Pro-arrhythmia metrics from in-silico action potential models

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CiPA Update Meeting
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Where does in-silico pro-arrhythmia evaluation fit into CiPA?

Throughput

Cost

Ion Channel Screens

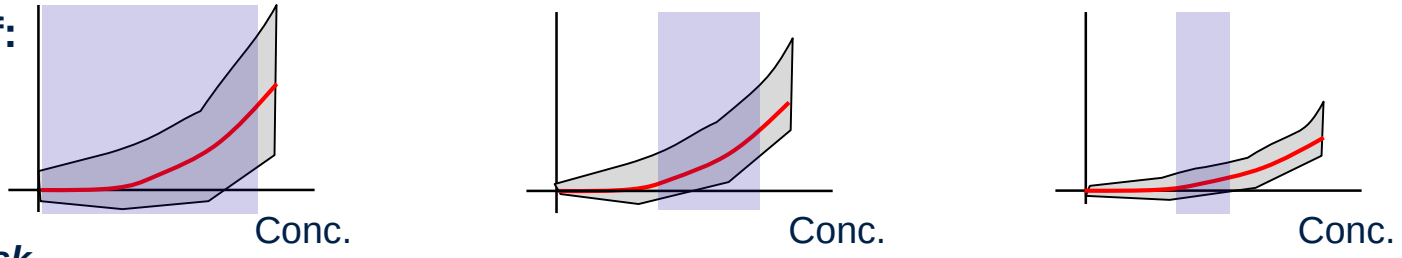
Stem-cell derived cardiomyocytes

In-vivo Testing / manual patch?

First Time In Human ECG

Simulation Predictions of:

- SC-CM recordings
- QT
- ***Arrhythmic risk***



Uncertainty

Accuracy

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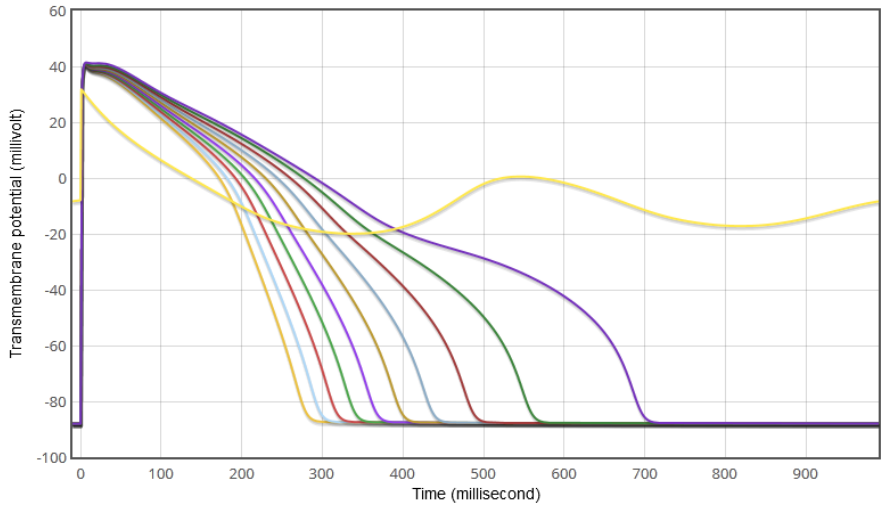
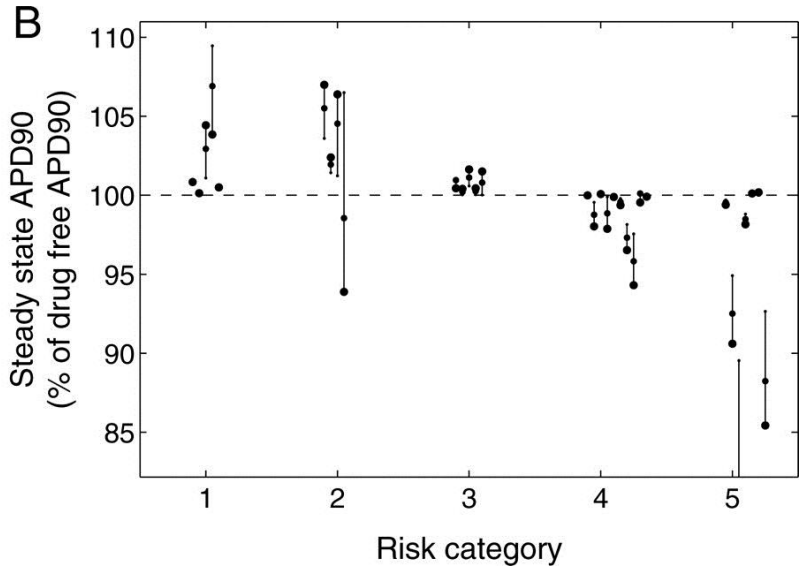
Possible Metrics: cell level

