Virtual tissue engineering of the heart: work in progress

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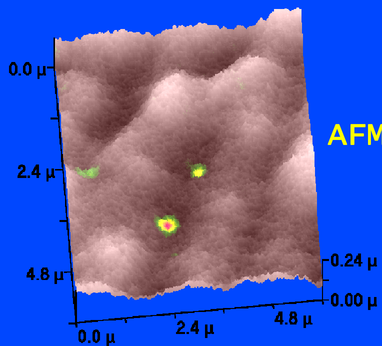
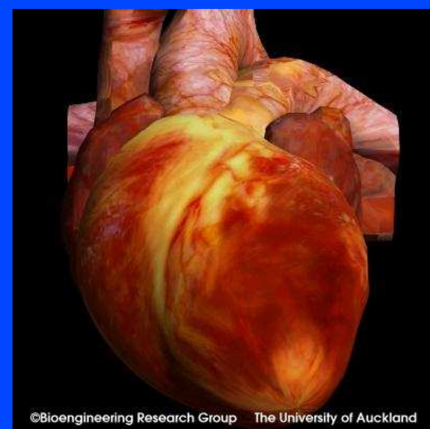
Modeling the beating heart

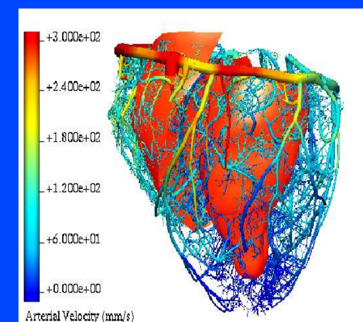
About 10^{14} floating point operations/beat *i.e.* /s



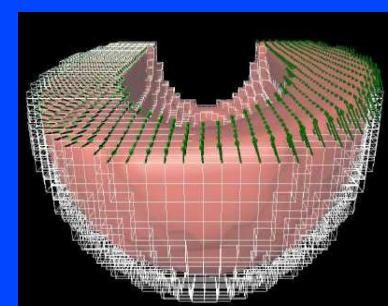
AFM

Patch and cell electrophysiology



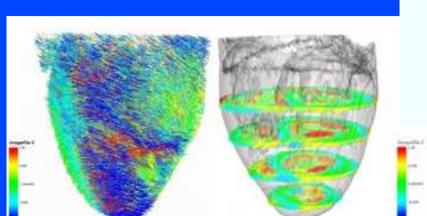


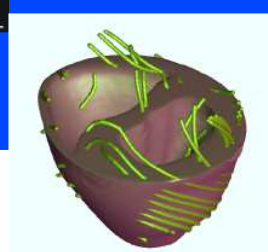
CFD



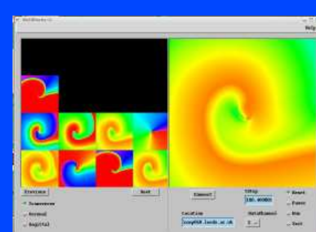
Computational electro-mechanics

DT-MRI

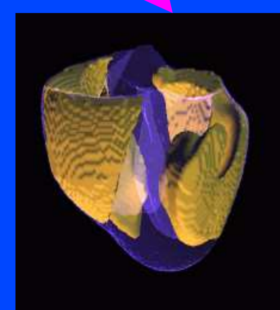




visualisation



Grid enabled Computational steering



Computational electrophysiology

Virtual tissue engineering

Biophysically detailed models of protein dynamics of cell

Histologically detailed tissue model

Spatial mapping of protein expression

Detailed anatomy

Validation of computational implementation

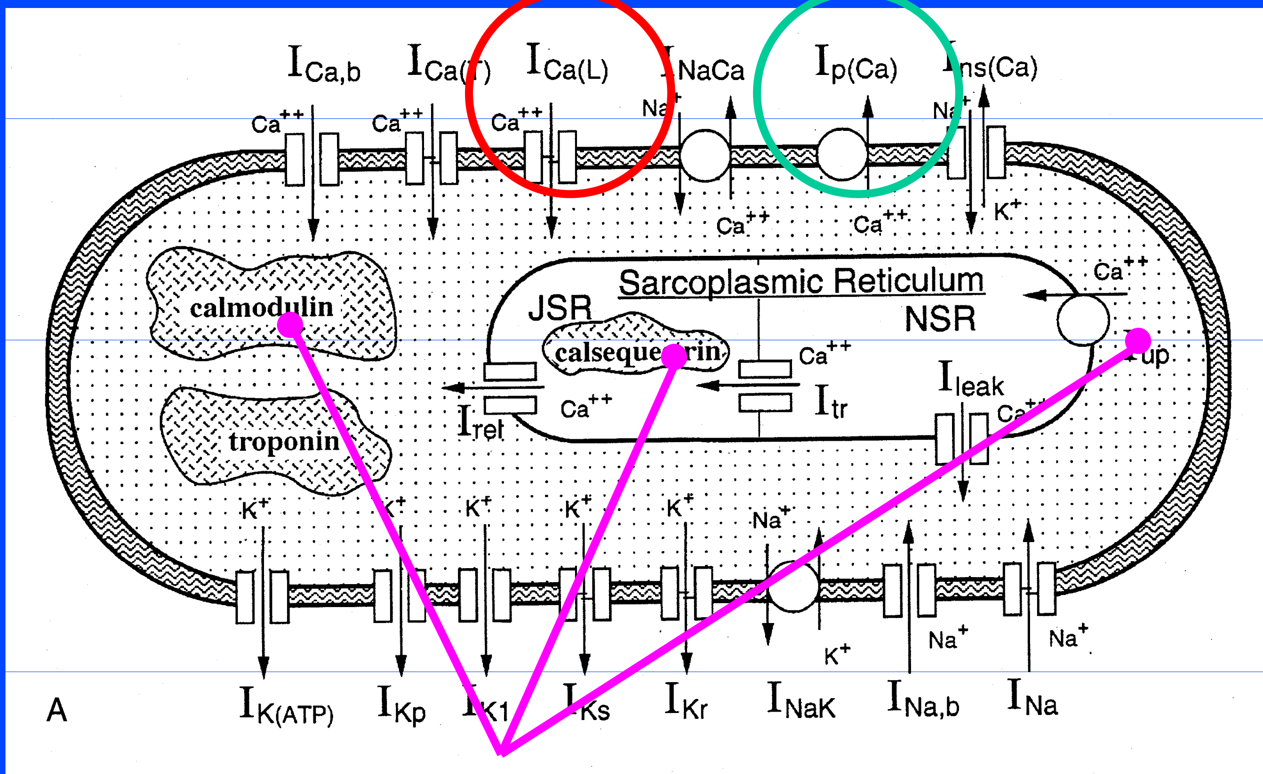
Visualisation of output : virtual reality

