dynamic processes in cells (a systems approach to biology)

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lecture 4
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recap

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

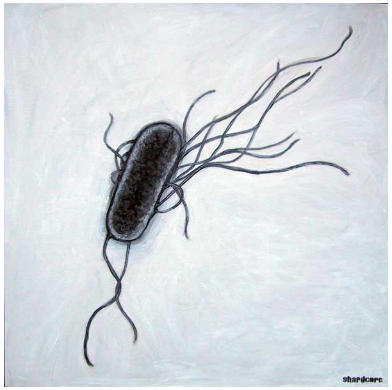
the Laplace transform converts differentiation by s (or t) into multiplication by t (or s)

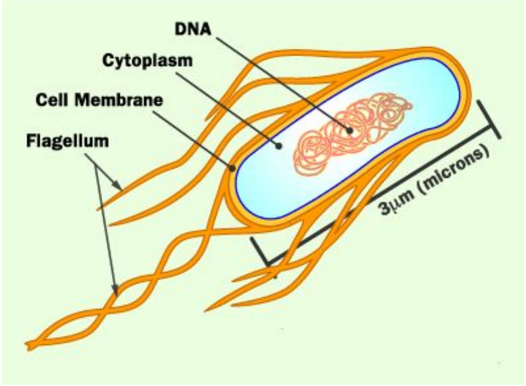
the solutions of a linear ODE are linear combinations of terms of the form $t^j e^{z_i t}$ where z_i are the roots of the characteristic equation

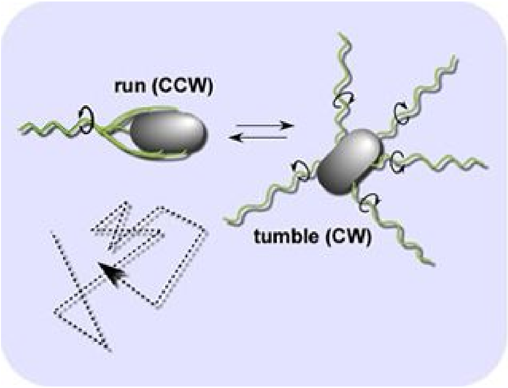
stable if, for all roots z_i , $\mathrm{Re}(z_i) < 0$

different kinds of negative feedback have different effects – redundancy can be more apparent than real

E coli chemotaxis



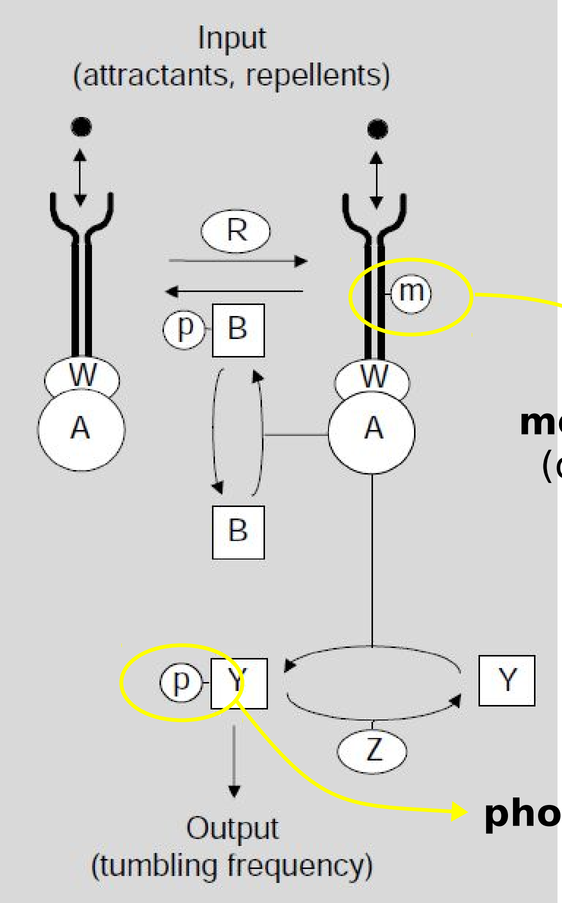




E coli navigates towards an attractant, or away from a repellent, by rotating its flagella, alternating between **“runs”** (flagella rotating together) and **“tumbles”** (flagella rotating apart). By changing the tumbling frequency, a bacterium can navigate along a chemotactic gradient.

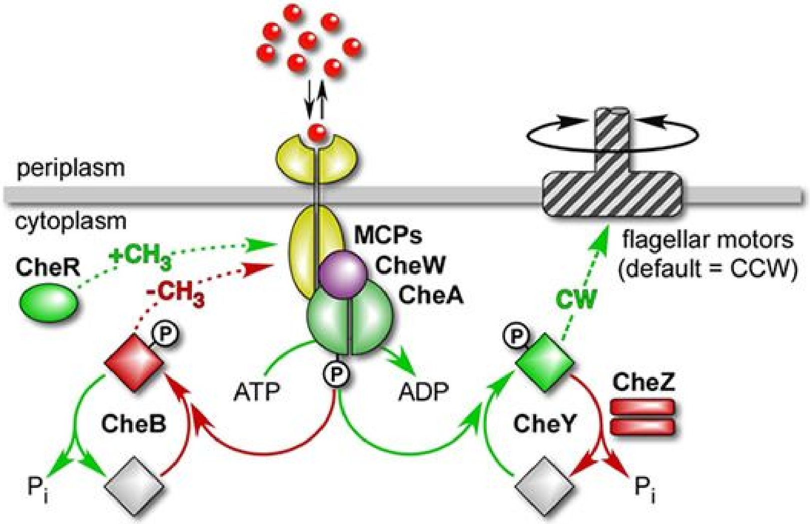
H Berg, **E coli in Motion**, Springer 2003

molecular circuitry of E coli chemotaxis



methylation
(on 4 sites)

