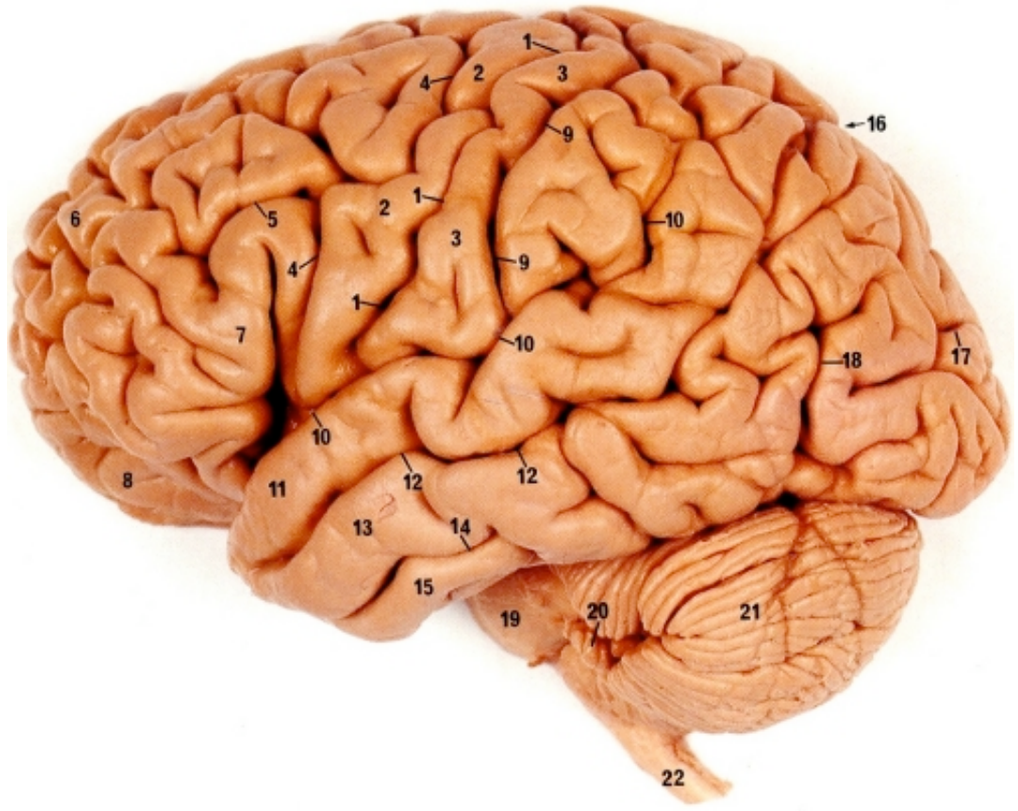
Dynamics and Evolution of Single Cell Cognition

David C. Krakauer.
Santa Fe Institute


1
4
2
3
16
9
6
5
2
1
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3
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7
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11
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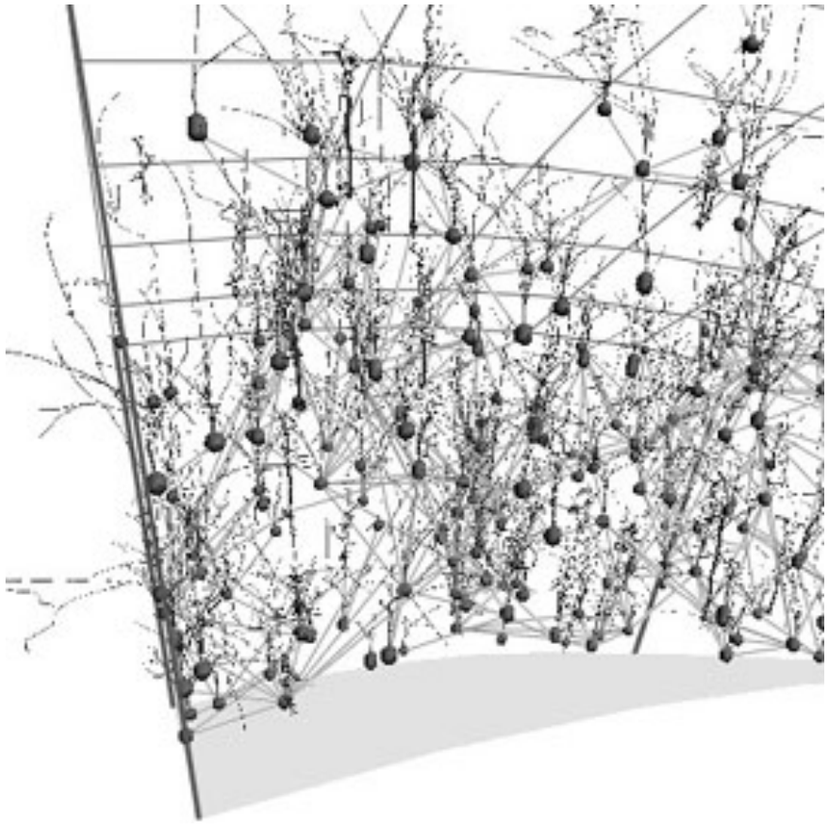
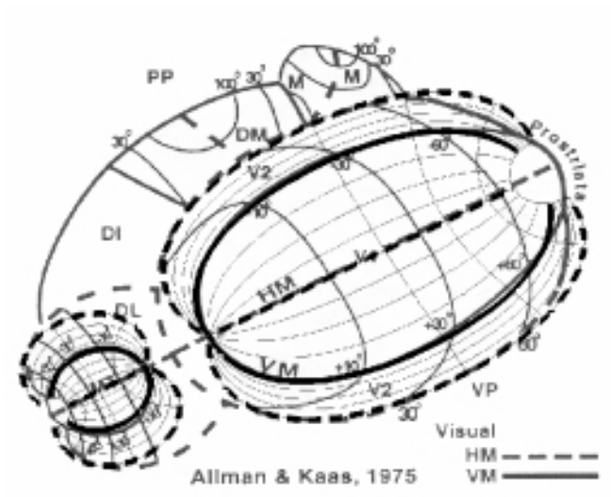
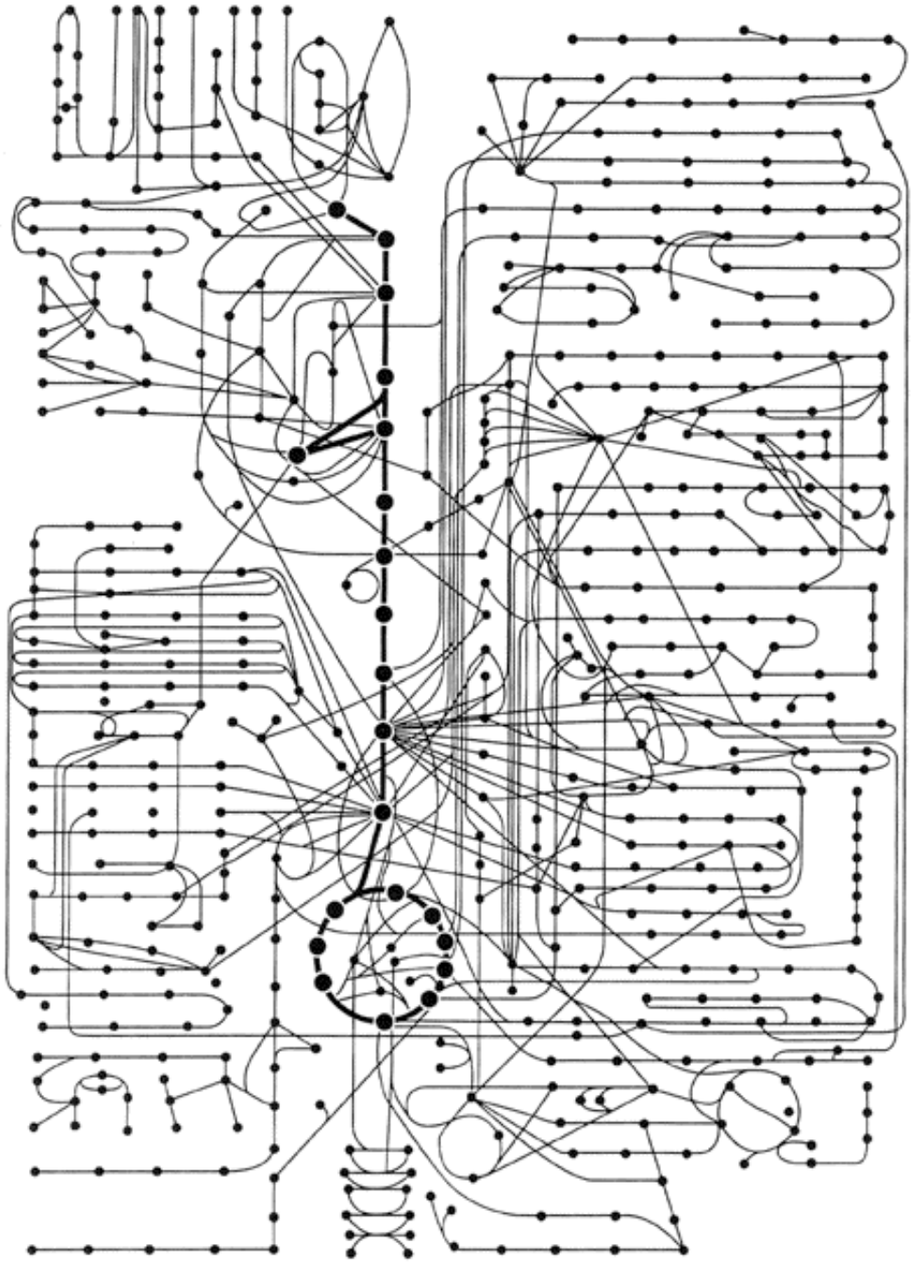
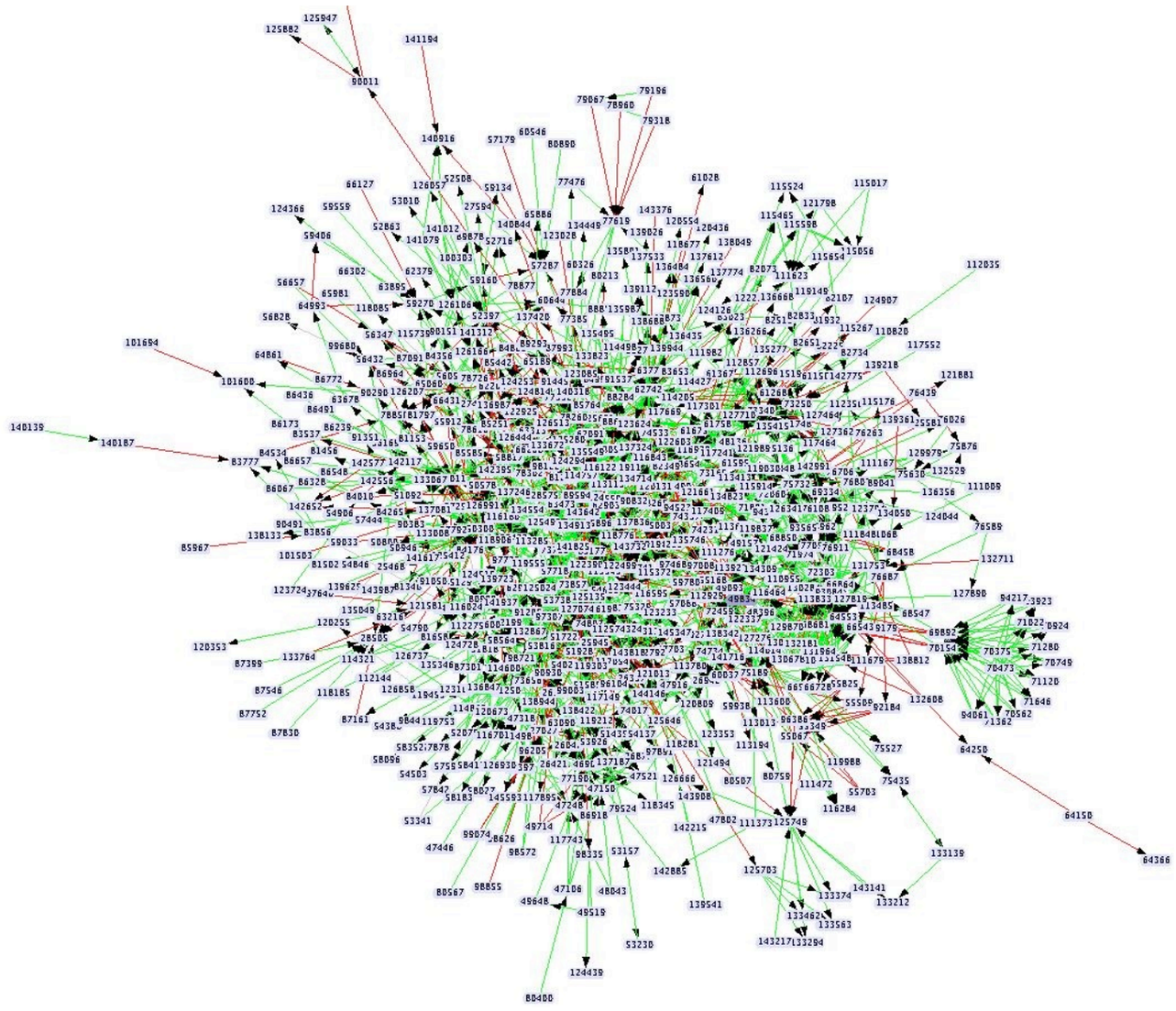
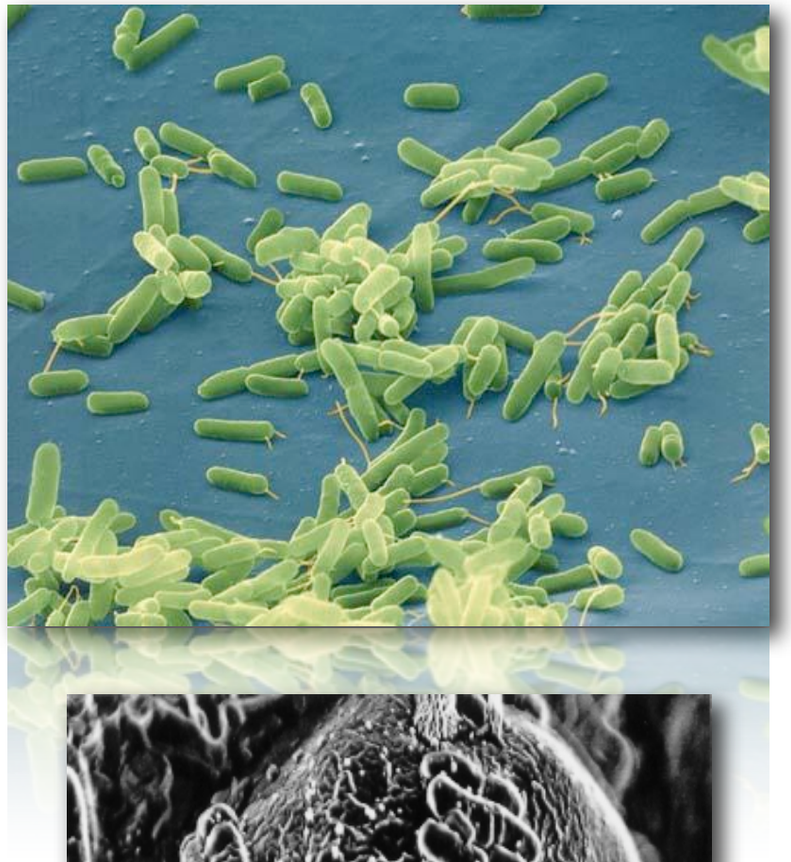
22

