dynamic processes in cells (a systems approach to biology)

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lecture 6

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Hardy's calculation

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 are stable

Hardy-Weinberg equilibrium

single locus, n alleles

alleles $A_1(p_1), A_2(p_2), \cdots, A_n(p_n)$

under random mating with no selection, mutation, migration, etc, the genotype frequencies become stable after one generation

their values are given by the respective terms in the expansion of

$$(p_1 + \cdots + p_n)^2$$

genotypes $A_iA_i(p_i^2)$ $A_iA_j(2p_ip_j)$

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

human polymorphisms at HW equilibrium

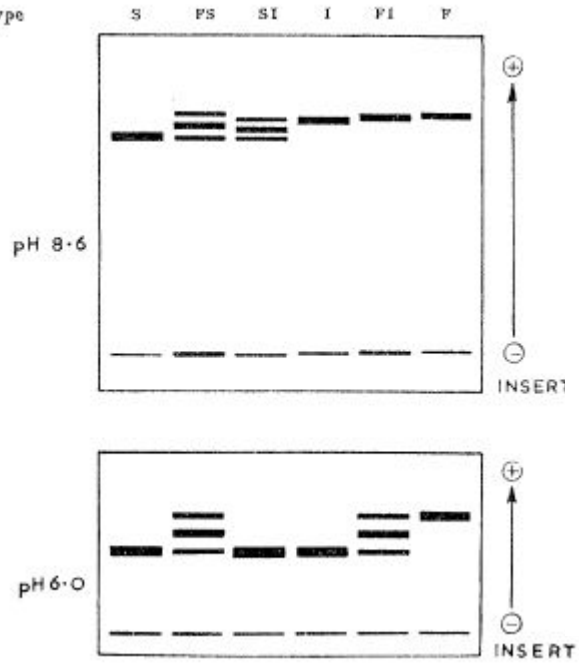


TABLE 9. OBSERVED AND EXPECTED NUMBERS OF PLACENTAL ALKALINE PHOSPHATASE TYPES IN A POPULATION SAMPLE ASSUMING A HARDY–WEINBERG EQUILIBRIUM **F I S**

($p = 0{\cdot}27$, $q = 0{\cdot}09$ and $r = 0{\cdot}64$)

placental alkaline phosphatase type	expected incidence		expected numbers in population sample	observed numbers in population sample
S	r^2	0·410	135·9	141
SF	$2pr$	0·346	114·7	111
F	p^2	0·073	24·2	28
SI	$2qr$	0·115	38·2	32
FI	$2pq$	0·049	16·1	15
I	q^2	0·008	2·7	5
totals	$(p+q+r)^2$	1·001	331·8	332

"Although one can hardly draw firm numerical conclusions from such a small series, it seems likely, unless we have been excessively lucky in our choice of enzymes, that polymorphism to a similar degree may be a fairly common phenomenon among the very large number of enzymes that occur in the human organism"

Henry Harris, "*Enzyme polymorphisms in man*", Proc Roy Soc Lond B, **164**:289-310 1966

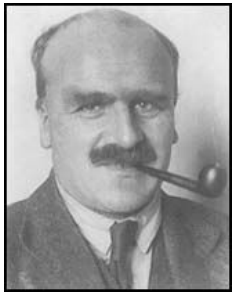
mathematical population genetics

how do allele frequencies change in populations under the influence of selection, mutation, migration, population structure, etc?

two alleles (a, A) at a single locus:

Fisher | Wright | Haldane





1890-1962 *1889-1988* *1892-1964*

selection coefficient

dominance

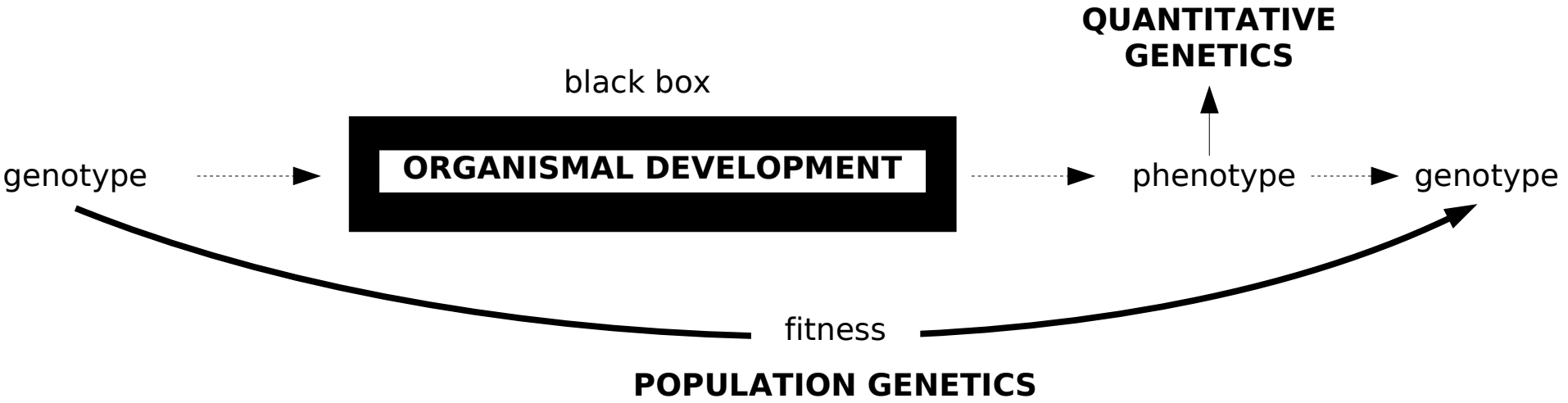
genotypes	AA	Aa	aa
relative fitness	*1 - s*	*1 - hs*	*1*

