GSTDMB 2010: Dynamical Modelling for Biology and Medicine

University of Nottingham
17–18 May 2010

Markus Owen

Course Outline

Aims:

- To introduce modelling and quantitative approaches to biology
- To explain where equations come from and what they mean, placing the mathematics into a context that is relevant for the life scientist.
- To enable life scientists to gain a better understanding of what a model is, and how to go about building one.

Objectives - By the end of the session, participants will:

- understand key concepts in how to build models of biological systems
- know how to investigate the behaviour of those models
- be able to interpret the results of those models.

KEY THEMES

- The kinds of behaviour that dynamic models can exhibit (e.g. exponential growth or decay, steady states, oscillations), and their stability.

- Single variable models: How to work out their dynamics by sketching one simple graph - applications, including to population growth and gene regulation.

- Multi-variable models: Interacting populations, signalling networks and biochemical reactions. How to turn a set of reactions into a mathematical model with the law of mass action. More about transcriptional and translational regulation. How to work out a lot about their dynamics by sketching two (or more) graphs.

Course Schedule

Day 1 (Monday 17 May 2010):

09:30 Lecture 1.1: Data, networks and models (Pope C17)
10:30 Coffee (Pope C17)
11:00 Lecture 1.2: Introduction to modelling with differential equations (Pope C17)
12:30 Lunch
13:30 Practical 1.1: Introduction to MATLAB (Pope A16)
15:00 Coffee (Pope C17)
15:30 Practical 1.2: Qualitative and quantitative model analysis (Pope A16)

Day 2 (Tuesday 18 May 2010):

09:30 Lecture 2.1: Multi-variable models (Pope C17)
10:30 Coffee (Pope C17)
11:00 Practical 2.1: Building multi-variable models in MATLAB (Pope A16)
12:30 Lunch
13:30 Lecture 2.2: Parameter estimation and sensitivity analysis (Pope C17)
15:00 Coffee (Pope C17)
15:30 Practical 2.2: Parameter estimation and sensitivity analysis (Pope A16)

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GSTDMB Dynamical Modelling for Biology and Medicine

Lecture 1.1
Data, Networks and Models

Markus Owen

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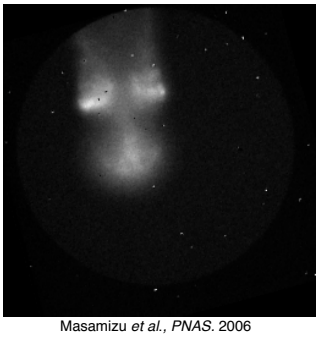
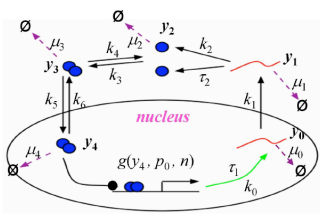
Mechanistic Process Models



Masamizu *et al., PNAS.* 2006

Hes1 (and other Notch pathway genes) oscillate in the presomitic mesoderm of developing vertebrate embryos.



- Biological processes understood as emergent properties of complex networks of interacting components.
- *Question:* what are the mechanisms regulating emergence?

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What kinds of processes?

How to make a switch?

- Important for Cell differentiation, quorum sensing, lac operon inducible system, lysis-lysogeny decision by phage Lambda, ...
- Delta-Notch signalling is a simple example. Negative feedback + coupling selects a subpopulation of cells for a neuronal fate.

How to make an oscillator?

- Cell cycle, circadian rhythms, cardiac action-potential

How to make an organism?

- Fate determination + cell movements, proliferation, etc, etc, ...

Population growth and interactions

- From bacteria to humans; cancer (mutant cells *invading* a normal host); epidemiology; ecology; ...

A Systems Approach

- ***Choose*** the process/system and characterise it
  - Scoring; boundary drawing; (quantitative) data availability
- ***Map out*** the interaction network:
  - "Parts list" (components)
  - Topology (pairwise interactions)
  - Functional characterisation of interactions
- ***Model***: explore how observed behaviour can emerge from the network
  - Need to identify *appropriate* questions that can be addressed
- ***Validate*** the model: focused experimental studies
  - Works best if *quantification* is possible

System Characterisation: State

- As a first step, we need to identify measurable properties of the system that we believe to be relevant (and preferably fairly comprehensive) indicators of its nature, and make measurements of these.
- Examples: mRNA concentration, protein concentration, cell volume, membrane potential, population density, …
- This gives us knowledge of the **state** of the system.
- But we seek **understanding**. In particular, we want to **understand the past and present and predict the future**.
- To achieve this, we need a **model**.

