MSc course: Practical Systems Biology

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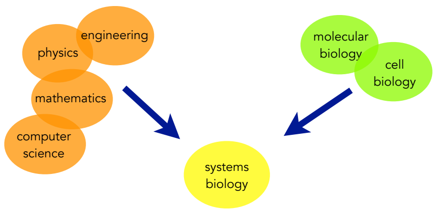
THE UNIVERSITY *of* EDINBURGH

This course will provide *an introduction to systems biology* by focusing on the behaviours expected from interactions between only a few genes, taking examples from microbes to mammals.

Cells are dynamic systems, and we will build intuition about the types of responses expected from different gene circuits *by running, adapting, and analysing computer simulations.*



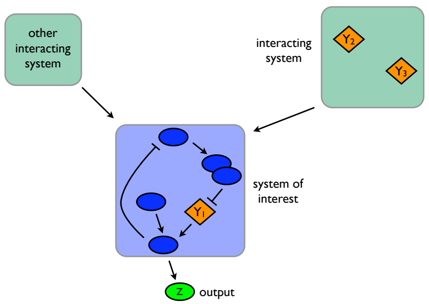
SynthSys Centre for Synthetic and Systems Biology

Overview

1. What is systems biology and why do we need it?
2. An introduction using three examples:
   a. Learning and memory
   b. Single-cell responses to stress
   c. Social behaviour in bacteria
3. A summary of the course structure

Although systems biology cannot be easily defined, a system can.

By a system, we simply mean some subset of the entire world **whose behaviour, and whose interaction with the rest of the world**, we believe can be sensibly described. (Kuipers, 1994)



These interactions be intra- or extracellular.

For many, systems biology started with this 1999 review

From molecular
to modular cell biology

Leland H. Hartwell, John J. Hopfield, Stanislas Leibler and Andrew W. Murray

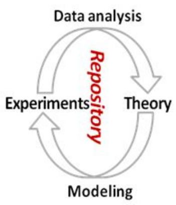
Cellular functions, such as signal transmission, are carried out by **'modules'** made up of many species of interacting molecules ...

General principles that govern the structure and behaviour of modules may be discovered with help from synthetic sciences such as engineering and computer science, from stronger interactions between experiment and theory in cell biology, and from an appreciation of evolutionary constraints.

Nature, 1999

Initial definitions of systems biology were mostly operational

Systems biology studies biological systems by systematically perturbing them (biologically, genetically, or chemically); monitoring the gene, protein, and informational pathway responses; integrating these data; and ultimately, formulating mathematical models that describe the structure of the system and its response to individual perturbations. (Ideker et al, 2001)

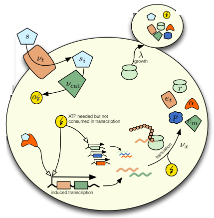


To understand complex biological systems requires the integration of experimental and computational research – in other words a systems biology approach. (Kitano, 2002)

the objective of systems biology [can be] defined as the understanding of network behavior, and in particular their dynamic aspects, which requires the utilization of methematical modeling tightly linked to experiment. (Cassman, 2005)

More inspiring definitions emerged later

What distinguishes systems biology from earlier traditions is the tendency **to define importance** less in operational terms (e.g., necessary or sufficient to produce a behavior) than **in terms of relevance to the goals of a system**. (Lander, 2007)



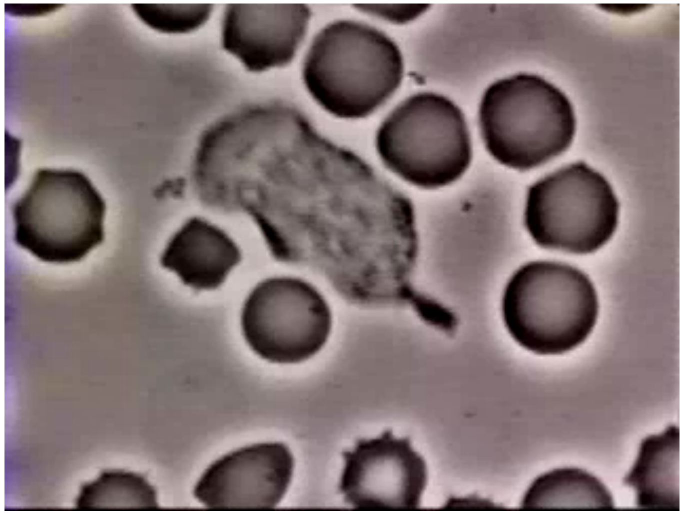
By discovering how function arises in dynamic interactions, systems biology **addresses the missing links between molecules and physiology**. (Bruggeman and Westerhoff, 2007)

Why do we need systems biology?

The sequencing of the human genome has given us a list of the parts of the cell (the genes and proteins).

