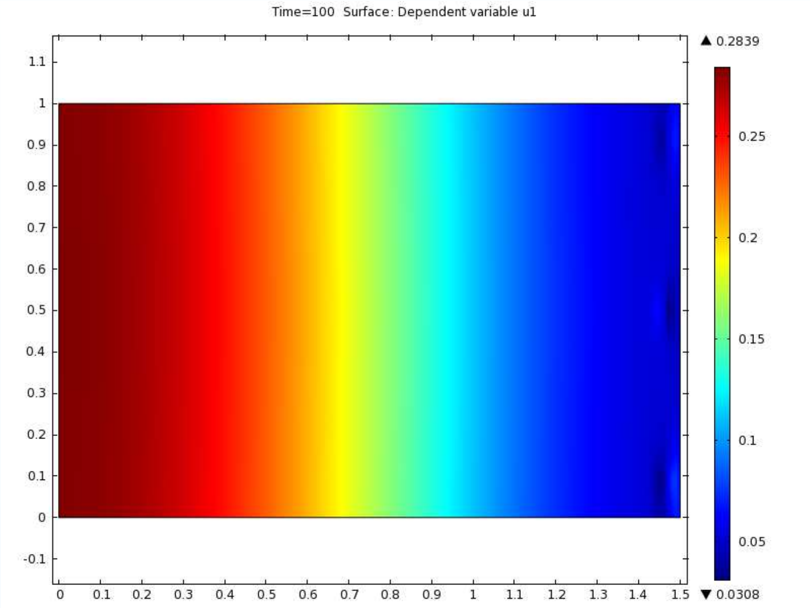


$\chi 3$

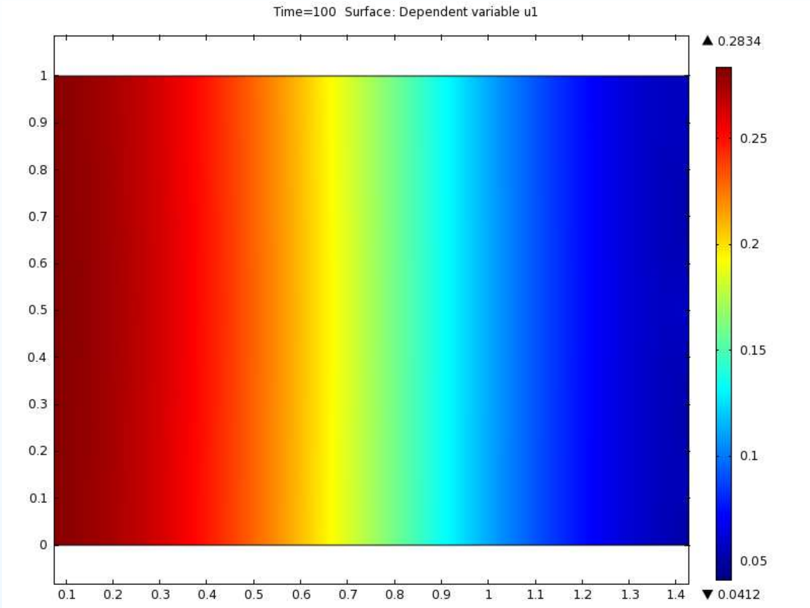


$\chi 4$

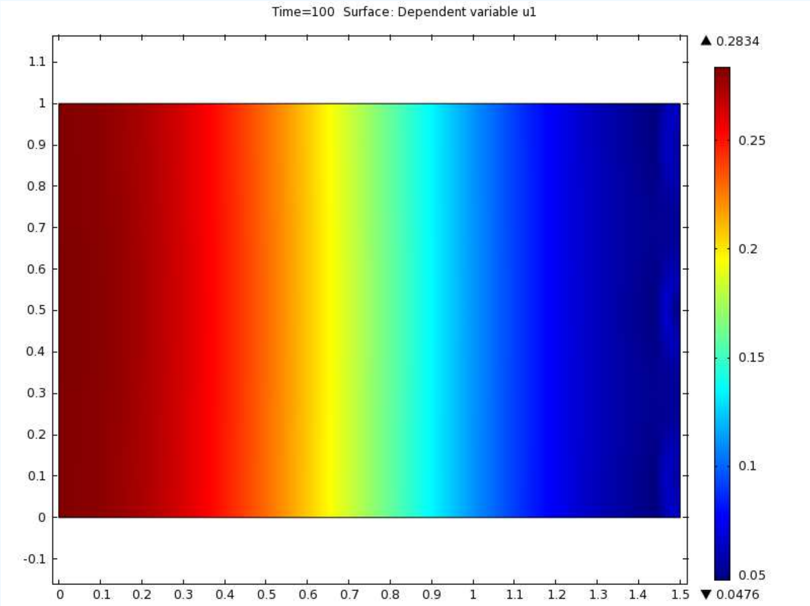
Solution $s(t,x)$ for M3ef, Parameter case 1, $T = 100$



