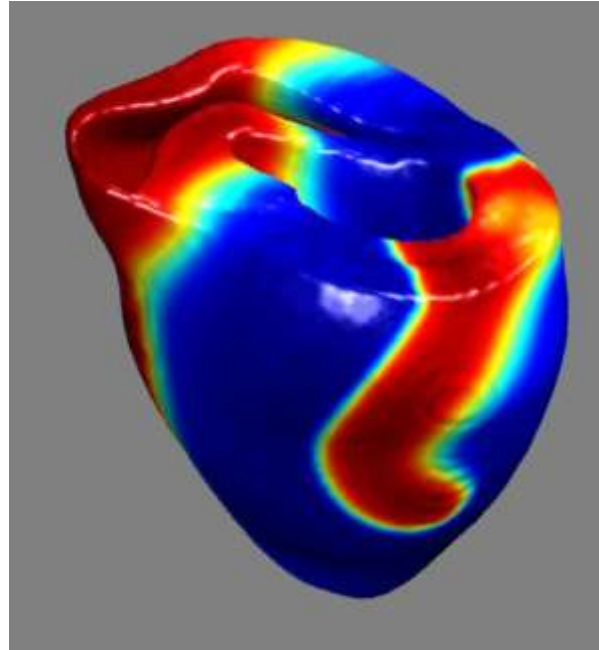


Mathematical modelling



Richard Clayton
University of Sheffield

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?

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 = $\frac{1}{2} m v^2$

v = velocity

When the apple hits the ground
potential energy = kinetic energy

So,

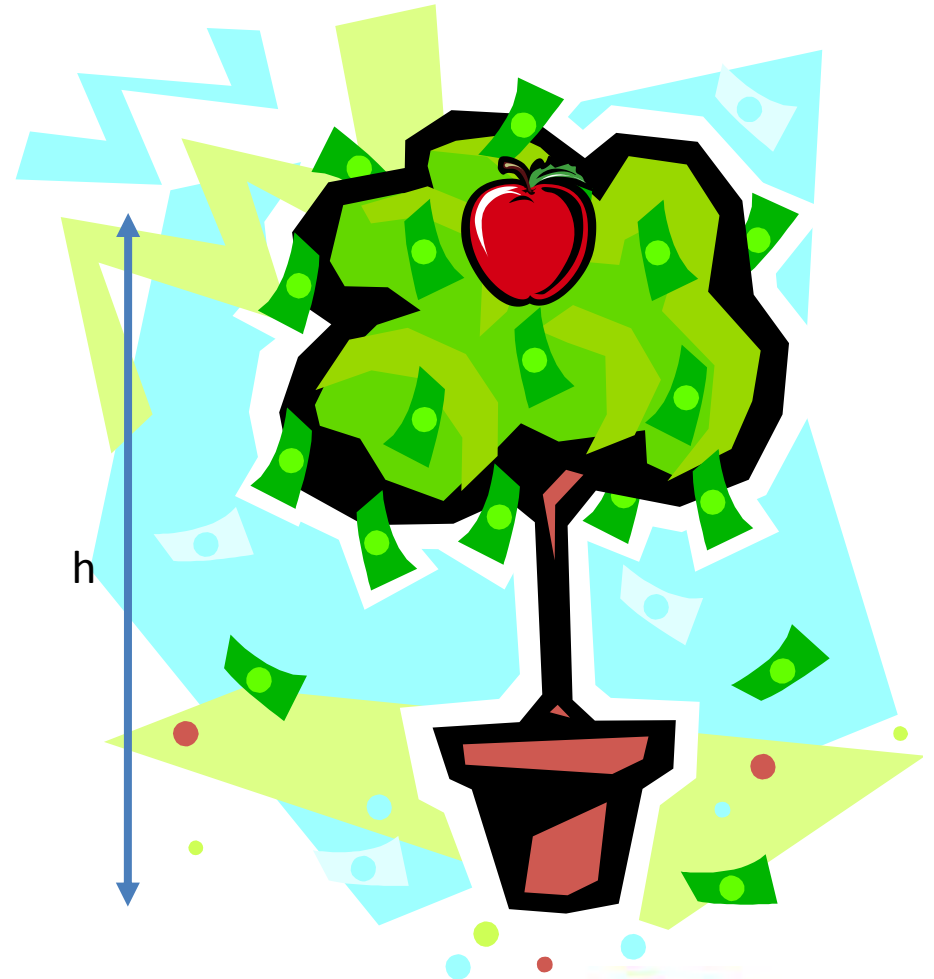
$$\frac{1}{2} m v^2 = m g h, \quad \frac{1}{2} v^2 = g h$$

