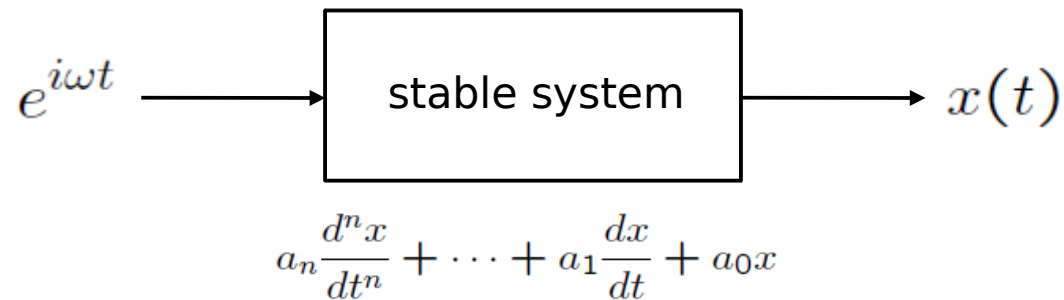


dynamic processes in cells
(a systems approach to biology)

jeremy gunawardena
department of systems biology
harvard medical school

lecture 5
15 september 2016

recap - interrogation by following the sines



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

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

initial conditions = 0

Bode amplitude plot

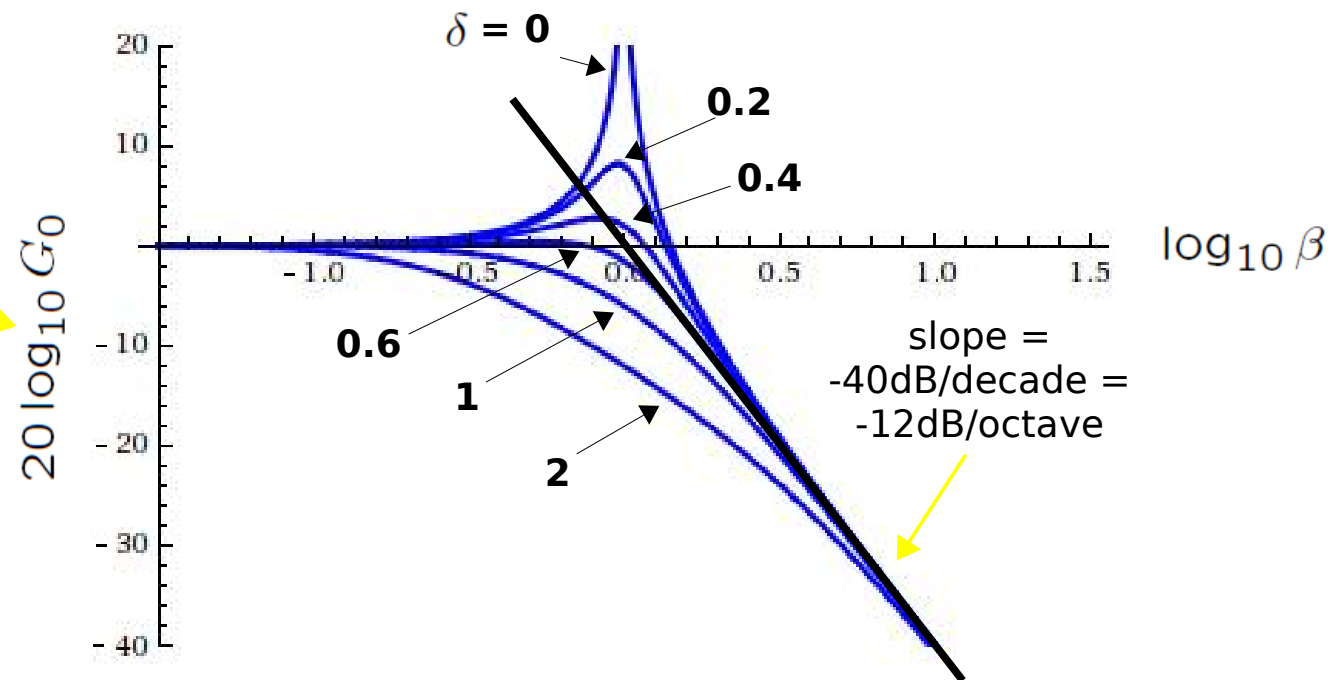
negative feedback systems considered earlier

