Simulation of abnormal colonic cell dynamics using a multiscale method

G. Romanazzi[1] I.N. Figueiredo[1] C. Leal[1]

[1]CMUC, Department of Mathematics, University of Coimbra, Portugal

UTAustin — Portugal
Workshop on Modeling and Simulation of Physiological Systems

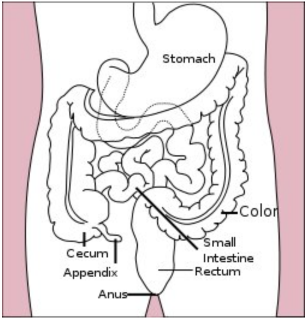
UT Austin | Portugal
International Collaboratory for Emerging Technologies, CoLab

cmuc
Centre for Mathematics
University of Coimbra

Outline

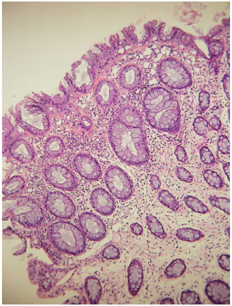
Colorectal Cancer

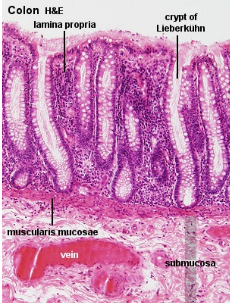
Malignant tumor in the large intestine (colon) or in the rectum (end of the colon)



Crypts

Colorectal Cancer is initiated in the **Crypts** that line the colon as a consequence of genetic mutations in normal cells.



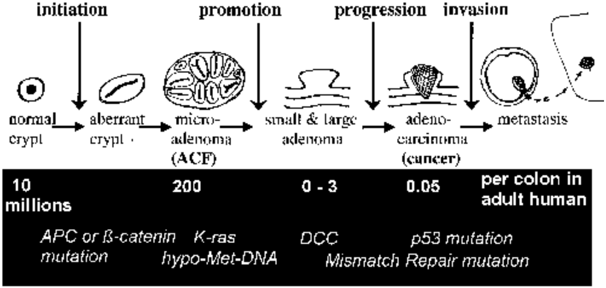


Images Source (left and right): UWA Blue Histology. Copyright Lutz Slomianka 1998-2009;

(centre): Faculty of Medicine, University of Coimbra, and HUC, Hospitais da Universidade de Coimbra

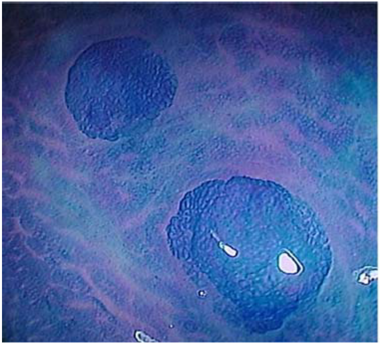
Aberrant Crypt Foci (ACF) and Colorectal Polypus

- The crypts, due to some mutation, can have dysplastic cells that deform the crypt (Aberrant Crypt). When this deformation appears in a set of adjacent crypts we have an Aberrant Crypt Foci (ACF).



Aberrant Crypt Foci (ACF) and Colorectal Polypus

- ACF are precursors in the formation of colorectal cancer



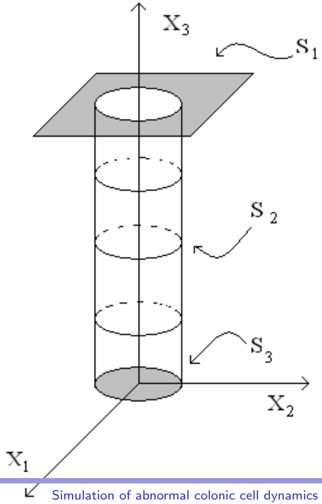
Images Source : Int J Colorectal Dis, #Springer-Verlag 2008

Motivation

- Model and Simulate the dynamics of a set of abnormal cells (that interact with normal cells) inside the colon using Multiscale PDE Equations.

