Tissue models 2: Virtual tissue engineering of the beating human heart

Arun V Holden
Computational Biology, Leeds

arun@cbiol.leeds.ac.uk

KITP, Santa Barbara
November 2003

Outline

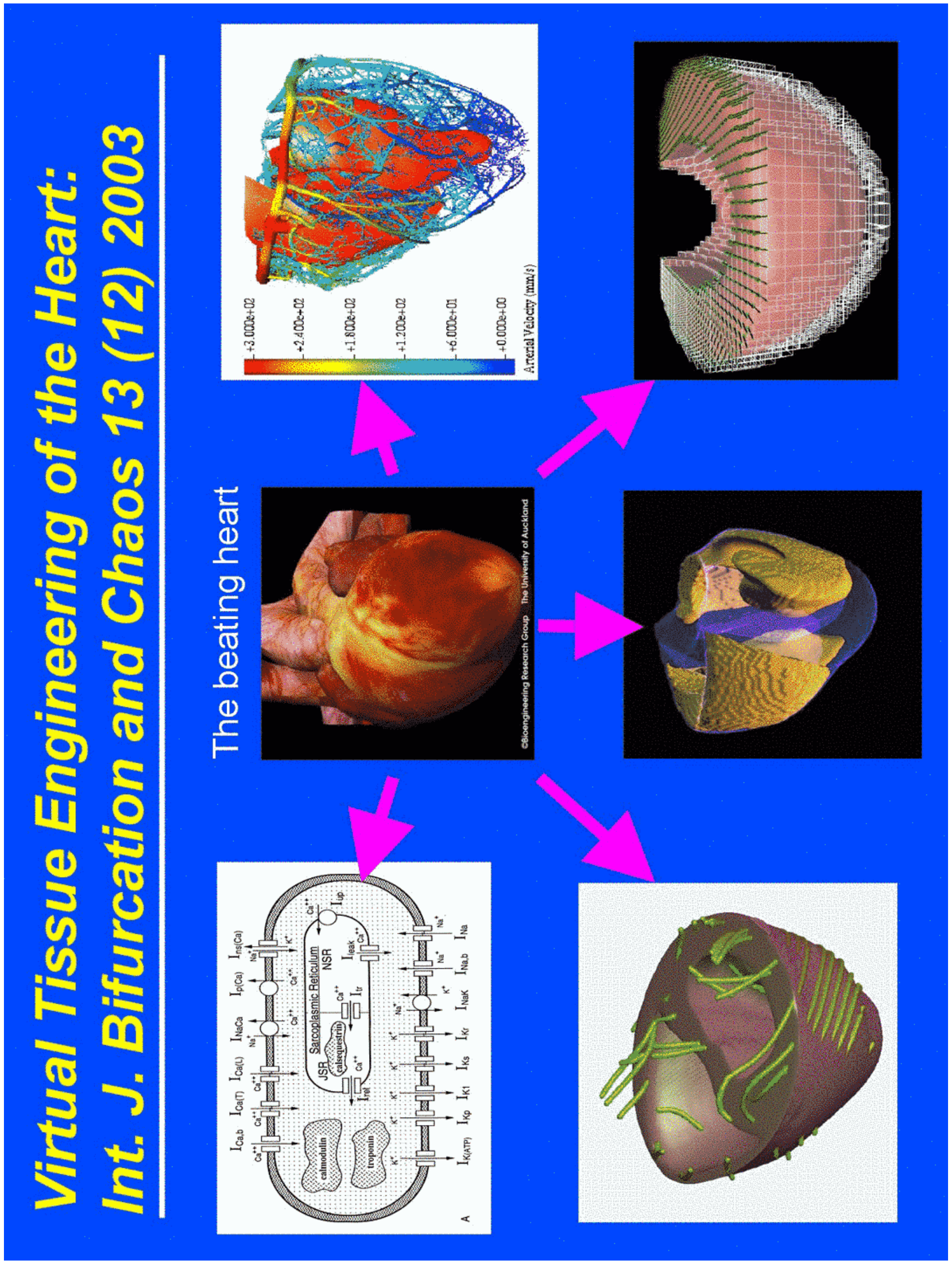
- Virtual cardiac tissue engineering and arrhythmmias: re-entry and fibrillation.
- Human virtual cardiac tissues and clinical illustrations
- Loop analysis of disease processes and application to CHD

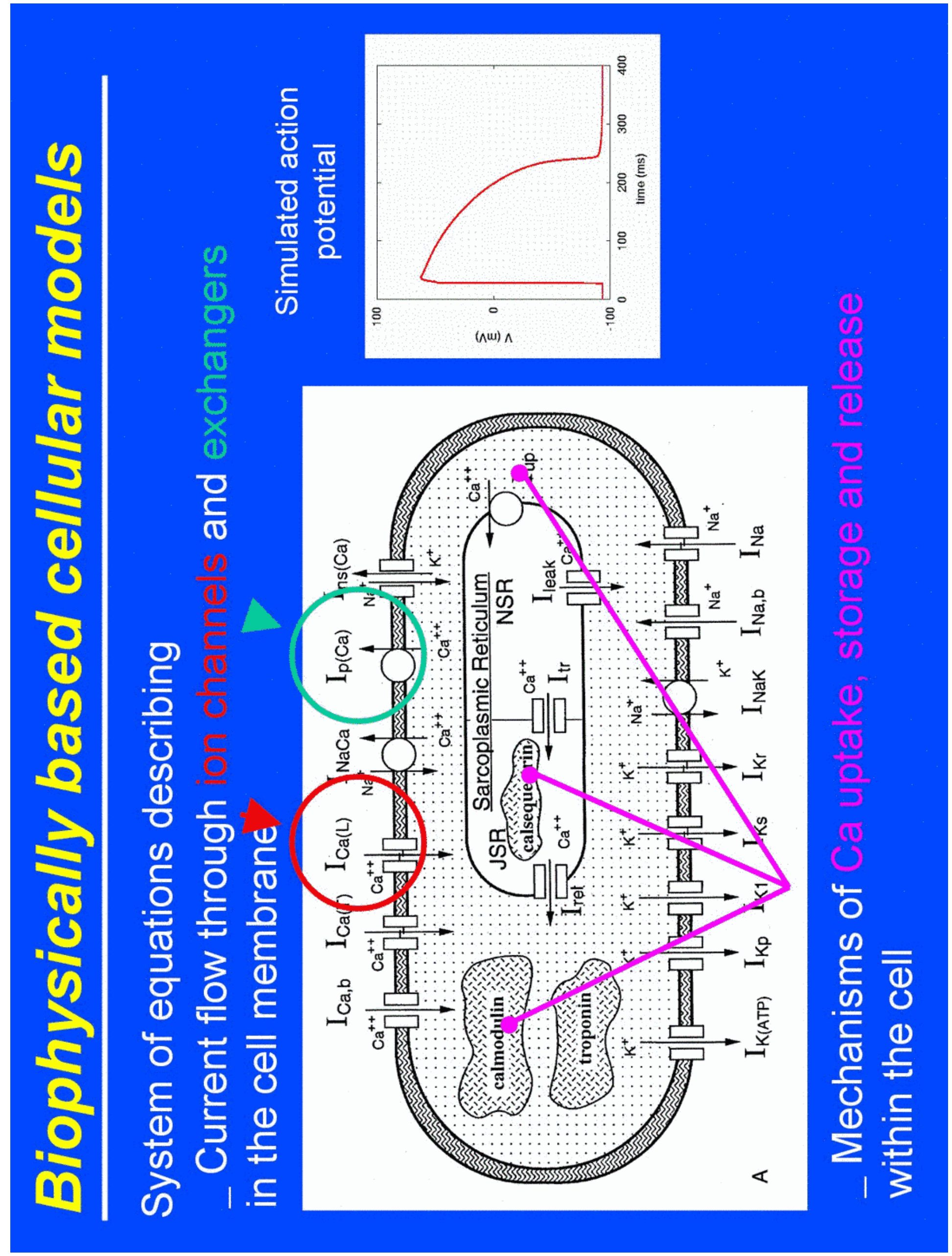
Virtual tissue engineering

- 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

Goals: Cardiac virtual tissue engineering

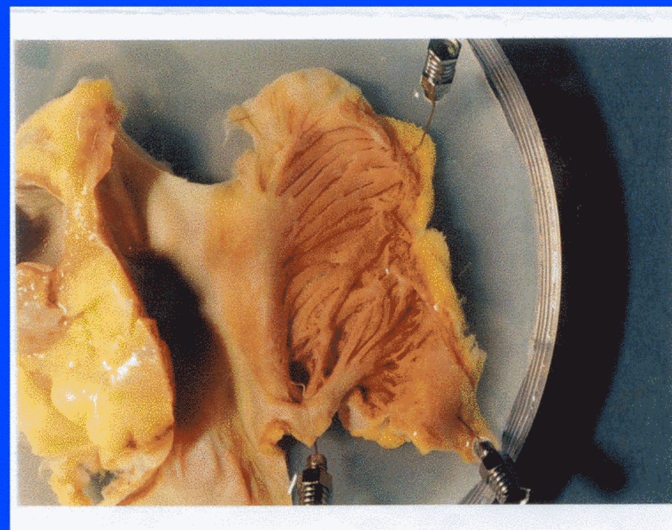
- Construction and validation of models for normal, abnormal, mammalian and human hearts
- Understand mechanisms of onset, persistence and termination of arrhythmmias
- Design low voltage defibrillation techniques
- Identify targets for antiarrhythmics
- **Provide tools for reducing mortality rate**
  - •England CVD target: >40% reduction by 2010
  - •Scotland CVD target: 50% reduction by 2010
  - **•VTE target: by at least an order of magnitude, within a decade**


Virtual Tissue Engineering of the Heart:
Int. J. Bifurcation and Chaos 13 (12) 2003
The beating heart
Arterial Velocity (mm/s)

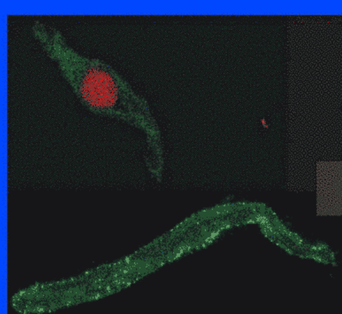

Biophysically based cellular models
System of equations describing
– Current flow through ion channels and exchangers
in the cell membrane
Simulated action potential
V (mV)
time (ms)
Sarcoplasmic Reticulum
NSR
JSR
calsequestrin
calmodulin
troponin
– Mechanisms of Ca uptake, storage and release
within the cell

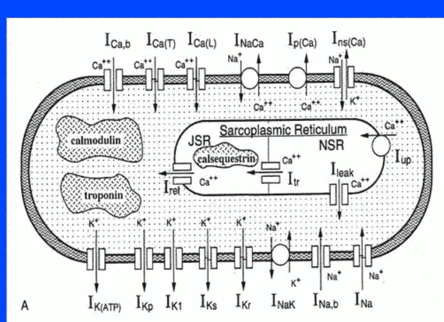
Cardiac pacemaker: sinoatrial node

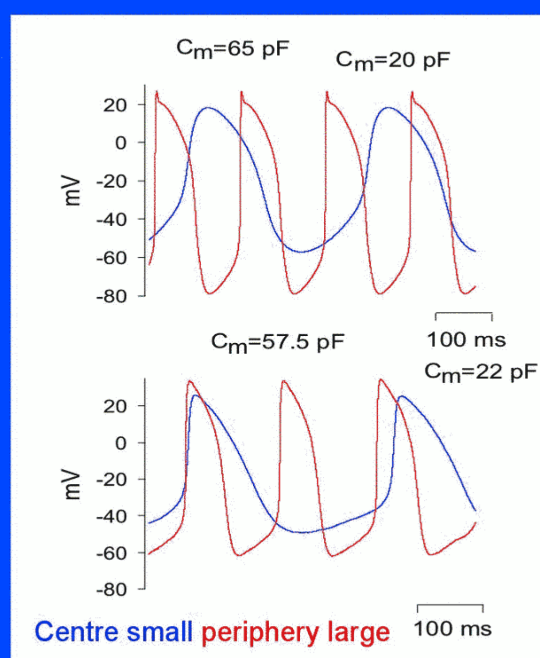
- Anatomy
- Molecular mapping
- Electrophysiology
- Simulation
- Pharmacology, pathology



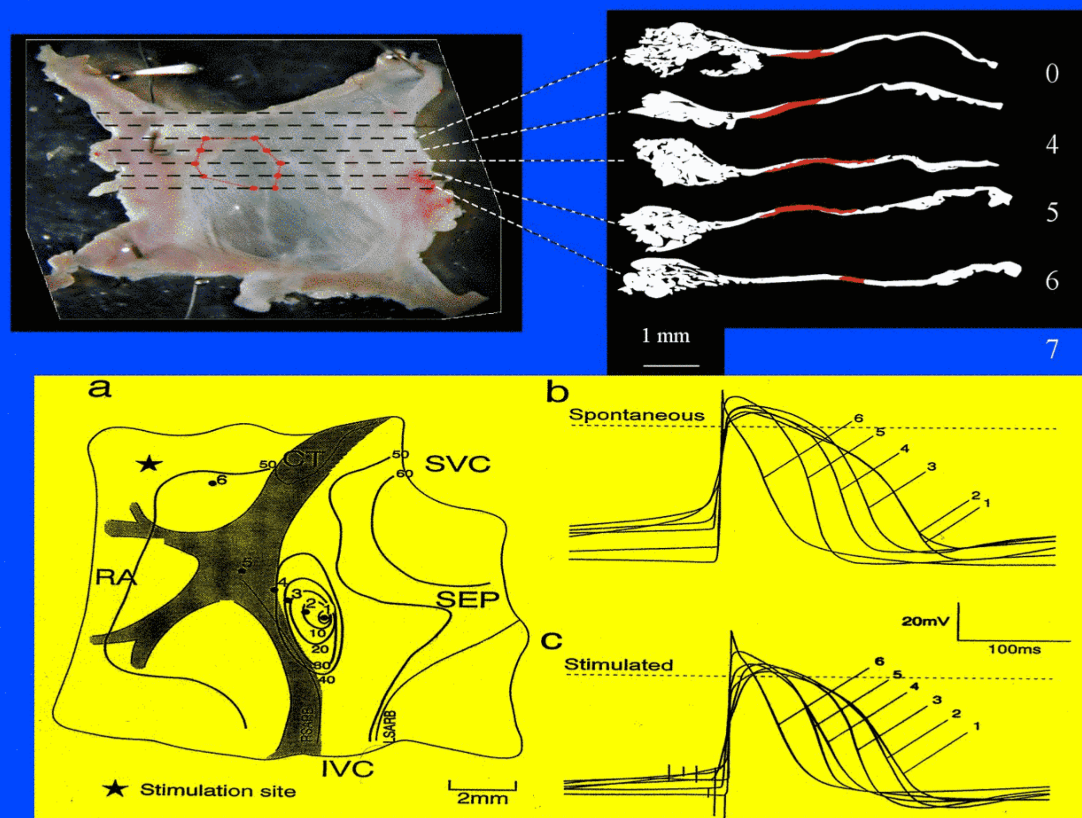
Virtual cell engineering







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

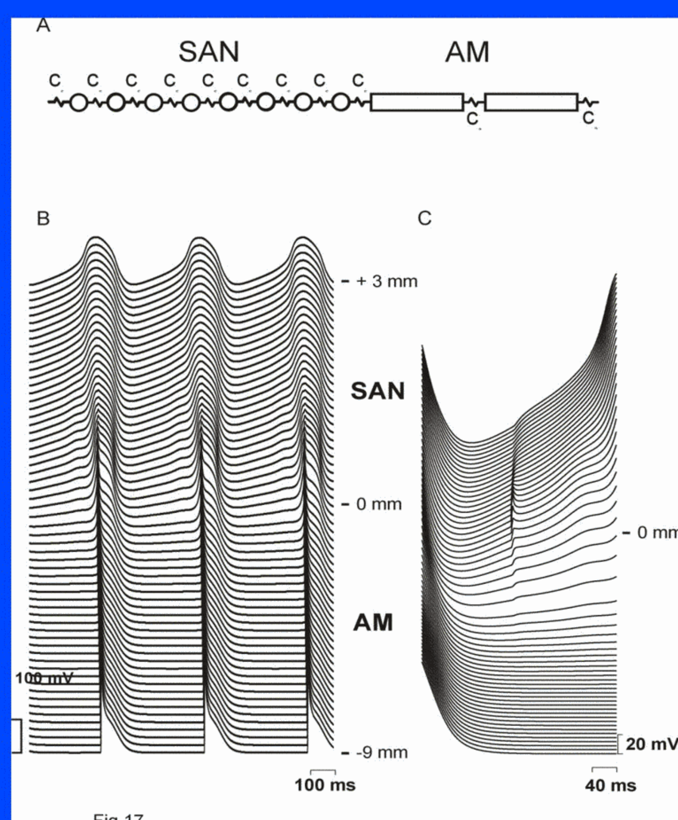


Zhang, Holden, Kodama, Honjo, Lei, Varghese, Boyett Am J Physiol Heart Circ (2000) 279 H 397-H421

