Towards multiscale modelling in Systems Biology

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Overview

- Computational modelling & analysis of biochemical networks:
  - ***Explain*** behaviours and mechanisms
  - ***Predict*** behaviour of a system under different conditions.
- Represent biological systems as networks often containing regular structures, i.e. ***repeated occurrences of network patterns***.
- ***Hierarchical organisation*** reflecting physical & spatial organisation of the organism, intracellular to the intercellular level and beyond (tissues, organs etc.).
- ***Multiscale modeling***: solving physical problems which have important features at multiple scales, particularly multiple spatial and/or temporal.
- ***Focus on spatial aspects*** – multiscale time comes 'for free'.
- Current modelling approaches, including Petri nets: limitated to relatively small networks.
- ***Hierarchy + colour*** in Petri nets: supports modelling of large and complex biological systems.

BioModel Engineering

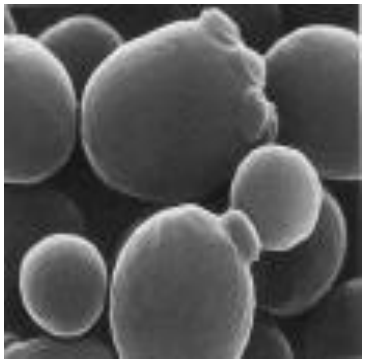
- Takes place at the interface of computing science, mathematics, engineering and biology.
- A systematic approach for **designing**, **constructing** and **analyzing** computational models of biological systems.
- Some inspiration from efficient software engineering strategies.
- Not engineering biological systems *per se,* but
  - describes their structure and behaviour,
  - in particular at the level of intracellular molecular processes,
  - using computational tools and techniques in a principled way.

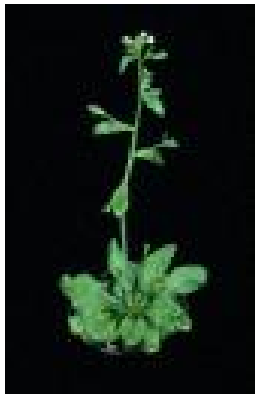
Rainer Breitling, David Gilbert, Monika Heiner, Richard Orton (2008). A structured approach for the engineering of biochemical network models, illustrated for signalling pathways. Briefings in Bioinformatics

David Gilbert, Rainer Breitling, Monika Heiner, and Robin Donaldson (2009). An introduction to BioModel Engineering, illustrated for signal transduction pathways, 9th International Workshop, WMC 2008, Edinburgh, UK LNCS Volume 539, pp13-28

Rainer Breitling, Robin Donaldson, David Gilbert, Monika Heiner (2010): Biomodel Engineering - From Structure to Behavior; : Trans. Comp Systems Biology XII, Springer LNBI 5945, pp. 1-12

What about scaling up?



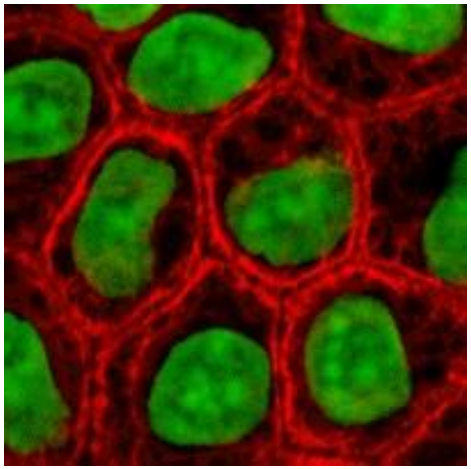


Multiscale modelling challenges

- ***Repetition*** – multiple components with similar definitions
- ***Variation*** – genetic mutants; random variants
- ***Spatial organisation -*** regular / irregular patterns in 1, 2 or 3 dimensions
- ***Communication*** – short & long distance
- ***Hierarchical organisation*** – intra or inter cellular (tissues, organs, …)
- **Movement** – mobility (passive) & motility (active)
- **Replication** - reproduction
- **Exchange** of genetic information
- **Death** – apoptosis, necrosis, etc (quiescence, senescence)

