A comparison of discrete and continuum models of cardiac electrophysiology

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Outline

1. Introduction
   - Biological Background
   - Research Questions
2. Past
   - Physiology of gap junctions
   - Adapting models to include gap junctions
   - Results of simulations
   - Conclusions
3. Present
   - The homogenised conductivity tensors
4. Future
   - Hybrid Modelling
5. Summary

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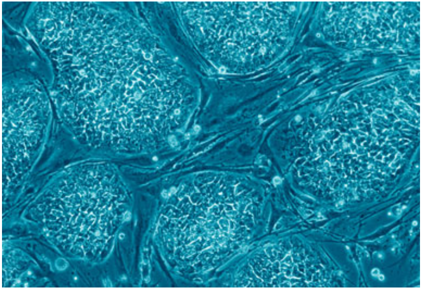
Discrete Modelling

Many phenomena in biology are discrete:

- For example, biological tissue consists of discrete cells
- These cells lie in an extracellular matrix



Discrete Modelling

- Different sets of equations usually apply in intracellular and extracellular regions
- Thus, we must model each cell individually
- This is not practical at organ or tissue level

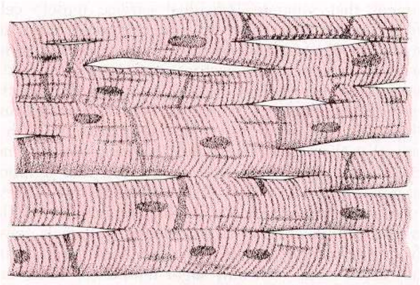
Continuum Modelling

To overcome this, we often model the tissue as a continuum:

- 'Average' the quantities we are solving for
- Retain their small-scale behaviours
- Process known as homogenisation

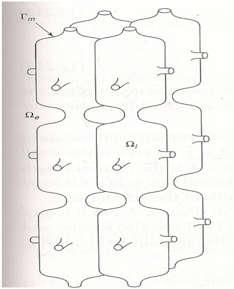
Modelling Cardiac Tissue

An example of cardiac cells:

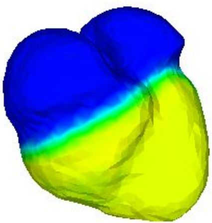


Modelling Cardiac Tissue

From discrete:



To continuum:



What assumptions are made in this process?

Assumptions in the Homogenisation Process

- Problem naturally defined on two scales:
  - Macroscale — Tissue-level
  - Microscale — Cell-level
- Parameter introduced — ratio of the two scales
  - It is assumed very small
- More precisely: parameter = $\frac{\text{Typical cell length}}{\text{Typical solution lengthscale}} \rightarrow 0$

Resulting Governing Equations

Discrete: Laplace's equation in each region

$$\nabla \cdot (\sigma_i \nabla \phi_i) = 0, \quad \mathbf{X} \in \Omega_i, \qquad -\sigma_i \nabla \phi_i \cdot \mathbf{n} = I_m(\mathbf{X}), \quad \mathbf{X} \in \Gamma_m,$$
$$\nabla \cdot (\sigma_e \nabla \phi_e) = 0, \quad \mathbf{X} \in \Omega_e, \qquad \sigma_e \nabla \phi_e \cdot \mathbf{n} = I_m(\mathbf{X}), \quad \mathbf{X} \in \Gamma_m.$$

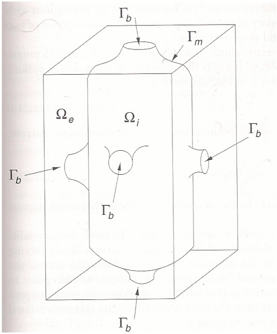
Continuum: The Bidomain Equations

$$\chi c_m \frac{\partial V}{\partial t} = \nabla_{\mathbf{x}} \cdot (\Sigma_i \nabla_{\mathbf{x}} (V + \Phi_e)) - \chi I_{ion},$$
$$0 = \nabla_{\mathbf{x}} \cdot ((\Sigma_i + \Sigma_e) \nabla_{\mathbf{x}} \Phi_e + \Sigma_i \nabla_{\mathbf{x}} V).$$

With appropriate (zero flux) boundary conditions on the tissue surface.