Variables and Dynamic Models

- The first step of modelling is to pose questions.
  e.g. Given a set of observations and/or measurements today, what will be the result of making those observations and/or measurements tomorrow?

- A **model** is a representation of the system that we can use to answer such questions. If the state of the system is changing in time, then the model is **dynamical** — the properties of the representation change in time.

- In this case, the time-varying components of the system state are referred to as **variables**.

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State evolution models

- If the values of the model variables change in time, then we represent them as $x_1(t), x_2(t), ..., x_N(t)$, where t is time.

- The **state** of the model at time t is just the set of all the variables at time t:

$$S(t) = \{x_1(t), x_2(t), ..., x_N(t)\}.$$

- The form of model we shall study is:

$$S(t_2) = f(S(t_1); p_1, p_2, ..., p_M), \quad t_2 > t_1$$

where f is a function, and $p_1, p_2, ..., p_M$ are model **parameters**.

- This simply states that the future state of the system is some function of its past state (i.e. that the future is **predictable**).

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Parameters

- The model parameters are numerical values that encode other information about the system that is not included in the dynamic state.

- Typically, parameters are independent of the model state, and do not vary in time.

- Time-varying parameters are sometimes used (*e.g.* when a system property changes because of an influence external to the model — such as light input to a circadian clock).

- *e.g.* The concentration of a mRNA species is a variable; the linear degradation rate of the mRNA is a parameter.

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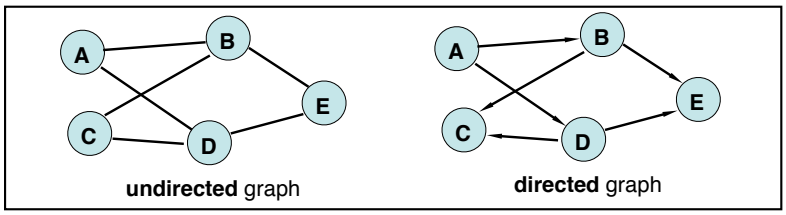
Networks

- In this course, we are interested in mechanistic models of processes occurring in cells, tissues, organisms and populations.
- The state of the system is defined by the quantities of each of the relevant components of the system (*e.g.* mRNAs, proteins, hormones, metabolites, number of bacteria, …)
- The functions in a state interaction model encode the mechanisms that regulate interactions between these components.
- The set of system components and their mutual interactions constitute a **network**.

Network terminology

- The components and interactions can be represented as a **graph**.
- Each node represents a system component (*e.g.* a type of mRNA).
- Each edge represents a pairwise interaction between two components. An edge need not encode the nature of the interaction.



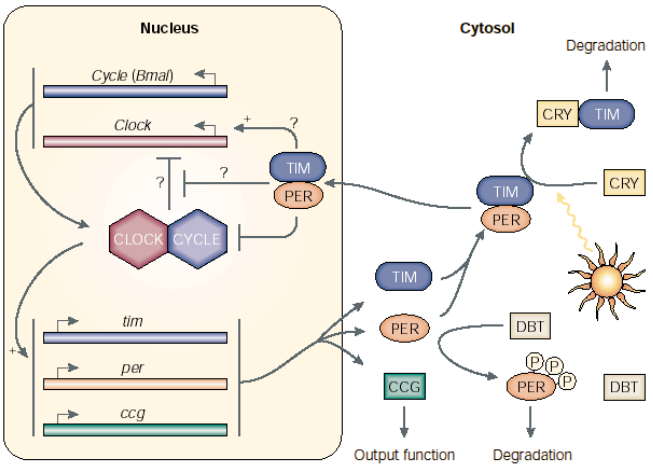
undirected graph **directed** graph

- **Undirected edge:** two components can interact with each other.
- **Directed edge:** one component has a causal influence on the other.
- *e.g. undirected*: protein A and protein B form a dimer (A——B)
  directed: protein A regulates the production of mRNA B (A→B)

Inferring Networks

- Components and interactions can be inferred from a wide range of data sources:
  - Genetic screens
  - RNAi screens
  - mRNA profiling (e.g. microarrays)
  - Metabolic profiling
  - Protein-protein interaction screens (e.g. yeast-two-hybrid, TAP mass spec.)
  - ChIP-on-chip analysis of transcription factor binding
  - Biochemistry
  - Population data (e.g. on predator-prey or epidemiological interactions)
- Each has strengths and limitations
- Integration of multiple data sources is important for reliable inference.

The Circadian Oscillator Network



Cermakian & Sassone-Corsi, *Nature Rev. Cell Molec. Biol.* **1**, 59–67 (2000).