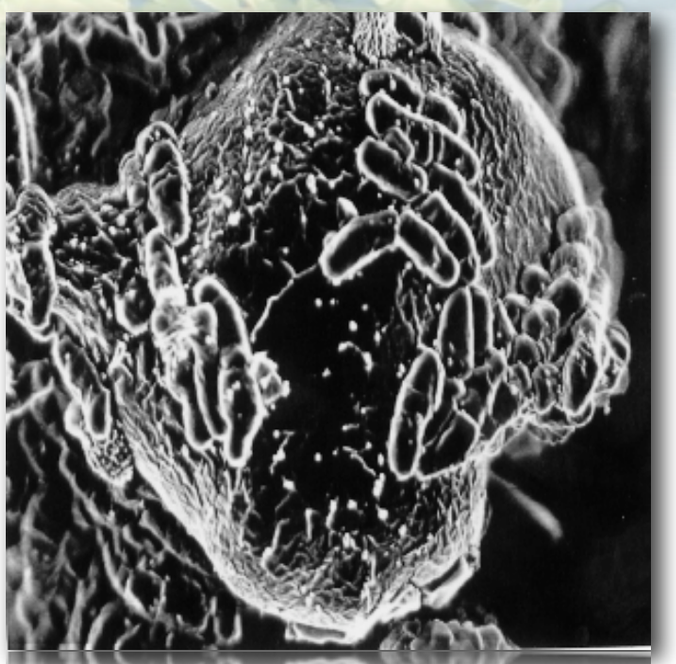


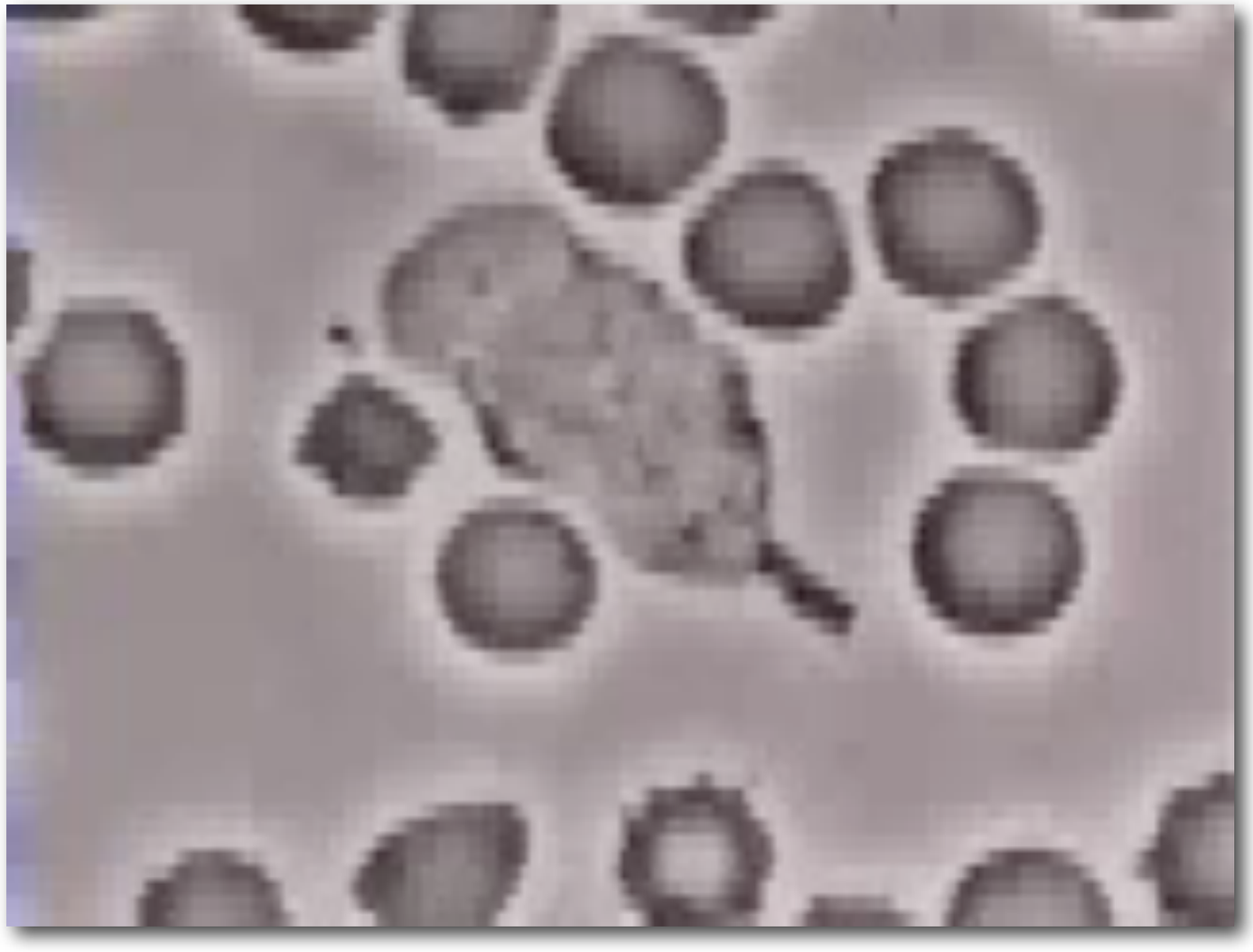

PP
M
M
DM
V2
DI
HM
DL
VM
V2
VP
Visual
HM
VM
Allman & Kaas, 1975

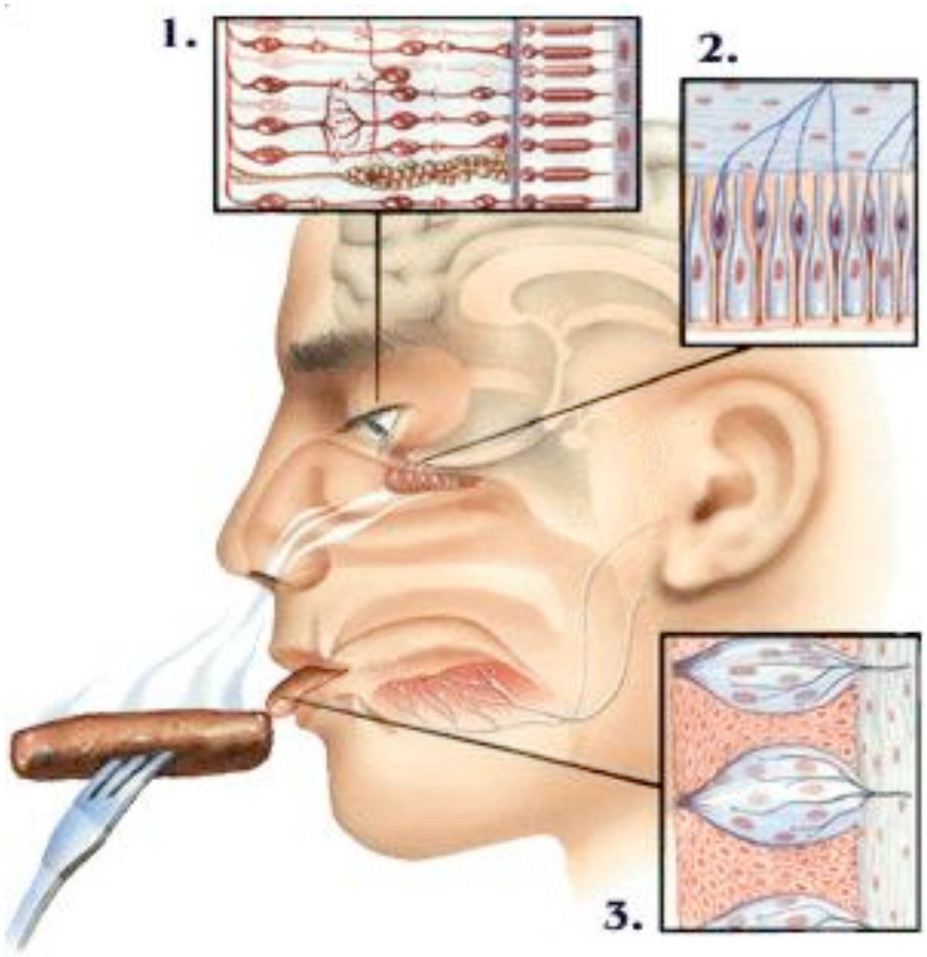


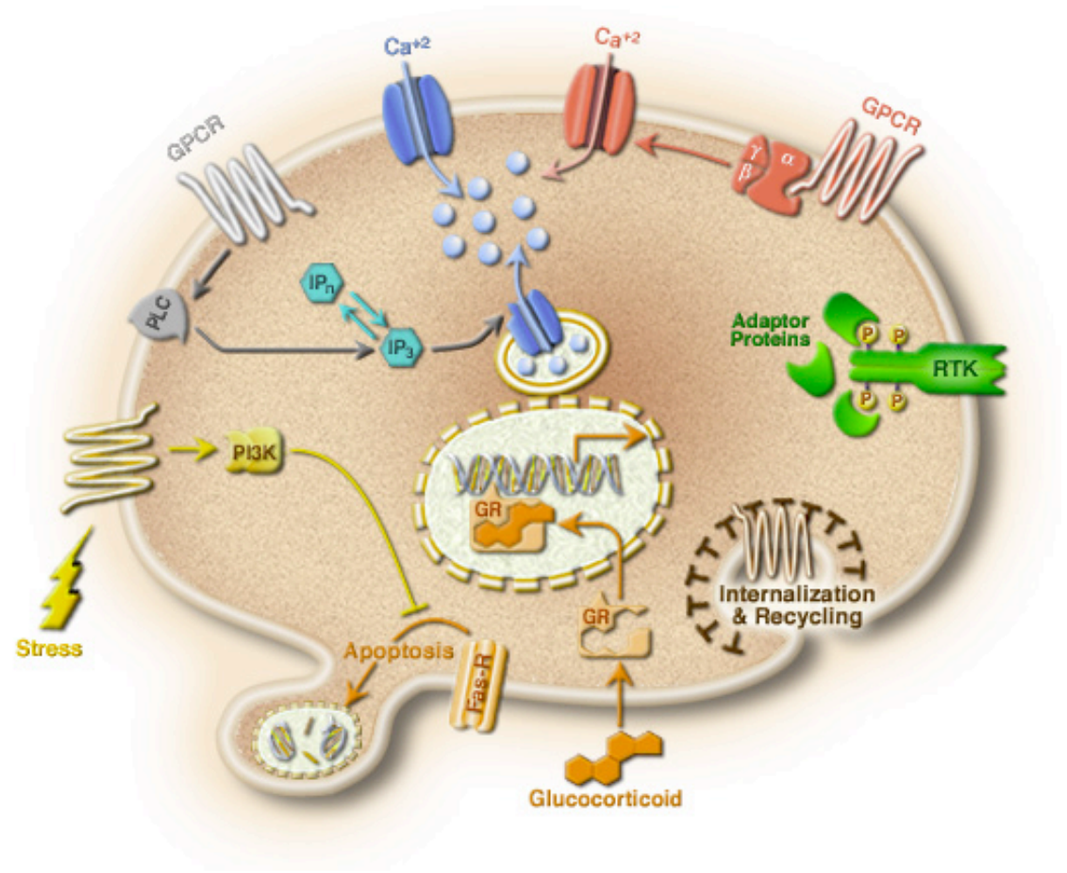


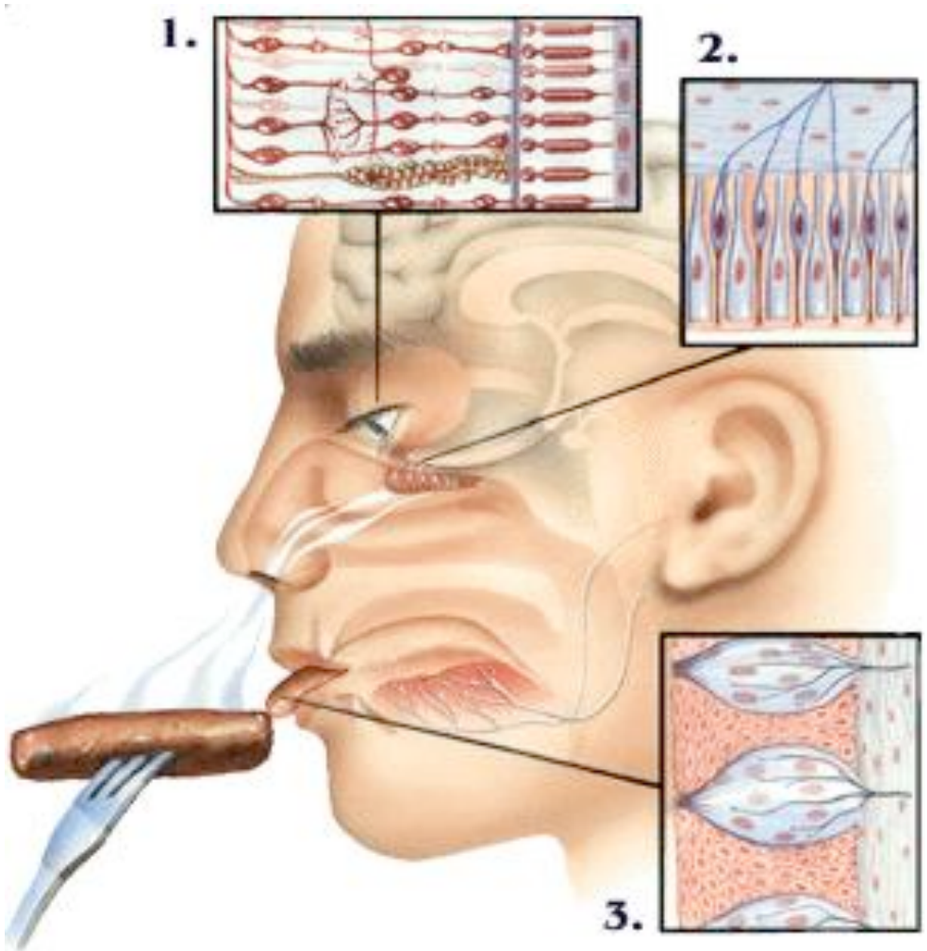


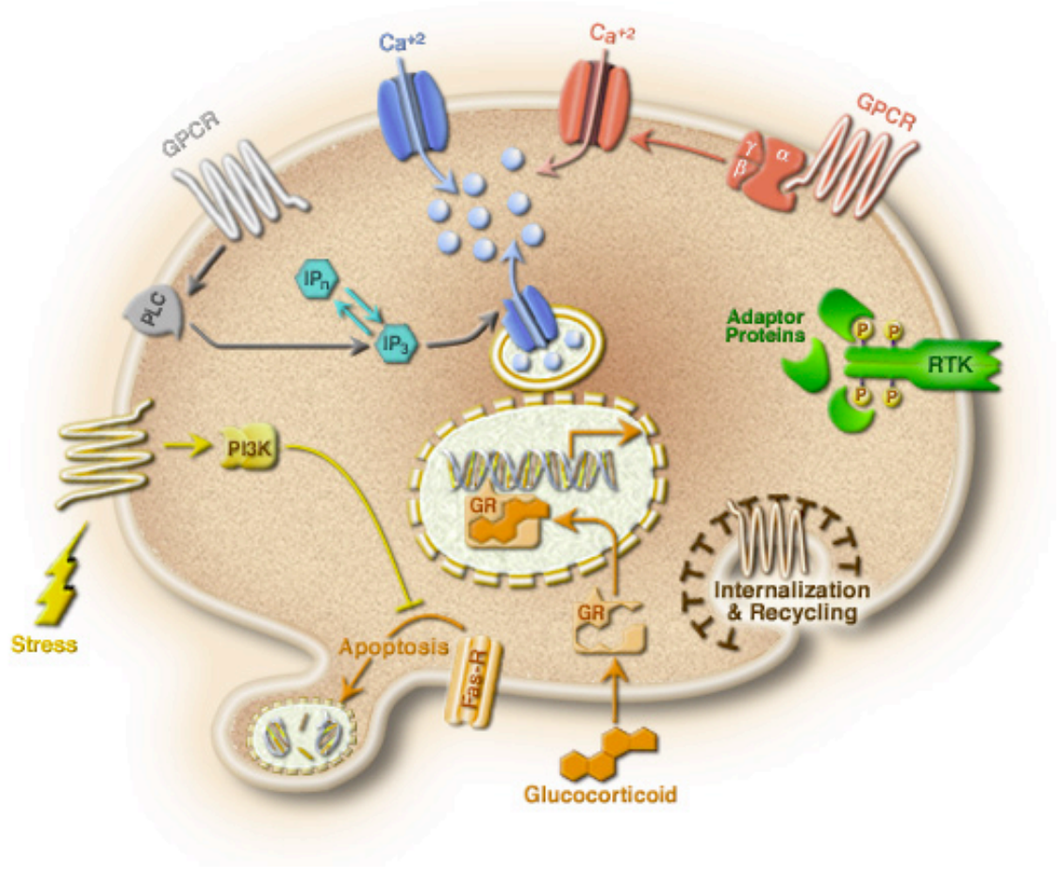





1.
2.
3.


