Gene Networks and the Evolution of Behavior

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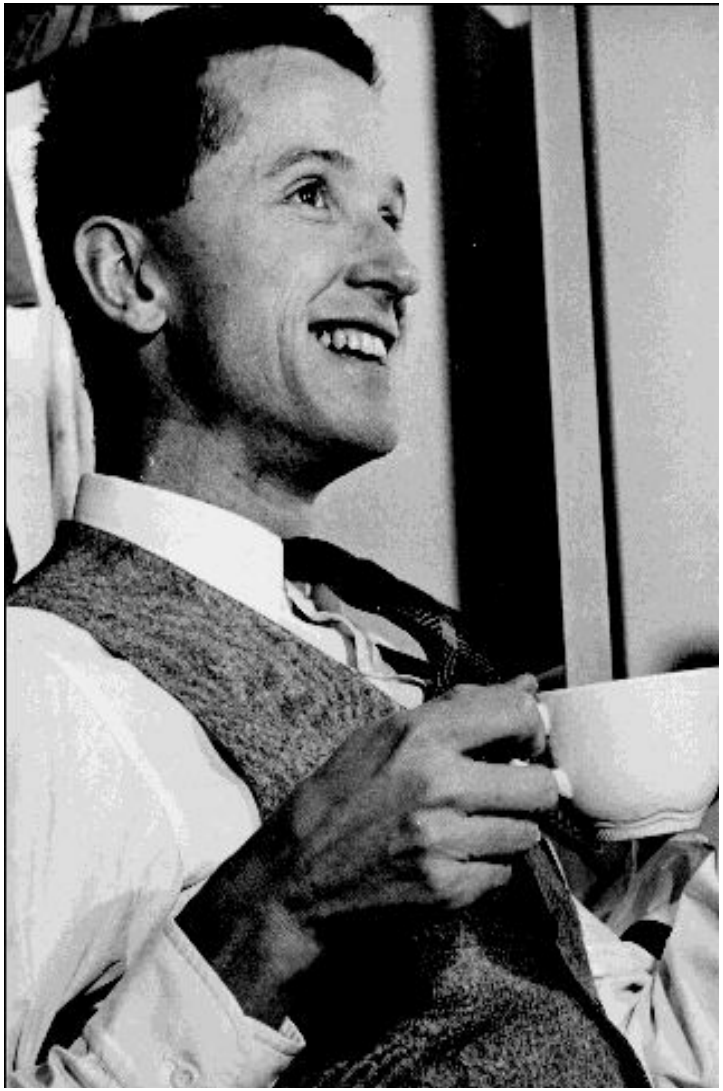
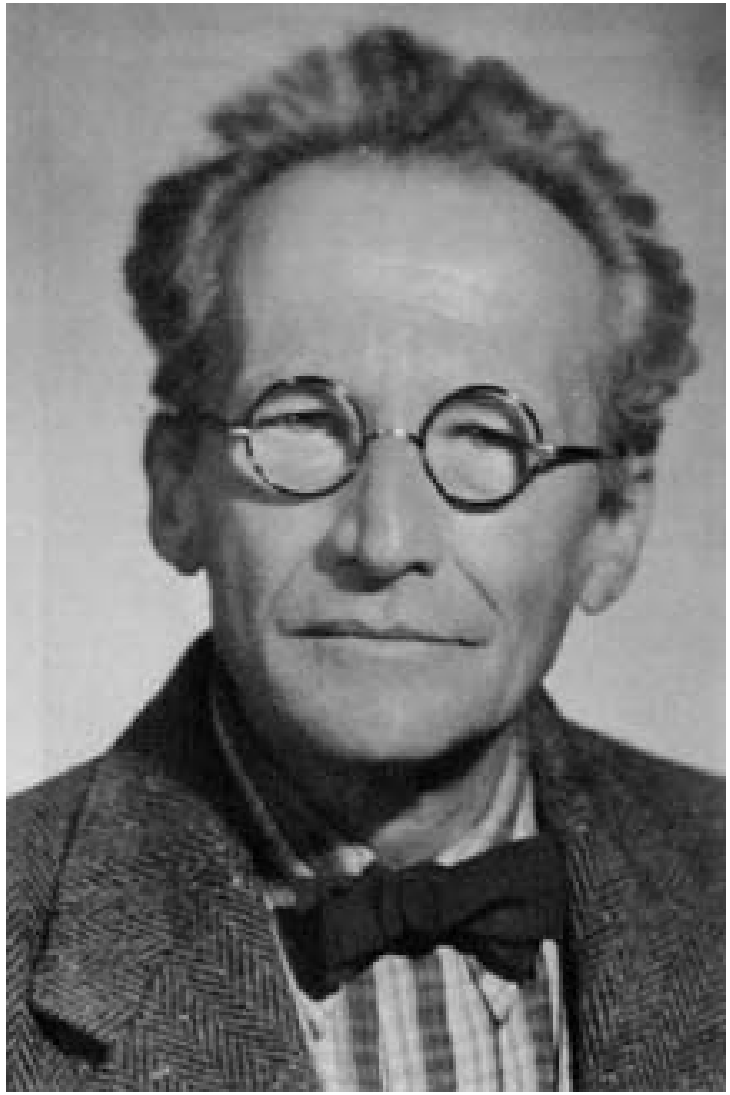
Waiting for the paradox

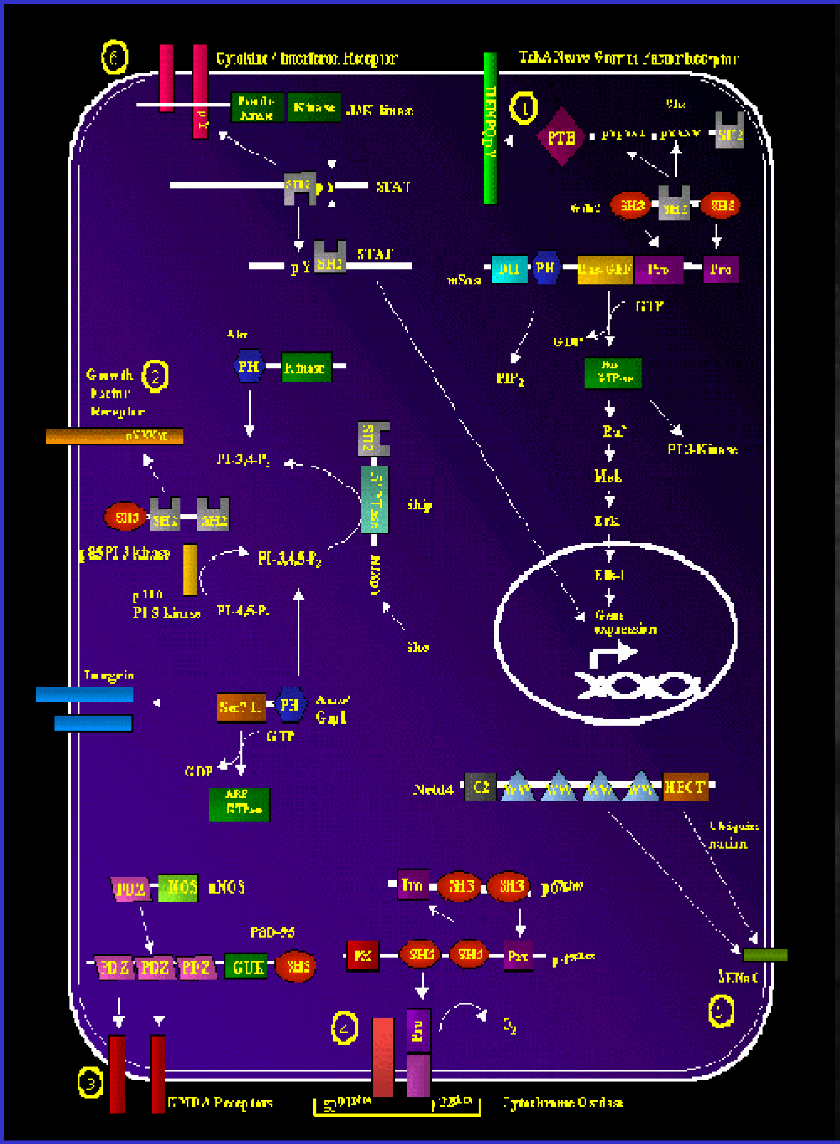
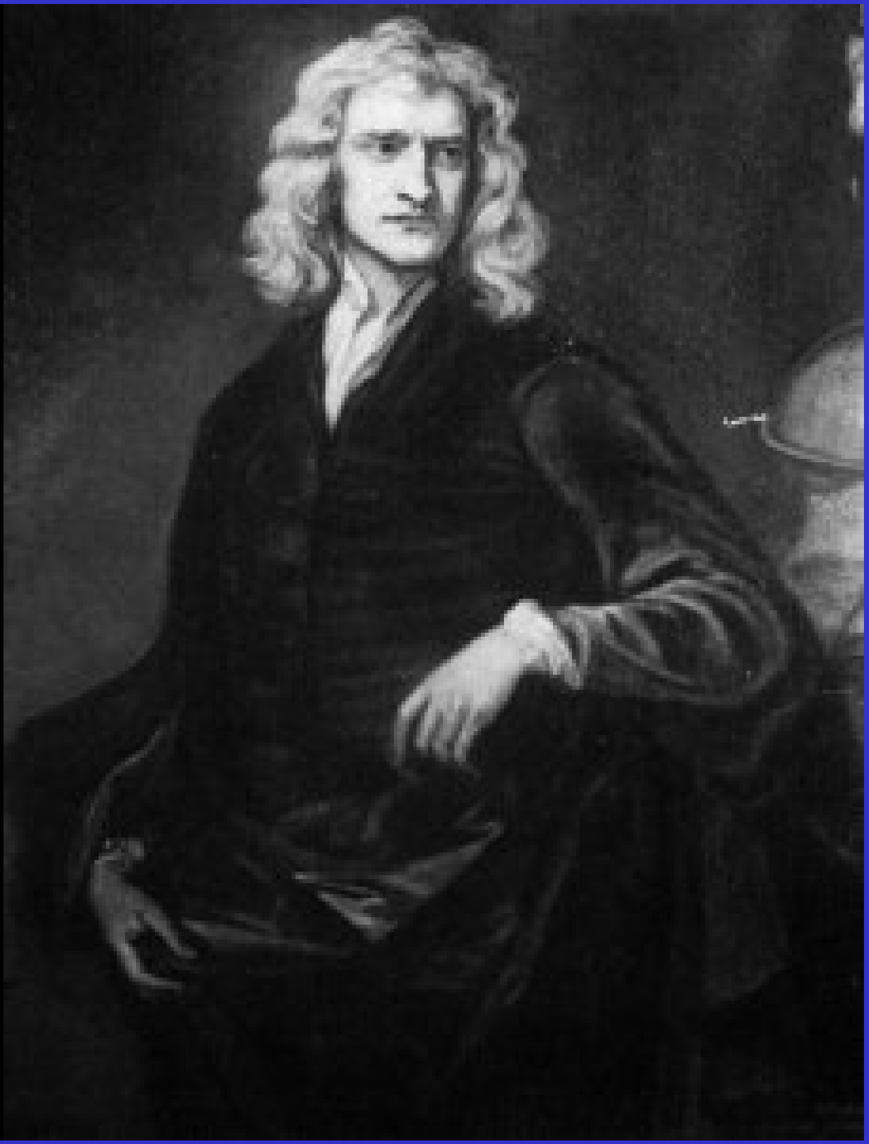


Delbrück

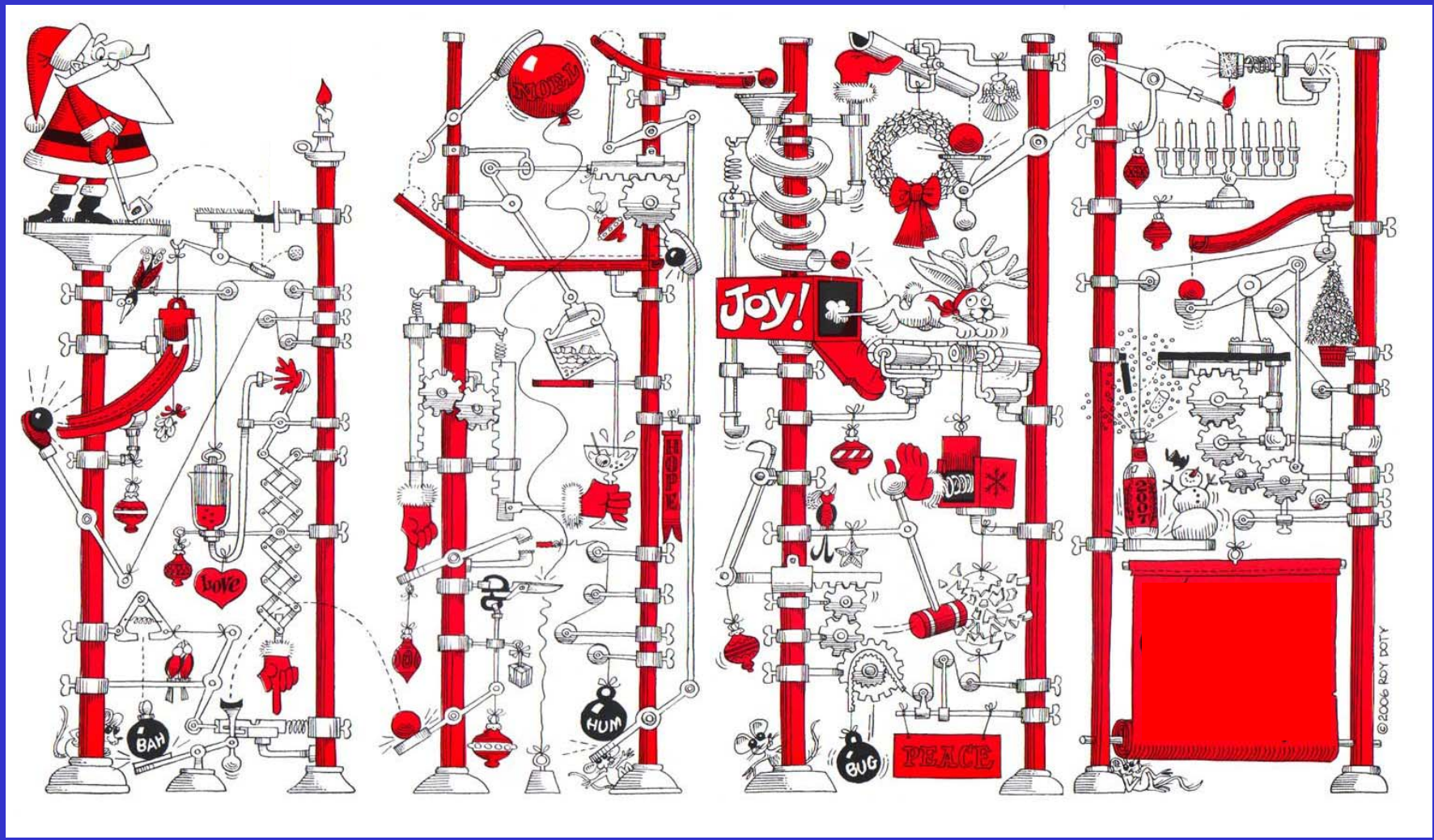


Schrödinger

The Pathway Paradigm


STAT
PTB
SH2
PH
Kinase
Growth Factor Receptor
Integrin
GTP
GDP
Raf
Mek
Erk
Gene expression
PI 3-Kinase
Nedd4
C2
HECT
nNOS
PSD-95
PDZ
GUK
SH3
Pro
ENaC
NMDA Receptors
Cytochrome Oxidase


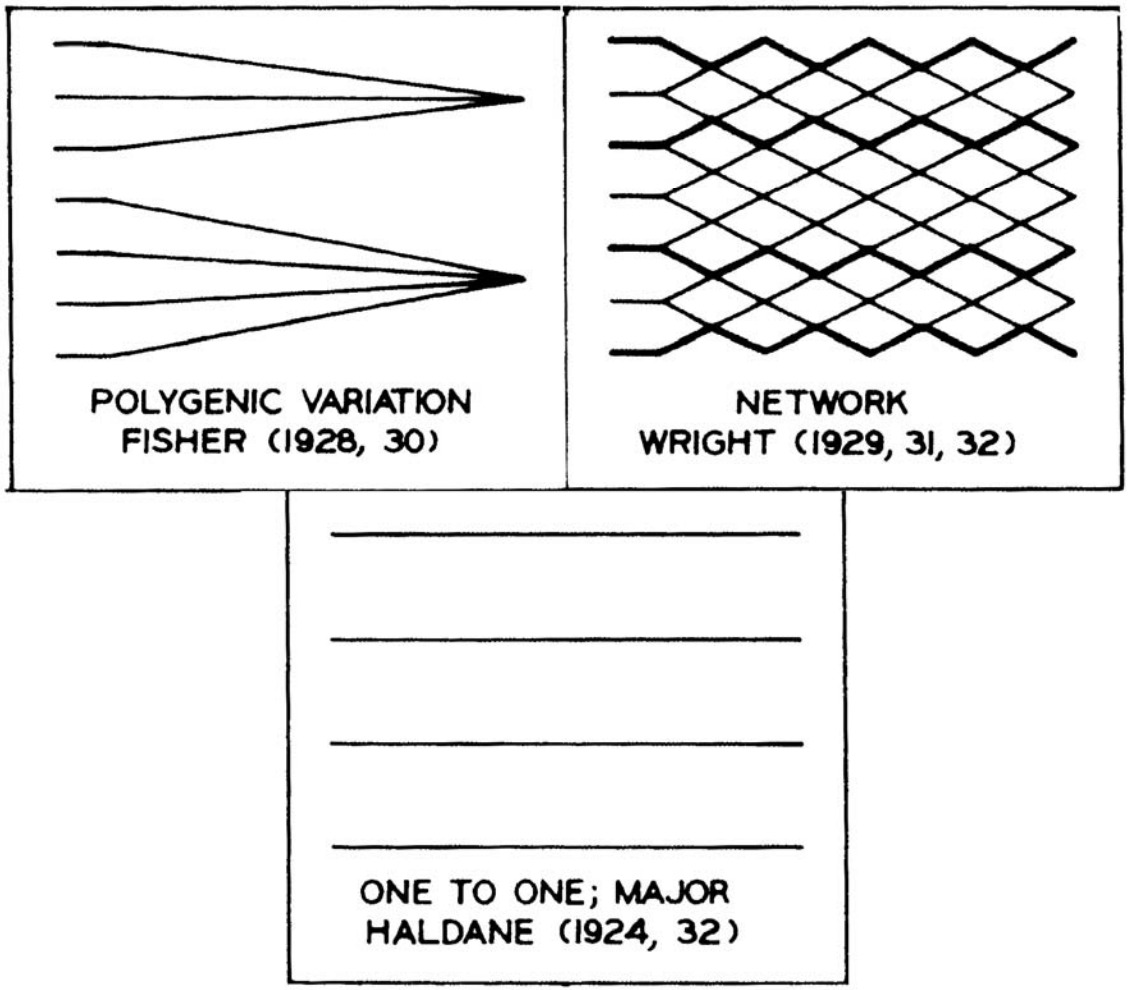
No paradox here, just a lot of stuff.



How does selection change genomes?

What can this tell us about genetic mechanisms?

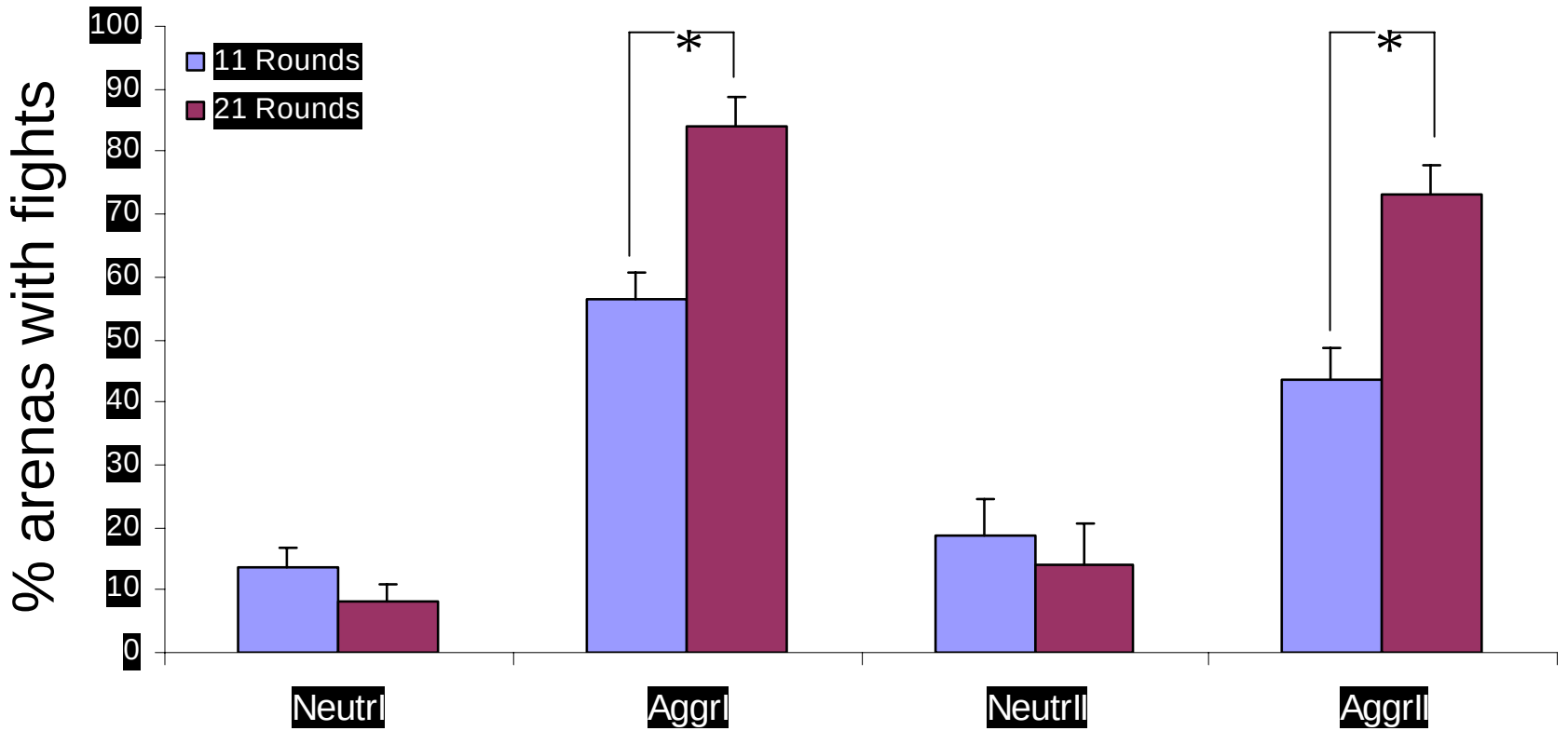
Genes, Selection, and Phenotypes



Short-term Selection

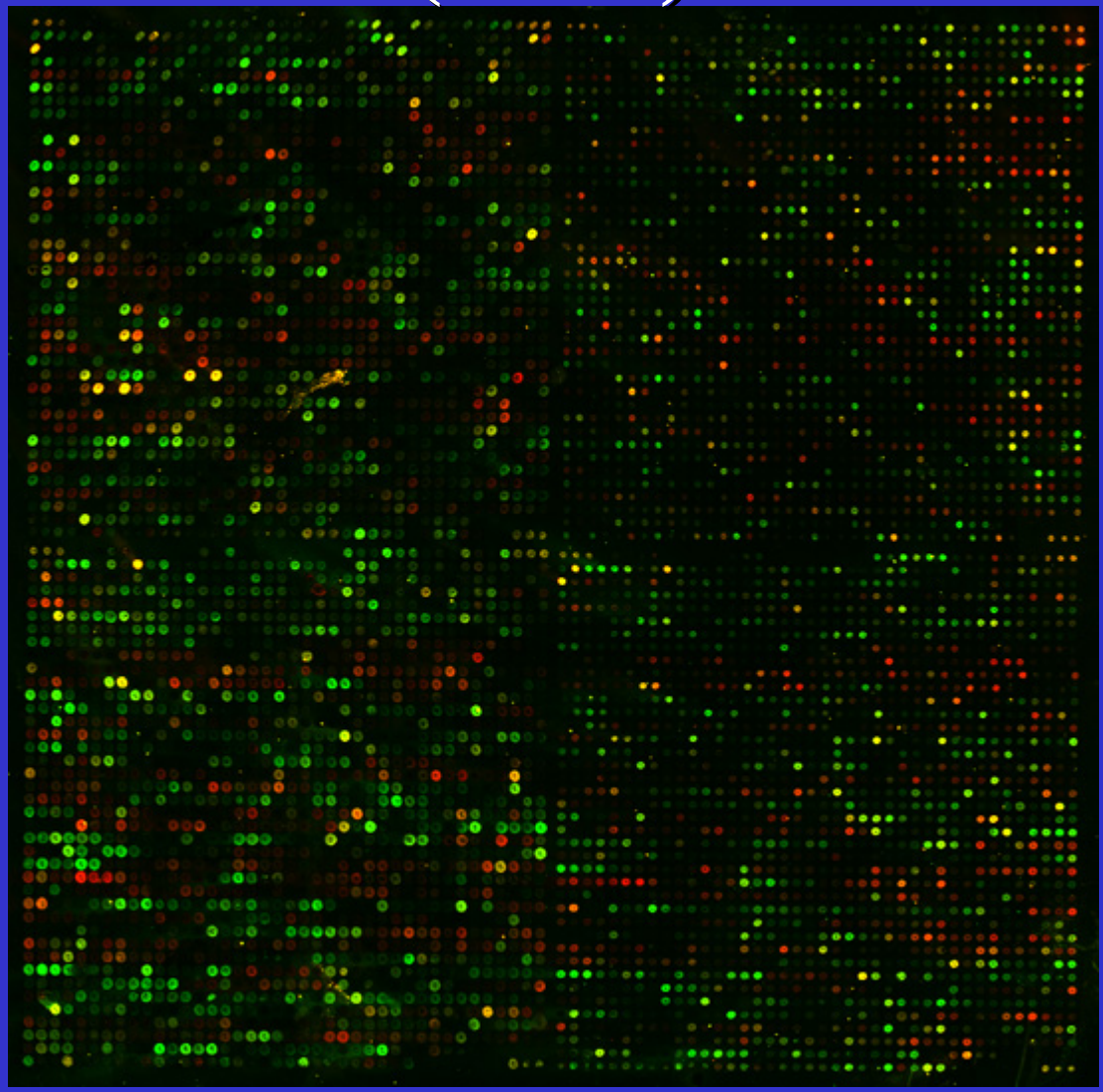
Aggression

After 21 generations



Dierick & Greenspan (2005)

Genes of all sorts
(heads)

