dynamic processes in cells (a systems approach to biology)

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lecture 5

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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)

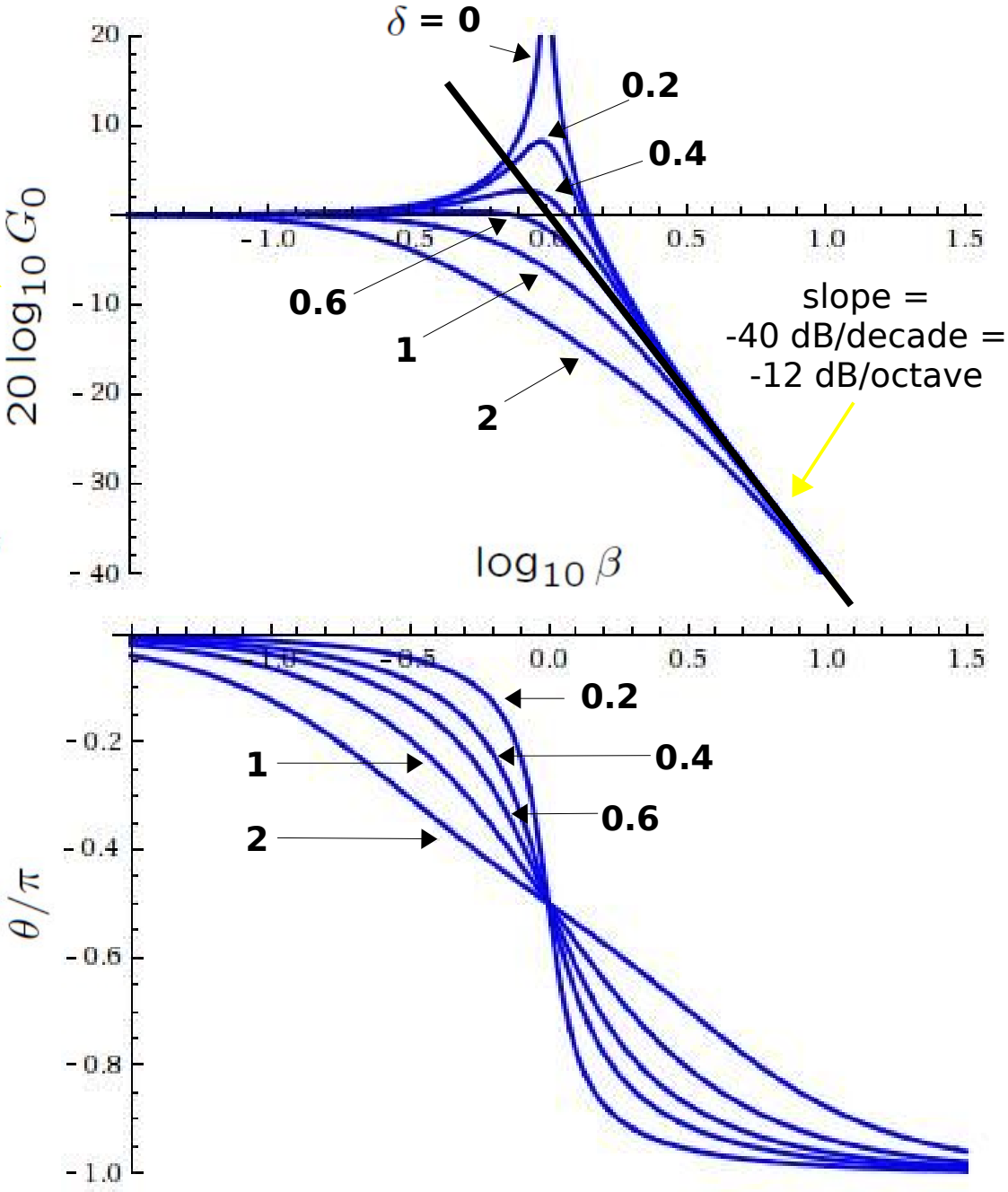
follow the sines ...

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

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

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

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



high-frequency interrogation gives the order

logarithmic derivative

$$h(u) = \log_a f(x), \quad x = a^u \qquad \frac{dh}{du} = \frac{d\log f}{d\log x} = \frac{x}{f}\frac{df}{dx}$$

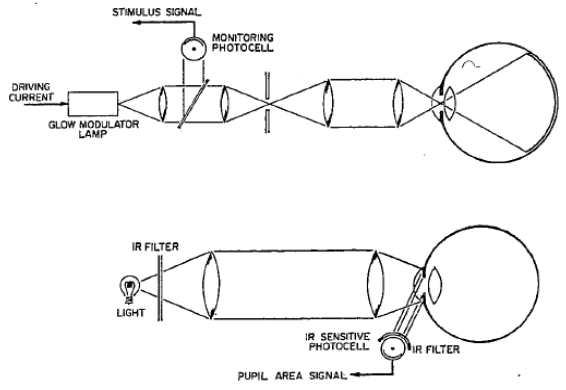
$$Z(i\omega) = a_n(i\omega)^n + \cdots + a_1(i\omega) + a_0 \qquad G(i\omega) = \frac{1}{Z(i\omega)} \qquad G_0 = \sqrt{G\overline{G}}$$