We also know that $v = g t$, so

$$\frac{1}{2} g^2 t^2 = g h, \text{ so}$$

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

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



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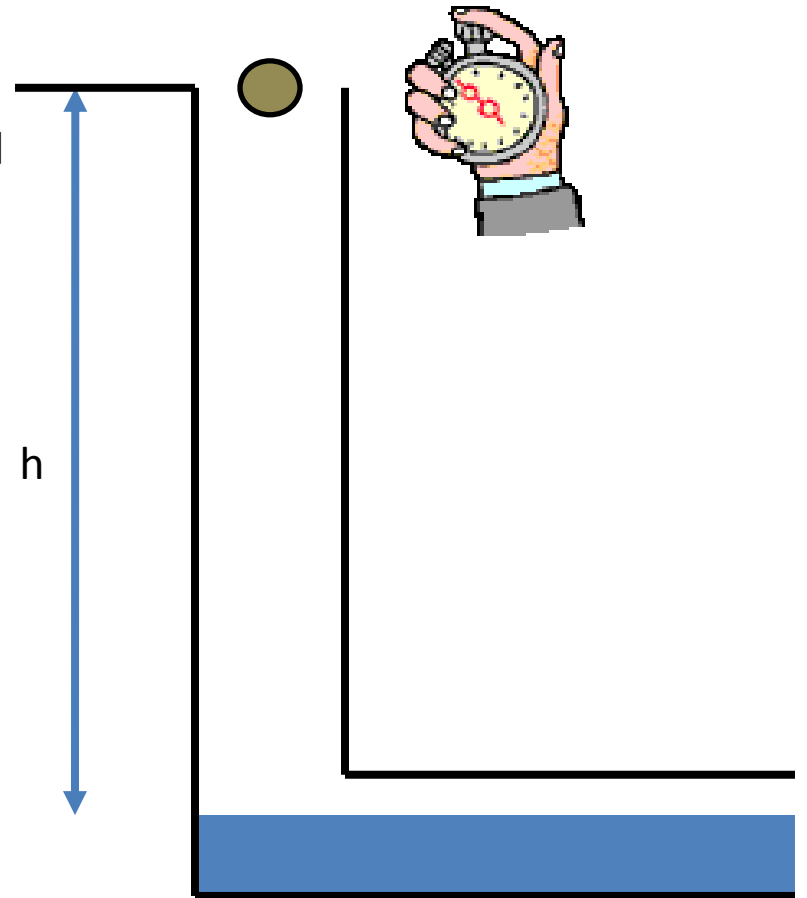
Generalisations

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



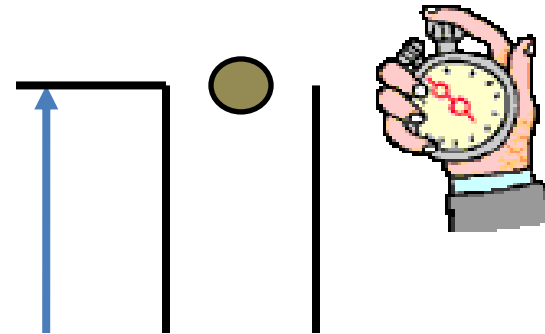
$$h = \frac{1}{2} g t^2, \text{ and } t = \sqrt{2h/g},$$

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



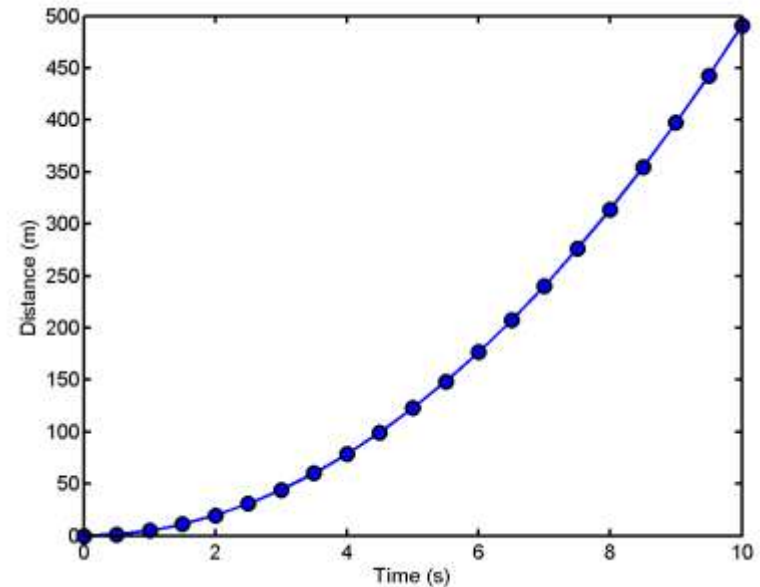
Generalisations

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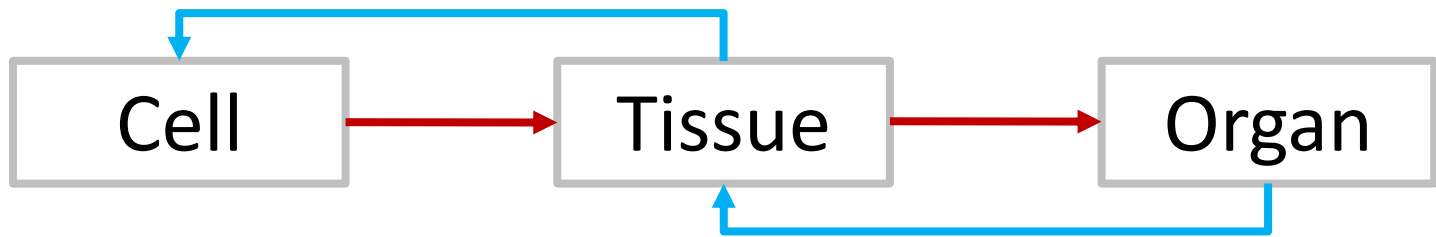
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$$\text{So if } t = 5 \text{ s, } h = \frac{1}{2} \times 9.81 \times 5^2 = 122 \text{ m}$$



What are models good for?