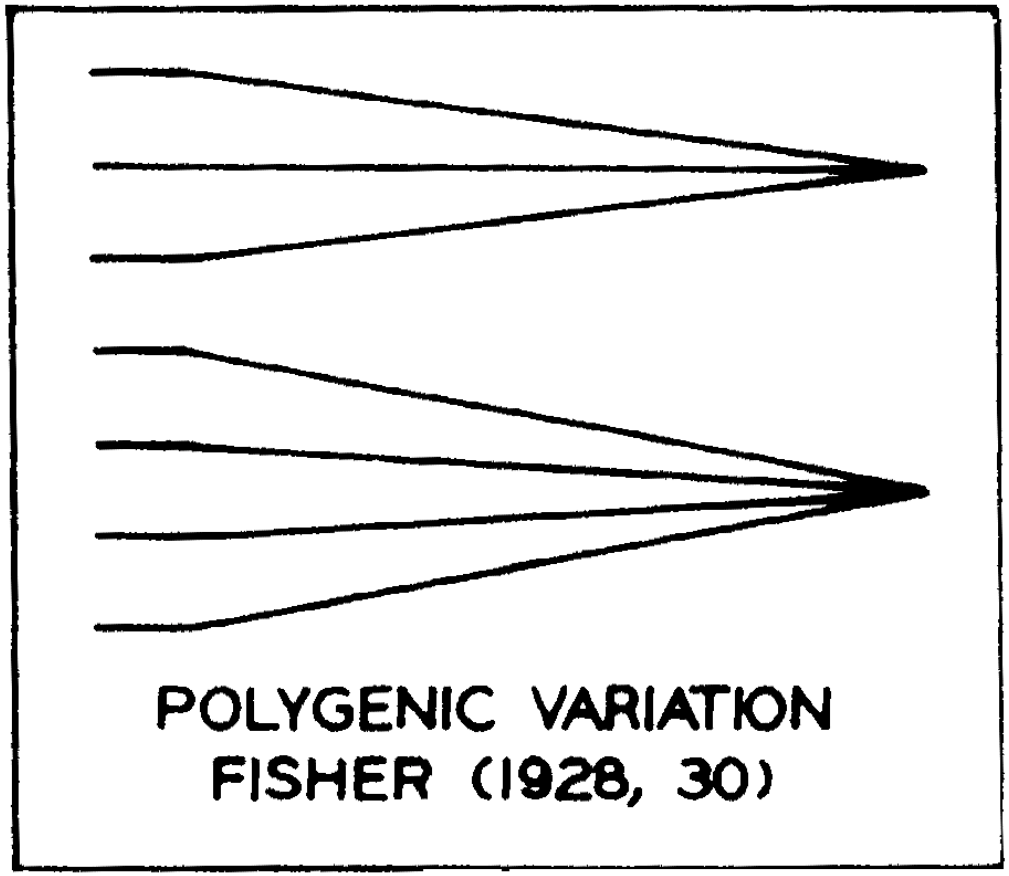


Gene	↑ in Aggr	Function	Gene	↓ in Aggr	Function
CG16978	2.55		Obp56a	2.50	odor binding
CG3397	2.10	K channel	CG11458	1.98	
Drs	2.08	immune	CG4825	1.66	
CG11899	1.61		Dh	1.63	diuretic hormone
CG7900	1.54		GNBP1	1.62	
Est8	1.53	esterase	CG10444	1.55	multivitamin trans
CG32444	1.53		CG13252	1.49	
CG5195	1.48	DNA binding	CG2555	1.47	
CG18162	1.48		Cyp6a20	1.46	cytochrome P450
CG5955	1.47		kek4	1.39	Egf-binding
CG2827	1.44		CG7529	1.36	
Snap	1.44	vesicle fusion	CG10098	1.35	
TpnC41C	1.43	troponinC	CG8942	1.34	Wnt binding
CG31475	1.42	Ca-binding	mub	1.29	mushroom body
CG11073	1.41		Gbeta76C	1.14	G-protein subunit
CG5104	1.38				
CG9295	1.38				
Mlc1	1.37	myosin LC			
CG6852	1.36				
CG5498	1.36				
CG1943	1.36				
CG7378	1.35	prot phosphatase			
CG15449	1.35				
Treh	1.35	trehalase			
Est1	1.34	esterase			
CG2767	1.33				
CG7331	1.33				
mfas	1.31	fasciclin			
Cam	1.16	calmodulin			
trpl	1.12	cation channel			

Known Drosophila aggression genes

Mutant/manipulation	function	evidence	reference
ebony	Increases α-alanine levels	Mutants more territorial	Jacobs (1978)
black	Decreases α-alanine levels	Mutants less territorial	"
fruitless	Regulates sex determination hierarchy pathway	Mutants engage in [illegible] head-to-head conflict	Lee & Hall (2000)
dissatisfaction	Regulates sex determination hierarchy pathway	Mutants [illegible] more head-to-head conflicts	"
octopamine null mutant	Neurotransmitter and neurohormone	[illegible] element generated nulls have low aggression	Baier et al. (2002)
dopamine levels increased or decreased by L-DOPA or 3-iodo-tyrosine	Neurotransmitter and hormone	Pharmacological manipulation changes aggression level	"
decreased synaptic output from mushroom body in P[GAL4] mb247 transgenic line	Brain bodies associated with learning and memory	decreased synaptic output lowers aggression	"
CheB42a-Gal4	Transgene partly defective for pheromone detection	transgenic line shows altered responses to social interactions	"

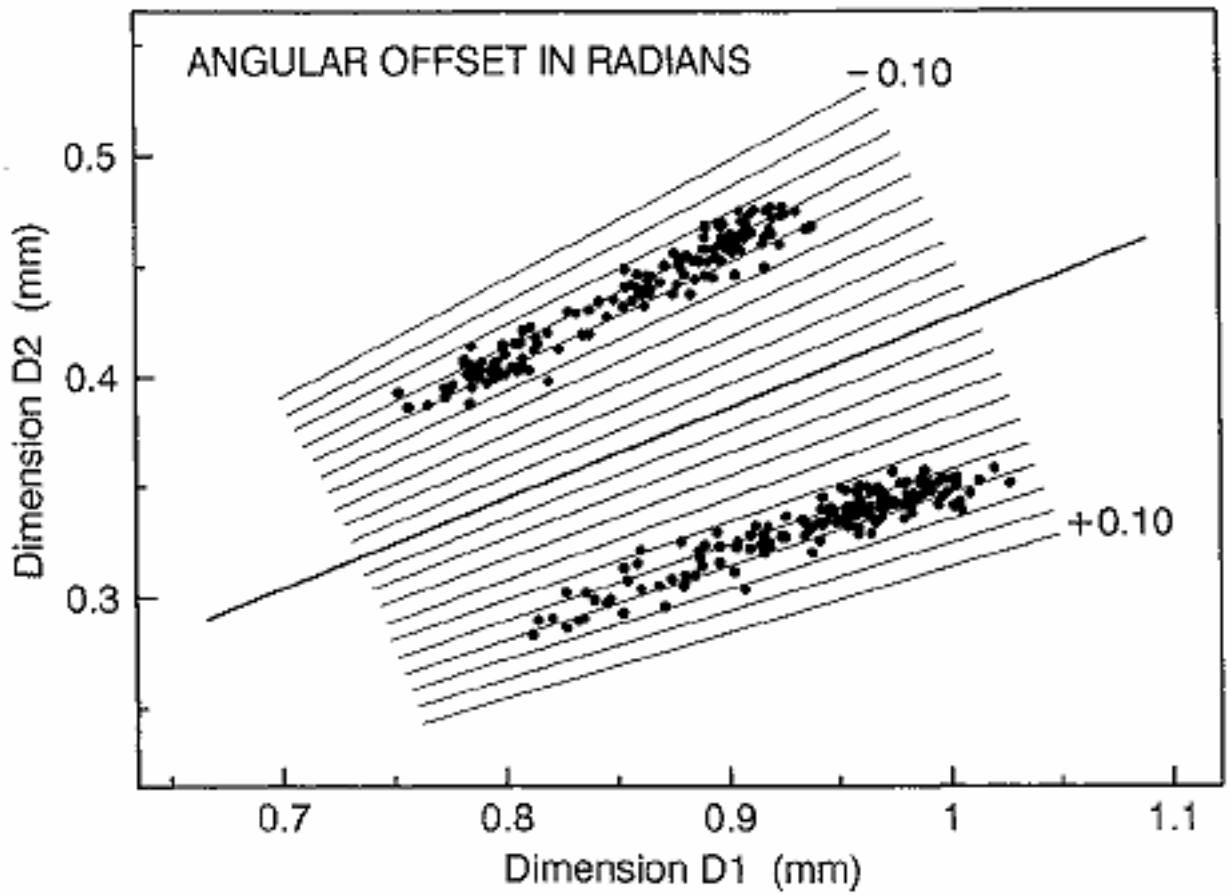
None of these

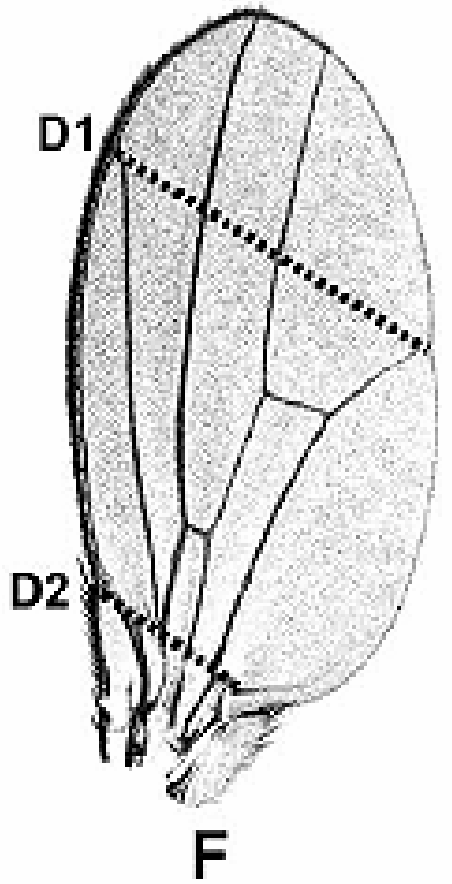


POLYGENIC VARIATION
FISHER (1928, 30)

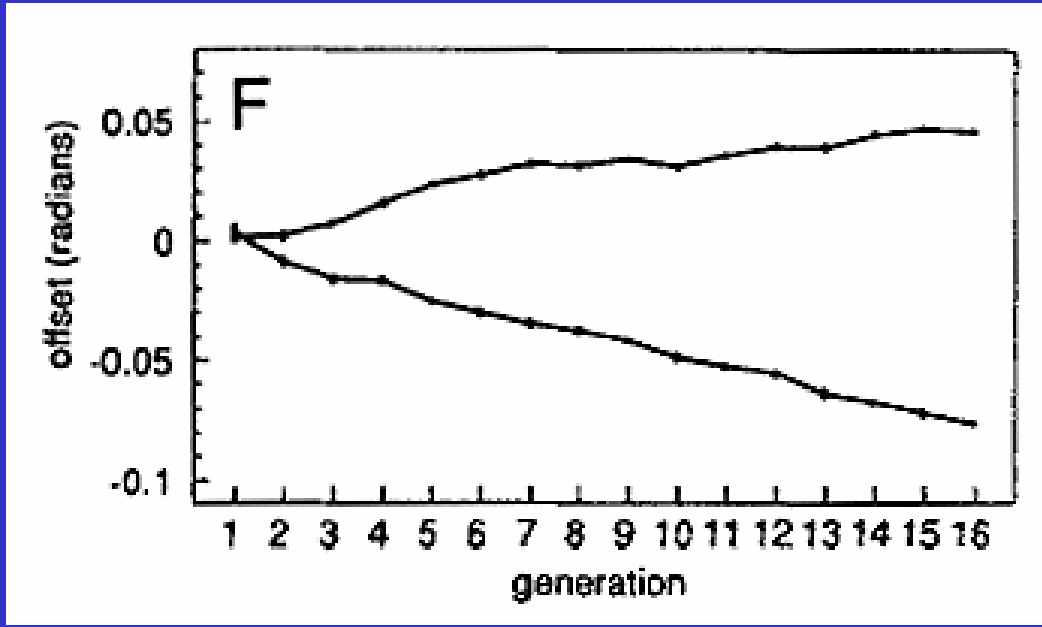
Medium-term Selection

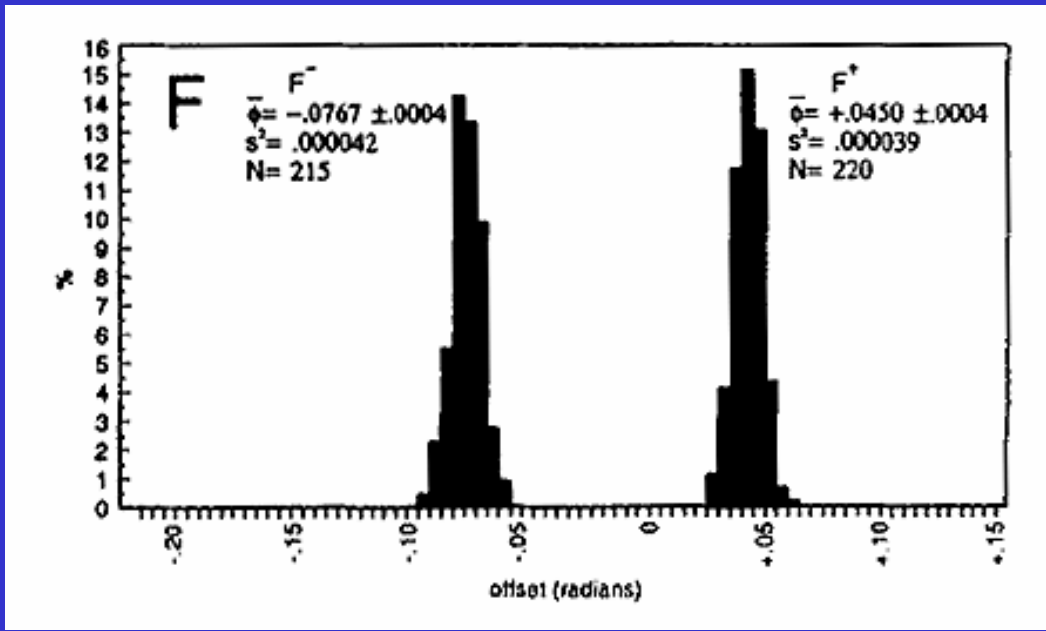
Wing Shape



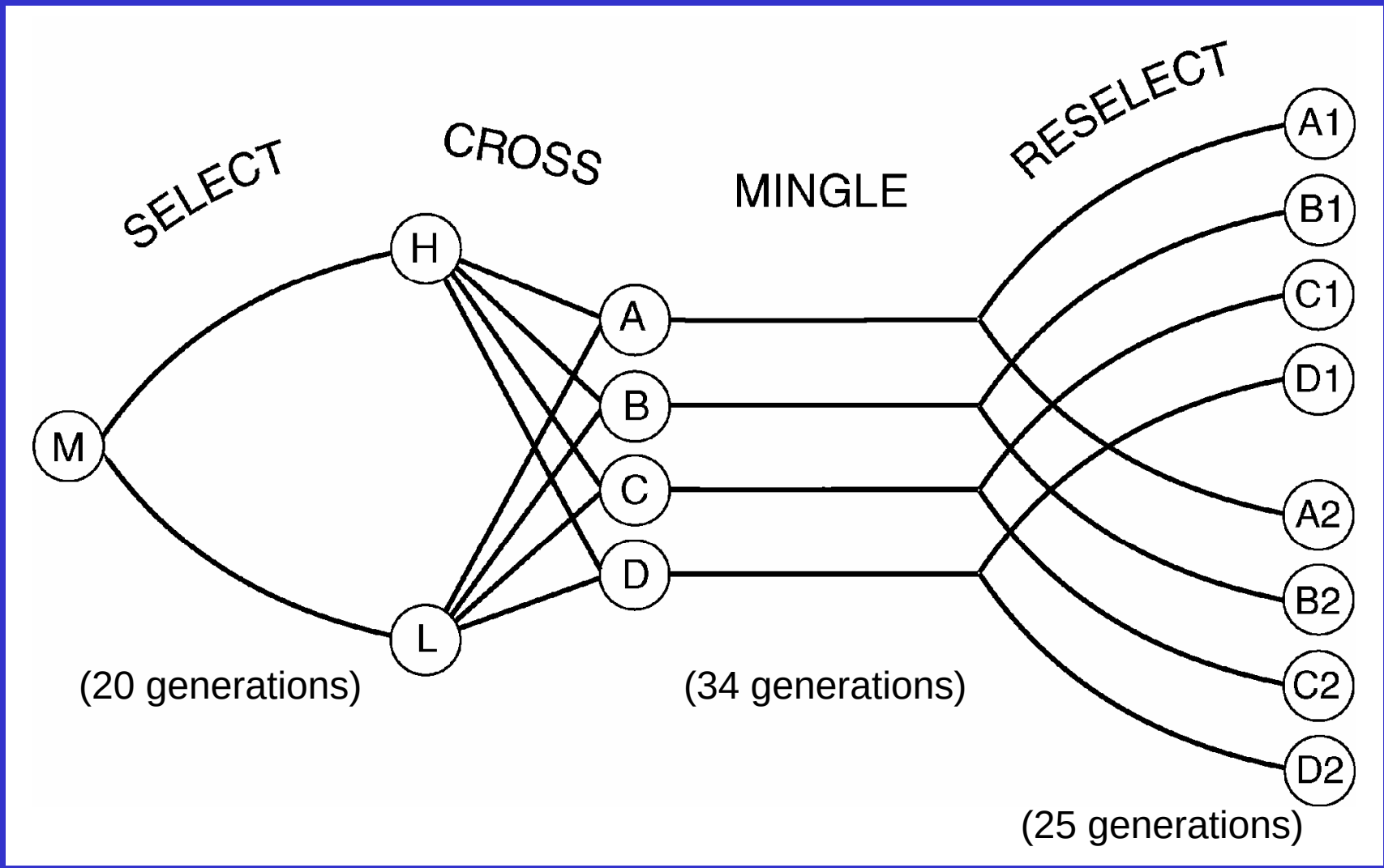


Weber, K.E. (1990)


F
0.05
0
-0.05
-0.1
offset (radians)
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
generation


F
F⁻
φ̄= −.0767 ±.0004
s²= .000042
N= 215
F⁺
φ̄= +.0450 ±.0004
s²= .000039
N= 220
%
offset (radians)

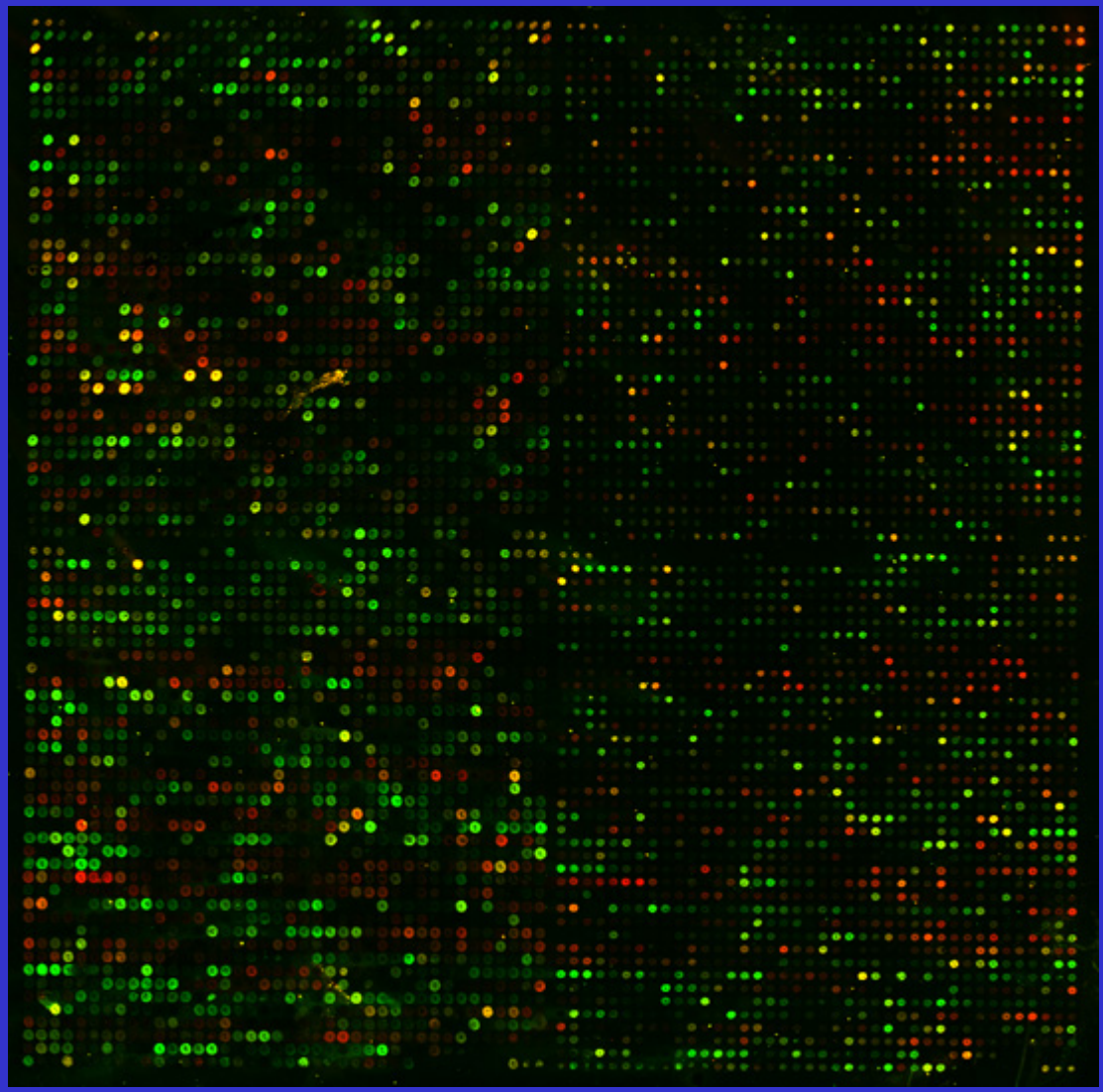
Mixed and Reselected



Weber, K.E., Greenspan, R.J. et al. (2007)

Genes of all sorts

(wing discs – restricted tissue)



Gene	Arm	Band	cM	Fold
CG3625	2L	21B7	0.4	+1.8
CG4291	2L	21D4	1.5	–1.7
CG3036	2L	25B1-2	14.2	+2.5
CG31918	2L	25C1-3	15.1	+2.1
CG31617	2L	39E1	54.6	–4.6
CG40293	2R	41C1-6	55.0	–1.5
CG10067 (*Act57B*)	2R	57B5	95.4	+4.2
CG17090	3L	61C3-5	0.1	–2.6
CG13895	3L	61C8	0.2	+1.9
CG2469	3L	61F5-6	0.4	–1.6
CG9186	3L	61F6	0.4	–2.1
CG2211	3L	61F6	0.4	+2.2
CG10359	3L	63E5	6.8	+4.2
CG32373	3L	66A8-12	23.0	+4.1
CG6776	3L	66D5	26.0	–3.3
CG13053	3L	72D10	43.6	+3.3
CG13023	3L	73D6	44.4	–1.7
CG4319 (*rpr*)	3L	75C6	46.1	–2.9
CG4144 (*GNBP2*)	3L	75D6	46.4	+2.2
CG31522	3R	82B2-3	47.2	–2.7
CG1163 (*Rpll18*)	3R	83A1	47.5	+1.5
CG10287 (*Gasp*)	3R	83D4	47.7	+2.0
CG18213	3R	89E10	59.1	–4.0
CG5184 (*mRpS11*)	3R	89E11	59.2	+1.9
CG6439	3R	93F13	73.9	+1.9
CG1471	3R	99F5-6	101.6	–1.9
CG32017	4	102F8	3.1	+9.1

