

# Multiscale modelling and numerical methods for the bioelectric activity of the heart

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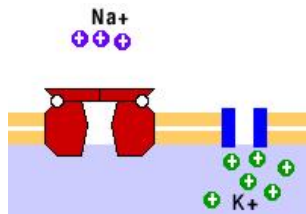
- Overview of the Problem
- Mathematical Models for the bioelectric activity of the heart
  - Microscopic Model
  - Macroscopic Model (Bidomain)
  - The derivation of the Macroscopic Model from the Microscopic properties of the tissue.
- Numerical Methods for the Bidomain Model

# The electrical activity of the heart

The bioelectric activity of cardiac cells is due to the flow of various ionic currents through the cellular membrane

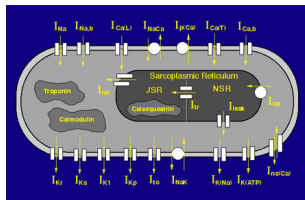
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membrane current per unit volume

$$I_m = c_m \frac{\partial v}{\partial t} + I_{ion}$$

$v$  is the transmembrane potential

$c_m$  surface capacitance

$I_{ion}$  is the ionic current depending on the membrane model chosen

# The Hodgkin-Huxley model for the ionic current

The first membrane model for ionic current was given by *Hodgkin-Huxley, J. Physiol. 1952* for nerve action potential.

Then models of Hodgkin-Huxley type have been developed for the cardiac action potential

# The Hodgkin-Huxley model for the ionic current

## Membrane ionic current

$$I_{ion}(v, w) = \sum_{k=1}^N G_k(v) \prod_{j=1}^M w_j^{p_{j_k}} (v - v_k(w))$$

- $w := (w_1, \dots, w_M)$  vector of the gating variables related to different ions flowing through membrane channels
- $G_k(w_k)$  conductance of the  $k$ -current
- $v_k$  is the equilibrium potential for the  $k$ -current
- $p_{j_k}$  are integers

## Dynamics of the gating and concentration variables

$$\frac{\partial w}{\partial t} = R(v, w) \quad \text{ODE's system}$$

$$R := (R_1, \dots, R_N)$$

$$R_K(v, w_k) := \alpha_k(v)(w_k - 1) + \beta_k(v)(w_k), \quad \alpha_k, \beta_k > 0$$

# Membrane models

Different models for

$$I_{ion}(v, w) = \sum_{k=1}^N G_k(v) \prod_{j=1}^M w_j^{p_{jk}} (v - v_k(w))$$

- Beeler–Reuter  $N = 4, M = 7$  (1977)
- phase-I Luo–Rudy  $N = 6, M = 7$  (1991)
- phase-II Luo–Rudy  $N = 10, M = 11$  (1994)
- etc.

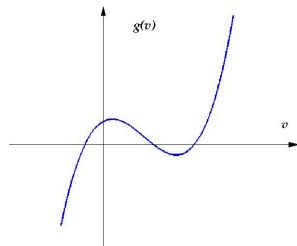
# Membrane models

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- etc.
- The simplified FitzHugh-Nagumo system ( $N=1, M=1$ )

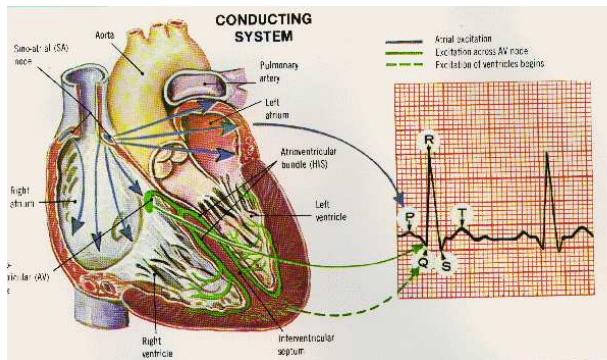
$$\begin{cases} I_{ion}(v, w) := g(v) + \beta w \\ R(v, w) := \eta w - \gamma v \end{cases}$$