1-D tissue model of sinoatrial node and atrium

Initiation & propagation of pacemaker activity with SAN-atrium

Sinoatrial node driving of atrial muscle

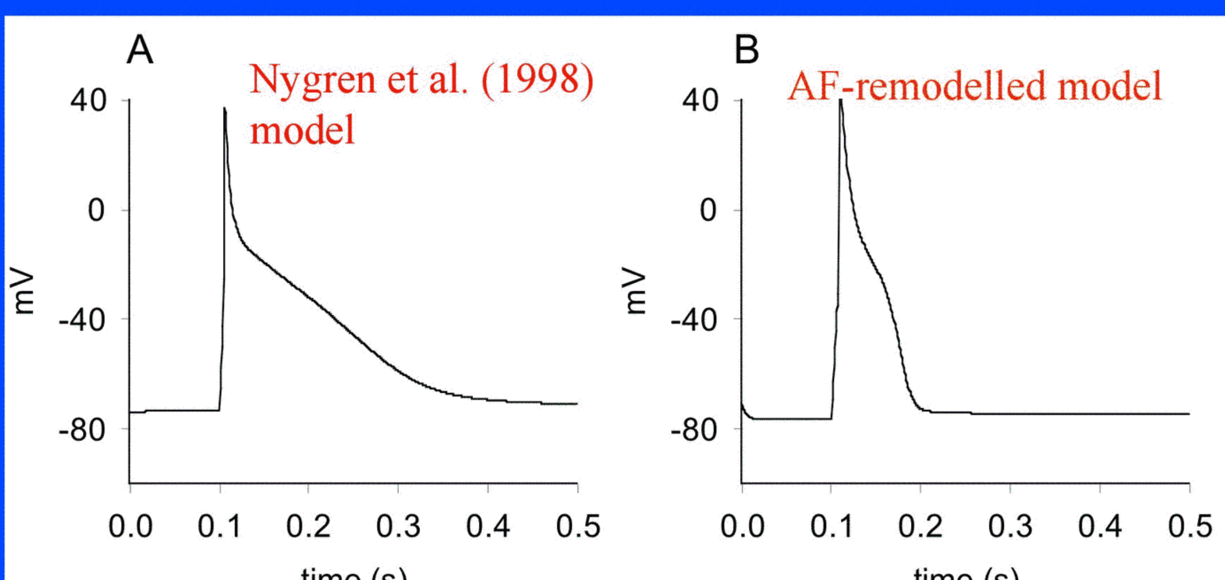


Chronic AF-induced remodelling of atrial ionic channels

	Regulation	Current density	Channel kinetics
$i_{Ca,L}$	Down ↓	74% ↓	$\tau_{inact,fast}$ 62% ↑
i_{to}	Down ↓	85% ↓	Activation curve shifted by 16 mV
$i_{K,sus}$	--	--	--
i_{Na}	--	--	Inactivation curve shifted by 10 mV
$i_{K,1}$	UP ↑	250% (-90 mV) ↑ 235% (-20 mV)	--

Bosch et al. (1999) Cardiovasc Res 44: 121-131

Simulation of AF-remodelling



Zhang Garratt Holden NASPE 2003

Remodelling of atrial action potential

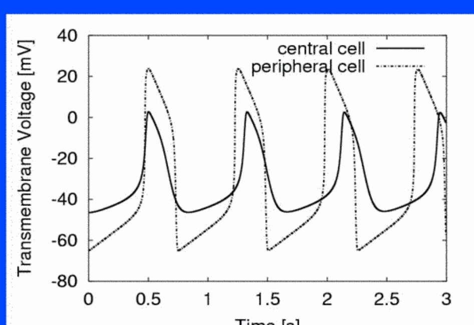
Simulation data

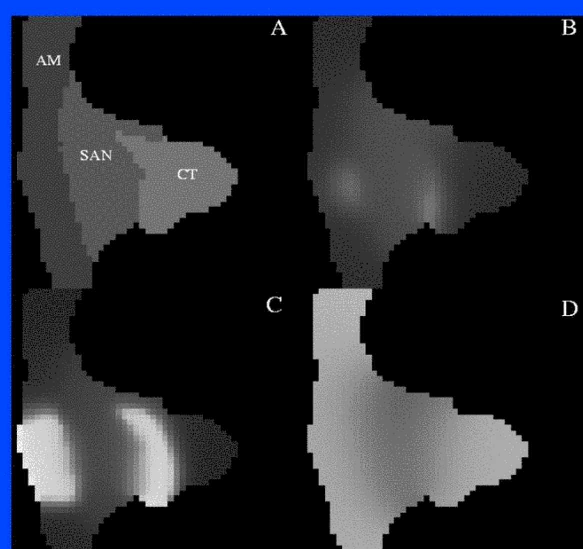
	RP (mV)	APD_{90} (ms) (0.2 Hz)
Nygren model	-74	300
AF remodeled model	-78	105
Change	-4 ↓	-65% ↓

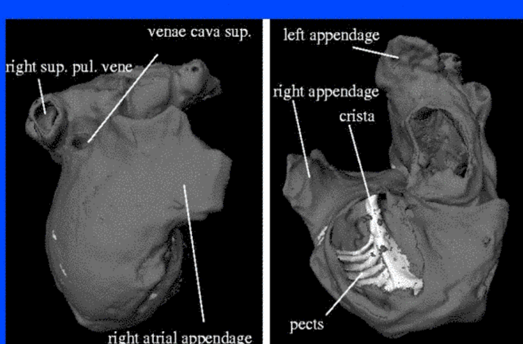
Experimental data (Bosch et al)

	RP (mV)	APD_{90} (ms) (0.2 Hz)
SR	-76.3±2.2	319 ±48
AF	-78.9 ±2.9	134 ±12
Change	-2.6 ↓	-58% ↓

Human SAN and atrial driving







Hoeper Seeman Sachse Zhang Dossel (Biomedzinische Technik Berlin 2003)

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

$$C_m \frac{\partial V_m}{\partial t} = \nabla(D \nabla V_m) - I_{ion}$$

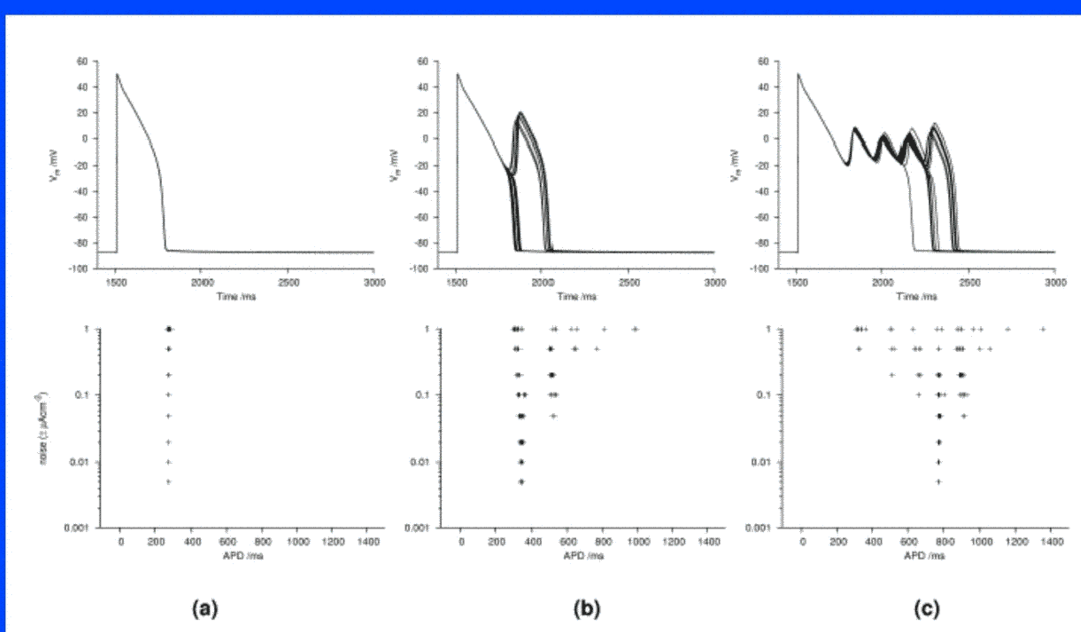
Propagation in homogenous isotropic virtual tissue

- Zero dimension: cell model
  - Action potential, APD restitution
- One dimensional: wave and wavefront
  - Propagation velocity, rate dependence
  - Vulnerable window
- Two dimensional: wavefront is a curve
  - Curvature effects, spiral waves,
- Three dimensional: wavefront is a surface
  - Scroll waves, and fibrillation

Propagation in one-dimensional virtual ventricular tissues

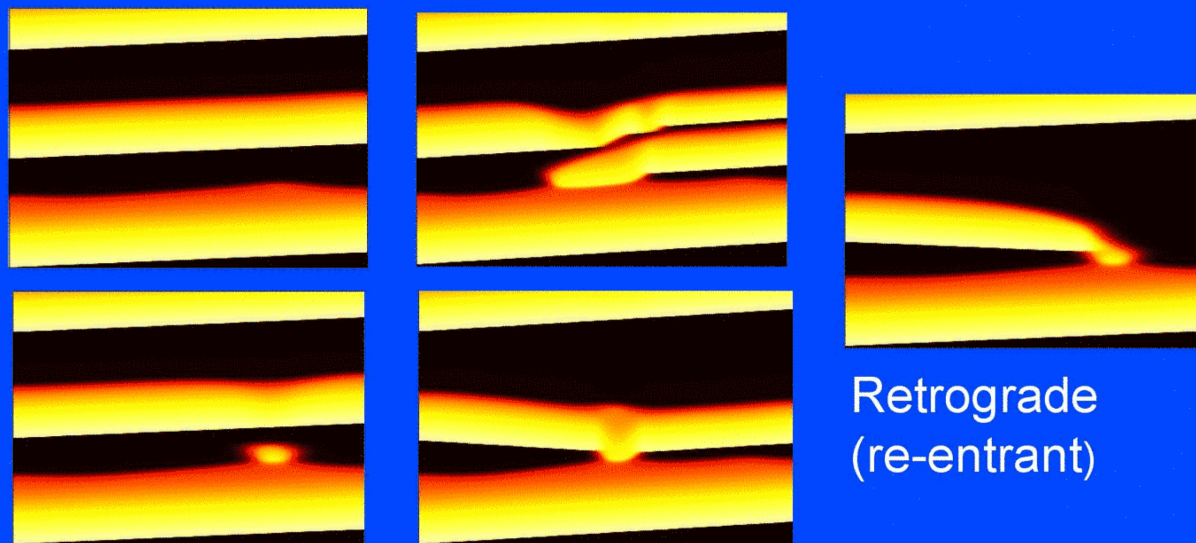
- Probability of arrhythmogenesis
- Transmural APD dispersion
- Sub-endocardial ischaemia and ST depression

Arrhythmogenesis: Noise induced early after-depolarisations



Clayton Holden Tong 2003 in press

Initiation of arrhythmias: Noise-induced propagating activity



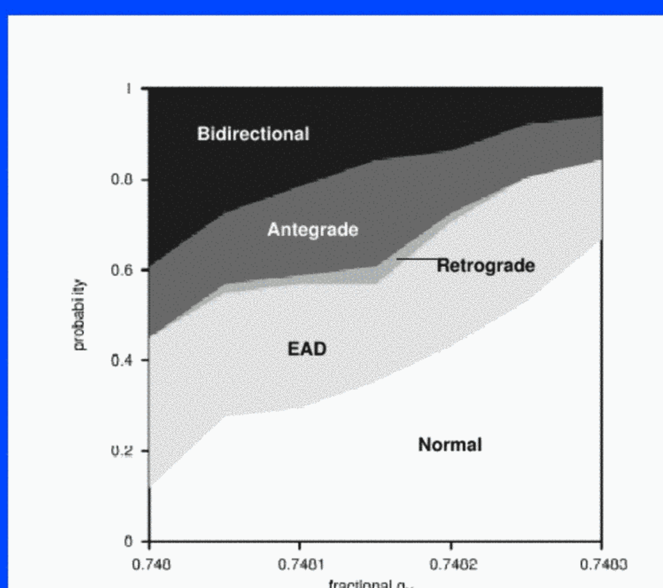
Retrograde (re-entrant)

Failure

Bi-directional or antegrade (ectopic)

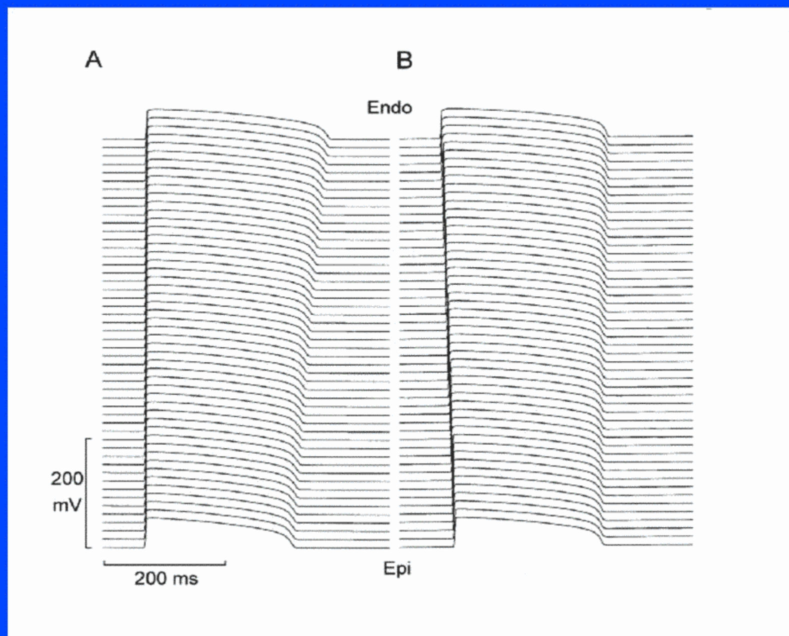
Clayton Holden Tong Int J Bifurc Chaos 13 (12) 2003