Model of the crypt

- The colon is defined by a periodic distribution of crypts
- A crypt $S = S_1 \cup S_2 \cup S_3$ has small dimensions, of order of ϵ (measurable in μm),



Medical Information

Two types of cells are considered

- Normal Cells, density $N(t)$
- Abnormal Cells, density $C(t)$
- $N(t) + C(t) = 1$ (overall density hypothesis)
- Inside the crypt, $S_2 \cup S_3$
  - Strong cellular activity with reproduction
  - Mitotic activity of normal cells causes a pressure-driven passive movement p
  - Diffusion by contact
- Outside the crypt, S_1
  - Apoptotic(died) normal cells are present, with no mitotic activity
  - Diffusion of abnormal cells
  - No pressure-driven movement, $p = 0$

Continuum Differential Model

- In $S_2 \cup S_3 \times (0, T)$ (inside each crypt)

$$\begin{cases} \dfrac{\partial N}{\partial t} - \nabla \cdot (\nabla p N) = \nabla \cdot (D_1 \nabla N) + \alpha_1 N - \beta_1 N(1-N) \\ \dfrac{\partial C}{\partial t} - \nabla \cdot (\nabla p C) = \nabla \cdot (D_2 \nabla C) + \beta_1 N(1-N) \end{cases} \tag{1}$$

  - p pressure
  - D_1, D_2 diffusion coefficients
  - α_1,β_1 rate of proliferation and mutation of normal cells

- In $S_1 \times (0, T)$ (intercryptal region)

$$\frac{\partial C}{\partial t} = \nabla \cdot (D_2^* \nabla C) + \beta_2 N(1-N) \tag{2}$$

Continuum Differential Model in $S \times (0, T)$

Summing the two equations of (1), and using $N = 1 - C$ we have in $S \times (0, T)$, with $S = S_1 \cup S_2 \cup S_3$

$$\begin{cases} \dfrac{\partial C}{\partial t} - \nabla \cdot (\nabla p C) = \nabla \cdot [D^S \nabla C] + \beta^S C(1 - C) & \text{in } S \times (0, T) \\ -\Delta p = \nabla \cdot (E^S \nabla C) + \alpha_1^S (1 - C) & \text{in } S \times (0, T) \end{cases}$$

with

$$D^S = \begin{cases} D_2 & \text{in} \quad S_2 \cup S_3 \\ D_2^* & \text{in} \quad S_1 \end{cases} , \qquad \beta^S = \begin{cases} \beta_1 & \text{in} \quad S_2 \cup S_3 \\ \beta_2 & \text{in} \quad S_1 \end{cases}$$

$$E^S = \begin{cases} D_2 - D_1 & \text{in} \quad S_2 \cup S_3 \\ 0 & \text{in} \quad S_1 \end{cases}$$

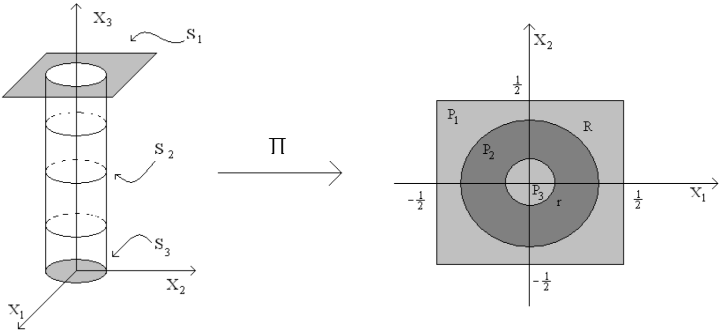
$$\alpha_1^S = \begin{cases} \alpha_1 & \text{in} \quad S_2 \cup S_3 \\ 0 & \text{in} \quad S_1 \end{cases}$$