Application to both scientific and practical problems

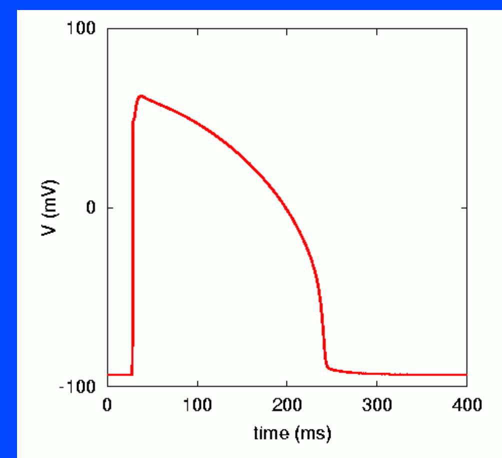
Biophysically based cellular models

System of equations describing

- Current flow through ion channels and exchangers in the cell membrane

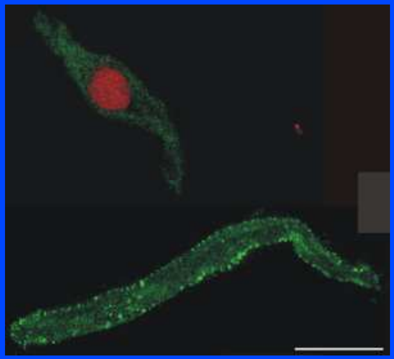


Simulated action potential



- Mechanisms of Ca uptake, storage and release within the cell

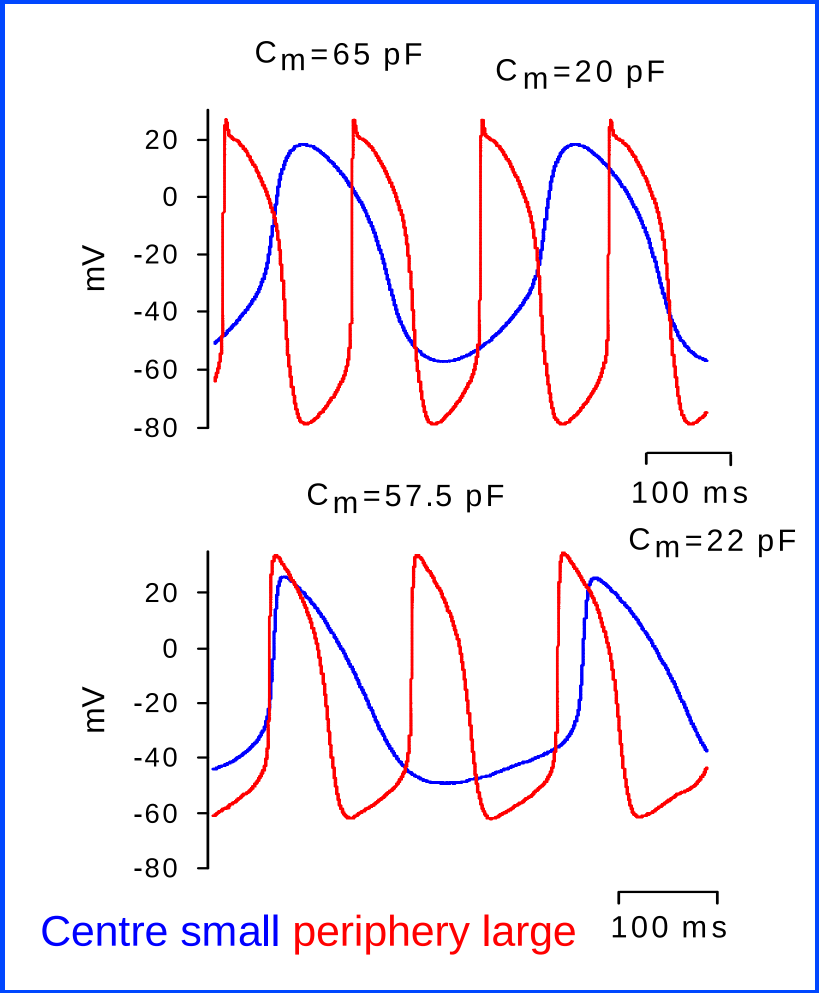
Virtual cell engineering: SAN



Zhang, Holden, Kodama, Honjo,
Lei, Varghese, Boyett
Am J Physiol Heart Circ
(2000) 279 H 397-H421

Intracellular Ca dynamics

2005-2010 BBSRC eScience programme



0-,1-,2-D (3-D) virtual tissues

- Atrium: AF remodelling, drugs acting on I_K
  - Human: Nygren, Courtemanche.
- Ventricles: re-entry,VF; pacemaking; ectopics; repolarisation arrhythmias; mutant channels; spatial (mostly transmural) changes in expression; patholgies (ischaemia, hypertrophy)
  - Luo-Rudy family
  - PriebeBeuckleman normal pathological human
  - OGPV,
  - Ten Tusscher human

