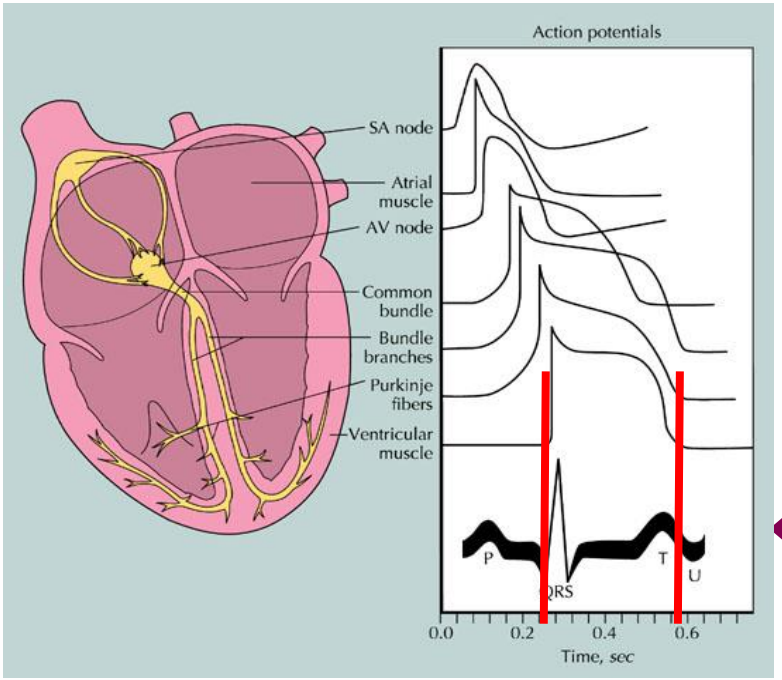
The application and evaluation of cardiac models for drug safety assessment, are we spoilt for choice?

Mark Davies PhD

Background

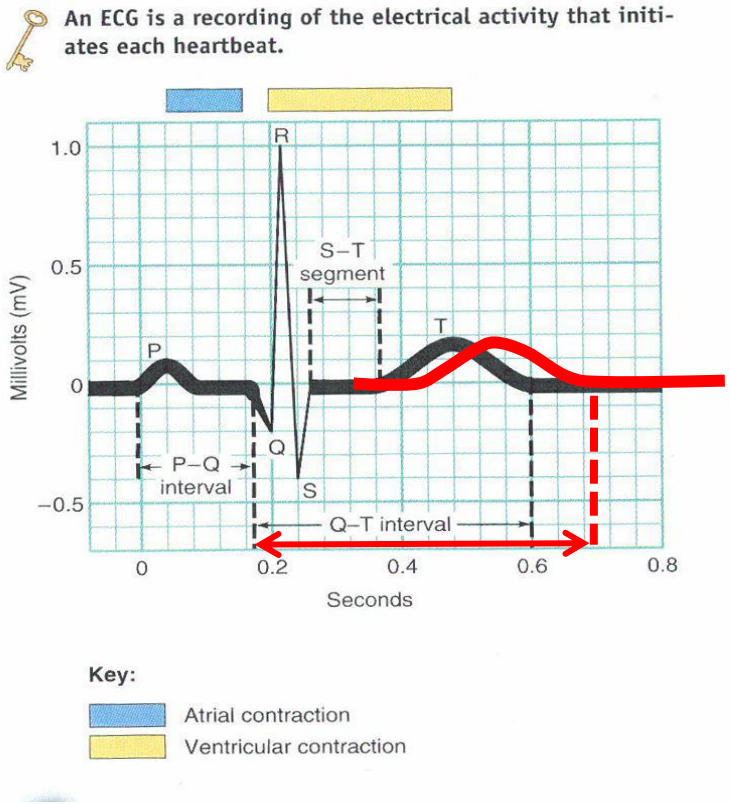
The ECG

- 1st action potential for each heart beat occurs in the Sino-Atrial node
- This initiates a wave of excitation that spreads through the heart and generates an electrical signal that can be detected at the body surface the electrocardiogram (ECG)

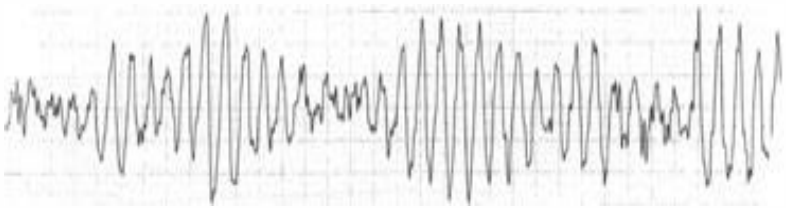


What is the risk of drug-induced effects on the ECG?

- Substantial number of drugs withdrawn from sale owing to QT interval prolongation & Torsades de Pointes (twisting of the points - QRS)

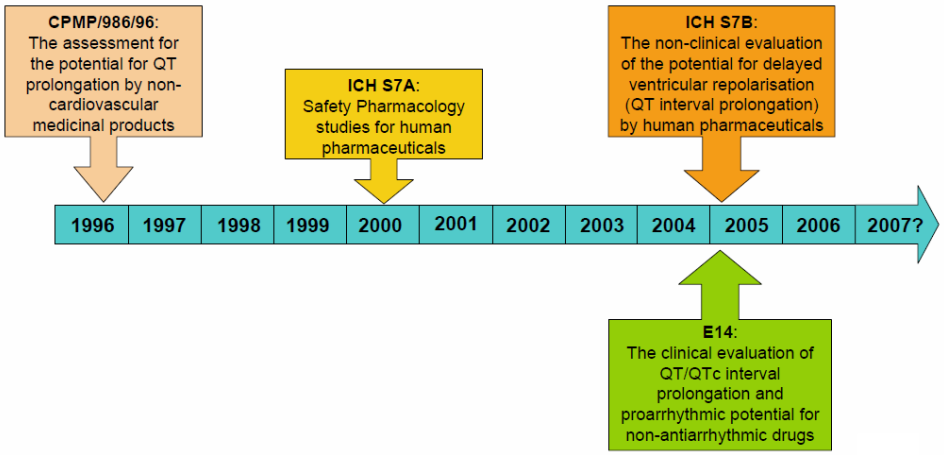


Drug-induced QT prolongation, in a very small % of people, leads to a potentially fatal arrhythmia: Torsades de Pointes



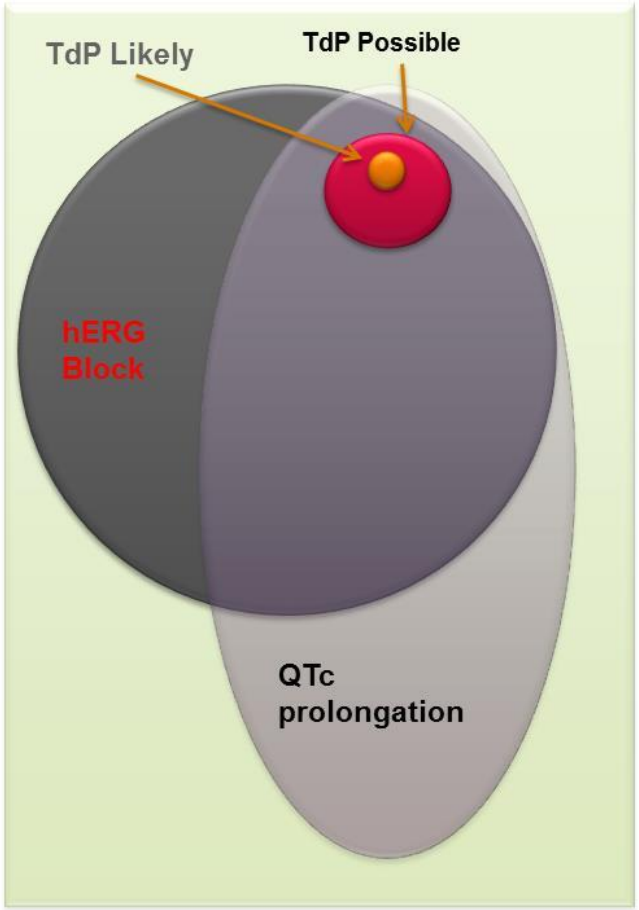
Development of cardiac risk strategy

- Genetic evidence – LQT disorders (e.g. Curran et al. 1995)
- Pharmacological evidence for withdrawn drugs i.e. linkage with hERG activity, e.g.
  - Terfenadine – Rampe et al 1993
  - Cisapride – Rampe et al 1997
  - ...
- Regulatory guidance and requirements, e.g.



