# *six lectures on systems biology*

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lecture 6
14 april 2011

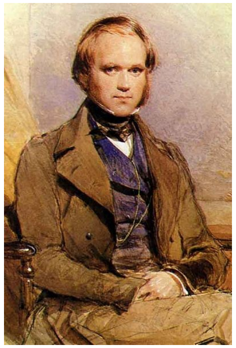
part 2 seminar room, department of genetics

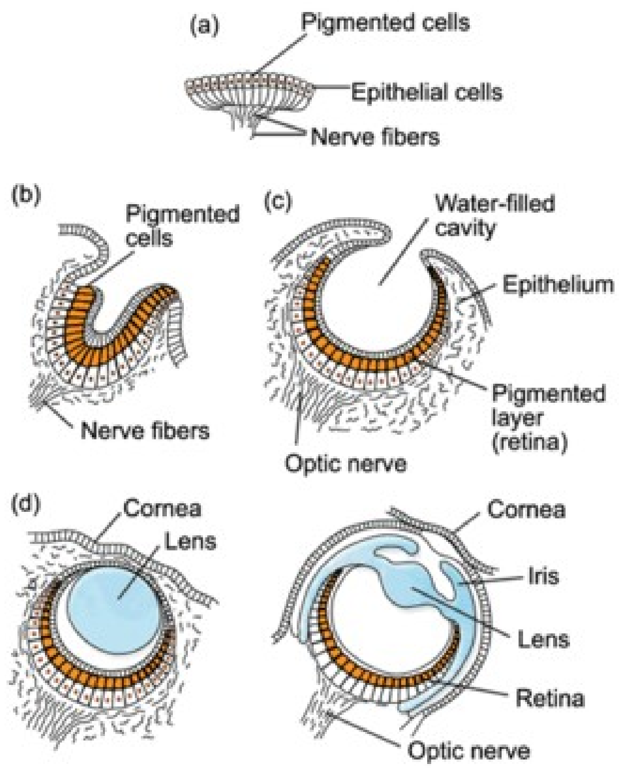
## a rather provisional syllabus

0. why mathematical models?
1. post-translational modification of proteins
2. microscopic cybernetics
3. modularity and evolution

# the evolution of complexity

*how can complex functionality emerge in nature?*






*“With these facts, here far too briefly and imperfectly given, which show that there is much graduated diversity in the eyes of living crustaceans, and bearing in mind how small the number of living animals is in proportion to those which have become extinct, 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.”*

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

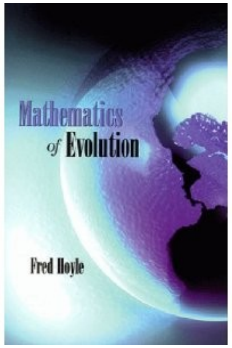
# the complexity of evolution

we do not perceive with our eyes but with our brains

to use a better eye seems to need a better brain

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

*"The chance that higher life forms might have emerged in this way is comparable to the chance that a tornado sweeping through a junkyard might assemble a Boeing 747 from the materials therein."*



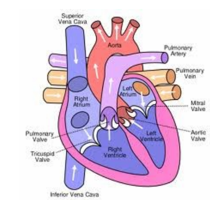

Fred Hoyle, **Mathematics of Evolution**, Acorn Enterprises 1999

# the neo-darwinian viewpoint

*"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."*

**genotype/phenotype relationship**

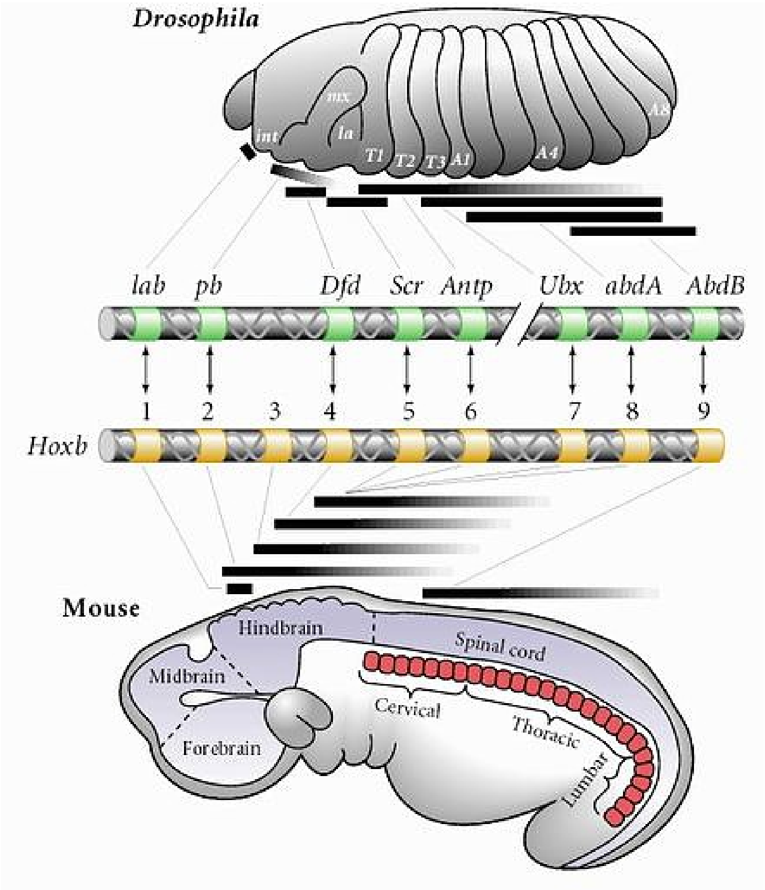
genes →  → 




fitness is simply assumed to arise. how it does so through development and physiology is not considered relevant

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

# is spectacularly wrong




there is deep conservation of certain genes and their protein functions between evolutionarily distant organisms

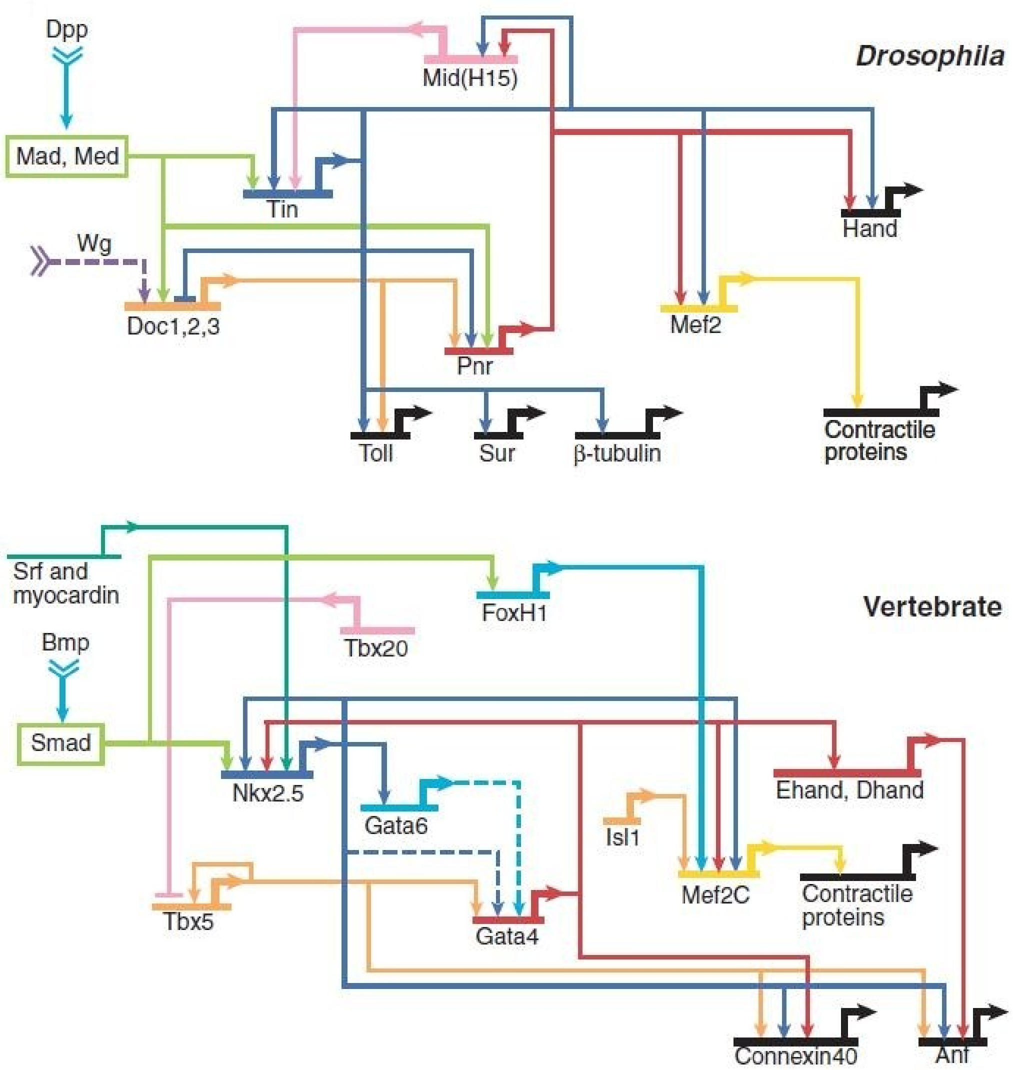
Lutz, Lu, Eichele, Miller, Kaufman, "*Rescue of Drosophila labial null mutant by the chicken ortholog Hoxb-1 demonstrates that the function of Hox genes is phylogenetically conserved*", Genes & Dev **10**:176-84 1996

