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Microscopic Modelling of the Non-Linear Gap Junction Channels

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On Gap Junctions

What is a Gap Junction?

- Cluster of gap junction channels
- Linking structure between neighbouring cells
- Provides direct passage of molecules and ions

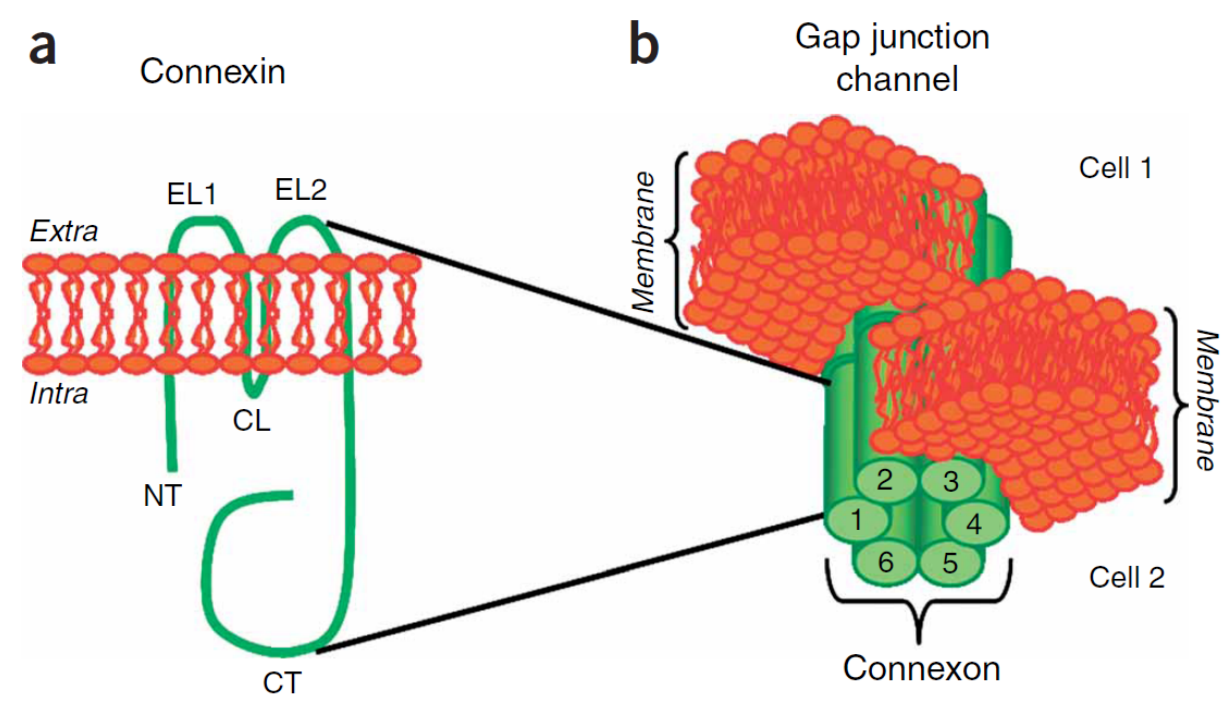


Figure : Schematic diagrams of a standard connexin molecule and gap junction channel. (Del Corso et. al., 2006)

What are they made of?

- Proteins connexins.
- 6 connexins = 1 connexon (hemichannel)
- 2 connexons = 1 gap junction channel
- Cardiac cell proteins: Cx43, Cx45 and Cx40.