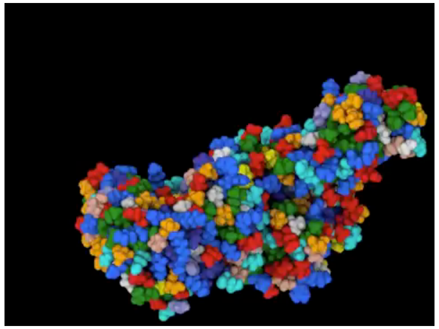
We need to understand how these parts interact to generate cellular behaviour if we wish to improve medicine and biotechnology.

Cellular behaviour can be remarkable...

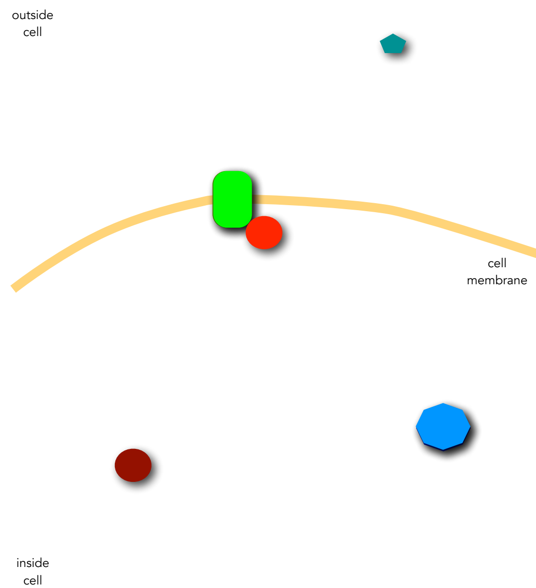


Cellular behaviour results from changes in proteins

Proteins can change shape, sometimes spontaneously and sometimes because of the binding of another molecule.



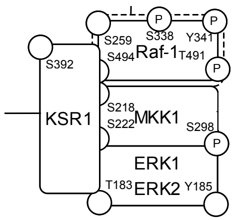
from Graham Johnson Medical Media



Information about the presence of an extracellular molecule is passed from protein to protein through changes in protein state or conformation.

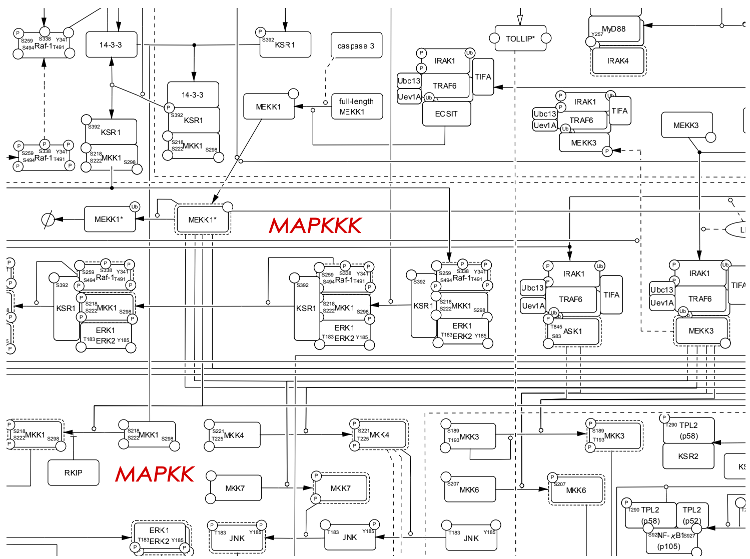
Biology is complex

For example, here are three proteins in a “cascade”: Raf-1 activates MKK1 and MKK1 activates ERK1



These proteins are part of the innate immune response and the figure is taken from a map of the innate immune system by Oda and Kitano.

Zooming out...



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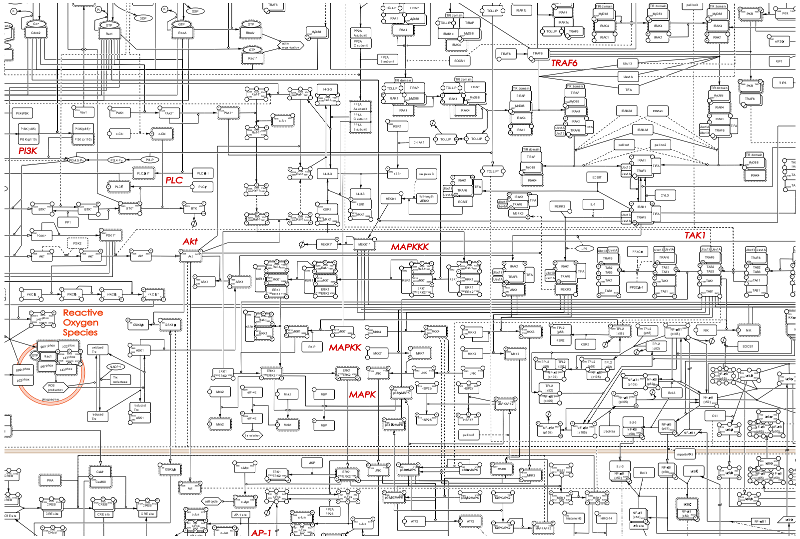