Ca+2
Ca+2
GPCR
GPCR
PLC
IP3
Adaptor Proteins
RTK
PI3K
GR
Internalization & Recycling
Stress
Apoptosis
Fas-R
GR
Glucocorticoid





	Connectivity	Density	Dynamics	Differentiation
Nervous system	Physical & Chemical	High	Variable time Constants	By Connection
Cell	Chemical	Sparse	Generally Rapid	By sequence

Genomic and Cellular Cognition

- Distributed Coding: Reading frame compression *(empirical e.g.)*
- Feature detection: Signal transduction and frequency filtering*(theory e.g.)*
- Elementary Logic: Switches & Base Systems *(theory e.g.)*
- Robustness: Population level redundancy*(theory e.g.)*
- Memory: Enzymatic feedback circuits *(theory e.g.)*

Coding & Compression

- Lillo, F. and Krakauer, D.C. A statistical analysis of the three-fold evolution of genomic compression through frame overlaps in prokaryotes. Biology Direct. doi:10.1186/1745-6150-2-22A. (2007)

Localization of Function

A syntactic specialization for Broca's area

David Embick*†‡, Alec Marantz*‡, Yasushi Miyashita*§, Wayne O'Neil*‡, and Kuniyoshi L. Sakai†¶‖

*Mind Articulation Project, International Cooperative Research Project, Japan Science and Technology Corporation, Tokyo 113-0034, Japan; †Department of Cognitive and Behavioral Science, the University of Tokyo, Komaba, Tokyo 153-8902, Japan; ‡Department of Linguistics and Philosophy, Massachusetts Institute of Technology, Cambridge, MA 02139; §Department of Physiology, the University of Tokyo School of Medicine, Tokyo 113-0033, Japan; and ¶Core Research for Evolutional Science and Technology, Japan Science and Technology Corporation, Kawaguchi-shi 332-0012, Japan

Communicated by Morris Halle, Massachusetts Institute of Technology, Cambridge, MA, March 7, 2000 (received for review February 15, 2000)

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Communicated by Morris Halle, Massachusetts Institute of Technology, Cambridge, MA, March 7, 2000 (received for review February 15, 2000)

Proc. Natl. Acad. Sci. USA
Vol. 93, pp. 9687–9692, September 1996
Genetics

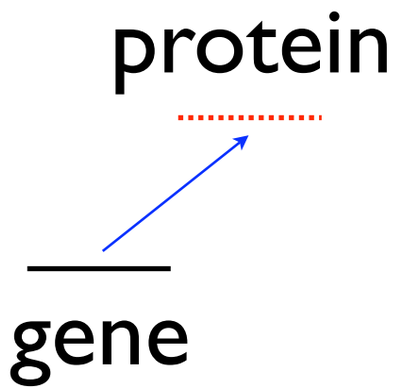
Sexual orientation in *Drosophila* is altered by the satori mutation in the sex-determination gene fruitless that encodes a zinc finger protein with a BTB domain

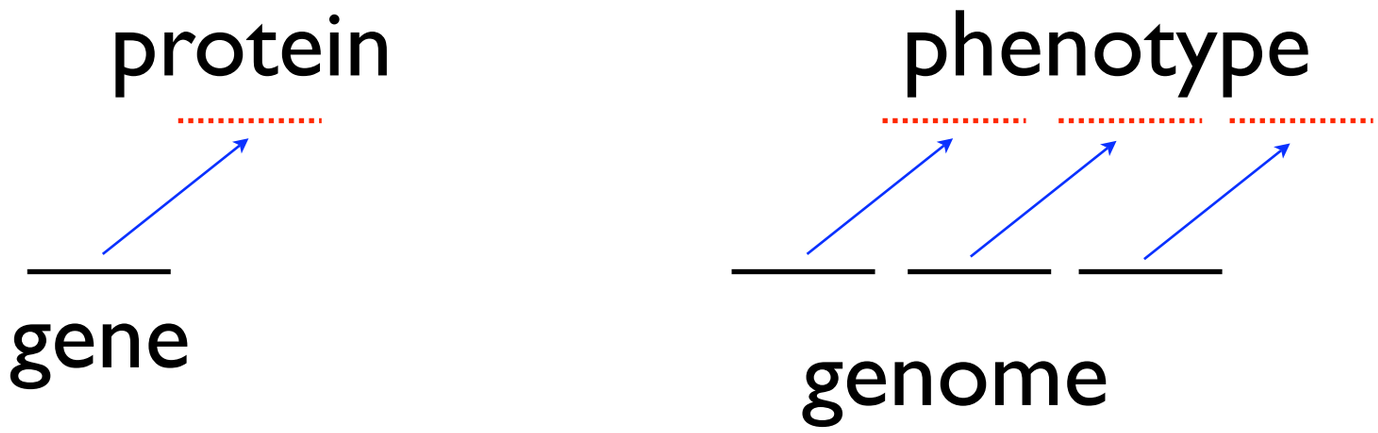
(homosexual courtship/muscle of Lawrence/transformer/mating behavior)

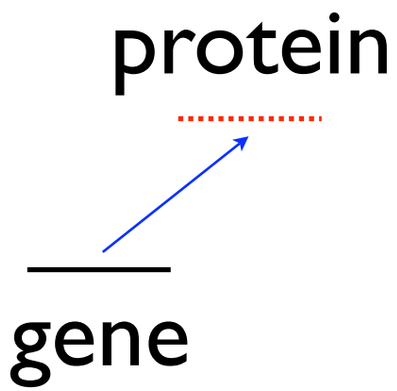
HIROKI ITO, KAZUKO FUJITANI, KAZUE USUI, KEIKO SHIMIZU-NISHIKAWA*, SHOJI TANAKA, AND DAISUKE YAMAMOTO†

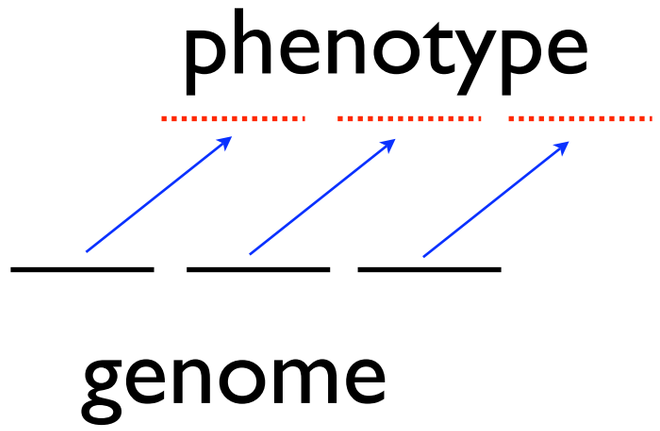
Yamamoto Behavior Genes Project, Exploratory Research for Advanced Technology (ERATO), Research Development Corporation of Japan, and Mitsubishi Kasei Institute of Life Sciences, 11 Minamiooya, Machida, Tokyo 194, Japan

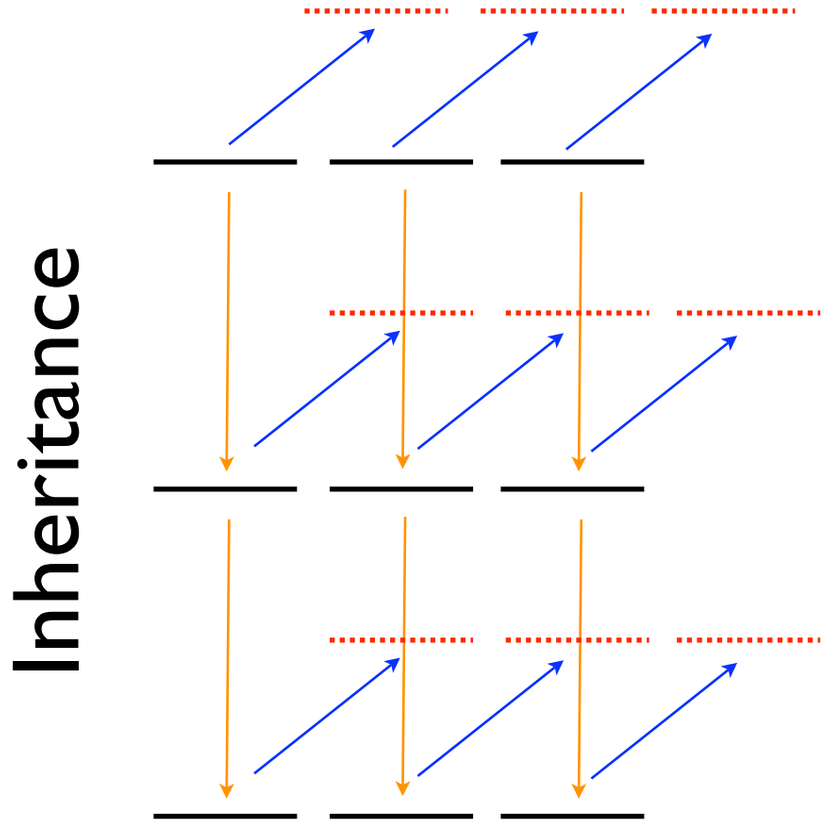
Communicated by Susumu Ohno, Beckman Research Institutes of the City of Hope, Duarte, CA, May 29, 1996 (received for review April 10, 1996)

