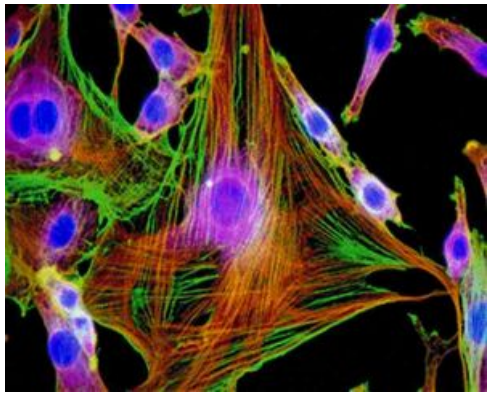
lecture 4
weak linkage and learning

jeremy gunawardena



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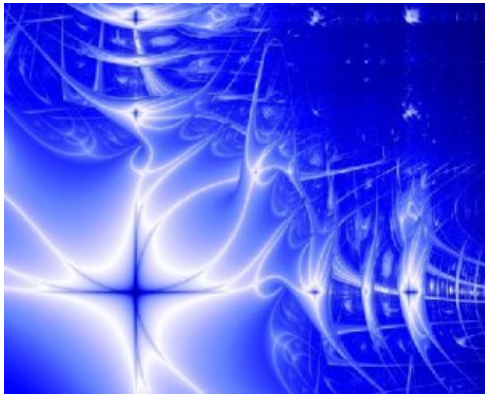


“A Systems Approach to Biology”, UBA Buenos Aires, 11-22 June 2018

syllabus

1. the role of mathematics in biology

2. homeostasis of the organism

3. the complexity of evolution 

4. weak linkage and learning 

5. timescale separation and the linear framework

evolutionary wars

1. why has evolutionary biology not answered the complexity question?

2. why do ridley and dawkins think they have answered it?

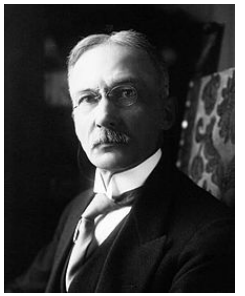
> *"At the heart of this exchange lie differences in perspective ... The skeptics probably represent the majority position: evolutionary processes are those that change gene frequencies. Advocates of NCT, in contrast, ... conceive of evolutionary processes more broadly, as anything that systematically biases the direction or rate of evolution. ... The skeptics among us embrace adaptationism, see natural selection as the ultimate source of organism-environment fit, have a gene-centered view of evolution ... NCT enthusiasts, in contrast are frequently sympathetic to a structuralist tradition that stems from developmental biology (e.g., Waddington 1959), which emphasizes not only constraints on adaptation but also the evolutionary significance of processes other than selection."*

conventional evolutionary thinking focusses only on the dynamical variables in population genetics – gene frequencies – and views the selection parameter as something which can be chosen at will, as justified by ecological selection, and lies outside the scope of theory.

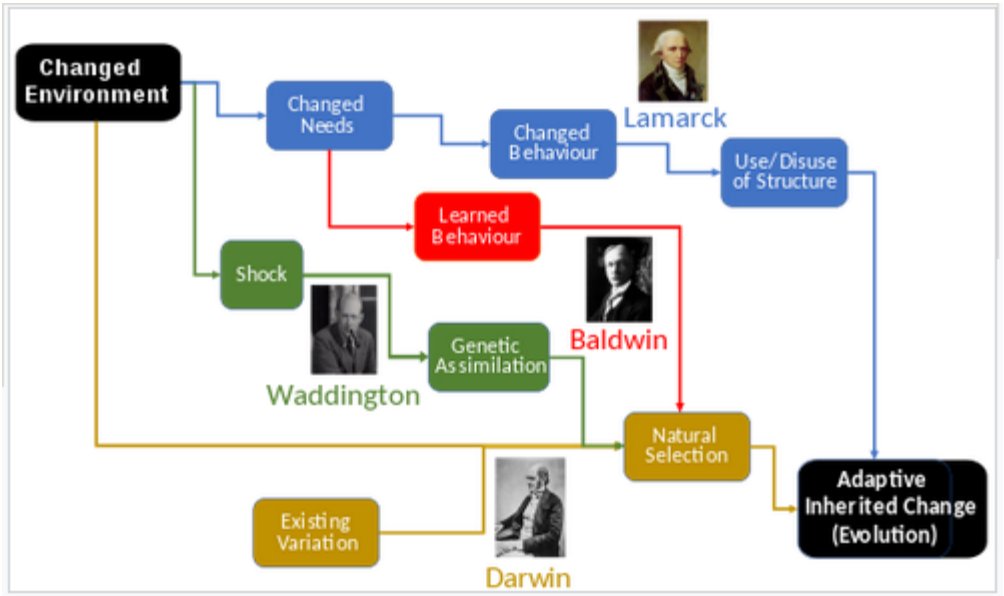
Scott-Phillips et al, "*The niche construction perspective: a critical apprasial*", Evolution **68**:1231-43 2013; Laland et al versus Wray et al, "*Does evolutionary theory need a rethink?*", Nature **514**:161-4 2014

the baldwin effect

individual organisms can learn how to cope with a changed environment and such learned behaviour can be passed on to offspring by education (non-genetically). the population can thereby survive the changes. this process creates a selection pressure in favour of organisms who can learn more efficiently. over time, the new behaviour can become genetically fixed.



1861-1934

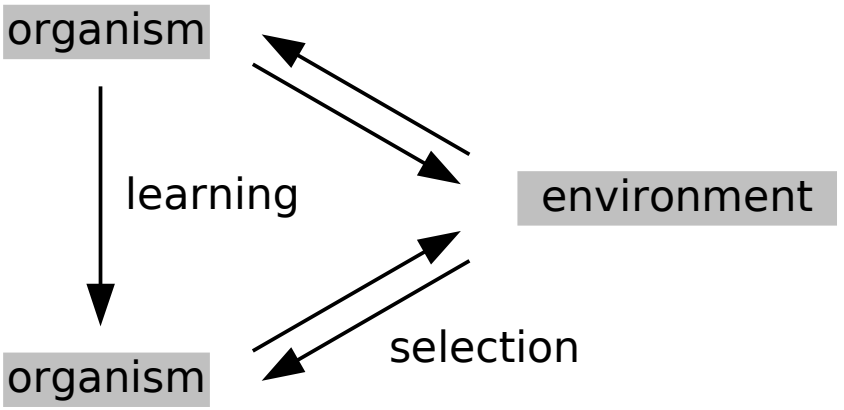


Baldwin, "*A new factor in evolution*", Amer Naturalist, **30**:441-51 1896

the organism as a learning agent

"Learning alters the shape of the search space in which evolution operates ... We demonstrate that this effect allows learning organisms to evolve much faster." (Hinton & Nowlan)

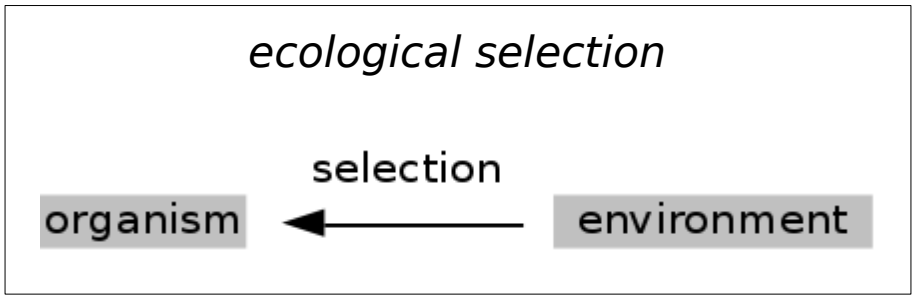
"Thanks to the Baldwin effect, species can be said to pretest the efficacy of particular different designs by phenotypic (individual) exploration of the space of nearby possibilities. If a particularly winning setting is thereby discovered, this discovery will create a new selection pressure: organisms that are closer in the adaptive landscape to that discovery will have a clear advantage over those more distant" (Daniel Dennett)

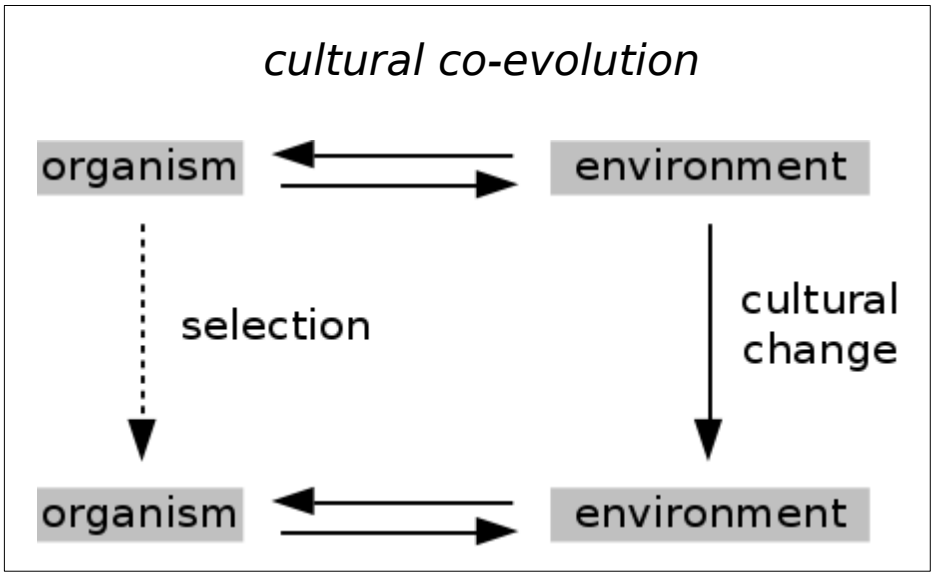


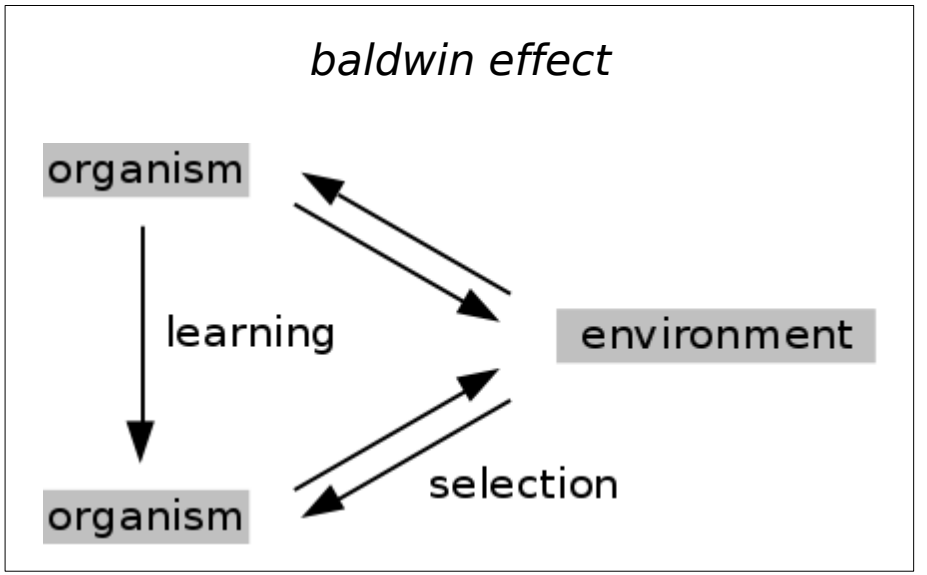
has been invoked (by Dennett and others) to understand human language evolution