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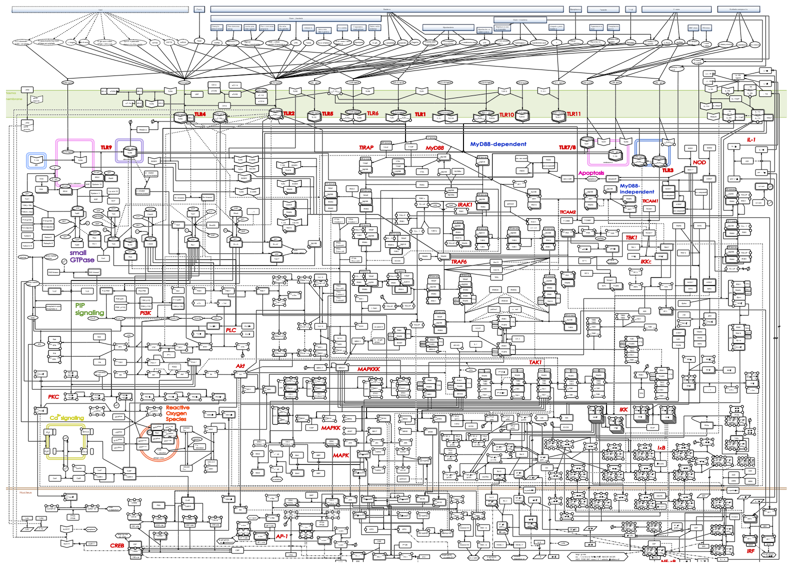
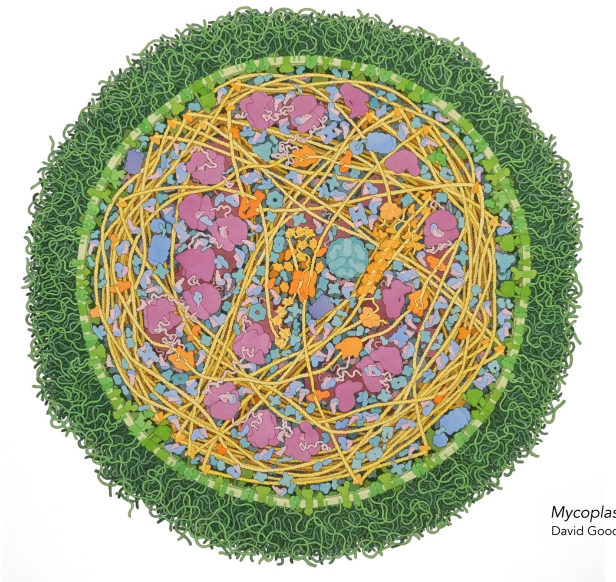


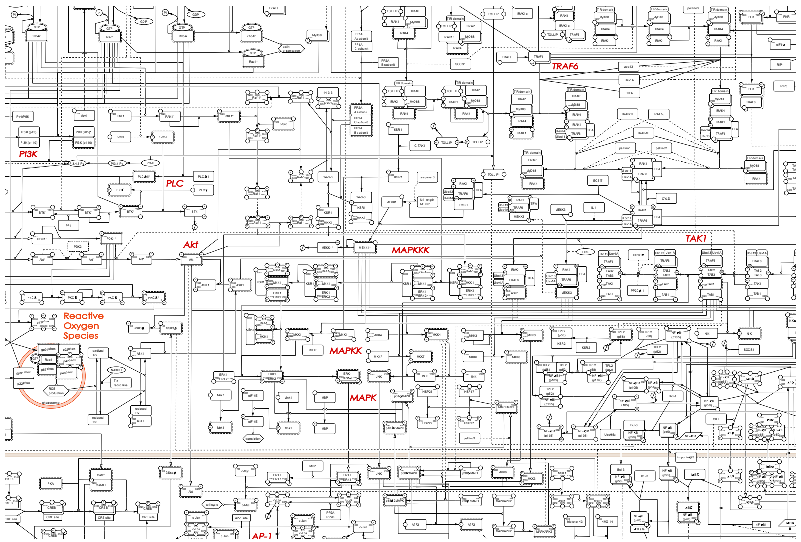
Biology is complex: cells are packed with proteins and other macromolecules

DNA
RNA polymerase
ribosome
lipoglycan



Mycoplasm mycoides
David Goodsell, Scripps Institute

It is because biology is so complex that we need a multidisciplinary approach.