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



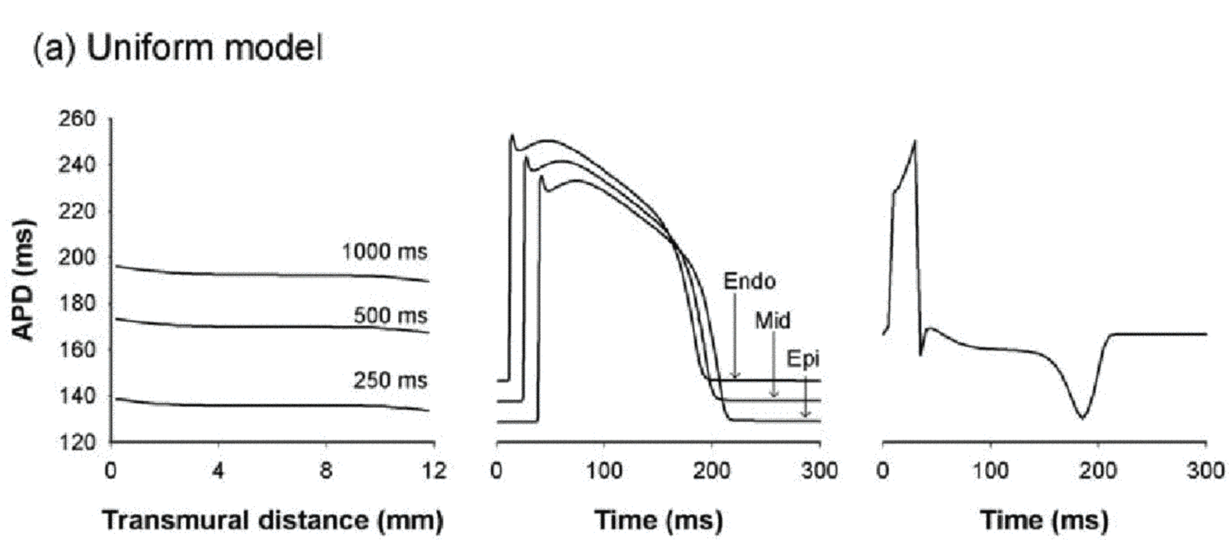
Clayton Holden Tong 2003 in press

Electrotonic couping reduces APD differences in heterogeneous wall

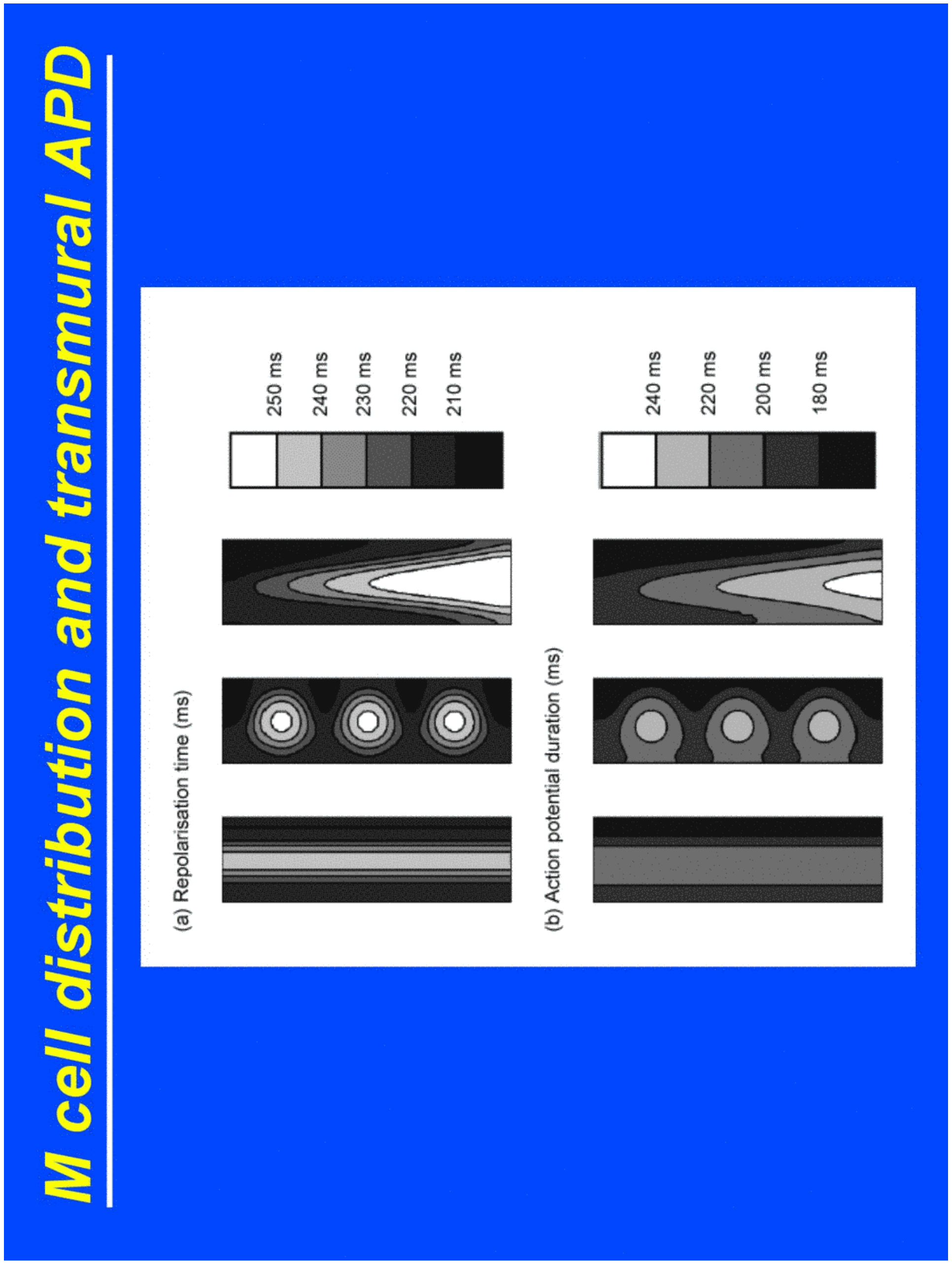


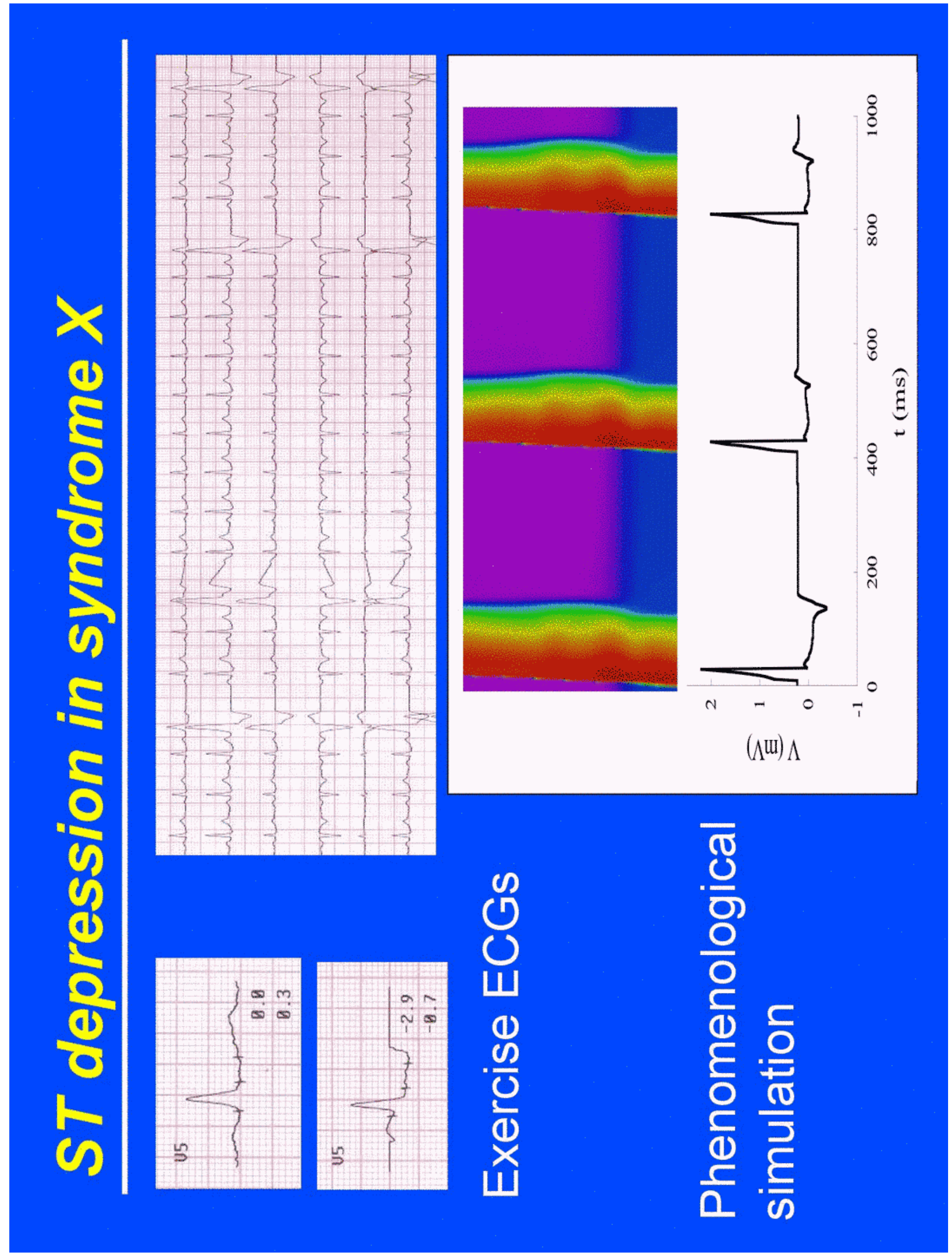
Holden Li Orchard 2001 EWGCCE 2001

Action potential duration dispersion in homogeneous 1D strand

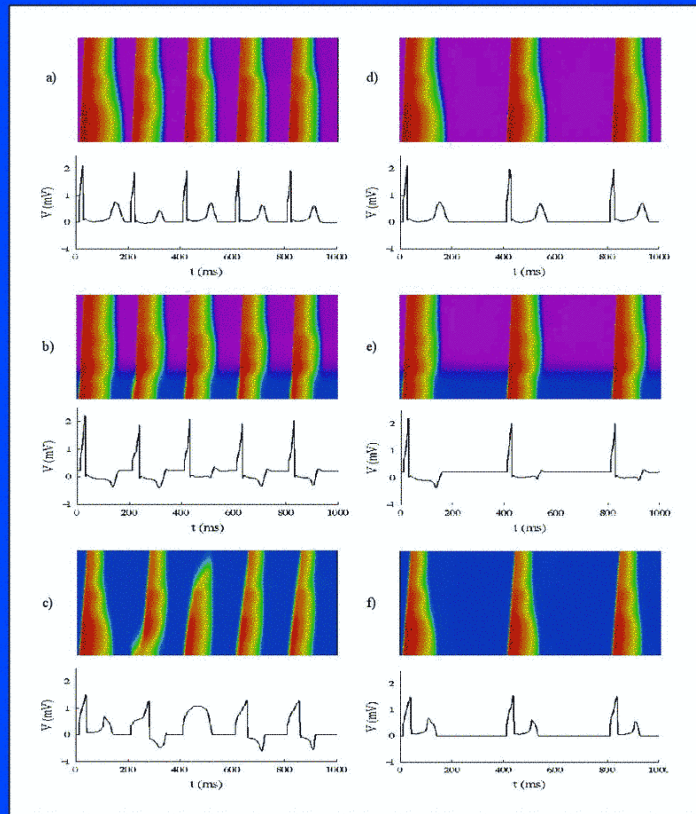


Clayton Holden Physics in Medicine and Biol (submitted)


M cell distribution and transmural APD
(a) Repolarisation time (ms)
250 ms
240 ms
230 ms
220 ms
210 ms
(b) Action potential duration (ms)
240 ms
220 ms
200 ms
180 ms

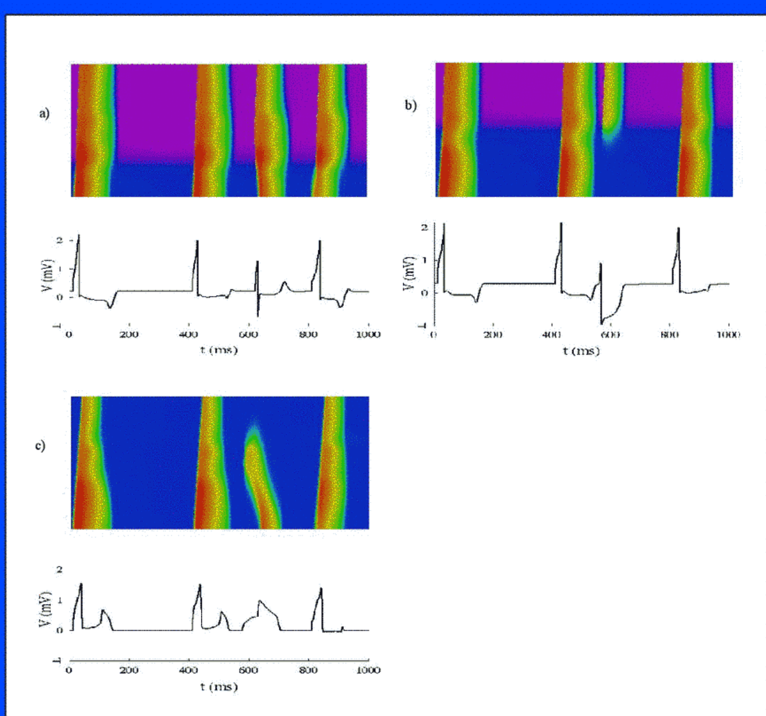

ST depression in syndrome X
Exercise ECGs
Phenomenological simulation
V (mV)
t (ms)

Partial transmural ischaemia a third endo-, M- and epicardial tissue



Space-time plots and pseudo-electrograms of transmural propagation in 1-D heterogeneous virtual ventricular wall. 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.
EWGCCE Utrecht 2003

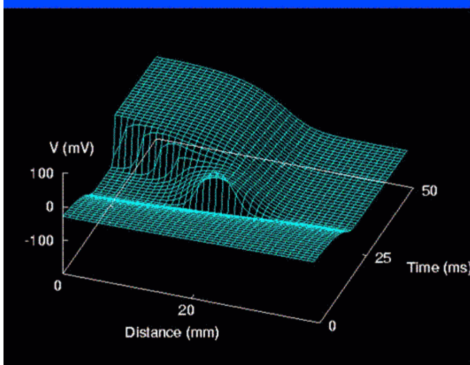
Focal initiation of arrhythmias

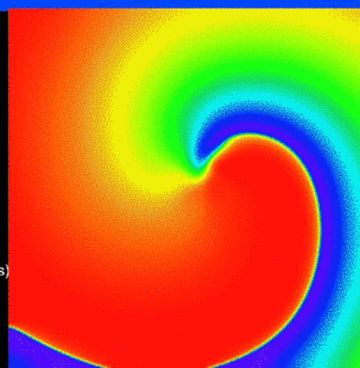


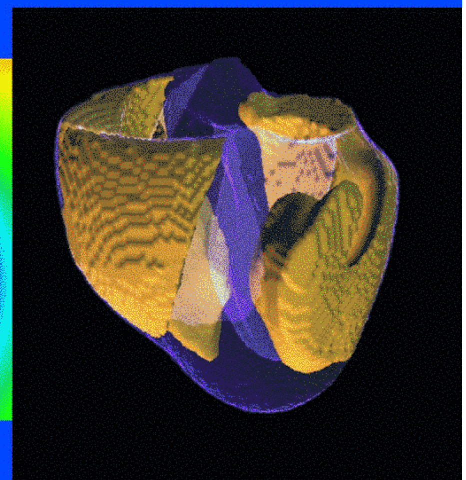
Space-time plots and electrograms of ectopic propagation in 1D heterogeneous virtual ventricular wall. Stimulation (S1) applied in subendocardial region at low-rate (BCL = 400 ms), ectopic (S2) initiated in mid M-cell region. (a) Bidirectional propagation; (b) unidirectional orthodromic propagation; (c) unidirectional antidromic propagation.

