



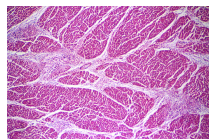
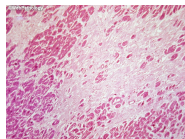
**Image-based modeling of the heterogeneity of  
propagation of the cardiac action potential.  
Example of rat heart high resolution MRI.**

**Anđela Davidović, Yves Coudière and Yves Bourgault**

# Introduction

Q: What is the goal?

A: Understanding the AP propagation in the hearts **with structural diseases**.



Q: Which models exist?

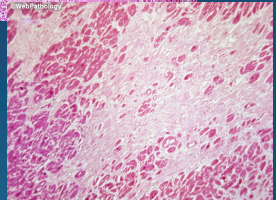
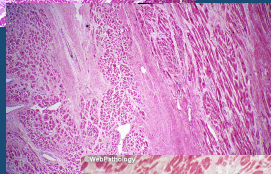
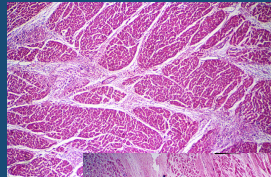
A: Bidomain and monodomain models. They have limitations. We propose a modifications to the bidomain model.

Q: Can it be applied on a real heart? Which tools are used?

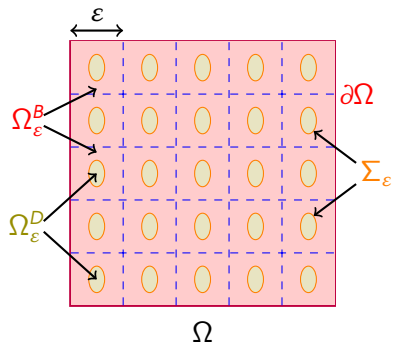
A: Yes. HR-MRI help in identifying useful informations about the structure of the tissue and to feed the model.

# Mesoscale model

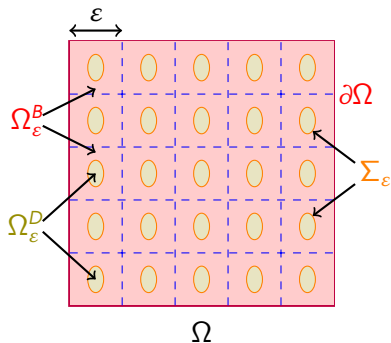
Influence of the diffusive inclusions  
in bidomain model



## Bidomain with periodic diffusive inclusions



## Bidomain with periodic diffusive inclusions

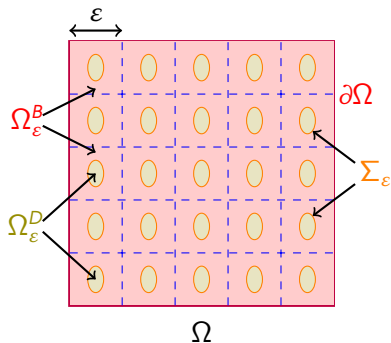


- ▶ Healthy tissue in  $\Omega_\epsilon^B$
- ▶ Diffusive inclusion in  $\Omega_\epsilon^D$
- ▶ Continuity of flux and potential on  $\Sigma_\epsilon$

$$\begin{aligned} \partial_t \mathbf{h}_\epsilon + \mathbf{g}(v_\epsilon, \mathbf{h}_\epsilon) &= 0, & \Omega_\epsilon^B \\ \partial_t v_\epsilon + I_{\text{ion}}(v_\epsilon, \mathbf{h}_\epsilon) &= \nabla \cdot (\sigma^j \nabla u_\epsilon^j), & \Omega_\epsilon^B \\ \partial_t v_\epsilon + I_{\text{ion}}(v_\epsilon, \mathbf{h}_\epsilon) &= \nabla \cdot (\sigma^e \nabla u_\epsilon^e), & \Omega_\epsilon^B \\ 0 &= \nabla \cdot (\sigma^d \nabla u_\epsilon^d), & \Omega_\epsilon^D \\ (\sigma^j \nabla u_\epsilon^j) \cdot \mathbf{n} &= 0, & \Sigma_\epsilon \\ (\sigma^e \nabla u_\epsilon^e) \cdot \mathbf{n} &= (\sigma^d \nabla u_\epsilon^d) \cdot \mathbf{n}, & \Sigma_\epsilon \\ u_\epsilon^e &= u_\epsilon^d. & \Sigma_\epsilon \end{aligned}$$

