Modelling repolarization and re-entrant arrhythmia

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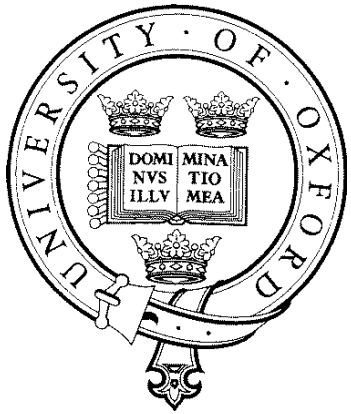
Basel Computational Biology Conference
From Information to Simulation

19 March 2004



The problem: drug-induced QT prolongation

- Major regulatory concern in drug development
- Impacts **all** therapeutic drug classes
- Responsible for nearly half of US FDA safety-based drug withdrawals since 1998
- Frequent cause of clinical holds, NDA withdrawals, delays in approval, and restricted labeling

Challenges in predicting QT safety

- No surrogate for the human heart
- No fully predictive pre-clinical assay
- Large number of experimental variables
- Effects of genetics, disease difficult to reproduce experimentally
  - ***Danger of false positives or false negatives***
  - ***Time and resource expenditures very significant***
  - ***Markers not conclusions***

This presentation will deal with

- Physiological basis of QT interval (action potential duration)
- Simulation of repolarization mechanisms
- Related arrhythmic indicators
- Where do we go after S7B (Draft Consensus Guideline)?

  - Page 2 "The development of new technologies and methodologies is encouraged"
  – I will ask how far modelling has got and where it could go.

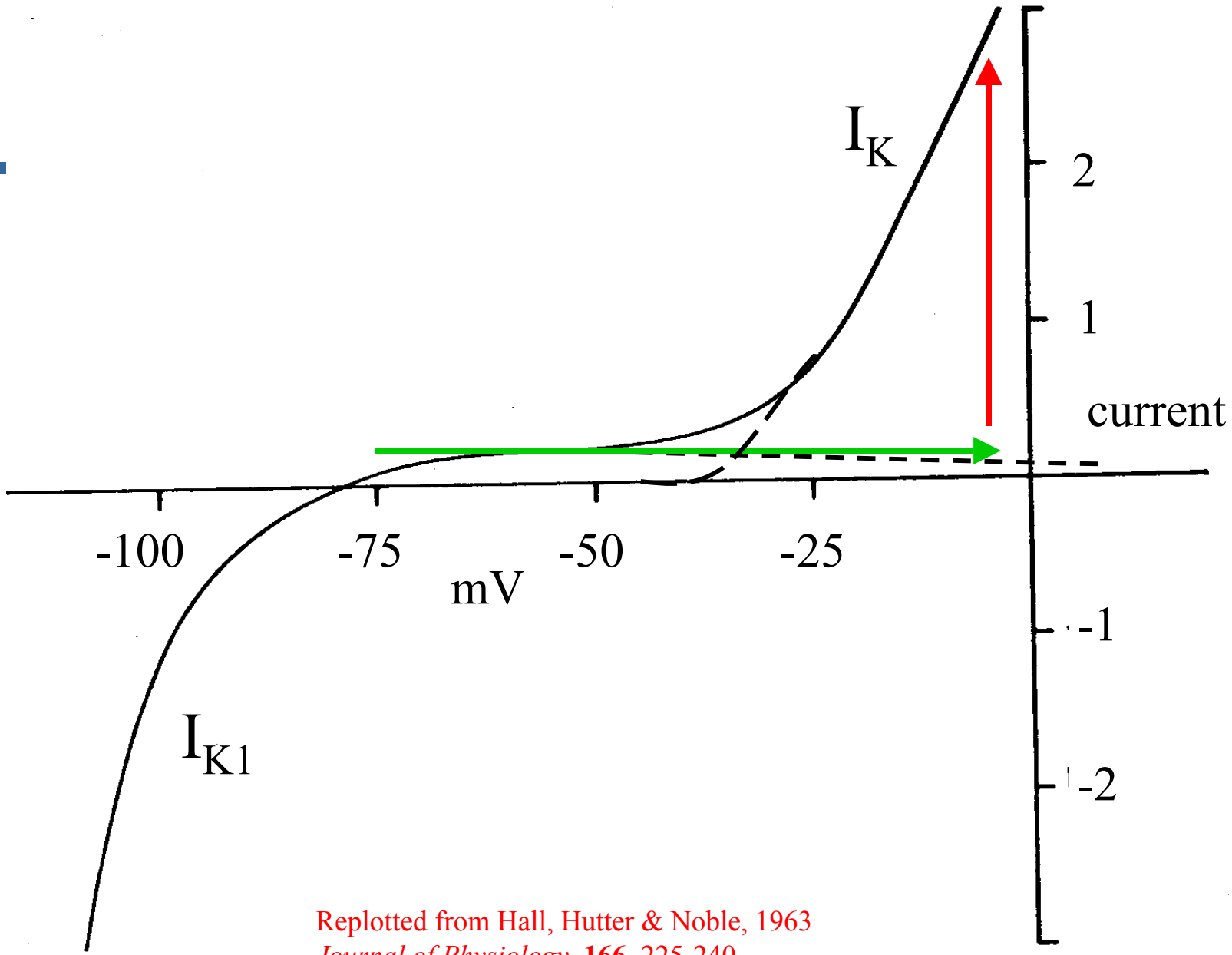
  - Page 6 "Evidence for repolarization impairment in nonclinical studies should not, however, preclude development of the candidate pharmaceutical"
  – I will illustrate such a case.

  - Page 21 "however, modelling of the clinical condition where pharmaceuticals elicit arrhythmia is complicated"
  – I will show that, while complicated, it is possible

Origin of the problem

Discovery of cardiac K^+ channels 1960

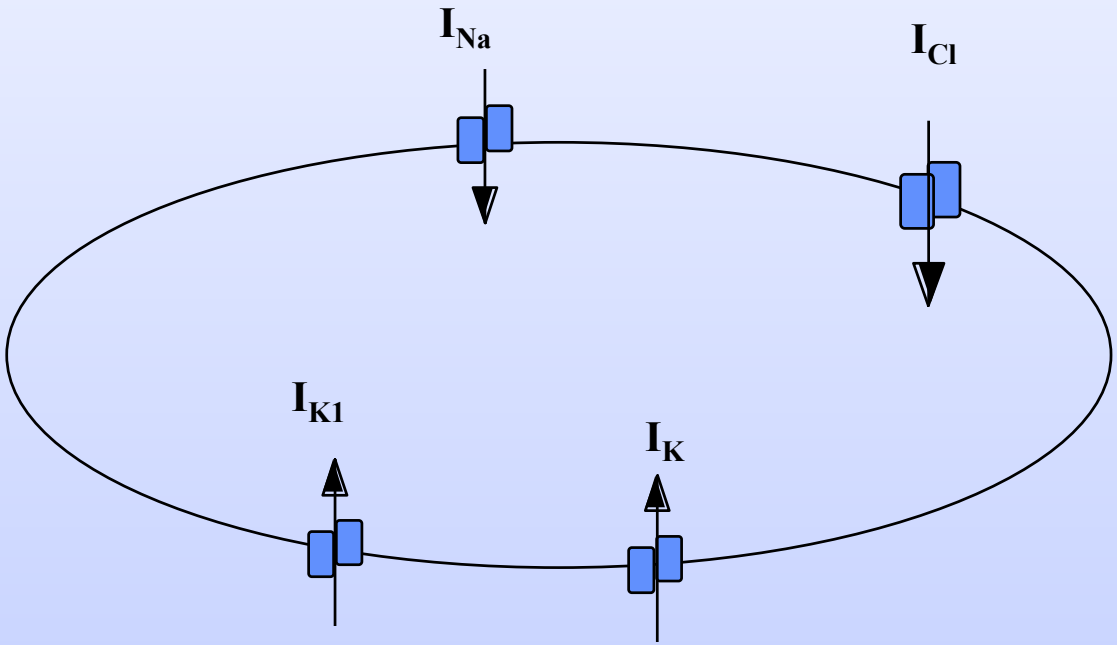
1960 : analysis of K^+ channels in the heart



