Development as a way of life: embedding cellular dynamics in physiological models

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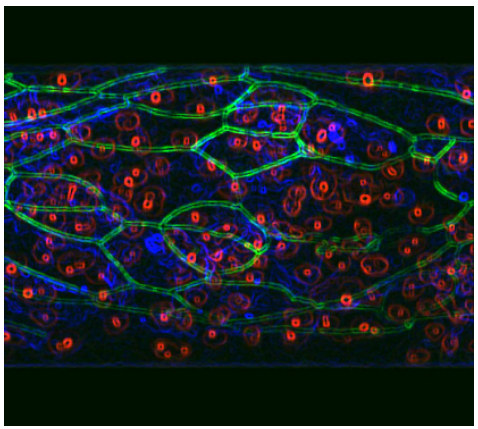
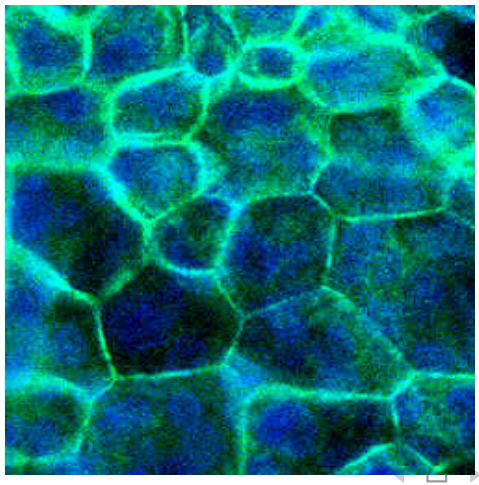
The scientific problem: how do we self-assemble?

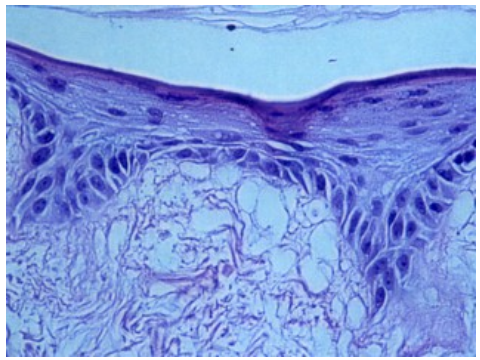
30,000 genes $\rightarrow$ 100,000 proteins $\rightarrow$ 10^{13} cells $\rightarrow$ 1 organism

- multiscale complexity
- there is a 1:n relationship between genes and proteins, so gene sequence alone does not specify which proteins are produced
- we do not know the relationship between structure, function and dynamics
- there is no blueprint at any level

A (possibly) manageable question – how does the emergent behaviour resulting from cell-cell interactions produce properly structured and functional tissues – with a particular focus on epithelial tissues