CiPA 2015?

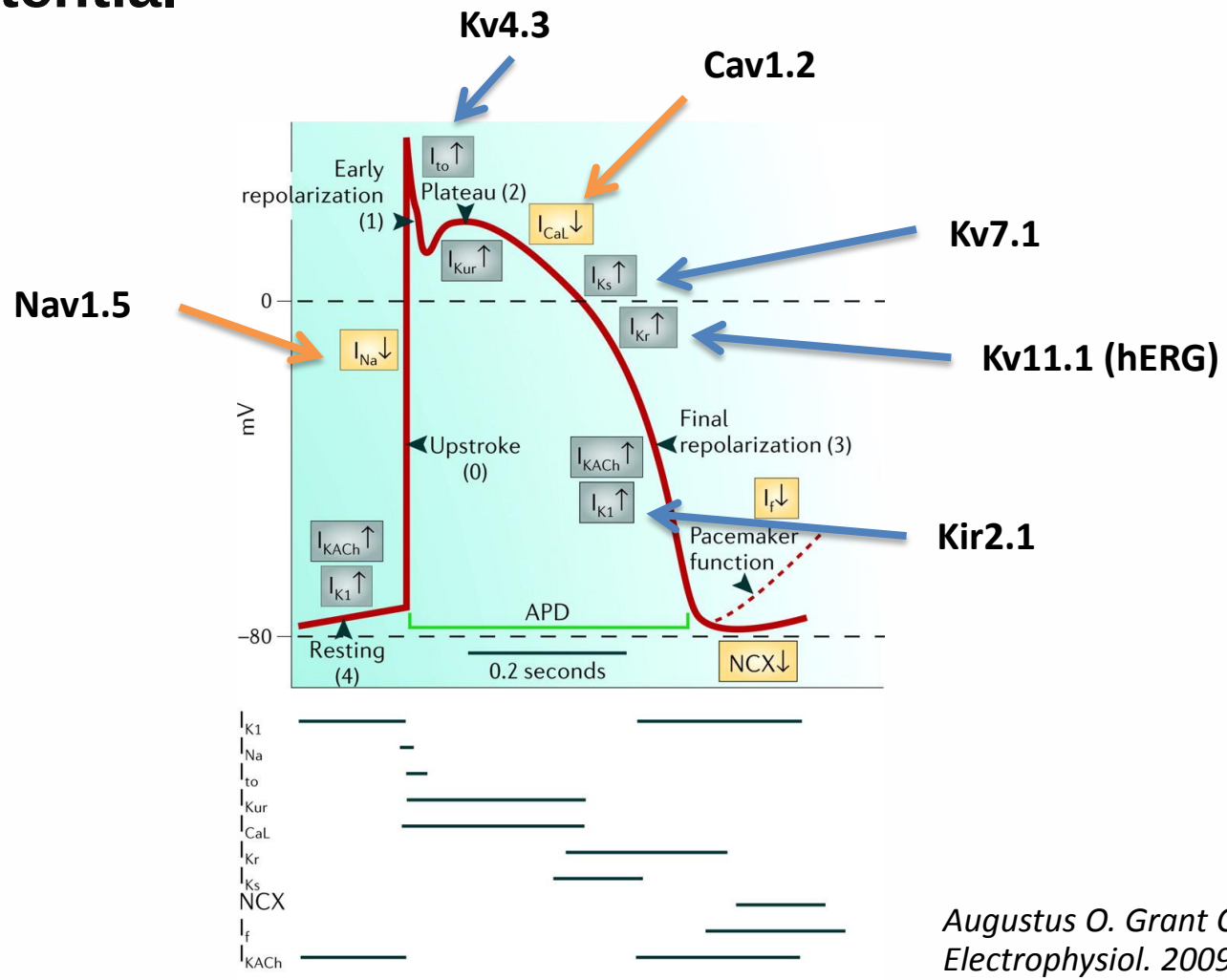
There's something else going on



- The paradigm that "hERG -> QT prolongation -> TdP" is no longer acceptable
- Increased understanding of cardiomyocyte electrophysiology has supported improved models of possible causation
- This has led to increased number of ion channel profiling in discovery projects (typically to include hERG, Nav1.5, Cav1.2)
- In-silico approaches to offer an interpretation of the multi-ion channel data

Valentin JP (from presentation at Computational Cardiovascular Science Workshop, Oxford, Sept 2014)

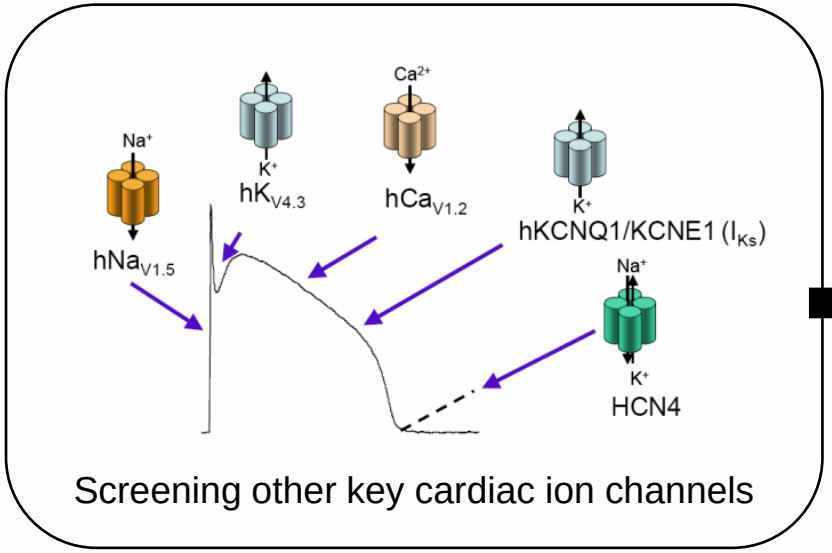
Membrane currents that generate a normal action potential



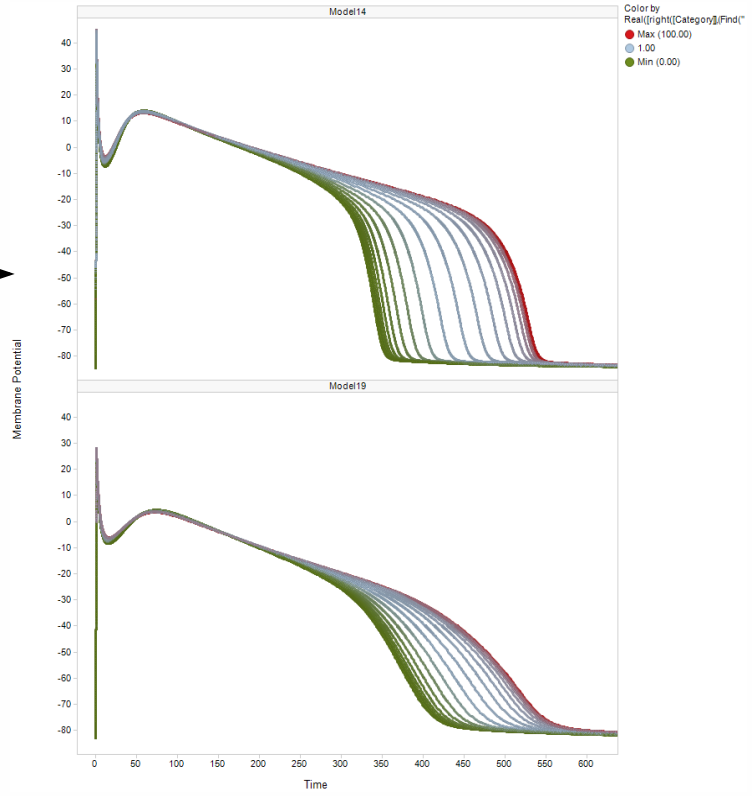
Augustus O. Grant Circ Arrhythm Electrophysiol. 2009;2:185-194

Limitations of “molecularising” the ventricular Action Potential

- Although able to generate inhibition curves for compound X against all the key channels in isolation, testing in an integrated system is needed

