dynamic processes in cells (a systems approach to biology)

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lecture 4

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recap – solving linear ODEs

$$a_n \frac{d^n x}{dt^n} + a_{n-1} \frac{d^{n-1} x}{dt^{n-1}} + \cdots + a_1 \frac{dx}{dt} + a_0 x = 0$$

has solutions which are linear combinations of terms of the form $t^j e^{z_i t}$

where z_i is a root of the characteristic polynomial

$$Z(s) = a_n s^n + a_{n-1} s^{n-1} + \cdots + a_1 s + a_0$$

and j is less than the number of times z_i is repeated as a root

stability and the roots of Z(s)

the solution with any initial condition is a linear combination of terms

$$t^j e^{z_u t}$$

$$z_u = a_u + i b_u$$

real part

imaginary part

$$t^j e^{z_u t} = t^j \boxed{e^{a_u t}} e^{i b_u t}$$

Euler's formula – sine or cosine

increasing power of t (if z_u is repeated)

increasing or decaying exponential depending on whether a_u is positive or negative, respectively

a decaying exponential of rate *a > 0*, no matter how small, will always overwhelm a power of *t*, no matter how large,

$$t^k e^{-at} \longrightarrow 0$$

hence, the solution with any initial condition will relax to 0 if all the roots of the characteristic equation have negative real parts

maxwell's criterion for stability

It will be seen that the motion of a machine with its governor consists in general of a uniform motion, combined with a disturbance which may be expressed as the sum of several component motions. These components may be of four different kinds :-

(1) The disturbance may continually increase.
(2) It may continually diminish.
(3) It may be an oscillation of continually increasing amplitude.
(4) It may be an oscillation of continually decreasing amplitude.

The first and third cases are evidently inconsistent with the stability of the motion; and the second and fourth alone are admissible in a good governor. This condition is mathematically equivalent to the condition that all the possible roots, and all the possible parts of the impossible roots, of a certain equation shall be negative.

1831-1879

a linear ODE is stable if the roots of its characteristic equation all have negative real parts

J C Mawell, *"On governors"*, Proc Roy Soc, **16**:270-83, 1868.

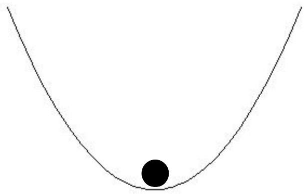
stability of negative feedback systems

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

since $a_0 \, , \; a_1 \, , \; a_2 > 0$ it is easy to check that, if z is a root, then

$$\mathrm{Re}(z) < 0$$

so, maxwell need not have lost any sleep over the systems we have considered – their steady states are all stable



stable

dynamical behaviour

a 2nd order negative feedback system can always be normalised as follows:

positive coefficient of *x* is +1

$$\left(\frac{1}{\omega^2}\right)\frac{d^2x}{dt^2} + \left(\frac{2\delta}{\omega}\right)\frac{dx}{dt} + x = 0$$

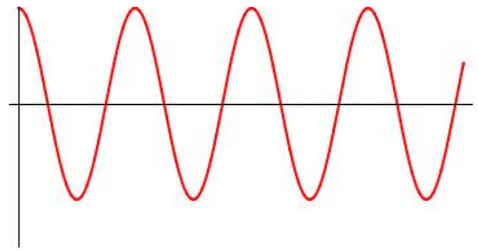
$\omega > 0$	fundamental frequency	(time)$^{-1}$
$\delta > 0$	damping ratio	dimensionless

with these choices the characteristic polynomial has the following two roots

$$s = \omega(-\delta \pm \sqrt{\delta^2 - 1})$$

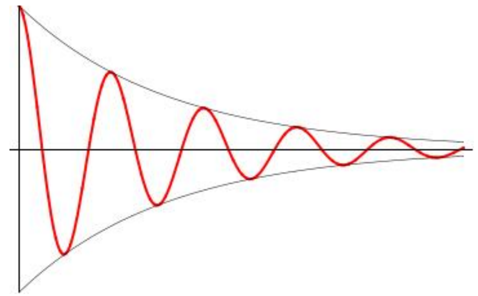
dynamical behaviour

$\delta = 0$ undamped



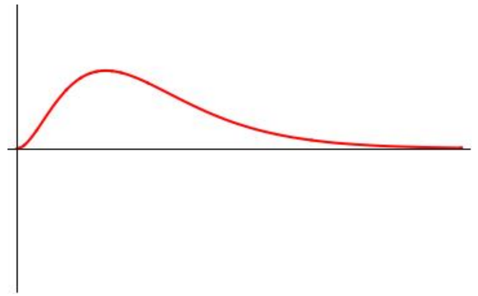
$\cos(\omega t)$

$0 < \delta < 1$ underdamped



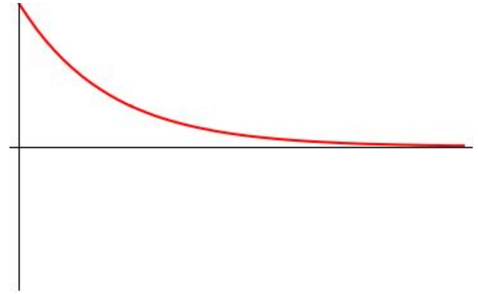
$e^{-\omega\delta t}\cos(\omega\sqrt{1-\delta^2}\,t)$