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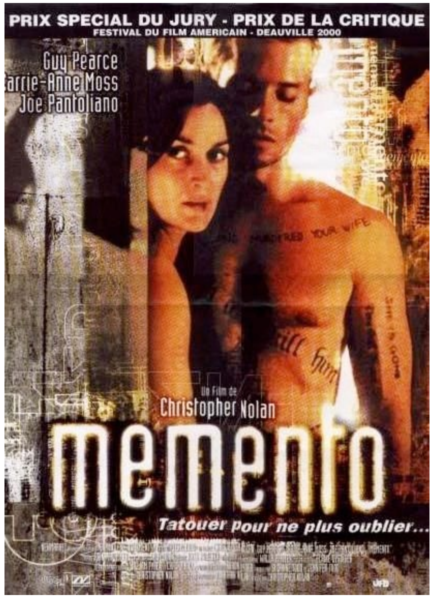
Nature, 1999

A memory module

The debilitating effects of memory loss are portrayed in the movie Momento (C Nolan, 2000).



Can cells remember?

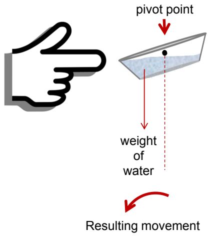
Early development of a fertilized egg of an African clawed toad:

H Williams and K Smith

Differentiated (specialised) cells "remember" to stay differentiated. They do not spontaneously undifferentiate.

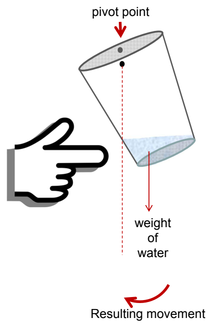
Cells remember through positive feedback

Positive feedback is a “runaway” process, where an effect enhances itself.



After a small perturbation, the moving water tips the bucket and causes the water to move more and tip the bucket further.

As opposed to negative feedback where an effect diminishes itself.



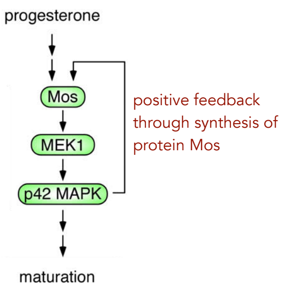
Positive feedback can be generated by the synthesis of new proteins that cause their own rate of synthesis to increase.

Example: maturation of frog oocytes

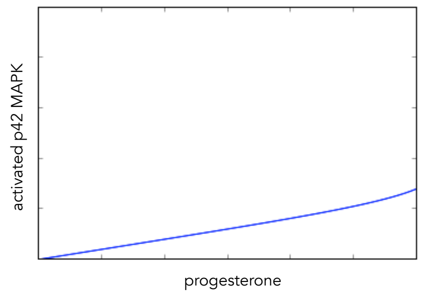
Very large single cells around 1mm in diameter.

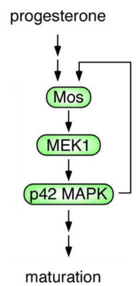
Progesterone induces the cells to mature after which they acquire a jelly coat and are laid by the frog.

A signalling cascade of three proteins

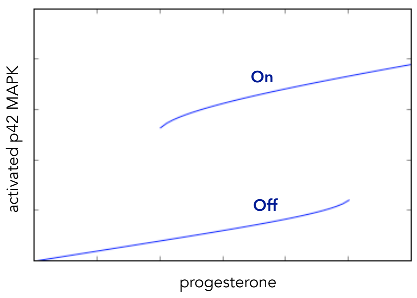


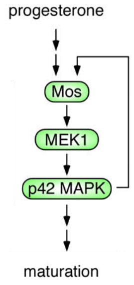
The last protein of the cascade becomes more active as levels of progesterone increase.





Increasing positive feedback allows the system to become either “on” or “off”





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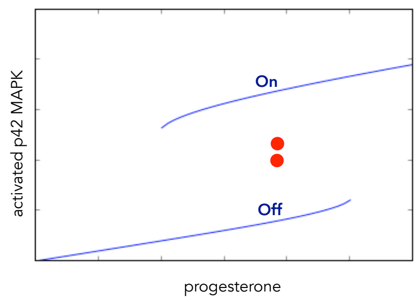
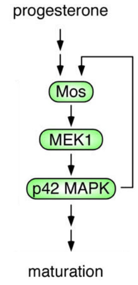
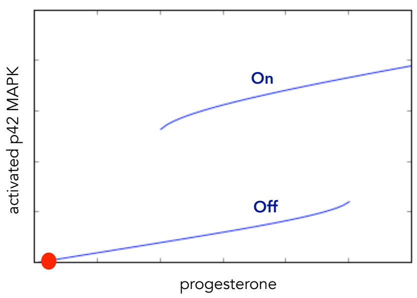
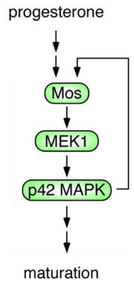




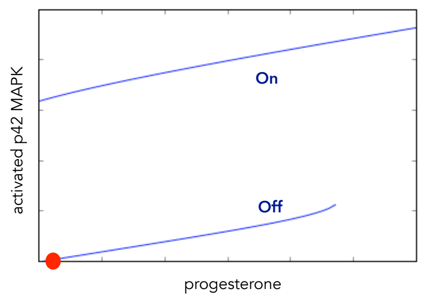
With both an *on* and an *off* state for the same level of progesterone, the system has memory.