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

amplitude

$$G_0 = \sqrt{GG}$$

decibels (dB)



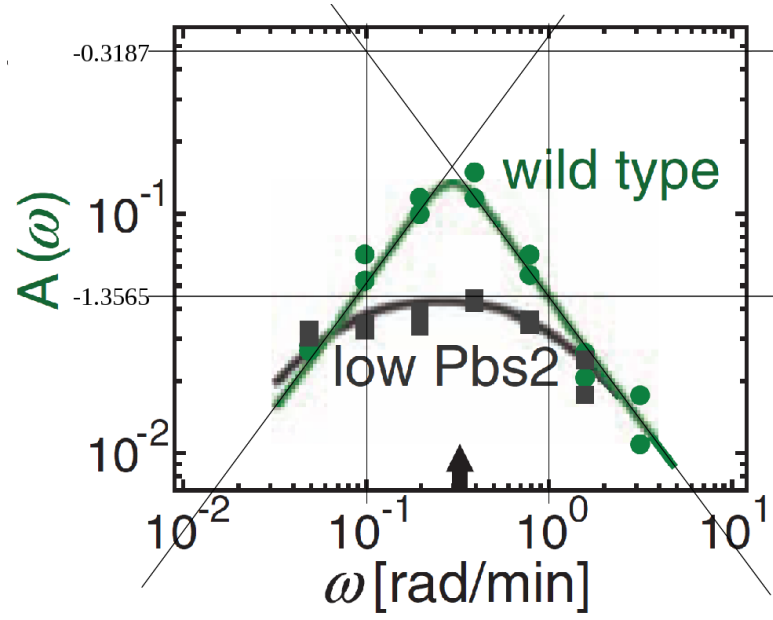
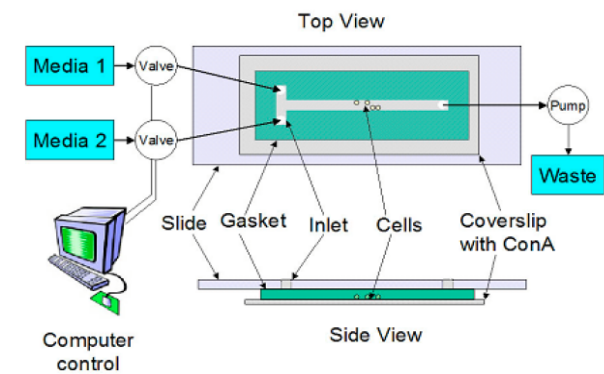
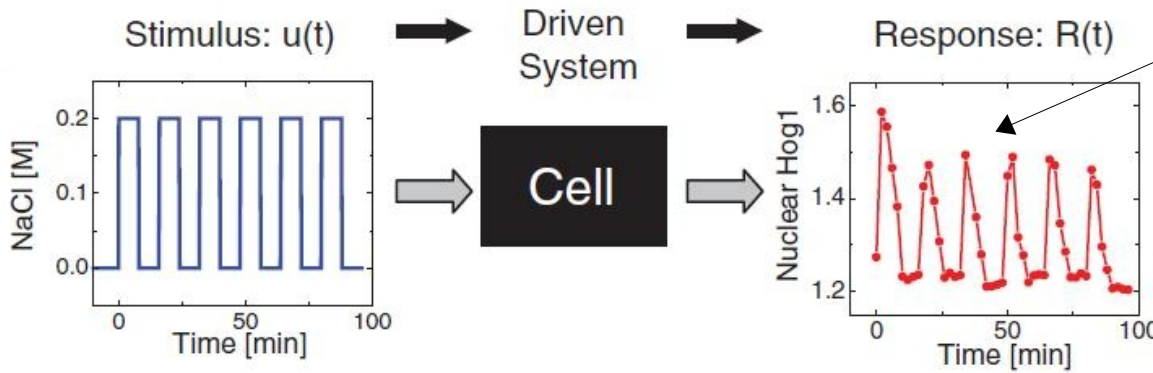
the secret of the shape

$$G(s) = \frac{P(s)}{Q(s)} = \frac{b_m s^m + \dots + b_1 s + b_0}{a_n s^n + \dots + a_1 s + a_0} \quad m < n$$

