Drug-induced effects on the heart: insights from HPC simulations

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July 1st, 2009

Acknowledgements

Esther Pueyo, Lucia Romero, Alberto Corrias, Martin Fink, David Gavaghan, Kevin Burrage

Chaste Team: Joe Pitt-Francis, Miguel Bernabeu among others: www.comlab.ox.ac.uk/chaste/theteam)

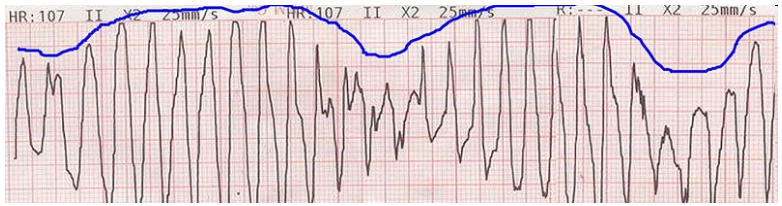
Image processing and Mesh generation: Vicente Grau, Martin Bishop, Gernot Plank

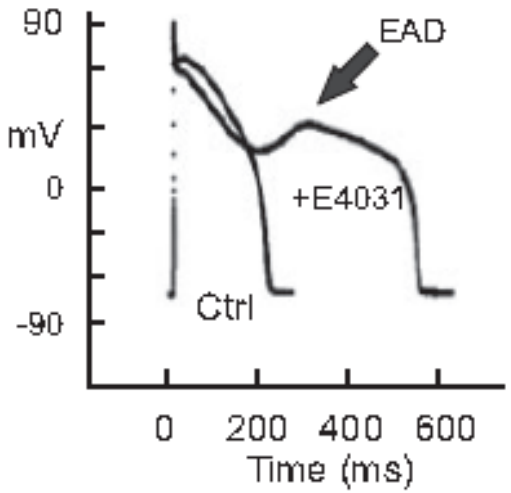
The Problem

£200 million, 13 years → Drug market approval (DiMasi et al., 2003).

Cardiotoxicity: unwanted side effects that can result in arrhythmia

Torsades de Pointes





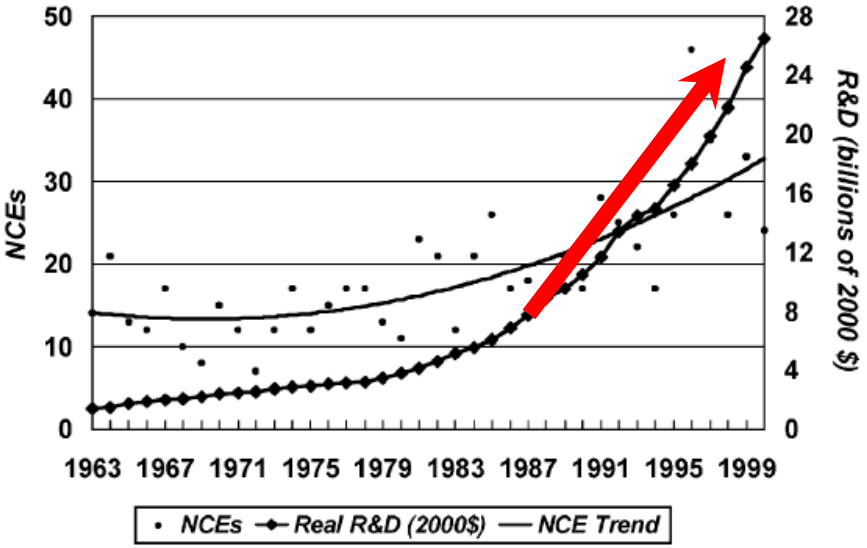
{Sims et al., 2008}

The Methods

Drugs that induce arrhythmias prolong APD and QT interval

Preclinical assessment of drug cardiotoxicity

Recordings of the HERG current (I_{Kr})
Action potential duration (at 1Hz)
In vivo QT interval



Something is not working…

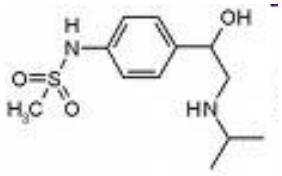
preDICT

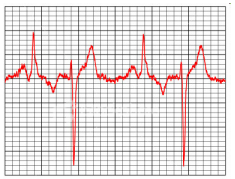
J.A. DiMasi et al./Journal of Health Economics 22 (2003) 151–185

The preDiCT project (EU VPH)

AIM

To identify **new biomarkers of drug-induced cardiotoxicity** using computational techniques





PARTNERS

Academic: University of Oxford, Universidad Politecnica de Valencia, CRS4 in Sardinia, University of Szeged

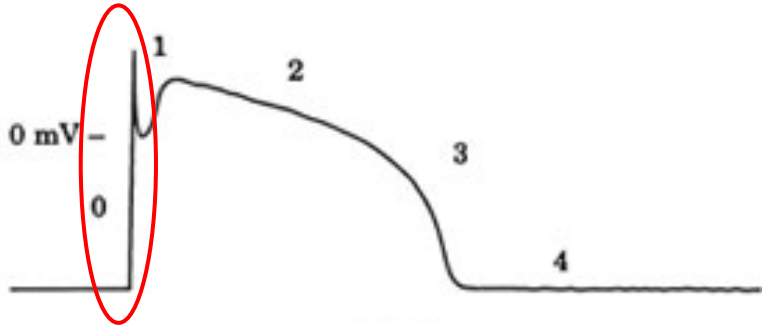
Industrial: Fujitsu, Aureus, GSK, Novartis, Roche, Pfizer, Astrazeneca

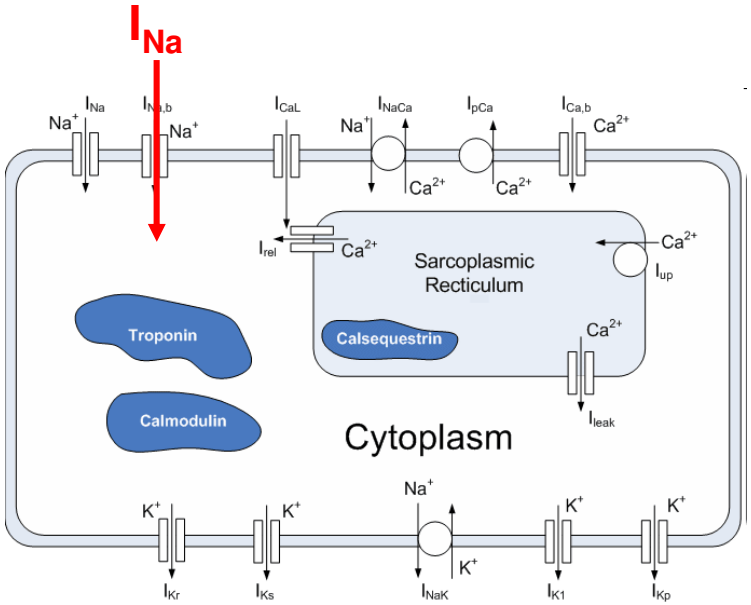
preDiCT

http://www.vph-predict.eu

Action Potential

Action Potential





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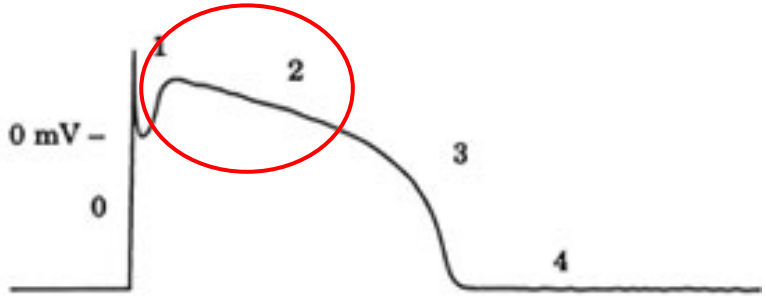