Re-entry

_ Stimuli in the vulnerable period give rise to re-entry

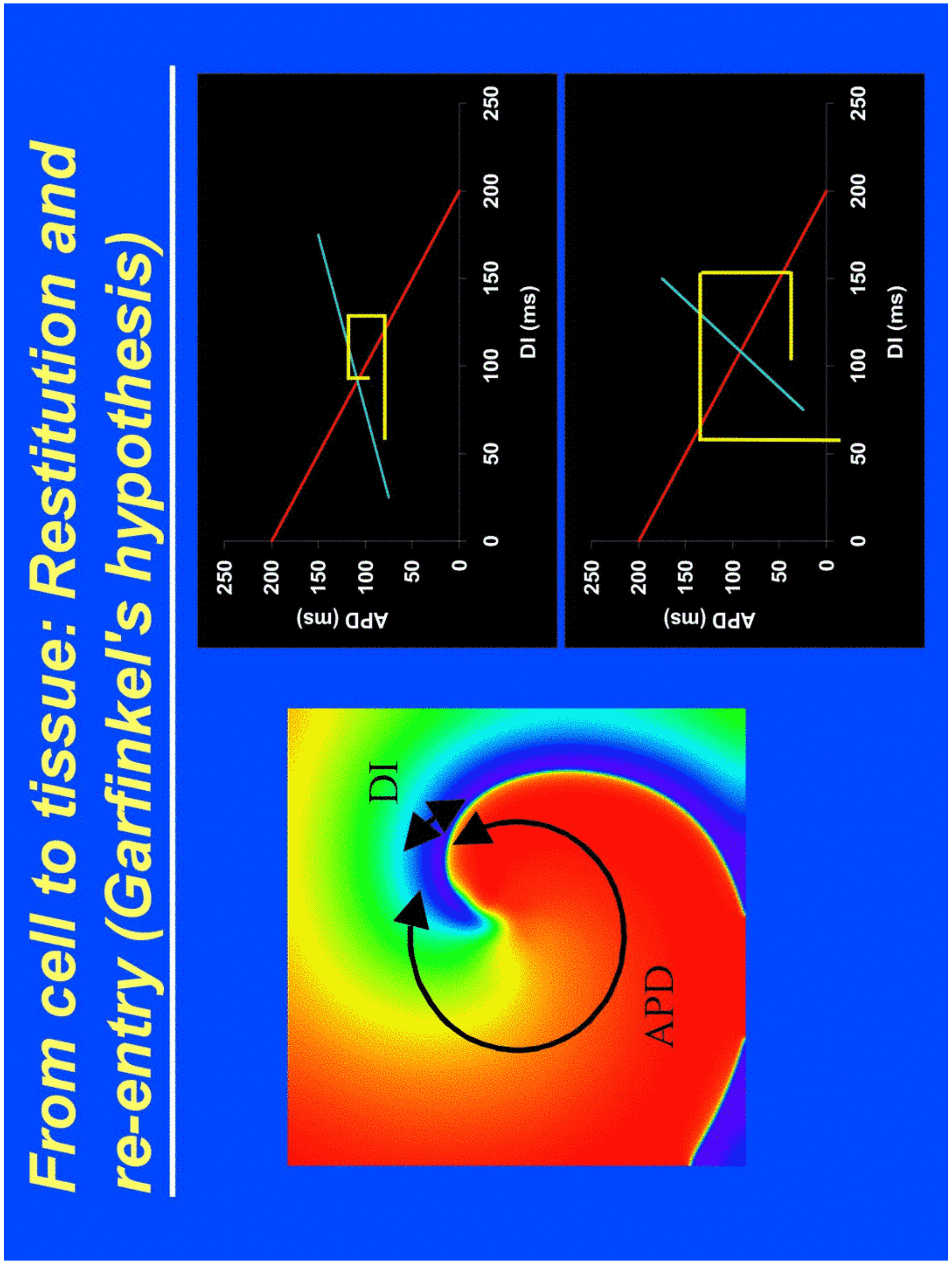


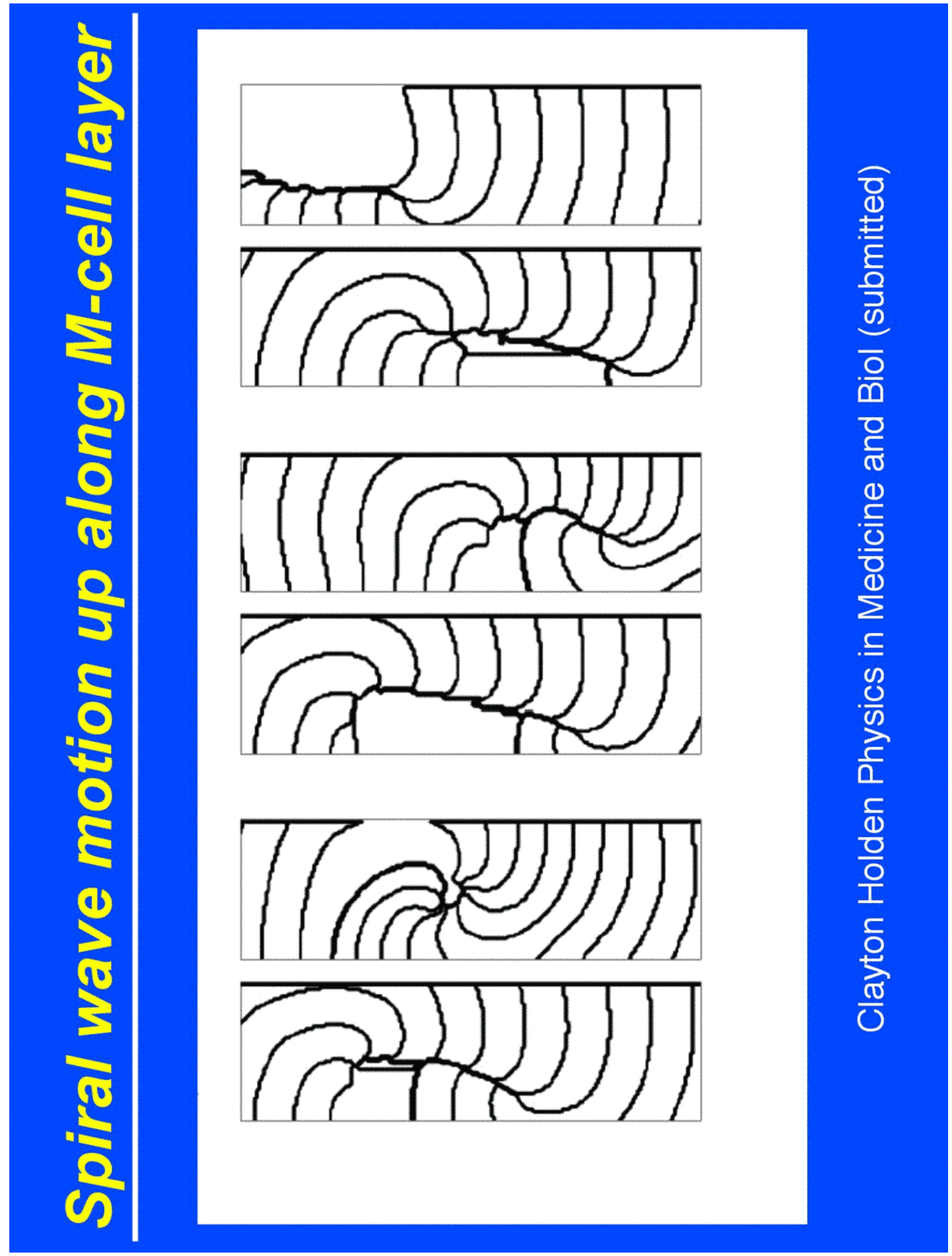


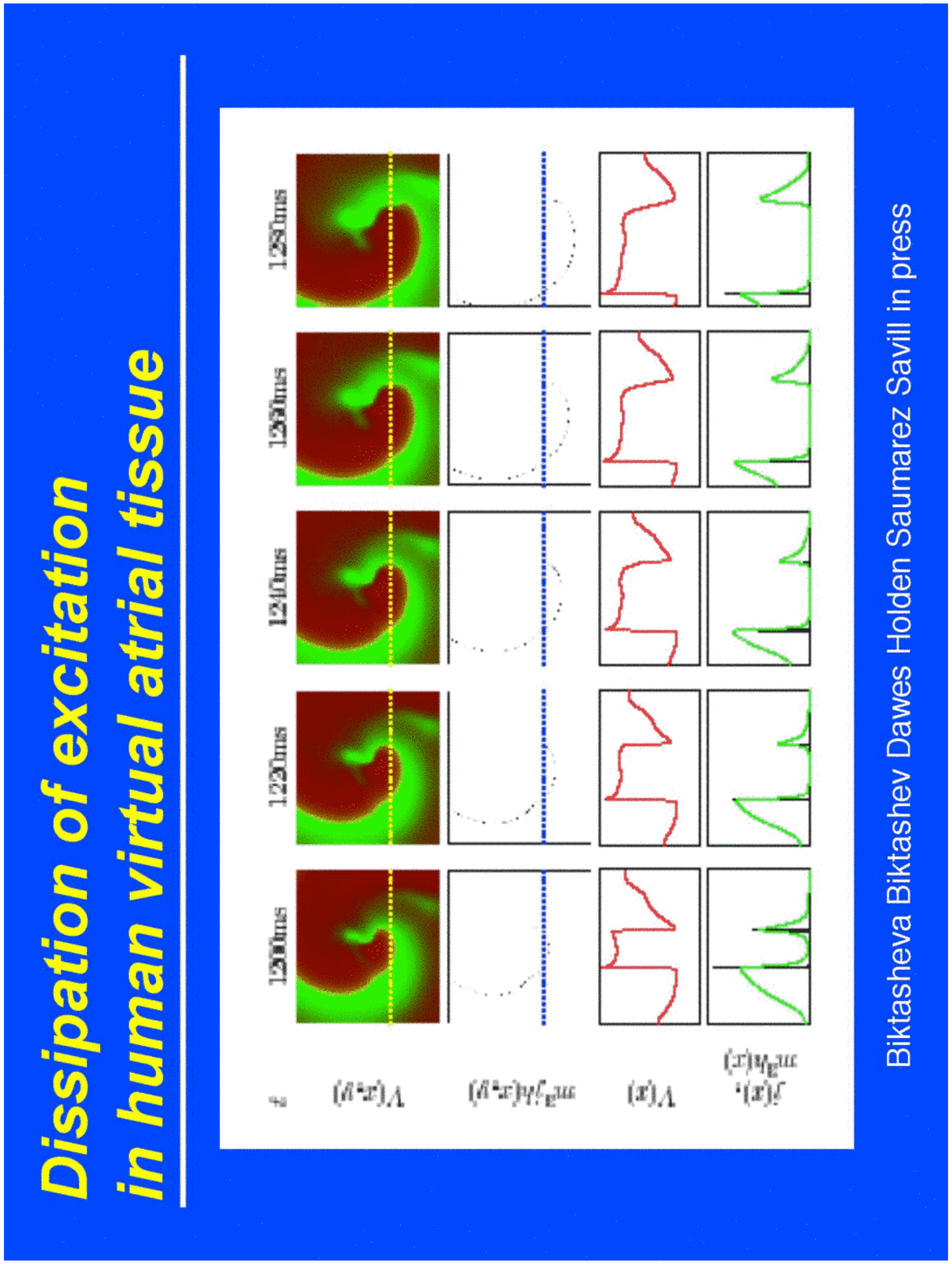


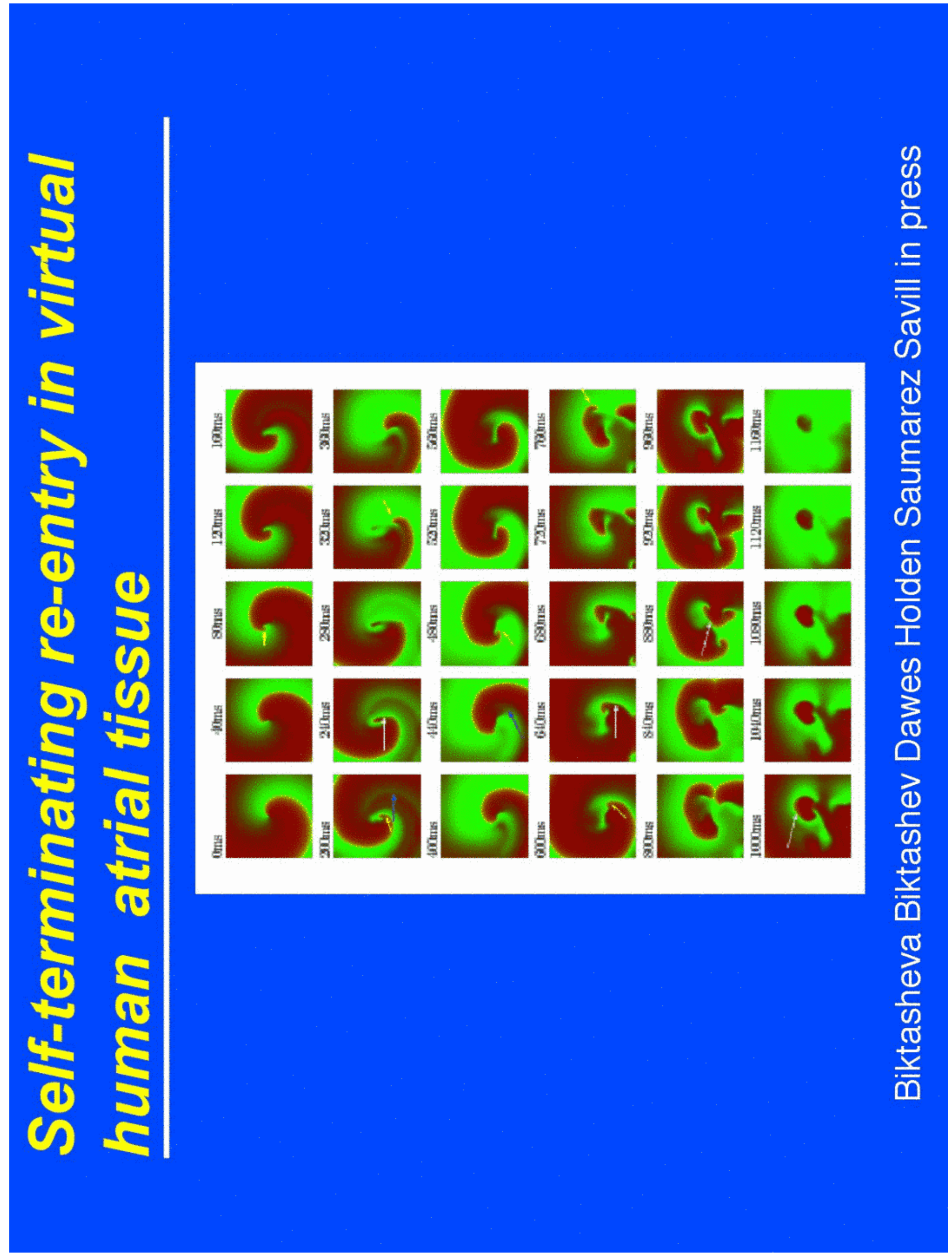
Propagation in two-dimensional virtual ventricular tissues

_ Restitution and re-entry
_ Intramural persistence of re-entry
_ Self-termination of re-entry by dissipation of excitation
_ LQT syndromes, meander and self-termination


From cell to tissue: Restitution and re-entry (Garfinkel's hypothesis)
DI
APD
APD (ms)
DI (ms)
0
50
100
150
200
250


Spiral wave motion up along M-cell layer
Clayton Holden Physics in Medicine and Biol (submitted)


Dissipation of excitation
in human virtual atrial tissue
1200ms
1220ms
1240ms
1260ms
1280ms
Biktasheva Biktashev Dawes Holden Saumarez Savill in press


Self-terminating re-entry in virtual
human atrial tissue
Biktasheva Biktashev Dawes Holden Saumarez Savill in press

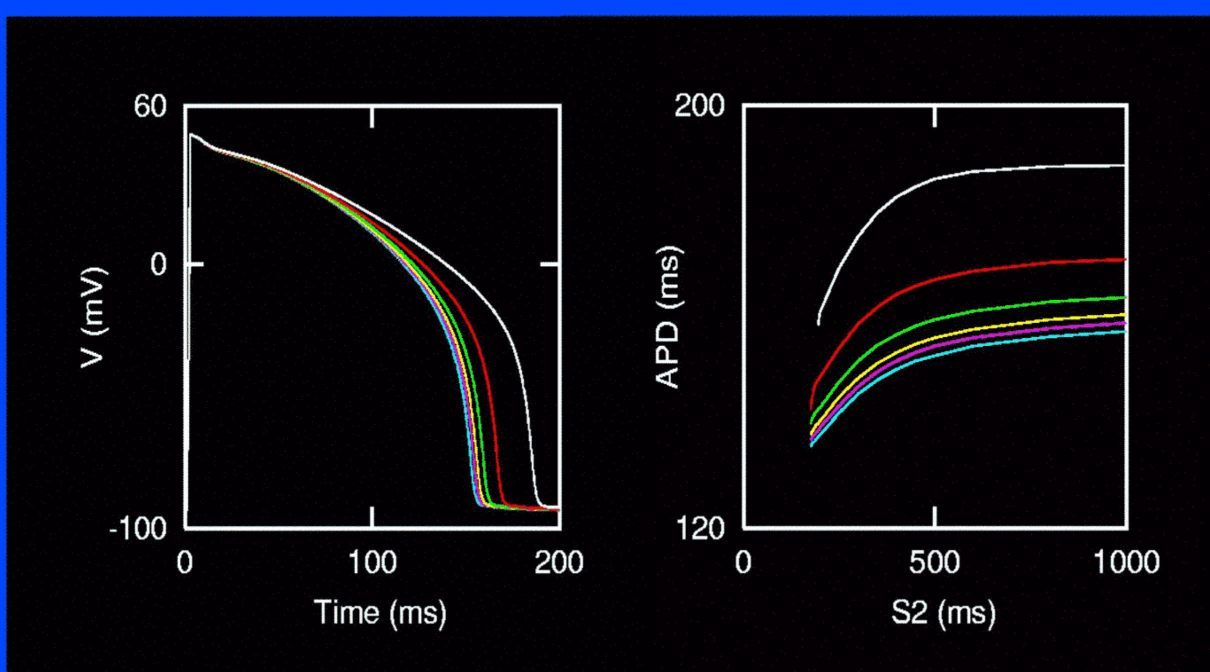
Inherited LQT syndromes

- Prolonged repolarisation
- Increased likelihood of ventricular arhythmia
- Associated with gene mutations

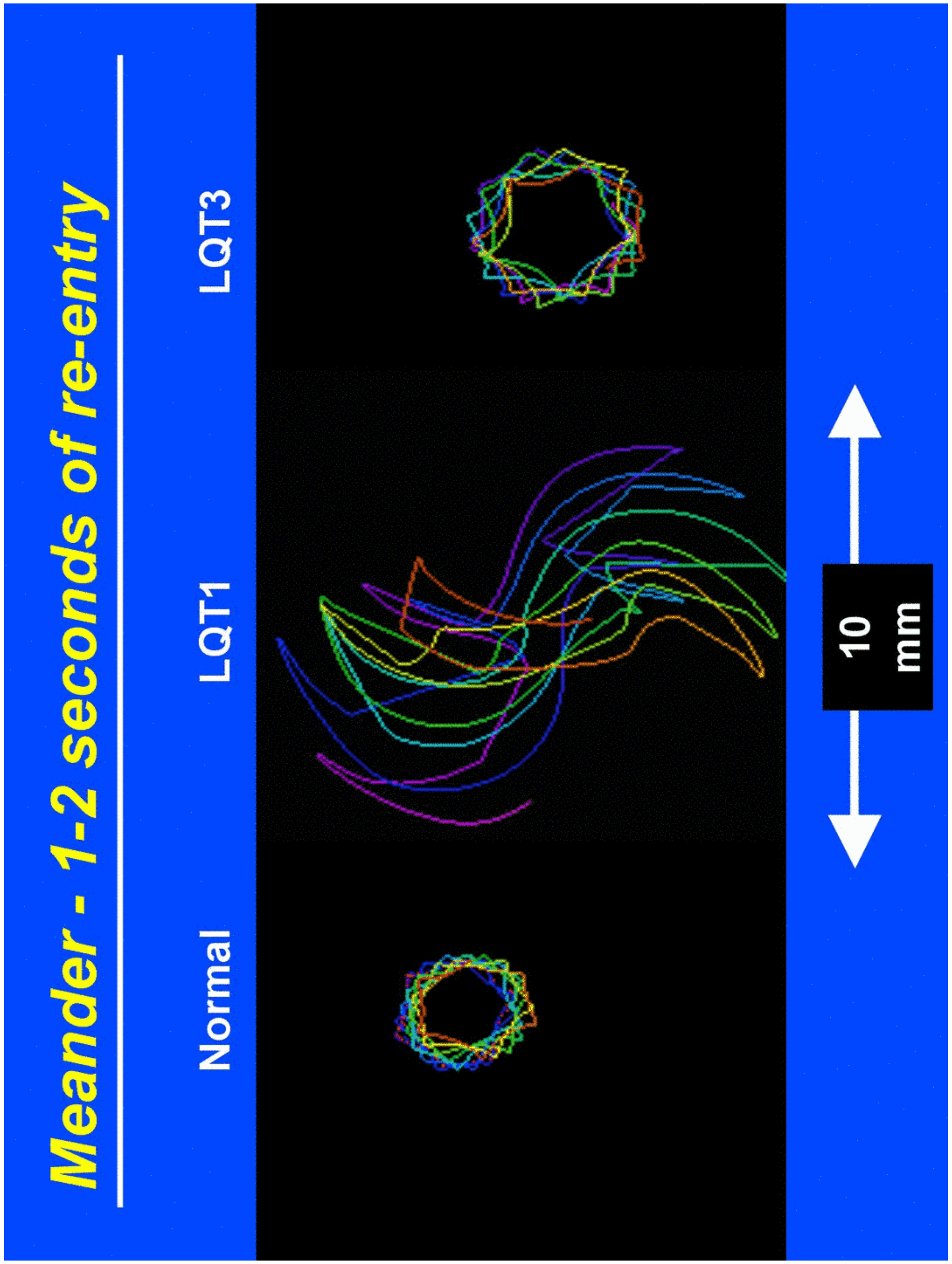
- LQT1 - inhibits I Ks channels
- LQT2 - inhibits I Kr channels
- LQT3 - prevents complete inactivation of I Na