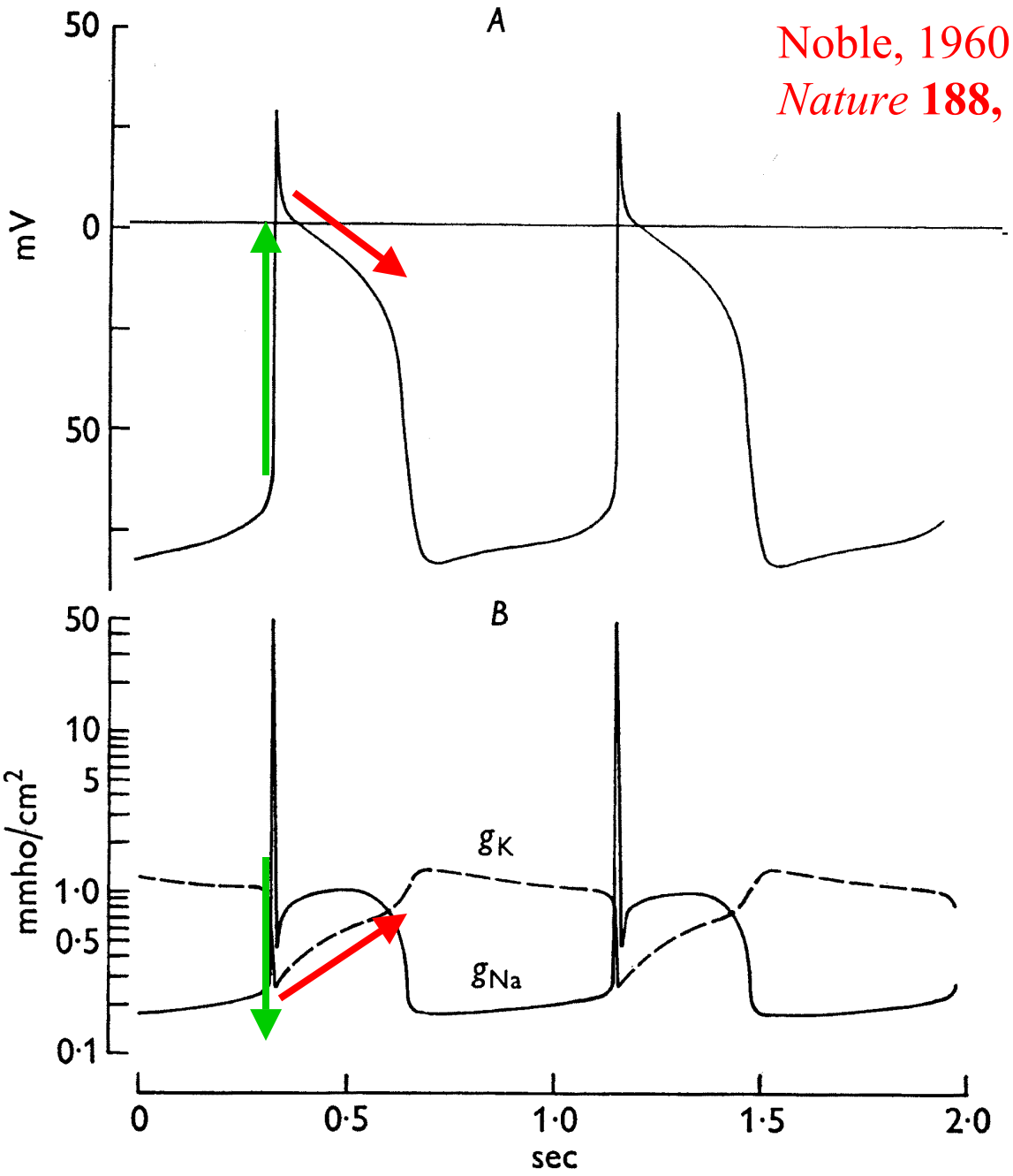
Replotted from Hall, Hutter & Noble, 1963
Journal of Physiology, **166**, 225-240

Model Construction 1960

Purkinje fibre Channels



Noble, 1960
Nature **188,** 495-497



Nature's pact with the devil:

1. The good news

The inward rectifier potassium current

i_{K1} (Kir2.x)

guarantees energy conservation

Nature's pact with the devil:

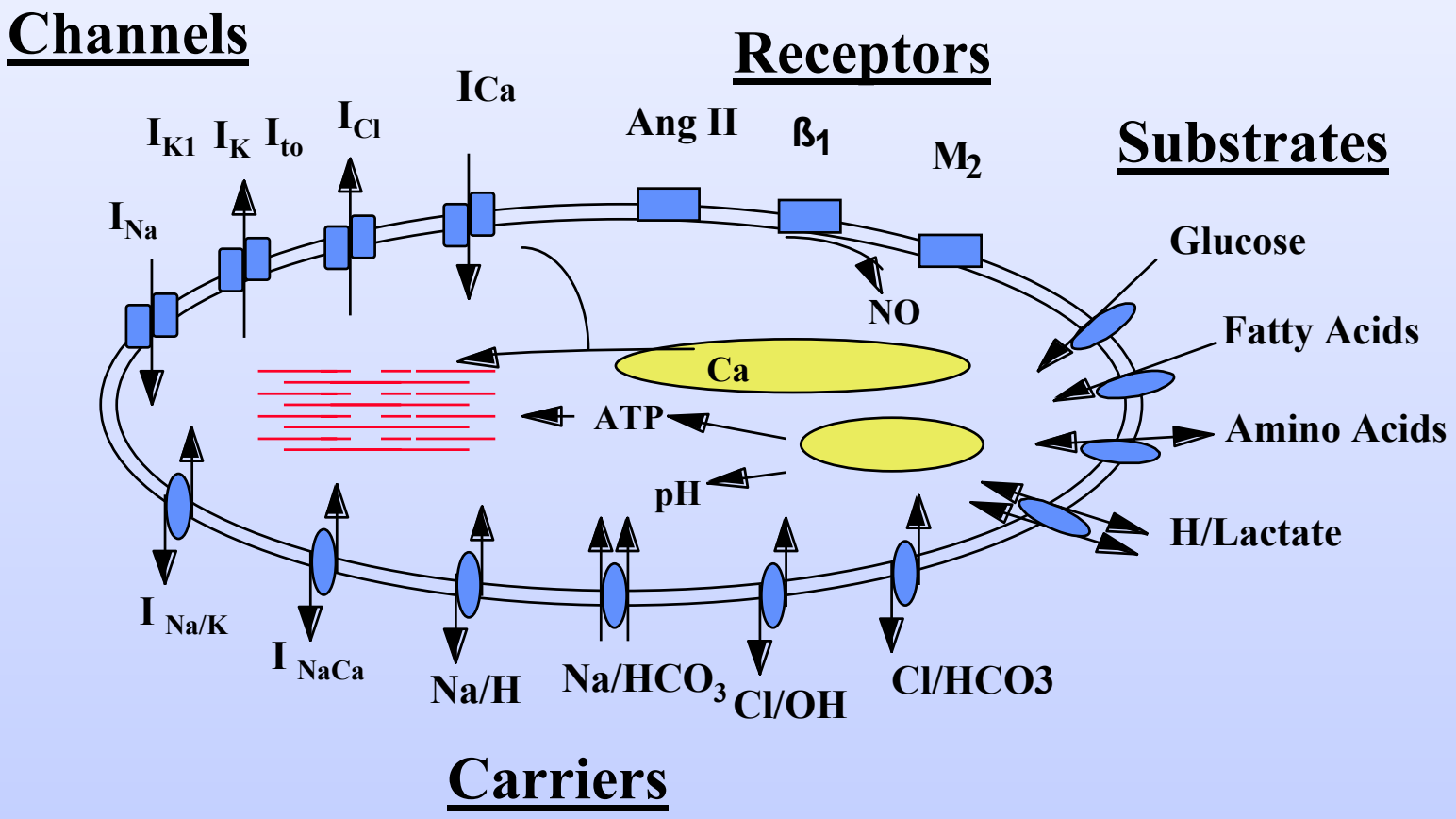
2. The bad news

The delayed potassium current

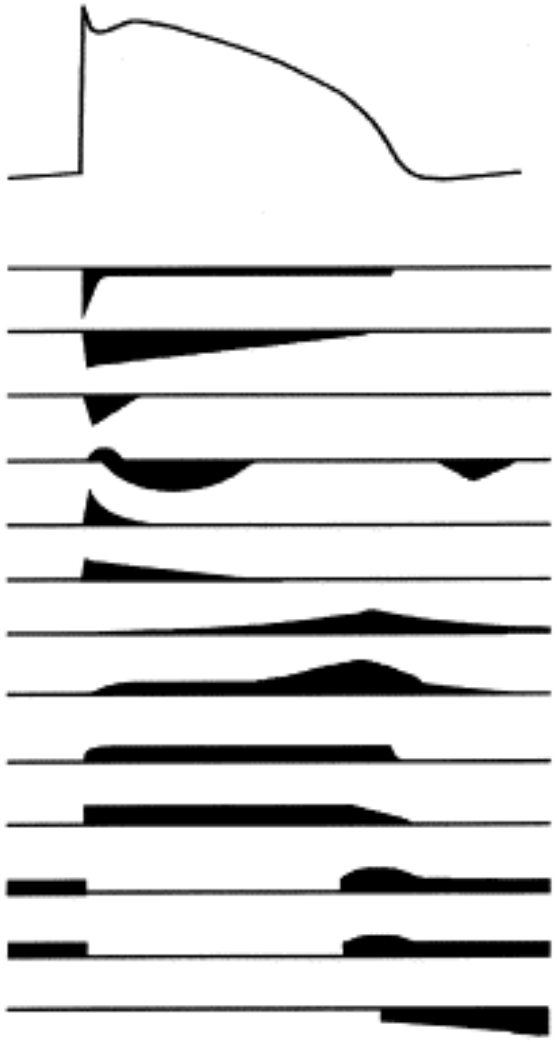
i_{Kr} (HERG +)

is highly promiscuous

Model Construction 2000

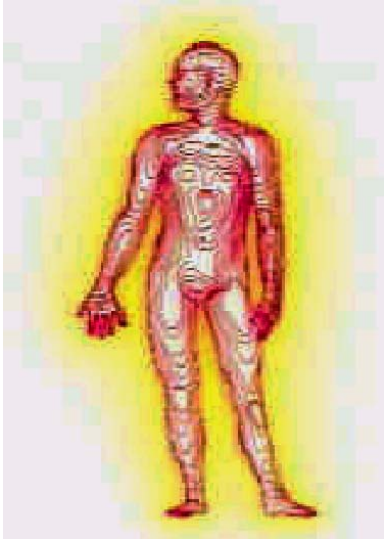


Cardiac ion currents and cloned subunits



Current	Probable clone
sodium current	hH1
L-type calcium current	α_{1C} dihydropyridine receptor
T-type calcium current	α_{1G}
Na-Ca exchange	Na-Ca exchanger
I_{TO1} (4-AP-sensitive)	Kv4.2/4.3
I_{TO2} (Ca-activated)	--
I_{Ks}	KvLQT1+minK
I_{Kr}	HERG + ?
I_{Kur} or I_{Kq}	Kv1.5
I_{Cl} or I_{Kp}	CFTR // TWIK
I_{K1} (inward rectifier)	Kir2 family
I_K ATP/ACh	GIRK1+4 / Kir6.2+SUR1
I_f (pacemaker)	HCN2

Human cell model



TEN TUSSCHER, K. H. W. J., NOBLE, D., NOBLE, P. J. & PANFILOV, A. V. (2003).

