six lectures on systems biology

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lecture 4

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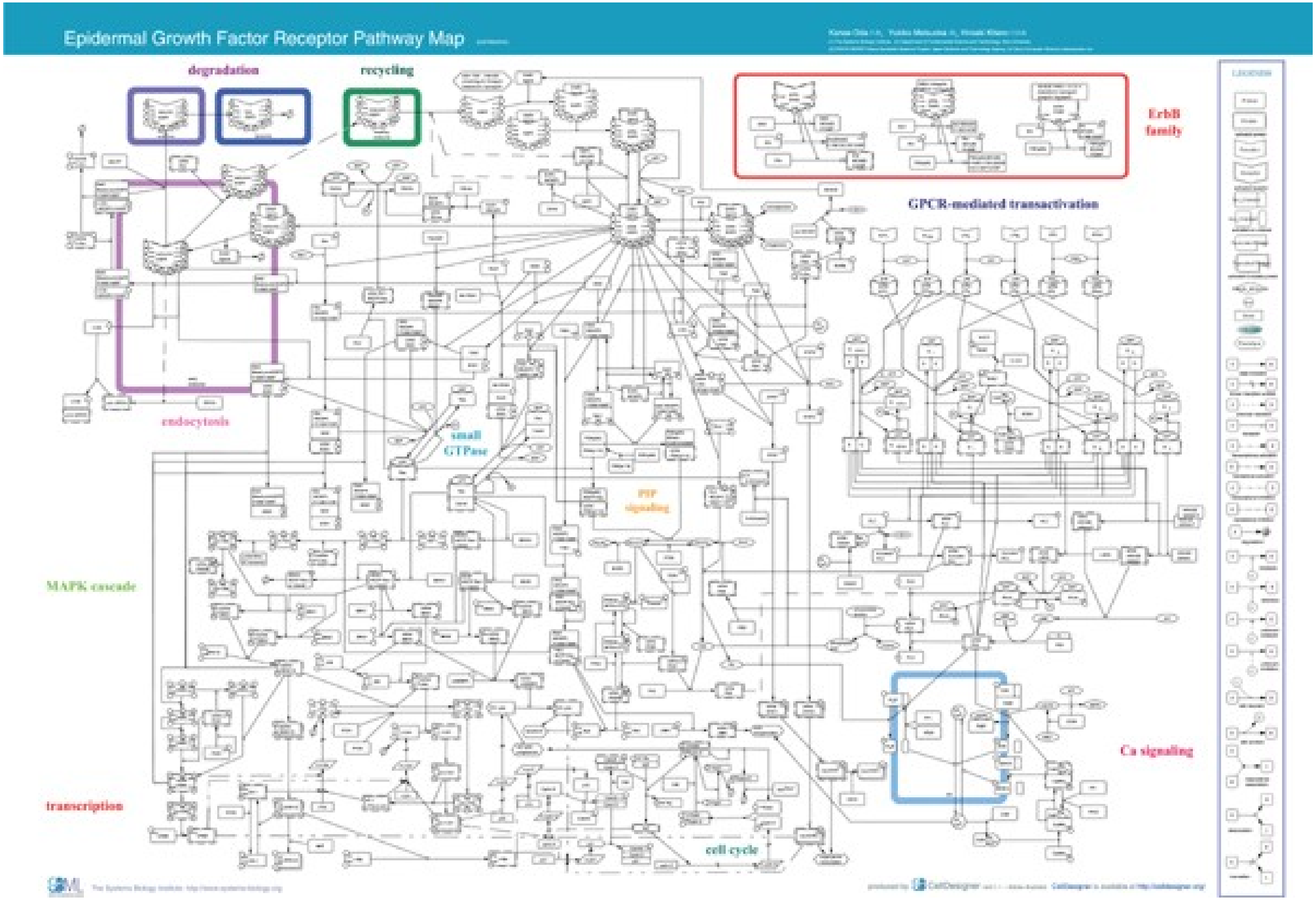
part 2 seminar room, department of genetics

a rather provisional syllabus

0. why mathematical models?
1. post-translational modification of proteins
2. microscopic cybernetics
3. development and evolution

functional purpose of molecular complexity?