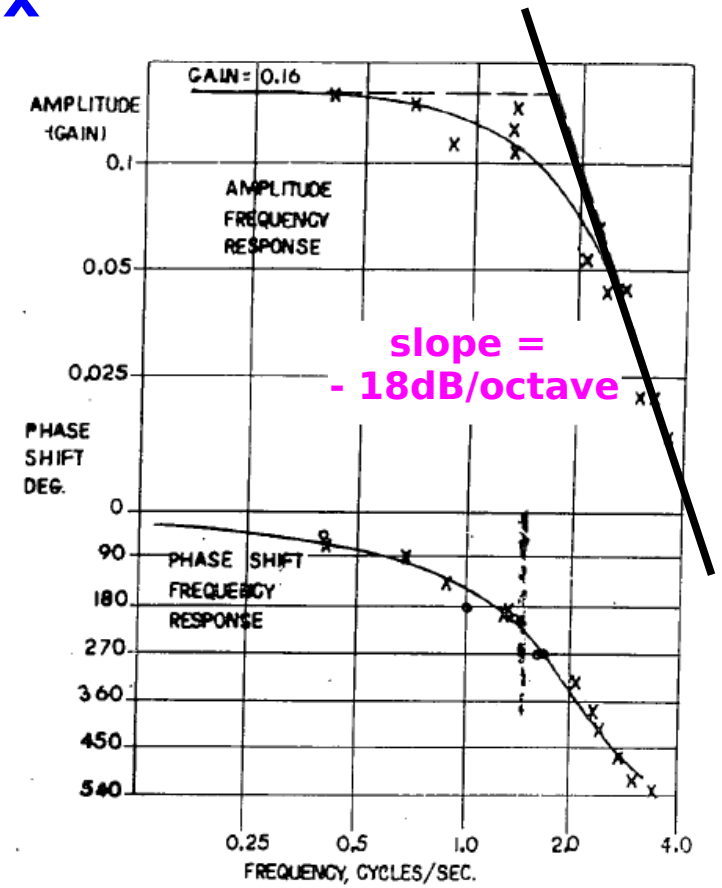
$$\frac{d\log G_0}{d\log \omega} = \frac{\omega}{G_0}\frac{dG_0}{d\omega} = \mathrm{Re}\left(-\frac{\omega}{Z}\frac{dZ}{d\omega}\right)$$

$$\mathrm{Re}\left(-\frac{na_n(i\omega)^n + \cdots + a_1(i\omega)}{a_n(i\omega)^n + \cdots + a_1(i\omega) + a_0}\right) \to -n \quad \text{as } \omega \to \infty$$

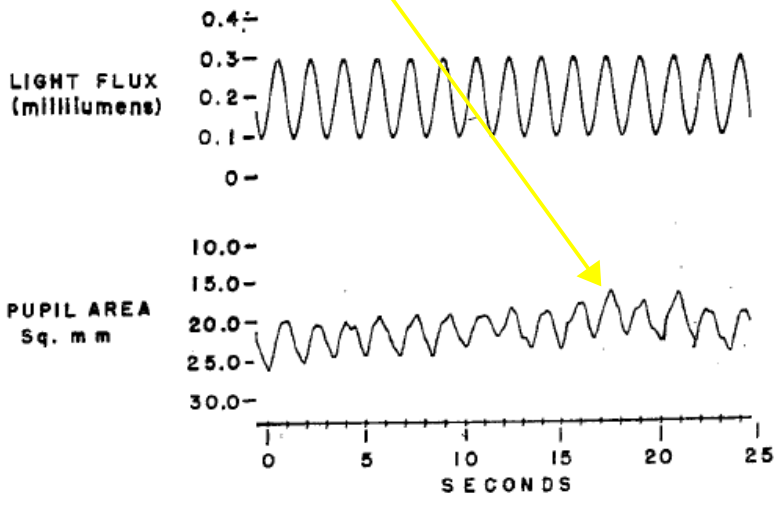
the asymptotic slope of the high-frequency gain is -20n dB/decade or -6n dB/octave, where n is the order of the system