Crypt Trasformation from 3-D to 2-D

Bijective function Π

$$\Pi: \; S \subset \mathbb{R}^3 \rightarrow \; P := \left[-\frac{1}{2}, \frac{1}{2}\right] \times \left[-\frac{1}{2}, \frac{1}{2}\right] \subset \mathbb{R}^2$$

where $P = P_1 \cup P_2 \cup P_3$, such that $\Pi(S_i) = P_i$ with $i = 1, 2, 3$



Crypt Trasformation from 3-D to 2-D

- With new variables in P, $(X_1, X_2) = \Pi(x_1, x_2, x_3)$

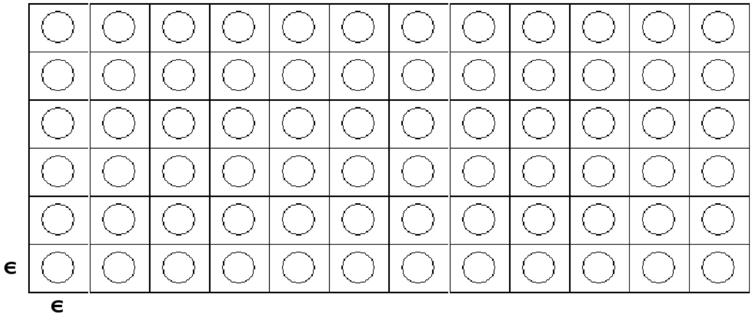
The problem in $P \times (0, T)$ is:
Determine $p^*, C^* : P \rightarrow \mathbb{R}$ such that

$$\begin{cases} \frac{\partial C^*}{\partial t} - \mathcal{A}^*_{ij} \frac{\partial}{\partial X_i}(C^* \frac{\partial p^*}{\partial X_j}) = \mathcal{A}^*_{ij} \frac{\partial}{\partial X_i}(D^* \frac{\partial C^*}{\partial X_j}) + \beta^* C^*(1 - C^*), \\ \\ -\mathcal{A}^*_{ij} \frac{\partial^2 p^*}{\partial X_i \partial X_j} = \mathcal{A}^*_{ij} \frac{\partial}{\partial X_i}(E^* \frac{\partial C^*}{\partial X_j}) + \alpha^*_1(1 - C^*) \end{cases} \tag{3}$$

where $D^* = D^S \circ \Pi^{-1}$, $\beta^* = \beta^S \circ \Pi^{-1}$, $E^* = E^S \circ \Pi^{-1}$, $\alpha^*_1 = \alpha^S_1 \circ \Pi^{-1}$.

Colon, Periodic structure in $\mathbb{R}^2$

- The colon is considered as a rectangle Ω with a crypt periodic structure ϵP,



Colon, Periodic structure in $\mathbb{R}^2$

- We rewrite the problem in all Ω extending the value of the P-parameters A^*_{ij} , D^*, E^*, α^*_1, β^* periodically in Ω,
- $$A^{\epsilon}_{ij}(X) = A_{ij}\left(\frac{X}{\epsilon}\right), \quad \forall X = (X_1, X_2) \in \Omega$$

  where

  $$A_{ij} = \begin{cases} \mathcal{A}^*_{ij}, \text{ in } P \\ \\ \text{by periodicity elsewhere} \end{cases}$$

Multiscale Problem

Determine C^ϵ, p^ϵ real functions in $\Omega \times (0, T)$ such that

$$\begin{cases} \dfrac{\partial C^\epsilon}{\partial t} - A^\epsilon_{ij}\dfrac{\partial}{\partial X_i}(C^\epsilon \dfrac{\partial p^\epsilon}{\partial X_j}) = A^\epsilon_{ij}\dfrac{\partial}{\partial X_i}(D^\epsilon \dfrac{\partial C^\epsilon}{\partial X_j}) + \beta^\epsilon C^\epsilon(1 - C^\epsilon) \\ \\ -A^\epsilon_{ij}\dfrac{\partial^2 p^\epsilon}{\partial X_i \partial X_j} = A^\epsilon_{ij}\dfrac{\partial}{\partial X_i}(E^\epsilon \dfrac{\partial C^\epsilon}{\partial X_j}) + \alpha^\epsilon_1(1 - C^\epsilon) \end{cases} \tag{4}$$

with a given initial condition C^ϵ_0 in Ω
and boundary conditions

$$p^\epsilon = 0, \quad C^\epsilon = 0, \text{ in } \partial\Omega \times (0, T)$$