# conserved core processes

| First arose in evolution | Conserved functional components and processes |
|---|---|
| Three billion years ago, in early prokaryotic organisms | Components of energy metabolism, biosynthesis of the 60 building blocks, DNA replication, DNA transcription to RNA, translation of RNA to protein, lipid membrane synthesis, transmembrane transport |
| Two billion years ago, in early eukaryotic cells | Components of the formation of microfilament and microtubule cytoskeletons, motor proteins moving materials along the cytoskeletons, contractility processes, movement of the cell by cilia and ruffling membrane action, shuttling of materials between intracellular organelles, phagocytosis, secretion, chromosome dynamics, a complex cell cycle driven by protein kinases and protein degradation, sexual reproduction with meiosis and cell fusion |
| One billion years ago, in early multicellular animal life forms | Components of 15–20 cell–cell signaling pathways, cell adhesion processes, apical basal polarization of cells, junction formation, epithelium formation, specialization of cells toward physiological ends, some developmental processes of the single-celled egg to the multicellular adult |
| Near pre-Cambrian, in animals with early body axes | Components of complex developmental patterning, such as anteroposterior axis formation (Wnt/Wnt antagonist gradients) and dorsoventral axis formation (Bmp/antagonist gradients), inductions, complex cell competence, additional specialized cell types, formation of the body plan's map of selector gene compartments (both transcription factors and signaling proteins), various regulatory processes |

John Gerhart & Marc Kirschner, "*The theory of facilitated variation*", PNAS **104**:8582-9 2007

# conserved core processes

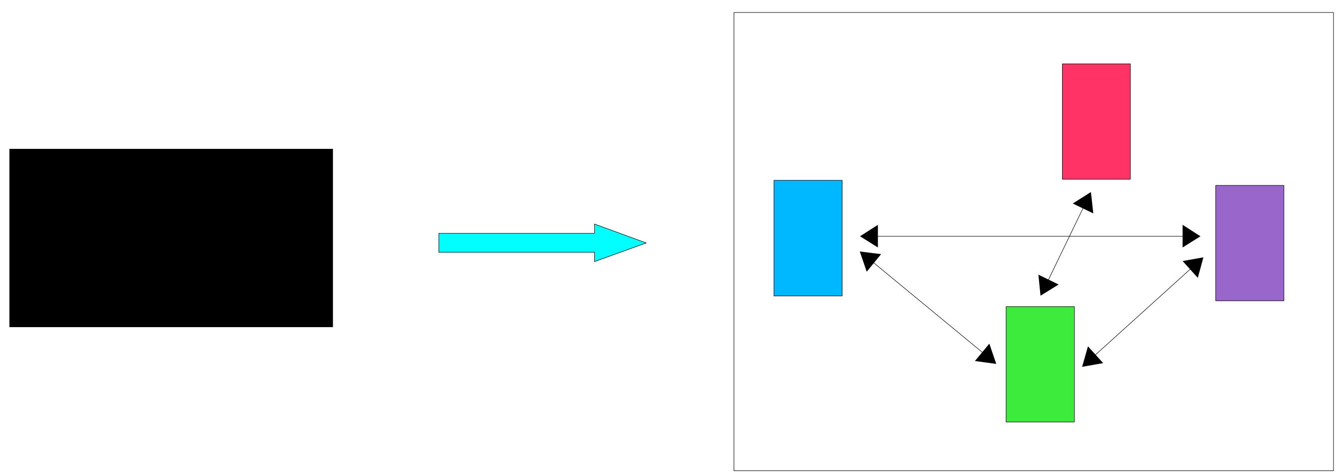



putative kernel network
for heart specification

Eric Davidson, Douglas Erwin, “*Gene regulatory networks and the evolution of animal body plans*”, Science **311**:796-800 2006

# modularity in biology

evolutionary diversification (at least in animals) arises from the reuse and reorganisation of existing core modules



modularity is necessary for evolvability

# but what is a module?

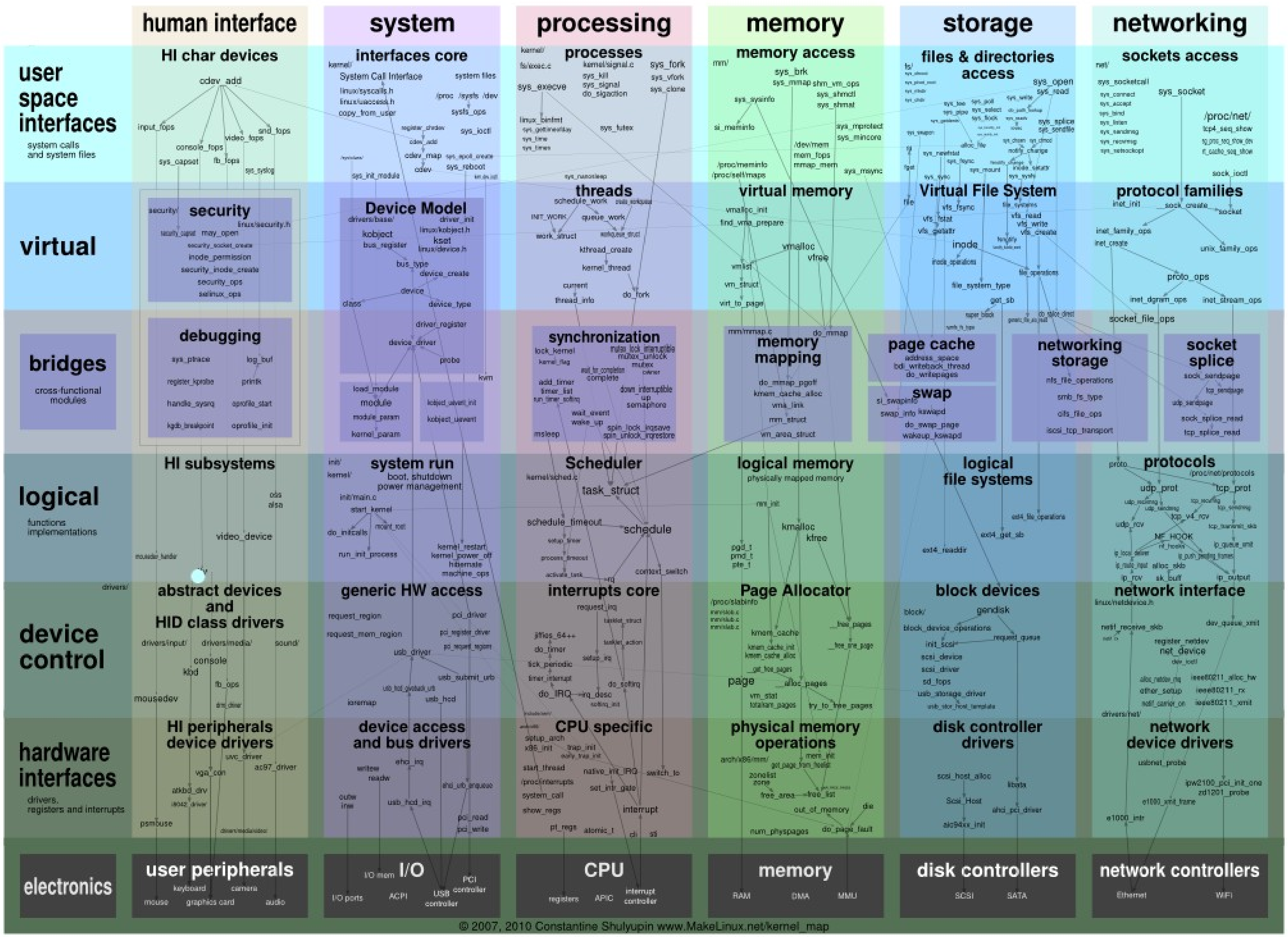
| | |
|---|---|
| a process, or set of components, that shows conservation between distinct organisms | MAP kinase cascade |
| a statistically over-represented sub-graph (motif) | feed-forward loop |
| a sub-graph that is more strongly connected internally than externally | ribosomes ? |

Alon, “*Network motifs: theory and experimental approaches*”, Nature Rev Genetics, **8**:450-61 2007

Wagner, Pavlicev, Cheverud, “*The road to modularity*”, Nature Rev Genetics, **8**:921-31 2007