change in frequency (*p*) of allele A

$$\Delta p = \frac{pqs[ph + q(1-h)]}{1 - 2pqhs - q^2 s}$$

John Gillespie, **Population Genetics**, JHU Press, 2004; Sean Rice, **Evolutionary Theory: Mathematical and Conceptual Foundations**, Sinauer Associates, 2004

the heart of the problem



in population genetics, fitness is assumed to be a function of the genotype, not the phenotype. this unrealistic assumption yields a theory based on the dynamics of gene frequencies, which is extremely successful at answering certain questions

but it does so at the cost of ignoring the development of the organism

out of sight, out of mind – the dark side of model building

the modern ("neo-darwinian") synthesis

the "modern synthesis" built upon population genetics to explain (**a**) the data from field experiments on natural populations of animals and plants; (**b**) the existence of species and phyla; and (**c**) the fossil record

Dobzhansky

1900-1975

Mayr

1904-2005

Simpson

1902-1984

"Nothing in biology makes sense except in the light of evolution"

except for organismal development .. which was left out of the evolutionary synthesis, except for the work of a few heretics

Goldschmidt

1878-1958

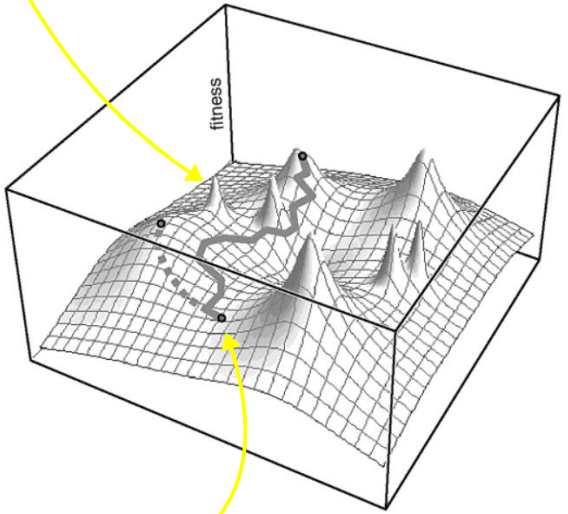
Waddington

1905-1975

Ernst Mayr & William Provine, **The Evolutionary Synthesis: Perspectives on the Unification of Biology**, Harvard Univ Press, 1980; Slack "*Conrad Hal Waddington: the last renaissance biologist*", Nature Rev Genet **3**:889-95 2002.

the bigger picture

fisher – in large populations, even weak positive selection will lead to an allele becoming fixed in the population, while deleterious alleles are quickly lost. under suitable conditions, the average fitness increases monotonically to an optimum.



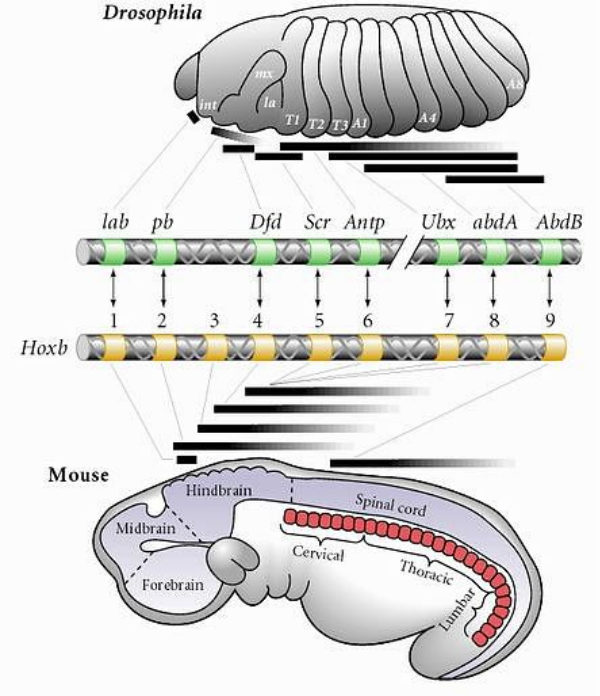
wright – in small populations, random processes (drift, mutation, recombination) dominate over selection. deleterious alleles can become fixed, while beneficial ones can be lost. average fitness may decrease.