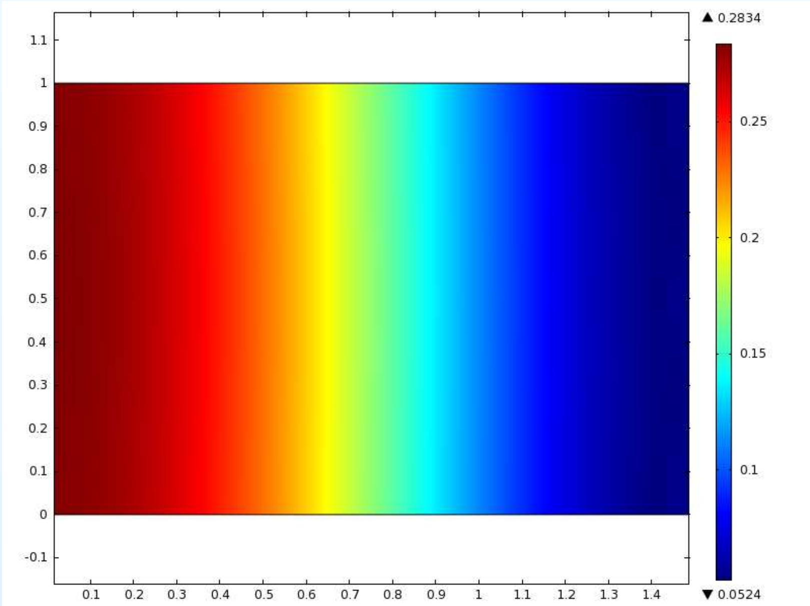
χ_1



χ_2

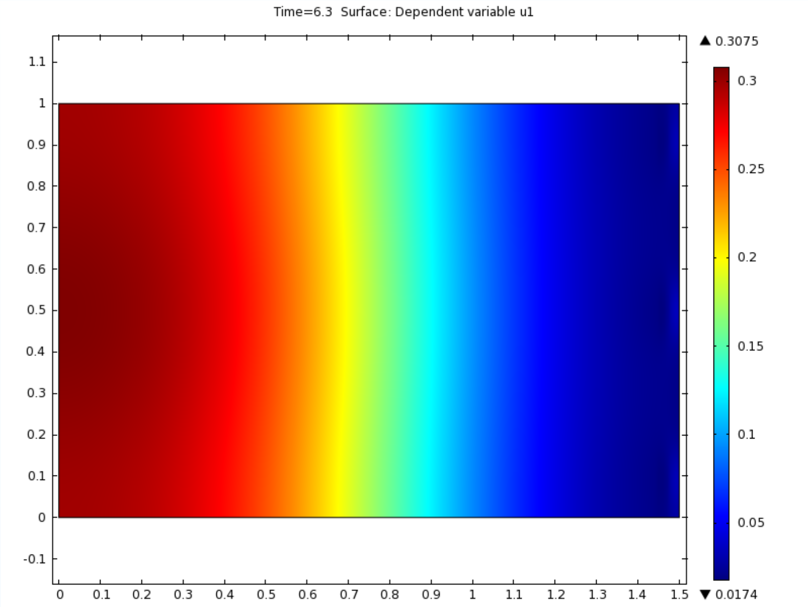


χ_3

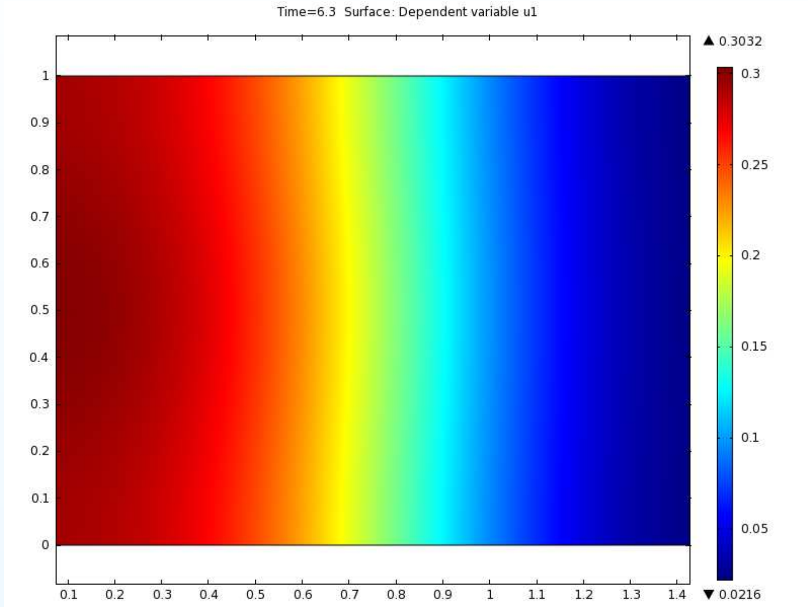


χ_4

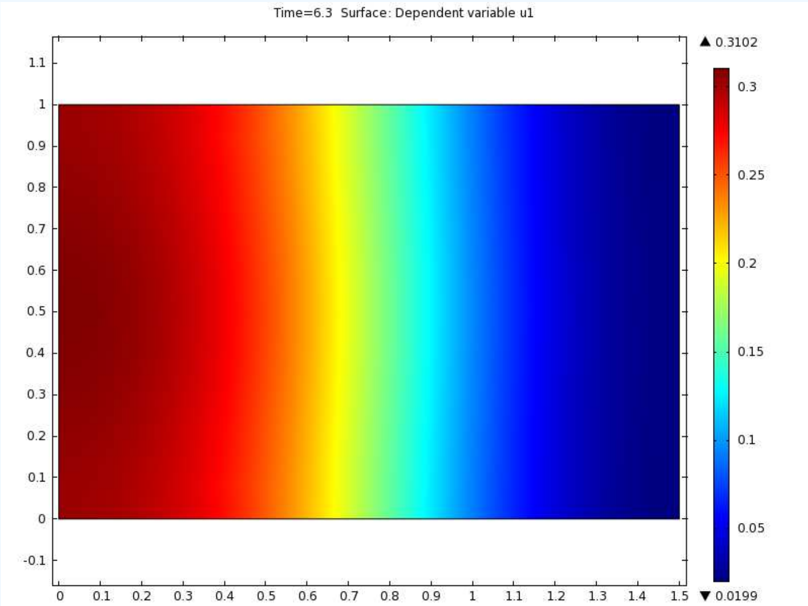
Solution $s(t,x)$ for M3ef, Parameter case 2, $T = 6.3$