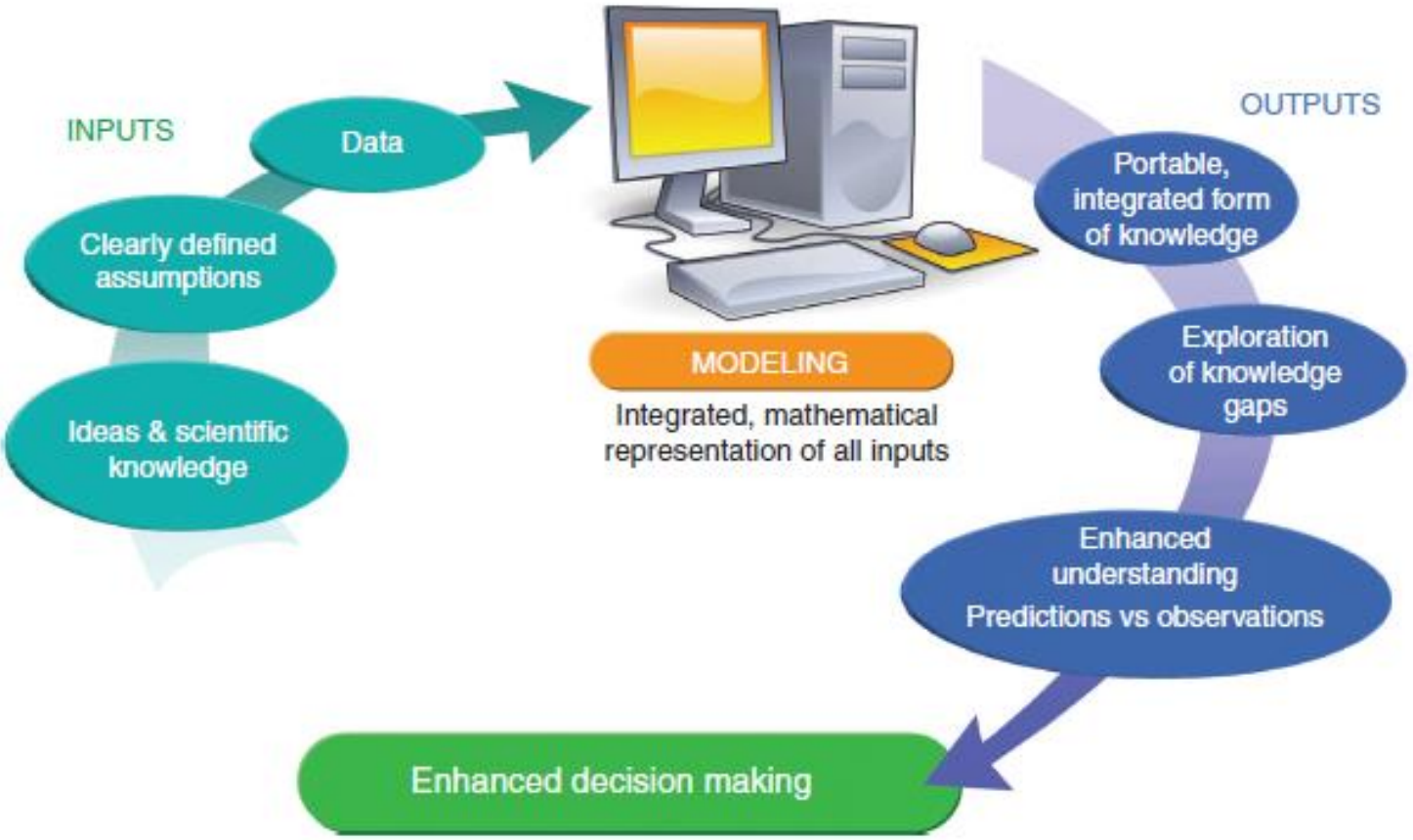


Screening other key cardiac ion channels



Virtual simulations provide an interpretation and a prediction of the integrated system from isolated ion channel screens

Where does M+S fit in decision making?

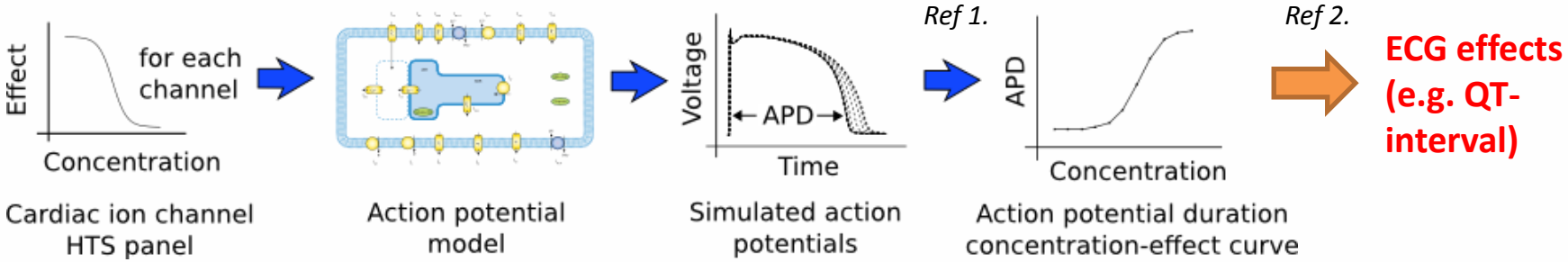


Visser et al (2014) CPT Pharmacometrics Syst. Pharmacol

Modelling approaches

Rationale and background

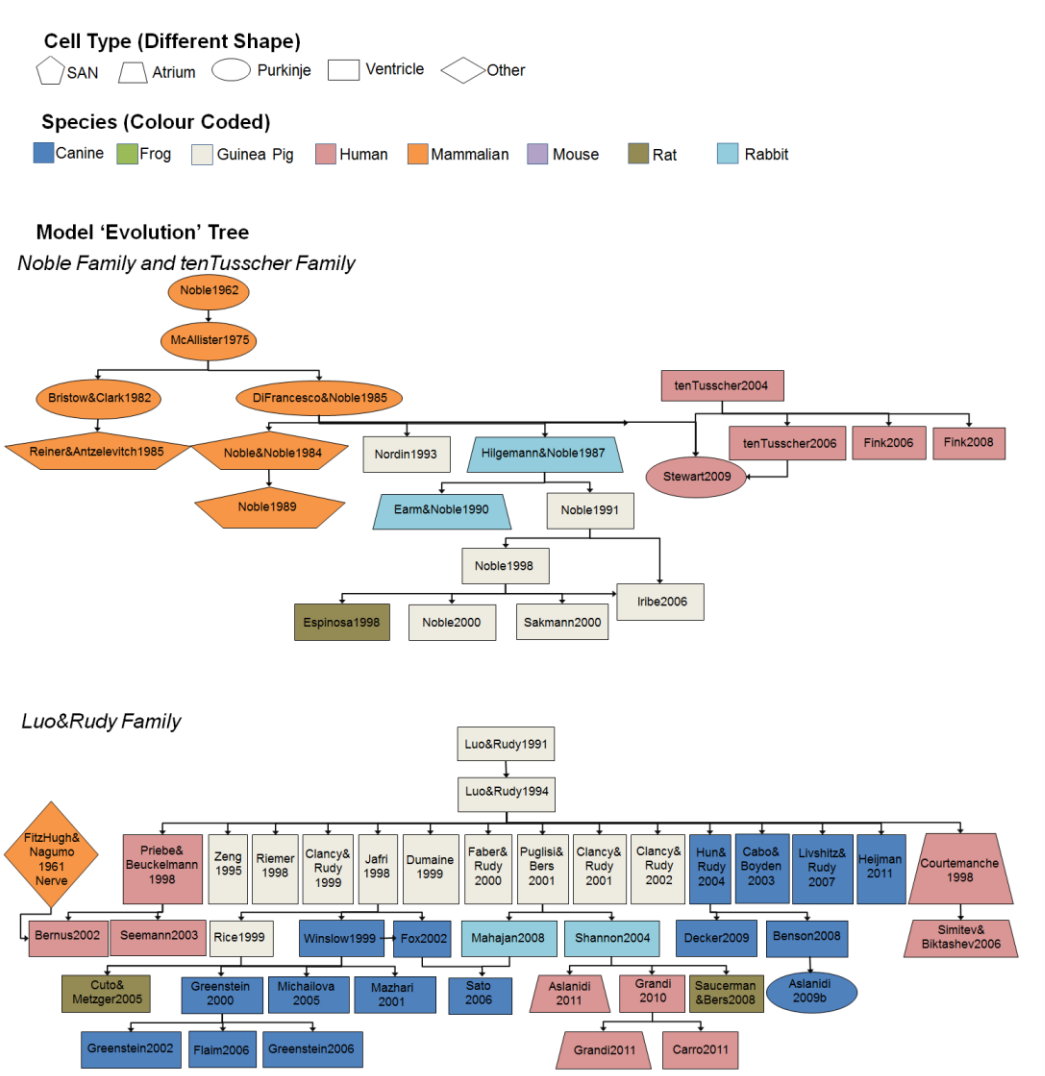
- Unlike some empirical models, mechanistic models are able to integrate individual ion channel effects measured using automated patch clamp systems (APC)
- The end of the action potential from left ventricular myocytes correlates with the end of the QT-interval on the ECG
- Therefore action potential simulations are a useful surrogate for ECG effects
- However, recent initiatives e.g. CiPA present a greater opportunity of usage of in-silico models
- Furthermore these models provide an excellent means for developing novel biomarkers for predicting beyond QT e.g. TdP/proarryhthmia risk