$v_\epsilon = u_\epsilon^j - u_\epsilon^e$  - transmembrane voltage  
 $\mathbf{h}_\epsilon$  - state variables of ionic model  
 $\sigma^j, \sigma^e, \sigma^d$  - conductivities

## Bidomain with periodic diffusive inclusions



- ▶ Healthy tissue in  $\Omega_\epsilon^B$
- ▶ Diffusive inclusion in  $\Omega_\epsilon^D$
- ▶ Continuity of flux and potential on  $\Sigma_\epsilon$

$$\begin{aligned} \partial_t \mathbf{h}_\epsilon + \mathbf{g}(v_\epsilon, \mathbf{h}_\epsilon) &= 0, & \Omega_\epsilon^B \\ \partial_t v_\epsilon + I_{\text{ion}}(v_\epsilon, \mathbf{h}_\epsilon) &= \nabla \cdot (\sigma^i \nabla u_\epsilon^i), & \Omega_\epsilon^B \\ \partial_t v_\epsilon + I_{\text{ion}}(v_\epsilon, \mathbf{h}_\epsilon) &= \nabla \cdot (\sigma^e \nabla u_\epsilon^e), & \Omega_\epsilon^B \end{aligned}$$

$$0 = \nabla \cdot (\sigma^d \nabla u_\epsilon^d), \quad \Omega_\epsilon^D$$

$$\begin{aligned} (\sigma^i \nabla u_\epsilon^i) \cdot \mathbf{n} &= 0, & \Sigma_\epsilon \\ (\sigma^e \nabla u_\epsilon^e) \cdot \mathbf{n} &= (\sigma^d \nabla u_\epsilon^d) \cdot \mathbf{n}, & \Sigma_\epsilon \\ u_\epsilon^e &= u_\epsilon^d. & \Sigma_\epsilon \end{aligned}$$

$v_\epsilon = u_\epsilon^i - u_\epsilon^e$  - transmembrane voltage

$\mathbf{h}_\epsilon$  - state variables of ionic model

$\sigma^i, \sigma^e, \sigma^d$  - conductivities

**HOMOGENIZATION!**

# The homogenised macroscale model

Modified bidomain model

$$|Y_B| (\partial_t v + I_{ion}(v, h)) = \nabla \cdot (\sigma^{j*} \nabla u^j) \quad \text{in } \Omega$$

$$|Y_B| (\partial_t v + I_{ion}(v, h)) = -\nabla \cdot (\sigma^{e*} \nabla u) \quad \text{in } \Omega$$

$$\partial_t h + g(v, h) = 0 \quad \text{in } \Omega$$

where:  $v = u^j - u$ .

Modified conductivity tensors take into account tissue microstructure:

$$\sigma_{kj}^{j*} = \sigma_{kj}^j |Y_B| + (\sigma_{k1}^j A_{1j}^j + \sigma_{k2}^j A_{2j}^j + \sigma_{k3}^j A_{3j}^j),$$

$$\sigma_{kj}^{e*} = \sigma_{kj}^e |Y_B| + (\sigma_{k1}^e A_{1j}^e + \sigma_{k2}^e A_{2j}^e + \sigma_{k3}^e A_{3j}^e) + \sigma_{kj}^d |Y_D| + (\sigma_{k1}^d A_{1j}^d + \sigma_{k2}^d A_{2j}^d + \sigma_{k3}^d A_{3j}^d).$$

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

# The cell problems

- ▶ Derived from the equations  $u_1^i = W_i \cdot \nabla u_0^i$  and  $u_1 = W \cdot \nabla u_0$ .
- ▶ Static problems, solved **only once** on the unit cell  $Y$ .

