

A systems approach to biology

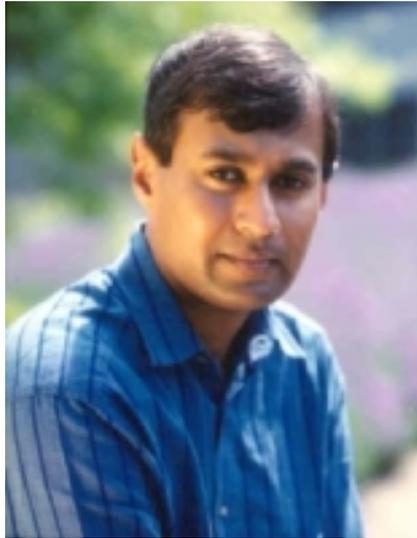
SB200

Lecture 1

16 September 2008

Jeremy Gunawardena

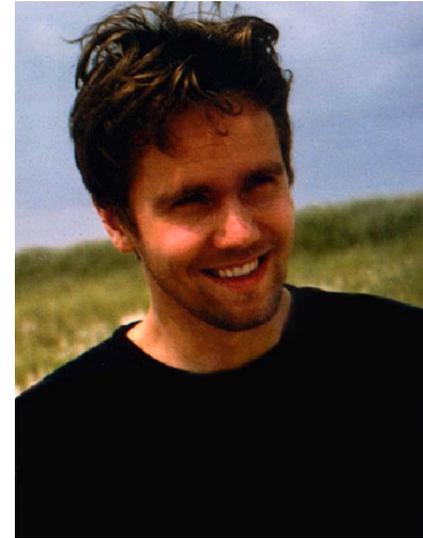
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*Jeremy
Gunawardena*



*Walter
Fonatana*



*Johan
Paulsson*

Topics for this lecture

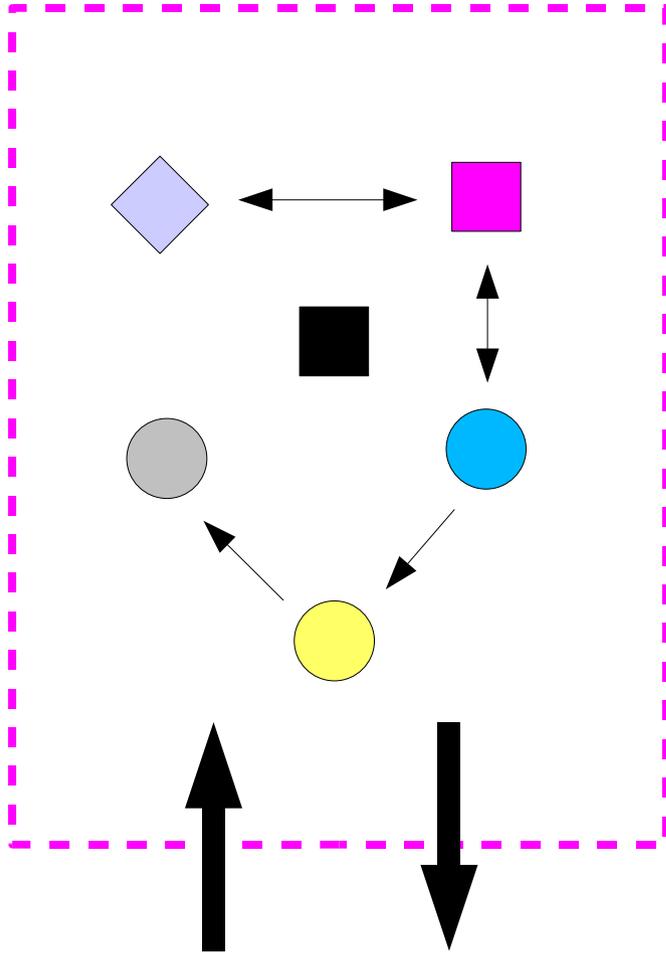
What is systems biology?

Why do we need mathematics and how is it used?

Mathematical foundations - dynamical systems.

Cellular decision making

What is systems biology?



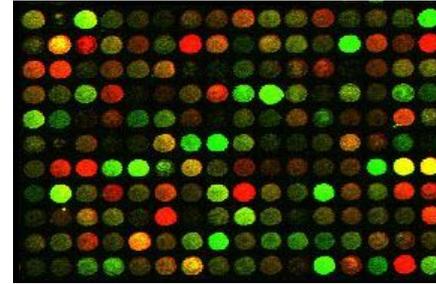
How do the collective interactions of the components give rise to the physiology and pathology of the system?

Marc Kirschner, "The meaning of systems biology," *Cell* 121:503-4 2005.

