Evaluation of Computational Modelling as a Preclinical Proarrhythmic Safety Assay

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Outline

- Where simulations could fit in the safety testing pipeline
- Mathematical models of cardiac electrophysiology
- Prediction of clinical Torsade Risk
- Rabbit QT simulations at GSK
- Results of simulation evaluation
Torsade-de-Pointes: “Pharmageddon”

- Torsade-de-Pointes (TdP) – a rare type of life threatening ventricular arrhythmia

- Patient safety consequences of unacceptable QT / TdP risk has led to
  1. the withdrawal of all of these medicines from the market:
     - Astemizole, Cisapride, Droperidol, Grepafloxacin, Prenylamine, Sertindole, Terfenadine, Terodiline, Thioridazine
  2. labelling restrictions on medicines
  3. failure of countless compounds during development
Drug / Ion Current Interaction and the ECG

control

50% $I_{Kr}$ block

![Graph showing voltage over time with labels for $I_{Na}$, $I_{CaL}$, and $I_{Kr}$]
Generic Progression strategy for QT and TdP risk

- **Phase I**
  - Pre-clinical Evaluation
  - In vitro assay: myocytes, Langendorff, wedge
  - HTS cardiac ion channels: $I_{Kr}$, $I_{Na}$, $I_{CaL}$
  - In vivo assay: simulation
  - Phase I ECG
  - Thorough QT study

- **Phase II**
  - Lead Optimisation
  - Computational models

- **Phase III**
  - Lead Discovery
  - Target Validation

- **Phase IV**
  - Registration & Launch
  - Adverse Event Reporting and monitoring
  - Actual TdP risk
The Ranolazine story

First targeted persistent Na current blocker developed by CV Therapeutics (USA)
Ranolazine (Ranoxa)

January 2006: Received FDA approval for treatment of chronic angina.

Undergoing trials as an anti-arrhythmic agent.
Ranolazine: a multi-channel blocker

90% block of $i_{Kr}$

simulation

control

90% block of $i_{Kr}$ + 50% block of $i_{pNa}$

Denis Noble & Penny Noble, *Heart*, 2006, 92, iv 1-5
A drug has **Inhibitory Concentration 50%** (IC50) values associated with different channel types.

**EFTPC** – Effective Free Therapeutic Plasma Concentration (our best guess for the concentration of the compound present at the cardiac ion channels).
Experimental data from GSK Safety

Redfern et al. (2003) categorisation of drugs:

1: repolarisation prolonging antiarrhythmics – may cause TdP but acceptable for cardiac drug.

2: unacceptable risk of TdP

3: measurable incidence of TdP in humans

4: isolated reports of TdP in humans

5: no reports of TdP in humans

<table>
<thead>
<tr>
<th>Drug</th>
<th>Risk</th>
<th>NaV1.5 IC50</th>
<th>CaV1.2 IC50</th>
<th>hERG IC50</th>
<th>EFTPC IC50</th>
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<td>8200</td>
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<td>1800</td>
<td>460</td>
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<td>300</td>
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<td>73000</td>
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<td>2300</td>
<td>8900</td>
<td>147</td>
<td>75–85</td>
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<td>Tocasil</td>
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<td>20000</td>
<td>n/a</td>
<td>2500</td>
<td>75–85</td>
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<td>Terfenadine</td>
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<td>970</td>
<td>375</td>
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<td>33</td>
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<td>Verapamil</td>
<td>5</td>
<td>41500</td>
<td>100</td>
<td>143</td>
<td>25–81</td>
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</table>

Are these IC\textsubscript{50} values predictive of TdP?
Current ‘best-practice’ marker

As suggested by Redfern et al (2003):

Note: All plots are for clinically relevant drug concentration ranges with 3 values shown for each drug: min, max and standard.
The importance of multi-channel effects
e.g. Simulation of the application of Verapamil up to therapeutic concentrations (hERG and CaL blocker).
Mathematical cardiac electrophysiology models

- **Cardiac cell models**
  - Change in voltage over time is dictated by the sum of the currents flowing across the membrane (which are themselves voltage dependent):
    \[
    \frac{dV}{dt} = -\frac{1}{C_m} \left( \sum_{\text{channels}} I_j + I_{\text{stim}} \right),
    \]

- **Incorporating drug-action:**
  - We model drug action by altering the maximum current that can flow through a particular channel according to IC$_{50}$ values, and a simulated dose.
    
  - Dose-response curve hill coefficient is assumed to be equal to one (~ one molecule of drug is sufficient to block one channel).
TdP risk correlation

Note: All plots are for clinically relevant drug concentration ranges with 3 values shown for each drug: min, max and standard.

False positive
False negative
Computational modelling trial at GSK

Compound Development

Existing QT assays
- QSAR in-silico statistical models
  - e.g. IonWorks Quattro

Very High-Throughput Ion Channel Screens
  - e.g. PatchXPress

High-Throughput Ion Channel Screens

Ex-vivo Rabbit Ventricular Wedge

Progress to in-vivo assays

Mathematical Models of Cardiac Electrophysiology

Input data

Predictions
Action Potential and QT Prolongation

% Change in QTc interval vs [Drug] uM

- Prep #1
- Prep #2
- shannon
- mahajan

UNIVERSITY OF OXFORD
Quantifying simulation results

<table>
<thead>
<tr>
<th></th>
<th>Simulation Shortener</th>
<th>Simulation No Effect</th>
<th>Simulation Prolonger</th>
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<tr>
<td><strong>Experiment</strong></td>
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<td>Shortener</td>
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<tr>
<td>No Effect</td>
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<tr>
<td>Prolonger</td>
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</tbody>
</table>