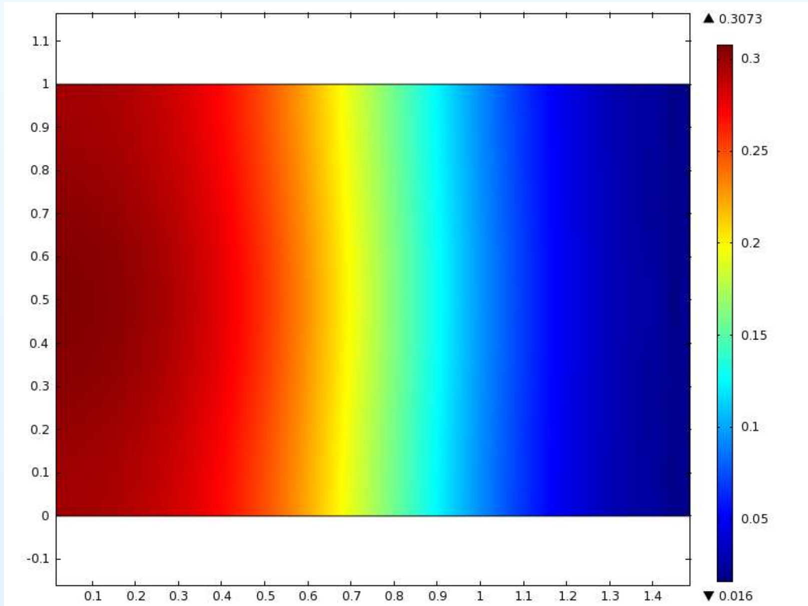
χ_1



χ_2

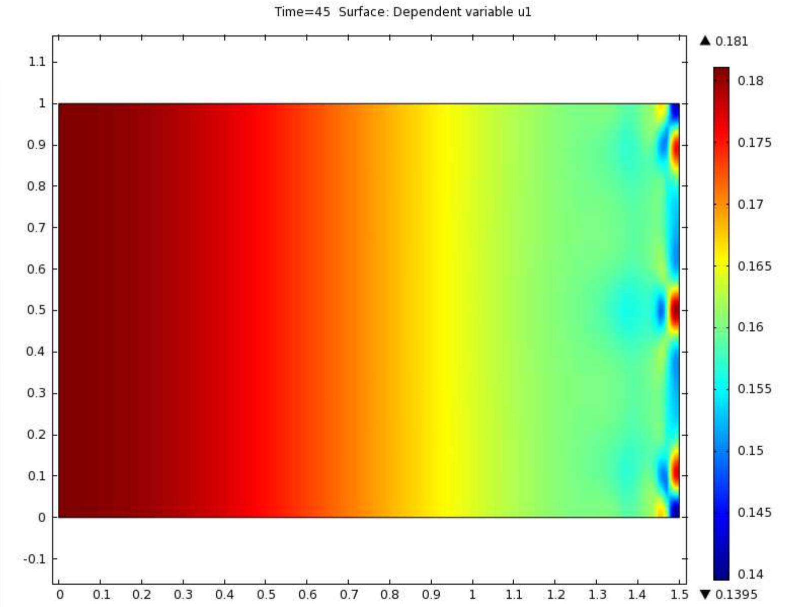


χ_3

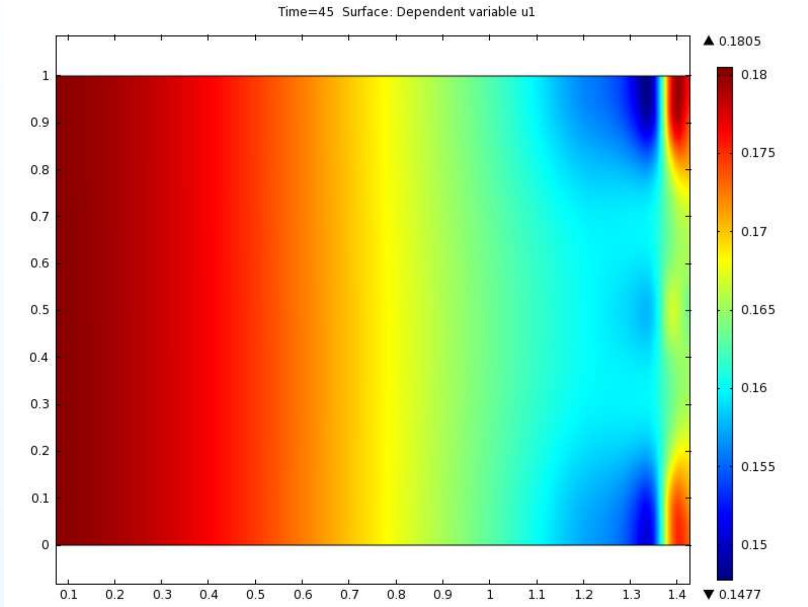


χ_4

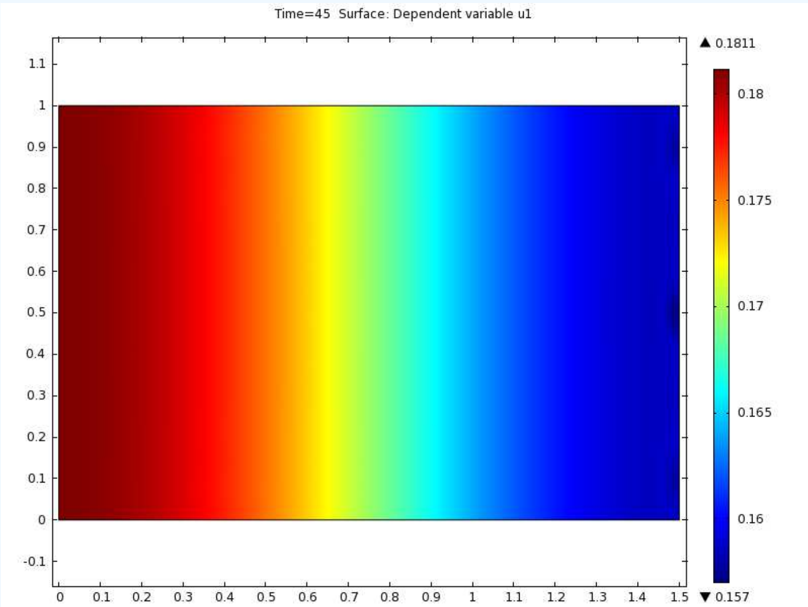
Solution $s(t,x)$ for M3ef, Parameter case 2, $T = 45$



