six lectures on systems biology

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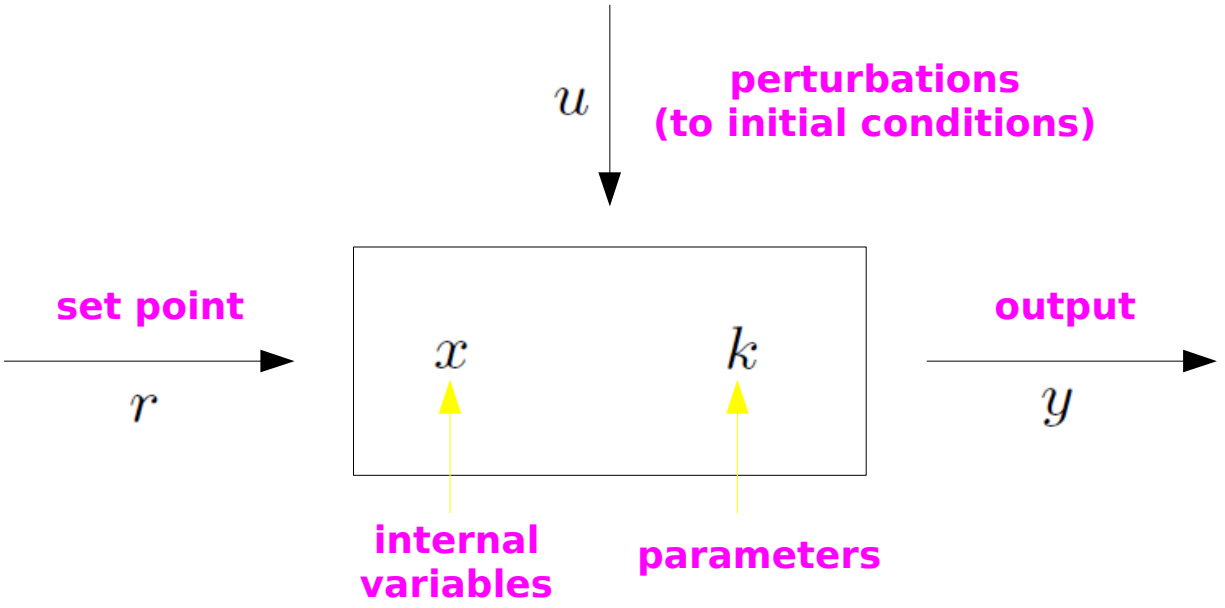
lecture 5
12 april 2011

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. modularity and evolution

homeostasis or perfect adaptation

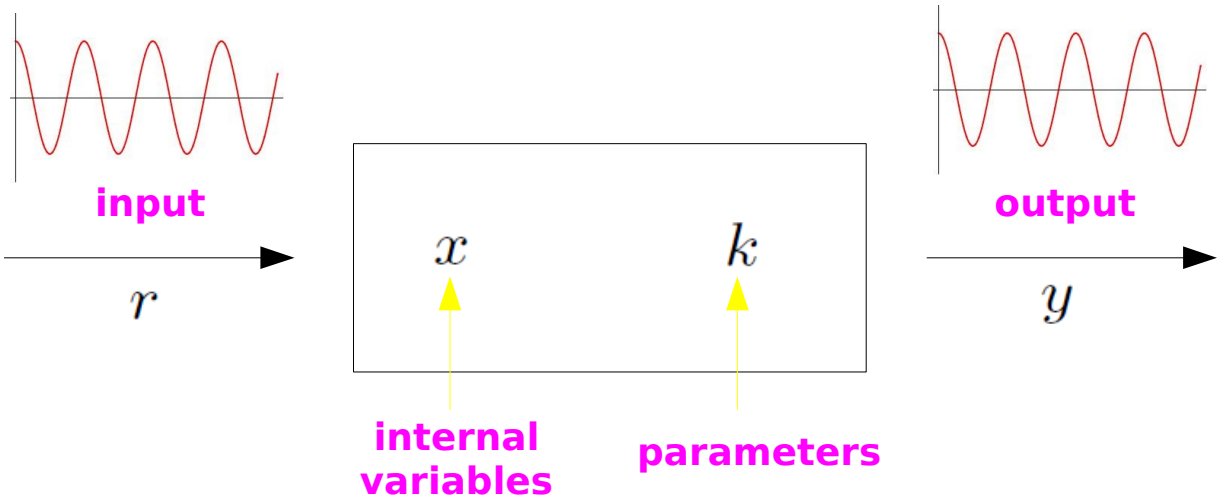


steady-state output matches set point (y = r)

robustly (ie: independently of parameter values)

in the face of perturbations

a more complex control problem



output at time t matches input at time t robustly

example – long-distance telephony

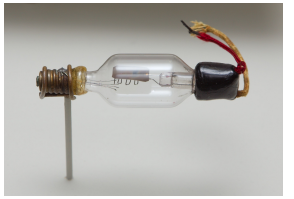
ATT's long-distance open-wire telephony, early 20th century

1915: NY to SF telephone service

130,000 poles, mostly open wire

loading coils every 8 miles

8 vacuum-tube amplifiers



$20 for 3 minutes

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

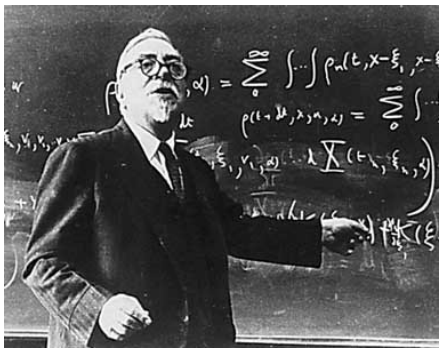
example – gunnery control

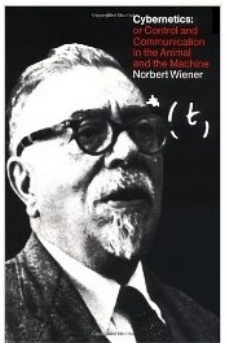
automatic gun control integrated the mechanical and electrical traditions and inspired post-war control theory