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



- Mechanistic insight by reconstruction of observations
- Add value

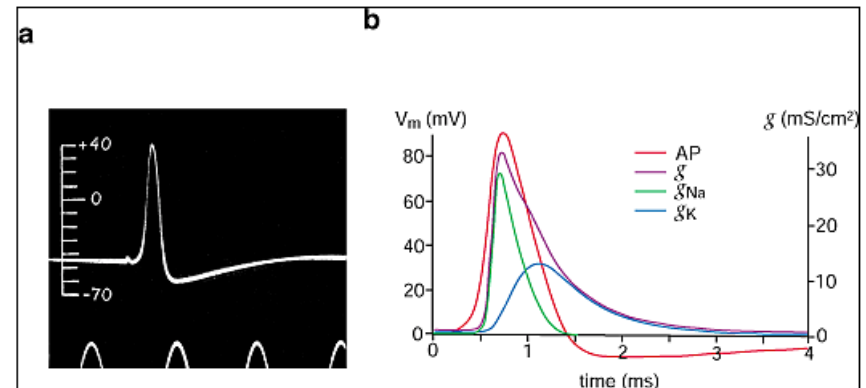


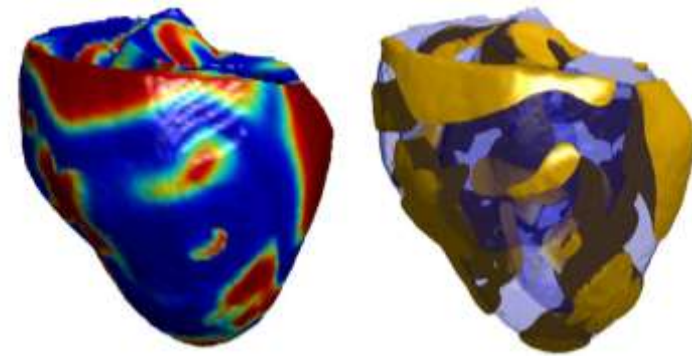
Figure 1: The action potential: from experiment to theory.

(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



Cell models



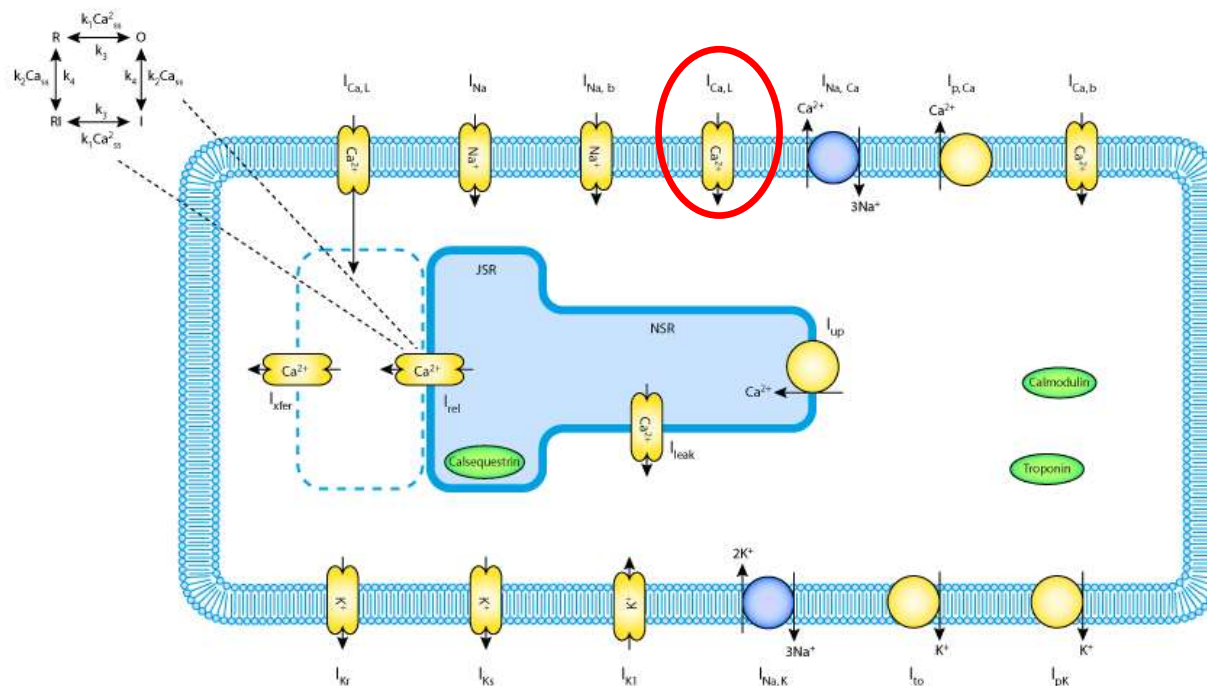
Am J Physiol Heart Circ Physiol 291: H1088–H1100, 2006.
First published March 24, 2006; doi:10.1152/ajpheart.00109.2006.

