Engineering Computational Biology

Bruce Gardiner
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Engineering Computational Biology

• Computational modelling of biological systems
• 6-8 academic members (incl. 4-5 postdocs)
• School of Computer Science and Software Engineering
  • Civil Engineers
  • Chemical Engineers
  • Physicists
  • Applied Mathematicians
  • Computer Scientists
  • Biologists
• Not bioinformatics or statistics
‘Integrative’ biology
Engineering Computational Biology

Computational models of biological systems including:
- Cell signalling pathways (e.g. IGF, Wnt/β-catenin, TGFβ, Rank)
- Cell-tissue interactions (e.g. tissue remodelling, mechanobiology)

Applications:
- Musculoskeletal systems
- Colon cancer, prostate cancer
- Renal physiology
- Wound healing following glaucoma surgery
Many roles for computational modelling in understanding biological systems

- Integration
- Prediction
- ‘value add’ data
- Abstraction
- Hypothesis testing
- Hypothesis formulation
- An organising ‘framework’
Counter-current vessels in the kidney

O’Connor et al. (2005)

AV
AA

Oxygen shunting

Nordsletten et al. (2006)
Need for integrative methods to understand regulation of renal $O_2$

- What is the relative importance of each interaction?
- Where is the anatomy?

Consumption $\text{VO}_2$

$z=0$  \hspace{3cm} z=L$

Change in total oxygen concentration along artery

Renal blood flow rate

$Q \frac{\partial C^A}{\partial z} = -\alpha D \left( c^A - c^V \right)$

Shunting

11 orders of arteries and veins arranged in a counter-current fashion

Based on published data from micro-computed tomography
Model predictions investigating the role of various factors influencing renal O$_2$

Arterial PO$_2$  

Blood flow  

Hemodilution

Gardiner et al. AJP: Renal Phys. (2011)
Model Prediction: For shunting to work best there will be a region surrounding artery-vein pair devoid of capillaries and tubules. (Hypothesis formulation!)

![Graph showing AV-shunting activity](graph.png)

- AV-shunting (nmol/m.min)
- Distance (μm)
- No capillaries or tubules near AV pair
- Capillaries and tubules near AV pair

Extracellular IGF transport and interactions in articular cartilage

Zhang et al. PLoS ONE 2013
Wnt/β-catenin intracellular signalling pathway

Can a biologist fix a radio?—Or, what I learned while studying apoptosis

RING Finger Domain
(RING: Really Interesting New Gene)
‘Tuning’ required for emergent properties

\[
\frac{\partial u}{\partial t} = D\delta \nabla^2 u + \alpha u(1 - r_1 v^2) + v(1 - r_2 u) \\
\frac{\partial v}{\partial t} = \delta \nabla^2 v + \beta v \left(1 + \frac{\alpha r_1}{\beta} uv\right) + u(\gamma + r_2 v),
\]

Figure 1. The radio that has been used in this study
Can a biologist fix a radio?—Or, what I learned while studying apoptosis

Yuri Lazebnik

CANCER CELL: SEPTEMBER 2002 · VOL. 2 · COPYRIGHT © 2002

Figure 1. The radio that has been used in this study

RING Finger Domain
(RING: Really Interesting New Gene)
Why might a cell have a two-step process in a ligand-receptor interaction?

- e.g. Wnt
- e.g. LRP5/6
- e.g. Frizzled
- e.g. beta-catenin degradation
Transient response
Transient response: ignores short duration signals.
Colon crypt regulation

Reya and Clevers (2005)
Abstraction and hypothesis testing in a model of epithelial cells in colon crypts

Alternate initial states

Alternate cell decisions

Abstraction and hypothesis testing in a model of epithelial cells in colon crypts

Pedigree versus Niche

Biological *in silico* lab
Wnt signalling and colon crypt project

• Targeted quantitative measurements of key Wnt signalling protein concentrations in a range of mammalian cells
  • Steady state
  • Transient response e.g. wnt stimulation, cyclohexamide
  • Cell compartmental concentrations
  • Crypt concentrations

• 4D Imaging of crypts and organoids in gell
  • Cell shape
  • Crypt shape
  • Crypt development
  • Development under mechanical and chemical perturbations

• Computational Modelling
  • Cell signalling pathways
  • Epithelial cell dynamics
  • Crypt development
What in the world is happening?