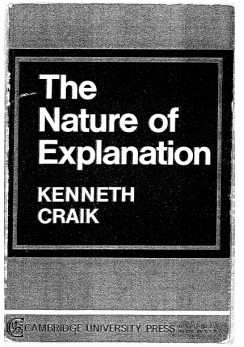
D Mindell, **Between Human and Machine: Feedback, Control and Computing before Cybernetics**, Johns Hopkins University Press, 2002.

example – gunnery control

it also had significant, but largely forgotten, implications for biology







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

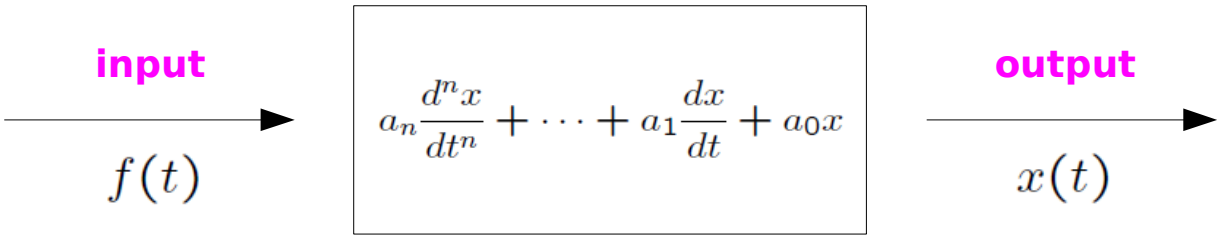
Kenneth Craik, **The Nature of Explanation**, CUP, 1943

frequency analysis

input/output analysis for linear systems

Harry Nyquist

Hendrik Bode



follow the propagation of a sinusoidal input through the system

complex exponentials

use complex numbers,

$$e^{i\omega t} = \cos(\omega t) + i \sin(\omega t)$$ **Euler's formula**

so that sinusoidal functions and exponentials can be treated as one

$$f(t) = Ae^{i\omega t}$$ **input**

$$a_n \frac{d^n x}{dt^n} + \cdots + a_1 \frac{dx}{dt} + a_0 x = Ae^{i\omega t}$$

assume the system is stable, so that transients die away

output frequency equals input frequency

try $x(t) = Be^{i\phi t}$  $\frac{d^k x}{dt^k} = (i\phi)^k Be^{i\phi t}$

$$(a_n(i\phi)^n + \cdots + a_1(i\phi) + a_0)Be^{i\phi t} = Ae^{i\omega t}$$

$$\phi = \omega$$

a stable linear system responds to a periodic forcing with a periodic output at the same frequency

transfer function

$$B = G(i\omega)A$$

$$G(s) = \left[\frac{1}{a_n s^n + \cdots + a_1 s + a_0}\right]$$ **transfer function**

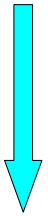
transfer functions may be more complicated functions of s (rational functions or with exponential factors)

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

input **output**

system identification

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



$$\left[\frac{1}{a_n s^n + \cdots + a_1 s + a_0} \right]$$ **powers of *s***

a stable linear system may be completely reconstructed by input/output analysis, without the need for any interventions inside the system

example - 2nd order systems

normalise, in terms of two new positive parameters

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

ω_f — **fundamental frequency**

δ — **damping**

the poles of the transfer function then occur at

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

$$\delta \begin{cases} < 1 & \text{underdamped} \\ = 1 & \text{critically damped} \\ > 1 & \text{overdamped} \end{cases}$$