Eugene Koonin, **The Logic of Chance: The Nature and Origin of Biological Evolution**, FT Press Science, New Jersey, 2012

the revenge of the organism

"Much that has been learned about gene physiology makes it evident that the search for homologous genes is quite futile except in very close relatives."

Ernst Mayr, **Animal Species and Evolution**, Harvard University Press, 1963



in fact, on the contrary, there is deep conservation of certain genes and their protein functions between evolutionarily very distant organisms

Lutz, Lu, Eichele, Miller, Kaufman, "*Rescue of Drosophila labial null mutant by the chicken ortholog Hoxb-1 demonstrates that the function of Hox genes is phylogenetically conserved*", Genes & Dev **10**:176-84 1996

“evo-devo” or misunderstanding?

“Since the Modern Synthesis, most expositions of the evolutionary process have focused on microevolutionary mechanisms. Millions of biology students have been taught the view (from population genetics) that ‘evolution is change in gene frequencies.’ Isn’t that an inspiring theme? This view forces the explanation toward mathematics and abstract descriptions of genes, and away from butterflies and zebras ... The evolution of form is the main drama of life’s story, both as found in the fossil record and in the diversity of living species. So, let’s teach that story. Instead of ‘change in gene frequencies,’ let’s try ‘evolution of form is change in development’.”

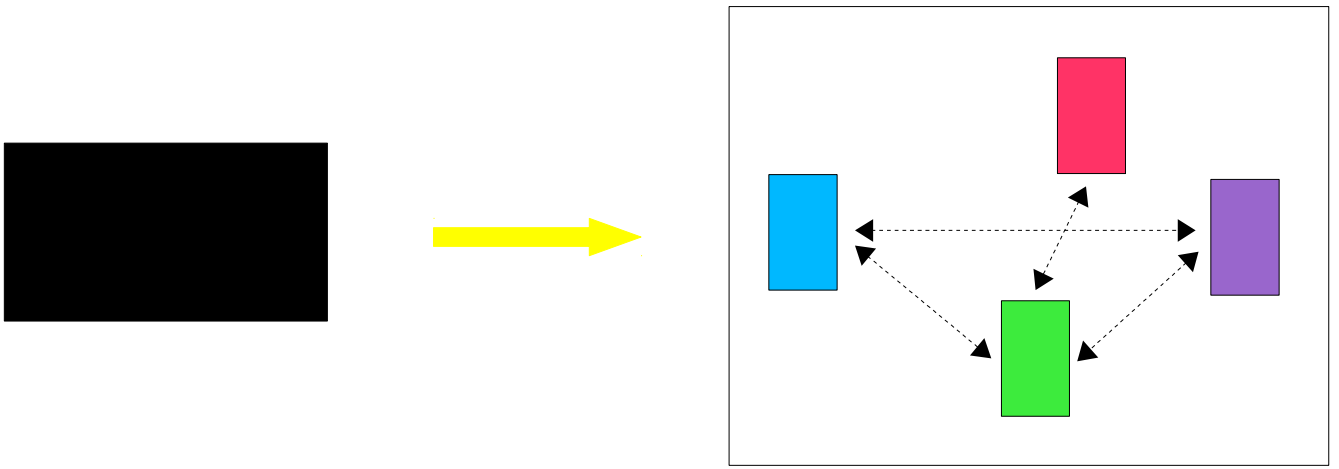
Sean Carroll, **Endless Forms Most Beautiful: The New Science of Evo-Devo**, W W Norton & Co, 2005

“Even ignoring the fact that most species are unicellular and differentiated mainly by metabolic features, this statement illustrates two fundamental misunderstandings. Evolutionary biology is not a story-telling exercise, and the goal of population genetics is not to be inspiring, but to be explanatory. ... Nothing in evolution makes sense except in the light of population genetics.”

Michael Lynch, “*The frailty of adaptive hypotheses for the origins of organismal complexity*”, PNAS **104**:8597-604 2007, commenting on Sean Carroll's comment

the evolution of complexity revisited

the evidence from molecular developmental biology suggests, in contrast to population genetics, that the “black box” must have specific properties in order for complexity to evolve