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

$$I_{\text{CaL}} = G_{\text{CaL}} d f f_2 f_{\text{CaSS}} A \frac{(V-15)F^2}{RT} \frac{0.25\text{Ca}_{\text{SS}} e^{2(V-15)F/RT} - \text{Ca}_o}{e^{2(V-15)F/RT} - 1} \quad (6)$$

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

$$f_{\text{CaSS}\infty} = \frac{0.6}{1 + \left(\frac{\text{Ca}_{\text{SS}}}{0.05}\right)^2} + 0.4 \quad (22)$$

$$\tau_{f\text{CaSS}} = \frac{80}{1 + \left(\frac{\text{Ca}_{\text{SS}}}{0.05}\right)^2} + 2 \quad (23)$$

Tools

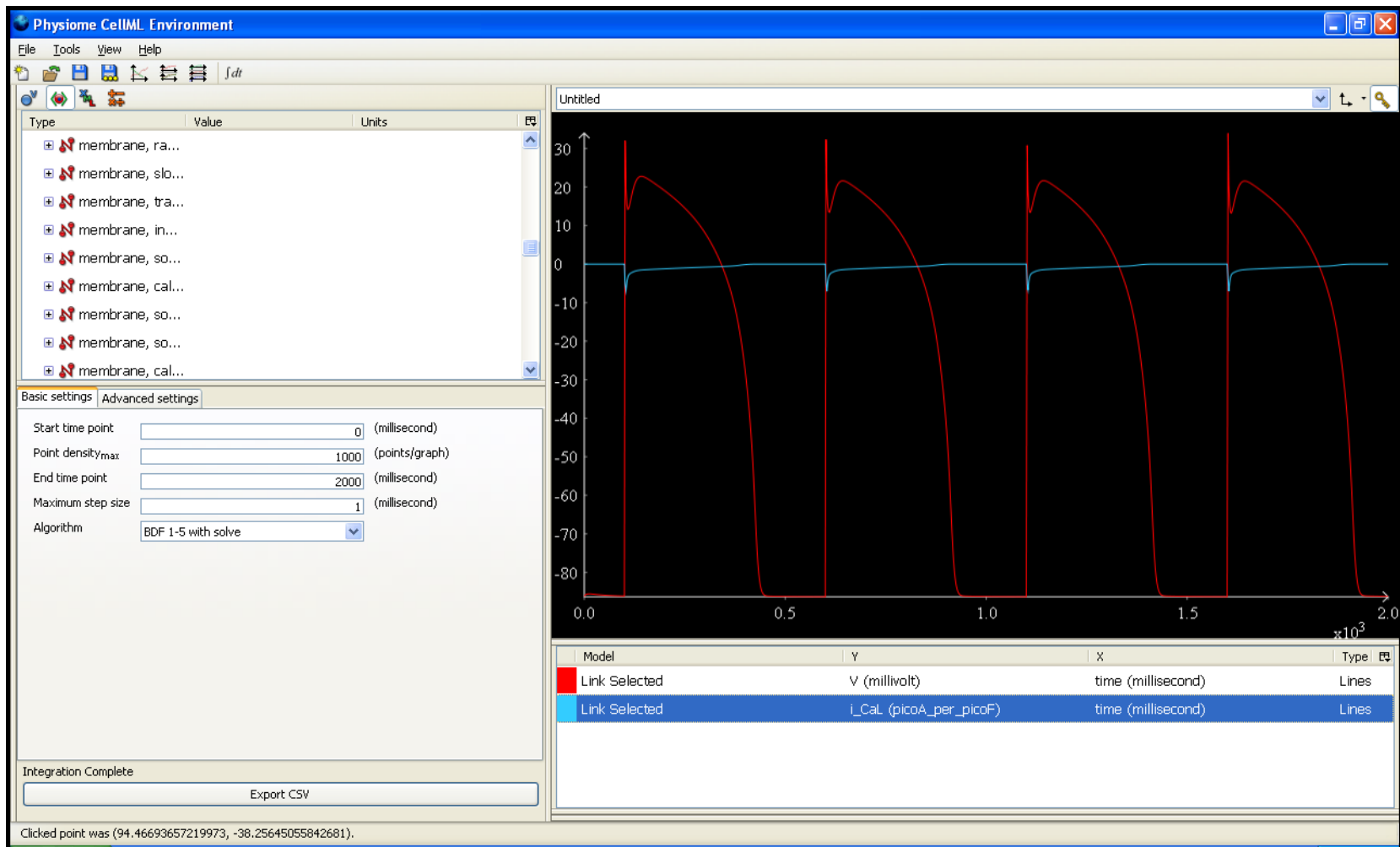
The CellML community is committed to providing freely available tools for creating, editing, and using CellML models.

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.

The screenshot shows the CellML website homepage. The browser window title is "The CellML project - CellML - Mozilla Firefox" and the address bar shows "http://www.cellml.org/". The website content is organized into several columns. The "Tools" section is circled in blue, and a blue arrow points from it to the "About CellML" section. Other sections include "Getting started", "Model repository", "Specifications", "Community", "Featured articles", "Funding agencies", and a news item for "OpenCell 0.7 and CellML API 1.7 Released" dated Mar 31, 2010. At the bottom, there are logos for various funding partners including EPSRC, ARUK, Wellcome, and others.