phosphorylation

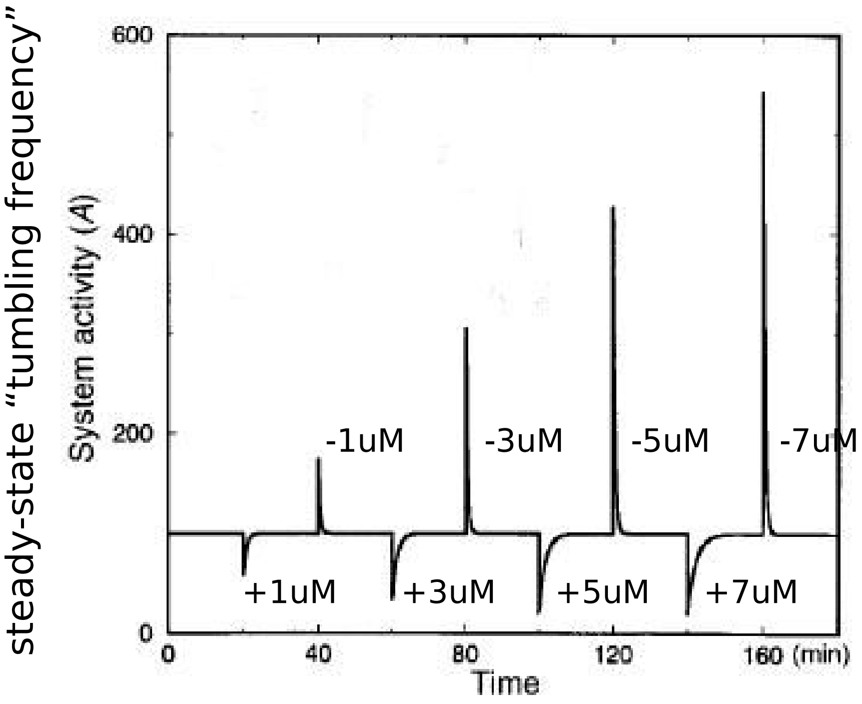


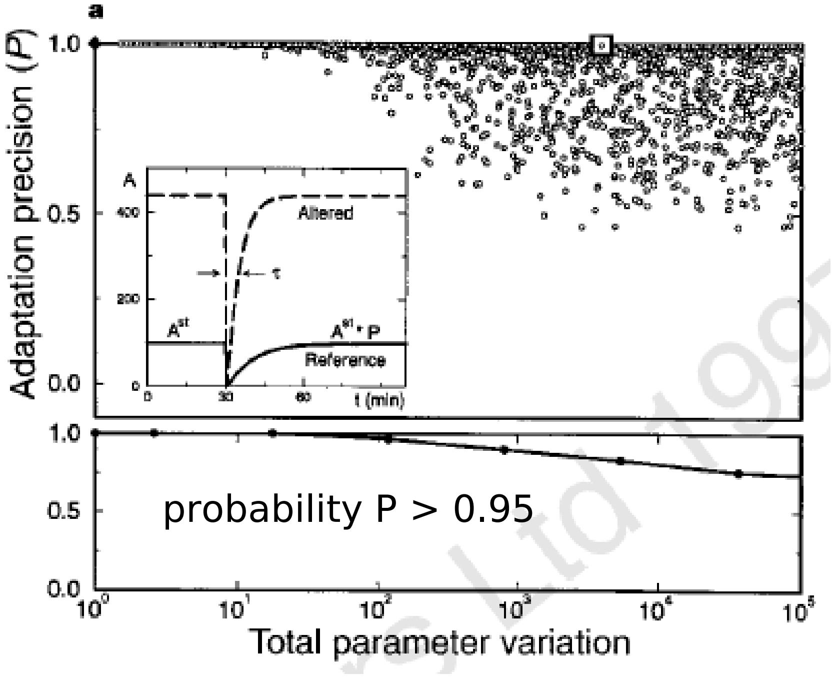
N Barkai, S Leibler, *“Robustness in simple biochemical networks”*, Nature **387**:913-7 1997

right hand image here and on the previous slide from Sandy Parkinson's lab @University of Utah – chemotaxis.biology.utah.edu/Parkinson_Lab/

perfect adaptation, in theory

steady-state tumbling frequency returns to its set point after a disturbance, with no steady-state error.



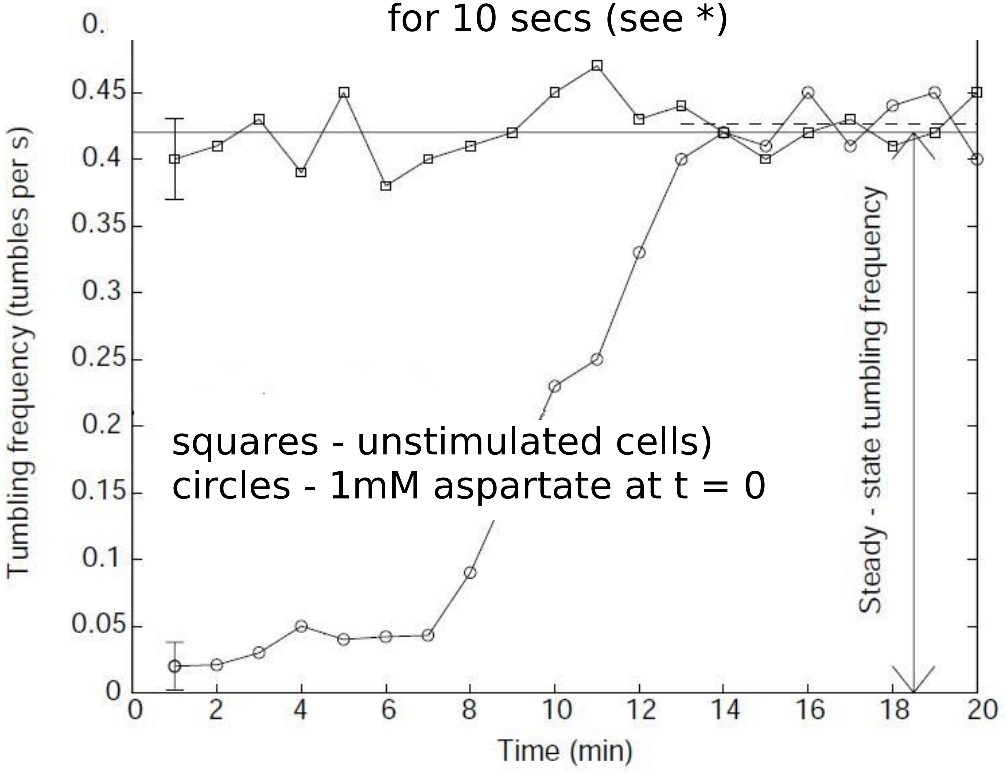


> *"Figure 3a illustrates the most striking result of the model … Typically, one can change simultaneously each of the rate constants several fold and still obtain, on average, only a few per cent deviation from perfect adaptation"*