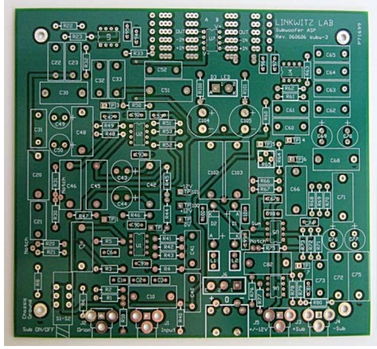


functional purpose of technological complexity?

suppose you know all about electromagnetism and Maxwell's equations but have no idea what a radio is for

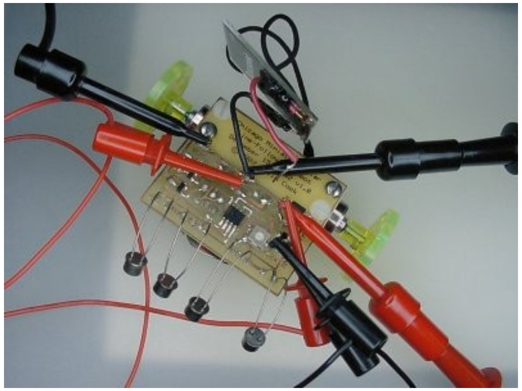
how would you find out?

radio de-construction for biologists

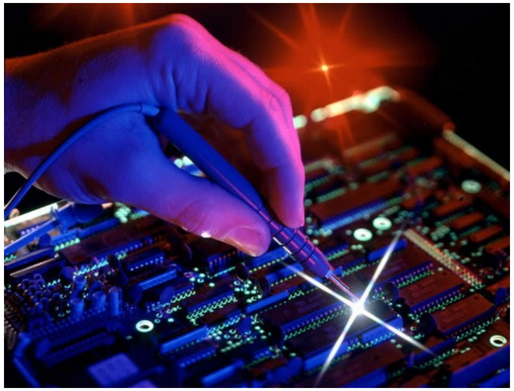


biochemistry

deletion



transfection

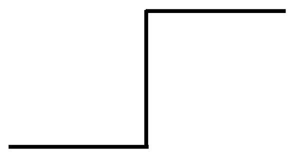


interference

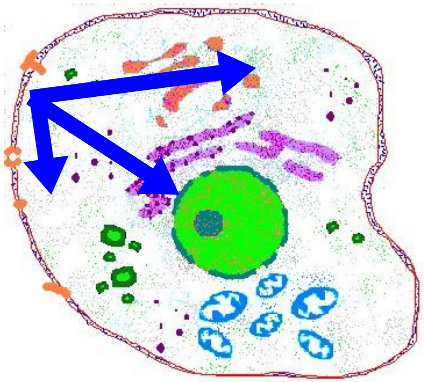
Yuri Lazebnik, *“Can a biologist fix a radio? — Or what I learned while studying apoptosis”*, Cancer Cell **2**:179–182 2002

radio de-construction for biologists

the conventional experiment in signal transduction



step function at saturating concentration



look to see what changes

even if we look at cells in an organism

the organism “knows” its internal environment but we do not

what is the spatial and temporal pattern of EGF in a developing embryo?

radio de-construction for systems biologists

the molecular complexity inside cells reflects the complexity of the environments in which those cells evolved

to understand this molecular complexity we have to integrate the environment into our conceptual and experimental methods

use the outside to learn about the inside

how do we turn this slogan into science?

how can we study cells from an input/output perspective?

the constancy of the “milieu intérieure”

“The fixity of the milieu supposes a perfection of the organism such that the external variations are at each instant compensated for and equilibrated.... All of the vital mechanisms, however varied they may be, have always one goal, to maintain the uniformity of the conditions of life in the internal environment .... ***The stability of the internal environment is the condition for the free and independent life****.”* *****

***** Claude Bernard, from **Lectures on the Phenomena Common to Animals and Plants**, 1978. Quoted in C Gross, *“Claude Bernard and the constancy of the internal environment”*, The Neuroscientist, **4**:380-5 1998

Claude Bernard, **Introduction to the Study of Experimental Medicine**, 1865

homeostasis

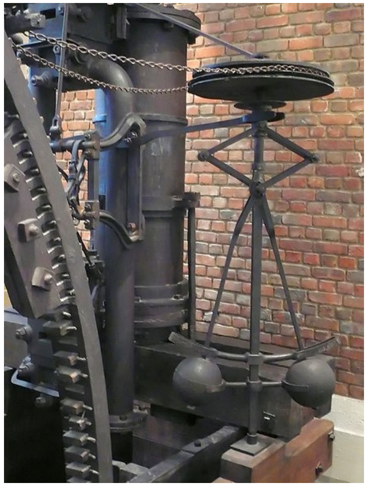
"The highly developed living being is an open system having many relations to its surroundings – in the respiratory and alimentary tracts and through surface receptors, neuromuscular organs and bony levers. Changes in the surroundings excite reactions in this system, or affect it directly, so that internal disturbances of the system are produced. ***Such disturbances are normally kept within narrow limits, because automatic adjustments within the system are brought into action, and thereby wide oscillations are prevented and the internal conditions are held fairly constant****."* *****

