Systems Biology of the Heart: Hope or Hype?

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2nd Year Medics 07 May 2013

Outline

- Concepts & Definitions
- Examples from the Heart
- Mission Impossible
- Praise of Failure

What is Systems Biology?

Perhaps surprisingly, a concise definition of *Systems Biology* that most of us can agree upon has yet to emerge.

Ruedi Aebersold
Institute for Systems Biology, Seattle

Systems Research

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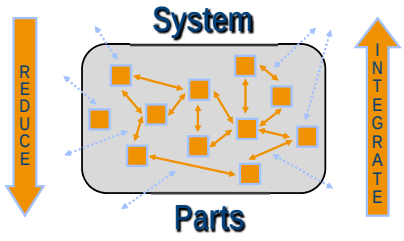
Definition (Ludwig von Bertalanffy, 1901-1972):
A system is an entity that maintains its existence through the mutual interaction of its parts.



Kohl P & Noble D. *Nature Molecular Systems Biology* 2009/5:292.

Systems Research in Biomedicine

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Systems Research: combines
(i) identification and
(ii) detailed characterisation of parts, with
(iii) exploration of their interactions with each other &
(iv) with the environment, to
(v) develop a systemic understanding of the entity, including its effects on (i) to (iv).

'Systems Biology': an *approach* that applies the principles of Systems Research to biological entities.

It is characterised by *dynamic integration of 'reduction' and 'integration'*.

Kohl P & Noble D. *Nature Molecular Systems Biology* 2009/5:292.

What are the Tools?

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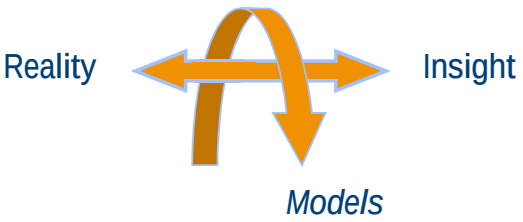

What is a Model?

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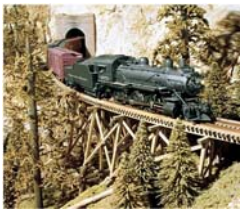

Model =

there is no one-to-one map between reality and models

Kohl P, Crampin E, Quinn TA & Noble D. *Nature Clinical Pharmacology & Therapeutics* 2010/88:25–33.

How to Pick 'the Right' Tools?

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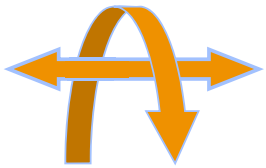
Reality  Insight

Models

- *Relevant*
- *Representative*
- *Reproducible*
- *Reasonable*

Models of Biological Systems

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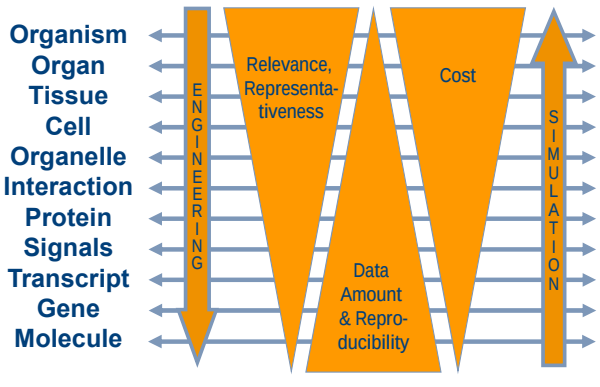

Kohl P, Bollensdorff C & Garny A. *Exp Physiol* 2006/91:307-321.

Surely Genes Determine Life?!

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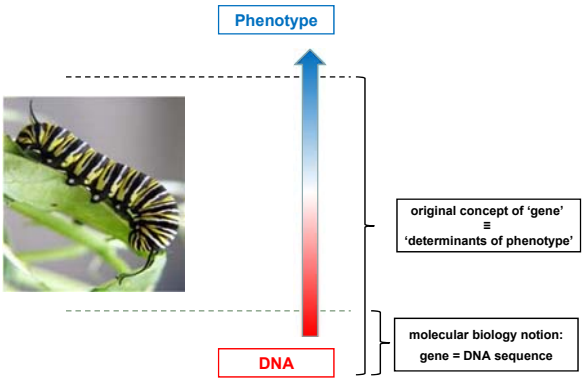

Kohl P, Crampin E, Quinn TA & Noble D. *Nature Clinical Pharmacology & Therapeutics* 2010/88:25–33.