- Repolarisation delay





  - Pros:
    - Correlation with risk is understood as per QT
    - Validation of mechanistic predictions is straightforward
      - [ish - see recent Mirams et al. 2014 JPTM paper]
  - Cons
    - APD/QT prolongation is not equal to pro-arrhythmic risk

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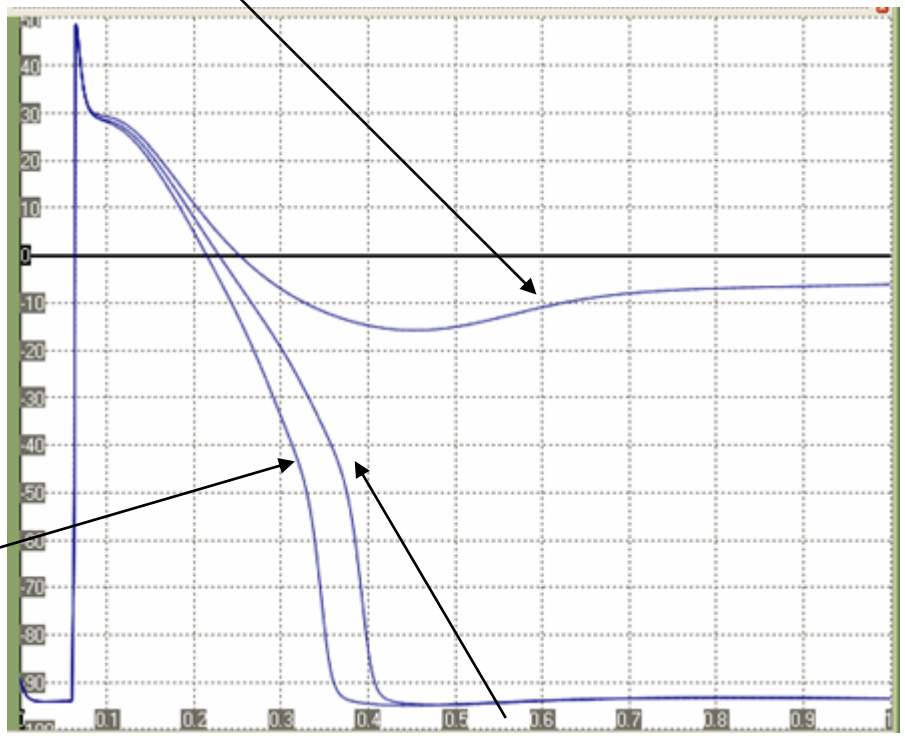
https://chaste.cs.ox.ac.uk/FunctionalCuration

Mirams *et al.*, Cardiovasc. Res., 2011

It's not all about hERG: Ranolazine

90% block of I_{Kr}



control

90% block of I_{Kr} + 50% block of I_{pNa}

Noble & Noble, *Heart*, **92**, iv1-5, (2006)
see also Moreno et al., Circ. Res. (2013)

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Can we do better than QT?

J. Physiol. (1969), **200**, *pp.* 255–265
With 4 text-figures
Printed in Great Britain

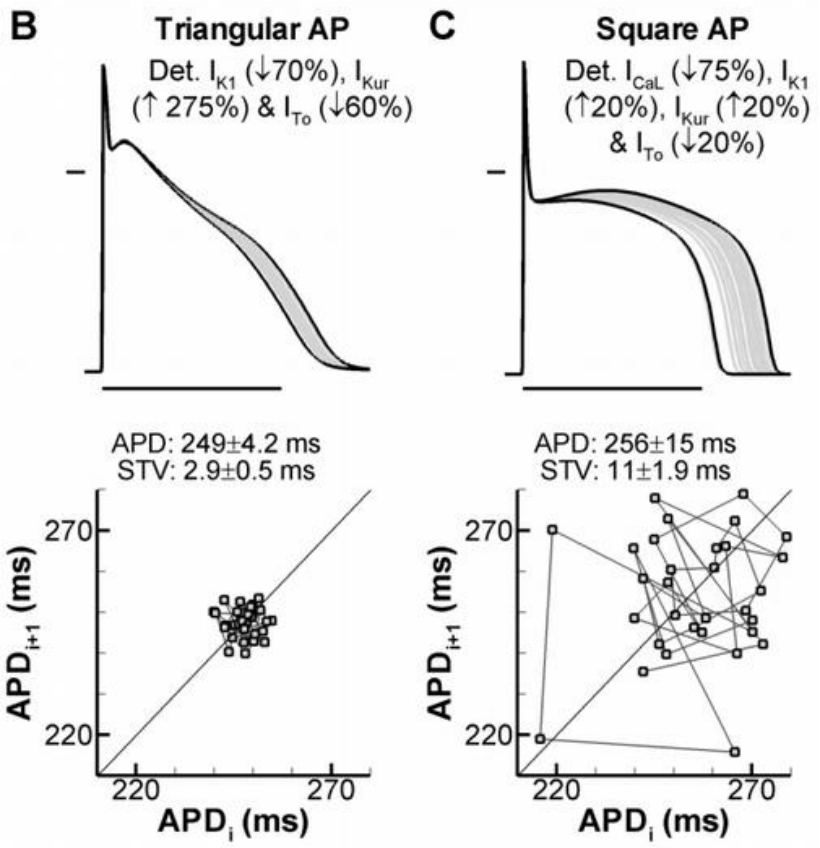
THE MECHANISM OF OSCILLATORY ACTIVITY AT LOW MEMBRANE POTENTIALS IN CARDIAC PURKINJE FIBRES