Top-down

“-omics”

system = whole cell / organism
model = statistical correlations
data = high-throughput, poor quality



too much data, not enough analysis

Bottom-up

“mechanistic”

system = network or pathway
model = mechanistic, biophysical
data = quantitative, single-cell

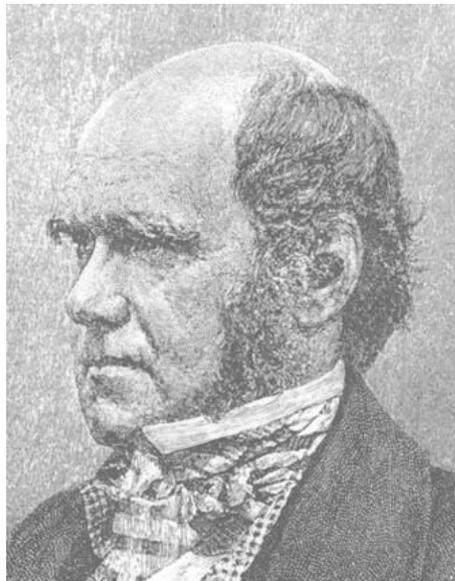
$$\frac{d}{dt}[ES] = a[E][S] - (b + c)[ES]$$

not enough data, too much analysis

Why do we need mathematics?

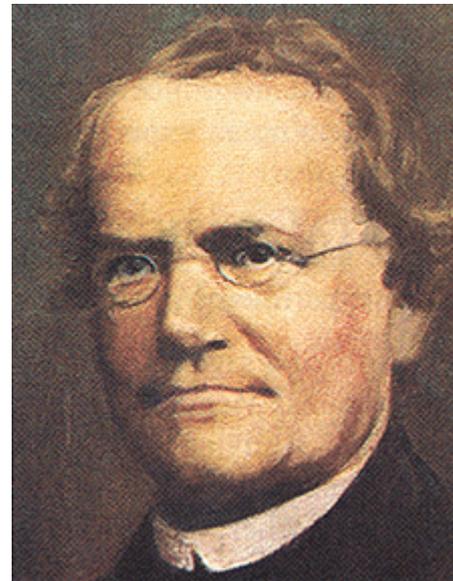
There have always been two traditions in biology ...

Descriptive



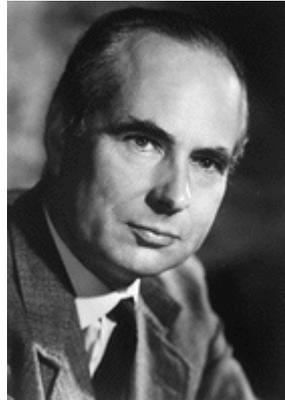
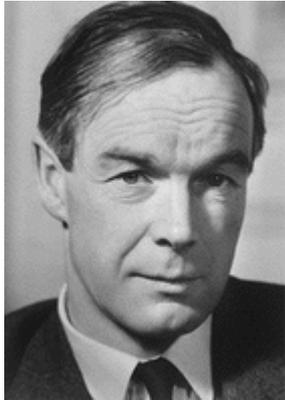
1809-1882

Analytical



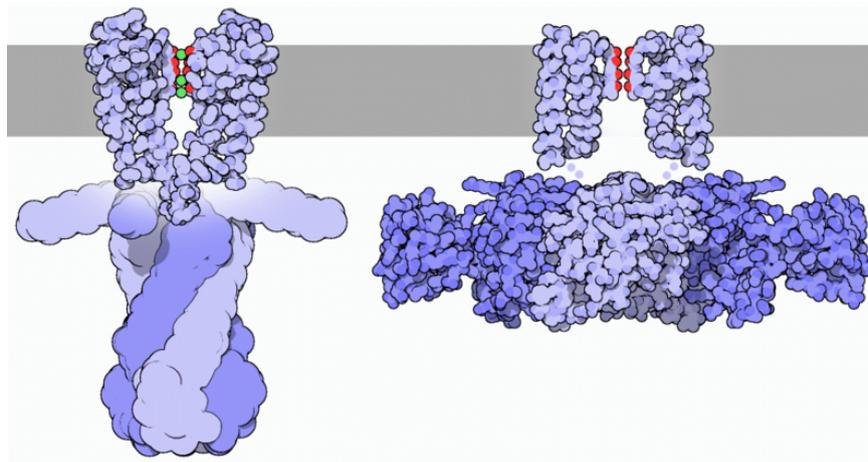
1822-1884

Mathematics allows you to guess the invisible components



$$I = C_M \frac{dV}{dt} + \bar{g}_K n^4 (V - V_K) + \bar{g}_{Na} m^3 h (V - V_{Na}) + \bar{g}_l (V - V_l),$$
$$\frac{dn}{dt} = \alpha_n (1 - n) - \beta_n n,$$
$$\frac{dm}{dt} = \alpha_m (1 - m) - \beta_m m,$$
$$\frac{dh}{dt} = \alpha_h (1 - h) - \beta_h h,$$

before anyone works out how to find them ...