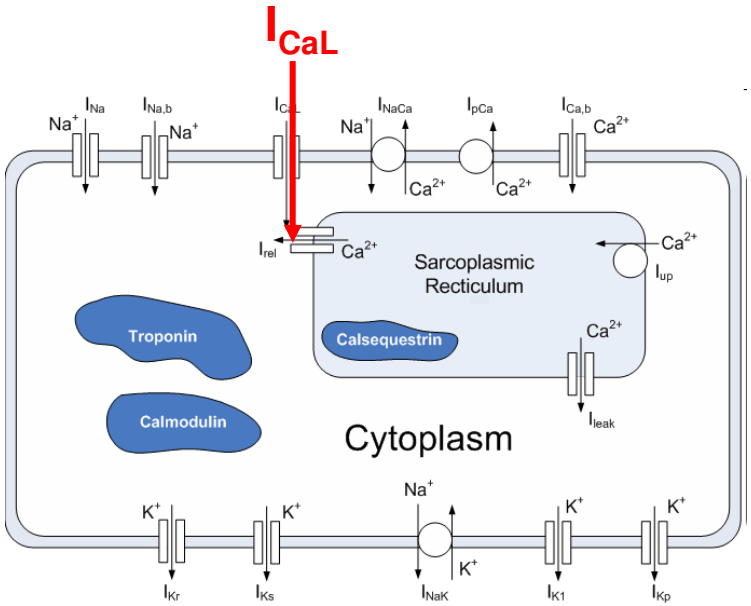

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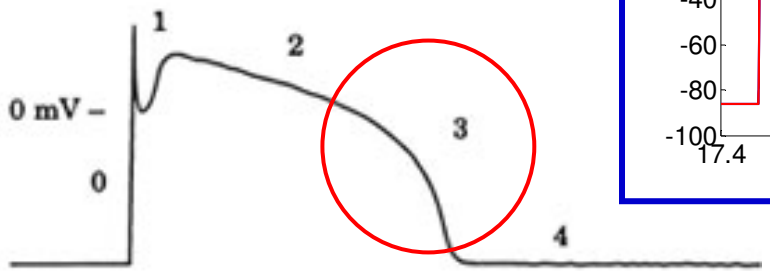
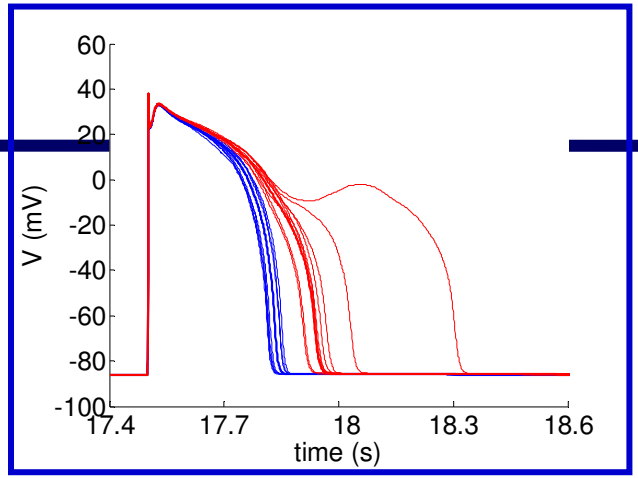
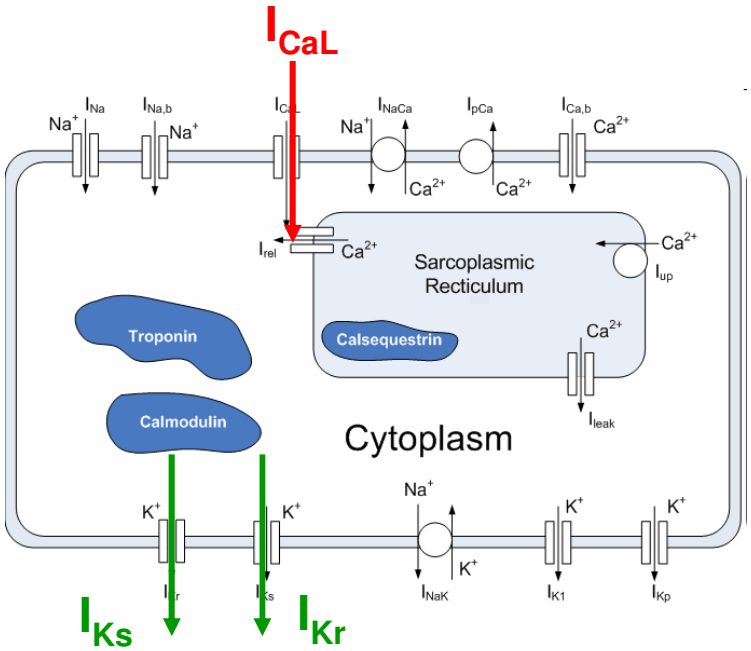
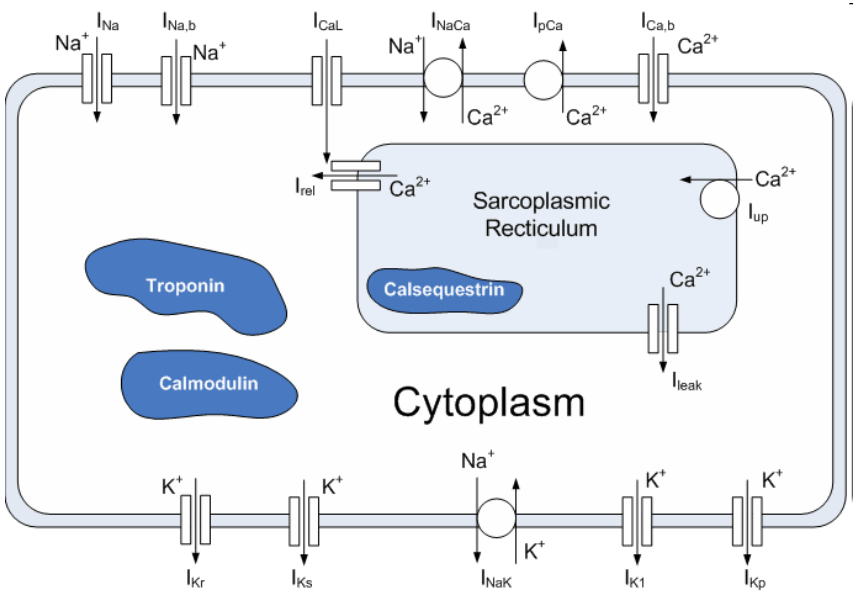






Ten Tussher Human Ventricular AP Model



Based on **human** data

"Average" human cell **behaviour**

Variability due to age, sex, location

How does variability in ionic current properties affect

APD?

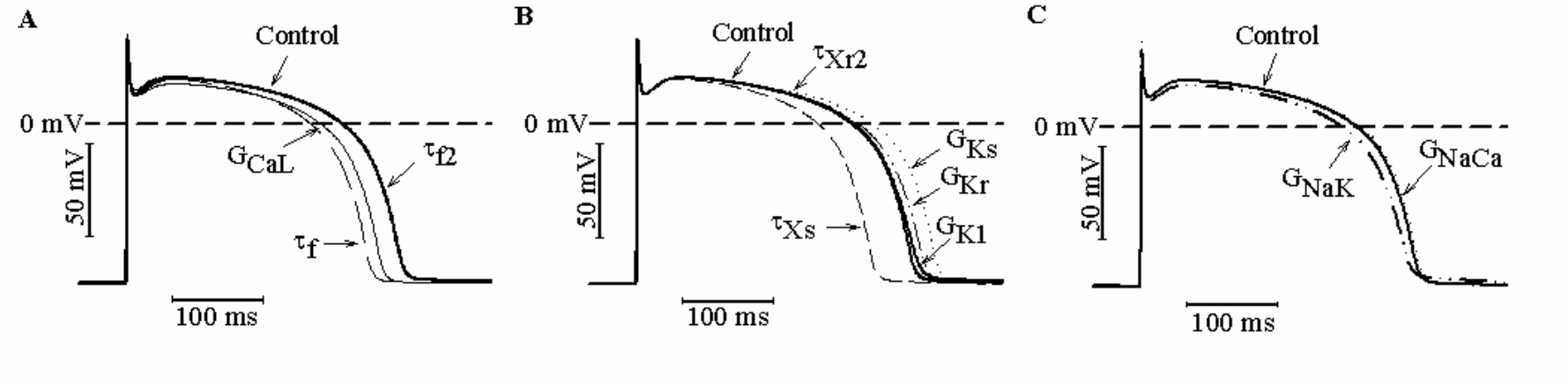
± 30% changes in properties of I_{Kr}, I_{Ks}, I_{K1}, I_{CaL}, I_{NaCa}, I_{NaK}:

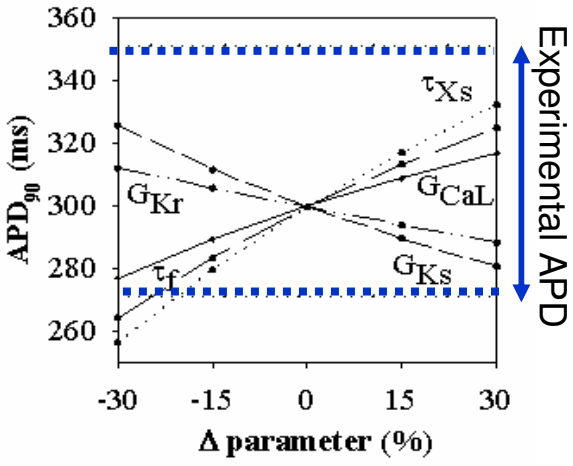
- maximum conductance (g)
- time constant of inactivation (τ)

