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## Modelling cardiac electrophysiology with structural heterogeneities and dynamical gap junctions

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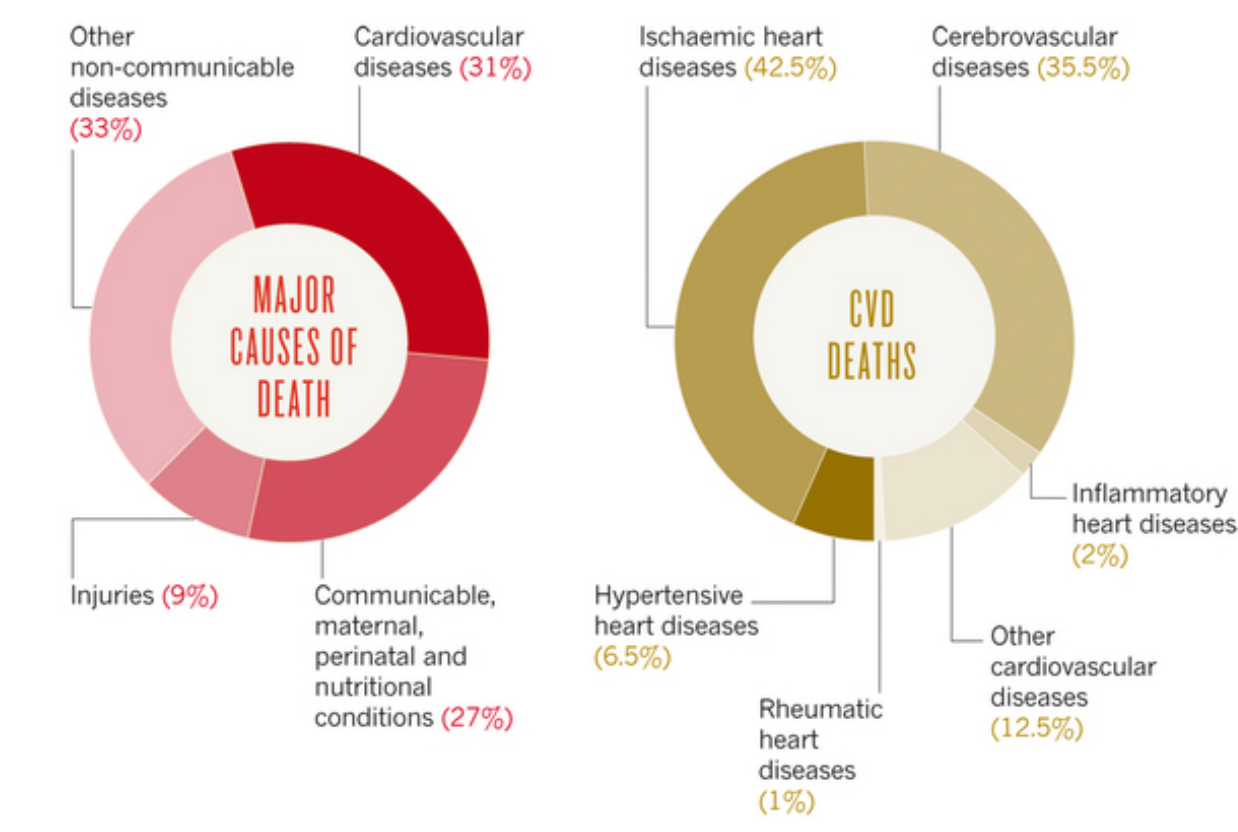
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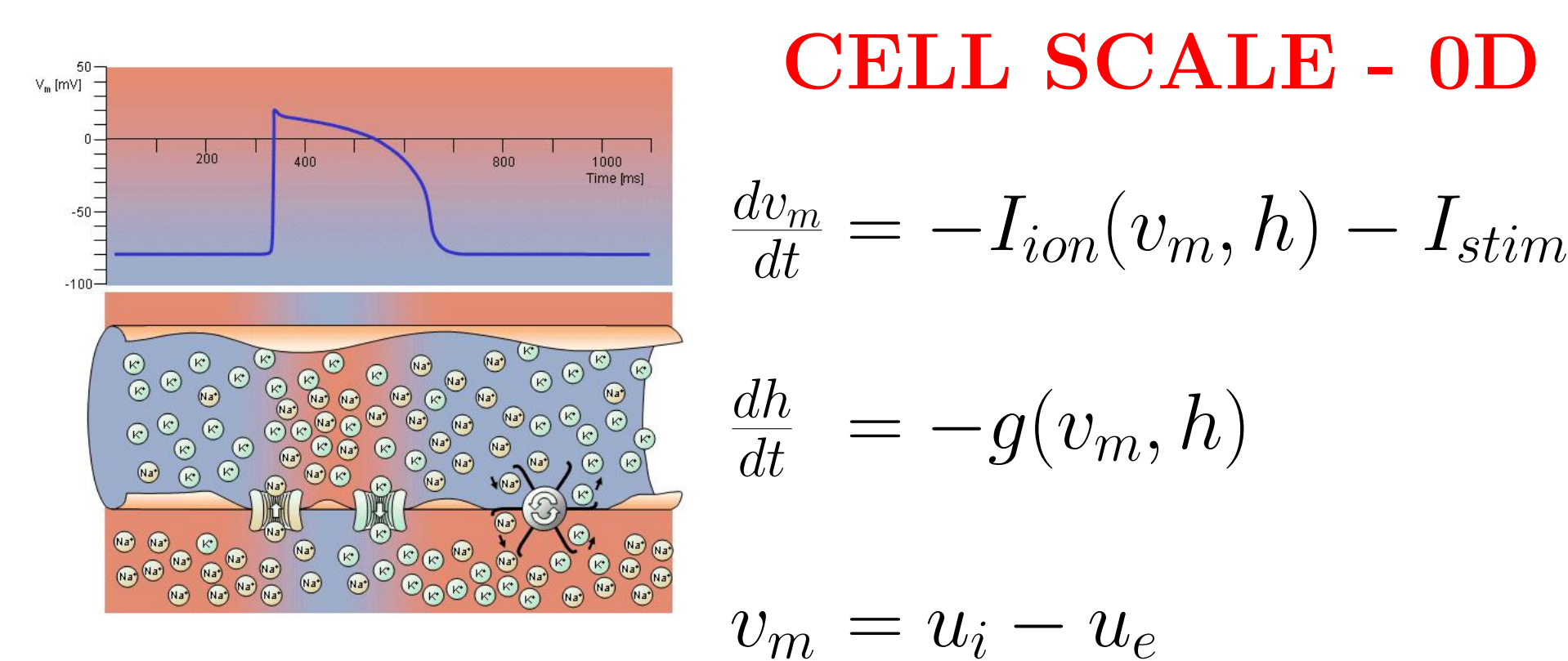