0-D

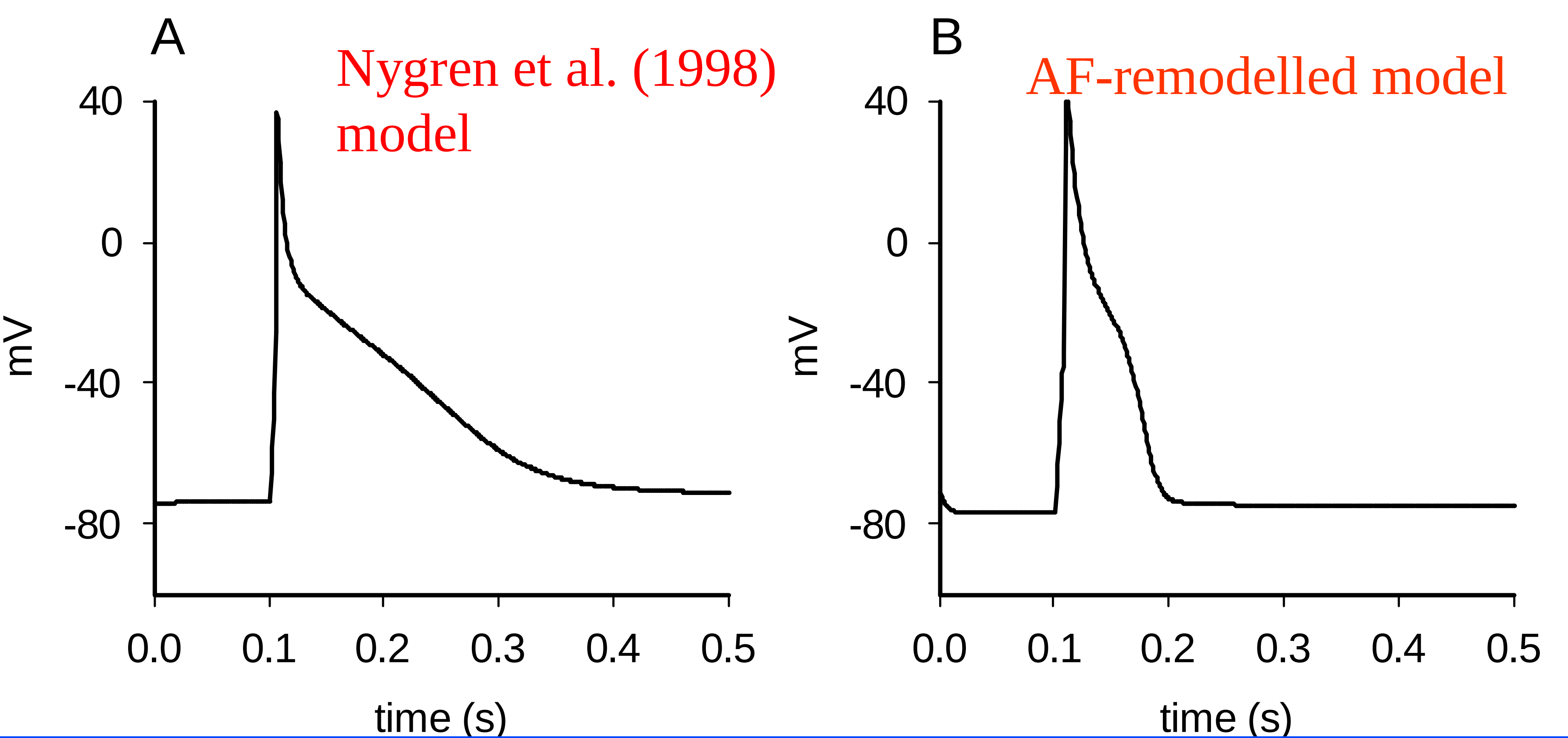
Cell models: change parameters

- Numerical solutions

AP waveform, APD restitution, dissect mechanisms

- Bifurcation analysis

AF remodelling

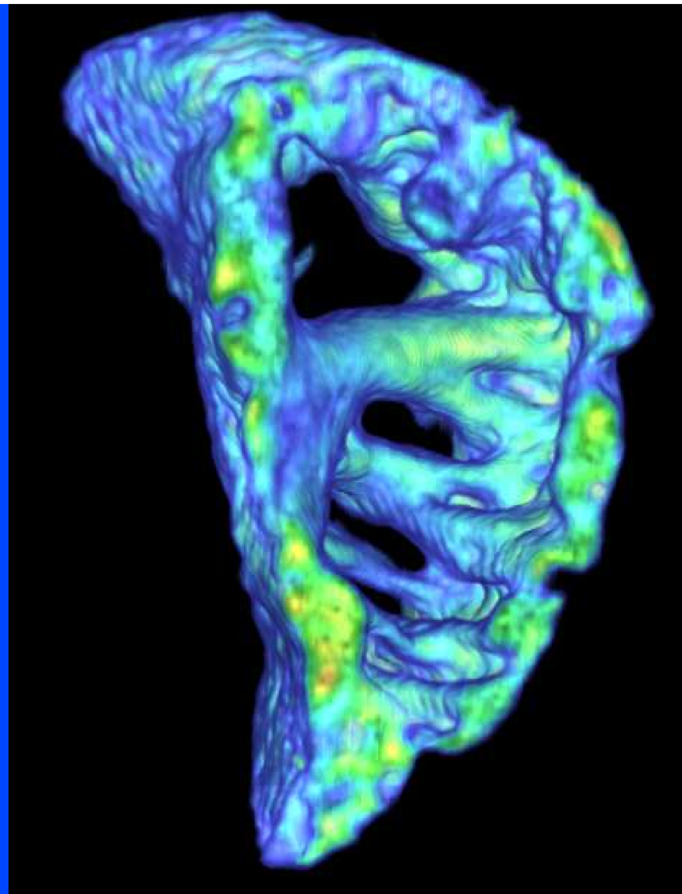


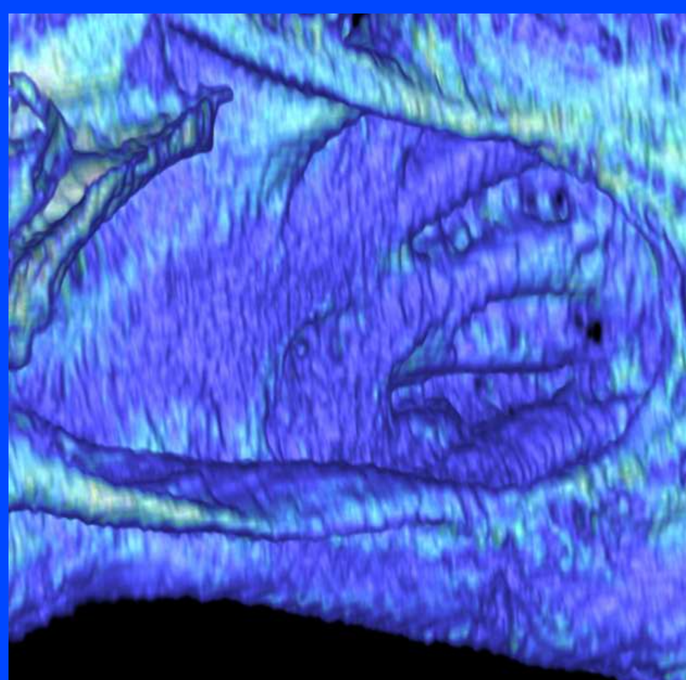
Zhang Garratt Holden CVR 2005: mostly due to g_{K1} upregulation
Connexin and ionic channel remodelling

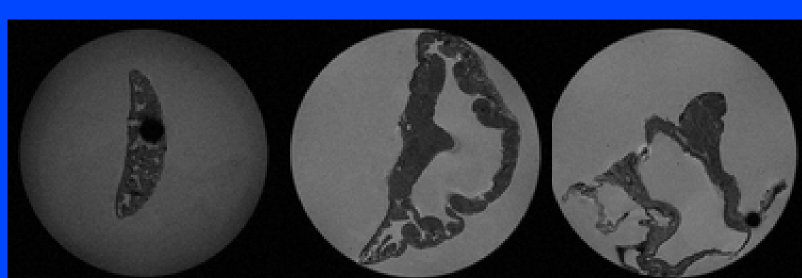
Human atrial electrophysiology

- Have cell, tissue models, (drug action) that can be incorporated into 3D atrial model
- Need high resolution normal/AF atrial geometries: postmortem DT-MRI. Access to clinical material and DTMRI.
- Need endocardial mapping of normal and atrial tachycardic activation

3D reconstruction from rabbit atrium MRI datasets







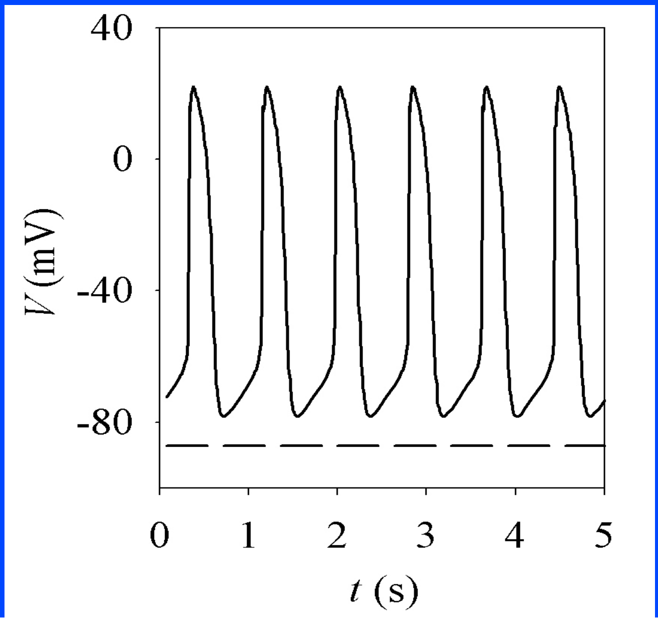
Ectopic pacemaking in human ventricular model

Experimental results:

- Expression of a genetic-engineered non-functional I_{K1} channels reduced I_{K1} current density and promote pacemaker activities in ventricular myocytes.

Miake *et al* (2002) Nature 419:132-133

Miake *et al* (2003) J. Clin. Invest 111:1529-1536



Modelling:

- These results can be reproduced by reducing I_{K1}: fractional g_{K1} = 1 (dash line) and fractional g_{K1} = 0 (solid line)

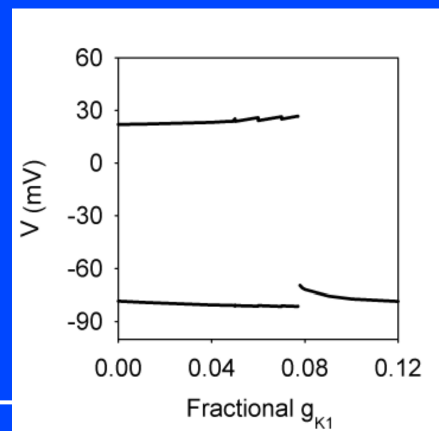
- Characterise how the pacemaker activity emerges, i.e., the location and nature of the bifurcation point, with two approaches: (1) numerical experiments and (2) XPPAUT

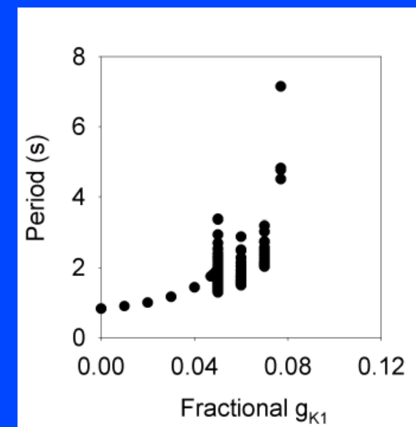
Ectopic pacemaking in human ventricular model

- Human ventricular model (ten Tusscher *et al* 2004)
- Fractional g_{K1} as the bifurcation parameter