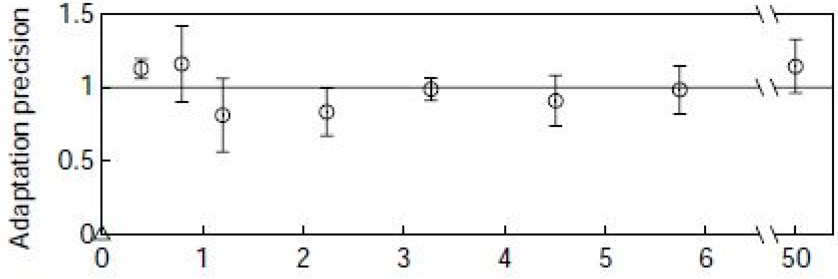
perfect adaptation, in practice

E coli RP437 strain

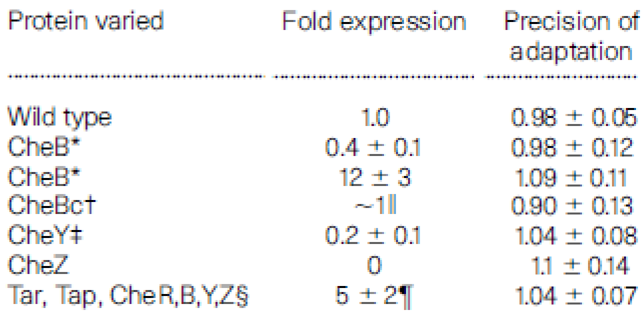
each data point averaged over 100-400 cells
for 10 secs (see *)



squares - unstimulated cells)
circles - 1mM aspartate at t = 0



CheR fold expression in CheR deletion strain



Protein varied	Fold expression	Precision of adaptation
Wild type	1.0	0.98 ± 0.05
CheB*	0.4 ± 0.1	0.98 ± 0.12
CheB*	12 ± 3	1.09 ± 0.11
CheBc†	~1‖	0.90 ± 0.13
CheY‡	0.2 ± 0.1	1.04 ± 0.08
CheZ	0	1.1 ± 0.14
Tar, Tap, CheR,B,Y,Z§	5 ± 2¶	1.04 ± 0.07

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

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

perfect adaptation arises from integral control

the Barkai-Leibler model implements integral control, in the sense that a generalised variable, z, can be identified for which

integral control variable

controlled variable

$$\frac{dz}{dt} = x - a$$

reference value

z is approximately the total receptor methylation level in the Barkai-Leibler model

furthermore, perfect adaptation implies integral control

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

matrix formulation

1 component, order n

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

n components, order 1

$$\frac{dx}{dt} = A.x \qquad x = (x_1, \cdots, x_n)^t$$

$$x_1 = x \,, \quad x_2 = \frac{dx}{dt}$$

$$\longrightarrow$$

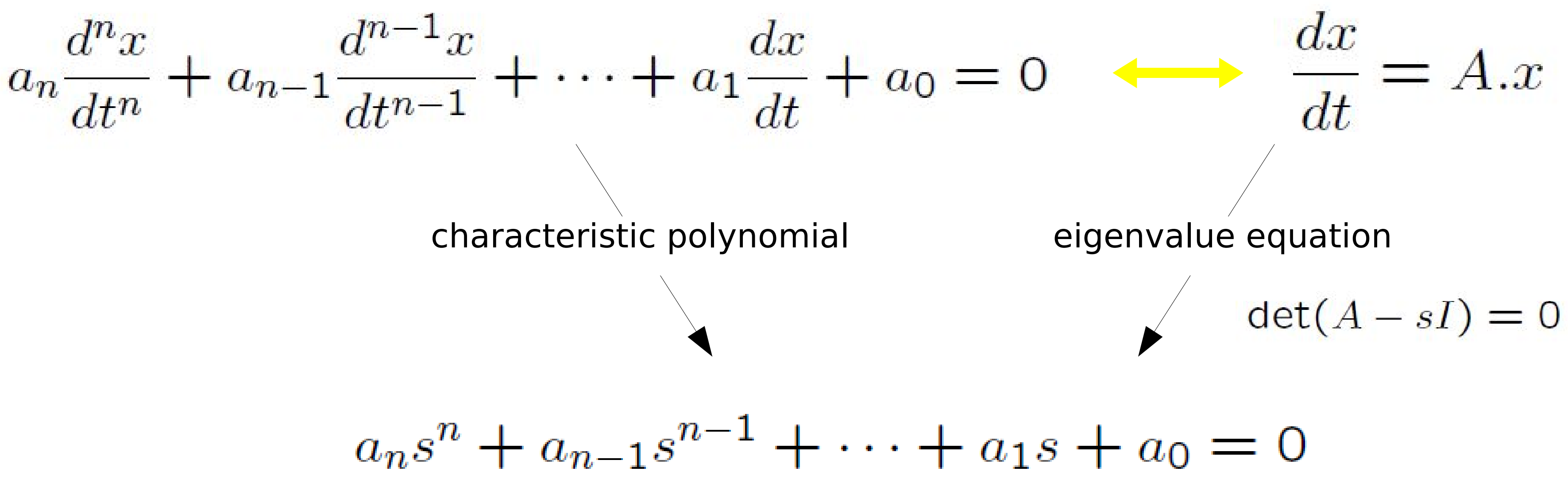
$$a_2 \frac{d^2 x}{dt^2} + a_1 \frac{dx}{dt} + a_0 x = 0 \qquad \frac{d}{dt} \begin{pmatrix} x_1 \\ x_2 \end{pmatrix} = \begin{pmatrix} 0 & 1 \\ -\frac{a_0}{a_2} & -\frac{a_1}{a_2} \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \end{pmatrix}$$