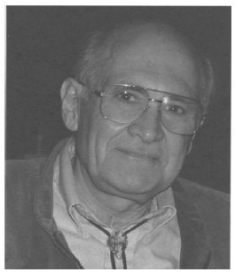
a golden oldie – the pupillary reflex





only the Fourier component of the response at the forcing frequency is used





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

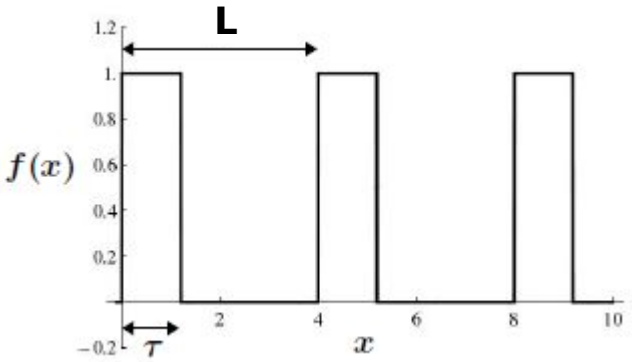
1926-2004

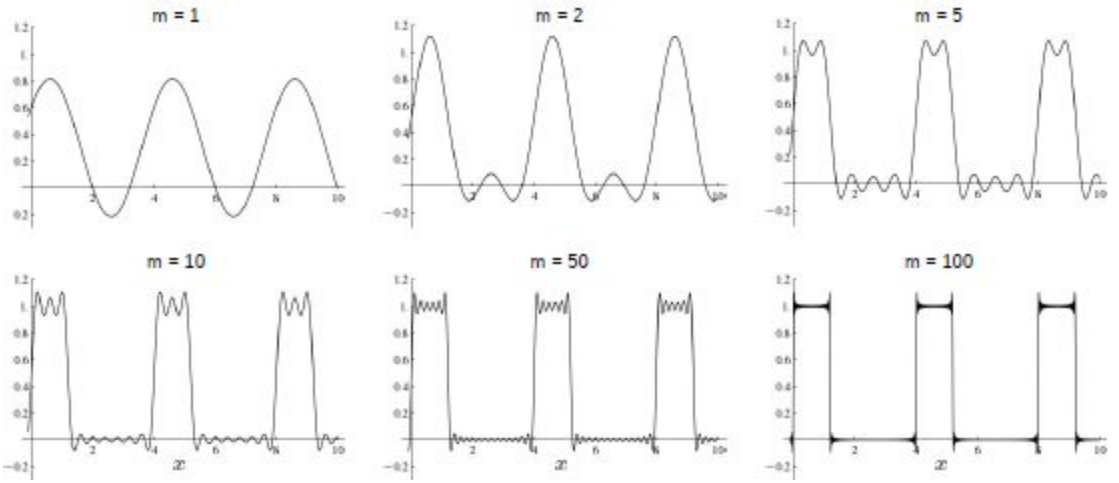
Fourier's theorem

a function which is periodic over an interval L can be decomposed into a (potentially infinite) sum of sine/cosine functions whose frequencies are multiples of 2π/L

1768-1830

$$f(x) = \sum_{-\infty<k<+\infty} c_k e^{k(2\pi i x/L)} \qquad c_k = \frac{1}{L}\int_o^L e^{-k(2\pi i u)/L} f(u)du$$





$$c_0 = \frac{\tau}{L} \qquad c_k = \frac{1 - e^{-k(2\pi i \tau)/L}}{2\pi i k}$$

$$\sum_{-m<k<+m} c_k e^{k(2\pi i x/L)}$$

measuring nerve feedback delay

the Laplace transform can be fitted to the data

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

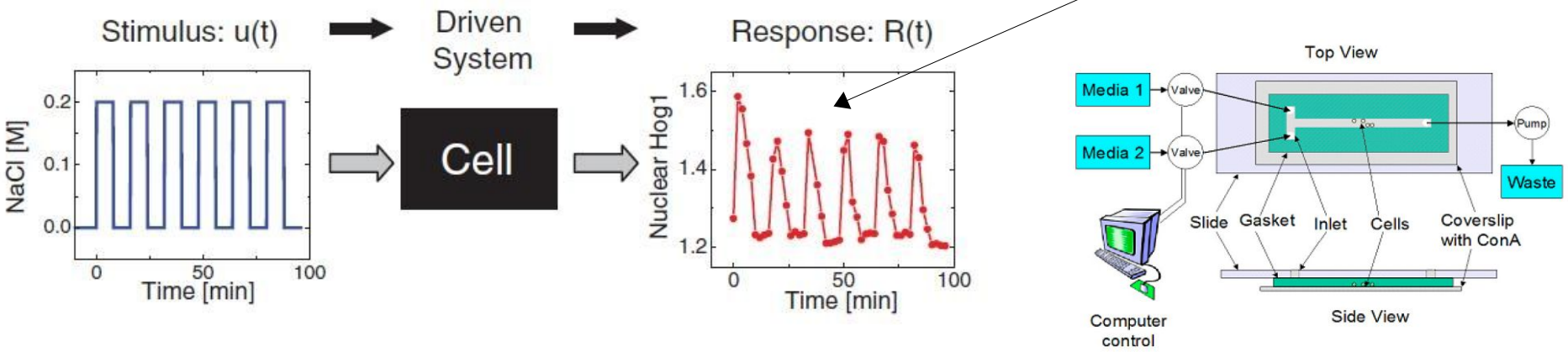
DELAY THEOREM: if the input signal is delayed by T time units then its Laplace transform is multiplied by