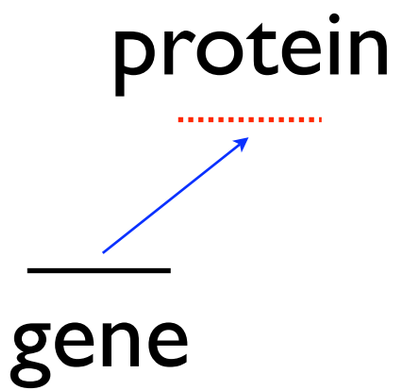

protein
gene

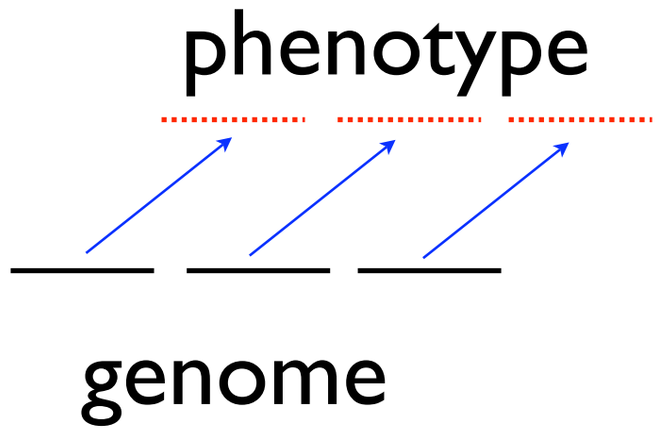

protein
gene
phenotype
genome

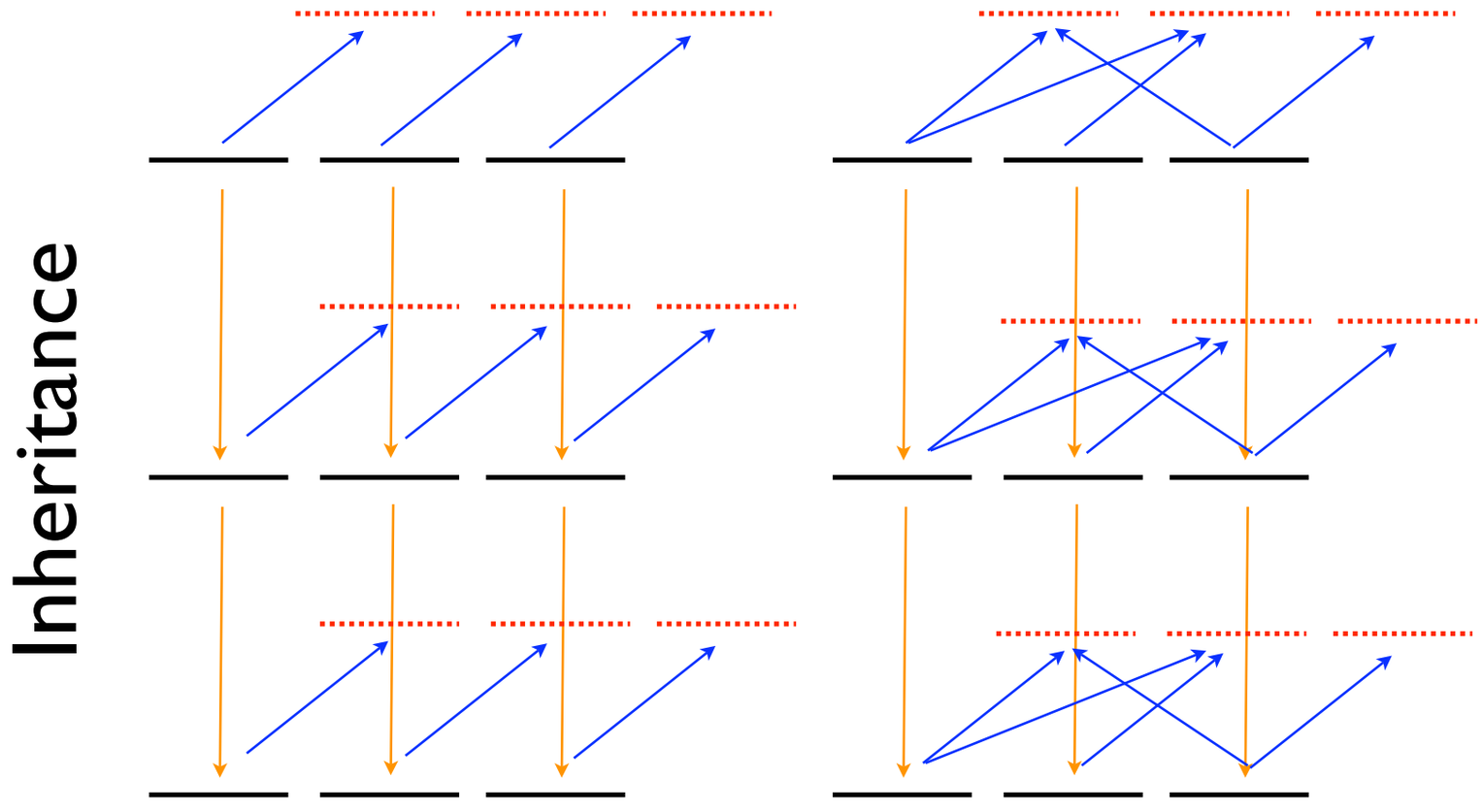

protein
gene

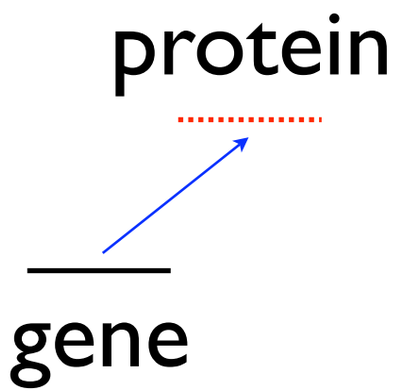

phenotype
genome

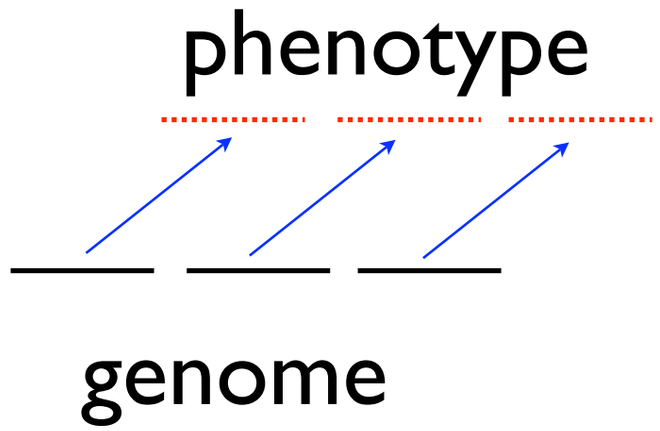

Inheritance

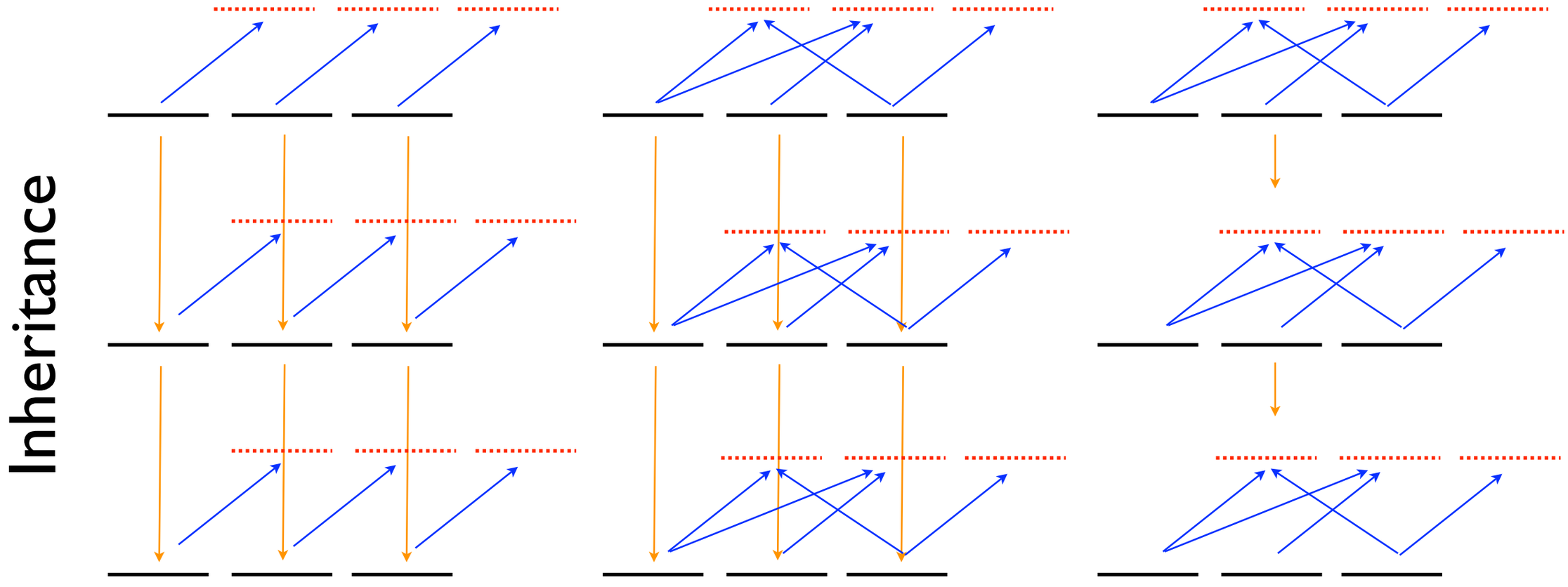

protein
gene

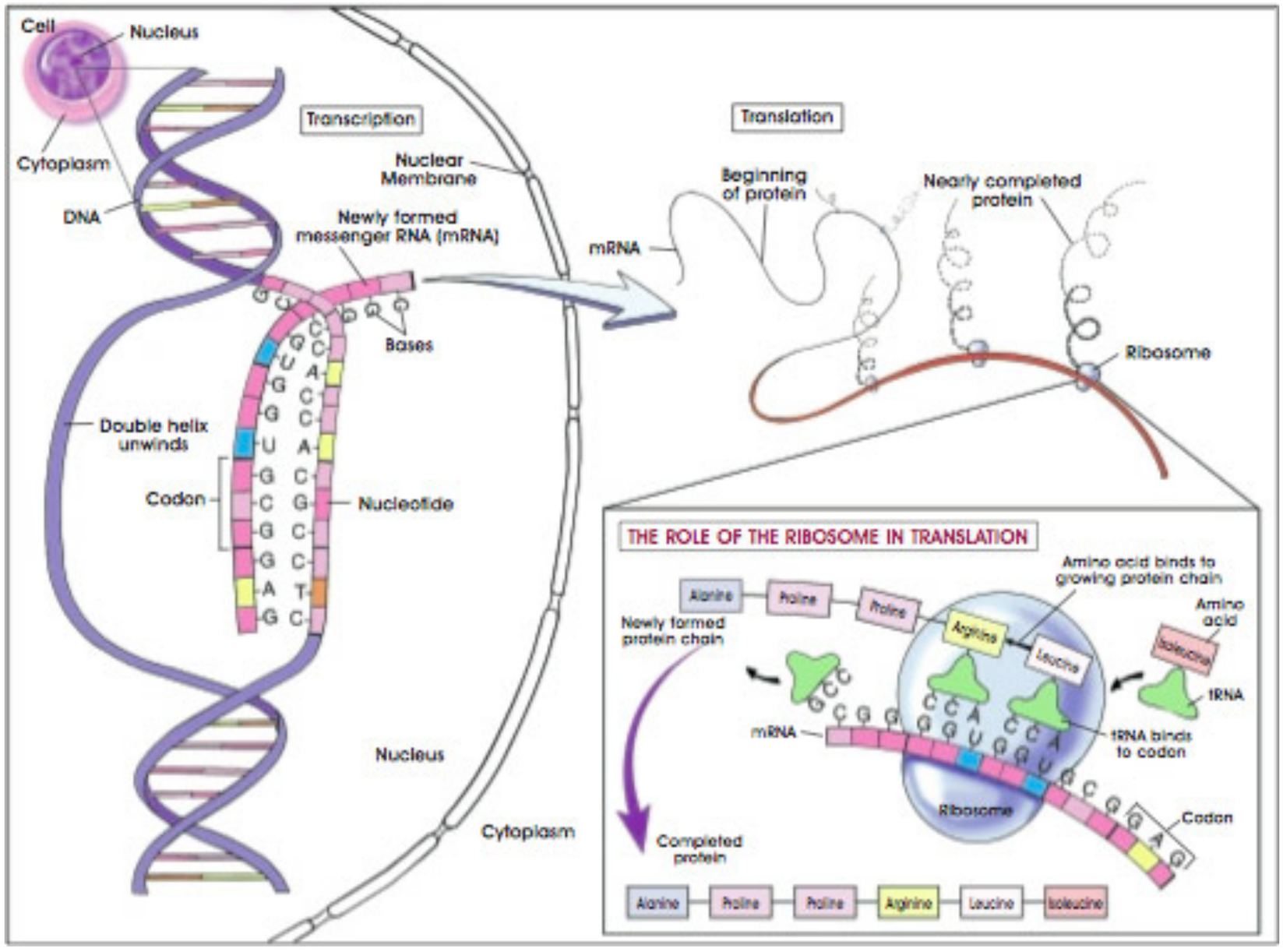

phenotype
genome


Inheritance


protein
gene


phenotype
genome


Inheritance


Cell
Nucleus
Cytoplasm
DNA
Transcription
Nuclear Membrane
Newly formed messenger RNA (mRNA)
Bases
Double helix unwinds
Codon
Nucleotide
Nucleus
Cytoplasm
Translation
mRNA
Beginning of protein
Nearly completed protein
Ribosome
THE ROLE OF THE RIBOSOME IN TRANSLATION
Amino acid binds to growing protein chain
Amino acid
Alanine
Proline
Proline
Arginine
Leucine
Isoleucine
tRNA
Newly formed protein chain
mRNA
tRNA binds to codon
Ribosome
Codon
Completed protein
Alanine
Proline
Proline
Arginine
Leucine
Isoleucine

The Genetic Code

Second letter

First letter	U	C	A	G	Third letter
U	UUU, UUC } Phe UUA, UUG } Leu	UCU, UCC, UCA, UCG } Ser	UAU, UAC } Tyr UAA Stop UAG Stop	UGU, UGC } Cys UGA Stop UGG Trp	U C A G
C	CUU, CUC, CUA, CUG } Leu	CCU, CCC, CCA, CCG } Pro	CAU, CAC } His CAA, CAG } Gln	CGU, CGC, CGA, CGG } Arg	U C A G
A	AUU, AUC, AUA } Ile AUG Met	ACU, ACC, ACA, ACG } Thr	AAU, AAC } Asn AAA, AAG } Lys	AGU, AGC } Ser AGA, AGG } Arg	U C A G
G	GUU, GUC, GUA, GUG } Val	GCU, GCC, GCA, GCG } Ala	GAU, GAC } Asp GAA, GAG } Glu	GGU, GGC, GGA, GGG } Gly	U C A G