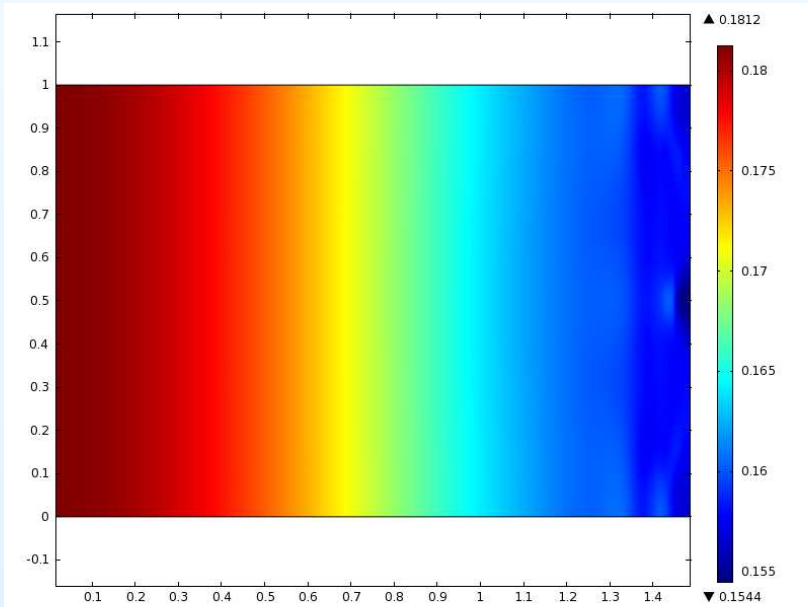
χ_1



χ_2

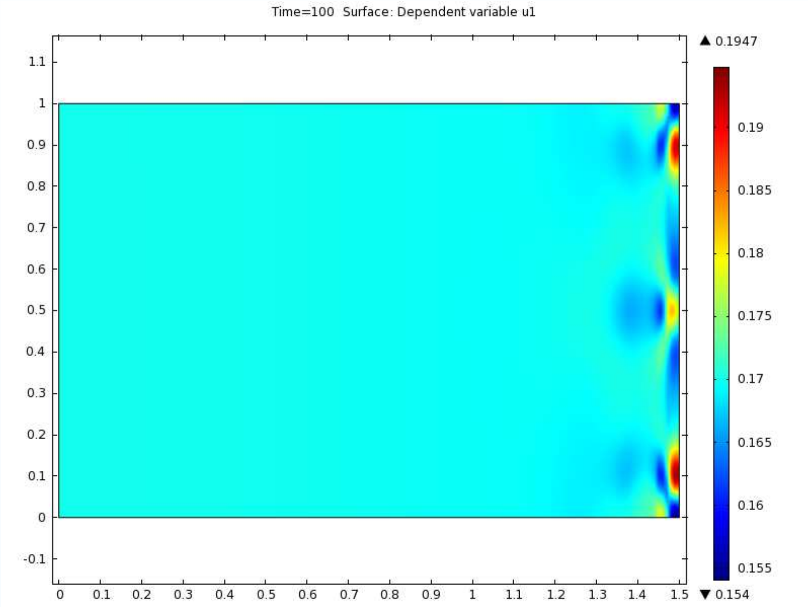


χ_3

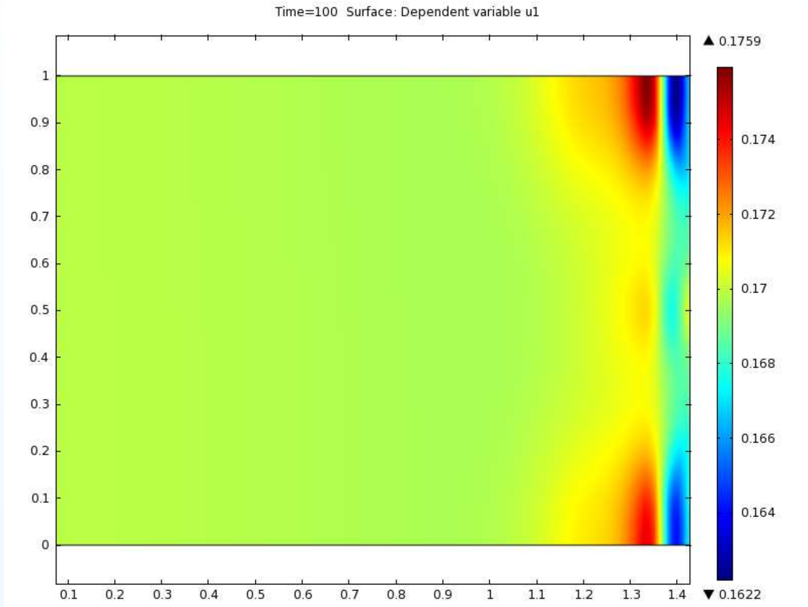


χ_4

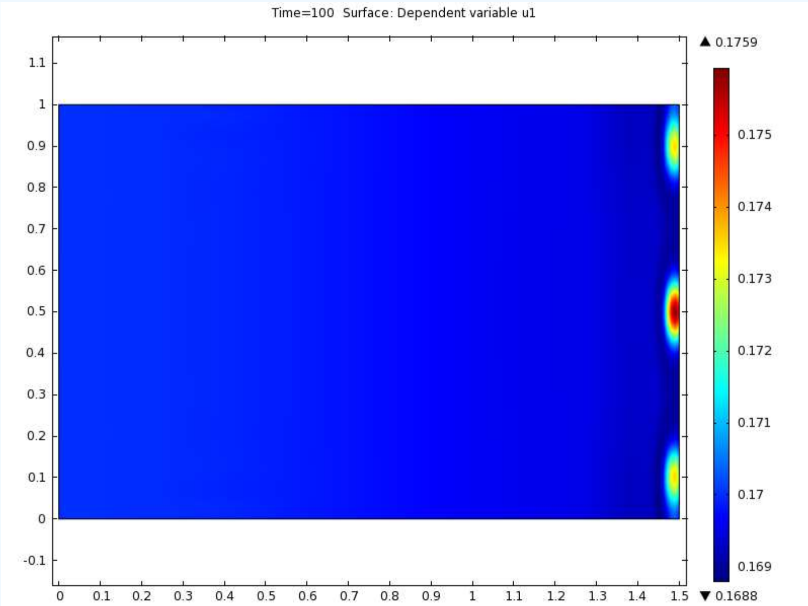
Solution $s(t, x)$ for M3ef, Parameter case 2, $T = 100$



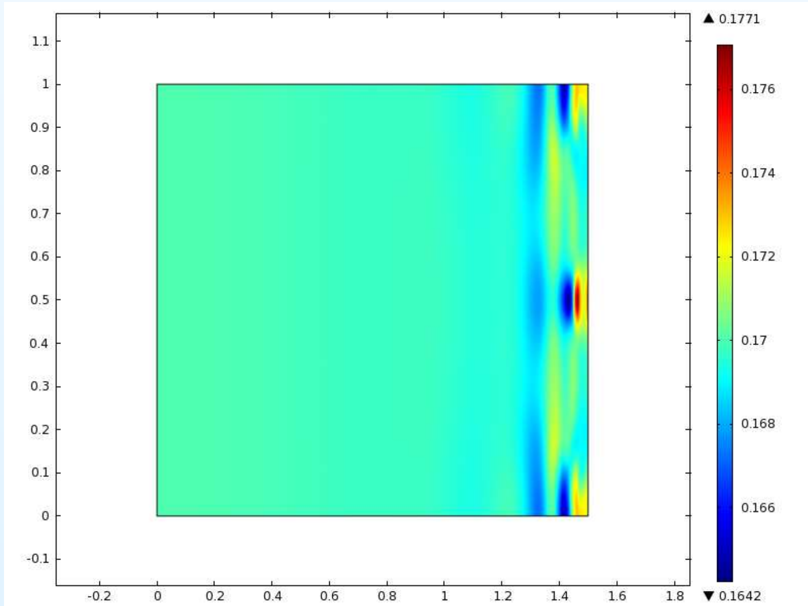
χ_1



χ_2



χ_3



χ_4

Remarks

- Observations:
  - Not always convergent
  - Negative values and oscillations for the solution
  - Initial model – the behaviour does not depend on the type of χ
  - Simplified model:
    - Parameter case 1: slight differences in the behaviour for χ_1, χ_3 (catch the initial distribution of a) compared to χ_2, χ_4
    - Parameter case 2: clear differnce in the behaviour for all χ
    - Negative values of the solution for $T < 6.3$
- Needed improvements in the direction of:
  - Extended model with appropirate space discretization
  - Robust discretization of nonlinear boundary conditions
  - Explicit efficient time integration