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Mathematical network representation

- The form of model we shall study (the state evolution equation) is:

$$S(t_2) = f\left(S(t_1); p_1, p_2, \ldots, p_M\right), \quad t_2 > t_1$$

This can be written in index notation as

$$x_i(t_2) = f_i\left(\left\{x_{\langle i\rangle}(t_1)\right\}; p_1, p_2, \ldots, p_M\right), \quad i = 1,2,\ldots,N$$

where $\langle i \rangle$ is the set of nodes that connect to node i in the graph (including i itself, if appropriate)

- The functions f_i encode the form of the interactions between components.
- In the context of network inference, these functions are hard to determine. There are no high-throughput methodologies for getting them.
- In practice, models are often based on a small set of standard representative forms for the f_i (see Lecture 1.2 for examples).

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Continuous Process Models

- In reality, the state of each network component should be represented by a discretely varying quantity (e.g. the number of molecules of a particular mRNA in a cell, the number of individuals in a population — an integer).
- Also, changes in state over time are discrete events (production or degradation of a network component, births/deaths in a population).
- In practice, if the amount of each component is sufficiently large, then its state can be approximated by a continuous variable that changes smoothly and continuously in time (e.g. concentration, population density).
- In doing this, we are essentially representing a continuous process rather than a set of events.

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Ordinary differential equations (ODEs)

- If we represent the network state $S(t)$ as continuous, then it has a well-defined **rate of change**: $\frac{dS}{dt}(t)$
- A (first order) **ordinary differential equation (ODE)** model is a set of equations that relate the rate of change of the system state at each moment in time to the state of the system at that time.
- In component form, an ODE representation of a network can be written

$$\frac{dx_i}{dt}(t) = f_i\left(\left\{x_{\langle i\rangle}(t)\right\}; p_1, p_2, \ldots, p_M\right), \quad i = 1,2,\ldots,n$$

where $<i>$ is the set of nodes that connect to node i in the graph (including i itself, if appropriate)

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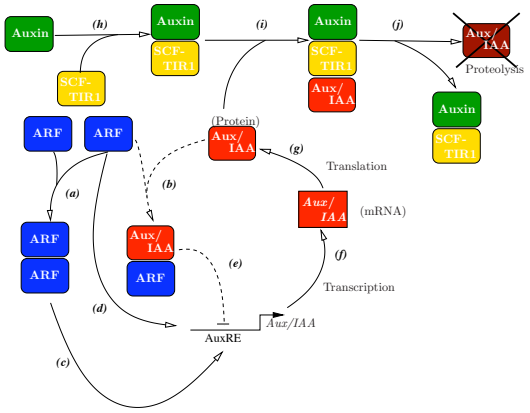
ODE Example - Auxin signalling



- Auxin is a plant hormone, which stimulates degradation of Aux/IAAs.
- Aux/IAAs repress their own transcription.
- Hence Auxin stimulates Aux/IAA transcription.

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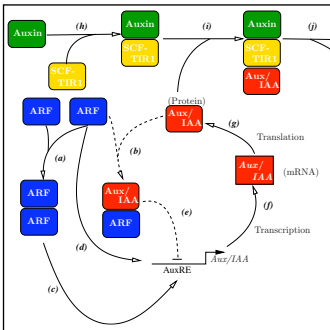

$$\frac{d[\mathrm{IAA_m}]}{dt} = \lambda_1 F_1([\mathrm{ARF}], [\mathrm{IAA_p}], [\mathrm{ARF\text{-}IAA}], [\mathrm{ARF_2}])$$
$$+ \lambda_2 F_2([\mathrm{ARF}], [\mathrm{IAA_p}], [\mathrm{ARF\text{-}IAA}], [\mathrm{ARF_2}]) - \mu_{\mathrm{IAA_m}}[\mathrm{IAA_m}],$$
$$\frac{d[\mathrm{IAA_p}]}{dt} = \delta[\mathrm{IAA_m}] - l_\mathrm{a}[\mathrm{IAA_p}][\mathrm{auxin\text{–}TIR1}] + l_\mathrm{d}[\mathrm{auxin\text{–}TIR1\text{–}IAA}] -$$
$$p_\mathrm{a}[\mathrm{IAA_p}][\mathrm{ARF}] + p_d[\mathrm{ARF\text{-}IAA}],$$
$$\frac{d[\mathrm{TIR1}]}{dt} = -k_\mathrm{a}[\mathrm{auxin}][\mathrm{TIR1}] + k_\mathrm{d}[\mathrm{auxin\text{–}TIR1}],$$
$$\frac{d[\mathrm{auxin\text{–}TIR1}]}{dt} = k_\mathrm{a}[\mathrm{auxin}][\mathrm{TIR1}] - k_\mathrm{d}[\mathrm{auxin\text{–}TIR1}]$$
$$+ (l_\mathrm{d} + l_\mathrm{m})[\mathrm{auxin\text{–}TIR1\text{–}IAA}] - l_\mathrm{a}[\mathrm{auxin\text{–}TIR1}][\mathrm{IAA_p}]$$
$$\frac{d[\mathrm{auxin\text{–}TIR1\text{–}IAA}]}{dt} = l_\mathrm{a}[\mathrm{IAA_p}][\mathrm{auxin\text{–}TIR1}] - (l_d + l_\mathrm{m})[\mathrm{auxin\text{–}TIR1\text{–}IAA}],$$