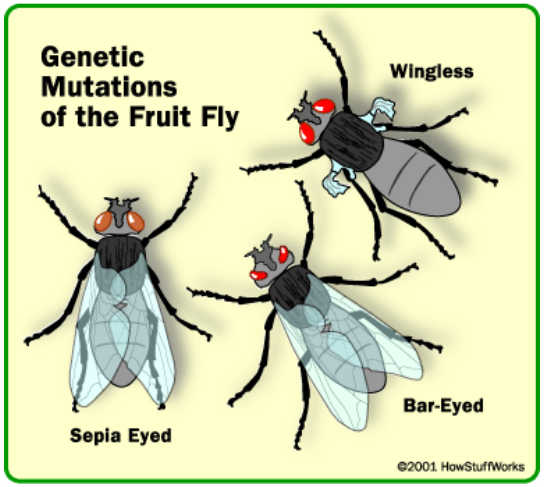
Repetition of individual components

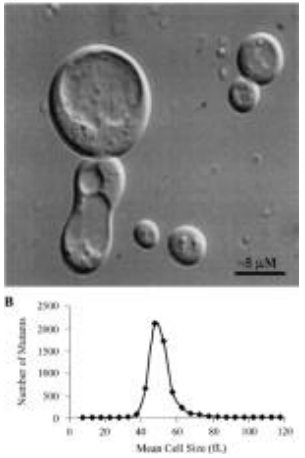
- Components within a cell (organelles etc)
- Multiple cells each of which having a similar definition
- Repeated tissue fragments
- Repeated organs (wings,…)
- Repeated individual organisms

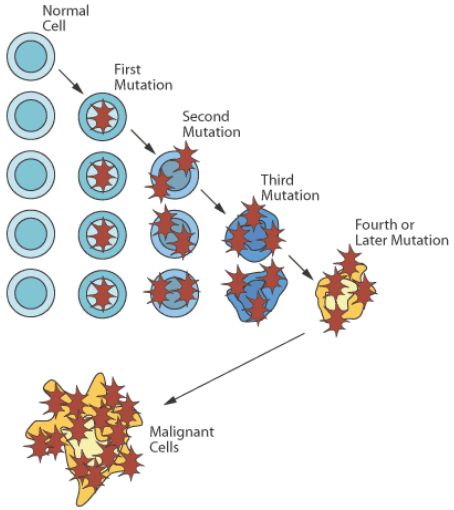


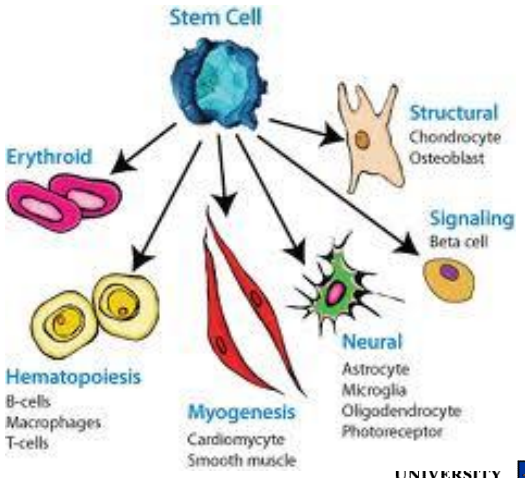
Variation

- Sets of similar components with defined variations
- Random mutation
- Genetic mutants
- Cancerous tissue
- Differentiation



