Role and modelling of some heterogeneities for cardiac electrophysiology

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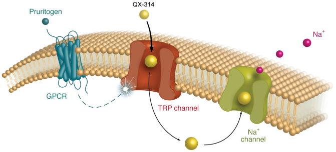
The first chapter

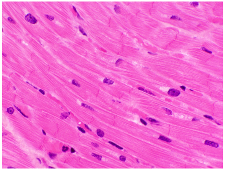
Modelling

Multiscale models

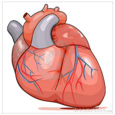
Cellular level



Tissue level

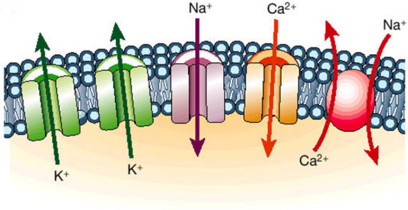


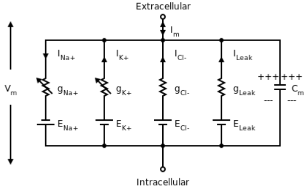
Organ level



Larger scale models depend on the smaller scale model.

The cellular level





$$I = \frac{dv}{dt} + I_{ion}(v)$$

- Cardiomyocytes - excitable cells, action potential (AP)
- Modelling
  - membrane - capacitor
  - ionic channels - conductors
  - ionic pump - source

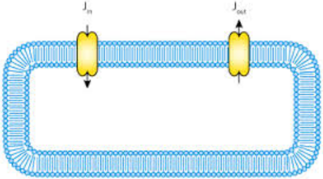
- I_{ion} - sum of ionic currents, ODEs
- Up to 15 different ionic currents

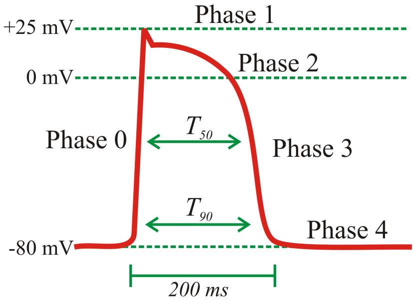
Mitchell-Schaeffer model

$$I_{ion}(v,h) = \frac{1}{\tau_{in}} h v^2 (v-1) - \frac{1}{\tau_{out}} v$$

$$\partial_t h + g(v,h) = 0$$

$$g(v,h) = \begin{cases} \frac{1-h}{\tau_{open}}, & \text{if } v < v_{gate}, \\ \frac{-h}{\tau_{close}}, & \text{if } v \geq v_{gate} \end{cases}$$





The tissue level

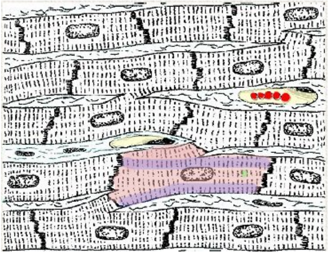
What do we model?

Propagation of AP

- Gap junctions
- Communication
- Coordinated contraction

Problem

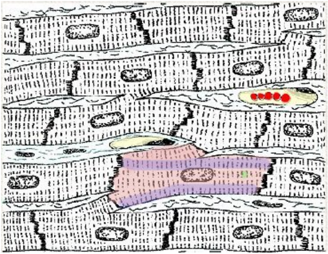
- Huge number of equations
- Huge number of transmission conditions
- Very small space step



The tissue level I

Mathematical assumptions:

- periodic micro-structure
- anisotropic intra- and extra-cellular spaces
- the transmembrane potential - cable equation



Microscale model $\longrightarrow^{homogenisation}\longrightarrow$ **BIDOMAIN MODEL**

The bidomain model

Degenerate parabolic reaction-diffusion system + ODE

$$\begin{aligned} \partial_t v + I_{ion}(v,h) &= \nabla \cdot (\sigma_i \nabla u_i), && \text{in } \Omega, \\ \partial_t v + I_{ion}(v,h) &= -\nabla \cdot (\sigma_e \nabla u_e), && \text{in } \Omega, \\ \partial_t h + g(v,h) &= 0, && \text{in } \Omega. \end{aligned}$$

$v = u_i - u_e$ - transmembrane potential

The standard boundary conditions for isolated heart:

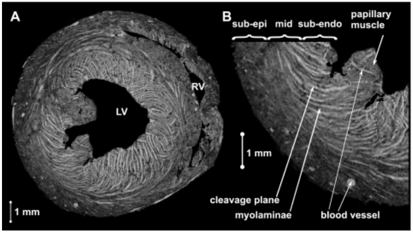
$$\begin{aligned} (\sigma_i \nabla u_i) \cdot n = 0, \ \text{on } \partial\Omega, \\ (\sigma_e \nabla u_e) \cdot n = 0, \ \text{on } \partial\Omega. \end{aligned}$$

The Gauge condition:

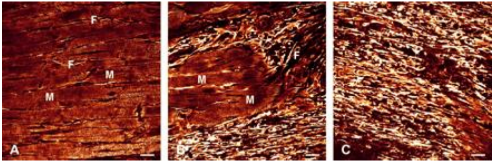
$$\int_\Omega u_e = 0.$$

Not a conclusive model - tissue heterogeneities

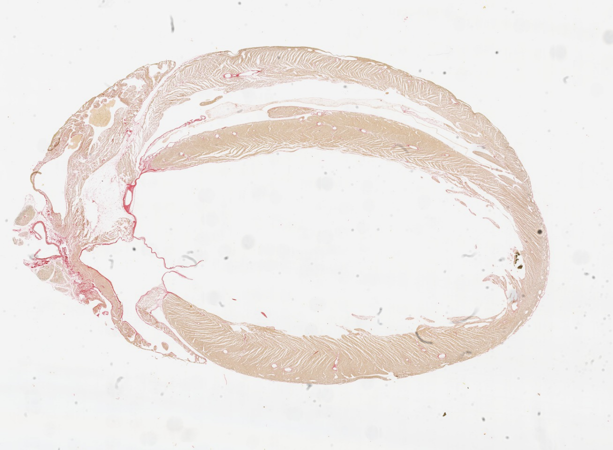
- Laminar stricture.