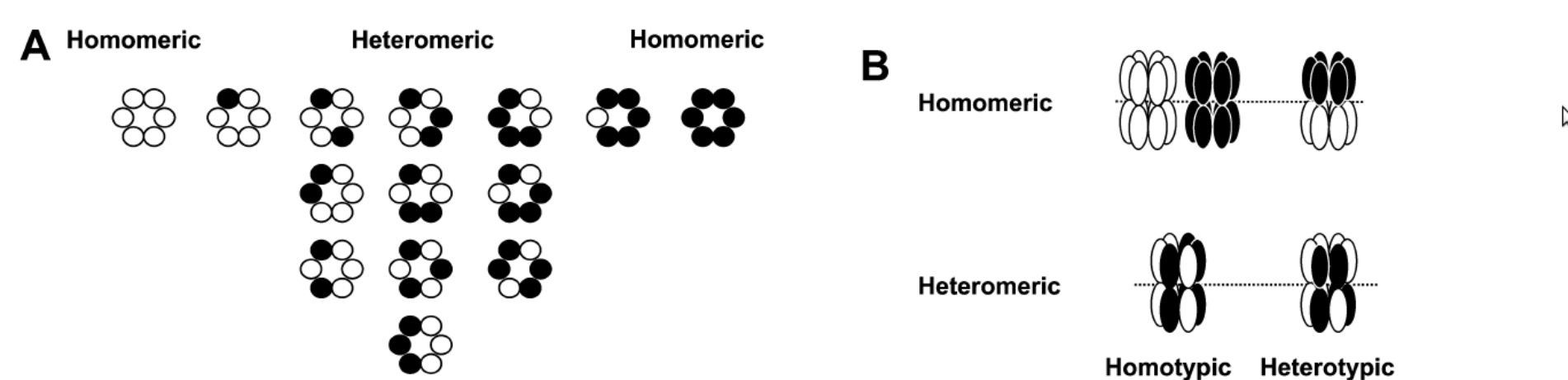


Figure : Predicted configurations of connexons and gap junction channels for two different connexins. (Desplantez, 2004)

Where are they located in cardiac cells?

- Mostly on the longitudinal ends where they compose the intercalated disks
- The behaviour of transversal GJ channels is not well understood

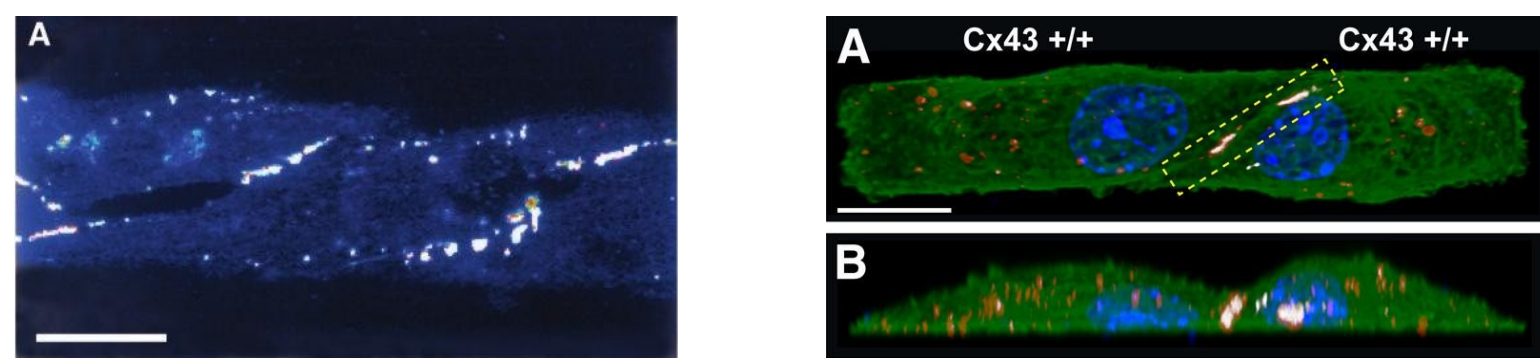


Figure : Immunohistochemical analysis of Cx43. Left: Bar = 10 μm. (Beauchamp, 2004) Right: top view(A), lateral view(B). Bar = 5 μm. (Beauchamp, 2012)

What about electrical behaviour?

- The dual voltage patch clamp
- Non-linear behaviour**
- Time dependence**
- Dependent on connexin arrangement.