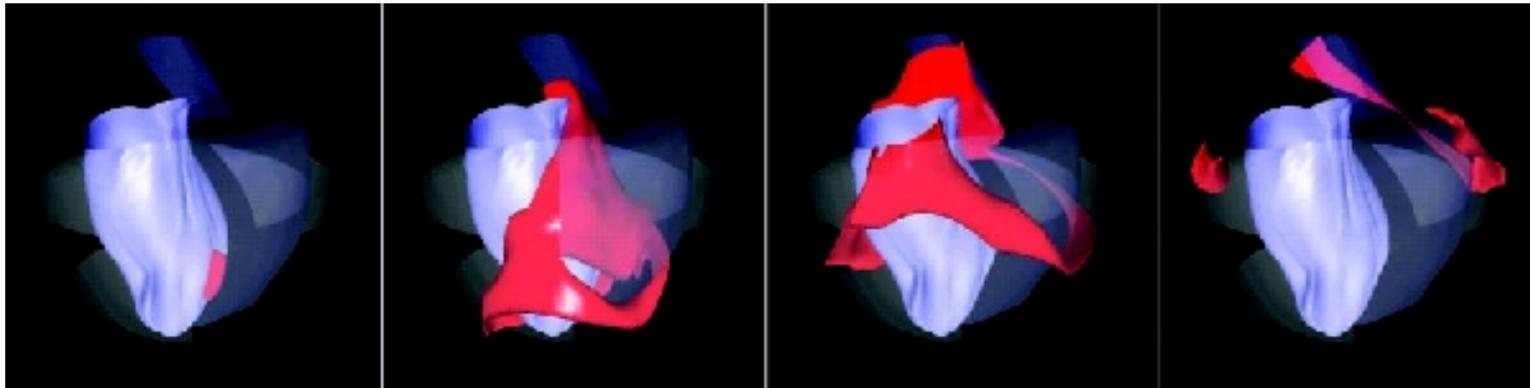


Bacterial potassium channel closed (left) and open (right) – Dutta & Goodsell, Mo lecule of the Month”, Feb 2003, PDB.

but these days we know many of the components
– and there are an awful lot of them –
so how are models used in systems biology?

Thick models

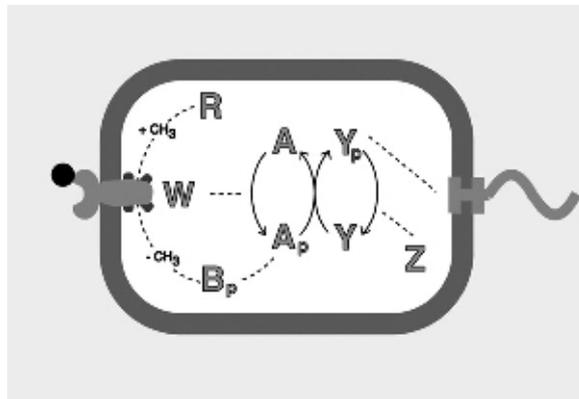
More detail leads to improved quantitative prediction



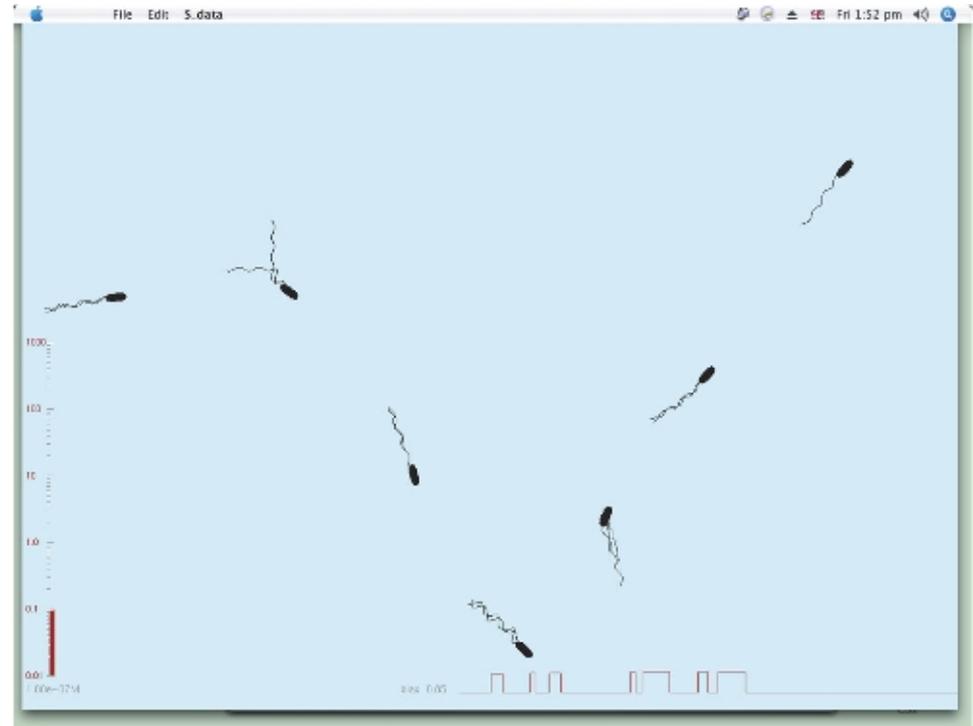
simulation of electrical activity in a mechanically realistic whole heart

Dennis Noble, *"Modeling the heart – from genes to cells to the whole organ"*, *Science* 295:1678-82 2002.