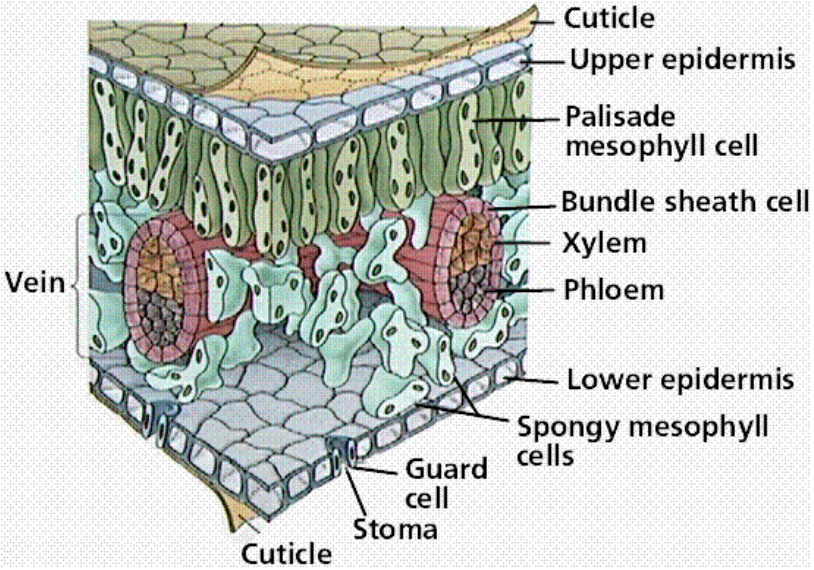




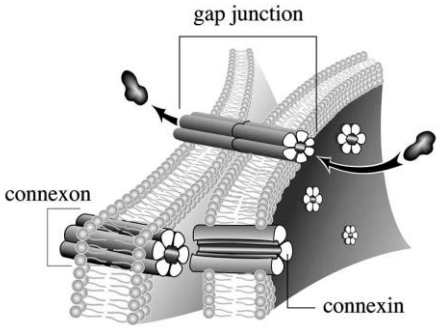


Spatial organisation

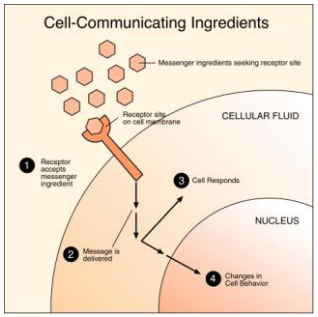
- Between cells
  - how they are organised into regular or irregular patterns over spatial networks in one, two or three dimensions.



Communication



- Between **immediate neighbours** (intracellular complexes)
- **Long-distance** (cytokines etc)



Further constraints:

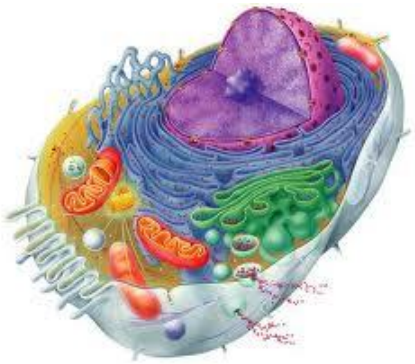
- Type of **relationship** between partners
- Type of component(s)
- History of component(s)
- **Position** of component(s) in spatial network.

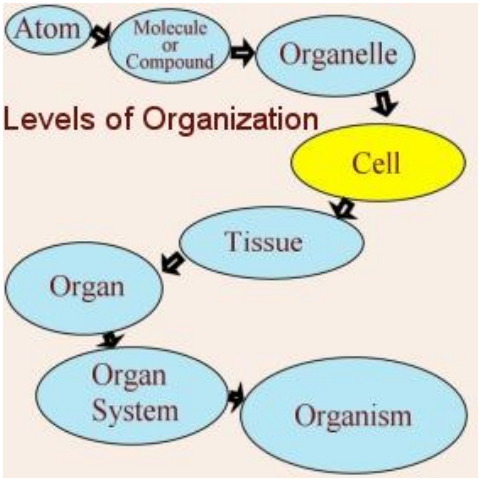
Hierarchical organisation

Components containing repeated sub-components

- Cell containing several compartments /components.