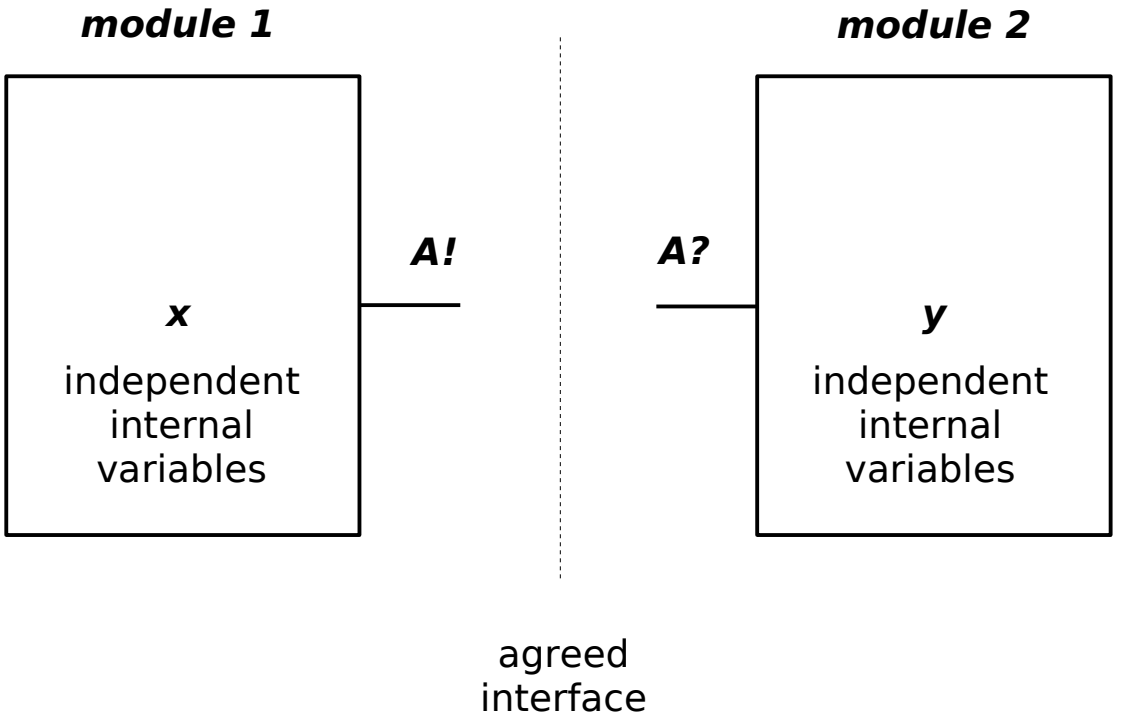
it has **MODULES** capable of some degree of independent reuse, modification and reorganisation and, furthermore, these modules are not tightly wired together but, rather, are **WEAKLY LINKED**, thereby allowing natural selection to act on individual modules and for complexity to evolve

Kirschner, Gerhart, **The Plausibility of Life**, Yale Univ Press 2006

linking modules together – in engineering

strong linkage

hierarchical encapsulation and hiding of internal state, with inter-module communication taking place through agreed interfaces

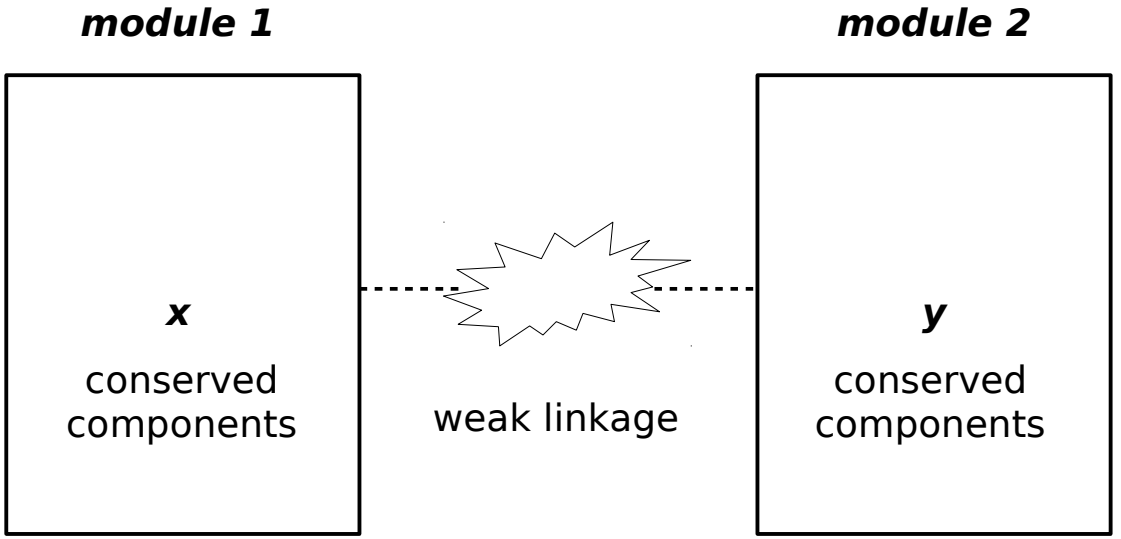


constrained interfaces allow de-constrained innovation within modules

linking modules together – in biology

weak linkage

modules are coupled by weak-linkage mechanisms rather than by instruction through a defined interface