Outline

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- Concept & Definitions
- Examples from the Heart
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- Praise of Failure

Heart Modelling

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- Currently best developed organ model
- High degree of spatio-temporal regularity
- High-quality structure and function data (ECG to patch clamp, histo to CT and MRI, etc.)
- Long history (Phillips light bulb model 1928; bio-physical cell models since 1960, bulk 3D cardiac geometry models 1990s, histo-anatomical models 2000s
- High relevance / visibility

Cell to Organ

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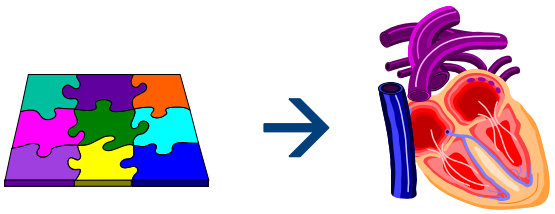

Cell to Organ

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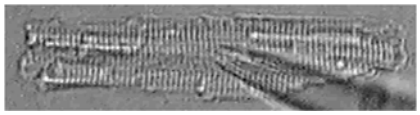

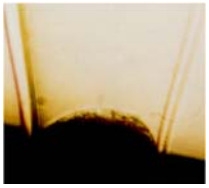

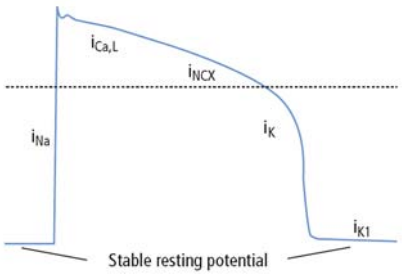

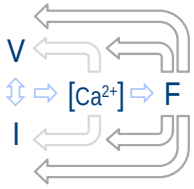

Cell EP Modelling I

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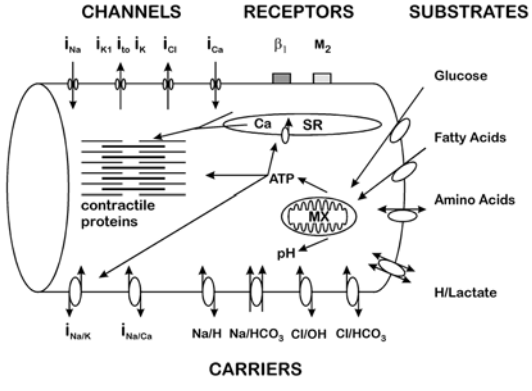

Noble D. *Nature* 1960/188:495-497. Iribe G *et al. Phil Trans Roy Soc Lond* 2006/364:1107-1133.

Cell EP Modelling II

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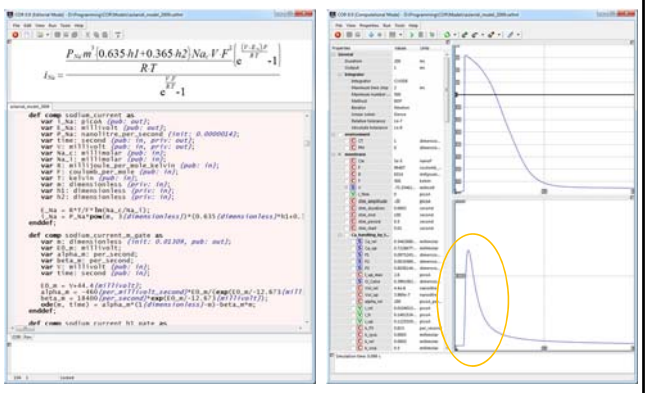

Garny A, Noble D, Hunter PJ & Kohl P. *Phil Trans Roy Soc A* 2009/367(1895):1885-1905.

Calcium Behaviour is Non-Homogeneous

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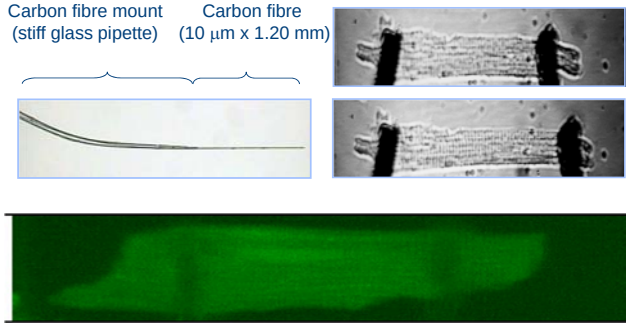
Carbon fibre mount (stiff glass pipette)

Carbon fibre (10 μm x 1.20 mm)



Iribe G *et al. Circulation Research* 2009/104:787-795.