***** Walter B Cannon, *"Organization for physiological homeostasis"*, Physiological Reviews, **9**:399-431, 1929.

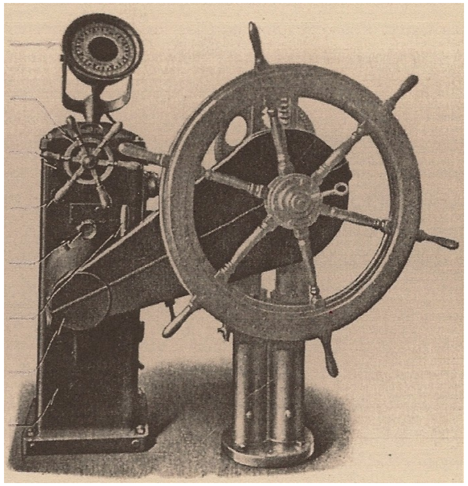
Walter B Cannon, **The Wisdom of the Body**, W W Norton & Co, 1932.

Walter B Cannon, *"The body physiologic and the body politic"*, Science, **93**:1, 1941.
Also, see the Epilogue to WOTB.

meanwhile, back in the real world



Watt's governor



“Metal Mike”

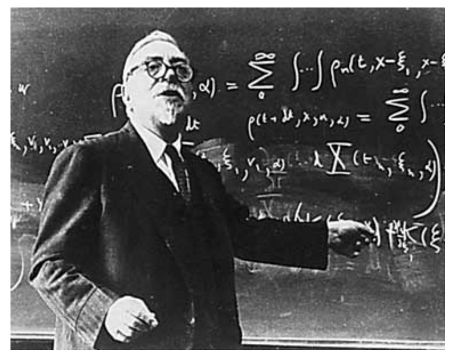
autopilot

engineers had already developed machines that could implement homeostatic behaviour

D Mindell, **Between Human and Machine: Feedback, Control and Computing before Cybernetics**, Johns Hopkins University Press, 2002.

and down the road at MIT

the analogy between machines and organisms was made explicit



in a famous rebuttal of vitalism *

* A Rosenblueth, N Wiener, J Bigelow, *“Behavior, purpose and teleology”*, Philosophy of Science 10:18-24 1943

N Wiener, **Cybernetics or Control and Communication in the Animal and the Machine**, MIT Press, 1948

linear approximation

near a steady state, a nonlinear system may be approximated by a linear one (the Hartman-Grobman Theorem)

nonlinear $$\frac{dx}{dt} = f(x)$$ ⇒ **linear** $$\frac{dy}{dt} = A.y$$

steady state x_{ss}

$$y = x - x_{ss}$$ **offset from the steady state**

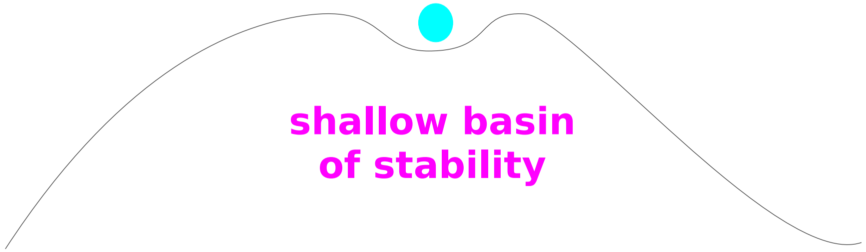
$$A_{i,j} = \left.\frac{\partial f_i}{\partial x_j}\right|_{x=x_{ss}}$$ **Jacobian matrix**

provided that no eigenvalue of the Jacobian has real part zero

stability of steady states

a steady state is stable if all the eigenvalues of the Jacobian, at the steady state, have negative real part

in this case, **sufficiently small** perturbations away from the steady state cause the system to return to the steady state



homeostasis requires stability of the steady state but stability is not sufficient to ensure homeostasis

linear systems

two equivalent ways of writing a system of linear differential equations

single variable, higher derivatives

$$a_2 \frac{d^2x}{dt^2} + a_1 \frac{dx}{dt} + a_0 x = 0$$

order = 2

matrix form

$$x_1 = x \quad x_2 = \frac{dx_1}{dt}$$

$$\frac{d}{dt}\begin{pmatrix} x_1 \\ x_2 \end{pmatrix} = \begin{pmatrix} 0 & 1 \\ -\frac{a_0}{a_2} & -\frac{a_1}{a_2} \end{pmatrix}\begin{pmatrix} x_1 \\ x_2 \end{pmatrix}$$