Intracellular:

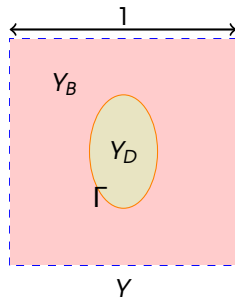
$$\begin{aligned}\nabla \cdot (\sigma_i \nabla w_j^i) &= 0, \text{ in } Y_B, \\ \sigma_i (\nabla w_j^i + e_j) \cdot n &= 0, \text{ on } \Gamma, \\ w_j^i &\text{ is } Y \text{ periodic.}\end{aligned}$$

Extracellular:

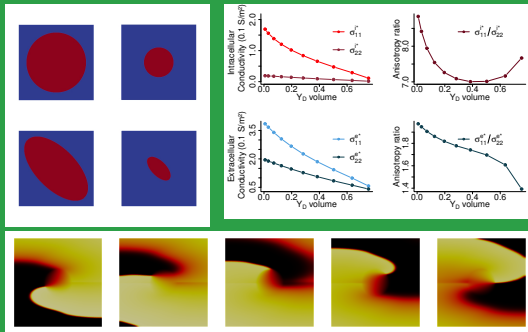
$$\begin{aligned}\nabla \cdot (\sigma \nabla w_j) &= 0, \text{ in } Y, \\ (\sigma_e - \sigma_d) (\nabla w_j + e_j) \cdot n &= 0, \text{ on } \Gamma, \\ w_j &\text{ is } Y \text{ periodic.}\end{aligned}$$

Matrices:

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





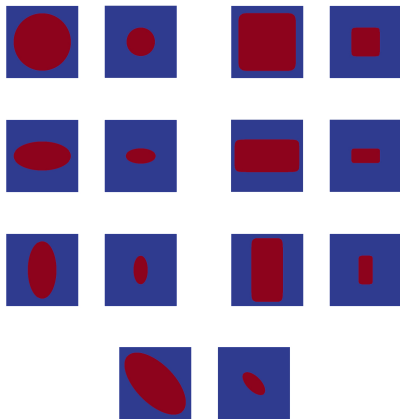


# Quantitative effects

depend on the shape, size and  $\sigma^d$

## Solving cell problems on different unit cells $Y$

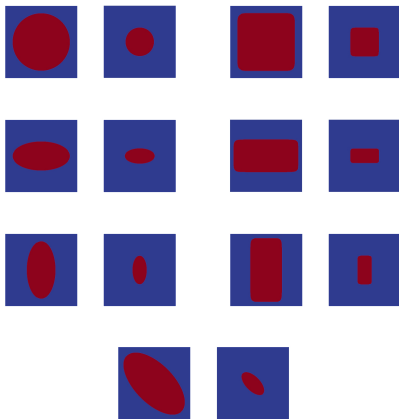
Fibers orientation:  $\longleftrightarrow$



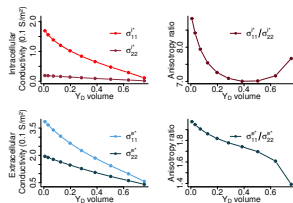
- ▶ blue is  $Y_B$ , red is  $Y_D$
- ▶ fibers orientation in  $Y_B$  domain is along x-axis
- ▶  $\sigma^{j*}$  and  $\sigma^{e*}$  depend on shape of periodic cells,  $|Y_B|$  and  $\sigma^d$ .

# Solving cell problems on different unit cells $Y$

Fibers orientation:  $\longleftrightarrow$

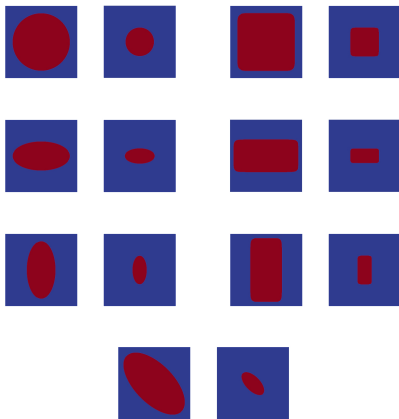


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- ▶  $\sigma^{I*}$  and  $\sigma^{E*}$  depend on shape of periodic cells,  $|Y_B|$  and  $\sigma^d$ .