$\delta = 1$ critically damped



$te^{-\omega\delta t}$

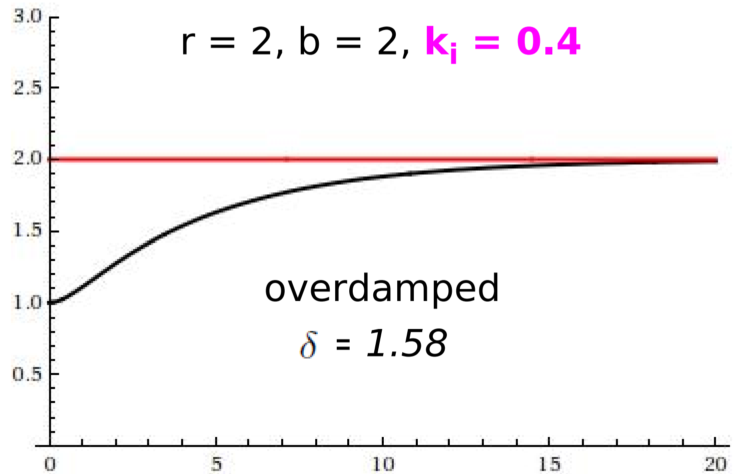
$1 < \delta$ overdamped

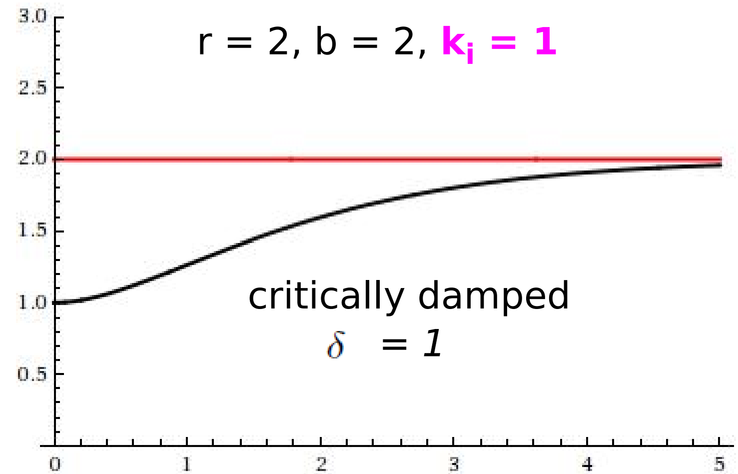


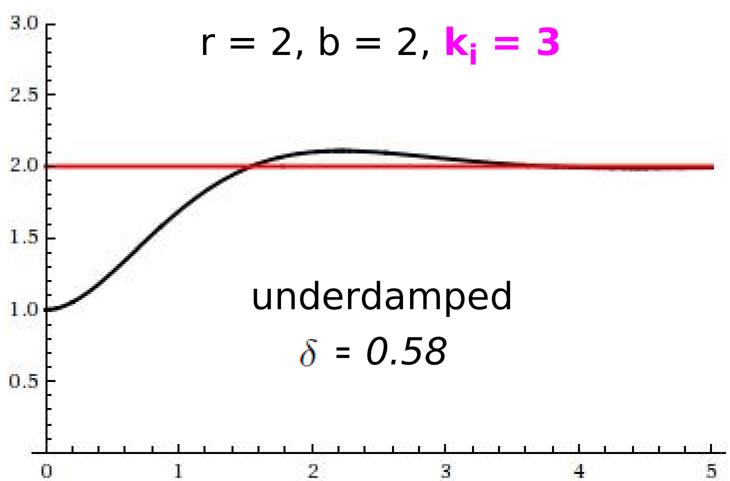
$e^{\omega(-\delta+\sqrt{\delta^2-1})t}$