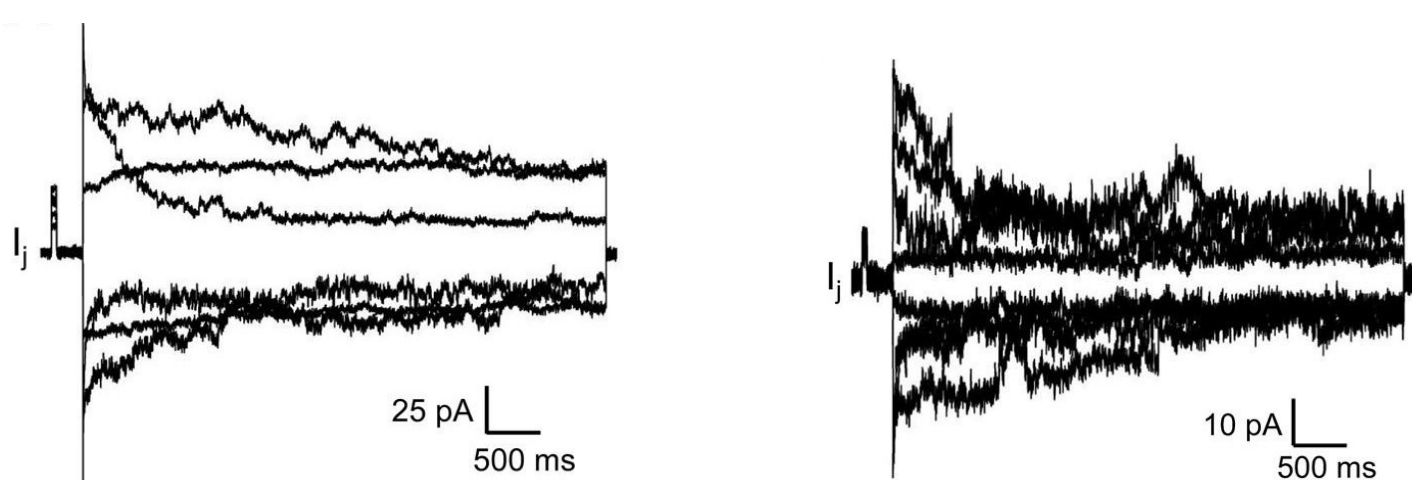
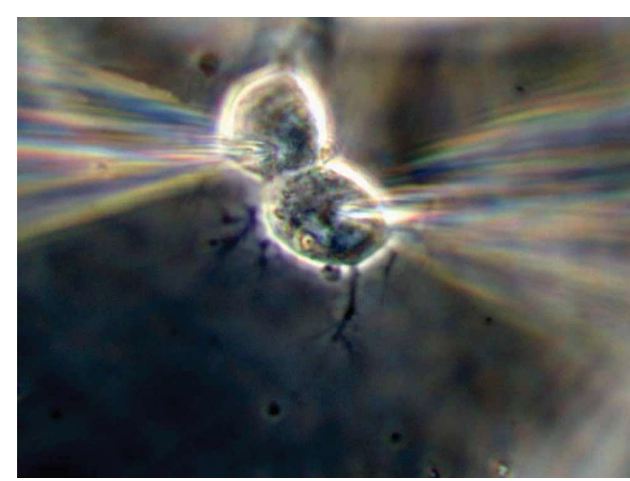


Figure : GJ currents in time, fixed V_j . Left: Homotypic Cx43/Cx43 cell pairs. Right: Cx43KO/Cx43KO cell pairs.

Macroscopic effects

- Primary cultures of Cx43 and Cx43KO ventricular myocytes.
- Macroscopic velocity calculated from the difference in activation times