BY O. HAUSWIRTH,* D. NOBLE AND R. W. TSIEN†
From the University Laboratory of Physiology, Oxford

Possible Metrics: cell level

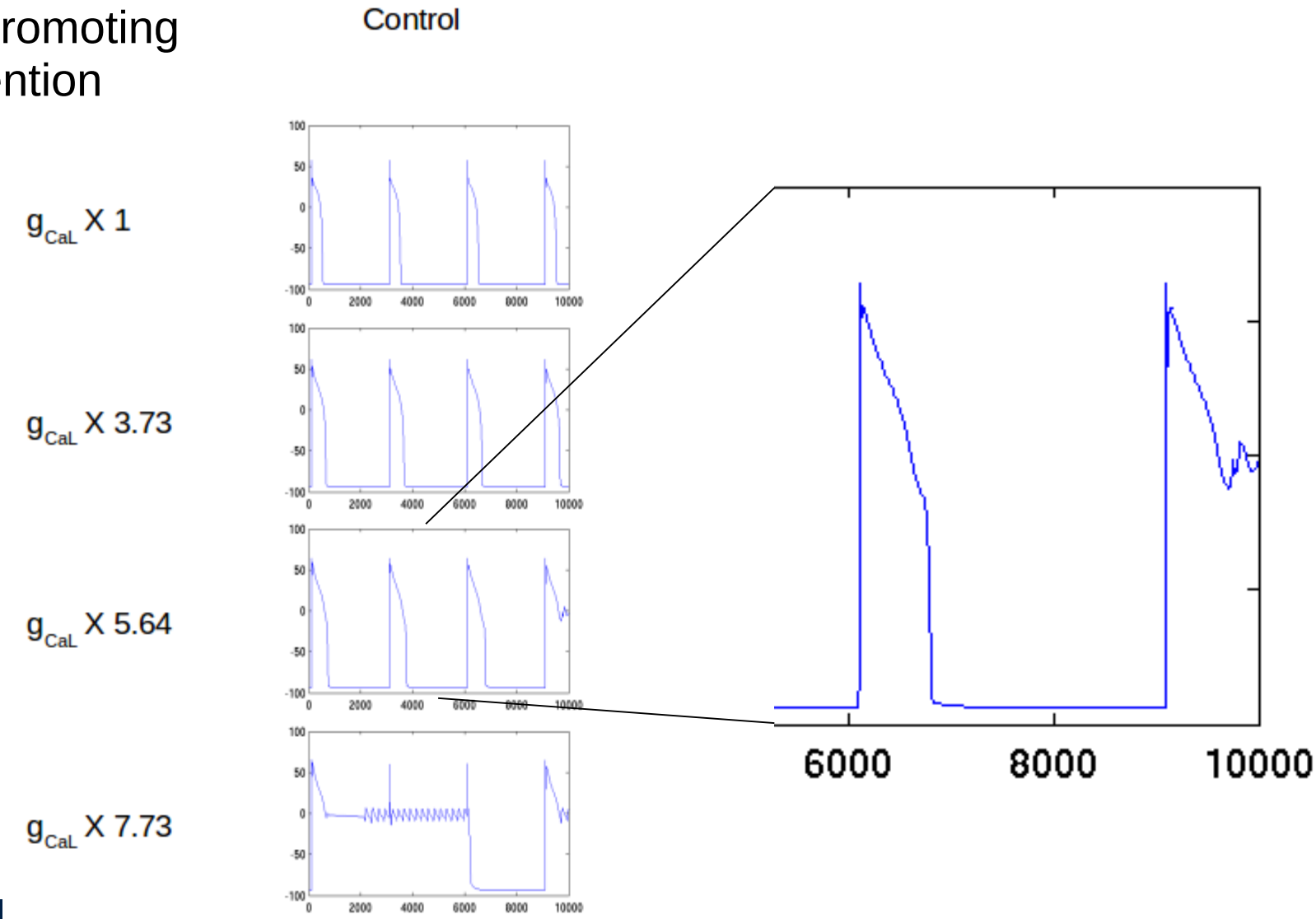
- Quantify ‘Repolarization Reserve’
- AP Triangulation
- Reverse-use dependence (Hondeghem et al. Circulation, 2001)
- Beat-to-beat stability (Heijman et al. PLoS Comp. Biol., 2013)
- ‘EAD tendency’
- ‘DAD tendency’
- Substrates and triggers