$$\longleftarrow$$

put matrix in triangular form by
Gaussian elimination

see “Matrix algebra for beginners, Parts I, II & III”

characteristic roots = eigenvalues



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

characteristic polynomial

eigenvalue equation

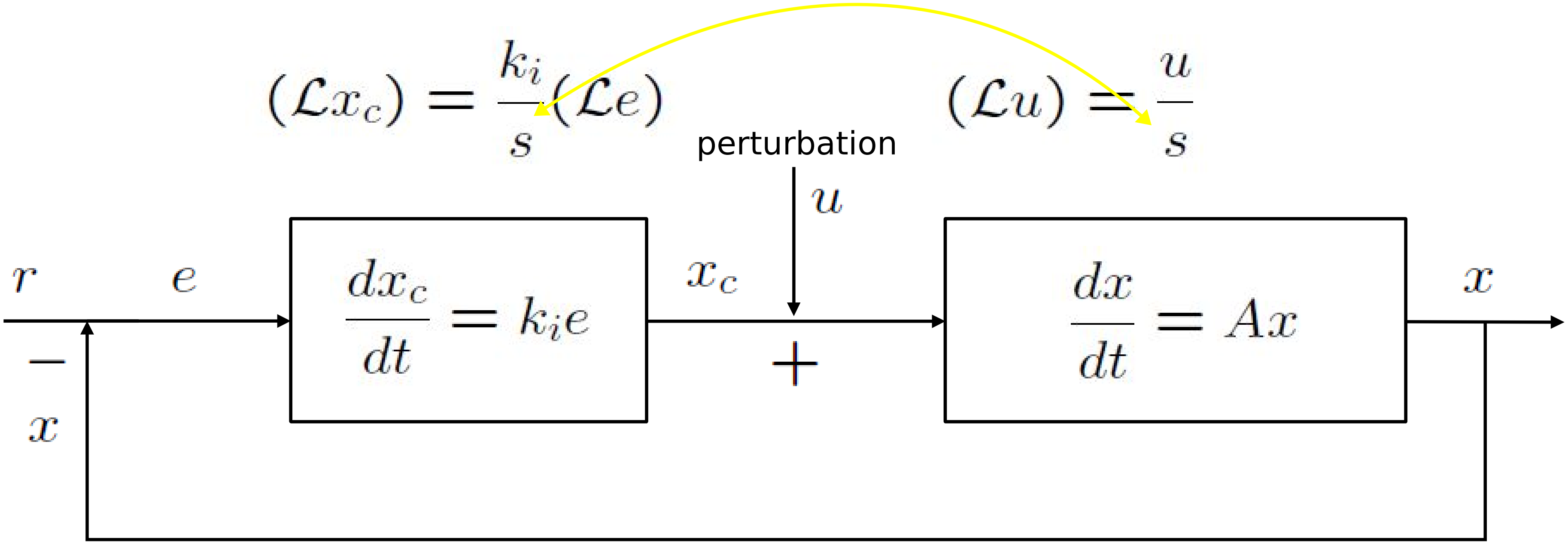
$$\det(A - sI) = 0$$

$$a_n s^n + a_{n-1} s^{n-1} + \cdots + a_1 s + a_0 = 0$$

in the matrix formulation, the stability condition is that all the eigenvalues of the matrix A have negative real parts

the internal models principle

a controller which perfectly adapts to an additive perturbation must contain an **internal model** of the perturbation



$$(\mathcal{L}x_c) = \frac{k_i}{s}(\mathcal{L}e) \qquad (\mathcal{L}u) = \frac{u}{s}$$

$$\frac{dx_c}{dt} = k_i e \qquad \frac{dx}{dt} = Ax$$

Francis, Wonham, “*The internal model principle of control theory*”, Automatica 12:457-465 1976; E Sontag, “*Adaptation and regulation with signal detection implies internal model*”, Systems & Control Letters, **50**:119-26 2003; M Kawato, “*Internal models for motor control and trajectory planning*”, Curr Opin Neurobiol **9**:718-27 1999.

linear systems approximate nonlinear systems

HARTMAN-GROBMAN THEOREM – in the vicinity of a hyperbolic steady state (all eigenvalues of the Jacobian have non-zero real part), a nonlinear system can be qualitatively approximated by a linear one