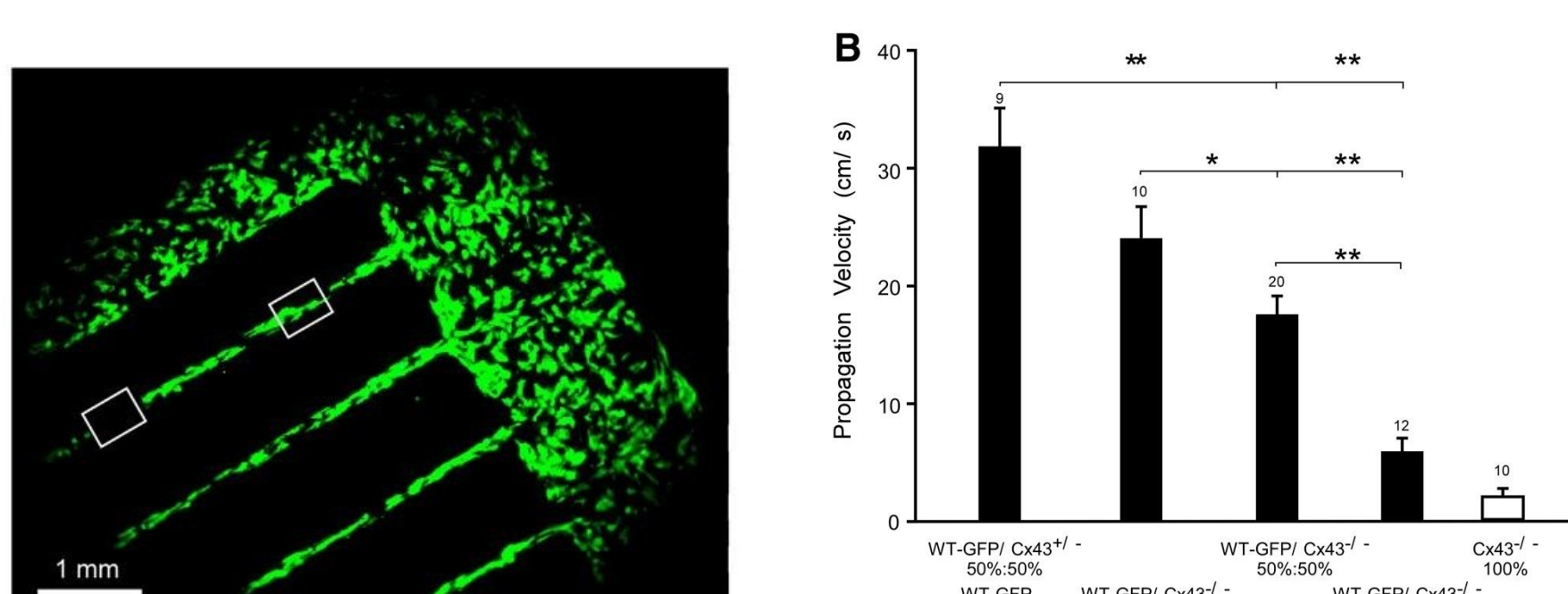


Figure : Left: A mixed patterned cell culture at low magnification. Right: Decrease in velocity of propagation w.r.t. presence of Cx43 cells.