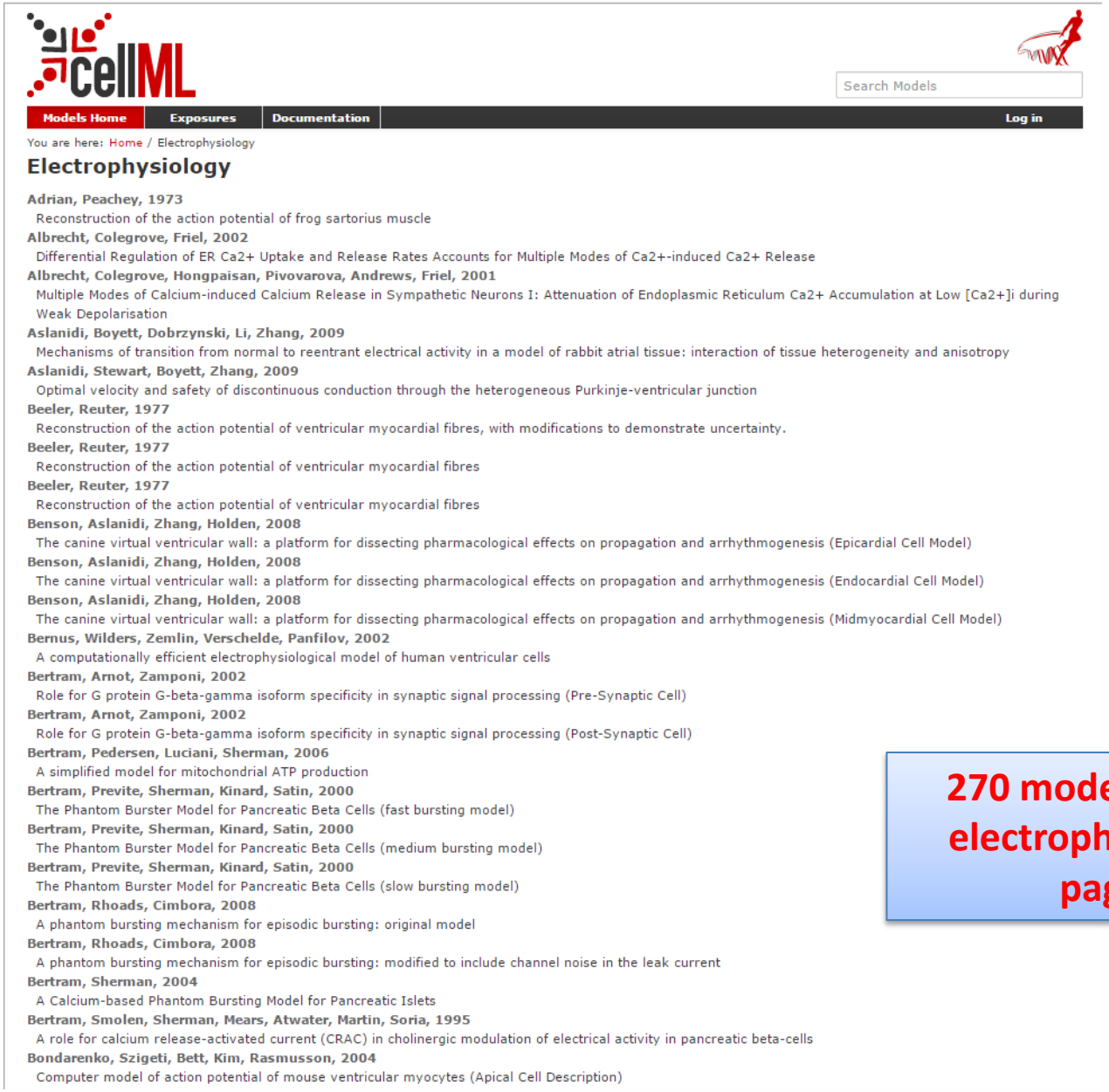
No. compounds screened experimentally: **1000's** **100's** **10's**

Ref.1 Davies et al. 2012 AJP-HCP
Ref.2 Mirams et al. 2014 JPTM

Which model to use?



Davies et al (2016)
Drug Discovery Today (in press)
&
Niederer et al (2009) Exp. Physiol.



270 models in the electrophysiology page

Is model granularity a function of processor speed?

- Cardiac model development has a rich history since the early ‘Noble’ models
- In general, models have increased in their computational complexity in line with computational power
- Does the improved complexity improve predictive score?
- **What is missing is the assessment of predictive capacity?**

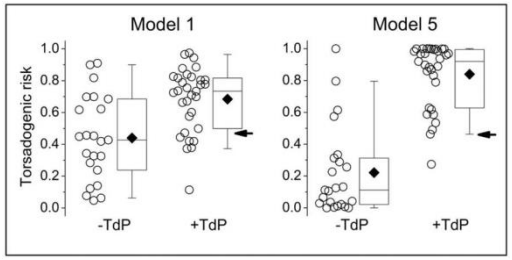
Figure 2: Generally, the size and complexity and mathematical models has increased over time in correlation with the availability of computational power.

Applying single cell models to drug development

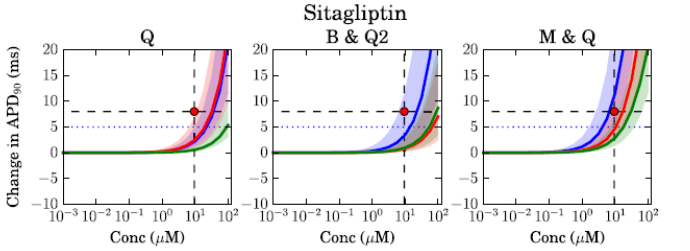
Previous in silico approaches

- **Several literature studies have implemented in silico approaches for categorising risk score, using statistical methods, mechanism based models and ensemble approaches:**

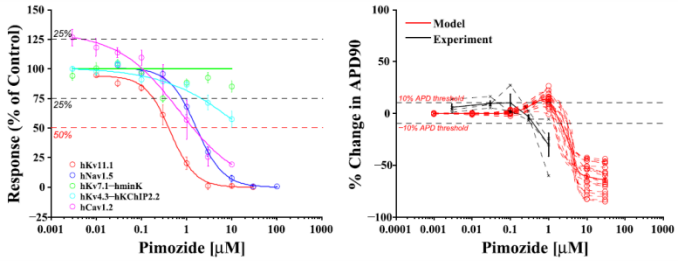
1. Kramer et al. (2013) integrating in a **statistical** model the data they obtained from APC platforms for compounds divided between TdP and non-TdP drugs



2. Mirams et al. (2014) combined ion channel screening data sets from multiple labs into different **mechanistic** models to evaluate the prediction of the outcome of the TQT study