{Ten Tussher and Panfilov, 2006}

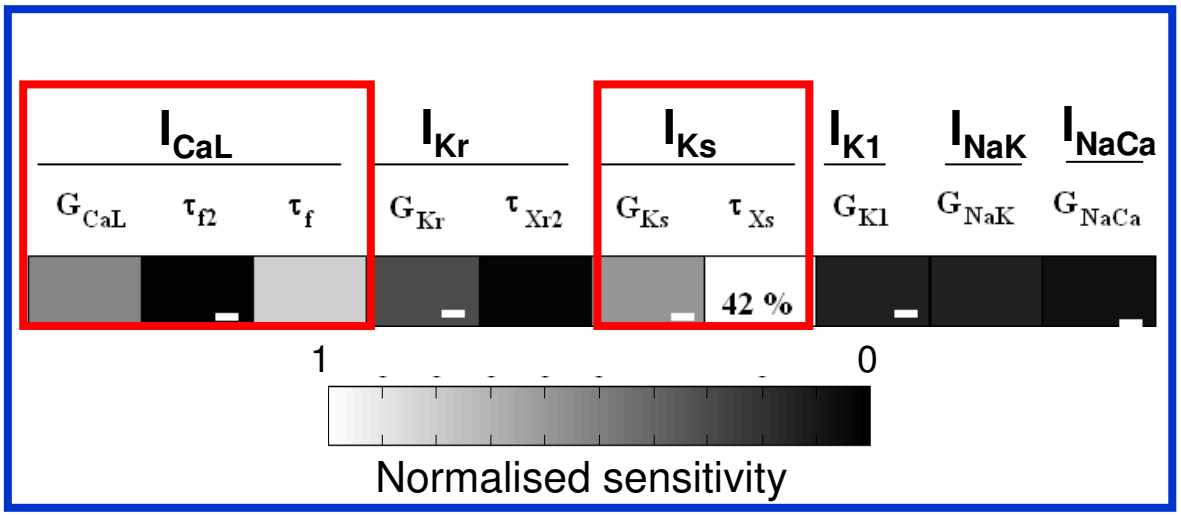
http://www.cellml.org/

Ionic Basis of Repolarization



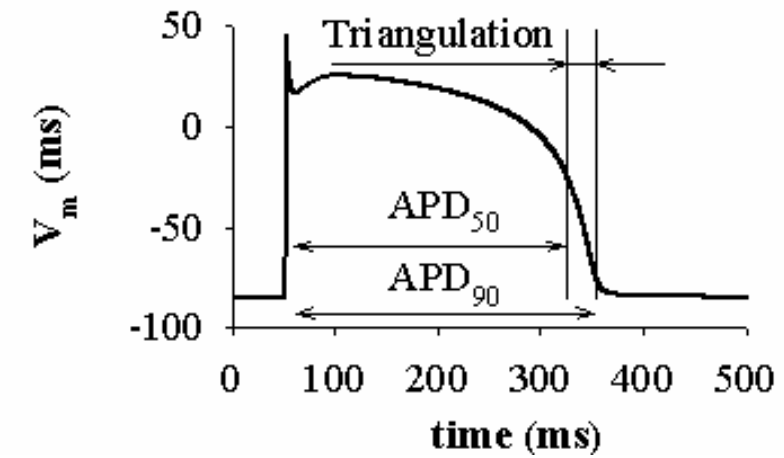


APD sensitivity to ± 30% changes

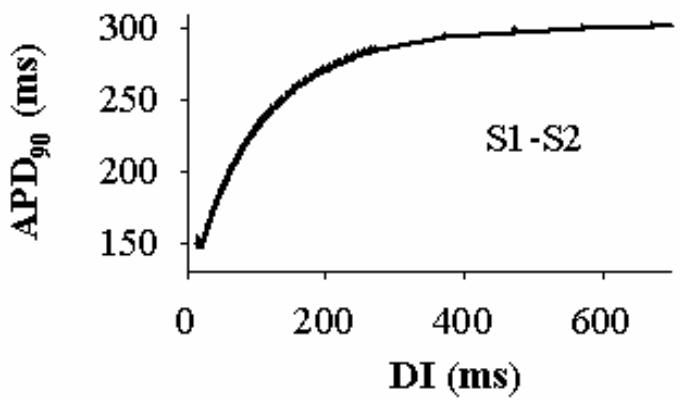


Preclinical Biomarkers

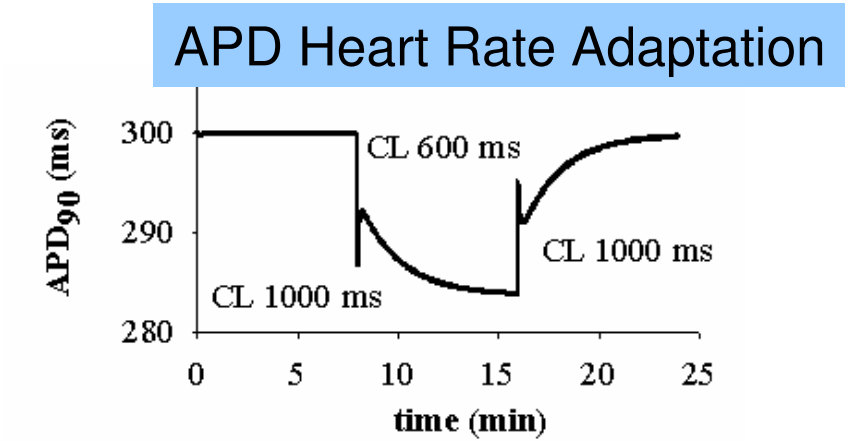
Action Potential at 1Hz

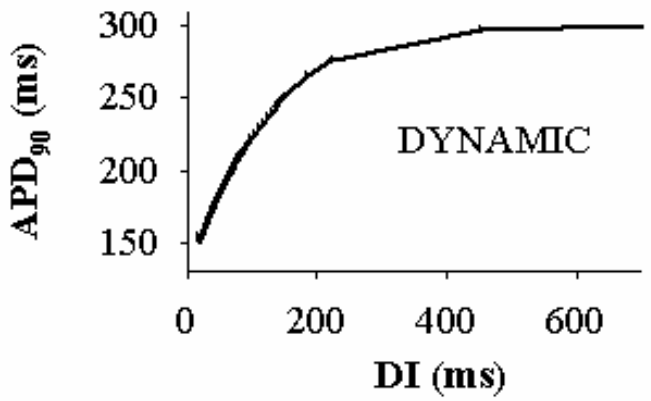


APD vs Heart Rate



APD Heart Rate Adaptation





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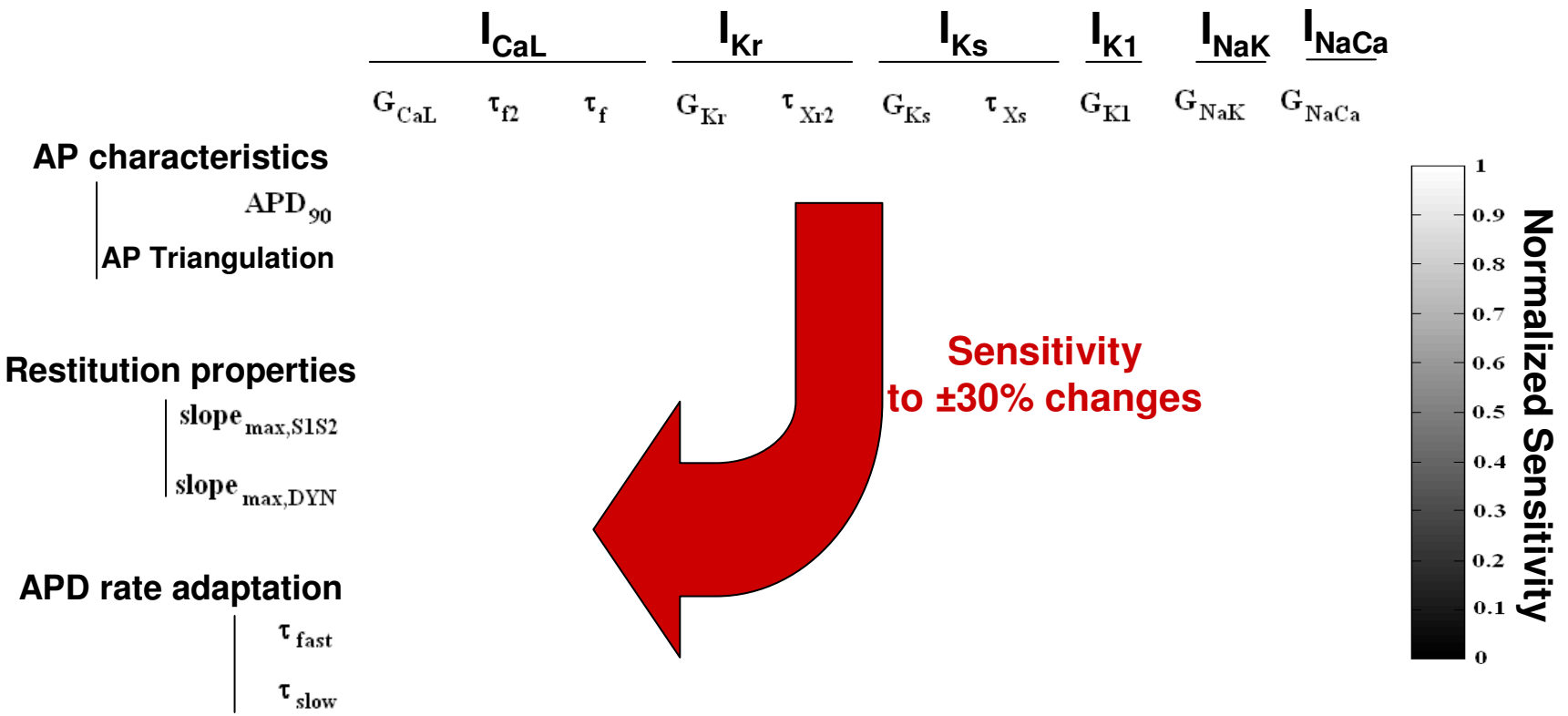