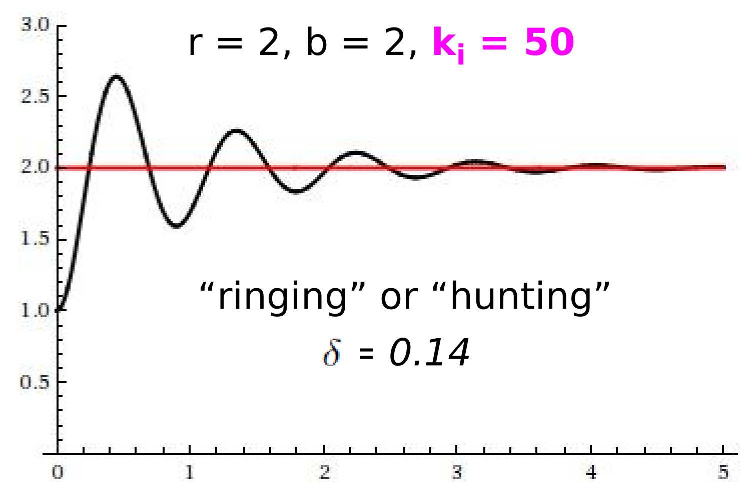
integral controllers

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



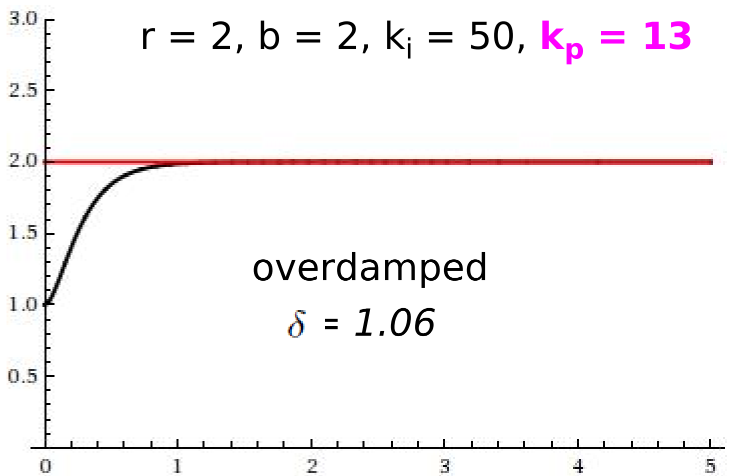


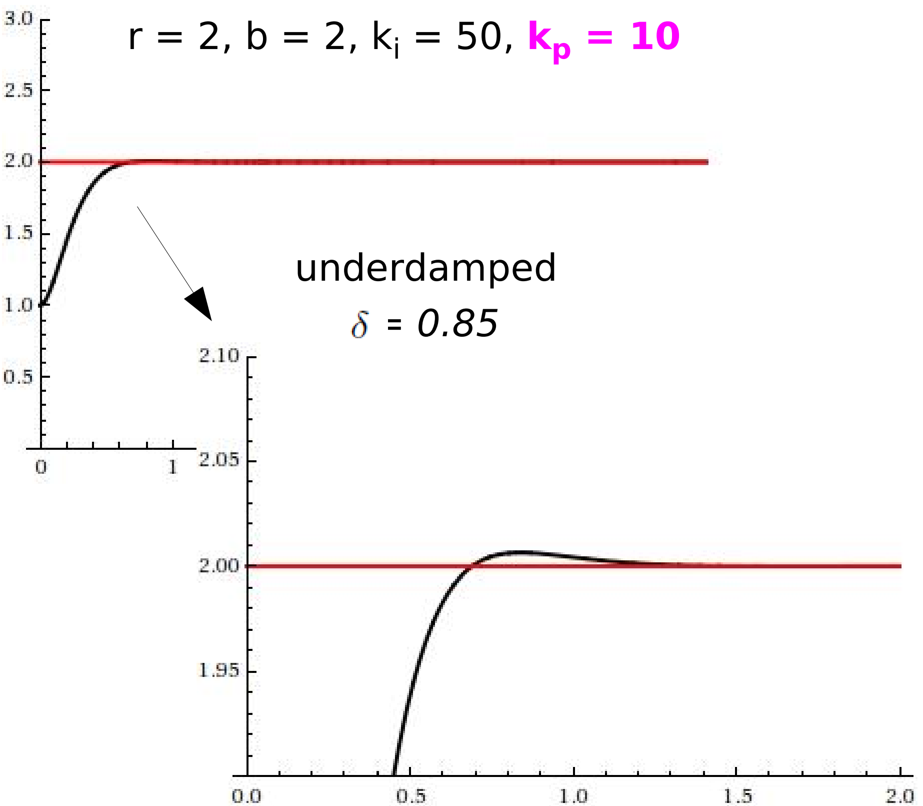




proportional integral controllers

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





PID controllers

we have considered the problem of controlling a very simple first-order system

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

but systems can be much more complicated

engineers have found that, it is usually sufficient to combine three mechanisms of negative feedback control – **proportional**, **integral** and **derivative** (PID control) – to achieve perfect adaptation with good dynamical behaviour

- integral control – responds to the past history of the system
- proportional control – responds to the current state of the system
- derivative control – responds to where the system is going in the future

in summary,

the Laplace transform converts differentiation by s (or t) into multiplication by t (or s)

the solutions of a linear ODE are linear combinations of terms of the form $t^j e^{z_i t}$ where z_i are the roots of the characteristic equation

the linear ODE is stable if, for all roots z_i , $\mathrm{Re}(z_i) < 0$

by combining different negative feedback mechanisms, such as PI or PID control, perfect adaptation can be achieved robustly and with good dynamical behaviour