Homogenised Conductivity Tensors

For a general unit cell (see right):



- Scalar conductivities $\sigma_{(i,e)}$
- Continuum tensors $\Sigma_{(i,e)}$ obtained via:

$$\Sigma_{(i,e)} = \frac{1}{V_{\text{unit}}} \int_{\Omega_{(i,e)}} \sigma_{(i,e)} \left(I + \frac{\partial \mathbf{W}^{(i,e)}}{\partial \mathbf{z}} \right) \mathrm{d}V_{\mathbf{z}},$$

- Functions $W_j^{(i,e)}$ satisfy:

$$\nabla_{\mathbf{z}} \cdot (\sigma_i \nabla_{\mathbf{z}} W_j^i) = -\frac{\partial \sigma_i}{\partial z_j}, \quad \nabla_{\mathbf{z}} \cdot (\sigma_i \nabla_{\mathbf{z}} W_j^e) = \frac{\partial \sigma_e}{\partial z_j}$$

- With boundary conditions:

$$\nabla_{\mathbf{z}} W_j^i \cdot \mathbf{n} = -n_j, \qquad \nabla_{\mathbf{z}} W_j^e \cdot \mathbf{n} = n_j$$

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Research Questions

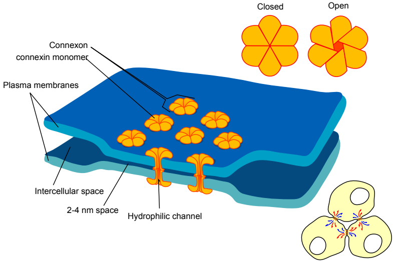
- How do gap junctions affect our system?
- When might the continuum assumptions be invalid?
- How does the histology of cardiac tissue affect the homogenisation process?
- Does a hybrid system provide a method of increasing accuracy whilst retaining efficiency?

Outline

How do gap junctions affect our system?

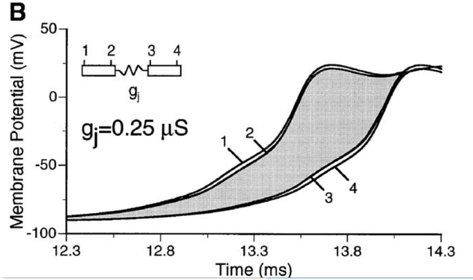
- Cells are electrically coupled via gap junctions
- Small hemichannels allowing molecules and ions to pass through them
- Distribution and number of junctions changes under diseased conditions

- *e.g.* ischemia, fibrosis, infarction



How do gap junctions affect our system?

- These channels provide larger resistance to flow than the cytoplasm
- Significant delay in propagation across junction
- Delay increases under diseases previously mentioned



Effect on continuum model

- Consider derivation of continuum model
- Key assumption: $\frac{\text{Typical cell length}}{\text{Typical solution lengthscale}} \longrightarrow 0$
- Solution varies rapidly as it passes through gap junction
- Assumption likely to be violated

Effect on continuum model

Additionally:

- Propagation speed nonuniform through tissue
- Continuum model 'averages' these effects
- Produces smooth, uniform solutions
- Thus, cannot capture the characteristics of discrete propagation

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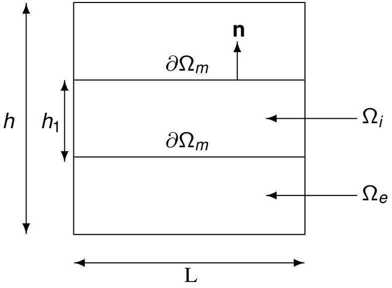
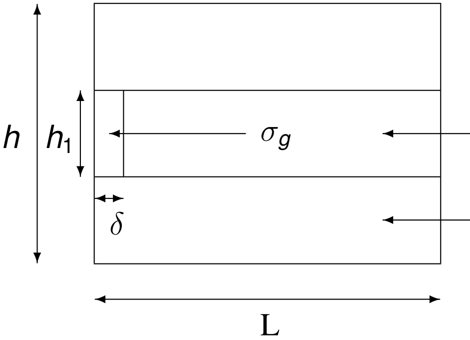
Solution geometry