Jacobian matrix

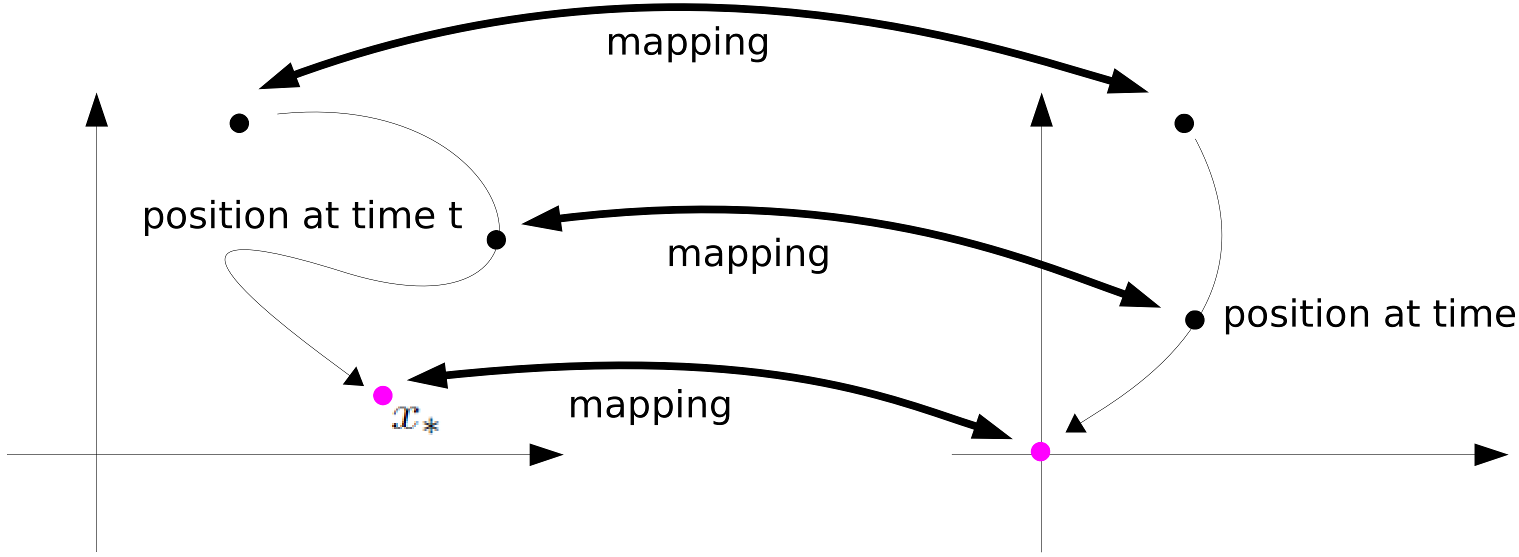
$$\frac{dx}{dt} = f(x) \quad f(x_*) = 0$$

$$\frac{dy}{dt} = A.y \qquad A = \left.\left(\frac{\partial f_i}{\partial x_j}\right)\right|_{x=x_*}$$