Hinton, Nowlan, "*How learning can guide evolution*", Complex Systems, **1**:495-502 1987; Daniel Dennett, "*The Baldwin effect: a crane, not a skyhook*", in Weber & Depew, **Evolution and Learning: The Baldwin Effect Reconsidered**, MIT Press 2003; Hauser et al, "*The mystery of language evolution"*, Front Psychol **5**:401 2014.

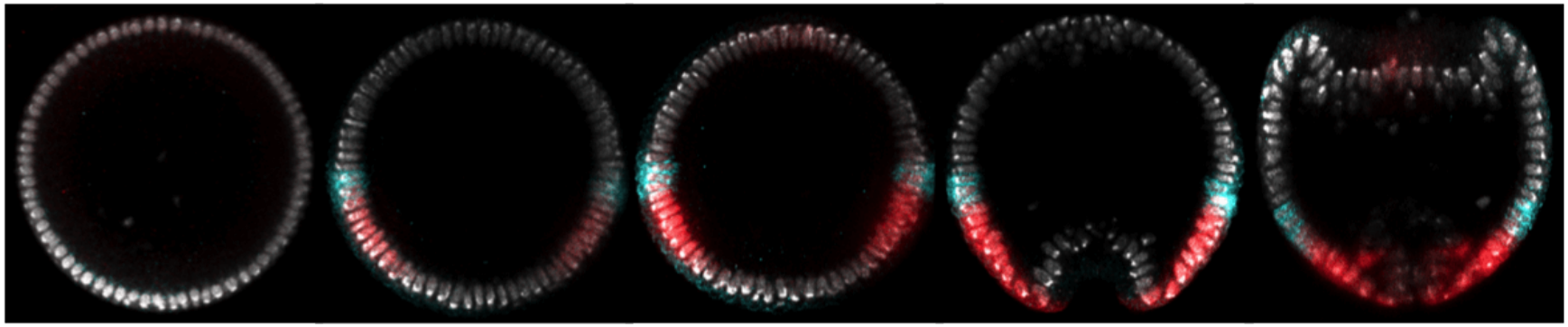
a taxonomy of natural selection





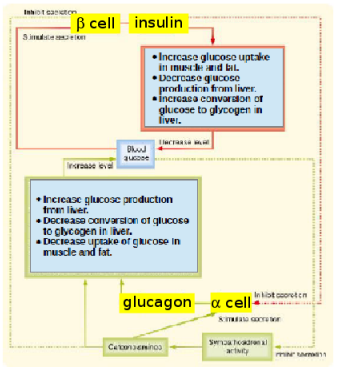


6. the missing biology - development

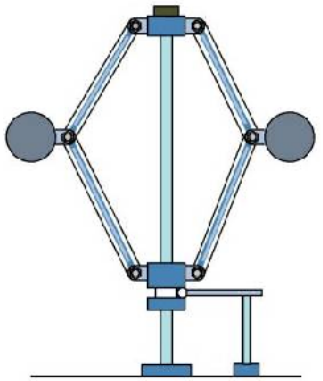


the mystery of organismal development

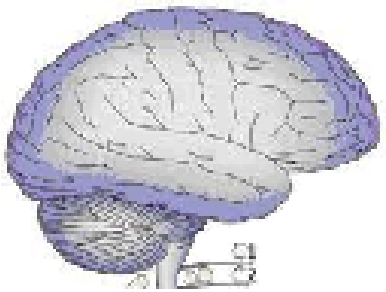
the development of the organism is a process of self-organisation for which we have no “machine analogy”



homeostasis

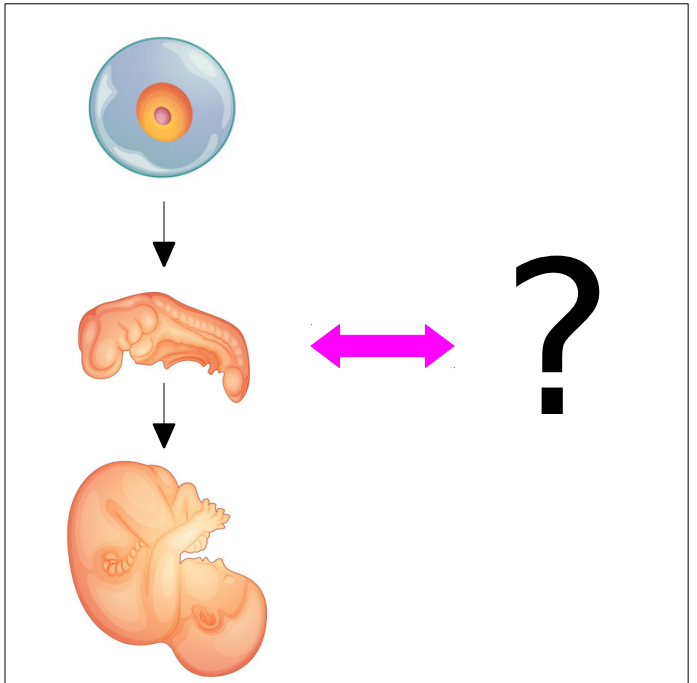


governor



brain

computer



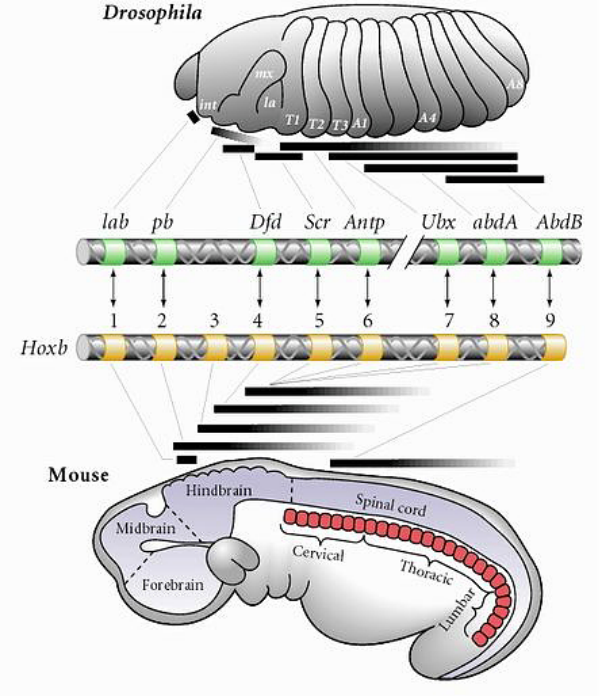
development

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

1904-2005



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 micro-evolutionary 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

Pigliucci, “*The proper role of population genetics in modern evolutionary theory*”, Biol Theory **3**:316-24 2009, tries to referee the fight

1. defining weak linkage

the evolution of complexity revisted

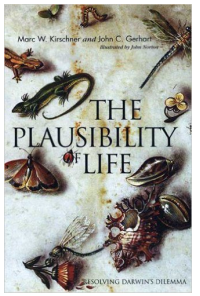
the evidence from developmental biology suggests, in contrast to population genetics, that the “black box” of the organism must have specific properties in order for selection to act and for complexity to evolve

1945 -

1938 -

weak linkage – biological processes can interact without having to know too much about each other ???

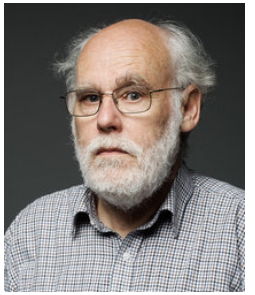
this facilitates “evolvability” by reducing constraints, increasing robustness and allowing the accumulation of genetic variation. evolvability may have been selected for during evolution.



Kirschner, Gerhart, “*Evolvability”,* PNAS **95**:8420-7 1998; Gerhart, KIrschner, “*The theory of facilitated variation*”, PNAS **104**:8582-9 2007; Kirschner, Gerhart, **The Plausibility of Life: Resolving Darwin's Dilemma**, Yale Univ Press 2005

mixed reception

"Until we have a predictive theory of developmental genetics, our understanding of the molecular basis of development sheds little light on what variation is potentially available for the use of selection. As a result, it is currently impossible to evaluate the idea that developmental systems have special properties that facilitate variation useful for evolution"



1945 -

Brian Charlesworth, "*On the origins of novelty and variation*", Science, **310**:1619-20 2005, book review of Kirschner, Gerhart, **The Plausibility of Life**

but kirschner & gerhart did not discuss an important problem – **how did weak linkage evolve?** - which resulted in a friendlier reception elsewhere ...