(1) Numerical experiment with full model

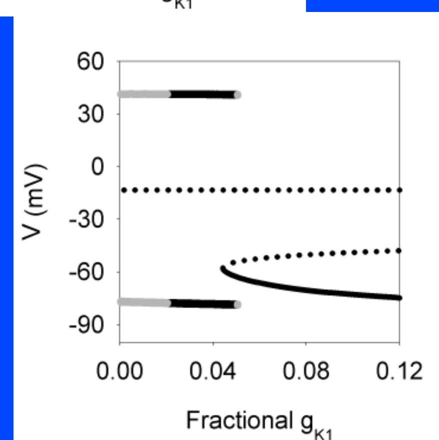
- Bifurcation point ≈ 0.077
- Bursting observed

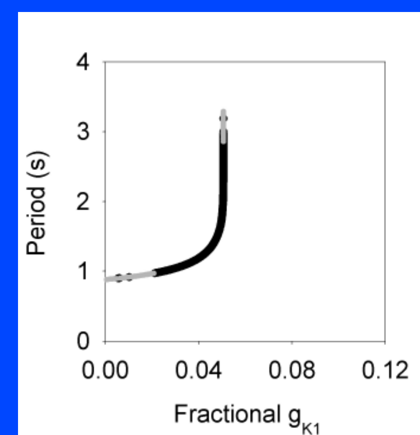




(2) XPPAUT on reduced model without concentration dynamics

- Bifurcation point ≈ 0.05
- Homoclinic bifurcation



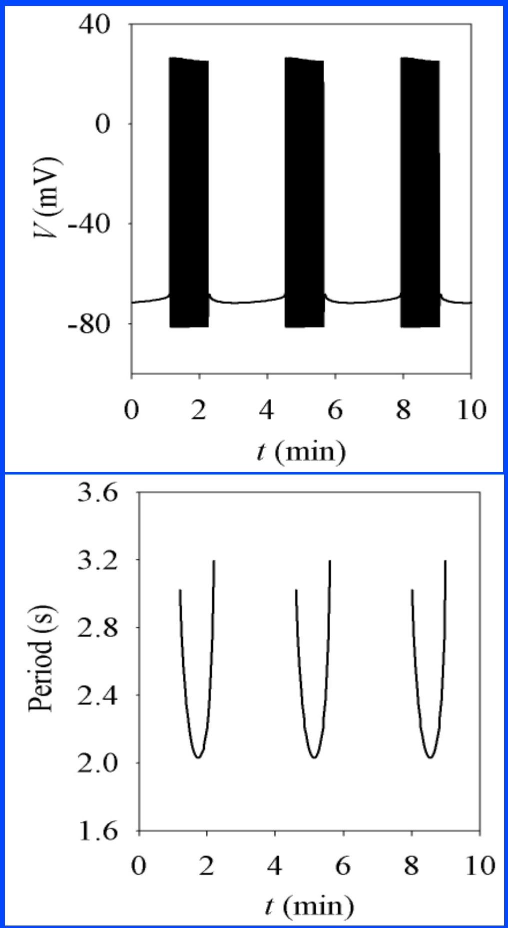


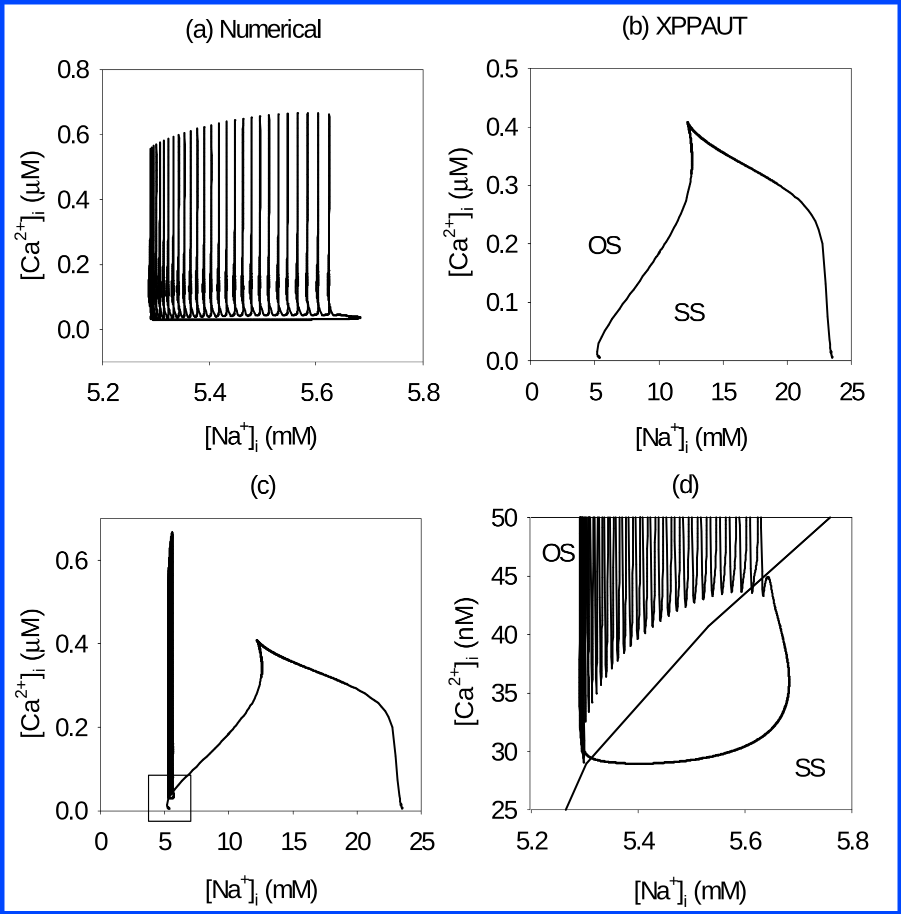
Qualitative similar behaviour is found in LRd00, with the bifurcation point ≈ 0.3. (Benson *et al* (2005) J. Physiol. (Proceedings) *In press*)

Ectopic pacemaking in human ventricular model Bursting

- Caused by slow variables dynamics
- Occur within a narrow parameter range (Fractional g_{K1}): 0.05-0.077
- Extremely pathological

fractional g_{K1} = 0.07





Tissue models

Generic equation for an excitable medium

Membrane voltage at a point depends on local voltage gradient and membrane current