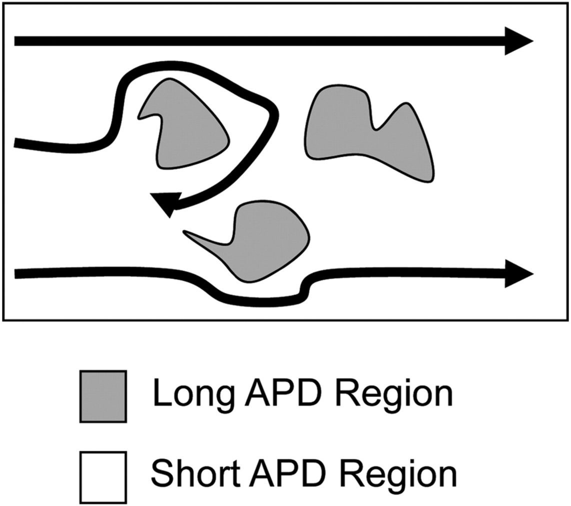
- The scar border zone.



Structural heterogeneities



Reentry



2
The second chapter

The new model

The new mesoscale model

Assumption: periodic diffusive inclusions

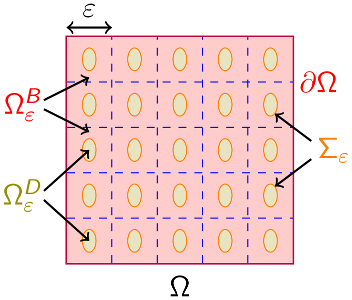


Figure: The 2D full domain Ω.

The new mesoscale model I

$$\left.\begin{aligned} \partial_t v_\varepsilon + I_{ion}(v_\varepsilon, h_\varepsilon) = \nabla \cdot (\sigma^i \nabla u_\varepsilon^i), \\ \partial_t v_\varepsilon + I_{ion}(v_\varepsilon, h_\varepsilon) = \nabla \cdot (\sigma^e \nabla u_\varepsilon^e), \\ \partial_t h_\varepsilon + g(v_\varepsilon, h_\varepsilon) = 0. \end{aligned}\right\} \text{Bidomain}$$

$$0 = \nabla \cdot (\sigma^d \nabla u_\varepsilon^d), \qquad \text{Diffusive incl.}$$

$v = u_i - u_e$ - transmembrane potential.

σ_i, σ_e - the standard anisotropic conductivities.

σ_d - the isotropic conductivity in the diffusive region.

$$\left.\begin{aligned} (\sigma^i \nabla u_\varepsilon^i) \cdot n = 0, \\ (\sigma^e \nabla u_\varepsilon^e) \cdot n = (\sigma^d \nabla u_\varepsilon^d) \cdot n, \\ u_\varepsilon^e = u_\varepsilon^d. \end{aligned}\right\} \underline{\text{on the inner boundary ??}}$$

The new mesoscale model II

We write

$$u_\varepsilon = \begin{cases} u_\varepsilon^e, & \text{in } \Omega_\varepsilon^B, \\ u_\varepsilon^d, & \text{in } \Omega_\varepsilon^D, \end{cases} \qquad \sigma = \begin{cases} \sigma_e, & \text{in } \Omega_\varepsilon^B, \\ \sigma_d, & \text{in } \Omega_\varepsilon^D. \end{cases}$$

The problem

$$\begin{aligned} \partial_t v_\varepsilon + I_{ion}(v_\varepsilon, h_\varepsilon) &= \nabla \cdot (\sigma^i \nabla u_\varepsilon^i), && \text{in } \Omega_\varepsilon^B, \\ \chi_{\Omega_\varepsilon^B}(\partial_t v_\varepsilon + I_{ion}(v_\varepsilon, h_\varepsilon)) &= \nabla \cdot (\sigma \nabla u_\varepsilon), && \text{in } \Omega, \\ \partial_t h_\varepsilon + g(v_\varepsilon, h_\varepsilon) &= 0, && \text{in } \Omega_\varepsilon^B. \end{aligned}$$

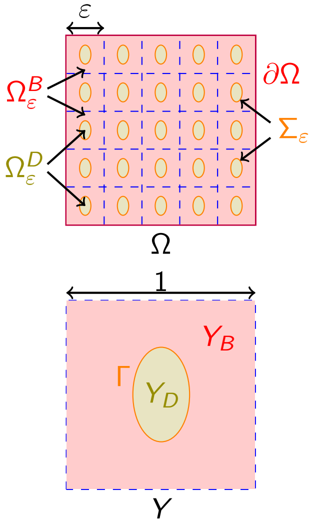
On the inner boundary

$$(\sigma^i \nabla u_\varepsilon^i) \cdot n = 0$$

Homogenisation

Main idea:

- Given model:
$$L_\varepsilon(u_\varepsilon) = f$$
- Assume: $u_\varepsilon \to u$
- Find L s.t.
$$L(u) = f$$



Formal approach

$$u_\varepsilon(x) = u_0(x) + \varepsilon u_1(x, x/\varepsilon) + \cdots$$
$$u_1(x, y) = w(y) \cdot \nabla u_0(x)$$

Twoscale convergence method (Allaire)

- Rigorous, exploits periodicity
- Solves two problems simultaneously
- New convergence definition - specific periodic test functions
- Requires: uniform *a priori* estimates, independent of ε

Method

1. Existence of $(v_\varepsilon, u^i_\varepsilon, u_\varepsilon)$ for fixed ε (Boulakia *et. al.*)
2. *A priori* bounds
   - energy estimates for $v_\varepsilon, h_\varepsilon, \nabla u^i_\varepsilon, \nabla u^e_\varepsilon$
   - bound on non-linear functions $I_{ion}(v, h)$ and $g(v, h)$

Method

3. Derivation of twoscale homogenisation system - var. form.
   - From the bounds

$$v_\varepsilon \twoheadrightarrow v_0, \qquad h_\varepsilon \twoheadrightarrow h_0$$

   - Derived convergence

$$\nabla u_\varepsilon^i \twoheadrightarrow \nabla u_0^i(x) + \nabla_y u_1^i(x,y), \qquad \nabla u_\varepsilon \twoheadrightarrow \nabla u_0(x) + \nabla_y u_1(x,y)$$

   - assume I_{ion} - Lipschitz function!

$$I_{ion}(v_\varepsilon, h_\varepsilon) \twoheadrightarrow I_{ion}(v_0, h_0), \qquad g(v_\varepsilon, h_\varepsilon) \twoheadrightarrow g(v_0, h_0)$$

4. Express $u_1^i = w_i \cdot \nabla u_0^i$ and $u_1 = w \cdot \nabla u_0$.
5. Read off the homogenised and the cell problems.

The new macroscale model

$$
\begin{aligned}
(\partial_t v_0 + I_{ion}(v_0, h_0)) &= \nabla \cdot (\sigma_i^* \nabla u_0^i), && \text{in } \Omega,\\
(\partial_t v_0 + I_{ion}(v_0, h_0)) &= -\nabla \cdot ((\sigma_e^* + \sigma_d^*) \nabla u_0), && \text{in } \Omega,\\
\partial_t h_0 + g(v_0, h_0) &= 0, && \text{in } \Omega.
\end{aligned}
$$

New effective conductivities

$$
\begin{aligned}
\sigma_{i_{kj}}^* &= \sigma_{i_{kj}} + \frac{1}{|Y_B|}(\sigma_{i_{k1}} A_{1j}^i + \sigma_{i_{k2}} A_{2j}^i + \sigma_{i_{k3}} A_{3j}^i),\\
\sigma_{e_{kj}}^* &= \sigma_{e_{kj}} + \frac{1}{|Y_B|}(\sigma_{e_{k1}} A_{1j}^e + \sigma_{e_{k2}} A_{2j}^e + \sigma_{e_{k3}} A_{3j}^e),\\
\sigma_{d_{kj}}^* &= \sigma_{d_{kj}} \frac{|Y_D|}{|Y_B|} + \frac{1}{|Y_B|}(\sigma_{d_{k1}} A_{1j}^d + \sigma_{d_{k2}} A_{2j}^d + \sigma_{d_{k3}} A_{3j}^d).
\end{aligned}
$$

$A_{kj}^i, A_{kj}^e, A_{kj}^d$ - from the cell problems.

The cell problems

Solved **only once** - on the unit cell Y.

Intracellular:

$$\nabla \cdot (\sigma_i \nabla w_j^i) = 0, \text{ in } Y_B,$$
$$\sigma_i(\nabla w_j^i + e_j) \cdot n = 0, \text{ on } \Gamma,$$
$$w_j^i \text{ is } Y \text{ periodic.}$$

Extracellular:

$$\nabla \cdot (\sigma \nabla w_j) = 0, \text{ in } Y,$$
$$[\sigma \nabla w_j \cdot n] + (\sigma_e - \sigma_d) e_j \cdot n = 0, \text{ on } \Gamma,$$
$$w_j \text{ is } Y \text{ periodic.}$$

Finally,

$$A_{kj}^i = \int_{Y_B} \partial_k w_j^i, \quad A_{kj}^e = \int_{Y_B} \partial_k w_j, \quad A_{kj}^d = \int_{Y_D} \partial_k w_j.$$

3
The third chapter
Numerics

2D Numerical experiments, convergence.

- Geometry:
  - square domain, circular and elliptical inclusions
  - $\varepsilon \in \{1/5, 1/10, \cdots, 1/40\}$
- Conductivities:

  $\sigma_{i_{11}} = 1.741, \sigma_{i_{22}} = 0.1934,\ \sigma_{e_{11}} = 3.906, \sigma_{e_{22}} = 1.970,$
  $\sigma_{d_{11}} = \sigma_{d_{22}} = 3.$
- Discretisation: $dt = 0.5$ and $dx \approx 0.3$