$$y = x - x_*$$

nonlinear dynamics

linear dynamics



mapping

position at time t

mapping

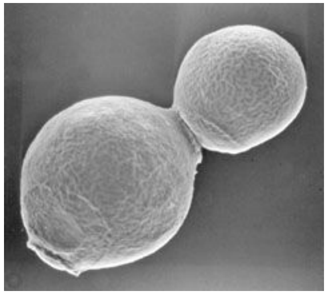
position at time t

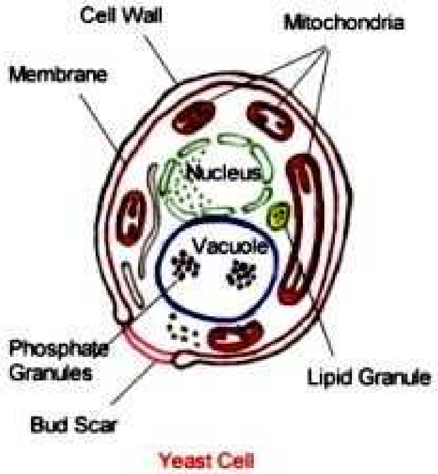
x_*

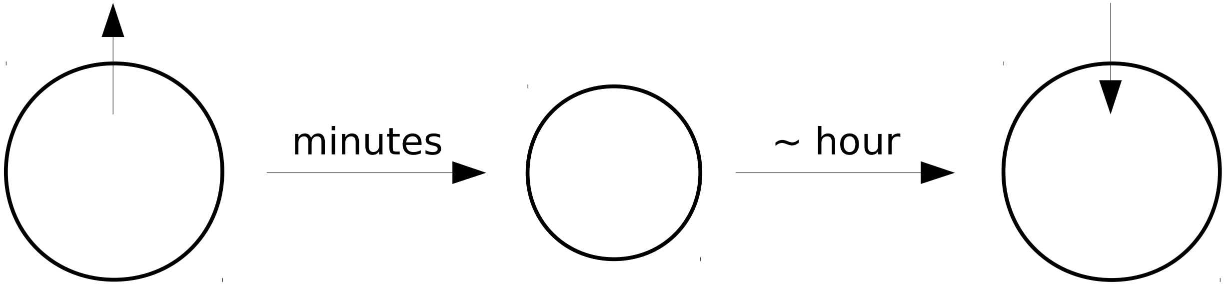
mapping

osmolarity regulation in S cerevisiae

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







water

water

minutes

~ hour

hyperosmotic shock

volume decrease

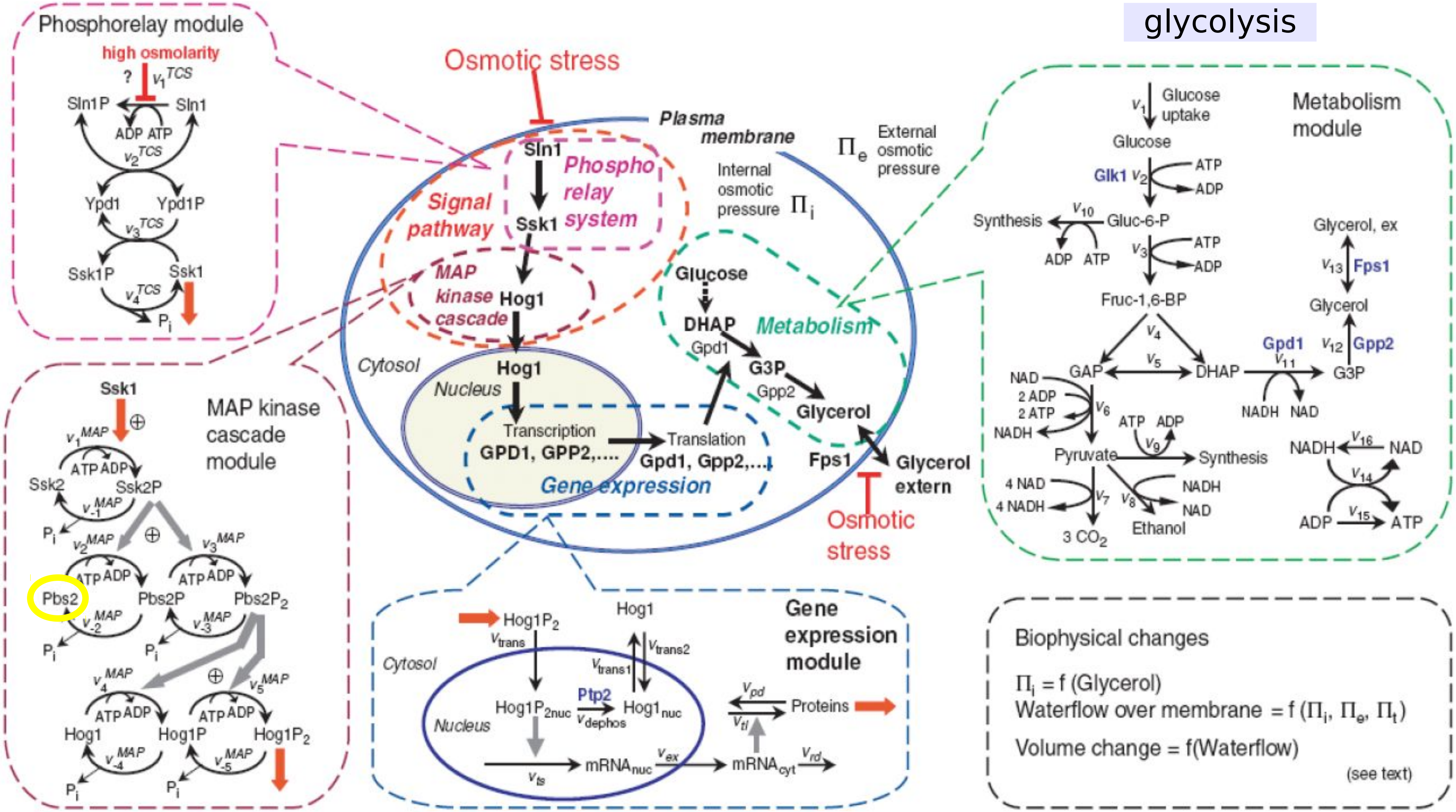
glycerol accumulation
volume recovery

detailed model of the molecular network

two-component signalling

glycolysis

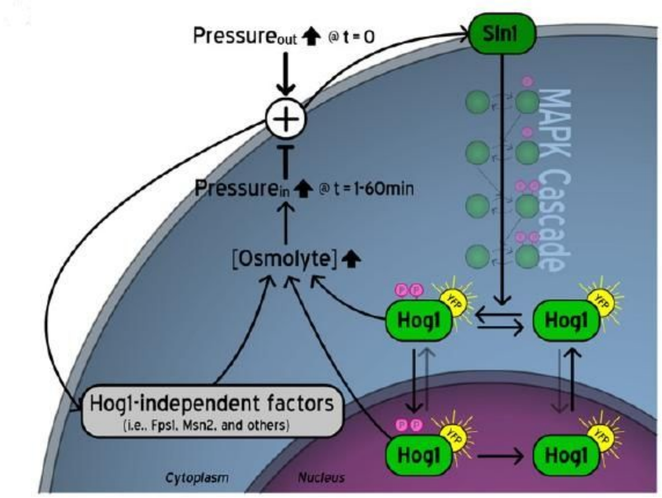
Mitogen Activated Protein (MAP) kinase cascade

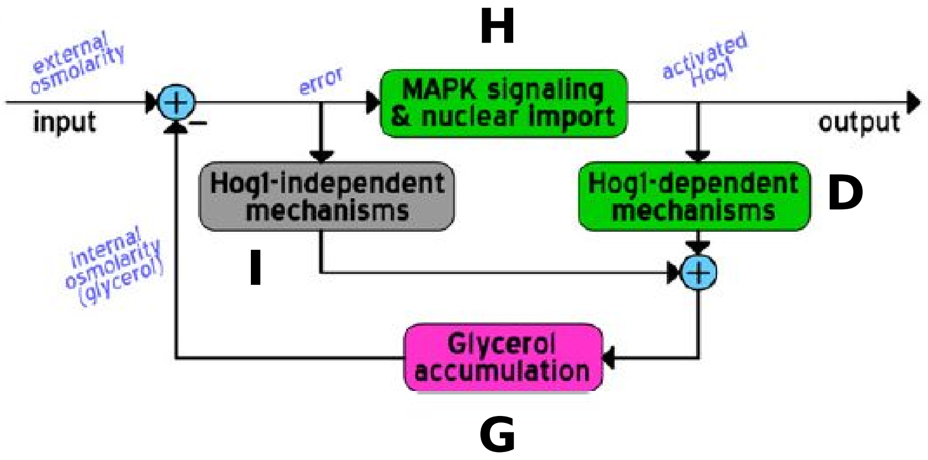


gene regulation

Klipp, Nordlander, Kruger, Gennemark, Hohmann, *“Integrative model of the response of yeast to osmotic shock”*, Nature Biotech **23**:975-82 2005

osmolarity regulation as a control system





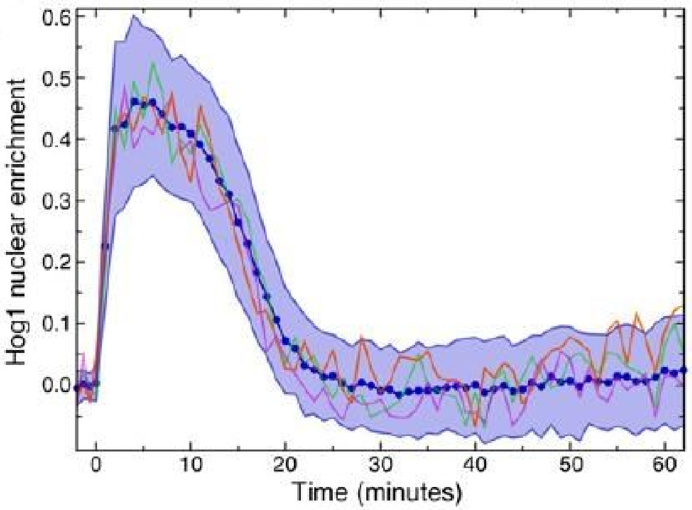
D Muzzey, C Gomez-Uribe, J T Mettetal, A van Oudenaarden, “*A systems-level analysis of perfect adaptation in yeast osmoregulation*”, Cell **138**:160-71 2009