Second-order finite volume approximation

Initial system in conservation form

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

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

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

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

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

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

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

$$\frac{\partial \mathbf{f}}{\partial \mathbf{U}}: \quad \lambda_1^{\mathbf{f}}(\mathbf{U}) = \frac{1}{2}\left(\chi p - \sqrt{4\omega + (\chi p)^2}\right),\ \lambda_2^{\mathbf{f}}(\mathbf{U}) = \frac{1}{2}\left(\chi p + \sqrt{4\omega + (\chi p)^2}\right),\ \lambda_{3,4}^{\mathbf{f}}(\mathbf{U}) = 0,$$

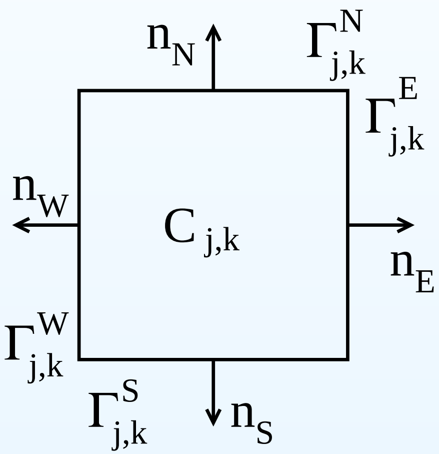
$$\frac{\partial \mathbf{g}}{\partial \mathbf{U}}: \quad \lambda_1^{\mathbf{g}}(\mathbf{U}) = \frac{1}{2}\left(\chi q - \sqrt{4\omega + (\chi q)^2}\right),\ \lambda_2^{\mathbf{g}}(\mathbf{U}) = \frac{1}{2}\left(\chi q + \sqrt{4\omega + (\chi q)^2}\right),\ \lambda_{3,4}^{\mathbf{g}}(\mathbf{U}) = 0.$$

Finite volume method

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

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

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



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

Semi-discrete scheme

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

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

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

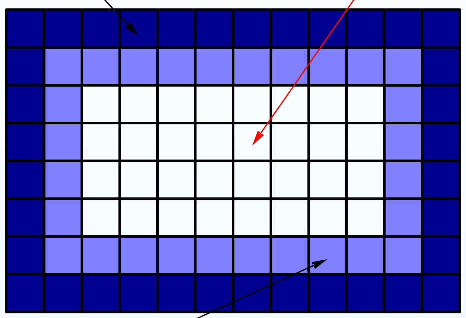
$$I^c_{j,k} + I^d_{j,k} = \int\limits_{\Gamma^E_{j,k}} (\mathbf{F}_c + \mathbf{F}_d) \cdot \mathbf{n}_E \, d\gamma + \int\limits_{\Gamma^W_{j,k}} (\mathbf{F}_c + \mathbf{F}_d) \cdot \mathbf{n}_W \, d\gamma$$

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

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 $j = 3, \dots N_x - 2, k = 3, \dots N_y - 2$

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



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

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

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

Semi-discrete scheme – interior cells (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 $\mathbf{U}^E_{j,k}$, $\mathbf{U}^W_{j+1,k}$, $\mathbf{U}^N_{j,k}$, $\mathbf{U}^S_{j,k+1}$

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

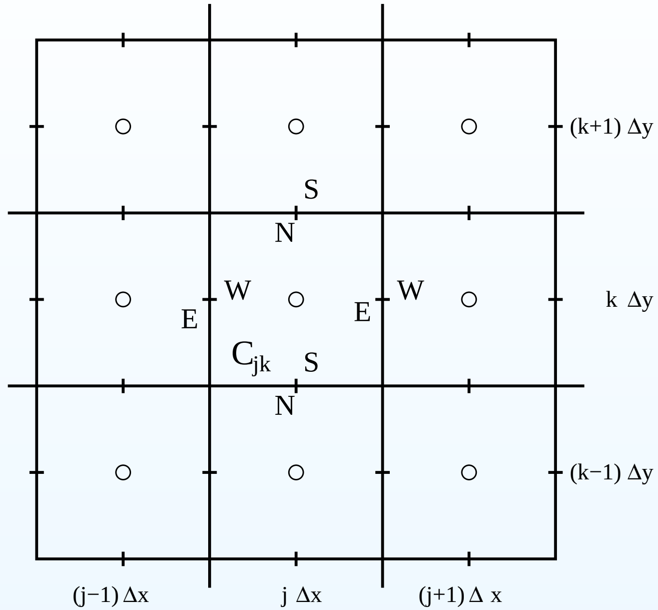
Semi-discrete scheme – interior cells (cont.)

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

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

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

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

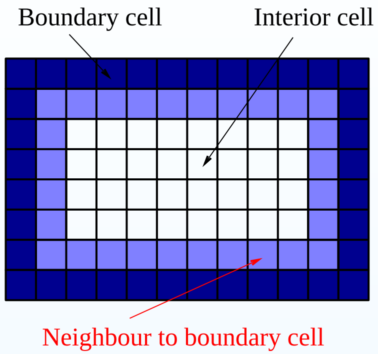


$$(\mathbf{U}_x)_{j,k} = \text{minmod}\left(\Theta\frac{\bar{\mathbf{U}}_{j,k} - \bar{\mathbf{U}}_{j-1,k}}{\Delta x}, \frac{\bar{\mathbf{U}}_{j+1,k} - \bar{\mathbf{U}}_{j-1,k}}{2\Delta x}, \Theta\frac{\bar{\mathbf{U}}_{j+1,k} - \bar{\mathbf{U}}_{j,k}}{\Delta x}\right)$$