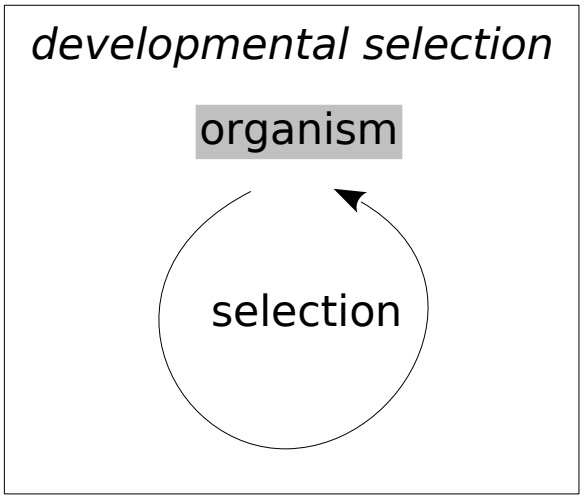
"The question of origin becomes especially acute under this new theory because the conserved core processes and the modular regulatory mechanisms have to already be in place before any evolution can occur. The new molecular evidence shows virtually all the main components of neo-Darwinian theory are wrong."

Alex Williams, "*Facilitated variation: a new paradigm in biology*", J Creation **22**:85-92 2008. available at https://creation.com/images/pdfs/tj/j22_1/j22_1_85-92.pdf

towards an answer to our scientific question

3**. how can complex functionality like the eye emerge in nature?**

weak linkage can be reinterpreted to show how selection can arise from within the organism, during the course of development.



there is evidence that these types of weak linkage are used during the development of structures like the eye and this may help to account for the evolution of complexity

defining “weak linkage”

a weak linkage mechanism is one that permits scalable integration of many inputs in to one, or many, outputs

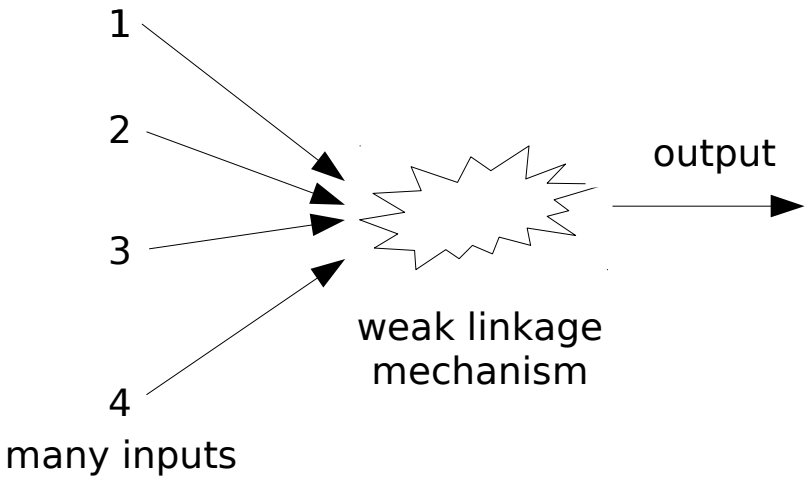
what does “scalable” mean?

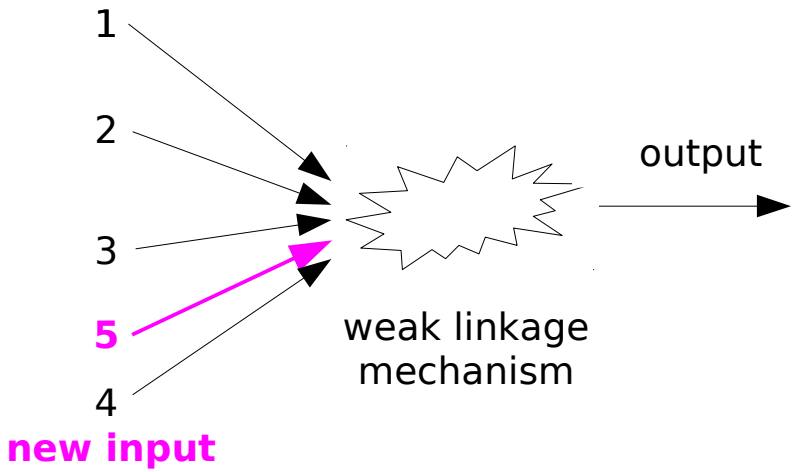
- accommodating new inputs
- accommodating changes to existing inputs

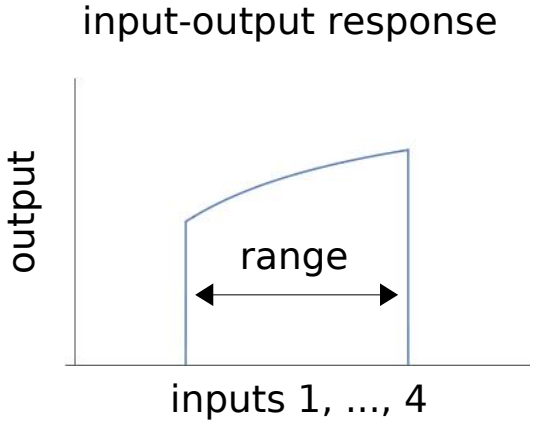
without disturbing (too much) the existing input-output relationship

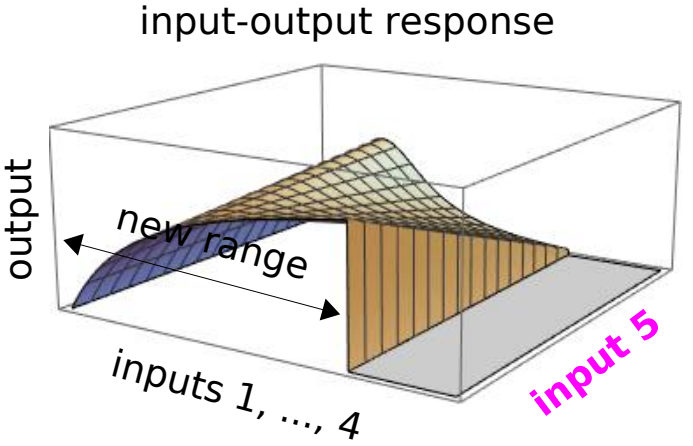
NOTE: not all the mechanisms considered by kirschner & gerhart to be “weak linkage” satisfy this definition