A model of the human ventricular myocyte.

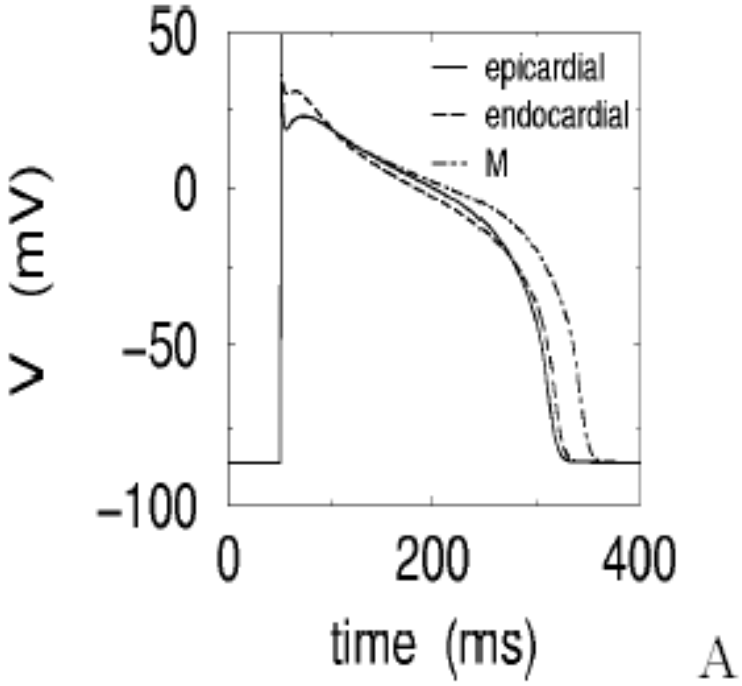
American Journal of Physiology

(published on-line December 4)

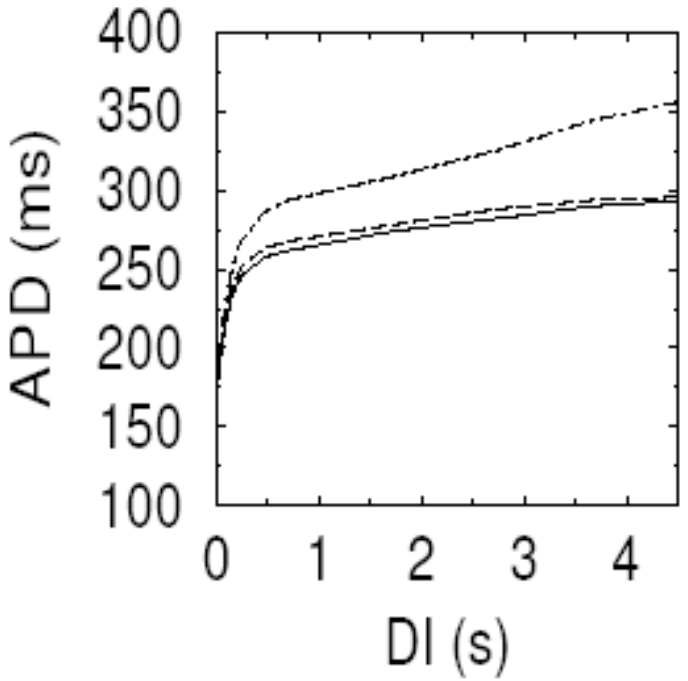
Detailed channel, transporter and SR equations, but computationally very efficient

Human cell model

The model includes regional expression differences.