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

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

Semi-discrete scheme – neighbour to boundary cells



$$j=2,\ j=N_x-1,\quad k=2,\ldots,N_y-1$$

$$j=2,\ldots,N_x-1,\quad k=2,\ k=N_y-1$$

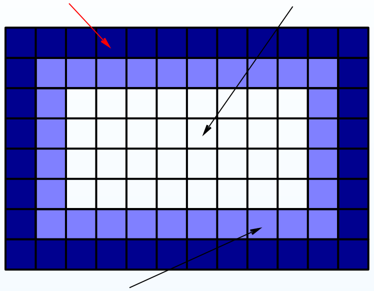
$$(\bar{\mathbf{U}}_{2,k})_t=-\frac{\mathbf{H}^x_{\frac{5}{2},k}-\mathbf{H}^x_{\frac{3}{2},k}}{\Delta x}-\frac{\mathbf{H}^y_{2,k+\frac{1}{2}}-\mathbf{H}^y_{2,k-\frac{1}{2}}}{\Delta y}+\frac{\mathbf{Q}^x_{\frac{5}{2},k}-\mathbf{Q}^x_{\frac{3}{2},k}}{\Delta x}+\frac{\mathbf{Q}^y_{2,k+\frac{1}{2}}-\mathbf{Q}^y_{2,k-\frac{1}{2}}}{\Delta y}+\bar{\mathbf{R}}_{2,k}$$

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

$$(\bar{\mathbf{U}}_{j,2})_t=-\frac{\mathbf{H}^x_{j+\frac{1}{2},2}-\mathbf{H}^x_{j-\frac{1}{2},2}}{\Delta x}-\frac{\mathbf{H}^y_{j,\frac{5}{2}}-\mathbf{H}^y_{j,\frac{3}{2}}}{\Delta y}+\frac{\mathbf{Q}^x_{j+\frac{1}{2},2}-\mathbf{Q}^x_{j-\frac{1}{2},2}}{\Delta x}+\frac{\mathbf{Q}^y_{j,\frac{5}{2}}-\mathbf{Q}^y_{j,\frac{3}{2}}}{\Delta y}+\bar{\mathbf{R}}_{j,2}$$

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

Semi-discrete scheme – boundary cells



$$\bar{\mathbf{h}}^l_{j,k} := \frac{1}{|\Gamma^l_{j,k}|}\int_{\Gamma^l_{j,k}} \mathbf{h}^l \, d\bar{\gamma}\,, \quad \begin{array}{l} l \in \{E, W, N, S\} \\ j = 1,\ j = N_x,\ k = 1, \ldots, N_y \\ j = 1, \ldots, N_x,\ k = 1,\ k = N_y \end{array}$$

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

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

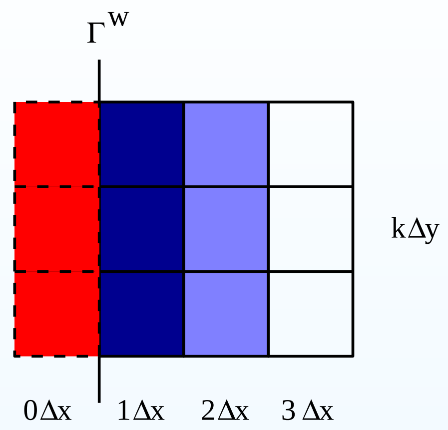
$$\left(\bar{\mathbf{U}}_{j,1}\right)_t = -\frac{\mathbf{H}^x_{j+\frac{1}{2},1} - \mathbf{H}^x_{j-\frac{1}{2},1}}{\Delta x} + \frac{\mathbf{Q}^y_{j,\frac{3}{2}} - \mathbf{H}^y_{j,\frac{3}{2}} - \bar{\mathbf{h}}^S_{j,1}}{\Delta y} + \frac{\mathbf{Q}^x_{j+\frac{1}{2},1} - \mathbf{Q}^x_{j-\frac{1}{2},1}}{\Delta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

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

Boundary cells and neighbours – case Γ^W

$$\bar{\mathbf{h}}^W_{1,k} := \frac{1}{|\Gamma^W_{1,k}|} \int_{\Gamma^W_{1,k}} \mathbf{h}^W \, d\bar{\gamma} = \mathbf{h}^W(\bar{\mathbf{U}}_{\frac{1}{2},k}, b_{\frac{1}{2},k}, x_{\frac{1}{2}}, y_k, t)$$

$$k = 1, \dots, N_y$$



$$\mathbf{H}^x_{\frac{3}{2},k} = \frac{a^+_{\frac{3}{2},k}\mathbf{f}(\mathbf{U}^E_{1,k}) - a^-_{\frac{3}{2},k}\mathbf{f}(\mathbf{U}^W_{2,k})}{a^+_{\frac{3}{2},k} - a^-_{\frac{3}{2},k}} + \frac{a^+_{\frac{3}{2},k}\, a^-_{\frac{3}{2},k}}{a^+_{\frac{3}{2},k} - a^-_{\frac{3}{2},k}} \left[\mathbf{U}^W_{2,k} - \mathbf{U}^E_{1,k}\right]$$

$$a^+_{\frac{3}{2},k} = \max(\lambda^{\mathbf{f}}_2(\mathbf{U}^E_{1,k}), \lambda^{\mathbf{f}}_2(\mathbf{U}^W_{2,k}), 0), \quad a^-_{\frac{3}{2},k} = \min(\lambda^{\mathbf{f}}_1(\mathbf{U}^E_{1,k}), \lambda^{\mathbf{f}}_1(\mathbf{U}^W_{2,k}), 0)$$