Thick models



E coli biochemical circuit



screen shot of simulated E coli swimming
in 0.1 μ M Asp

Bray, Levin & Lipkow, "*The chemotactic behaviour of computer-based surrogate bacteria*",
Curr Biol 17:12-9 2007.

Thick models

We need better tools – conceptual and computational – for specifying, building and analysing systems with high levels of molecular complexity. [See Walter's section.](#)

Hlavacek, Faeder, Blinov, Posner, Hucka, Fontana, *Rules for modelling signal transduction systems*, Sci STKE doi:10.1126/stke.3442006re6 2006.

Mallavarapu, Thomson, Ullian, Gunawardena, *Programming with models: modularity and abstraction provide powerful capabilities for systems biology*, Roy Soc Interface doi:10.1098/rsif.2008.0205 2008.

Thin models

Feedback control structures determine the robust system behaviours

negative feedback



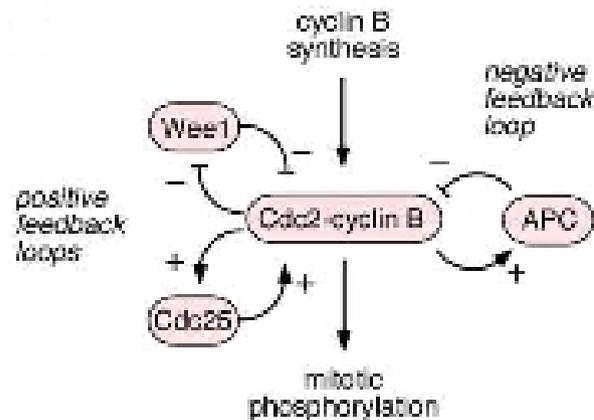
homeostasis

clocks & rhythms

positive feedback



decision making



Feedback control structure of the G2/M transition in Xenopus.

Pomerening, Kim & Ferrell, *Systems level dissection of the cell cycle oscillator*, Cell 122:565-78 2005.

“Very often my expectations turned out to be wrong and an important lesson I learned from these manual computations was the complete inadequacy of one's intuition in trying to deal with a system of this degree of complexity.”

Andrew Huxley

“The quantitative analysis of excitation and conduction in nerve”
Nobel Lecture, 11 December 1963

“All of this argues that in addition to the more typical intuitive interpretation of immunological data, it is now time to add the power of mathematics, systems analysis and quantitative cell-based modelling.”

Ron Germain

“The art of the probable: system control in the adaptive immune system”
Science **293**:240-5 2001

“Simple as they are such systems show surprising behaviours. To understand them, unaided intuition is not enough; we need mathematics.”

Julian Lewis

“Autoinhibition with transcriptional delay: a simple mechanism for the zebrafish somitogenesis oscillator”
Current Biology **13**:1398-408 2003

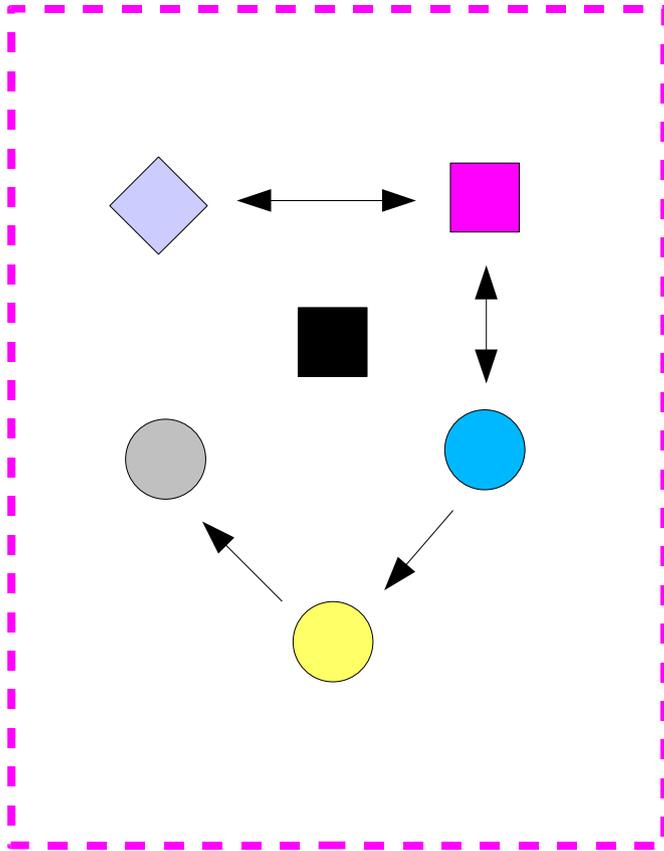
“Perhaps the most pressing need is to develop the appropriate theoretical approaches to analyse the management of information flow and to investigate the logic systems that are responsible for that flow”