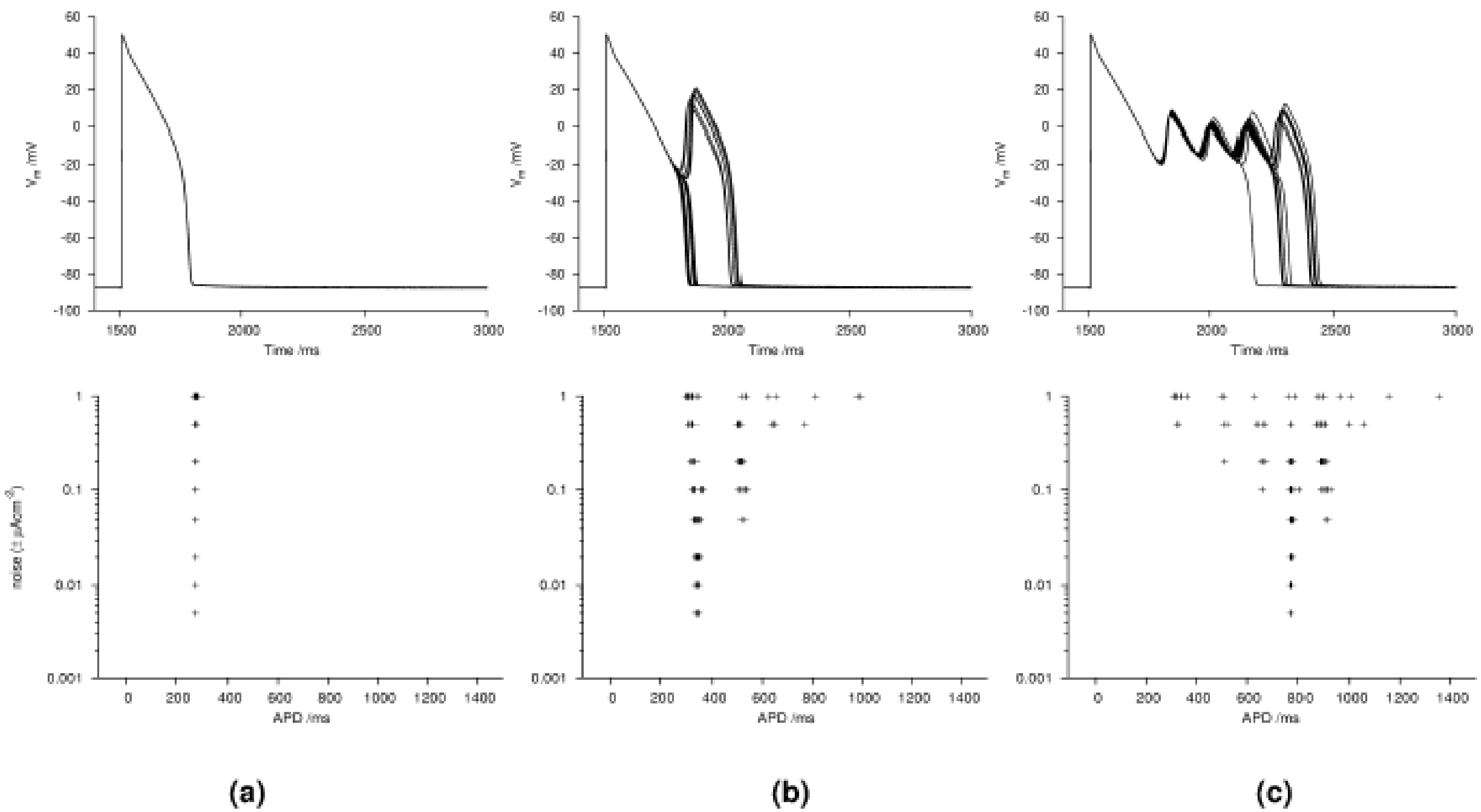
Assumes myocardium is a continuum

Can take account of anisotropic conduction

Plug in kinetics for I_{ion} models

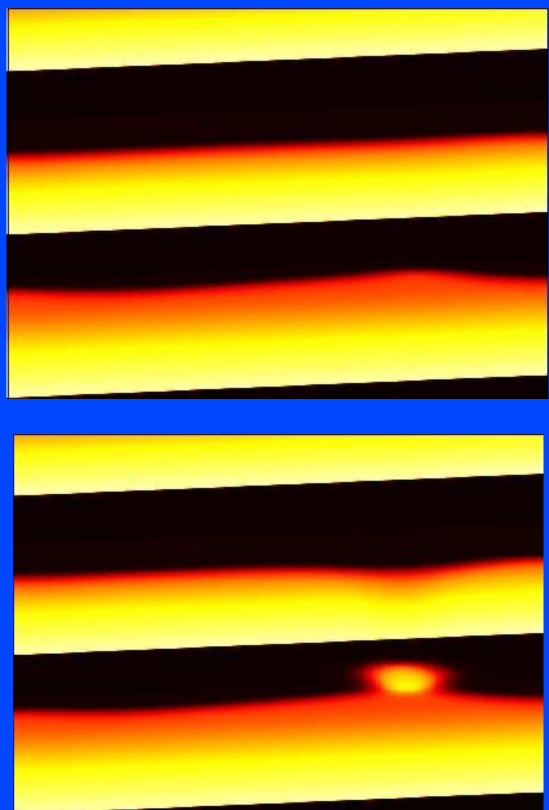
$$\frac{\partial V}{\partial t} = D\frac{\partial^2 V}{\partial x^2} - \frac{1}{C} I_{ion}$$

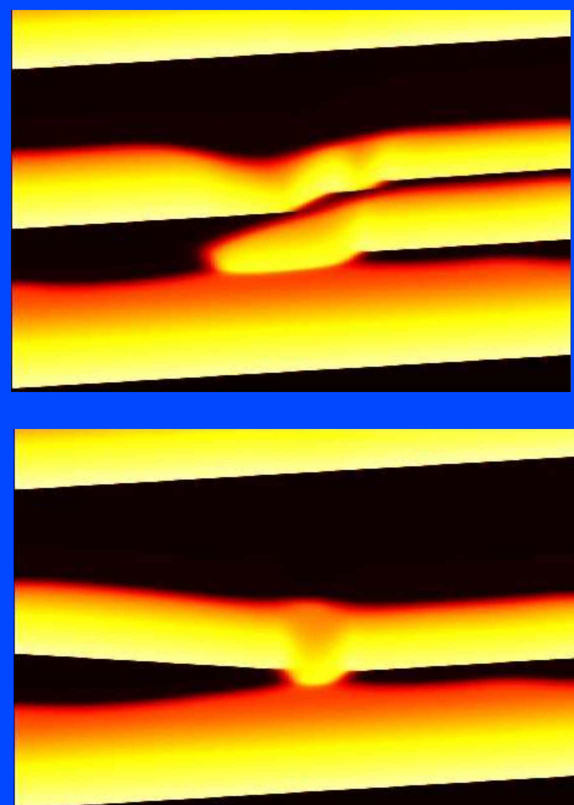
Probability of arrhythmogenesis:
Noise induced early after-depolarisations



Clayton Holden Tong IJBC 2003

Initiation of arrhythmias: Noise-induced propagating activity





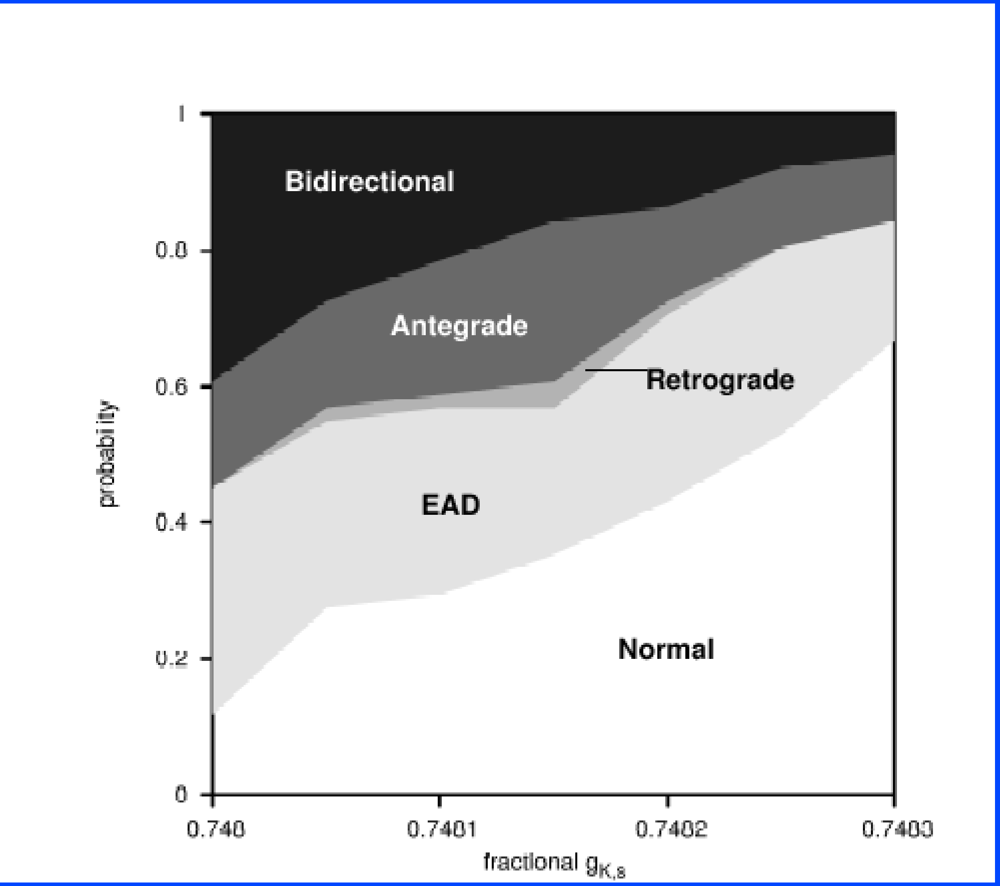
Retrograde (re-entrant)