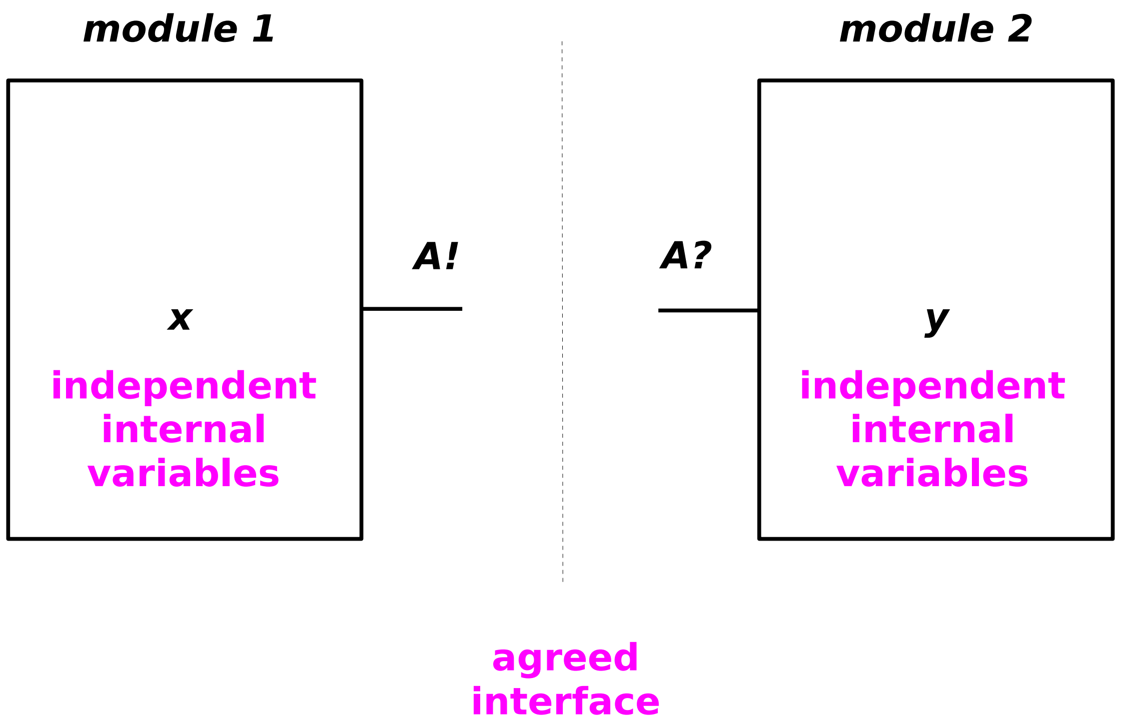
# modularity in engineering

linux OS – 15,000,000 lines of communally developed code



# modularity in engineering

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

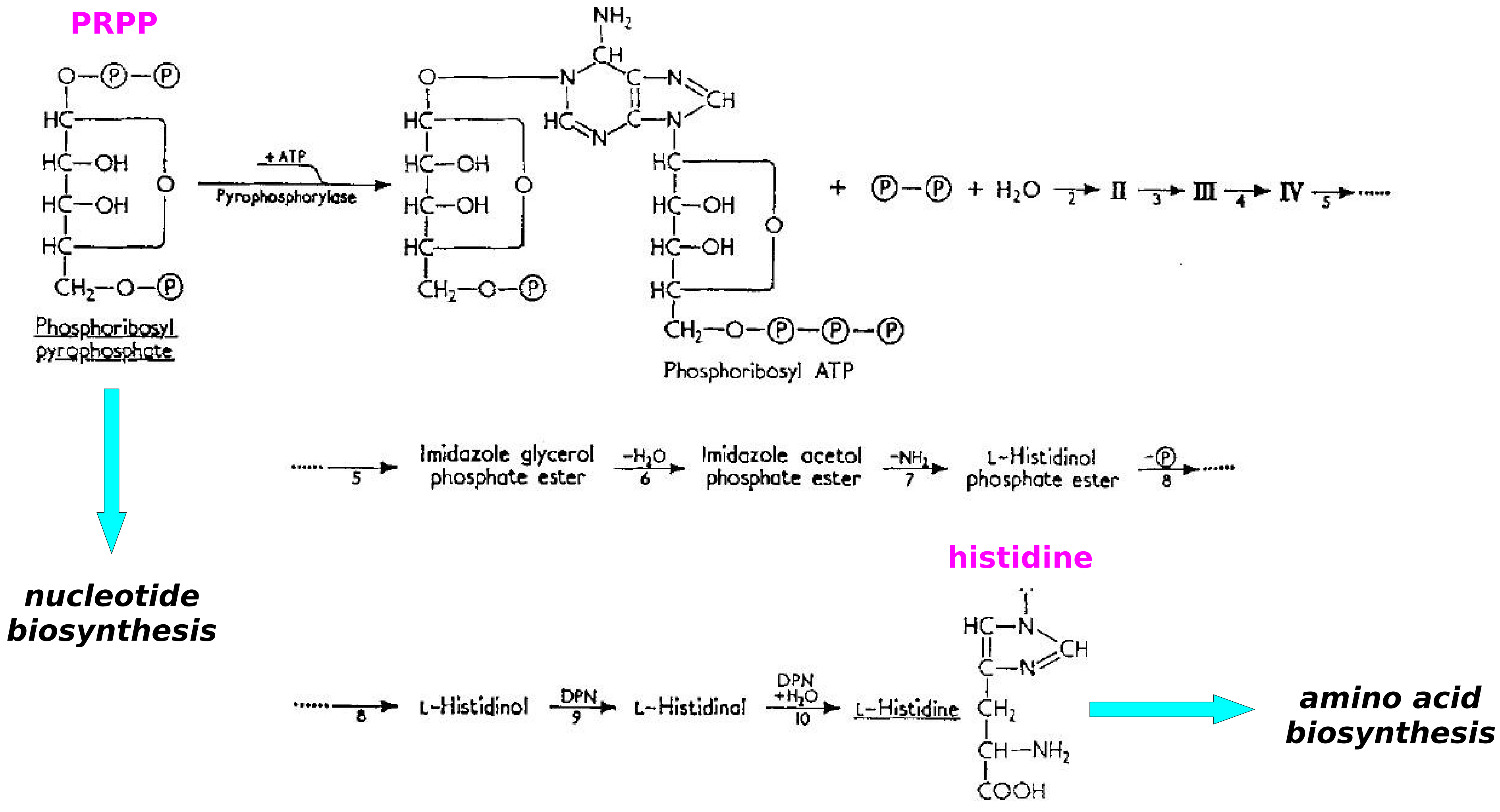



an instructive mechanism

*constrained interfaces allow de-constrained innovation within modules*

# the metabolic economy

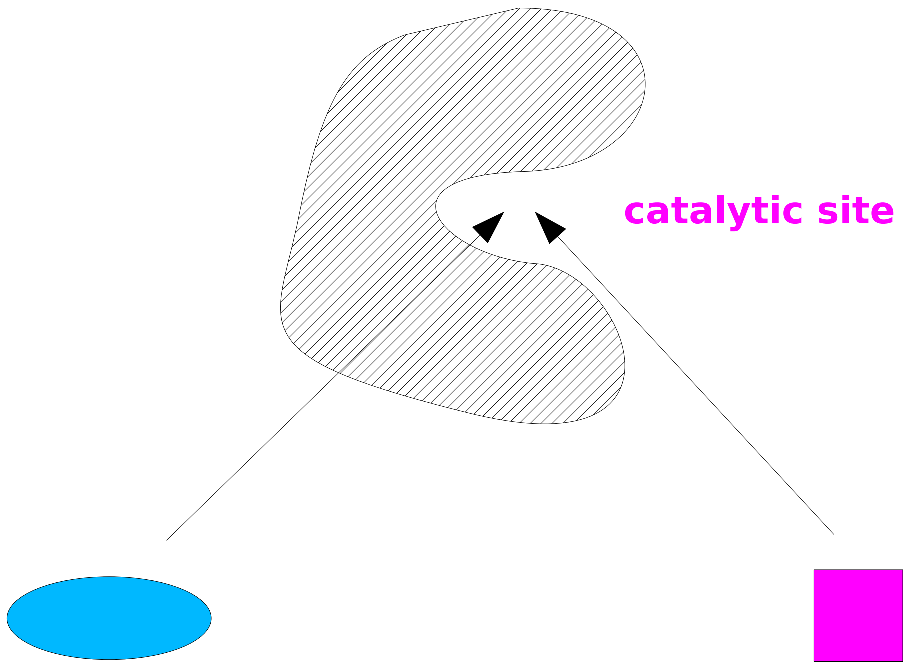
*how can metabolic modules be coupled so as to allow flux to vary 10-100 fold, while keeping intermediate concentrations constant?*



# feedback inhibition

Umbarger, Science 123:848 1956;  Yates & Pardee, J Biol Chem 222:757 1956

requires an enzyme that can both efficiently catalyse its substrate and be efficiently inhibited by a chemically distinct downstream product

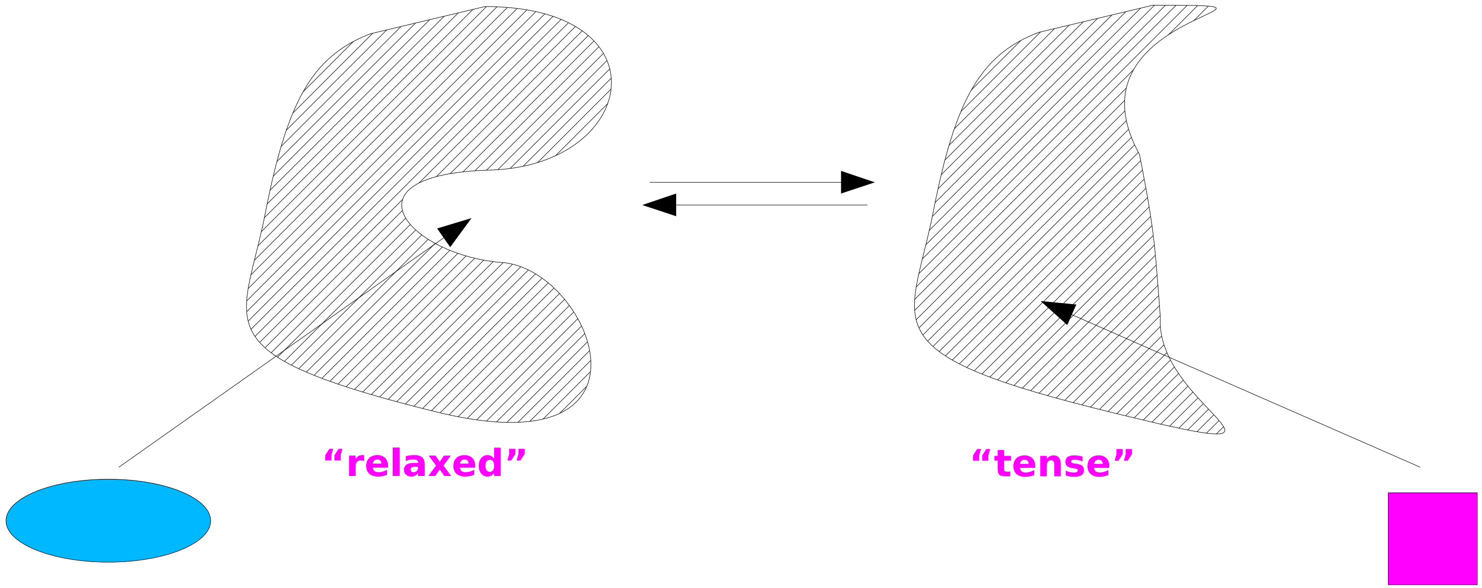



hard to make with a single structure and hard to evolve further if it can be made