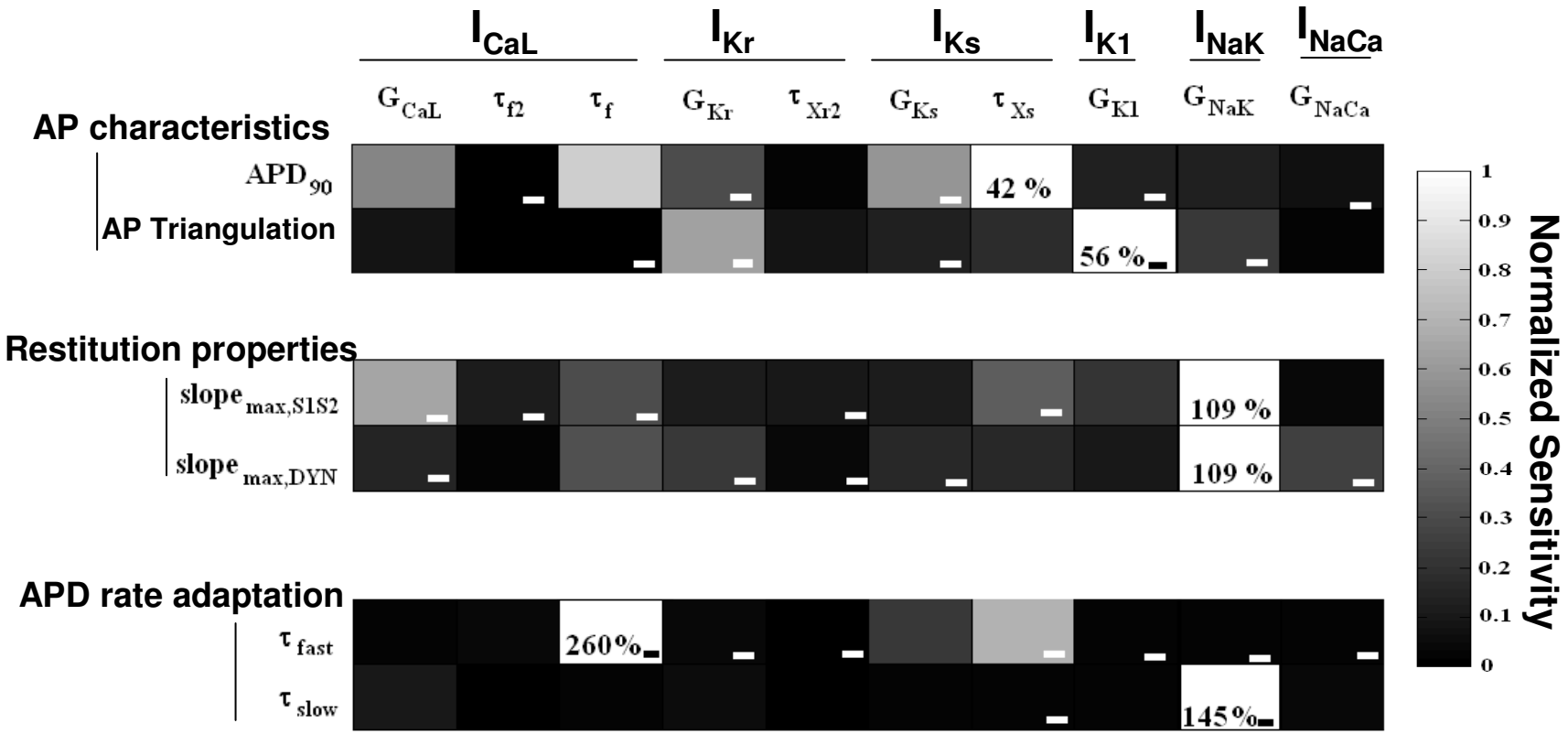
Ionic Basis of Preclinical Biomarkers



{Romero L, Pueyo E, Fink M, Rodriguez B, Am J Physiol, under review}

Ionic Basis of Preclinical Biomarkers



{Romero L, Pueyo E, Fink M, Rodriguez B, Am J Physiol, under review}

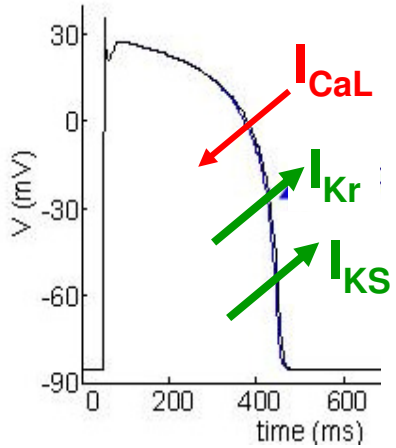
Repolarization reserve

Pro-arrhythmic drugs block I_{Kr} and prolong APD and QT

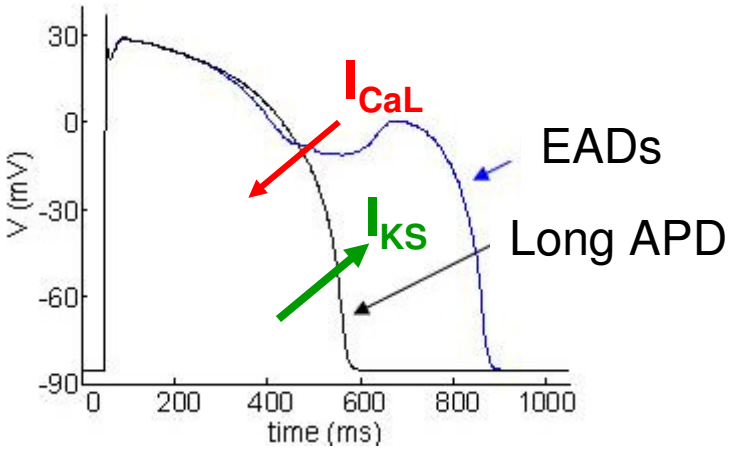
I_{Kr} block causes Torsades de Pointes

but not always…

then when?