Failure

Bi-directional or antegrade (ectopic)

Clayton Holden Tong Int J Bifurc Chaos 13 (12) 2003

Probability of ectopic or re-entrant source in 1-D virtual tissue

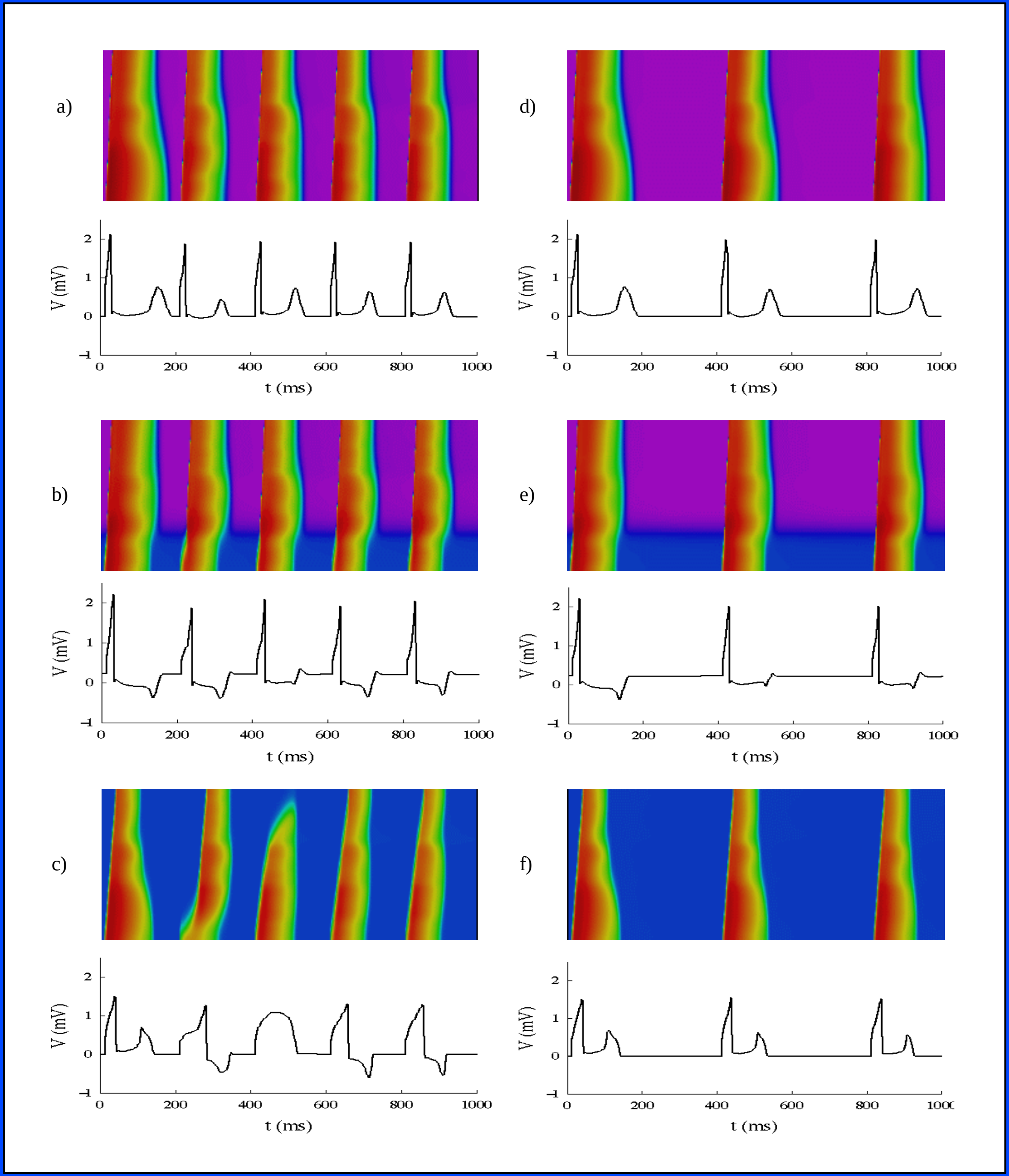


Clayton Holden Tong 2003 i

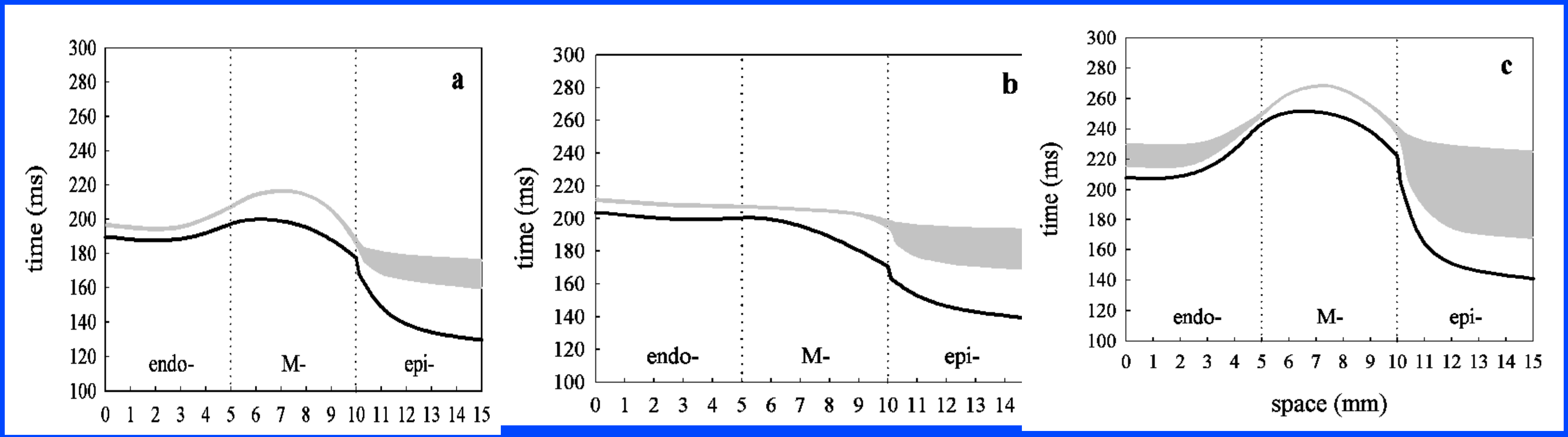
Transmural 1D and pseudo ventricular ECG

Space-time plots and pseudo-electrograms. Stimulation applied in subendocardial region is either high- (BCL = 200 ms) or low-rate (BCL = 400 ms). (a) Normal tissue, high-rate; (b) subendocardial ischaemia, high-rate; (c) global ischaemia, high-rate; (d) normal tissue, low-rate; (e) subendocardial ischaemia, low-rate; (f) global ischaemia, low-rate.
J theor Biol in press

?LQT1,2 to identify spatial characteristics ?predict QT interval and T wave changes induced by modified I_{Kr}