- a root of the numerator polynomial causes the slope of the Bode amplitude plot to increase by (approximately) 6 dB/octave (20 dB/decade)
- a root of the denominator (characteristic) polynomial causes the slope of the Bode amplitude plot to decrease by (approximately) 6 dB/octave
- the asymptotic (high-frequency) slope of the Bode amplitude plot is $6(m-n)$ dB/octave, where m is the degree of the numerator polynomial in the transfer function and n is the degree of the characteristic polynomial in the denominator

osmoregulation revisited

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



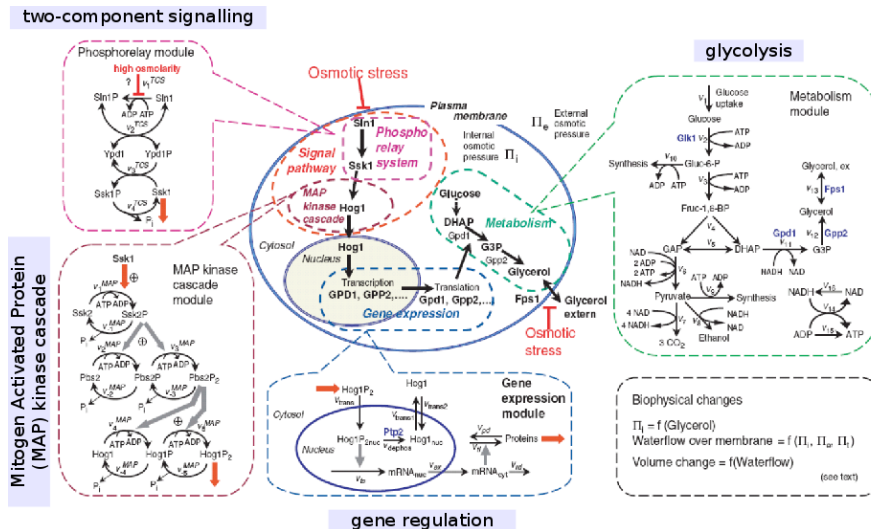
transfer function

$$m = 1$$

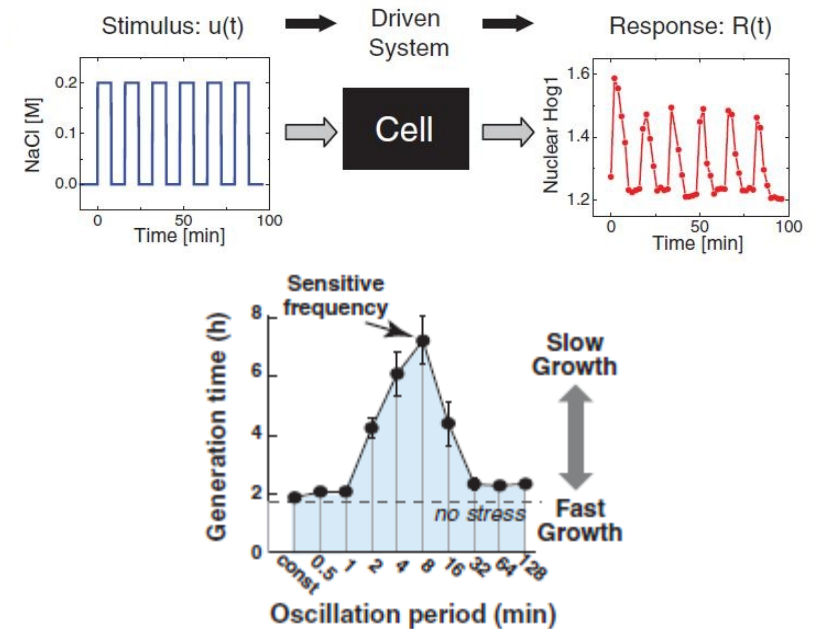
$$n = 2$$

what does linear analysis tell us?