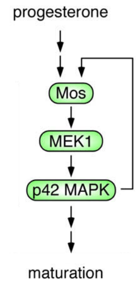




The cell remembers because the level of progesterone at which MAPK jumps to the other state depends on whether the cell was initially either *on* or *off*.

With strong feedback, the memory can become permanent.





Even when levels of progesterone fall to zero, the cell remains *on*. The cell has differentiated.

Summary

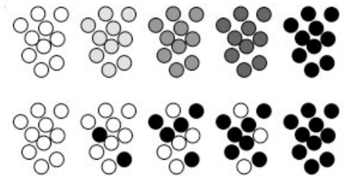
Biochemical systems can "remember" through positive feedback, where a sufficiently large stimulus causes a response that generates more response.

Such memory is important to ensure that cells stay differentiated.

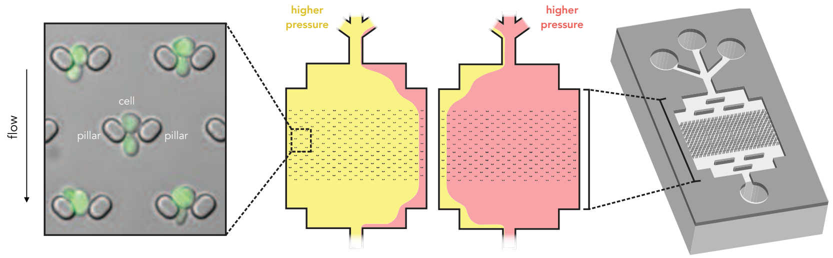
Similar ideas may apply to memory in neurons.

Cam kinase II

A focus of systems biology is on the behaviour of individual cells rather than the average behaviour of populations of cells

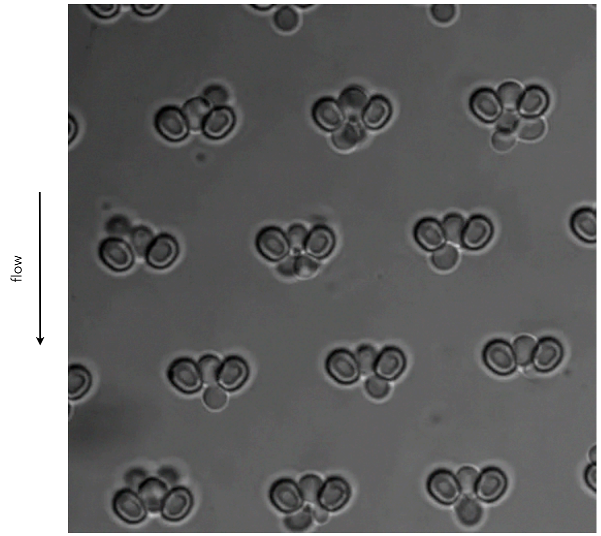


Microfluidic devices allow the responses of individual cells to be quantified in controlled dynamic environments

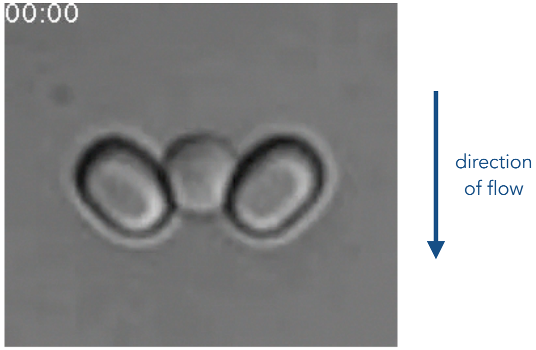


Crane et al., PLoS One 2014

With time-lapse microscopy, 100s of cells can be followed.



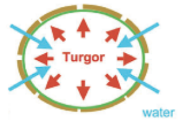
Yeast cells die of old age after 20 or so divisions



Cells must adapt to changing osmotic conditions

Cells maintain turgor as they grow.

Under hypo-osmotic conditions, cells swell and must lose water.



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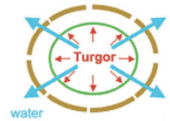
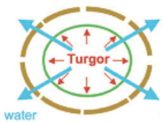


From Ziegler et al., 2010

Yeast change the concentration of glycerol to adapt to osmotic stress



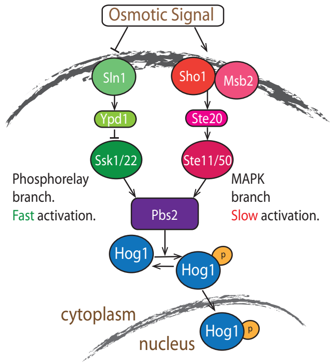
Cells must increase internal osmolytes to recover turgor