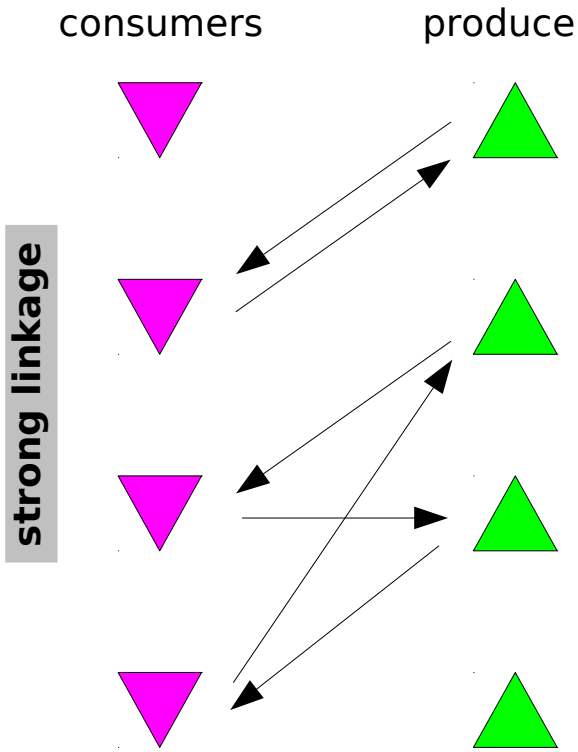


de-constrained interfaces allow conserved components to evolve new functionality within modules while maintaining overall system behaviour

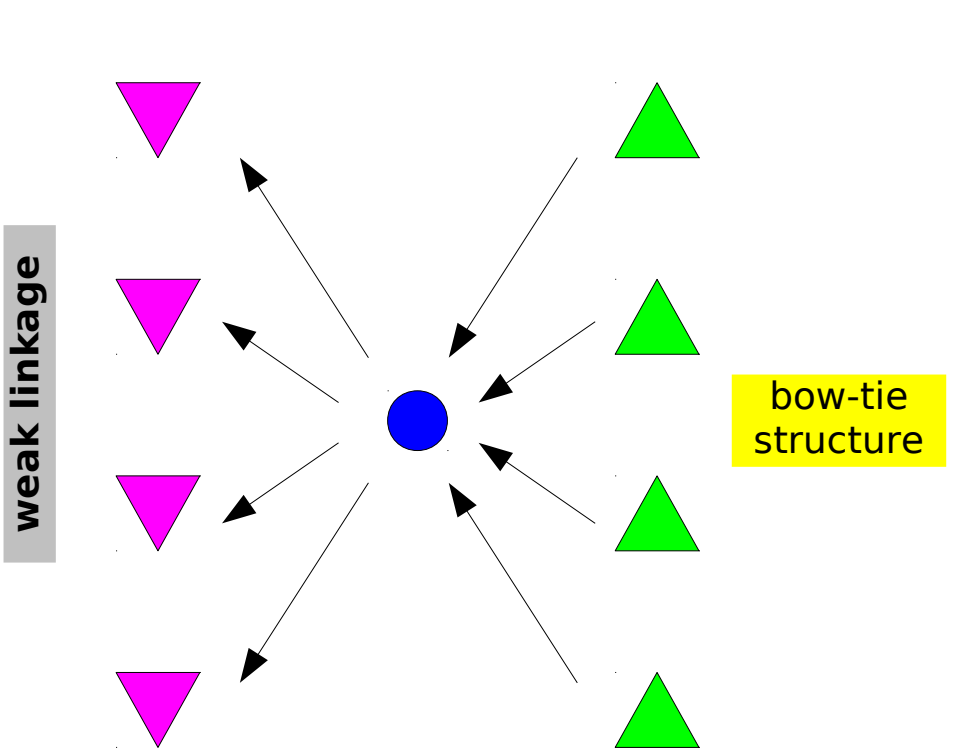
Gerhart & Kirschner, "*The theory of facilitated variation*", PNAS **104**:8582-9 2007;
Kirschner, Gerhart, **The Plausibility of Life**, Yale Univ Press 2006

weak linkage in metabolism

dehydrating condensations consume energy and must be coupled to energy-producing reactions



"barter economy"



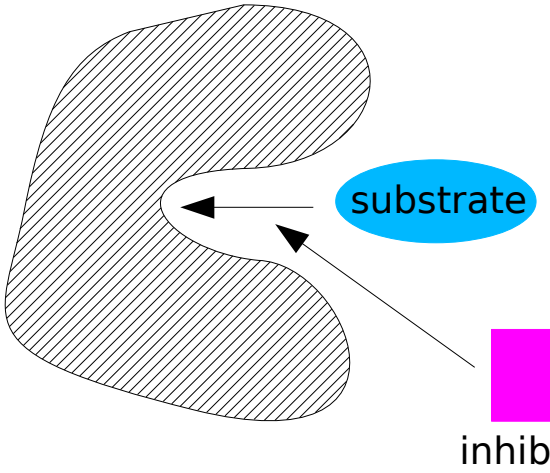
"invention of money"