Heterogeneous Multiscale Methods (HMM)

- HMM's have a cost that is independent of the size of micro-scale ϵ
- No need to compute a priori tensors of type a^0, on the opposite with respect the Homogenized problems
- Multiscale tensors a^ϵ are evaluated only in (small) sampling domains.
- Results of convergence are known for elliptic uniform problems in divergence form

HMM, Elliptic problem

Consider a second order elliptic equation

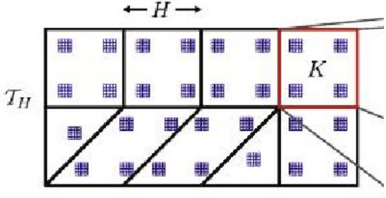
$$-\nabla \cdot (a^\epsilon \nabla u^\epsilon) = f$$
$$u^\epsilon = 0 \text{ in } \partial\Omega$$

$a^\epsilon(x)$ is an high oscillating parameter

- periodic with period ϵP
- symmetric, uniformly elliptic and bounded.

HMM, Discretization

- Classical Galerkin Methods (FEM, Finite Element Methods) need a full space discretization in Ω with stepsize $h < \epsilon$ in order to catch the oscillations of the multiscale parameter a^{ϵ}
- HMM-FEM use a micro scale discretization only around the **quadrature points**,
  used to approximate the integrals appearing in the Macro-Discretization of the Variational problem



(a) macro discretization with sampling domains (microproblems)

HMM-FEM, Macro Discretization

- H size of the Macro Discretization, $H >> \epsilon$,
- $\mathcal{T}_H$ partition of Ω with squares of edge H
- Macro Finite Element Space

$$V^H = \left\{ v^H \in H_0^1(\Omega) \mid u^H|_K \text{ is a (bi)linear polynomial } \forall K \in \mathcal{T}_H \right\}$$

- **Macro-scale** Problem
  Find u^H in V^H such that $\forall v^H \in V^H$

$$\int_\Omega a^\epsilon \cdot \nabla u^H \nabla v^H dx = \int_\Omega f v^H dx$$

that is

$$\sum_{K \in \mathcal{T}_H} \int_K a^\epsilon \cdot \nabla u^H \nabla v^H dx = \int_\Omega f v^H dx$$

HMM-FEM, Quadrature formulae for the Macro-Problem

- Let $K_{\delta_l} = x_{K_{\delta_l}} + \delta I$ be the square of edge $\delta \geq \epsilon$ with barycenter the quadrature point $x_{K_{\delta_l}}$,
- For each q^H, the following approximation is used

$$\int_K q^H(x)dx \approx \sum_{l \in \mathcal{L}} \omega_{K_l} q^H(x_{K_{\delta_l}}) \approx \sum_{l \in \mathcal{L}} \frac{\omega_{K_l}}{|K_{\delta_l}|} \int_{K_{\delta_l}} q^h(x)dx,$$

where q^h, $h < \epsilon << H$, are appropriate **micro-scale** functions defined in K_{δ_l}.