Upon hyper-osmotic stress, cells:

first:
- (i) stop dividing
- (ii) divert glycolytic flux towards glycerol synthesis
- (iii) close glycerol exporters

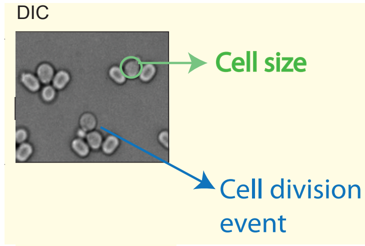
second:
- (i) increase expression of the enzymes for glycerol synthesis

The signalling network has a Y-shaped structure with two input branches leading to activation of a MAP kinase, Hog1

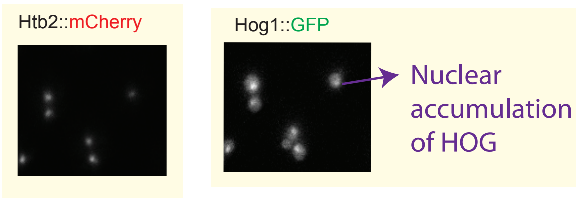


Using microfluidics, the volume and levels of nuclear Hog1 can be measured in single cells

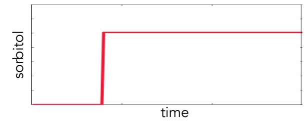
Cell volume and cell fitness is determined from DIC images

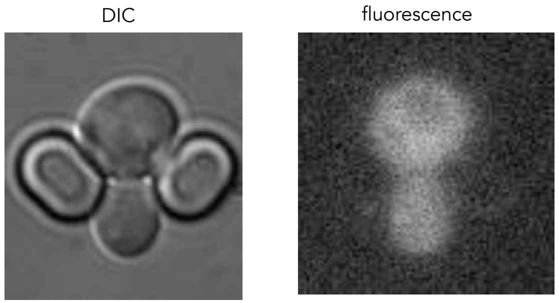


Nuclear Hog1 via a histone marker



Hog1 translocates in response to a step in the concentration of sorbitol



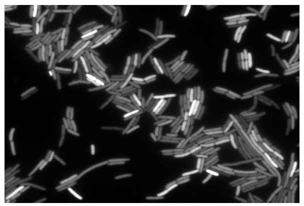


Summary

Individual cells can show behaviour far from average responses.

Microfluidics allows the study of single-cell responses in controlled dynamic environments.

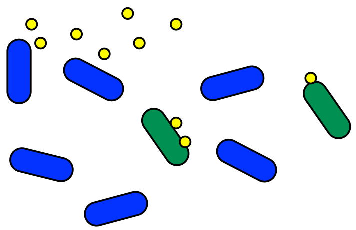
Signal transduction systems can specialize to particular dynamics of the cellular environment.



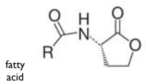
Systems biology goes beyond intracellular behaviour: communication and cooperation in bacteria

Even bacteria can "talk"

Bacteria can secrete molecules called autoinducers, which are sensed by other bacteria.

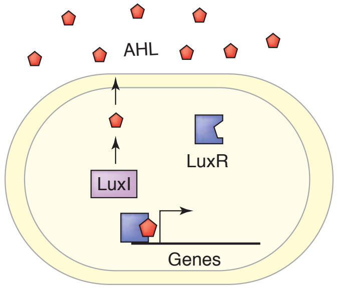


Bacteria that detect the autoinducers can initiate new gene expression.



Acyl-homoserine lactones (AHL) are the autoinducers secreted by gram-negative bacteria.

The biochemistry of auto induction involves positive feedback.

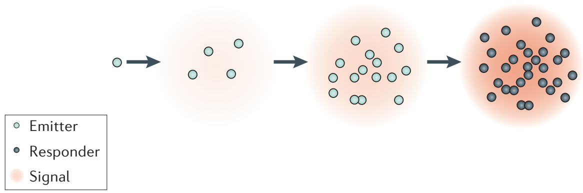


AHL is synthesized by LuxI and detected by LuxR, which activates expression of more LuxI.

from Henke & Bassler, 2004

Bacterial communication is called quorum-sensing.

Levels of autoinducer only become high for sufficiently dense populations – when the population of cells has reached a threshold size, or quorum.

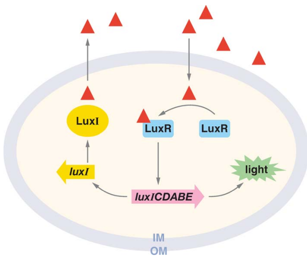


An example of positive feedback generating "all-or-none" behaviour.

A Hawaiian bobtail squid is luminescent because of quorum sensing by *Vibrio fischeri* bacteria.