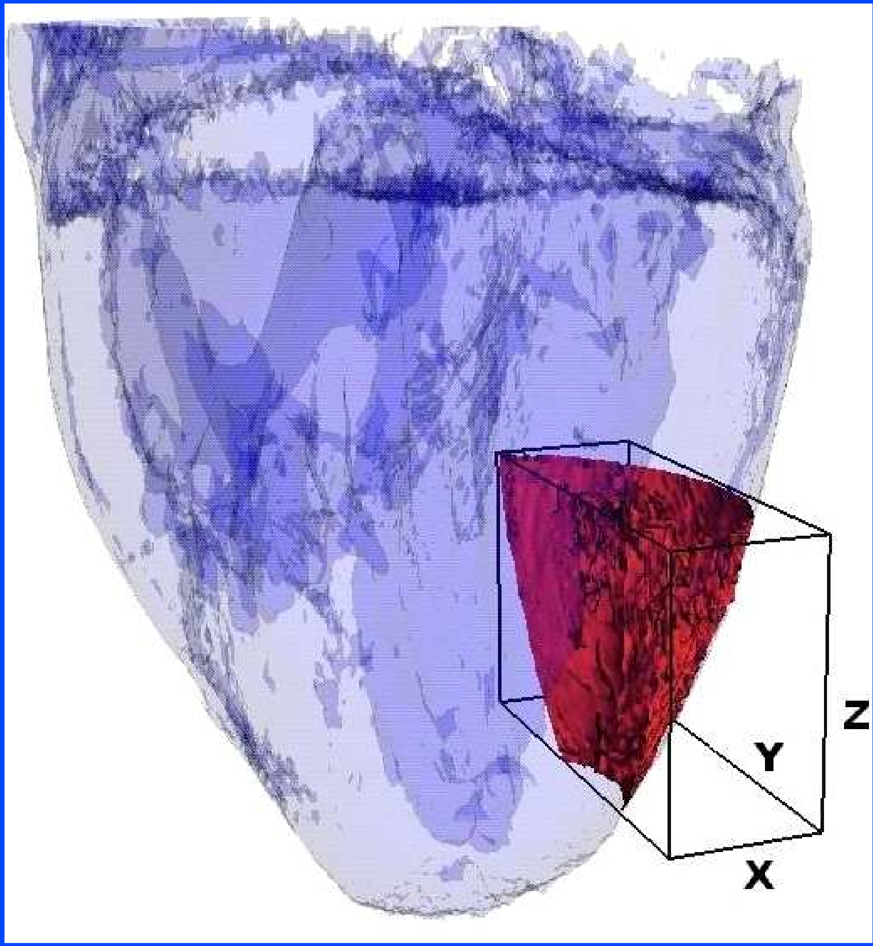


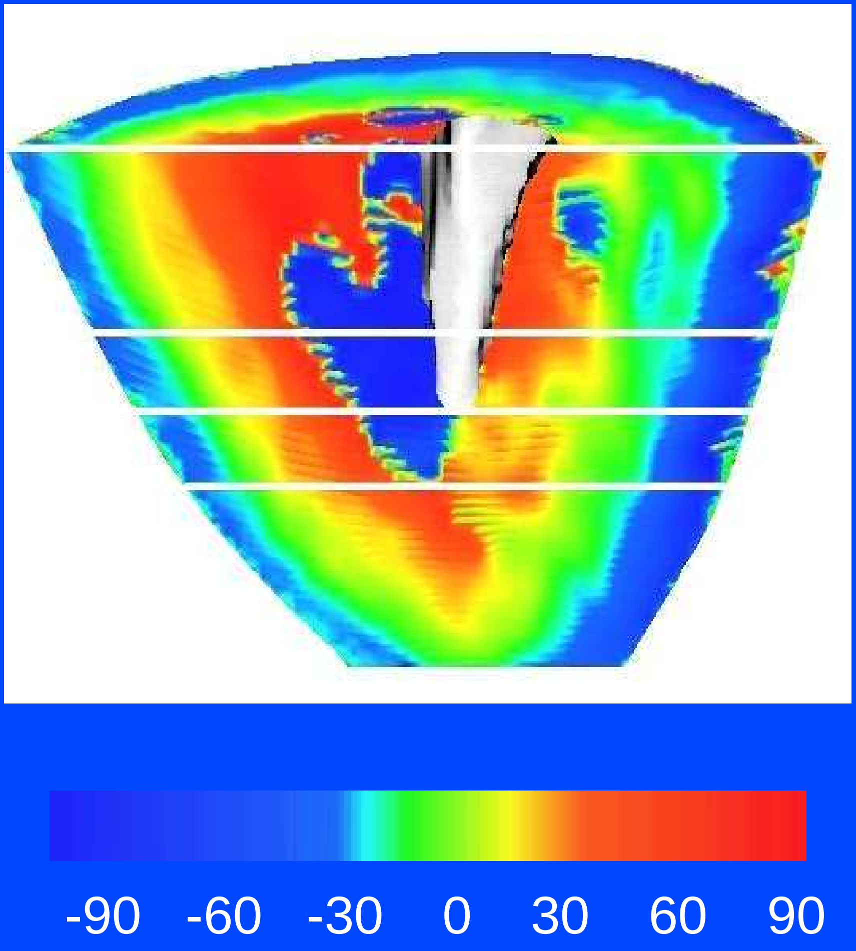
Transmural heterogeneity



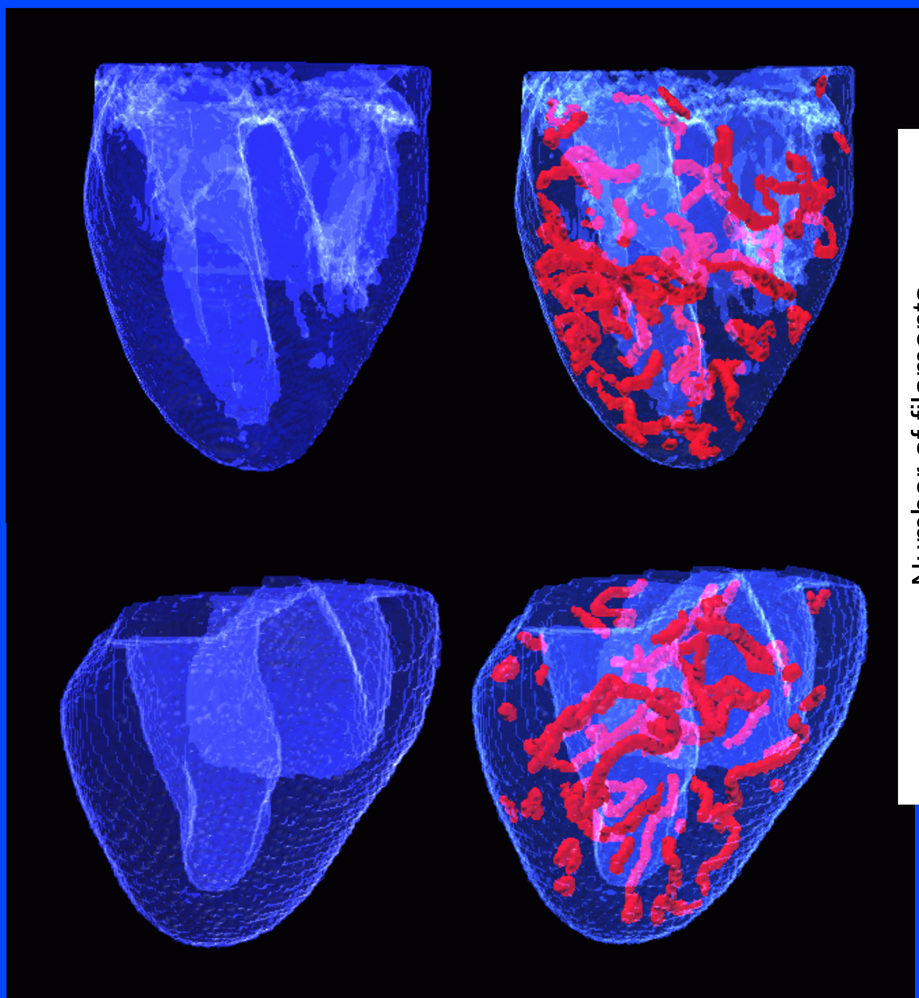
Transmural APD dispersion and vulnerability in 1D LRd virtual ventricular tissues: (a) normal tissue, (b) with amiodarone, (c) with d-sotalol. Spatial distributions of APD (solid lines) and VWs (grey areas).