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



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

www.thevirtualheart.org

The screenshot shows a web browser window displaying the website www.thevirtualheart.org. The browser's address bar and tabs are visible at the top. The website's navigation menu on the left includes: Home, Cardiac Rhythms, Cardiac Anatomy, Java Applets, 3D Museum, Movies, Who We Are, Publications, Awards & News, Links, Contact, and Updates. The main content area features a banner with the title "The Virtual Heart" and a 3D heart model. Below the banner, a large 3D heart model is shown on the left. To its right, the text reads: "The heart is a powerful muscle that pumps blood throughout the body by means of a coordinated contraction. The contraction is generated by an electrical activation, which is spread by a wave of bioelectricity that propagates in a coordinated manner throughout the heart. In this web site you will find information about the heart's function and structure along with information about some arrhythmias with many movies and interactive java applets." Below this text, a smaller 3D heart model is shown with three mouse icons labeled "Rotate", "Zoom", and "Pan" indicating interactive controls. A red "News" section states: "We were awarded first prize in the first Acrobat 3D PDF contest in the Technical Publishing category (March, 2005). Click [here](#) to view our 3D PDF interactive entry." At the bottom, a visitor count of "122,936" is shown, along with the date "visits since July 1, 2007" and the authors' names: "by Flavio A. Fenton and Elizabeth M. Cherry".



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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/>

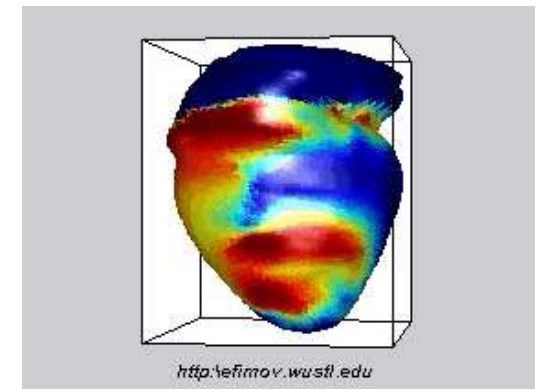
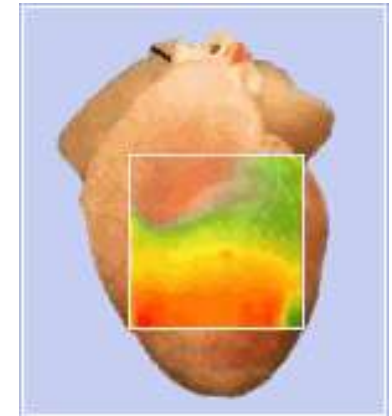
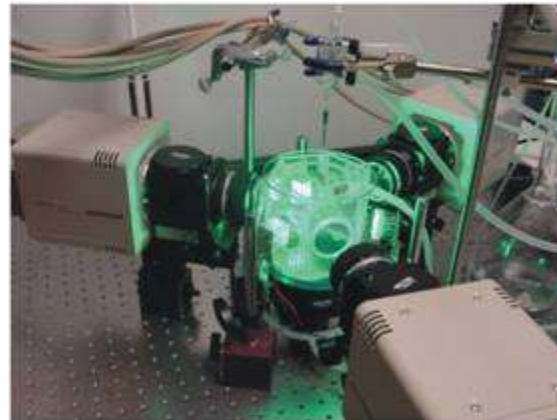
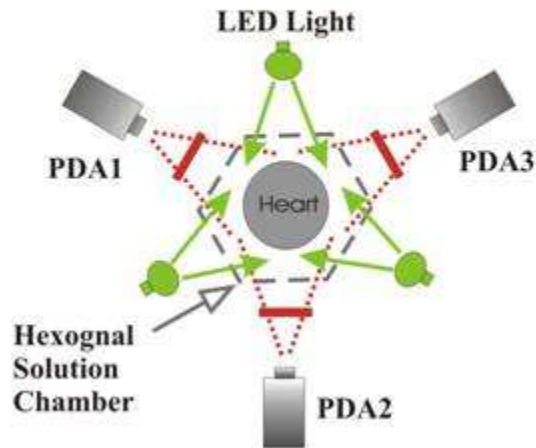
What are models good at?