evidence for integral control – glucose

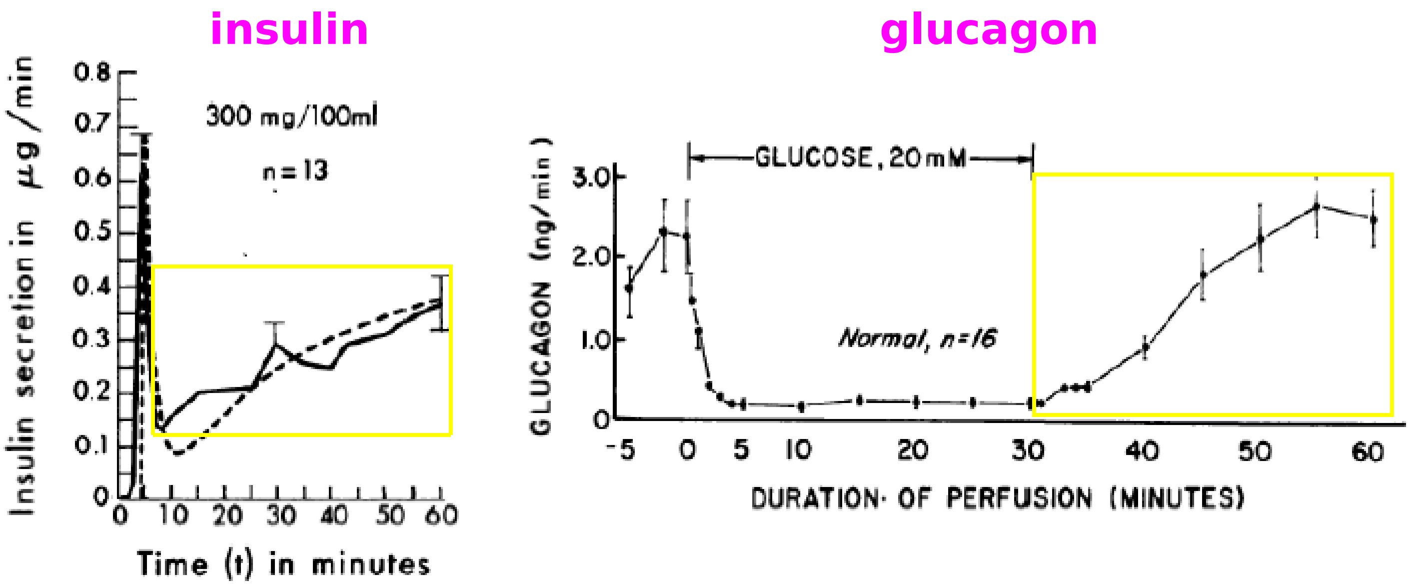


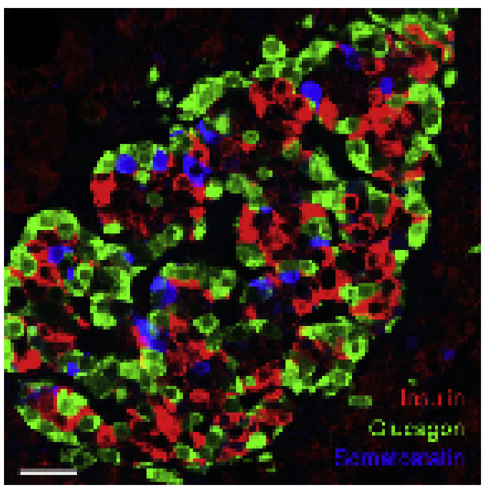
Figure 4.7: Evidence for integral control in glucose homeostasis, with the relevant data in the yellow boxes. a. Rate of insulin secretion, measured in μg/min, of an isolated rat pancreas continuously perfused with buffer containing 300 mg/dL = 16.7mM glucose (§1.6). Data points are mean $\pm$ the standard error of the mean from 13 normal rats. The dashed line shows the results of a simulation that is not discussed here. Adapted from [83, Figure 2]. b Rate of glucagon secretion, measured in ng/min, of an isolated rat pancreas continuously perfused with buffer containing no glucose. Glucose at 20mM was added to the buffer as shown from 0 to 30 minutes. Data points are mean $\pm$ the standard error of the mean from 16 normal rats. Adapted from [155, Figure 5].

Grodsky, *"A threshold distribution hypothesis for packet storage of insulin and its mathematical modeling"*, J Clin Invest **51**:2047-59 1972

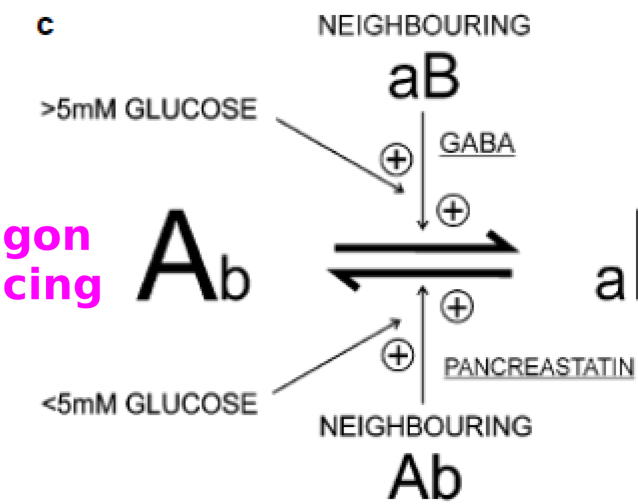
Pagliara, ..., Matschinsky, *"Insulin and glucose as modulators of the amino acid-induced glucagon release in the isolated pancreas of alloxan and streptozotocin diabetic rats"*, J Clin Invest **55**:244-55 1975

evidence for integral control – glucose

it is possible for two opposing integral controllers to perfectly adapt, provided they mutually inhibit each other



glucagon producing



insulin producing

Koeslag, Saunders, Terblanche, *“A reappraisal of the blood glucose homeostat which comprehensively explains the type 2 diabetes mellitus-syndrome X complex”*, J Physiol **549**:333-46 2003

