Modelling Aspects of Electrophysiology
- Tools and Test Studies

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SofTMech Progress Meeting
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Glasgow
Outline

1) Goals and Strategy

2) Modelling of single cardiomyocyte EP data
   i. Description of experimental data
   ii. Models of single-cell electrophysiology – detailed and reduced
   iii. Fitting of parameter values
   iv. Preliminary results

3) Modelling and simulation of transmural and whole heart EP data
   i. Description of experimental data
   ii. Bi/mono-domain equations
   iii. Numerical implementation
   iv. Preliminary Results

4) Conclusion
Summary of project tasks and objectives

SofTMech proposal Task 5.2 of WP-5

1) Formulate a multiscale mathematical model of whole left ventricle/heart.

2) Couple electrohysiology and mechanical response using
   (a) measured activation sequence,
   (b) detailed mathematical models with [Ca].
   (Mechanical models – including active tension and passive response)

3) Incorporate in Immersed Boundary Finite Element code.

4) Apply to Myocardial Infarction.
Available EP experimental data

Wealth of rabbit EP data is available from the Lab of Co-I Godfrey Smith as follows.

1) Isolated cardiomyocytes  
2) Transmural tissue slabs  
3) Whole heart/chamber data
Rabbit single cardiomyocyte electrical data


- Heterogeneous changes in action potential and intracellular Ca2+ in left ventricular myocyte sub-types from rabbits with heart failure.

- Sub-epicardial, midmyocardial, sub-endocardial cells.

- Control (healthy) and Heart Failure (MI).

- AP and Ca2+.

- A range of pacing rates.

- APD90 and CaD Restitution.
Models of the single-cell action potential

- Action Potential (transmembrane voltage potential) is controlled by the cell membrane.
- The cell membrane acts both as an insulator and as a conductor.
- This can be modeled as an electric circuit with a capacitor and a resistor connected in parallel

\[ C_m \frac{d}{dt} V = - \sum_S \left( g_S \prod_i (n_{S,i})^{k_{S,i}} (V - V_S) \right) - I_{\text{stim}}, \]

\[ \frac{d}{dt} n_{S,i} = \frac{1}{\tau_{n_{S,i}(V)}} (n_{S,i}(V) - n_{S,i}). \]

- The resistive current is a sum of \( S \) ionic currents, each modelled by an Ohmic relation and gated by \( i \) gates of multiplicity \( k_S \).
- Each gate has voltage-dependent rates of opening and closing.

- The set of ODE requires initial conditions—Typically in the form of a “Pacing protocol” for stimulation by current.
Single-cell models of the action potential - “second and third generation”

Ionic Mathematical Models

1st Generation
1. H-H formulation of $I_s$ and $O_s$
2. No pumps and exchangers
3. Slow inward current, depending on $[Ca]_i$

2nd Generation
1. H-H formulation of all ionic currents except $I_{Ca}$, $[Ca]_i \neq$ const
2. Pump and exchangers
3. Intracellular $[Ca^{2+}]_i$ dynamics.

3rd & future Generation
1. Variable $[S]_i$ and $[S]_e$
2. GHK const field equation for $I_s$
3. Markovian represent. for $O_s$
4. Improved $[Ca^{2+}]_i$ dynamics
5. The effect of contraction on channels conductivity
Mahajan et al. (2008) Biophys J. 94, 392-410

- “A Rabbit Ventricular Action Potential Model Replicating Cardiac Dynamics at Rapid Heart Rates”
- Rapid heart rates relevant to ventricular tachycardia and fibrillation.
- Used new experimental patch-clamp data to modify the L-type calcium (Ca) current (I(Ca,L)).
- Ca(i) cycling formulation – seven-state Markovian model.
- 35-37 degrees C.
- 26 differential equations; 9 currents; 62 parameters.
Re-fitting of parameter values

Need for refitting

- Despite their sophistication ionic models often fail to reproduce data other than the one they have been fitted to because

- Most parameter values are inherited from a “predecessor” model, possibly from different species, incompatible experimental protocols etc.

- Differences in experimental protocols.

- Not yet known physiology.

Parameter estimation and optimisation

- Straightforward approach – find the parameter values which minimise the mean relative error

$$ F = \frac{1}{M} \sum_{i=1}^{M} \frac{|x_i^{sim} - x_i^{target}|}{|x_i^{target}|} $$

- Use widely available standard methods and software, e.g. Matlab’s `fminsearch` – unconstrained minimisation of multivariable functions.