 # components = 2

the problem of homeostasis (with 1 component)

linear system with a stable steady state at $x = 0$

$$\frac{dx}{dt} = -bx$$

to be controlled so that it maintains the steady state $x = r$
against perturbations

set point

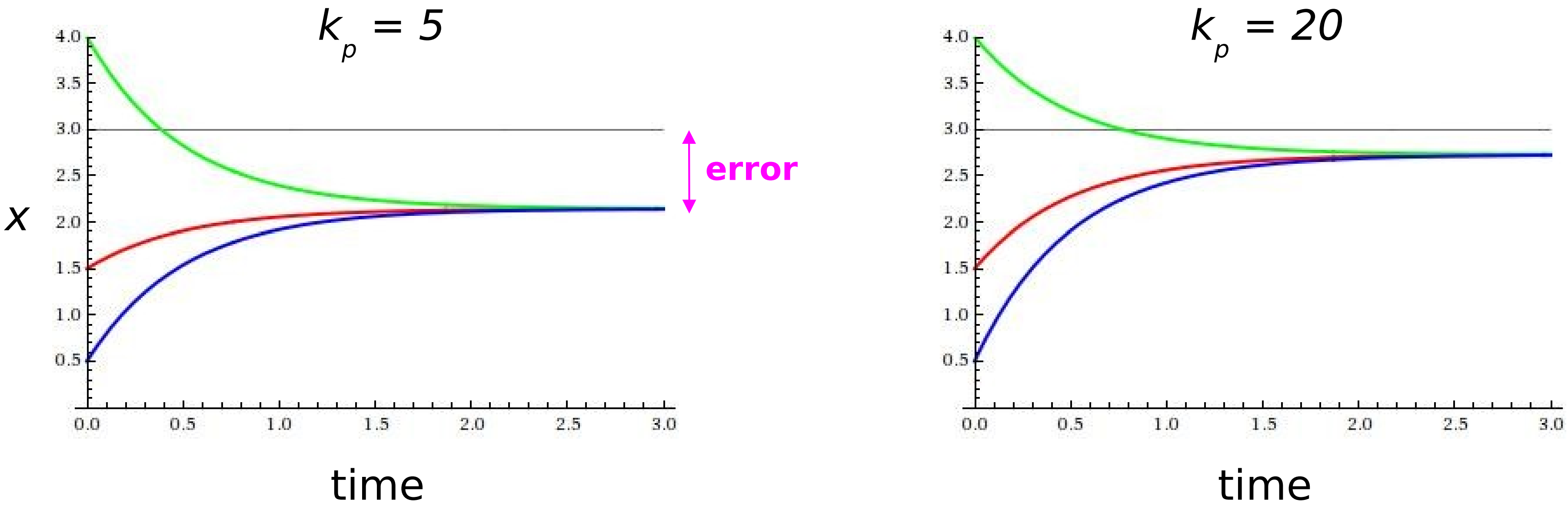
proportional control

apply negative feedback that is proportional to the discrepancy between *x* and *r*

controller gain

$$\frac{dx}{dt} = -bx + k_p(r - x)$$

b = 2, *r* = 3



proportional control

suffers from **steady state error** that can be minimised by increasing the controller gain

normalised

$$\left(\frac{1}{b + k_P}\right)\frac{dx}{dt} + x = \frac{r}{1 + b/k_P}$$

$$x_{ss} = \frac{r}{1 + b/k_P}$$

steady state of the controlled system

how can steady state error be avoided?

biased proportional control

add a bias, so that there is positive control when $x = r$

$$\frac{dx}{dt} = -bx + k_p(r - x) + \underset{\text{bias}}{c}$$

if $c = br$, then

$$x_{ss} = r$$

biased proportional control works but it is not a robust solution – the parameters have to be fine tuned

integral control

integral control variable

suppose there is another variable in the system, *y*, whose **rate of change** is proportional to the discrepancy between *x* and *r*

