In silico modelling: state of the art

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“[Mathematical] Models in analytical pharmacology are not meant to be descriptions, pathetic descriptions, of nature; they are designed to be accurate descriptions of our pathetic thinking about nature. They are meant to expose assumptions, define expectations and help us to devise new tests.”

James W. Black
Nobel Prize Lecture, 1988
• Imagine dropping a 1kg mass from between 8 and 12 m up a tower, and timing how long it takes to fall to the ground.

• You might get these recordings:

**Statistical model**
(line of best fit)

[Caution is required when using outside training data]
But if we have a hypothesis for the underlying processes we can make a [bio]physical model.

\[ h = \frac{1}{2}gt^2 \]

This is the CiPA approach: reliable for extrapolation to situations we haven’t seen before if we have captured biophysics well…
• Voltage-gated ion channel currents (& pumps and exchangers)

\[
\frac{dV}{dt} = - \frac{1}{C_m} \left( \sum_{\text{channels}} I_j + I_{\text{stim}} \right),
\]

• Cell

• Tissue / organ

• Body surface markers

Zemzemi et al., British Journal of Pharmacology, 2013
• **Hodgkin & Huxley, 1952:** First applied to cardiac cells by Denis Noble in 1958-60.

• **First quantitative biophysical model of membrane excitability**

• Describes dependence of currents on membrane voltage and time. Excitable voltage waveform *emerges* from interaction of these currents.
Electrophysiology Models

- Luo-Rudy 1991

- Widely used simple model which includes major ionic currents

- Contains a phenomenological description of calcium dynamics
Electrophysiology Models

- Noble et al. 1998

- Includes the Sarcoplasmic Reticulum (SR), the cell’s intracellular calcium store

- Distinct rapid and slow potassium currents (Ikr/hERG and IKs)
Modern Cardiac Models

- O’Hara et al. (2011)
- Based on human cell and tissue data
- Calcium sub-space gives rise to calcium induced calcium release and afterdepolarisation behaviour

a) Obtain patch clamp data on human cardiac ion channels contributing to TdP risk,
b) Use these data as inputs to an *in silico* model of the human ventricular myocyte,
c) Run simulations and calculate a metric that classifies the level of TdP risk,
d) Check predictions of electrophysiological changes in Phase I ECG and iPSC-CMs.

**Ion Channel → In Silico Workflow in CiPA**

<table>
<thead>
<tr>
<th>In vitro Assessment of Drug Effects in Multiple Ionic Currents</th>
<th>In silico Computer Modeling to Predict Risk</th>
<th>In vivo ECG Biomarker in Phase 1 Clinical Trials</th>
<th>In vitro effects on Human Stem Cell Derived Ventricular Cardiomyocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium Calcium hERG Potassium</td>
<td>$I_{\text{sim}} = C \frac{dV_m}{dt} + I_m$</td>
<td><img src="image" alt="ECG baseline on drug" /></td>
<td><img src="image" alt="Cardiomyocytes" /></td>
</tr>
<tr>
<td>$I_{Ks}$ and $I_{Na}$ Peak in specific situations</td>
<td>![Torsade Metric Score (qNET)]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Torsade Metric Score (qNET)</td>
<td><img src="image" alt="Check for unanticipated human effects, confirm mixed channel effects using JT_{peakc}" /></td>
<td></td>
<td>Can be considered for unanticipated nonclinical effects, or if human ECG data is insufficient</td>
</tr>
</tbody>
</table>
CiPA’s created something of a research field
A quick review (very rough numbers of articles)

- 20 – Simulation studies of one or two drug compounds
- 16 – Possible/improved TdP risk markers/classifiers
- 8 – Larger-scale tissue simulations
- 5 – Testing/re-calibration/validation of adult human AP model
- 5 – hiPSC-CM modelling and translation work
- 3 – Testing/re-calibration/validation of baseline ion channel models
- 4 – Work on measuring/fitting/predicting ion channel/drug binding kinetics
Temperature dependence of kinetics of drug block of hERG channels are compound specific and an important factor for proarrhythmic risk prediction. Windley et al. 2018. Molecular Pharmacology (in press)

doi:10.1124/mol.117.111534
A personal take on where we are

- FDA have done a stringent validation exercise that you will hear about (good separation of training and validation).

- Most of the gains/improvements in risk markers are fairly marginal now – it’s difficult to say statistically that one is better than another.
  - More validation compounds always helps though – perhaps some recent real-world pharma compounds.

- We should focus some efforts on improving the biophysics of the parts of the models we can test easily – APs under block, baseline ion channel kinetics, drug binding.

- Efforts to assist in interpretation of hiPSC-CM results will be very useful for CiPA when it is in daily use.
Acknowledgements

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Resources

- Action potential prediction portal: https://chaste.cs.ox.ac.uk/ActionPotential

- Cardiac Web Lab for exploring and comparing action potential models: https://chaste.cs.ox.ac.uk/WebLab