Pacing rate: 3Hz (333ms)

<table>
<thead>
<tr>
<th>Parameters (unit)</th>
<th>Default value</th>
<th>Epicardial cell (Healthy)</th>
<th>Epicardial cell (MI)</th>
<th>M-cell (Healthy)</th>
<th>M-cell (MI)</th>
<th>Endocardial cell (Healthy)</th>
<th>Endocardial cell (MI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T, Temperature (kelvin)</td>
<td>30B</td>
<td>426.92</td>
<td>299.70</td>
<td>253.44</td>
<td>240.18</td>
<td>491.24</td>
<td>292.69</td>
</tr>
<tr>
<td>F, Faraday constant (C/mmol)</td>
<td>96.48</td>
<td>136.92</td>
<td>400.26</td>
<td>89.24</td>
<td>75.83</td>
<td>60.36</td>
<td>96.06</td>
</tr>
<tr>
<td>K_o, External potassium concentration (mM)</td>
<td>5.4</td>
<td>6.5947</td>
<td>5.8137</td>
<td>4.5865</td>
<td>4.3087</td>
<td>6.9387</td>
<td>6.1138</td>
</tr>
<tr>
<td>Ca_o, External calcium concentration (mM)</td>
<td>1.8</td>
<td>2.0206</td>
<td>1.8078</td>
<td>2.0467</td>
<td>2.5678</td>
<td>2.2806</td>
<td>1.8902</td>
</tr>
<tr>
<td>Na_o, External sodium concentration (mM)</td>
<td>136</td>
<td>145.77</td>
<td>143.07</td>
<td>146.30</td>
<td>165.71</td>
<td>150.57</td>
<td>123.71</td>
</tr>
<tr>
<td>gna, Peak INa conductance (mS/μF)</td>
<td>12</td>
<td>14</td>
<td>12</td>
<td>14</td>
<td>12</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>gca, Strength of Ca current flux (mmol/(cm C))</td>
<td>182</td>
<td>50.48</td>
<td>209.92</td>
<td>259.86</td>
<td>193.23</td>
<td>203.08</td>
<td>228.22</td>
</tr>
<tr>
<td>pca, Constant in ICaL (cm/s)</td>
<td>0.00054</td>
<td>0.0003</td>
<td>0.0006</td>
<td>0.0002</td>
<td>0.0008</td>
<td>0.0008</td>
<td>0.0006</td>
</tr>
<tr>
<td>r1, opening rate in ICaL ()</td>
<td>0.3</td>
<td>0.6359</td>
<td>0.3438</td>
<td>0.4804</td>
<td>0.3546</td>
<td>0.4972</td>
<td>0.3022</td>
</tr>
<tr>
<td>r2, closing rate in ICaL ()</td>
<td>3</td>
<td>1.312</td>
<td>2.4229</td>
<td>2.8285</td>
<td>2.8694</td>
<td>2.7551</td>
<td>2.4839</td>
</tr>
<tr>
<td>gk1x, Peak IK1 conductance (mS/μF)</td>
<td>0.3</td>
<td>0.2553</td>
<td>0.2742</td>
<td>0.4400</td>
<td>0.2604</td>
<td>0.2777</td>
<td>0.2539</td>
</tr>
<tr>
<td>gtof, Peak Ito conductance (mS/μF)</td>
<td>0.11</td>
<td>0.0072</td>
<td>0.0912</td>
<td>0.0221</td>
<td>0.0421</td>
<td>0.0833</td>
<td>0.0933</td>
</tr>
<tr>
<td>(Global) root mean square error</td>
<td>-</td>
<td>0.0848</td>
<td>0.1028</td>
<td>0.0133</td>
<td>0.1070</td>
<td>0.0283</td>
<td>0.1018</td>
</tr>
</tbody>
</table>
Generic reduced model of cardiac excitability

Caricature Model

\[
\begin{align*}
\frac{dE}{dt} &= \frac{1}{\epsilon_1 \epsilon_2} G_{Na}(E_{Na} - E) H(E - E_*) h + \frac{1}{\epsilon_2} \left( \tilde{g}_2(E) n + \tilde{G}(E) \right) \\
\frac{dh}{dt} &= \frac{1}{\epsilon_1 \epsilon_2} F_h(H(E^*_1 - E) - h) \\
\frac{dn}{dt} &= F_n(E)(H(E - E^*_1) - n) \\
\tilde{g}_2(E) &= g_{21} H(E^*_1 - E) + g_{22} H(E - E^*_1), \\
\tilde{G}(E) &= \begin{cases} \\
k_1(E_1 - E), & E \in (-\infty, E^*_1), \\
k_2(E - E_2), & E \in [E^*_1, E_*), \\
k_3(E - E_3), & E \in [E_*, +\infty), \\
\end{cases}
\end{align*}
\]