HMM-FEM, Microfunctions v^h

Macro-scale Problem becomes: Determine u^H such that $\forall v^H \in V^H$

$$\sum_{K \in \mathcal{T}_H} \sum_{l \in \mathcal{L}} \frac{\omega_{K_l}}{\|K_{\delta_l}\|} \int_{K_{\delta_l}} a^{\epsilon}(x) \nabla u^h \nabla v^h dx = \int_{\Omega} f v^H dx \qquad (5)$$

where microfunctions $u^h, \; v^h : K_{\delta_l} \to \mathbb{R}$ satisfy

- $$v^h - v^H|_{K_{\delta_l}} \in S = S(K_{\delta_l}, \mathcal{T}_h) \qquad (6)$$

  with
  $$S := \{z : K_{\delta_l} \to \mathbb{R} : \forall T \in \mathcal{T}_h \; z|_T \text{ is linear, } z \text{ is periodic in } K_{\delta_l} \text{ and } \int_{K_{\delta_l}} z dx = 0\}$$

- $$\int_{K_{\delta_l}} a^{\epsilon}(x) \nabla v^h \nabla z^h dx = 0 \quad \forall z^h \in S \qquad (7)$$

Microfunctions v^h, Dual problem

- Find v^h that satisfies

$$\int_{K_{\delta_l}} a^\epsilon(x)\nabla v^h \nabla z^h dx = 0 \quad \forall z^h \in S$$

implies to determine v^h such that $F'_\epsilon(v^h)(z^h) = 0 \quad \forall z^h \in S$ where

$$F_\epsilon(v^h) := \frac{1}{2}A^\epsilon(v^h, v^h) := \frac{1}{2}\int a^\epsilon \nabla v^h \nabla v^h dx$$

$F'_\epsilon(v^h)$ is the Frechet derivative of the functional F_ϵ in v^h.

- Since $A^\epsilon(\cdot,\cdot)$ is an operator in $S \times S$ bilinear and symmetric this problem is equivalent to the minimum problem

$$w = argmin_{\left\{ v^h, v^h - v^H|_{K_{\delta_l}} \in S \right\}} F_\epsilon(v^h),$$

that can be solved using the technique of Lagrange multipliers

HMM, Integrals in the Micro-Problems

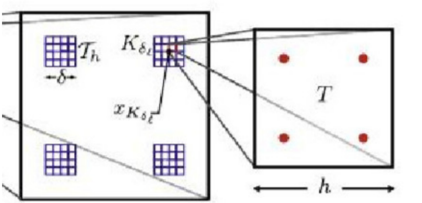
The **micro-scale** integrals in

$$\sum_{K\in\mathcal{T}_H}\sum_{l\in\mathcal{L}}\frac{\omega_{K_l}}{\|K_{\delta_l}\|}\int_{K_{\delta_l}} a^{\epsilon}(x)\nabla u^h\nabla v^h dx = \int_{\Omega} f v^H dx$$

are approximated using

$$\int_{K_{\delta_l}} q(x) \approx \sum_{T\in\mathcal{T}_h}\sum_{z\in\mathcal{L}}\omega_{z,T}\, q(x_{z,T})$$

that is same quadrature formula for the Macro-scale elements



(b) microproblems (c) example of quadrature for a microproblem

HMM-FE, Computation and Convergence

- The number of computations not depends on the ϵ-size
- **Convergence**

$$\|u^{\epsilon} - u^{H,\epsilon}\| \leq C(H + \sqrt{\epsilon} + \frac{h}{\epsilon})$$

using the semi-norm in H^1, $\|u\| = \left(\sum_{K \in \mathcal{T}_H} \|\nabla u\|^2_{L^2(K)}\right)^{\frac{1}{2}}$

HMM, Coupled multiscale problem

$$-A^{\epsilon}_{ij}\frac{\partial^2 p^{\epsilon}}{\partial X_i \partial X_j} = A^{\epsilon}_{ij}\frac{\partial}{\partial X_i}(E^{\epsilon}\frac{\partial C^{\epsilon}}{\partial X_j}) + \alpha^{\epsilon}_1(1 - C^{\epsilon}), \quad \text{in} \quad \Omega\times]0, T[$$

can be discretized in V^H with basis $\{\phi_m\}_m$.
The variational problem becomes an algebraic problem in p^H

$$(F_1 + G_1)p^H = -(F_{E^{\epsilon}} + G_{E^{\epsilon}})C^H + Mass(\alpha_1)(1 - C^H) \qquad (8)$$

with

$$F_{a^{\epsilon}} = \left(\int_{\Omega} a^{\epsilon}(x)\phi_k \sum_{i}^{2} \frac{\partial A^{\epsilon}_i}{\partial x_i}\nabla\phi_l dx\right)_{k,l}$$

We use an algorithm where C^H is solved before than p^H. The second member of (8) is then known.