US National Centers for Systems Biology, (NIH and NIGMS)
- [http://www.systemscenters.org/](http://www.systemscenters.org/)
- 2013 10th Anniversary.

NIH: Predictive Multiscale Models for Biomedical, Biological, Behavioral, Environmental and Clinical Research (Interagency U01)

**SystemsX:ch:** Swiss initiative on Systems Biology,
- 120 million Swiss Francs (2008-2012)
- 100 million Swiss Francs (2013-2016)
- ~Aus$40million per year, Swiss pop: ~8million,
- ‘largest ever public research initiative in Switzerland’
**Acknowledgements**

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Prof Alan Grodzinsky (MIT)
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(WEHI, Melbourne)

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Jennifer Ngo (Monash)
Dr Paul O’Connor (Georgia)

**UWA**
W/Prof David Smith
Dr Saptarshi Kar (kidney)
Dr Kelvin Wong (colon)
Dr Francis Woodhouse (cartilage)

Dr Richard van Der Wath (colon)
Dr John Davidson (cartilage)
Dr Sarah Thompson (kidney)

**Funding**
NHMRC, ARC
<table>
<thead>
<tr>
<th>Grant Type</th>
<th>Years</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>ARC Discovery</td>
<td>2014-2016</td>
<td>The comparative physiology of oxygen delivery to the kidney</td>
</tr>
<tr>
<td>NHMRC Project</td>
<td>2013-2015</td>
<td>Bridging the gap between cartilage biology and osteoarthritis risk prediction</td>
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<td>NHMRC Project</td>
<td>2013-2015</td>
<td>Glycomic control of cartilage extra cellular matrix turnover</td>
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<td>NHMRC Project</td>
<td>2012-2014</td>
<td>Investigating the roles of the wnt and notch signalling systems in the colon</td>
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<tr>
<td>ARC Linkage</td>
<td>2011-2014</td>
<td>Bioengineered bioscaffolds for Achilles tendinopathy treatment</td>
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<td>NHMRC Project</td>
<td>2010-2012</td>
<td>Hypoxia is the common pathway to renal failure</td>
</tr>
<tr>
<td>ARC Discovery</td>
<td>2009-2011</td>
<td>Engineering cartilage homeostasis in health and disease</td>
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<td>NHMRC Project</td>
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<td>Stimulations of colon cancer</td>
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<td>NHMRC Project</td>
<td>2009-2011</td>
<td>Regulating fluid mechanics to improve the outcome of glaucoma surgery</td>
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<td>Prostate Cancer</td>
<td>2009-2010</td>
<td>Integrative systems modelling of prostate cancer bone metastases</td>
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Synchrotron-based micro computed tomography

James Pearson
Mechano-chemical environment of chondrocytes

Nutrients, growth factors, waste etc

Solute transport

Chemical microenvironment

ECM Production

Enhance/inhibit?

Mechanical microenvironment

ECM Degradation

Enhance/inhibit?

Applied load/strain
This thrusts biology into a new era. For the past century the tools and concepts of chemistry have driven biology. This is so much a part of the landscape of modern biology that it will be shocking to many when, in the next century, biology becomes largely driven by engineering and physics. This is a consequence of the fact that understanding the dynamics of even the simplest biological networks requires the application of mathematical approaches and the generation of models and simulations. These mathematical tools are not now part of the average biologists’ training. Indeed, biology has almost become the province of those who want to do science without learning mathematics. Consequently, two major issues in the evolving field of systems biology are needed to create functional collaborations between engineers, physicists, and biologists, and to produce a new generation of scientists that will be conversant with both the mathematical tools and the biological systems. Both of these issues were a major concern of the study.
Multiscale, patient specific modelling of cartilage

Stage 1: Morphing 3D Lower Limb Model (UAuck)

Stage 2: Create consistent musculoskeletal and knee joint FEM models (UAuck, UWA)

Stage 3: Neuro-musculoskeletal (UWA)

Stage 4: Joint elastic and cartilage poroelastic FEM (UWA, UMelb)

Stage 5: Cartilage Cellular Signalling (UWA, UMelb)

Chemical environment

Chondrocyte

Biosynthesis

Mechanical environment