Constant parameters : 
\[\epsilon_1, \epsilon_2, G_{Na}, E_{Na}, E_*, E^*_1, g_{21}, g_{22}, k_1, k_2, k_3, E_1, E_2, E_3, F_h, f_n, r\]


Reduction method

- Obtained from the model of Noble (1962) by
  - Preserving essential asymptotic structure
  - Replacing, quasi-stationary equilibria and timescaling functions by piecewise linear approximations.

Advantages

- Easy to understand
  - Few parameters
  - Allows asymptotic solution
  - Allows exact solution
- Cheap to simulate
- Efficient numerical methods may be developed?
Sensitivity analysis of the Caricature Noble model

- Steepness of upstroke: $G_{Na}, \epsilon_1, F_h$
- Steepness of plateau: $k_3$
- Steepness of repolarization: $\epsilon_2$

Parameters:
- $r_1$
- $r_2$
- $G_{Na}$
- $k_1$
- $k_2$
- $k_3$
- $E_1$
- $I_n$
- $F_n$
- $g_{21}$
- $g_{22}$
- $r$

Graph showing the effect of these parameters over time ($t$ in ms).
Fitting of AP of Caricature Noble model to measurements of McIntosh, Cobbe, Smith (2000)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Default</th>
<th>Pacing 3Hz</th>
<th>Pacing 0.3Hz</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edag</td>
<td>-80</td>
<td>-50</td>
<td>-60</td>
</tr>
<tr>
<td>East</td>
<td>-10</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>k1</td>
<td>0.075</td>
<td>0.0575</td>
<td>0.0225</td>
</tr>
<tr>
<td>k2</td>
<td>0.04</td>
<td>0.0246</td>
<td>0.0074</td>
</tr>
<tr>
<td>k3</td>
<td>0.10</td>
<td>0.086</td>
<td>0.0195</td>
</tr>
<tr>
<td>E1</td>
<td>-280/3</td>
<td>-245/3</td>
<td>-245/3</td>
</tr>
<tr>
<td>fn</td>
<td>1/270</td>
<td>1/270</td>
<td>1/270</td>
</tr>
<tr>
<td>g21</td>
<td>-1.0</td>
<td>0.4764</td>
<td>0.0406</td>
</tr>
<tr>
<td>g22</td>
<td>-9.0</td>
<td>0.3828</td>
<td>-0.404</td>
</tr>
</tbody>
</table>
Rabbit transmural slab electrical measurements


- Transmural action potential measurements.
- Control and MI hearts.
- Temperatures: 37°C and 31°C.
- Measurements of Voltage.
- Measurements of Activation Times.
- Measurements of Conduction Velocity.
- Transmural distance (wall thickness).
- Data from peri-infarct and infarct zone.
The bidomain model is essentially a two- or three-dimensional cable model.

It is a continuum model – describes the electrical behaviour averaged over many cells.

Accounts for the different electrical conductivities of the intracellular and extracellular space.

The tissue is regarded as as a two-phase medium as if every point is composed of a fraction of intra and extracellular space.

To every point two electrical potentials $V_i$ and $V_e$, two current densities $I_i$ and $I_e$ and two conductivity tensors $\sigma_i$ and $\sigma_e$ are assigned.

### Bidomain equations for propagation of excitation

\[
\nabla \cdot \left( \sigma_i \nabla V_i + \sigma_e \nabla V_e \right) = 0,
\]

Transmembrane current = current leaving intercellular region:

\[
\xi \left[ C_m \partial_t V + I_{ion} \right] = \nabla \cdot (\sigma_i \nabla V_i),
\]

\[
V = V_i - V_e,
\]

Boundary conditions on $x = \partial \Omega$

Continuity of extracellular current:

\[
\mathbf{n}_h \cdot (\sigma_0 \nabla V_{bath}) = \mathbf{n}_h \cdot (\sigma_e \nabla V_e),
\]

Vanishing intracellular current:

\[
\mathbf{n}_h \cdot (\sigma_i \nabla V_i) = 0.
\]
Monodomain reduction and further choices

Monodomain reduction
If \( \sigma_i = \alpha \sigma_e \) and \( \alpha = \text{const} \) then

\[
\xi(C_m \partial_t V + I_{\text{ion}}) = \nabla \cdot (\sigma \nabla V),
\]

where \( \sigma = \sigma_i \left( \sigma_i + \sigma_e \right)^{-1} \sigma_e \).