# allostery

an enzyme with two equilibriating structures, one being catalytically incompetent, ignoring the inhibitor

allow the inhibitor to bind more tightly to the incompetent structure (anywhere), ignoring the catalytic site

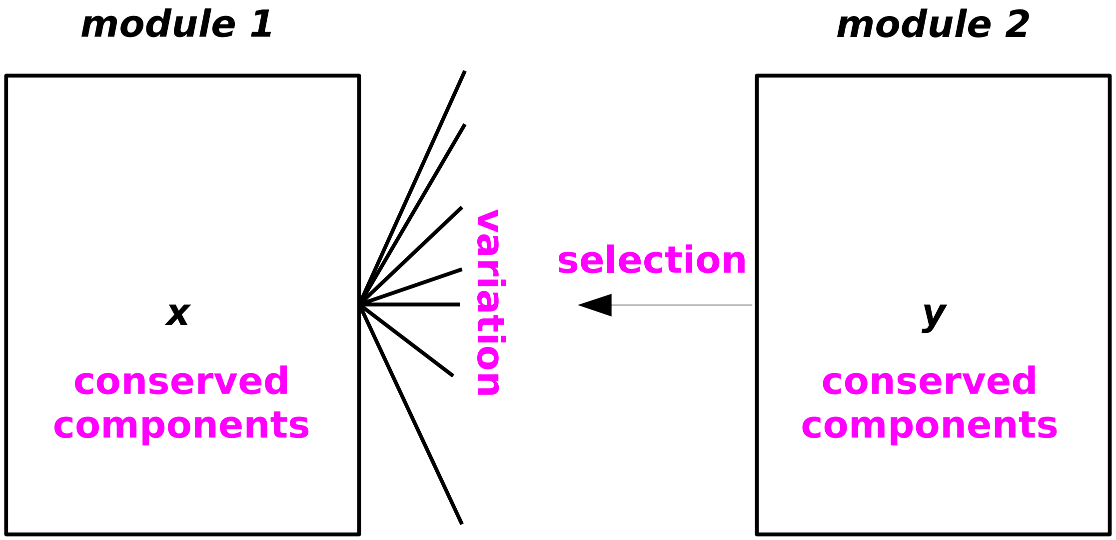



easier to make and to evolve further

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

# weak linkage

modules are coupled by exploratory variation/selection mechanisms

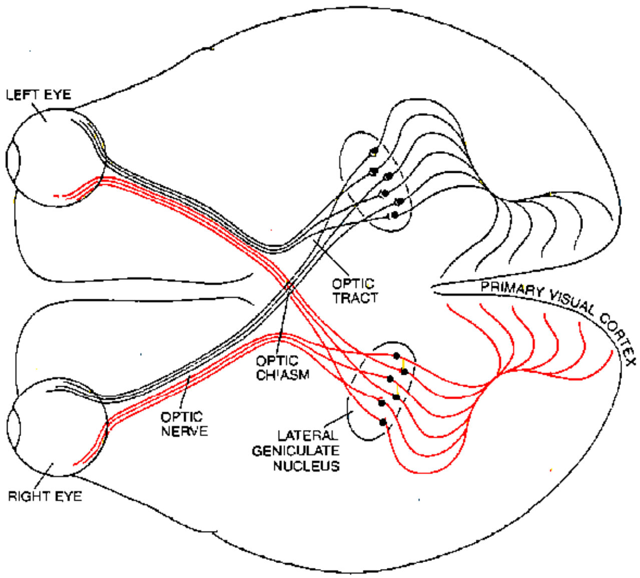



de-constrained interfaces facilitate phenotypic variation and evolvability, despite conservation of modules

*evoloved biological modularity is the inverse of engineering modularity!*

John Gerhart & Marc Kirschner, "*The theory of facilitated variation*", PNAS **104**:8582-9 2007

# weak linkage in physiology




the visual centres of the brain accept whatever the eyes send them and learn from these images, allowing eye and brain to evolve independently

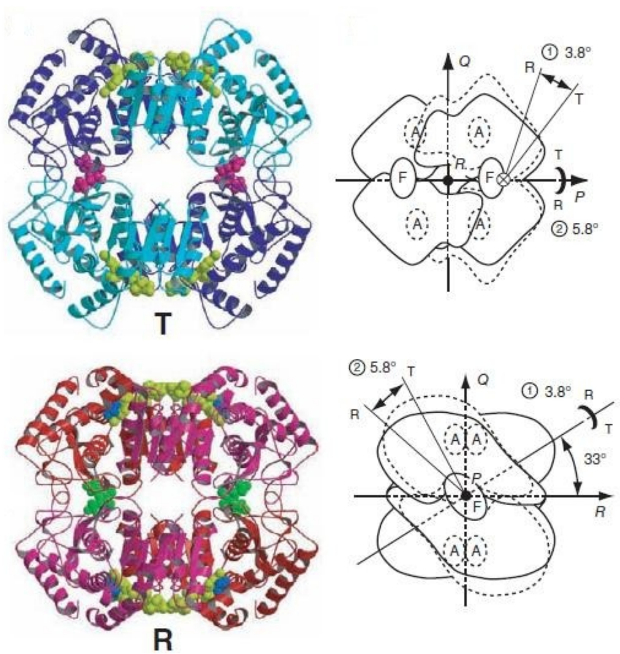
**polydactly**

bone, muscle, nerves and vasculature adapt to what each other are doing

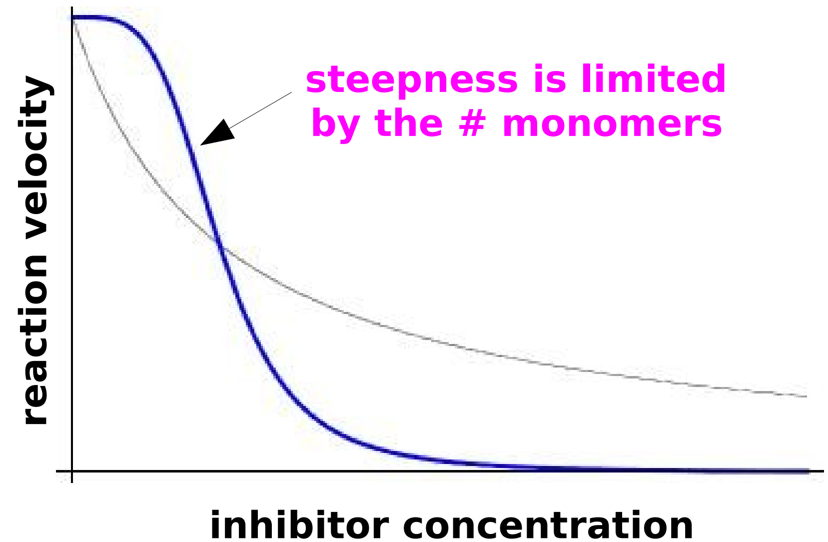
# allostery

requires quaternary structures

creates ultrasensitivity




**lactate dehydrogenase**




Changeux, Edelstein, *“Allosteric mechanisms of signal transduction”*, Science **6**:1424-8 2005