## Why?



- > 17 000 000 people die every year
- medical care - millions of EUR

## Multiscale Modelling



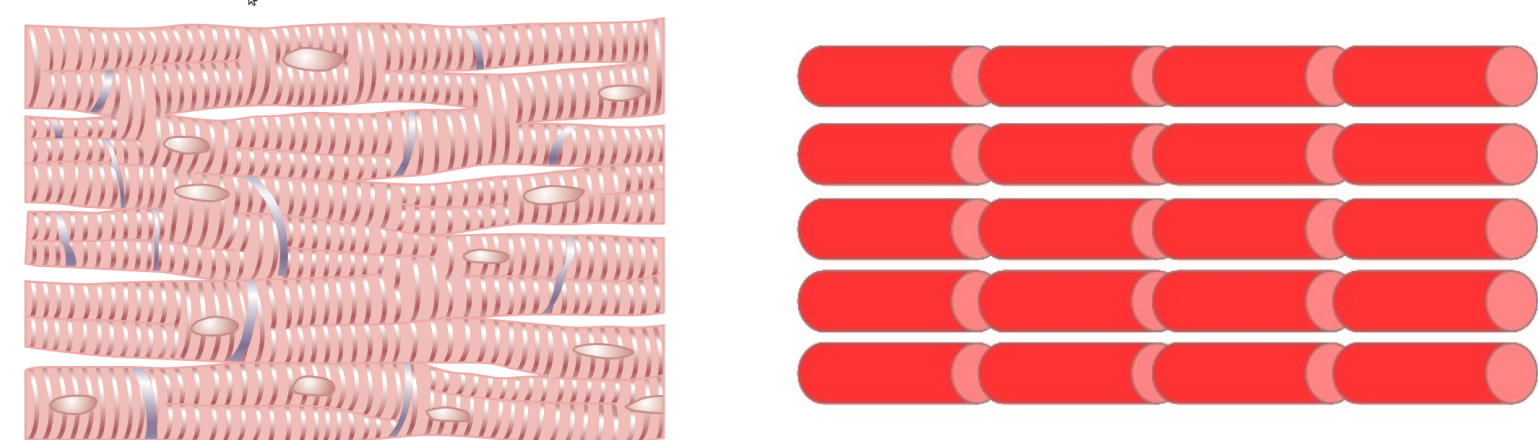
### CELL SCALE - 0D

$$\frac{dv_m}{dt} = -I_{ion}(v_m, h) - I_{stim}$$

$$\frac{dh}{dt} = -g(v_m, h)$$

$$v_m = u_i - u_e$$

### TISSUE SCALE - 2D or 3D



- Bidomain model (Neu-Krassowska, 1993)

$$\begin{aligned} \partial_t h + g(v_m, h) &= 0 \\ \partial_t v_m + I_{ion}(v_m, h) &= \nabla \cdot (\sigma^i \nabla u^i) \\ \partial_t v_m + I_{ion}(v_m, h) &= -\nabla \cdot (\sigma^e \nabla u^e) \end{aligned}$$

- generalised cable equation
- derived from microscopic equations
- anisotropic model

## SCARS - BLACK BOXES

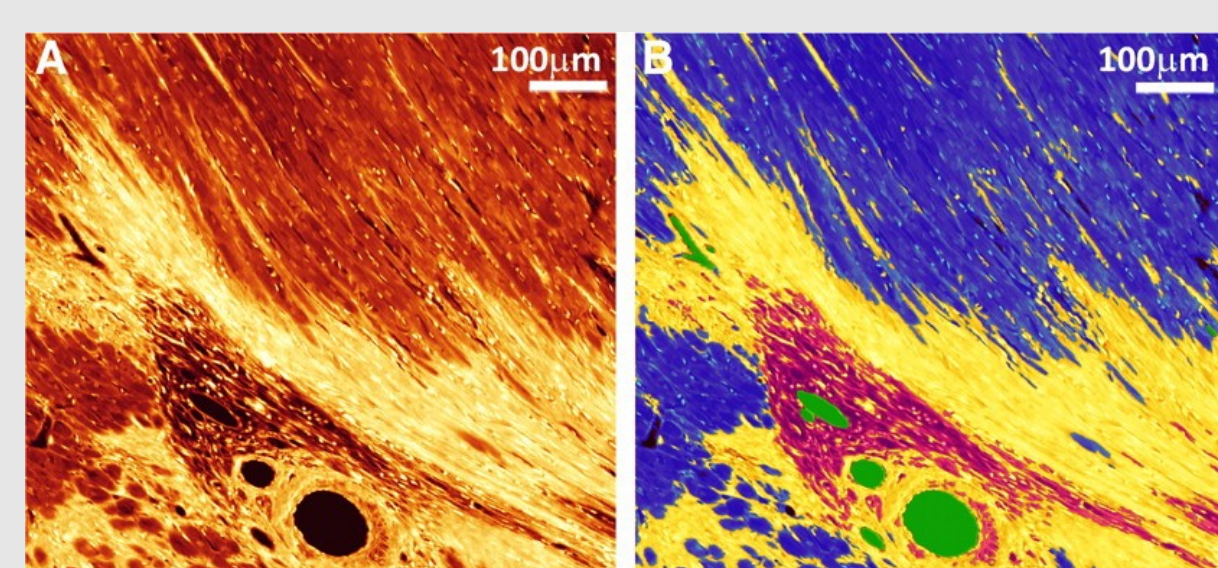


Figure : The infarct border zone. (Rutherford, 2012)