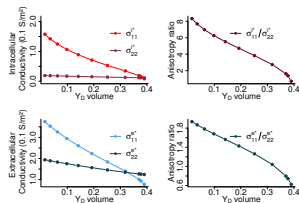


# Solving cell problems on different unit cells $Y$

Fibers orientation:  $\longleftrightarrow$



- ▶ blue is  $Y_B$ , red is  $Y_D$
- ▶ fibers orientation in  $Y_B$  domain is along x-axis
- ▶  $\sigma^{l*}$  and  $\sigma^{e*}$  depend on shape of periodic cells,  $|Y_B|$  and  $\sigma^d$ .



For

more details: PhD thesis A. Davidovic, 2016.

# Change in speed and direction of the wavefront for fixed $|Y_B|$ .

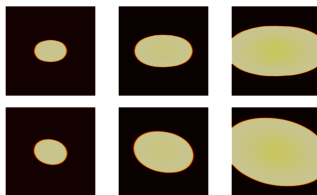
Fibers orientation:  $\longleftrightarrow$

Standard bidomain simulation, i.e.  $|Y_B| = 1$ :



Shape of periodic cells:

Modified bidomain simulation, with  $|Y_B| < 0.5$ :



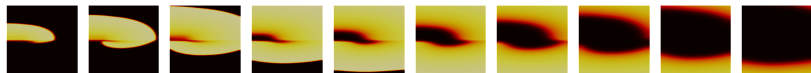
20ms

50ms

100ms

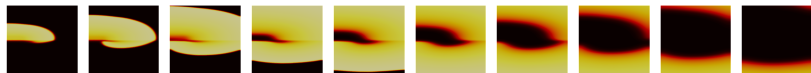
## Effects on a heterogeneous tissue patch and spiral waves.

Healthy tissue patch:

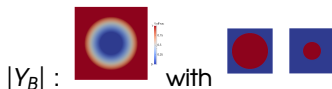


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Healthy tissue patch:

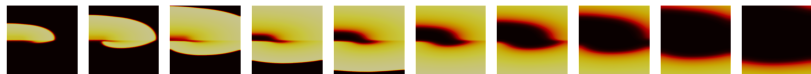


Heterogeneous tissue patch with different periodic cells:

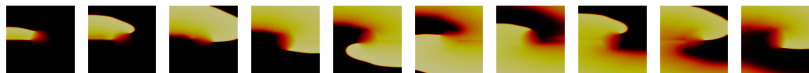
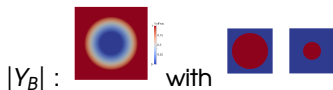


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Healthy tissue patch:



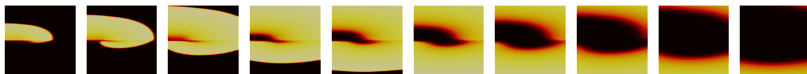
Heterogeneous tissue patch with different periodic cells:



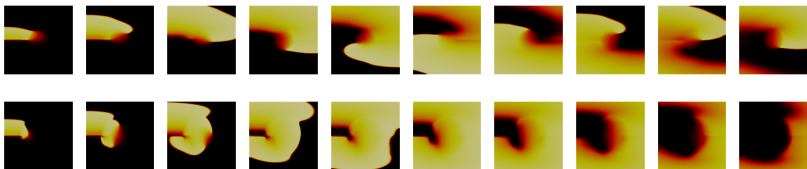


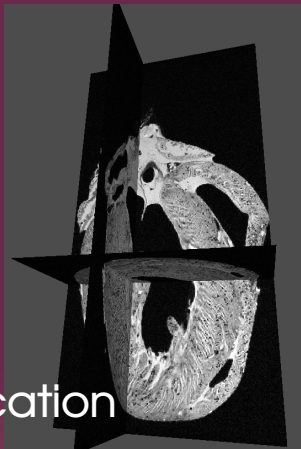
# Effects on a heterogeneous tissue patch and spiral waves.

Healthy tissue patch:



Heterogeneous tissue patch with different periodic cells:





# Rat heart application

## From HR MR Imaging to Simulation

# Modified bidomain model adapted for the rat heart

Steps:

1. Fit MS ionic model to the rat heart model

- ▶ Pongui Ngoma et al, Adjustment of Parameters in Ionic Models Using Optimal Control Problems. FIMH 2017.