evidence for integral control – eye movement

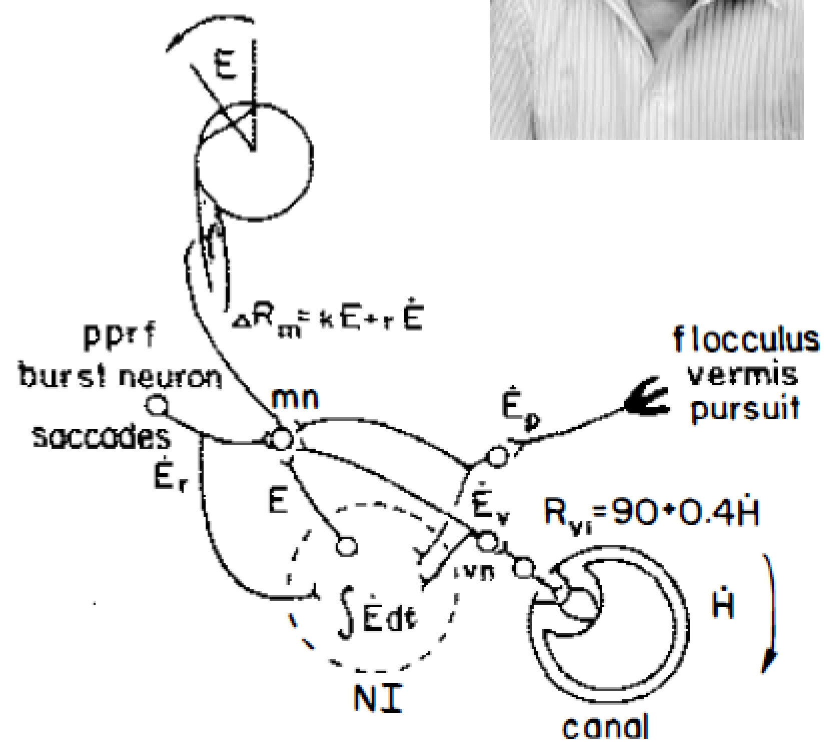
INTEGRATING WITH NEURONS

D. A. Robinson

Ann. Rev. Neurosci. 1989. 12:33–45

Department of Ophthalmology and Biomedical Engineering, The Johns Hopkins University, School of Medicine, Baltimore, Maryland 21205

“The retina sense the error between the eye (fovea) and the target and the system turns the eye until the error is zero – a simple negative feedback scheme. Moreover, when the goal is reached, a constant eye deviation (output) is maintained while the error (input) is zero. But that is just whan an integrator does.”



the internal models principle

does perfect adaptation imply integral control?

if a **linear** system shows perfect adaptation to a set point, r , in some internal variable, x , when some parameter changes in a sustained manner, then the system includes an integral controller

$$\frac{dx_c}{dt} = k(r - x)$$

for a proof, see (*) or the handout

Francis, Wonham, "*The internal model principle of control theory*", Automatica 12:457-465 1976

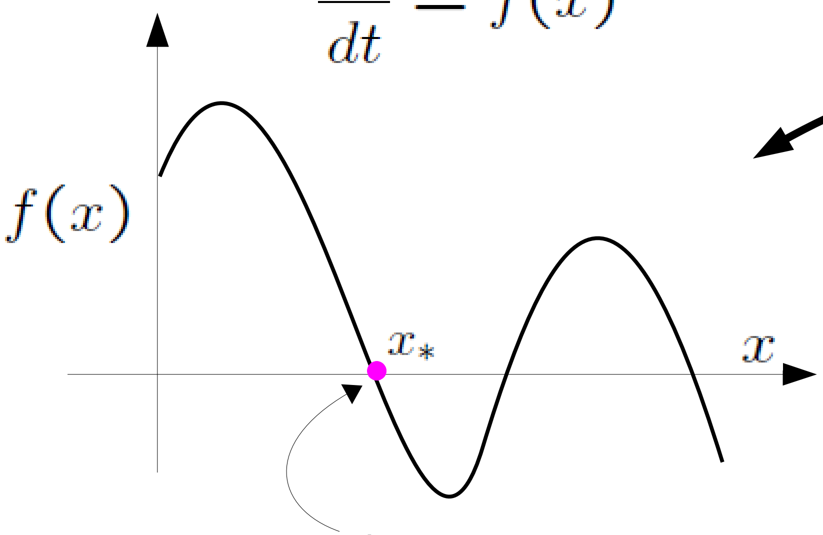
(*) T-M Yi, Y Huang, M I Simon, J Doyle, *"Robust perfect adaptation in bacterial chemotaxis through integral feedback control*", PNAS **97**:4649-53 2000

linearisation at a steady state

if a **nonlinear** system has a steady state, then its dynamical behaviour in the vicinity of the steady state can be approximated by a linear system