scalable integration

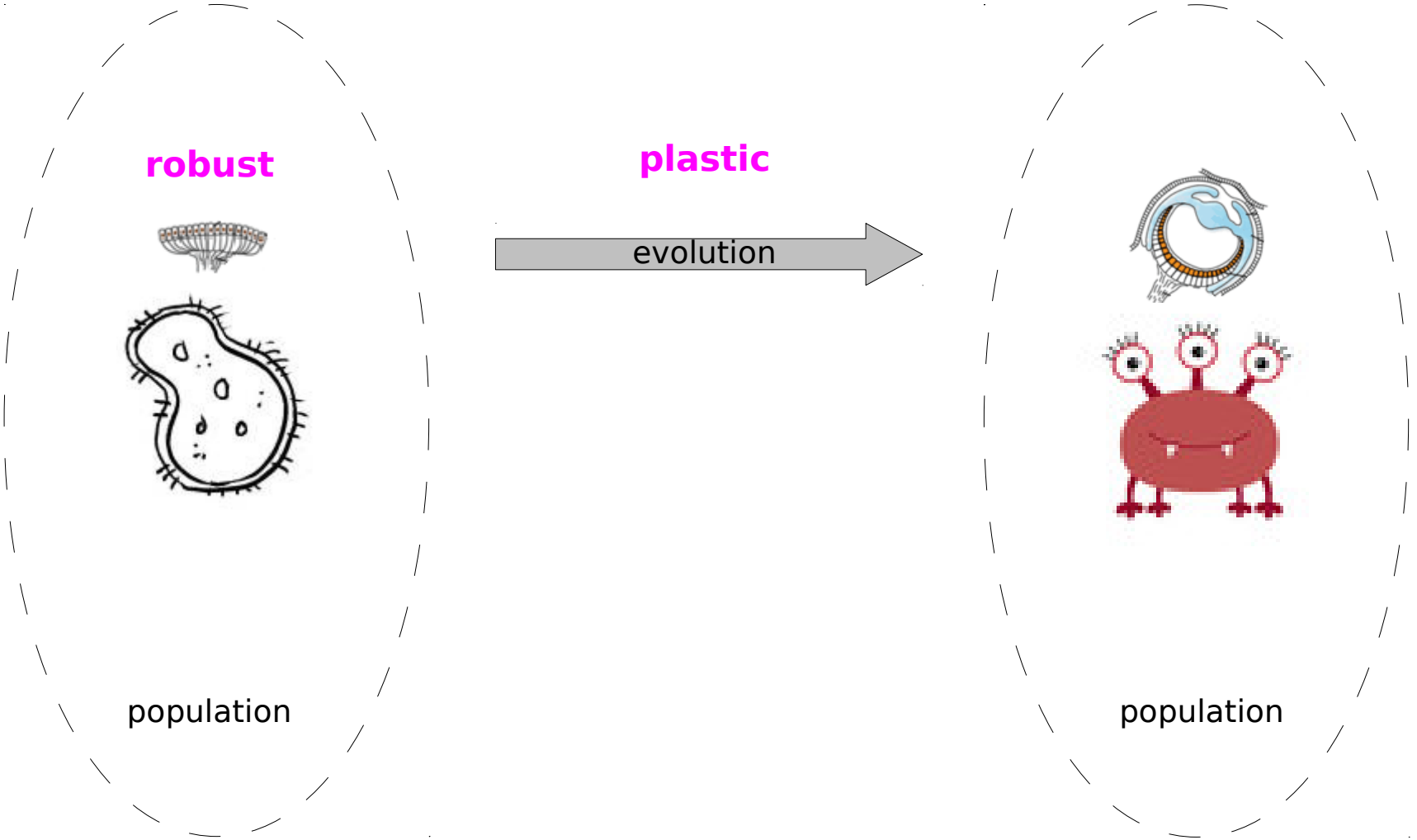








scalability allows neutrality

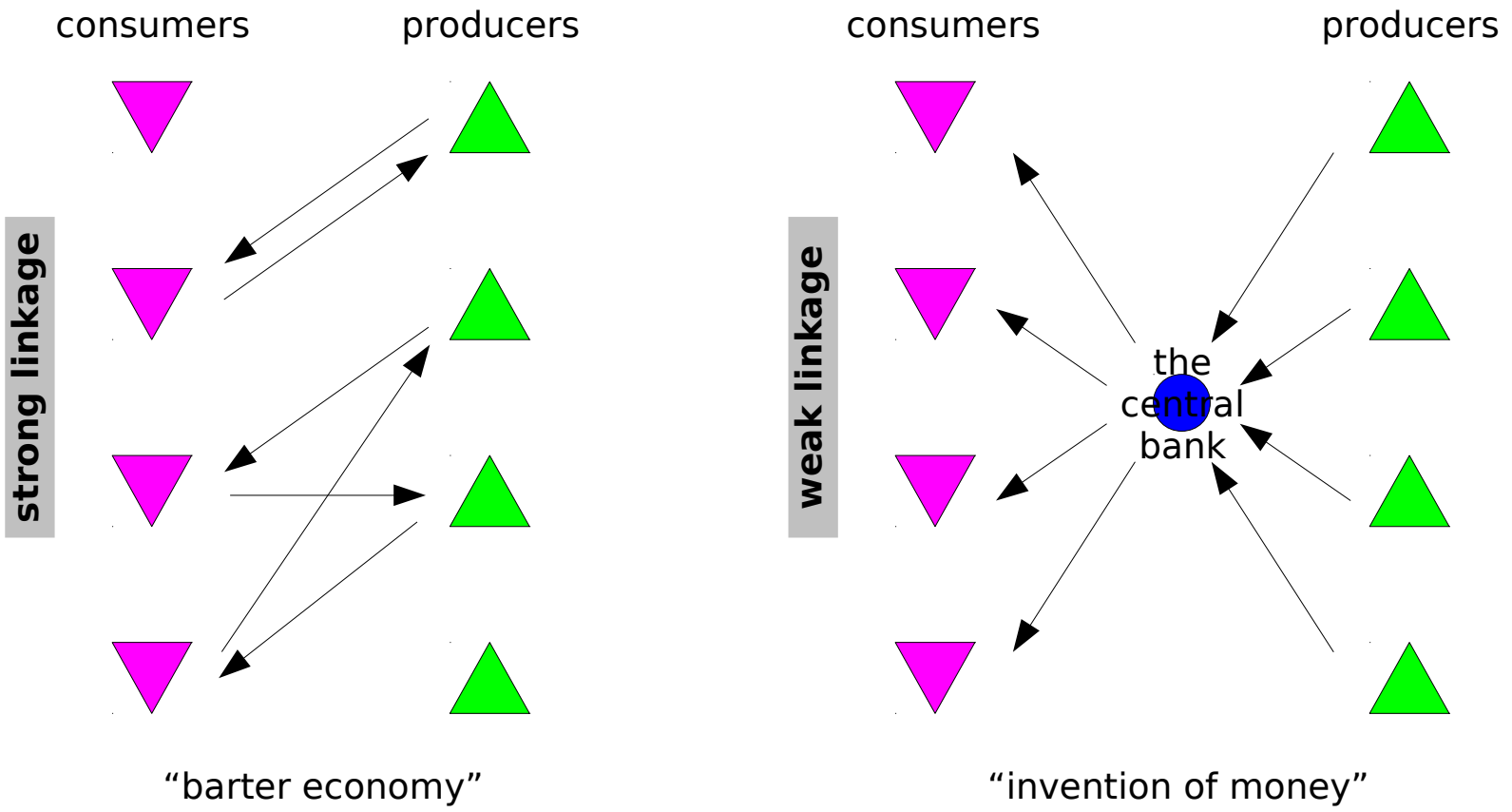


changes are accommodated without disturbing existing function. there is no selective disadvantage (but there may not be a selective advantage – for this, more is needed, as we will see later).

2. examples of weak linkage

ATP = money

the metabolic economy runs on energy



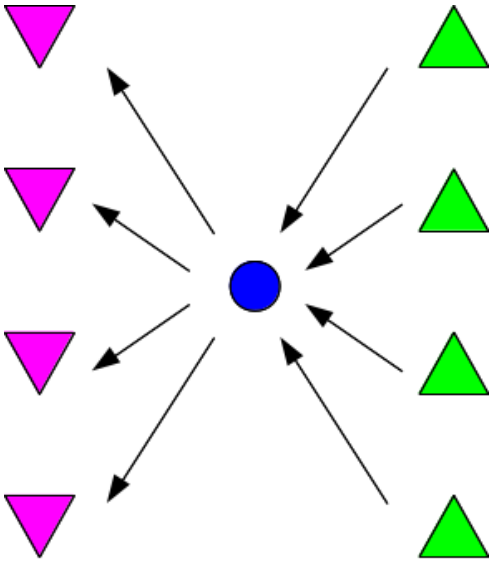
“barter economy”

“invention of money”

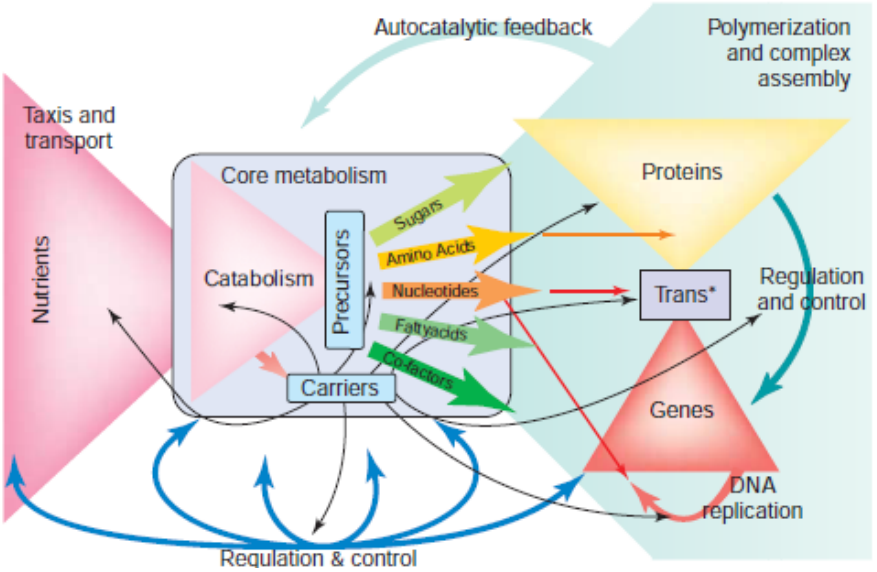
bow tie architectures

weak-linkage mechanisms which inter-connect many inputs to many outputs have a characteristic “bow-tie” architecture

bow-tie structure



“fan-out” “fan-in”

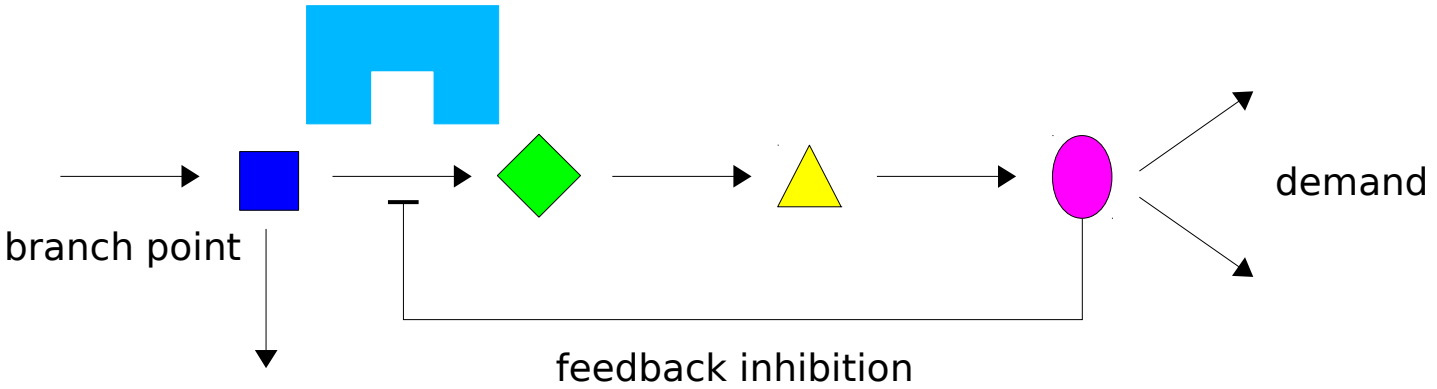


john doyle has argued that these architectures exhibit special properties of robustness and are widely found in complex systems.

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

enzyme regulation

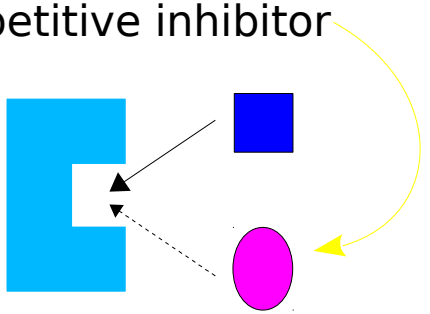
the enzyme catalysing the first committed step in a biosynthetic pathway is usually inhibited by the terminal metabolite in the pathway



Pardee, Yates, J Biol Chem **221**:757-70 1956; Umbarger, Science **123**:848 1956

but the terminal metabolite is structurally very different from the enzyme's substrate and binds the enzyme far from the catalytic site, unlike a competitive inhibitor

how is information conveyed from a distal inhibitor site to the catalytic site?