HMM, Rewrite Multiscale problem

Unfortunately terms $F_{a^\epsilon}(\cdot,\cdot)$ are not symmetric

- We add an anti-symmetric operator

$$F^t_{a^\epsilon} := \left(\int_\Omega a^\epsilon(x) \phi_l \sum_i^2 \frac{\partial A_i^\epsilon}{\partial x_i} \nabla \phi_k dx \right)_{k,l}$$

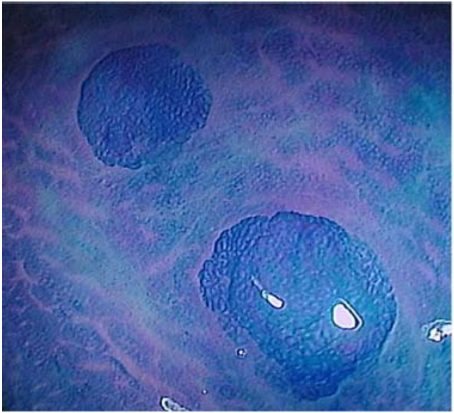
  with $a^\epsilon = 1$, the problem is now

$$(F_1 + F_1^t + G_1) p^H = -(F_{E^\epsilon} + G_{E^\epsilon}) C^H + Mass(\alpha_1)(1 - C^H) + F_1^t p^H_{old}$$

  the first member has now a symmetric, bilinear operator.

- The dual problem can be solved to approximate each integral
- We added $F_1^t p^H_{old}$ in the second member, instead of $F_1^t p^H$, in order to have a known right hand side.

Initial Condition



Numerical results

Parameters in the Numerical Simulations

$$\Omega = [-2, 2] \times [-1, 1]$$
$$\delta = \epsilon = 5e - 05$$

$$H = 0.125 \qquad (Macroscale\ step - size)$$

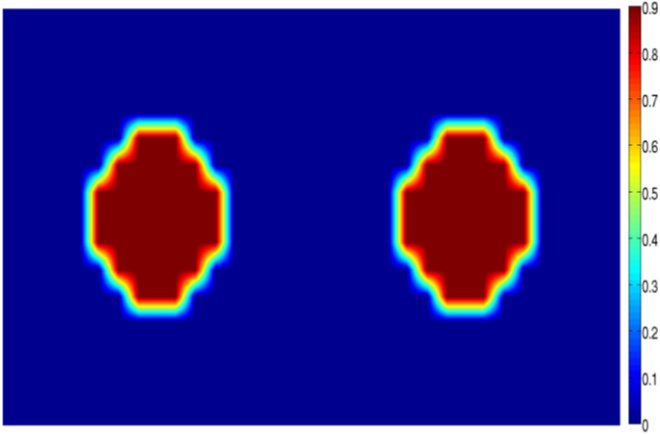
$$h = \frac{\epsilon}{6} \qquad (microscale\ step - size)$$