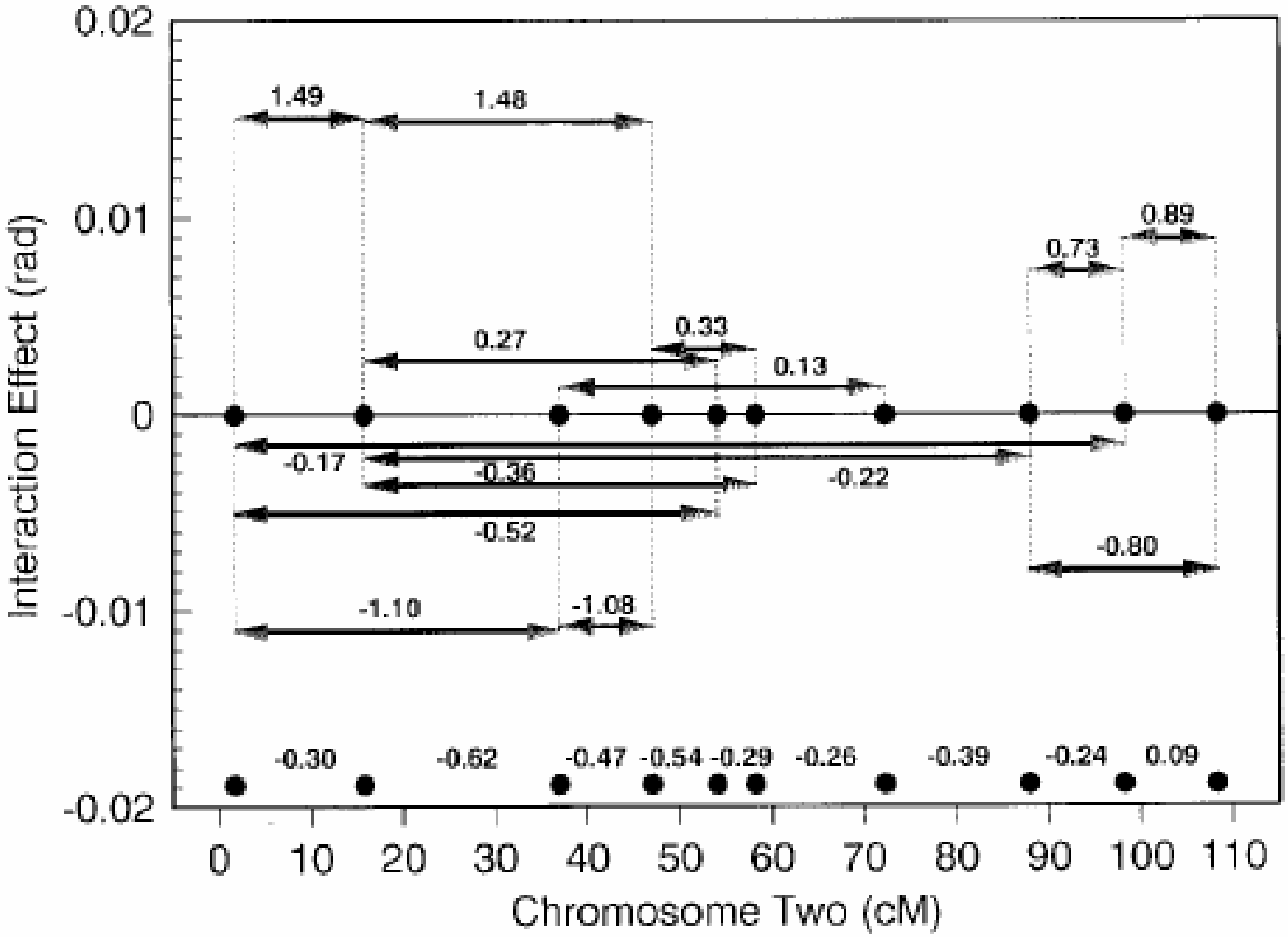
Known wing development genes

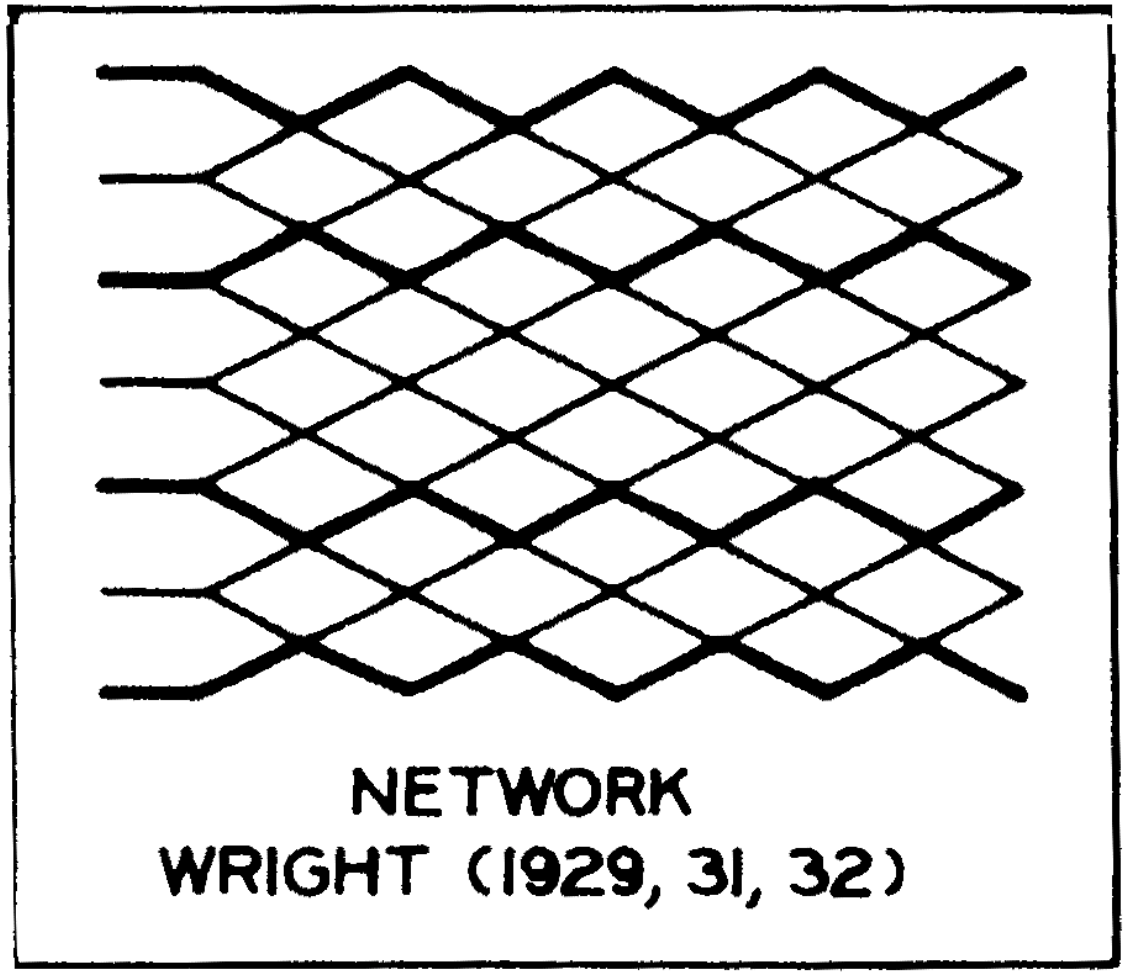
Abl oncogene
abrupt
absent
APClhomologue
Antennapedia
Apaf-1-related-killer
apterous
araucan
arc
Argos
aristaless
arrow
Arrowhead
atonal
Axin
baboon
bantam
BarH1 and BarH2
Beadex
blistered
blistery
brahma
brain tumor
brinker
broad
bursicon
canoe
Capicua
capricious
capulet
caupolican
Cdc42
charlatan
chico
Chip
combgap
corkscrew
costa
cousin of atonal
crossveinless 2
cut
Cyclin-dependent kinase
dachsous
daughterless
Daughters against dpp
death executioner Bcl-2 homologue
decapentaplegic
Dfrizzled-3
diego
discs lost
dispatched
distal-less
division abnormally delayed
Dorsocross
drifter
E(spl) region transcript m7
E2F transcription factor
E2F transcription factor 2
ecdysone receptor
echinoid & friend of echinoid
Egf-r
elbow
engrailed
Enhancer of split complex
escargot
expanded
extra machrochaete
extradenticle
eyelid
fat
Fibroblast growth factor receptor
four-jointed
fringe
frizzled
furrowed
G protein salpha
G protein-coupled receptor kinase 2
gigas
Glutactin
grain
grainy head
Grunge
guftagu
headcase
hedgehog
held out wings
hemipterous
Hepatocyte growth factor regulated tyrosine kinas
substrate
hephaestus
hibris
hiiragi
hippo
HMG Coenzyme A reductase
homothorax
hopscotch
hyperplastic discs
inflated - see myospheroid
Inositol 1,4,5,-tris-phosphate receptor
inscuteable
Insulin-like receptor
Integrin linked kinase
invected
karst
kekkon-1
klumpfuss
knot
Laminin A
legless
lethal (2) giant
liquid fac
longitud ls la ing
Ly
m elle
ma
dea
Merlin
mind-bomb
Mnt
Moesin-like
moira
Mothers against dpp
multiple edematious wings - see myospheroid
muscle segment homeobox
Myb
Myosin-binding substrate
myospheroid
nemo
NEM-sensitive fusion protein 2
net
Neurofibromin 1
nicastrin
Nitric oxide synthase
not enough muscle
O-fucosyltransferase 1
Optix
opto blind
outs - a potential ligand
box neuro
kinase
angolin
pannier
Pcaf
pdm-1
pickpocket 25
pitchoune
polyhomeotic
prickle
Protein tyrosine phosphatase 69D
Pten
puckered
punt
pygopus
Rac1
RacGAP50C
reversed polarity
Rfx
Rheb
Rho1
rho-associated kinase
rhomboid
rolled - also known as MAP kinase
roughest
RPS6-p70-protein kinase
rugose
SANT domain protein
saxophone
scalloped
schnurri
scribbler
Serum response factor
Sex combs on midleg
shifted
short gastrulation
sightless
skittles
slingshot
small wing
snail
Snf5-related 1
spalt
spineless
split ends
ß3 tubulin
Star
starry night
strabismus
string
supernumerary limbs
Suppressor of fused
Syntaxin 1A
Talin
target of Pox-n
TBP-associated factor 250kD
thick veins
Tiggrin
TNF-receptor-associated factor 1
tolloid-related
tricornered
twins
ultraspiracle
u-shaped
vein
vestigial
vrille
warts
wingless
wishful thinking
Wrinkled
yorkie
zipper
Zn finger homeodomain 2

None of these

Total = 214 genes

Gene interactions in selected strains

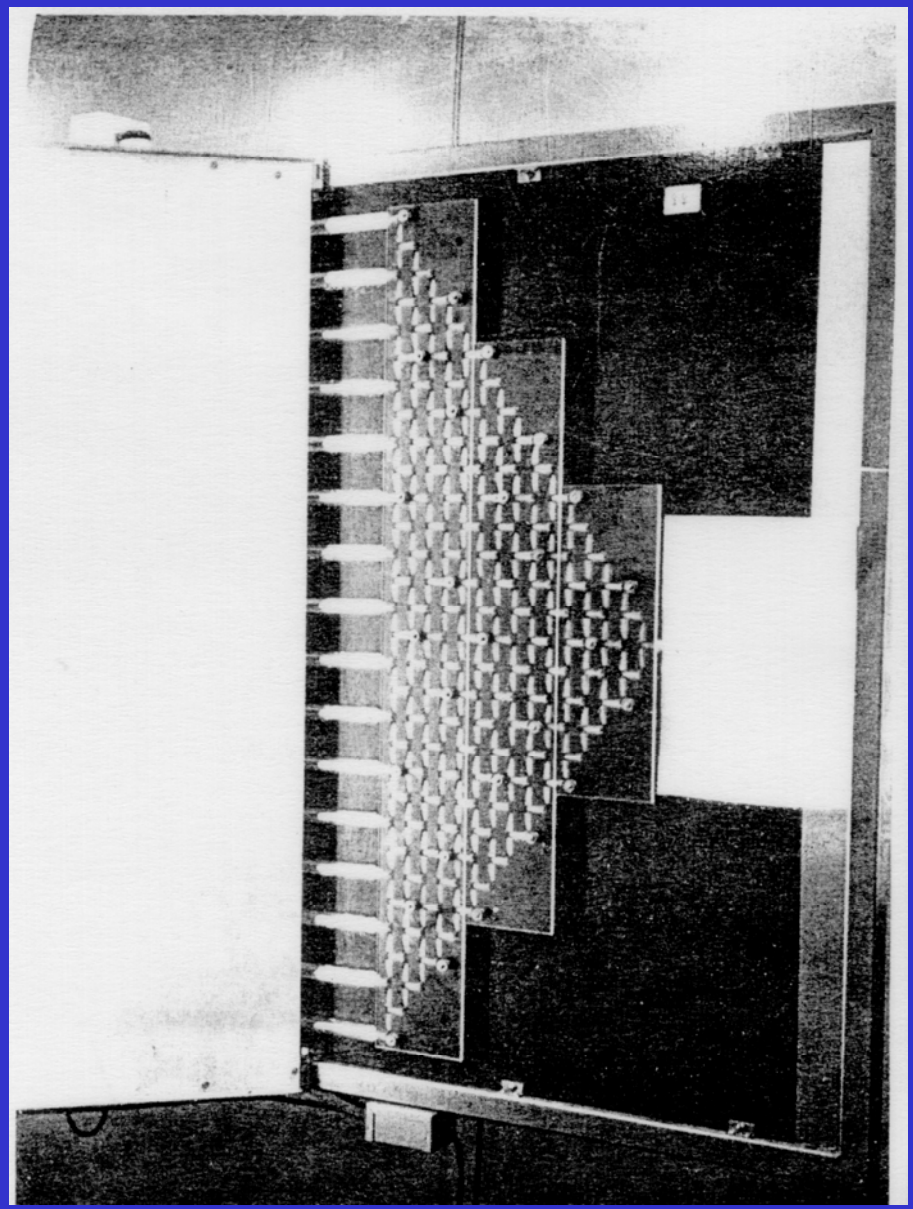




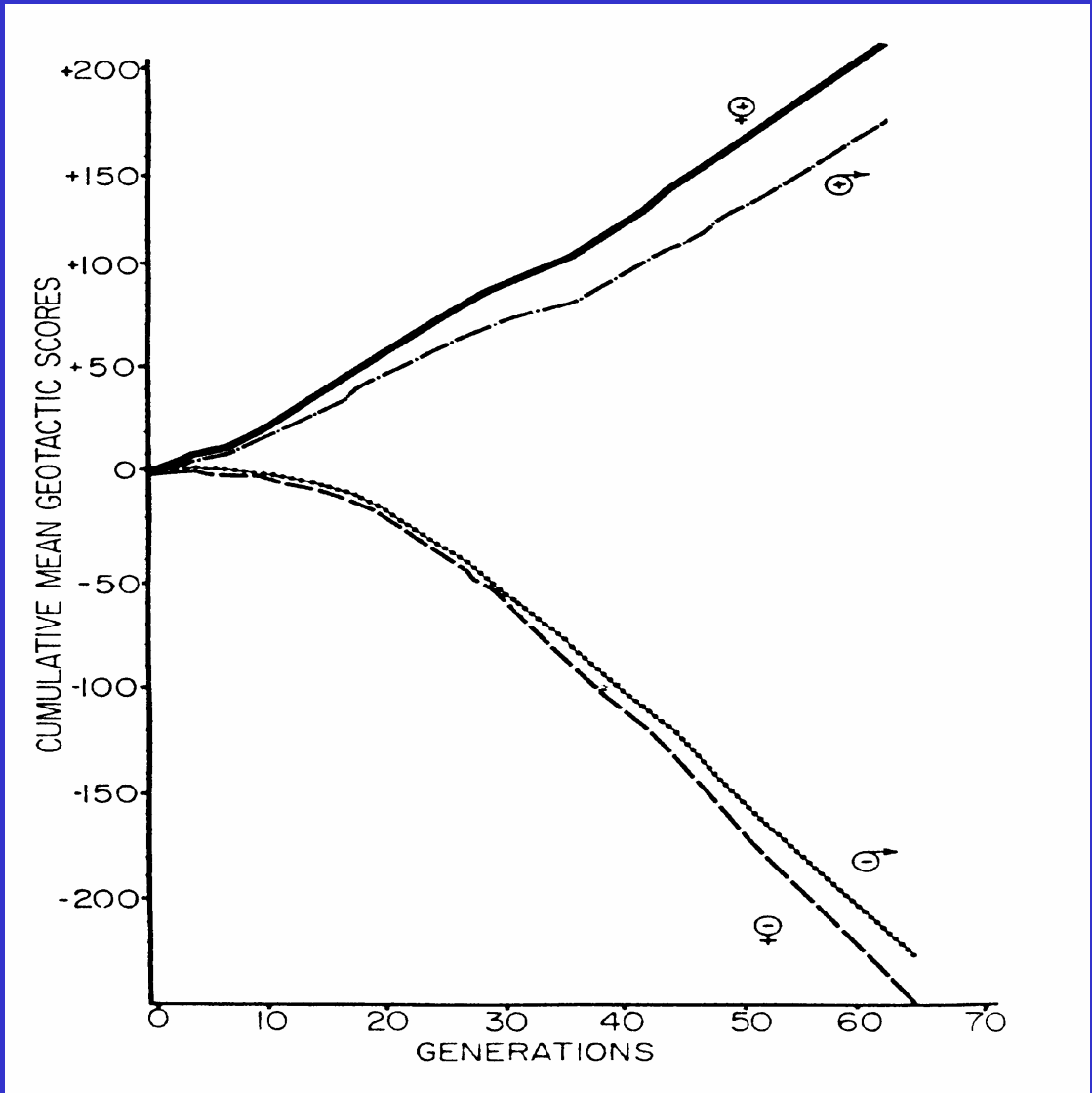
NETWORK
WRIGHT (1929, 31, 32)

Long-term Selection

Geotaxis

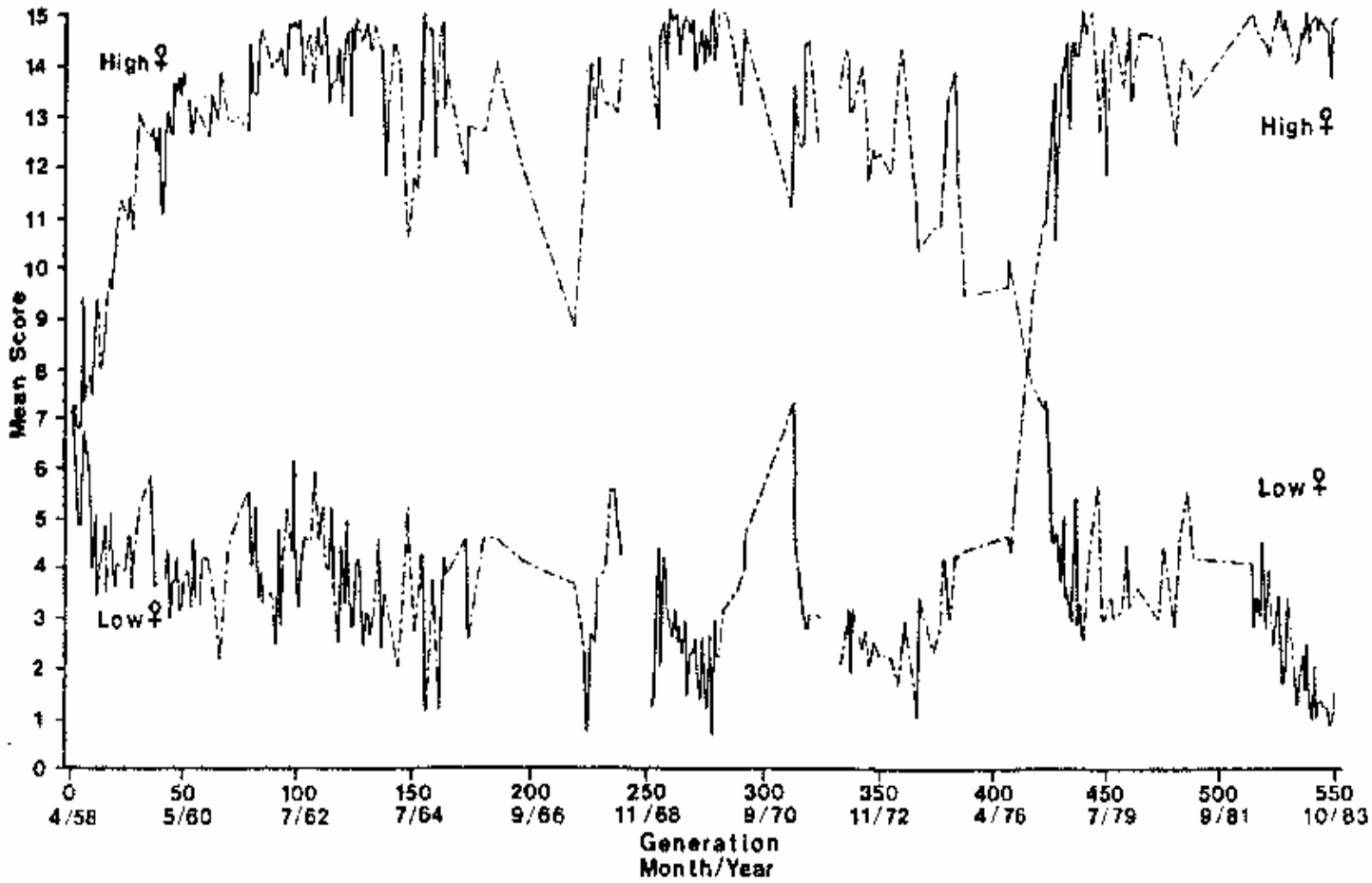


Bidirectional Selection



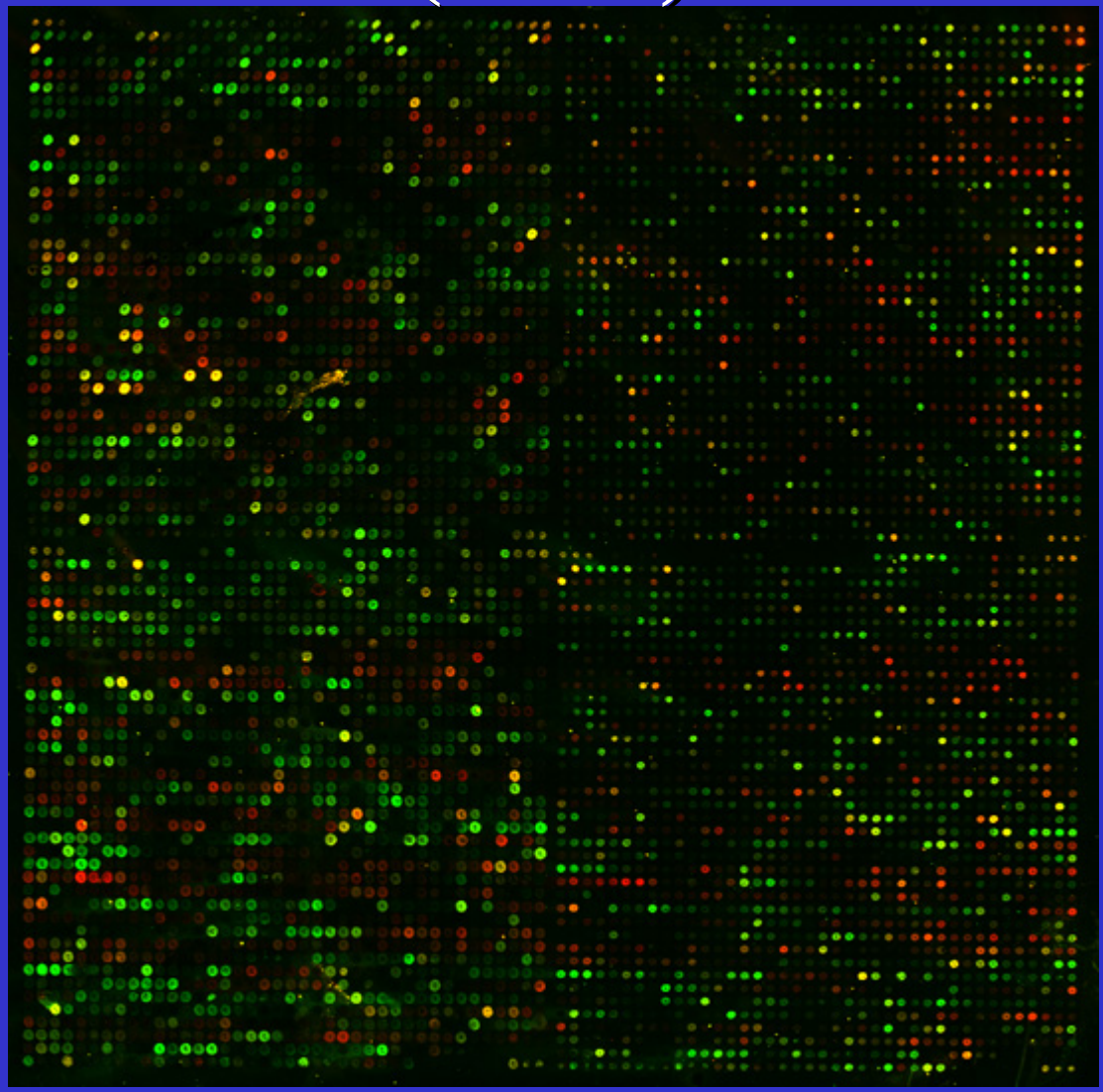
Hirsch, J. & Erlenmeyer-Kimling, L.F. (1962)

Selection response of *Hi* and *Lo* lines for first 25 years



Ricker and Hirsch (1985)

Genes of all sorts
(heads)



Gene expression

swallow	RNA binding protein
prospero	homeodomain protein

Signal transduction

nemo	serine/threonine protein kinase

Circadian rhythms

Pigment-dispersing factor	neuropeptide
cryptochrome	photoreceptor protein

Axon guidance

abLIM	actin-binding protein

Immune system

Attacin-A	immune defense protein
croquemort	macrophage receptor

Cytoskeleton & protein localization

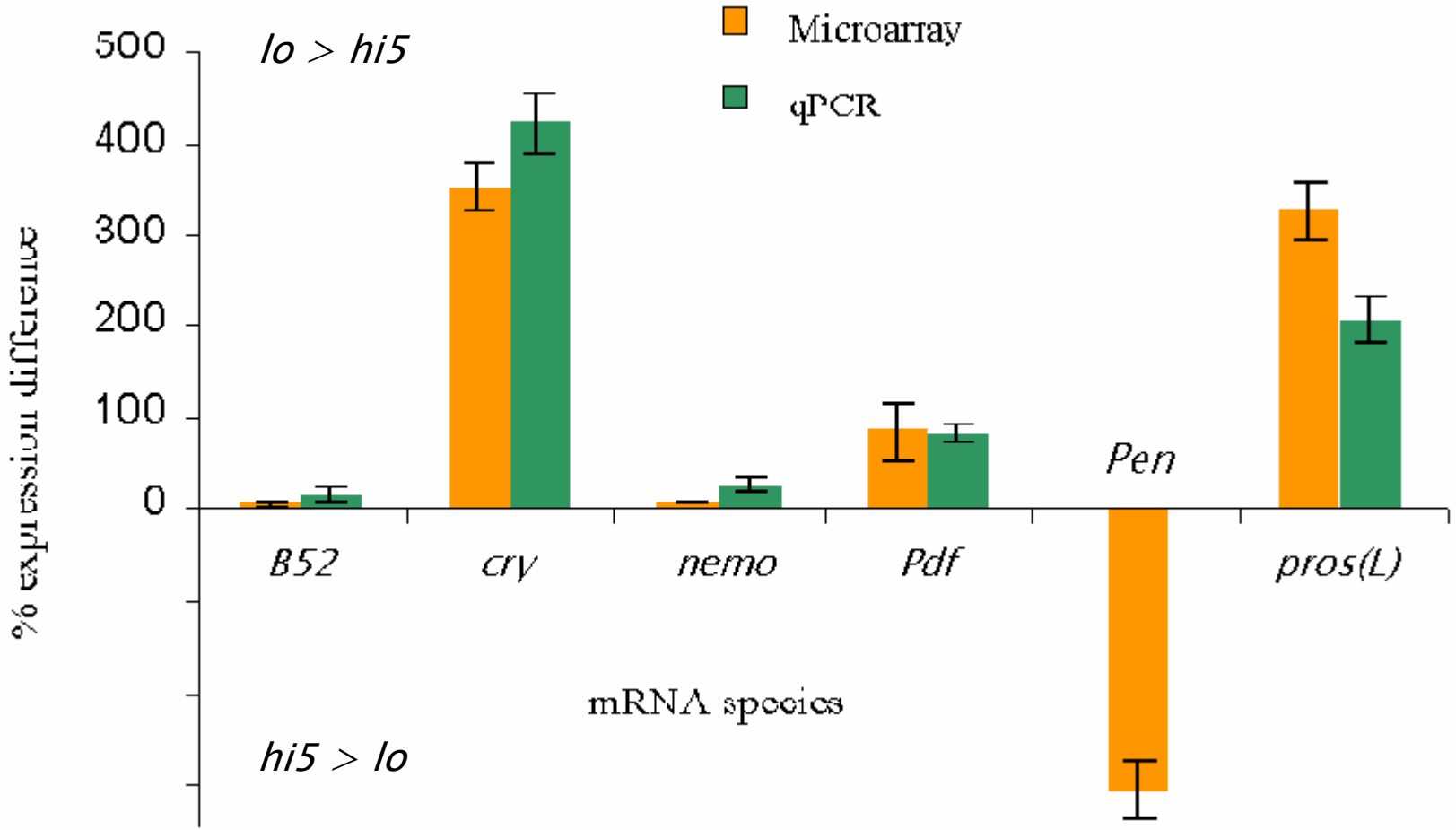
Pendulin	nuclear importin α2-subunit
zipper	cytoplasmic myosin II heavy chain
Klp67A	kinesin-like protein