nonlinear system

$$\frac{dx}{dt} = f(x)$$



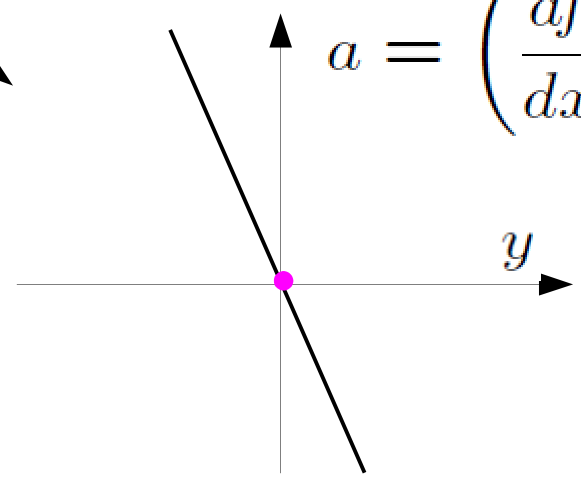
steady state

$$f(x_*) = 0$$

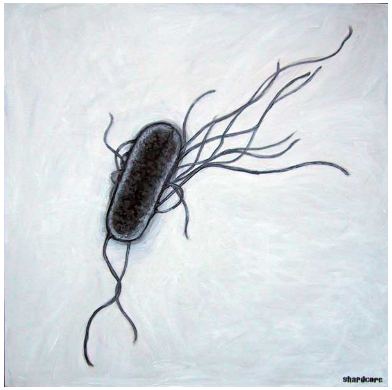
linear system

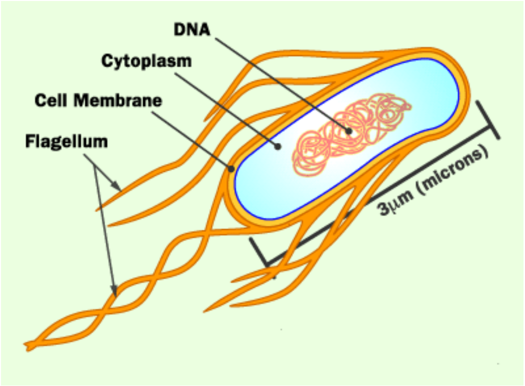
$$\frac{dy}{dt} = ay \qquad y = x - x_*$$

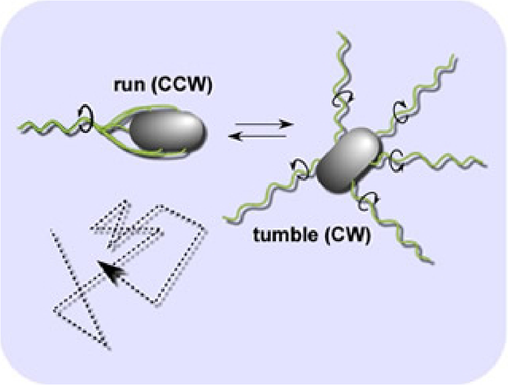
$$a = \left(\frac{df}{dx}\right)\bigg|_{x=x_*}$$



E coli chemotaxis







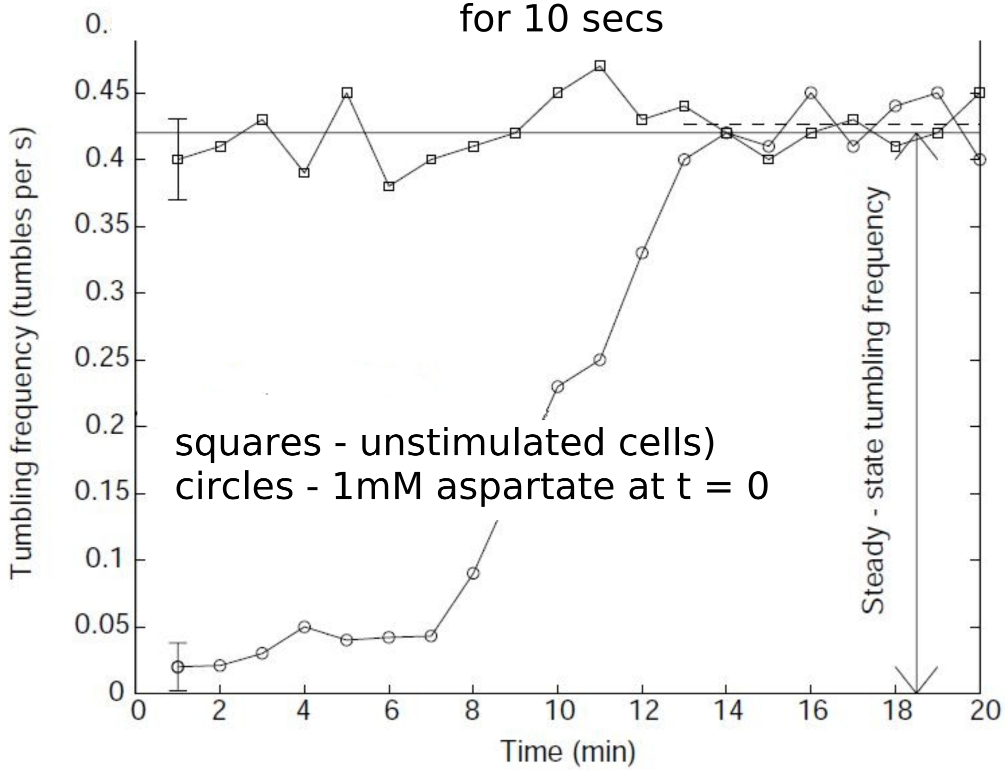
E coli navigates towards an attractant, or away from a repellent, by rotating its flagella, alternating between **“runs”** (flagella rotating together) and **“tumbles”** (flagella rotating apart). By changing the tumbling frequency, a bacterium can navigate along a chemotactic gradient.