$$\frac{dy}{dt} = k_i(r - x)$$

then, in any steady state,

$$x_{ss} = r$$

$$y(t) = \int_0^t k_i(r - x(u))du$$

integral control

use *y* as the control variable

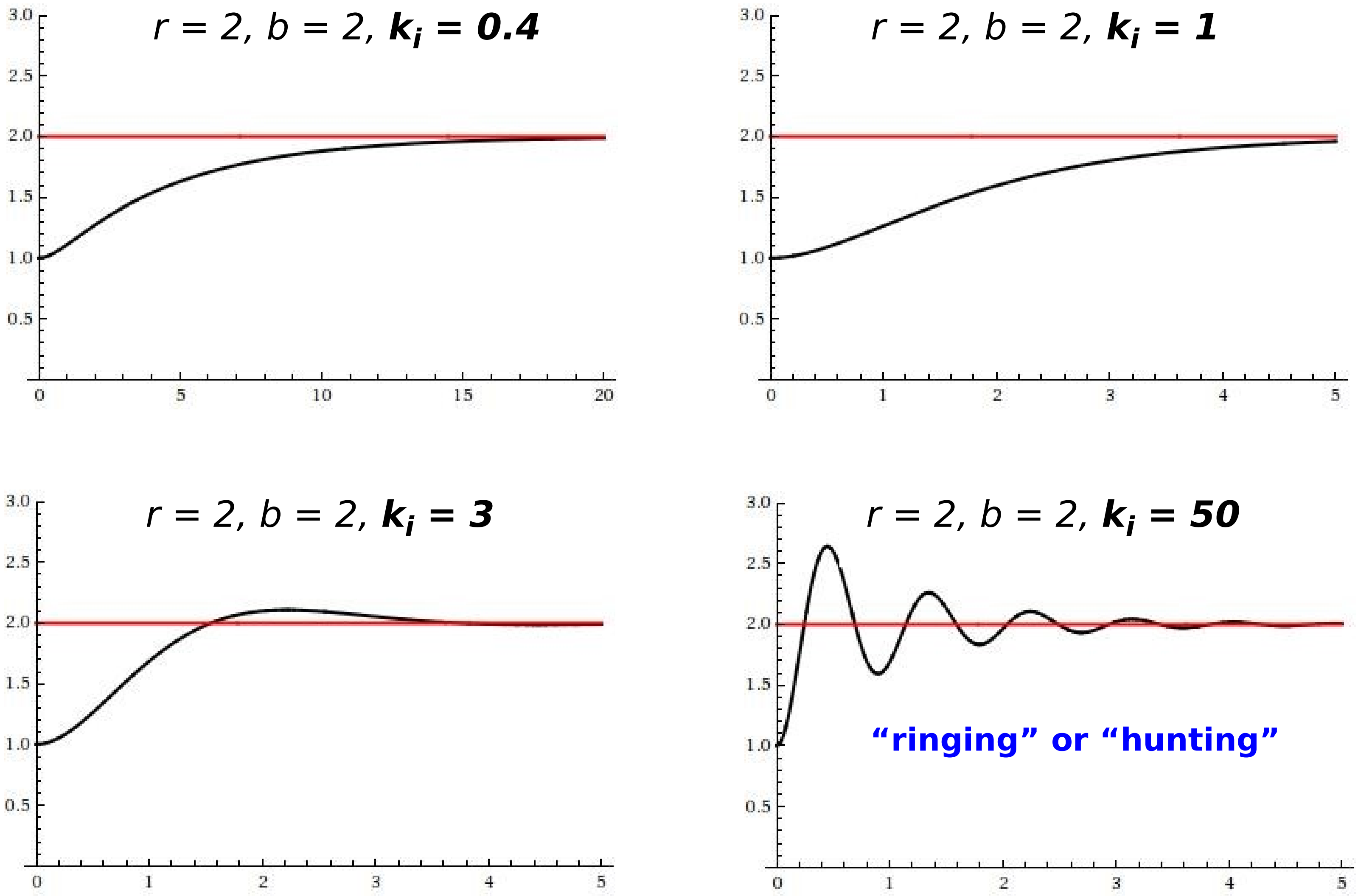
$$\frac{dx}{dt} = -bx + \int_0^t k_i(r - x(u))du$$

$$\left(\frac{1}{k_i}\right)\frac{d^2x}{dt^2} + \left(\frac{b}{k_i}\right)\frac{dx}{dt} + x = r$$

integral control provides a robust implementation of homeostasis

at the price of increasing the number of components

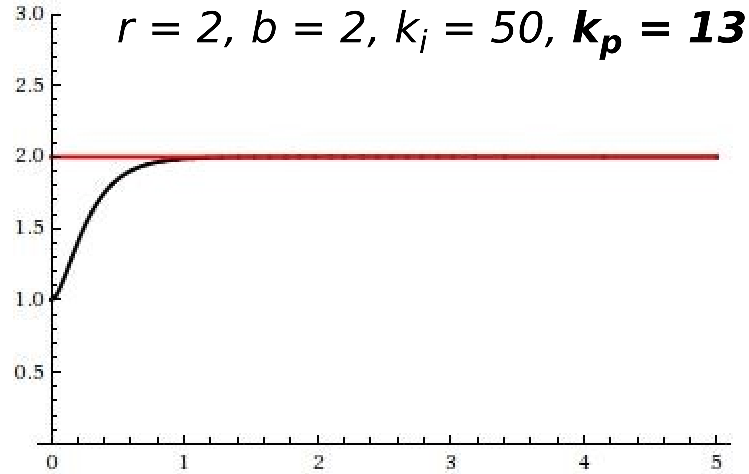
integral control – transient behaviour



PI and PID control

transient behaviour can be improved by adding proportional control

$$\left(\frac{1}{k_i}\right)\frac{d^2x}{dt^2} + \left(\frac{b+k_p}{k_i}\right)\frac{dx}{dt} + x = r$$



and shaped further by adding derivative control (PID control)

evolution anticipated engineering

Robust perfect adaptation in bacterial chemotaxis through integral feedback control