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

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

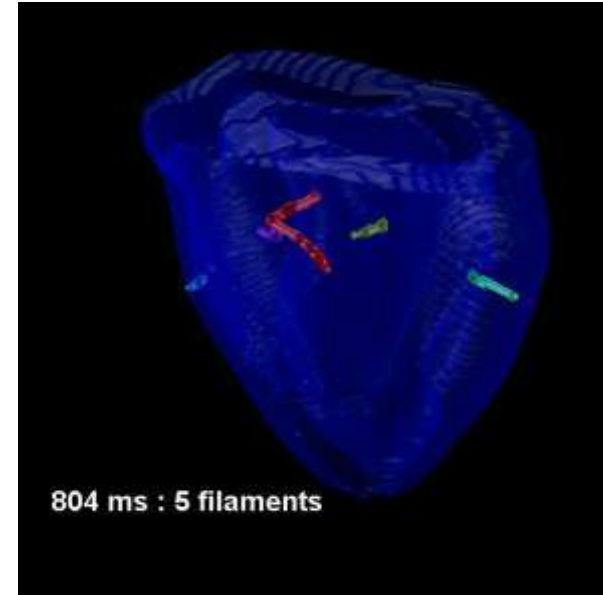
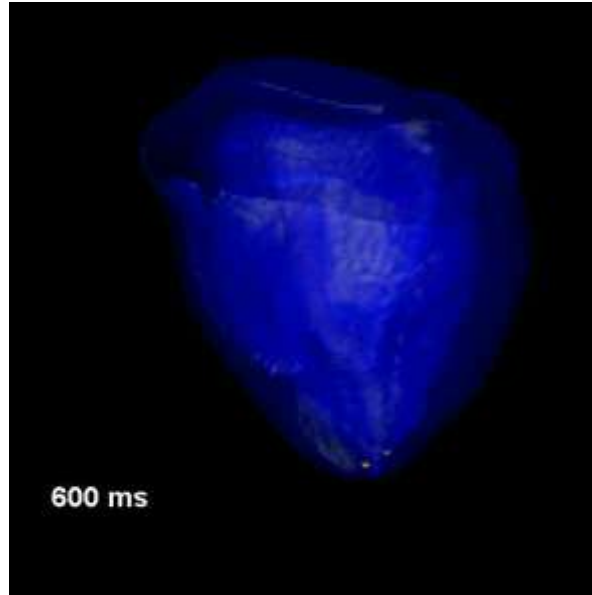
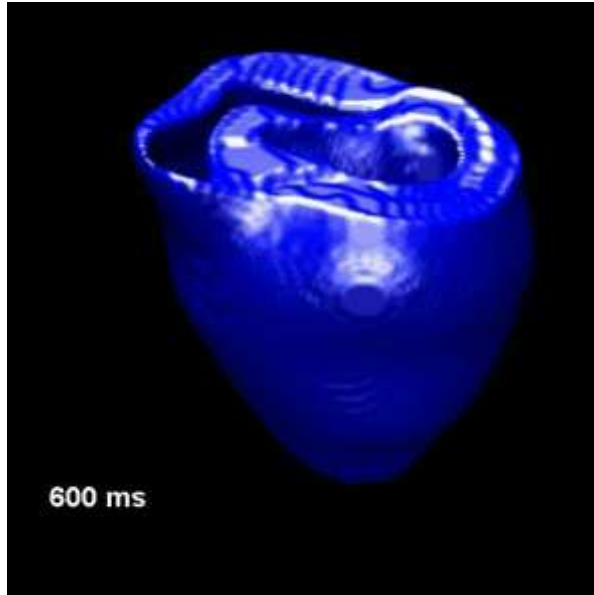


But what is going on inside the tissue



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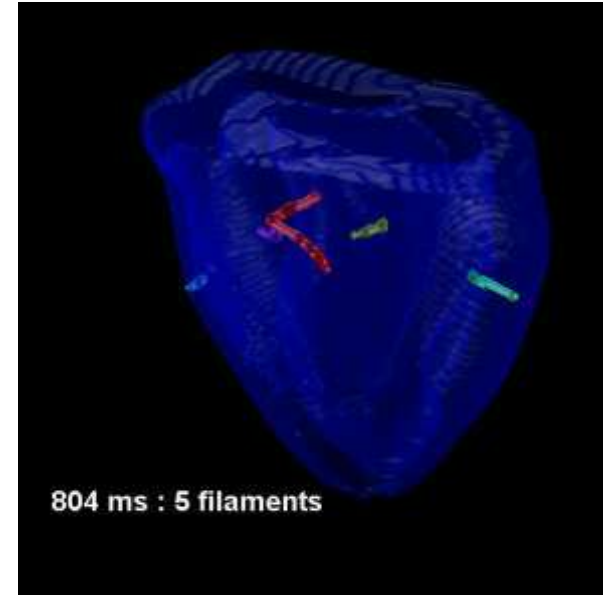
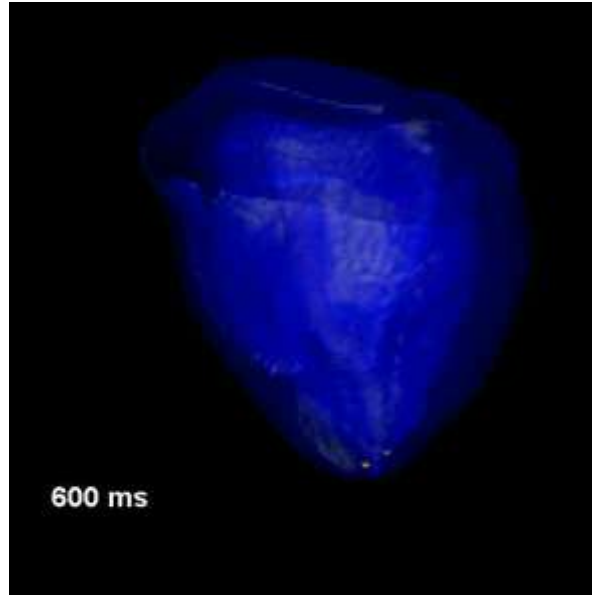
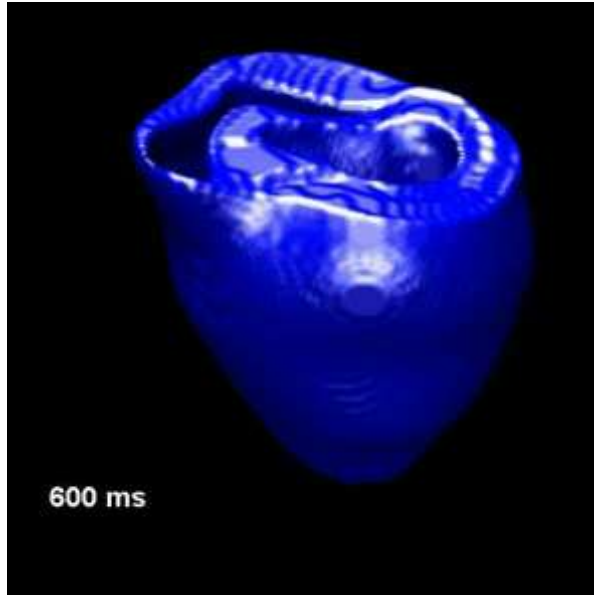
Re-entry in a whole heart