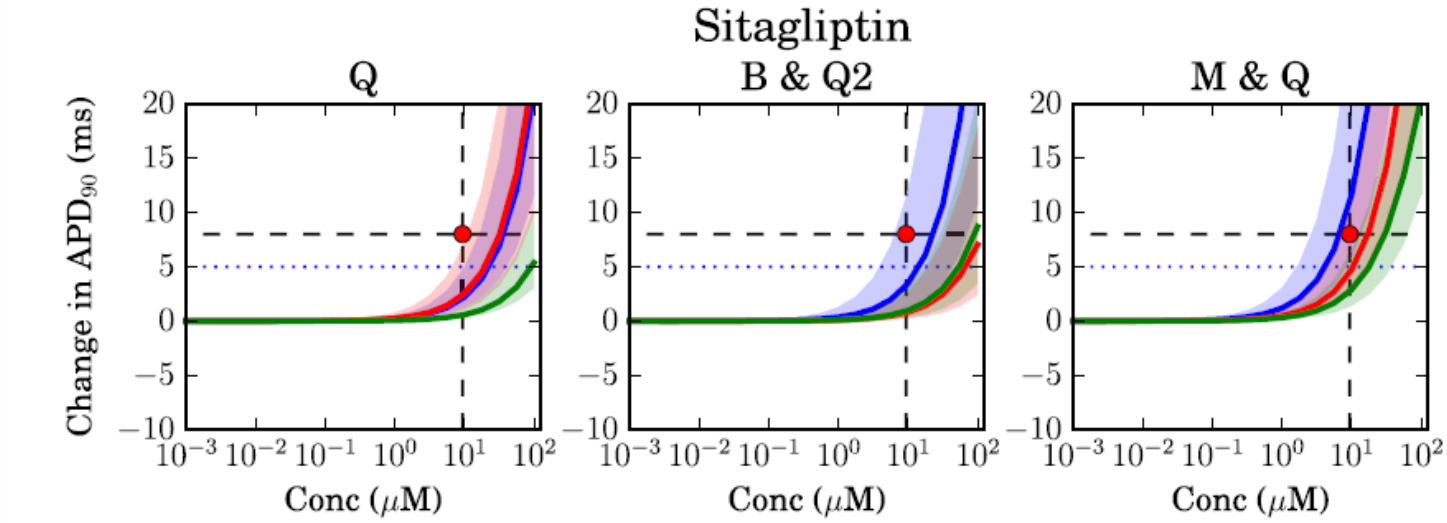
3. Davies et al. (2012) used an **ensemble** of a mechanistic model to integrate multichannel data to predict action potential changes from a canine cardiomyocyte assay



Case study 1 - Sitagliptin

- Model predicts prolongation
- Clinical study shows prolongation
- Consistent prediction across datasets and model structures

Right prediction, right dose

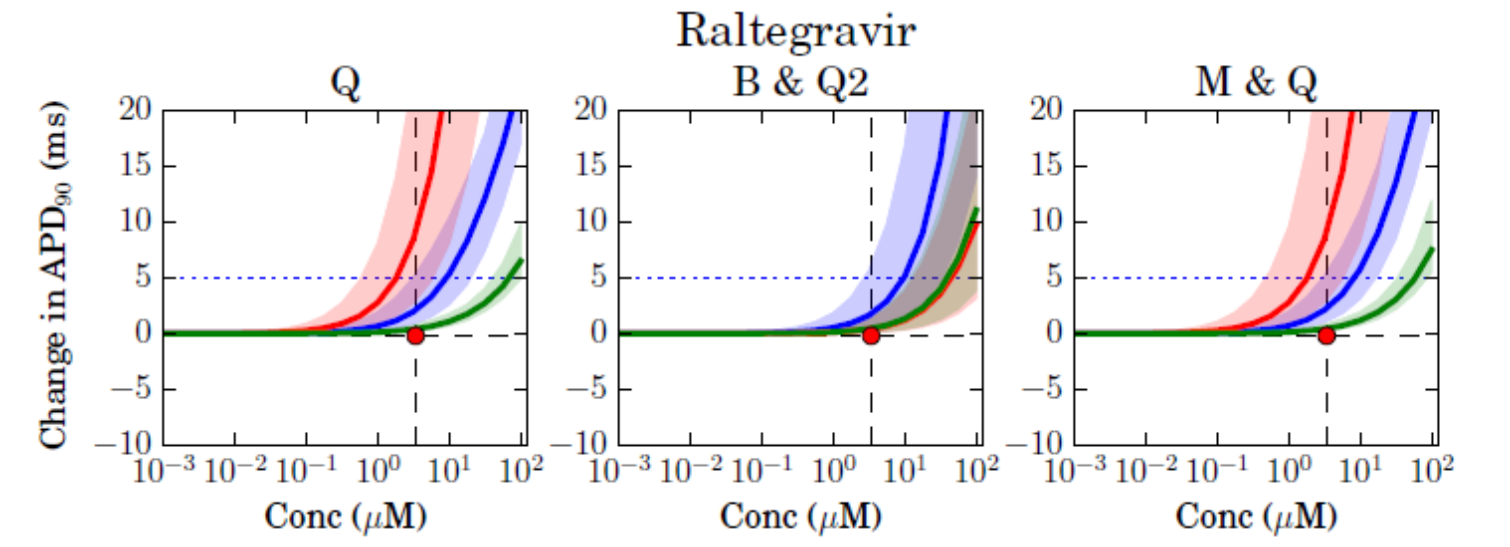


Mirams et al (2014) JPTM

Case study 2 - Raltegravir

- Models predict prolongation
- Clinical study shows no effect
- Does the model suggest that an effect would be seen at higher clinical concentrations? Or False positive
- Consistent prediction across datasets and model structures

Wrong prediction? wrong dose?



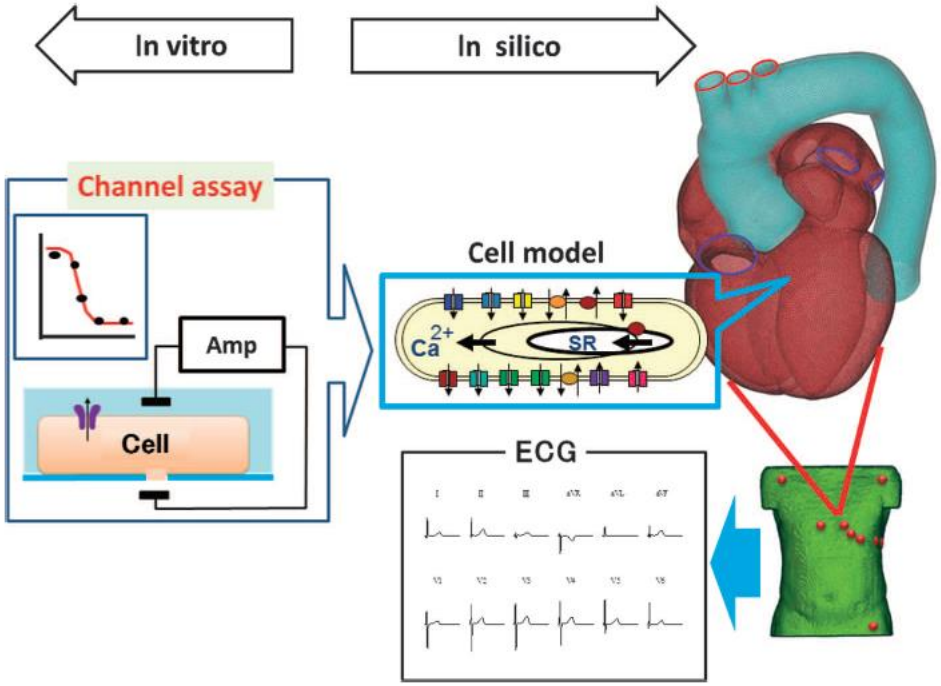
Mirams et al (2014) JPTM

Modelling the interpretation?

- How do we provide guidance to the interpreter when there is uncertainty in the predictions
- Dependent upon multiple other *human* factors, such as:
  - Individual scientist or project leader,
  - Their own understanding of modelling techniques (prior exposure)
  - Project motivations
- E.g. For Case study 2, what should the project have done?

3D heart modelling

- These model systems assume that emergent properties will be predicted when considering the physiological environment
- But which is represented and how should we interpret such results?