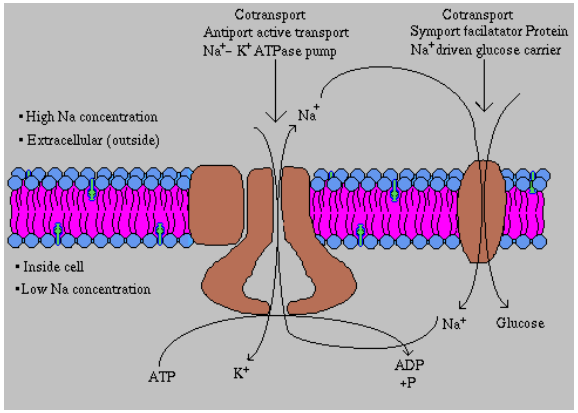
Enables the use of abstraction over level of detail used to describe components



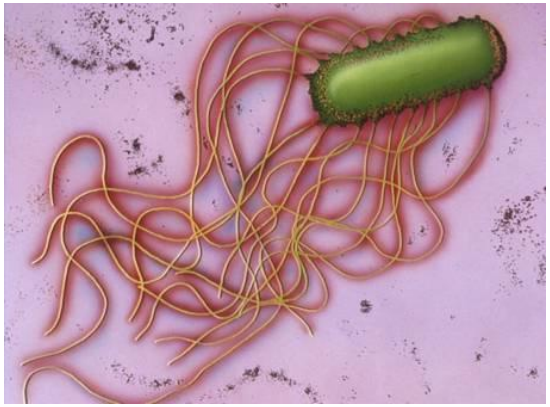


Movement

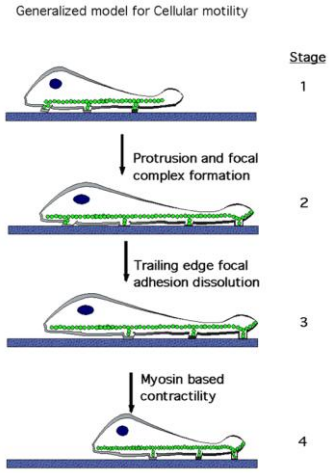
- Mobility – passive movement.
  - Protein transport
  - Sodium transport



- Motility – active movement.
  - Cells using organelles (flagellae)