Bode plots

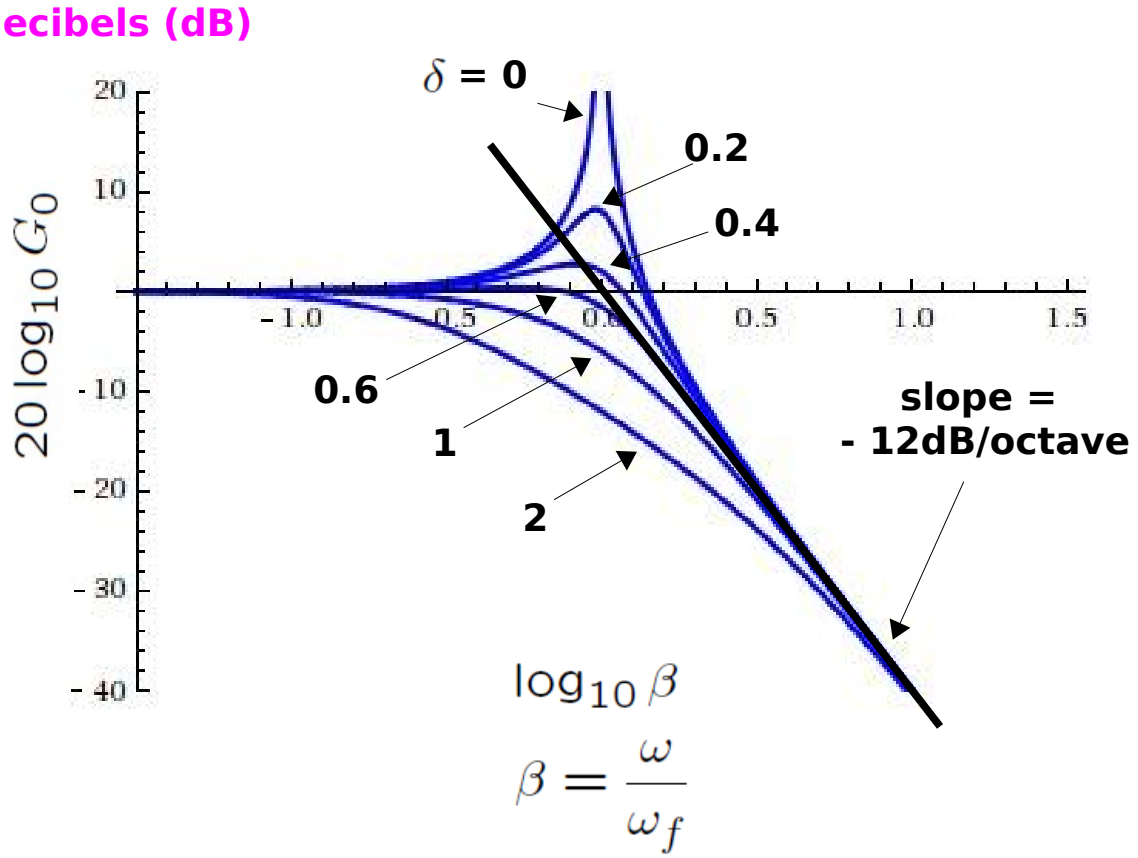
$$x(t) = G(i\omega)Ae^{i\omega t}$$

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

$$x(t) = G_0 Ae^{i(\omega t+\theta)}$$

gain

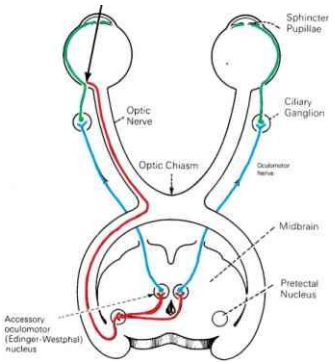
phase lag or lead

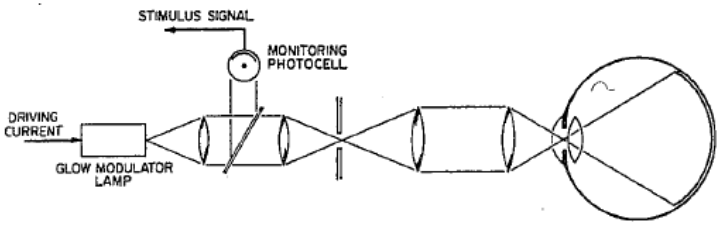


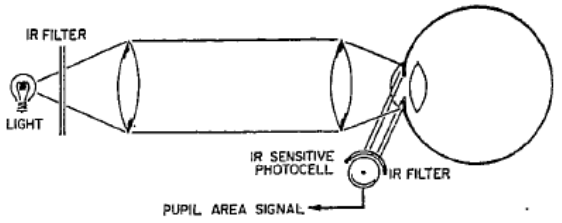
for simple transfer functions, the slope of the gain at high frequencies becomes n(-6dB), where n is the order of the system

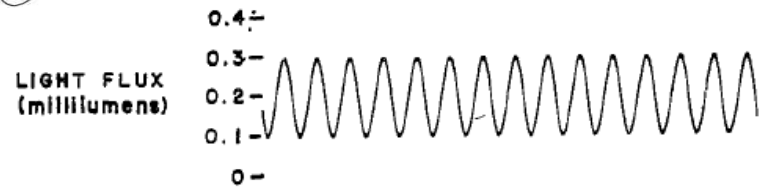
example – a golden oldie

input/output analysis and control theory played a key role in the quantitative analysis of physiological systems

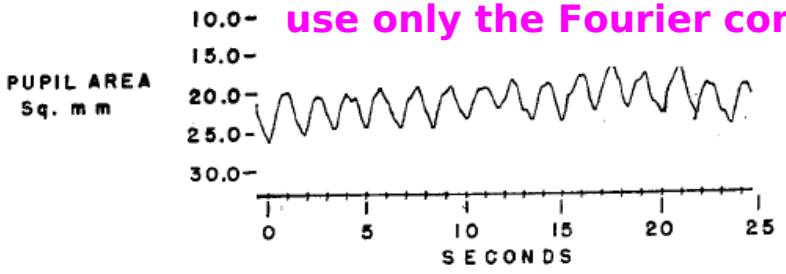


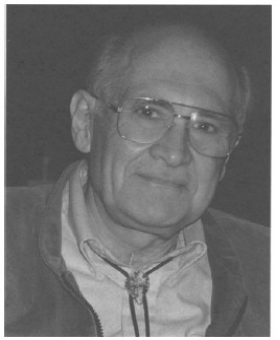






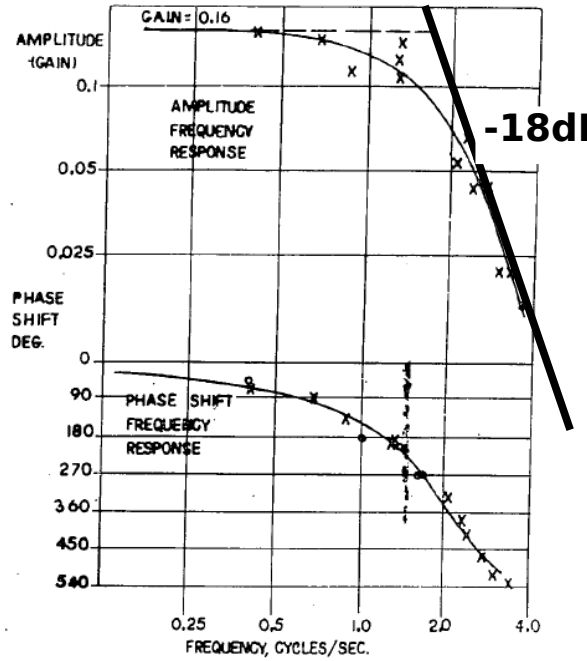
use only the Fourier component at the forcing frequency