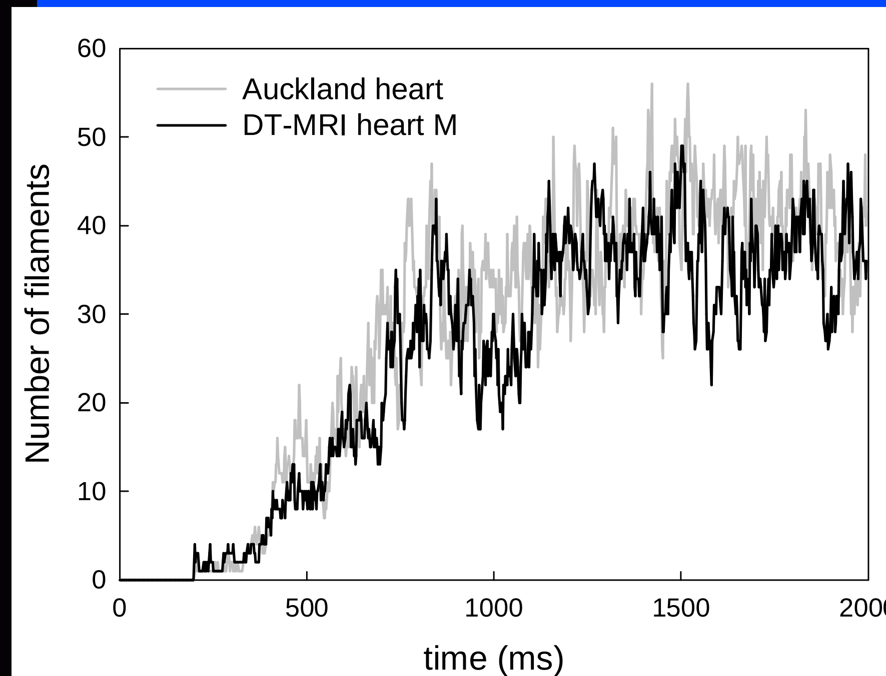
DT MRImaging of canine ventricle





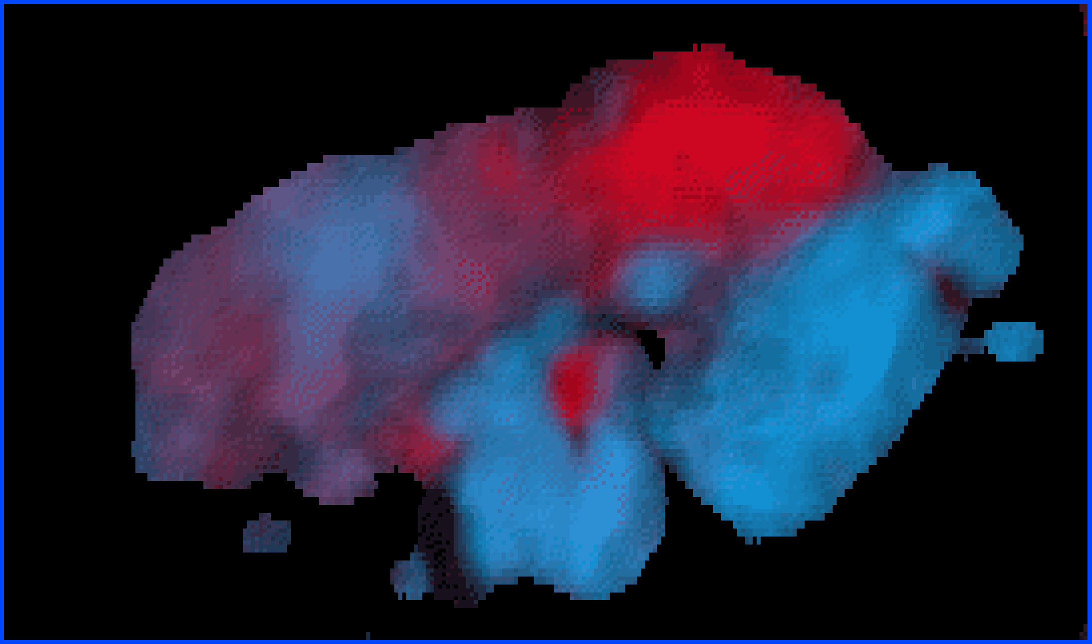
VF in Auckland and DTI canine geometries





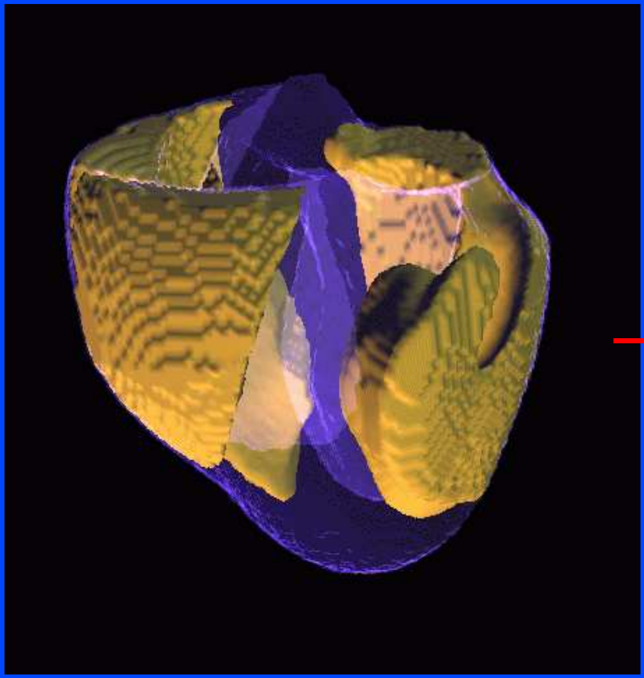
Fibrillatory conduction with domains

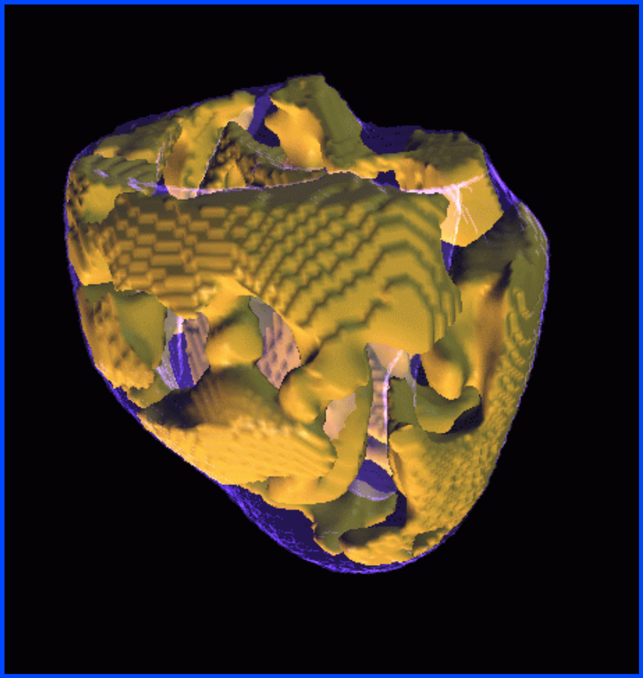
- Frequency analysis of spatial activity reveals domains fibrillating at different frequencies



- Could the domains be driven by a single re-entrant source?

VF mechanisms in individual DTMRI hearts: canine, hypertrophic canine, human.





Need library of normal, pathological human DTMRI data sets

Grid-enabled visualisation: n concurrent 2 d simulations.