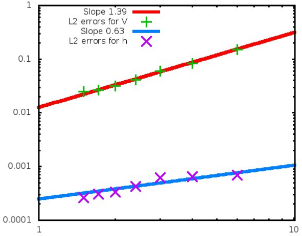
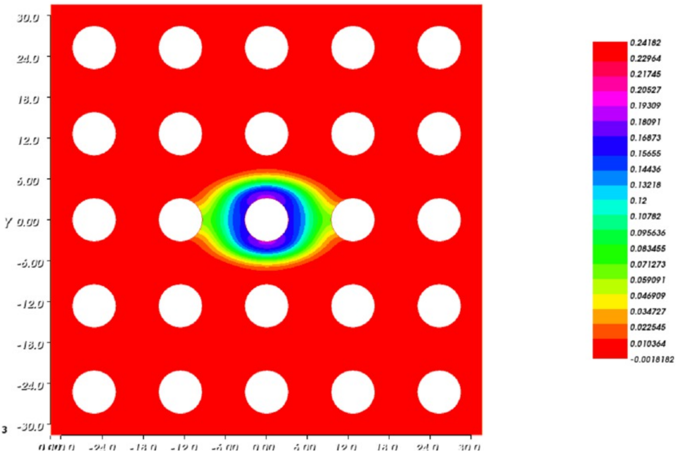


Figure: Convergence rate: 1.39 for V, 0.63 for h.