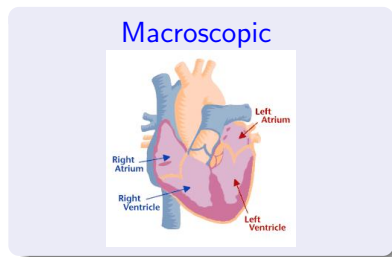
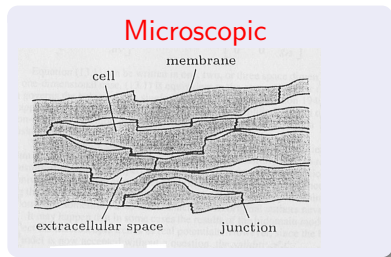
$g$  is a *cubic like* function,  $\beta, \gamma > 0$ .

# Aims

- **Simulations of the Cardiac Excitation Process**
- **Efficient modeling tool** for
  - potential maps
  - ElectroCardioGrams (ECGs)



# Multiscale Modelling



The macroscopic model can be derived from the microscopic properties of the tissue

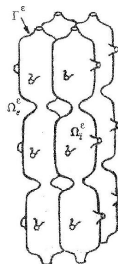
**formal derivation:** Neu, Krassowska 1993, Keener, Panfilov 1996, Keener 1998, Colli-Franzone, Savaré 2000

**rigorous mathematical derivation:** Pennacchio, Savarè, Colli Franzone, 2006

# The microscopic model

$\Omega^\varepsilon \in \mathbb{R}^3$ : domain modeling the heart

$$\Omega^\varepsilon := \Omega_i^\varepsilon \cup \Omega_e^\varepsilon \cup \Gamma^\varepsilon$$



$\Omega_i^\varepsilon$ : intracellular tissue with conductivity  $\sigma_i(x) > 0$

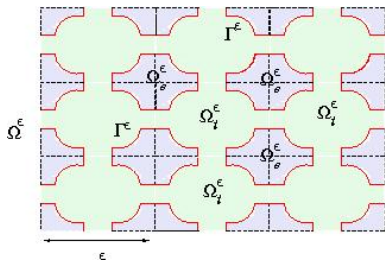
$\Omega_e^\varepsilon$ : extracellular tissue with conductivity  $\sigma_e(x) > 0$

$\Gamma^\varepsilon$  the cellular membrane

$u_i^\varepsilon$ : intracellular potential       $u_e^\varepsilon$ : extracellular potential

$v^\varepsilon = u_i^\varepsilon - u_e^\varepsilon$ : transmembrane potential

# The Microscopic model



Bidimensional section of the simplified 3-D periodic network of interconnected cells

## Microscopic model

$$-\operatorname{div}(\sigma_i^\varepsilon \nabla u_i^\varepsilon) = 0$$

$$\text{in } \Omega_i^\varepsilon \times (0, T)$$

$$-\operatorname{div}(\sigma_e^\varepsilon \nabla u_e^\varepsilon) = 0$$

$$\text{in } \Omega_e^\varepsilon \times (0, T)$$

$$\left. \begin{array}{l} -\sigma_i^\varepsilon \nabla u_i^\varepsilon \cdot \mathbf{n}_i \\ \sigma_e^\varepsilon \nabla u_e^\varepsilon \cdot \mathbf{n}_e \end{array} \right\} = \varepsilon (\partial_t v^\varepsilon + I_{ion}(v^\varepsilon, w^\varepsilon)) \quad \text{on } \Gamma^\varepsilon \times (0, T)$$

$$\partial_t w^\varepsilon = R(v^\varepsilon, w^\varepsilon) \quad \text{on } \Gamma^\varepsilon \times (0, T)$$

+ boundary and initial conditions

# The Macroscopic Model

## The Bidomain model

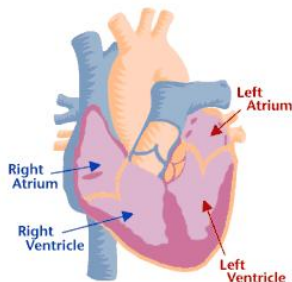
Cardiac Tissue: two anisotropic superimposed media, one **intracellular** and the other **extracellular** which occupy the same volume and are separated by the cellular membrane.