Lawrence Stark, **Neurological Control Systems**, Plenum Press, 1968

Bode plots for the pupillary reflex



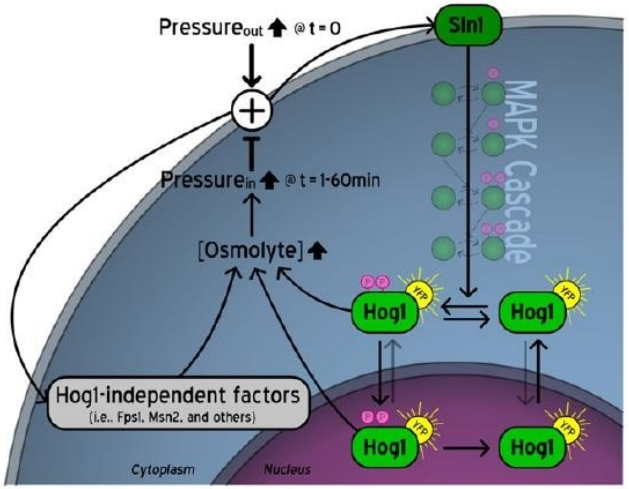
-18dB/octave

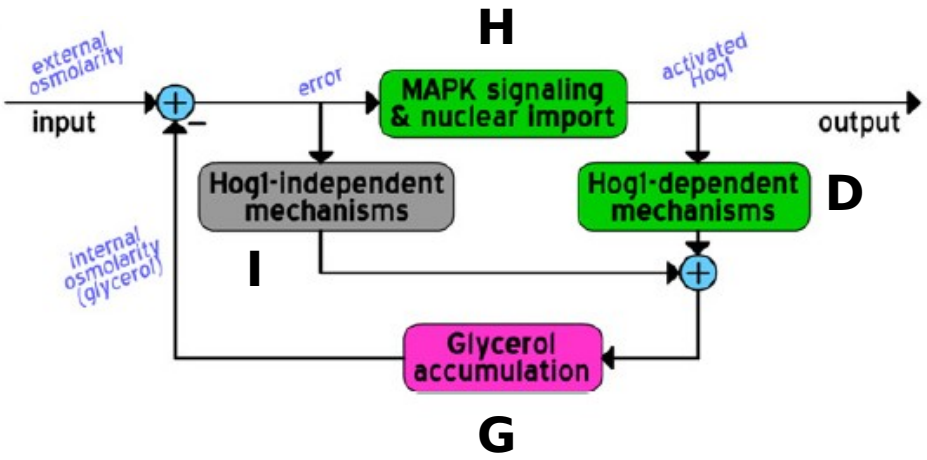
time delay

$$\frac{0.16e^{-0.18s}}{(1+0.1s)^3}$$

transfer function

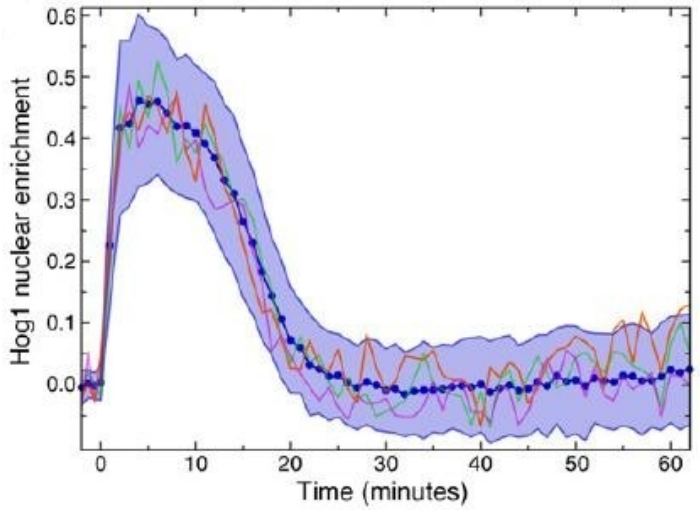
example – osmolarity control in yeast

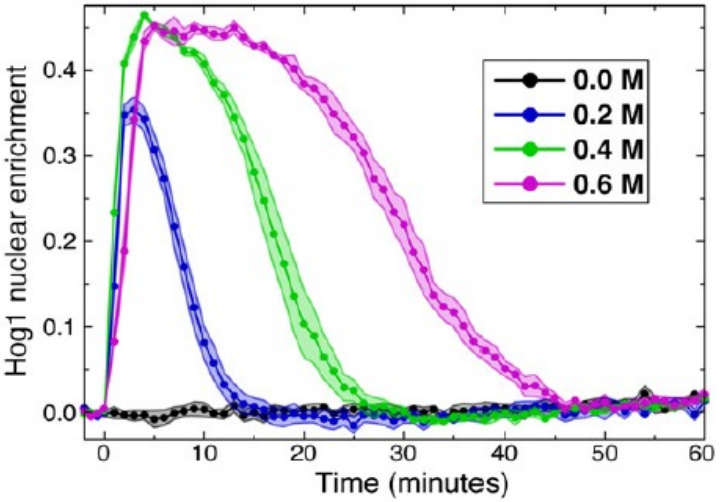




J T Mettetal, D Muzzey, C Gomez-Uribe, A van Oudenaarden, "*The frequency dependence of osmo-adaptation in Saccharomyces cerevisiae*", Science **319**:482-4 2008