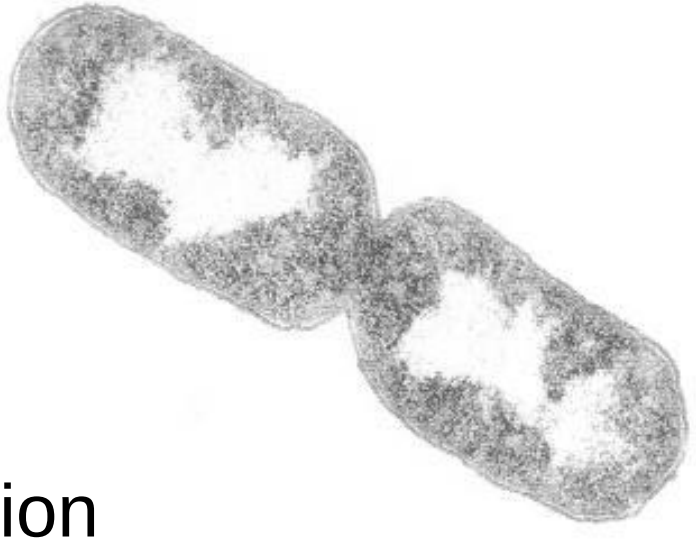


General cellular motility



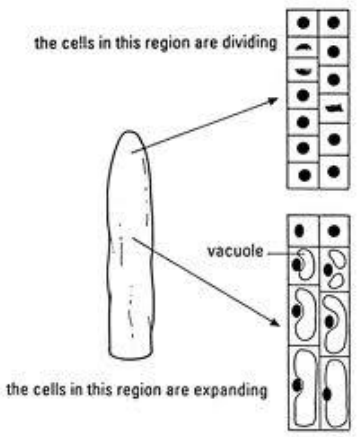
Replication

- E.g. cell division



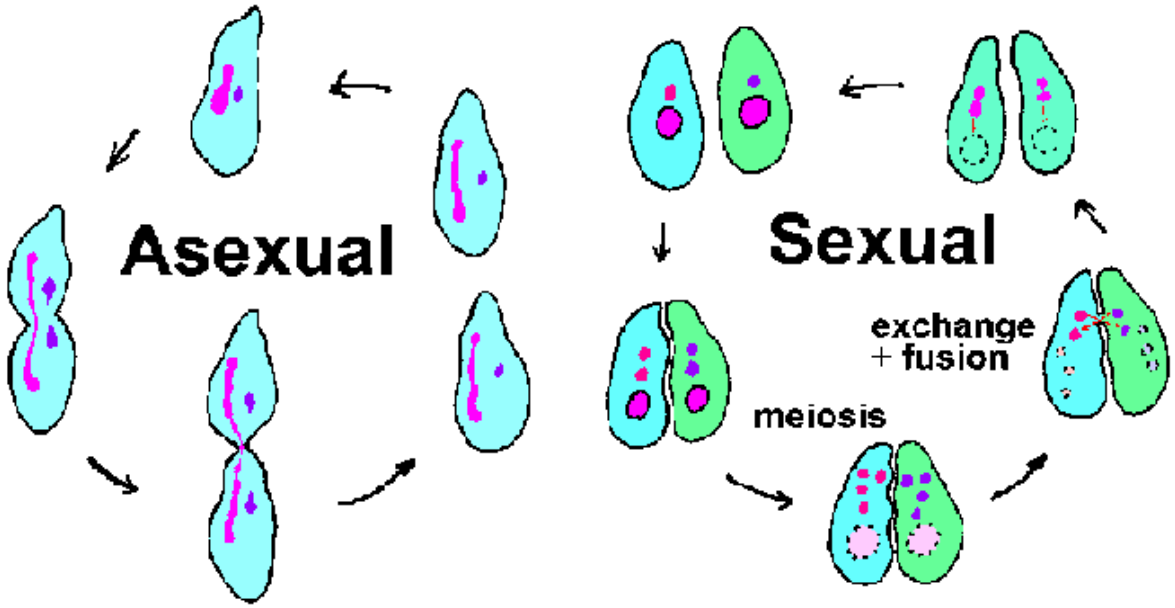
Can take into account:

- Mutation
- Spatial organisation / position



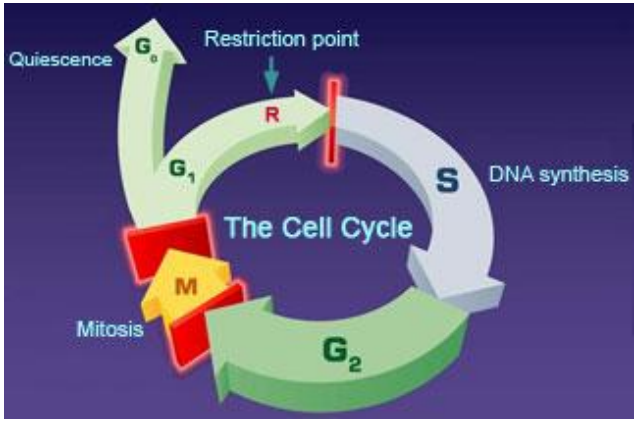
Exchange

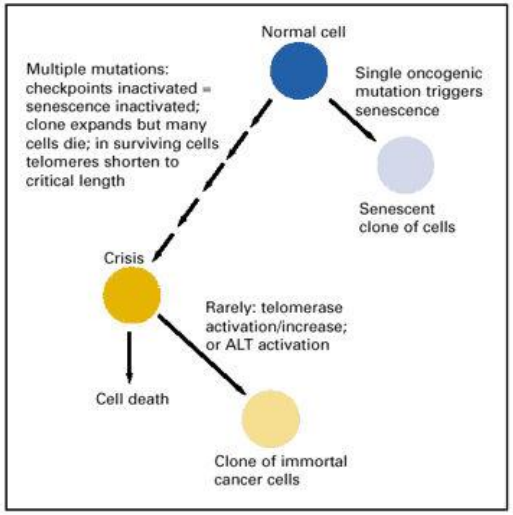
- Exchange of (genetic) information
- Sexual
- Asexual

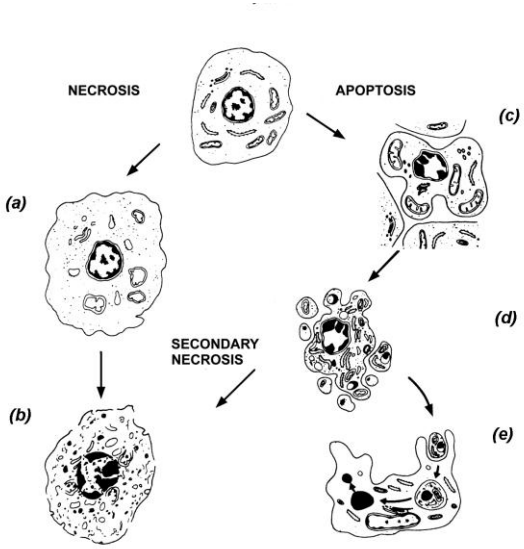


Death etc

- Cell death:
  - apoptosis (programmed), necrosis (traumatic)
- Quiescence
- Senility







Modelling challenges

How to:

- Design & construct models
- Simulate models
- Visualise results
- Check models
- Analyse models
- Validate models

Day 2: Multiscale Systems Biology

8.30 – 9.00: Welcome Coffee

9.00 – 11.10:

BioModel Engineering via modular, protein-oriented modeling [Mary Ann Blätke]

Introduction: *Moving to the multiscale in systems biology modeling*. [David Gilbert]

Advanced modeling concepts:

Coloured, and hierarchically coloured Petri nets + Exercise [Monika Heiner]

Detailed discussion and analysis of examples:

C.elegans and calcium channels [Fei Liu]

11.10 – 11.40: Coffee Break

11.40 – 13.30:

Detailed discussion and analysis of examples:

Halobacterium salinarum [Wolfgang Marwan]

Drosophila melanogaster - planar cell polarity in tissues [Qian Gao, Esther Bamigboye]

Analysis techniques for multiscale models [Mary Ann Blätke, Daniele Maccagnola]

Discussion: Challenges in multi-scale modeling for systems biology

13.30 – 14.00: Lunch

Some references

Qian Gao, Fei Liu, David Gilbert, Monika Heiner, David Gilbert (2011). **A Multiscale Approach to Modelling Planar Cell Polarity in Drosophila Wing using Hierarchically Coloured Petri Nets,** CMSB 2011

Robin Donaldson and David Gilbert (2008)**. A Model Checking Approach to the Parameter Estimation of Biochemical Pathways**. CMSB 2008, LNCS 5307/2008, pp269-287.

Monika Heiner, David Gilbert, and Robin Donaldson (2008), **Petri Nets for Systems and Synthetic Biology**. Formal Methods for Systems Biology SFM 2008, LNCS 5016, pp. 215-264

David Gilbert, Monika Heiner and Sebastian Lehrack (2007). **A Unifying Framework for Modelling and Analysing Biochemical Pathways Using Petri Nets** CMSB 2007, LNCS/LNBI 4695, pp. 200-216.

David Gilbert and Monika Heiner, (2006)**. From Petri Nets to Differential Equations - an Integrative Approach for Biochemical Network Analysis,** (ATPN06), LNCS 4024 / 2006, pp. 181-200