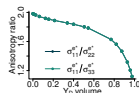
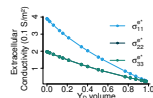
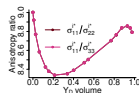
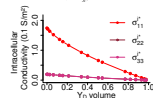
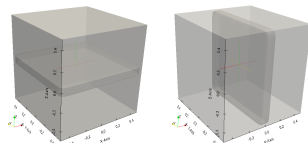
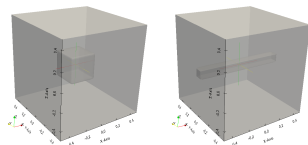
# Modified bidomain model adapted for the rat heart

Steps:

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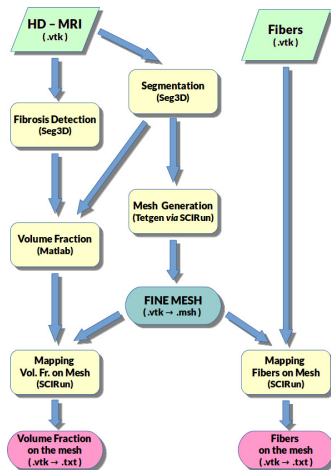
2. Solve the cell problems on 3D unit cell for given  $\sigma^d$ , and varying  $|Y_B| \in [0.02, 1]$



# Modified bidomain model adapted for the rat heart

Steps:

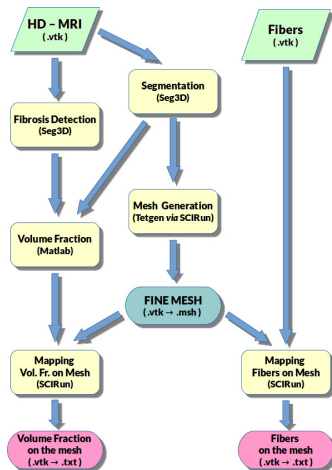
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  - ▶ Pongui Ngoma et al, Adjustment of Parameters in Ionic Models Using Optimal Control Problems. FIMH 2017.
2. Solve the cell problems on 3D unit cell for given  $\sigma^d$ , and varying  $|Y_B| \in [0.02, 1]$
3. Image processing
  - ▶ segmentation
  - ▶ mesh generation
  - ▶ define diffusive inclusions
  - ▶ compute  $|Y_B|$
  - ▶ map  $|Y_B|$  and fibers on the mesh



# Modified bidomain model adapted for the rat heart

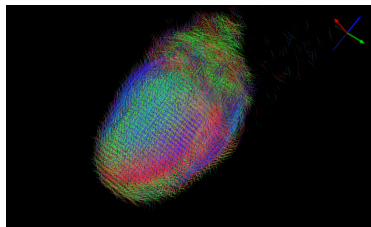
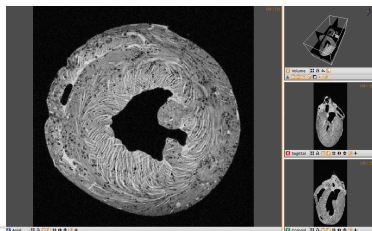
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3. Image processing
  - ▶ segmentation
  - ▶ mesh generation
  - ▶ define diffusive inclusions
  - ▶ compute  $|Y_B|$
  - ▶ map  $|Y_B|$  and fibers on the mesh
4. Define  $\sigma^{f*}$  and  $\sigma^{e*}$  using Step 2 and  $|Y_B|$ .
5. Run simulation.

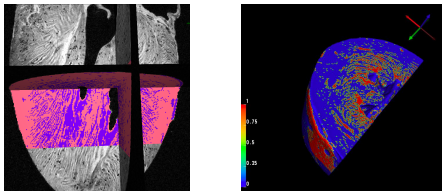


## HR MRI data and DT MRI fibers orientation

- ▶ Data provided by Stephen Gilbert and IHU-Liryc, Bordeaux.
  - ▶ Gilbert SH, et al. American Journal of Physiology-Heart and Circulatory Physiology. 2012; 302(1):H287-98.
- ▶ male Wistar rat heart, imaged using a T1 weighted FLASH (Fast Low Angle SHot) MRI sequence in a 9.4T spectroscope.
- ▶ HR MR images:
  - ▶ resolution of  $50 \times 50 \times 50 \mu m$
  - ▶ matrix of  $256 \times 256 \times 512$  voxels
  - ▶ view field of  $12.8 \times 12.8 \times 25.6 mm$
- ▶ DT MR images:  $64 \times 64 \times 128$  voxels on the same view field



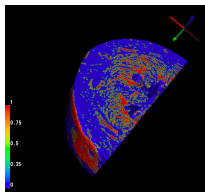
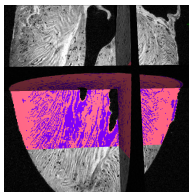
## Segmentation, diffusive inclusions detection and meshing.