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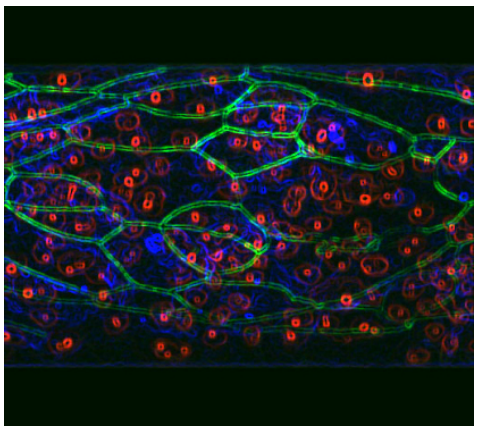
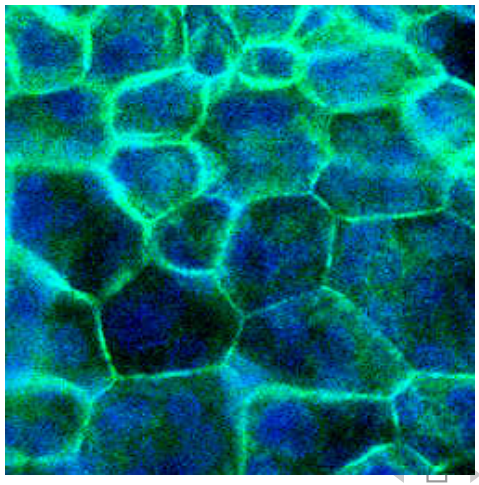
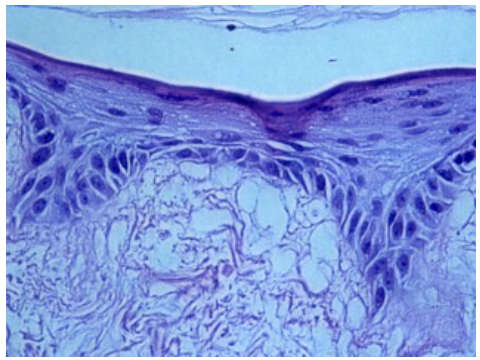
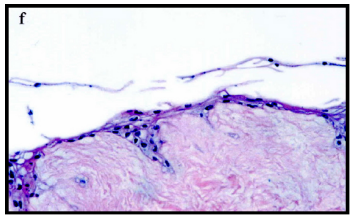
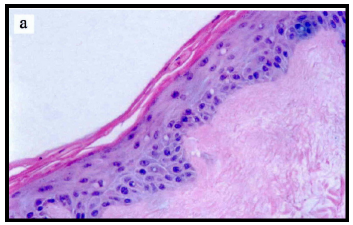


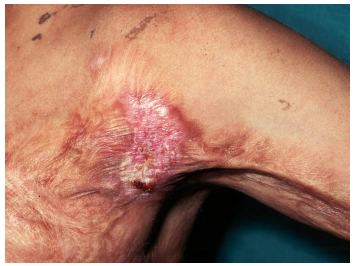


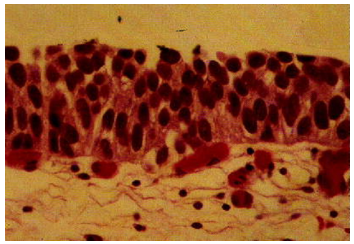


Clinical problems of cellular behaviour in epithelial tissues









- Cells behaving well
  - how does properly structured and functional tissue self-assemble
  - how does homeostasis work
- Cells behaving badly
  - why do wounds not heal
  - what controls the development of neoplasms
- Problem driven (medium to long term)
- Aim is fundamental understanding leading to rational design of therapy
- Very close coupling of biologists and physicists/engineers/computer scientists
- Environment provides the route from laboratory to commercial exploitation/clinic

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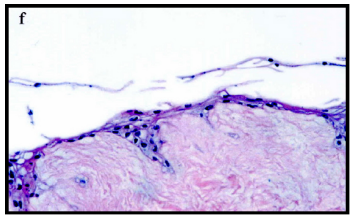

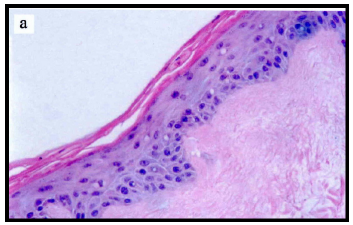

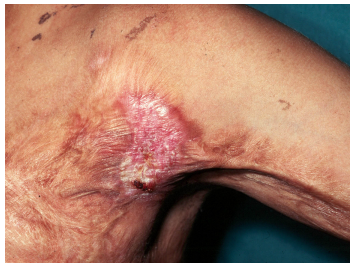

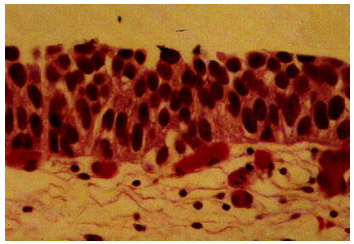

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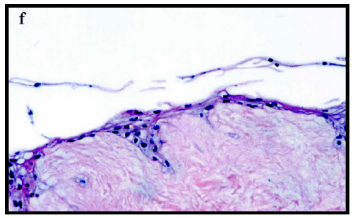