Genomes Store Information

Genomes Store Information

Genomes Store Information

$$H_i = -\sum_j p_j^{(i)} \log_4 p_j^{(i)}$$

Genomes Store Information

$$H_i = -\sum_j p_j^{(i)} \log_4 p_j^{(i)}$$

$$I_i = H_{max} - H_i$$

Genomes Store Information

$$H_i = -\sum_j p_j^{(i)} \log_4 p_j^{(i)}$$

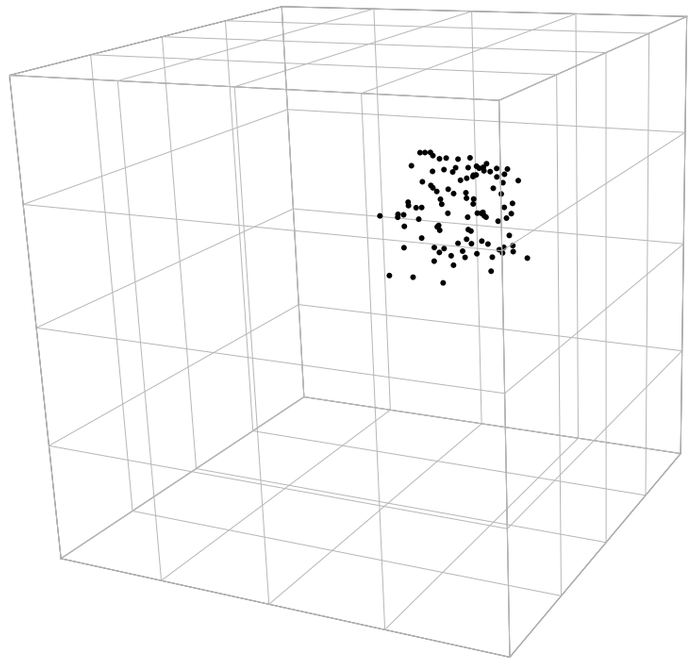
$$I_i = H_{max} - H_i$$

Information in Population of genomes

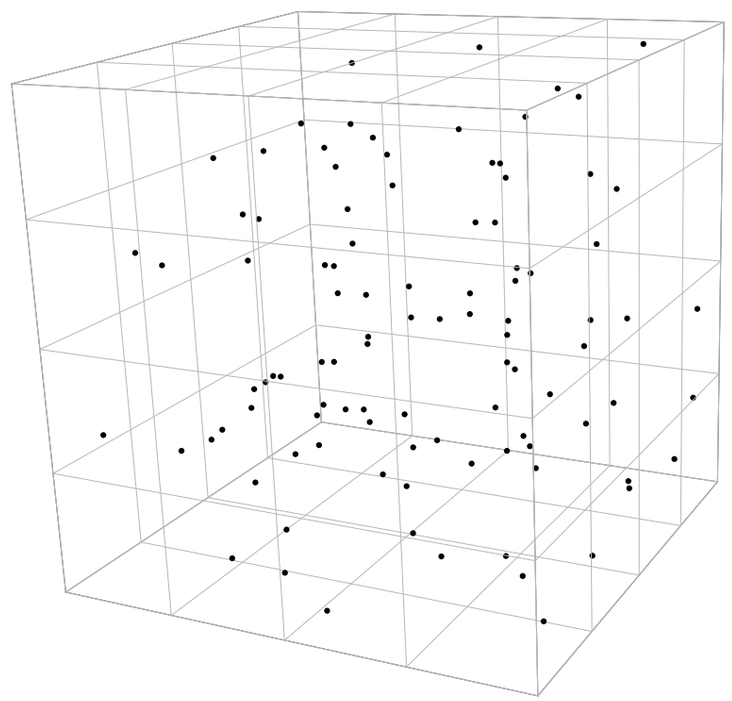
$$C = L - \sum_i H_i$$

Evolutionary Information Storage

Information Conserved



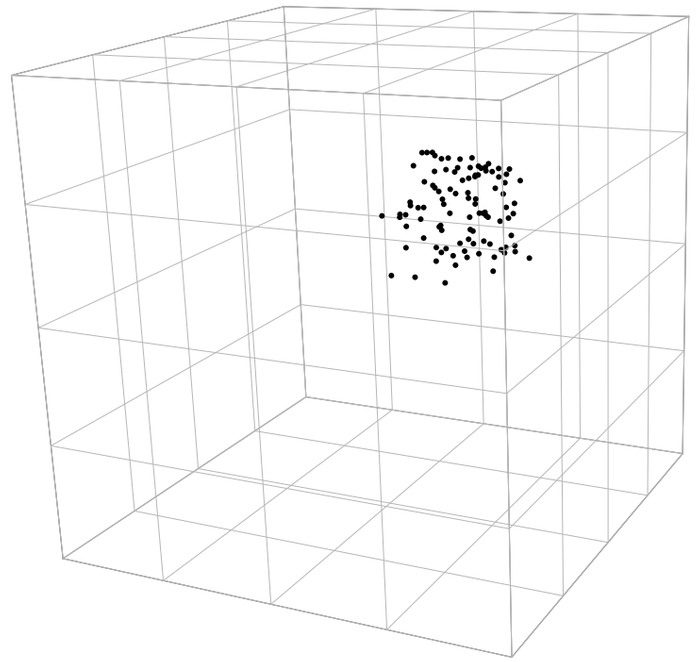
Information Lost



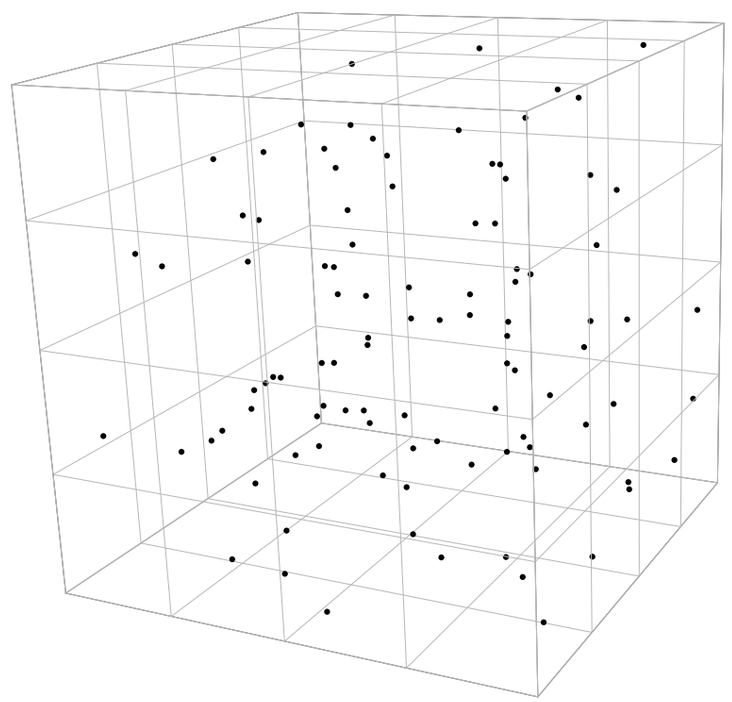
Evolutionary Information Storage

Information Conserved

$$s \geq \frac{\mu L}{N}$$

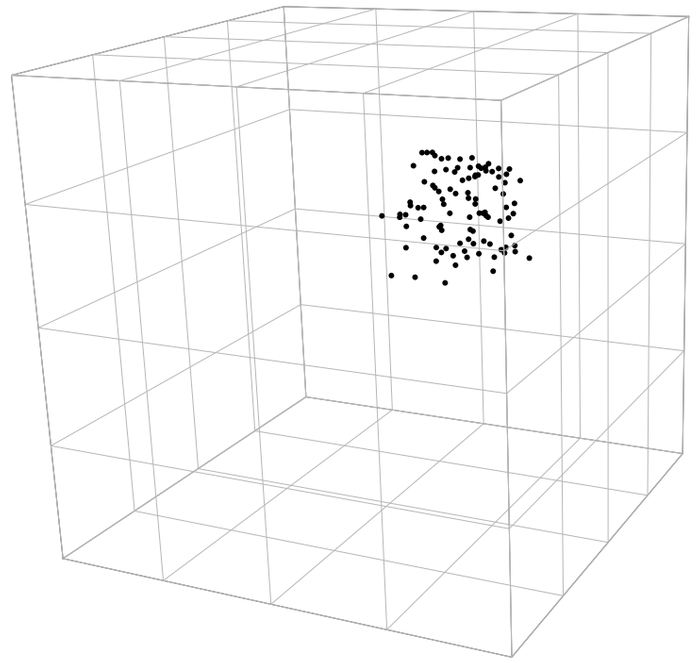


Information Lost



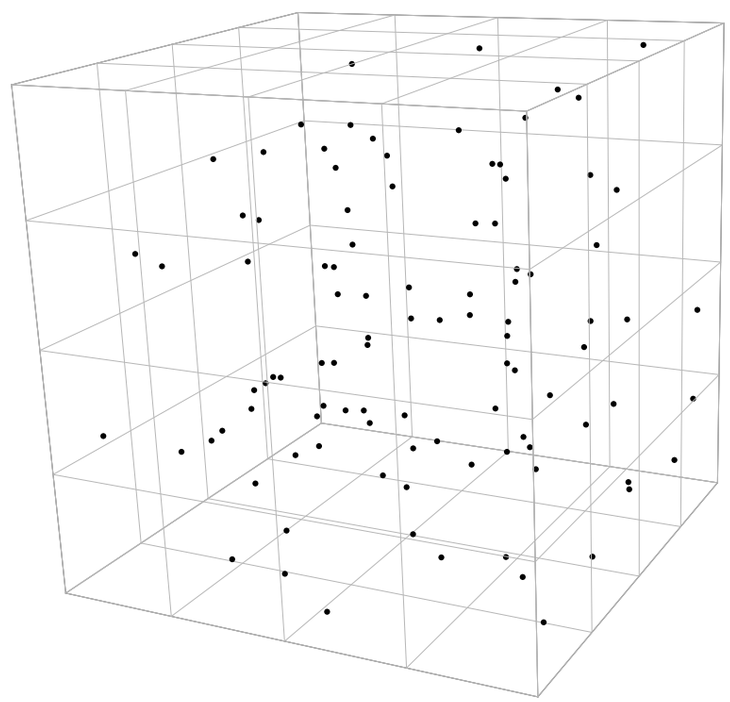
Evolutionary Information Storage

Information Conserved



$$s \geq \frac{\mu L}{N}$$

Information Lost



$$s < \frac{\mu L}{N}$$

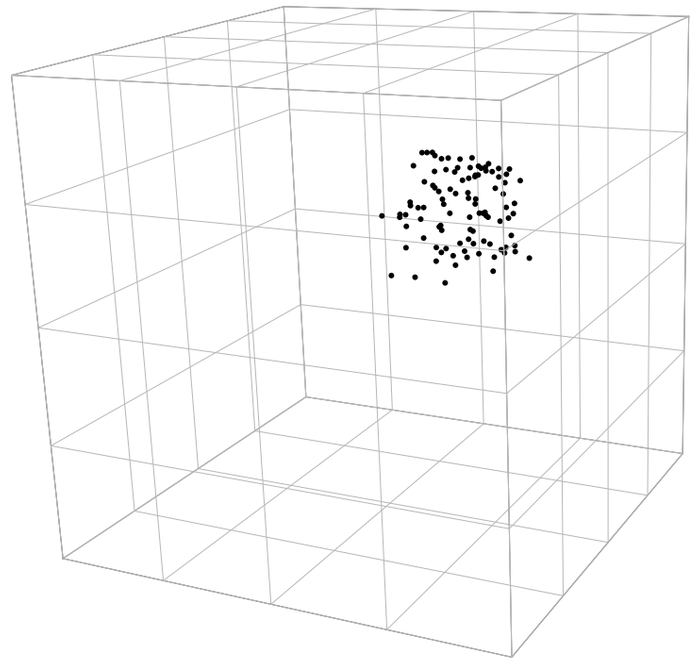
Evolutionary Information Storage

Information Conserved

organismal regularity

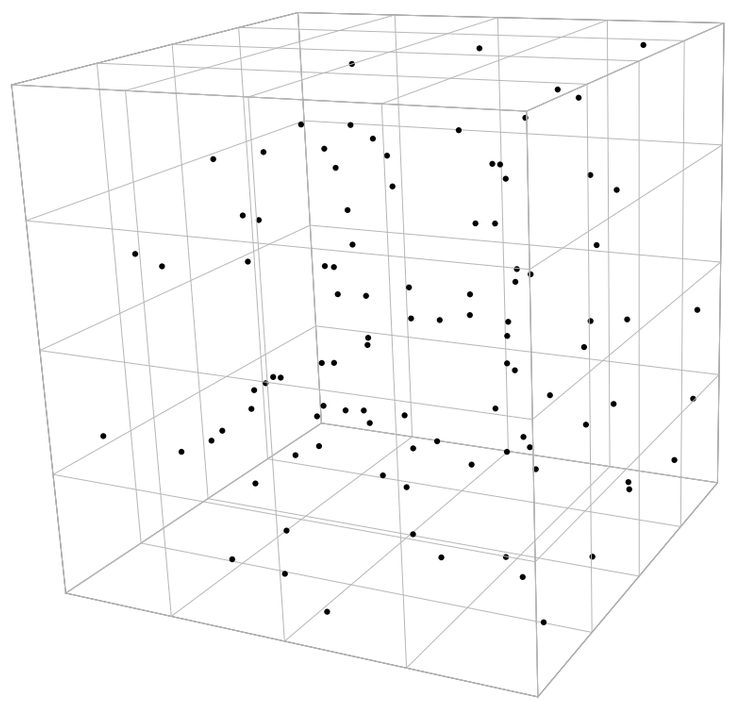
Environmental regularity

$$s \geq \frac{\mu L}{N}$$



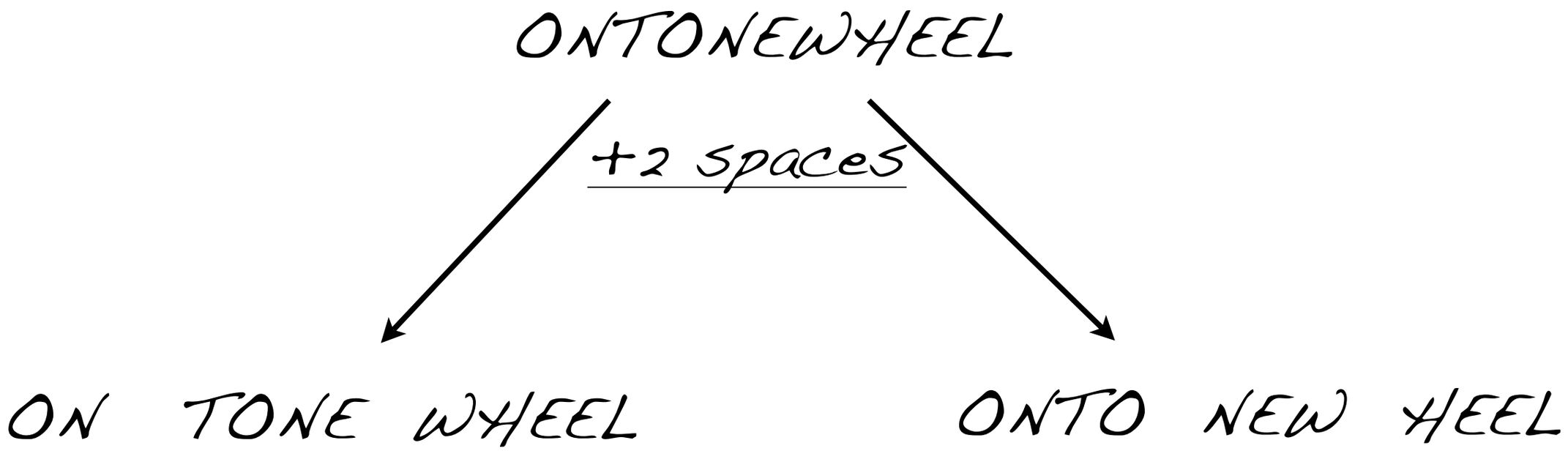
Information Lost

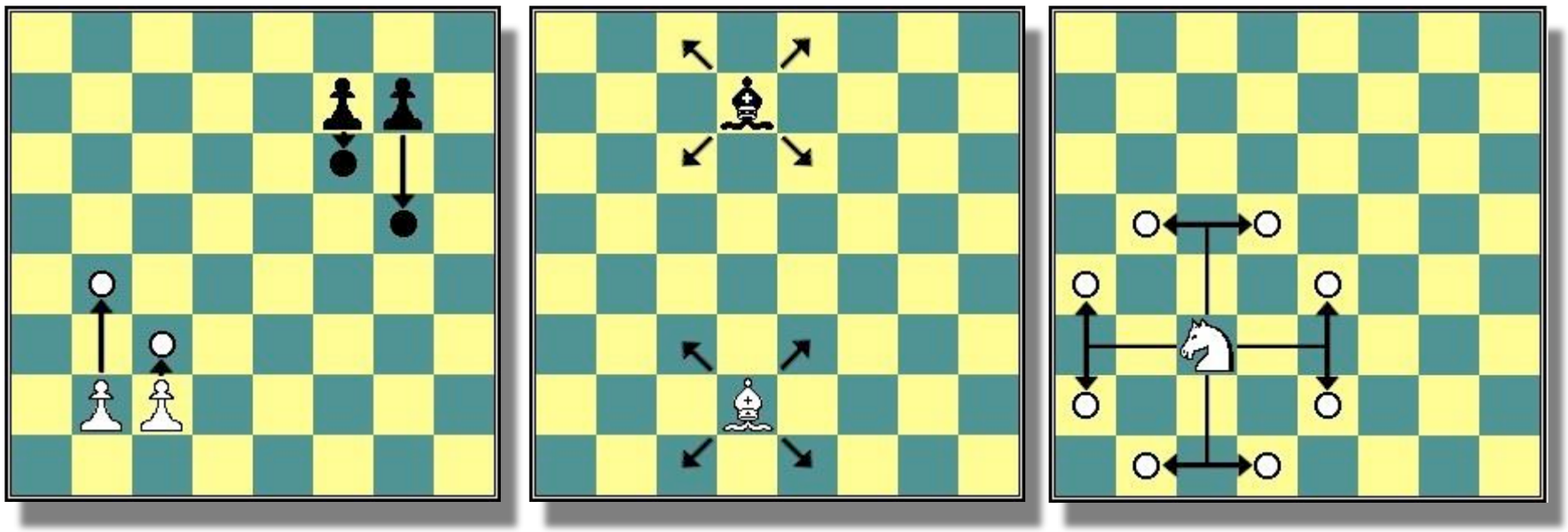
$$s < \frac{\mu L}{N}$$



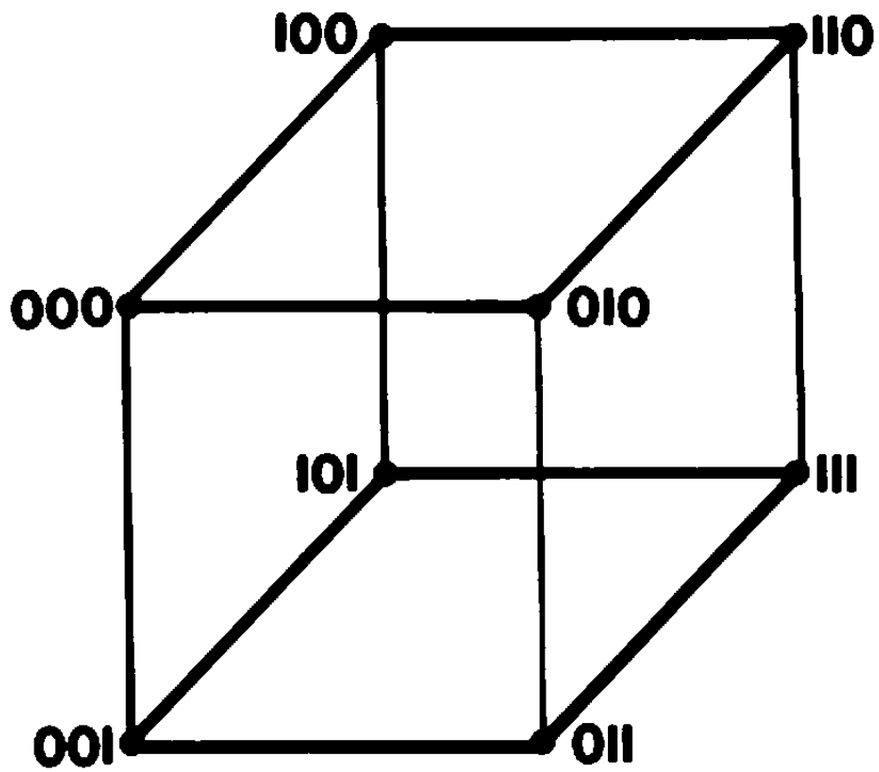
Phase	Alignment
-2	3213213213213213213213
	3213213213213213213213
	3213213213213213213213
0	123123123123123123123
	123123123123123123123
2	123123123123123123123