“detailed” nonlinear model
38 components



linear model near the steady state
2 components



models are accurate descriptions of our pathetic assumptions!

reduced linear models capture dynamical behaviour close to steady state with far fewer components than a “detailed” biochemical model

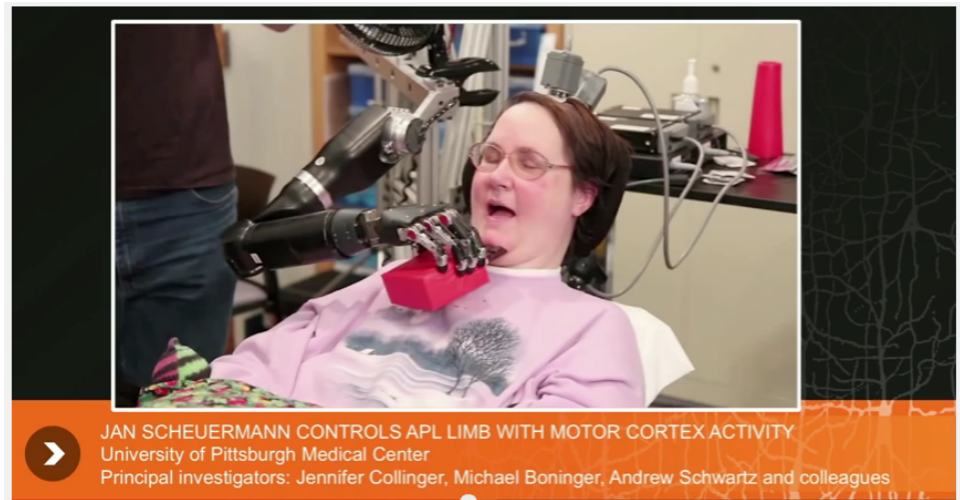
Klipp, Nordlander, Kruger, Gennemark, Hohmann, “Integrative model of the response of yeast to osmotic shock”, Nature Biotech **23**:975-82 2005; Mitchell, Wei, Lim, “Oscillatory stress stimulation uncovers an Achilles’ heel of the yeast MAPK signaling network”, Science **350**:1379-83 2016

