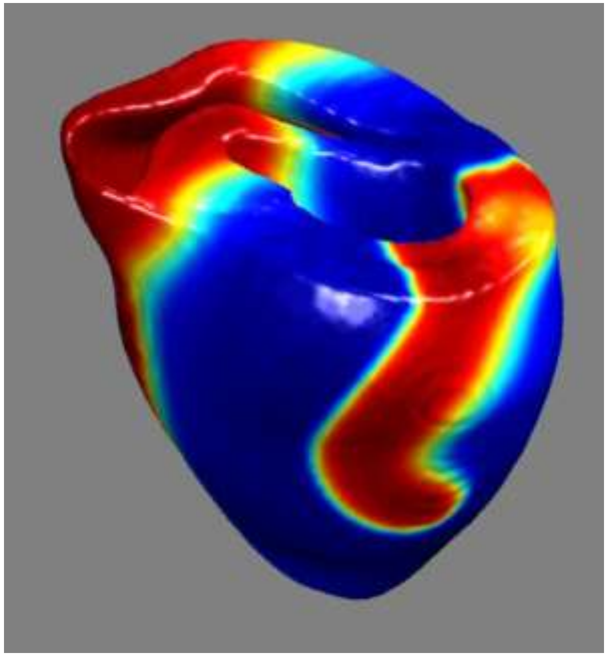
Mathematical modelling



Richard Clayton

University of Sheffield

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Introductory

Personal background:

- BSc in Applied Physics and Electronics
- PhD and Post Doctoral work in NHS Medical Physics (Newcastle-upon-Tyne)
- Academic in Physiology (Leeds) 1998-2002
- Academic in Computer Science (Sheffield) since Jan 2003

Talk outline:

- What is a mathematical model and what can we use it for?
- Why bother with mathematical modelling of cardiac cells and tissue?
- How?

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What is a model?

"A scientific model is a simplified abstract view of complex reality.

A scientific model represents empirical objects, phenomena, and physical processes in a logical way"

– Wikipedia

Falling apples

Physical principles

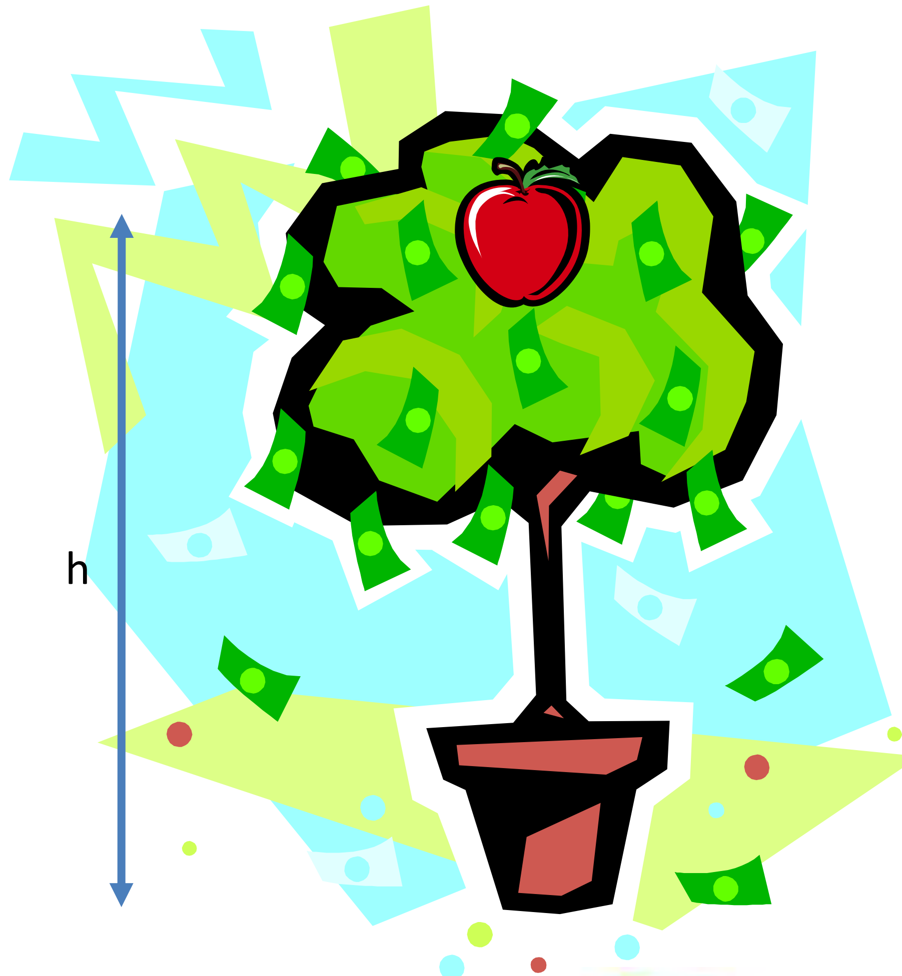
Potential energy = m g h
m = mass of apple
g = acceleration due to gravity
h = height of apple above ground

Kinetic energy = ½ m v^2
V = velocity

When the apple hits the ground
potential energy = kinetic energy
So,
$\frac{1}{2} m v^2 = m g h$, $\frac{1}{2} v^2 = g h$

We also know that v = g t, so
$\frac{1}{2} g^2 t^2 = g h$, so
$h = \frac{1}{2} g t^2$, and

$$t = \sqrt{2h/g}$$



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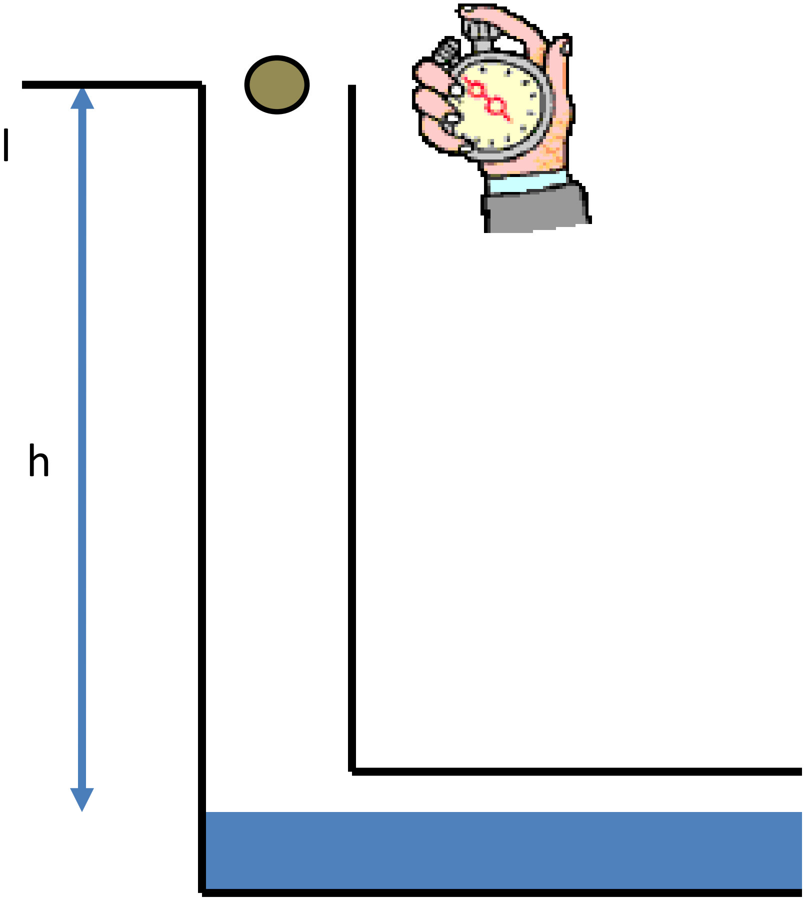
Generalisations