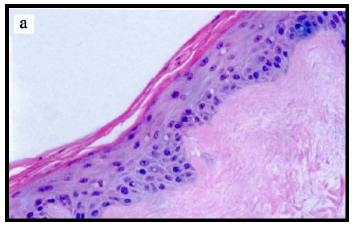

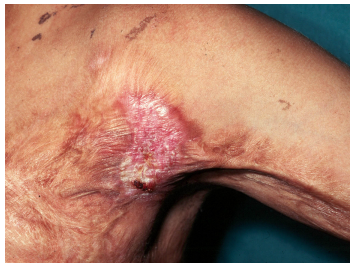

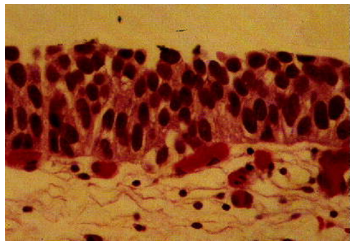

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Movies to illustrate system behaviour

Three movies to illustrate system behaviour *in vitro*:

- Gemma's wound model
- Zac's calcium signalling model
- Salem and Sun Tao's computational model

Components of the biological system

If we consider skin, we have the following components and behaviours:

- dermis/supporting structure – muscle, connective tissue etc – physical properties, diffusion, bonding
- basement lamina/membrane – collagen, bonds, signalling
- cells – grow, divide, die, differentiate
- signalling – intra/inter cellular, gap junction, surface ligands and receptors, diffusion through extra-cellular space, mechanotransduction
- forces – cell organisation, mechanotransduction

physical models

physical and signalling models

cell-cycle model, gene networks, proteomics

signalling models

coupled cell-tissue physical models

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The modelling paradigm – cell-centric development of tissues

The cell is the smallest unit that contains all the information (genes) and machinery (protein factory) that is required for replication
and
there is no information at a higher level than the cell – the structure and function of multi-cellular organisms is the result of the behaviour and interaction of individual cells

so:

- we represent individual cells by a software construct (an agent)
- the agent (cell) behaviour is controlled by a set of functions (mathematical or logical)
- space can be discrete (a lattice) or continuous
- can potentially have a large number of individuals (millions)
- can be many types of individuals
- the model has no information or imposed behaviour above the level of the cell (question - at what level are we interested in emergent behaviour?)
- the higher-level behaviour is therefore an emergent property of cell interaction

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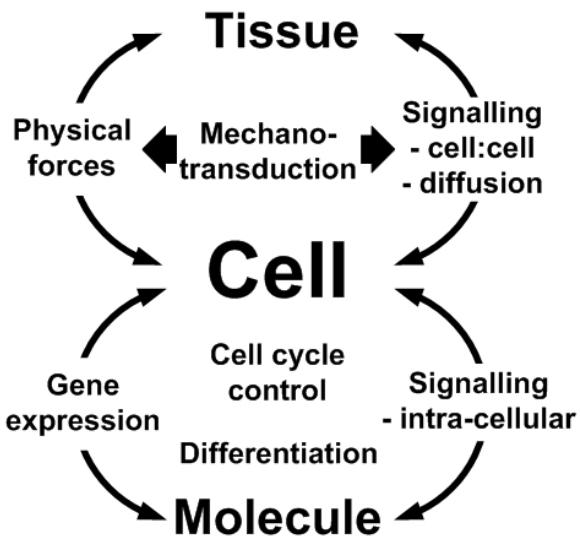
What we don't want and what we might need in a model:

We do not want a model that contains everything in the real cell:

- we don't know everything
- it really is too complex
- might just as well use the real cell – it computes faster!
- we learn by abstraction

We might need:

- a memory to store cell phenotypes (more gene expression than genes per se)
- the cell cycle
- physical forces
  - growth
  - cell-cell and cell-substrate bonds
  - motility
- cellular machinery
- signalling
  - inter- and intra-cellular
  - mechanotransduction
- modularity/extensibility
- ability to link to or embed other models