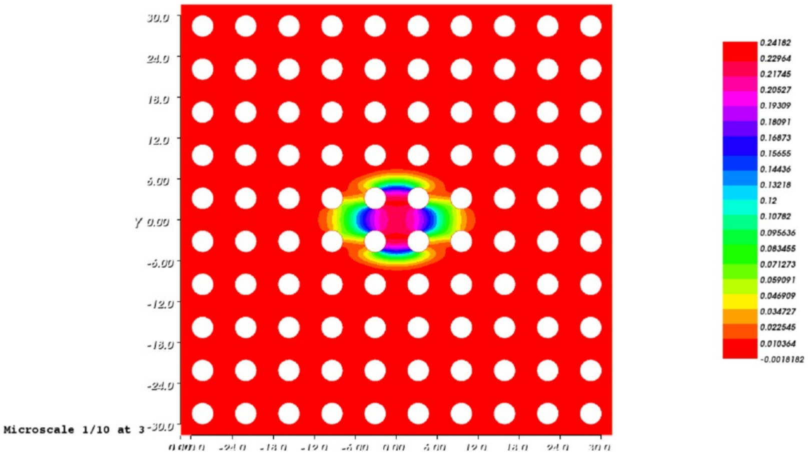
The numerical results

Homogenisation process - $\varepsilon = \frac{1}{5}$



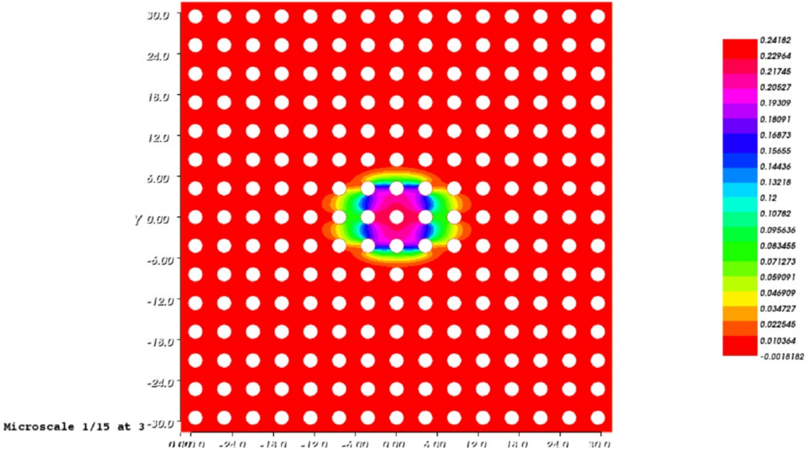
The numerical results

Homogenisation process - $\varepsilon = \frac{1}{10}$



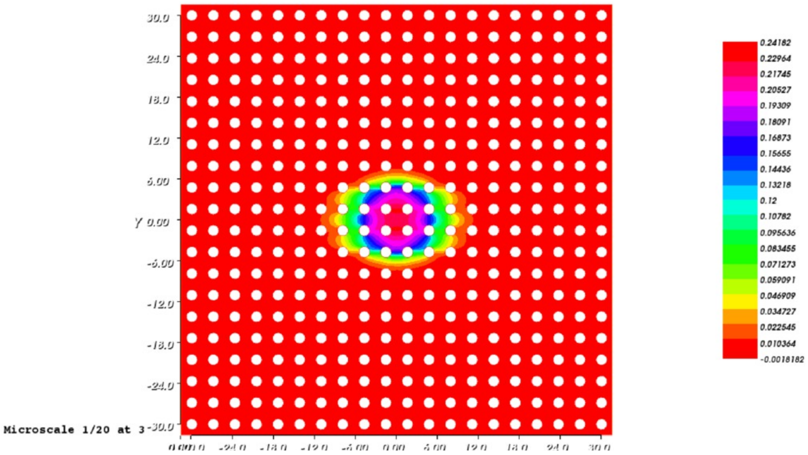
The numerical results

Homogenisation process - $\varepsilon = \frac{1}{15}$



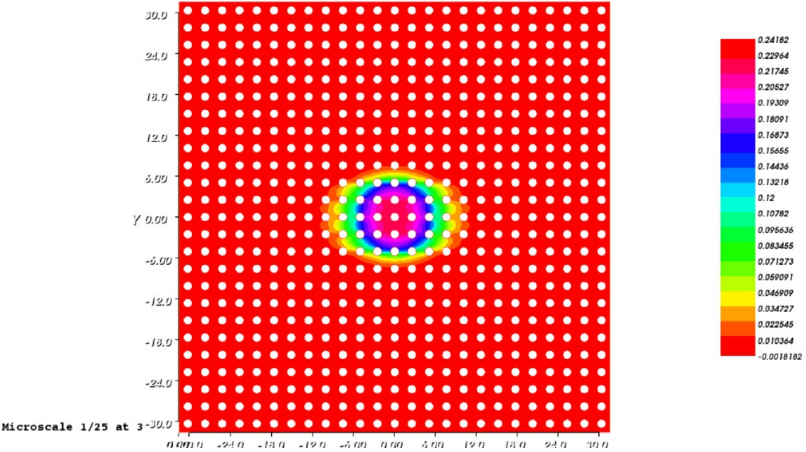
The numerical results

Homogenisation process - $\varepsilon = \frac{1}{20}$



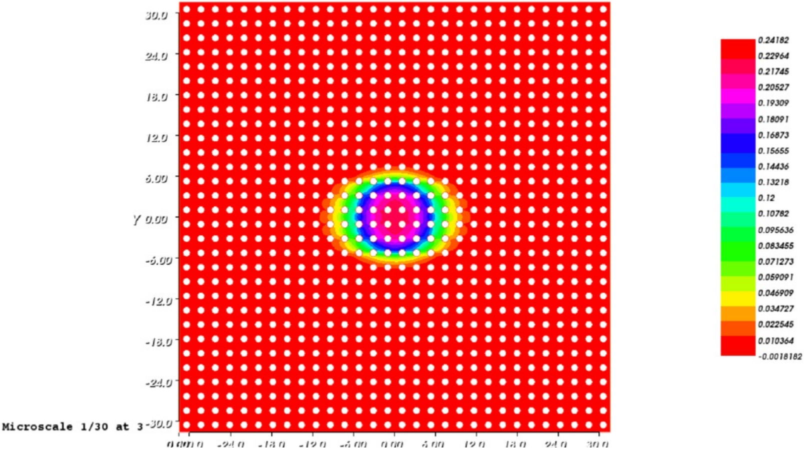
The numerical results

Homogenisation process - $\varepsilon = \frac{1}{25}$



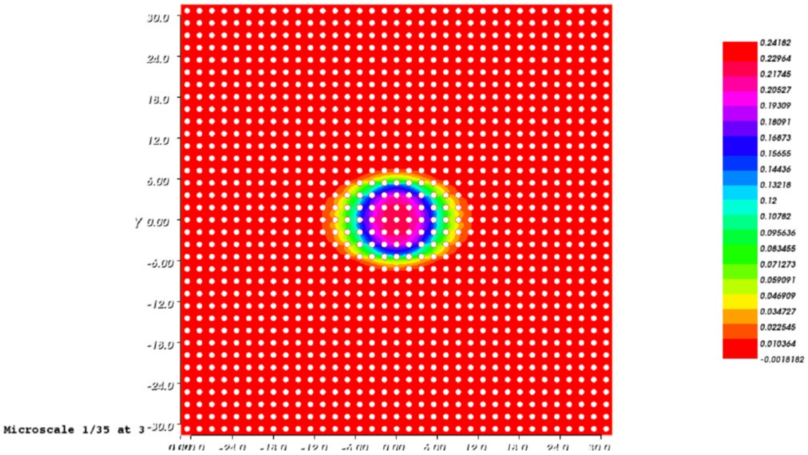
The numerical results

Homogenisation process - $\varepsilon = \frac{1}{30}$



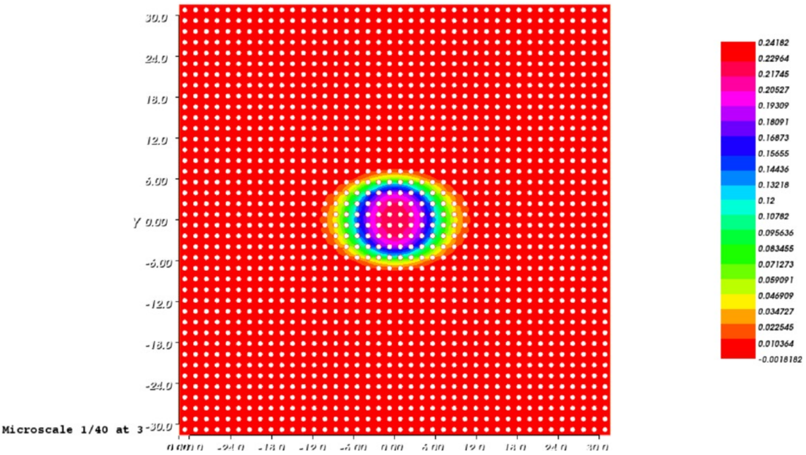
The numerical results

Homogenisation process - $\varepsilon = \frac{1}{35}$



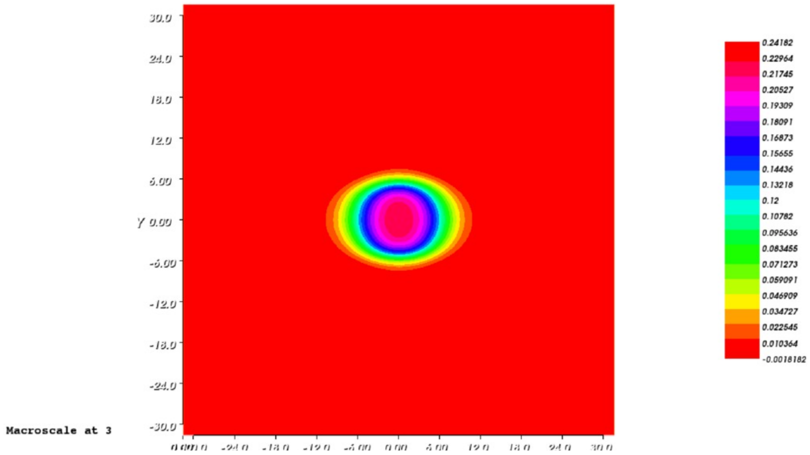
The numerical results

Homogenisation process - $\varepsilon = \frac{1}{40}$



The numerical results

Homogenisation process - $\varepsilon = \frac{1}{\infty}$



The numerical results, conductivities.