A

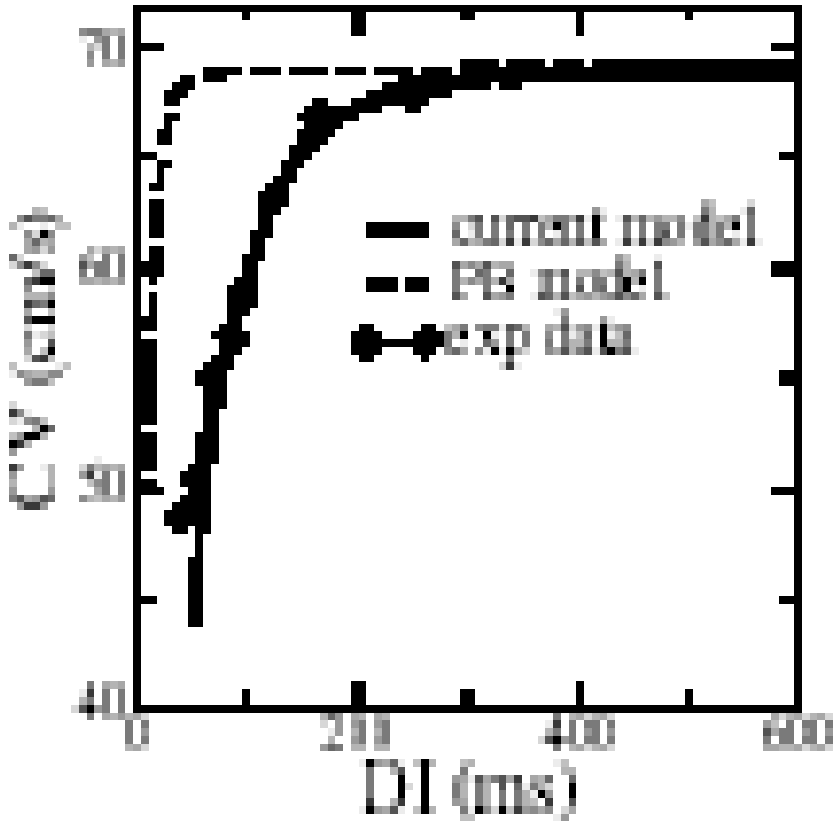


B

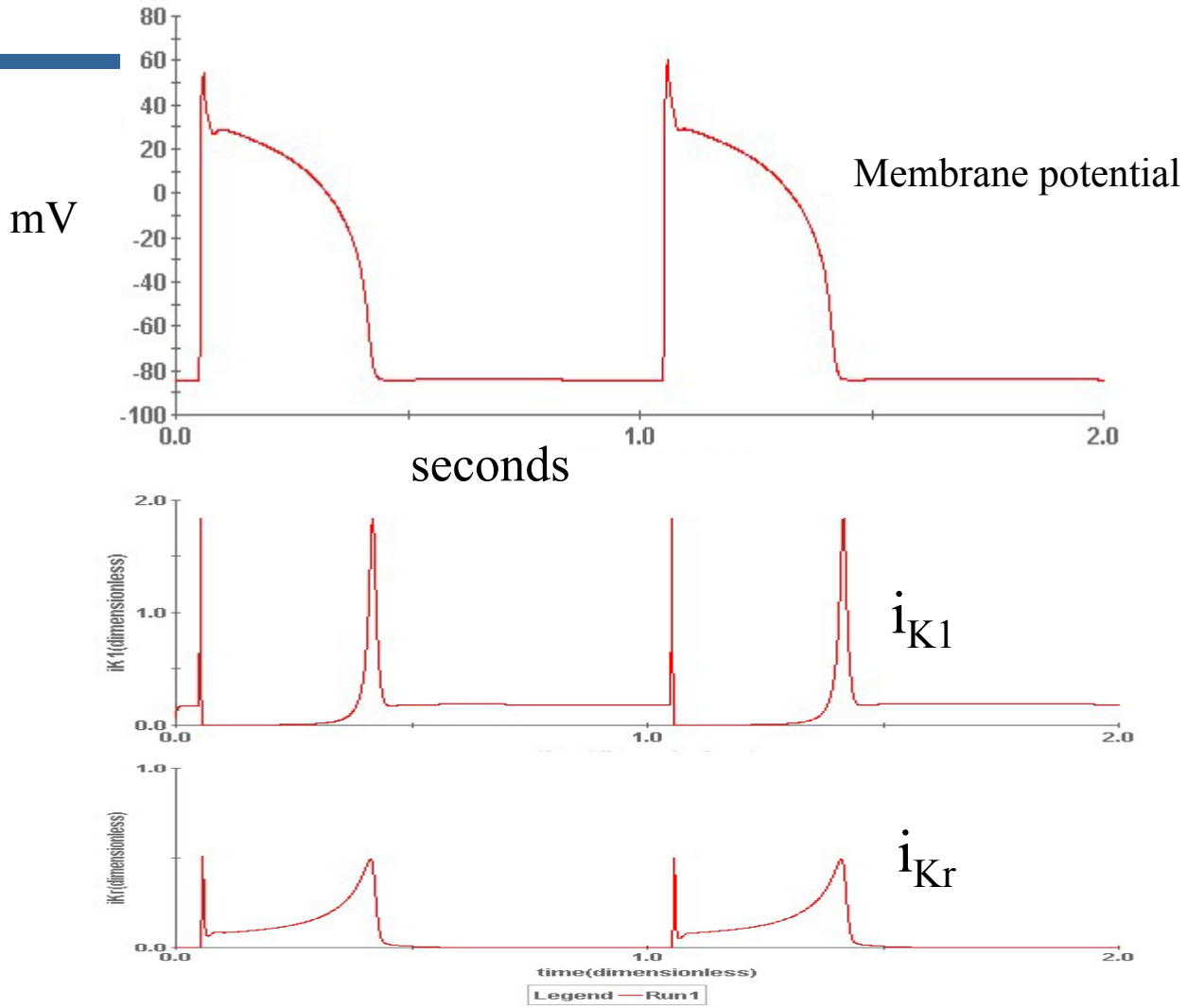
Human cell model

Comparison with Priebe-Beuckelman 1998

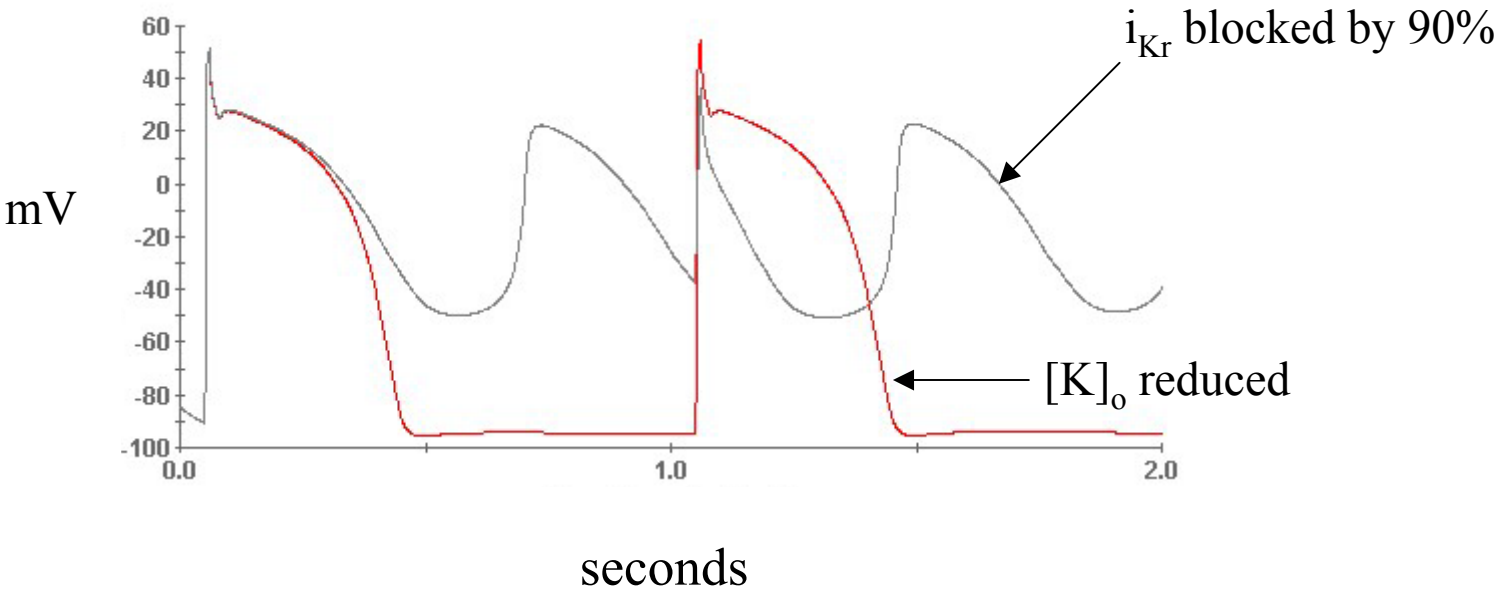
Slower recovery of conduction velocity, as seen experimentally