# The Macroscopic Model

## The Bidomain model

Cardiac Tissue: two anisotropic superimposed media, one **intracellular** and the other **extracellular** which occupy the same volume and are separated by the cellular membrane.

- Let  $\Omega \in \mathbf{R}^3$  the heart tissue

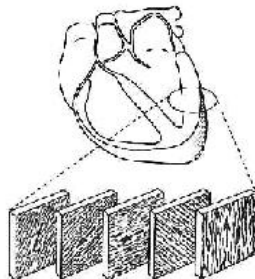


# The Macroscopic Model

## The Bidomain model

Cardiac Tissue: two anisotropic superimposed media, one **intracellular** and the other **extracellular** which occupy the same volume and are separated by the cellular membrane.

- Let  $\Omega \in \mathbf{R}^3$  the heart tissue
- Fiber structure:  
 $M_i, M_e$  intra-extracellular  
anisotropic conductivity tensors

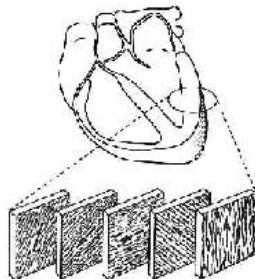


# The Macroscopic Model

## The Bidomain model

Cardiac Tissue: two anisotropic superimposed media, one **intracellular** and the other **extracellular** which occupy the same volume and are separated by the cellular membrane.

- Let  $\Omega \in \mathbf{R}^3$  the heart tissue
- Fiber structure:  
 $M_i, M_e$  intra-extracellular  
anisotropic conductivity tensors
- $u_i, u_e$  intra-extracellular  
potential

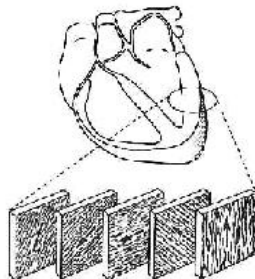


# The Macroscopic Model

## The Bidomain model

Cardiac Tissue: two anisotropic superimposed media, one **intracellular** and the other **extracellular** which occupy the same volume and are separated by the cellular membrane.

- Let  $\Omega \in \mathbf{R}^3$  the heart tissue
- Fiber structure:  
 $M_i, M_e$  intra-extracellular anisotropic conductivity tensors
- $u_i, u_e$  intra-extracellular potential
- $v = u_i - u_e$  transmembrane potential



# The Bidomain Model

## Reaction–Diffusion System

$$c_m \partial_t v - \operatorname{div} M_i \nabla u_i + I_{ion} = I_{app} \quad \text{in } \Omega \times ]0, T[$$

$$c_m \partial_t v + \operatorname{div} M_e \nabla u_e + I_{ion} = I_{app} \quad \text{in } \Omega \times ]0, T[$$

$$\partial_t w = R(v, w) \quad \text{in } \Omega \times ]0, T[$$

+ boundary and initial conditions

nonlinear degenerate parabolic system

$I_{ion}$  non-linear reaction term  
*related to the model of membrane*

$c_m$  cellular membrane capacitance

$I_{app}$  applied current

# The derivation of the macroscopic model

## Microscopic model

$$\begin{aligned} -\operatorname{div}(\sigma_i^\varepsilon \nabla u_i^\varepsilon) &= 0 && \text{in } \Omega_i^\varepsilon \times (0, T) \\ -\operatorname{div}(\sigma_e^\varepsilon \nabla u_e^\varepsilon) &= 0 && \text{in } \Omega_e^\varepsilon \times (0, T) \\ \left. \begin{aligned} -\sigma_i^\varepsilon \nabla u_i^\varepsilon \cdot \mathbf{n}_i \\ \sigma_e^\varepsilon \nabla u_e^\varepsilon \cdot \mathbf{n}_e \end{aligned} \right\} &= \varepsilon (\partial_t v^\varepsilon + I_{ion}) && \text{on } \Gamma^\varepsilon \times (0, T) \\ \partial_t w^\varepsilon &= R(v^\varepsilon, w^\varepsilon) && \text{on } \Gamma^\varepsilon \times (0, T) \end{aligned}$$

$$\downarrow \quad \varepsilon \rightarrow 0$$

$\Gamma$ -convergence

*Pennacchio, Savaré, Colli Franzone*  
*SIAM J. Math. Anal.*, (2006)  
vol. 37, (4), 1333-1370