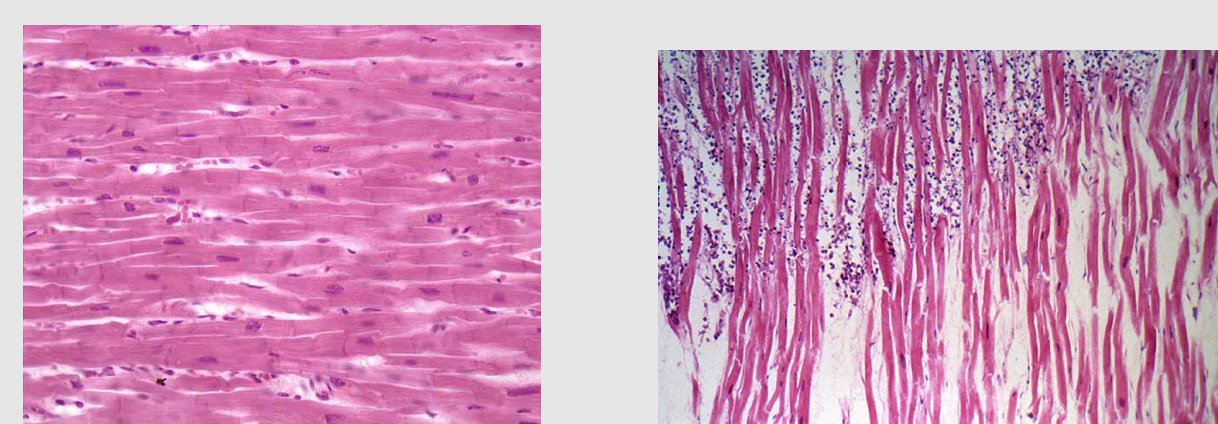


Figure : Normal vs myocardial infarction in human.

## MAIN FACTORS

- Nonlinear ionic currents
- MICROSTRUCTURE**
- Gap Junctions (resistors?)

## Assumptions

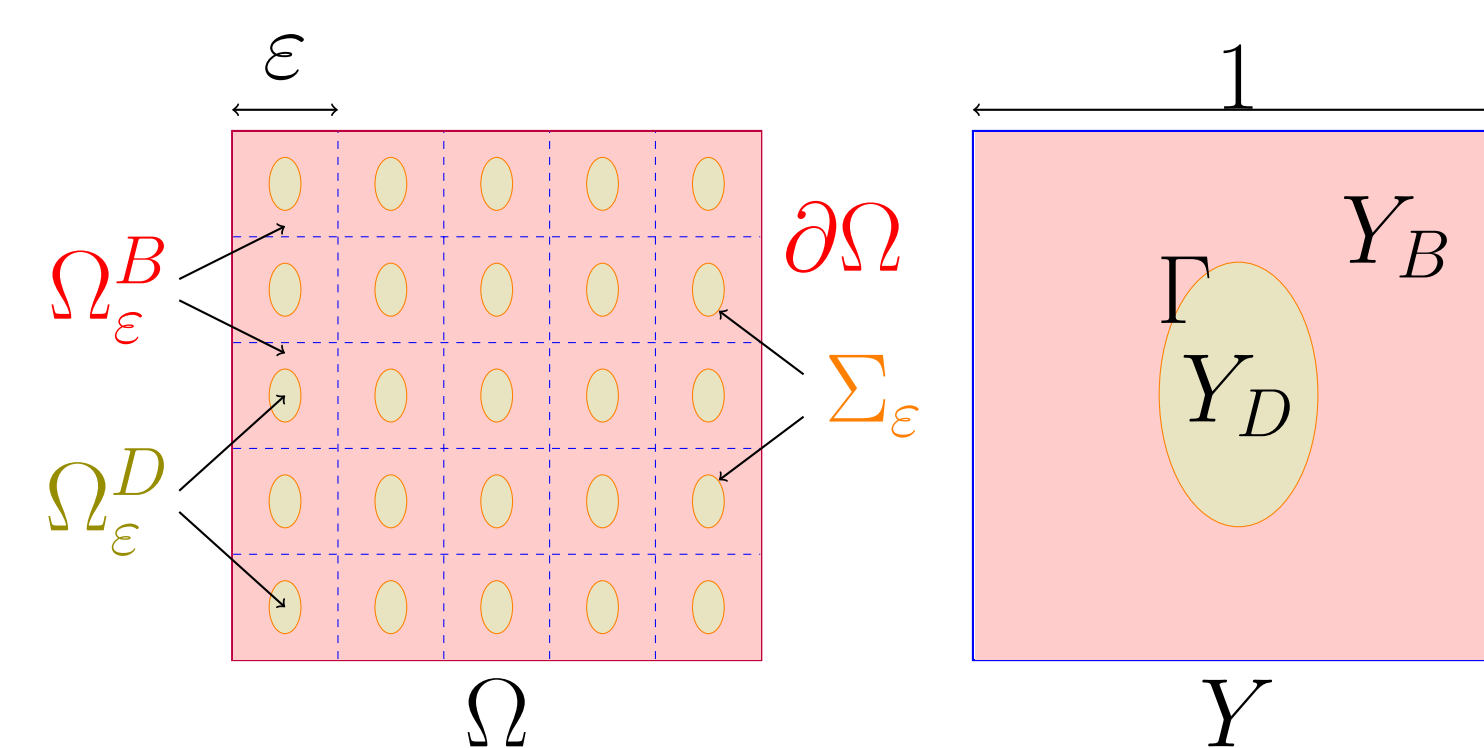
- Periodic** inclusions of size  $\varepsilon$ .
- Isotropic conductivity in the inclusions.
- No cells in the inclusions - **passive conductors**.
- Standard transmission conditions.