- Begin with simplified 2D structure
- Periodically repeated to form tissue slab
- Homogeneous intracellular space (Ω_i) and membrane ($\partial\Omega_m$)



Solution geometry

- Across a gap junction, continuity of flux
- $\Longrightarrow$ junction can be treated as part of the intracellular space
- narrow region at one end of cell with different conductivity (σ_g vs. σ_i)
- membrane will have different properties



Mathematical formulation

Discrete model:

- Intracellular conductivity: was constant scalar σ_i, becomes

$$\sigma(\mathbf{x}) = \begin{cases} \sigma_i & \mathbf{x} \in \text{cell}, \\ \sigma_g & \mathbf{x} \in \text{gap junction}. \end{cases}$$

- Transmembrane current: was $c_m \frac{\partial v}{\partial t} + I_{ion}$, now

$$I_m = \begin{cases} c_i \frac{\partial v}{\partial t} + I_{ion} & \mathbf{x} \in \text{cell}, \\ c_g \frac{\partial v}{\partial t} + I_g I_{ion} & \mathbf{x} \in \text{gap junction}. \end{cases}$$

- c_g = capacitance of gap junction membrane, I_g = boolean switch. Both are modified to study effect on propagation.

Mathematical formulation

Continuum model:

- Began with bidomain equations:

$$\chi c_m \frac{\partial V}{\partial t} = \nabla_{\mathbf{x}} \cdot (\Sigma_i \nabla_{\mathbf{x}} (V + \Phi_e)) - \chi I_{ion},$$
$$0 = \nabla_{\mathbf{x}} \cdot ((\Sigma_i + \Sigma_e) \nabla_{\mathbf{x}} \Phi_e + \Sigma_i \nabla_{\mathbf{x}} V).$$

- Modified to become:

$$(\chi_i c_i + \chi_g c_g) \frac{\partial V}{\partial t} = \nabla_{\mathbf{x}} \cdot (\Sigma_i \nabla_{\mathbf{x}} (V + \Phi_e)) - (\chi_i + l_g \chi_g) I_{ion},$$
$$0 = \nabla_{\mathbf{x}} \cdot ((\Sigma_i + \Sigma_e) \nabla_{\mathbf{x}} \Phi_e + \Sigma_i \nabla_{\mathbf{x}} V).$$

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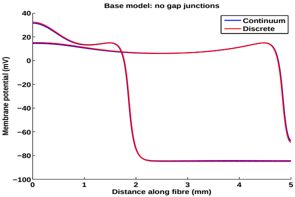
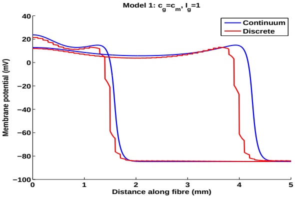
Simple gap junctions

- Junctions modelled just as reduced conductivity
- Results snapshot at 15 ms & 30 ms (Beeler-Reuter kinetics)
- Discrete wavefront highly irregular
- Underlying conduction velocities different



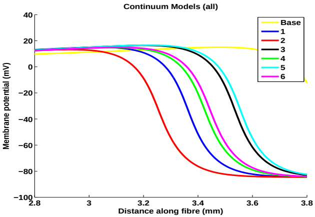


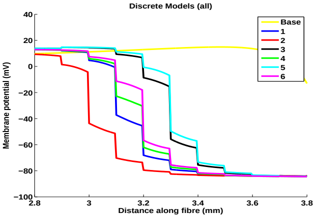
Different gap junction implementations

- Varied new parameters c_g and l_g as follows:

Parameter values used			
Model	σ_g	c_g	l_g
Base	0.25 $(=\sigma_i)$	0.01	1
1	0.0025	0.01	1
2	0.0025	0.01	0
3	0.0025	0.001	1
4	0.0025	0.001	0
5	0.0025	0	1
6	0.0025	0	0

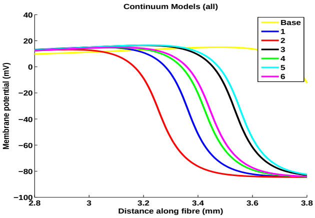
- Magnification of results at 30ms
- Continuum models on top, discrete below

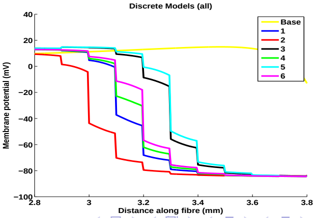




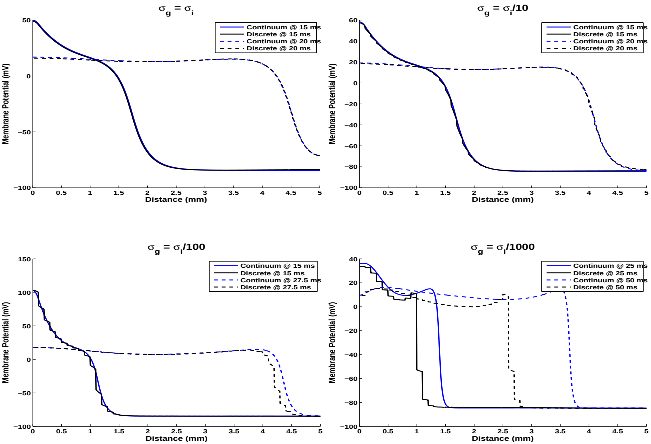
Different gap junction implementations

- Differences between models smaller than effect of reduced conductivity
- Switching ionic current off slows speed, equal in both models
- Reducing capacitance slows speed, equal in both models
- Zeroing capacitance has little extra effect



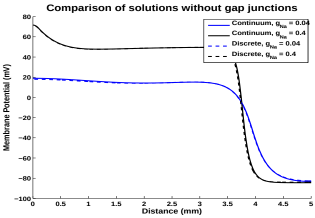


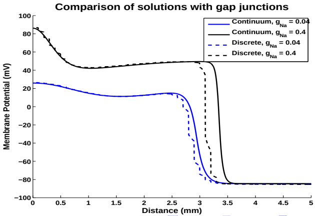
Effect of changing gap junction conductivity



Effect of changing sodium conductance

- Steepness of upstroke related to ionic model parameter g_{Na}
- Increase by a factor of 10 and look and results of simluations
- No gap junctions: models still match up
- Gap junctions: larger discrepancy with increased upstroke velocity





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Conclusions

- Gap junctions cause discrepancy in propagation speed & characteristics between discrete and continuum models
- Main area is around upstroke of action potential
- Capacitance and ionic current of junction has no effect on discrepancy
- Reduction in gap junction conductivity increases discrepancy
- Increase in upstroke velocity increases discrepancy

Outline

What affects the homogenised conductivity tensors?

Recap:

- Scalar conductivities $\sigma_{(i,e)}$
- Continuum tensors $\Sigma_{(i,e)}$ obtained via:

$$\Sigma_{(i,e)} = \frac{1}{V_{\text{cell}}} \int_{\Omega_{(i,e)}} \sigma_{(i,e)} \left(I + \frac{\partial \mathbf{W}^{(i,e)}}{\partial \mathbf{z}} \right) \mathrm{d}V_{\mathbf{z}},$$

- Functions $W_j^{(i,e)}$ satisfy:

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- With boundary conditions:

$$\nabla_{\mathbf{z}} W_j^i \cdot \mathbf{n} = -n_j, \qquad \nabla_{\mathbf{z}} W_j^e \cdot \mathbf{n} = n_j$$