Human ventricular cell model



Human ventricular cell model
Class III induced EAD

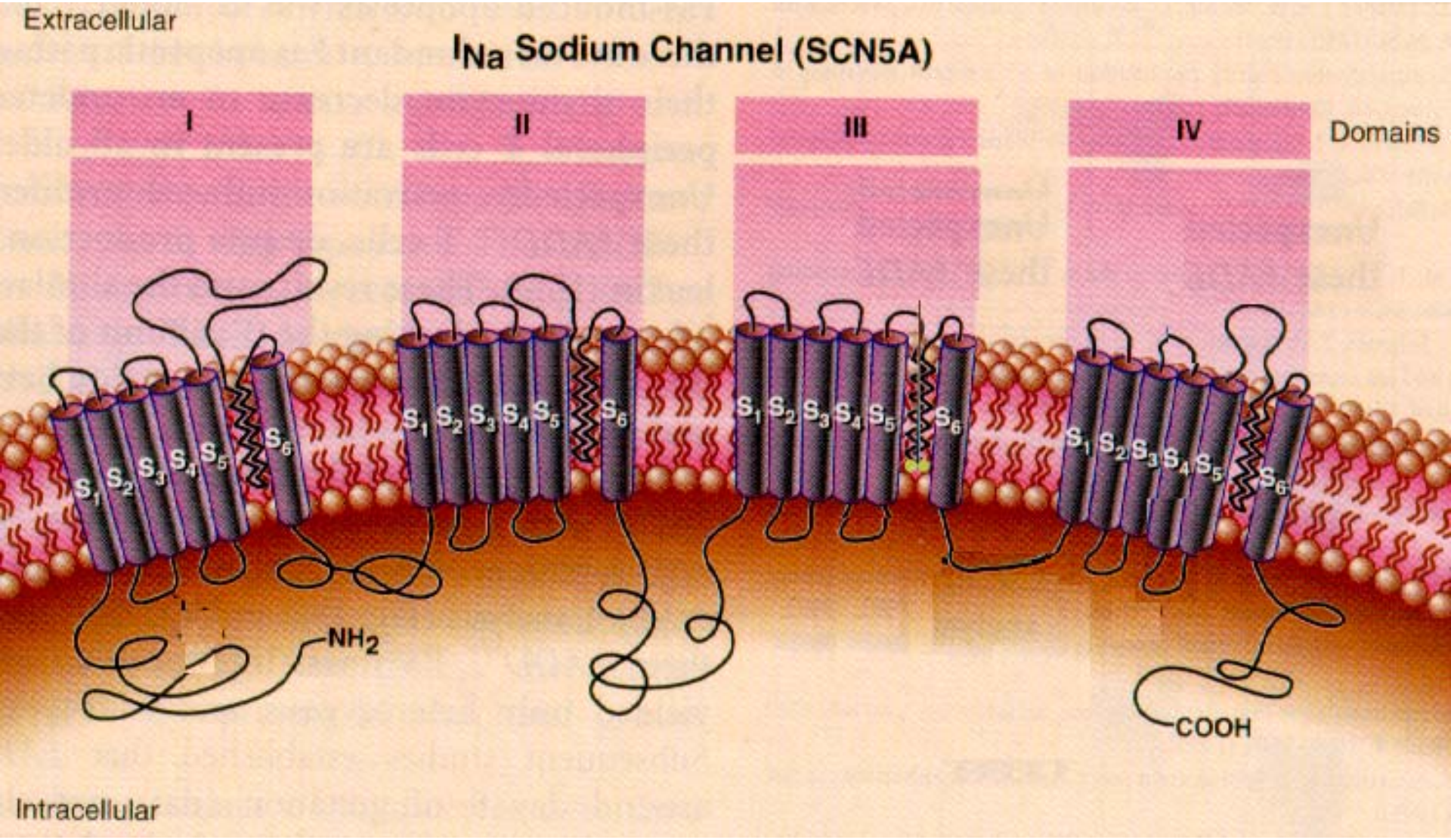


$[K]_o$ reduced from 5.4 mM to 2.7 mM
Then i_{Kr} blocked by 90%

Genetically-induced Repolarization failure

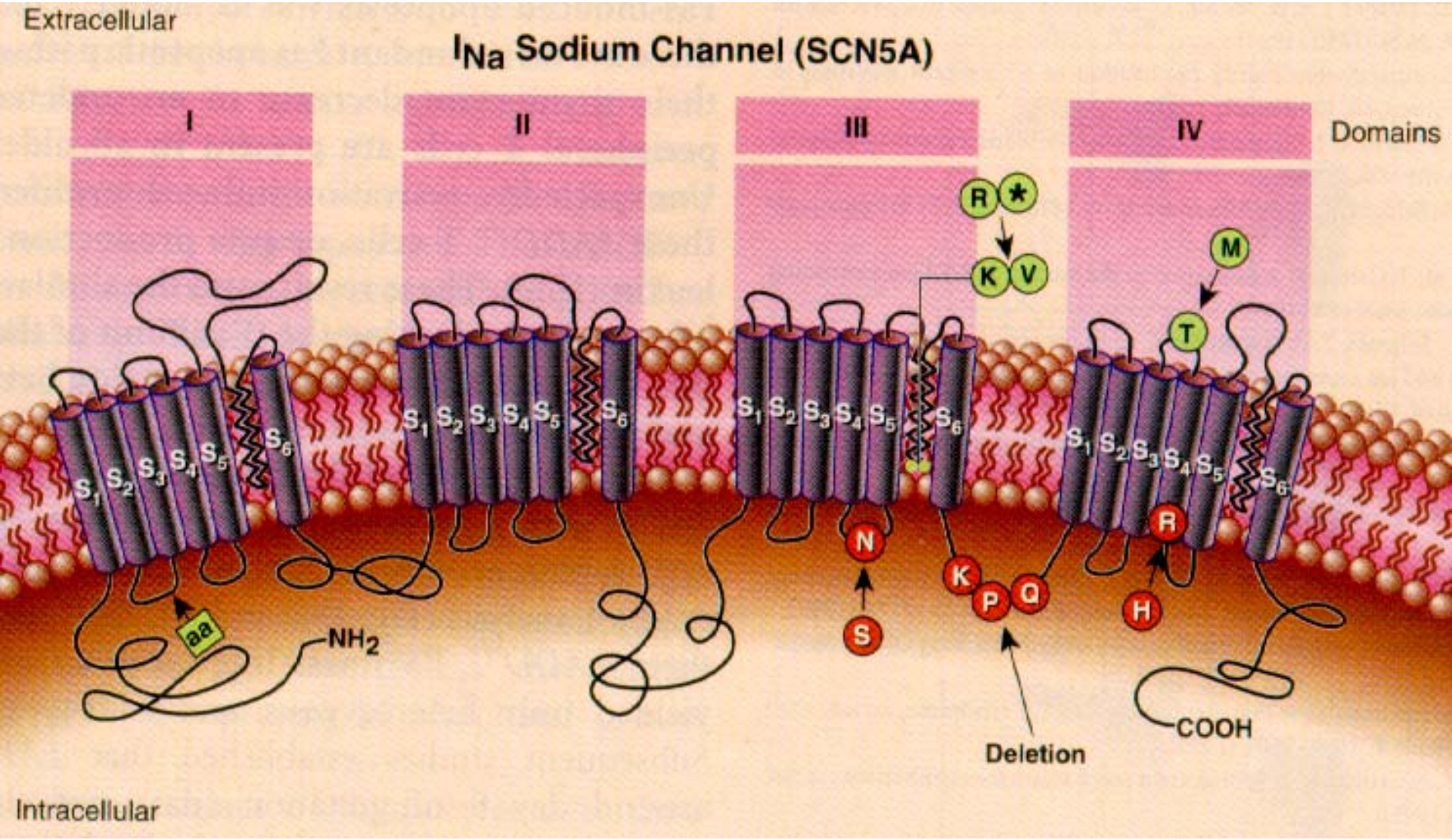
Mutations in various ionic channels can predispose to repolarization failure

This simulation is of a sodium channel mis-sense mutation responsible for idiopathic ventricular fibrillation



Sodium channel molecular structure

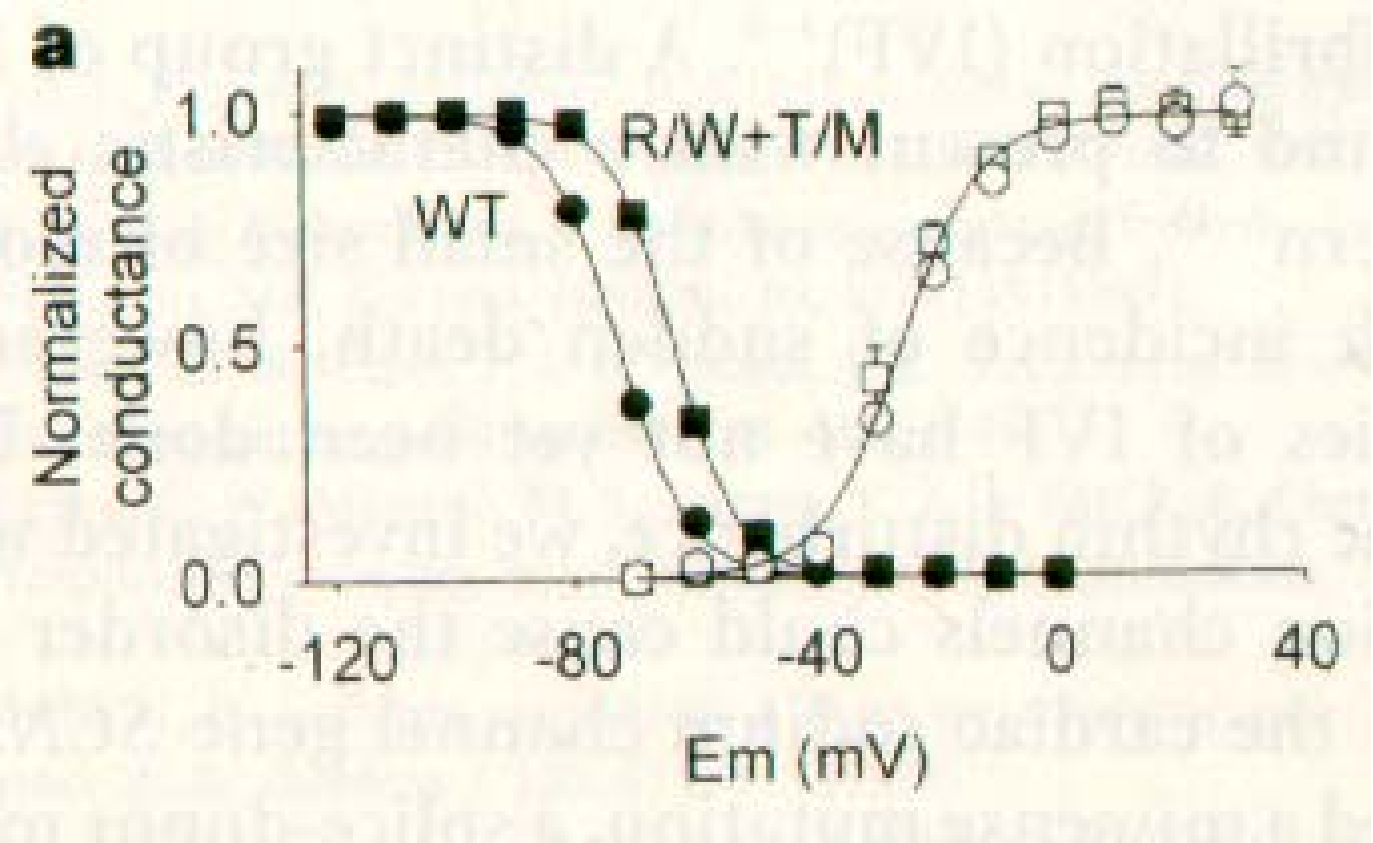
Four transmembrane domains each with six subunits



Heart sodium channel mutations

green : IVF mutations red : long QT mutations

(Chen et al, *Nature*, 19 March 1998)

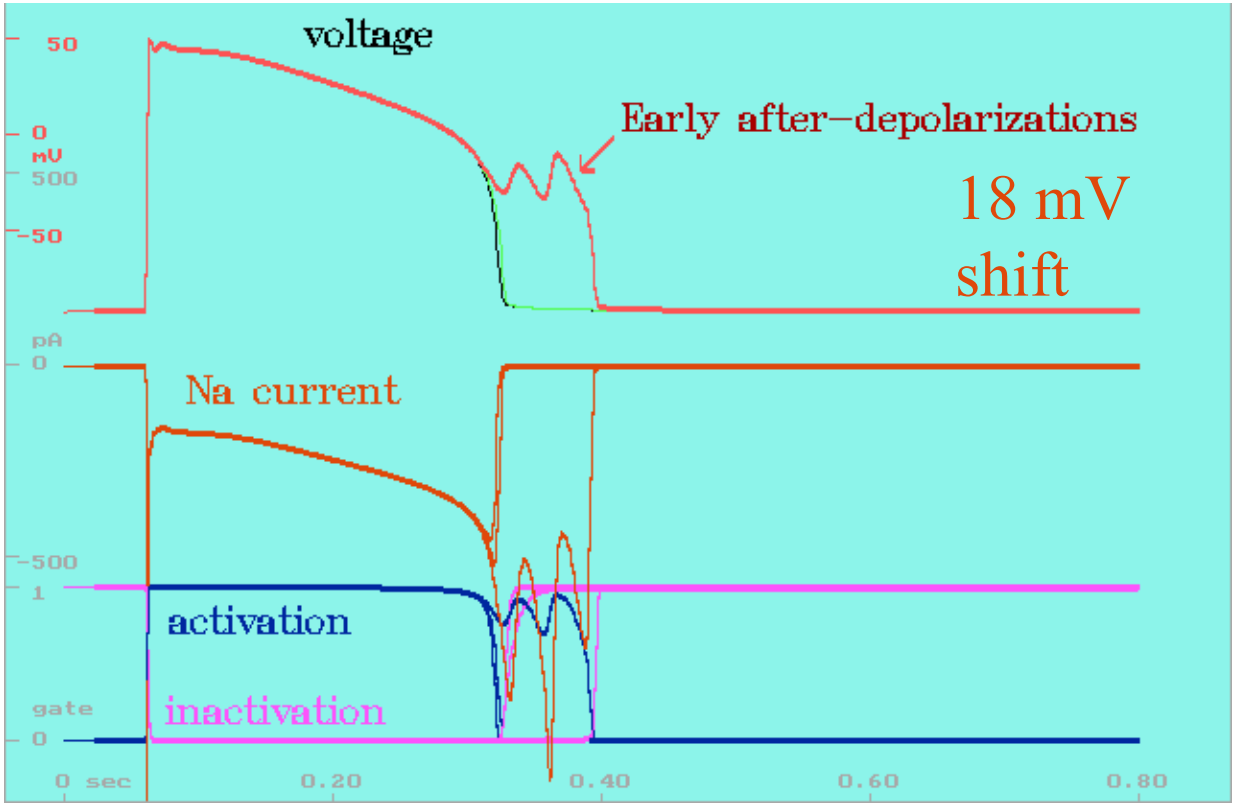


Expressed sodium channel kinetics

(Chen et al, *Nature*, 19 March 1998)