$F_0(123,123)$ $F_{-2}(123,321)$ $F_2(123,231)$

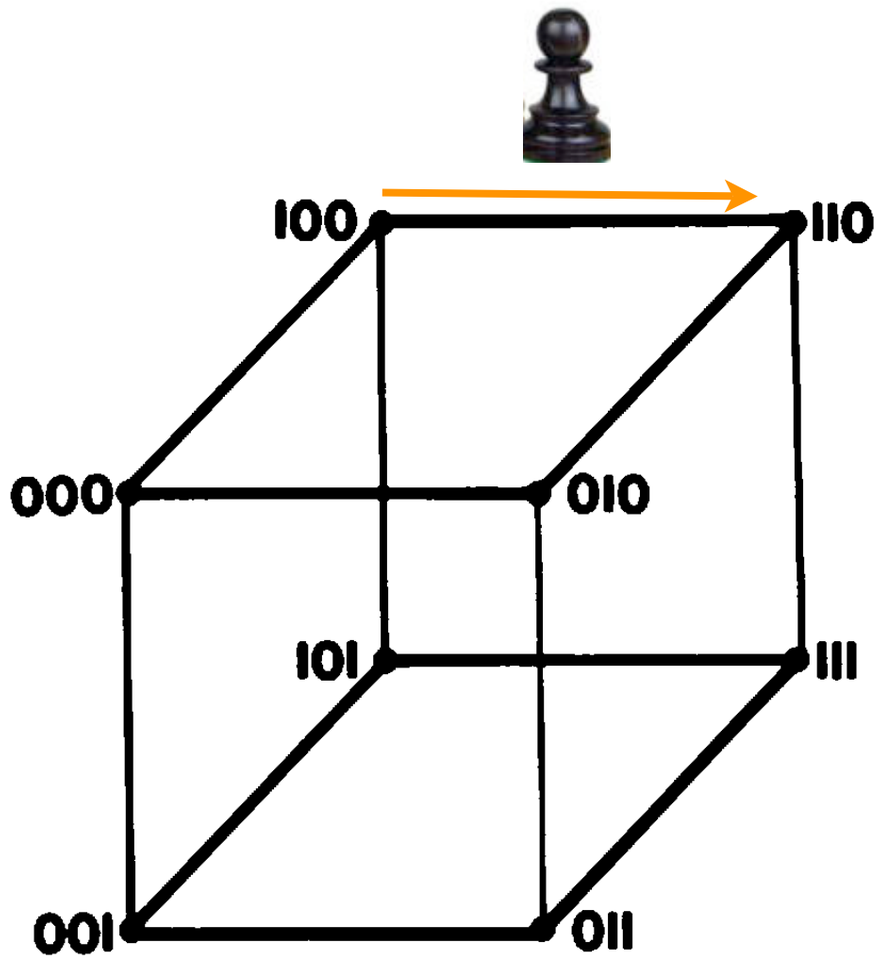

ONTONEWHEEL
+2 spaces
ON TONE WHEEL
ONTO NEW HEEL



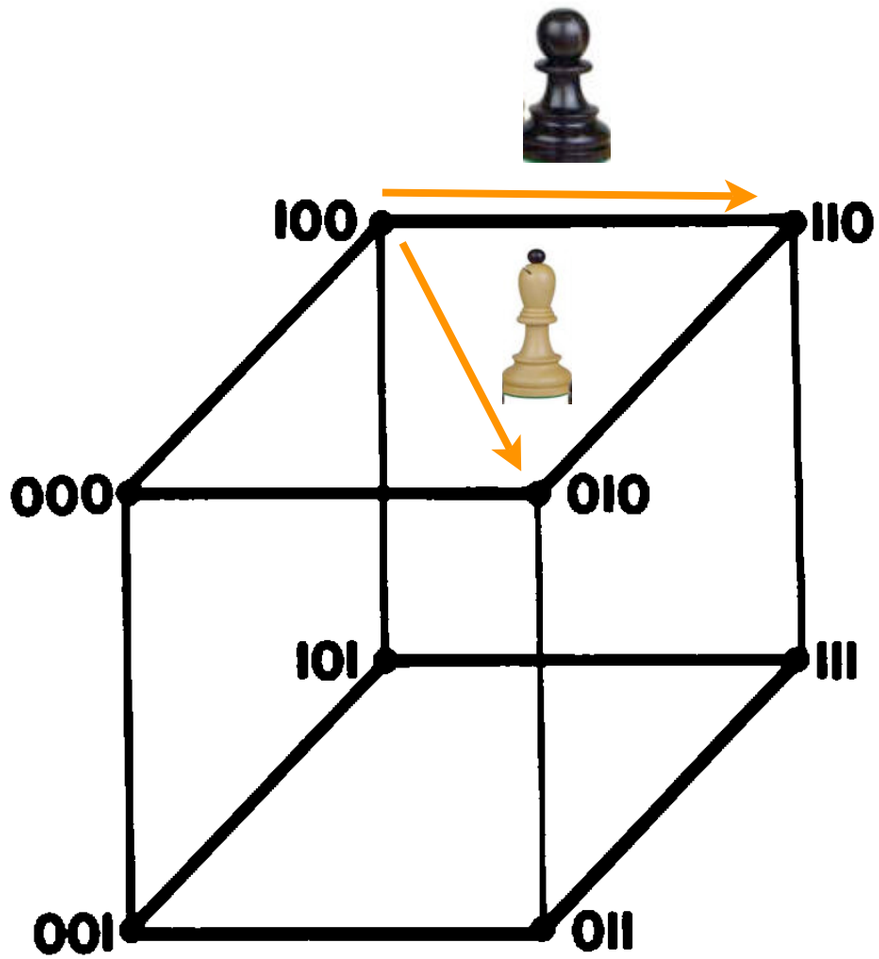
Functional Sequence Space



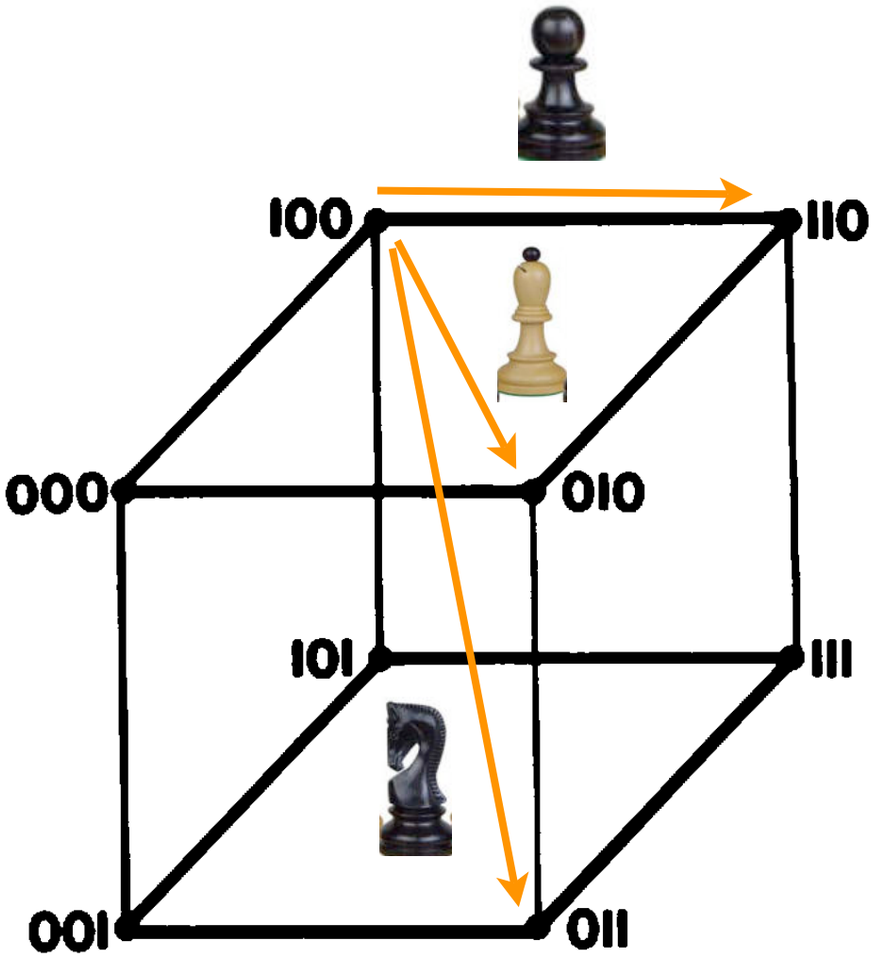
Functional Sequence Space

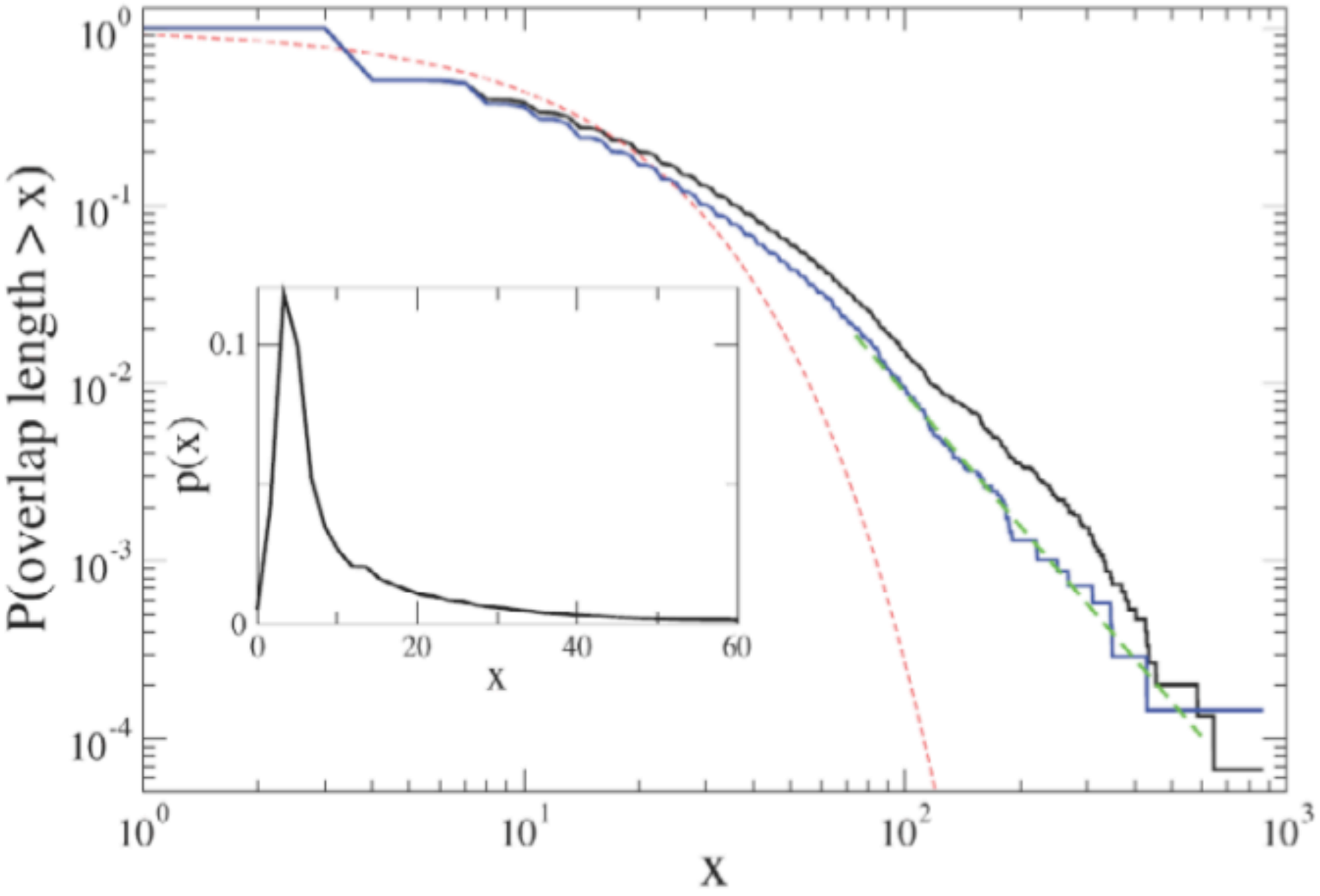


Functional Sequence Space



Functional Sequence Space



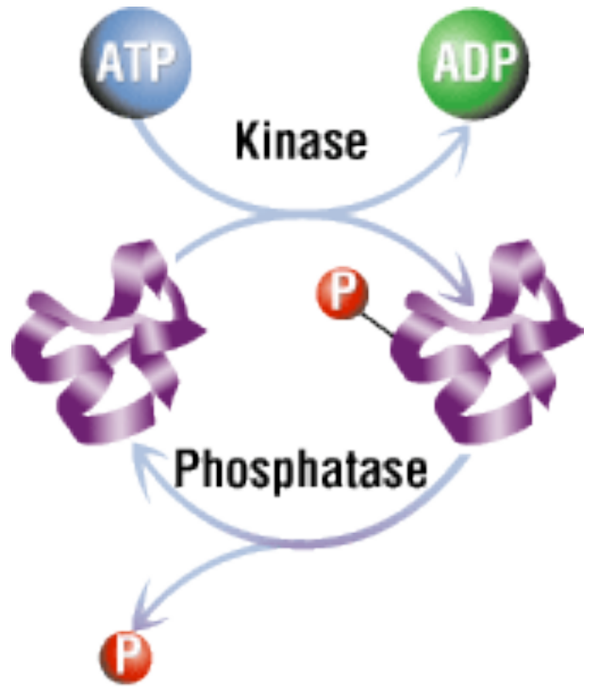

P(overlap length > x)
10^0
10^{-1}
10^{-2}
10^{-3}
10^{-4}
10^0
10^1
10^2
10^3
X
p(x)
0.1
0
0
20
40
60
X

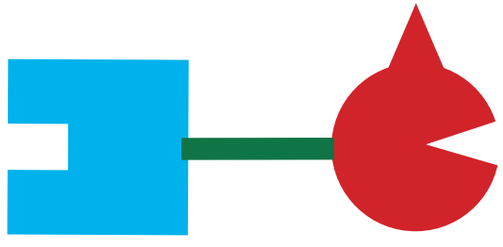
Logic & Stochastic Switches

- Krishnamurthy, S., Smith, E.D, Krakauer, D.C. and Fontana, W. The stochastic behavior of a molecular switching circuit with feedback. 2:13-25 Biology Direct. (2007)

Phosphorylation:

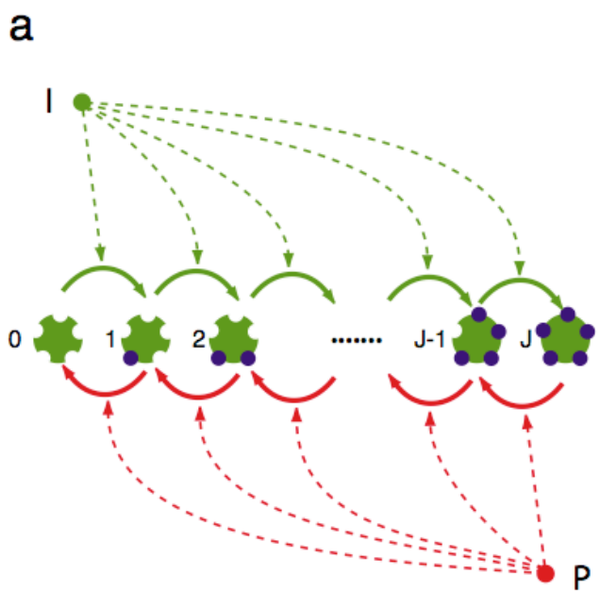
Modulation of Protein Function

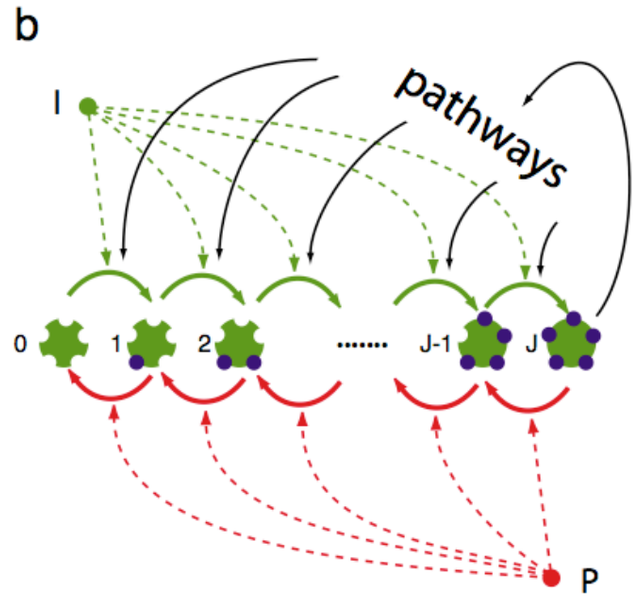


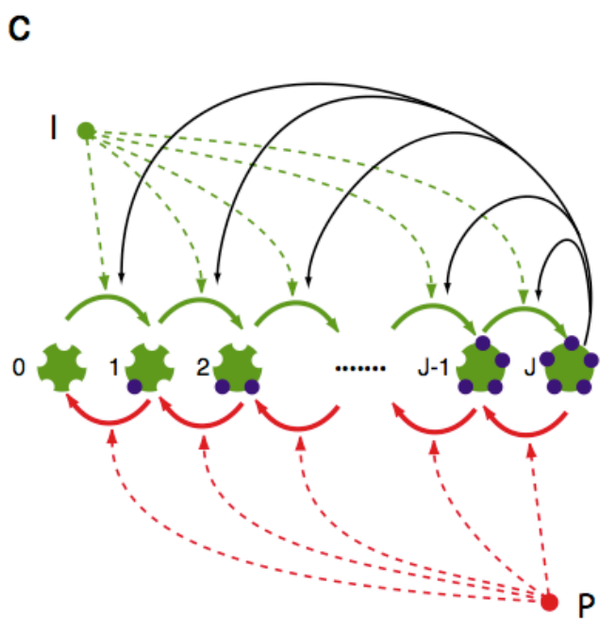


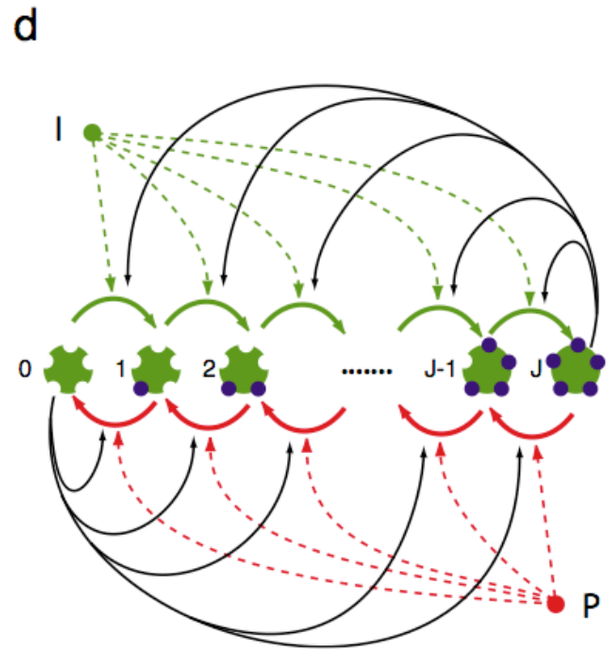
Variable Binding Domain

Conserved Catalytic Domain


a
I
0
1
2
.....
J-1
J
P


b
pathways
I
0
1
2
.....
J-1
J
P


c
I
0
1
2
.....
J-1
J
P

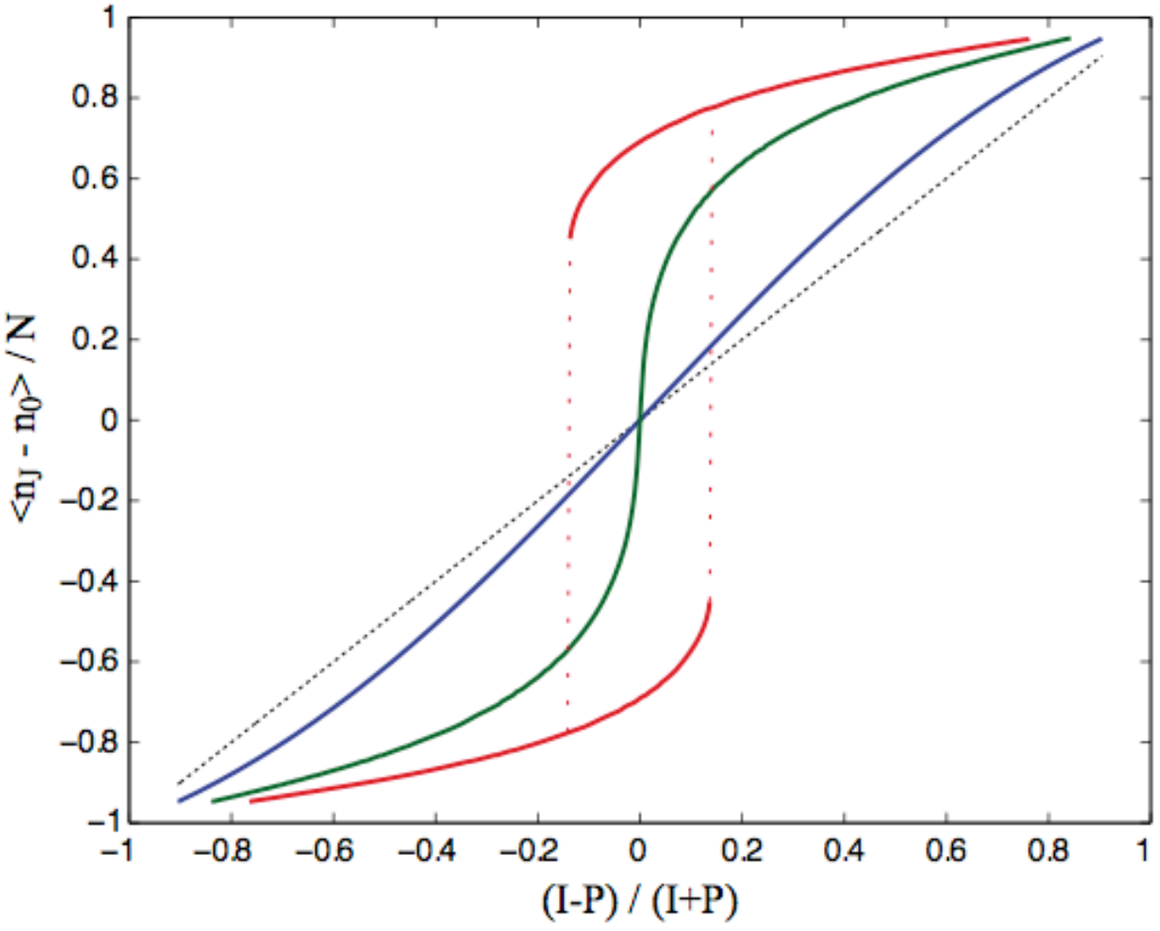

d
I
0
1
2
.....
J-1
J
P

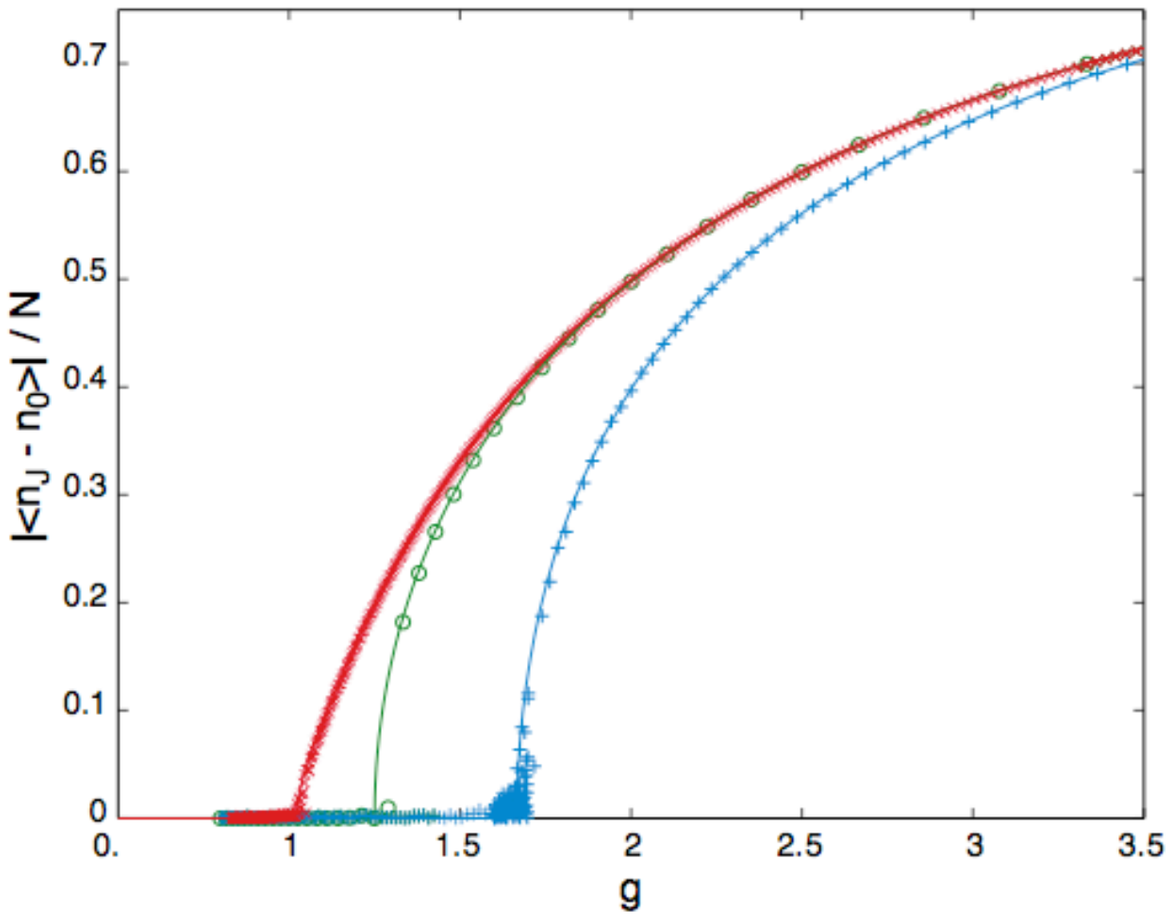
$$\frac{d}{dt}\Pr(n) = \sum_{j=0}^{J-1}\Big[(I+n_J-\delta_{J,j+1})(n_j+1)\Pr(n+1_j-1_{j+1}) - (I+n_J)n_j\Pr(n)$$