Okada et al (2015) Sci Adv

Example of semi-mechanistic (black box) model

$$S_x = 1 - \frac{1}{1 + \left(\frac{IC_{50}}{[D]}\right)^n},$$

- **Q.** Which compounds will show cardiac risk, which ones will not?
- The underlying mechanisms are unknown

$$Z = \frac{1 + a_0 S_{CaL} + a_1 S_{Na}}{1 + a_2 S_{Kr}}$$

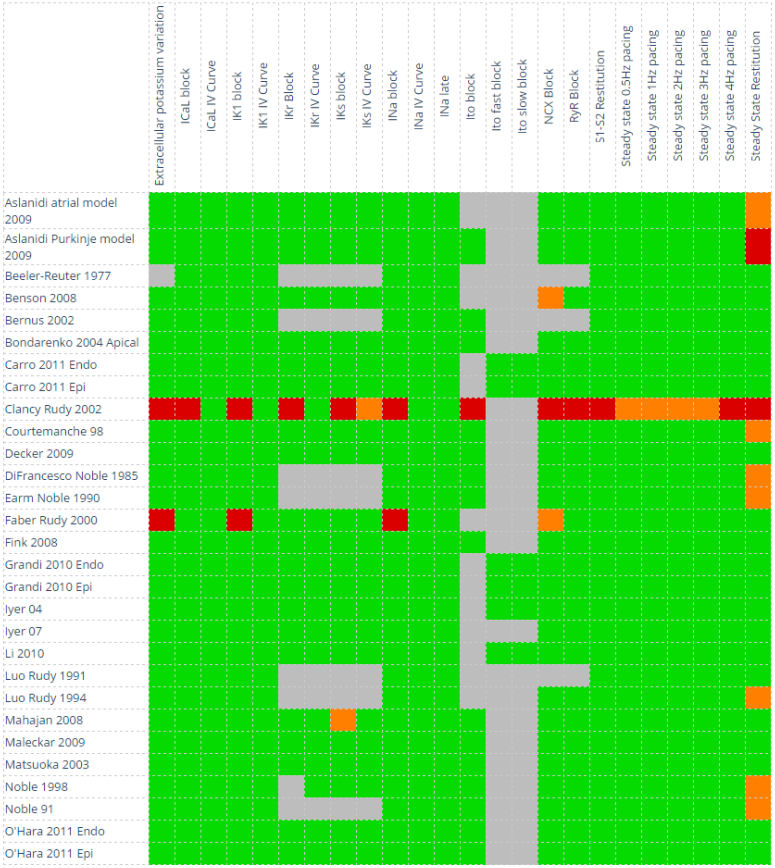
Data-set Binary Test Question (Yes/No)	Sensitivity%		Specificity%		Balanced Accuracy%	
	This model	Original model	This model	Original model	This model	Original model
Human 1 Torsade de Pointes Risk	97	97	91	83	94	90
Human 2 Torsade de Pointes Risks	93	100	97	97	95	98.5
Human 3 QTc Prolongation	57	50	90	85	73.5	67.5
Rabbit Prolongation	96	72	73	81	84.5	66.5
Rabbit Shortening	50	31	87	80	67.5	60
Dog Prolongation	67	60	84	76	75.5	68
Dog Shortening	67	48	78	87	72.5	67.5

Better metrics are highlighted in green. Worse metrics are highlighted in red.

Mistry et al (2015) Front. Pharmacol.

So which should we use?

- ‘Simple’ Statistical/QSP models: Kramer/Mistry/Cardiotox Predictor
- Mechanistically detailed ‘QSP’ models?
  - But which one, evaluate all is a tricky task in itself:
- 3D models (UT-Heart/Predict)
- Modular approach (Certara CSS)



https://travis.cs.ox.ac.uk/FunctionalCuration/db.html

External environment

What is CiPA

- HESI Mission: Engage scientists from academia, government and industry to identify and resolve global health and environmental issues.
- Of which the Cardiac Safety Technical Committee proposes a new paradigm for a *mechanistic* assessment of proarrhythmia that is not measured exclusively by potency of hERG block and not at all by QT prolongation
- CIPA initiative will ultimately require the modification or replacement of the existing ICH S7a/b guidelines and elimination of E14 guidelines
- CIPA *could* eliminate the need for a TQT study for compounds entering clinical development, based upon on the assessment in the proposed studies:
  - 1. *In vitro* drug effects on multiple cardiac ion channels (currently **7** proposed)
  - 2. *In silico* reconstruction of electrical effects
  - 3. *In vitro* drug effects on human stem-cell derived cardiomyocytes

What are the options and what opportunities

- Clear desire to extensively evaluate compounds (ongoing and over next 12-18 months), both *in silico* and *in vitro*
- CiPA have therefore published a list of 29 compounds covering different cardiac safety risk categories that will result in a community driven screening and evaluation against a core set of compounds
- The data generated by this initiative could be used to support new/existing models for the translational challenges† and safety evaluation of drugs.
  - Standardizing/reproducibility of ion channel screening
  - *In silico* model selection, calibration and evaluation exercises, (however O'Hara model is a preferred candidate)
  - Stem cell study sensitivity/robustness
- But we wish to avoid data being available only by way of conference/ journal article PDF tables!

† – *e.g. from Gintant presentation* - http://www.cardiac-safety.org.php53-3.ord1-1.websitetestlink.com/wp-content/uploads/2014/12/3.-CiPA-Overview-Workstreams-Gintant-Rechanneling_Dec-11-2014_FINAL.pdf

Data sets and Evaluation

Previous *in silico* assessments have not studied a consistent set of compounds

Study	Compounds in common with at least 1 other study[a]	No. unique *in silico* study compounds	Compounds common to CiPA list[b]
Mirams 2014 (39 cmpds)	11	28	1
Kramer 2013 (55 cmpds)	28	27	20
Davies 2012 (53 cmpds)	6	47	5
Mirams 2011 (31 cmpds)	18	13	13

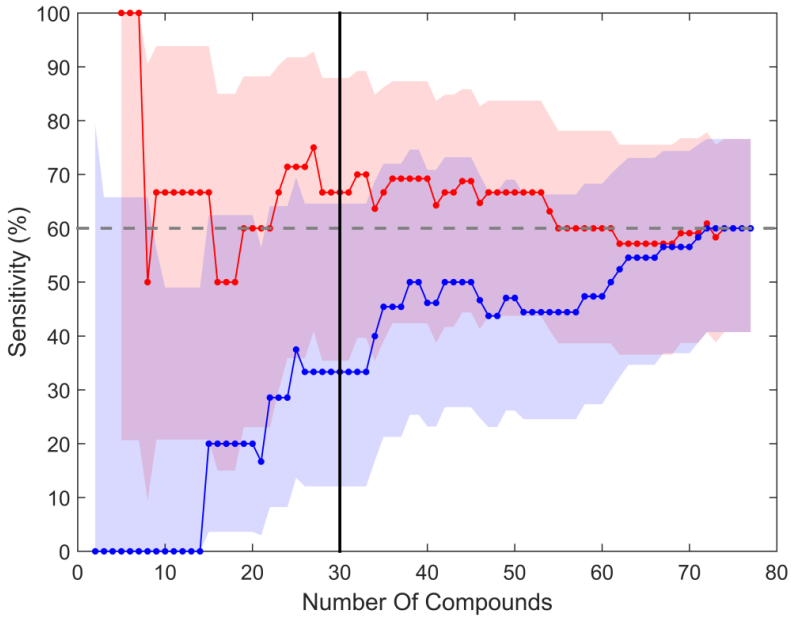
[a] *7 compounds have appeared in more than 2 studies, amiodarone, cisapride, dofetilide, nifedipine, pimozide, quinidine and terfenadine. No compounds have been used in every study.*

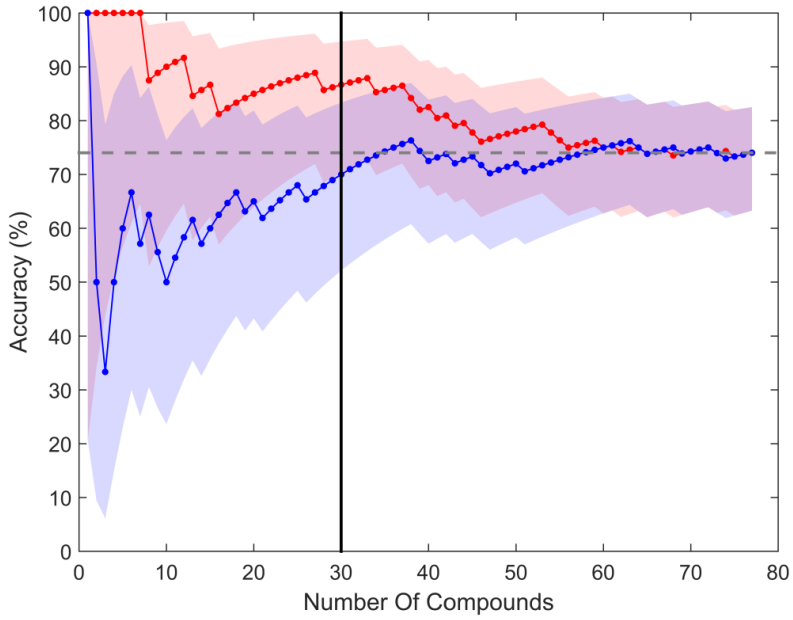
[b] *8 compounds (azimilide, clarithromycin, domperidone, metoprolol, ondansetron, ranolazine, tamoxifen, vandetanib) from the CiPA list have not previously been the subject of an in silico cardiac study.*