Computer model prediction

- Sodium channel missense mutation
- 12 and 18 mV voltage shifts
- Using digital cell ventricular model



Unravelling genetics of arrhythmia

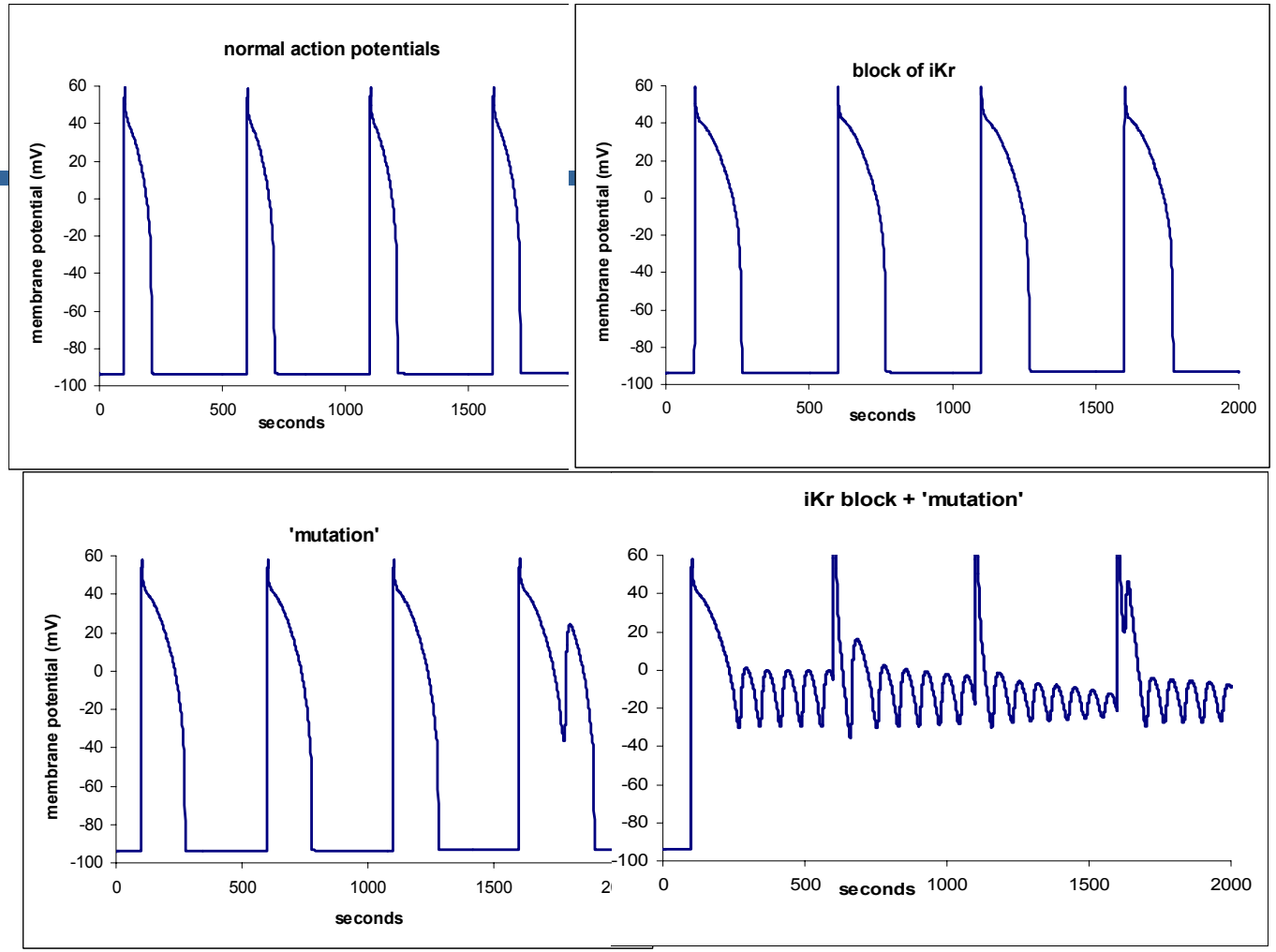
This approach has now been used for a substantial number of gene manipulations in heart cells and can account for genetic susceptibility to fatal cardiac arrhythmia

Including interactions with drugs causing long QT and arrhythmia in clinical trials

Genetic typing to screen out those susceptible to drugs causing QT problems is therefore a foreseeable possibility

Noble D (2002) Unravelling the genetics and mechanisms of cardiac arrhythmia. *Proc Natl Acad Sci USA* **99**, 5755-6

Drug-gene interaction



Threshold for EADs = 23 mV

Threshold for EADs = 17 mV

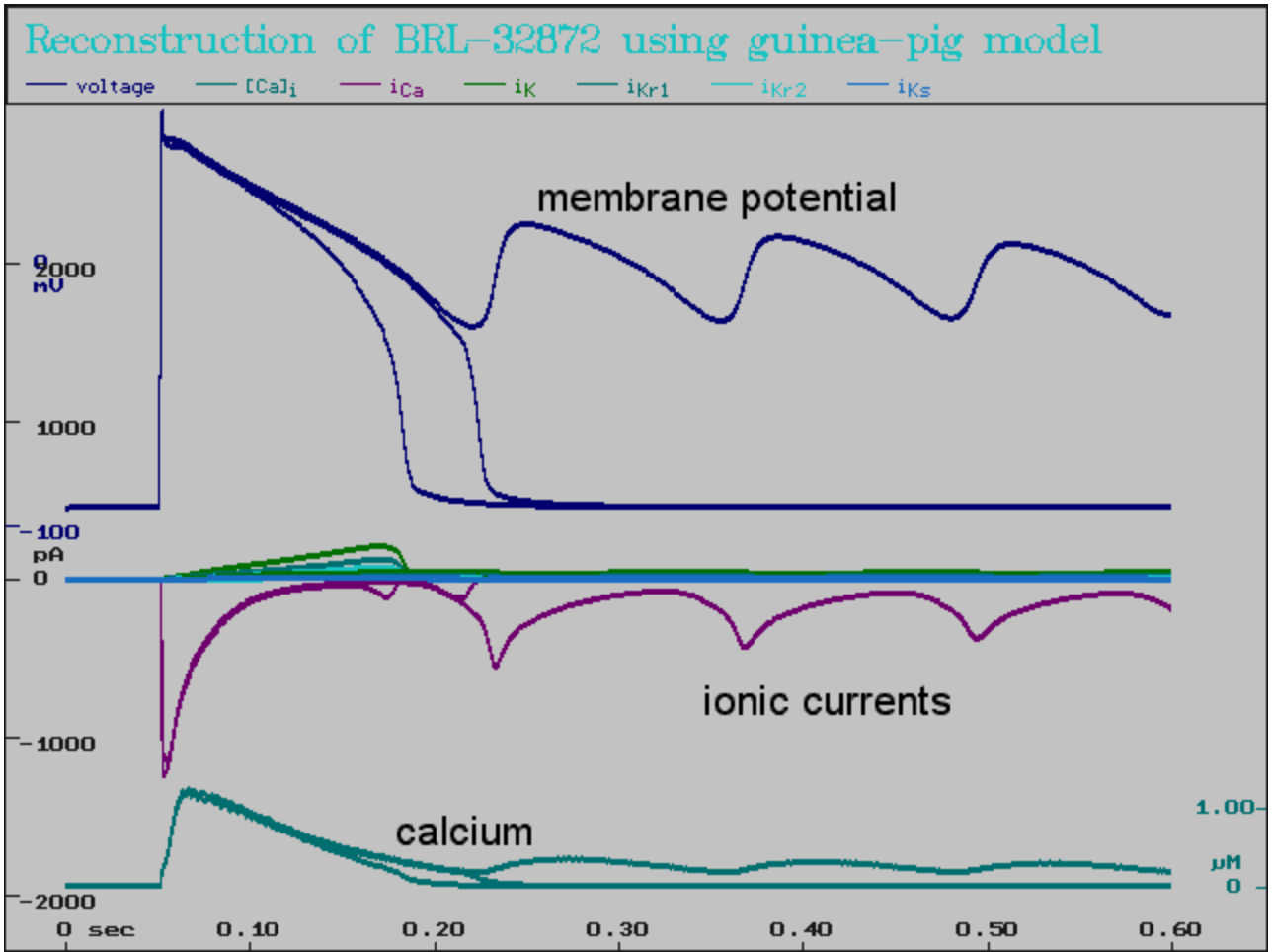
NOBLE, D. (2003). Will Genomics revolutionise pharmaceutical research and development? *Trends in Biotechnology* **21,** 333-337.

Multiple site drugs: QT prolongation without arrhythmia?