We can use this simple model to predict the depth of a flooded mineshaft – or well



$h = \frac{1}{2} g t^2$, and $t = \sqrt{2h/g}$,

So if $t = 5$ s, $h = \frac{1}{2} \times 9.81 \times 5^2 = 122$ m

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Generalisations

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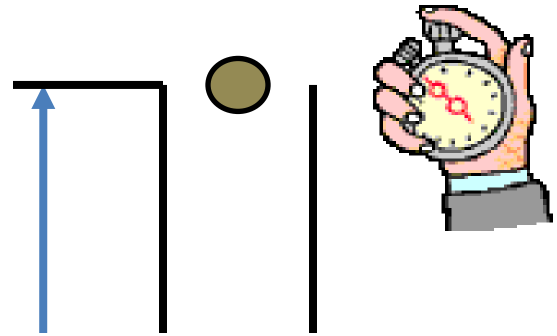

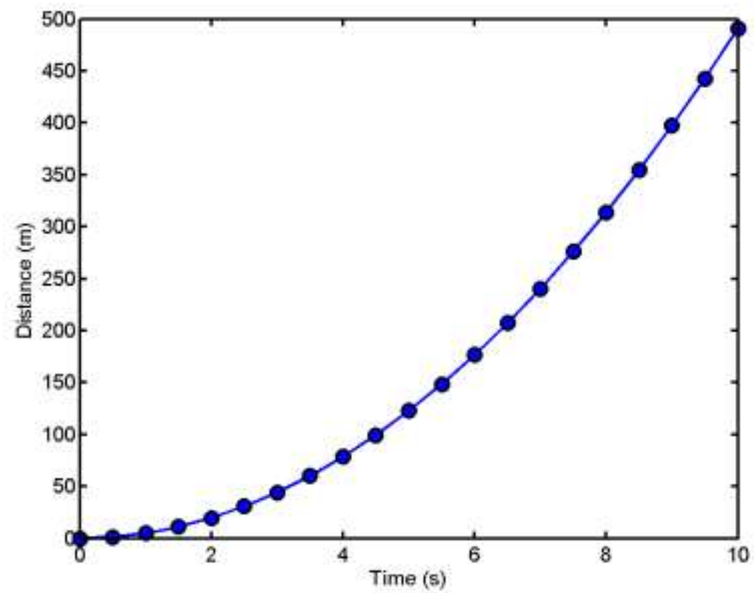

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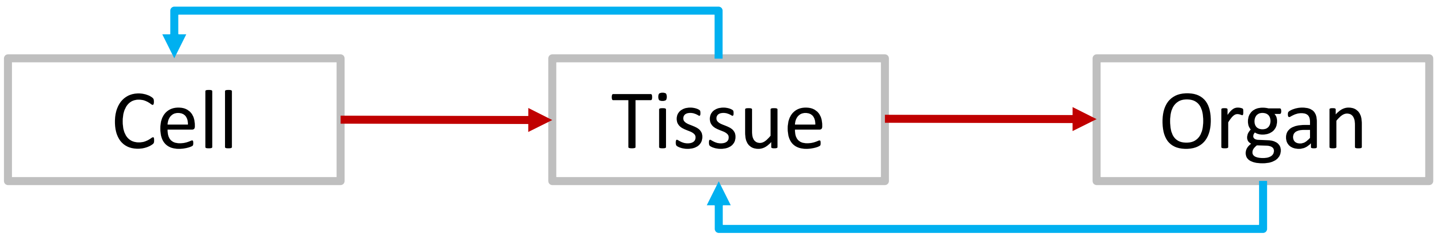
What are models good for?

- Prediction – “what-if?” scenarios
- Integration and coupling across scales



- Mechanistic insight by reconstruction of observations
- Add value

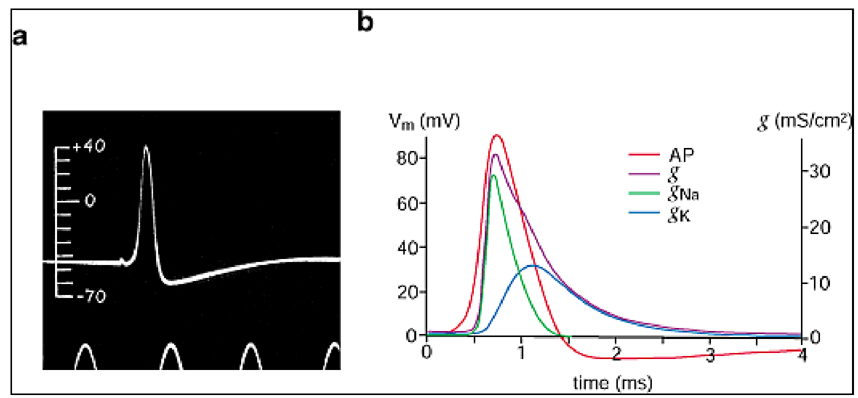
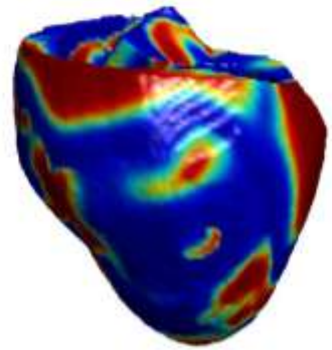
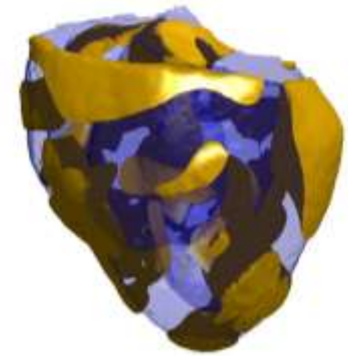


Figure 1: The action potential: from experiment to theory.

(**a**) The first intracellular recording of an action potential, from squid axon. Time calibration, 2 ms. Modified from ref. 2. (**b**) Separation of ionic conductances underlying the action potential (AP) in the H-H model. Modified from ref. 6.