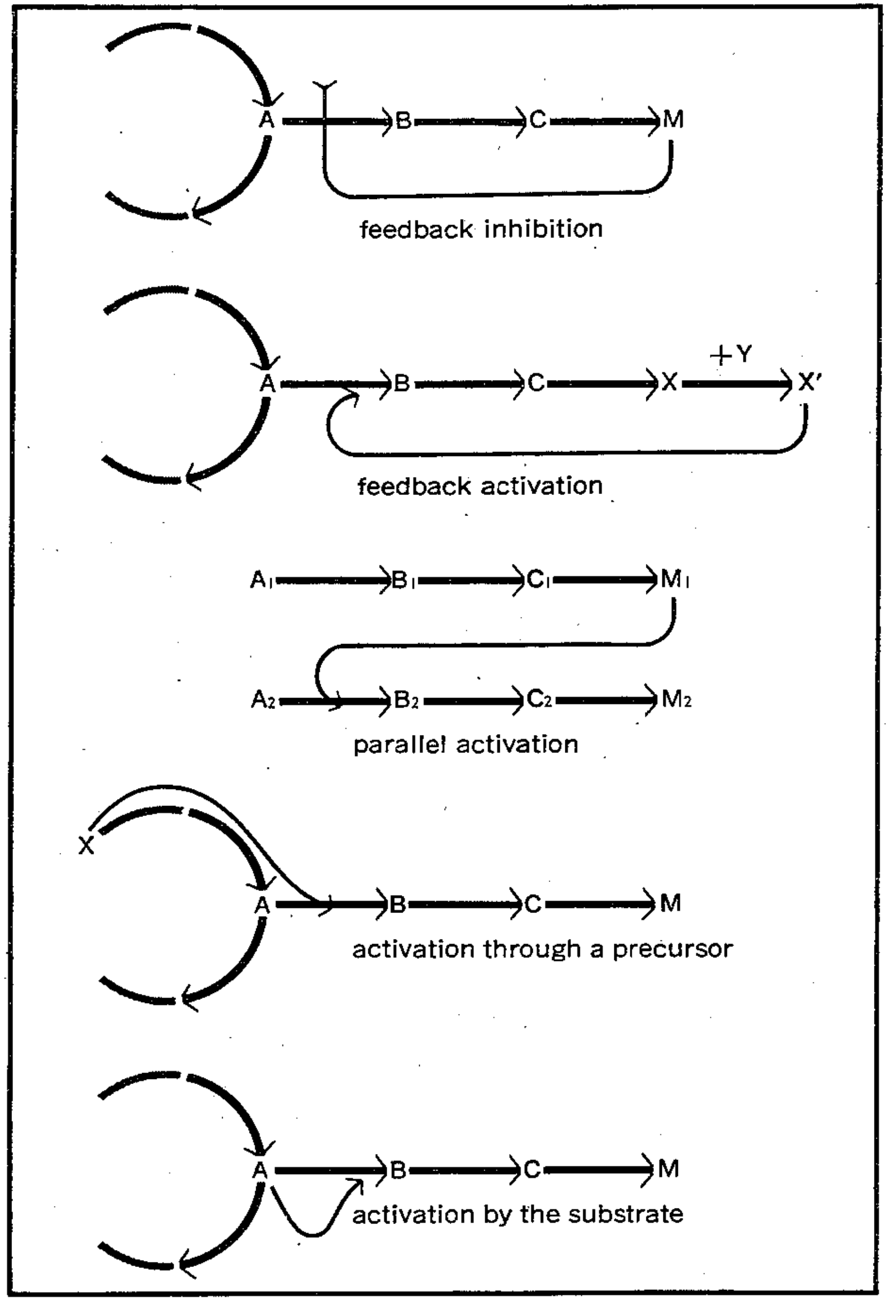
Monod, Wyman, Changeux, *“On the nature of allosteric transitions: a plausible model”*, J Mol Biol, **12**:88-188 1965

# microscopic cybernetics

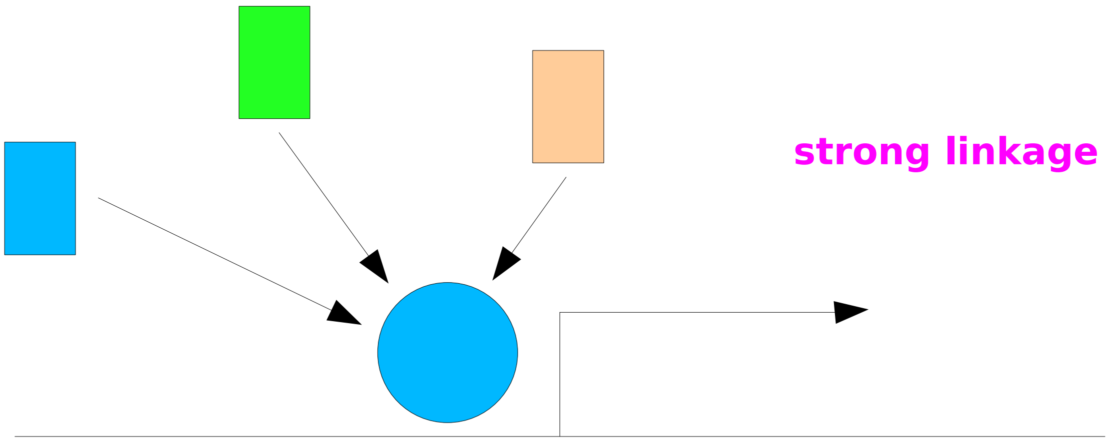
(**Chapter 4 of Chance and Necessity**)

Monod called allostery *"the second secret of life"* and envisioned a theory of metabolic regulation inspired by cybernetics.

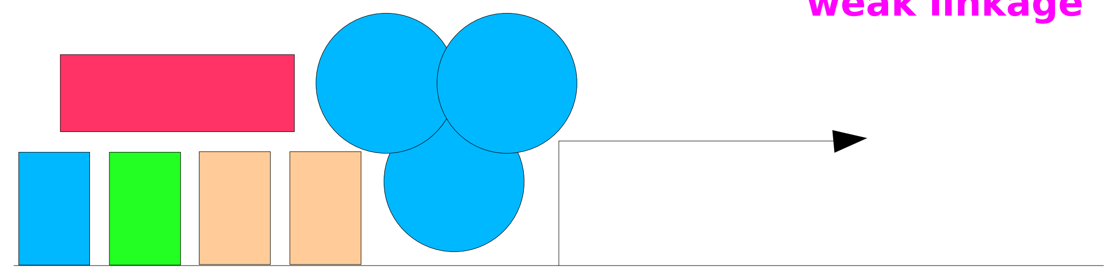
Jacques Monod, **Chance and Necessity: on the Natural Philosophy of Modern Biology**, Alfred Knopf, 1971 (French original, 1970)