Davies et al (2016) Drug Discovery Today (in press)

Consequences of different compound sets

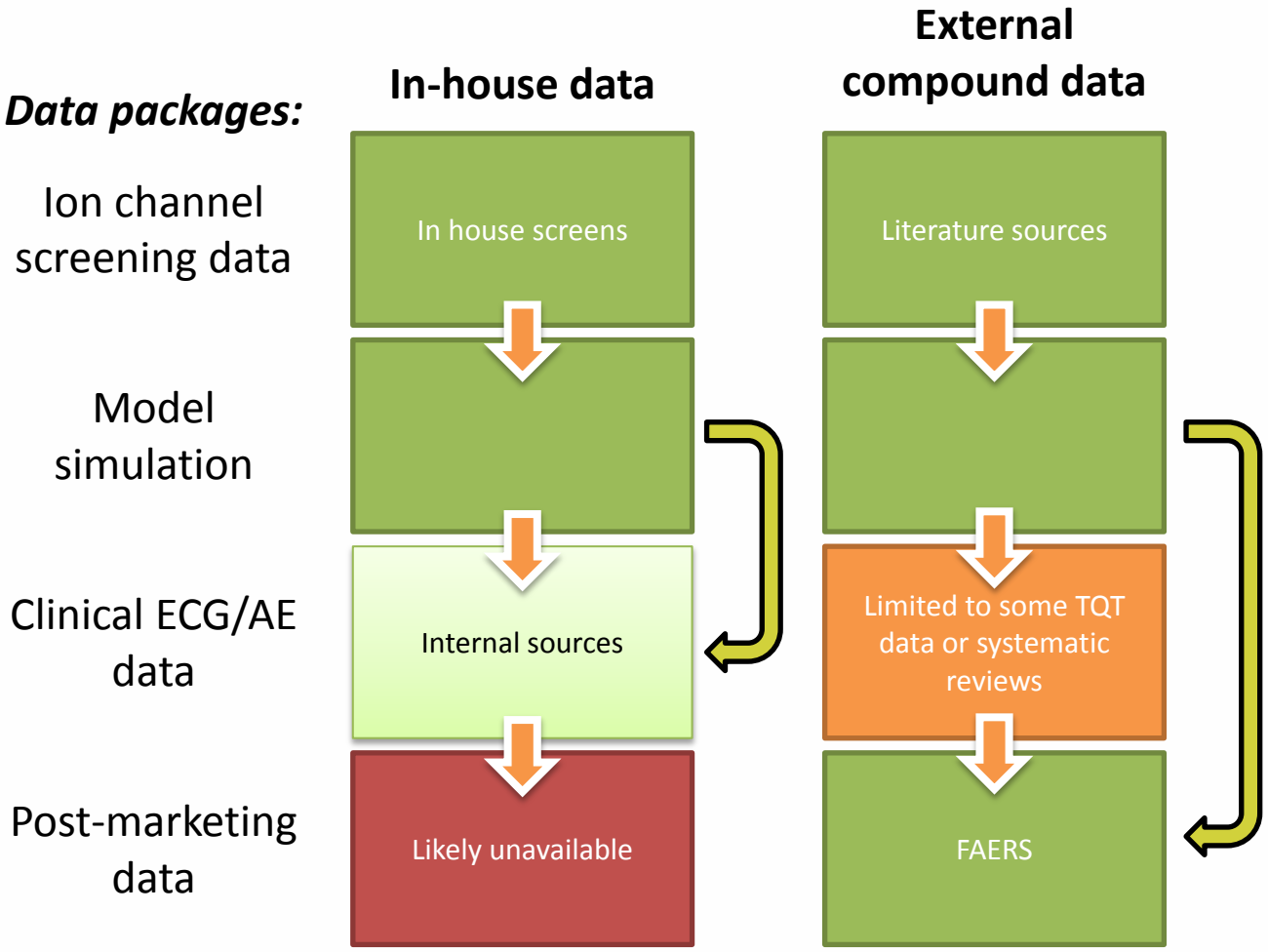
- Different compounds used for these studies means comparison across in silico tools is difficult
- The composition of the compound sets heavily influences the model performance





Davies et al (2016) Drug Discovery Today (in press)

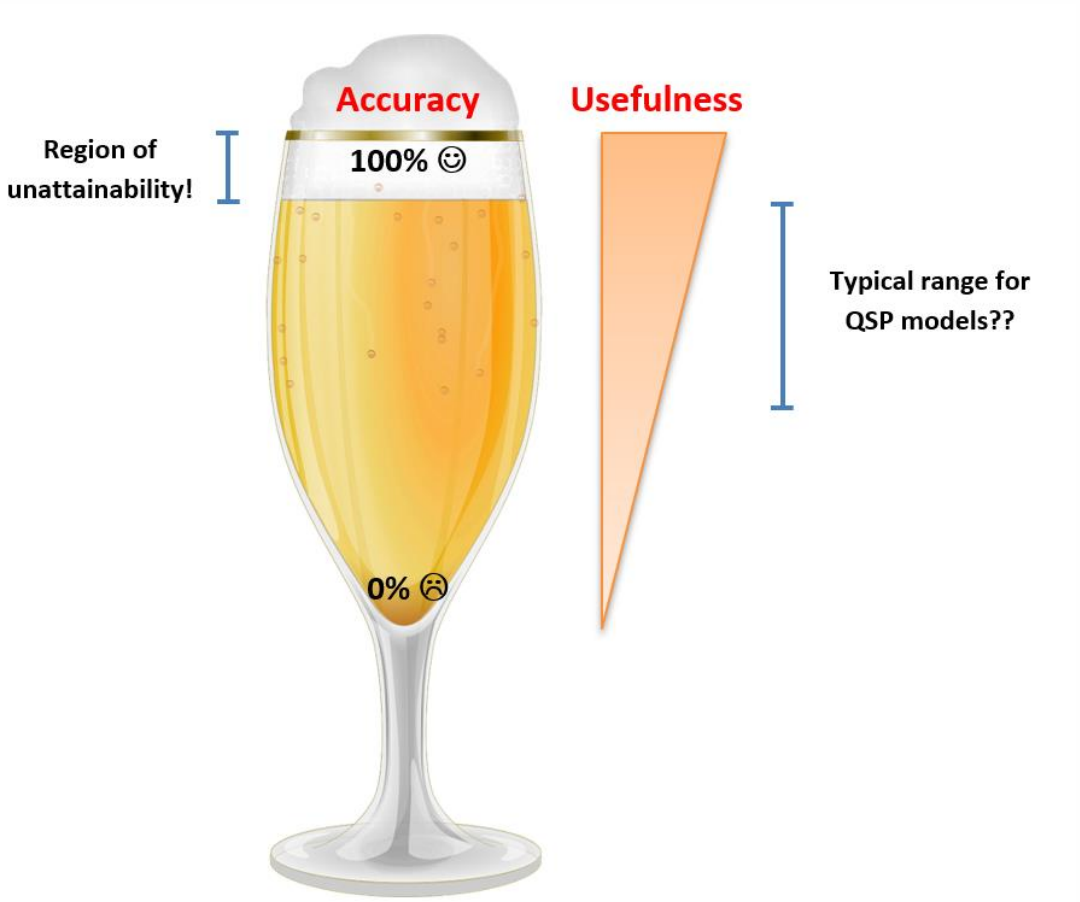
Improved data sharing would allow more joined-up/ translational model evaluation



What do we do with the results

- Does the score have the final say?
- We need to think about this up front?
- What if we don’t like the results!!