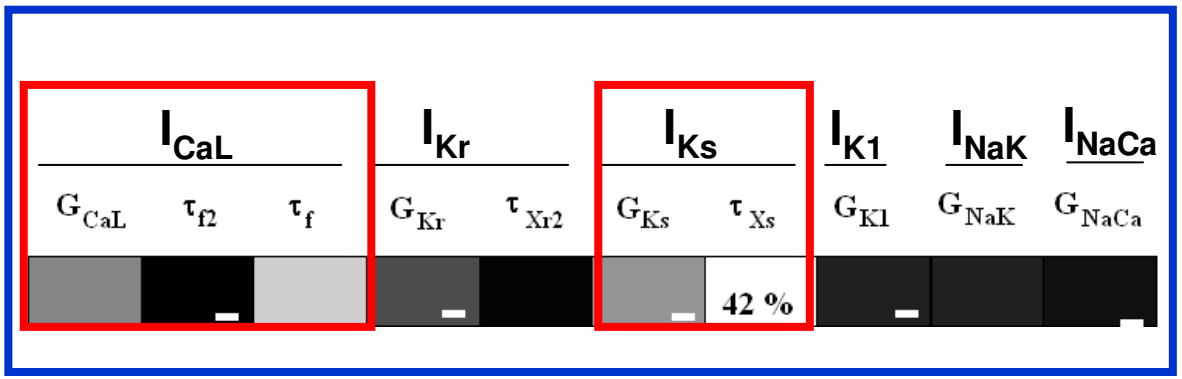
I_{Kr} block

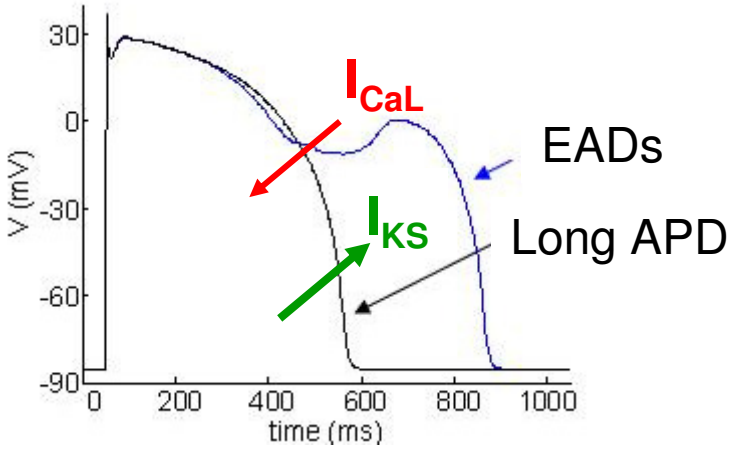


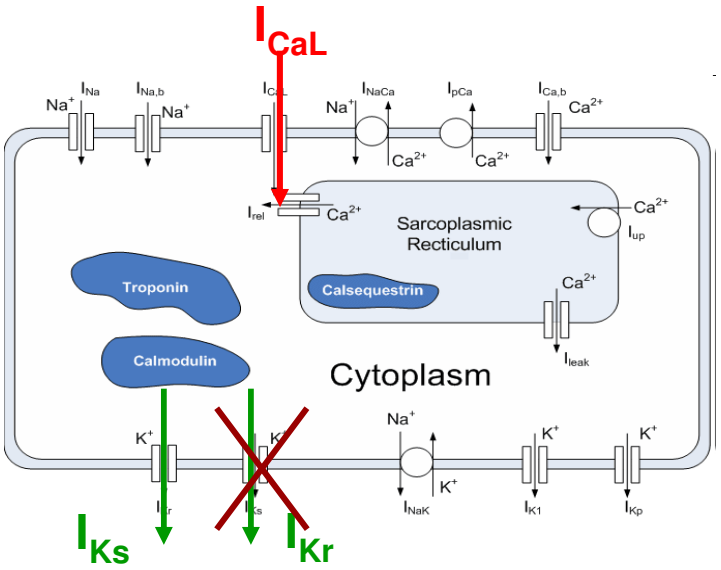
{Pueyo E, Corrias A, Gavaghan D, Burrage K, Rodriguez B, Heart Rhythm, 2009}

Repolarization Reserve

APD sensitivity to ± 30% changes



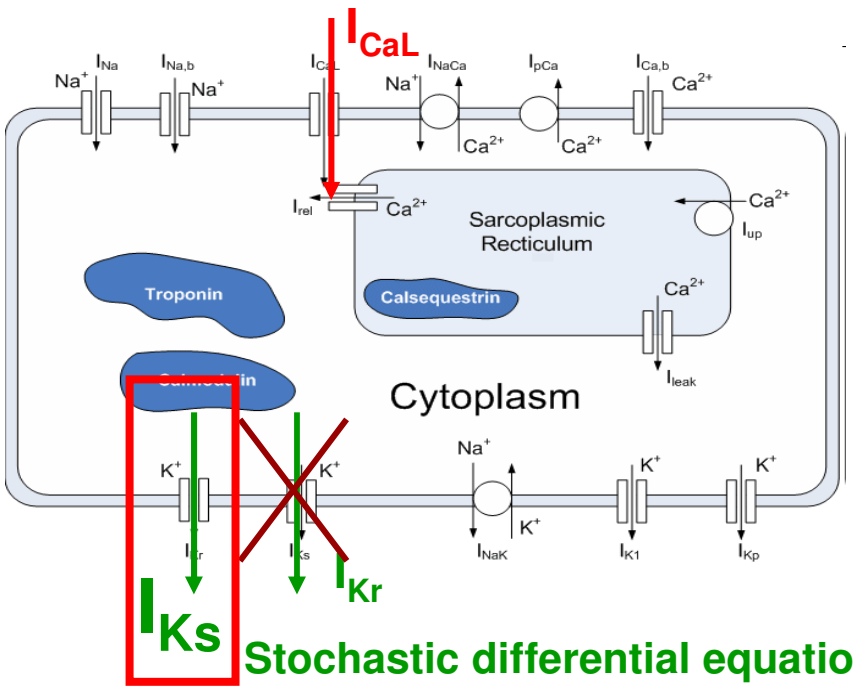




What is the role of I_{Ks} and I_{CaL} in repolarization reserve?

IKs stochastic behavior

Human ventricular model

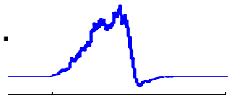


I_{Ks} variability

varies with location in the ventricles (↓midmyocardial cells→long APD)

• increases during 24h exposure to I_{Kr} blocker {Xiao et al., 2008}

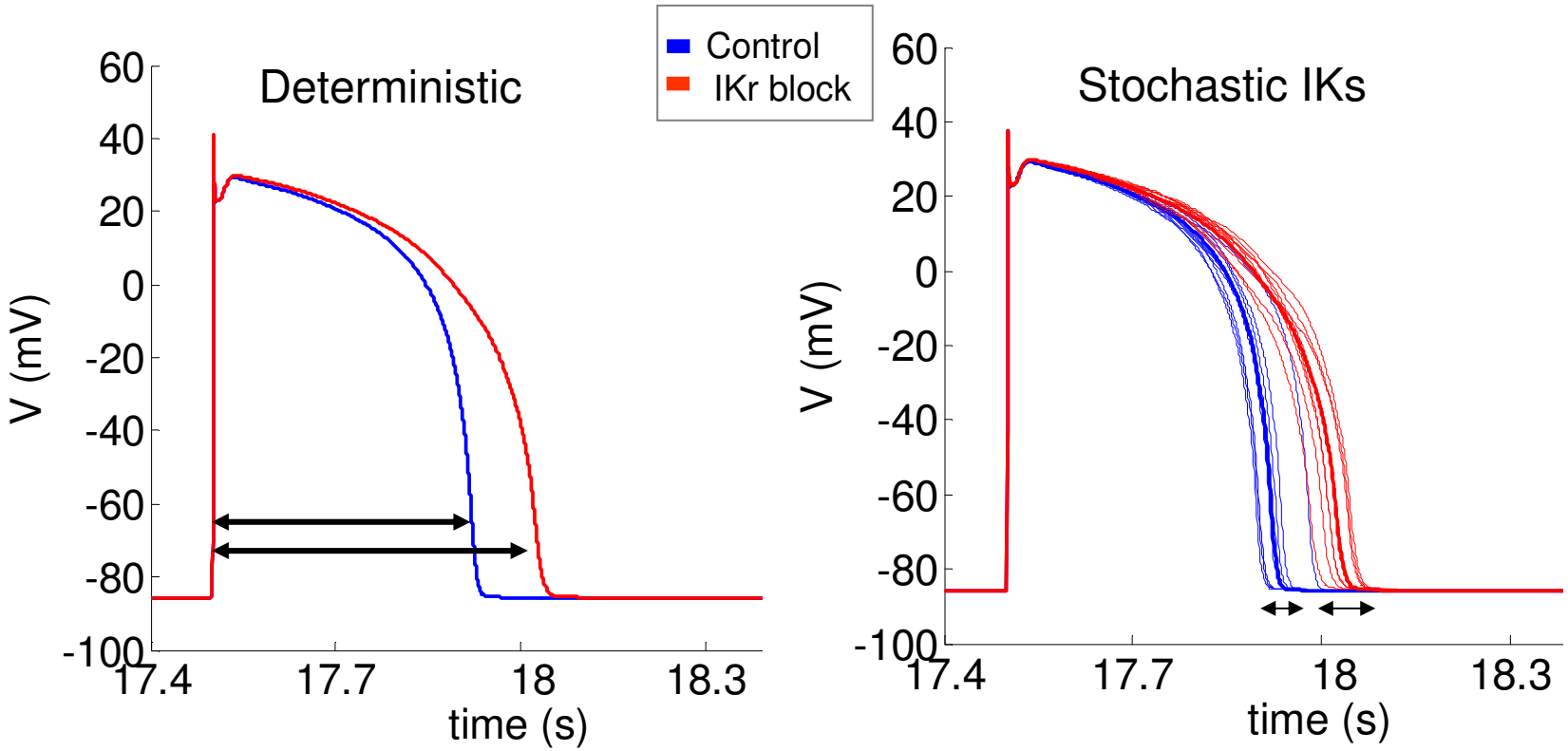
•Small number of channels →**ion channel stochastic behaviour** manifests itself at macroscopic ionic current level {Krogh-Madsen, 2004}.