## MESOSCALE MODEL

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

$$\nabla \cdot (\sigma_\varepsilon^d \nabla u_\varepsilon^d) = 0, \quad \text{in } \Omega_\varepsilon^D.$$

$$\left. \begin{aligned} \sigma_\varepsilon^i \nabla u_\varepsilon^i \cdot \mathbf{n}_{\Sigma_\varepsilon} &= 0, \\ \sigma_\varepsilon^e \nabla u_\varepsilon^e \cdot \mathbf{n}_{\Sigma_\varepsilon} &= \sigma_\varepsilon^d \nabla u_\varepsilon^d \cdot \mathbf{n}_{\Sigma_\varepsilon}, \\ u_\varepsilon^e &= u_\varepsilon^d, \end{aligned} \right\} \quad \text{on } \Sigma_\varepsilon.$$



## MODIFIED BIDOMAIN MODEL

- Limit macroscale model

$$\begin{aligned} \partial_t h_0 + g(v_0, h_0) &= 0, \\ |Y_B|(\partial_t v_0 + I_{ion}(v_0, h_0)) &= \nabla \cdot (\tilde{\sigma}_i \nabla u_0^i), \\ |Y_B|(\partial_t v_0 + I_{ion}(v_0, h_0)) &= -\nabla \cdot (\tilde{\sigma}_e \nabla u_0^e). \end{aligned}$$

$$\begin{aligned} \tilde{\sigma}_i &= \sigma^i |Y_B| + A^i(\sigma_i, w^i), \\ \tilde{\sigma}_e &= \sigma^e |Y_B| + \sigma^d |Y_D| + A(\sigma_e, \sigma_d, w) \end{aligned}$$

- UPDATED CONDUCTIVITIES!**
- $A_i$ ,  $A$  matrices obtained by solving the cell problems on  $Y$  for  $w^i$  and  $w$ .
- volume fraction AND geometry

## A word on homogenisation..

- Full problem depends on  $\varepsilon \Rightarrow$  very expensive**
- Averaging solution:  
Let  $\varepsilon \rightarrow 0$

$$L_\varepsilon u_\varepsilon = f \rightarrow Lu = f$$

- Formal asymptotic expansion

$$u_\varepsilon(t, x) = u_0(t, x, x/\varepsilon) + \varepsilon u_1(t, x, x/\varepsilon) + \dots$$

$\Rightarrow$  Cascade PDE systems

- Cell problems** for new variables  $w$  - define dependence of  $u_1$  on  $u_0$  - solved once.
- Homogenised problem** - limit macroscale problem on  $u_0$  that does not depend on  $\varepsilon$ .
- A priori estimates** ensure two scale convergence (Allaire, 1992)
- Difficulty - **nonlinear** ionic functions

## Numerical results

- FreeFem++* and *gnuplot*
- Mitchell Schaeffer ionic model
- 2D simulations on rectangle, SBDF2 scheme
- Circular and elliptical inclusions

Table : Modified conductivities. C - circles, E - ellipses.