Chaperones

Hsp90	*Hsp60*	*Hsp22*
Hsp70	*Hsp27*	

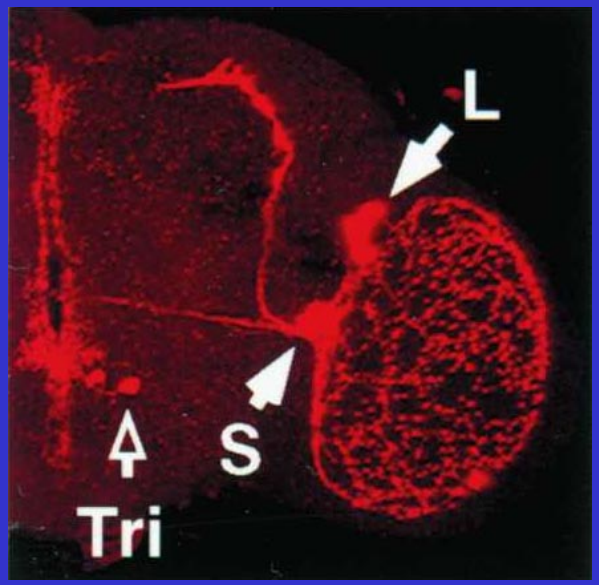
Toma et al. (2002)

mRNA levels in *hi5* vs. *lo* lines

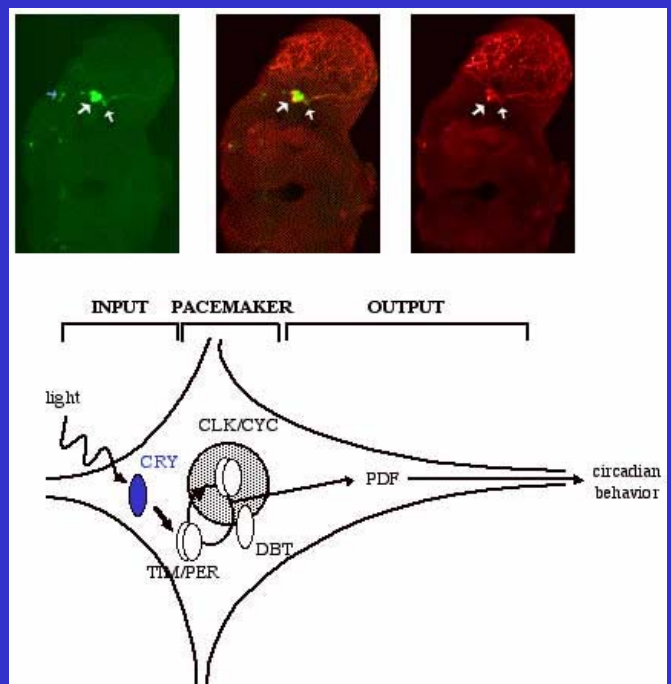


Large Effects

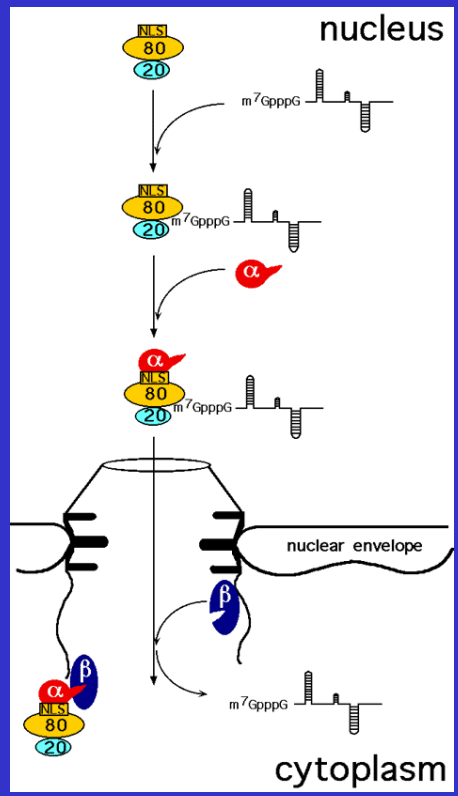
Pigment Dispersing Factor (Pdf)

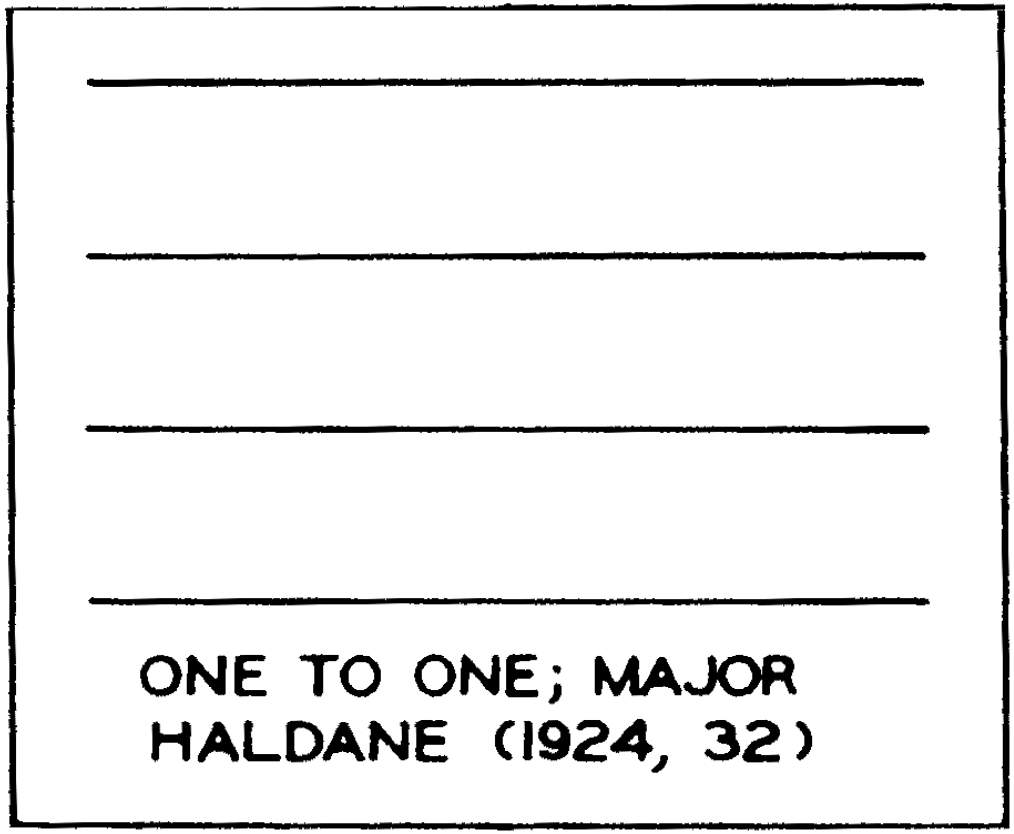


cryptochrome (cry)



Importin-α *(Pendulin)*




ONE TO ONE; MAJOR
HALDANE (1924, 32)

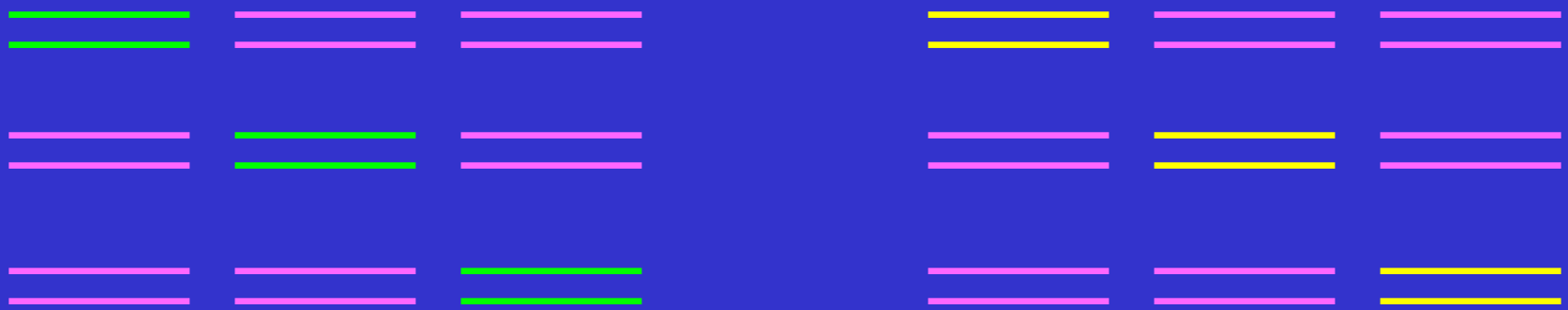
Chromosome Substitution Lines

Lo

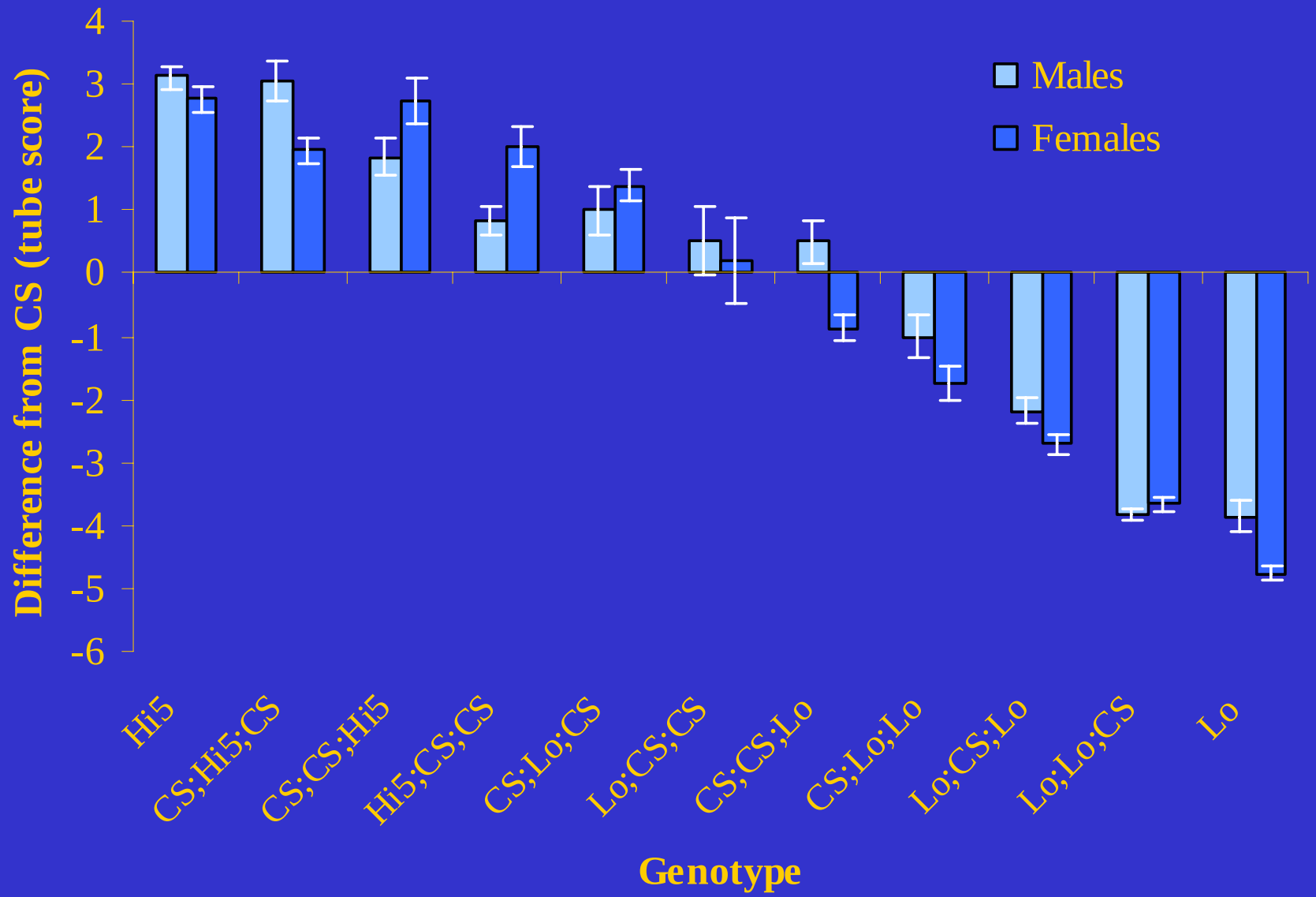
Hi5

X

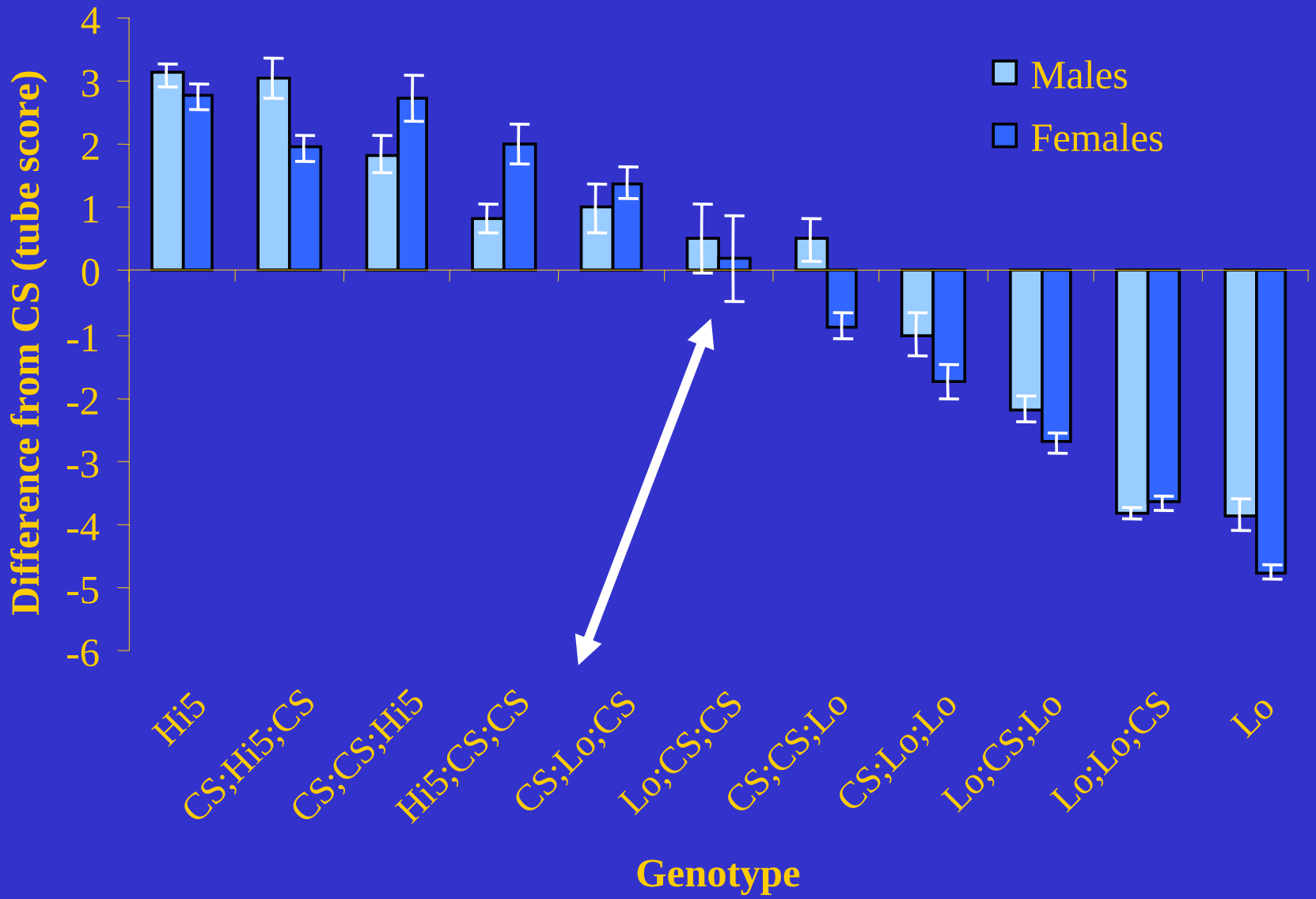
CS



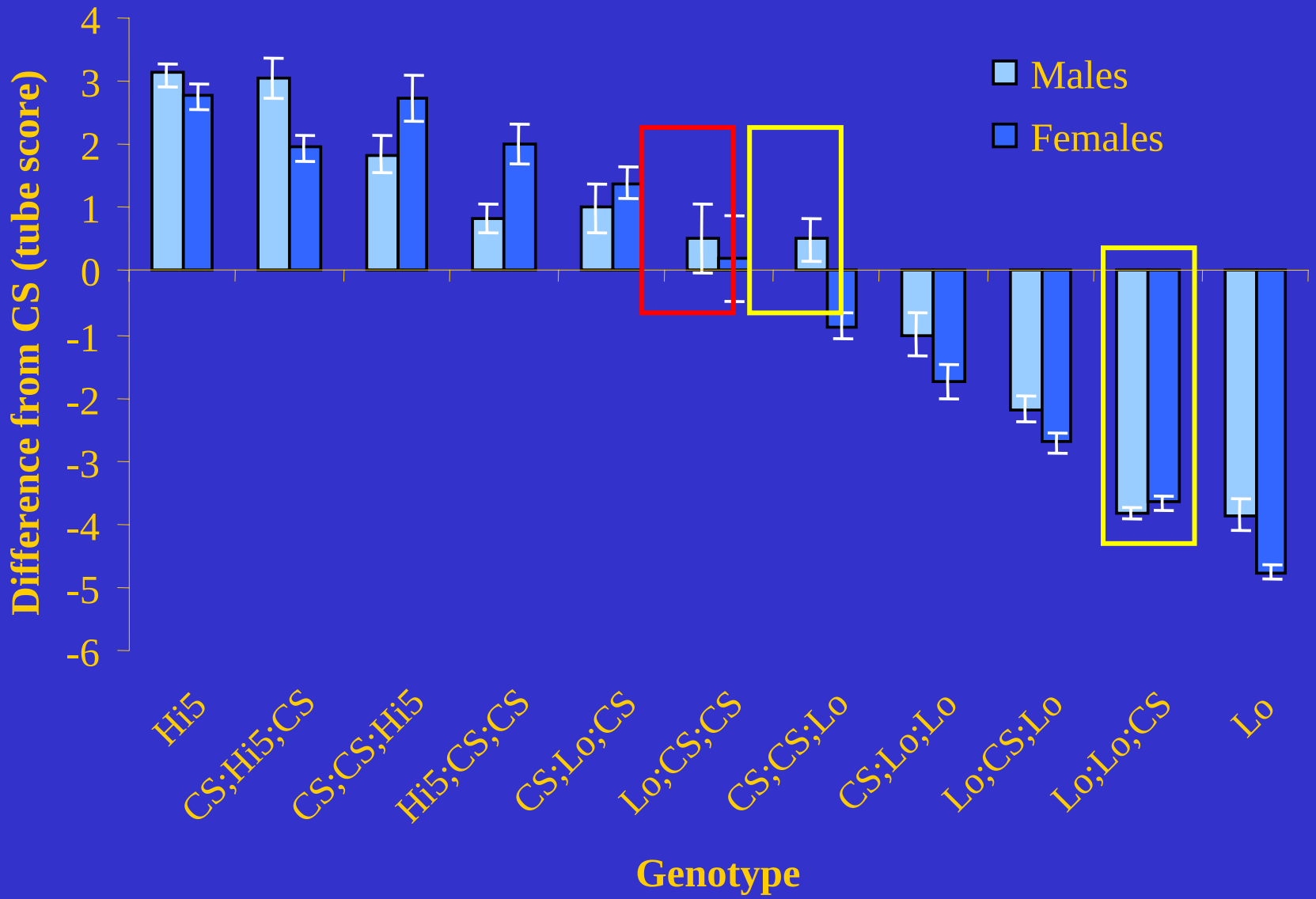
Epistatic Interactions



Non-additive interactions



Non-additive interactions

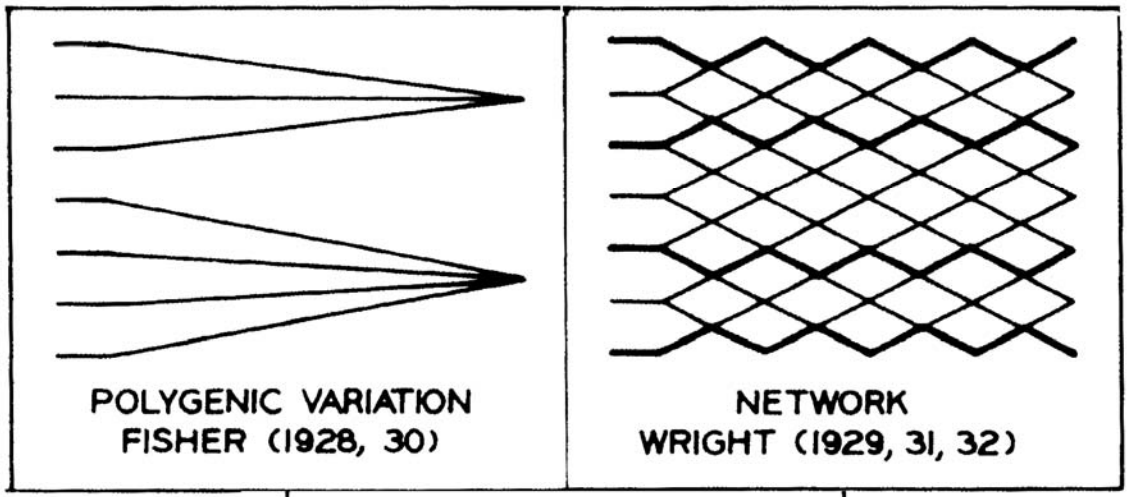


Known Drosophila genes

Gene	Protein Function
[b]broad (br)	Zinc-finger class transcription factor
[b]off-track (otk)	Receptor tyrosine kinase with role in neural pathfinding (Human homologs are Trk neurotrophin receptors)
[b]discslarge (dlg1)	MAGUK class protein with guanylate kinase, PDZ, SH3 and P-loop domains with role in synapse structure (Human homolog is [illegible] 10)
[b]escargot (esg)	Zinc-finger class transcription factor with role in peripheral nervous system development (Human homolog is SLUG)
[b]Connector of kinase to AP-1 (Cka)	WD-40 domain protein, part of JNK signaling cascade (Human homologs are striatin, zinedin and cell cycle autoantigen SG2NA)
[c]period (per)	Transcription factor that regulates circadian rhythm (Human homolog is PER3)
[c]timeless (tim)	Transcription factor that regulates circadian rhythm (Human homolog is hTimeless)
[c]dunce (dnc)	Phosphodiesterase that regulates cAMP levels (Human homolog is cAMP-specific 3', 5'-cyclic phosphodiesterase 4D)
[c]rutabaga (rut)	Adenylate cyclase responsible for cAMP synthesis (Human homolog is brain adenylate cyclase 1)
[c]I'm not dead yet (indy)	Sodium dicarboxylate cotransporter implicated in longevity (Human homolog is NADC3)
[c]G-salpha60A	Component of transmembrane receptor signal transduction cascade involved in associative learning in mushroom body
Pdf receptor (Pdfr)	Receptor for neuropeptide Pdf.

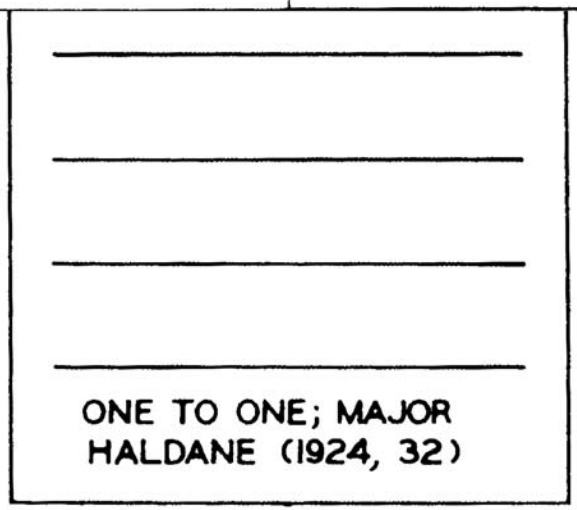
None of these

The Seasons of Selection



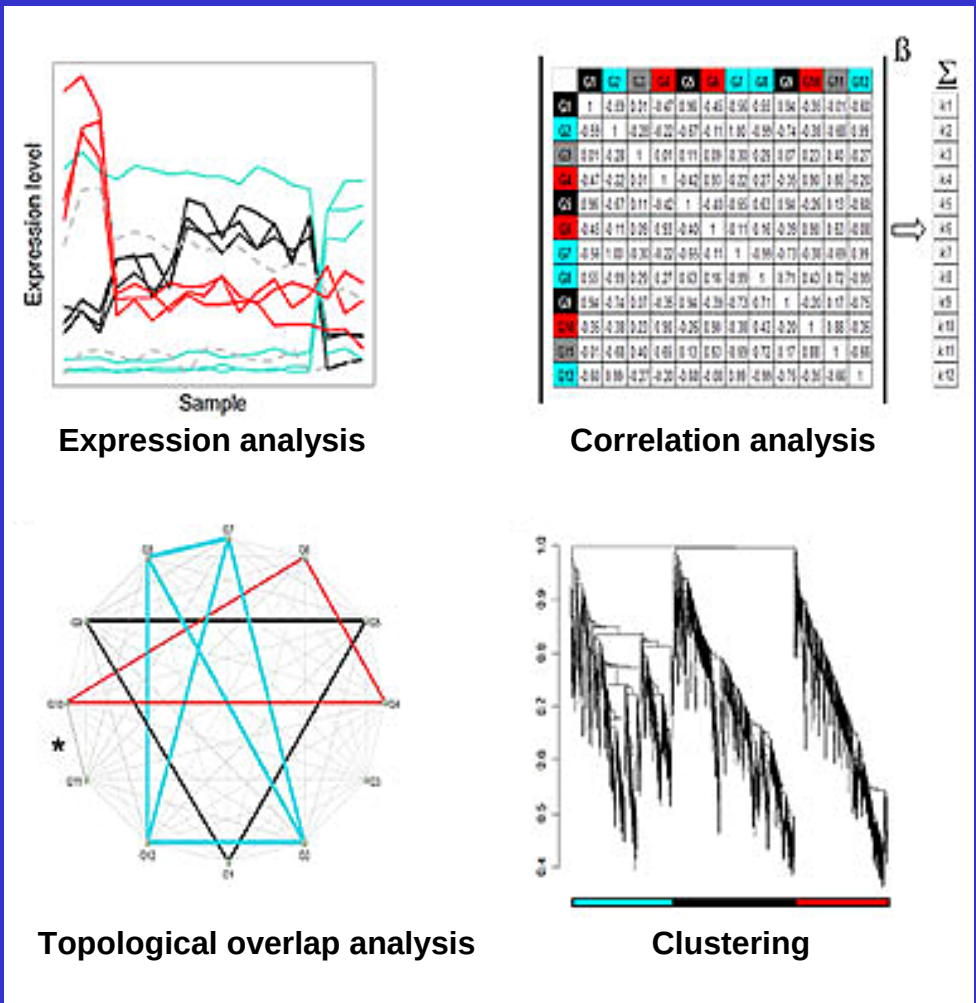
Short-term?

Medium-term?



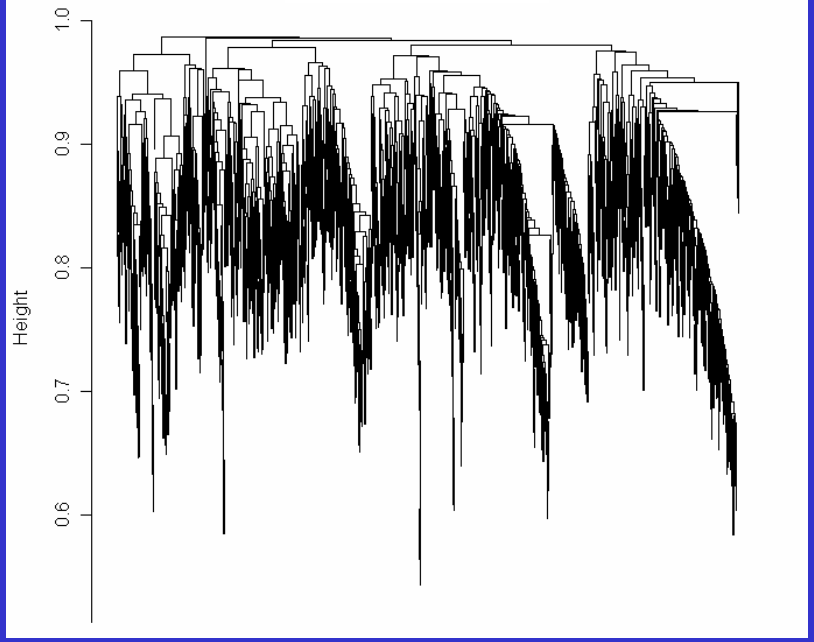
Long-term?