From Häusser Nature Neuroscience 3, 1165 - 1165 (2000)

Components of a cardiac model

- Sub-cellular
  - Ca^{2+} storage, uptake, and release
- Cell
  - Electrophysiology
  - Tension development
- Tissue
  - Action potential propagation
  - Passive and active mechanics
- Whole organ
  - Anatomy
- External effects
  - Pacing
  - Fluids
  - Nervous system

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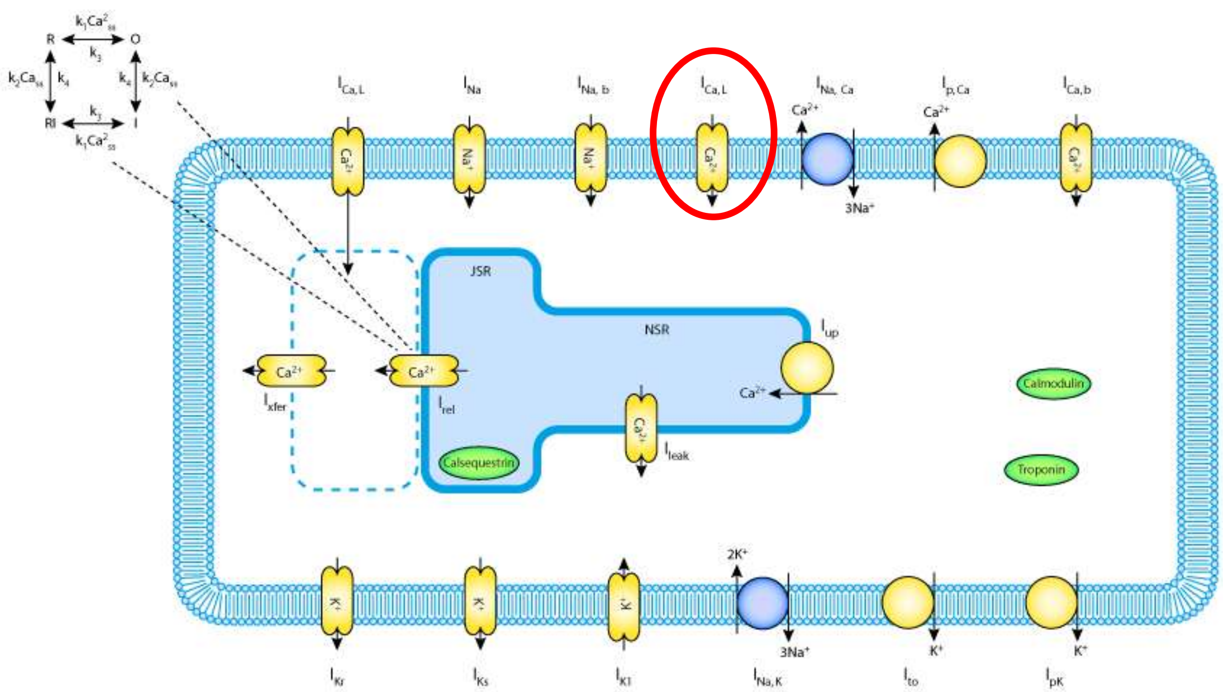
Cell models

Am J Physiol Heart Circ Physiol 291: H1088–H1100, 2006.
First published March 24, 2006; doi:10.1152/ajpheart.00109.2006.

Alternans and spiral breakup in a human ventricular tissue model

K. H. W. J. ten Tusscher and A. V. Panfilov
Department of Theoretical Biology, Utrecht University, Utrecht, The Netherlands

Submitted 30 January 2006; accepted in final form 5 March 2006



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Cell models

Equations for just one (out of eight) ion channel currents – L-type Ca^{2+} channel

L-Type Ca^{2+} Current

$$I_{CaL} = G_{CaL} d f f_2 f_{cass} 4 \frac{(V-15)F^2}{RT} \frac{0.25 Ca_{ss} e^{2(V-15)F/RT} - Ca_o}{e^{2(V-15)F/RT} - 1} \quad (6)$$

$$d_\infty = \frac{1}{1 + e^{(-8-V)/7.5}} \quad (7)$$

$$\alpha_d = \frac{1.4}{1 + e^{(-35-V)/13}} + 0.25 \quad (8)$$

$$\beta_d = \frac{1.4}{1 + e^{(V+5)/5}} \quad (9)$$

$$\gamma_d = \frac{1}{1 + e^{(50-V)/20}} \quad (10)$$

$$\tau_d = \alpha_d \beta_d + \gamma_d \quad (11)$$

$$f_\infty = \frac{1}{1 + e^{(V+20)/7}} \quad (12)$$

$$\alpha_f = 1102.5 e^{-\left(\frac{V+27}{15}\right)^2} \quad (13)$$

$$\beta_f = \frac{200}{1 + e^{(13-V)/10}} \quad (14)$$

$$\gamma_f = \frac{180}{1 + e^{(V+30)/10}} + 20 \quad (15)$$

$$\tau_f = \alpha_f + \beta_f + \gamma_f \quad (16)$$

$$f_\infty = \frac{1}{1 + e^{(V+20)/7}} \quad (12)$$

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$$\gamma_f = \frac{180}{1 + e^{(V+30)/10}} + 20 \quad (15)$$

$$\tau_f = \alpha_f + \beta_f + \gamma_f \quad (16)$$

$$f_{2\infty} = \frac{0.67}{1 + e^{(V+35)/7}} + 0.33 \quad (17)$$

$$\alpha_{f2} = 600 e^{-\frac{(V+25)^2}{170}} \quad (18)$$

$$\beta_{f2} = \frac{31}{1 + e^{(25-V)/10}} \quad (19)$$

$$\gamma_{f2} = \frac{16}{1 + e^{(V+30)/10}} \quad (20)$$

$$\tau_{f2} = \alpha_{f2} + \beta_{f2} + \gamma_{f2} \quad (21)$$

$$f_{cass\infty} = \frac{0.6}{1 + \left(\frac{Ca_{ss}}{0.05}\right)^2} + 0.4 \quad (22)$$

$$\tau_{fcass} = \frac{80}{1 + \left(\frac{Ca_{ss}}{0.05}\right)^2} + 2 \quad (23)$$