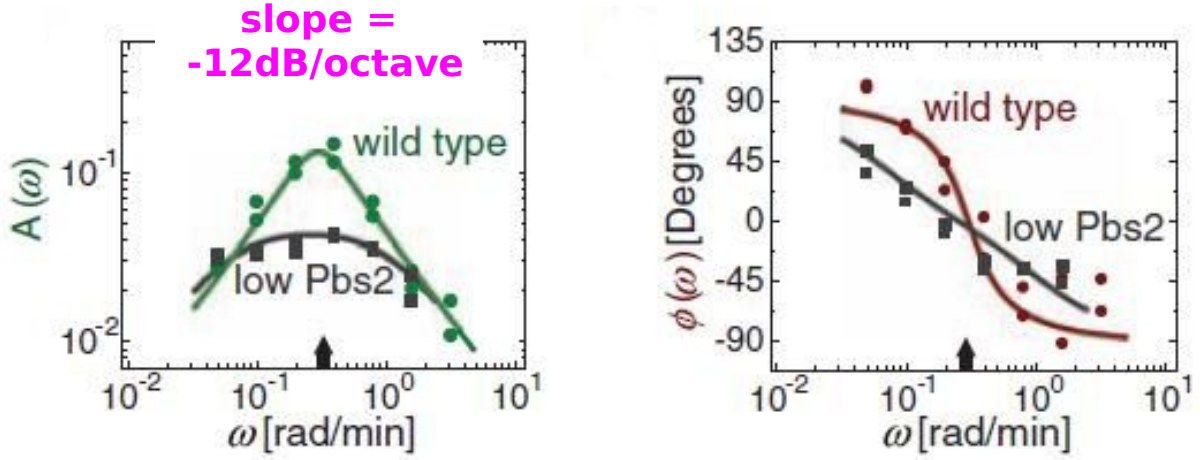
$$e^{-Ts}$$

the delay represents the time it takes for the feedback signal to reach the brainstem and spinal cord and return to the pupil

osmoregulation revisited

only the Fourier component of the response at the forcing frequency is used





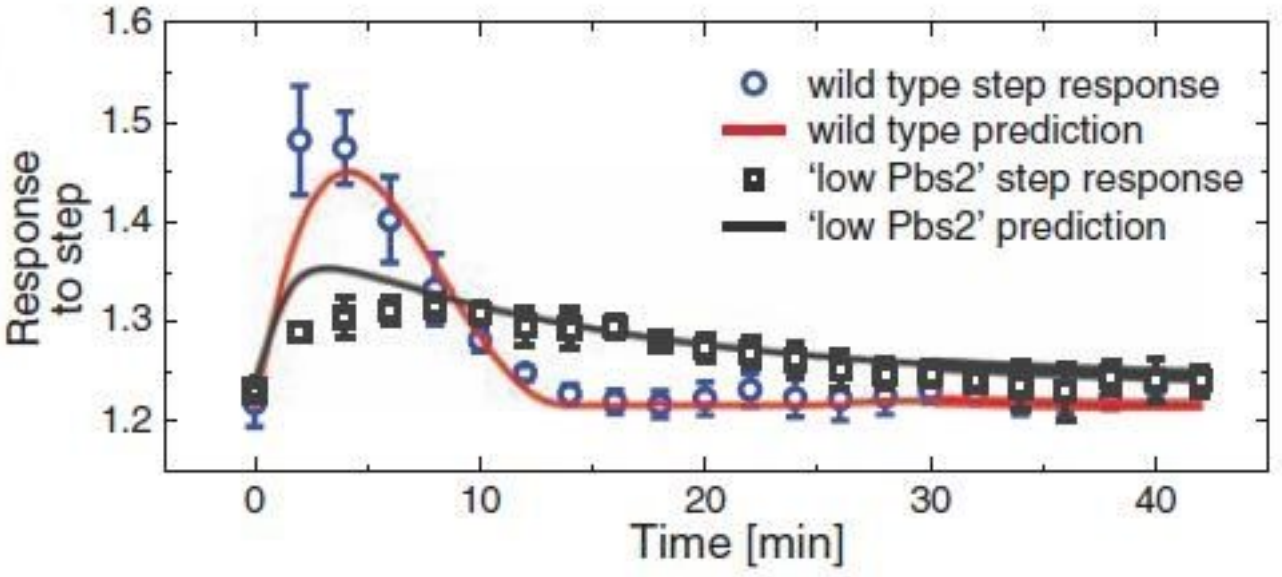
J T Mettetal, D Muzzey, C Gomez-Uribe, A van Oudenaarden, "*The frequency dependence of osmo-adaptation in Saccharomyces cerevisiae*", Science **319**:482-4 2008

osmoregulation revisited

an approximate linear model, with just **two components**, can be accurately fitted to the transient response to a step increase of 0.2M NaCl for both the wild type and the mutant strain