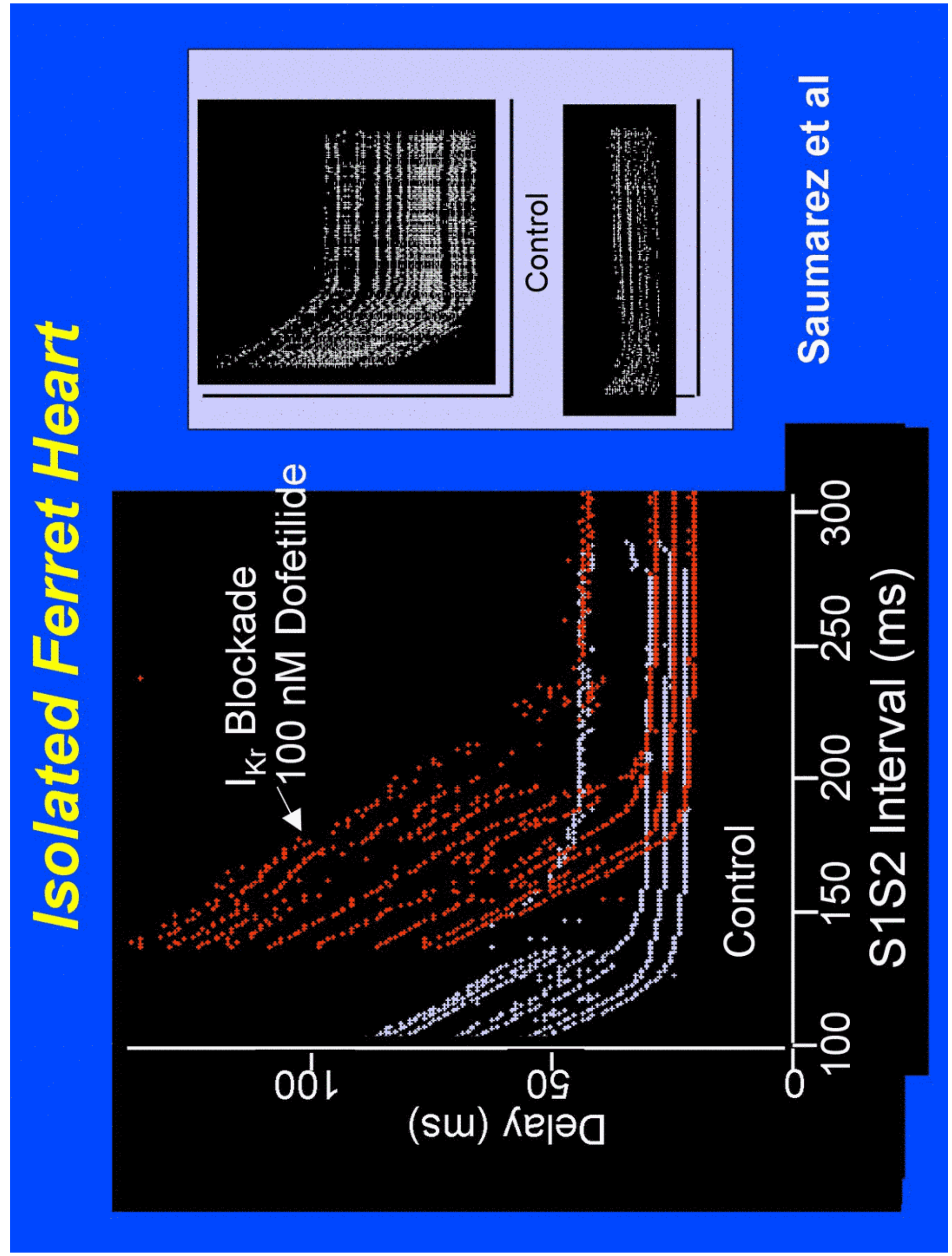
Patients with LQT3 are more likely than patients with LQT1 to suffer arrhythmias, but LQT1 arrhythmias are more likely to self-terminate

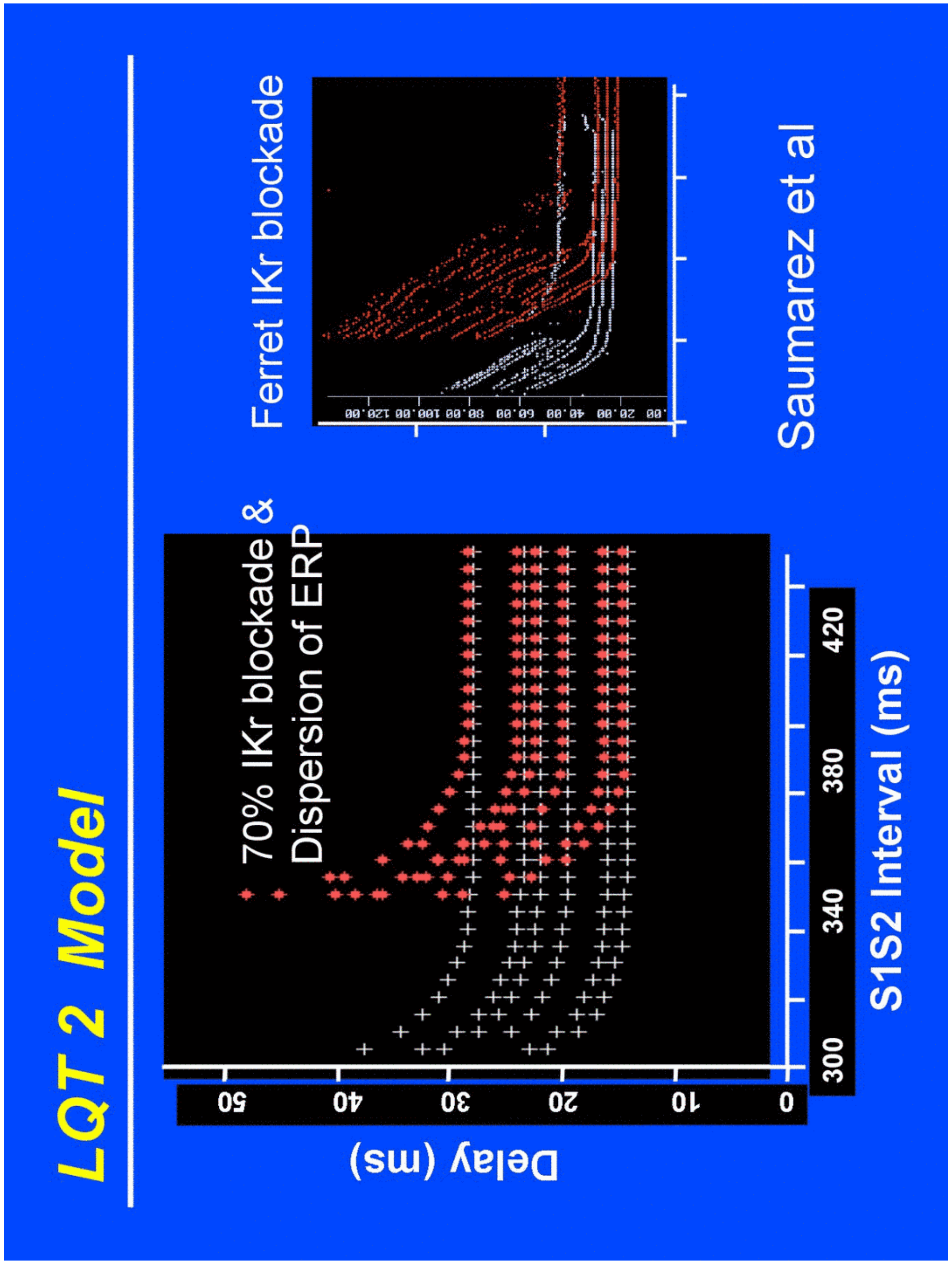
LQT3 simulation - increase gB on APD restitution



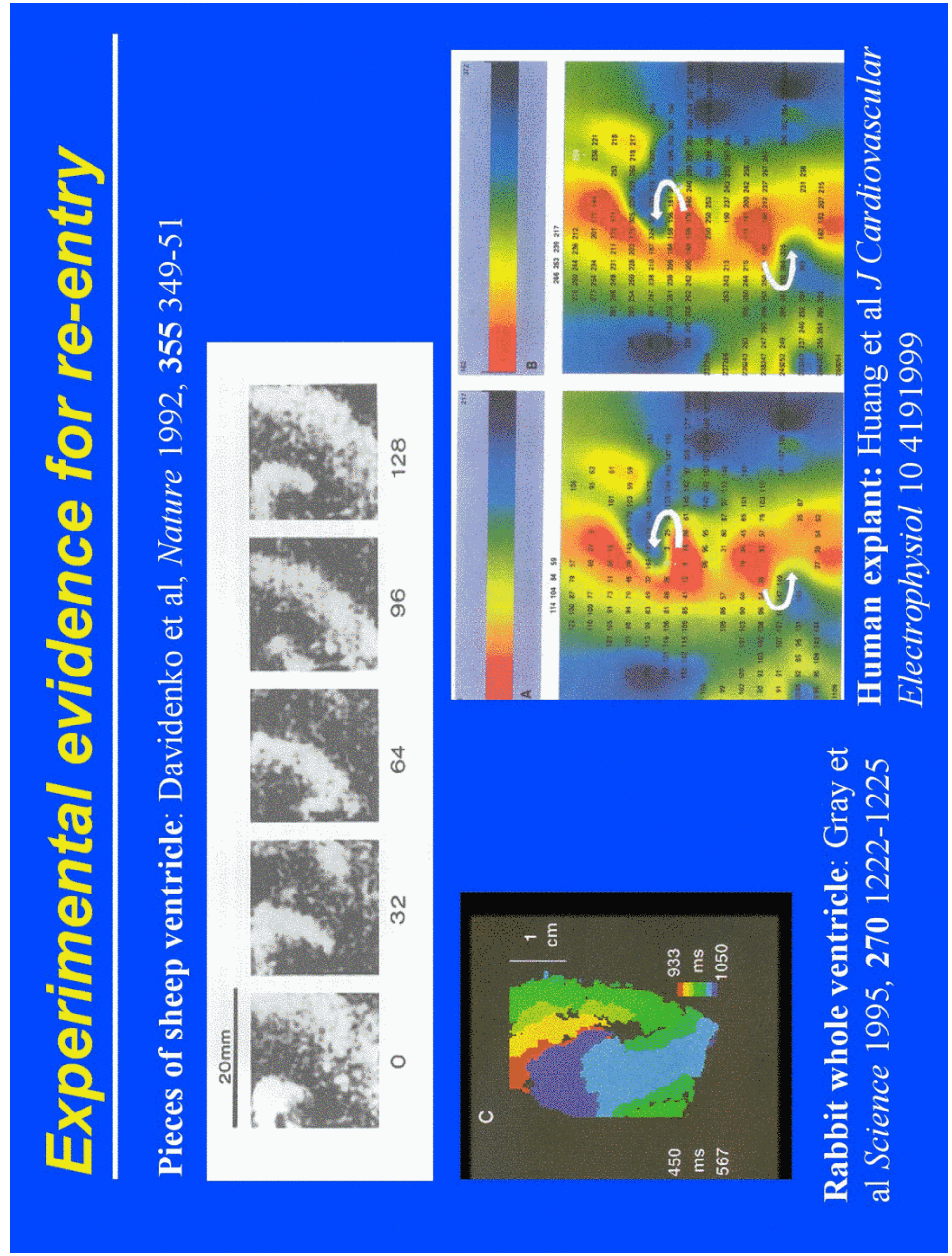
Clayton Bailey Biktashev Holden J Theoretical Biol (2001) 208 215-225


Meander - 1-2 seconds of re-entry
Normal
LQT1
LQT3
10 mm


Isolated Ferret Heart
I_{Kr} Blockade
100 nM Dofetilide
Control
Delay (ms)
0
50
100
100
150
200
250
300
S1S2 Interval (ms)
Control
Saumarez et al



LQT 2 Model
70% IKr blockade &
Dispersion of ERP
Delay (ms)
0
10
20
30
40
50
300
340
380
420
S1S2 Interval (ms)
Ferret IKr blockade
Saumarez et al



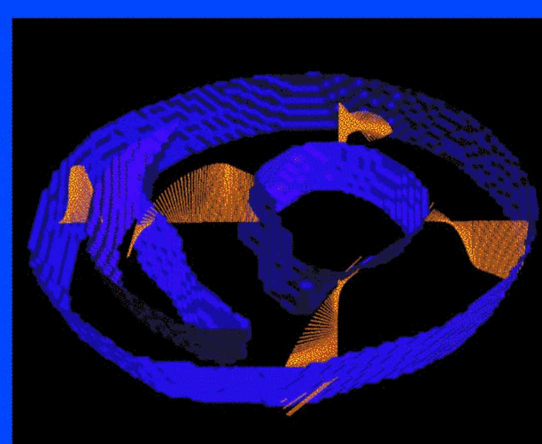
Experimental evidence for re-entry
Pieces of sheep ventricle: Davidenko et al, *Nature* 1992, **355** 349-51
20mm
0
32
64
96
128
C
1 cm
450 ms 567
933 ms 1050
A
B
Rabbit whole ventricle: Gray et al *Science* 1995, **270** 1222-1225
Human explant: Huang et al *J Cardiovascular Electrophysiol* 10 4191999

Propagation in three-dimensional virtual ventricular tissues

- Ventricular anisotropy
- Normal activation
- Filament breakdown
- Domain structure of VF
- Defibrillation strategies