Before setting out on evaluating our models we need to consider the consequences?



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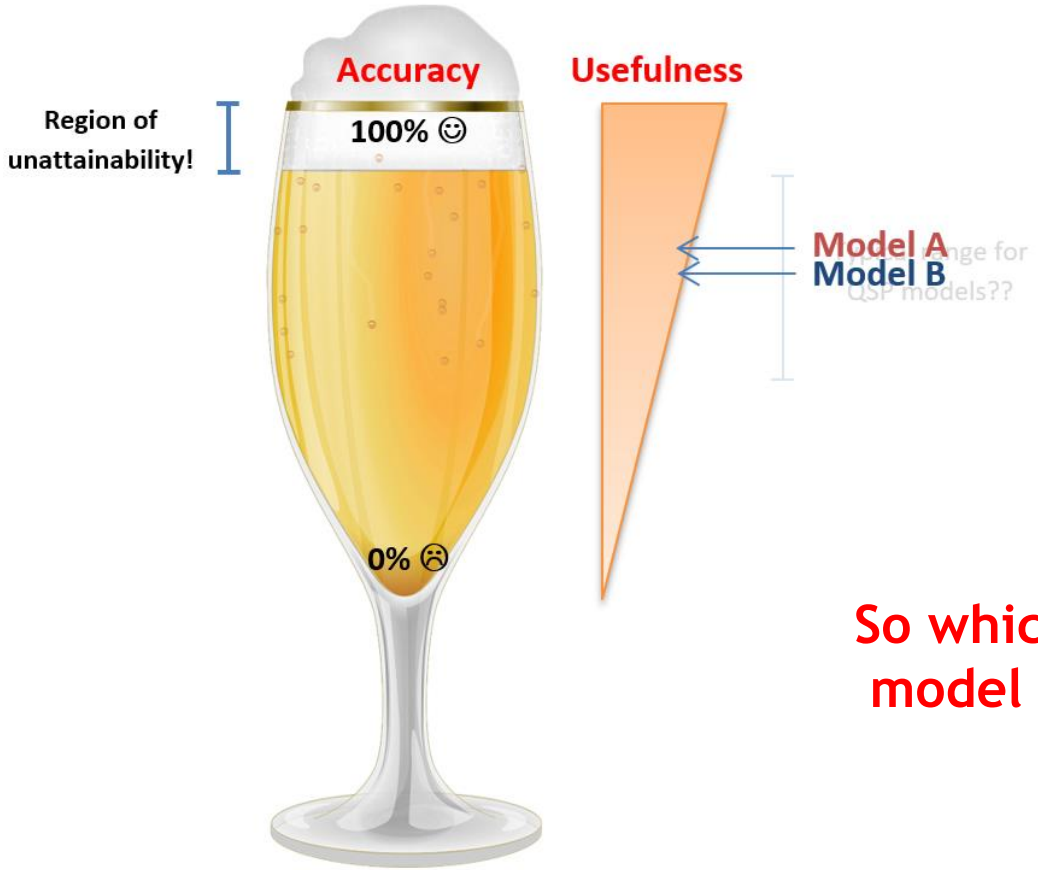


So which is the model to use?

Deciding which model to choose?

- In fact there are many, many models rather than just A and B
- What if model A (the higher scoring model) was actually an older (rabbit) model and model B was the ‘preferred’ (human) model?
- Does credibility of the model (i.e. underlying data, maturity) mitigate for a slightly lower accuracy?
- Which is more important, prediction accuracy or confidence in the model structure?
- How much should we consider the onward user – e.g. attempt to define a rule set for supporting onward decision making

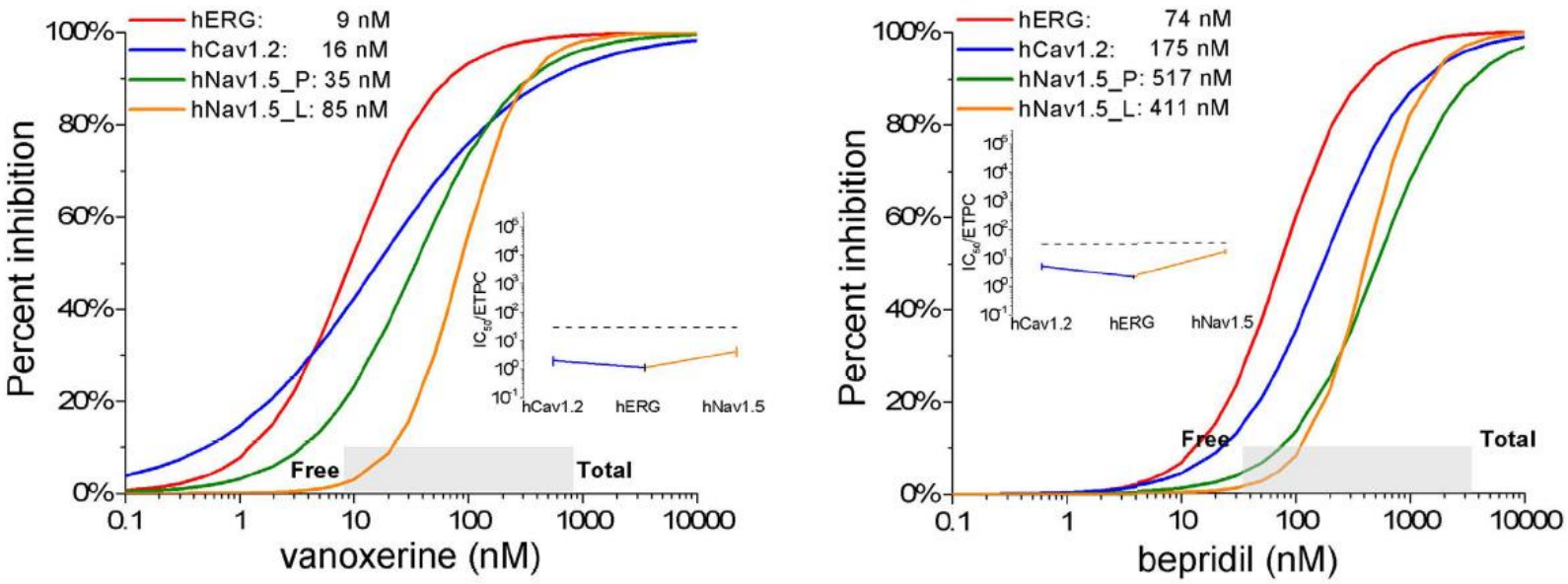
Summary

Summary and Questions:

- In the cardiac field we not only have different modelling types (and scales) to choose from but also a multitude of different structural (and differentially parameterised) models
- Choosing the representative model(s) is tricky and requires evaluation
- A carefully designed and tailored set of compounds and outcomes are essential for a reasonable evaluation of these models for the purpose of decision making
- Consideration for the outcomes of an evaluation is important in advance to reduce potential bias
- Can we go back (supposing the score directs us) from more physiologically detailed models?
- Can different granular models peacefully co-habit?
- Should mechanism based models be used as a black box model?

Reminder: CiPA initiative

- The cardiac in vitro proarrhythmia assay proposes to replace TQT studies with a combination of **in silico** (O'Hara model) and in vitro tests
- Important for 'Modelling and Simulation' to support getting this right
- Vanoxerine story: How to unpick those safe from those risky? They can look mighty similar



Obejero-Paz et al (2015) Sci. Rep.

The (Financial) Modelers' Hippocratic Oath

- I will remember that I didn't make the world, and it doesn't satisfy my equations.
- Though I will use models boldly to estimate value, I will not be overly impressed by mathematics.
- I will never sacrifice reality for elegance without explaining why I have done so.
- Nor will I give the people who use my model false comfort about its accuracy. Instead, I will make explicit its assumptions and oversights.
- I understand that my work may have enormous effects on society and the economy, many of them beyond my comprehension.

Emanuel Derman and Paul Wilmott, January 7 2009
http://www.wilmott.com/blogs/eman/index.cfm/2009/1/8/The-Financial-Modelers-Manifesto

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Chris Pollard
Jonathan Swinton

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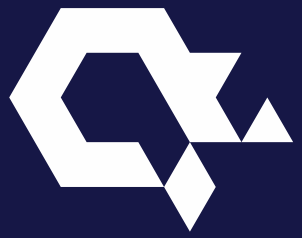

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