Csete, Doyle, "*Bow ties, metabolism and disease*", Trends Biotechnol **22**:446-50 2004

weak linkage in enzyme regulation

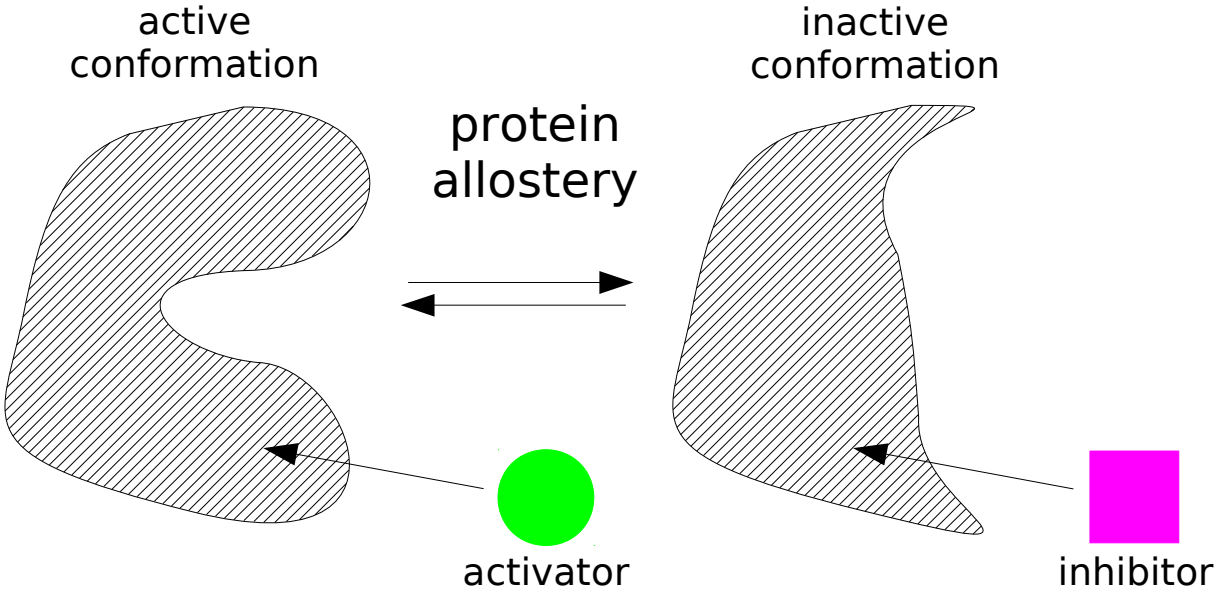
instruction – competitive inhibition of enzyme activity

strong linkage



variation/selection

weak linkage

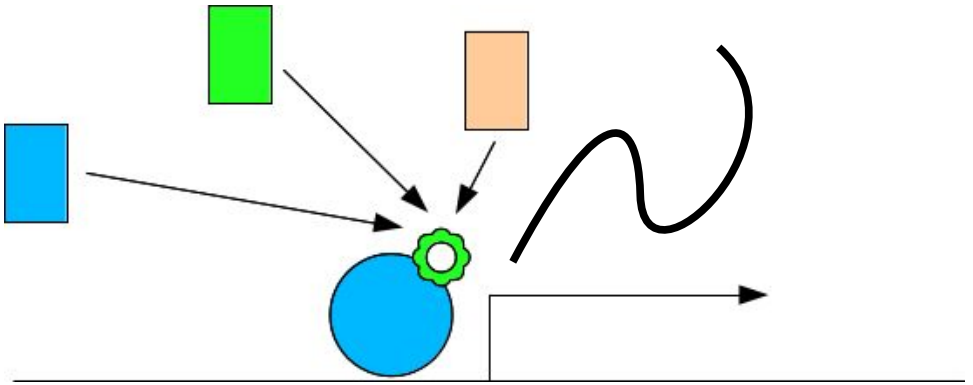


Monod, Changeux, Jacob, "*Allosteric proteins and cellular control systems*", J Mol Biol **6**:306-29 1963

weak linkage in gene expression

gene transcription requires both catalytic production of mRNA and regulation of transcription by cellular processes acting through transcription factors