Coexpression Analysis – Network Structure

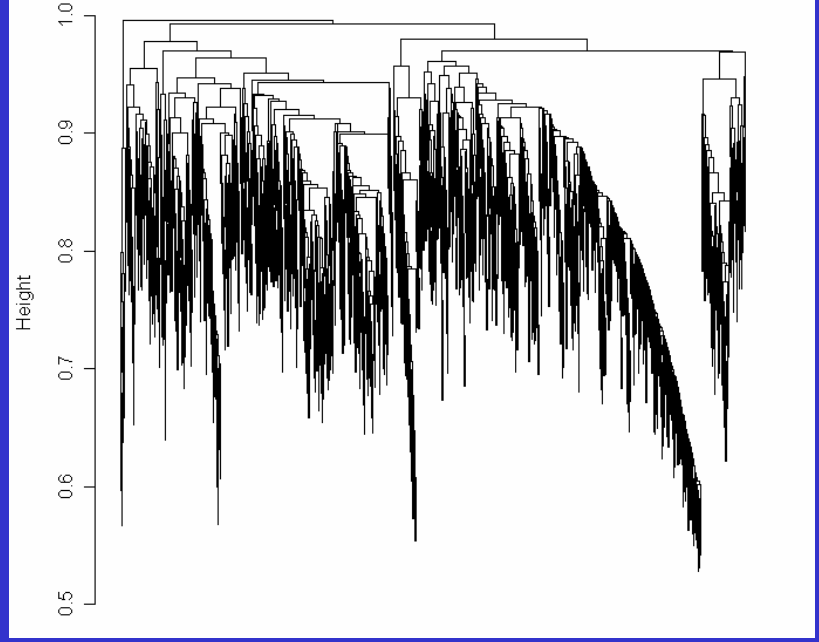


Oldham, Horvath & Geschwind (2006)
Zhang & Horvath (2005)

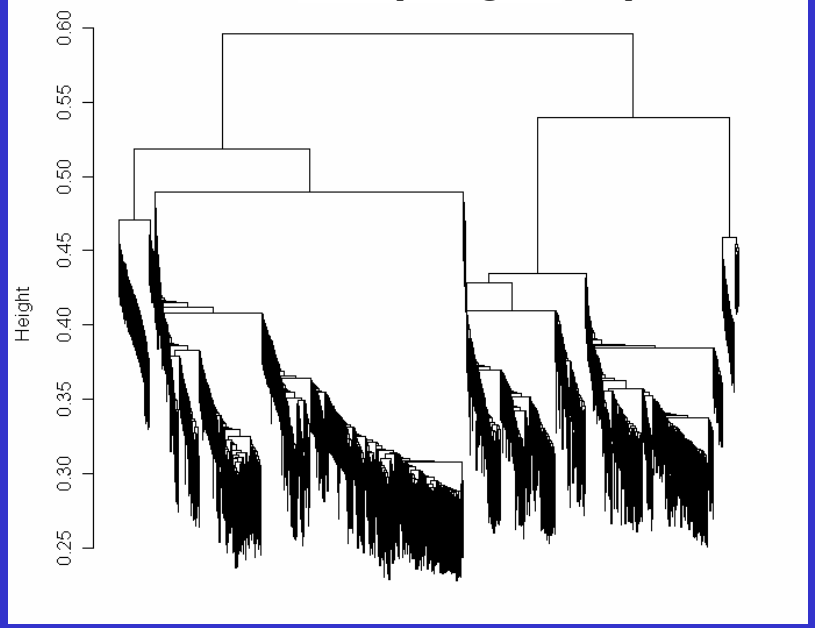
Aggression (short-term)



Wing shape (medium-term)



Geotaxis (long-term)

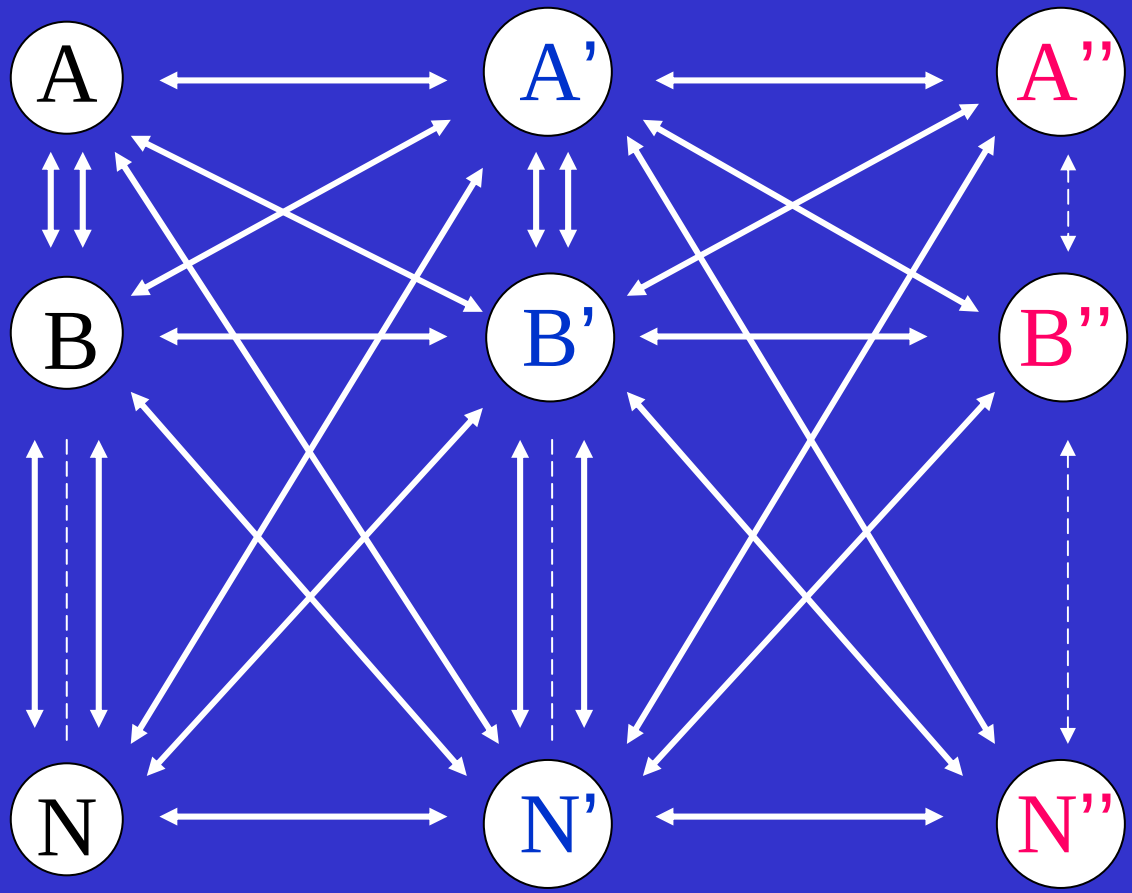


Why so different from mutant screens?

Why so different from mutant screens?

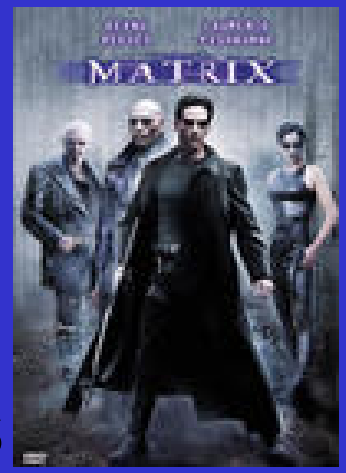
$\Rightarrow$ wide-ranging network for any phenotype

Genes **Cells** **Phenotype**



Can you affect any phenotype from anywhere in the genome?

“The Matrix”

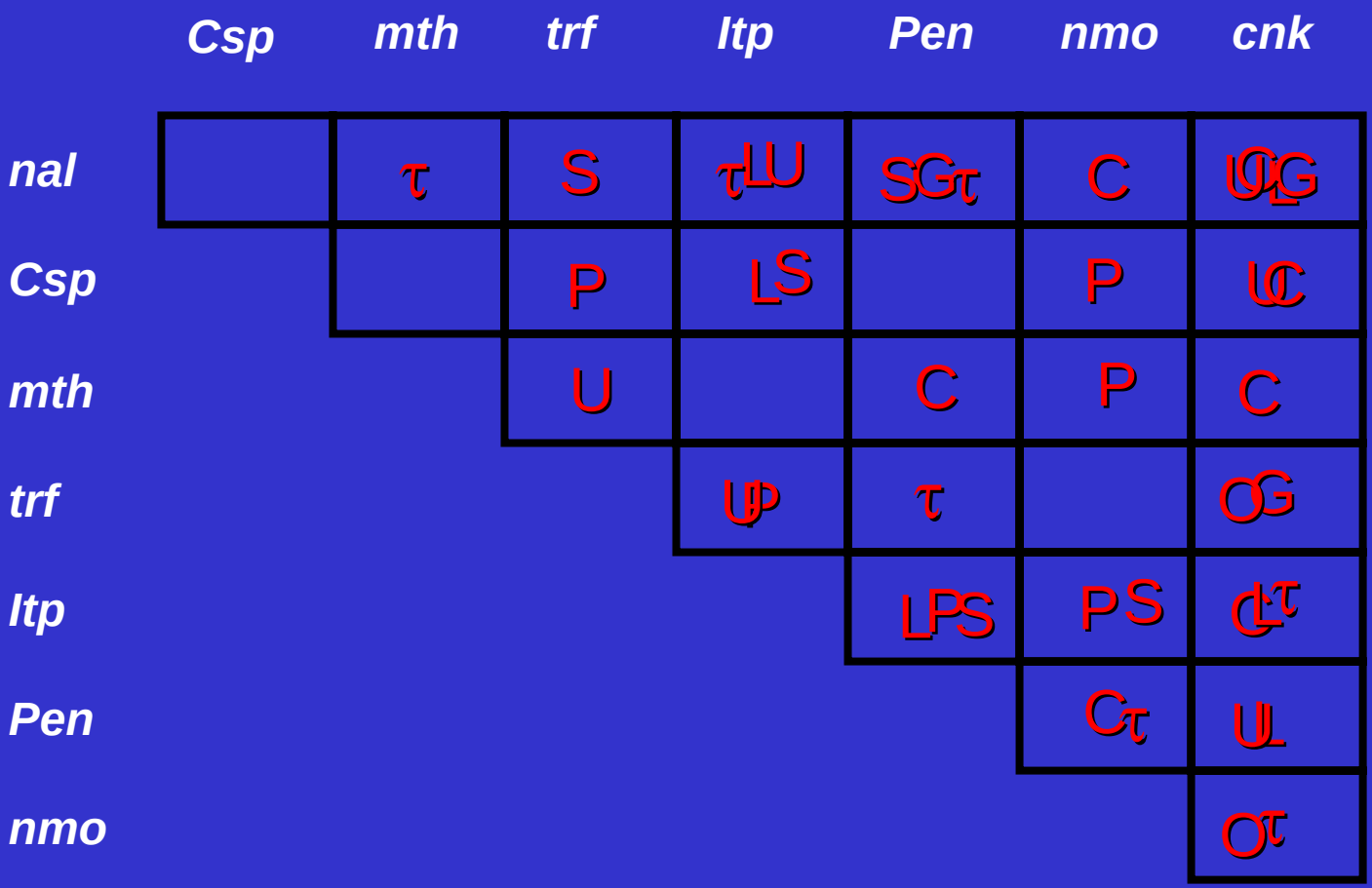


- 8 “random” loci
- range of functions and phenotypes
- all expressed in the nervous system
- place on common genetic background
- test all pairwise combinations