How does **noise in I_{Ks}** kinetics due to ion channel **stochastic behaviour** affect **repolarization reserve?**

{Pueyo E, Corrias A, Gavaghan D, Burrage K, Rodriguez B, Heart Rhythm, 2009}

I_{Kr} Block and I_{Ks} stochastic properties

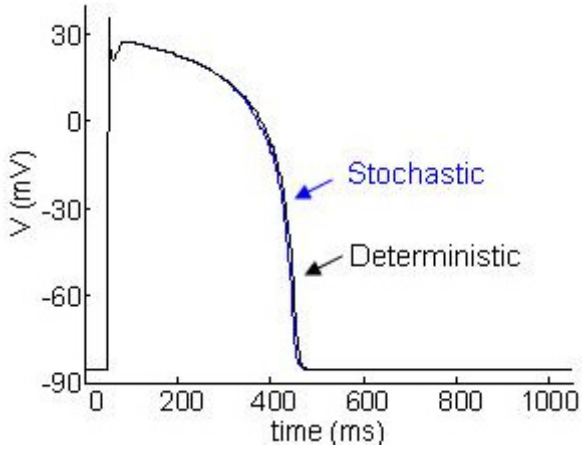


I_{Kr} block ⇨ **APD prolongation**

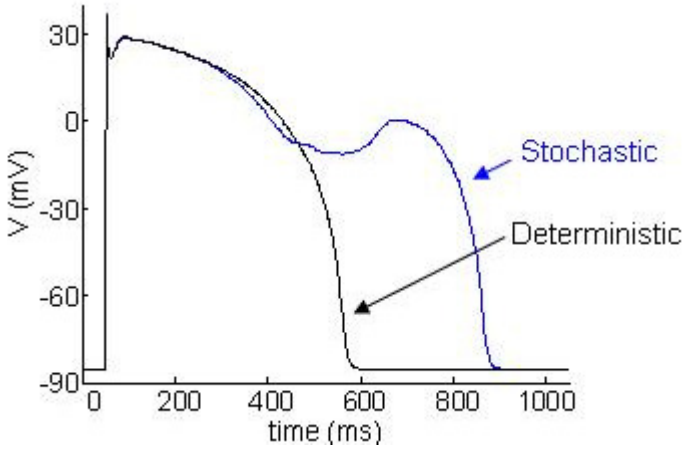
Increased dispersion in APD

I_{Kr} Block and I_{Ks} stochastic properties

Control



LQT2 (I_{Kr} block)



IKs stochastic behaviour might contribute to arrhythmogenesis in LQT2 due to:

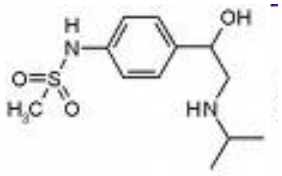
- EADs generation (probability=0.2)
- Increased dispersion of APD

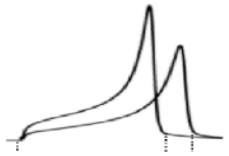
preDICT

{Pueyo E, Corrias A, Gavaghan D, Burrage K, Rodriguez B, Heart Rhythm, 2009}

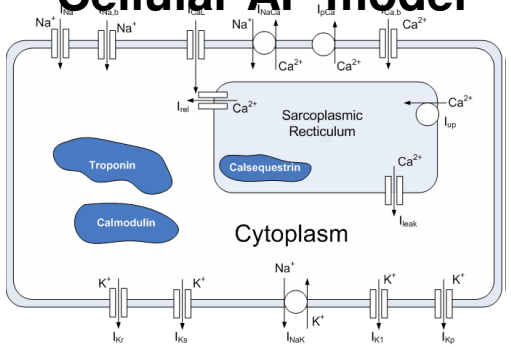
Multi-scale Modelling of Drug-induced Effects

Drug/Ion Channel model

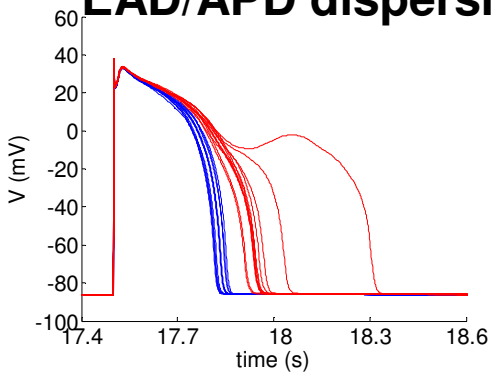




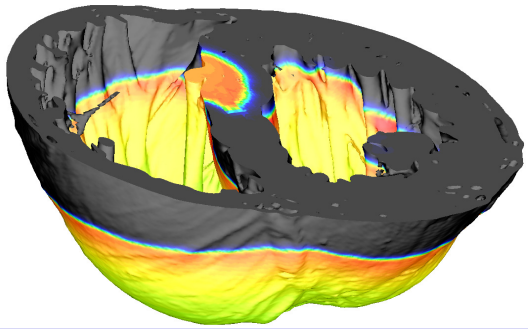
Cellular AP model



EAD/APD dispersion



Ventricular model



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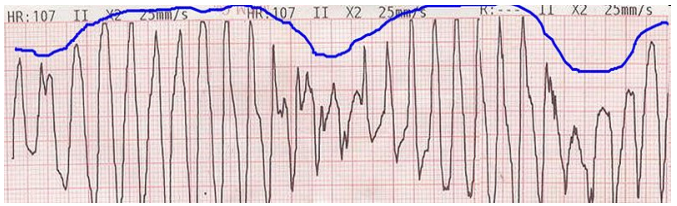