Stretch Effects on Calcium Sparks

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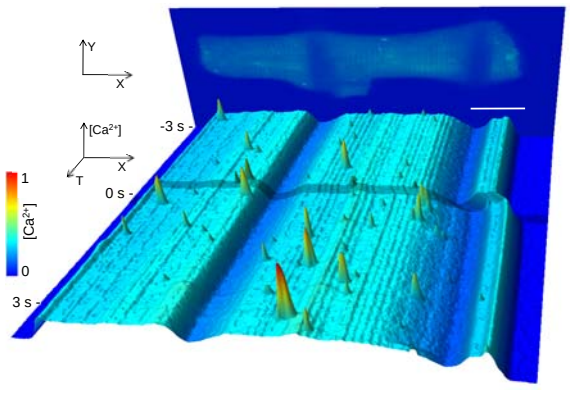

Iribe G *et al. Circulation Research* 2009/104:787-795.

3D Nanoscale: the Missing Link

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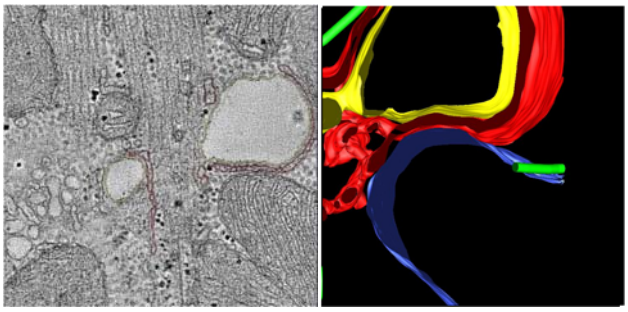

EM Tomography (4 nm)

Iribe G *et al. Circulation Research* 2009/104:787-795.

Cell to ECG

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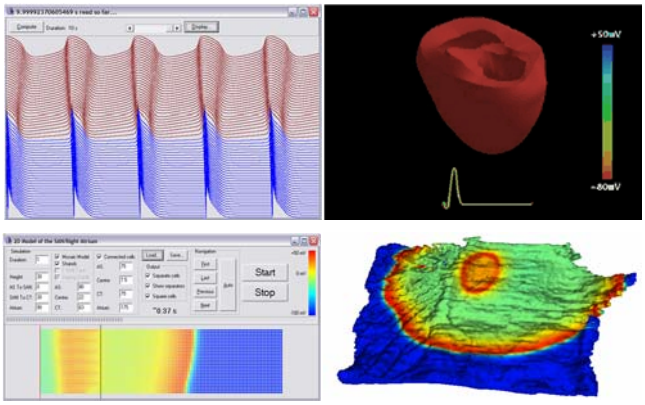

Garny A et al. *Intl J Bifurcation & Chaos* 2003/13:3579-3590.

Winslow lab, JHU, ca. 1998.

What Cell? Muscle is Non-Homogeneous!

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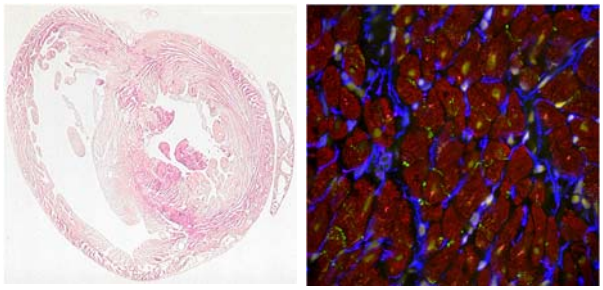

Largest by volume: cardiomyocytes.

Largest by numbers: fibroblasts.

...plus endothelium, vascular smooth muscle, blood & immune cells, neurones.