Hog1 nuclear enrichment shows perfect adaptation

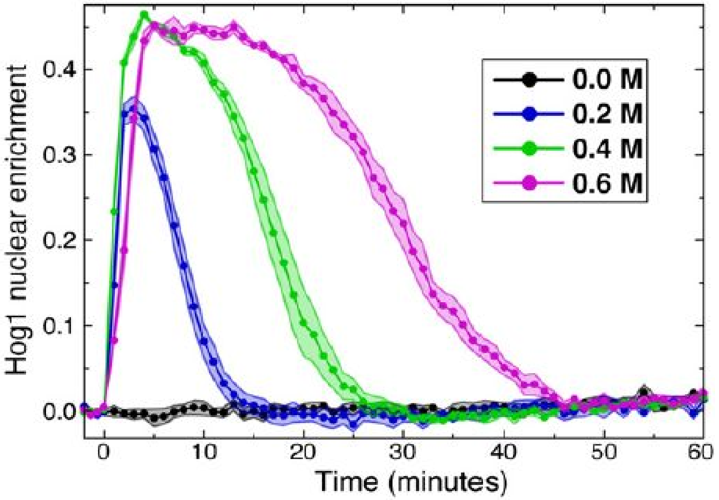
Hog1-YFP, haploid *SHO1-* cells

SHO1 deletion disables the
non-Sln1 pathway of Hog1
activation

homeostatic response to step-function increase in external NaCl



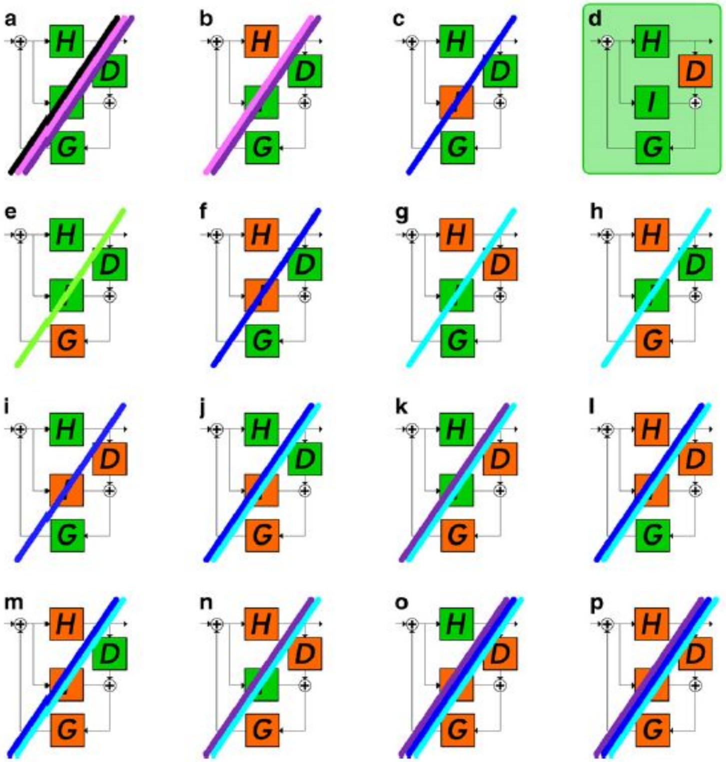
cell-to-cell variation is low



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

perfect adaptation implies integral control in the linear approximation

locating the integral feedback



there is a single integrator, localised to the Hog1-dependent module D

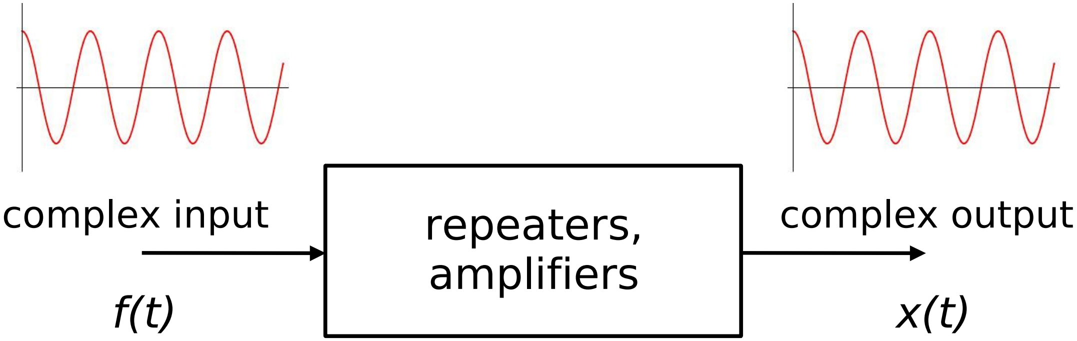
integral control requires Hog1 kinase (Pbs2) activity

further analysis and extension to *Candida albicans*:

You, ..., Brown, “*A systems biology analysis of long and short-term memories of osmotic stress adaptation in fungi*”, BMC Res Notes **5**:258 2012

a more complex control problem

trans-continental telephony, early 20th century,



complex input

$f(t)$

repeaters, amplifiers

complex output

$x(t)$

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

need to ensure that the output recapitulates the input with “high fidelity”

need to understand the input/output behaviour of a highly complex system without knowing all the internal details

follow the sines

Harry Nyquist

1889-1976

Hendrik Bode

1905-1982

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

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

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

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

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

stable system has output at same frequency

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

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

$$= \frac{B}{s-i\omega} + \sum_{i=1}^{k}\left(\sum_{u=1}^{r_i}\frac{C_{i,u}}{(s-z_i)^u}\right) + \sum_{i=1}^{k}\left(\sum_{u=1}^{r_i}\frac{D_{i,u}}{(s-z_i)^u}\right)$$