Paul Nurse

“Life, logic and information”
Nature **454**:424-6 2008

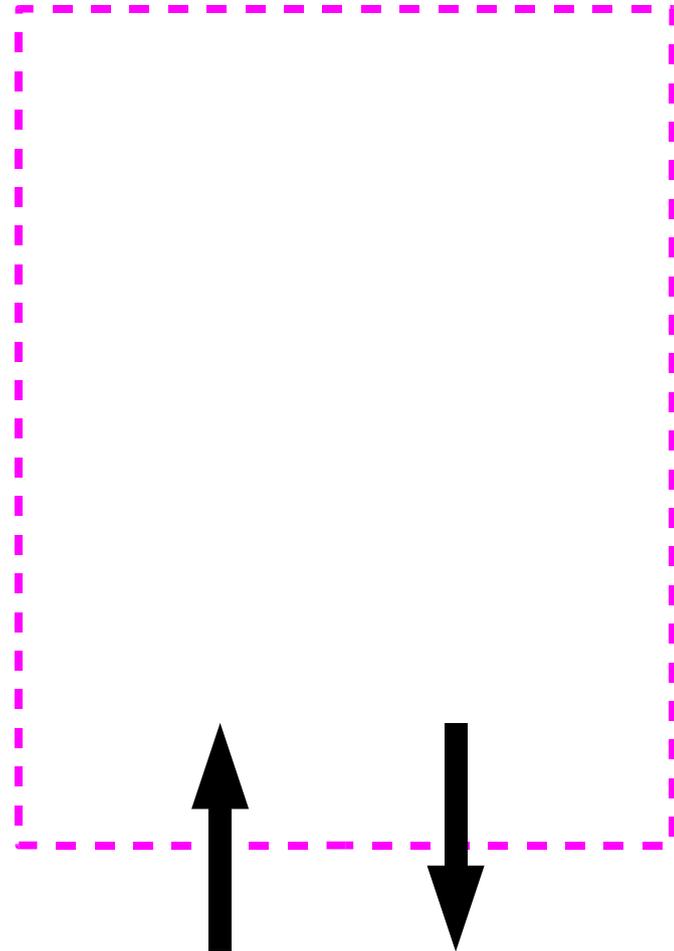
mathematical foundations

Dynamical system



explicit representation of internal state

Input-output system



Representation of internal state



deterministic

concentration of X as a function of time

spatial

concentration of X as a function of space and time

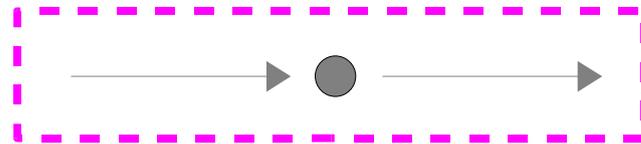
stochastic (Johan's section)

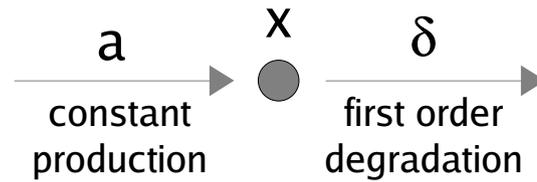
probability of a certain number of X as a function of time (or space and time)

agent-based (Walter's section)