cybernetics redux ... in neuroscience

~1968



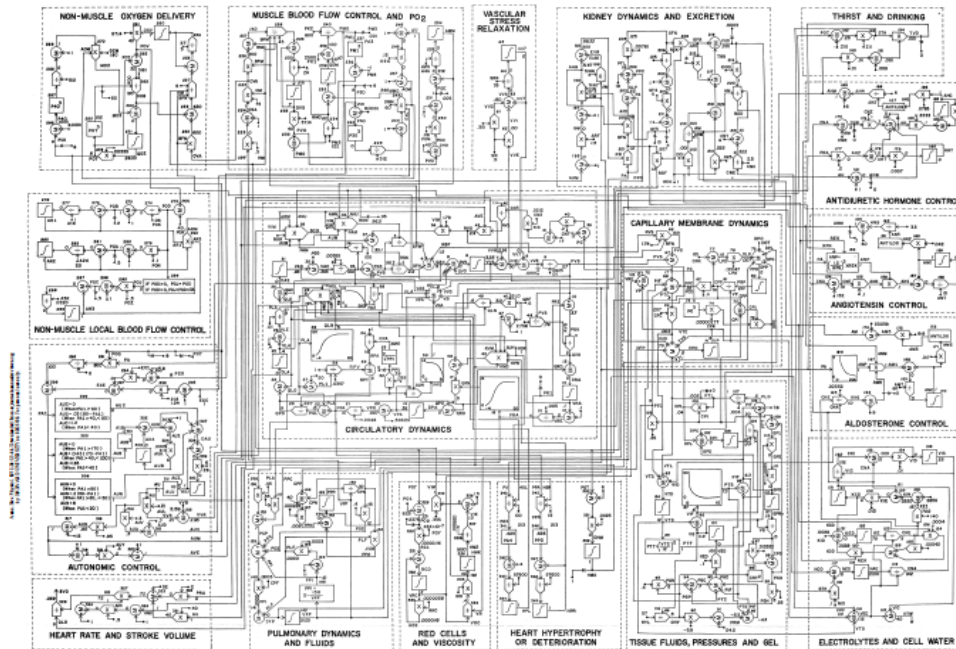
~2012



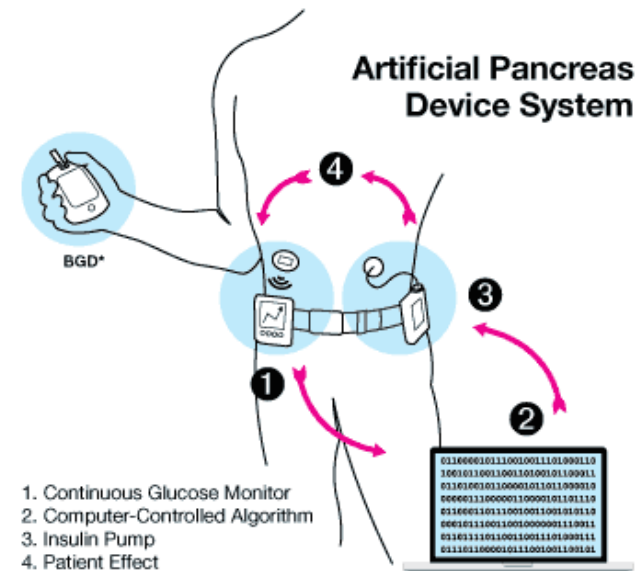
Collinger, ..., Schwarz, "High-performance neuroprosthetic control by an individual with tetraplegia", Lancet **381**:557-64 2013; see also <http://schwartzlab.neurobio.pitt.edu/index.php>

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

1972
Guyton model of the circulation



2012
FDA guidance for industry



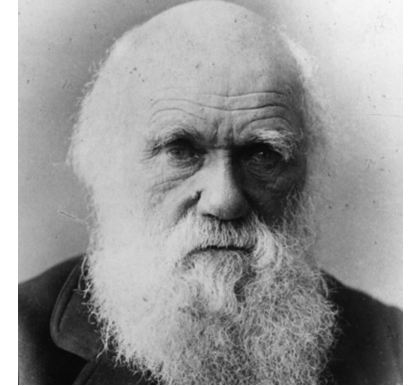
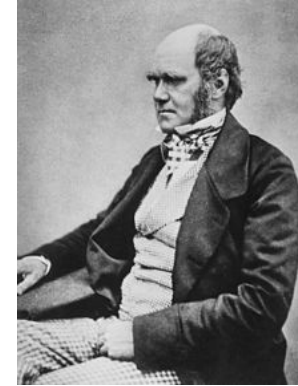
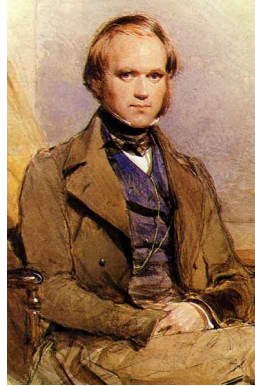
Guyton, Coleman, Granger, "Circulation: overall regulation", Annu Rev Physiol **34**:13-44 1972

Pinsker, ..., Doyle, "Randomized crossover comparison of personalized MPC and PID control algorithms for the artificial pancreas", Diabetes Care **39**:1135-42 2016.

2. evolution, modularity & weak linkage

natural selection

" ... any being, if it vary however slightly in any manner profitable to itself, under the complex and sometimes varying conditions of life, will have a better chance of surviving and thus be naturally selected. From the strong principle of inheritance, any selected variety will tend to propagate its new and modified form."