Geom	Vol fr	σ^d	$\sigma^*_{i_{11}}$	$\sigma^*_{i_{22}}$	$\sigma^*_{e_{11}}$	$\sigma^*_{e_{12}}$	$\sigma^*_{e_{21}}$	$\sigma^*_{e_{22}}$
-	-	-	1.74	0.19	3.9	0	0	1.97
circle	0.2	0.1	1.26	0.17	2.85	0.00	0.005	1.81
circle	0.2	1	1.26	0.17	2.99	0.01	0.005	2.02
circle	0.2	6	1.26	0.17	3.73	0.04	0.005	3.27
circle	0.2	3	1.26	0.17	3.29	0.02	0.005	2.53
circle	0.4	3	1.07	0.15	3.42	-0.17	0.02	3.53
circle	0.7	3	0.69	0.09	5.08	-2.09	-0.01	7.89
ellipse	0.2	3	1.13	0.18	2.82	0.06	0.00	2.58
ellipse	0.4	3	0.81	0.16	2.53	-0.03	-0.01	3.70
ellipse2	0.2	3	0.86	0.18	2.09	0.06	0.00	2.64

The numerical results, comparison.

Time t = 0.5

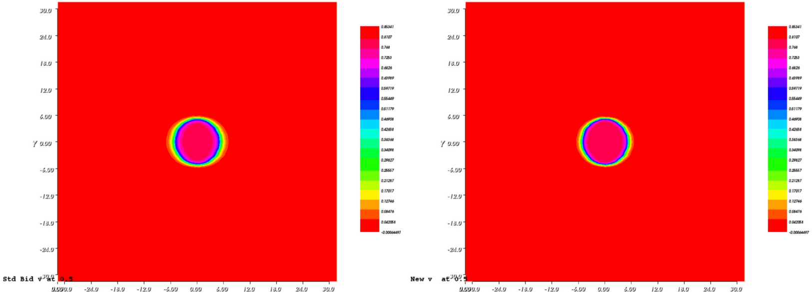


Figure: (Left) Standard bidomain. (Right) New model.

The numerical results, comparison.

Time t = 1.0

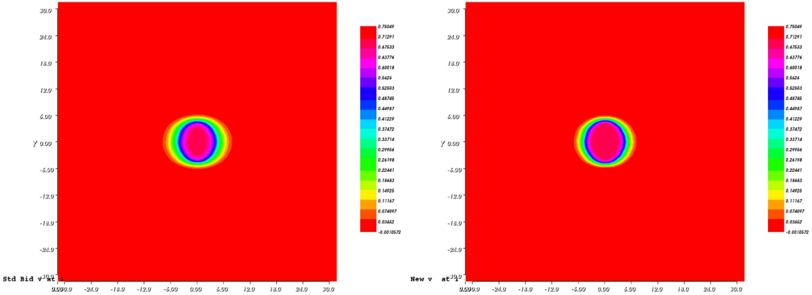


Figure: (Left) Standard bidomain. (Right) New model.

The numerical results, comparison.

Time $t = 1.5$

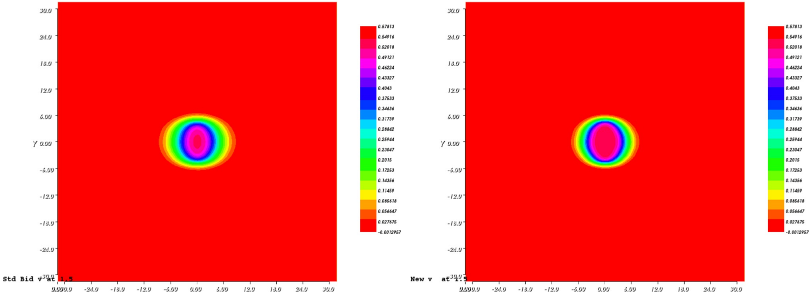


Figure: (Left) Standard bidomain. (Right) New model.

The numerical results, comparison.

Time t = 2.0

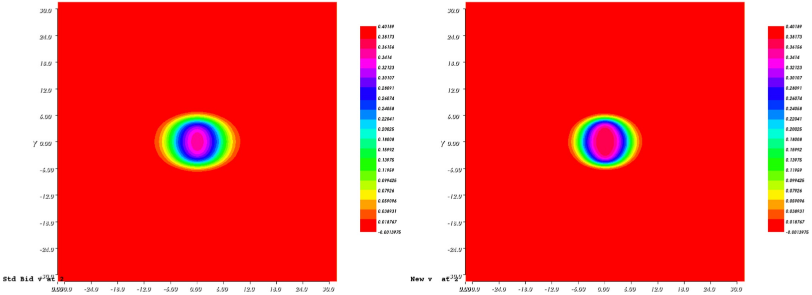


Figure: (Left) Standard bidomain. (Right) New model.