each individual molecule is independently represented

Simple example of production and degradation





state variable

parameters

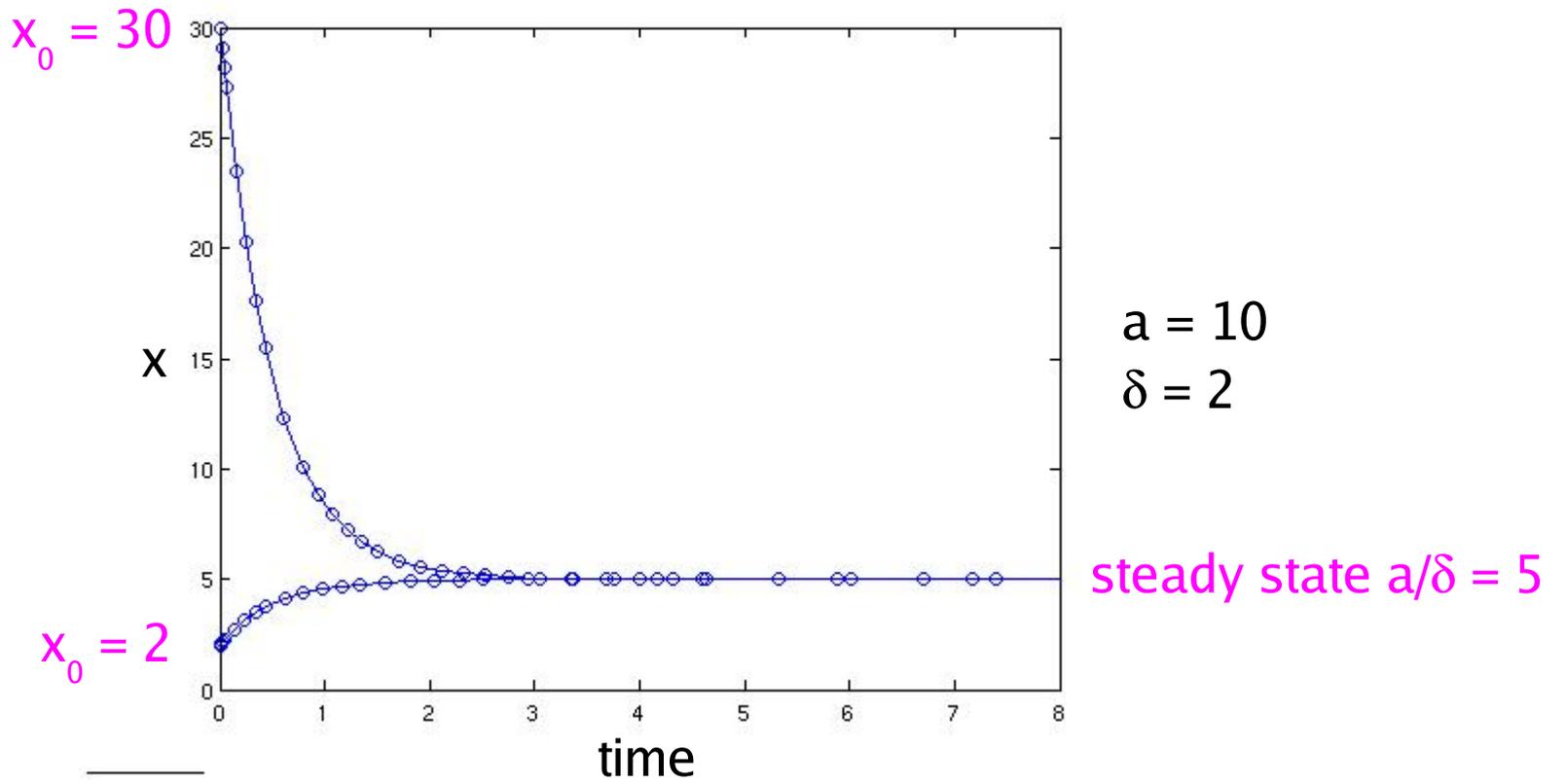
$$\frac{dx}{dt} = \text{production} - \text{degradation} = a - \delta x$$