- Pros:
  - more mechanistic links to TdP different ways’ to be captured
- Cons:
  - validation of the mechanistic p experiments that would be nee



EAD Tendency

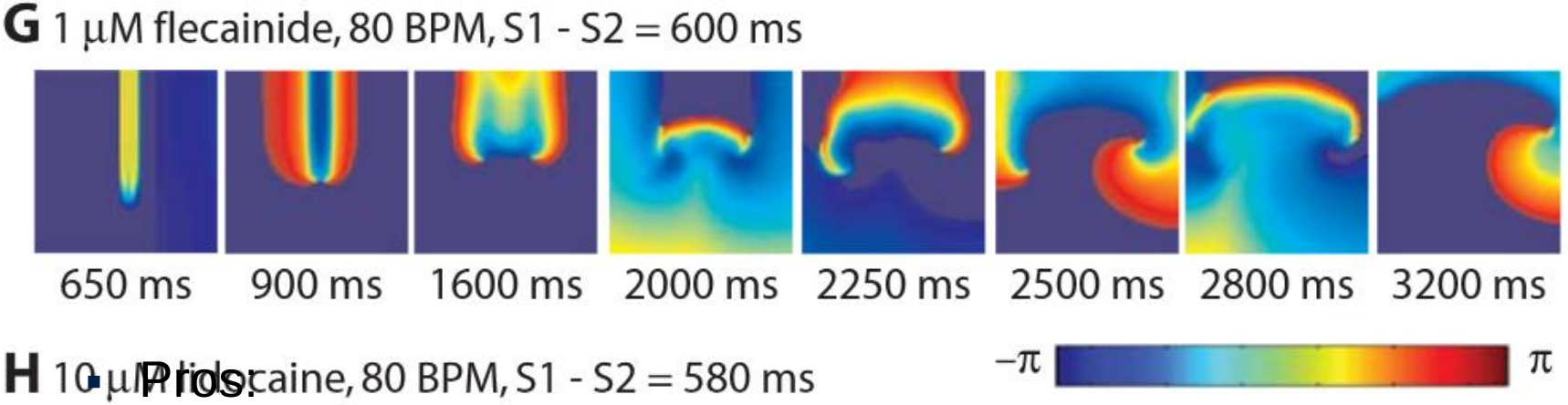
EAD-promoting intervention



Ten Tusscher ‘06 in low extracellular potassium, unpublished

Possible Metrics: tissue and organ level

- Dispersion of repolarization
- Vulnerable period (see Starmer papers)
- Spiral Wave induction and breakup (e.g. Moreno et al. 2011)



- Pros:
  - Higher level integration could be the key to some types of arrhythmias.
- Cons:
  - More unknowns in terms of tissue coupling, heterogeneity, fibre directions, patient specificity. Validation of the mechanisms behind these predictions is very difficult

Challenges

- What would success look like?
  - Limited number of CiPA ref compounds. 3 risk categories
- Characterisation and variability of SC-CM electrophysiology
- Capturing ion channel ‘drug kinetics’ is very complicated
  - We’ll only really know if it helps once we’ve tried it
- Will high-throughput machines be accurate enough to capture what can be a delicate balance of current block?

  (Elkins et al. 2013)
- **Quantify uncertainty** in predictions

Putting the ‘C’ in CiPA...

- Lots of possible markers – perhaps we shouldn’t be looking for one...
- Patient subgroups
  - Genetic:
    - Sex
    - Ion channel mutations
    - etc.
  - Disease:
    - Under various heart failure and ischaemic electrophysiology situations
- Co-administration of drugs
- Risk assessment for the patient not the pill

Acknowledgements

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wellcome trust Fellow

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