$$\begin{pmatrix} m1 & + \\ + & m2 \end{pmatrix}$$

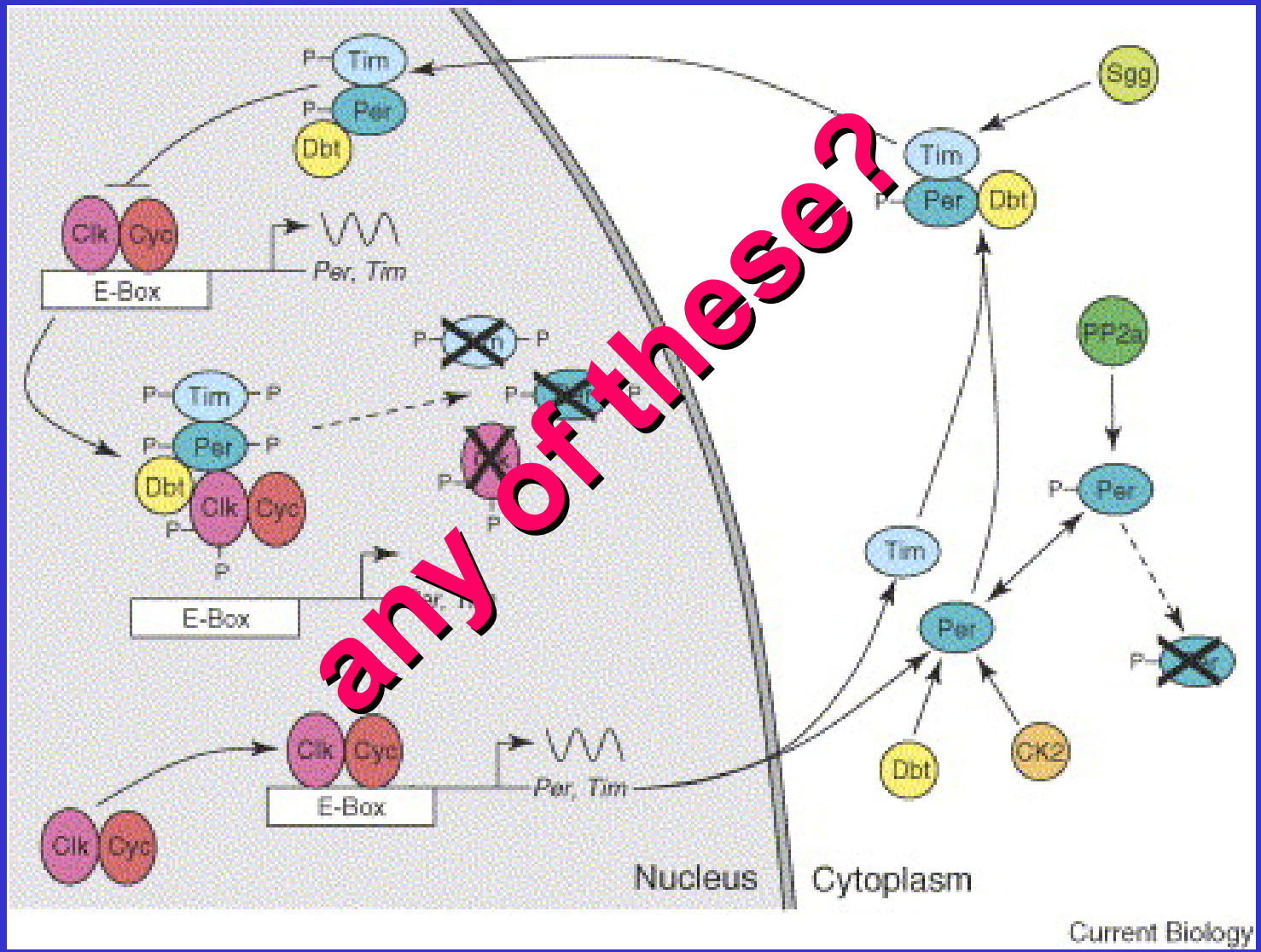
for different behaviors

Significant Effects

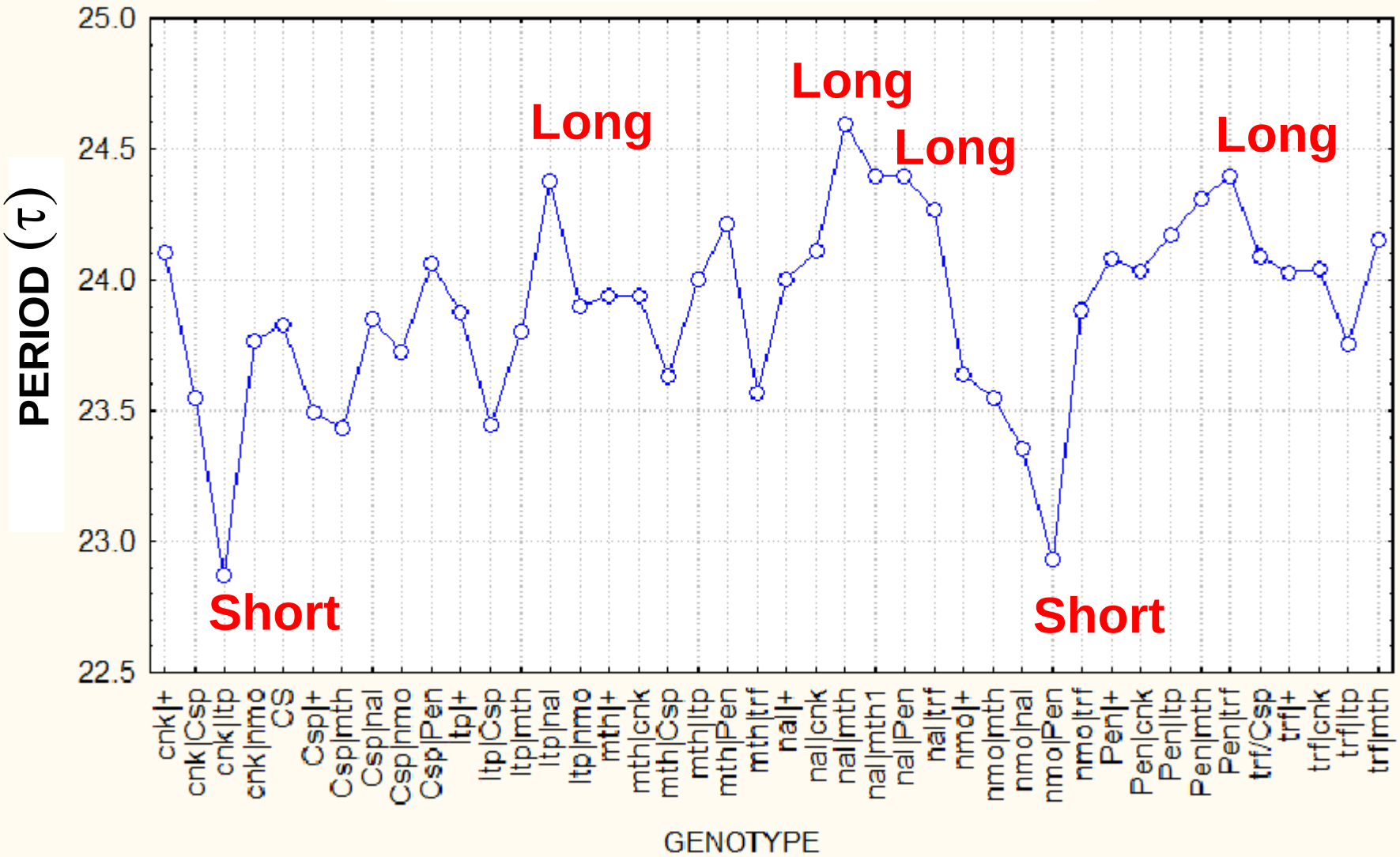


mostly combinatorial

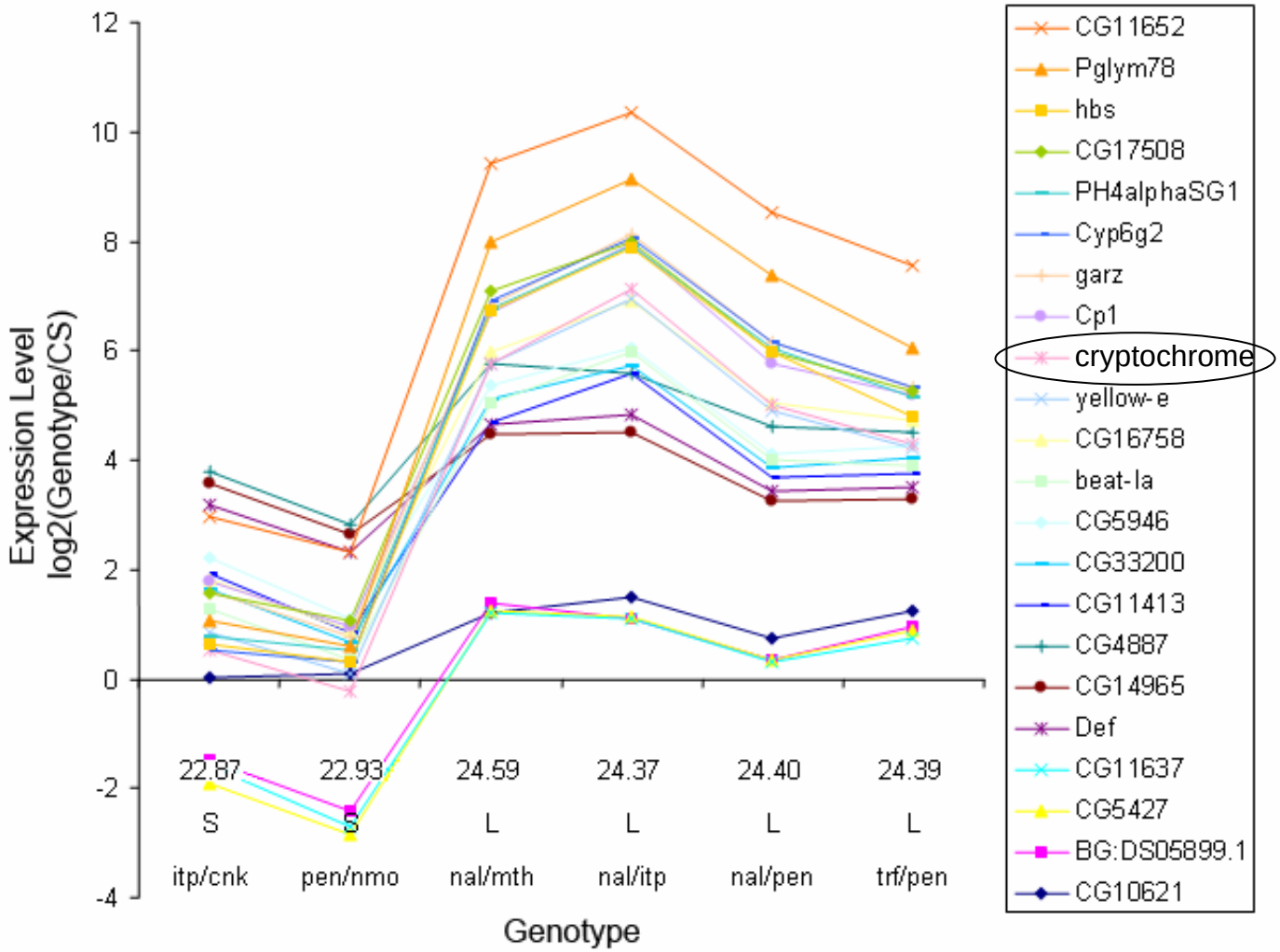
The Canonical Rhythms Pathway



Circadian Rhythms

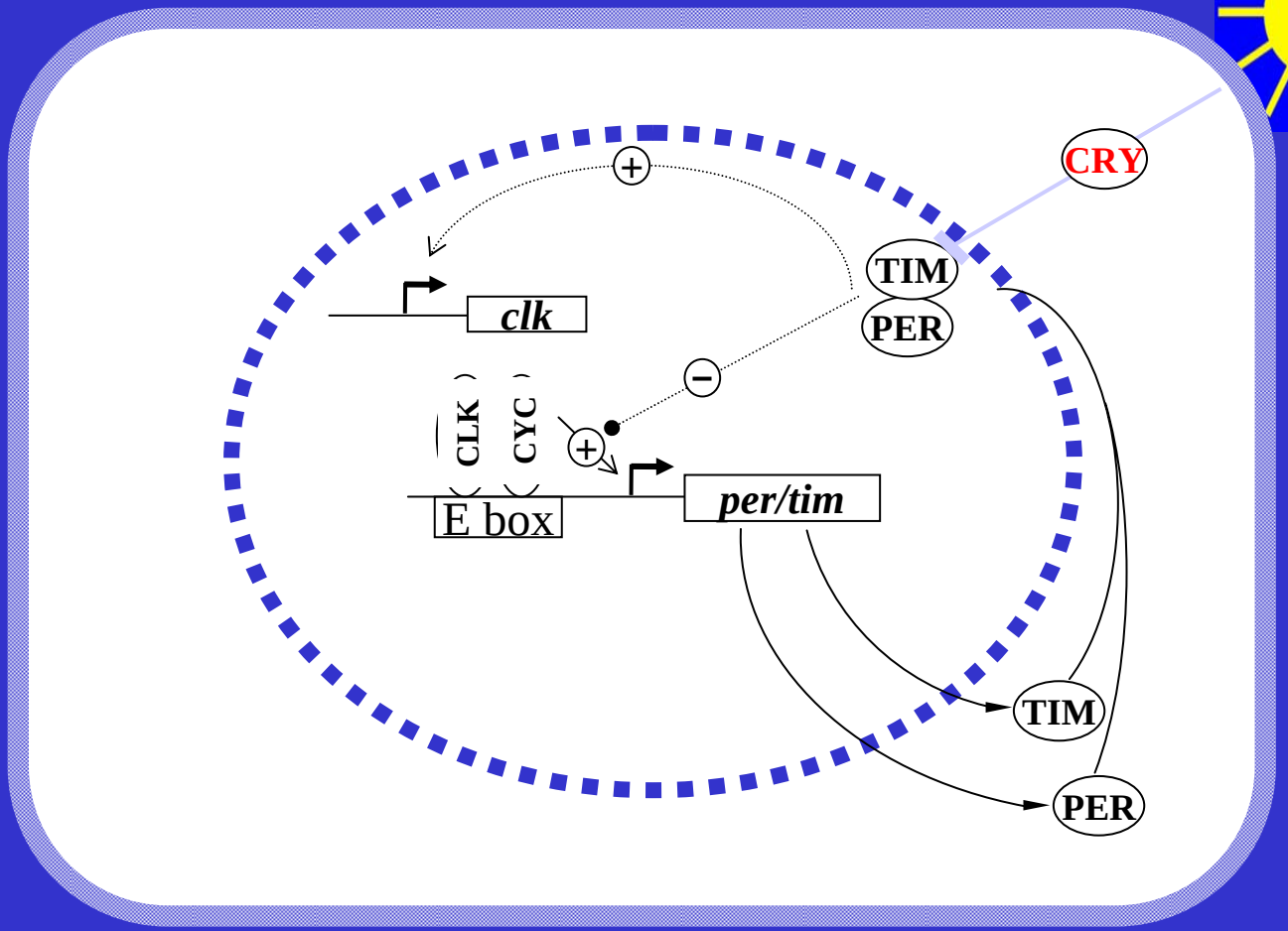


Differential Gene Expression in Short vs. Long

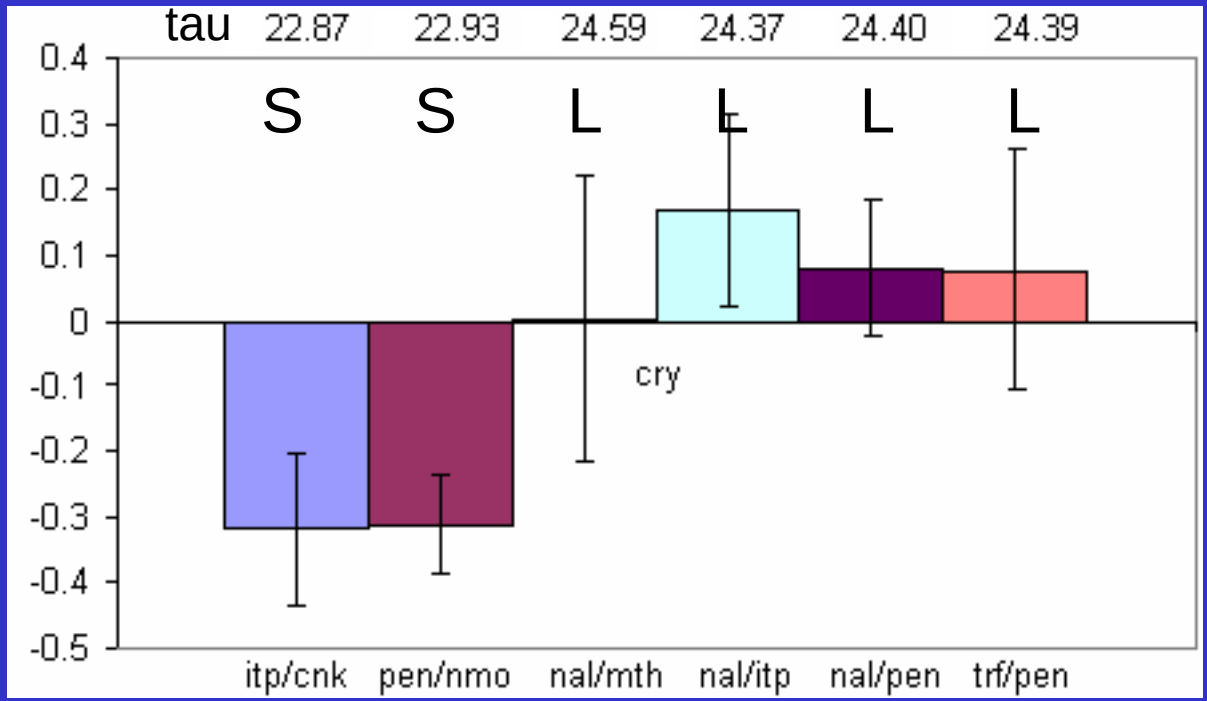


cryptochrome

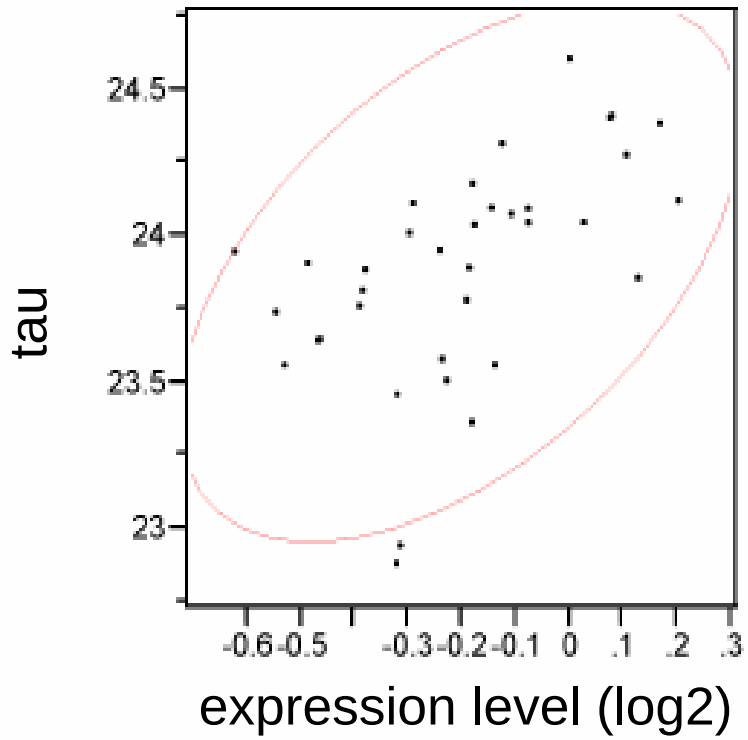
not part of the core clock,
but entrains the clock to light



cryptochrome levels in Short vs. Long



cryptochrome-tau correlation (all genotypes)

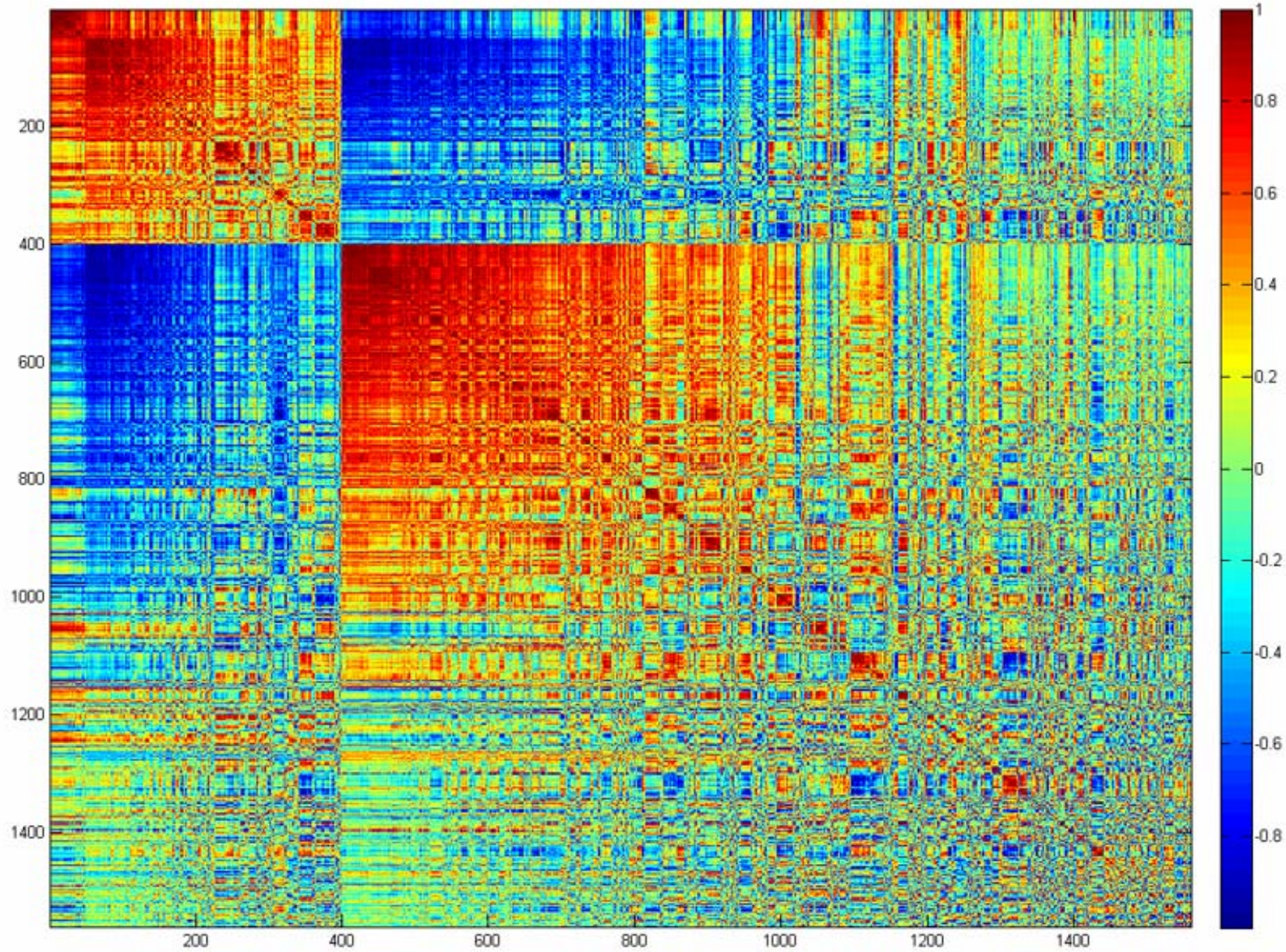


Pairwise Correlations

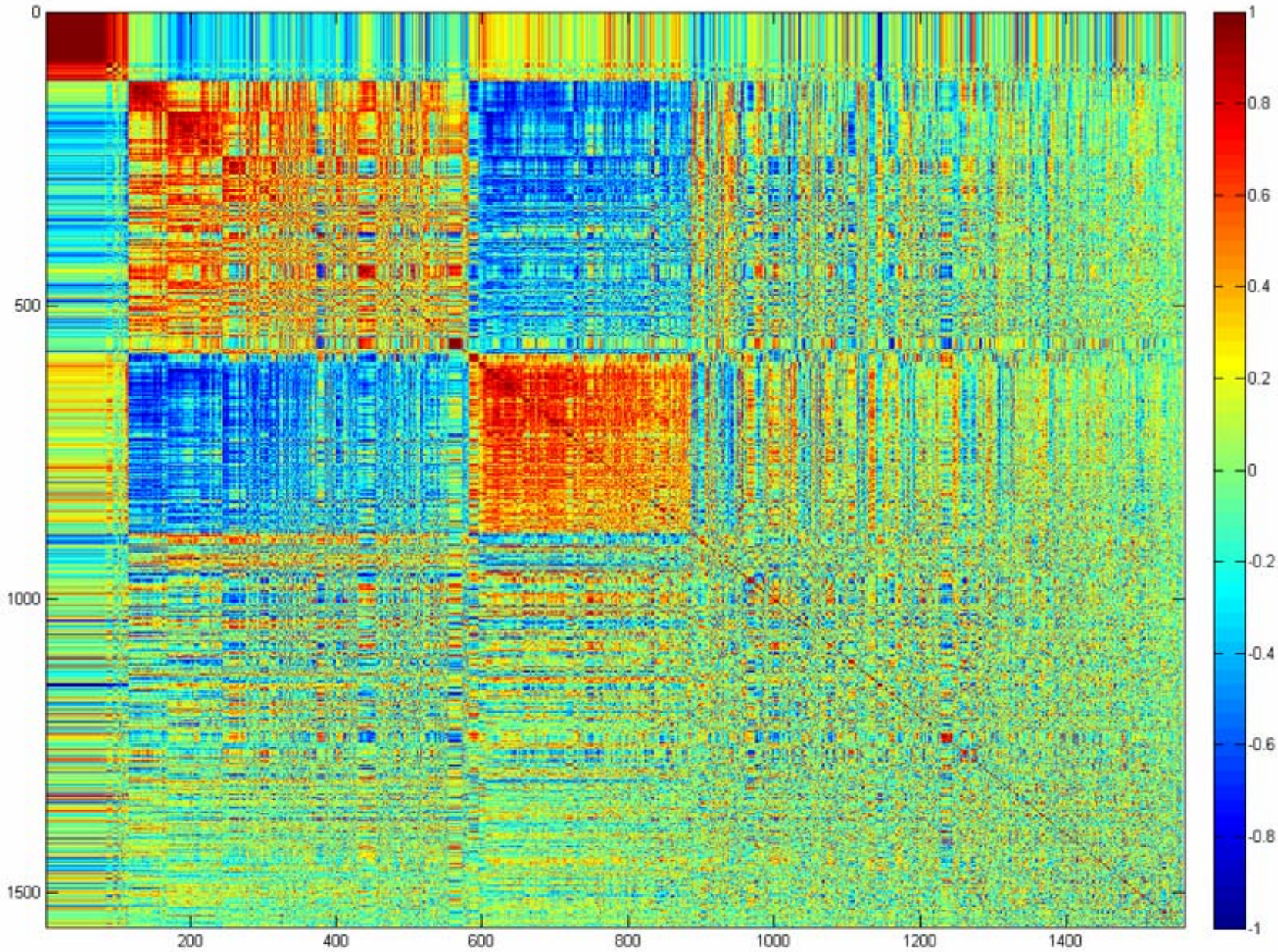
Variable	by Variable	Correlation	Count	Signif Prob
tau	cry	0.5310	36	0.0009

-.8 -.6 -.4 -.2 0 .2 .4 .6 .8

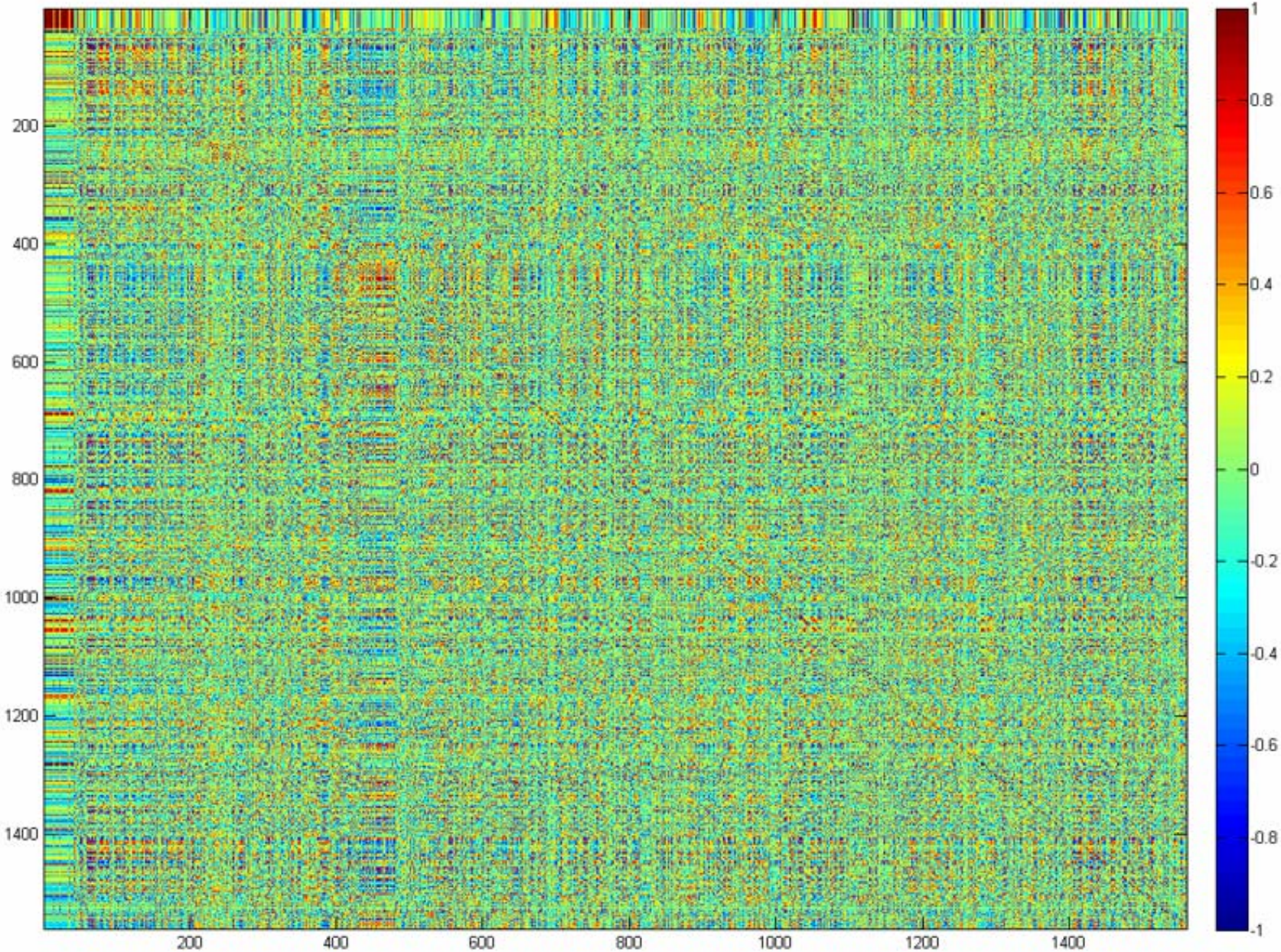
“Short” correlation matrix



“Long” correlation matrix

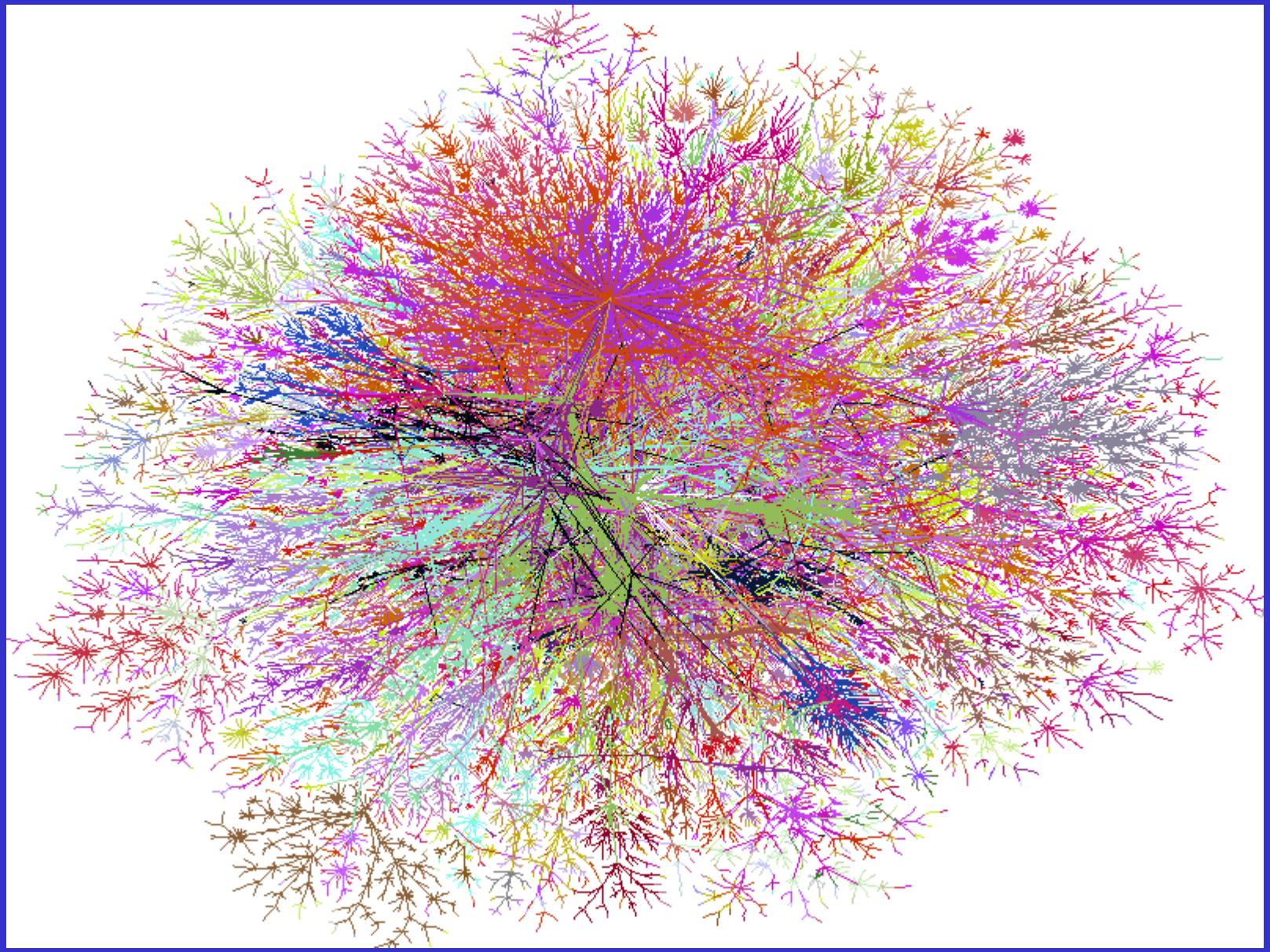


“Long” correlation matrix indexed as “Short”



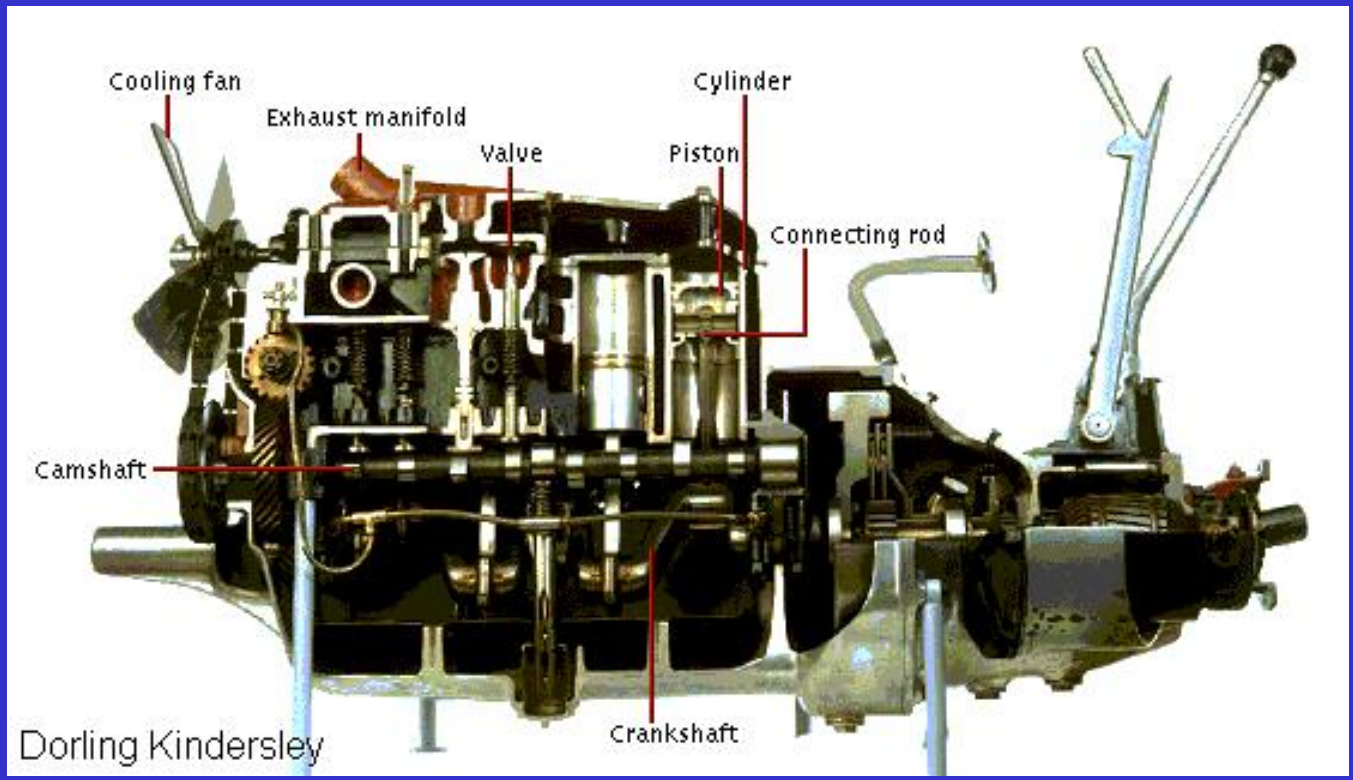
Gene networks appear to be responsive to changes (even mild changes) anywhere in the system.

Small effects, properly connected, can make a big difference.

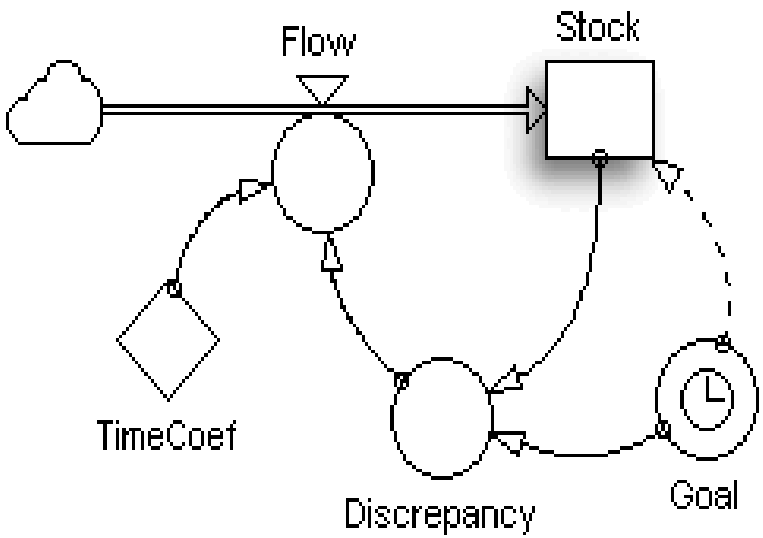


What is the appropriate paradigm?