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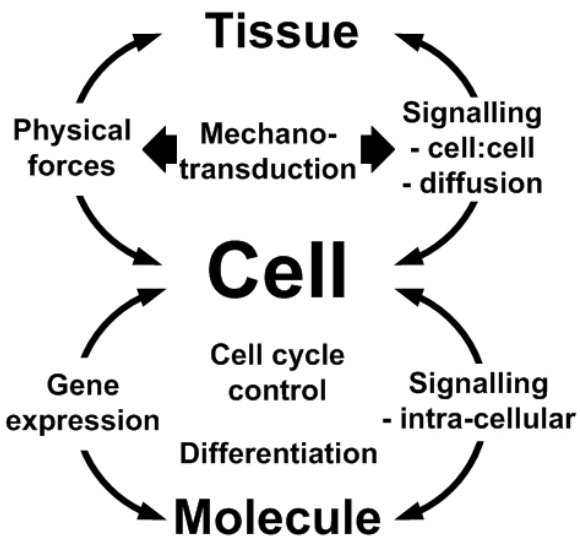

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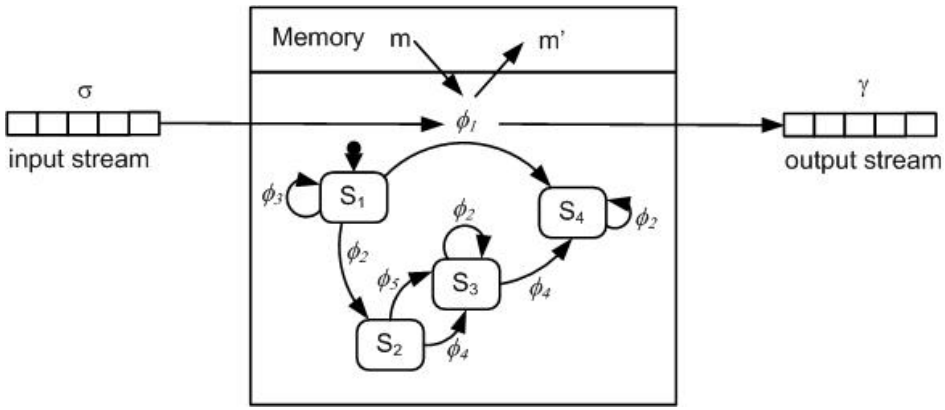
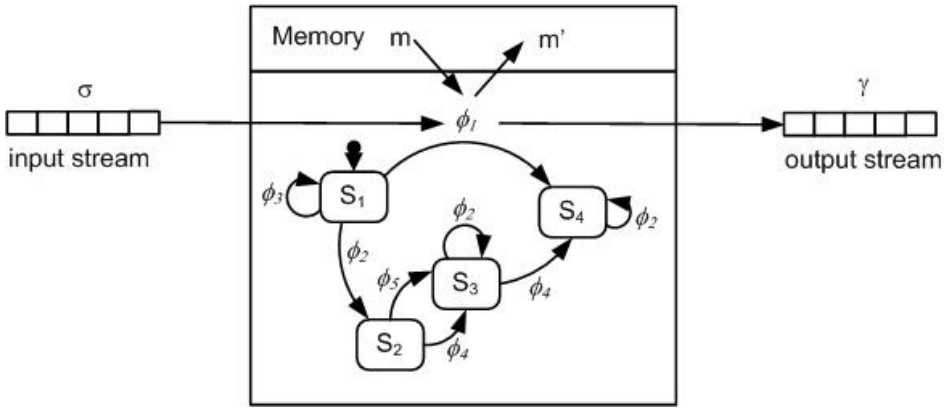
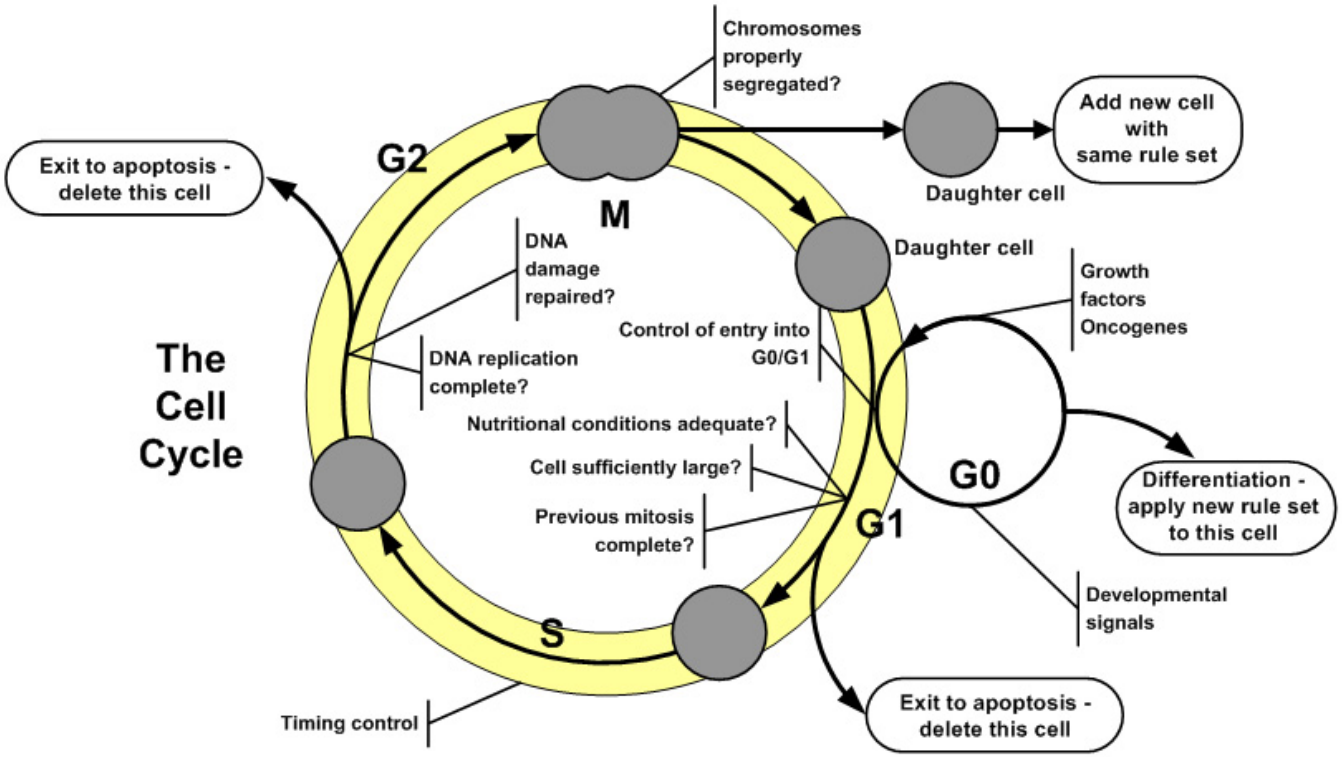
A formal approach to modelling individual cells