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

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

the transfer function

but what is the amplitude, 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

linear frequency analysis

the amplitude is the transfer function, evaluated at the forcing frequency

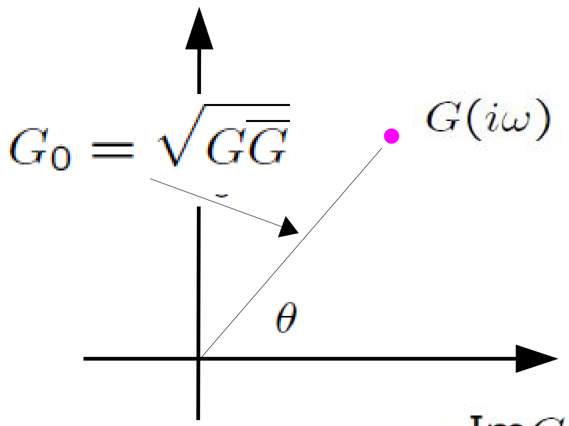
$$f(t) = Ae^{i\omega t} \qquad x(t) = G(i\omega)Ae^{i\omega t}$$

$$G(i\omega) = G_0 e^{i\theta}$$

$$x(t) = G_o A e^{i(\omega t + \theta)}$$

gain

phase lag or lead



$$\theta = \tan^{-1}\frac{\mathrm{Im}G(i\omega)}{\mathrm{Re}G(i\omega)}$$

for high fidelity, the gain and the phase lag/lead should change little with frequency

second-order linear ODEs

consider a system normalised the way physicists prefer

positive

coefficent of *x* is +1

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

$\omega_f > 0$	fundamental frequency	$(\text{time})^{-1}$
δ	damping ratio	dimensionless

with these choices the characteristic polynomial has the following two roots

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

and the system is stable provided that $\delta > 0$

Bode plots

decibels (dB)

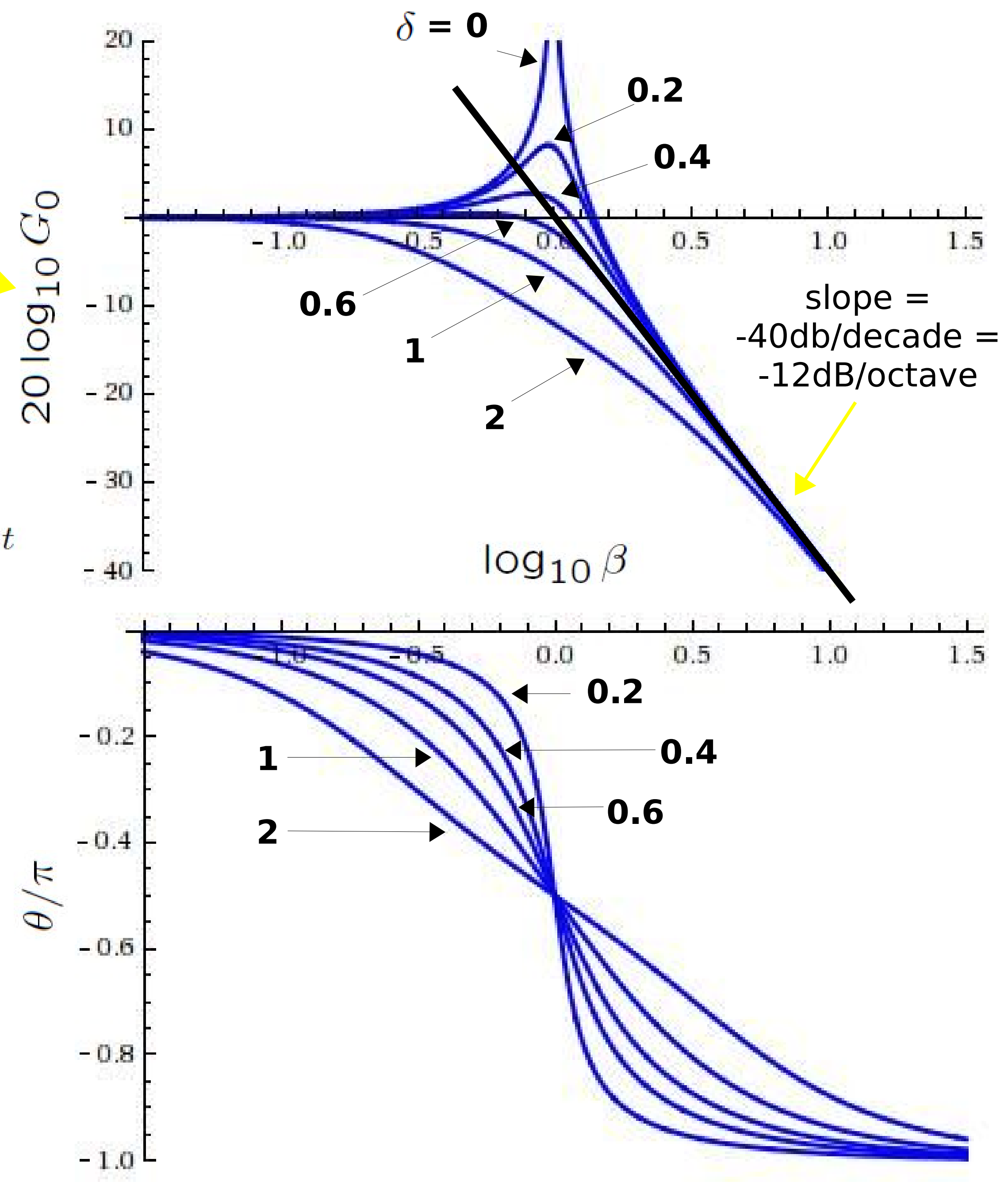
follow the sines ...

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

$$\beta=\frac{\omega}{\omega_f}$$

$$G(i\omega)=(1-\beta^2+2\delta\beta i)^{-1}$$

$$G_0=\sqrt{G\overline{G}}$$



slope =
-40db/decade =
-12dB/octave