The Systems Biology Paradigm



The Control Theory Paradigm



Stock(t) = Stock(t-DT) + DT * (Flow) [Units]

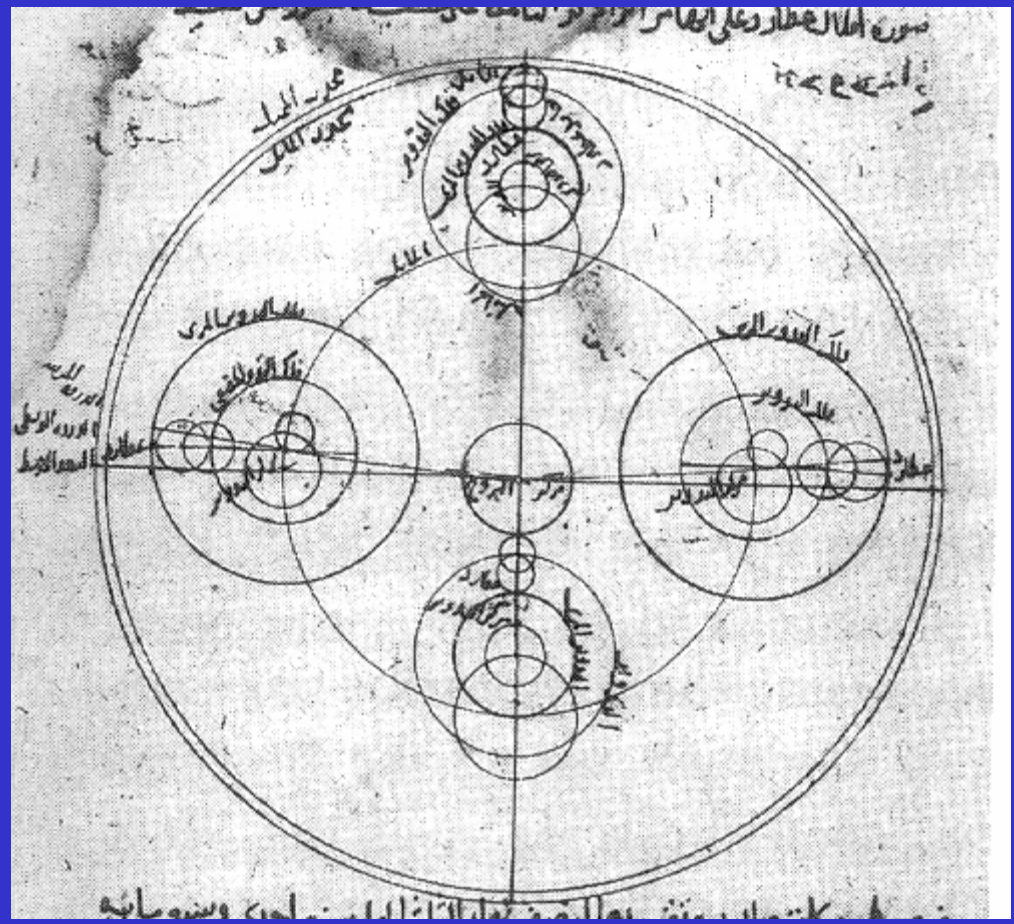
Flow = Discrepancy/TimeCoef [Units/Time Units]

Goal = 10 + STEP(5,1) [Units]

Discrepancy = Goal-Stock [Units]

TimeCoef = 2 [Time Units]

Ptolemy

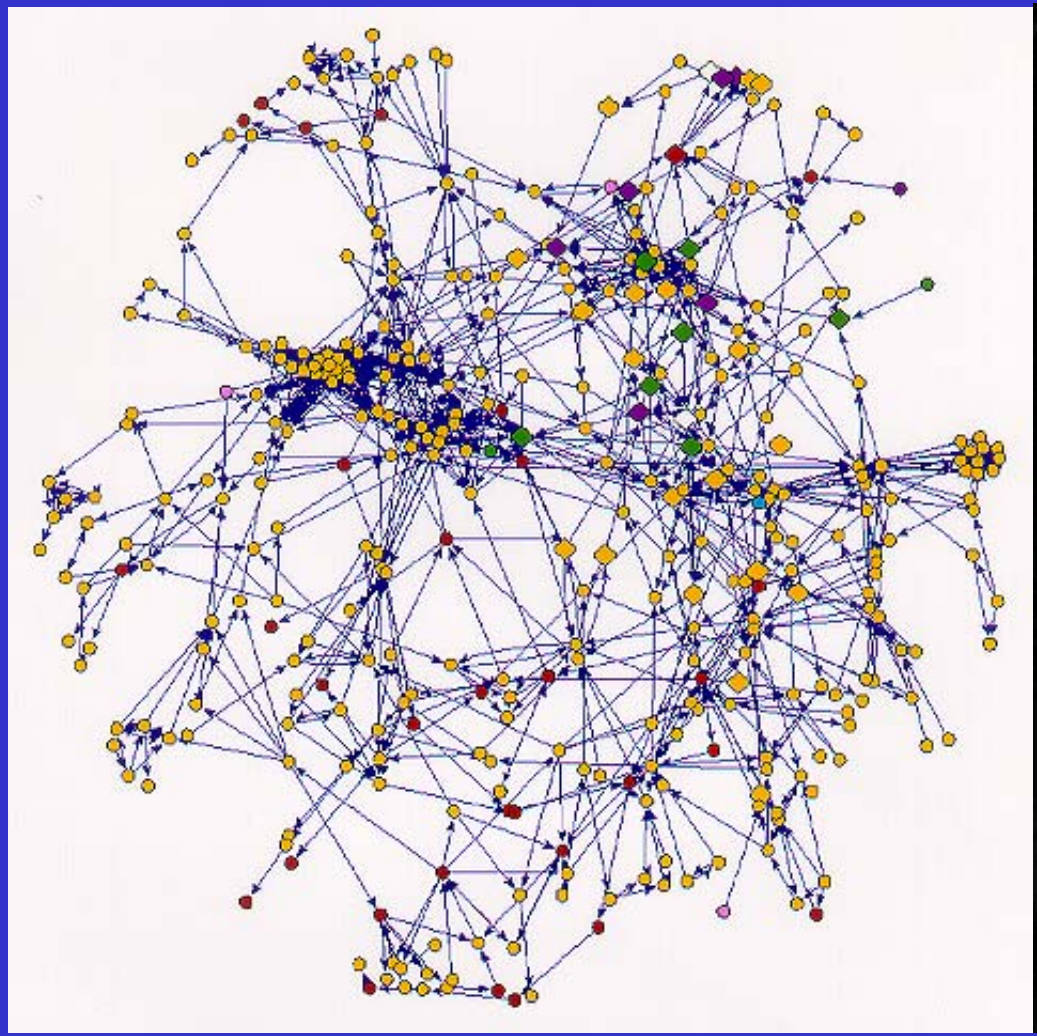


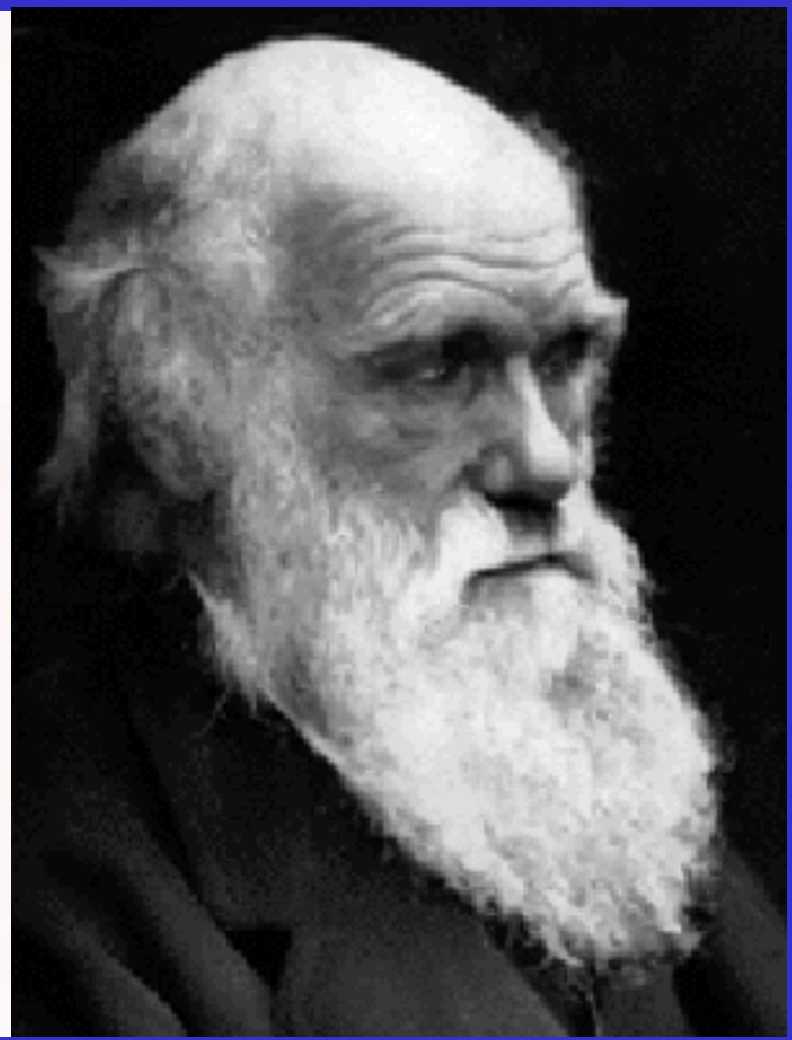
Epicycles

Is there a such a thing

as a Darwinian conception

of biological mechanism?





Darwinian mechanism

Heterogeneity

Clustering

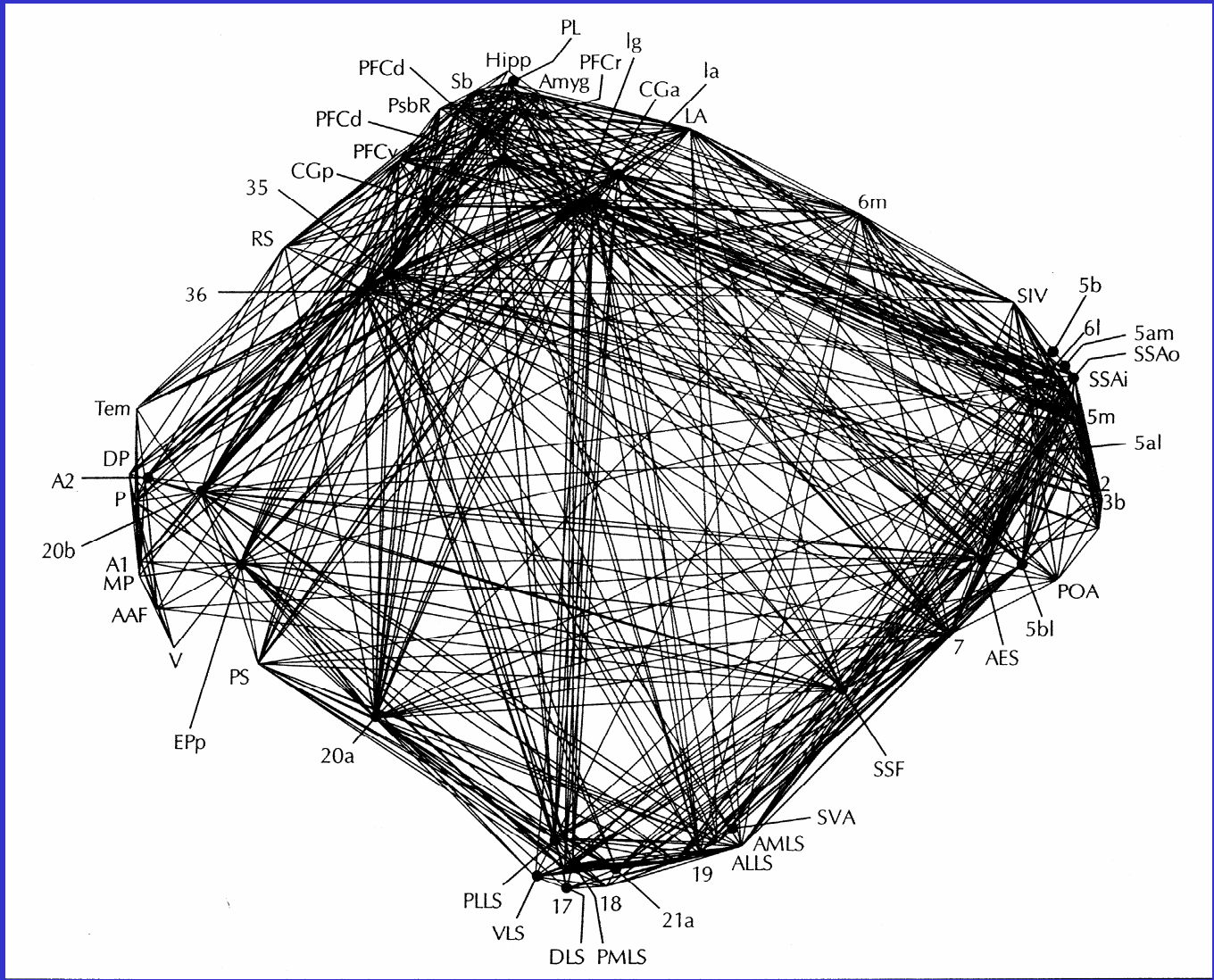
Flexible relationships

Degeneracy

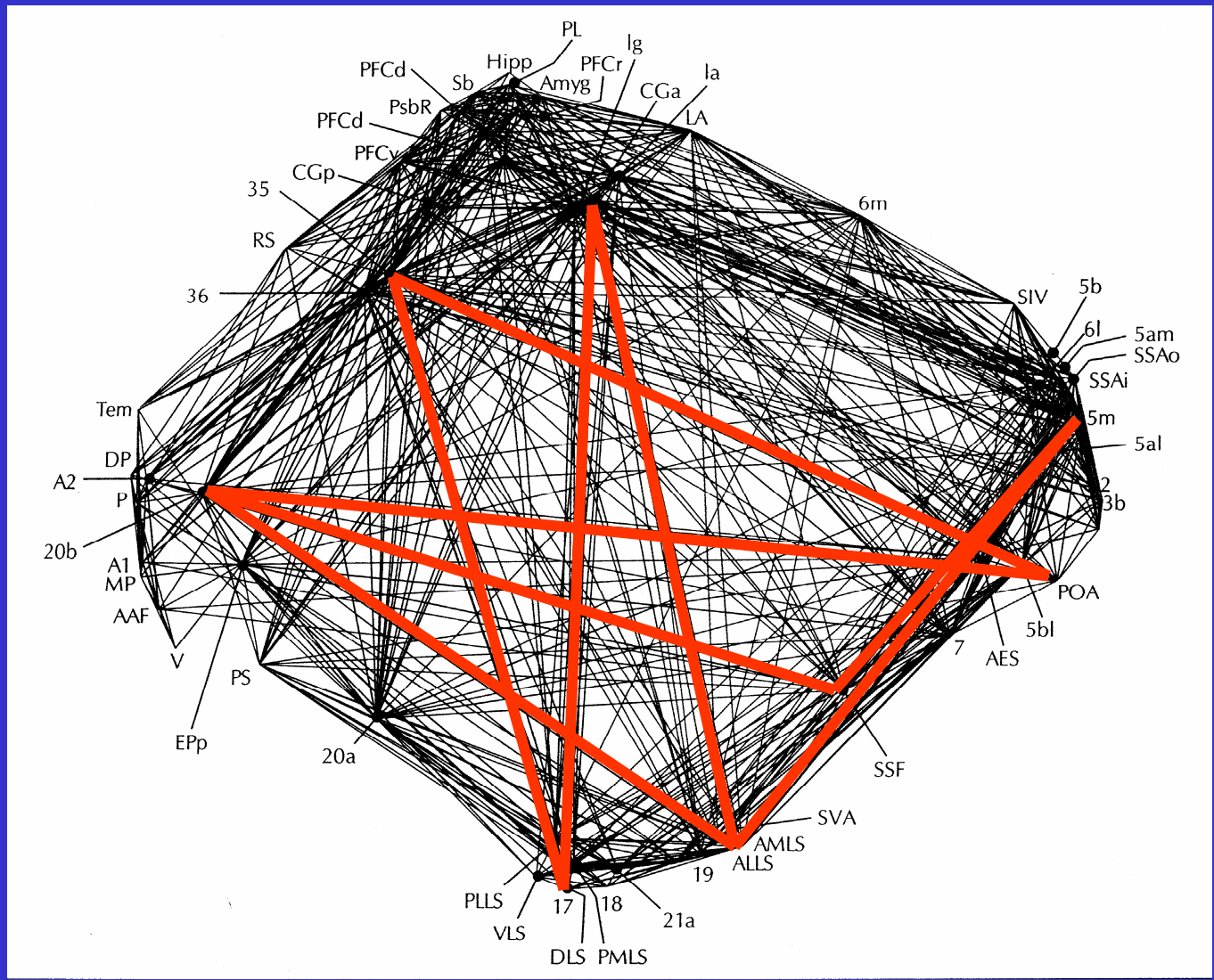
Selection from repertoire of states

Relational system

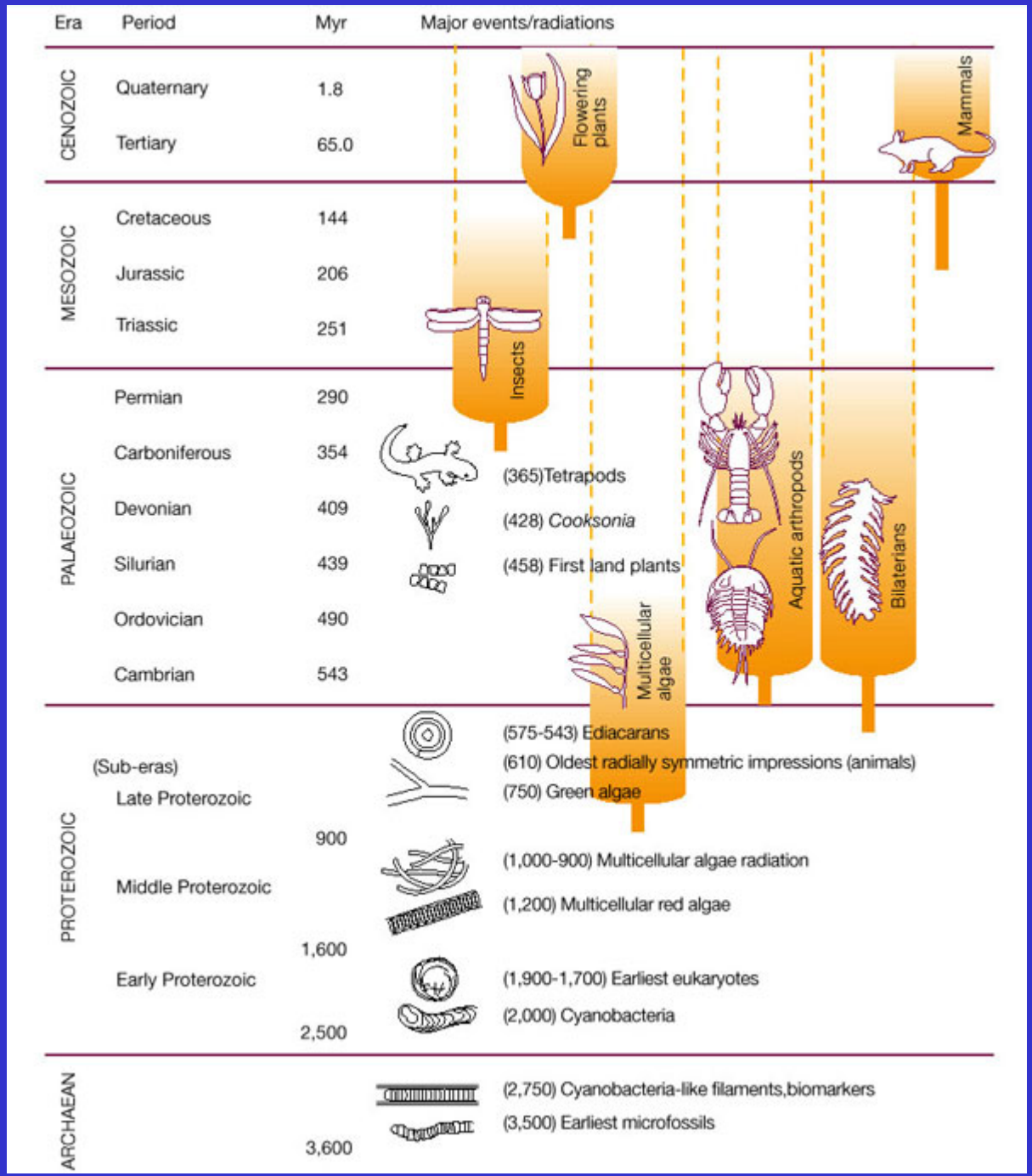
Repertoires



A relational system



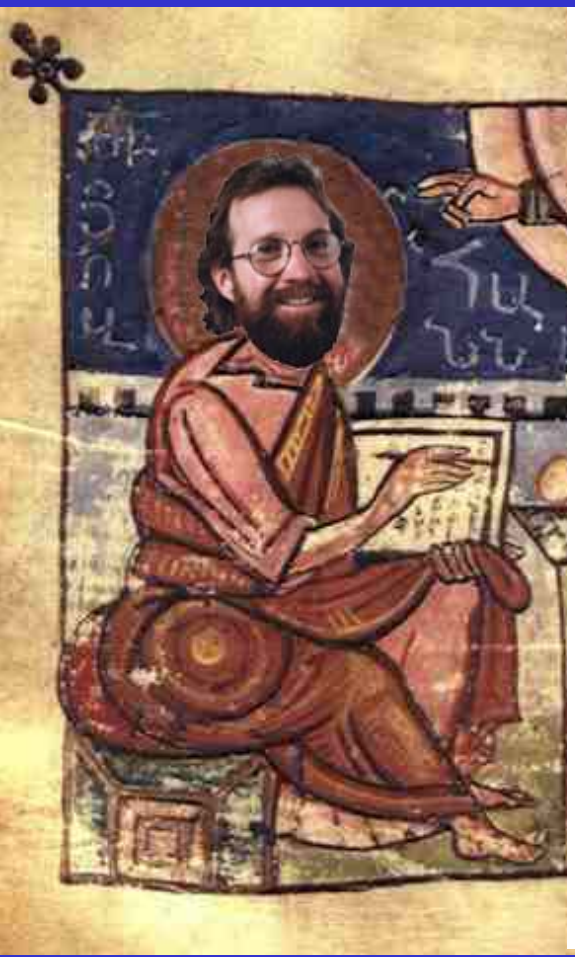
Some implications

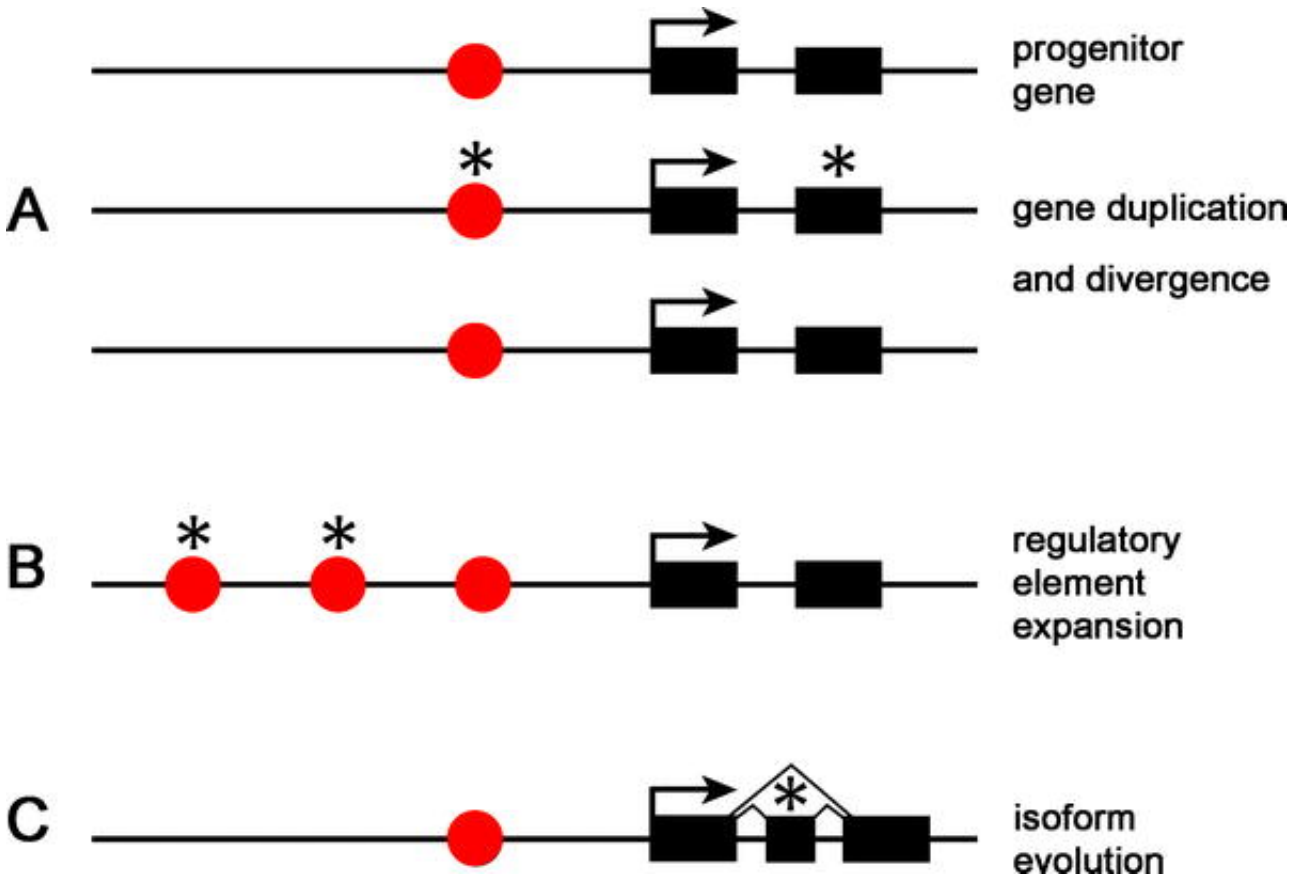


Macro-Evolution:

The Final Frontier

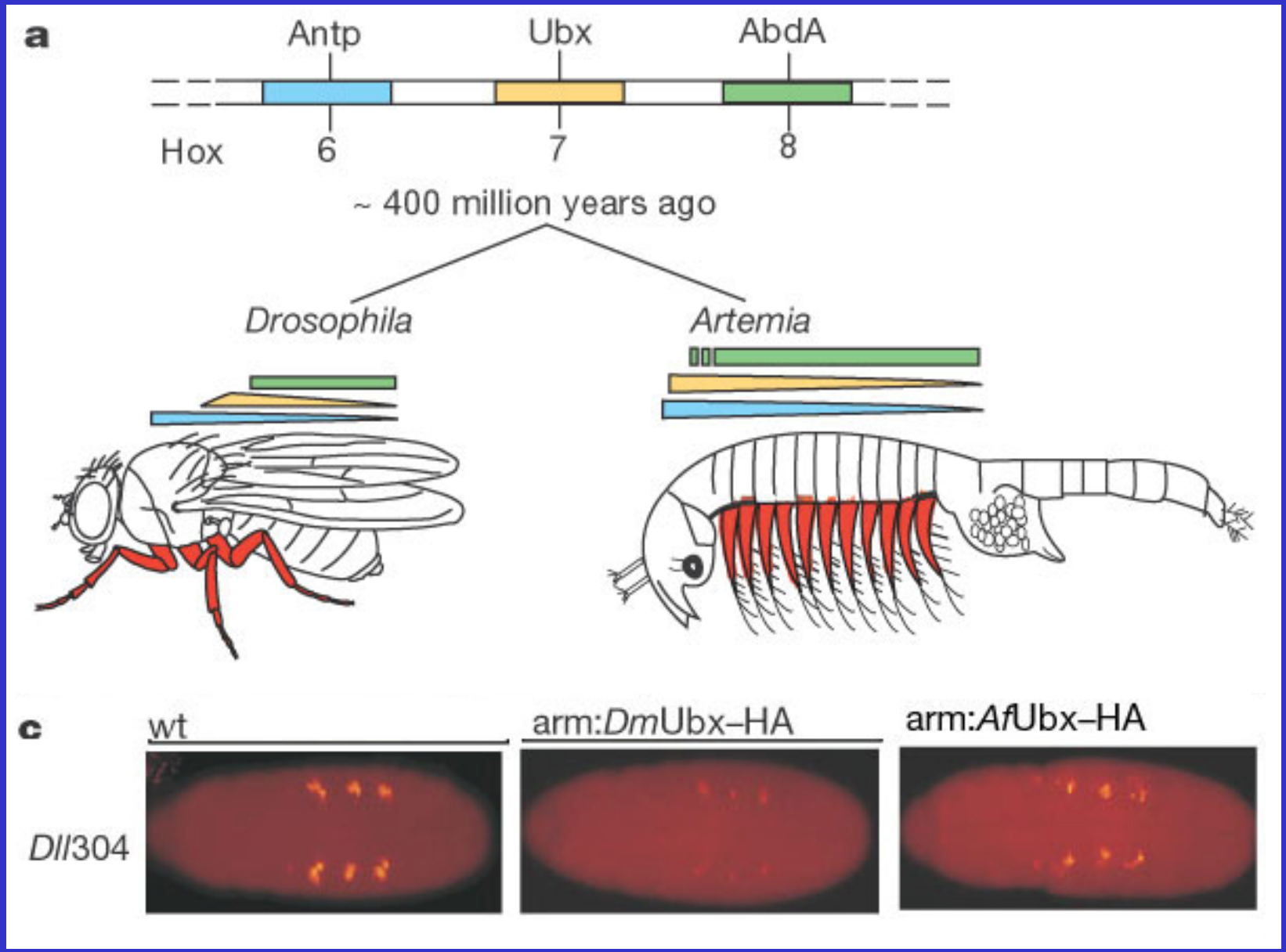
The Gospel According to Sean Carroll



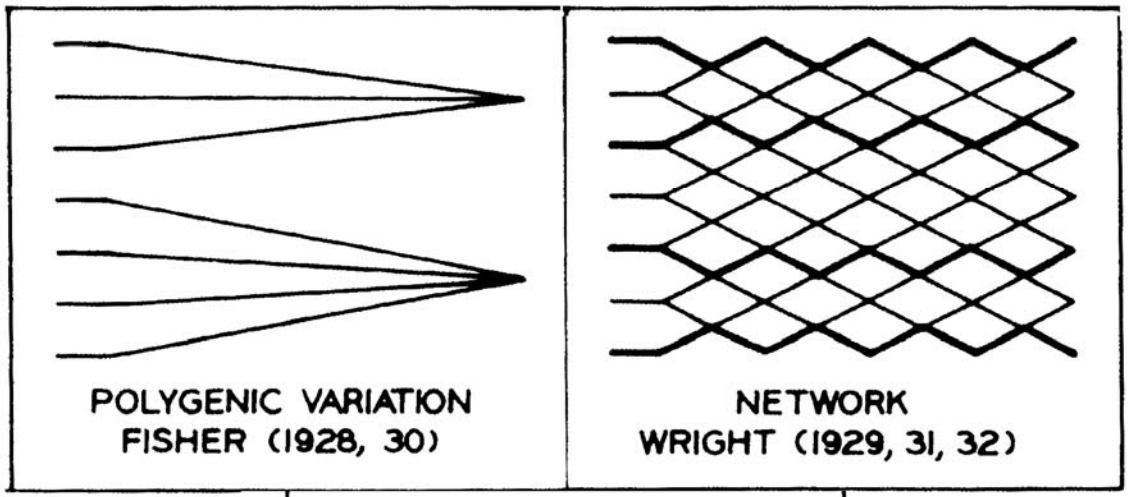


Is it likely that such changes just pop up and work?