- we use a formally-defined state machine – a communicating stream X-machine (originally described by Eilenberg, and extended by Holcombe et al) – and formal software-engineering methods to build the models
- the formality is a result of our aim to inform intervention in clinical problems
- formal verification (even at individual cell level) is impractical – we need to gain some understanding of constraints on emergent systems
- the modelling frameworks – either FLAME (http://www.flame.ac.uk) or MUSCLE (http://muscle.berlios.de) – explicitly allow the building of multiscale, multiparadigm models

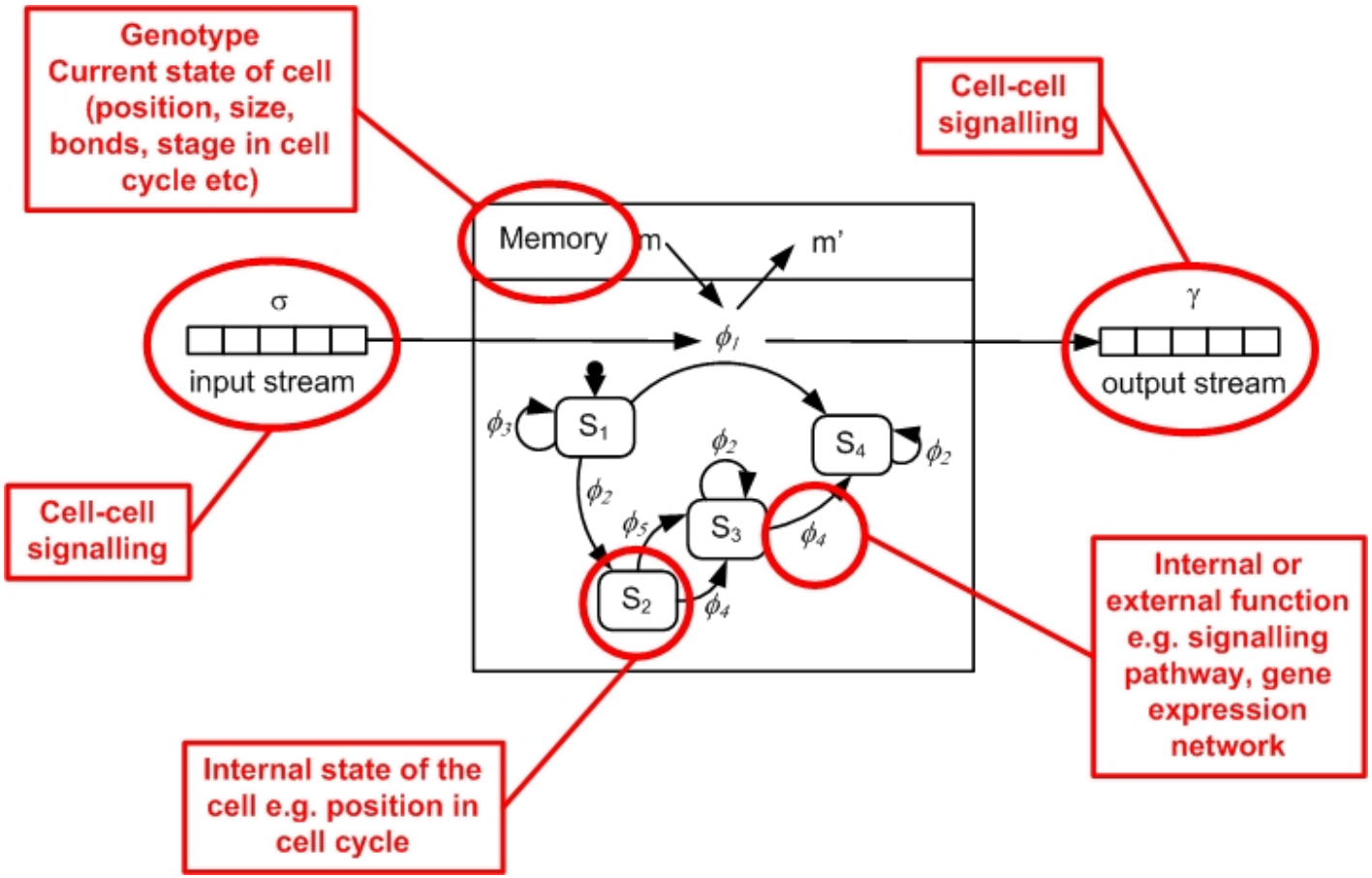


The cell as a state machine





The state machine as a cell



Modelling deficiencies

- no formal metamodel or graphical description language to describe the structure and processes of the model – we can do this as natural language (which is the cell biologists' description)
- the only way to see what emerges is to let it emerge – no way to predict outputs from a list of components and interactions other than running the model
- need a virtual biology interface – like Simulink – so biologists can play
- need to be able to robustly abstract models so they will run in 30 minutes on a desktop machine – otherwise they will not be used in clinic and pharma

Experimental deficiencies

- noisy/incomplete biological data
- inability to track cells in 3D
- inability to identify cell type non-invasively (phenotype is more a process than a state)

Inputs and outputs

- Models have many uses, and the user interface is a function of the use:
  - understanding complex systems – which are not necessarily biological
  - understanding a particular problem
  - predicting behaviour
  - teaching
- components, interactions, structure, processes and initial conditions need to be defined
- the starting point might be a model that has been run until it reaches a stable state (homeostasis), which is used as a basis for perturbation
- post-processing should give graphs/images that are quantitative and can be directly compared to outputs of biological experiments