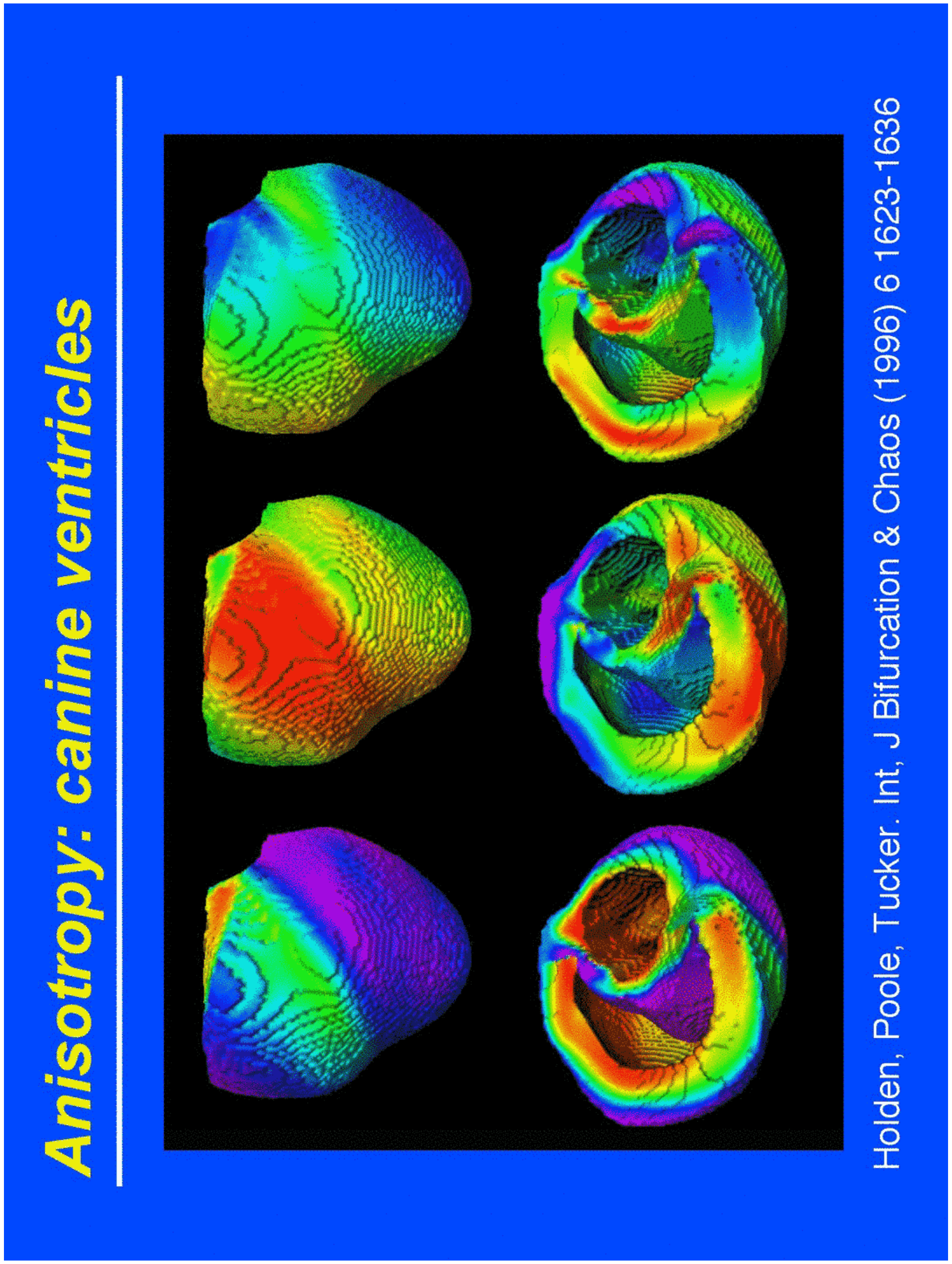
Anisotropy of cardiac muscle

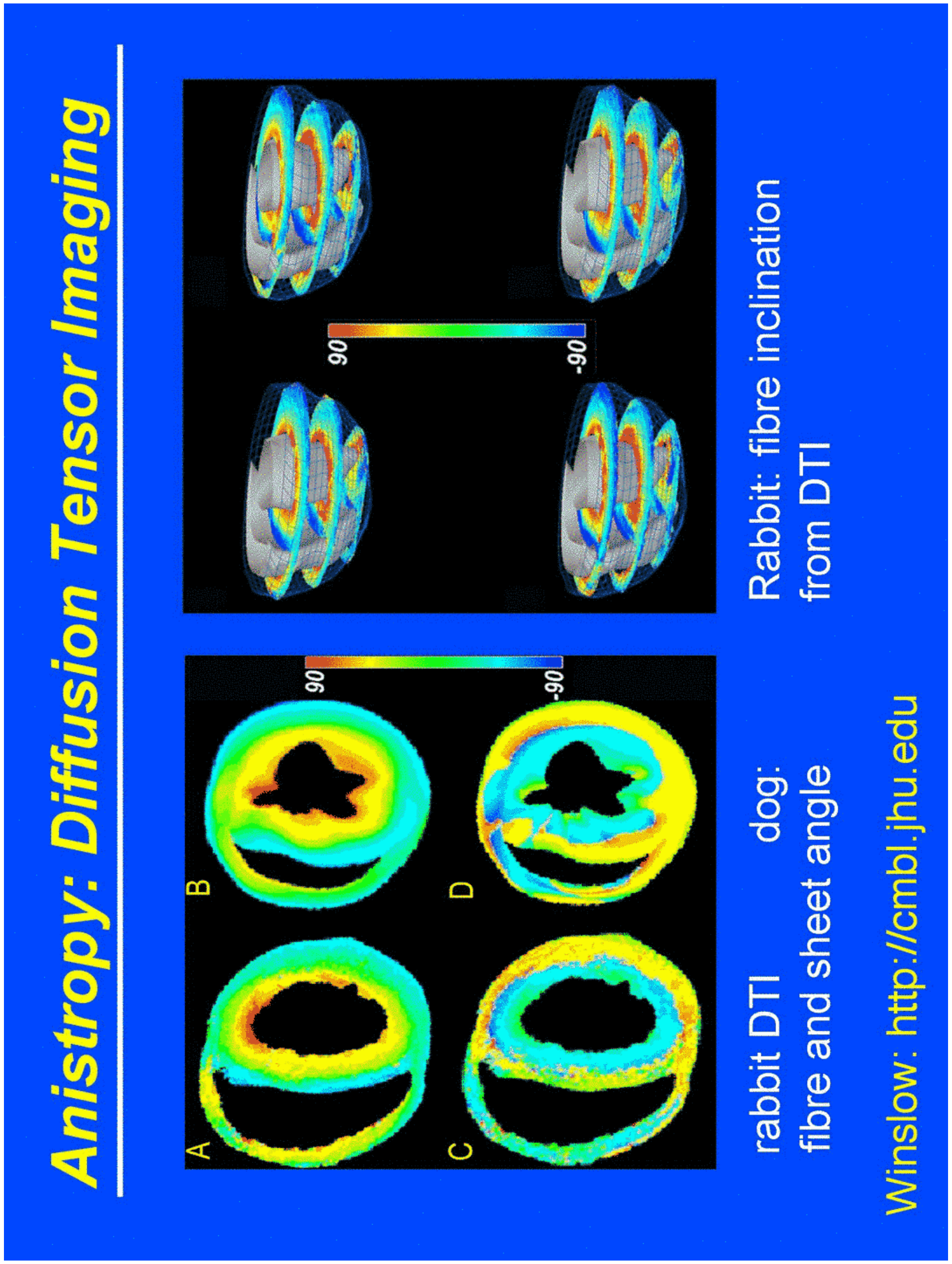
Cardiac cells are arranged in fibres and electrically connected to nearest neighbours by gap junctions at their ends



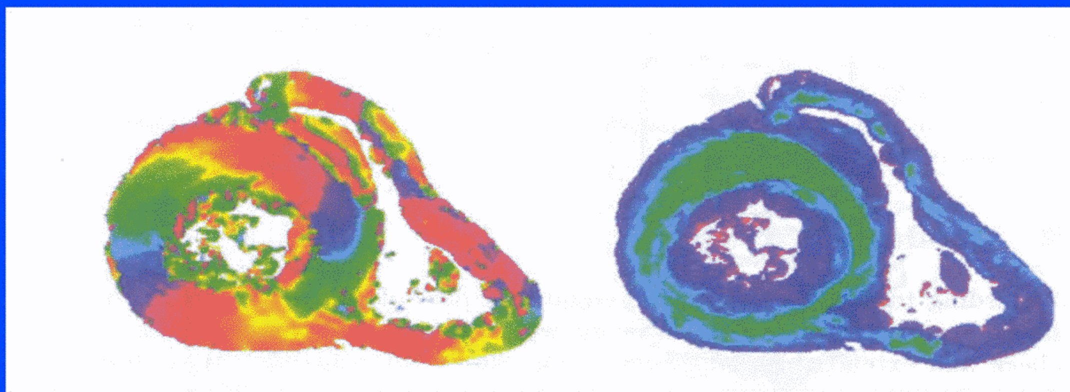
Rotational transmural anisotropy Fibre orientation varies within the ventricular wall.

$$C_m \frac{\partial V_m}{\partial t} = \nabla(D\,\nabla V_m) - I_{ion}$$


Anisotropy: canine ventricles
Holden, Poole, Tucker. Int. J Bifurcation & Chaos (1996) 6 1623-1636


Anistropy: Diffusion Tensor Imaging
A
B
C
D
90
-90
90
-90
rabbit DTI
dog:
fibre and sheet angle
Rabbit: fibre inclination
from DTI
Winslow: http://cmbl.jhu.edu

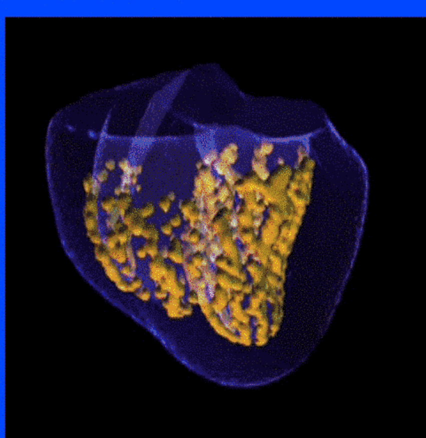
Anisotropy: human foetal heart, by plane of polarisation



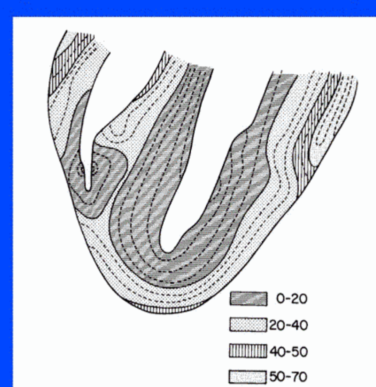
Mourad et al (2001) In Functional Imaging and Modeling of the Heart, Lecture Notes in Compter Science 2230 p 32-38 Springer

Propagation of a normal beat

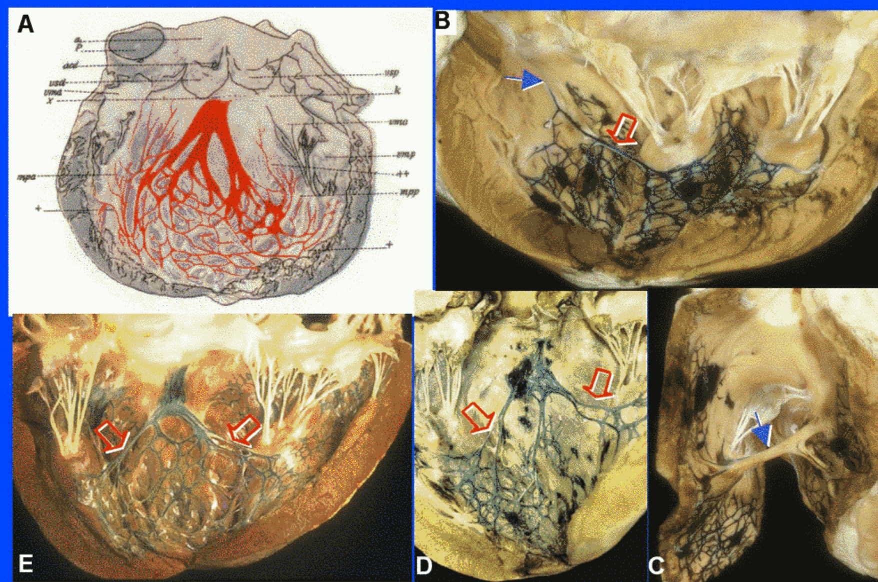
Simulation - canine ventricle



Experiment - human ventricle (Durrer et al 1970)