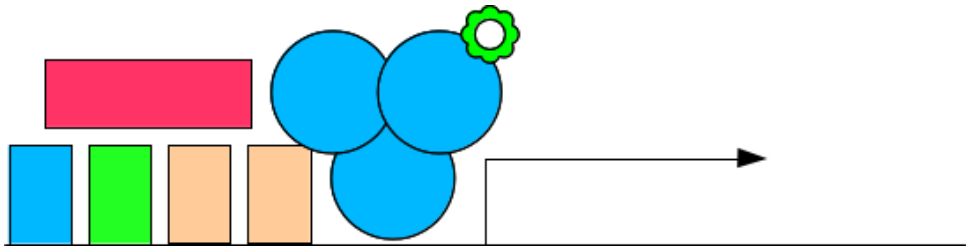
direct activation/inhibition of RNA polymerase



strong linkage

indirect binding to DNA and recruitment of factors that activate/inhibit transcription

combinatorial complexity emerges in gene regulation

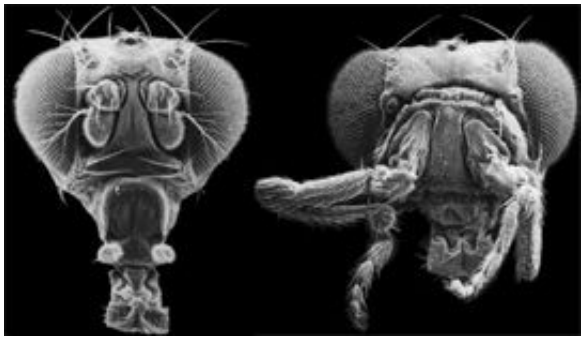


weak linkage

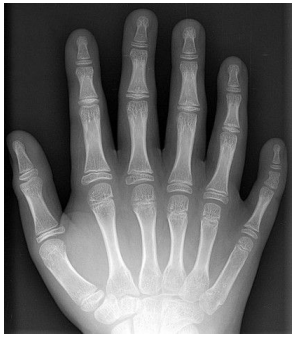
polymerase becomes more complicated

weak linkage in development

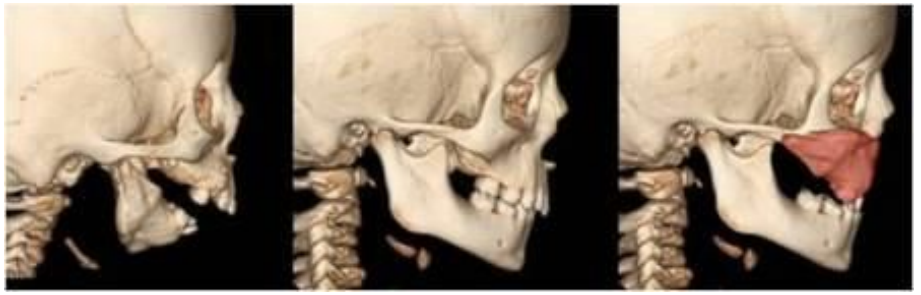
homeotic mutations lead to reorganisation of body parts



antennapedia



polydactly



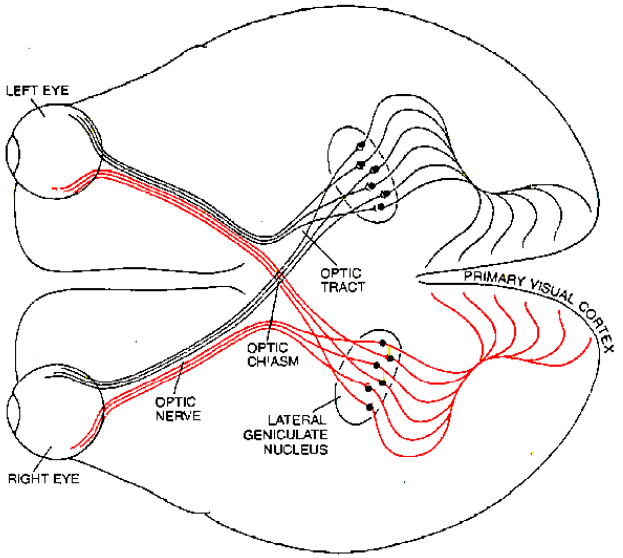
auriculocondylar syndrome

weak linkage: bone, muscle, nerves, vasculature adapt to what each other are doing

evolution of the eye, again

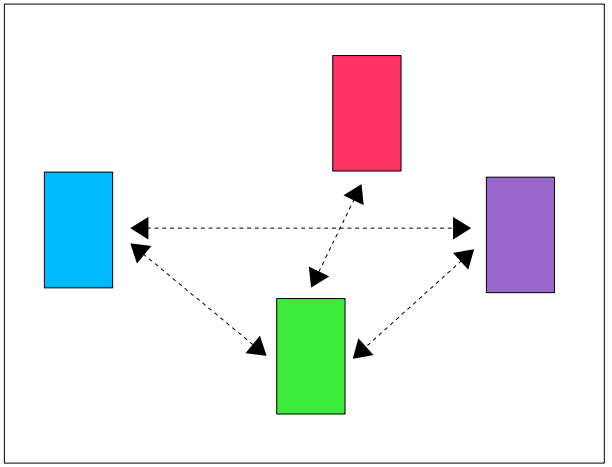
during organismal development, there is a “critical window” during which neuronal connections are formed in an activity-dependent manner.