Biological and computational outputs

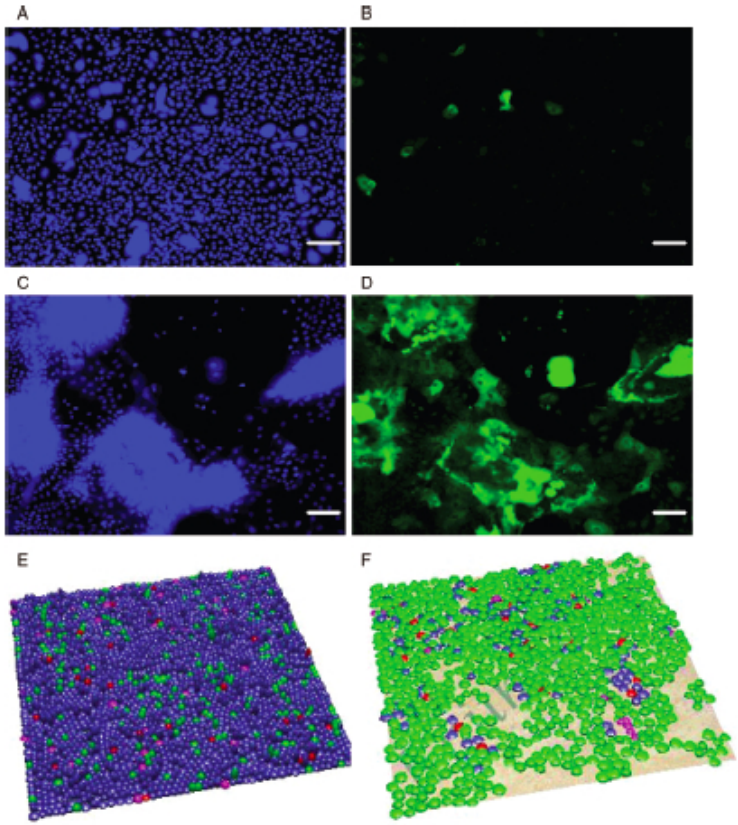


FIG. 5. Micrographs of **(A)** 4′,6-diamidino-2-phenylindole dihydrochloride (DAPI)-stained and **(B)** involucrin-immunostained normal human keratinocytes cultured in medium with low calcium, **(C)** DAPI-stained and **(D)** involucrin-immunostained normal human keratinocytes cultured in medium with high calcium. **(E** and **F)** Plots of modeled normal human keratinocytes after 12 days of simulated time in 0.05 mM calcium **(E)** and 2.0 mM calcium **(F)**. Red: stem cell; blue: transit-amplifying cell; pink: mitotic cell; green: terminally differentiated cell.