- 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



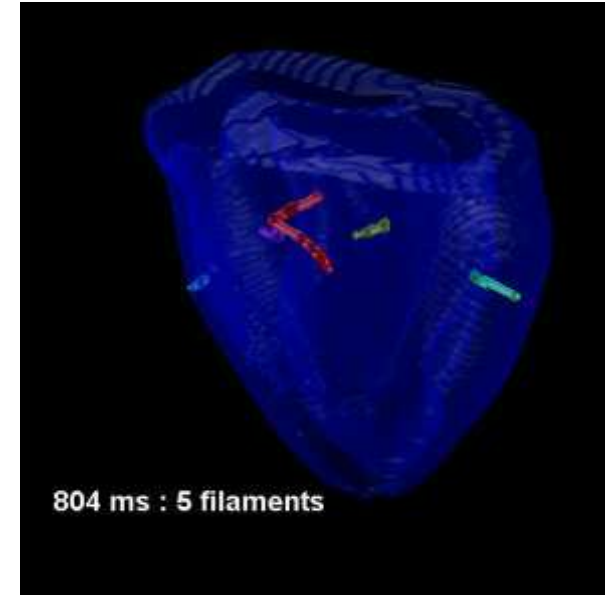
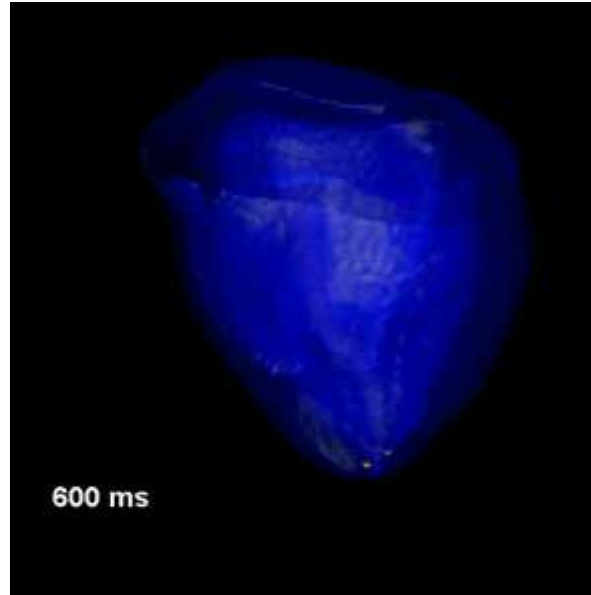
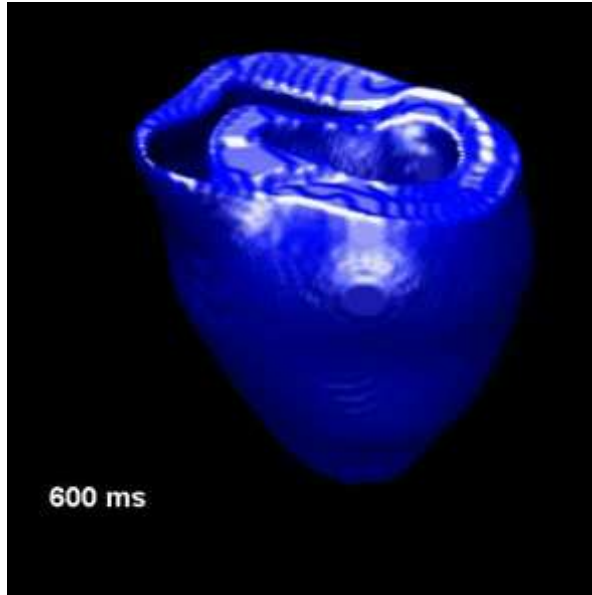
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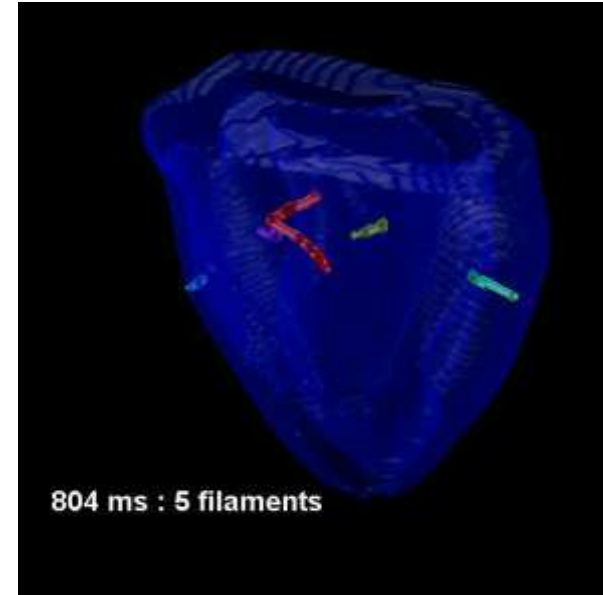
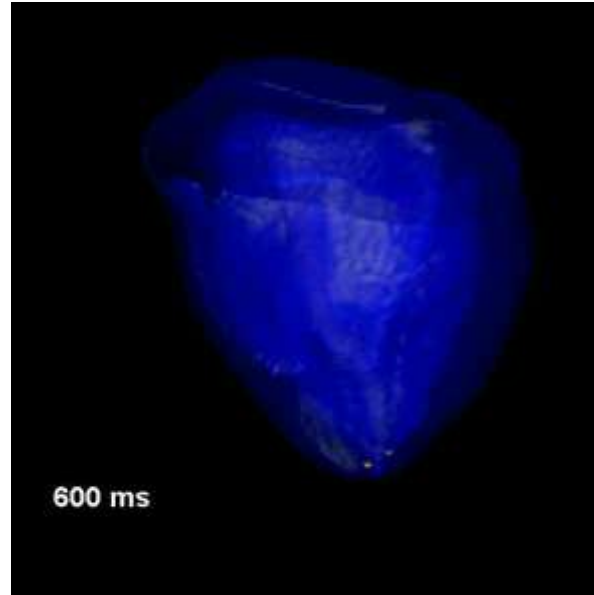
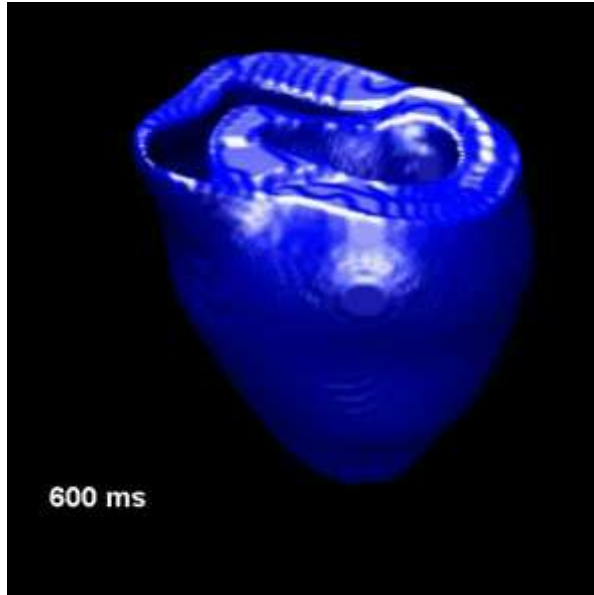
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Re-entry in a whole heart