Camelliti P & Kohl P. *Heart Rhythm* 2012/9:461-464

Organ Models with Para-Cellular Resolution

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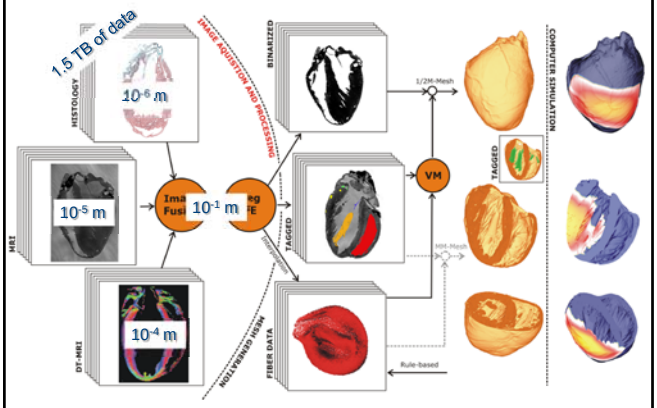

Plank et al. *Phil Trans Roy Soc A* 2009/367:2257-2292.

Organ to Cell

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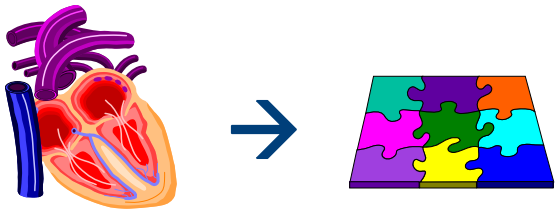

Model-Guided Parameter Extraction

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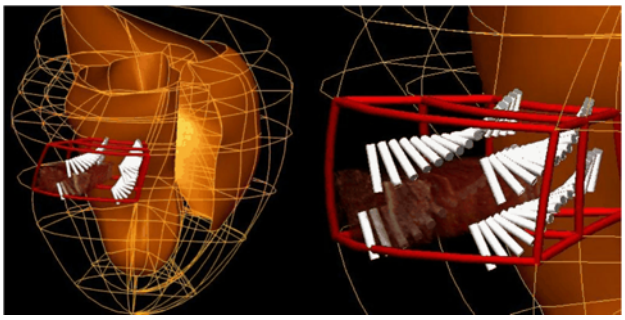

Nash MP & Hunter PJ. J *Elasticity* 2001/61:113-141.

Pressure-Volume → Force-Length

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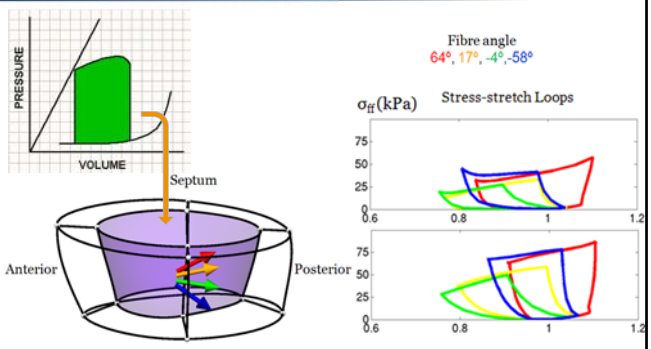

Homogeneous pressure-volume loops in the ventricles are associated with *inhomogeneous* force-length loops at cell levels.

Wang VY *et al.* In: *Cardiac MEC and Arrhythmias* (2nd ed.). OUP Oxford. 2011/pp.241-250.

Building Models to Match

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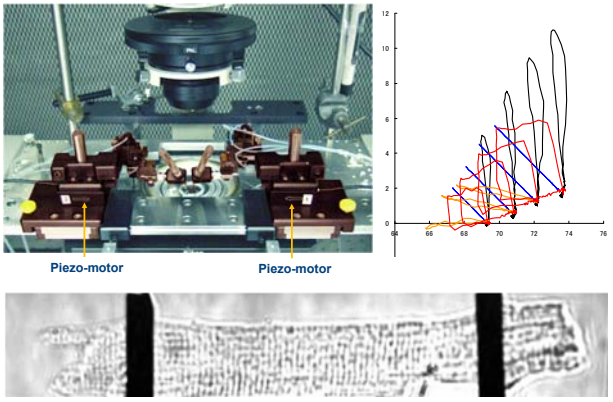

Iribe, Helmes & Kohl. *AJP* 2007/292:1487-1497.