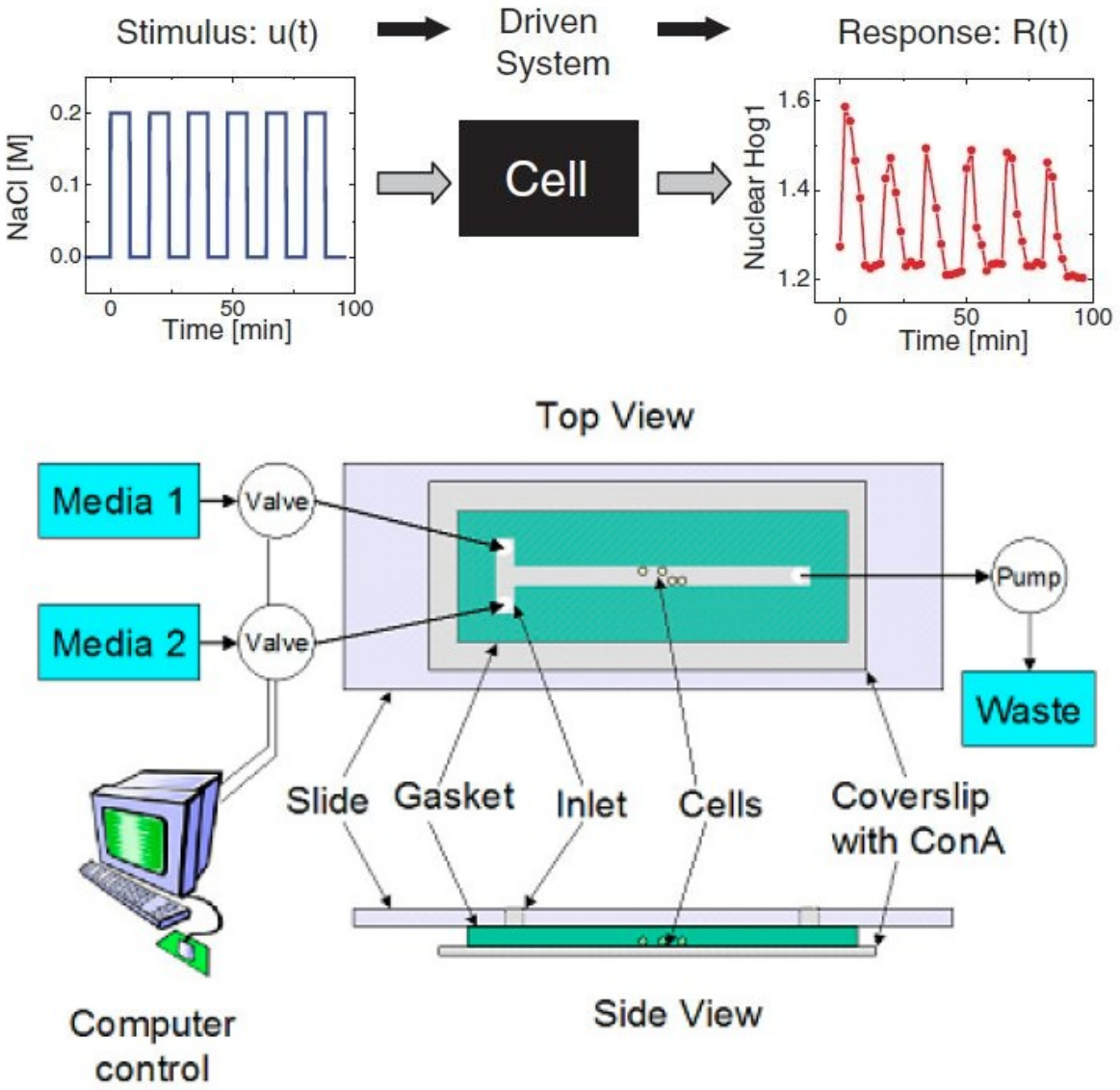
perfect adaptation at single-cell level





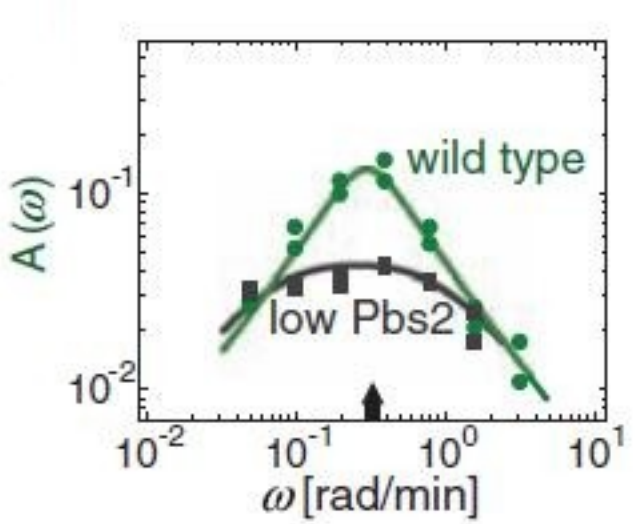
D Muzzey, C Gomez-Uribe, J T Mettetal, A van Oudenaarden, "*A systems-level analysis of perfect adaptation in yeast osmoregulation*", Cell **138**:160-71 2009

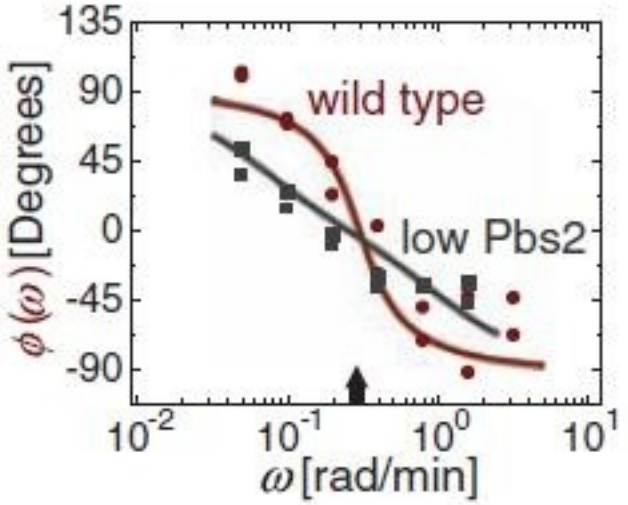
frequency analysis



J T Mettetal, D Muzzey, C Gomez-Uribe, A van Oudenaarden, "*The frequency dependence of osmo-adaptation in Saccharomyces cerevisiae*", Science **319**:482-4 2008

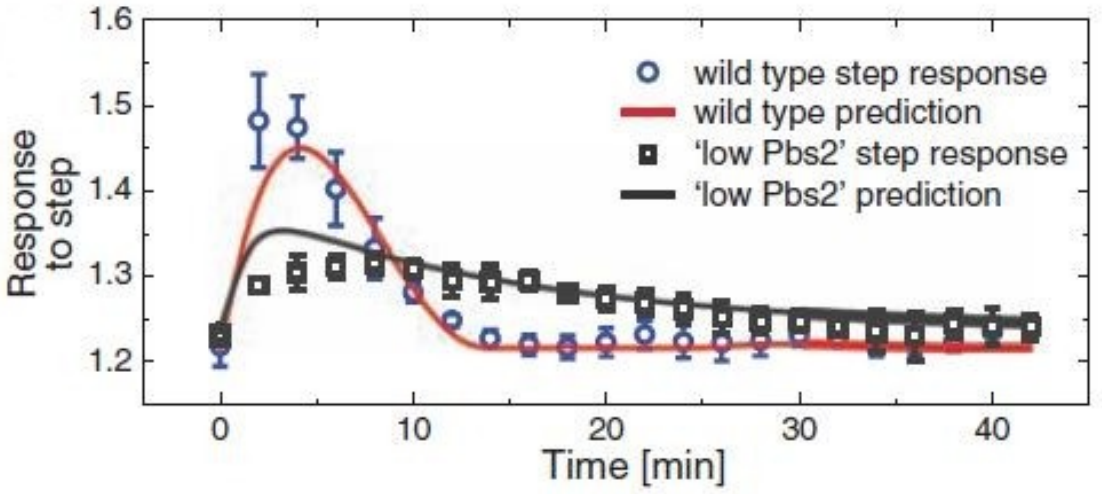
Bode plots for the osmolarity regulator





$$\dot{y} = (A_0 u - x) - \gamma y$$

$$\dot{x} = \alpha(A_0 u - x) + \beta y$$



the challenge of non-linearity

linear frequency analysis can work well, in the vicinity of a steady state

the challenge is to extend it to regions far from a steady state or to non-linear behaviours that cannot be linearly approximated

nonlinear limit-cycle oscillators, arising from interlinked positive and negative feedback loops, are believed to underlie key cellular processes