- **Specificity** = \(\frac{5}{5+8+2}\)
- **Sensitivity** = \(\frac{15}{15+6+2}\)
- **Negative Predicted Value** = \(\frac{5}{5+3+2}\)
- **Positive Predicted Value** = \(\frac{15}{15+6+2}\)
- **Accuracy** = \(\frac{5+24+15}{5+8+2+3+24+6+2+8+15}\)
## Evaluation of simulation results

<table>
<thead>
<tr>
<th></th>
<th>Overall Accuracy</th>
<th>Kappa Value</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predicted Value</th>
<th>Negative Predicted Value</th>
<th>Enrichment Over Chance (Positive)</th>
<th>Enrichment Over Chance (Negative)</th>
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<tbody>
<tr>
<td><strong>PatchXpress</strong></td>
<td><strong>60.27%</strong> (46.3-72.8)</td>
<td><strong>0.36</strong> (0.17-0.54)</td>
<td><strong>60.0%</strong> (36.9-79.4)</td>
<td><strong>33.3%</strong> (12.7-63.2)</td>
<td><strong>65.2%</strong> (40.7-83.7)</td>
<td><strong>50.0%</strong> (19.8-80.2)</td>
<td><strong>1.90</strong></td>
<td><strong>2.43</strong></td>
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<tr>
<td><strong>(73 Compounds)</strong></td>
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<tr>
<td><strong>IonWorks/FLIPR</strong></td>
<td><strong>59.4%</strong> (47.8-70.1)</td>
<td><strong>0.36</strong> (0.22-0.51)</td>
<td><strong>77.4%</strong> (56.1-90.2)</td>
<td><strong>26.9%</strong> (11.8-50.4)</td>
<td><strong>58.5%</strong> (40.2-74.8)</td>
<td><strong>48.3%</strong> (20.0-70.9)</td>
<td><strong>2.00</strong></td>
<td><strong>1.78</strong></td>
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<td><strong>(106 Compounds)</strong></td>
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<tr>
<td><strong>QSAR</strong></td>
<td><strong>56.1%</strong> (0.50-0.62)</td>
<td><strong>0.24</strong> (0.15-0.33)</td>
<td><strong>89.9%</strong> (0.82-0.94)</td>
<td><strong>12.7%</strong> (0.05-0.27)</td>
<td><strong>51.5%</strong> (0.44-0.59)</td>
<td><strong>46.7%</strong> (0.21-0.74)</td>
<td><strong>1.17</strong></td>
<td><strong>2.86</strong></td>
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<td><strong>(337 Compounds)</strong></td>
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</table>
Multi-scale mathematical models

Tissue/Organ (Optical mapping, MRI)

Cell (Microelectrode)

Ionic current (Voltage-clamp)

Propagation model
\[ \nabla \cdot \sigma_i \nabla \Phi_i = \beta \cdot I_m - I_{st_i} \]
\[ \nabla \cdot \sigma_e \nabla \Phi_e = -\beta \cdot I_m \]

Action potential model
\[ I_{\text{stim}} = C \frac{dV_m}{dt} + I_m \]

Ionic current models
\[ I_{Na} = g_{Na\text{max}} \cdot m^3 h^* j^* (V_m - E_{Na}) \]
\[ \frac{dx}{dt} = \alpha_x (1 - x) - \beta_x x \]
\[ \alpha_x = \alpha_x (V_m) ; \beta_x = \beta_x (V_m) \]

Slide courtesy of Dr Blanca Rodriguez
Building models from experimental data

MRI images → Ventricular surfaces → Tetrahedral mesh → Electromech. activity

Image segmentation → Mesh generation → Simulation

Plotkowiak et al. LNCS, 2008; Bishop et al., 2009; Bordas et al., 2010
Detailed Heart Simulations

Human models:
Ion channel to tissue propagation
Fibre orientation
Heterogeneity

100ms of bidomain simulation
5 min in 1024 processors
12 hours on a 4-core desktop

Produced by our specialised open-source cardiac simulation library

www.cs.ox.ac.uk/chaste

Bordas R et al. PBMB (2011)
Future possibilities

Zemzemi et al., British Journal of Pharmacology, 2012
Future Plans

- Simulation portal software to be released in the near future.

- Currently examining variability in high-throughput screening, and consequences for mathematical model predictions.

- We have just been awarded an NC3Rs grant to work with AZ and GSK to investigate how well multiple channel screens and models can predict the results of human QT trials.
with thanks to...

Denis Noble, Blanca Rodriguez, Esther Pueyo, Alberto Corrias, Kylie Beattie, Alex Quinn, Phil Gemmel, Lucia Romero, Carlos Sanchez, Matt Gibb, Alfonso Bueno, Nejib Zemzemi

Heart Rhythm Mechanisms

Experimental data

Mathematical models

Numerical algorithms

Scientific computing

Kevin Burrage

Ciara Dangerfield

Alberto Corrias

Simulation Software

Simulation results

Yi Cui, Nick McMahon, Peter Kohl, Jurgen Schneider, Andras Varro, Istvan Bascko, Peter Taggart

Raf Bordas, Martin Bishop, Vicente Grau John Walmsley, Mikael Wallman, Ana Minchole

Miguel Bernabeu, David Kay, Geoff Williams, Jonathan Cooper, Chris Arthurs, Joe Pitt-Francis, David Gavaghan