# weak linkage – gene regulation

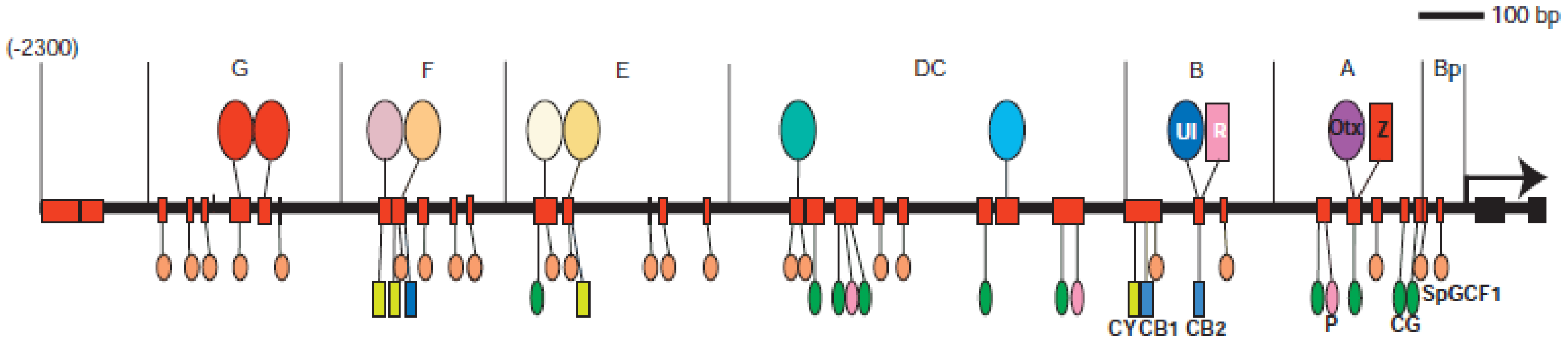


strong linkage

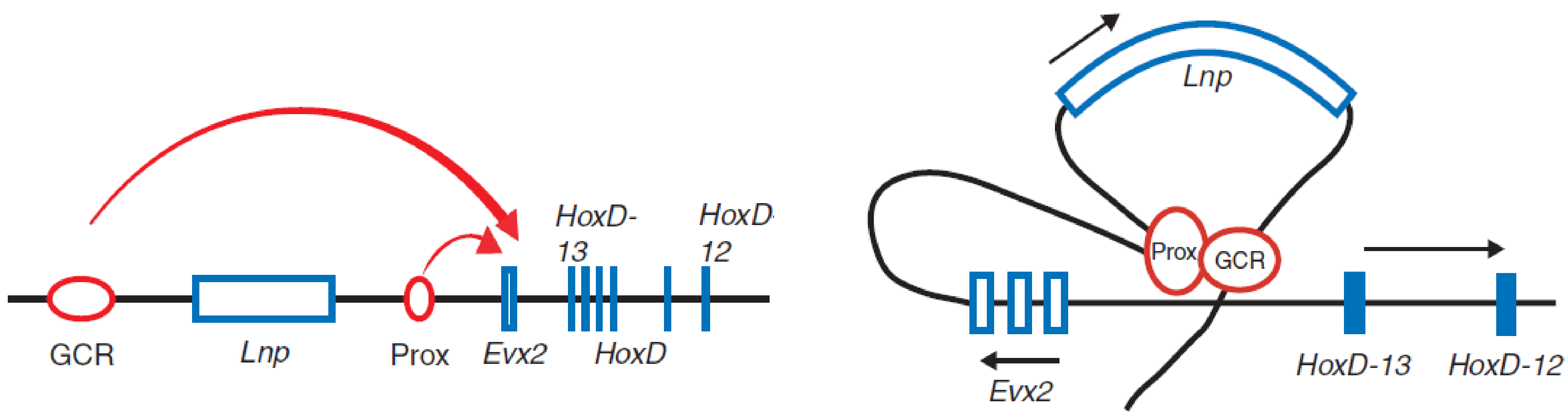


weak linkage

# exuberant exploration




**endo-16 promoter region in sea urchin endoderm specification**

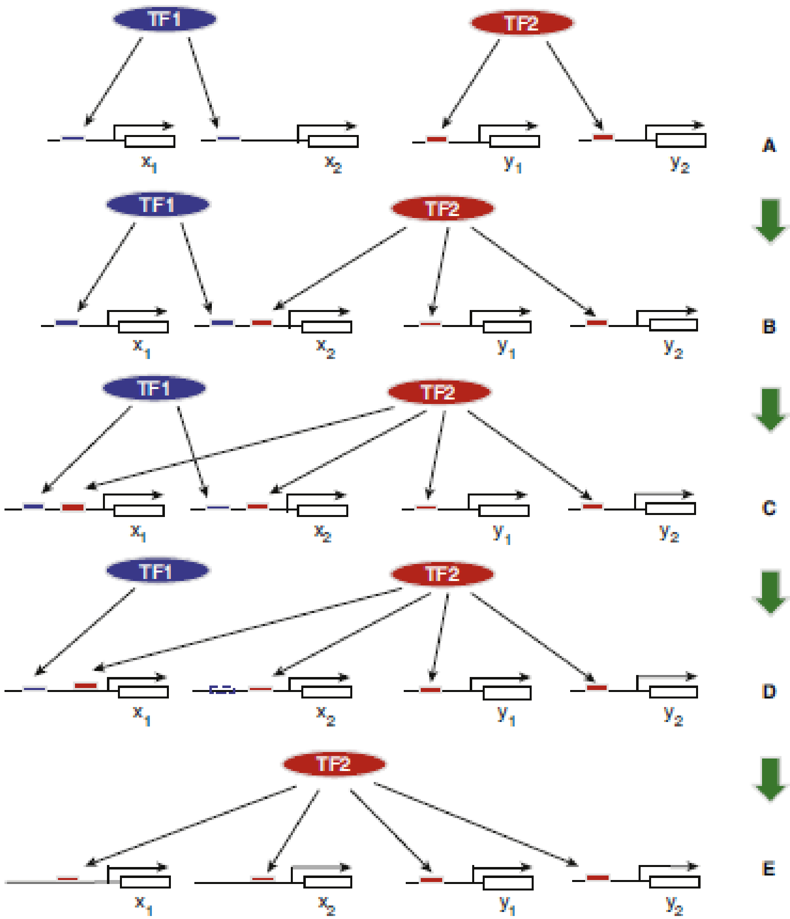



**HoxD enhancers in digit specification**

Yuh, Bolouri, Davidson, *“cis-regulatory logic in the endo-16 gene”*, Development **128**:617-29 2001

Wagner, Vargas, *“On the nature of thumbs”*, Genome Biol **9**:213 2008

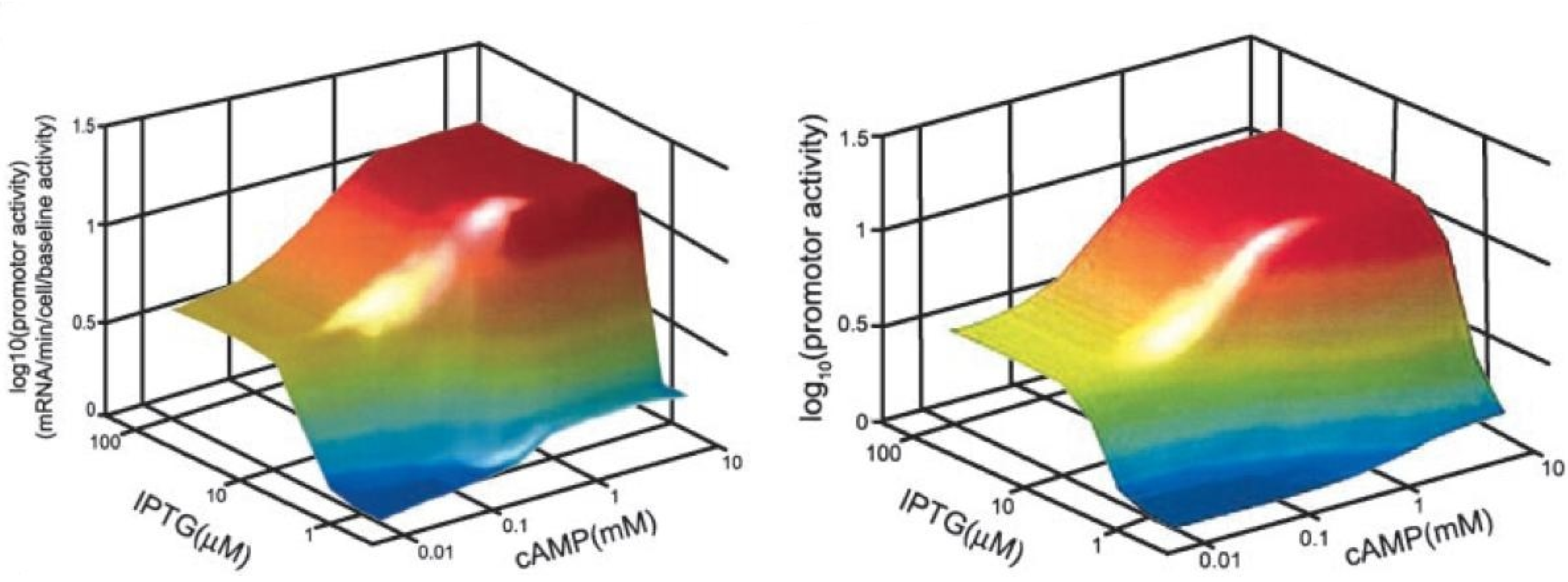
# evolutionary flexibility




Li, Johnson, *"Evolution of transcription networks – lessons from yeast"*, Curr Biol **20**:R746-53 2010

# but what are its functional capabilities?

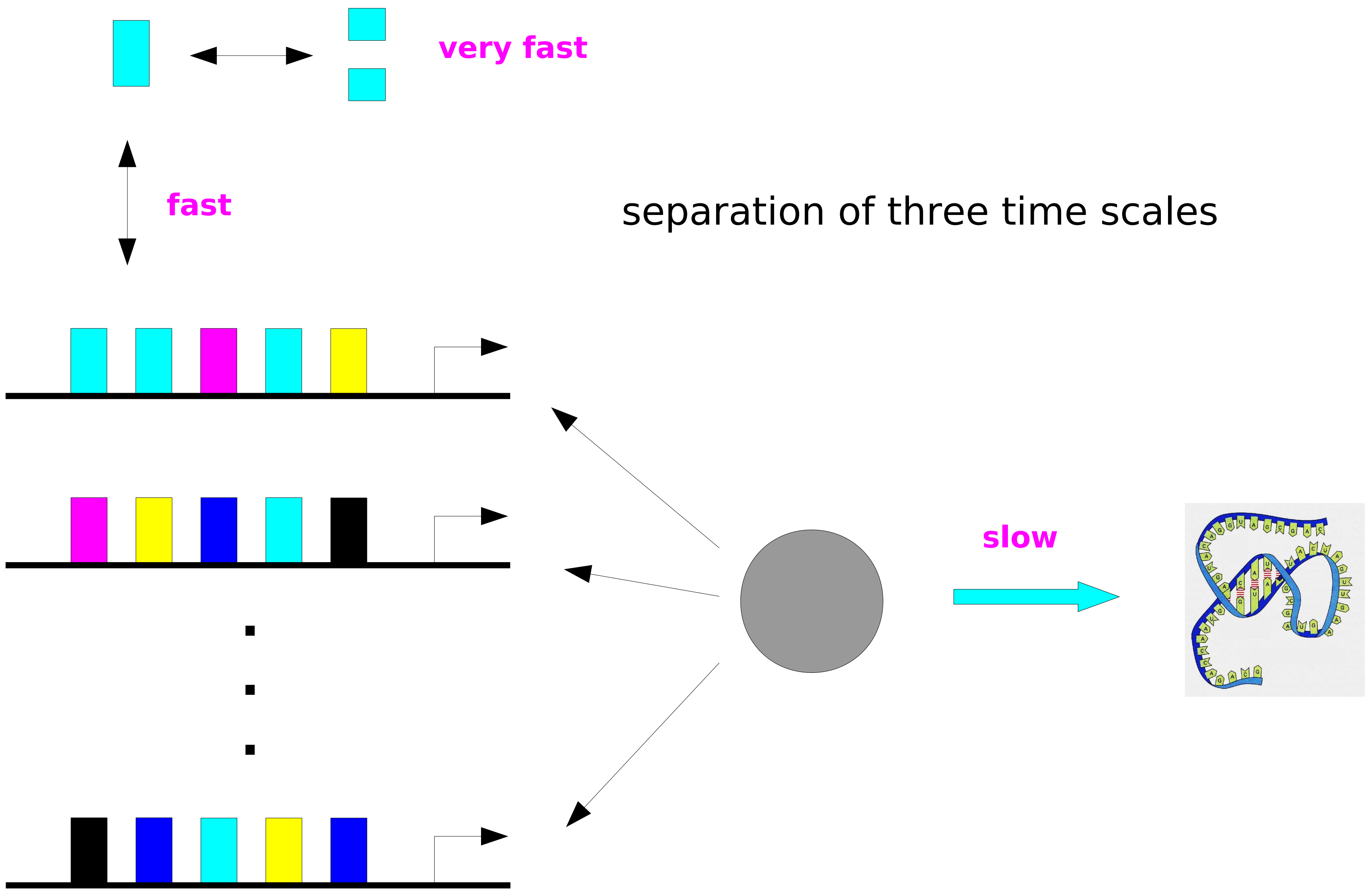
the lac operon of E coli responding to cAMP and IPTG