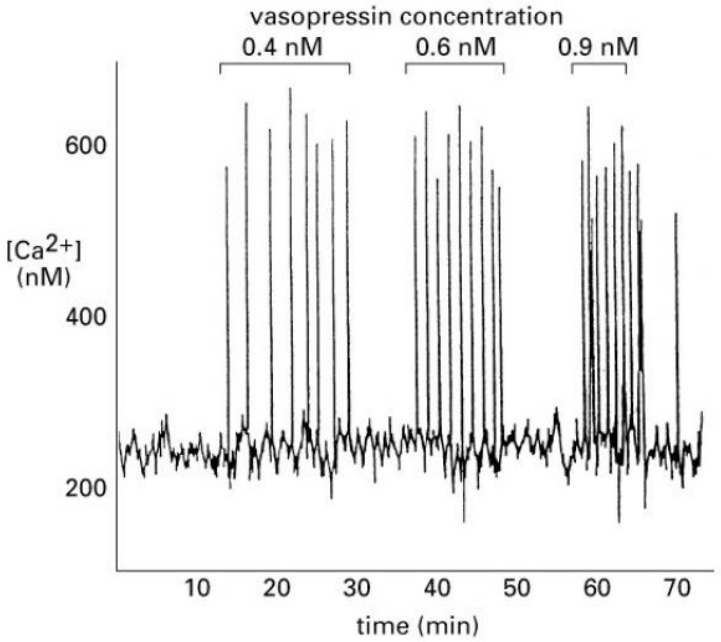
1. circadian oscillator
2. cell cycle
3. calcium spiking

Barkai & Leibler, *"Circadian clocks limited by noise",* Nature **403**:267-8 1999

example – calcium signalling

in many cell types, hormone stimulation elicits repetitive calcium spiking

step function

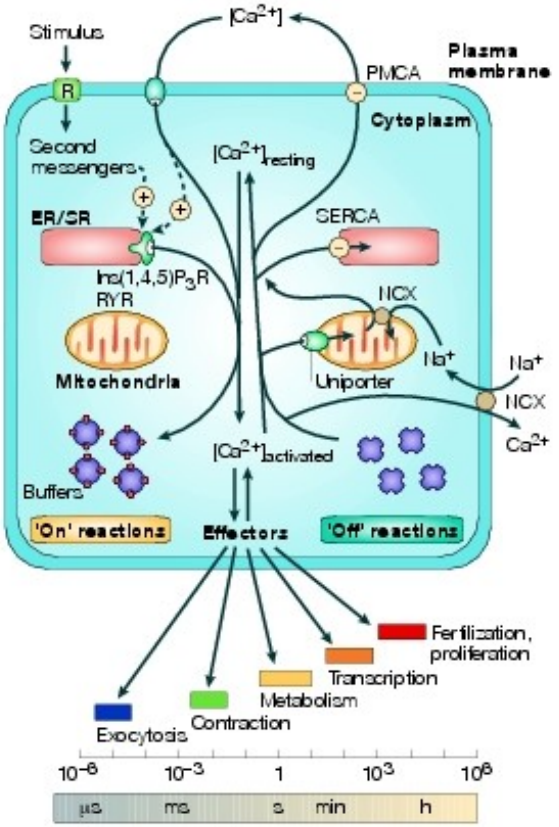


different spiking frequencies elicit different downstream responses

Woods, Cuthbertson, Cobbold, *"Repetitive transient rises in cytoplasmic free calcium in hormone-stimulated hepatocytes"*, Nature **319**:600-2 1986

different cell types may use different mechanisms

there is a “calcium signalling toolkit” from which cells mix and match components to orchestrate physiological responses

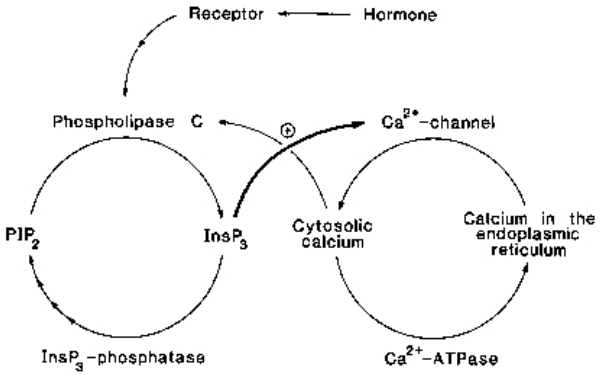


Berridge, Bootman, Roderick, “*Calcium signalling: dynamics, homeostasis, remodelling*”, Nature Rev Mol Cell Biol **4**:517-29 2003

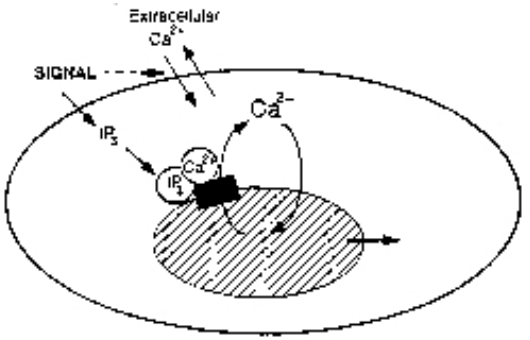
nonlinear input/output analysis

in-silico frequency analysis shows that it is possible to robustly distinguish between different biochemical assumptions about the spiking mechanism

phospholipase C (PLC)



calcium-induced calcium release (CICR)