$$\mathbf{U}^E_{1,k} = \bar{\mathbf{U}}_{1,k} + \frac{\Delta x}{2}(\mathbf{U}_x)_{1,k}, \quad \mathbf{U}^W_{2,k} = \bar{\mathbf{U}}_{2,k} - \frac{\Delta x}{2}(\mathbf{U}_x)_{2,k}$$

$$(\mathbf{U}_x)_{1,k} = \text{minmod}\left(\Theta\frac{\bar{\mathbf{U}}_{1,k} - \bar{\mathbf{U}}_{0,k}}{\Delta x}, \frac{\bar{\mathbf{U}}_{2,k} - \bar{\mathbf{U}}_{0,k}}{2\Delta x}, \Theta\frac{\bar{\mathbf{U}}_{2,k} - \bar{\mathbf{U}}_{1,k}}{\Delta x}\right)$$

$$(\mathbf{U}_x)_{2,k} = \text{minmod}\left(\Theta\frac{\bar{\mathbf{U}}_{2,k} - \bar{\mathbf{U}}_{1,k}}{\Delta x}, \frac{\bar{\mathbf{U}}_{3,k} - \bar{\mathbf{U}}_{1,k}}{2\Delta x}, \Theta\frac{\bar{\mathbf{U}}_{3,k} - \bar{\mathbf{U}}_{2,k}}{\Delta x}\right)$$

Evaluation of $\bar{\mathrm{U}}_{0,k}$ and $\bar{\mathrm{U}}_{\frac{1}{2},k}$, $\mathbf{x} \in \Gamma^W \in \Gamma_1$, $\chi(a) = \chi a$

$$-(\varepsilon\partial_\nu U^1 - U^1\chi'(U^2)\partial_\nu U^2) = c_1 U^1 - c_2 b \qquad \varepsilon\frac{\partial U^1}{\partial x} + U^1\chi\frac{-\partial U^2}{\partial x} = c_1 U^1 - c_2 b\,,$$

$$D_a\partial_\nu U^i = B_i(\beta(t,b)c(\mathbf{x})), i = 2,3,4 \quad \Rightarrow \quad -\frac{\partial U^i}{\partial x} = \frac{1}{D_a}B_i(\beta(t,b)c(\mathbf{x}))$$

$$\left.\frac{\partial \mathbf{U}^1}{\partial x}\right|_{(\frac{1}{2},k)} + \mathbf{U}^1_{\frac{1}{2},k}\,\frac{1}{\varepsilon}\left.\left(\frac{\chi\beta(t,b)c(\mathbf{x})}{D_a} - c_1\right)\right|_{(\frac{1}{2},k)} = -\left.\frac{c_2}{\varepsilon}b\right|_{(\frac{1}{2},k)}$$

$$\left.\frac{\partial \mathbf{U}^i}{\partial x}\right|_{(\frac{1}{2},k)} = -\left.\frac{1}{D_a}B_i(\beta(t,b)c(\mathbf{x}))\right|_{(\frac{1}{2},k)},\; i = 2,3,4$$

$$\left.\frac{\partial \mathbf{U}^i}{\partial x}\right|_{(\frac{1}{2},k)} = \frac{\mathbf{U}^i_{1,k} - \mathbf{U}^i_{0,k}}{\Delta x} + \mathcal{O}(\Delta x^2),\; \mathbf{U}^1_{\frac{1}{2},k} = \frac{3\mathbf{U}^1_{0,k} + 6\mathbf{U}^1_{1,k} - \mathbf{U}^1_{2,k}}{8} + \mathcal{O}(\Delta x^2)$$

$$\frac{\mathbf{U}^1_{1,k} - \mathbf{U}^1_{0,k}}{\Delta x} + \frac{3\mathbf{U}^1_{0,k} + 6\mathbf{U}^1_{1,k} - \mathbf{U}^1_{2,k}}{8}\,\frac{1}{\varepsilon}\left.\left(\frac{\chi\beta(t,b)c(\mathbf{x})}{D_a} - c_1\right)\right|_{(\frac{1}{2},k)} = -\left.\frac{c_2}{\varepsilon}b\right|_{(\frac{1}{2},k)}$$

$$\frac{\mathbf{U}^i_{1,k} - \mathbf{U}^i_{0,k}}{\Delta x} = -\left.\frac{1}{D_a}B_i(\beta(t,b)c(\mathbf{x}))\right|_{(\frac{1}{2},k)},\; i = 2,3,4$$

Time integration

- Semi-discrete system: $\frac{d}{dt}\bar{\mathbf{U}}(t) = F(\bar{\mathbf{U}}, t)$
- Implicit schemes
  - high computational costs
  - in some cases require time step restrictions
- Explicit Euler/ IMEX scheme (A. Chertock, A. Kurganov, 2008)
  - firts order accuracy
  - integration with the smallest time-step:

$$\Delta t_{EE} \le \min\left(\frac{\Delta x}{8a}, \frac{\Delta y}{8b}, c\right), \quad \Delta t_{IMEX} \le \min\left(\frac{\Delta x}{4a}, \frac{\Delta y}{4b}\right)$$

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

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

- 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
  - Numerical study of the ranges for parameters where the model works or fails
  - Sensitivity analysis and parameter estimation
  - Parallel implementation of the numerical scheme

Thank you for your attention!