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

tumbling frequency shows perfect adaptation

E coli RP437 strain

each data point averaged over 100-400 cells
for 10 secs



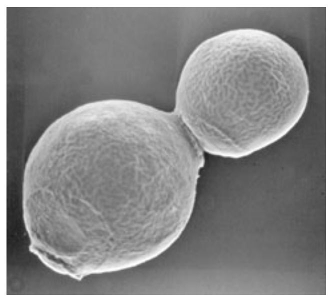
population average
returns to its set point

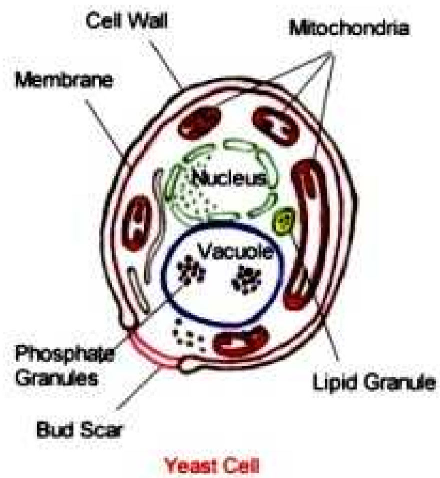
U Alon, M G Surette, N Barkai, S Leibler, *“Robustness in bacterial chemotaxis”*, Nature **397**:168-71 1999

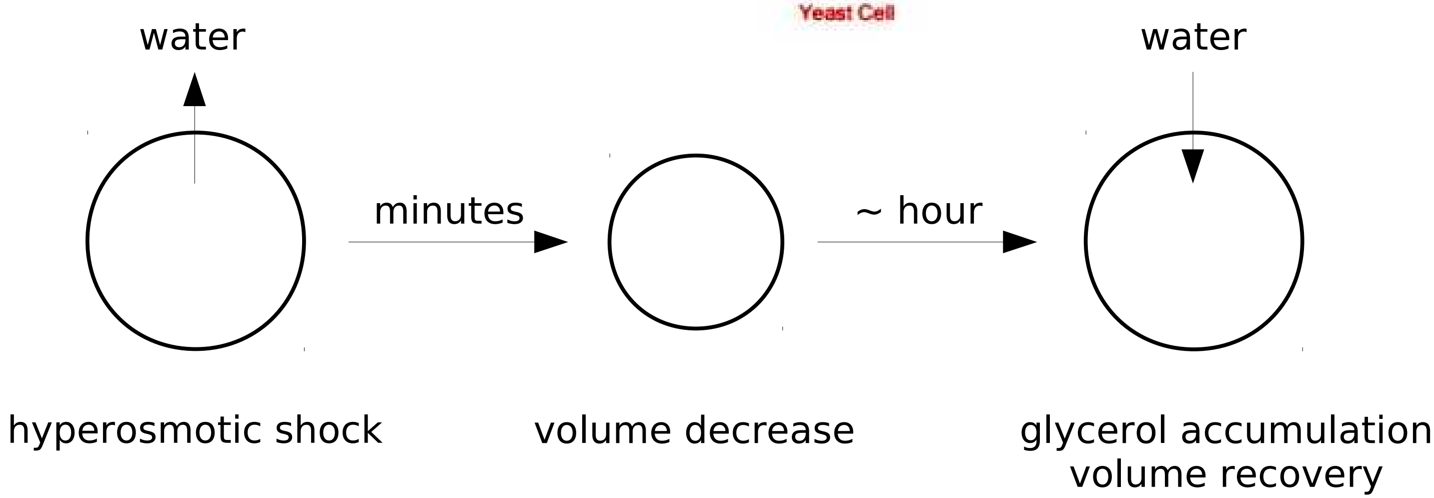
T-M Yi, Y Huang, M I Simon, J Doyle, *“Robust perfect adaptation in bacterial chemotaxis through integral feedback control”*, PNAS **97**:4649-53 2000

S cerevisiae osmolarity regulation

yeast are unicellular fungi whose external environment can exhibit changes in osmolarity on fast and slow time scales