$$\frac{d[\mathrm{IAA^*}]}{dt} = l_\mathrm{m}[\mathrm{auxin\text{–}TIR1\text{–}IAA}] - \mu_{\mathrm{IAA^*}}[\mathrm{IAA^*}],$$
$$\frac{d[\mathrm{ARF}]}{dt} = -2q_\mathrm{a}[\mathrm{ARF}]^2 + 2q_\mathrm{d}[\mathrm{ARF_2}] - p_\mathrm{a}[\mathrm{ARF}][\mathrm{IAA_p}] + p_\mathrm{d}[\mathrm{ARF\text{-}IAA}],$$
$$\frac{d[\mathrm{ARF\text{-}IAA}]}{dt} = p_\mathrm{a}[\mathrm{ARF}][\mathrm{IAA_p}] - p_\mathrm{d}[\mathrm{ARF\text{-}IAA}],$$
$$\frac{d[\mathrm{ARF_2}]}{dt} = q_\mathrm{a}[\mathrm{ARF}]^2 - q_\mathrm{d}[\mathrm{ARF_2}],$$
$$\frac{d[\mathrm{auxin}]}{dt} = \omega + k_\mathrm{d}[\mathrm{auxin\text{–}TIR1}] - k_\mathrm{a}[\mathrm{auxin}][\mathrm{TIR1}] - \mu_\mathrm{Auxin}[\mathrm{auxin}].$$

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ODE Models: Basic assumptions

Assumption	Relaxation
The numbers of each molecular species are large enough to represent as continuous variables	Discrete models
Production and degradation processes are continuous	Discrete models
Outputs of processes begin to change as soon as the inputs change	Delay differential equations
Processes are deterministic	Stochastic differential equations
Spatial distribution in a cellular compartment is not important	Partial differential equations

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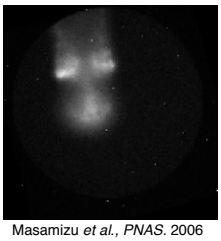
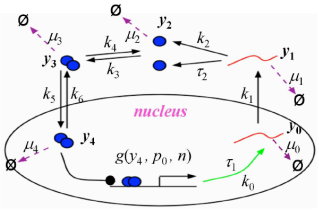
Hes1 oscillations: somites



Masamizu *et al., PNAS.* 2006



- Hes1 (and other Notch pathway genes) oscillate in the presomitic mesoderm of developing vertebrate embryos.
- Can we understand the origin of these oscillations using simple models?

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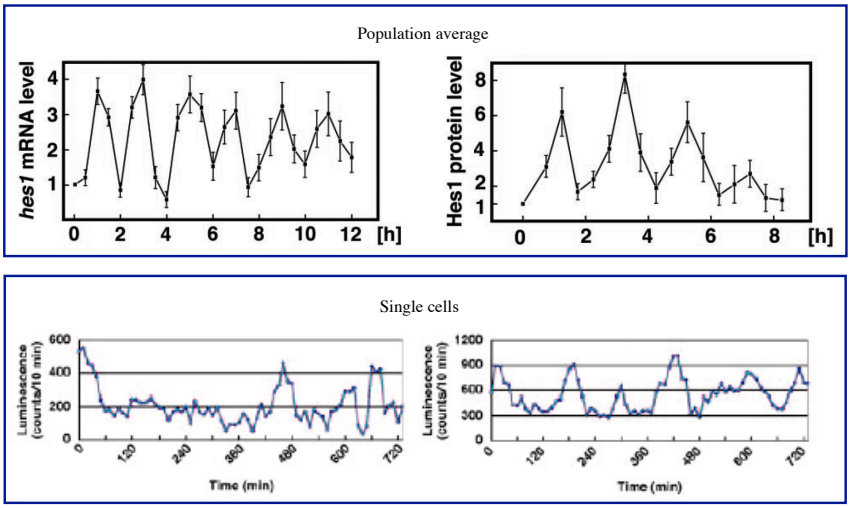
Quantitative Data: Hes1 in mouse fibroblasts



Hirata *et al., Science* **298**, 840–843 (2002); Masamizu *et al., PNAS.* **103**, 1313–1318 (2006).