$$dt = 0.005$$

$$D_1 = 0.1 \qquad D_2 = D_2^* = 0.2$$

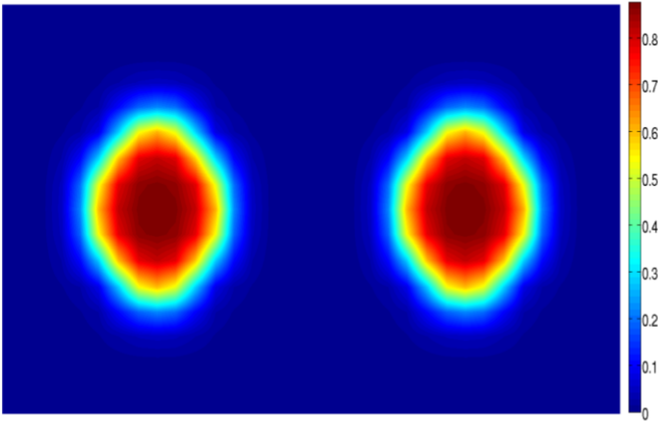
Numerical results, Density C

$t = 0$



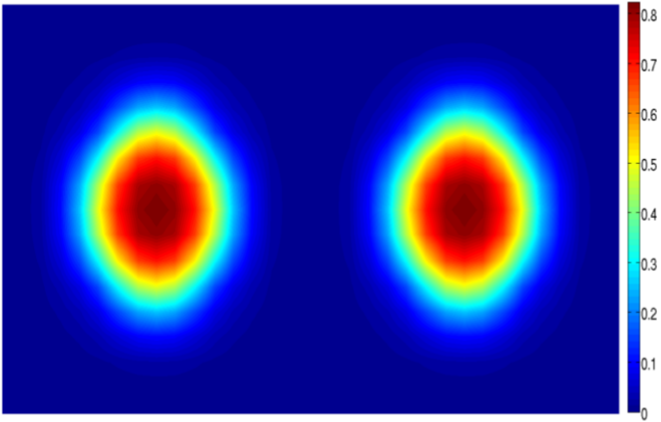
Numerical results, Density C

$t = 0.05$



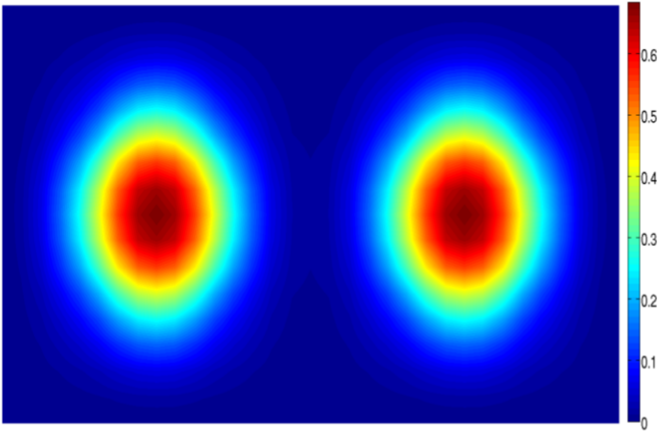
Numerical results, Density C

$t = 0.1$



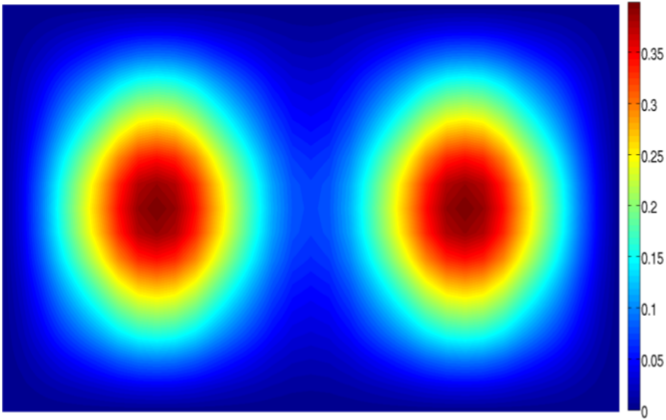
Numerical results, Density C

$t = 0.2$



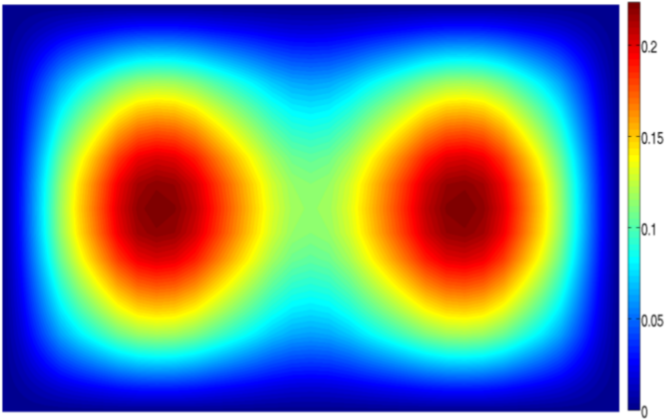
Numerical results, Density C

$t = 0.5$

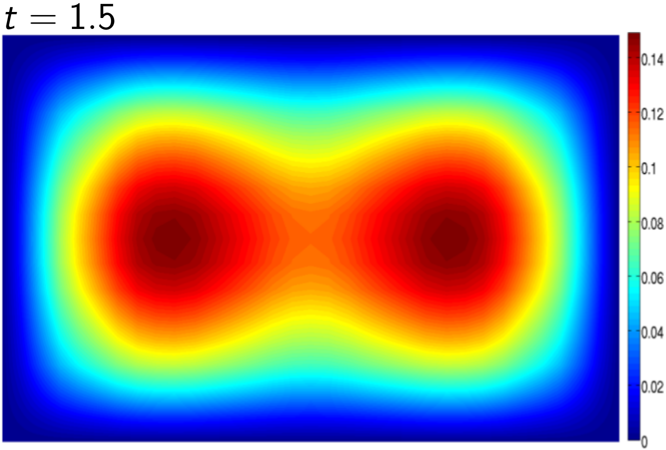


Numerical results, Density C

$t = 1$

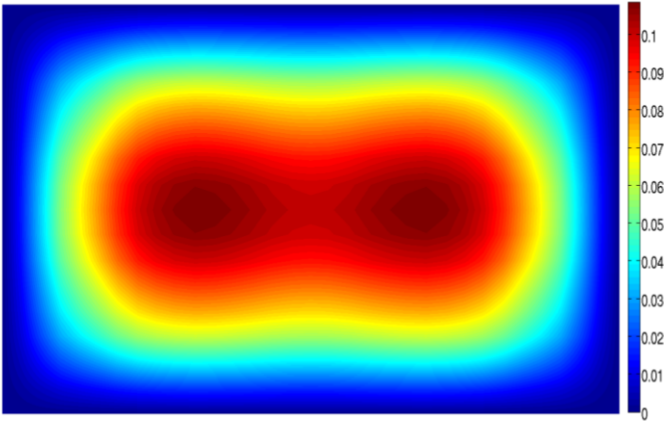


Numerical results, Density C