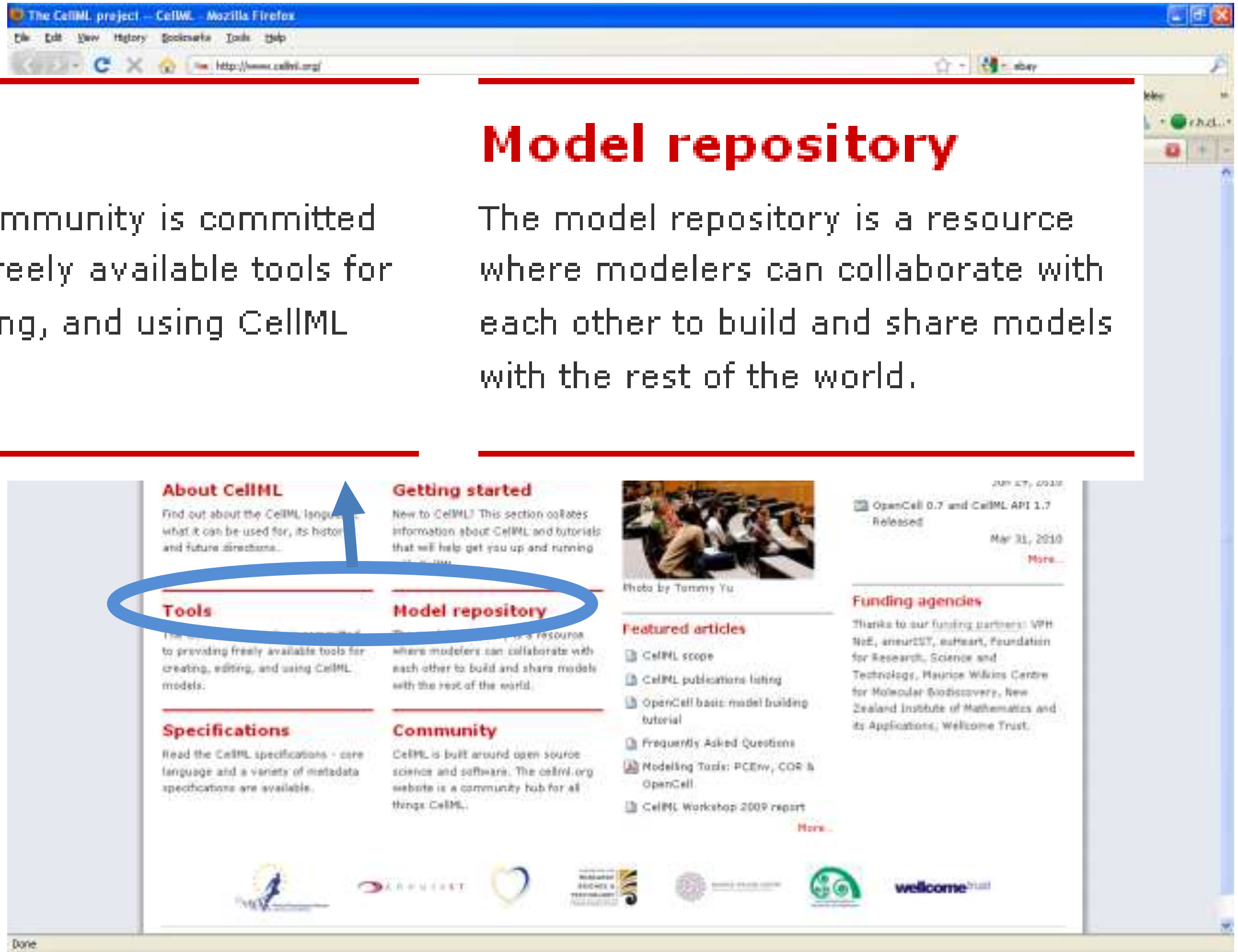
www.cellml.org

Tools

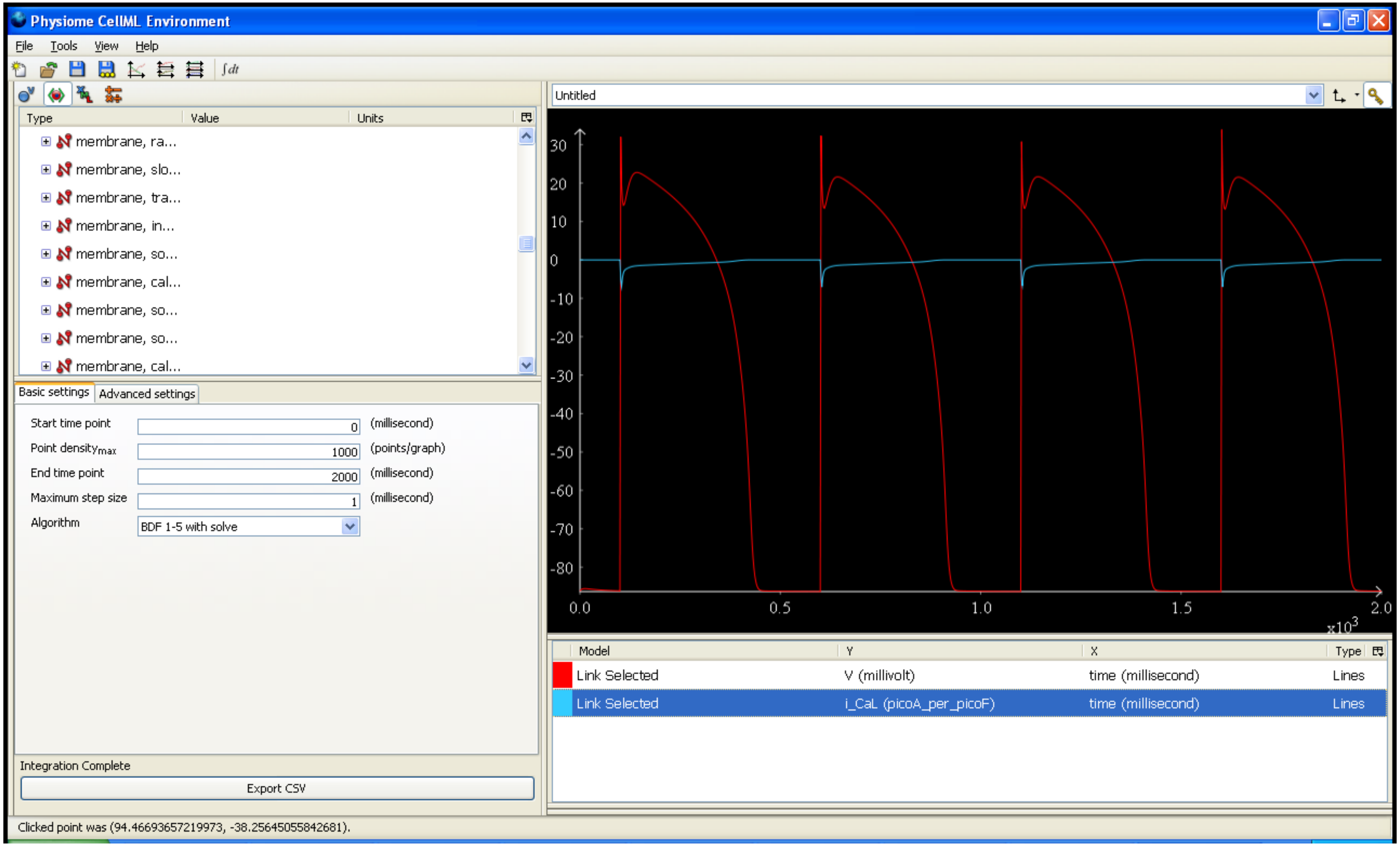
The CellML community is committed to providing freely available tools for creating, editing, and using CellML models.