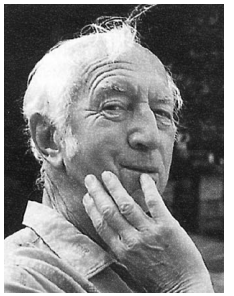


strong linkage

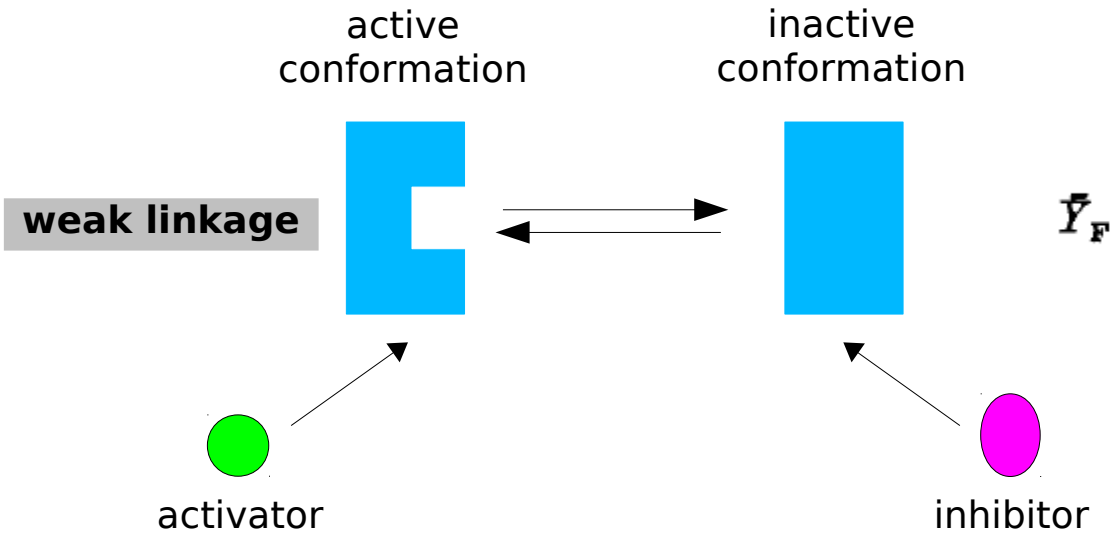
protein allostery

the enzyme exists in two conformations which differ in their catalytic efficiency. inhibitors bind preferentially to any site in the inactive conformation. activators bind preferentially to any site in the active conformation


1910 - 1976


1901 - 1995


1936 -



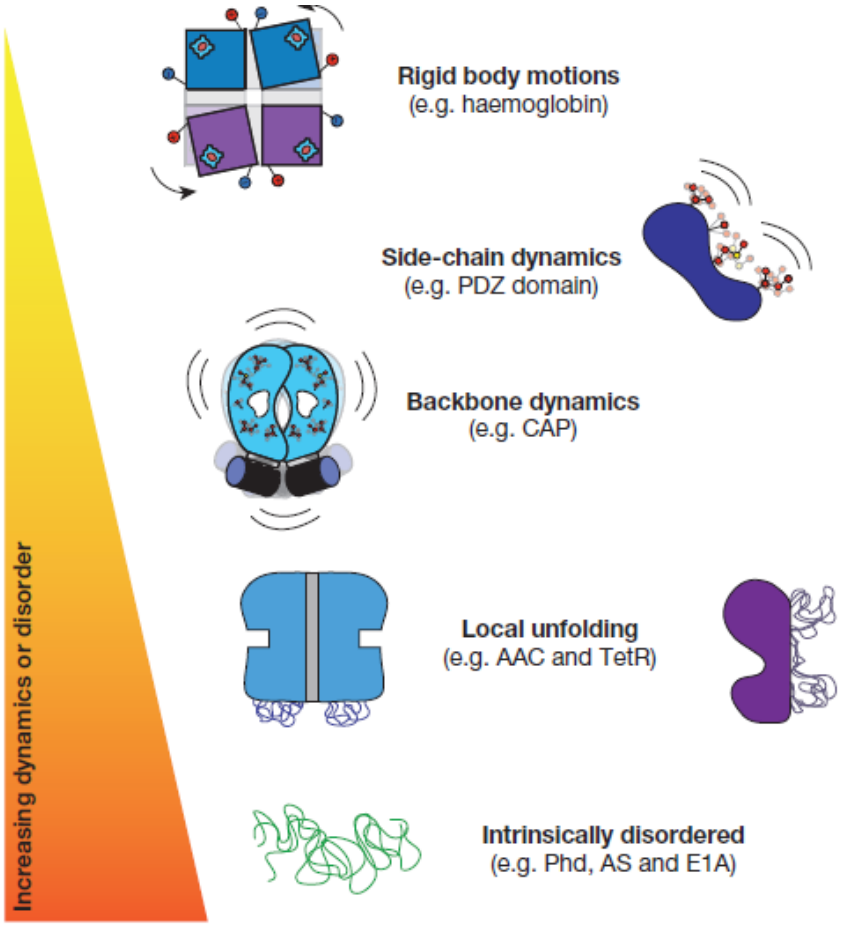
$$\bar{Y}_F = \frac{Lc\alpha(1+c\alpha)^{n-1} + \alpha(1+\alpha)^{n-1}}{L(1+c\alpha)^n + (1+\alpha)^n}$$

MWC formula

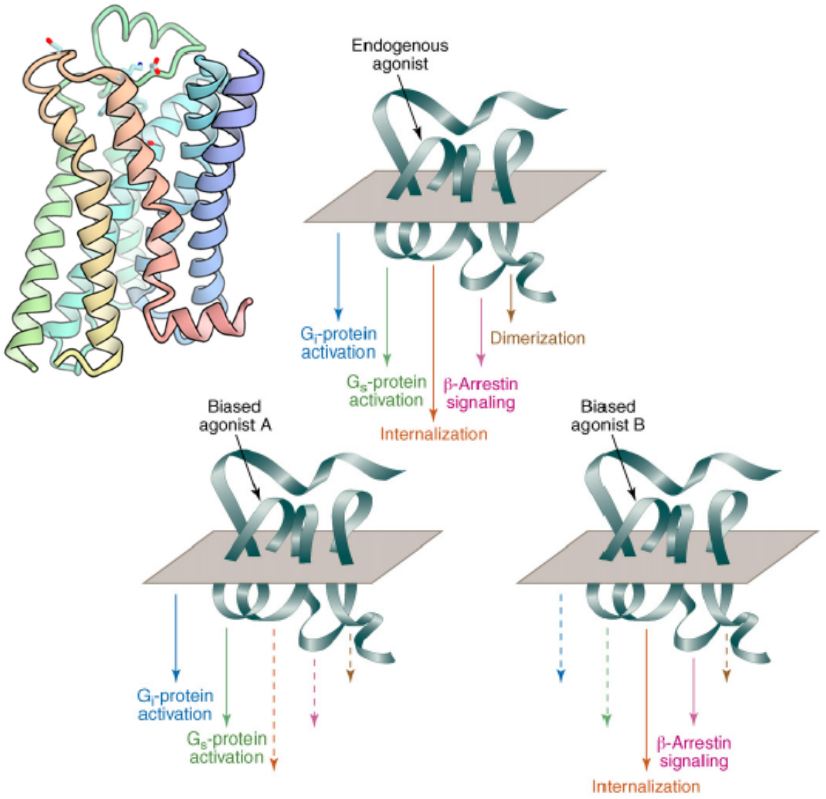
"the second secret of life"

Monod, Wyman, Changeux, "*On the nature of allosteric transitions: a plausible model*", J Mol Biol **12**:88-118 1965; Agnes Ullmann, "*In memoriam: Jacques Monod (1910 - 1976)*", Genome Biol Evol **3**:1025-33 2011

allostery everywhere



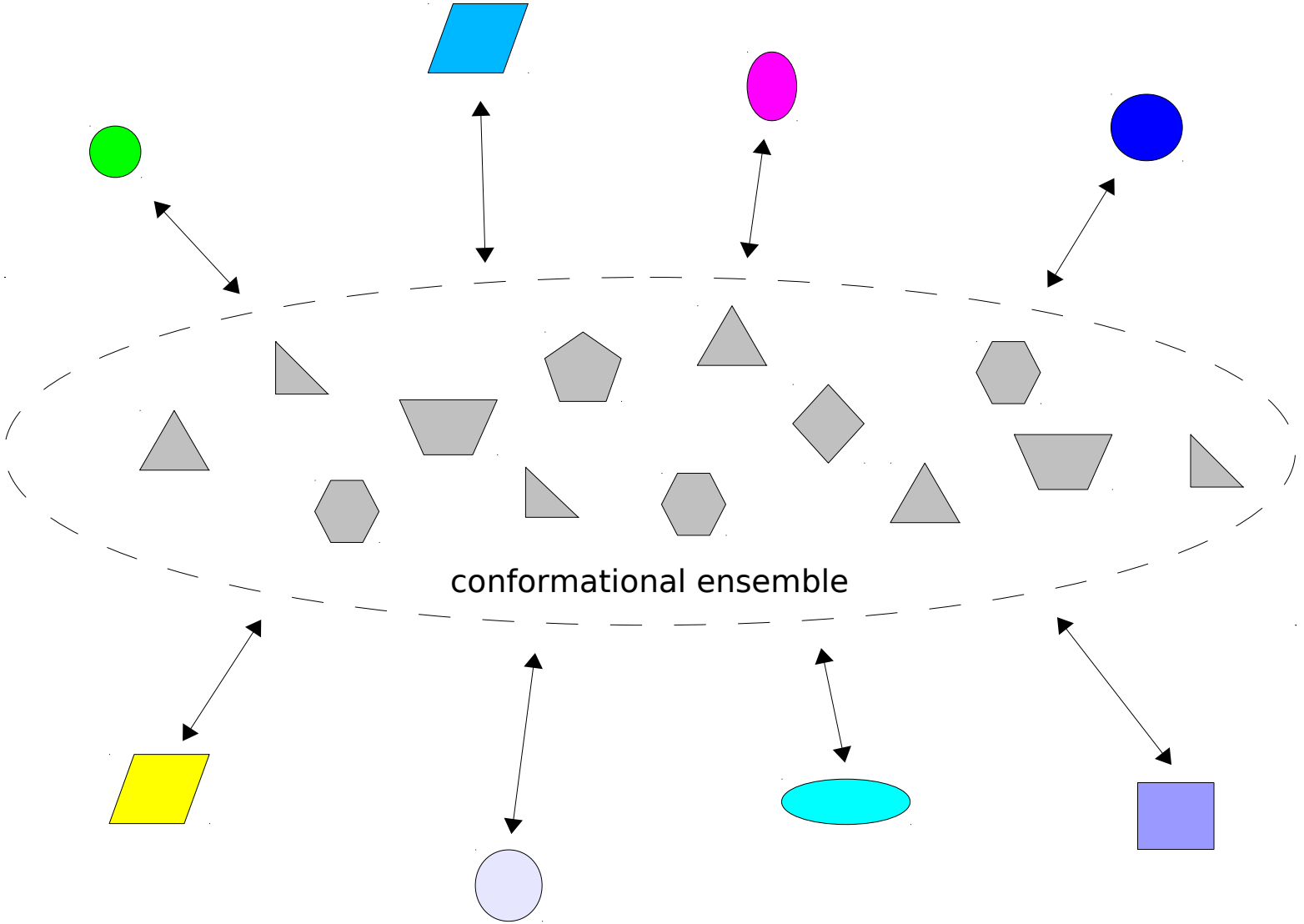
G-protein coupled receptors



“biased agonism” or “collateral efficacy” or “functional selectivity”