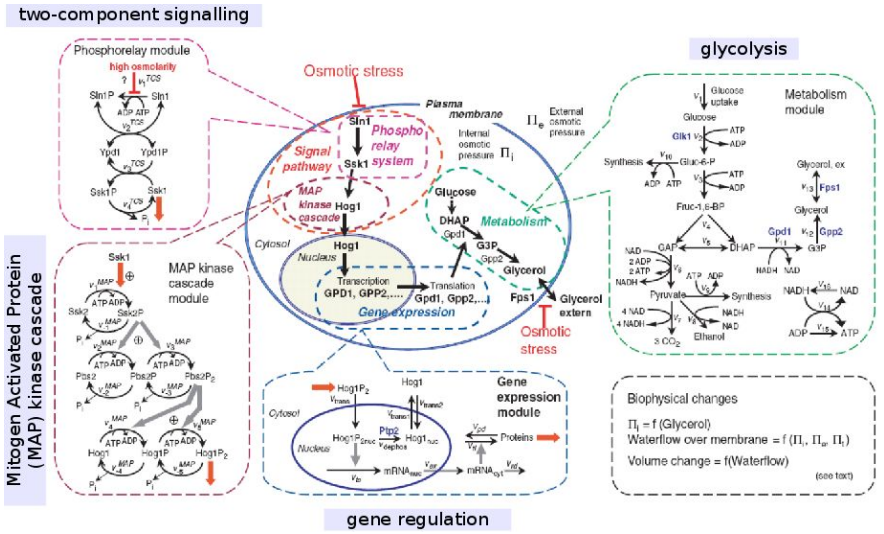
$$\dot{y} = (A_0 u - x) - \gamma y$$

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

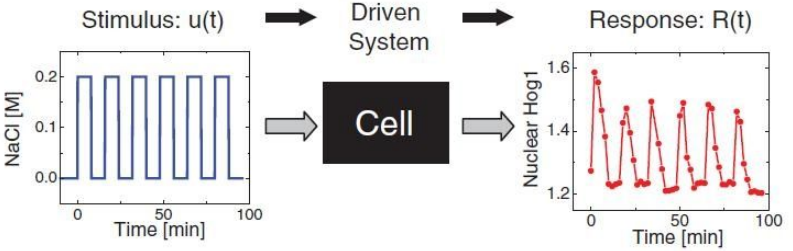


what does linear frequency analysis tell us?

~100 components



2 components



existence of an integral controller; **existence of a reduced linear model**

how accurate is the reduced model close to the set point?

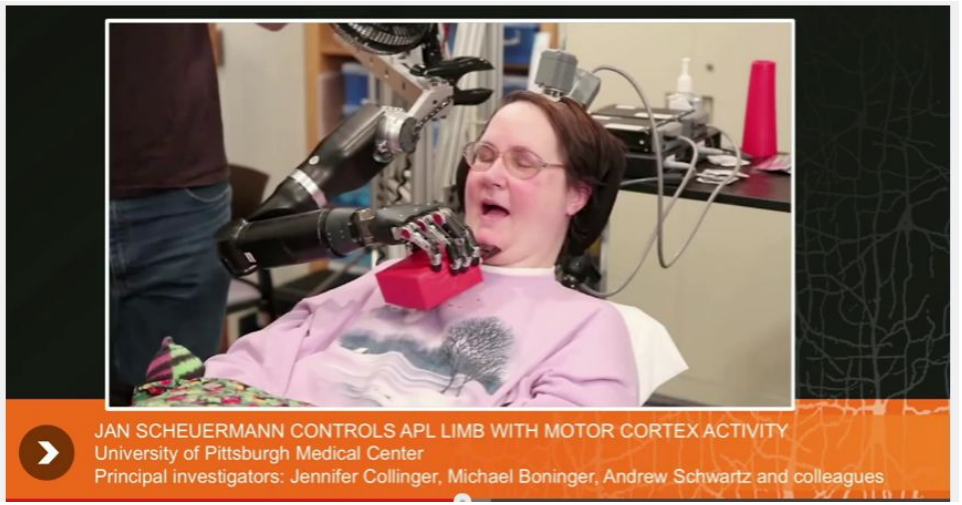
how are the components of the reduced model related to the molecular components?

what are all the other components for?

cybernetics redux ... in neuroscience

~1968

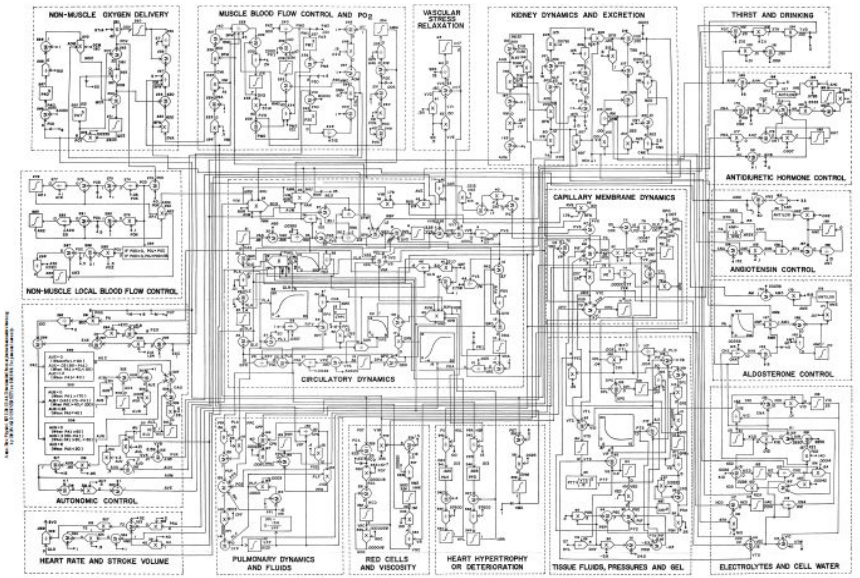
~2012



Aflalo, ..., Andersen, "*Decoding motor imagery from the posterior parietal cortex of a tetraplegic human*", Science **348**:906-10 2015; and see the Andersen lab @Caltech