Inclusions	Vol. fraction	$\sigma_{i11}^*$	$\sigma_{i22}^*$	$\sigma_{e11}^*$	$\sigma_{e22}^*$
none	0.0	1.74	0.19	3.9	1.97
C	0.18	1.29	0.18	3.28	2.45
C	0.2	1.26	0.17	3.29	2.53
C	0.4	1.07	0.15	3.42	3.53
C	0.7	0.69	0.09	5.08	7.89
E - long	0.18	0.31	0.19	0.75	2.61
E - short	0.2	1.13	0.18	2.82	2.58
E - medium	0.2	0.86	0.18	2.09	2.64
E - short	0.4	0.81	0.16	2.53	3.70

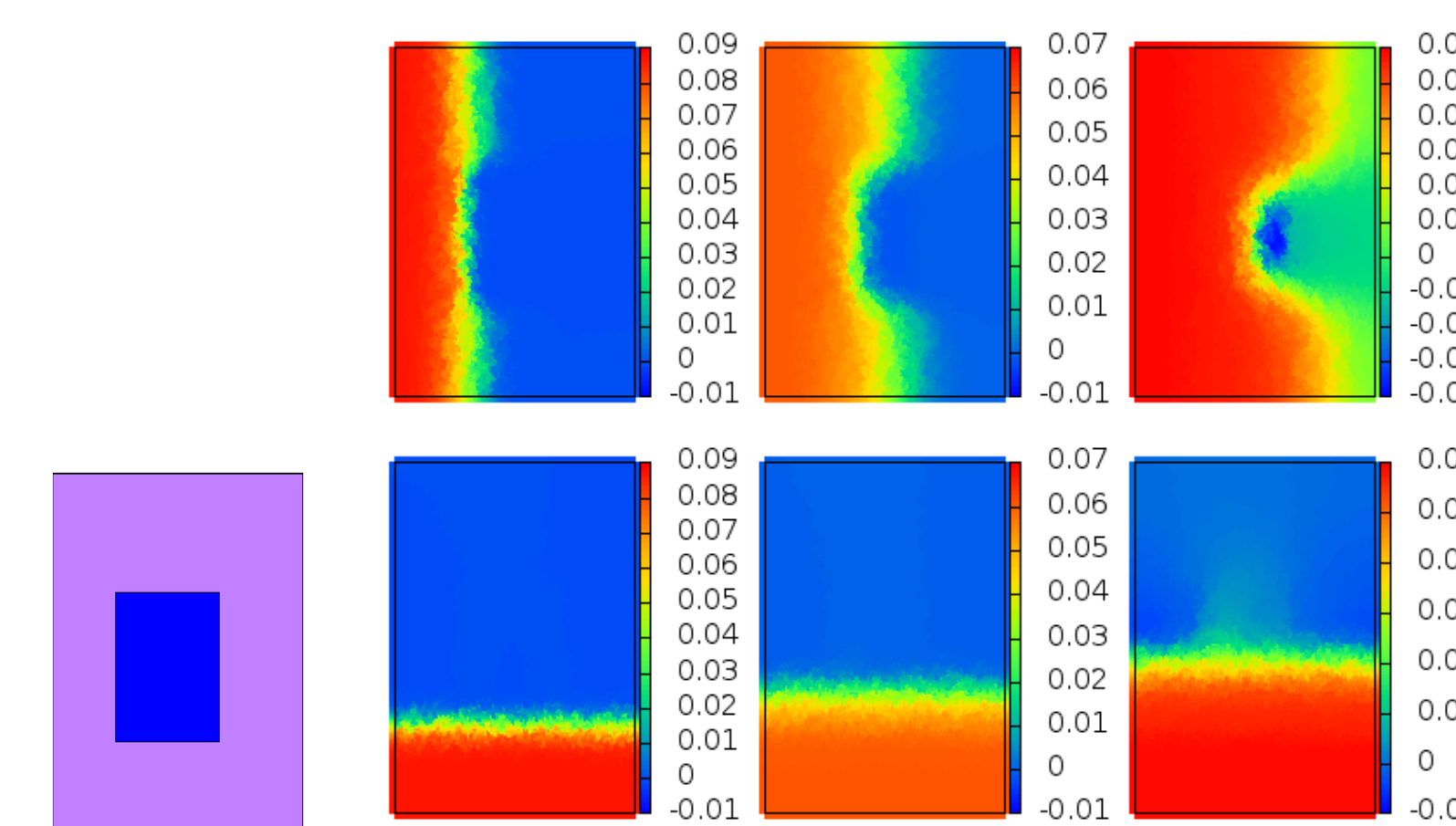


Figure : Propagation of  $v_m$  in heterogeneous tissue.