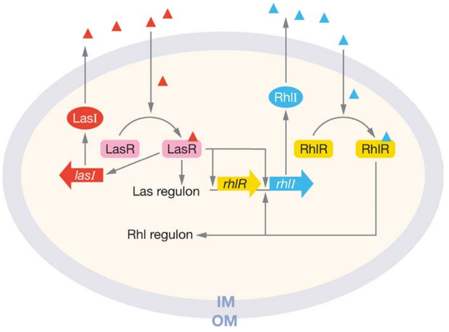
The bacteria are supplied with nutrients in an internal organ of the squid. The squid hunts at night and hides its shadow from predators by controlling the level of bioluminescence emitted.

The bacteria only reach high densities in the squid, not in the open ocean, and use quorum sensing to appropriately initiate bioluminescence.



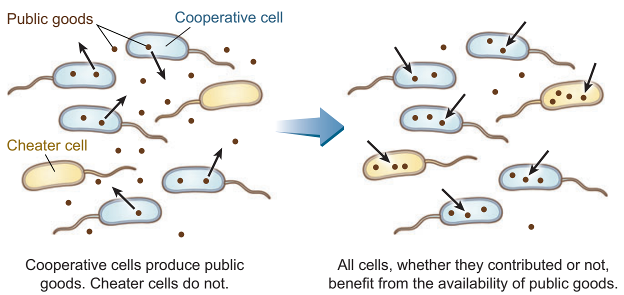
from Waters & Bassler, 2005

Two quorum sensing circuits control the expression of virulence factors in the opportunistic pathogen *Pseudomonas aeruginosa*.



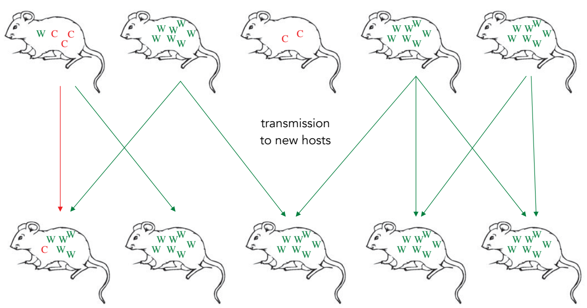
P aeruginosa is the major pathogen for people with cystic fibrosis.

Secreted products can lead to the "tragedy of the commons", where cheats dominate and the fitness of the population falls.



from West *et al.*, 2007

For *P aeruginosa*, cooperators persist because populations of cooperators are more infectious than populations of cheaters.

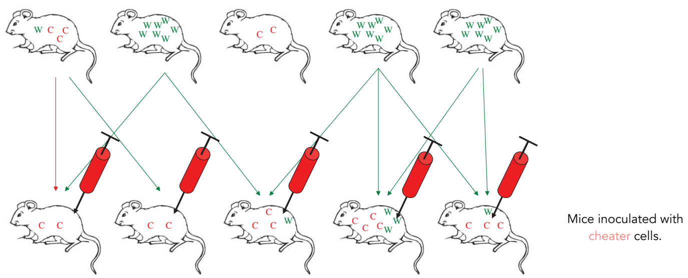


Wild-type cells secrete exoproducts; cheater cells do not.

from Brown *et al.*, 2009

Quorum sensing and cooperative behaviour of pathogens suggest new therapies.

For example, creating cheater cells and inoculating mice with cheaters, which should out-compete wild-type cells:



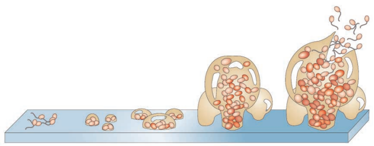
The resulting bacteria populations are less virulent and more vulnerable to the immune system.

Summary

Microbes can communicate through secreting and sensing extracellular products.

Autoinducers are used by bacteria to estimate cell densities.

Such communication is important in biofilms and for determining when pathogenic bacteria become virulent.



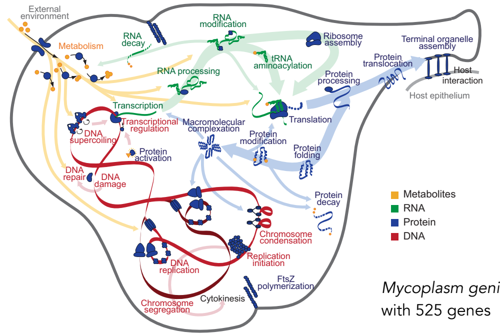
Formation of a biofilm (Davies, 2003)

Moving beyond individual modules, the first whole-cell model was published in 2012.