## Macroscopic Model (Bidomain)

$$\begin{aligned} c_m \partial_t v - \operatorname{div} M_i \nabla u_i + I_{ion} &= 0 && \text{in } \Omega \times ]0, T[ \\ c_m \partial_t v + \operatorname{div} M_e \nabla u_e + I_{ion} &= 0 && \text{in } \Omega \times ]0, T[ \\ \partial_t w &= R(v, w) && \text{in } \Omega \times ]0, T[ \end{aligned}$$

# Equivalent Bidomain models

## $(u_i, u_e)$ formulation - Theoretical Analysis

nonlinear degenerate parabolic system

$$\begin{aligned}c_m \partial_t v - \operatorname{div} M_i \nabla u_i + I_{ion} &= I_{app} \\c_m \partial_t v + \operatorname{div} M_e \nabla u_e + I_{ion} &= I_{app}\end{aligned}$$

$$v = u_i - u_e \quad M = M_i + M_e$$

## $(v, u_e)$ formulation - Numerical simulations

parabolic and elliptic equation

$$\begin{aligned}c_m \partial_t v - \operatorname{div} M_i \nabla v + I_{ion} &= \operatorname{div} M_i \nabla u_e + I_{app} \\-\operatorname{div} M \nabla u_e &= \operatorname{div} M_i \nabla v\end{aligned}$$

**Which formulation for computational efficiency?**

# Which formulation for computational efficiency?

A comparison of the two formulations with Finite Element Method in a 3-D block of myocardium showed the best performance of the  $(u_i, u_e)$  formulation

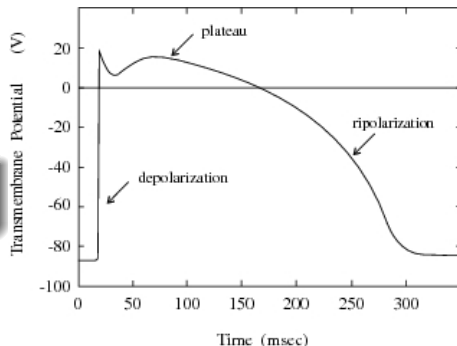
- At each time step we have to solve a **large linear algebraic system** whose computational cost is dominant with respect to the other parts of the computation
- The matrix associated to the  $(u_i, u_e)$  formulation can be reordered in such a way to be more sparse
- $(u_i, u_e)$  formulation is computationally more efficient than  $(v, u_e)$  formulation

*M. Pennacchio and V. Simoncini*

*J. Comput. Math. Appl., vol. 145, n. 1, pag. 49-70 (2002)*

# Numerical Methods

$v(\mathbf{x}, t)$  : sharp variation from a resting to a plateau value



time step  $\simeq 10^{-2}$  msec

space step  $\simeq 10^{-1}$  mm



3-D Large Scale Simulations are still too costly

# How to solve efficiently the bidomain model?

In literature we can find:

## Non Adaptive methods

- fixed time and space steps  $\Rightarrow$  discrete problems with at least  $O(10^7)$  unknowns
- the resulting numerical method is too costly
- many papers related to simulations in small block of the myocardium

## Adaptive methods

- space and time adaptivity to follow the cardiac excitation wavefront
- few works in literature:  
Cherry, Greenside, Henriquez 2000  
Lines, Grottun, Tveito, 2003  
Trangestein. Kim 2004  
Colli Franzone, Deuffhard, Ermann, Lang, Pavarino 2006

## Domain Decomposition Methods

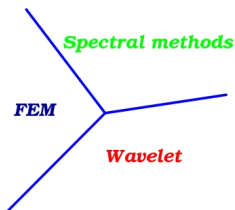
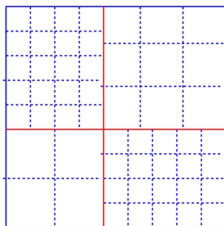
- The domain is decomposed into subdomains  $\rightarrow$  parallel computers
- Different papers for conforming domain decompositions

# How to combine the advantages of the previous methods?

## Mortar Method

a non-conforming non-overlapping Domain Decomposition method.