The numerical results, comparison.

Time t = 2.5

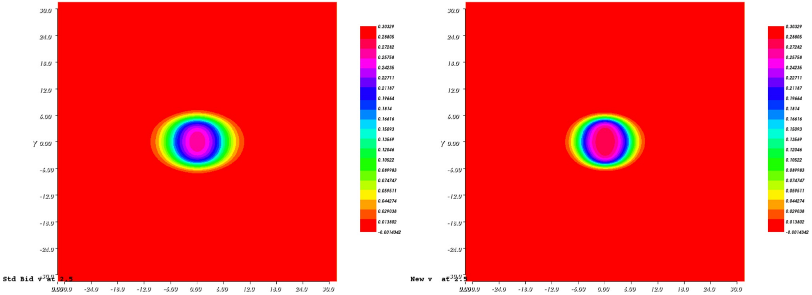


Figure: (Left) Standard bidomain. (Right) New model.

The numerical results, comparison.

Time t = 3.0

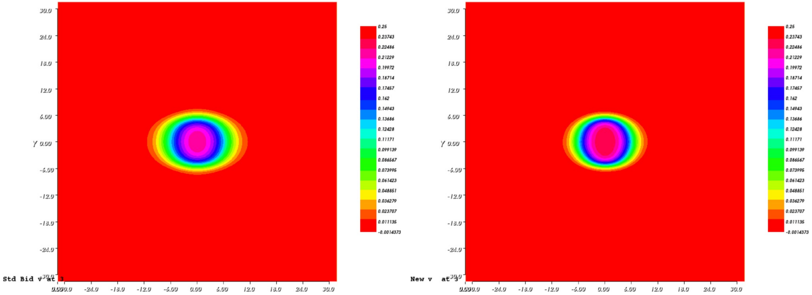


Figure: (Left) Standard bidomain. (Right) New model.

The numerical results, comparison.

Time t = 3.5

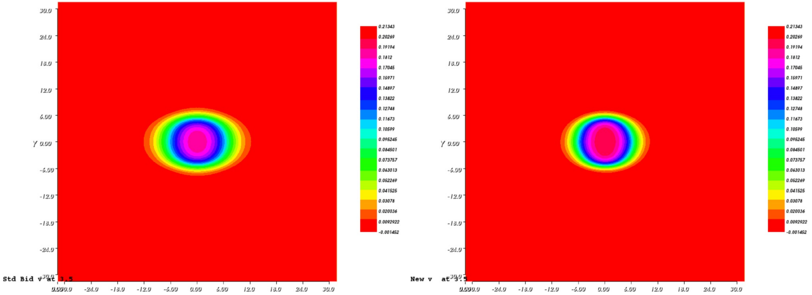


Figure: (Left) Standard bidomain. (Right) New model.

The numerical results, comparison.

Time t = 4.0

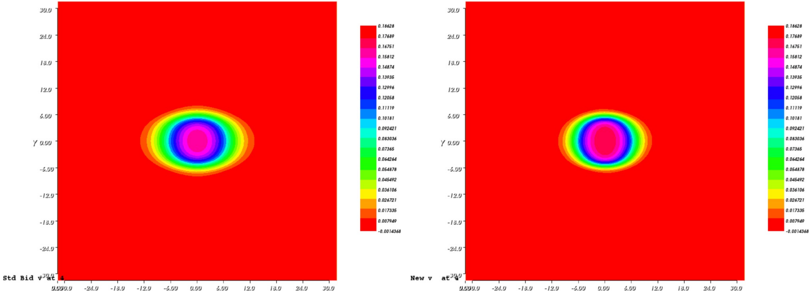
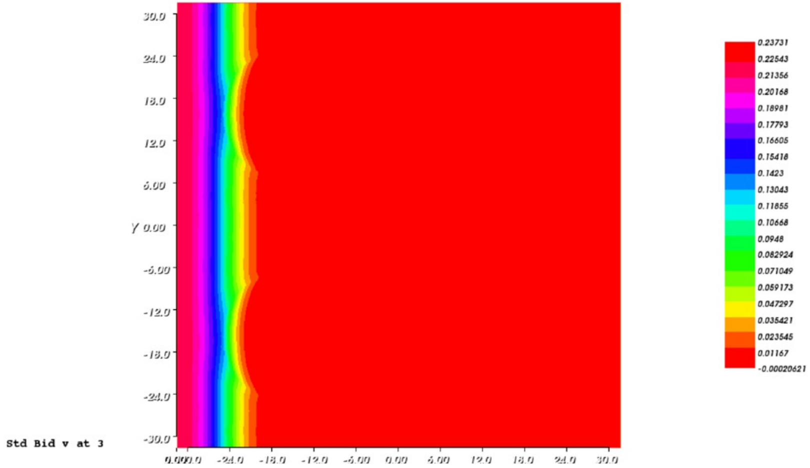


Figure: (Left) Standard bidomain. (Right) New model.