Tau-Mu Yi*†, Yun Huang†‡, Melvin I. Simon*§, and John Doyle‡

Calcium Homeostasis and Parturient Hypocalcemia: An Integral Feedback Perspective

H. El-Samad*, J. P. Goff† and M. Khammash*‡

perfect adaptation = homeostasis

A Systems-Level Analysis of Perfect Adaptation in Yeast Osmoregulation

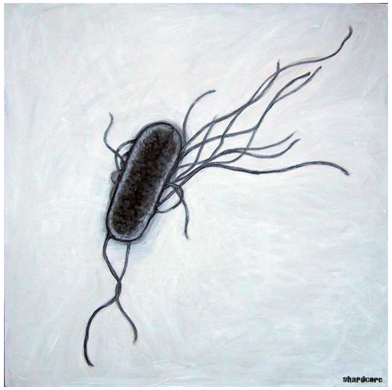
Dale Muzzey,[1,4,5] Carlos A. Gómez-Uribe,[1,2,5] Jerome T. Mettetal,[1] and Alexander van Oudenaarden[1,3,*]

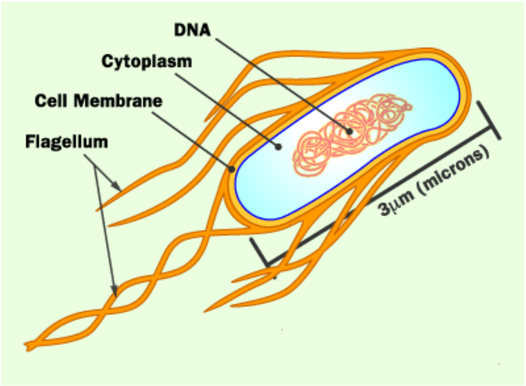
Yi, Huang, Simon, Doyle, PNAS **97**:469-53 2000

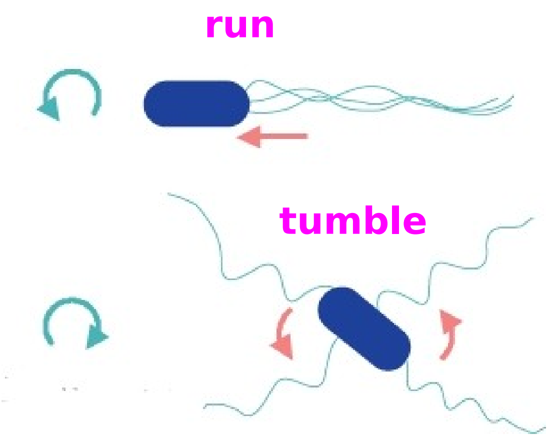
El-Samad, Goff, Khammash, J Theor Biol **214**:17-29 2002