- 1 The domain is decomposed into subdomains
- 2 Different discretizations and/or methods can be considered in each subdomain



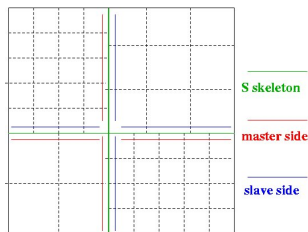
- 3 Using the **Mortar Method** the matching of different discretizations on adjacent subdomains is weakly enforced.

# Mortar Method

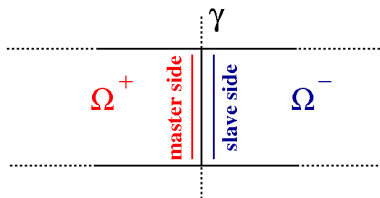
$\{\Omega_I\}_{I=1}^L$ : partition of  $\Omega \subset \mathbf{R}^2$

- $\Omega_I$  non-overlapping subdomains
- $\Gamma_{Ik} = \partial\Omega_I \cap \partial\Omega_k$
- $S = \cup \Gamma_{Ik}$  skeleton of the decomposition

On each  $\Gamma_{Ik}$ , one **master** side and one **slave** side is chosen.



## Jump constraint

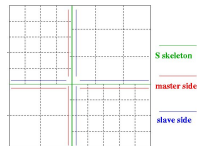


$u_h^-$  is determined once  $u_h^+$  is given, through the **constraint**:

$$\int_{\gamma} (u_h^- - u_h^+) \lambda_h = 0, \quad \forall \lambda_h \in \Lambda_h$$

- implementation requires computing the constraint

# Mortar Method



- The actual degrees of freedom  $\mathbf{u}^M$  are

- ① coefficients corresponding to basis functions on  $\Omega_I$
- ② coefficients corresponding to a master side

The value of those coefficients corresponding to basis functions “living” on **slave sides** is uniquely determined by the remaining coefficients through the jump condition.

- Let  $\mathbf{u}^S$  be these constrained coefficients then

$$\mathbf{u} = \begin{pmatrix} \mathbf{u}^M \\ \mathbf{u}^S \end{pmatrix} \quad \text{and} \quad \mathbf{u}^S = \mathbf{C} \mathbf{u}^M$$

with **C** matrix expressing the constraint.

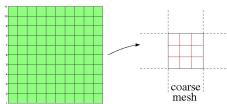
# Mortar Method in computational electrocardiology

*M. Pennacchio, J. Sci. Comput. , vol. 20, (2), pag. 191-210 (2004)*

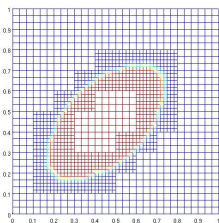
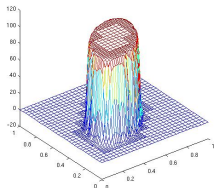
*M. Pennacchio, Computers in Cardiology 2004; vol. 31: 509-512*

## Domain decomposition in

- regions of high and low electrical activity



- Identification of the domains crossed by the cardiac wavefront:  
 $v$  transmembrane potential



# Mortar Method in Computational Electrophysiology

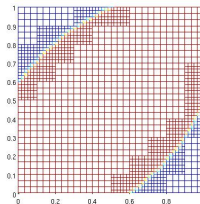
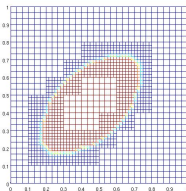
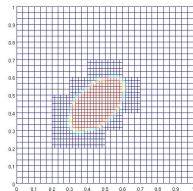
**Coarse**

**Refined**

- Refinement of these domains



- Mesh at different time instants:



# Discretization

- In each subdomain: **FEM** + **semi-implicit scheme**
- Each time step we have to solve:

$$C^T B C \mathbf{u}^{k+1} = C^T \mathbf{b}$$

$$C$$

Constraint matrix

$$B = M_t + A$$

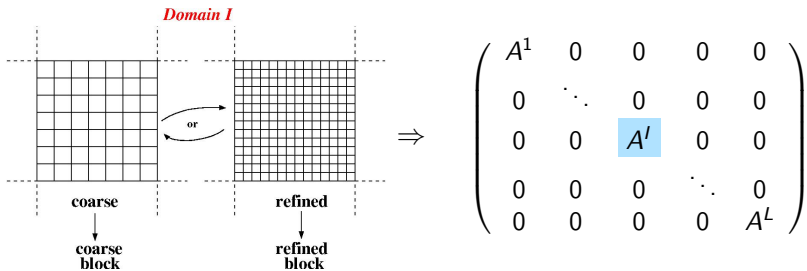
$M_t = \frac{c_m}{\tau} M$ ,  $\tau$  time step

$M$  lumped mass matrix

$A$  stiffness matrix = 
$$\begin{pmatrix} A^1 & 0 & 0 \\ 0 & \ddots & 0 \\ 0 & 0 & A^L \end{pmatrix}$$

If the mesh changes the matrices  $A$ ,  $M$  and  $C$  have to be rebuilt, but not completely. Indeed

**$A$  is block-diagonal**  $\Rightarrow$  only the block corresponding to a subdomain that is refined or derefined has to be changed



The coarse and the refined block are computed only once:  
at the beginning

# Results

- Square domain  $\Omega = 1 \text{ cm} \times 1 \text{ cm}$
- Uniform mesh in each domain

Domain not crossed  
by the wavefront



coarse mesh  
space step  $dx = 3.33 \cdot 10^{-1} \text{ cm}$

Domain crossed by  
the wavefront

Refinement



Level 1



Level 2



Level 3

...

- At level 5 of refinement:  
space step  $dx = 2.08 \cdot 10^{-3} \text{ cm}$  close to the wavefront
- Time step fixed:  $dt = 4 \cdot 10^{-2} \text{ msec}$

# Comparison with the standard conforming FEM

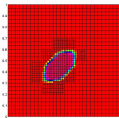
Conjugate Gradient with an Incomplete Cholesky preconditioner

Substructuring preconditioner: *M. Pennacchio, V. Simoncini 2006*

Two cases are considered:

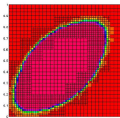
- **“Small” wavefront:** 10 msec after stimulation  $\Rightarrow$  250 time steps

**16 refined  
subdomains**



- **“Large” wavefront:** 30 msec after stimulation  $\Rightarrow$  750 time steps

**max number (45)  
of refined  
subdomains**



“Small” Wavefront: 16 refined subdomains / 250 time steps

		# elem	cputime (sec.)	cputime reduction
LEVEL 1	mortar	900	11.3	NO
	conf. FEM	900	5.9	
LEVEL 2	mortar	927/1332	17	23 %
	conf. FEM	3600	22	
LEVEL 3	mortar	1035/3060	26	73 %
	conf. FEM	14440	98	
LEVEL 4	mortar	1467/9972	62	89 %
	conf. FEM	57600	584	
LEVEL 5	mortar	3195/37620	220	92 %
	conf. FEM	240000	2887	

“Large” Wavefront: **45 refined subdomains / 750 time steps**

		# elem	cputime (sec.)	cputime reduction
LEVEL 1	mortar	900	34.2	NO
	conf. FEM	900	17.9	
LEVEL 2	mortar	927/2115	66	1 %
	conf. FEM	3600	67	
LEVEL 3	mortar	1035/6975	150	48 %
	conf. FEM	14440	290	
LEVEL 4	mortar	1467/26415	613	59 %
	conf. FEM	57600	1510	
LEVEL 5	mortar	3195/104175	2679	69 %
	conf. FEM	240000	8558	

## Conclusions

The proposed numerical method:

- concentrates the computational work only in regions of high electrical activity.
- allows more accurate computation with a lower computational cost
- is adaptive but can maintain the easiness of implementation and the properties of methods based on uniform structured grids
- The efficiency of the method may be improved since **parallelization should be taken into account**