1809 - 1882

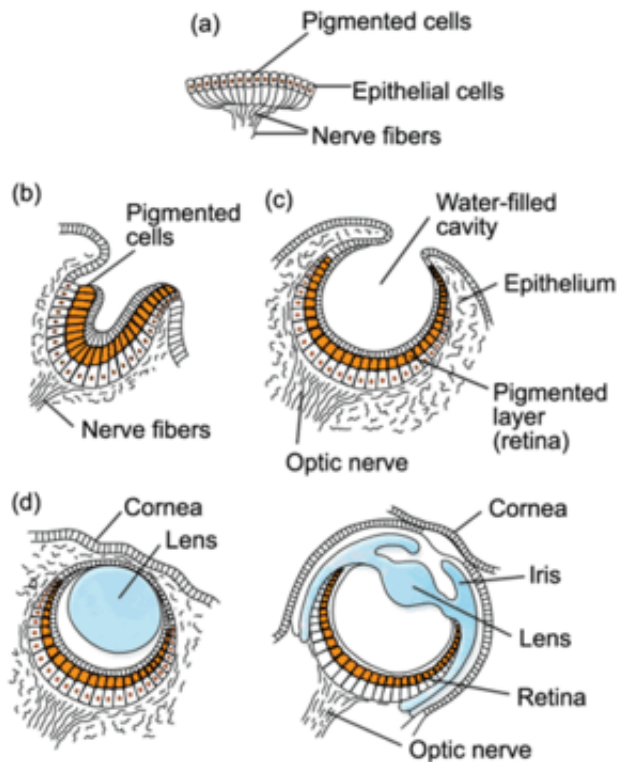
darwinian dynamics - can arise when the reproductive success of an individual is influenced by a property whose variation in the population shows heritability.

"How extremely stupid not to have thought of that!" T H Huxley

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 evolution of complexity

how can complex functionality emerge in nature?



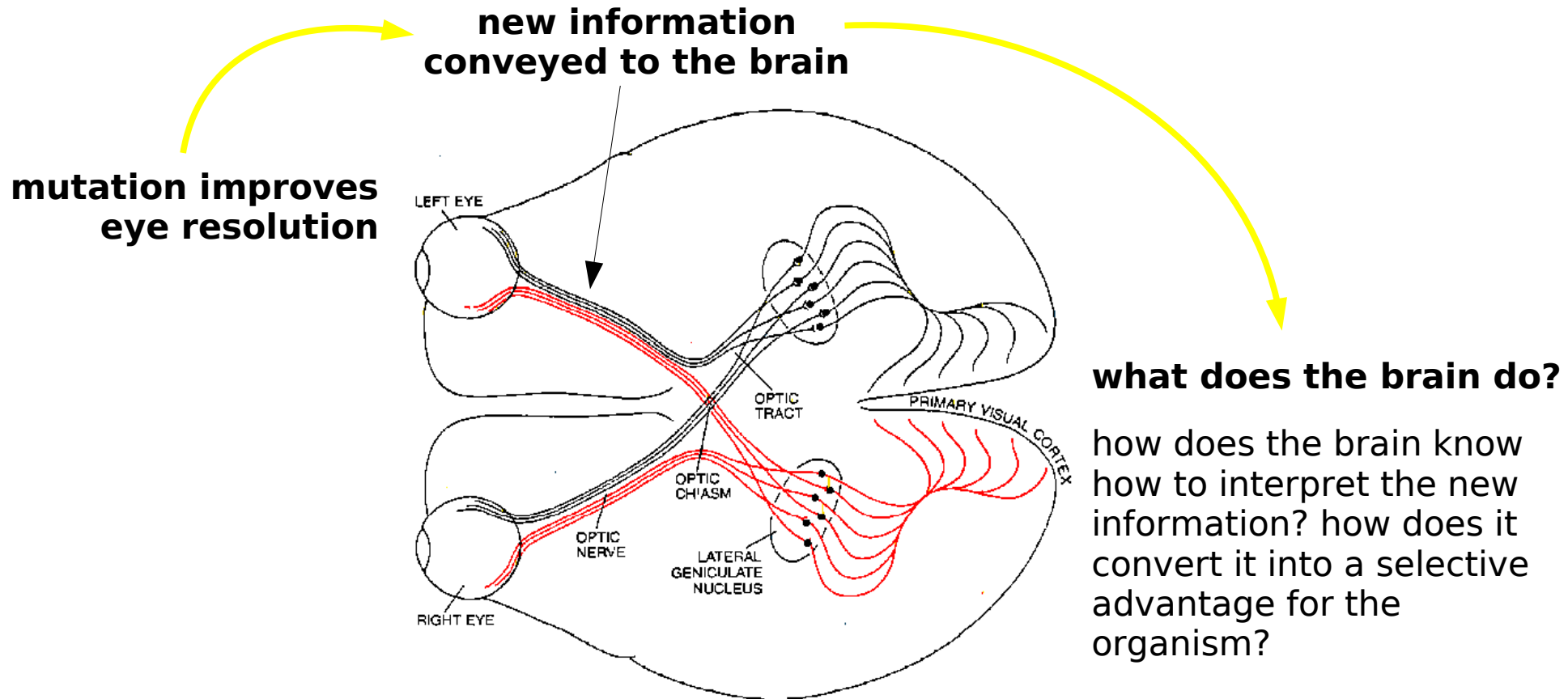
“To suppose that the eye, with all its inimitable contrivances ... could have been formed by natural selection, seems, I freely confess, absurd in the highest possible degree.”