A Whole-Cell Computational Model Predicts Phenotype from Genotype

Jonathan R. Karr,[1,4] Jayodita C. Sanghvi,[2,4] Derek N. Macklin,[2] Miriam V. Gutschow,[2] Jared M. Jacobs,[2] Benjamin Bolival, Jr.,[2] Nacyra Assad-Garcia,[3] John I. Glass,[3] and Markus W. Covert[2,*]

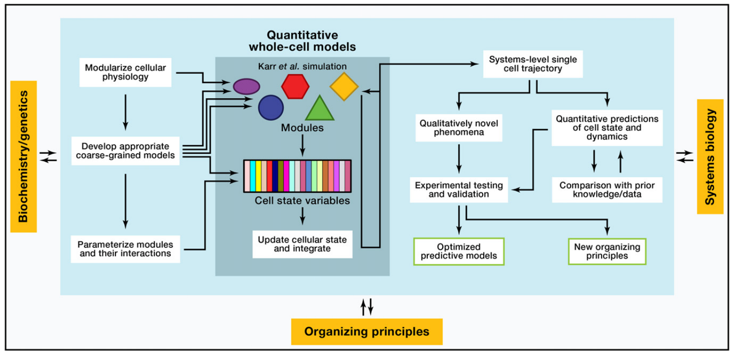
Cell, 2012



Mycoplasm genitalium
with 525 genes

A challenge was to make different types of models "talk" to each other.

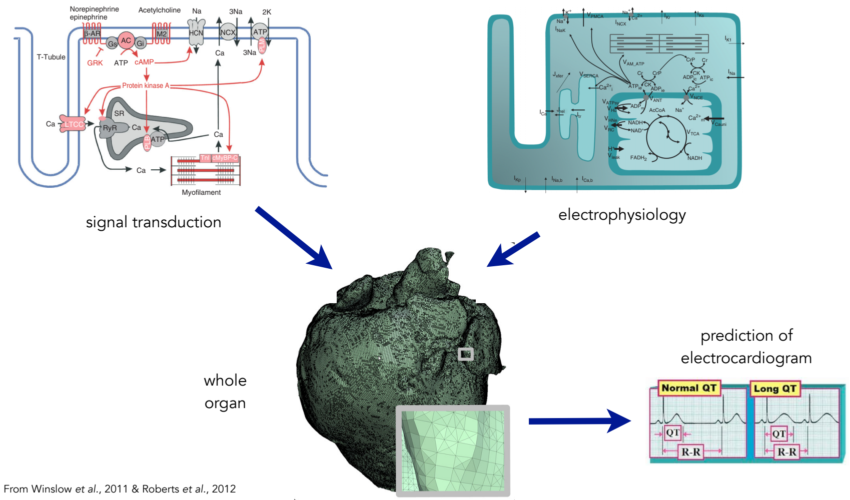
Such models will be repositories of information and enable the cycle of experiment and prediction that underpins systems biology.



Freddolino & Tavazoie, Cell 2012

The future: from genes to cells to whole organs

Models of the heart incorporate gene expression, signal transduction, and electrophysiology with three dimensional models of the whole organ.



From Winslow *et al.*, 2011 & Roberts *et al.*, 2012

Outcomes of the course

You will be able to:

(i) design a systems approach

(ii) understand and predict the dynamics of simple modules

(iii) formulate and simulate mathematical models

(iv) write programs in Python to test biological hypotheses

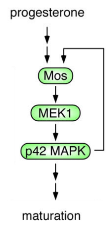
Main learning outcome:

To use the free computer language Python to test biological hypotheses by creating, simulating and analysing mathematical models of biological processes.

Assessment:

Two assignments (step-by-step computational analyses of a model of a biological system – 20% each)

A research project (selecting a model from the literature and simulating and adapting that mode to test a novel hypothesis – 60%)



Further information:

swainlab.bio.ed.ac.uk/psb

Lecture Outlines

Week 1 ***What is systems biology?***
The general systems approach with examples. Why a systems approach is important for molecular and cellular biology.

Weeks 2-5 ***Fundamentals of modelling biochemical networks***
Mathematical modelling of biochemical reactions, the law of mass action, and a discussion on ultrasensitivity, cooperativity, and Hill numbers.

Weeks 6 ***Modelling gene expression***
Modelling the rate of transcription for genes controlled by activators and repressors.

Weeks 7-8 ***Positive feedback and genetic switches***
Positive feedback and MAP kinase cascades, bifurcations and hysteresis, cellular memory and bistable genetic networks.

Weeks 9-10 ***Negative feedback and oscillations***
Circadian rhythms, the Tyson model of the circadian clock in the fruit fly, relaxation oscillations, and oscillations through positive and negative feedback.

Week 11 **Stochastic simulations and model-fitting**
Depending on interest.

Structure of the course

Systems biology	Python
Modelling biochemical networks	Basic programming
Enzyme kinetics	Loops, lists, and functions
Ultrasensitivity and allostery	Plotting data
Modelling gene expression	Scientific computing with arrays
Biochemical switches	Generating random numbers
Negative feedback	Simulating biochemical networks
Genetic oscillators	Stochastic simulations
Stochastic gene expression	Fitting data

References

U Alon, *An introduction to systems biology: design principles of biological circuits*

H Langtangen, *A primer on scientific computing with Python*

JM Kinder & P Nelson, *Python for physical modeling*

D Bray, *Wetware: a computer in every living cell*

B Ingalls, *Mathematical modeling in systems biology: an introduction*

R Phillips *et al.*, *Physical biology of the cell*