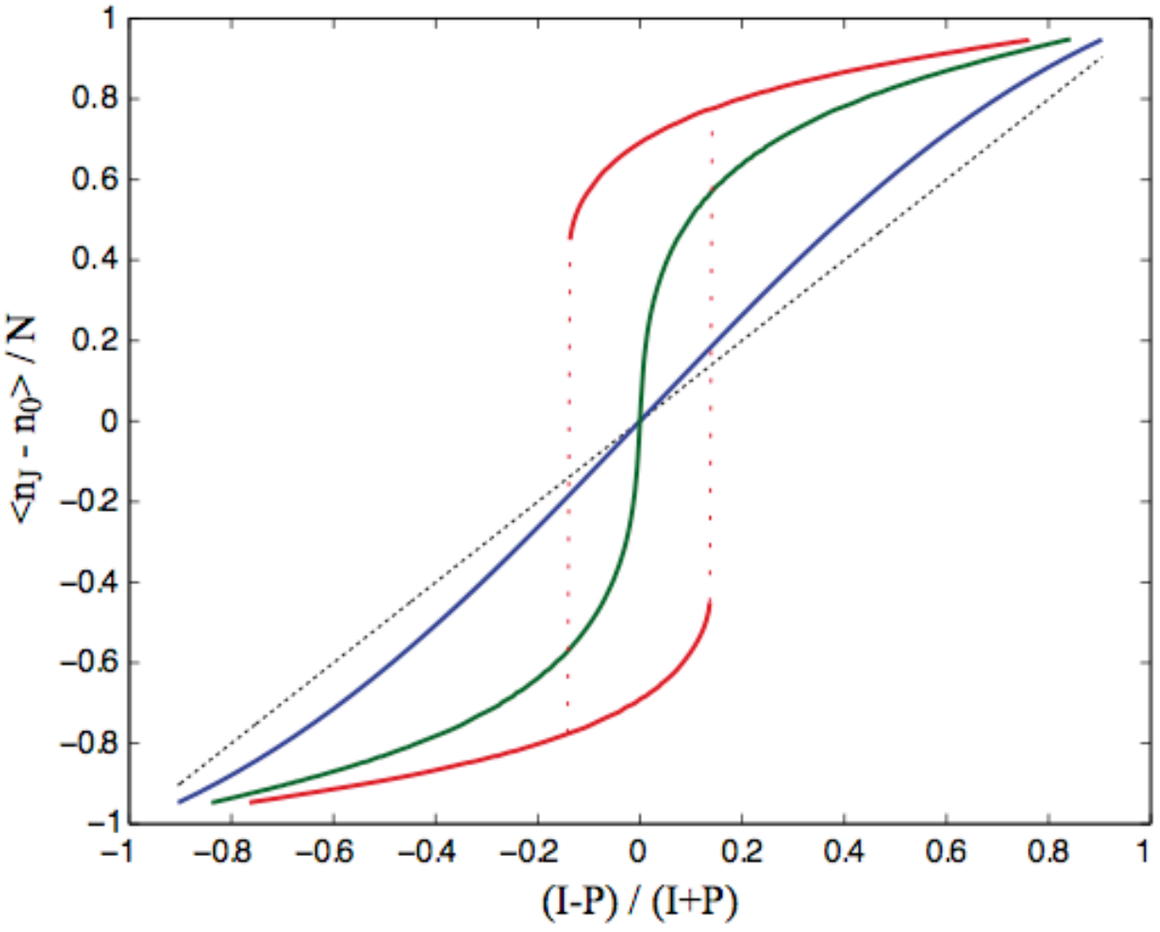
$$+(P+n_0-\delta_{0,j})(n_{j+1}+1)\Pr(n-1_j+1_{j+1}) - (P+n_0)n_{j+1}\Pr(n)\Big].$$

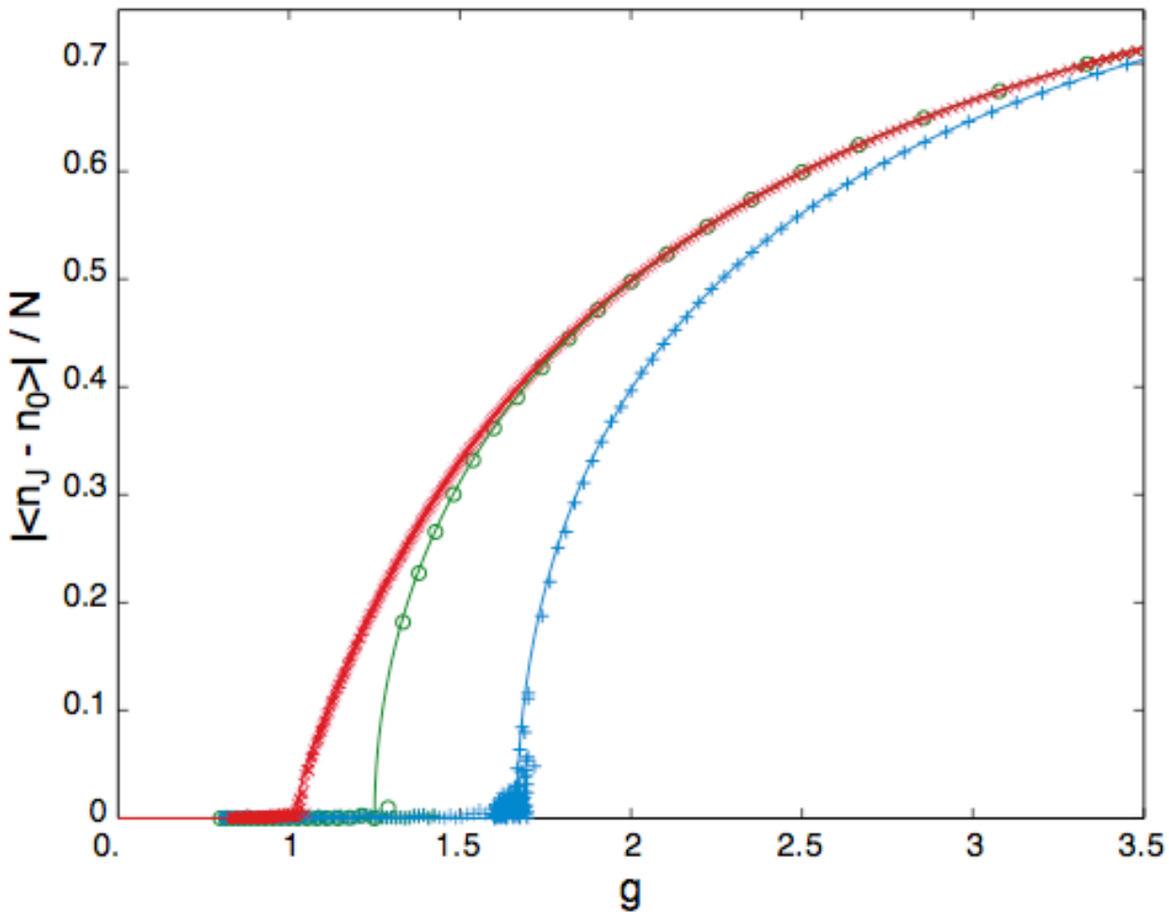
$$\frac{d}{dt}\Pr(n) = \sum_{j=0}^{J-1}\Big[(I+n_J-\delta_{J,j+1})(n_j+1)\Pr(n+1_j-1_{j+1}) - (I+n_J)n_j\Pr(n)$$

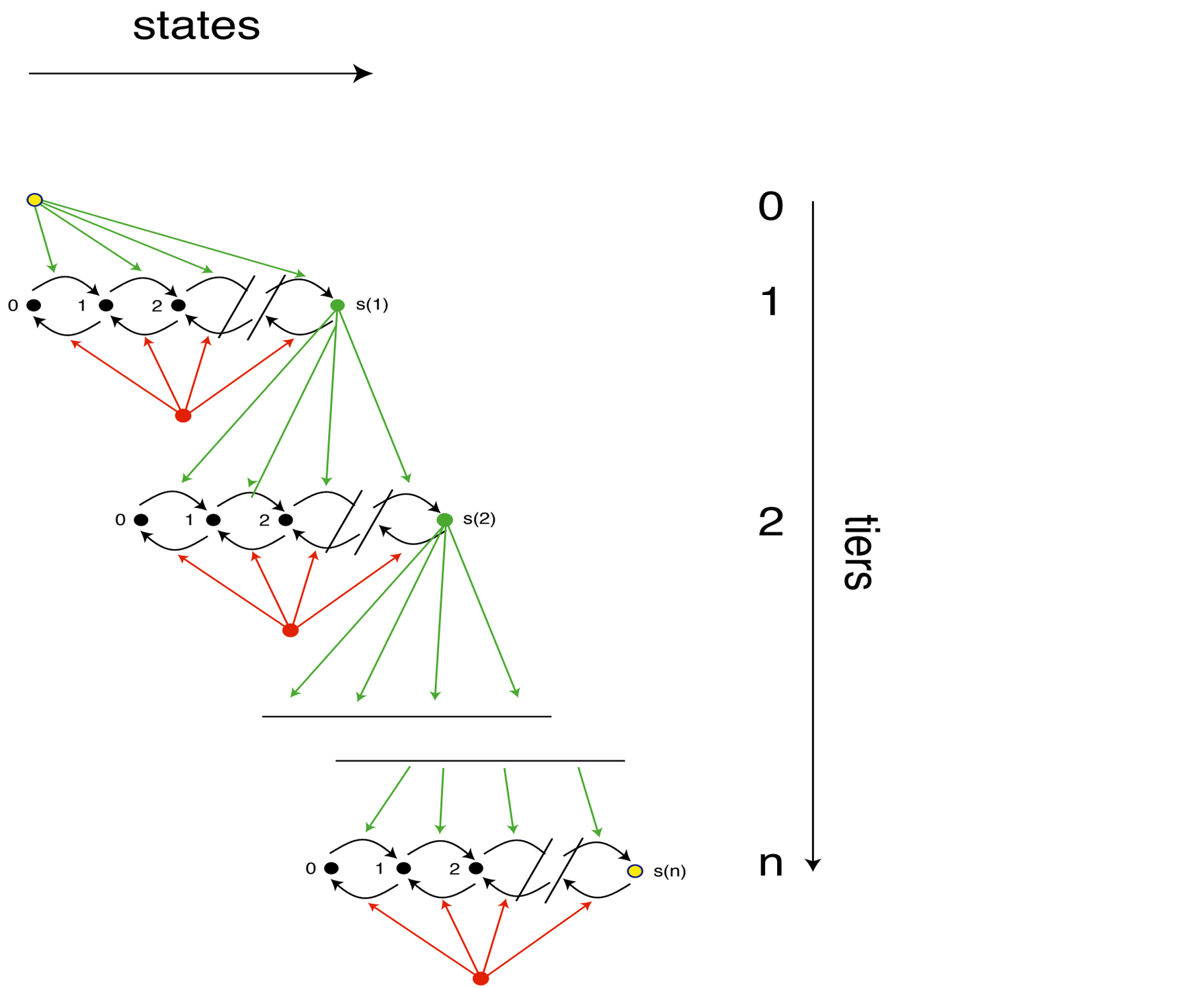
$$+(P+n_0-\delta_{0,j})(n_{j+1}+1)\Pr(n-1_j+1_{j+1}) - (P+n_0)n_{j+1}\Pr(n)\Big].$$