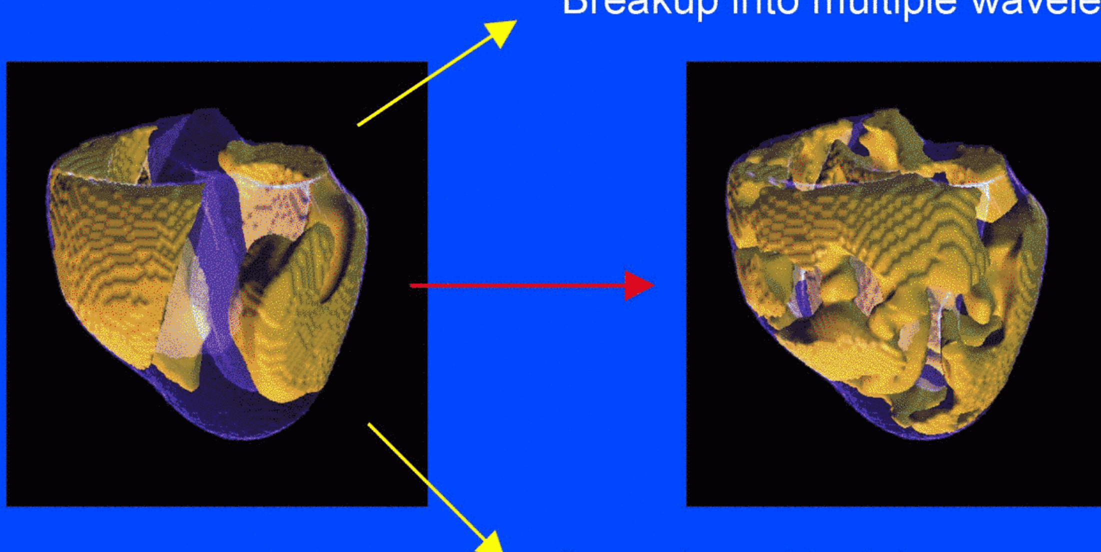


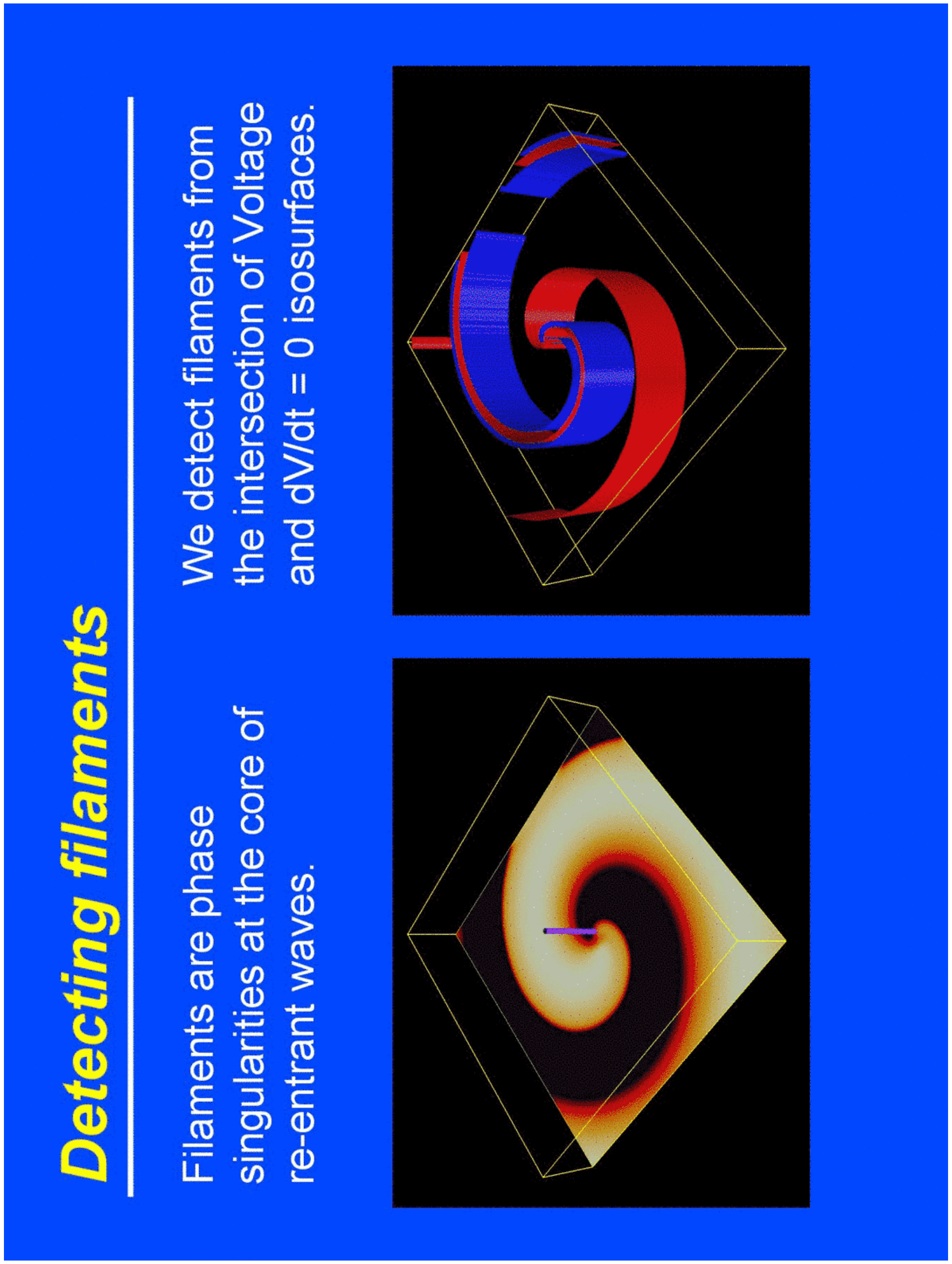
Purkinje fibre distribution

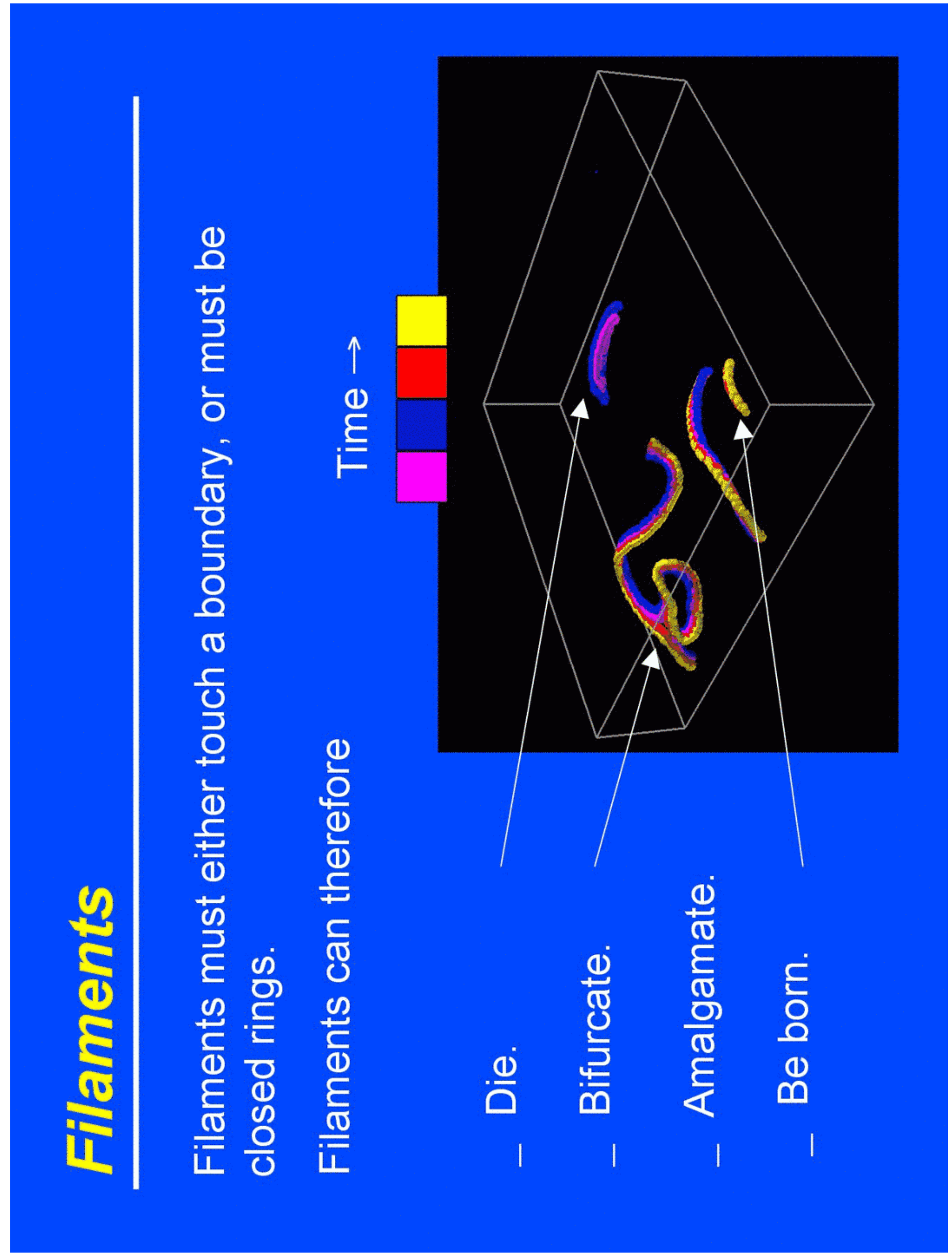


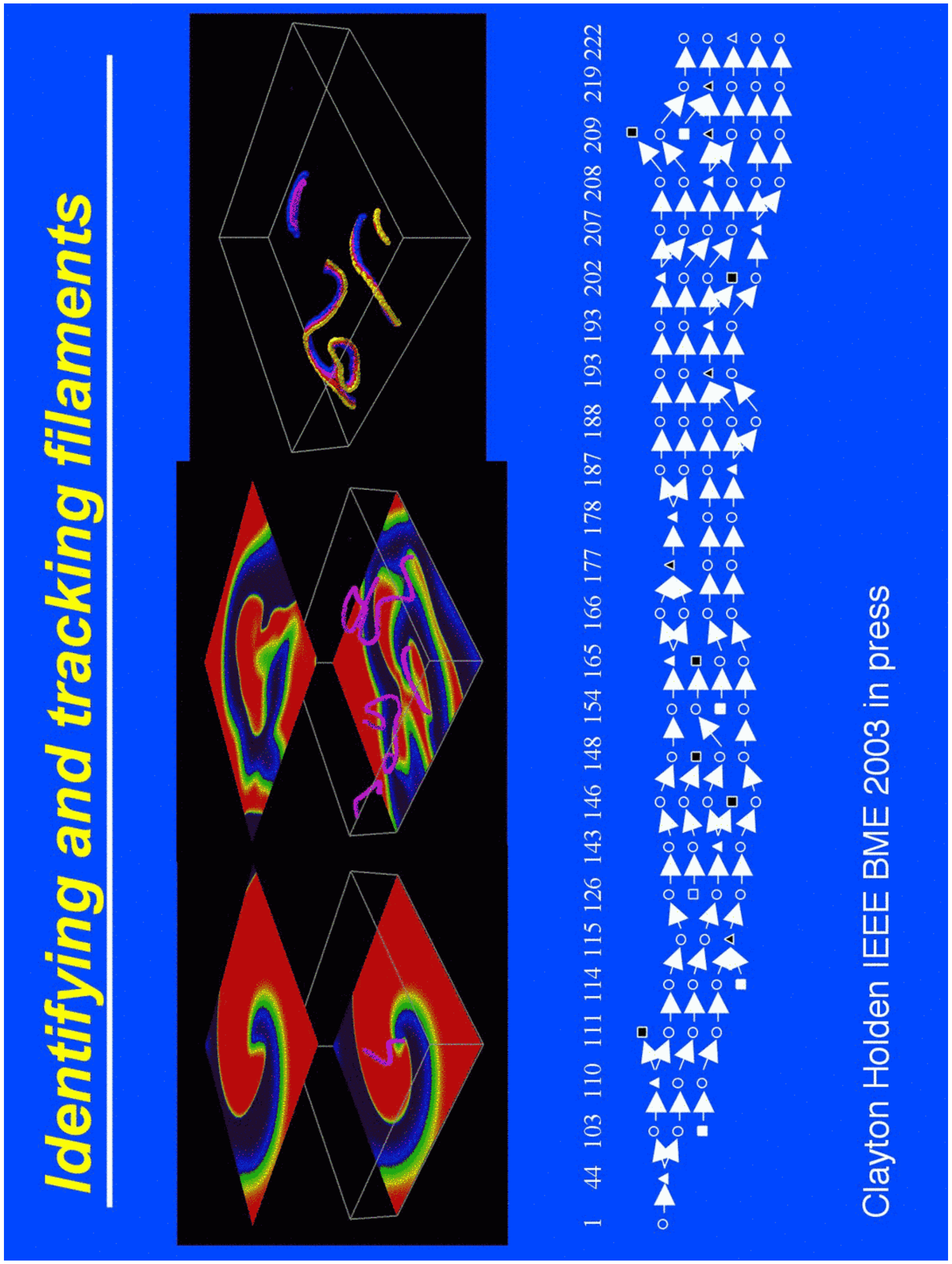
Yen Ho et al Int J Bif Chaos in press 2003 13(12)

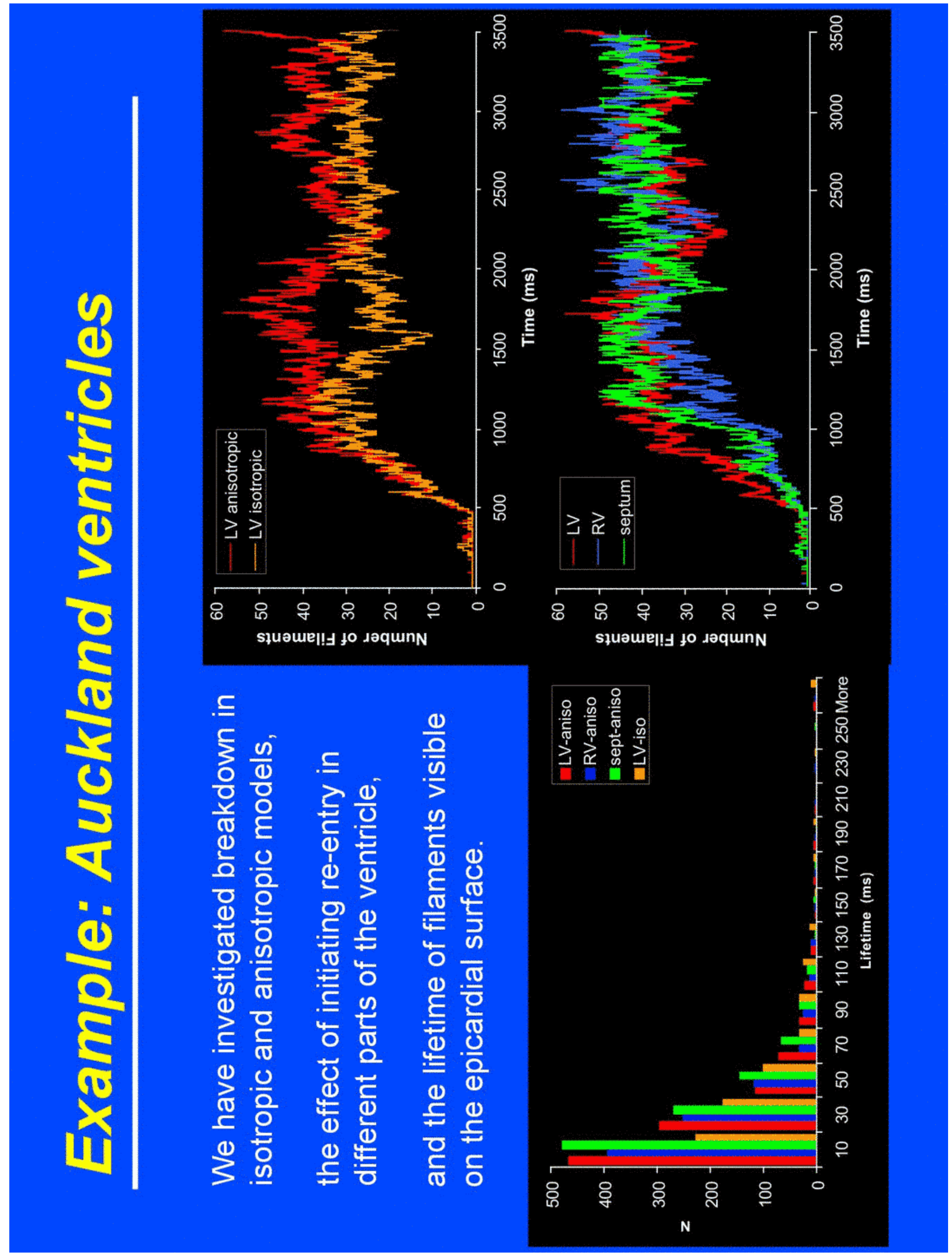
Possible mechanisms of VF




Detecting filaments
Filaments are phase singularities at the core of re-entrant waves.
We detect filaments from the intersection of Voltage and dV/dt = 0 isosurfaces.

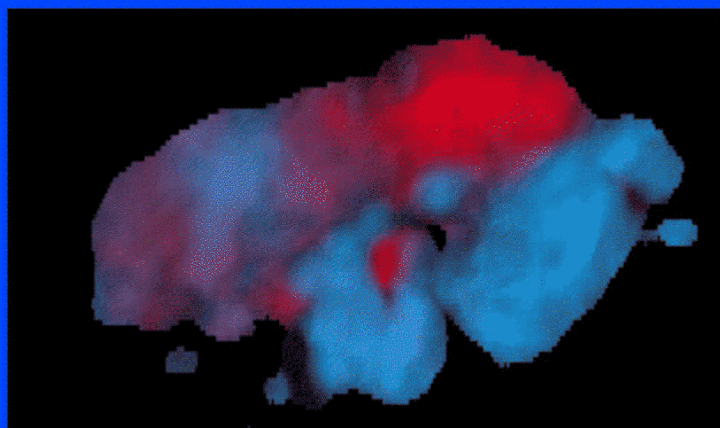

Filaments
Filaments must either touch a boundary, or must be closed rings.
Filaments can therefore
– Die.
– Bifurcate.
– Amalgamate.
– Be born.
Time →


Identifying and tracking filaments
1 44 103 110 111 114 115 126 143 146 148 154 165 166 177 178 187 188 193 193 202 207 208 209 219 222
Clayton Holden IEEE BME 2003 in press


Example: Auckland ventricles
We have investigated breakdown in isotropic and anisotropic models,
the effect of initiating re-entry in different parts of the ventricle,
and the lifetime of filaments visible on the epicardial surface.
LV anisotropic
LV isotropic
Number of Filaments
Time (ms)
LV
RV
septum
LV-aniso
RV-aniso
sept-aniso
LV-iso
N
Lifetime (ms)

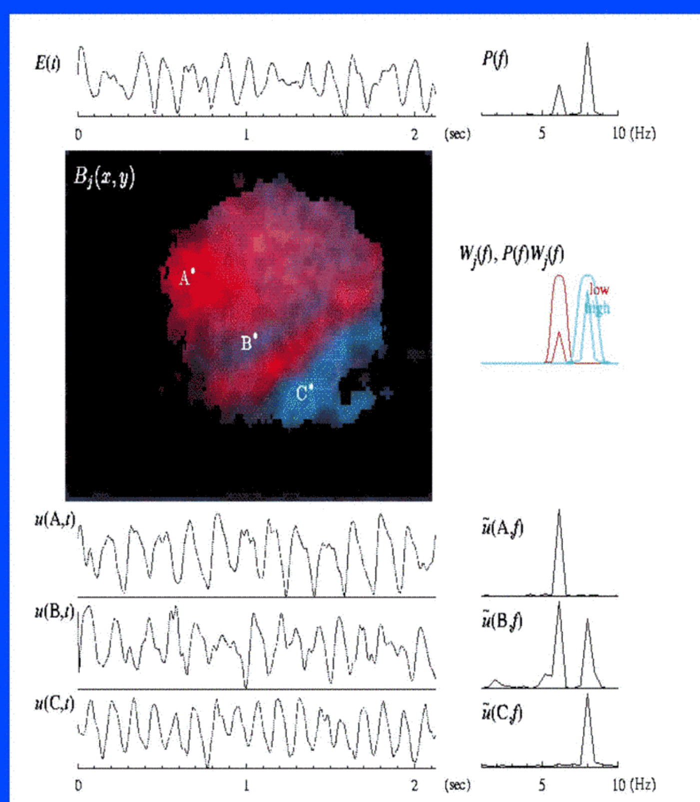
Fibrillatory conduction with domains

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

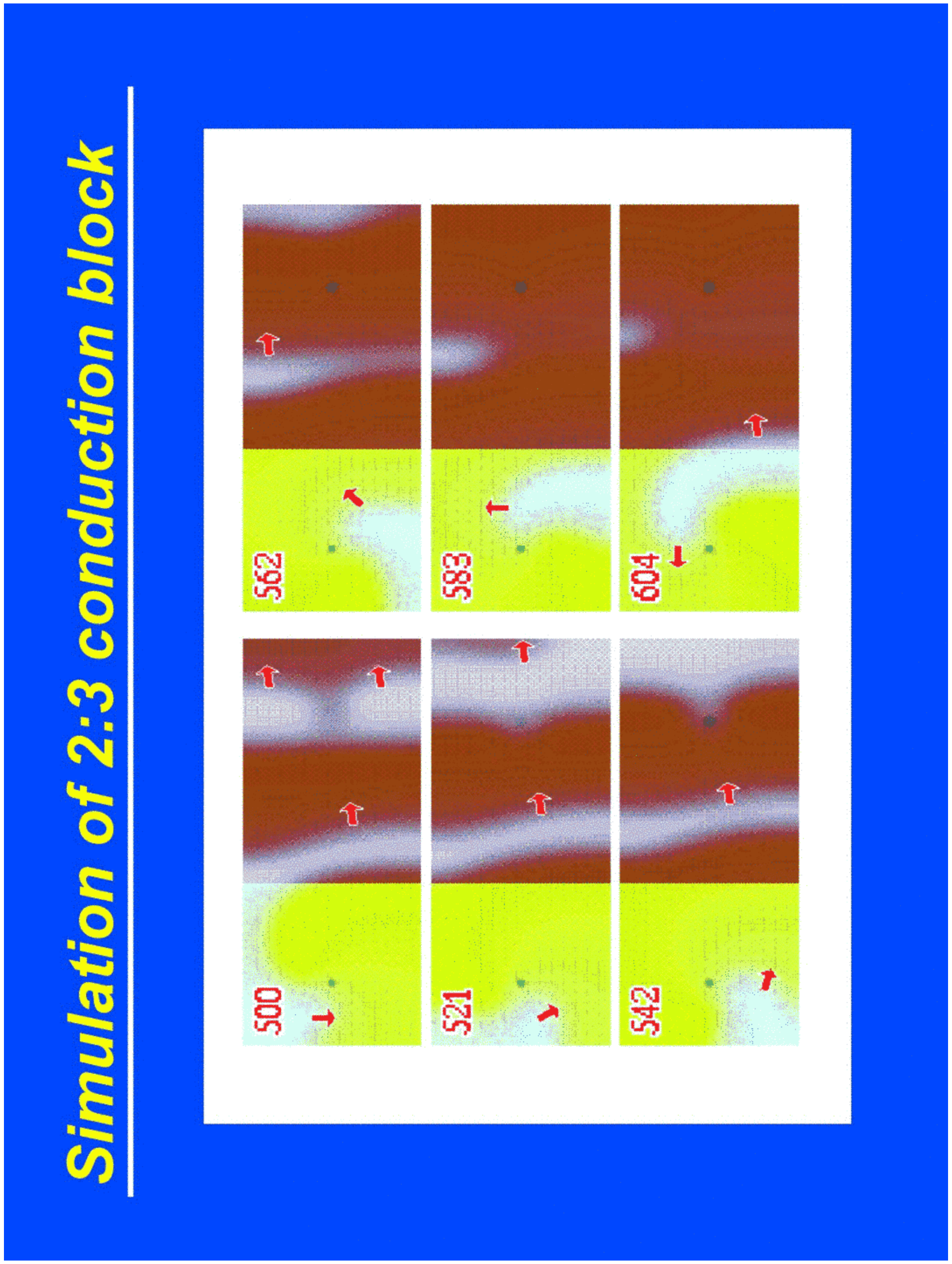


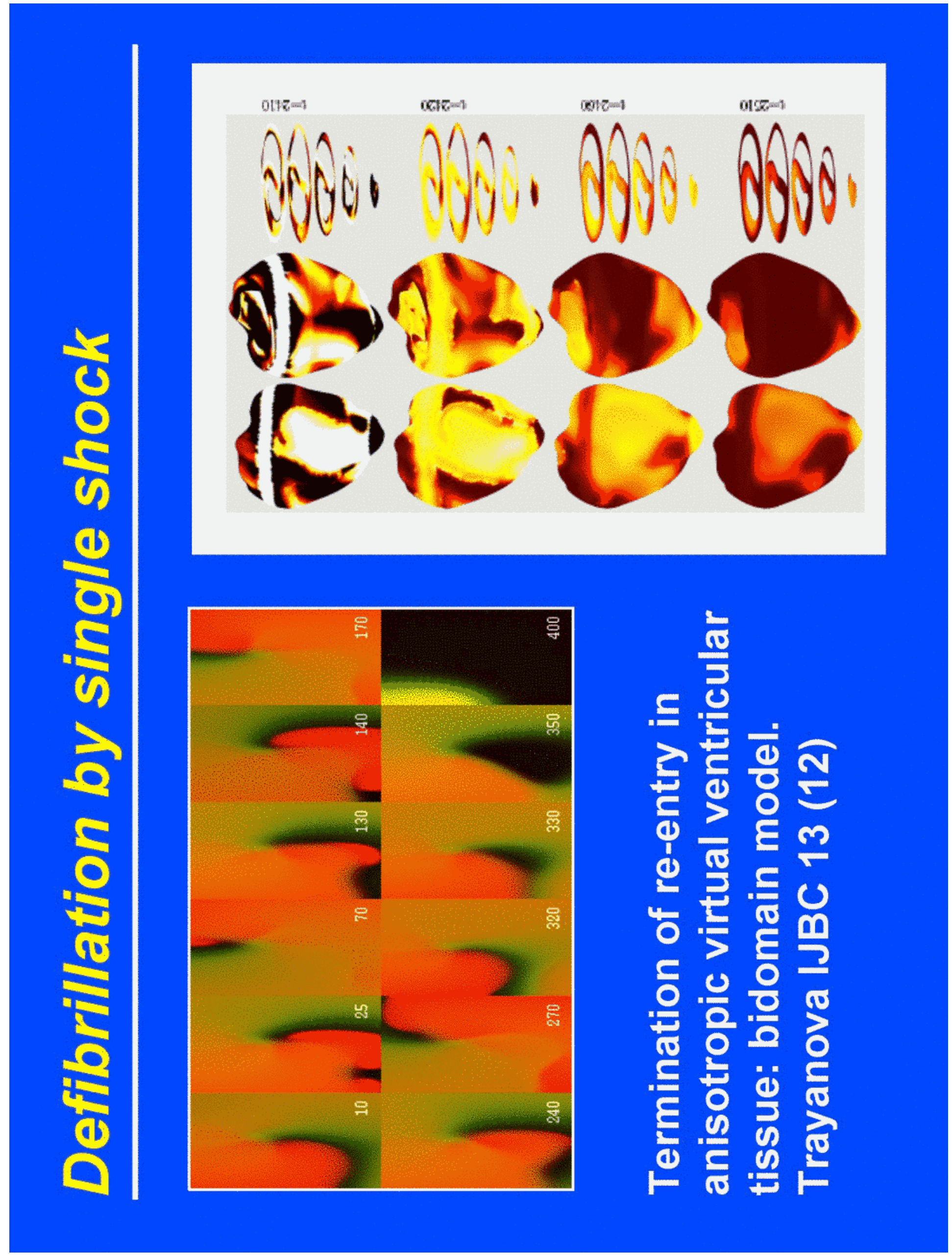
- Could the domains be driven by a single re-entrant source?