Muzzey, Gomez-Uribe, Mettetal, van Oudenaarden, Cell **138**:160-71 2009

chemotaxis in *E coli*





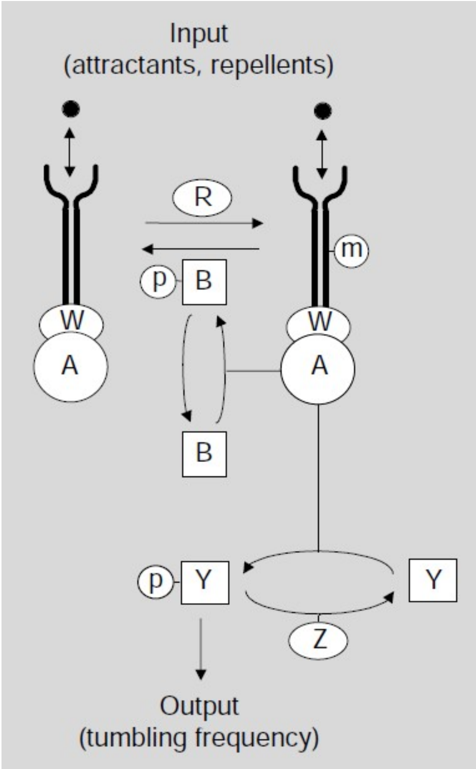


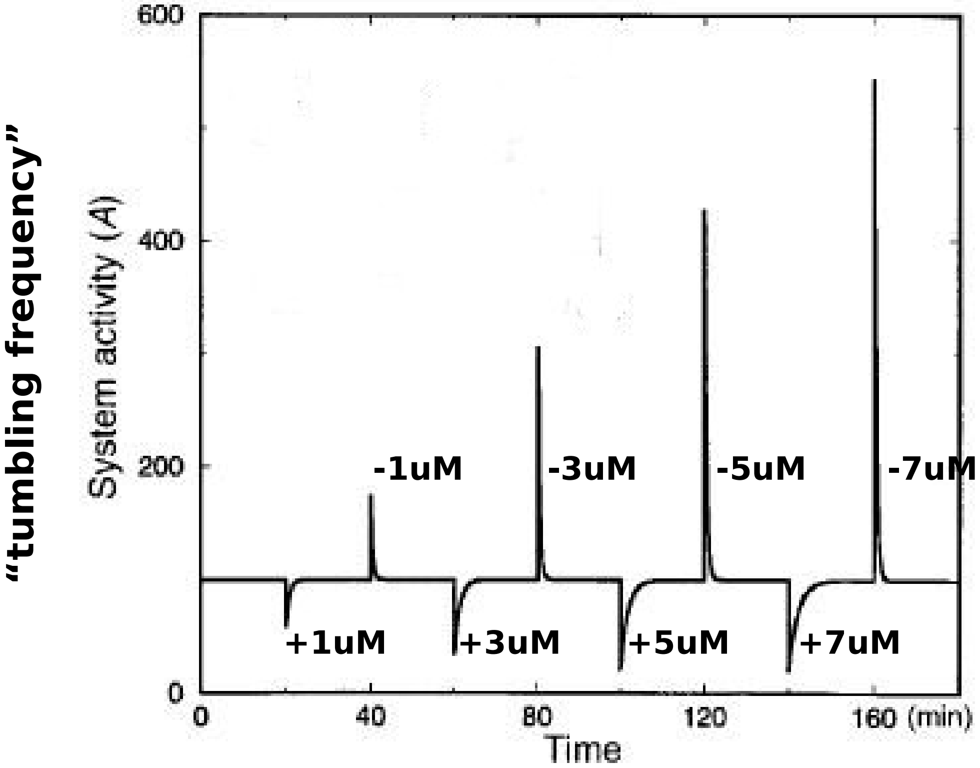
E coli navigates towards an attractant, or away from a repellent, by rotating its flagella, alternating between **"runs"** (flagella rotating together) and **"tumbles"** (flagella rotating apart).

By changing the tumbling frequency, a bacterium can navigate along a chemotactic gradient.

H Berg, **E coli in Motion**, Springer 2003

perfect adaptation in theory

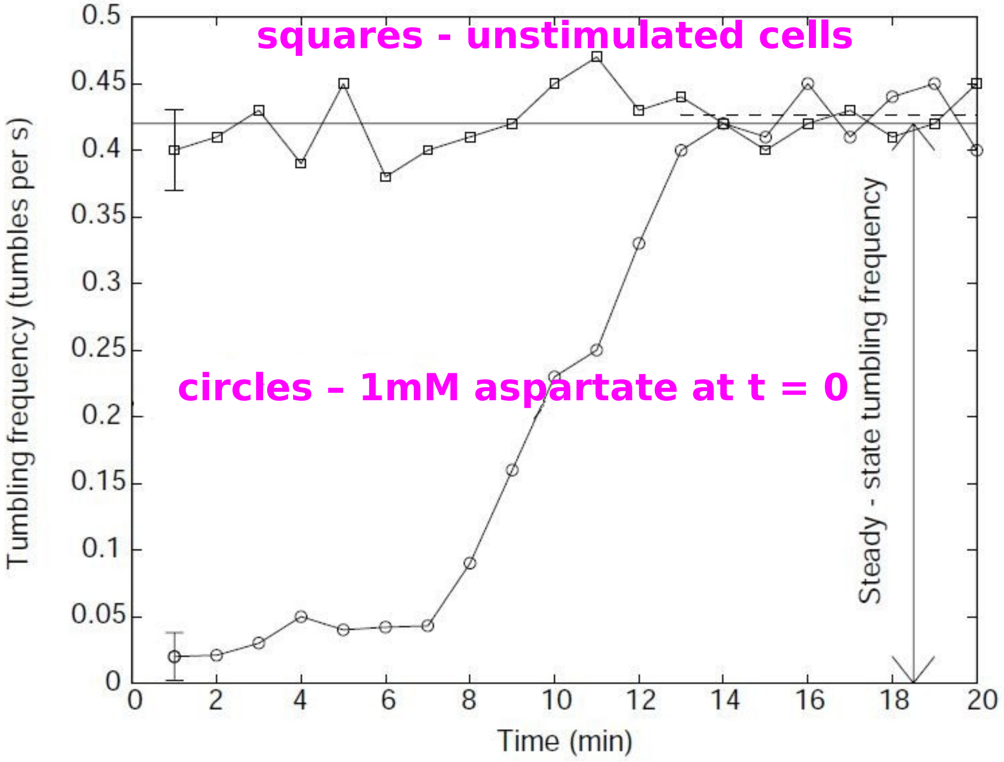




N Barkai, S Leibler, *"Robustness in simple biochemical networks"*, Nature **387**:913-7 1997