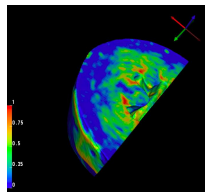
segmentation



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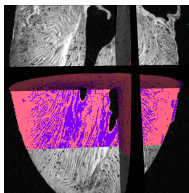
segmentation



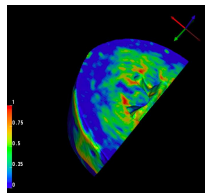
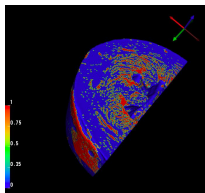
volume fraction  $|Y_D|$

- ▶ On the mask use a moving window  $[5 \times 5 \times 5]$  to compute local volume fraction  $|Y_D|$ . Note:  $|Y_D|$  depends on
  1. threshold used to determine  $Y_D$
  2. size of the moving window

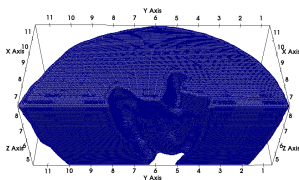
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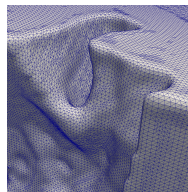
segmentation



volume fraction  $|Y_D|$



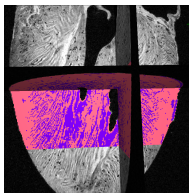
mesh



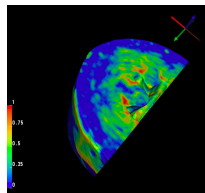
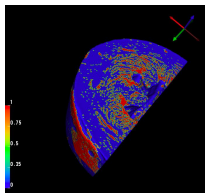
mesh detail

- ▶ Mesh size: 351 706 nodes, 1 924 747 tetrahedra

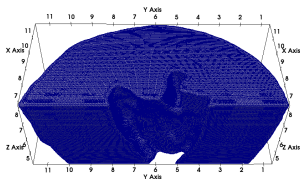
## Segmentation, diffusive inclusions detection and meshing.



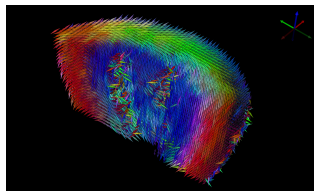
segmentation



volume fraction  $|Y_D|$



mesh

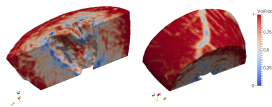


fibers on the segmentation

- ▶ Project volume fraction  $|Y_D|$  and fibers orientations on the mesh.

## Effective conductivities

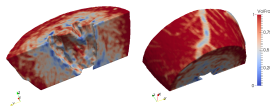
- ▶ Use volume fraction  $1 - |Y_D| = |Y_B| \in [0, 1]$
- ▶ Assume same shape of inclusions everywhere (smooth box)



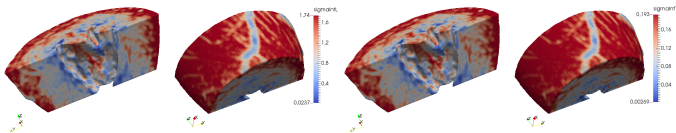
volume fraction  $|Y_B|$

# Effective conductivities

- ▶ Use volume fraction  $1 - |Y_D| = |Y_B| \in [0, 1]$
- ▶ Assume same shape of inclusions everywhere (smooth box)
- ▶ For  $\sigma^d = 0.2$