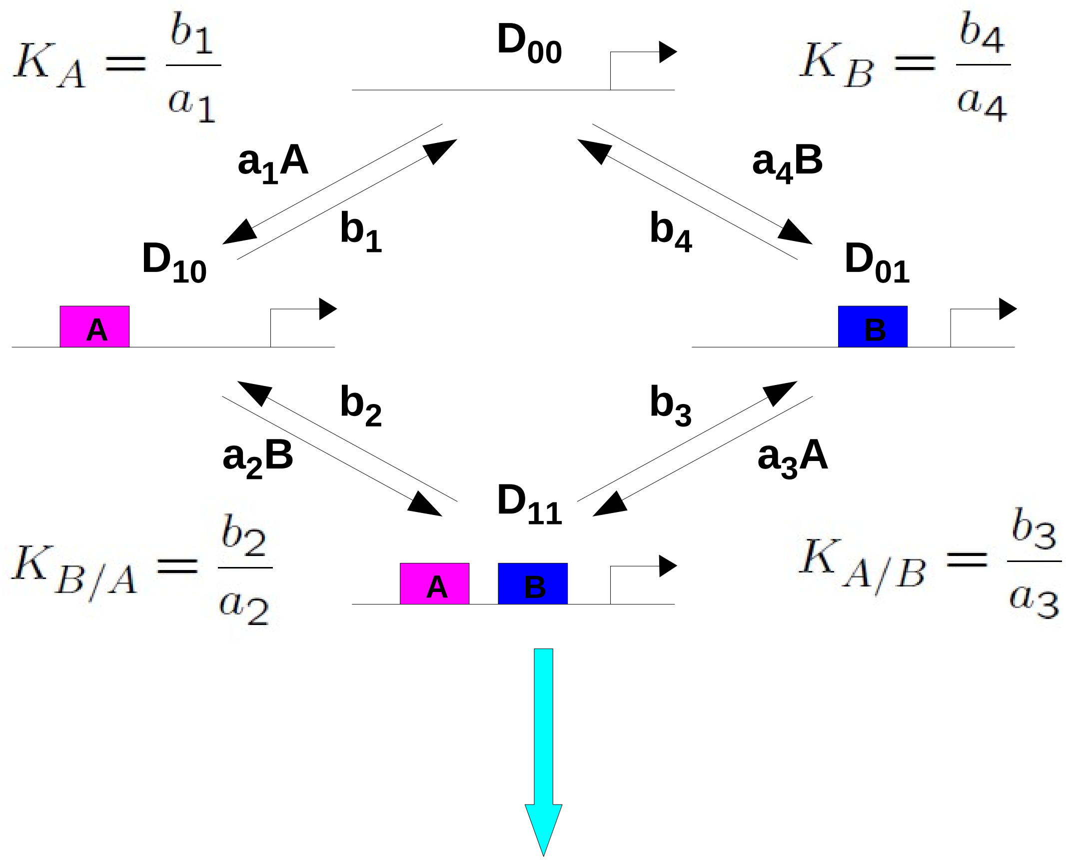

**experiment** **simulation**

Setty, Mayo, Surette, Alon, *"Detailed map of a cis-regulatory input function"*, PNAS **100**:7702-7 2003

# the graphical framework (lecture 3)



# labelled directed graph




$$R(A,B) = \frac{r_{00} + r_{10}\left(\frac{A}{K_A}\right) + r_{01}\left(\frac{B}{K_B}\right) + r_{11}\omega\left(\frac{A}{K_A}\right)\left(\frac{B}{K_B}\right)}{1 + \left(\frac{A}{K_A}\right) + \left(\frac{B}{K_B}\right) + \omega\left(\frac{A}{K_A}\right)\left(\frac{B}{K_B}\right)}$$

rate of gene expression

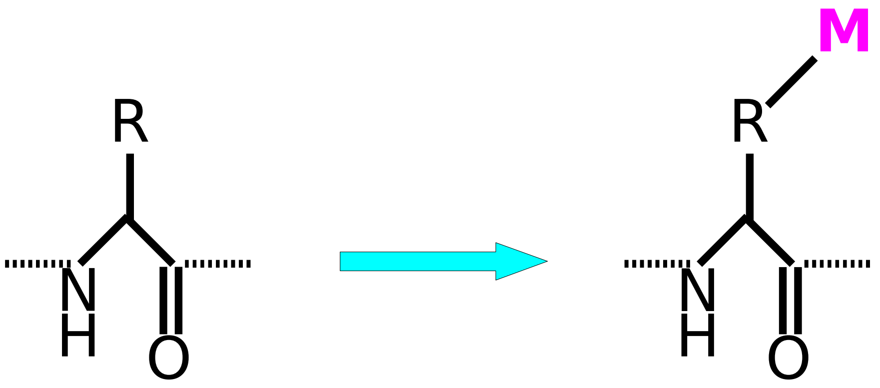
$$\omega = \frac{K_A}{K_{A/B}} = \frac{K_B}{K_{B/A}}$$

cooperativity

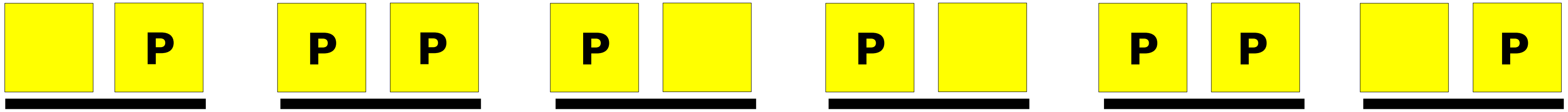
# weak linkage – post-translational modification

allostery may have been evolutionarily sufficient for coupling metabolic modules (small molecules to protein enzymes) but the functional capabilities of oligomerisation are limited

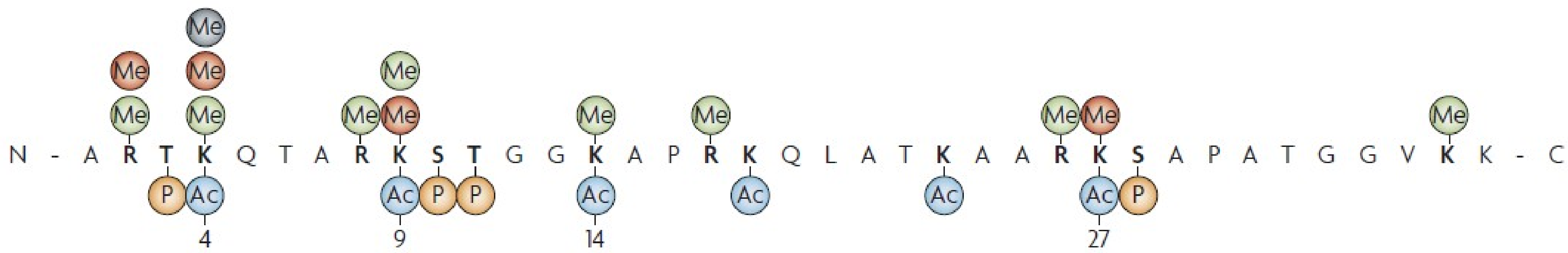
for coupling protein modules, a different structural alteration arose