Challenges

Ventricular geometry

Chaste simulator

Bidomain equations

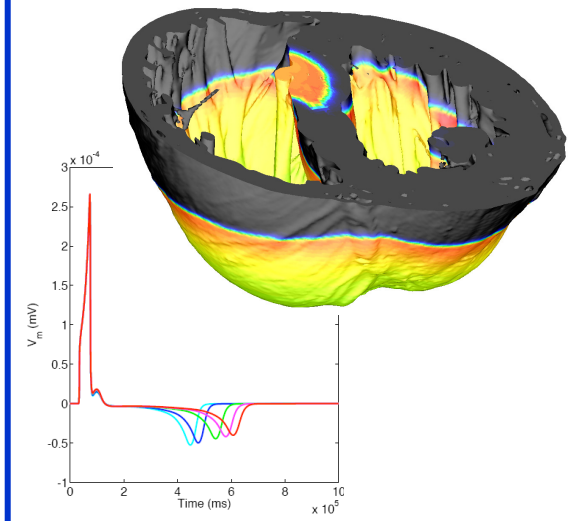
2 PDEs

$$\nabla\bullet(\sigma_i\nabla\Phi_l)=I_m+I_{stim,i}$$

$$\nabla\bullet(\sigma_e\nabla\Phi_e)=-I_m-I_{stim,e}$$

20 ODEs

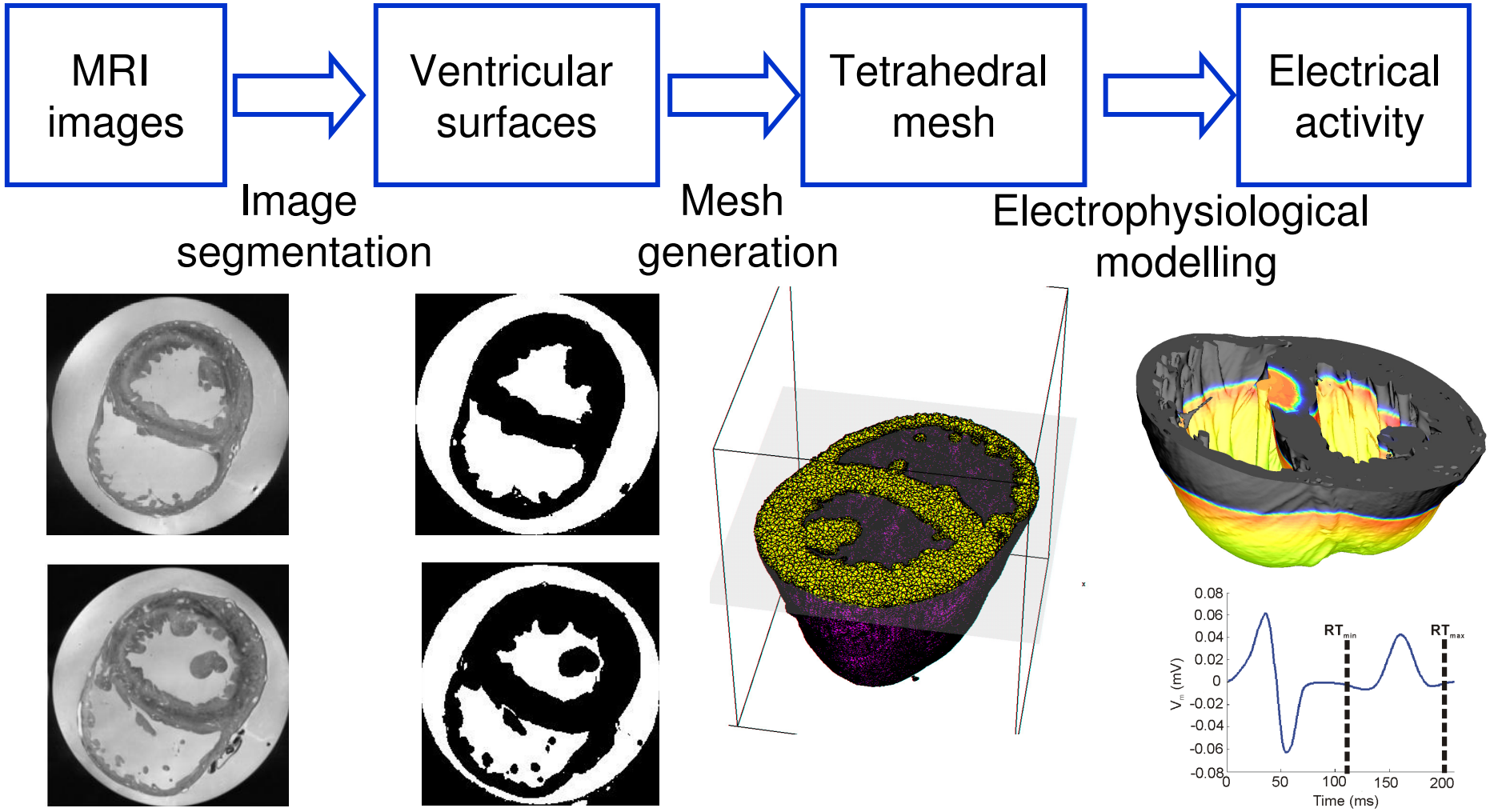
Modelling & Simulation



New Biomarkers for Drug Cardiotoxicity

preDICT

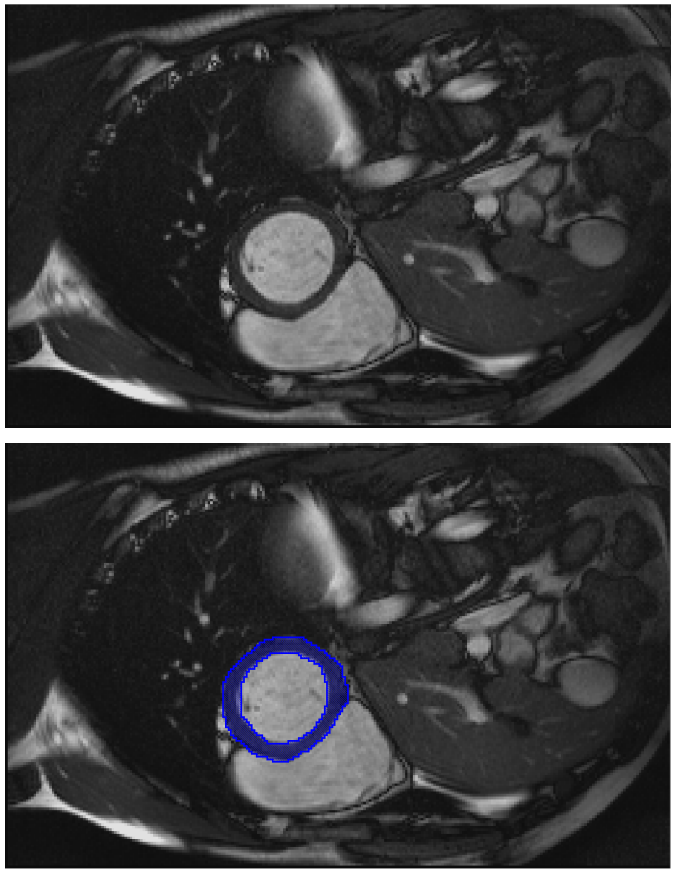
From MRI Images to Cardiac Models



{Plotkowiak, Rodriguez, Plank, Scheneider, Gavaghan, Kohl, Grau. LNCS, 2008}

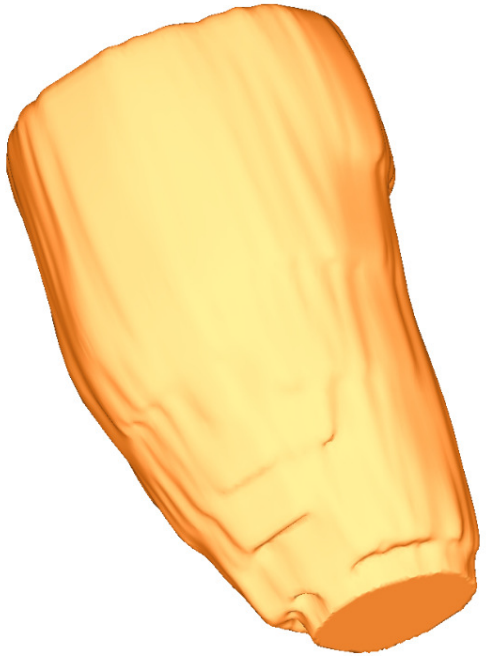
From Clinical MRI to Human Models

Short Axis Slices



{Images courtesy of Matthew Robson}

Volume reconstruction using Short axis MRI

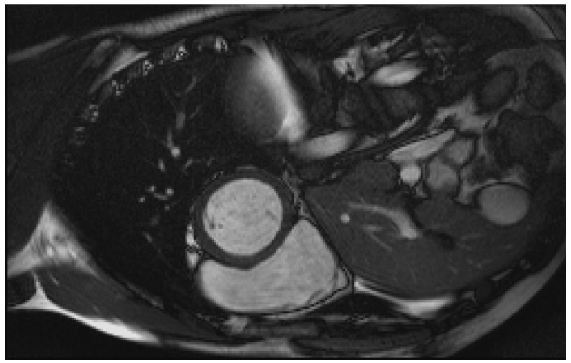


Resolution: 1mm intraslice; 1cm interslice

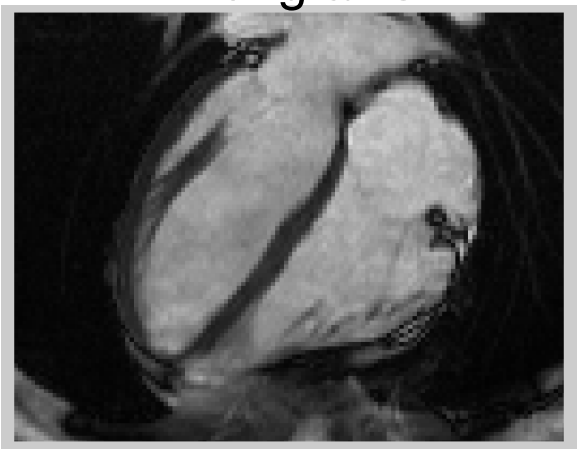
{Phil Prior, Blanca Rodriguez, Vicente Grau. Computers in Cardiology, 2009}