Summary

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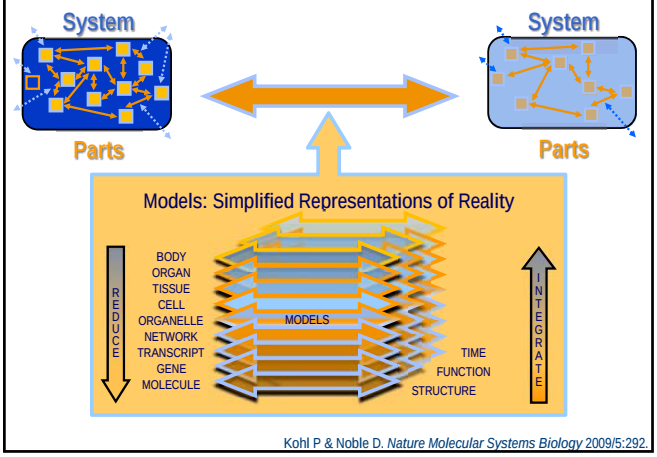

Kohl P & Noble D. *Nature Molecular Systems Biology* 2009/5:292.

Challenges

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- Noninvasive imaging (preferably human)
- Structure mapping
- Motion = artifact
- L: Nano-to-Micro 0.1 nm to 100 μm (10^6)
- L: Micro-to-Macro 1 μm to m (10^6)
- High spatio-temporal resolution
- Function prediction
- No motion = exitus
- T: Nano-to-Micro ns to seconds (10^9)
- T: Micro-to-Macro ms to months (10^9)

Kohl P & Noble D. *Nature Molecular Systems Biology* 2009/5:292.

Mission Imperative!

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No alternative for quantitative study of dynamic structure-function interactions in complex systems, but beware of 'plausibility trap'.

Quantitative 'dry' models *can* guide insight if conducted in iteration with 'wet' experiments / observations for data input and hypothesis validation.

System behaviour is 'multi-scale'.

There is no 'privileged' level of insight (although the cell is a pragmatically useful reference point for many biological systems).

Kohl P & Noble D. *Nature Molecular Systems Biology* 2009/5:292.

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- Mission ~~Impossible~~ imperative
- Praise of Failure

Praise of Failure

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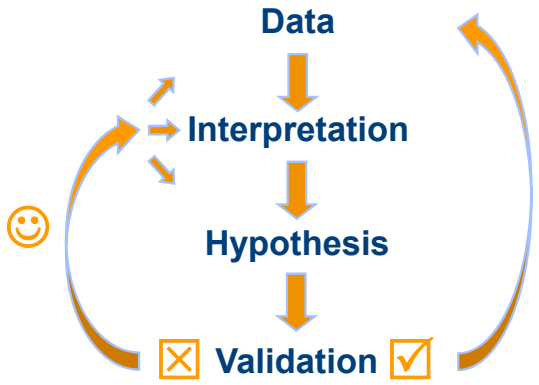

Kohl P, Crampin E, Quinn TA & Noble D. *Nature Clinical Pharmacology & Therapeutics* 2010/88:25–33.

Acknowledgements

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Cardiac Biophysics:	*Carlos Afonso, Rebecca Bayliss, Christian Bollensdorff, Katherine Fletcher, Skye Kelly-Barrett, Remi Peyronnet, Alex Quinn, Urszula Siedlecka, Ken Wang*
Alumni:	*Gil Bub, Rebecca Burton, Patrizia Camelliti, Patricia Cooper Alan Garny, Michiel Helmes, Gentaro Iribe, Peter Lee*
University of Oxford:	*Ramón Casero Cañas, Sara Dutta, David Gavaghan, Vicente Grau, Gary Mirams, Denis Noble, Blanca Rodriguez, Jürgen Schneider*
Ann Arbour:	*José Jalife*
Auckland:	*Peter Hunter, Colin Green, Hilary Holloway*
Uni Colorado:	*Andy Hoenger*
Connecticut:	*Leslie Loew, Ping Yan*
EMBL Heidelberg:	*Christian Boulin*
Ekaterinburg:	*Vladimir Markhasin, Olga Solovyova*
Johns Hopkins:	*Rai Winslow, Natalia Trayanova, Brian O'Rourke*
Maastricht:	*Uli Schotten*
Okayama:	*Gentaro Iribe*
Pordenone:	*Tommaso Pellis*
Stanford:	*Euan Ashley, Chris Woods*

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The Magdi Yacoub Institute