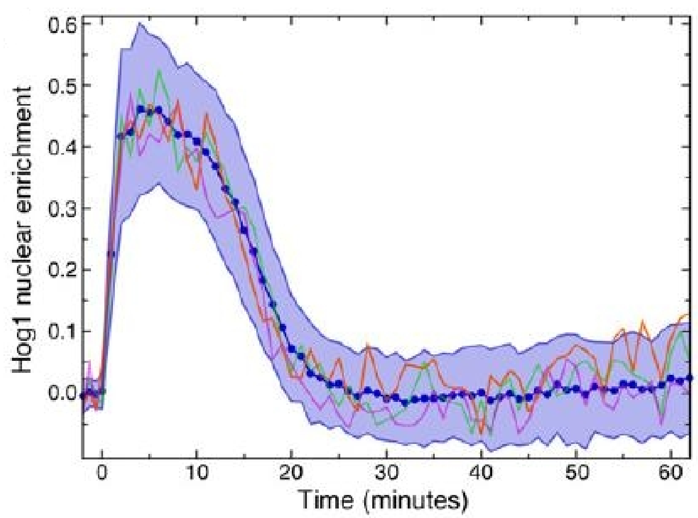




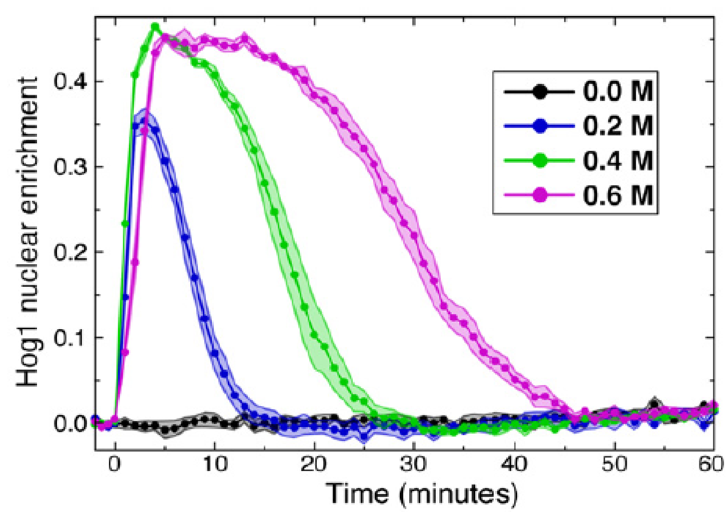
Hog1 nuclear enrichment shows perfect adaptation

SHO1 deletion disables one of the two pathways of Hog1 activation

in haploid SHO1- cells, sustained increase in external NaCl leads to transient nuclear accumulation of the activated MAP kinase Hog1, measured by Hog1-YFP "nuclear enrichment"



cell-to-cell variation is low

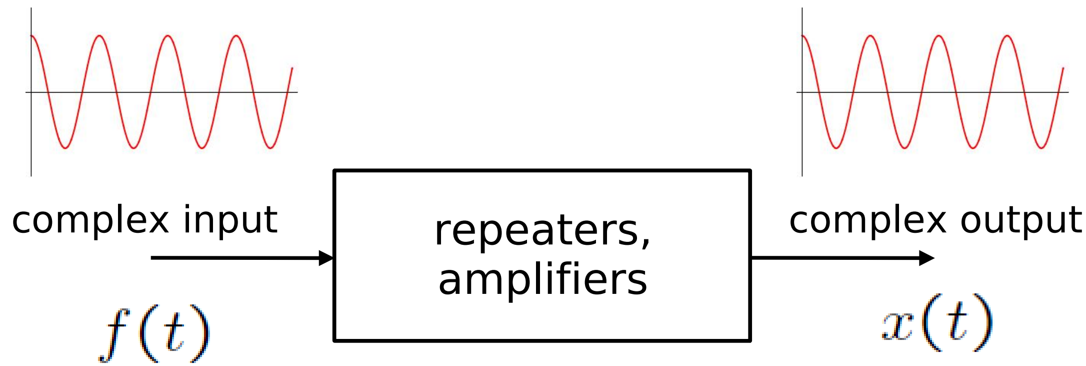


population average returns to its set point
perfect adaptation - no steady-state error

D Muzzey, C Gomez-Uribe, J T Mettetal, A van Oudenaarden, "*A systems-level analysis of perfect adaptation in yeast osmoregulation*", Cell **138**:160-71 2009

learning the inside from the outside

a linear system can be **interrogated** in such a way that its internal architecture can be determined by its response to certain stimuli



$$a_n \frac{d^n x}{dt^n} + \cdots + a_1 \frac{dx}{dt} + a_0 x$$

force the system with a sinusoidal input and look at the output

$$f(t) = e^{i\omega t}$$

1889-1976

1905-1982

Hendrik Bode, **Network Analysis and Feedback Amplifier Design**, Van Nostrand, New York 1945

follow the sines

$$f(t) = e^{i\omega t} \quad (\mathcal{L}f)(s) = \frac{1}{s - i\omega}$$

$$(\mathcal{L}x)(s) = \frac{(\mathcal{L}f) + c(s)}{Z(s)} = \frac{1}{(s - i\omega)Z(s)} + \frac{c(s)}{Z(s)}$$

if the system is stable, the roots of the characteristic polynomial, $Z(s)$, have negative real parts, so $i\omega$ cannot be a repeated root

$$x(t) = Be^{i\omega t} + \underbrace{\sum_i C_i' t^{r_i} e^{z_i t} + \sum_i D_i' t^{r_i} e^{z_i t}}_{\to 0, \text{ as } t \to \infty}$$

because of stability

after the transients have died down, the response of a stable linear system to sinusoidal forcing is a sinusoidal output at the same frequency

but what is the (complex) factor B?

$$\left(a_n \frac{d^n}{dt^n} + a_{n-1}\frac{d^{n-1}}{dt^{n-1}} + \cdots + a_1 \frac{d}{dt} + a_0\right)\left(Be^{i\omega t}\right) = Ae^{i\omega t}$$

$$B(a_n(i\omega)^n + a_{n-1}(i\omega)^{n-1} + \cdots + a_1(i\omega) + a_0) = A$$

$$B = \left(\frac{1}{Z(i\omega)}\right) A = G(i\omega)A$$

the **transfer function** is the reciprocal of the characteristic polynomial

$$G(s) = \frac{(\mathcal{L}x)(s)}{(\mathcal{L}f)(s)} = \frac{1}{Z(s)}$$

or the ratio of the laplace transform of the output to the laplace transform of the input, when the initial conditions are all zero

transfer functionology

it is easy to work out transfer functions from a modular description