Model components

- Models of conductivity tensors
- Geometry
- Single-cell EP model
- Stimulation protocol
- Fitting of parameter values
Open source solvers available

- Chaste, Continuity, Beatbox, acCELLerate, CARP, (via SofTMech collaborator G Plank).

GlasgowHeart_EP –

- In-house FE code developed by within SofTMech Hao Gao based on code by B. Griffith.

- Uses LibMesh, PETSc, tetGen for computing electrophysiology in heart.

- Supports parallel computing.

- Visualisation via Visit or Paraview.

  - Capable of importing any EP model from CellML.

- Capable of simulating simplified and realistic geometries.
Results - Toy transmural scar problem

**Experiment**

- **Geometry:** rectangular box
- **Resolution:** 100 x 35 x 15 elements
- **Timestep:** 0.005
- **Model ten Tuscher-Panfilov simplified model.**
- **Conductivity tensor in tissue**
  \[
  \sigma \approx \begin{pmatrix}
  1.33 & 0 & 0 \\
  0 & 0.176 & 0 \\
  0 & 0 & 0.176
  \end{pmatrix}
  \]
- **Conductivity tensor in scar**
  \[
  \sigma \approx \begin{pmatrix}
  0.3 & 0 & 0 \\
  0 & 0.008 & 0 \\
  0 & 0 & 0.008
  \end{pmatrix}
  \]
Results - Toy transmural scar problem

B. Endocardial stimulation

[Graphs showing activation times and calcium concentration]

- Perfused whole heart preparation.
- Optical mapping – voltage sensitive dyes.
- Both Left and Right Ventricles.
- Temperature: 37 degrees C.
- Several stimulation protocols and locations.
- Measurements on the whole epicardium and at fixed locations of the following
  - Action Voltage Potential,
  - Activation times,
  - APD(90),
- Control (healthy) and MI hearts.

**Preparation**

- Perfused whole heart preparation.
- Optical mapping – voltage sensitive dyes.
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- Several stimulation protocols and locations.
- Measurements on the whole epicardium and at fixed locations of the following
  - Action Voltage Potential,
  - Activation times,
  - APD(90),
- Control (healthy) and MI hearts.

**Stimulation protocol**
Wealth of rabbit EP data is available from the Lab of Co-I Godfrey Smith.

In addition to Andrew Allan's data,

- **Ng, André (1998) PhD thesis**, University of Glasgow. “Mechanical performance, intracellular \( \text{Ca}^{2+} \) handling and ventricular repolarisation in isolated hearts from rabbits with heart failure.”
  - Calcium data from LV epicardial surface in both control and MI hearts (Andre Ng, Thesis and Papers).
  - Epicardial measurements of conduction velocity at 37°C, 31°C and 17°C in control hearts (Dietrichs 2017 – submitted).

https://www.dropbox.com/home/Rabbit%20Heart%20Data/Single%20Cell%20Measurements/Electrical
Results - Toy rabbit LV simulation

- Geometry: LV geometry is from a healthy volunteer based on CMR images
- Timestep: 0.005
- Model: Mahajan-Weiss detailed rabbit model.
- Conductivity tensor

\[
\sigma \approx \begin{pmatrix}
0.0154, & 0, & 0 \\
0, & 0.0154, & 0 \\
0, & 0, & 0.0154
\end{pmatrix}
\]
Results - Toy rabbit LV simulation

- Activation Times (ms)
- Voltage (mV)
- Calcium Concentration (mM)
Conclusions

We have been **building tools and methodology** required to address the overall aims of SofTMech WP5 and to model detailed experimental data.

- Identified appropriate EP models at different scales.
- Developed reduced single cell model.
- Developed methodology for parameter fitting of single cell models to experimental data.
- Configured and simulated test cases closely matching experimental setups.

Future work

- Parameter estimation
  - in complex measurement protocols,
  - in tissue and organ level
  (support from statistical analysts welcome!)
- Addressing meaningful physiological questions
  (guidance from physiologists welcome!)