Model repository

The model repository is a resource where modelers can collaborate with each other to build and share models with the rest of the world.



http://www.cellml.org/tools/downloads/opencell



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OpenCell

- Runs on PC, Mac, Linux
- Free
- You don’t need to worry about how the equations are solved
- Easy to change model parameters
- Outputs to spreadsheet etc

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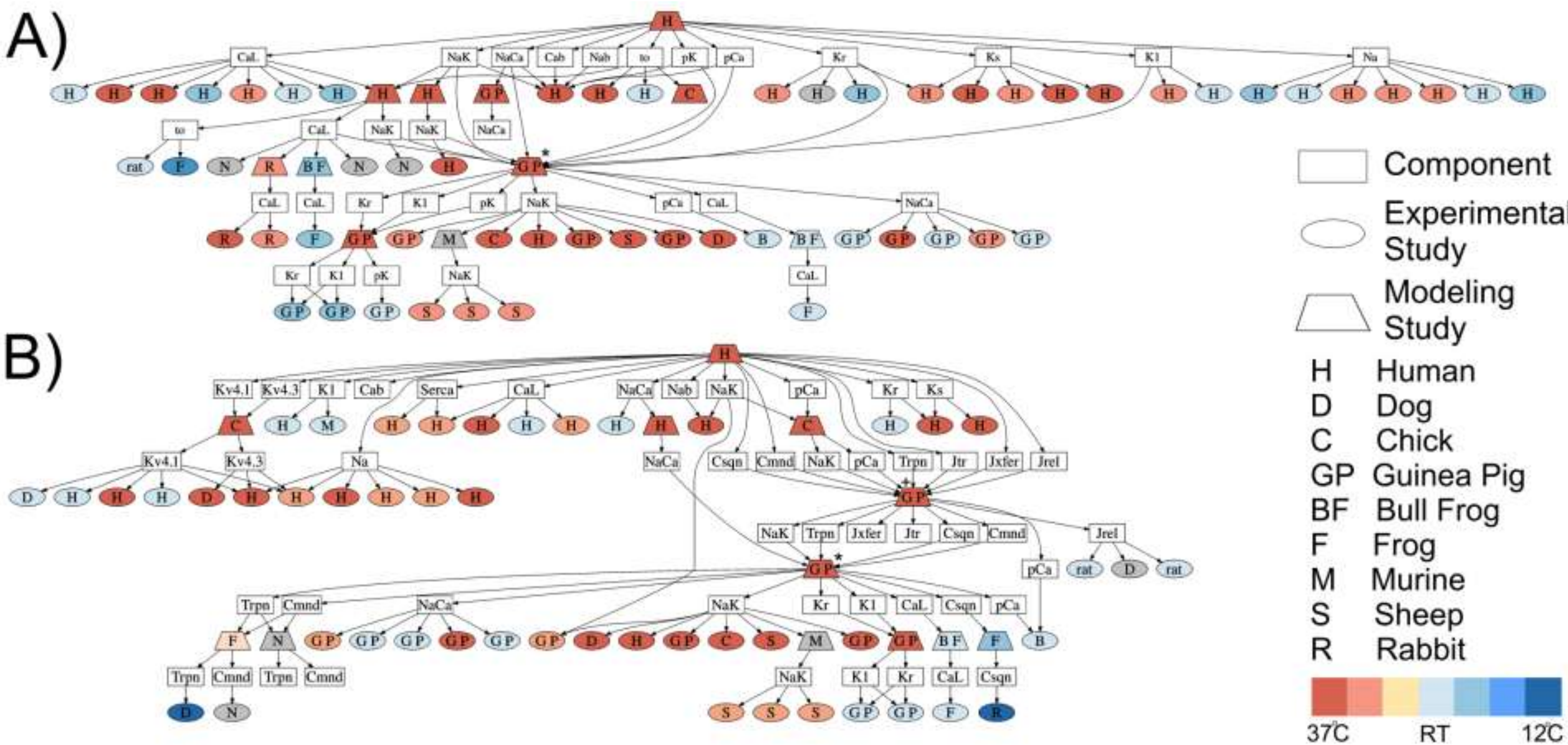
Figure 1. Phylogenetic schematic for (A) the ten Tusscher et al and (B) Iyer et al models of human ventricular myocyctes



Niederer S. A. et.al. Exp Physiol;2009;94:486-495

Experimental Physiology
Translation and Integration

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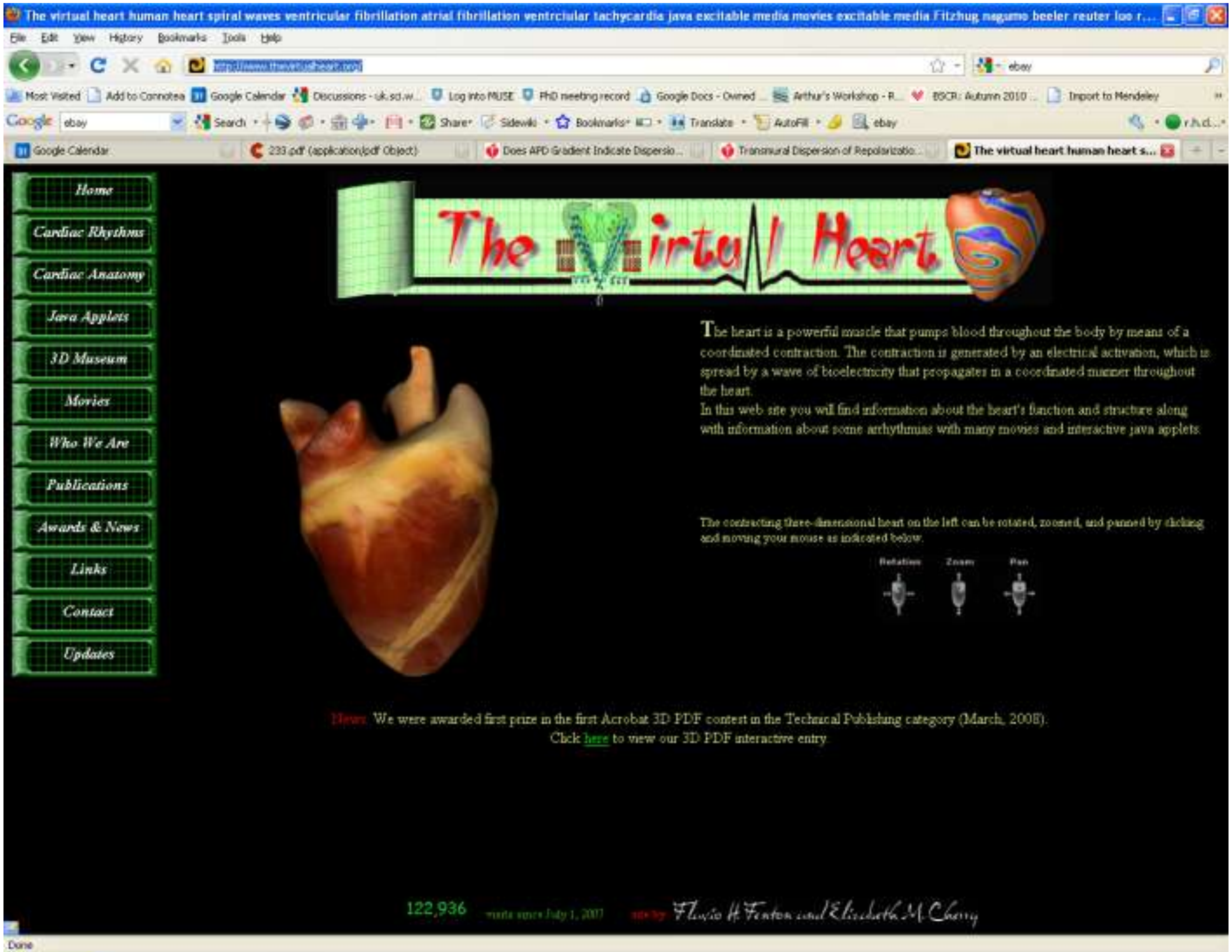
www.thevirtualheart.org