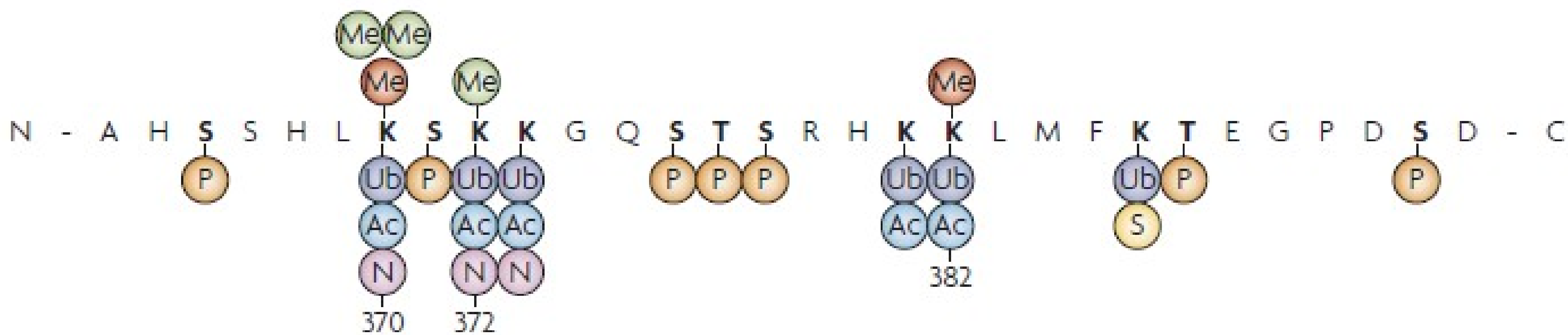


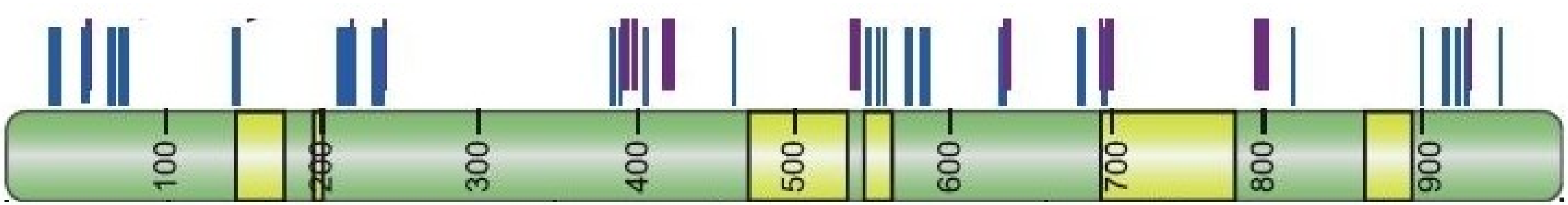

the mod-form distribution creates a vast landscape for variation



# exuberant exploration

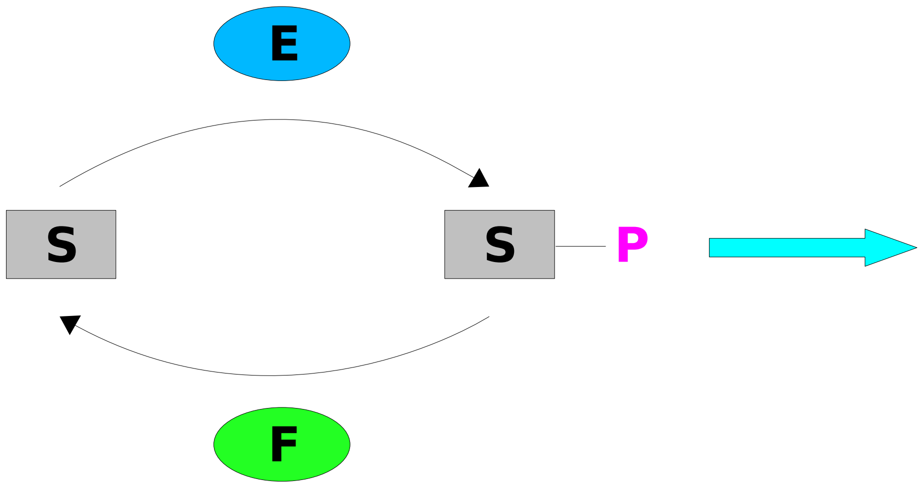


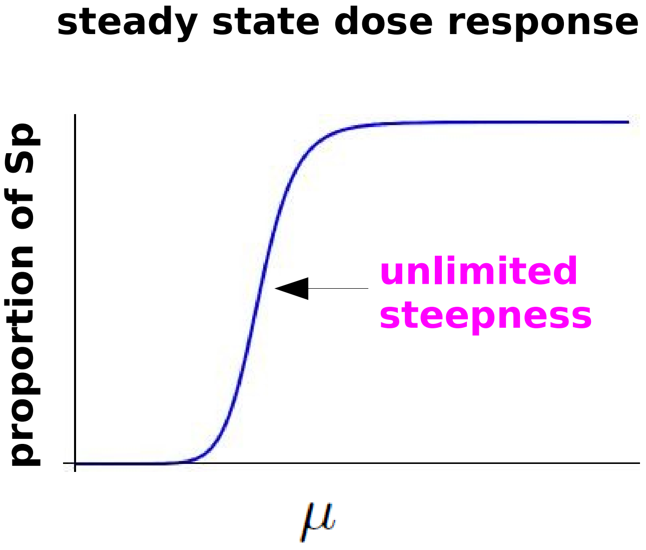



# but what are its functional capabilities?

Goldbeter-Koshland ultrasensitivity



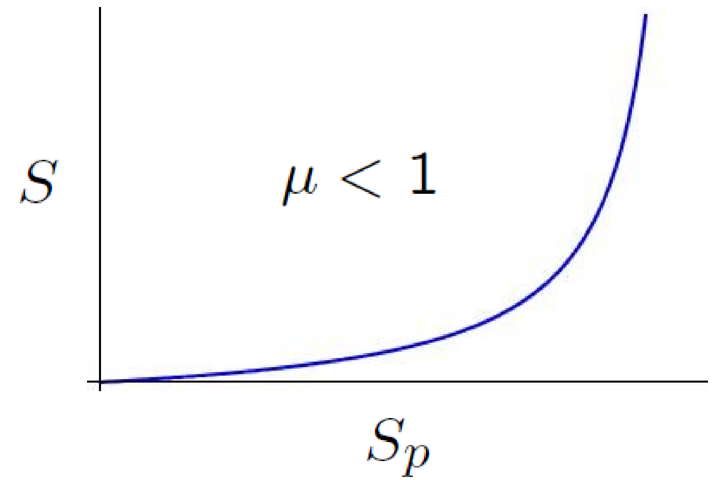

$$\mu = \frac{c_E E_{tot}}{c_F F_{tot}}$$

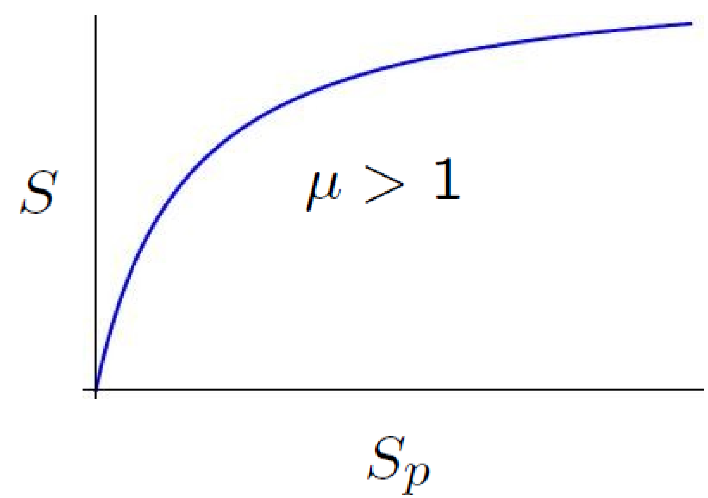
Goldbeter, Koshland, *“An amplified sensitivity arising from covalent modification in biological systems”*, PNAS **78**:6840-4 1981

# apply the graphical framework

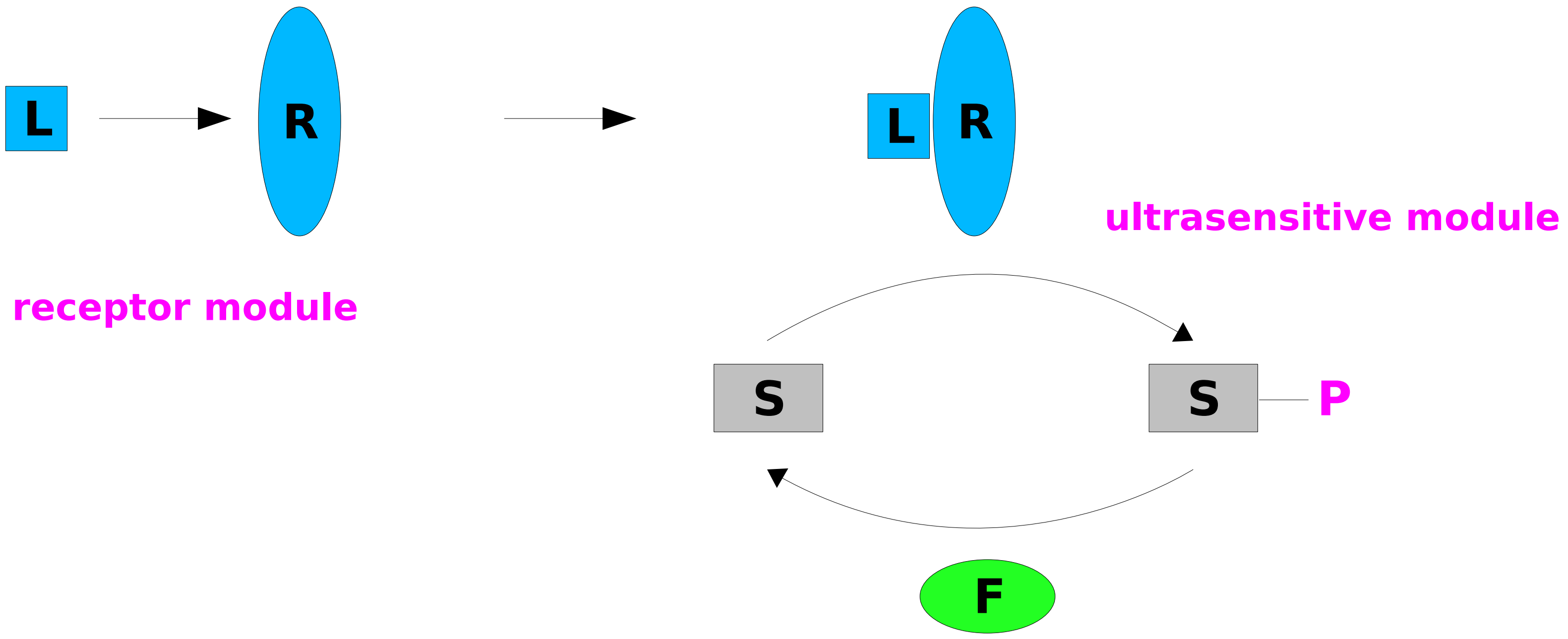
$$S = \frac{K_E S_p}{\mu K_F + (\mu - 1) S_p}$$

ultrasensitivity arises
from a singularity at $\mu = 1$



# coupling modules can change behaviour




$$S = \frac{(1 + K_R/L) K_E S_p}{\mu K_F + (\mu - 1) S_p}$$

at steady state, the ligand, L, does not influence the singularity – ultrasensitivity disappears!

***structural modularity may not imply functional modularity***

Xu, Gunawardena, *“Ultrasensitivity and modularity depend on network context”*, in preparation, 2011

## summing up

1. *biological modularity is the inverse of engineering modularity*

2. *weak linkage facilitates variation and evolution*

3. *PTM is a weak-linkage mechanism for coupling protein networks*

4. *but structural modularity may not imply functional modularity*

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