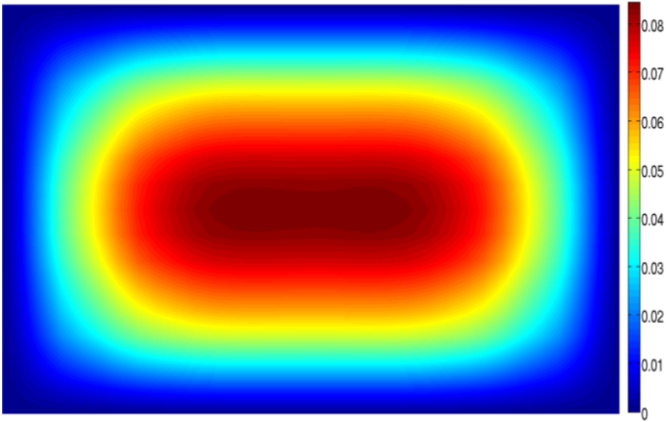
Numerical results, Density C

$t = 2$



Numerical results, Density C

$t = 2.5$



Conclusions

- Implementation of an HMM method for a coupled PDE multiscale medical problem
- HMM methods are computationally efficient approaches for PDE problems with high oscillating parameters,
  with respect of Classical Numerical Methods (using fine grids) or Homogenized Methods
- Existence and Convergence theories are missing for complex Multiscale Problems
- Future Work:
  - Analysis of errors with respect Homogenized and Fine grid solutions

Thank you for your attention!