weak linkage: the neurons in the CNS can learn from the signals which the eyes send them, thereby extracting new information and enabling a fitness advantage for the organism to arise from mutations which improve the optics of the eye



Dale Purves, **Brains: How They Seem to Work**, FT Press, 2010

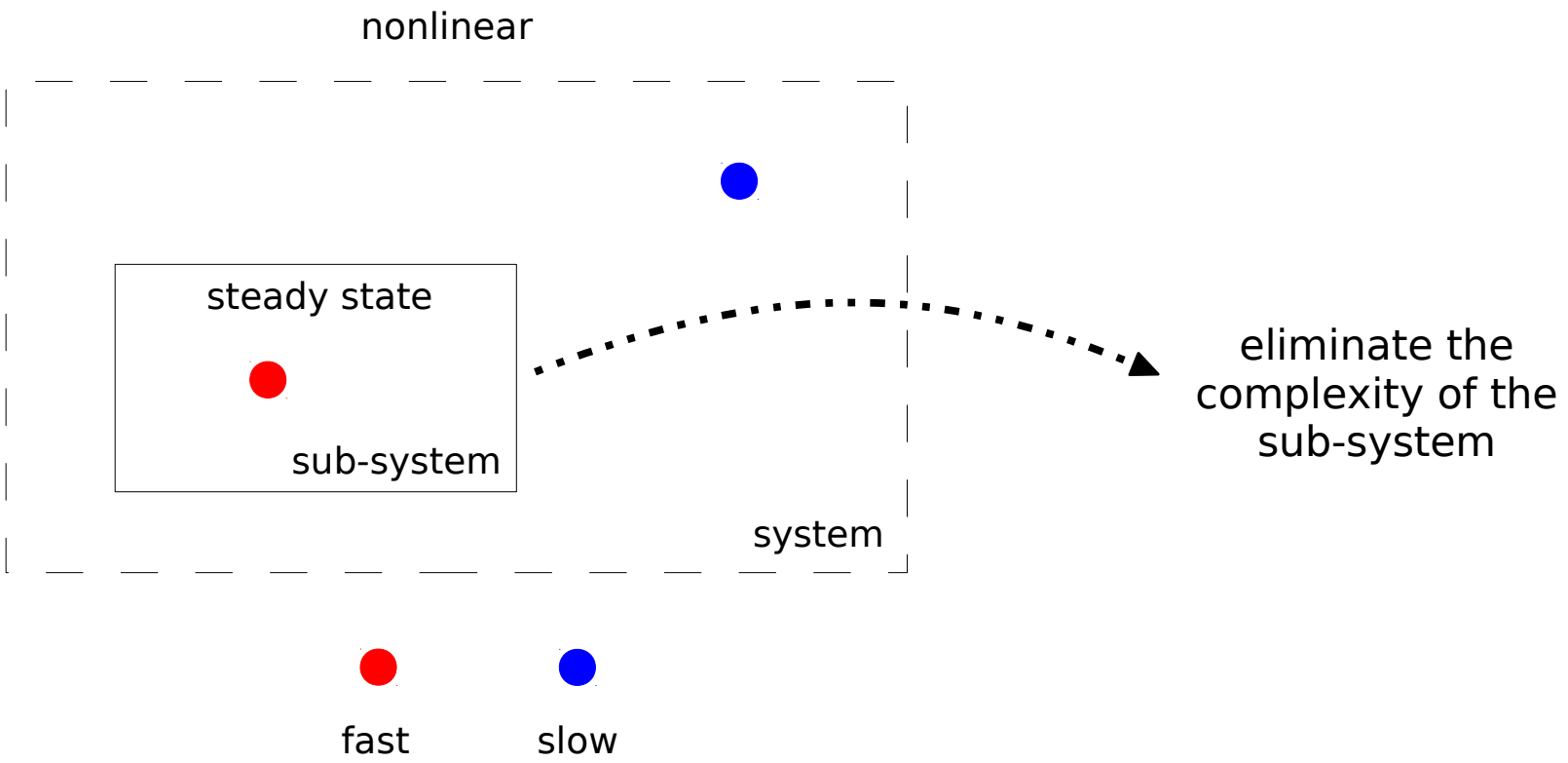
weak linkage facilitates variation and evolution



- weak linkage allows mutations to occur within modules without compromising the organism as a whole
- such mutations give rise to genetic variation which is neutral or only mildly deleterious or, through learning and physiological adaptation, potentially advantageous
- such genetic variation can proliferate and mix in the population by mating and recombination, providing the raw material for subsequent selection
- but how did weak linkage mechanisms evolve in the first place … ?

3. time-scale separation & the linear framework

time-scale separation



$$E + S \rightleftharpoons ES \rightarrow E + P$$