Non linear GJ model - 0D

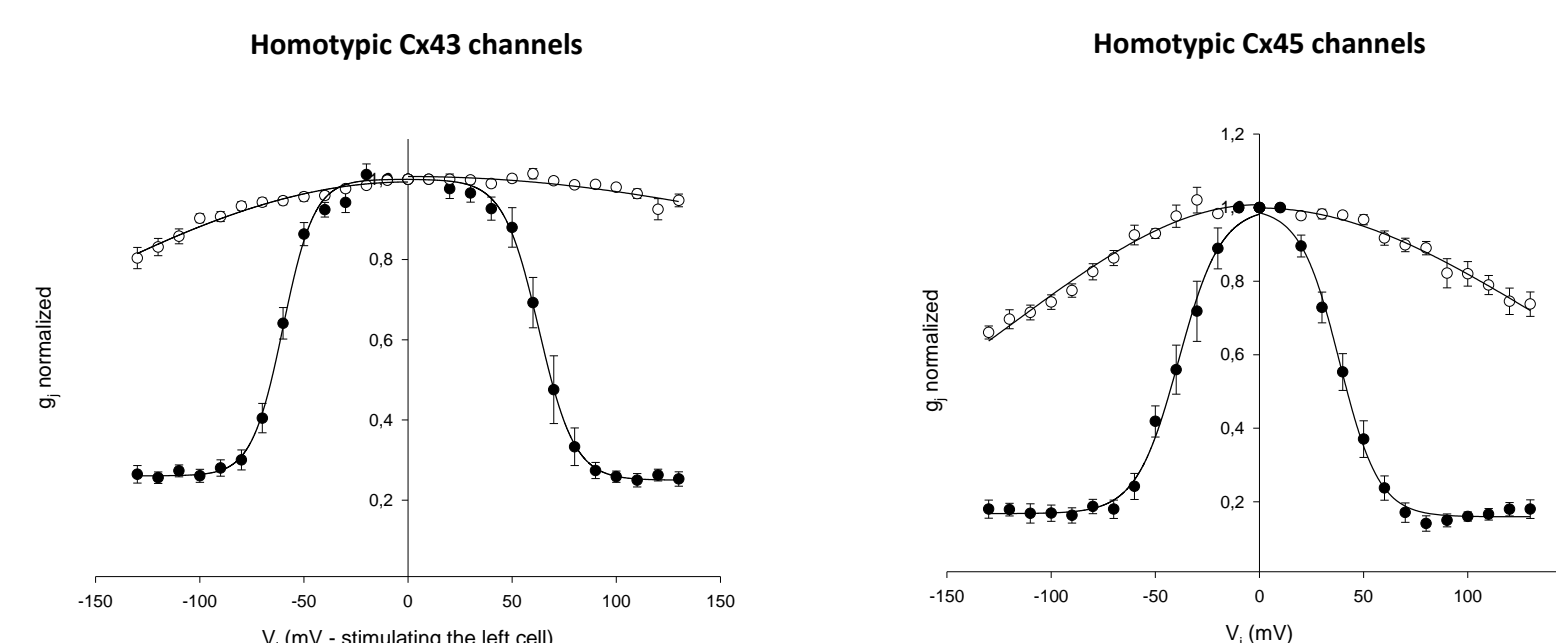
- GJ current:

$$I_j = G_j(t, V_j) V_j,$$

where:

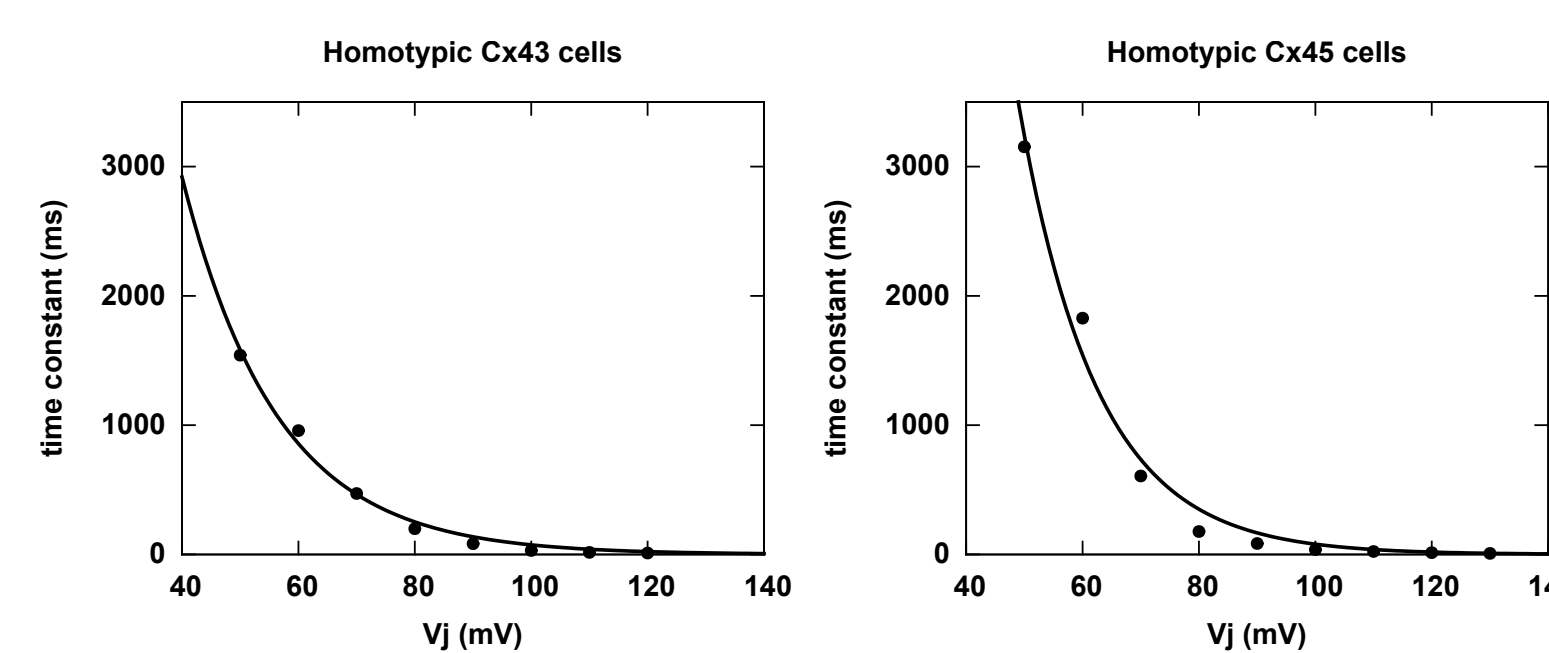
- V_j transjunctional voltage.
 - Conductance: $G_j(t, V_j) = g_{j,0} g_j(t, V_j)$.
 - The amplitude of the junctional conductance: $g_{j,0} = 68 nS$ for Cx43 cells, i.e. $g_{j,0} = 2 nS$ for Cx43KO.
 - Gating variable: $g_j = g_j(t, V_j)$
- $$\frac{dg_j}{dt} = \frac{g_\infty(V_j) - g_j}{\tau_\infty(V_j)}$$