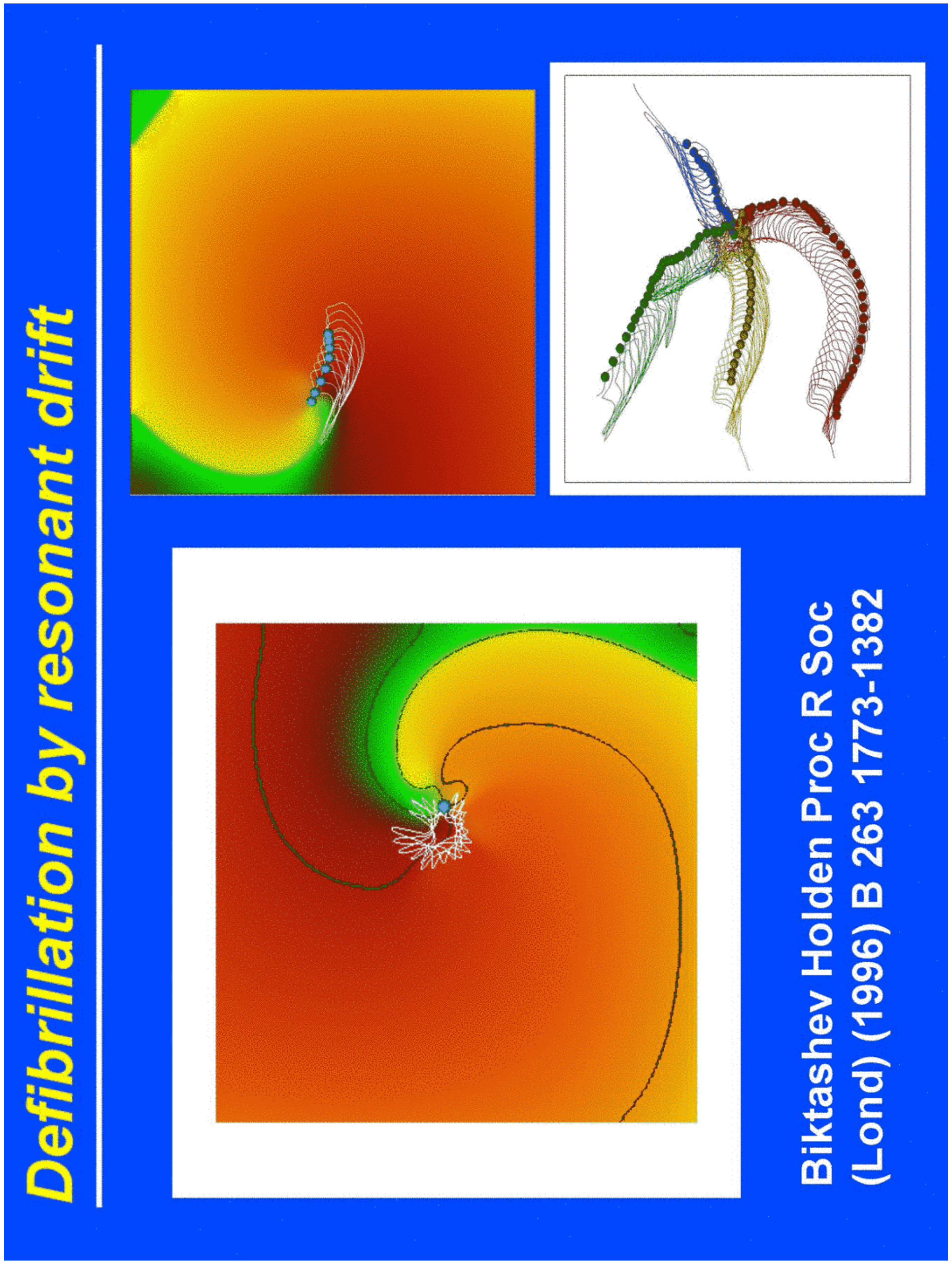
Domains in VF

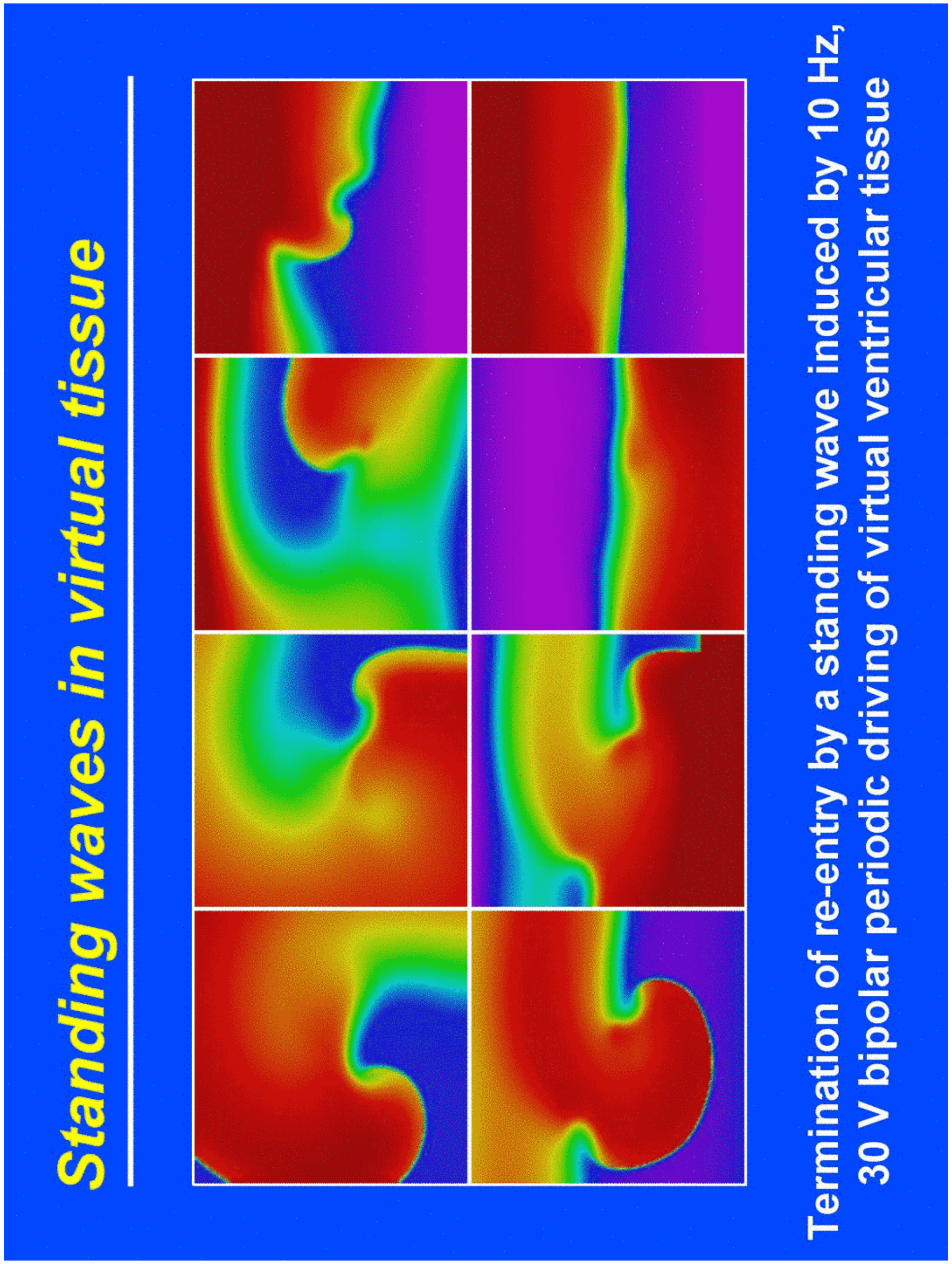


Biktashev Holden
Mironov Pertsov Zaitsev
Int J Bifurcation & Chaos
(2001) 11 1035-1051

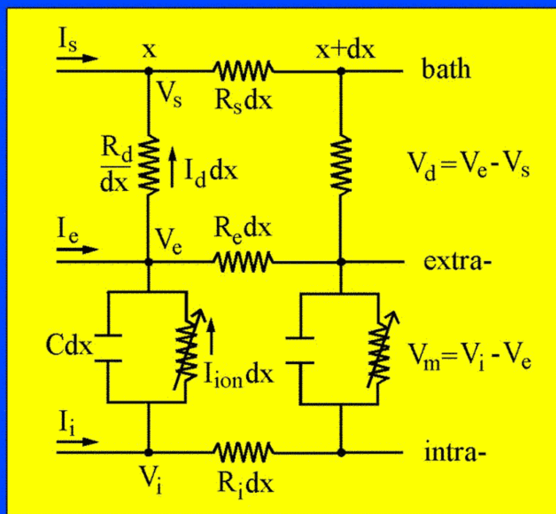

Simulation of 2:3 conduction block
500
521
542
562
583
604

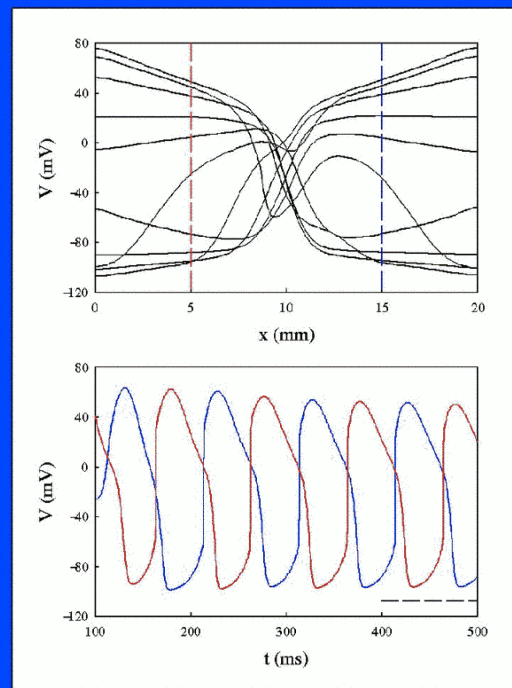

Defibrillation by single shock
10
25
70
130
140
170
240
270
320
330
350
400
Termination of re-entry in anisotropic virtual ventricular tissue: bidomain model.
Trayanova IJBC 13 (12)


Defibrillation by resonant drift
Biktashev Holden Proc R Soc
(Lond) (1996) B 263 1773-1382


Standing waves in virtual tissue
Termination of re-entry by a standing wave induced by 10 Hz,
30 V bipolar periodic driving of virtual ventricular tissue

Bidomain virtual tissue with a bath

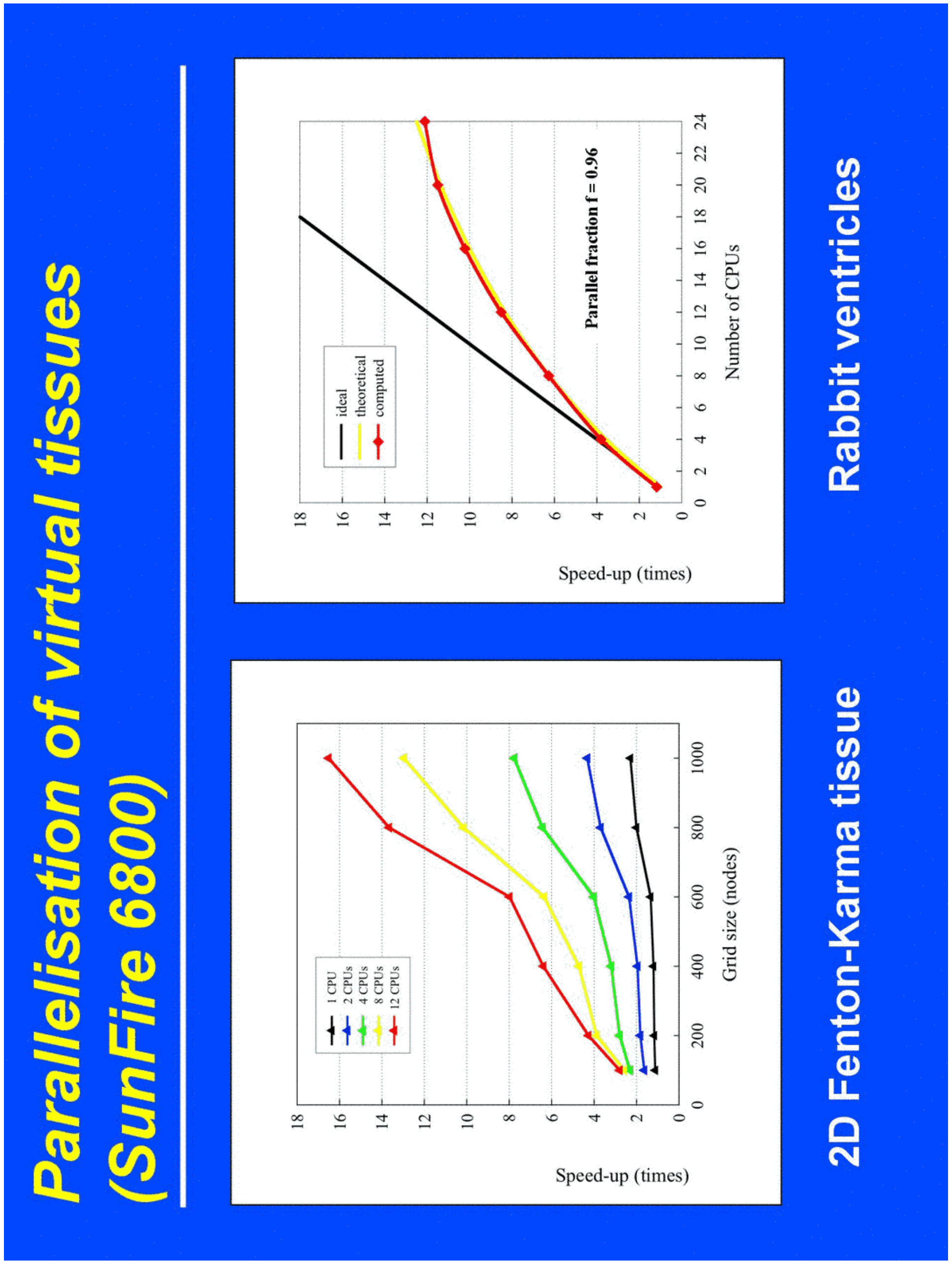




Gray et al. Phys Rev Lett 2001;87:8104-08
Aslanidi et al. Eur J Physiol 2002;443:S259

Summary

- Virtual mammalian and human cardiac tissues have been constructed and validated
- As researchtools can be used to identify mechanisms
- For clinically applied arrhythmia research, need significant HPC resources
- Coupling with clinical streams and and population data bases will enhance impact on CHD death rates


Parallelisation of virtual tissues (SunFire 6800)
Speed-up (times)
Grid size (nodes)
1 CPU
2 CPUs
4 CPUs
8 CPUs
12 CPUs
2D Fenton-Karma tissue
Speed-up (times)
Number of CPUs
ideal
theoretical
computed
Parallel fraction f = 0.96
Rabbit ventricles