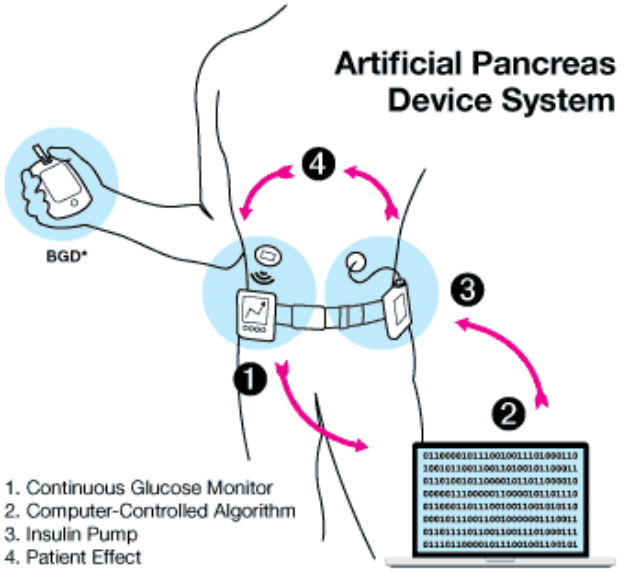
but still a long way to go in physiology ...

1972
Guyton model of the circulation



a systems understanding
but no molecules

2012
FDA guidance for industry

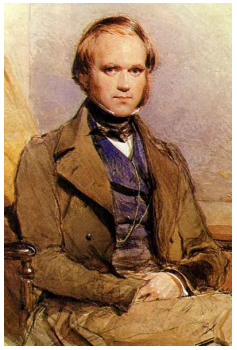


many molecules but little systems
understanding

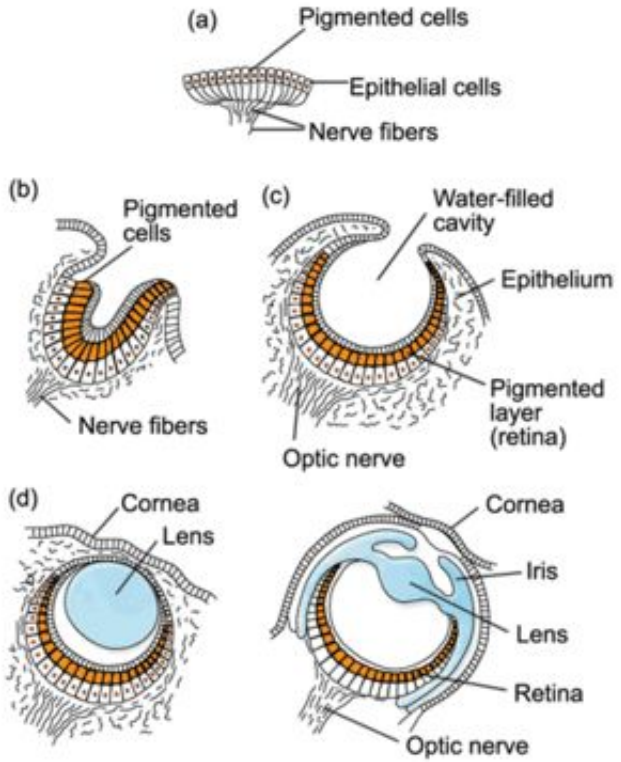
Guyton, Coleman, Granger, "*Circulation: overall regulation*", Annu Rev Physiol **34**:13-44 1972

2. evolution, modularity & weak linkage

the evolution of complexity – by Darwin



how can complex functionality emerge in nature?



"To suppose that the eye, with all its inimitable contrivances ... could have been formed by natural selection, seems, I freely confess, absurd in the highest possible degree."

"With these facts, here far too briefly and imperfectly given ... I can see no very great difficulty (not more than in the case of many other structures) in believing that natural selection has converted the simple apparatus of an optic nerve merely coated with pigment and invested by transparent membrane, into an optical instrument as perfect as is possessed by any member of the great Articulate class."