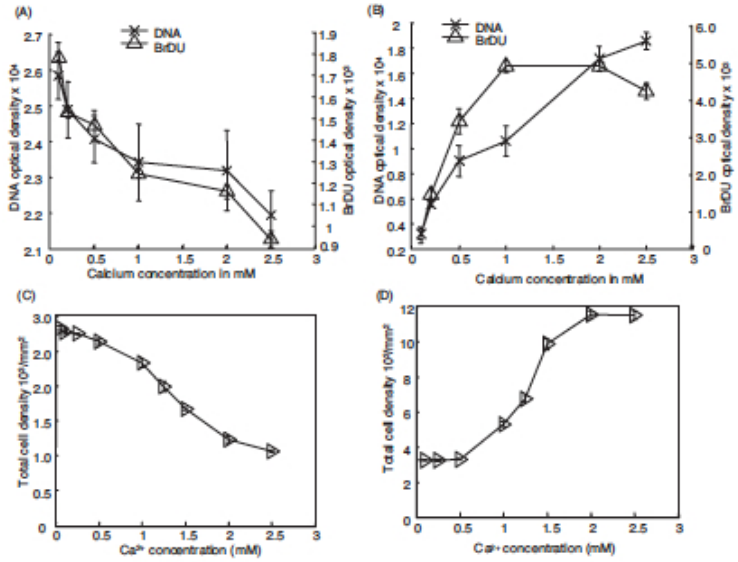
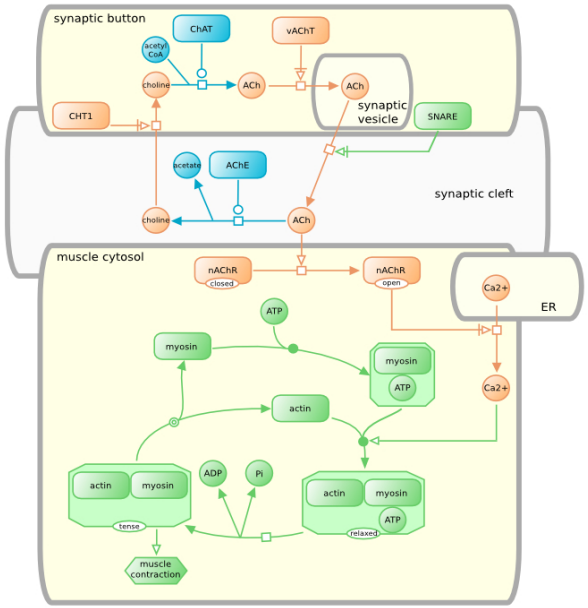


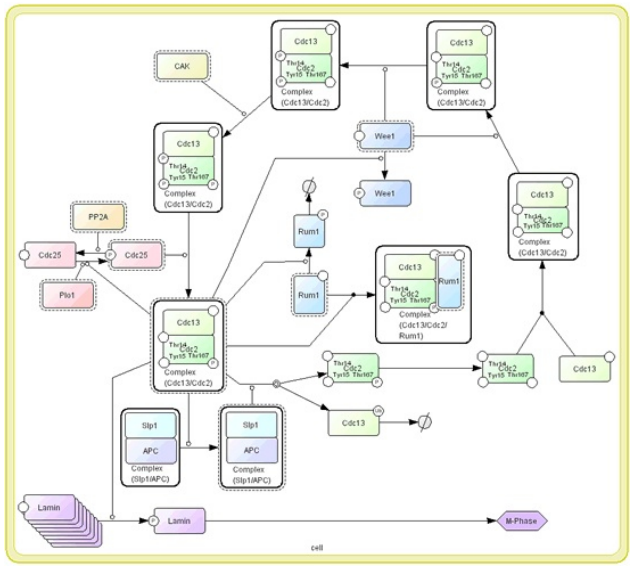
FIG. 4. Total population DNA of normal human keratinocytes **(A)** and HaCat cells **(B)** cultured in medium with varying levels of calcium. Virtual DNA assay (total modeled cell density vs calcium concentration in mM) for normal human keratinocytes **(C)** and HaCat cells **(D)**.

CBO/CBMSL/repository

What can we learn from others?

- a super-set of the Systems Biology Graphical Notation (SBGN) to provide diagrams of cell behaviour?
- the concept of three orthogonal languages in SBGN:
  - Process Description language
  - Entity Relationship language
  - Activity Flow language
- link to other ontologies (GO, OPB etc) to describe model components and interactions
- need to describe model assembly, starting conditions, boundary conditions etc
- model sharing (repository) is essential





Ackowledgements

The opinions expressed are my own, but have benefited from discussions with and work by:

- Jenny Southgate (urothelial cell biology)
- Mike Holcombe (X-machine guru)
- Sheila Mac Neil (skin biology)
- Dawn Walker (the original epithelial tissue model)
- Simon Coakley (FLAME, the modelling framework)
- Mark Pogson (cell signalling)
- Tao Sun (cell biology and the skin model)
- Zac Shabir (calcium signalling)
- Nik Georgopoulos (urothelial cell biology)
- Phil McMinn (verification and skin modelling)
- Salem Adra (functions and skin modelling)
- Des Ryan (generic cell model)
- Goodarz Kodabakshi (physical models)
- Rod Hose (physical modelling guru)
- Pat Lawford (numerate biology)

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