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Other tissue modelling packages

Open CMISS http://www.cmiss.org/openCMISS

Chaste http://web.comlab.ox.ac.uk/chaste/

Continuity http://www.continuity.ucsd.edu/

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What are models good at?

- Synthesising information at different scales
  - Structure and function
- Adding value
- Reconstructing mechanisms
- Examples:
  - Mechanisms of ventricular fibrillation
  - Cellular electrophysiology of long QT syndrome

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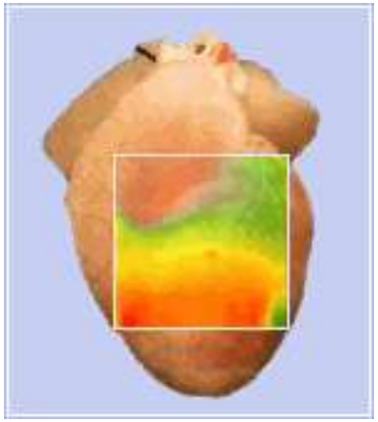
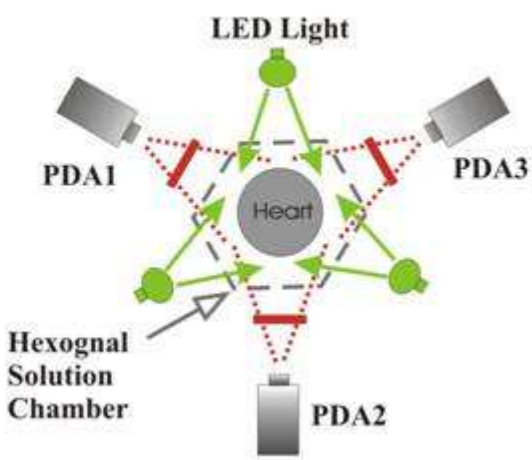
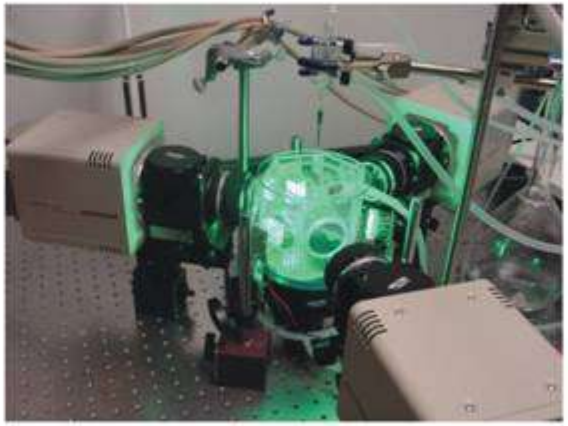
Experimental VF research

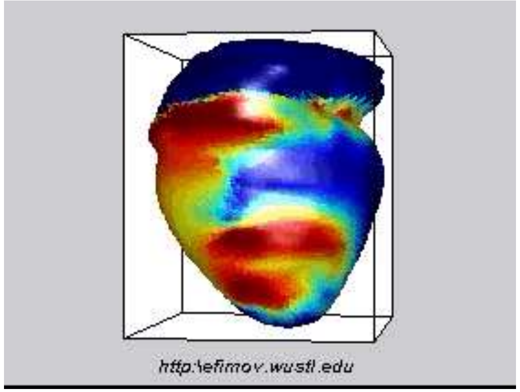
- Optical imaging using voltage sensitive fluorescent dyes (images and data from Igor Efimov's lab - http://efimov.wustl.edu)



Panoramic Fast Fluorescence Imaging System







But what is going on inside the tissue ?

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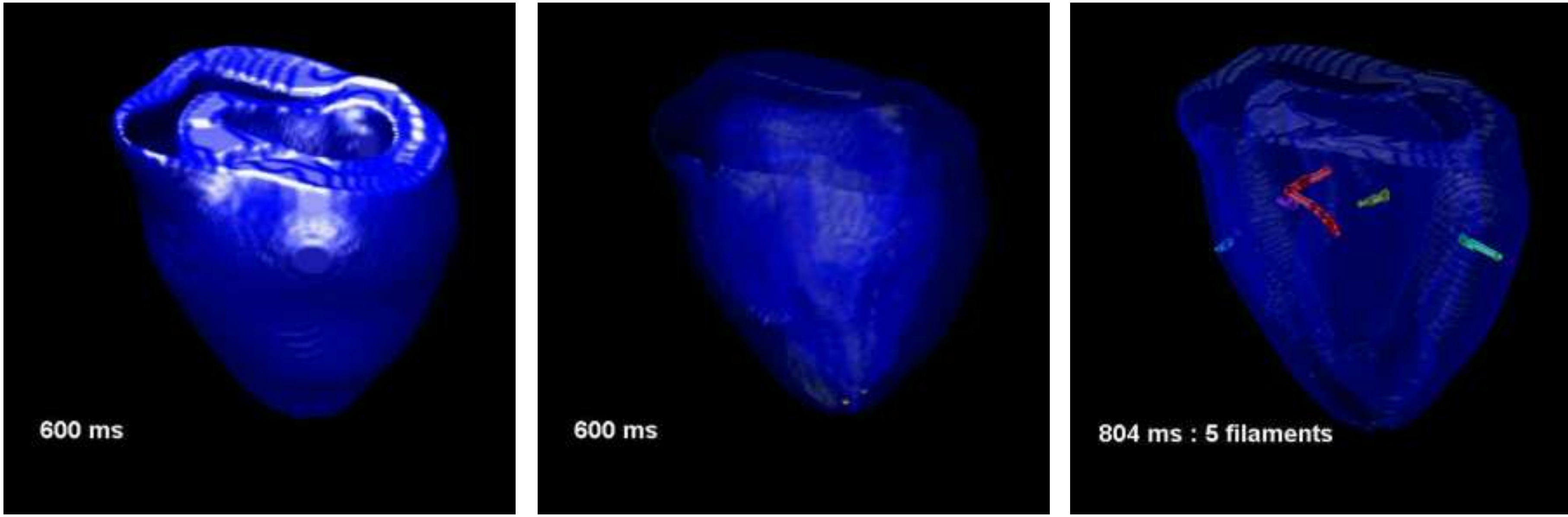
Re-entry in a whole heart