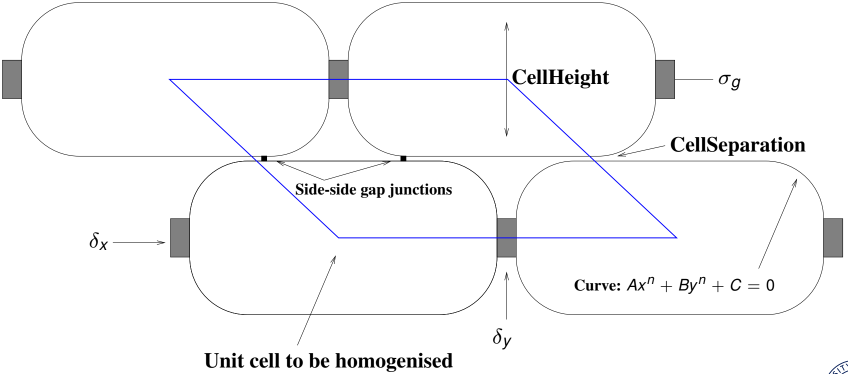
What affects the homogenised conductivity tensors?

Thus, tensors affected by:

- Scalar conductivity — gap junctions changing intracellular conductivity
- Size & shape of cell membrane
- Proportions of intra- and extracellular space

For bidomain equations, quantities of interest are Σ_i/χ and $(\Sigma_i + \Sigma_e)/\chi$.

Building a unit cell in 2D



Performing calculations

- We can calculate tensors for all possible parameter values
- Huge parameter space with little physiological meaning
- Need to isolate which values vary and by how much
- Liaising with experimentalists to determine these
- Combine with sensitivity analysis

Limitations to 2D approach

- No side-side gap junctions: propagation only in fibre direction
- Side-side junctions included: no extracellular propagation
- However, between these methods we should be able to extract the relevant answers
- 3D approach removes the problem, currently working on this

Initial thoughts/results

- Change one variable at a time, keep others at a ‘default’ level
- Height of cell has large effect on $(\Sigma_i + \Sigma_e)/\chi$
- Gap junction height δ_x also does
- Looking to combine this with experimental data

How does the choice of unit cell affect results?

- Length of cells: distribution of lengths in fibre & off-fibre direction
- Compare results with those expected using mean values
- Again combine with experimental data

Outline

Creation of New Hybrid Models

We know what might case a discrepancy between discrete & continuum systems

- Gap junctions (especially if lowered conductivity)
- Steepness of upstroke (specific to cell type)
- Cell shape & size? Results of previous section will elucidate

We propose a hybrid solution method

- Use continuum model (*e.g.* bidomain) where possible
- Use discrete model if continuum assumptions invalid

Creation of New Hybrid Models

First, we must:

- Find the appropriate discrete parameters (conductivities *etc.*)
- Derive the corresponding continuum model
- Get a ‘feel’ for under what conditions the continuum model does not replicate the discrete model
- *i.e.* perform simulations using both models individually
- Convert this into mathematical criteria

Hybrid Modelling

A possible method for implementation:

- Solve continuum system everywhere
- Look for regions where solution varies rapidly
- *i.e.* $\dot{V}_{max} >=$ some threshold
- Re-solve, using discrete model in such regions

Motivated by work of Hand *et al.* (*)

- They have 1D (cable/monodomain) model of this form
- We wish to extend to 2D & 3D
- Incorporating more realistic geometries (driven by homogenised tensor data)

(*) Hand PE, Griffith BE: **Adaptive multiscale model for simulating cardiac conduction**. *Proceedings of the National Academy of Sciences* 2012, **107**(33):14603-14608

Summary

- Inclusion of gap junctions causes discrepancy between discrete & continuum models
- Hybrid model may be appropriate: requires investigation into suitable criteria
- Shape of cell boundary also likely to be relevant — considering homogenised conductivity tensors in more detail