“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

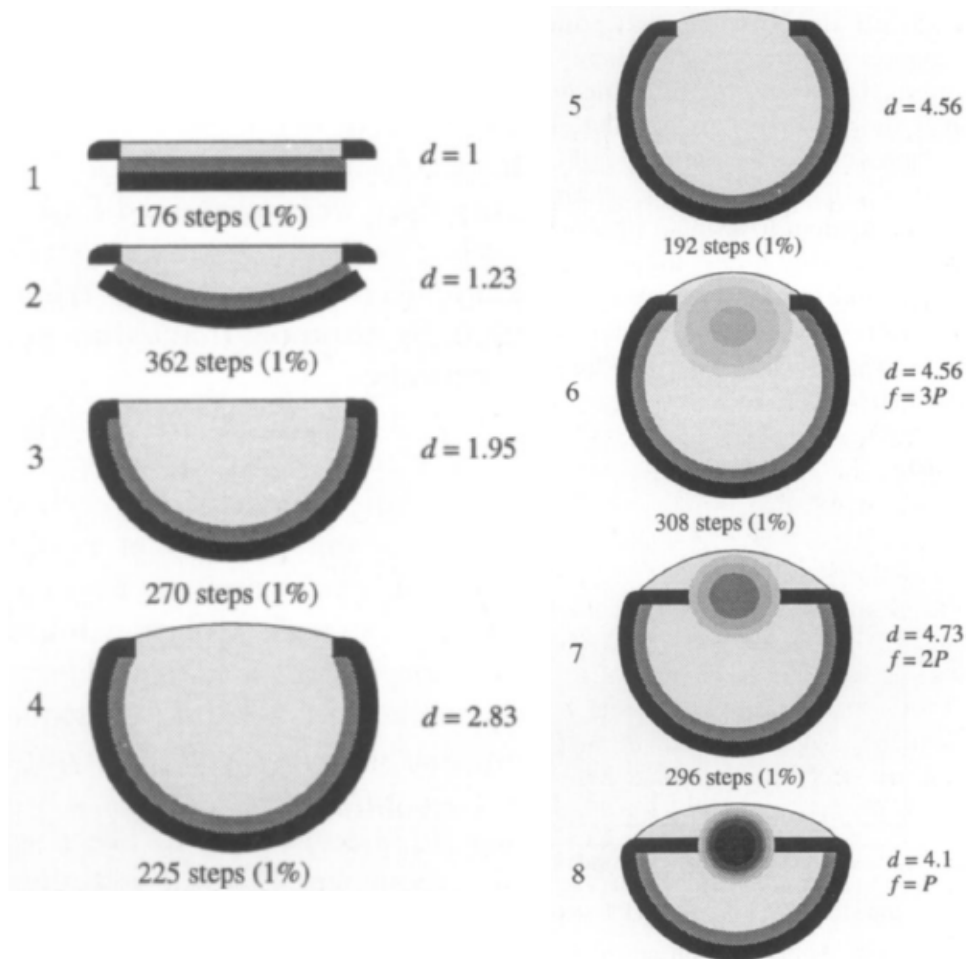
the complexity of evolution

we do not perceive with our eyes but with our brain



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

the evolution of complexity - in the modern era

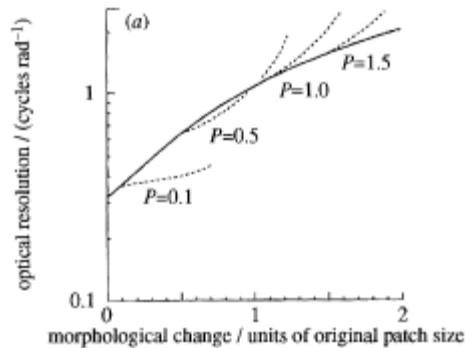


according to Ridley

"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."

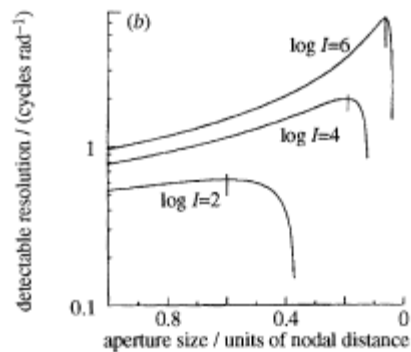
Mark Ridley, **Evolution**, 2nd ed, Blackwell Science, 1996; see also Richard Dawkins, **The Blind Watchmaker**, Norton, 1988; Nilsson, Pelger, "A pessimistic estimate of the time required for an eye to evolve", Proc Roy Soc Lond B, **256**:53-8 1994

wishful thinking?



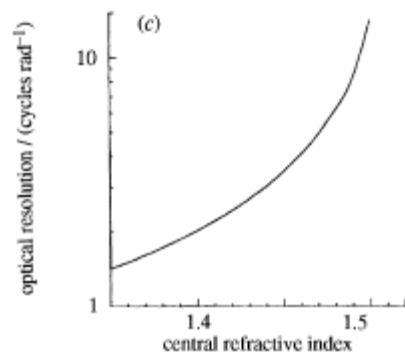
“The relative effects that *depression* and *constriction* have on the eye's optical resolution are compared in figure 1a”

“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.”



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