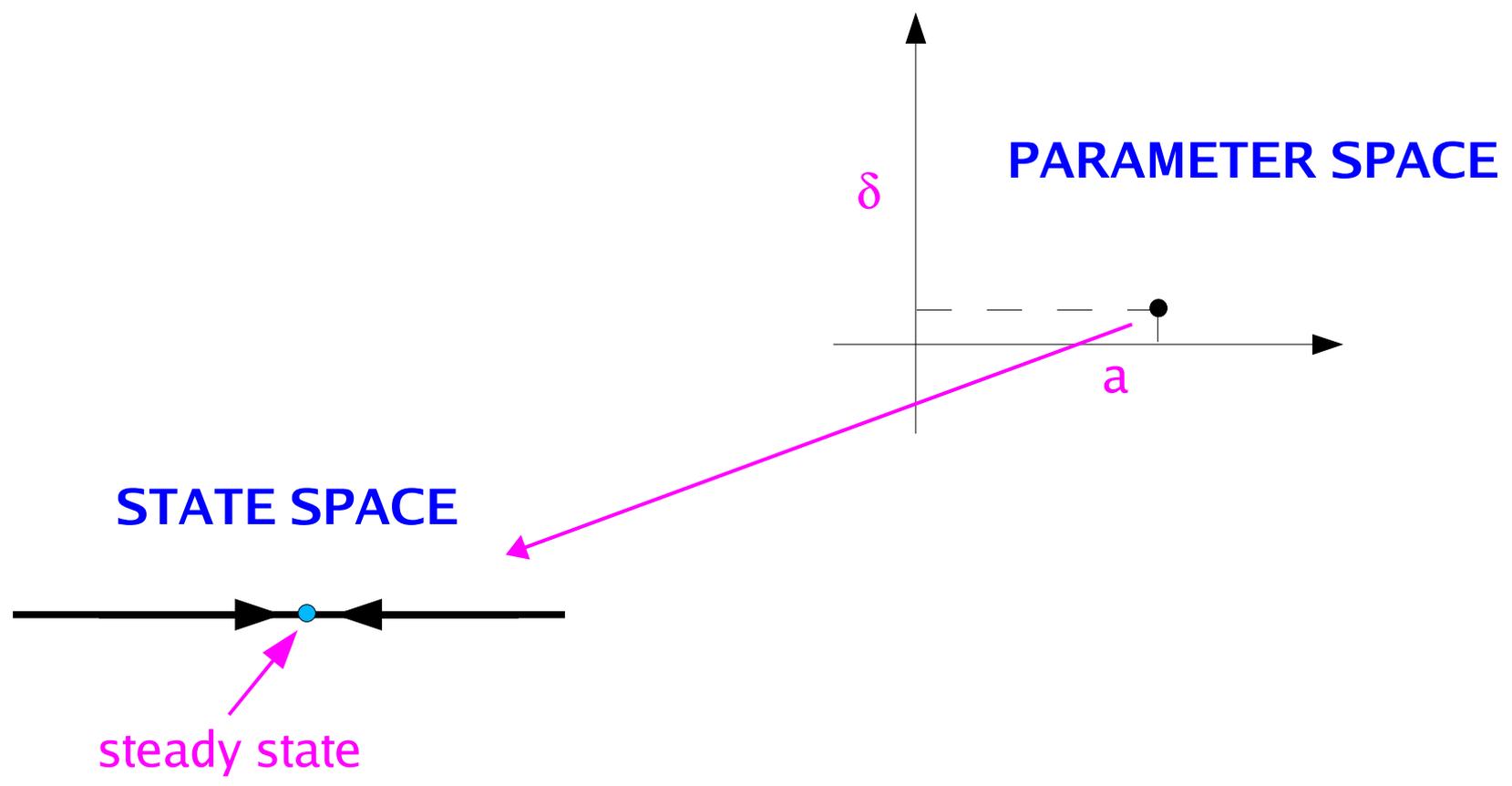
$$x_t = \frac{a}{\delta} + \left(x_0 - \frac{a}{\delta} \right) \exp(-\delta t)$$

initial condition

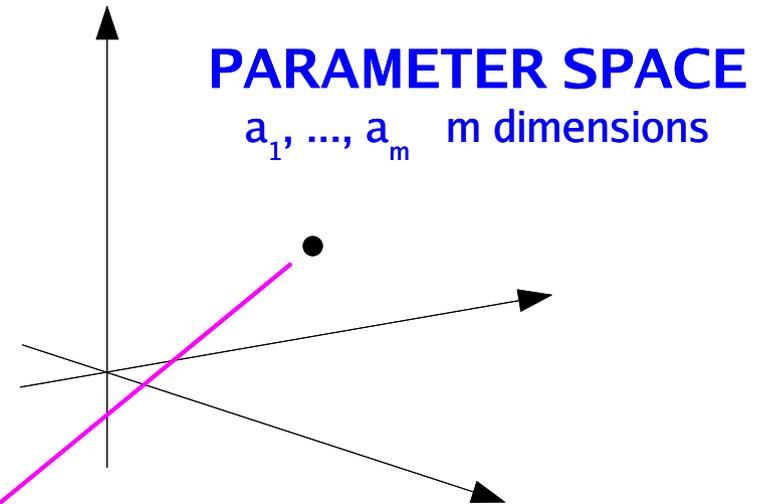
If $x_0 = a/\delta$, then $x_t = a/\delta$ for all t . This is a **steady state**.