arthropods

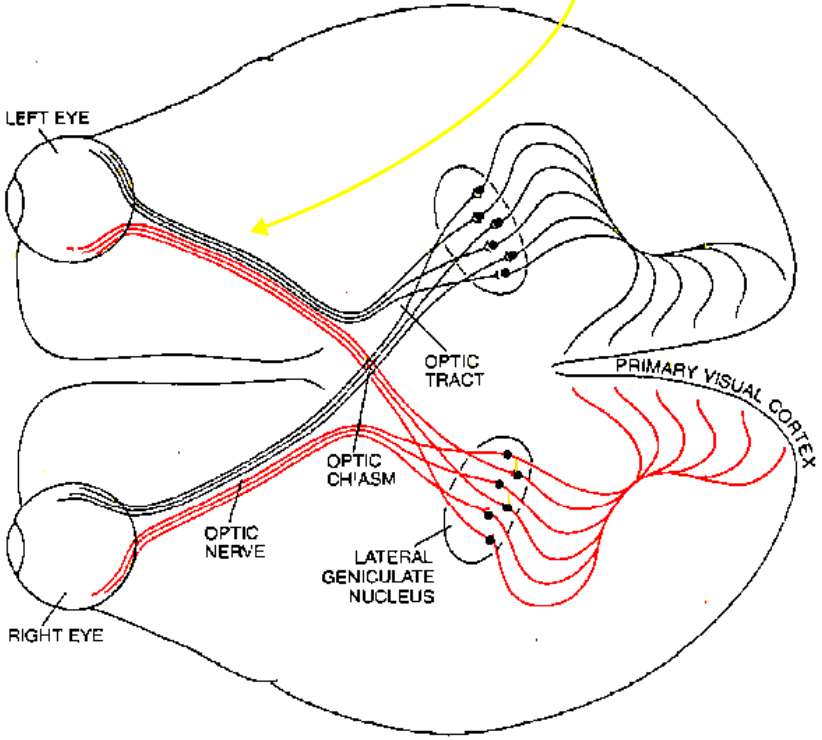
Charles Darwin, **On the Origin of Species by Means of Natural Selection, or the Preservation of Favoured Races in the Struggle for Life**, John Murray, London, 1859

the complexity of evolution

we do not perceive with our eyes but with our brain

new information
conveyed to the brain

mutation improves
eye resolution

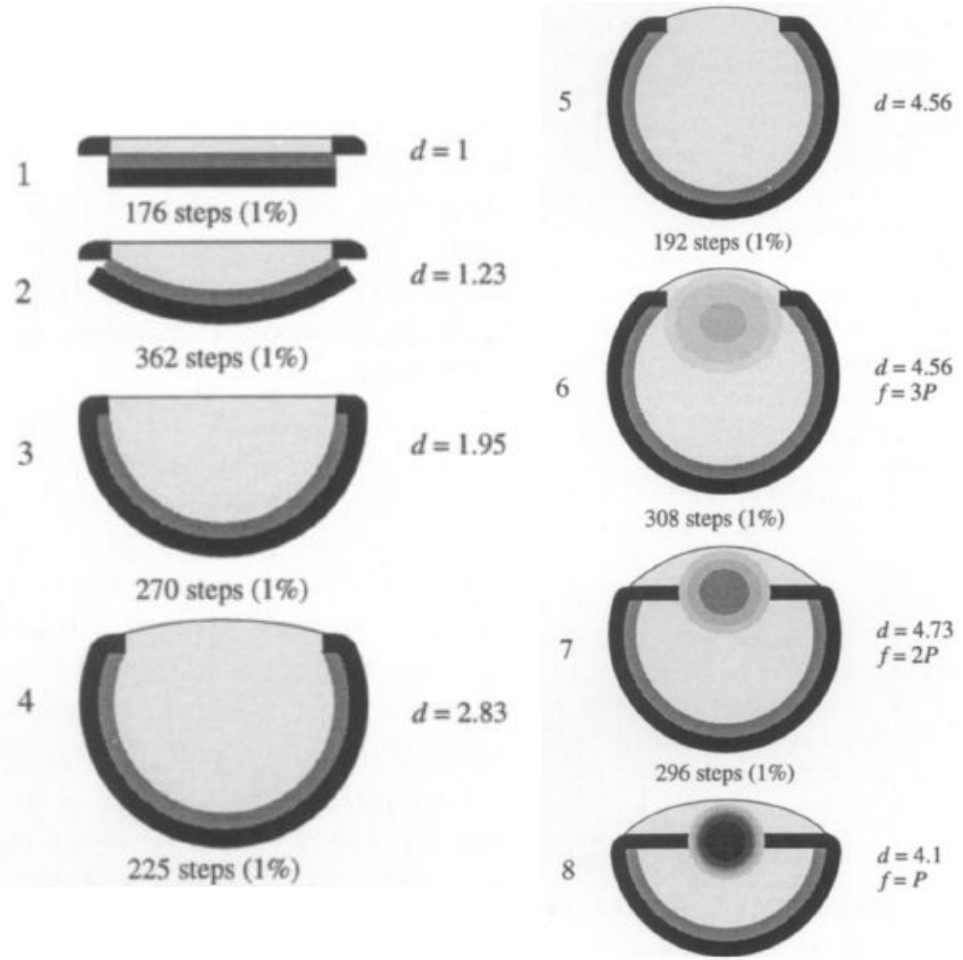


what does the brain do?

how does the brain know how to interpret the new information? how does it convert it into a fitness advantage for the organism?

how does evolution avoid the need for multiple changes – to both eye and brain – in order to gain a fitness advantage?

the evolution of complexity – in the modern era

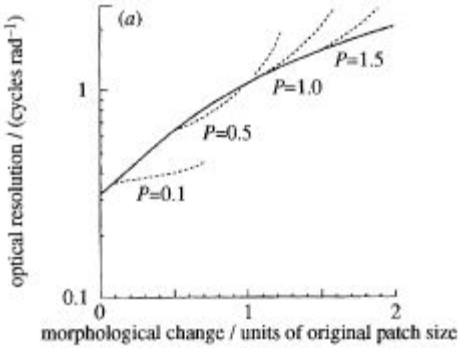


according to Ridley

"Nilsson and Pelger allowed the shape of the model eye to change at random, in steps no more than 1% change at a time ... The model eye then evolved in the computer, with each new generation formed from the optically superior eyes in the previous generation; changes that made the optics worse were rejected, as selection would reject them in nature."