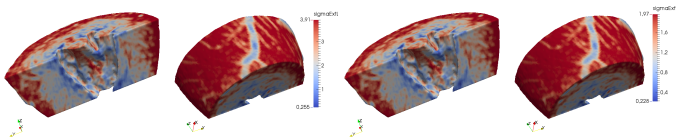


volume fraction  $|Y_B|$



Intracellular

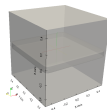
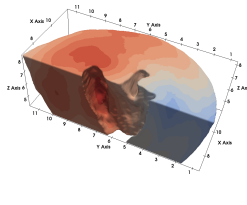
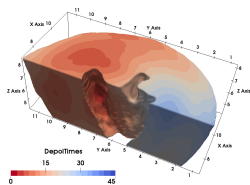
- ▶  $\sigma_l^{j*} \in [0, 1.74]$
- ▶  $\sigma_n^{j*} \in [0, 0.19]$



Extracellular

- ▶  $\sigma_l^{e*} \in [0.2, 3.9]$
- ▶  $\sigma_n^{e*} \in [0.2, 1.97]$

## Simulation of the modified bidomain model, isochrones.



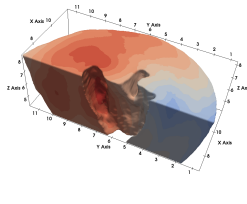
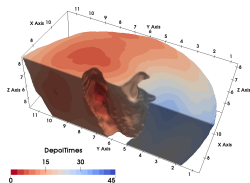
Isochrones with  $dt = 2.5ms$

Without inclusions,  $|Y_B| = 1$

vs.

With inclusions (parallel to fibers)

# Simulation of the modified bidomain model, isochrones.



Isochrones with  $dt = 2.5ms$

Without inclusions,  $|Y_B| = 1$

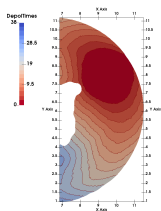
vs.

With inclusions (parallel to fibers)

**Table:** Various test cases and total depolarization time,  $T_D$ .

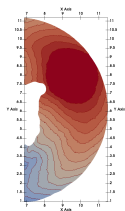
shapes	ref	Volume fraction from HR-MRI								
		sticks ( $\parallel$ )		plates ( $\parallel$ )		plates ( $\perp$ )		cubes		
$\sigma_d [Sm^{-1}]$	-	0.02	0.3	0.02	0.3	0.02	0.3	0.02	0.15	0.3
$T_D [ms]$	32.66	33.02	31.75	32.26	30.99	44.89	44.07	34.31	32.49	33.3
%	-	1,1%	2,7%	1,2 %	5,1%	37,4%	34,9%	5%	0,5%	1,9%

# Simulation of the modified bidomain model, isochrones.



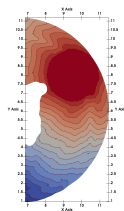
Without inclusions

vs.



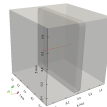
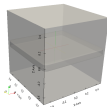
With inclusions parallel with fibers

vs.



With inclusions perp. to fibers

Isochrones with  $dt = 2ms$



**Table:** Various test cases and total depolarization time,  $T_D$ .

shapes	ref	Volume fraction from HR-MRI								
		sticks ( $\parallel$ )		plates ( $\parallel$ )		plates ( $\perp$ )		cubes		
$\sigma_d [Sm^{-1}]$	-	0.02	0.3	0.02	0.3	0.02	0.3	0.02	0.15	0.3
$T_D [ms]$	32.66	33.02	31.75	32.26	30.99	44.89	44.07	34.31	32.49	33.3
%	-	1,1%	2,7%	1,2 %	5,1%	37,4%	34,9%	5%	0,5%	1,9%



# Conclusions

1. Proposed extension of the bidomain model
2. Studied the quantitative effects: changes due to the size, shape and conductivity of diffusive inclusions
3. Applied on a slab of the rat heart

On going:

1. Use whole heart with realistic activation times
2. Simplification of the process using MUSIC and CEPS

To do:

1. Realistic shapes of inclusions
2. Use data with fibrosis, scars etc..
3. Validation: missing electrical data
4. Add other kinds of cells in inclusion, e.g. fibroblasts
5. Non-periodic homogenisation (stochastic approach)

Thank you. Merci.



informatics mathematics  
*Inria*

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12 June 2017