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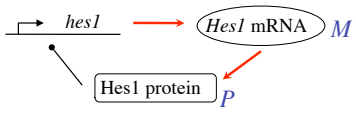
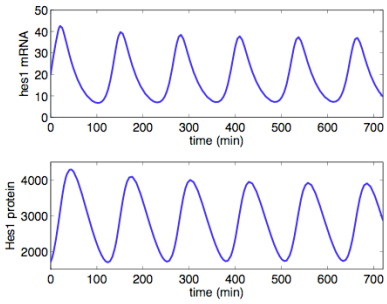
Hes1: direct intracellular negative feedback



$$dM/dt = k_M G[P(t-\tau_1)] - d_M M(t)$$
$$dP/dt = k_P M(t-\tau_2) - d_P P(t)$$

- k_M, k_P: transcription/translation rates
- d_M, d_P: linear degradation rates
- τ_1, τ_2: transcription/translation delays
- G: transcriptional repression function ($G' < 0$) e.g. Hill function

- $\tau_1 = 16\text{min}$, $\tau_2 = 2.5\text{min}$
- G = decreasing Hill function ($n = 5$)



Monk. *Curr. Biol.* **13**, 1409–1413 (2003).

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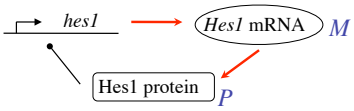
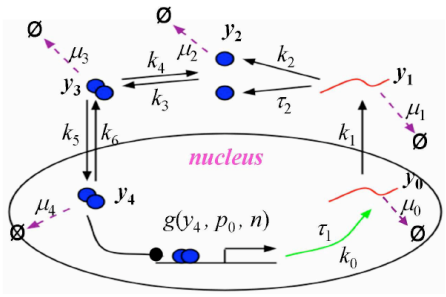
Which mechanisms do we need to model?





- Simple model (basic mechanisms we know to be involved) has 16 parameters, each of which would require substantial effort to measure.
- Explore model behaviour to find parameters that affect amplitude.

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Summary

- The properties of a system can be represented by a set of variables that collectively constitute the state of a model
- In dynamic models, the state is a dynamical variable (i.e. changes in time)
- State evolution models encode mathematically the way that the state changes over time
- ODEs are based on the assumption that the state changes continuously, at a rate that depends only on the current state

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Success stories in Mathematical Biology

- R.M. Anderson, G.F. Medley, R.M. May, A.M. Johnson: A preliminary study of the transmission dynamics of the human immunodeficiency virus (HIV), the causative agent of AIDS. *Math. Med. Biol.* **3**(4):229-263 (1986).
- N. Barkai, S. Leibler: Robustness in simple biochemical networks. *Nature* **387**(6636):913-917 (1997).
- G. Dupont, A. Goldbeter: One-pool model for ca2+ oscillations involving ca2+ and inositol 1,4,5-trisphosphate as co-agonists for ca2+ release. *Cell Calcium* **14**(4):311-322, (1993).
- P. Hahnfeldt, D. Panigrahy, J. Folkman, L. Hlatky: Tumor development under angiogenic signaling: A dynamical theory of tumor growth, treatment response, and postvascular dormancy. *Cancer Research* **59**(19):4770-4775 (1999).
- A.L. Hodgkin, A.F. Huxley: A quantitative description of membrane current and its application to conduction and excitation in nerve. *J. Physiology*, **117**(4):500-544 (1952).

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Success stories in Mathematical Biology

- A.D. Lander, Q. Nie, F.W.M. Wan: Do morphogen gradients arise by diffusion. *Dev. Cell.* **2**:785-796 (2002).
- M. Mackey, L. Glass: Oscillation and chaos in physiological control systems. *Science* **197**(4300):287-289 (1977).
- N.A.M. Monk: Oscillatory expression of Hes1, p53, and NF-κB driven by transcriptional time delays. *Curr. Biol.* **13**:1409-1413 (2003).
- A.M. Turing: The chemical basis of morphogenesis. *Phil. Trans. R. Soc. Lond. B*, **237**:37-72 (1952).
- J.J. Tyson, B. Novak: Regulation of the eukaryotic cell cycle: Molecular antagonism, hysteresis, and irreversible transitions. *J. Theor. Biol.* **210**:249-263, 2001.
- ... AND MANY MORE ...

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