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Effects of non-linear GJ channels on the AP propagation : a modelling insight

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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

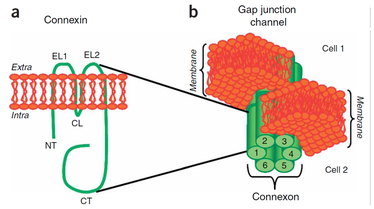


Figure : Schematic diagrams of a standard connexin molecule and gap junction channel. (Del Corso et. al., 2006)

- **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.

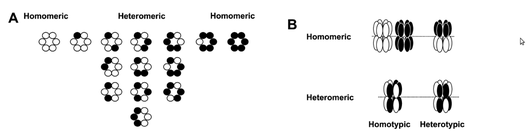


Figure : Predicted configurations of connexons and gap junction channels for two different connexins. (Desplantez, 2004)

- **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

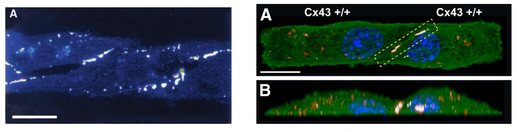
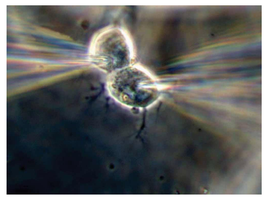


Figure : Immunohistochemical analysis of Cx43. Left: Bar = $10\mu m$. (Beauchamp, 2004) Right: top view(A), lateral view(B). Bar = $5\mu m$. (Beauchamp, 2012)

- **Electrical behaviour?**
  - The dual voltage patch clamp
  - Non-linear behaviour - gating of channels
  - Dependent on connexin arrangement.



Non linear GJ model - 0D

- GJ current: $I_j = G_j(t, V_j)V_j$, where V_j transjunctional voltage.

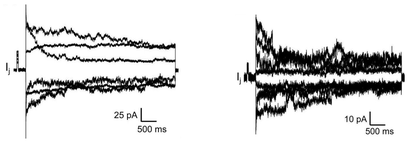
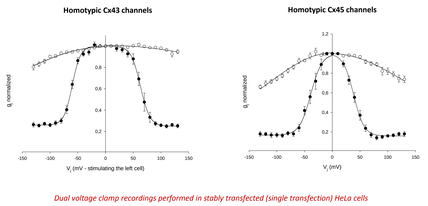


Figure : GJ currents in time, fixed V_j. Left: Homotypic Cx43/Cx43 cell pairs. Right: Cx43KO/Cx43KO cell pairs.

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

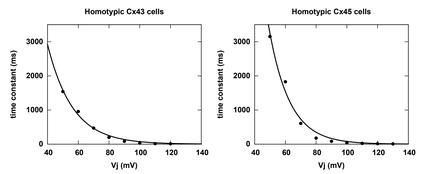
$$\frac{dg_j}{dt} = \frac{g_\infty(V_j) - g_j}{\tau_\infty(V_j)}$$

- 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 $\tau_\infty(V_j)$.



Macroscopic effects

- Primary cultures of Cx43 WT and Cx43KO ventricular myocytes.
- Macroscopic velocity was calculated from the difference in mean activation time within regions of interest.

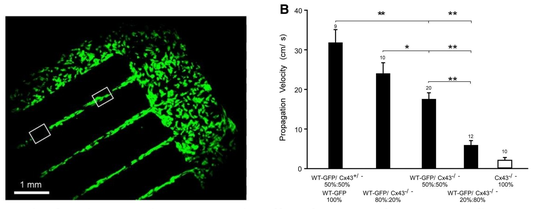


Figure : Left: A mixed patterned cell culture at low magnification. Right: Decrease in velocity of propagation w.r.t. presence of Cx43 cells.

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/3D mathematical microscopic model

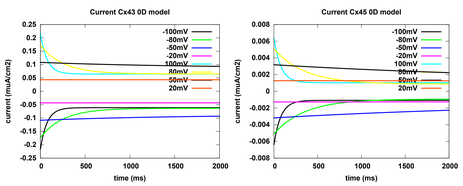
- σ_i, σ_e intra and extracellular conductivities
- $\mathbf{h}$ gating variables for ionic model
- $V_m = u_i - u_e$ transmembrane potential, $V_j = [u_i]$ transjunctional potential.

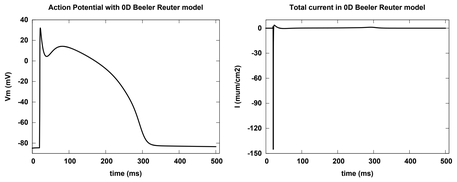
$$\begin{aligned} \sigma^i \Delta u^i &= 0, && \text{in } \Omega_i, \\ \sigma^e \Delta u^e &= 0, && \text{in } \Omega_e, \end{aligned}$$

$$\sigma^e \nabla u^e \cdot n = I_{app}(t), \qquad \text{on } \partial\Omega_e$$

$$\left.\begin{aligned} \partial_t V_m + I_{ion}(V_m, \mathbf{h}) &= \sigma^i \nabla u^i \cdot \mathbf{n}, \\ \partial_t V_m + I_{ion}(V_m, \mathbf{h}) &= -\sigma^e \nabla u^e \cdot \mathbf{n}, \\ \partial_t \mathbf{h} &= f_{ion}(V_j, \mathbf{h}), \end{aligned}\right\} \text{ on } \Gamma_{ion}.$$

$$\left.\begin{aligned} G_j(V_j, g_j) \cdot V_j &= \sigma^i \nabla u^i \cdot \mathbf{n}, \\ \partial_t g_j &= f_j(V_m, g_j), \end{aligned}\right\} \quad \text{on } \Gamma_j.$$





Numerical analysis - 2D

- Tests on: 2×1, 4×1 and 10×1 cells, cell size $100 \times 20\mu m$. Mesh step: $dx = 0.005mm$.
- Time: $T = 300ms$, time step: $dt = 0.001ms$. Explicit FE time scheme. Iterative method.
- Execution time on 10×1 domain $\approx 10h$.

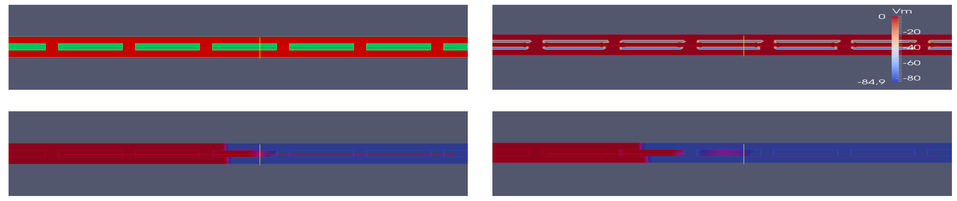


Figure : Up: domain of simulation and initial tansmembrane potential. Bottom: propagation of the potential.

Observations and Future work

- GJ facilitated the propagation in intracellular space.
- Almost NO change in GJ gates - mostly open. Hard to observe dynamics.
- Very small difference due to different GJ channels.

We need:

- Improve the model?
- Longer simulations. Larger domain.
- Try to observe dynamics of GJ channels by applying multiple stimuli.
- Move to HOMOGENISED model!