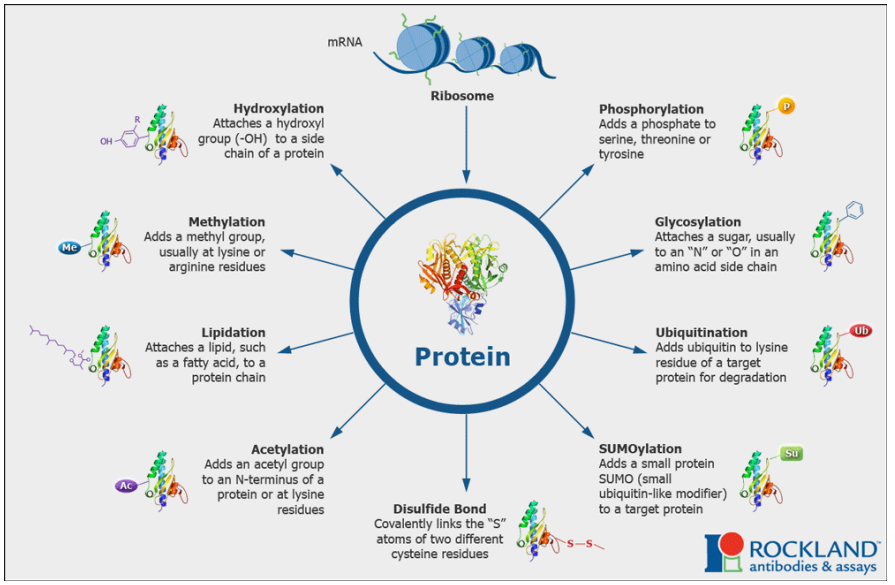
Motlagh, Wrabl, Li, Hilser, Nature **508**:331-9 2014; Nussinov, Tsai, Ma, Annu Rev Biophys **42**:169-89 2013; Kenakin, Trends Pharmacol Sci 28:407-15 2007.

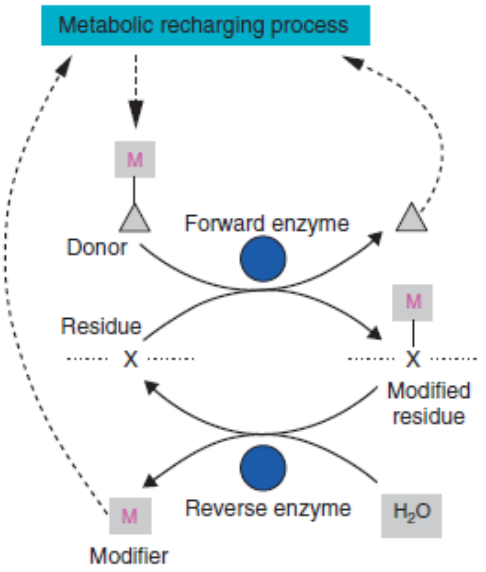
scalable many-to-many integration



post-translational modification (PTM)

enzymatic covalent modification of amino-acid residues by small molecule (eg: phosphate) or polypeptide (eg: ubiquitin) moieties

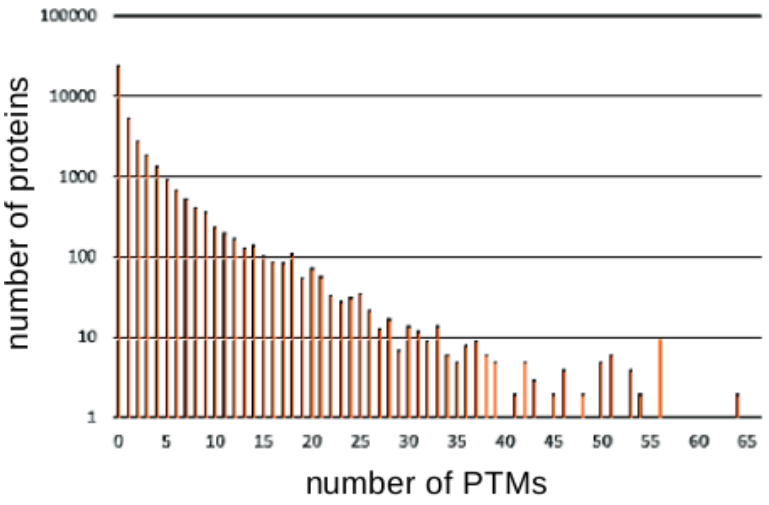




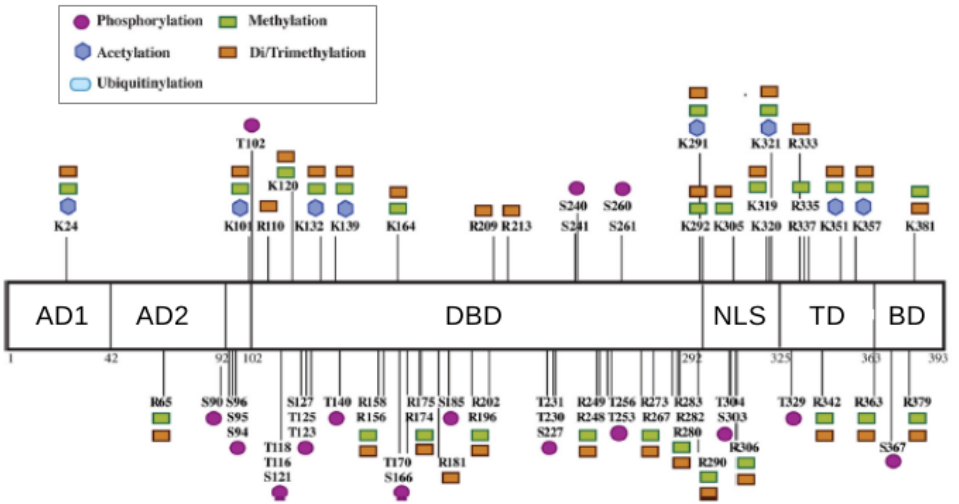
the process of modification and demodification is dissipative – it consumes free energy, which must be continuously supplied by background biochemical processes

enhanced input-output functionality can be achieved by energy expenditure

PTMs are also everywhere



~20,000 human SwissProt entries

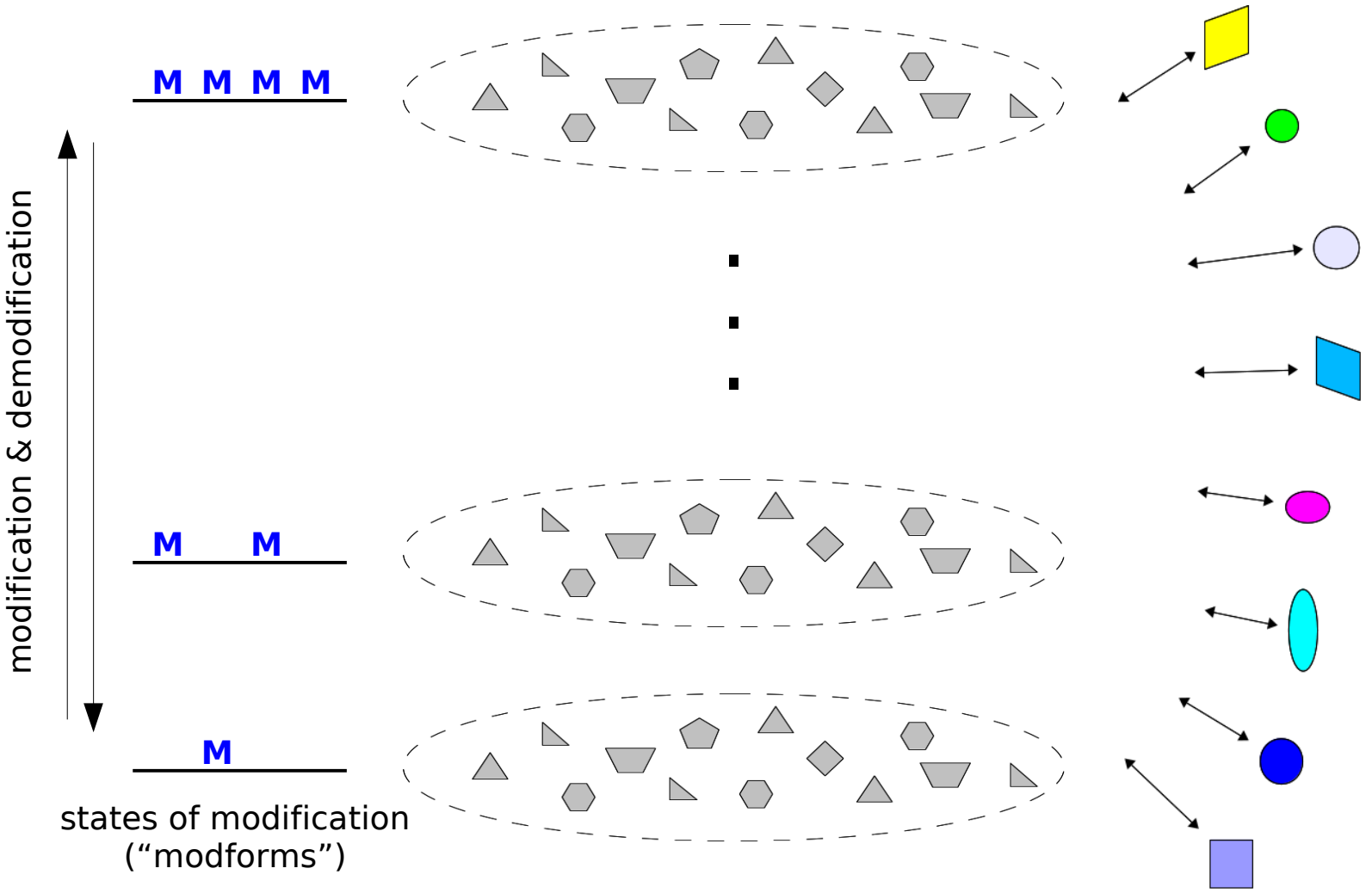


tumour suppressor p53
(over 100 sites of modification)