This example shows

- effect of 90% block of I_K alone (pure class III)
- effect of additional 20% block of $I_{ca,L}$

- Normal action potential
- Block of I_K alone
- Partial block of I_{CaL}



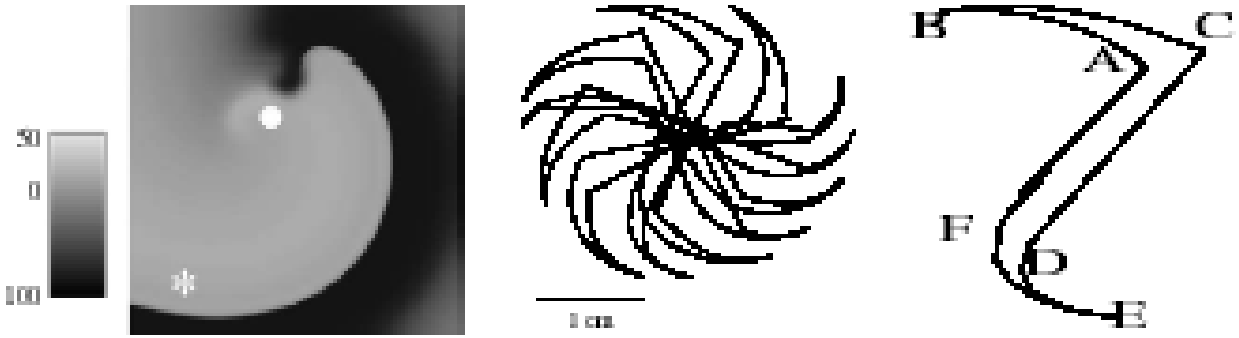
Re-entrant arrhythmia

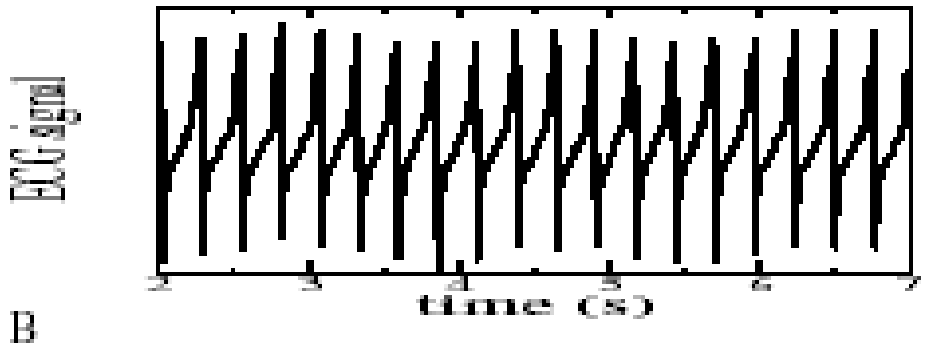
Incorporation of cellular models into tissue and organ models

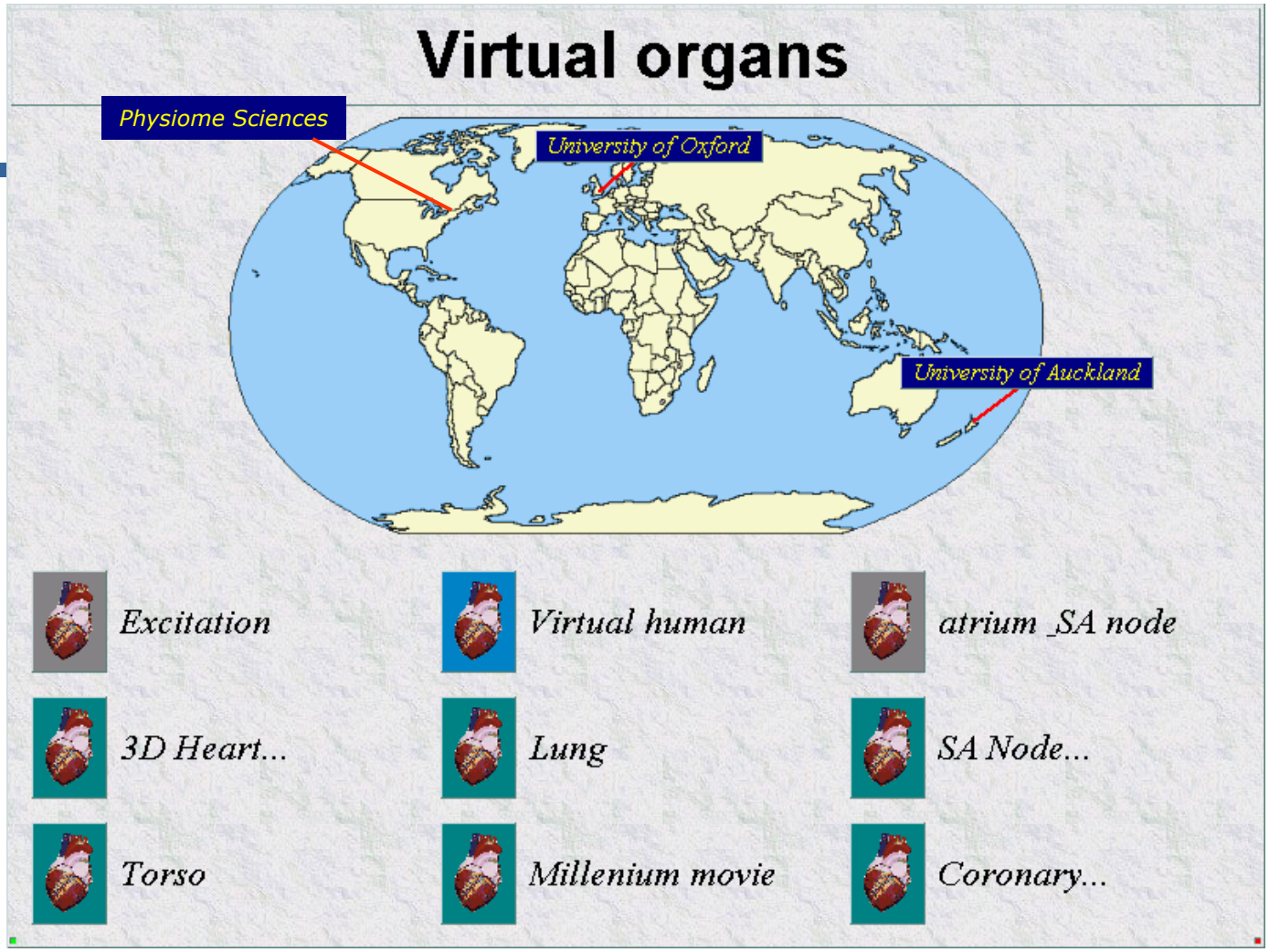
Re-entrant arrhythmia using human cell model

Spiral wave in 600 x 600 2D lattice

TEN TUSSCHER, NOBLE, D., NOBLE, P. J. & PANFILOV (2003).





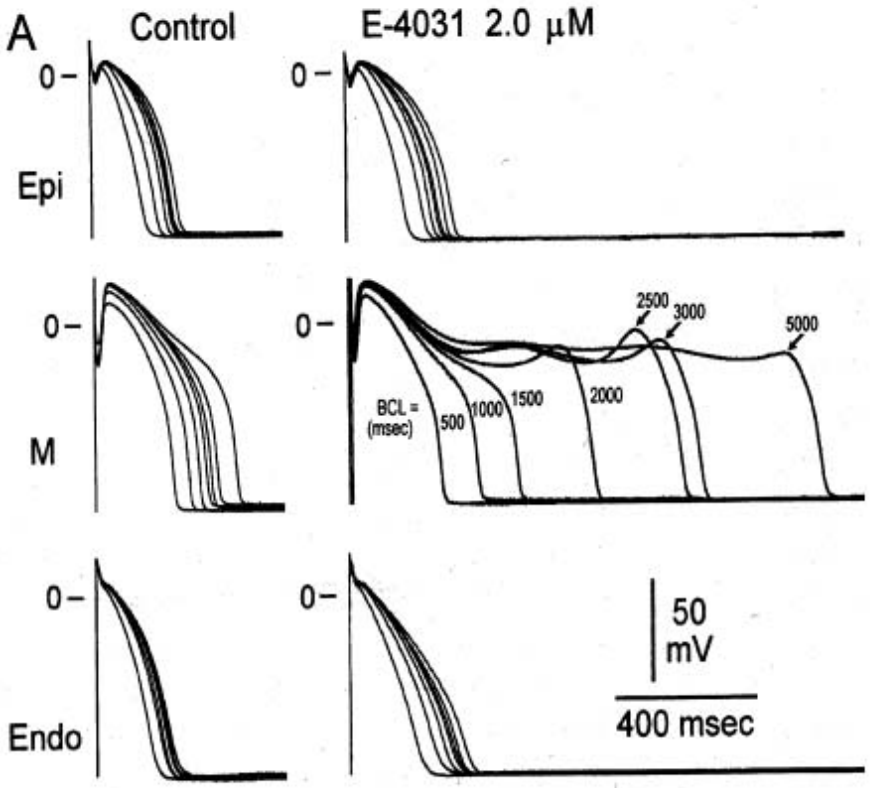


Noble D (2002) Modelling the heart: from genes to cells to the whole organ. *Science* **295**, 1678-1682