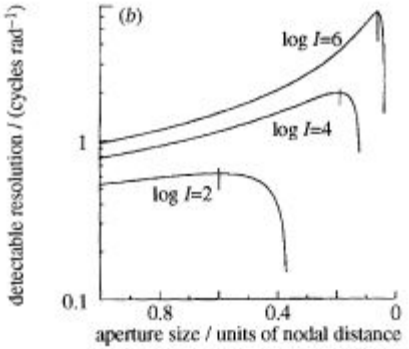
Mark Ridley, **Evolution**, 2nd ed, Blackwell Science, 1996; see also Richard Dawkins, **The Blind Watchmaker**, Norton, 1988; Nilsson, Pelger, "*A pessimistic estimate of the time required for an eye to evolve*", Proc Roy Soc Lond B, **256**:53-8 1994

wishful thinking?



"The relative effects that depression and constriction have on the eye's optical resolution are compared in figure 1a"

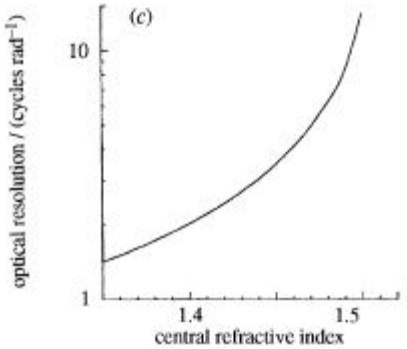
"We would thus expect selection first to favour depression and invagination of the light-sensitive patch, and then gradually change to favour constriction of the aperture."



$$\nu_{\max} = (0.375P/A)\,[\ln(0.746A^2\sqrt{I})]^{\frac{1}{2}},$$

"We can now use this relation to plot resolution against aperture diameter (figure lb)."

"When the aperture has reached the diameter which is optimal for the intensity at which the eye is used, there can be no further improvement of resolution unless a lens is introduced."



"The effect this has on resolution was calculated by using the theory of Fletcher et al. (1954) for an ideal graded-index lens (figure 1 c)"

"Based on the principles outlined above, we made a model sequence of which representative stages are presented in figure 2"

the complexity of evolutionary science

Does evolutionary theory need a rethink?

Researchers are divided over what processes should be considered fundamental.

POINT

Yes, urgently

Without an extended evolutionary framework, the theory neglects key processes, say Kevin Laland *and colleagues.*

COUNTERPOINT

No, all is well

Theory accommodates evidence through relentless synthesis, say Gregory A. Wray, Hopi E. Hoekstra *and colleagues.*

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the rediscovery of Mendelian genetics

much of our evidence for evolution and the mechanisms underlying it, rests on the mathematical theory of population genetics that emerged from the rediscovery of Mendelian algebra.

shortness of digits

"To THE EDITOR OF SCIENCE: I am reluctant to intrude in a discussion concerning matters of which I have no expert knowledge, and I should have expected the very simple point which I wish to make to have been familiar to biologists. ... Mr. Yule is reported to have suggested, as a criticism of the Mendelian position, that if brachydactyly is dominant 'in the course of time one would expect, in the absence of counteracting factors, to get three brachydactylous persons to one normal'. It is not difficult to prove, however, that such an expectation would be quite groundless."

1877-1947

G H Hardy, "*Mendelian proportions in a mixed population*", Science, **28**:49-50 1908.

Hardy-Weinberg equilibrium

two alleles (a, A) at a single locus

probabilities/frequencies

genotypes $\mathrm{AA}(P) \quad \mathrm{Aa}(Q) \quad \mathrm{aa}(R) \qquad P+Q+R=1$

alleles $\mathrm{A}\left(P+\frac{Q}{2}\right) \qquad \mathrm{a}\left(R+\frac{Q}{2}\right)$

under random mating in an infinite population with non-overlapping generations, in the absence of selection, mutation, migration, etc, the next generation looks like

genotypes

AA	Aa	aa
$\left(P+\frac{Q}{2}\right)^2$	$2\left(P+\frac{Q}{2}\right)\left(R+\frac{Q}{2}\right)$	$\left(R+\frac{Q}{2}\right)^2$

alleles $\mathrm{A}\left(P+\frac{Q}{2}\right) \qquad \mathrm{a}\left(R+\frac{Q}{2}\right)$ no change

provided $Q^2 = 4PR$, the genotype frequencies do not change. hence, they become stable after just one generation – **genetic variation persists**

C Stern, "*The Hardy-Weinberg law*", Science, **97**:137-38 1943.