- Models of electrical activity in the heart can indicate 3D activity that can account for 2D observations
- Models can be dissected in space and time at high resolution.
- Complexity of re-entrant (spiral) activity can be measured using filaments

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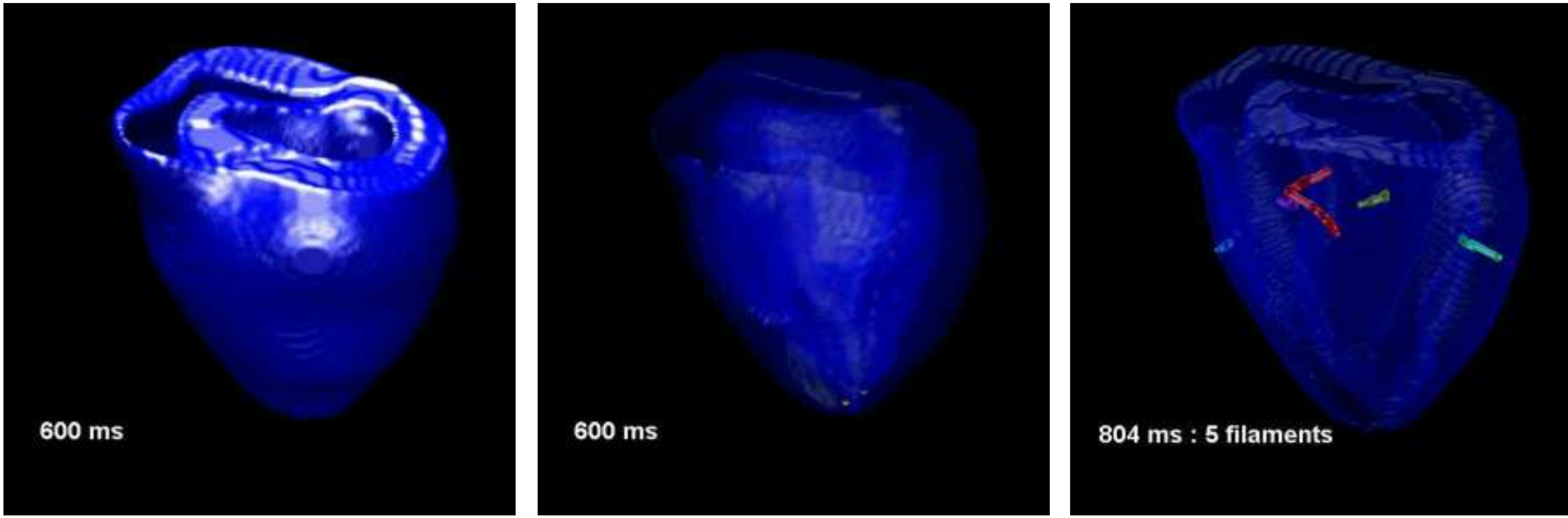
Re-entry in a whole heart



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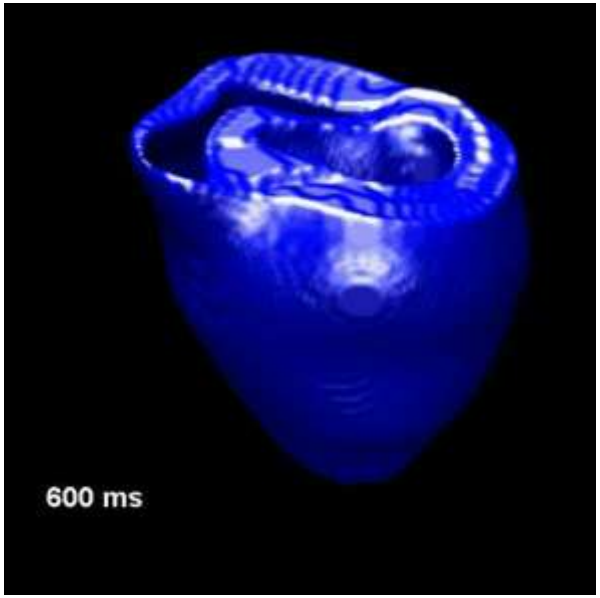