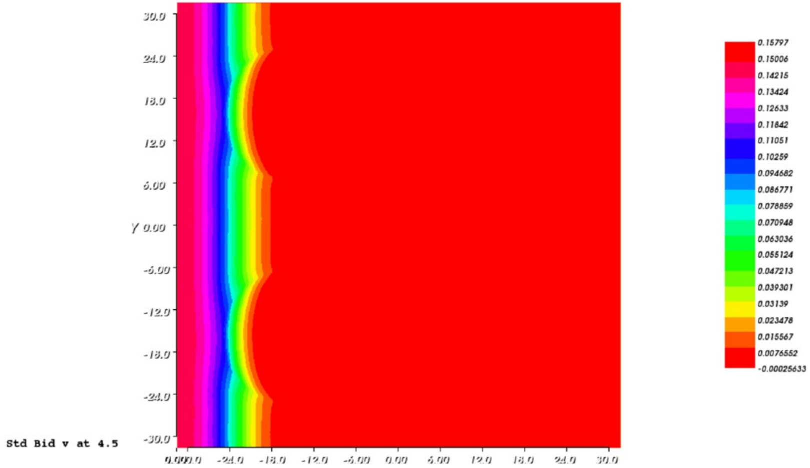
The numerical results, scars.

Time t = 3.0



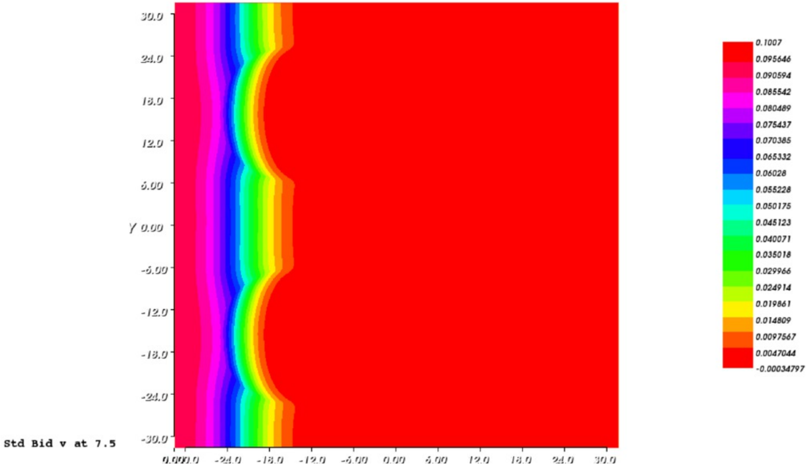
The numerical results, scars.

Time t = 4.5



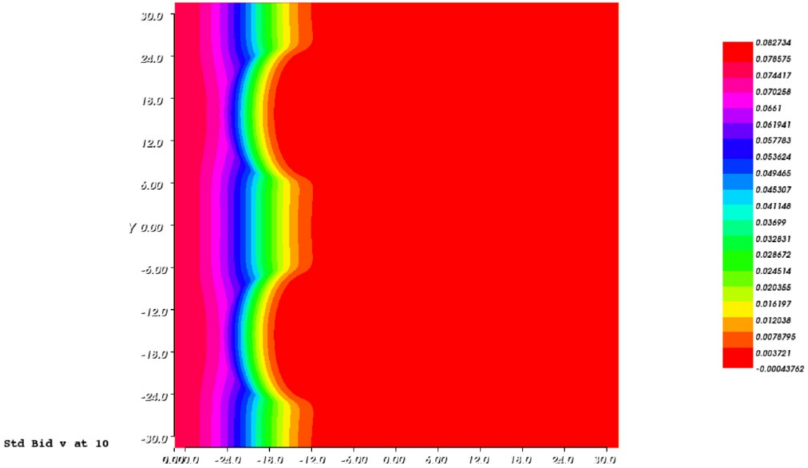
The numerical results, scars.

Time t = 7.5



The numerical results, scars.

Time t = 10.0

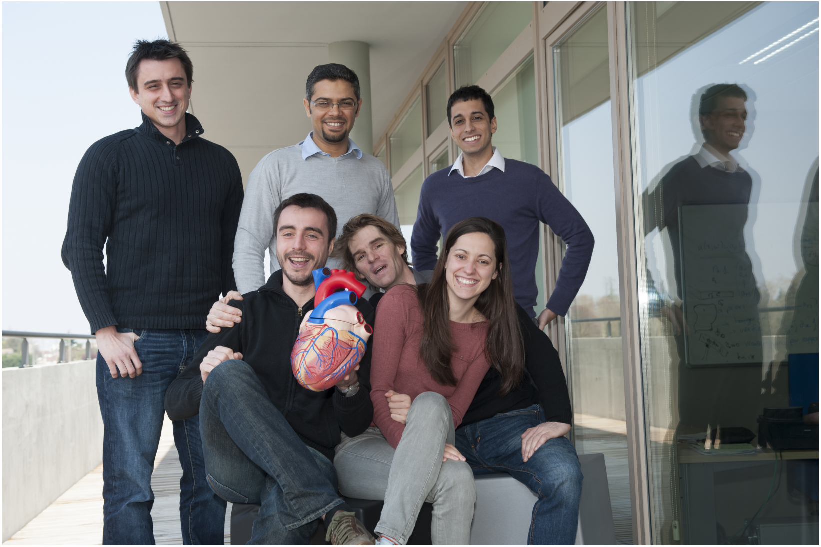


4
Conclusions

Discussion and further work

- New model $\neq$ standard bidomain model
- Depends on
  - value of σ^d
  - volume fraction - larger inclusions bigger difference
  - geometry of inclusions
- Future work
  - Simulations for 3D model
  - The real geometries
  - The data reading - MRI? σ_d?
  - The impact on the dynamics of spiral waves?
  - Can we trigger the re-entrant waves?

CARMEN team



Thank You.

Andjela Davidović
L'Aquila

September 7, 2014