## What about GAP JUNCTIONS?

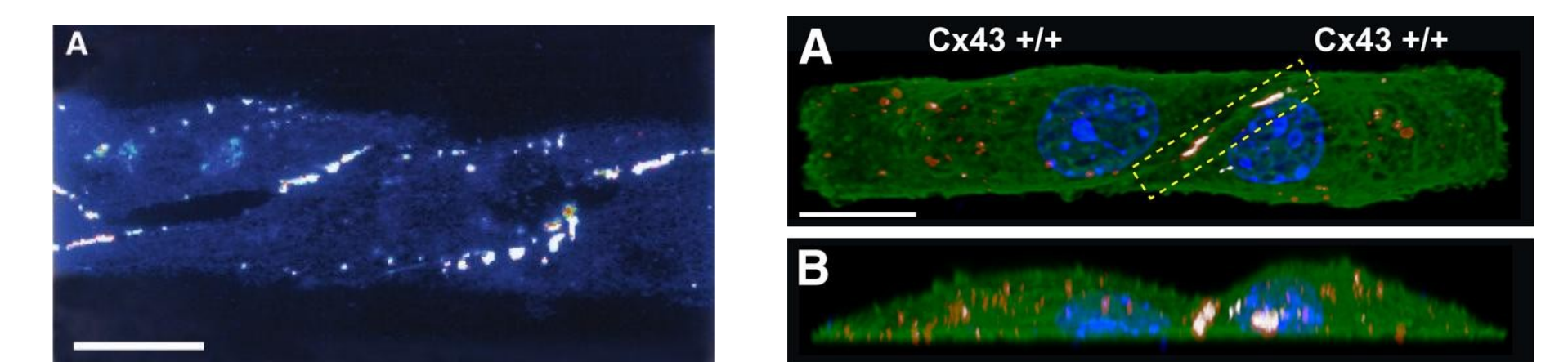


Figure : Immunohistochemical analysis of Cx43. Left: Bar =  $10\mu m$ . (Beauchamp, 2004) Right: top view(A), lateral view(B). Bar =  $5\mu m$ . (Beauchamp, 2012)

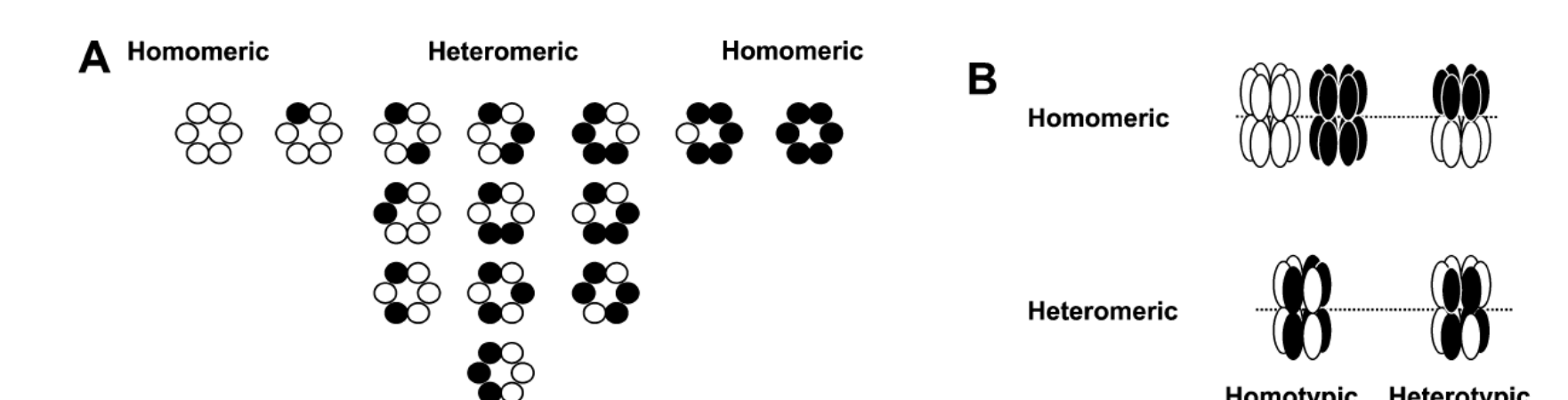


Figure : Predicted configurations of connexons and gap junction channels for two different connexins. (Desplantez, 2004)