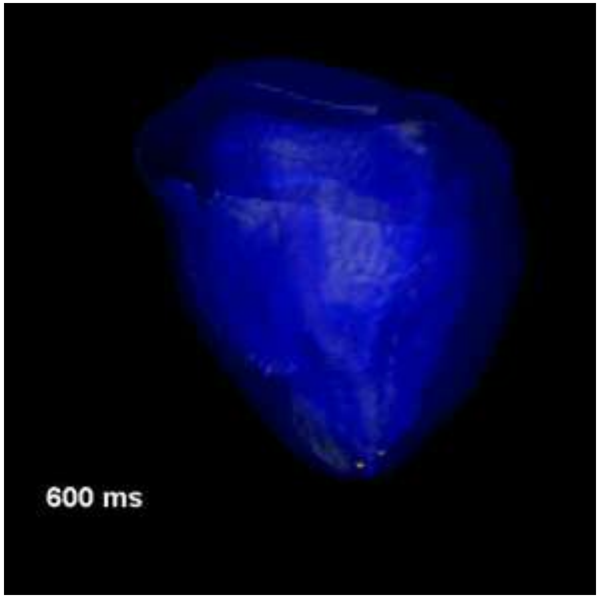

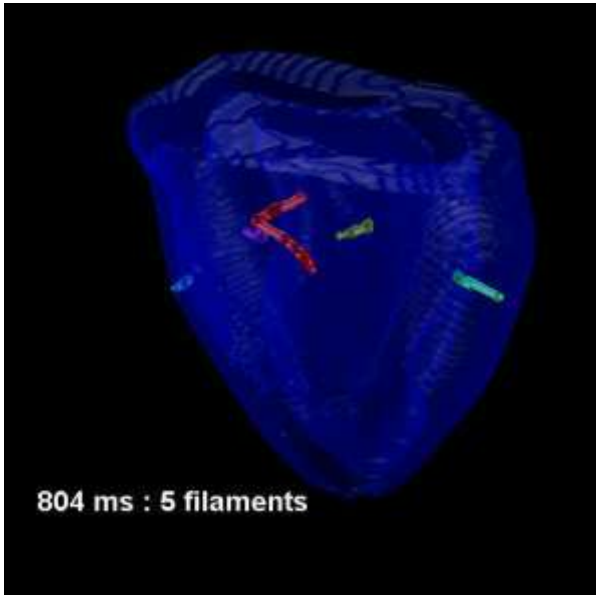

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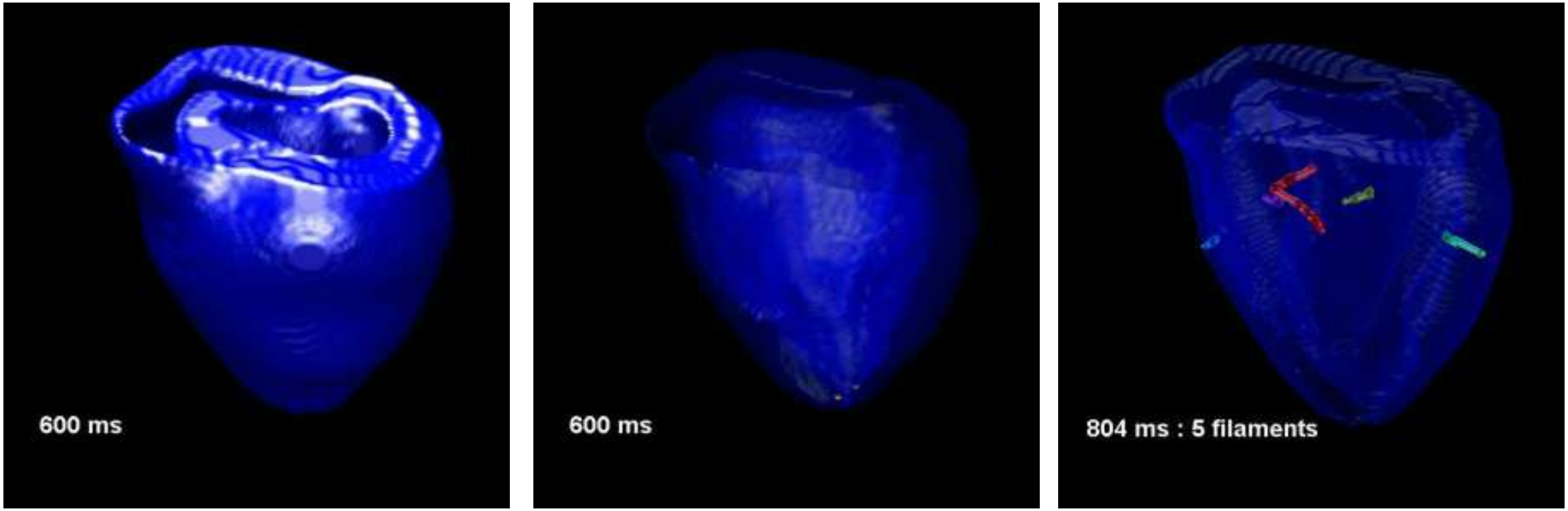

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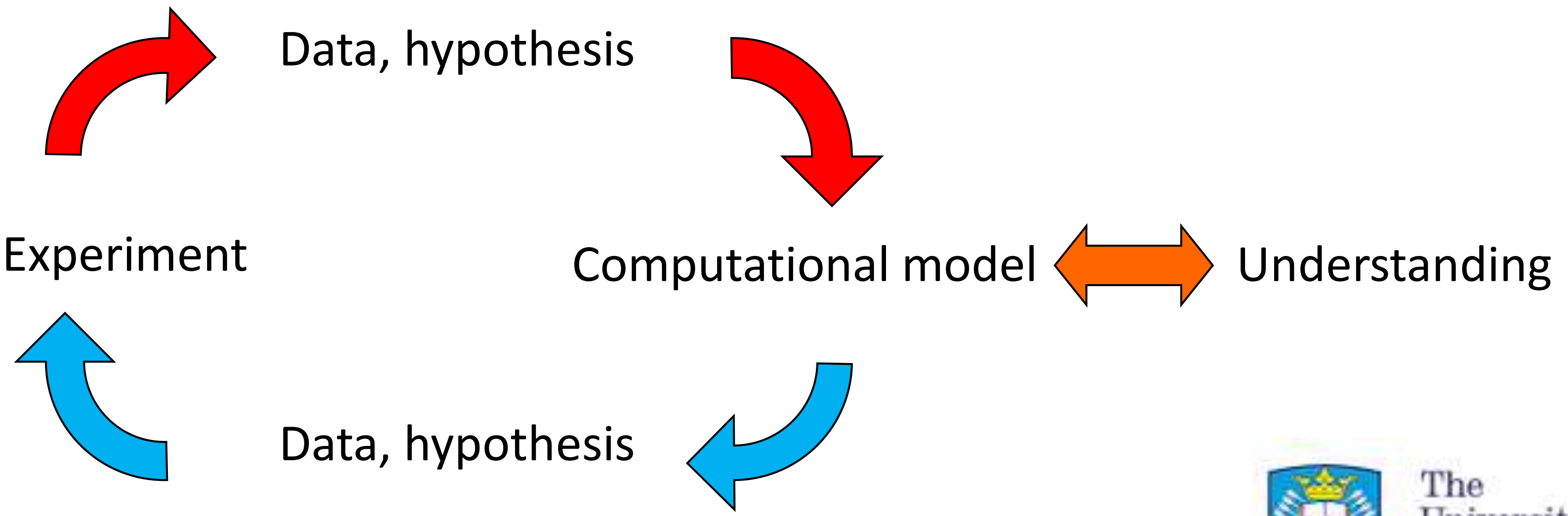
What are models bad at?

- Inverse problems
  - Which LQT mechanism has prolonged APD
  - Epicardial potentials from body surface electrodes
- Tackling unfocussed questions



Concluding thoughts

"All models are wrong, but some are useful"

George Box

"If you are an experimentalist ***no-one*** *believes your data, but if you are a modeller* ***everyone*** *believes your model"*

Alan Garfinkel

- ❖ Models are becoming a valuable research tool for basic science
- ❖ But not yet for clinical research …
- ❖ Open access to models and software is making it easier to get started
- ❖ Cell and tissue models still have limitations

r.h.clayton@sheffield.ac.uk http://www.dcs.shef.ac.uk/~richard

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