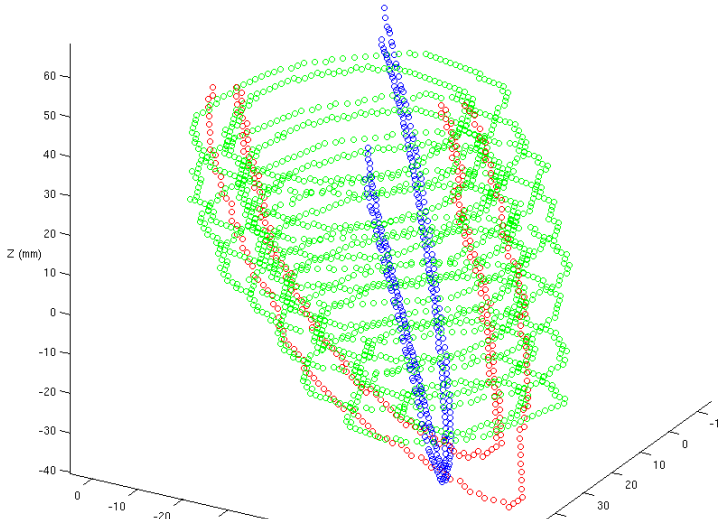
From Clinical MRI to Human Models

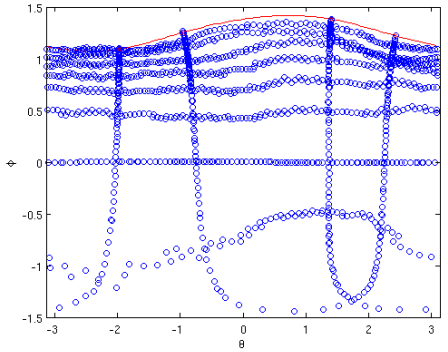
Short axis

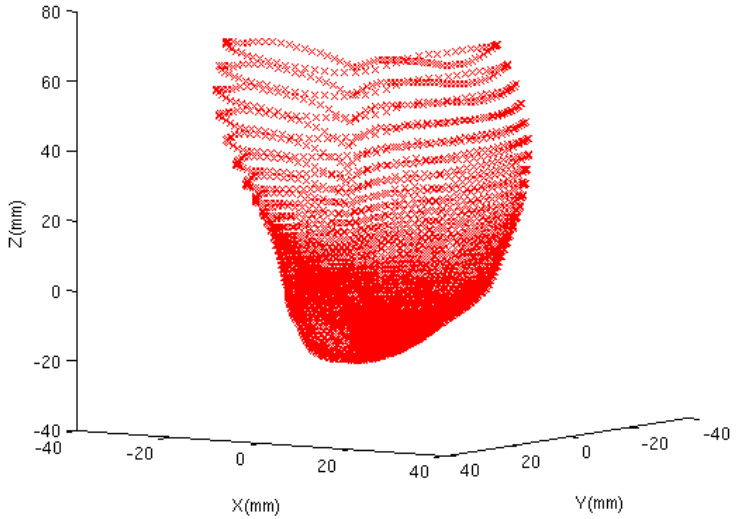


Long axis









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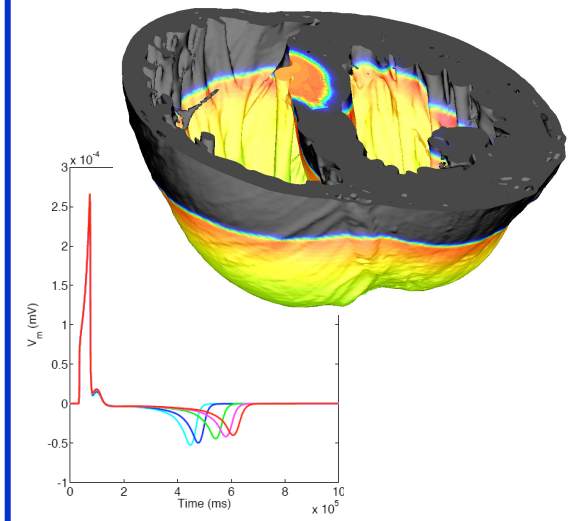
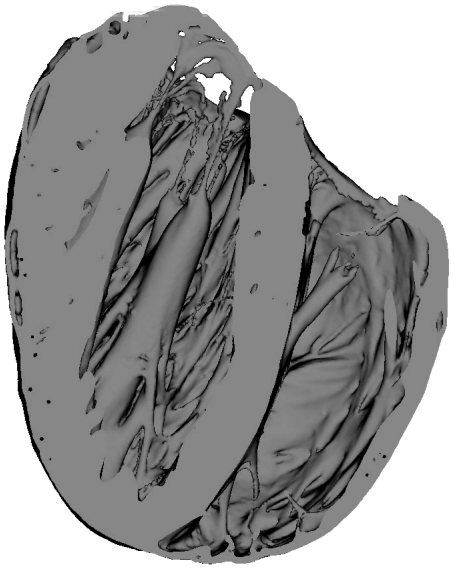


New Biomarkers for Drug Cardiotoxicity

preDICT

The Chaste project

Cancer **Heart** and Soft-Tissue Software Environment



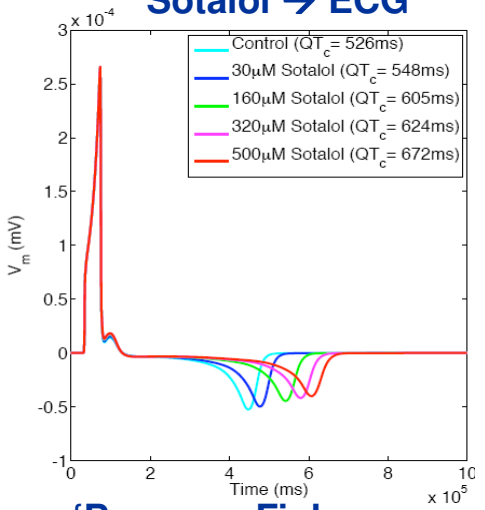
Features:

- Cardiac electrophysiology simulator (monodomain/bidoma
- Open source (www.comlab.ox.ac.uk/chaste)
- Professional software engineering methods (Xtreme progra
- State-of-the-art FEM solutions
- Maximum efficiency on HPC platforms
- Easy integration of cell models using CellML with PyCML
- XML for input definition

Contributors:

University of Oxford
Fujitsu Laboratories Europe
CSR4

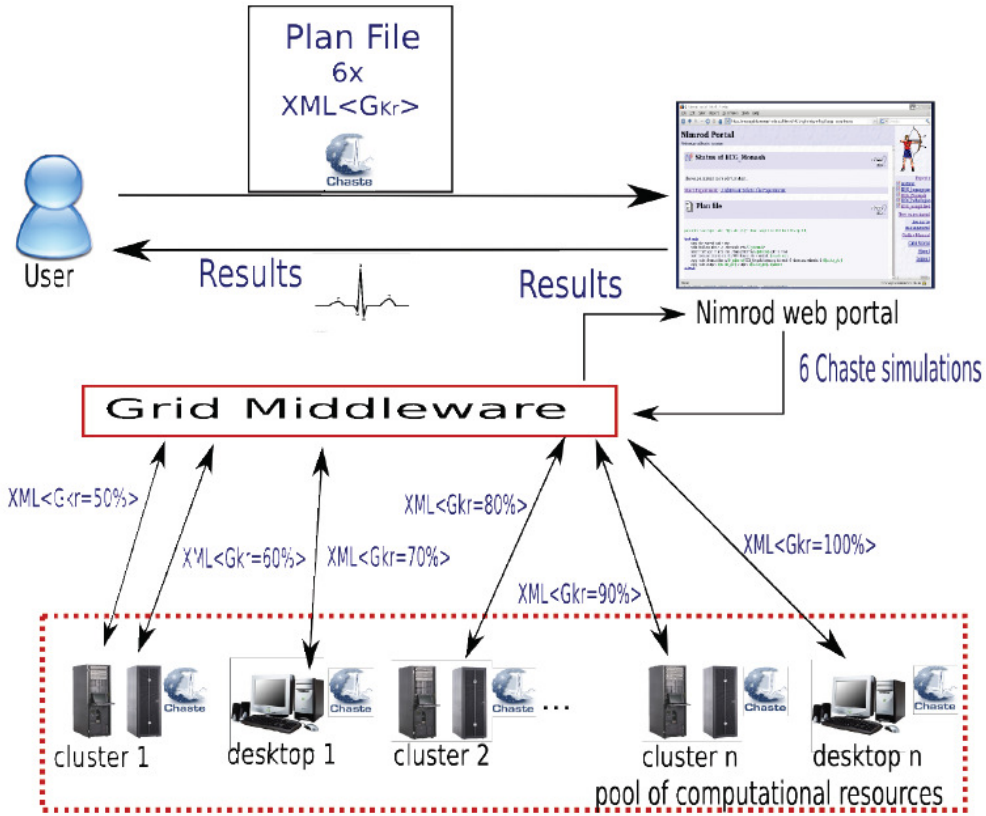
Sotalol → ECG

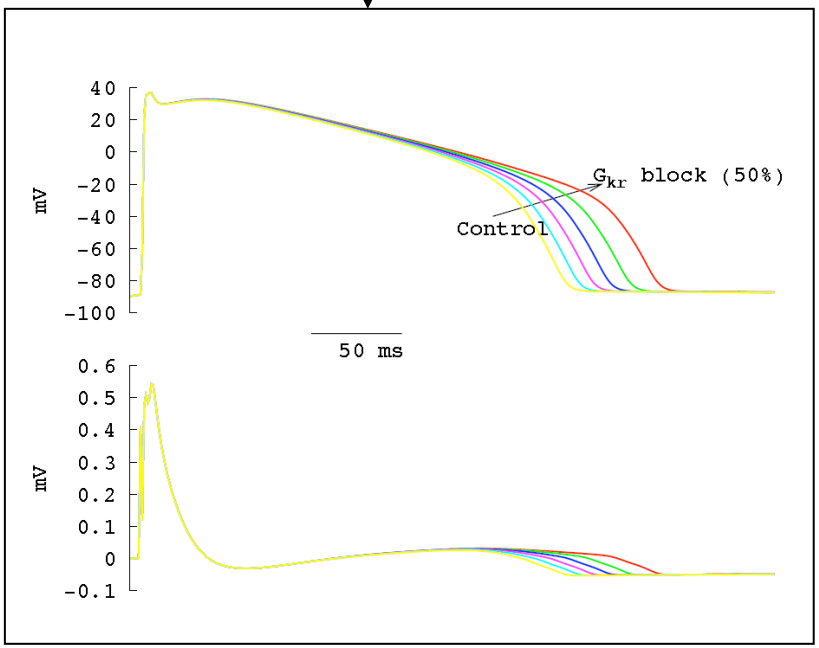


{**Brennan, Fink, Rodriguez**, EJPS, 2009}

preDICT **(www.comlab.ox.ac.uk/chaste_workshop_2009)**

Nimrod and Chaste





{Bernabeu, Corrias et al. Computers in Cardiology, 2009}

Summary

Ventricular geometry

Chaste simulator

Bidomain equations

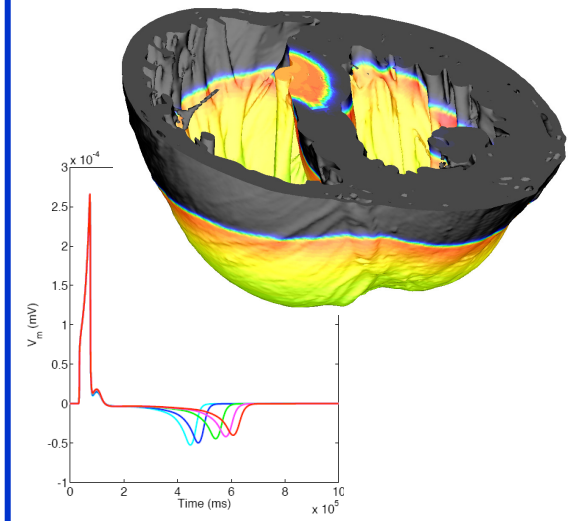
2 PDEs

$$\nabla\bullet(\sigma_i\nabla\Phi_l)=I_m+I_{stim,i}$$

$$\nabla\bullet(\sigma_e\nabla\Phi_e)=-I_m-I_{stim,e}$$

20 ODEs

Modelling & Simulation



New Biomarkers for Drug Cardiotoxicity

preDICT