- Distributed around the cell perimeters.
- Expressed in ventricles: Cx43, Cx45 and Cx40.
- In recent models:

$$I_j = g_j V_j$$

with  $g_j = const$  and  $V_j$  - transjunctional voltage.

## NON LINEAR MODEL

- Gating variable:  $g_j = g_j(t, V_j)$
- Fit experimental data to find  $g_\infty/g_0$  and  $\tau_\infty$ .

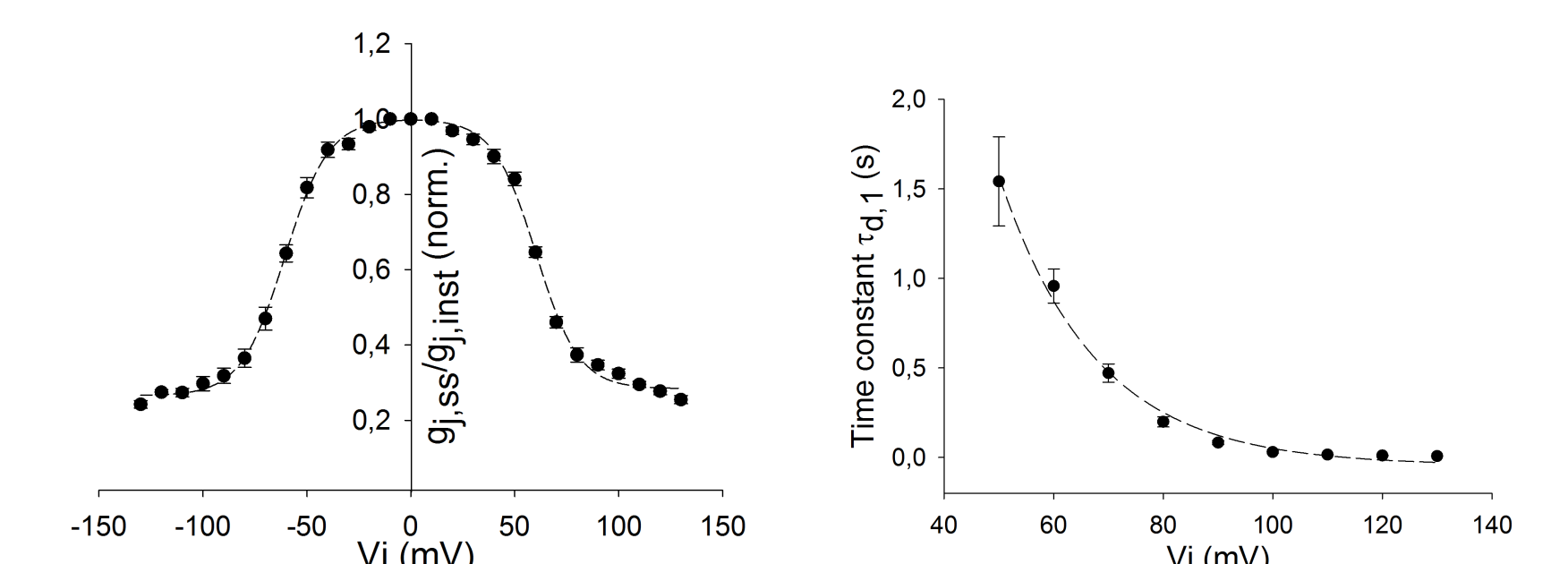


Figure : Fitting the non-linear model to the experimental data for the homomeric Cx43 gap junction in rodent.

$$g_j = g_\infty + (g_0 - g_\infty)e^{-\frac{t}{\tau_\infty}}$$

## Work in progress... and beyond

- Current work: including GJ model
  - as boundary condition
  - rescaling propagation front
- Future work:
  - SCAR modelling
  - Late enhancement MRI