Compton, Kelleher, Gunawardena, "*Estimating the distribution of protein post-translational modification states by mass spectrometry*", J Proteome Res, to appear

scalable many-to-many integration

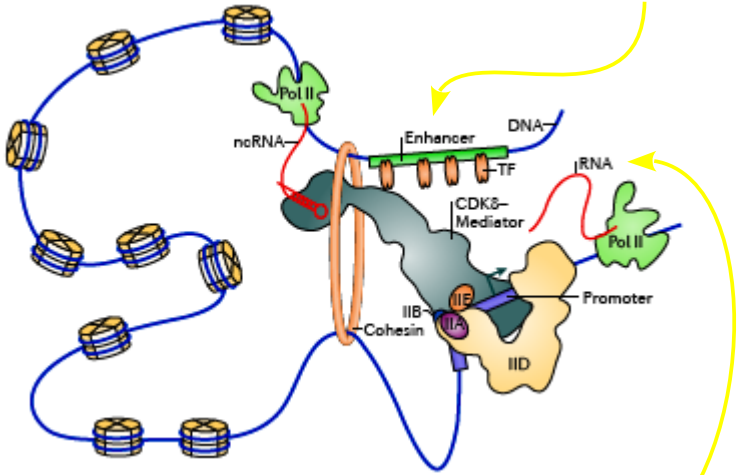
PTM create an enlarged conformational ensemble



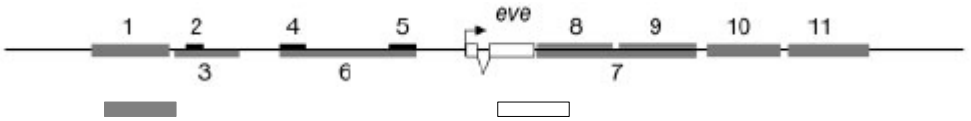
3. the gene-neuron analogy

genes & neurons – scalable many-to-one integration

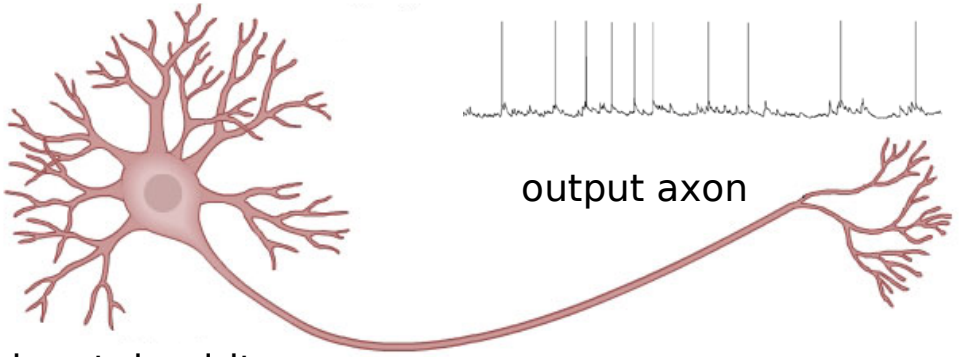
input transcription factor (TF)
binding at enhancers



output mRNA
production

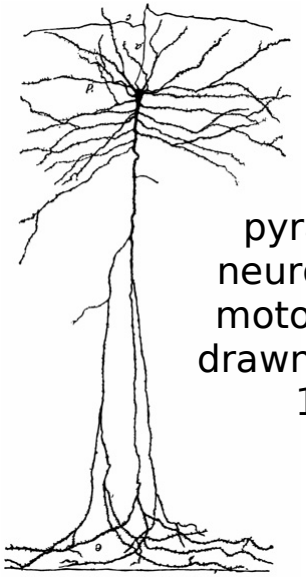


regulatory region exon



output axon

input dendrites

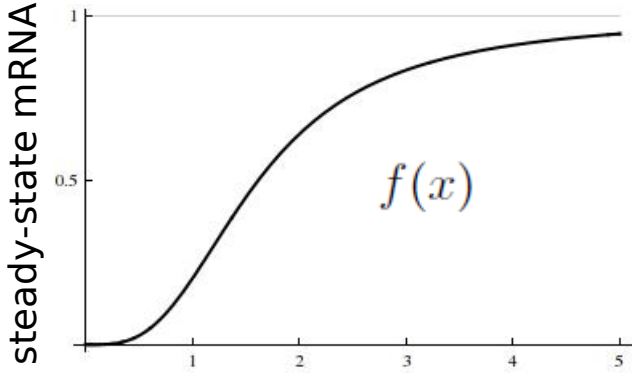


pyramidial
neuron in the
motor cortex,
drawn by Cajal,
1900

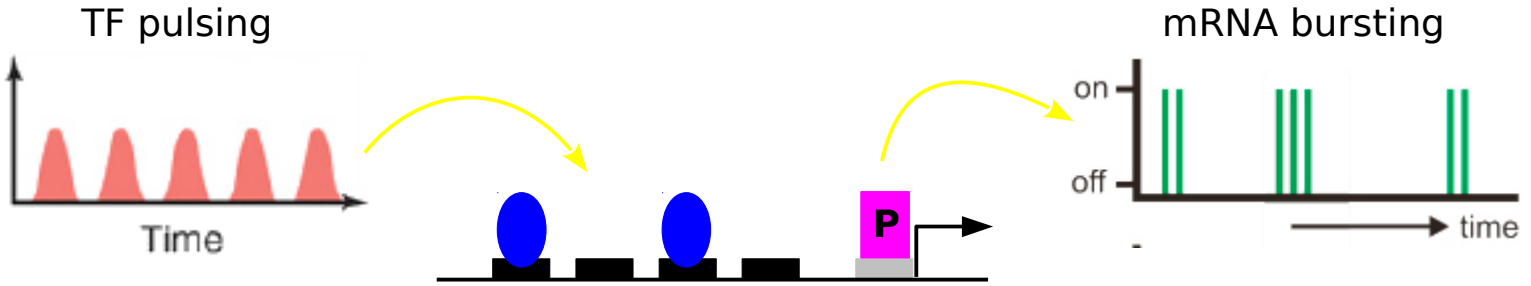
Wray et al, Mol Biol Evoll **20**:1377-419 2003

genetic information is also time-varying

genetic input-output is usually analysed at steady state

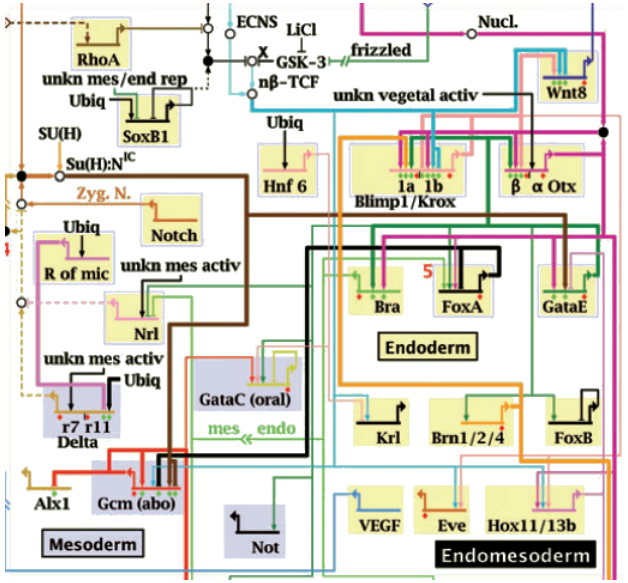


but both inputs and outputs may be time varying

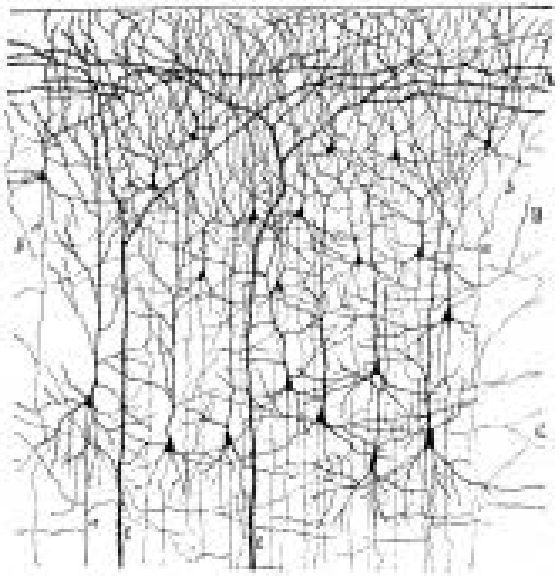


Purvis, Lahav, "*Encoding and decoding cellular information through signaling dynamics*", Cell **152**:945-56 2013

networks – scalable many-to-many integration



gene regulatory network
for endomesoderm
development in sea urchin



neuronal network in
the cerebral cortex,
drawn by Cajal

de Leon, Davidson, "*Gene regulation: gene control network in development*", Annu Rev Biophys Biomol Struct **36**:191-212 2007