Conclusions

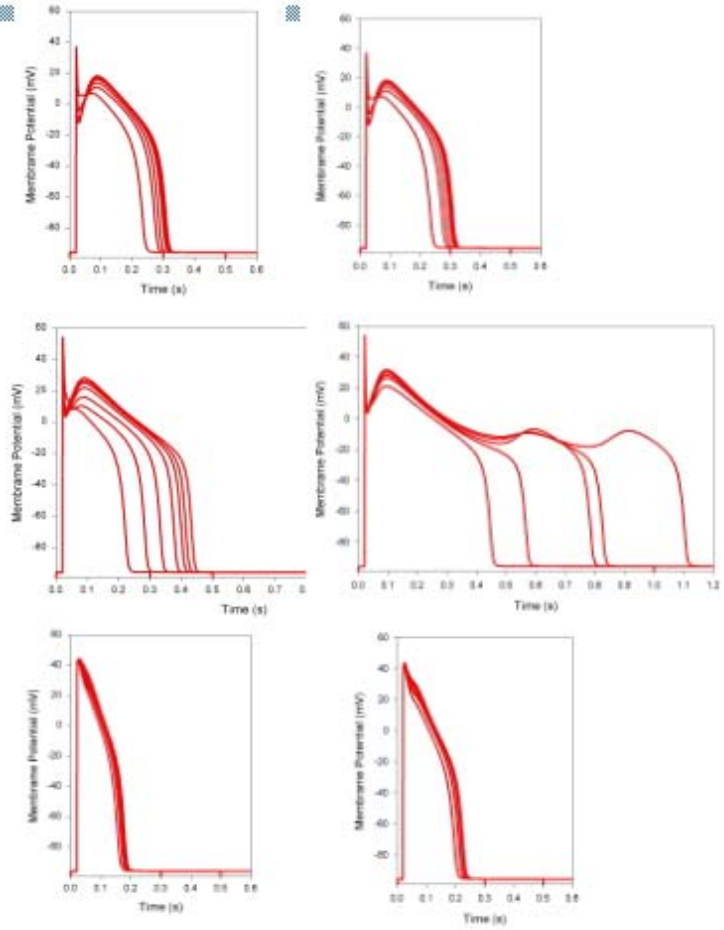
- QT is a very poor marker – can be prolonged without arrhythmia – can be shortened with arrhythmia – all combinations are possible – hence the mess and confusion.
- HERG also a poor marker – i_{Kr} block could be part of a multiple action therapeutic agent
- Arrhythmia would be a better marker
- Cellular mechanisms now well-established
- Need therefore for systematic modeling of arrhythmic mechanisms at tissue and organ levels
- This problem is soluble. LET'S DO IT!

CardioPrism™ model verification
Response to I_{Kr} block



Experimental data

Burashnikov and Antzelevitch, 1998



Simulations

BCL = 300, 500, 1000, 2000, 4000, 6000 msec

CardioPrism™ case study:
Sex-based differences

D-Sotalol (SWORD trial):

- Trial resulted in loss of interesting compound
- Disproportionate deaths of women

Women exhibit:

- a longer QT interval at baseline
- greater response to QT prolonging drugs; increased risk of TdP

JGSM The Journal of Gender-Specific Medicine

Use our archive to search for previous articles.

The Official Journal of the Partnership for Women's Health

The Electrocardiographic QT Interval and Its Prolongation in Response to Medications: Differences Between Men and Women

Janice B. Schwartz, MD

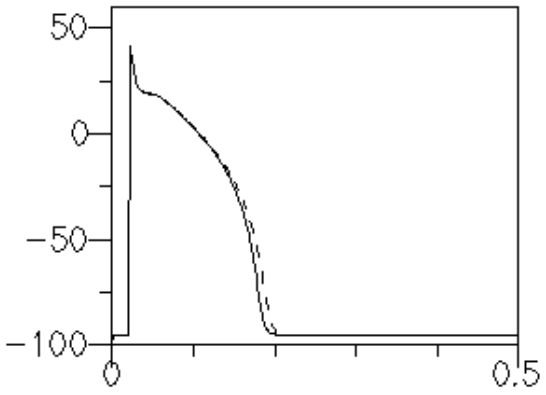
Dr. Schwartz is Professor of Medicine, Northwestern University Medical School, Chicago, IL. Address for correspondence: Janice B. Schwartz, MD, #1 Miraflores Ln, Tiburon, CA 94920.

Gender Differences in the QT Interval

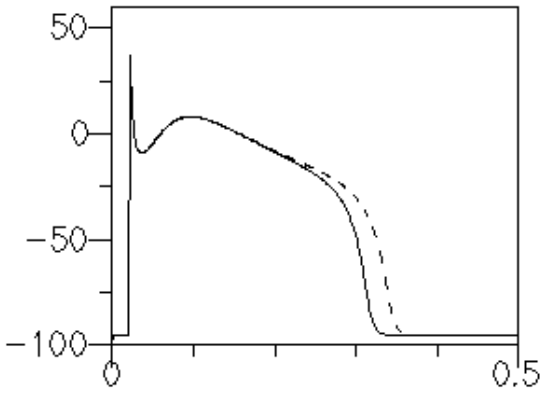
The QT interval on an electrocardiogram reflects the time required for cardiac repolarization. The duration of the QT interval is affected by a number of factors, including heart rate, transmembrane cardiac ion flux, disease states, electrolyte abnormalities, temperature abnormalities, medications, and genetics. During normal conditions, the changes in QT interval that occur with heart rate are so dominant that normal ranges for surface electrocardiogram QT intervals are corrected for heart rate (QTc). The initial descriptions by Bazett[1] of a

CardioPrism™ Case Study:
Sex-based differences

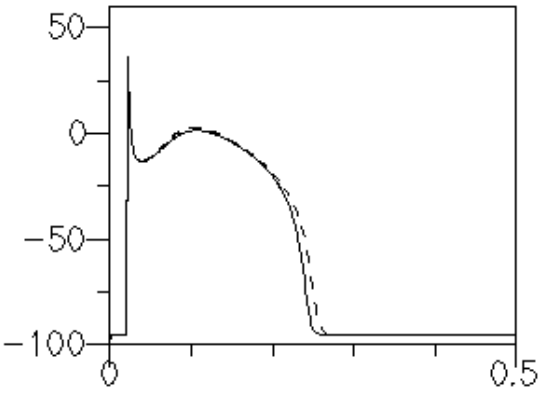
Male Female



Endocardial cell



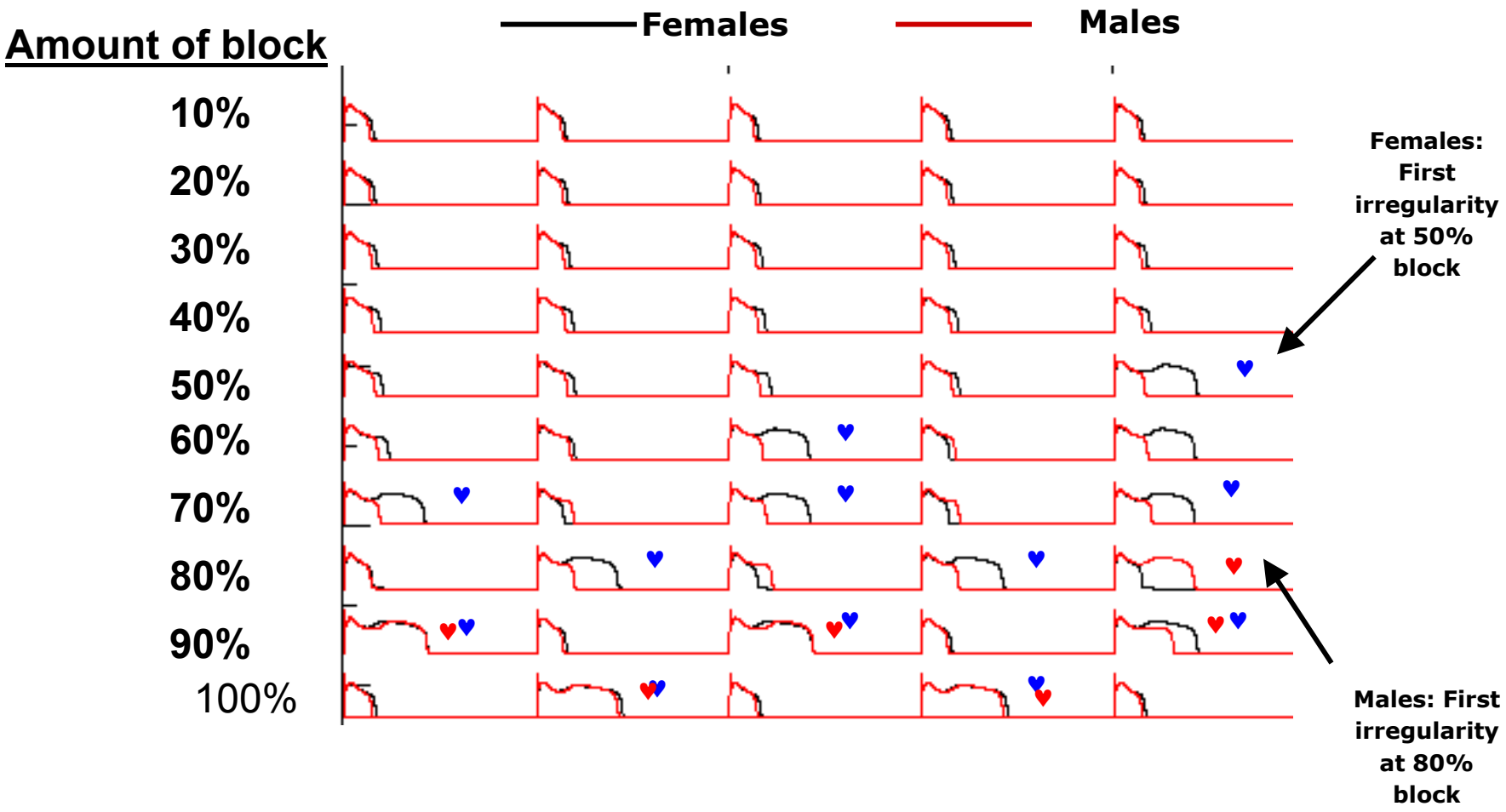
M-cell



Epicardial cell

Female: 15% reduction IKr + 13% reduction IK1
BCL = 1000 msec

CardioPrism™ Case Study:
Response to IKr block with sex-based differences



CardioPrism™ Case Study:
Females have lower threshold for drug-induced proarrhythmia