perfect adaptation in fact

E coli RP437

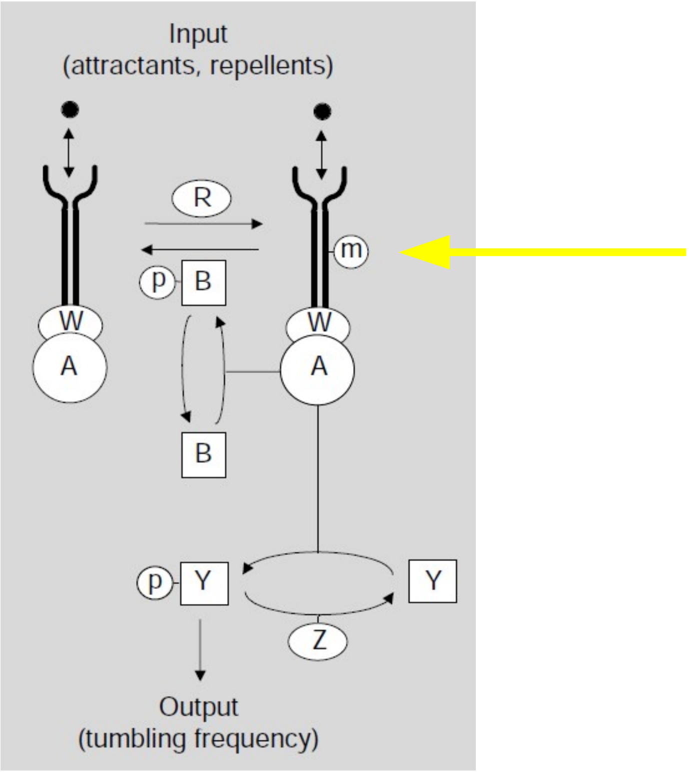


each data point averaged over 100-400 cells

U Alon, M G Surette, N Barkai, S Leibler, *"Robustness in bacterial chemotaxis"*, Nature **397**:168-71 1999

perfect adaptation as integral control

total receptor methylation acts as an integral control variable



4 methylation sites

T-M Yi, Y Huang, M I Simon, J Doyle, *“Robust perfect adaptation in bacterial chemotaxis through integral feedback control*”, PNAS **97**:4649-53 2000

linear system with *n* components

external stimulus

$$\frac{dx_1}{dt} = A_{11}x_1 + \cdots + A_{1n}x_n + b_1u$$

$$\frac{dx_2}{dt} = A_{21}x_1 + \cdots + A_{2n}x_n + b_2u$$

$$\vdots \quad \vdots \quad \vdots$$

$$\frac{dx_n}{dt} = A_{n1}x_1 + \cdots + A_{nn}x_n + b_nu$$

$$y = c_1x_1 + \cdots + c_nx_n + du$$

observed output variable

$$\frac{dx}{dt} = Ax + bu$$

$$y = cx + du$$

integral control is necessary for perfect adaptation

“perfect adaptation” is taken to mean that the steady state value of the observed output variable, *y*, is independent of the stimulus, *u*

provided the underlying system is stable, then perfect adaptation implies the existence of a generalised internal variable

$$z = k_1 x_1 + \cdots + k_n x_n$$

that implements integral control $$\frac{dz}{dt} = y$$ **set point = 0**

T-M Yi, Y Huang, M I Simon, J Doyle, *“Robust perfect adaptation in bacterial chemotaxis through integral feedback control*”, PNAS **97**:4649-53 2000 – see the Appendix, for which the following formula is helpful

$$\det \begin{pmatrix} A & b \\ c & d \end{pmatrix} = (d - cA^{-1}b) \det A$$

summing up

1. *molecular complexity reflects the complexity of external environments*

2. *we need to integrate complex environments into our conceptual and experimental approaches – an input/output perspective*

3. *the origins of such ideas go back to physiology and engineering*

4. *nonlinear systems can be approximated by linear ones, in the vicinity of a reasonable steady state (Hartman-Grobman Theorem)*

5. *homeostasis can be robustly implemented by integral feedback control*

6. *homeostasis (perfect adaptation) requires integral control, at least from a linear perspective*