Drosophila vs. *Artemia* body plan

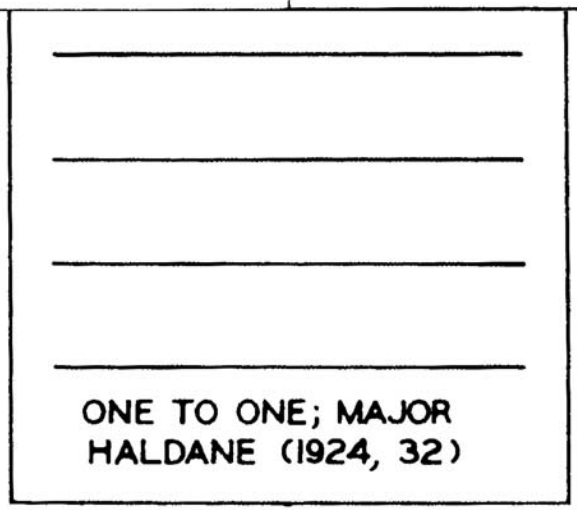


The Seasons of Selection



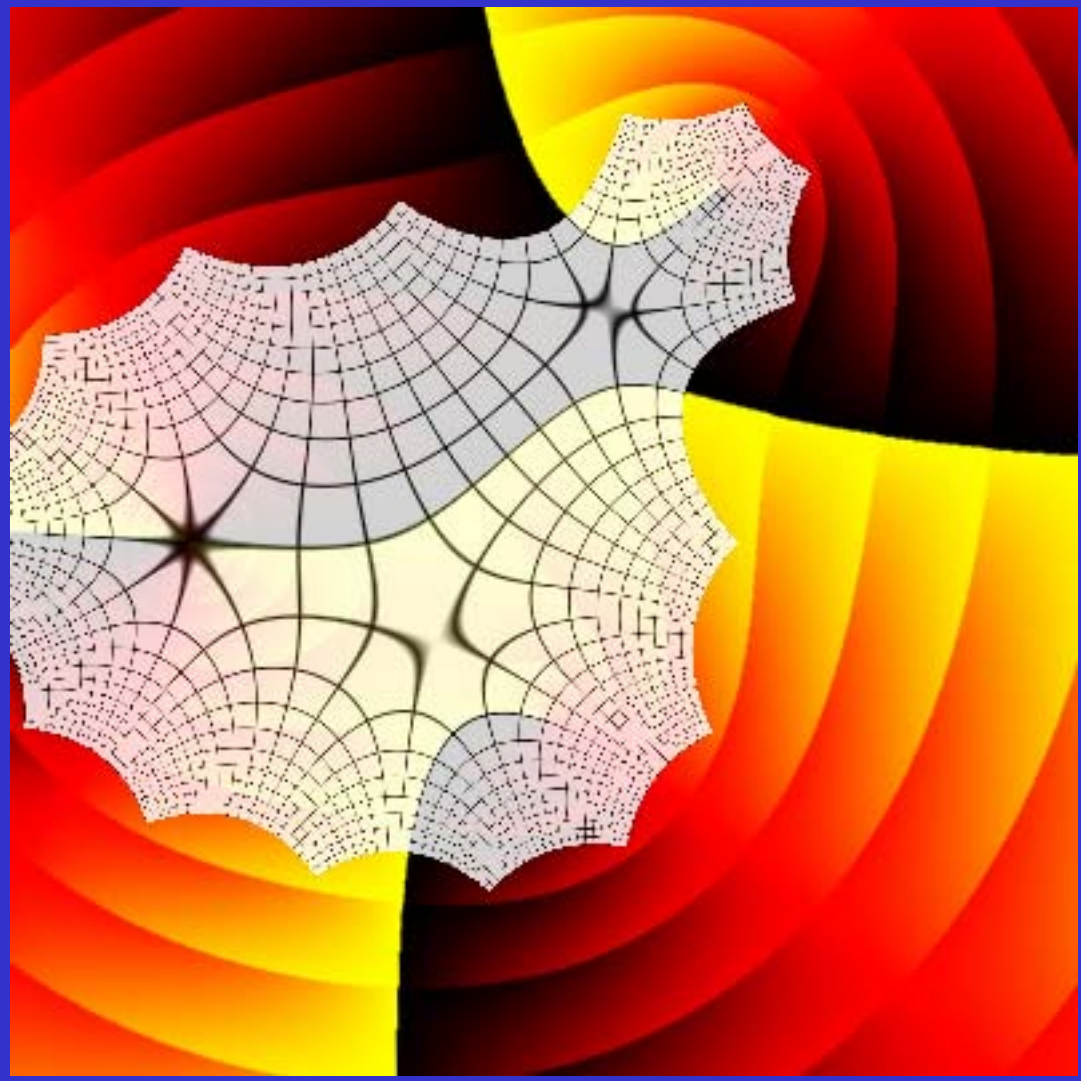
Short-term?

Medium-term?

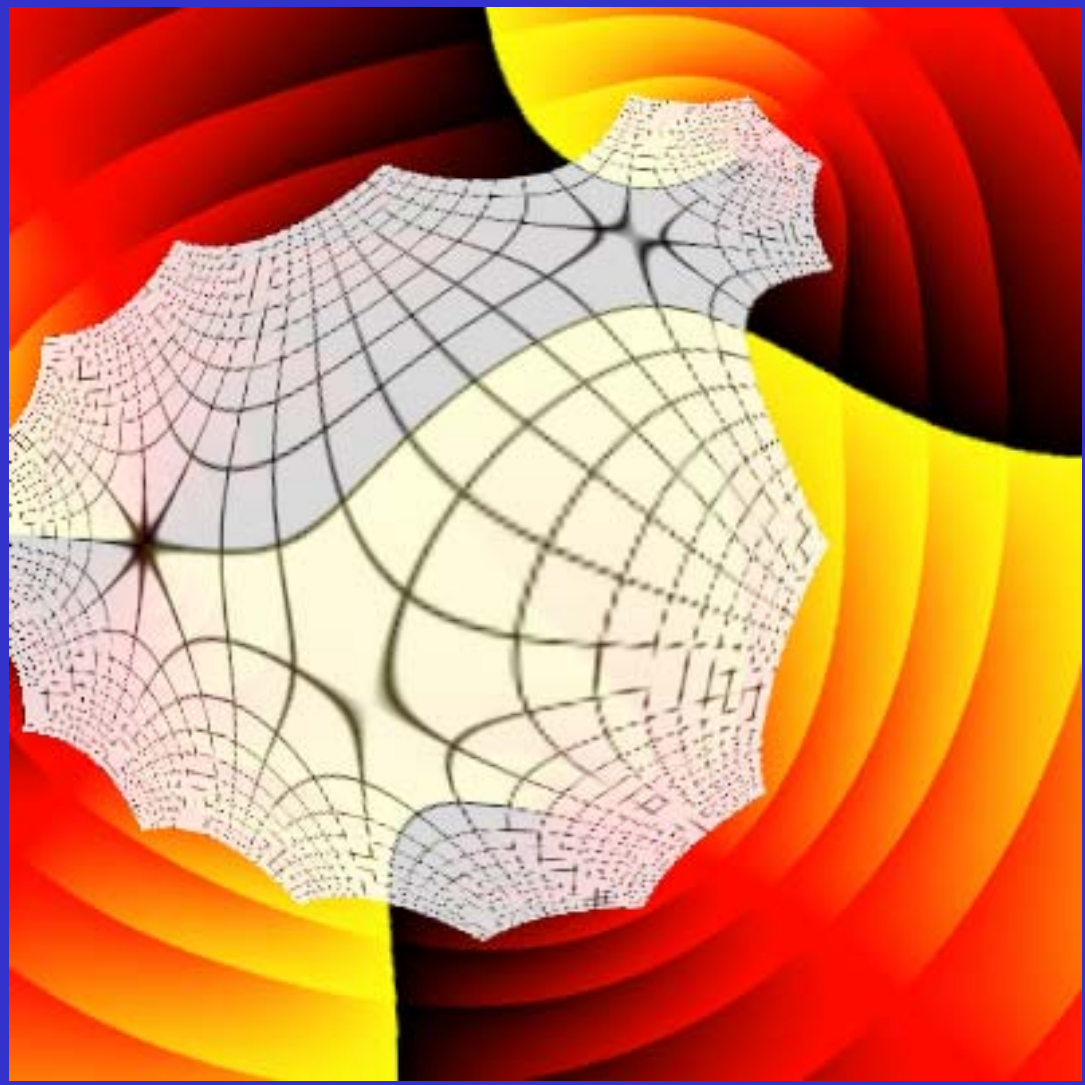


Long-term?

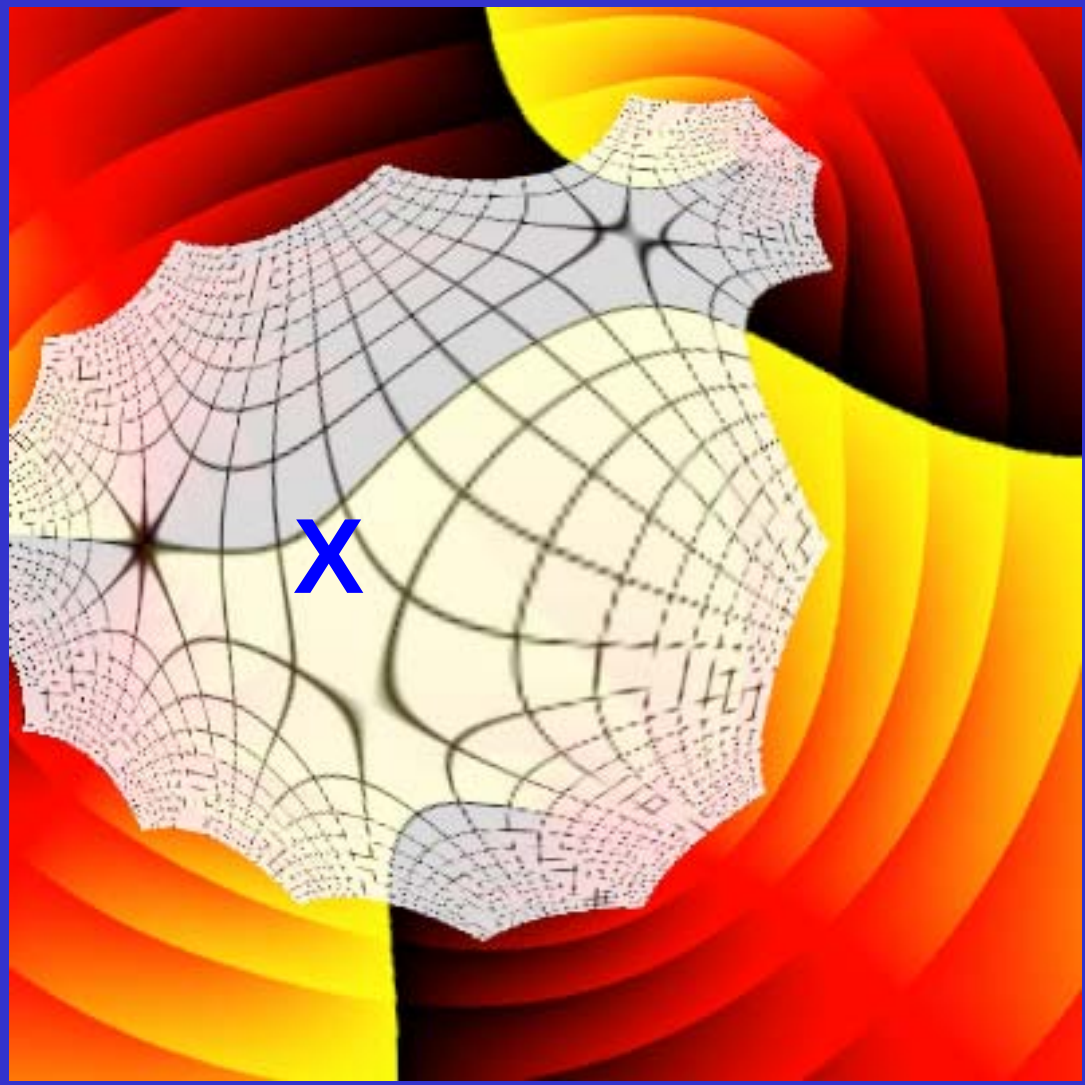
The gene network underlying a phenotype



Selection gradually distorts that network

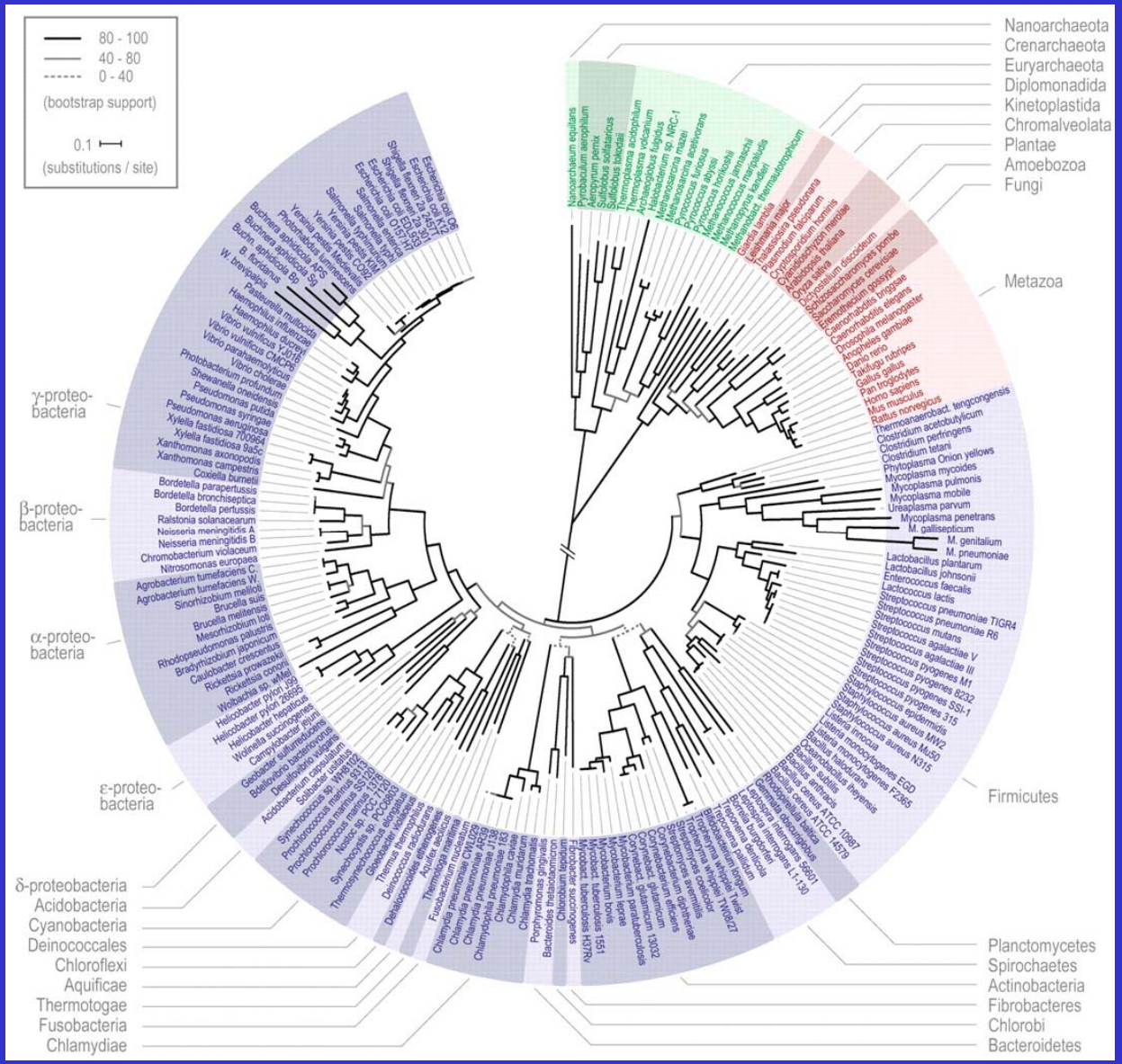


Making it capable of tolerating a major mutation

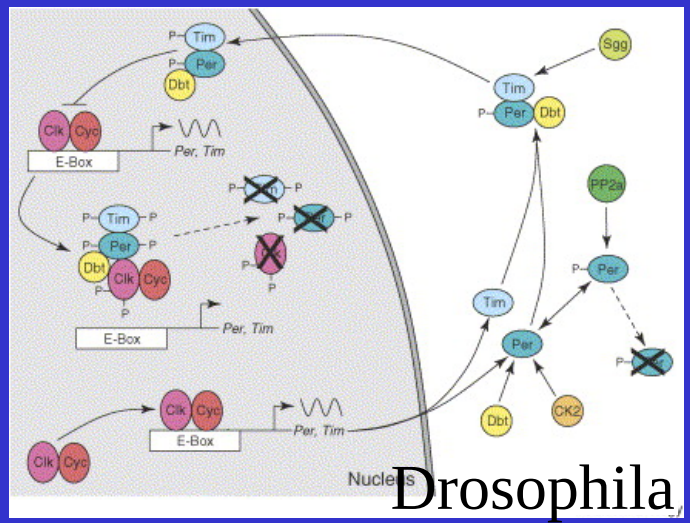


How might a behavioral mechanism evolve?

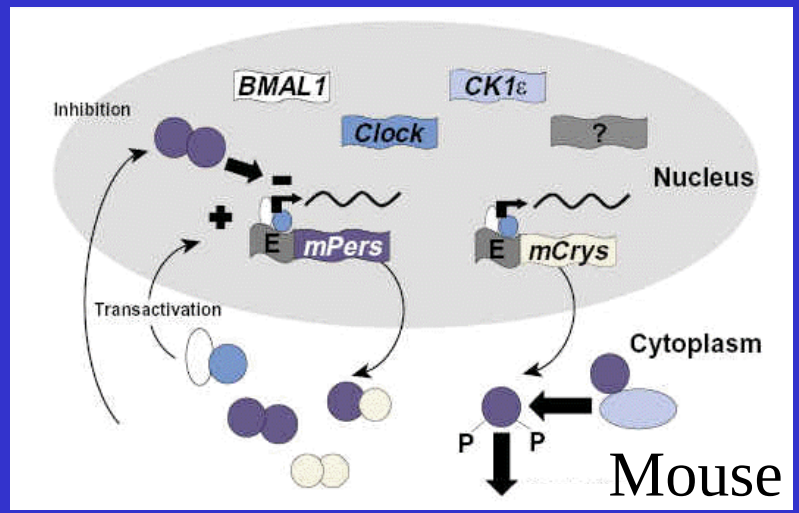
Circadian rhythms are nearly universal



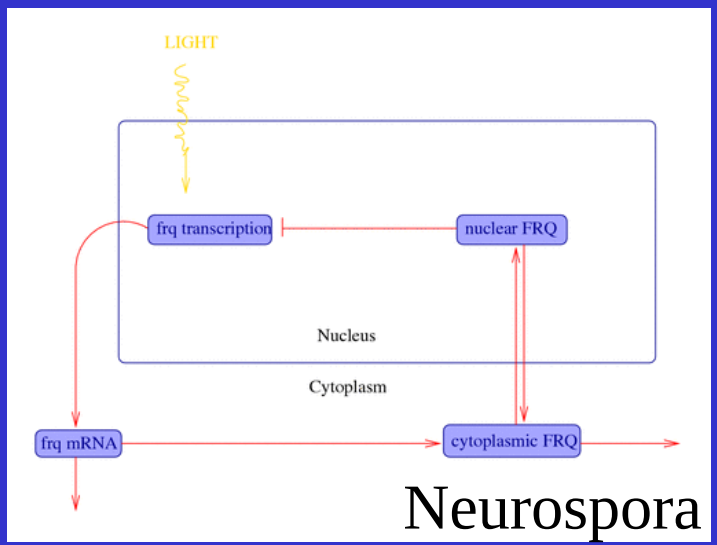
Relationships are conserved, not just molecules



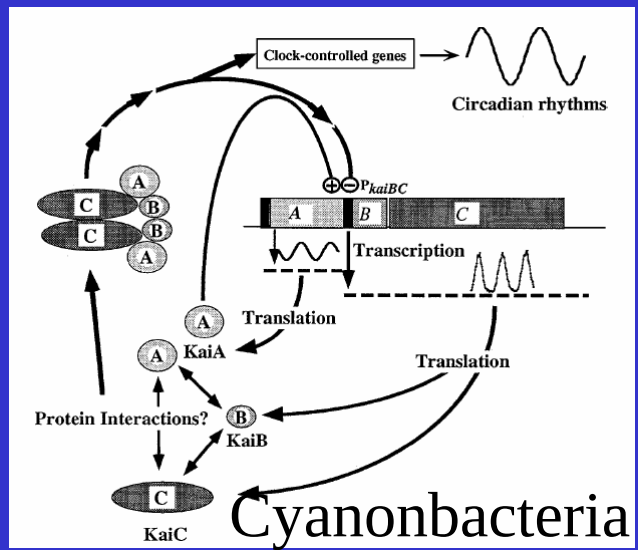
Drosophila



Mouse

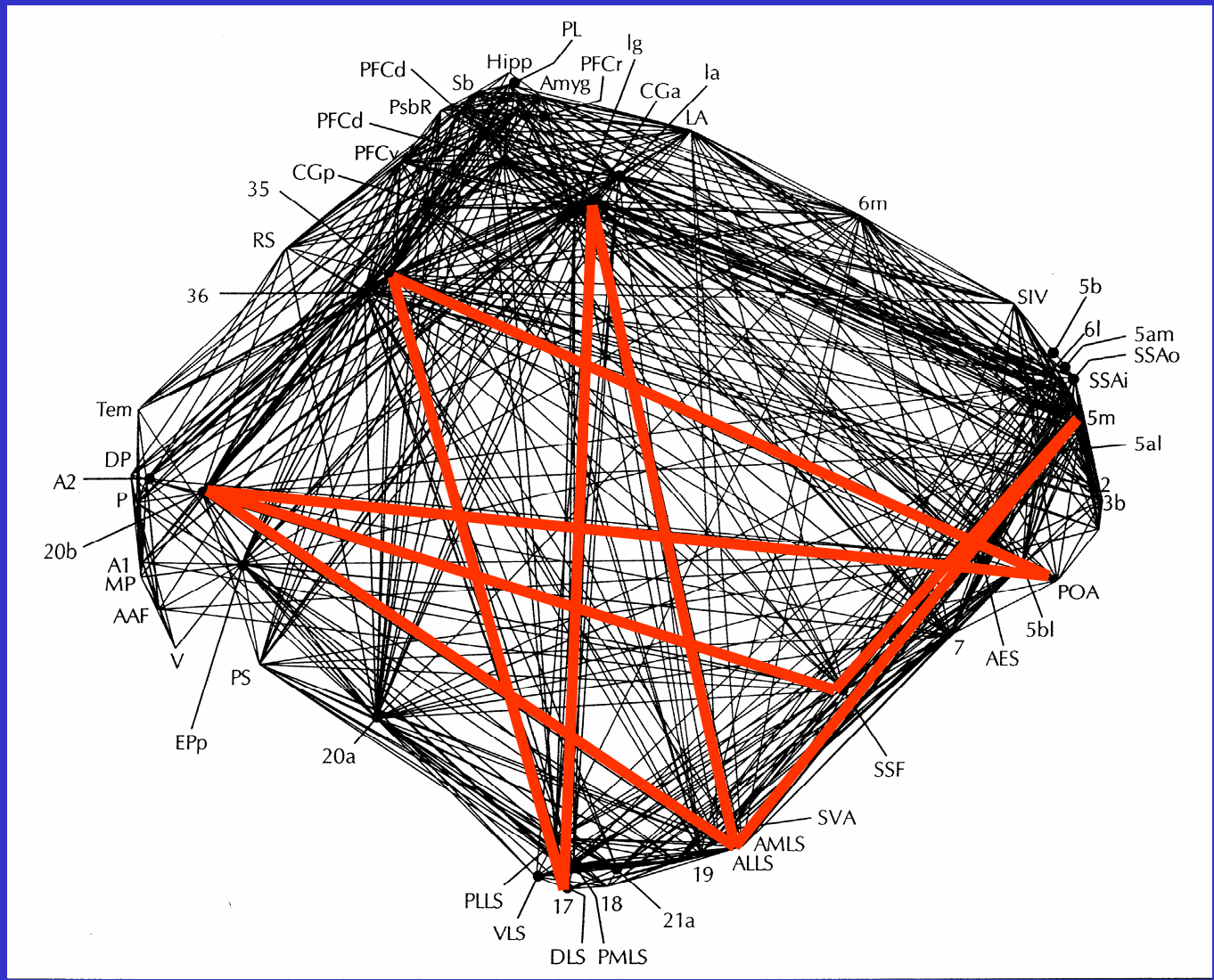


Neurospora



Cyanonbacteria

A relational system – what are its principles?



Dramatis Personae

Rozi Andretic	NSI
Herman Dierick	
Bruno van Swinderen	
Dan Toma	
Jenée Wagner	
Bambos Kyriacou	U. Leicester
Ed Green	
Kevin White	Yale U.
Richard Cross	
Ken Weber	U. Southern Maine