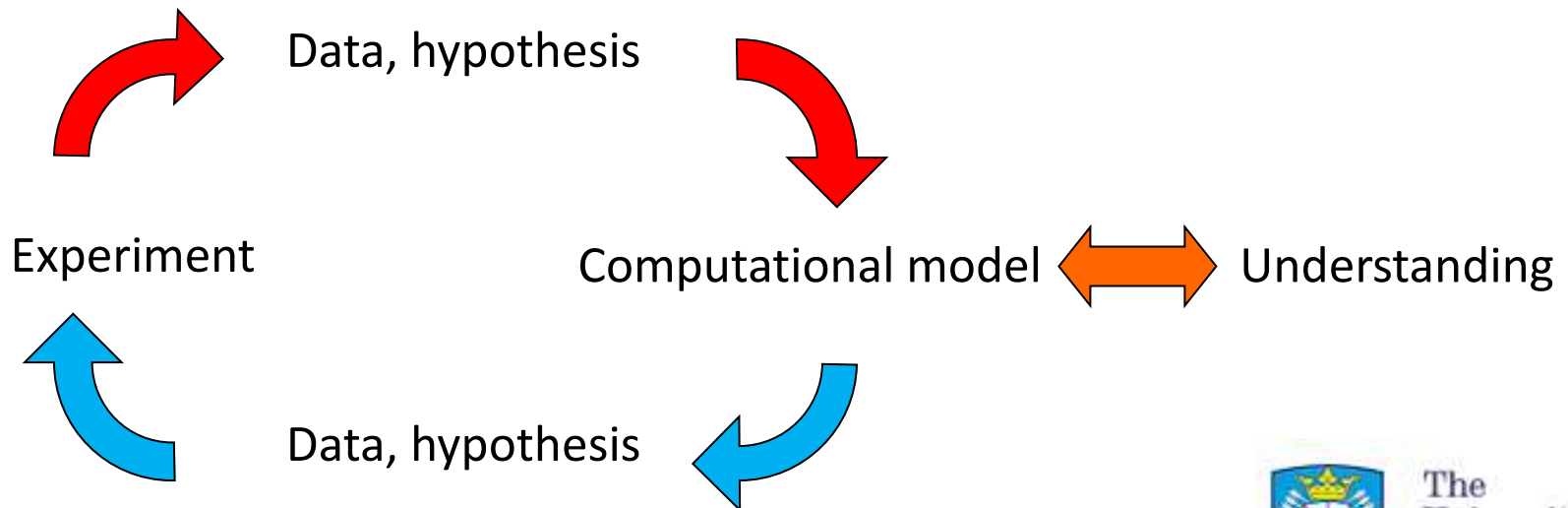


- Models of electrical activity in the heart can indicate 3D activity that can account for 2D observations
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- Complexity of re-entrant (spiral) activity can be measured using filaments



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>