“We can now use this relation to plot resolution against aperture diameter (figure 1b).”



“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.

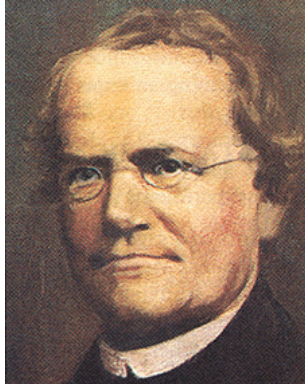
COUNTERPOINT

No, all is well

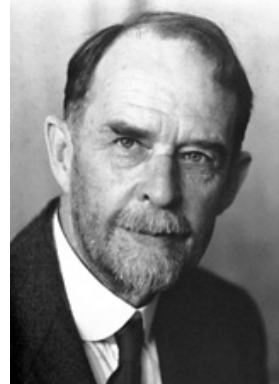
Theory accommodates evidence through relentless synthesis, say Gregory A. Wray, Hopi E. Hoekstra and colleagues.

9 OCTOBER 2014 | VOL 514 | NATURE

the rediscovery of Mendelian genetics



1822 - 1884



1866 - 1945



1902 - 1992

genes are mathematical abstractions that explain data ...

“Frankly, these are questions with which the working geneticist has not much concern himself ... There is no consensus of opinion as to what the genes are—whether they are real or purely fictitious.”

but are closely associated in some way with chromosomes ...

“Pairing chromosomes, heteromorphic in two regions, have been shown to exchange parts at the same time they exchange genes assigned to those regions.”

Creighton, McClintock, “A correlation of cytological and genetical crossing over in *Zea mays*”, PNAS **17**:492-7 1931.