- Fit experimental data to find normalised $g_\infty(V_j)$.



Dual voltage clamp recordings performed in stably transfected (single transfection) HeLa cells

- Fit experimental data to find $\tau_\infty(V_j)$.



Numerical simulation

- Assume uniform distribution of GJ channels over given area (see 2D model)

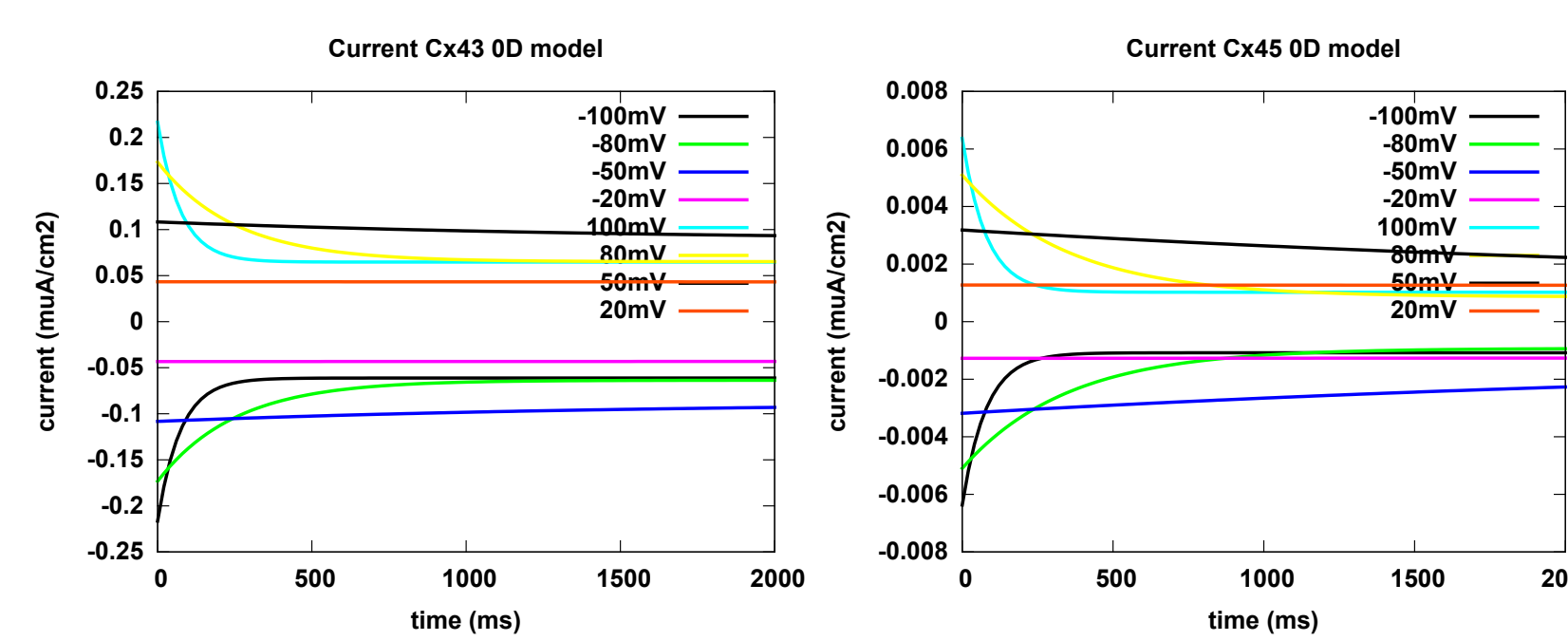
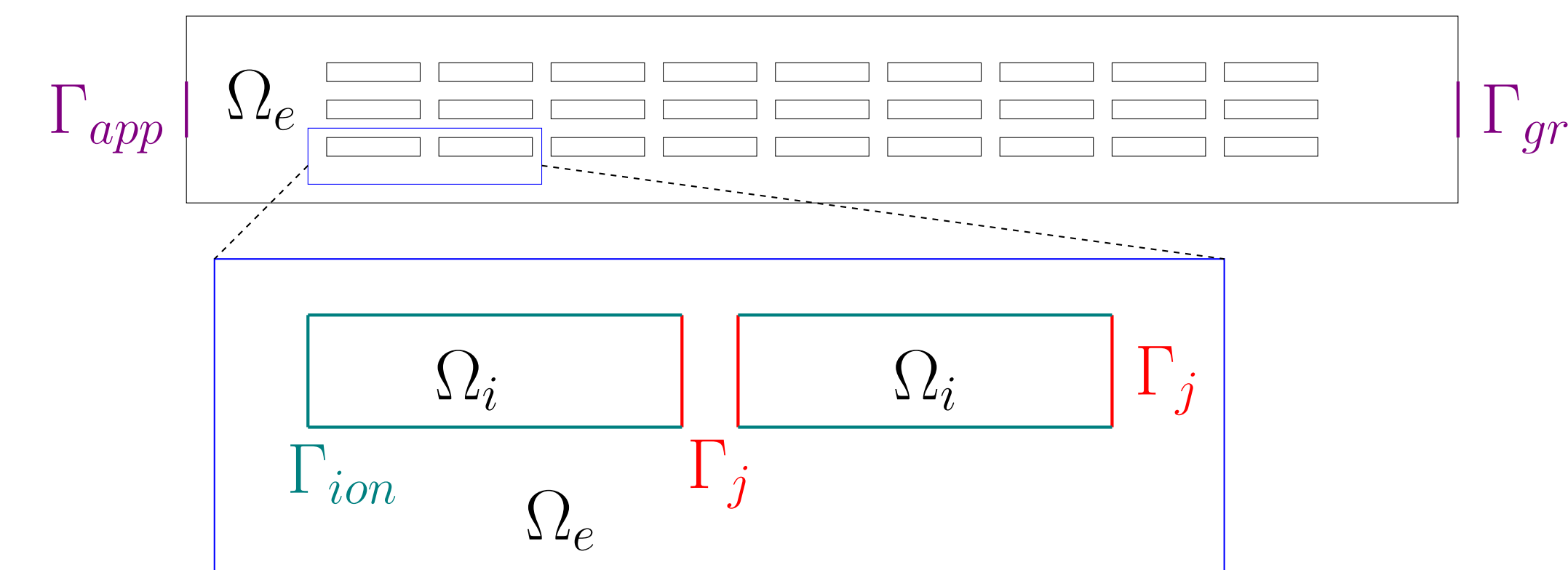


Figure : Simulated GJ current per unit area w.r.t. the time for the fixed V_j .

Assumptions

- Use only homotypic Cx43 and Cx45 GJ channels.
- GJ channels are at the perimeters of the cells, on the membrane.
- The rest of the membrane has only ionic channels. Use Beeler Reuter ionic model.