$$\text{steady state} \Leftrightarrow dx/dt = 0.$$

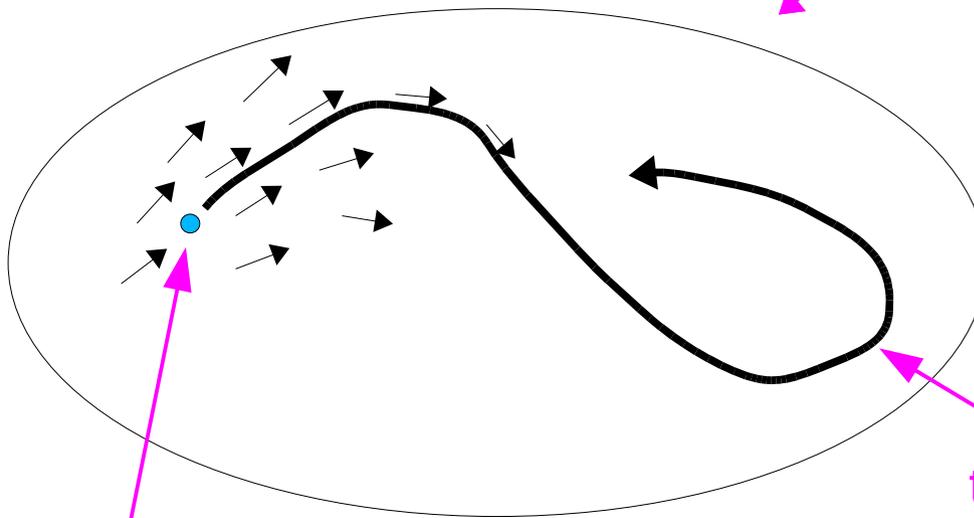




$$\begin{aligned} \frac{dx_1}{dt} &= f_1(x_1, x_2, \dots, x_n; a_1, \dots, a_m) \\ \frac{dx_2}{dt} &= f_2(x_1, x_2, \dots, x_n; a_1, \dots, a_m) \\ &\vdots \\ \frac{dx_n}{dt} &= f_n(x_1, x_2, \dots, x_n; a_1, \dots, a_m) \end{aligned}$$



STATE SPACE
 x_1, \dots, x_n n dimensions



- trajectories always exist
- they never cross
- but they usually **cannot be written down analytically**

initial condition

trajectory

two important issues that we will not discuss in this section

- the parameter problem
- cell-to-cell variability

the parameter problem

PHYSICIST – avoid them

ENGINEER – fit them

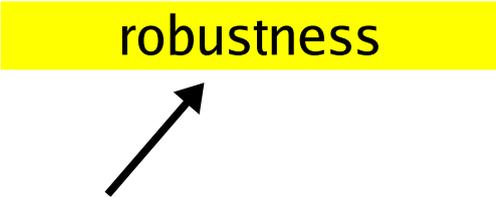
MATHEMATICIAN – (1) reduce them (2) ignore them

BIOCHEMIST – measure them

CHEMIST – calculate them

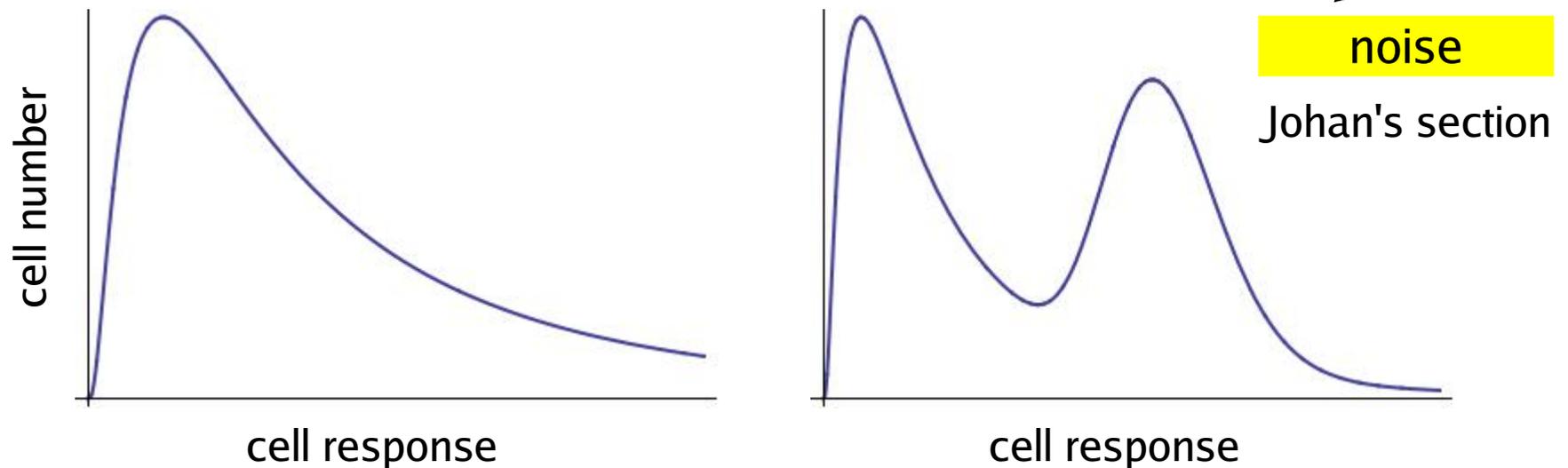
SYSTEMS BIOLOGIST – all of the above

robustness



cell-to-cell variability

a model of a molecular network describes what happens in a single cell but each cell in a population or tissue may behave differently



average is not representative of any cell

Lahav, Rosenfeld, Sigal, Geva-Zatorsky, Levine, Elowitz, Alon, *Dynamics of the p53-Mdm2 feedback loop in individual cells*, Nat Genet 32:142-50 2004.

Korobkova, Emonet, Vilar, Shimizu, Cluzel, *From molecular to behavioural variability in a single bacterium*, Nature 428:574-8 2004.