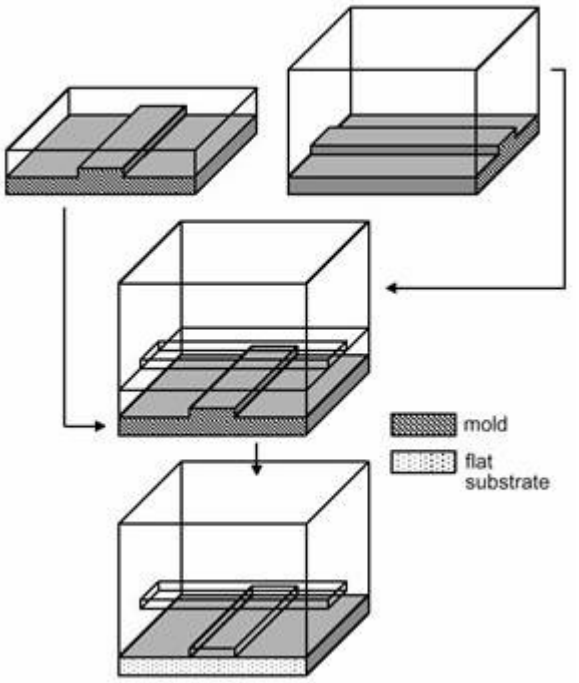


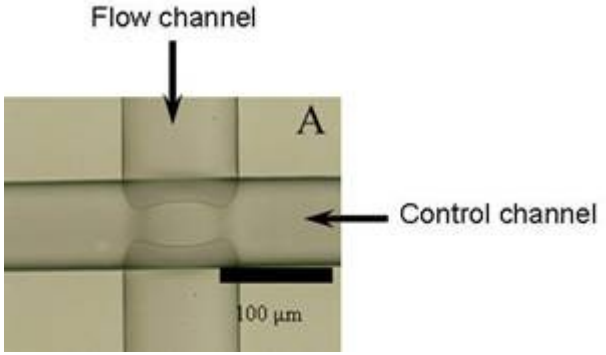
by asking cells the right question, their answers can tell us what is going on inside the cells

N Andrew, F Chang, J Esparza, F Gnad, V Sant, D Gibson, J Gunawardena, in preparation, 2011

microfluidics

reproducible application of high frequencies (~1Hz) requires multi-layer PDMS devices with on-chip fluid handling

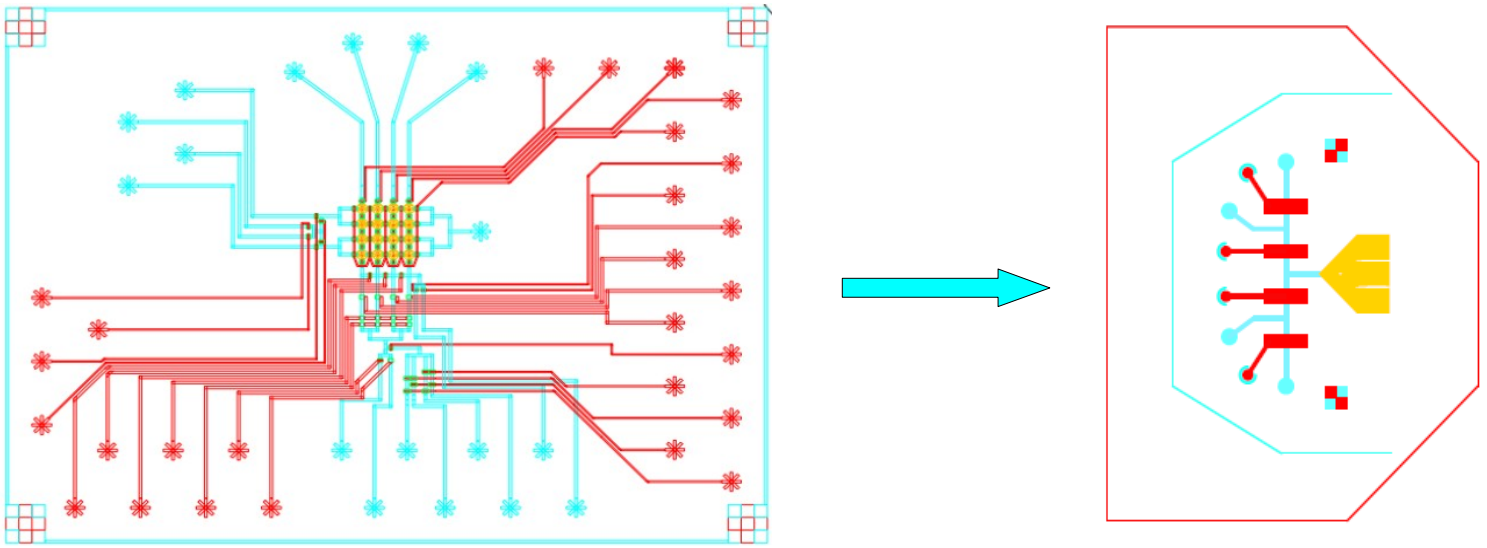




Todd Thorsen, Sebastian Maerkl, Stephen Quake, *"Microfluidic large-scale integration"*, Science 298:580-84 2002