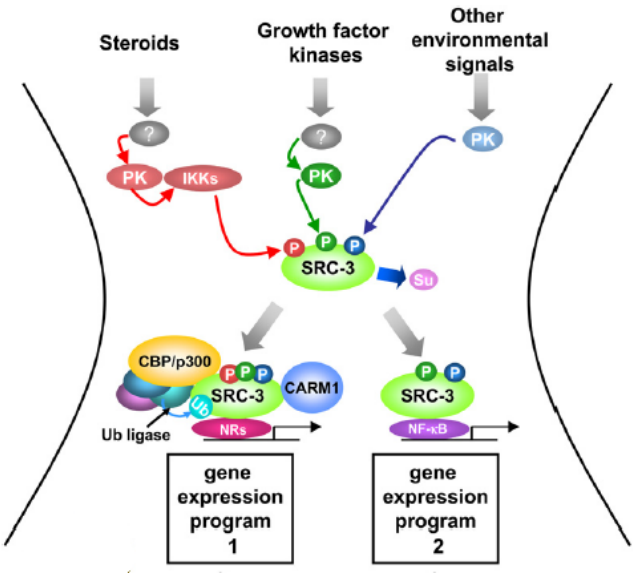
the weak linkage hierarchy

neurons are implemented by gene regulatory networks

gene regulation is implemented by allostery and PTM

PTM is implemented on top of conformational ensembles

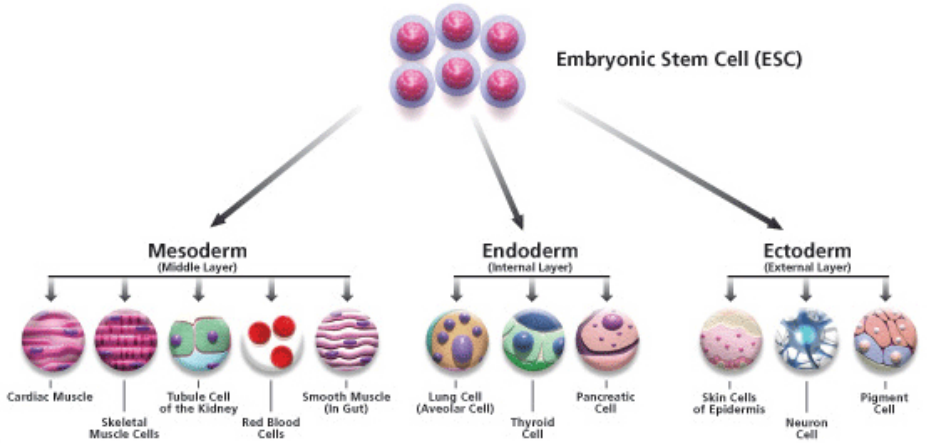
PTM is implemented by ATP and other cellular “currencies”

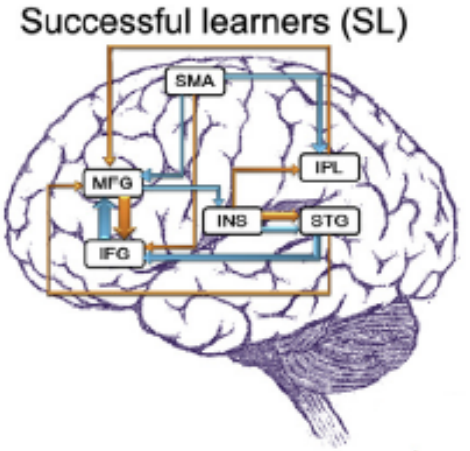


Lonard, O'Malley, *“Nuclear receptor co-regulators: judges, juries and executioners of cellular regulation”*, Development **128**:617-29 2001

4. learning and positive selection

gene & neuronal networks can learn



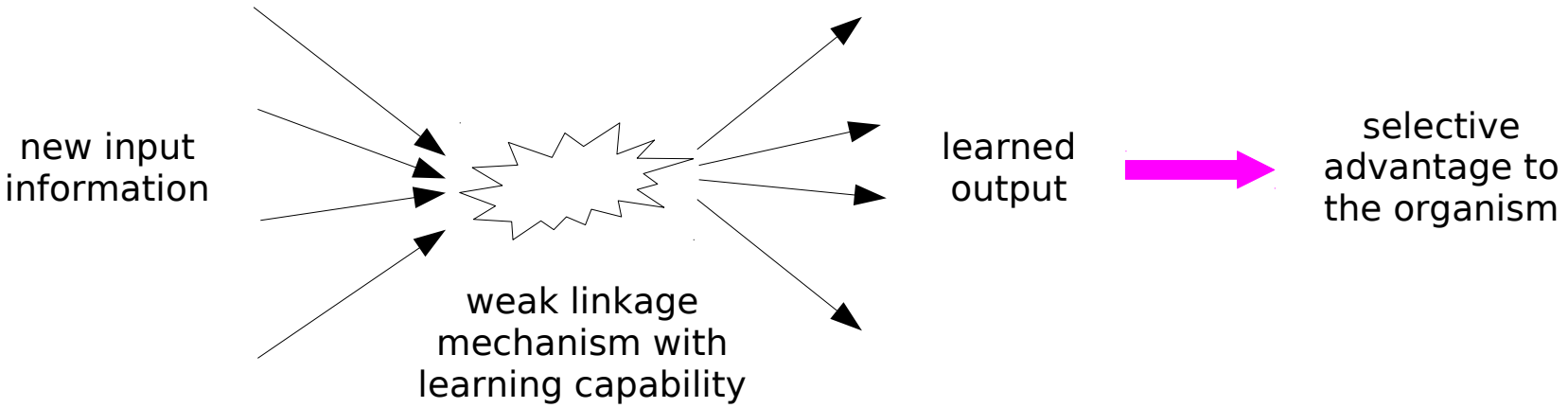


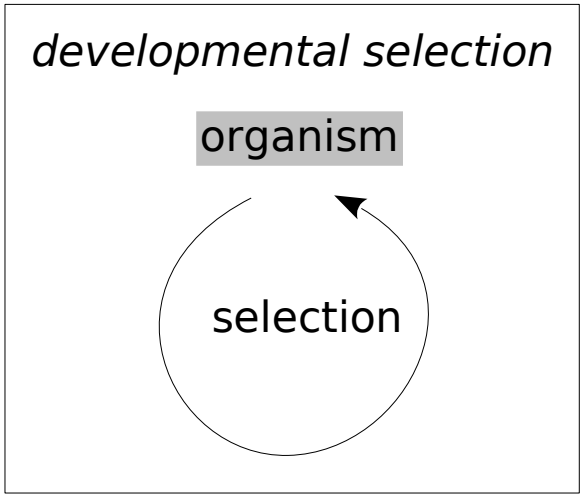
cell identity is learned during development and inherited by progenitor cells. the identity information is represented primarily by the gene regulatory network

learning in the brain is thought to be implemented hierarchically by (epigenetic) changes to gene regulatory networks in neurons

Yang, Gates, Molenaar, Li, *"Neural changes underlying successful second language word learning"*, J Neurolinguistics **33**:29-49 2015; Day, Sweatt, "*Epigenetic mechanisms in cognition*", Neuron **70**:813-29 2011

learning allows positive selection



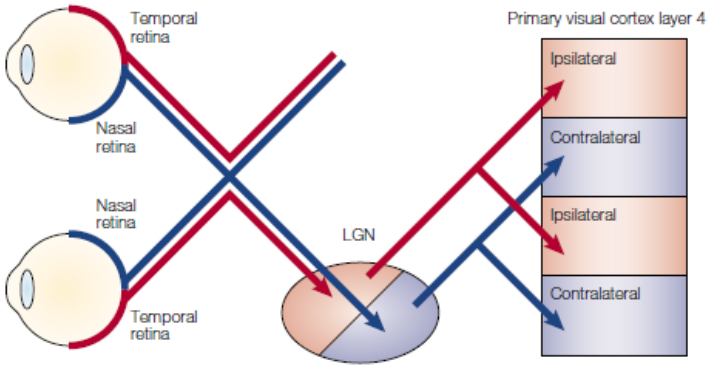


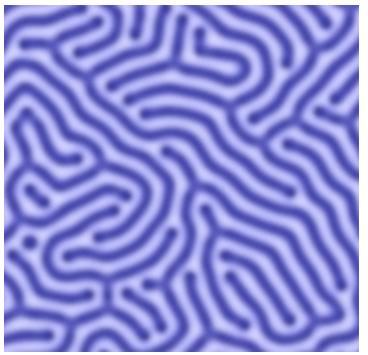
visual learning during a critical period

organisms exhibit “critical windows” during post-natal development, in which certain behaviours are learned with high efficiency (eg: language in humans).

hubel & wiesel showed that critical windows also occur in the development of the brain itself. ocular dominance columns in the visual system of the cat are disrupted by monocular deprivation during the first months of life.

1926 - 2013 1924 -





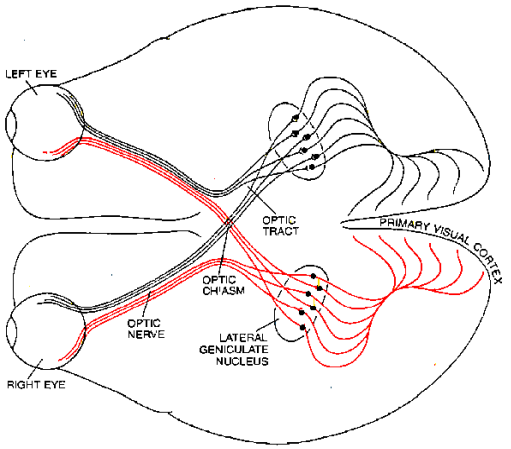
simulated pattern of ocular dominance

“With maturation of the sense organs, the developing brain relies ... increasingly on sensory experience”

Katz, Crowley, *“Development of cortical circuits: lessons from ocular dominance columns”*, Nat Rev Neuro **3**:34-42 2002; Katz, Shatz, “*Synaptic activity and the construction of cortical circuits*”, Science **274**:1133-8 1996

and, finally, back to where we started

3. **how can complex functionality like the eye emerge in nature?**



an improvement to the eye, arising from a novel mutation, sends new information to the brain along the eye-brain neuronal network.

this network exhibits weak linkage, thereby accommodating the new information without breaking, or otherwise imposing a selective disadvantage on the organism.

but the network can also learn, perhaps during a critical period, to correlating the new information against memories and actions

this gives the organism a positive selective advantage, allowing the eye mutation to become fixed in the population and complexity to evolve.