2D microscopic model



Main problem:

$$\begin{aligned} \sigma^i \Delta u_i &= 0, & \text{in } \Omega_i, \\ \sigma^e \Delta u_e &= 0, & \text{in } \Omega_e. \end{aligned}$$

Ionic model:

$$\left. \begin{aligned} \partial_t V_m + I_{ion}(V_m, \mathbf{h}) &= -\sigma_i \nabla u_i \cdot \mathbf{n}, \\ \partial_t V_m + I_{ion}(V_m, \mathbf{h}) &= -\sigma_e \nabla u_e \cdot \mathbf{n}, \\ \partial_t \mathbf{h} &= f_{ion}(V_j, \mathbf{h}), \end{aligned} \right\} \text{ on } \Gamma_{ion}.$$

GJ model:

$$\left. \begin{aligned} G_j(V_j, g_j) \cdot V_j &= -\sigma_i \nabla u_i \cdot \mathbf{n}, \\ \partial_t g_j &= f_j(V_m, g_j), \end{aligned} \right\} \text{ on } \Gamma_j.$$

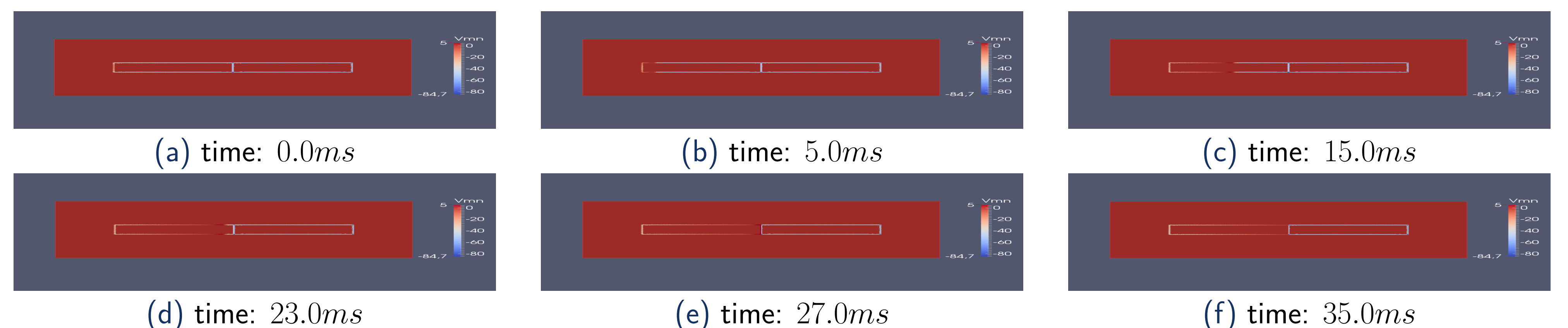
Boundary conditions and stimulus:

$$\begin{aligned} \sigma_e \nabla u_e \cdot \mathbf{n} &= 0, & \text{on } \partial \Omega_e \setminus \Gamma_{ion}, \\ u_e &= 0, & \text{on } \Gamma_{gr}, \\ \text{for } t \in [t_0, t_0 + t_{stim}], \\ u_e &= U_{app}, & \text{on } \Gamma_{app}. \end{aligned}$$

- σ_i, σ_e intra and extracellular conductivities
- \mathbf{h} gating variables for ionic model
- $V_m = u_i - u_e$ transmembrane potential
- $V_j = [u_i]$ transjunctional potential

Numerical analysis - 2D test case

- Domain: 2×1 cells, cell size $100 \times 20 \mu m$, distance $1 \mu m$. Mesh and time step: $dx = 1 \mu m, dt = 0.02 ms$.
- BR ionic model. Semi-implicit time scheme. FEM. Iterative method. Test: **no gap junctions**.



On going work

- Current observations: without GJ there is no AP propagation from cell to cell.
- To be tested: finer mesh, smaller cell distances.
- Include different types of GJCs on larger domains.
- Compare velocities with the experimental observations.

Future work:

- Move to homogenised model.

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