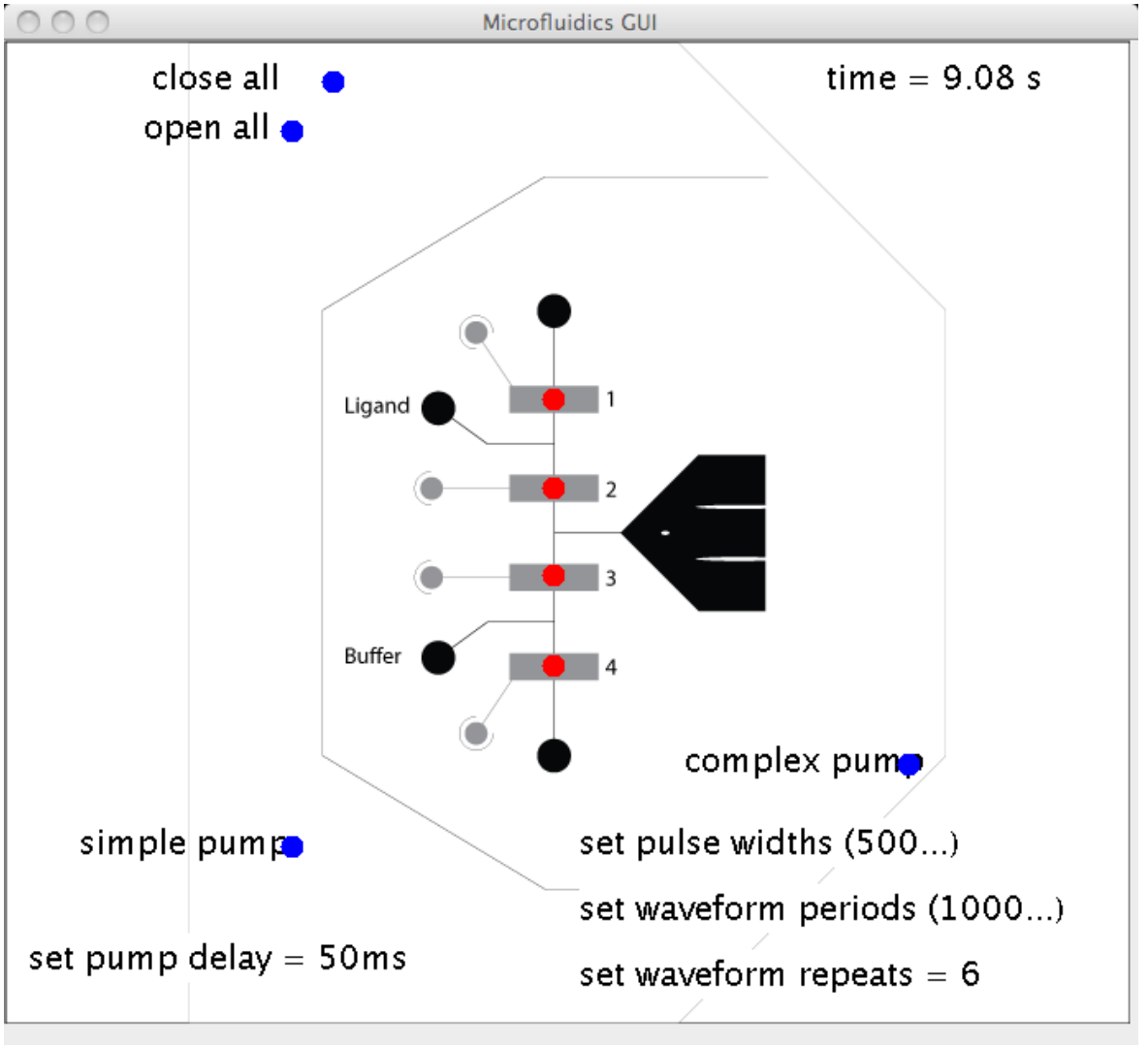
first law of microfluidic design

KISS – Keep It (extremely) Simple, Stupid



building the devices is one thing but getting cells to live happily on them is another matter

programmable experimentation



input/output analysis as practice

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

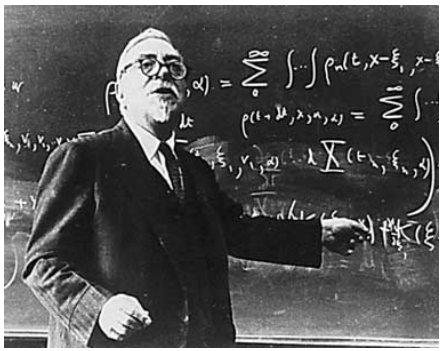
use the outside to learn about the inside

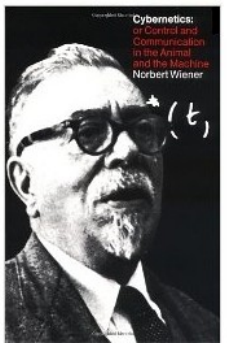
1. perfect adaptation implies an integral control mechanism

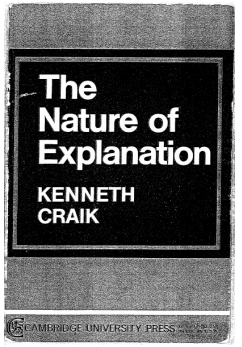
2. frequency analysis leads to a simplified linear model

3. frequency interrogation discriminates between nonlinear mechanisms

input/output analysis as principle: internal models







Norbert Wiener and, especially, Kenneth Craik articulated a mechanistic view about how the outside influences the inside

the internal complexity inside cells is a representation, or "internal model", of the external environment, that can predict what the environment will do

Philip Johnson-Laird, **Mental Models**, Harvard University Press, 1986

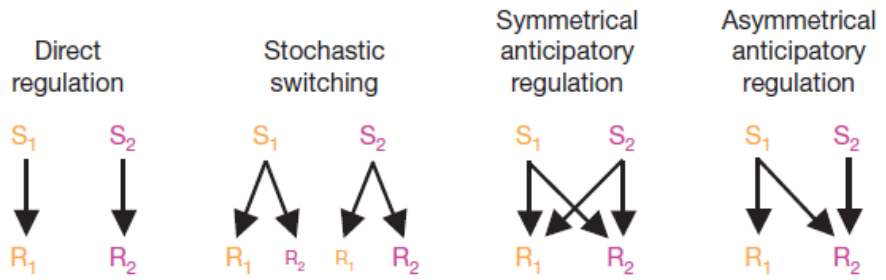
microbial prediction

Predictive Behavior Within Microbial Genetic Networks

Ilias Tagkopoulos,[1,2]* Yir-Chung Liu,[2,3]* Saeed Tavazoie[2,3]†

Adaptive prediction of environmental changes by microorganisms

Amir Mitchell[1], Gal H. Romano[2], Bella Groisman[1], Avihu Yona[1], Erez Dekel[3], Martin Kupiec[2], Orna Dahan[1]* & Yitzhak Pilpel[1,4]*



Tagkopoulos *et al*, Science **320**:1313-7 2008; Mitchell *et al*, Nature **460**:220-4 2009

summing up

1. molecular complexity reflects the complexity of external environments

2. linear frequency analysis can reveal aspects of the internal mechanisms, near a steady state, without having to intervene inside the cell

3. nonlinear frequency analysis can robustly discriminate between mechanisms by asking cells “the right question”

4. this requires new experimental capabailities, such as multi-layer microfluidics, to examine the high-frequency regime

5. the molecular complexity inside a cell may encode internal models that predict the cell's environment