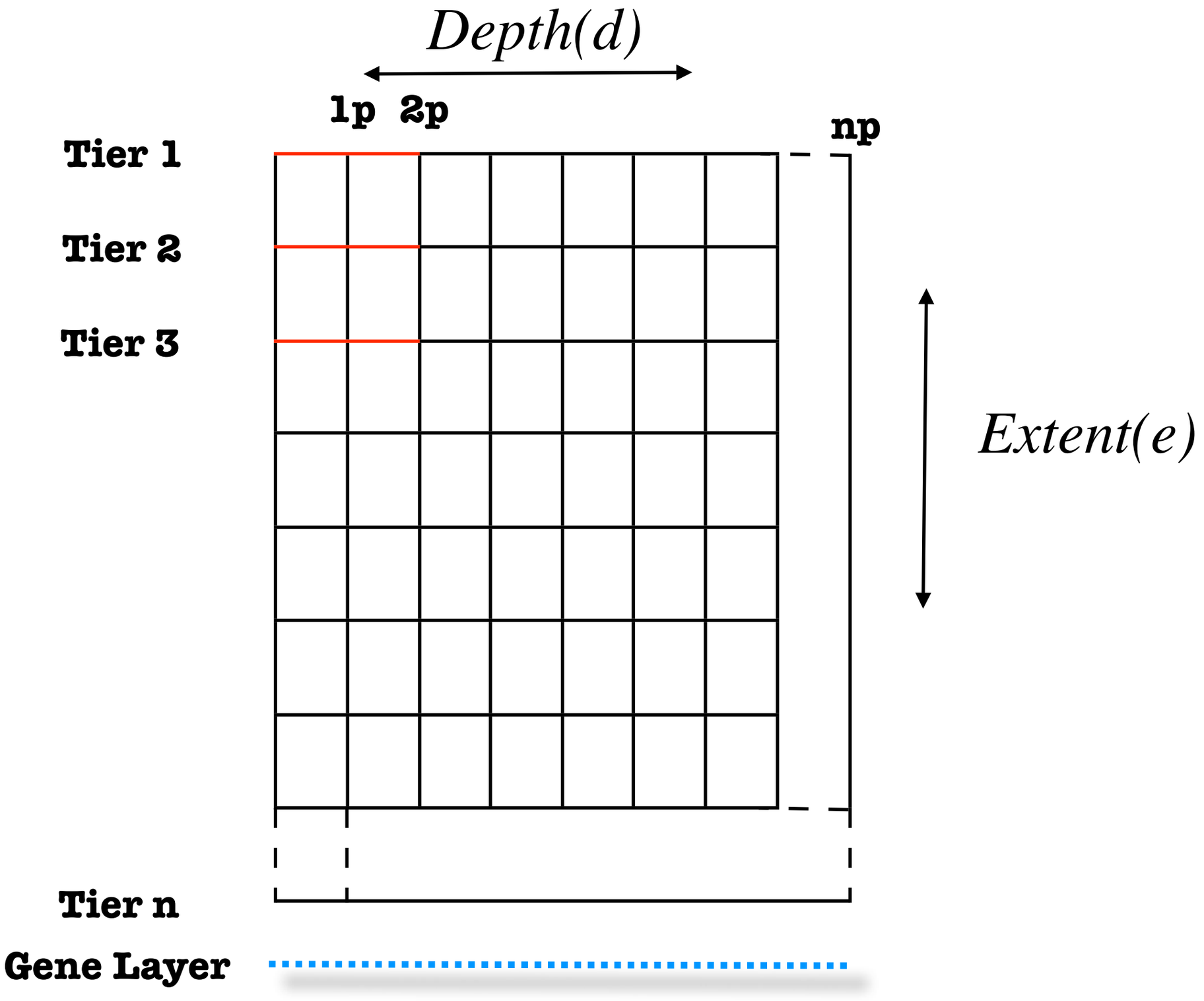


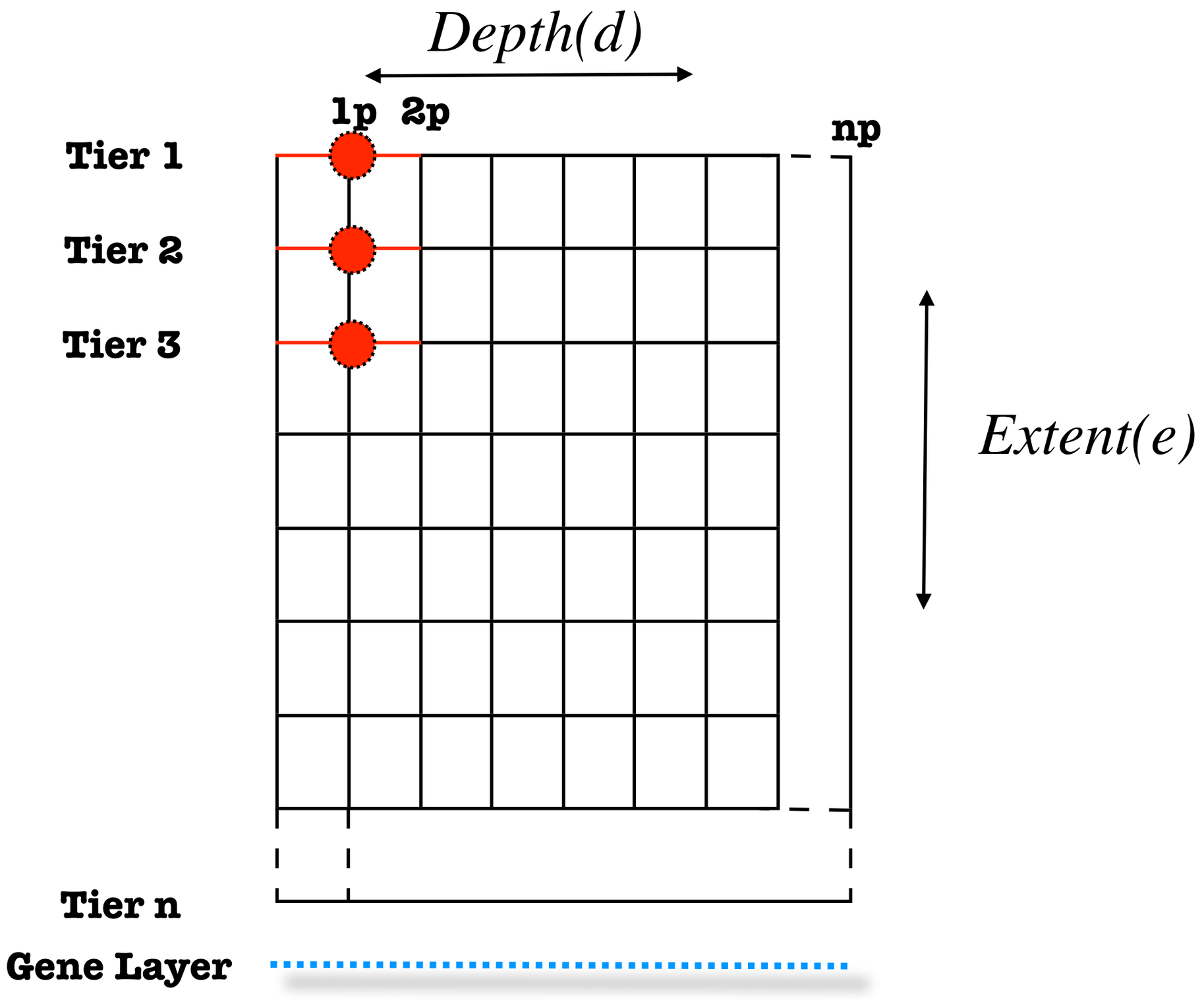


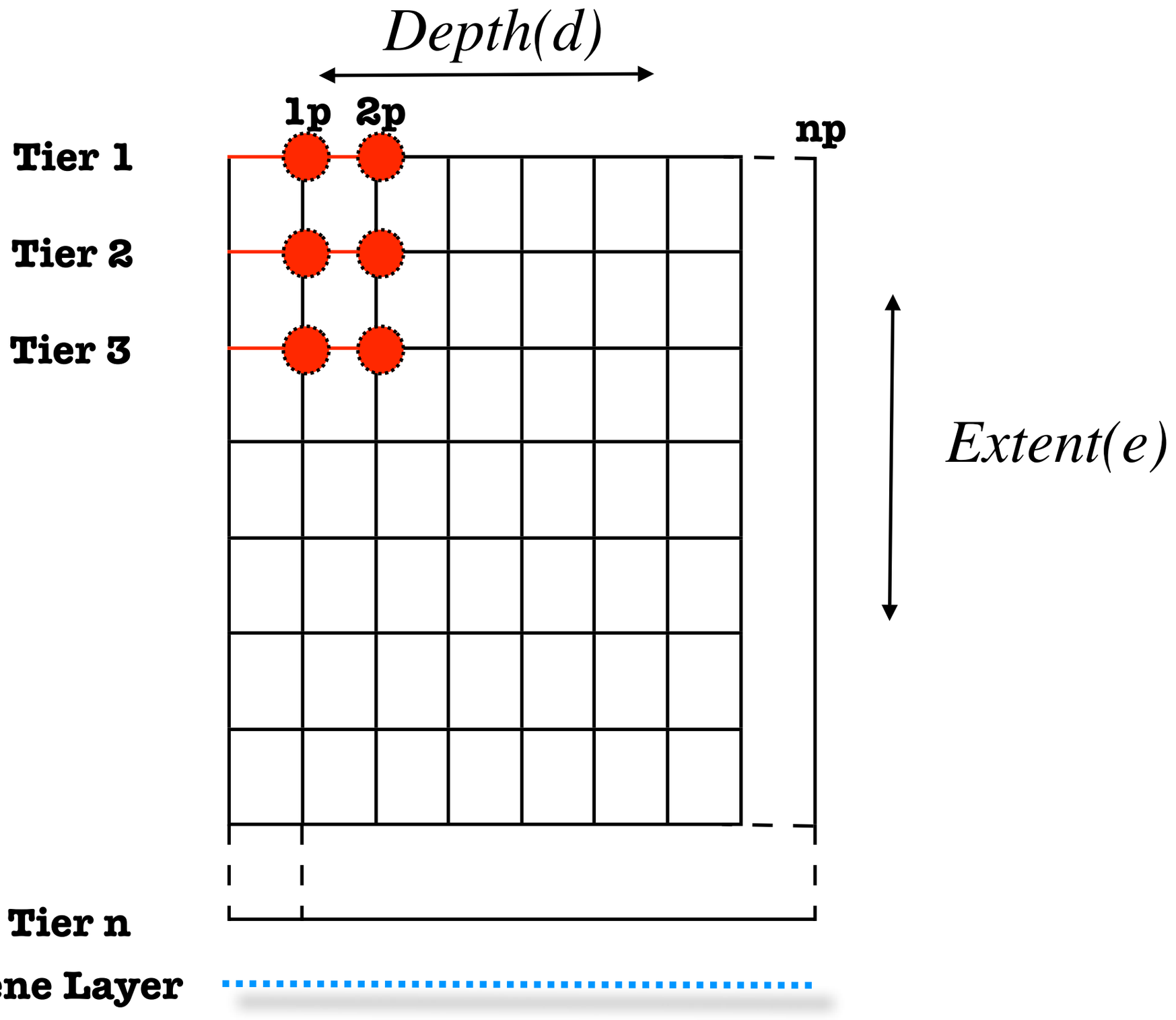

1
0.8
0.6
0.4
0.2
0
−0.2
−0.4
−0.6
−0.8
−1
−1
−0.8
−0.6
−0.4
−0.2
0
0.2
0.4
0.6
0.8
1
<nJ - n0> / N
(I-P) / (I+P)


0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.
1
1.5
2
2.5
3
3.5
|<nJ - n0>| / N
g

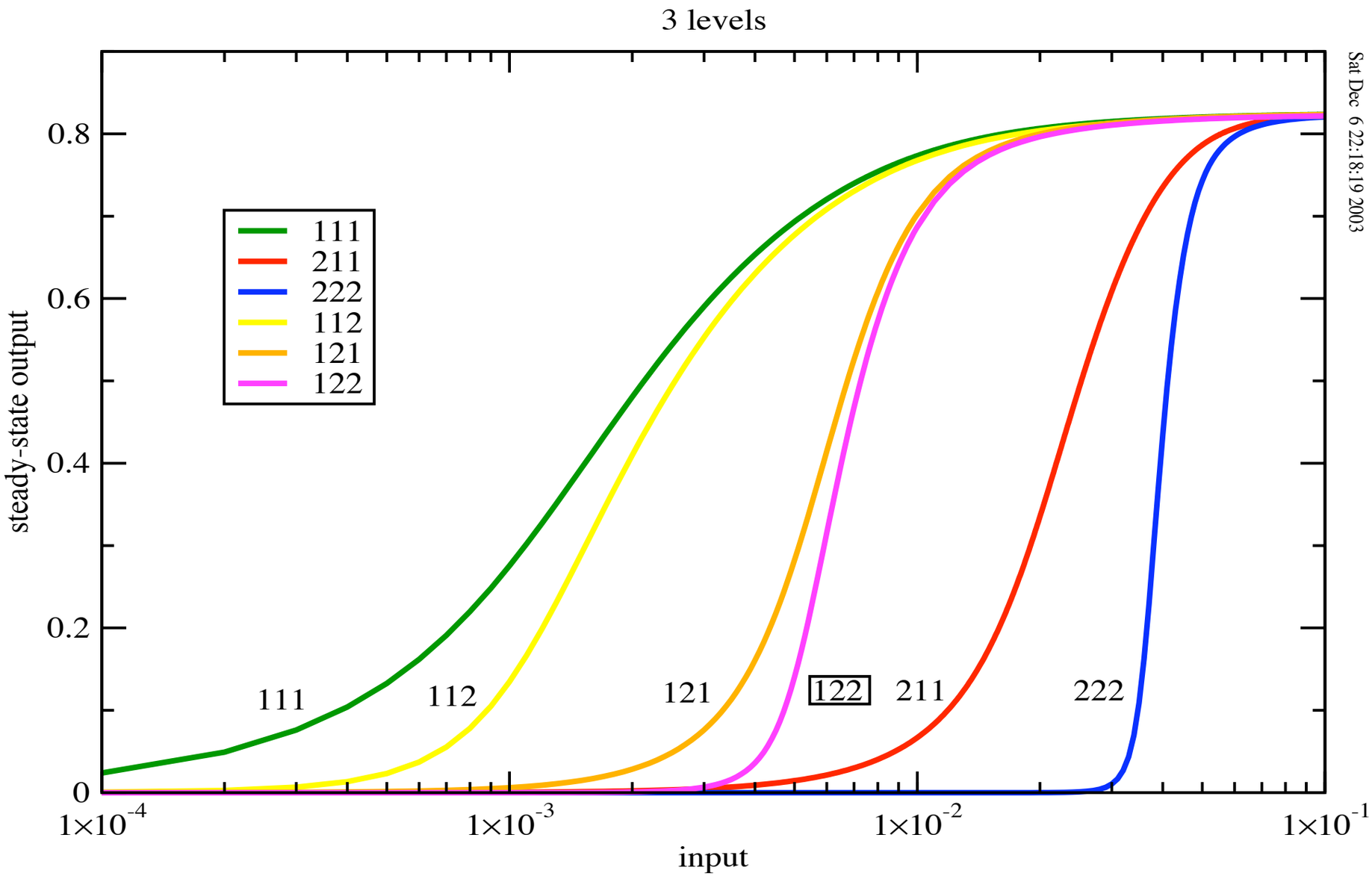

states
0
1
2
s(1)
0
1
2
s(2)
0
1
2
s(n)
0
1
2
n
tiers


Depth(d)
1p
2p
np
Tier 1
Tier 2
Tier 3
Tier n
Extent(e)
Gene Layer


Depth(d)
1p
2p
np
Tier 1
Tier 2
Tier 3
Tier n
Extent(e)
Gene Layer

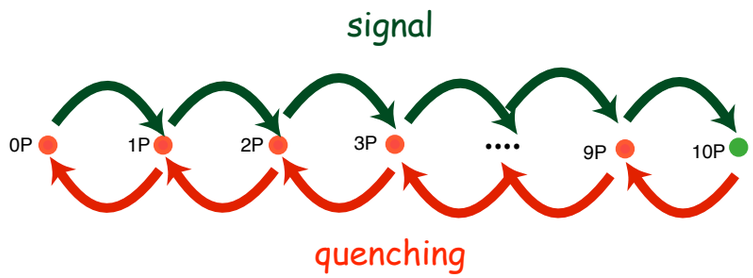

Depth(d)
1p
2p
np
Tier 1
Tier 2
Tier 3
Tier n
Extent(e)
Gene Layer

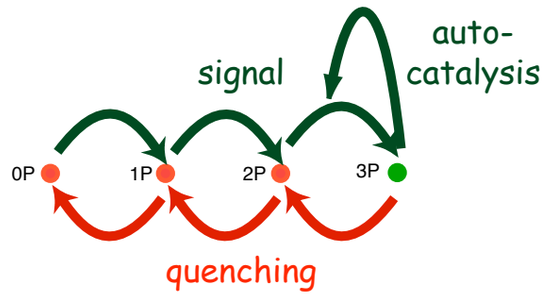
Kinase Lattice Logic

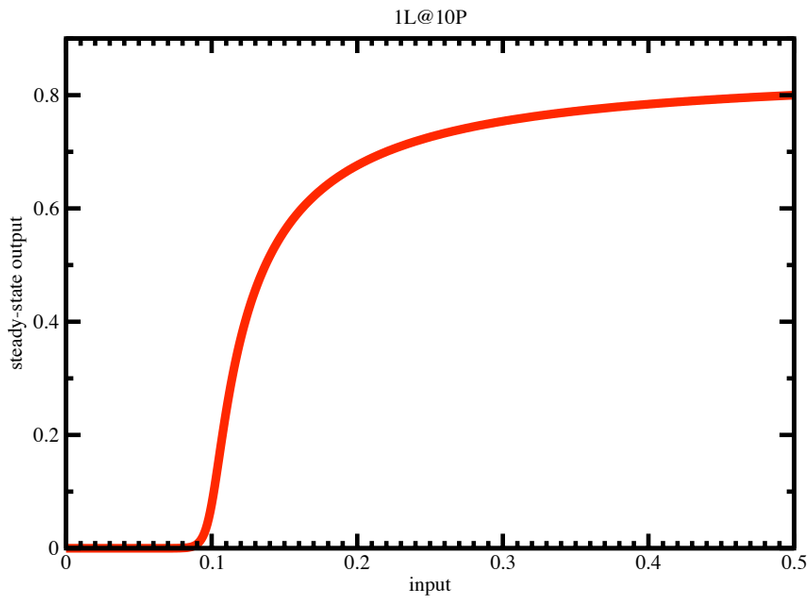


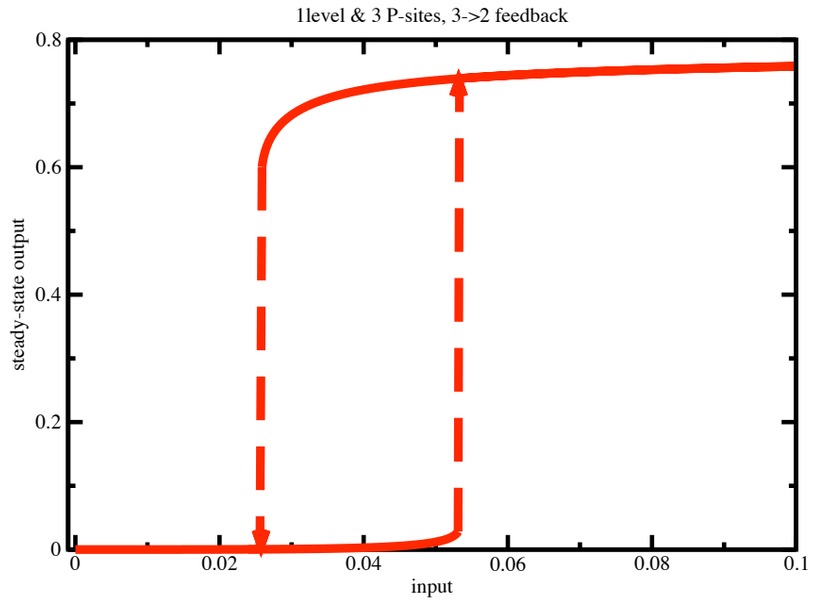
I(222) > I(211)> I(122)>I(121)>I(112)>I(111)

Protein Memory



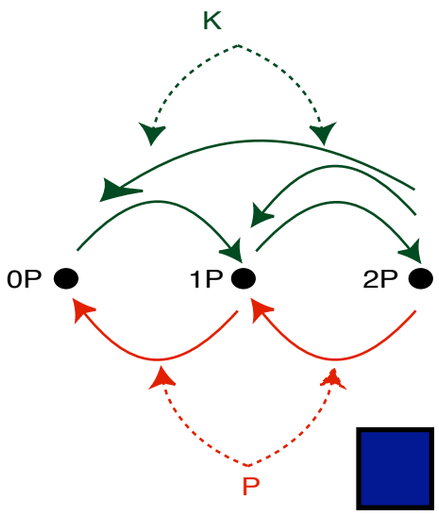


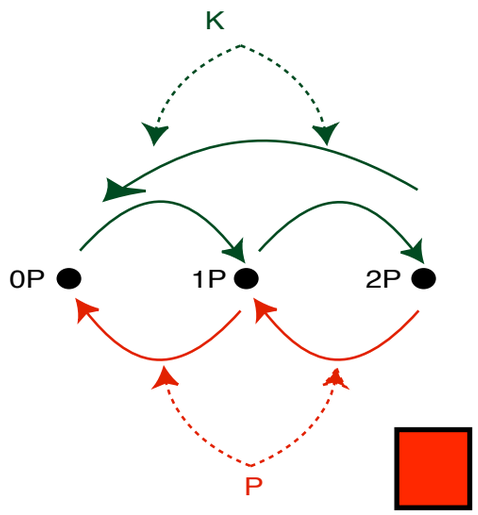


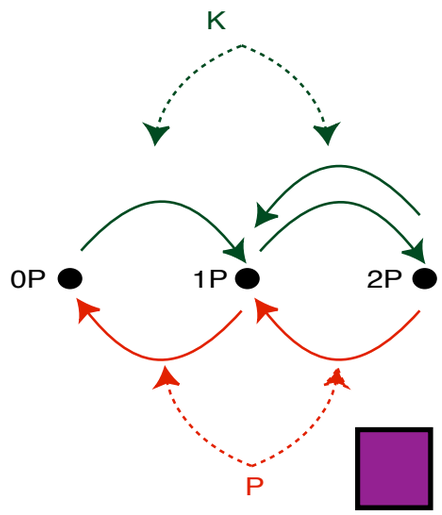


hypersensitivity

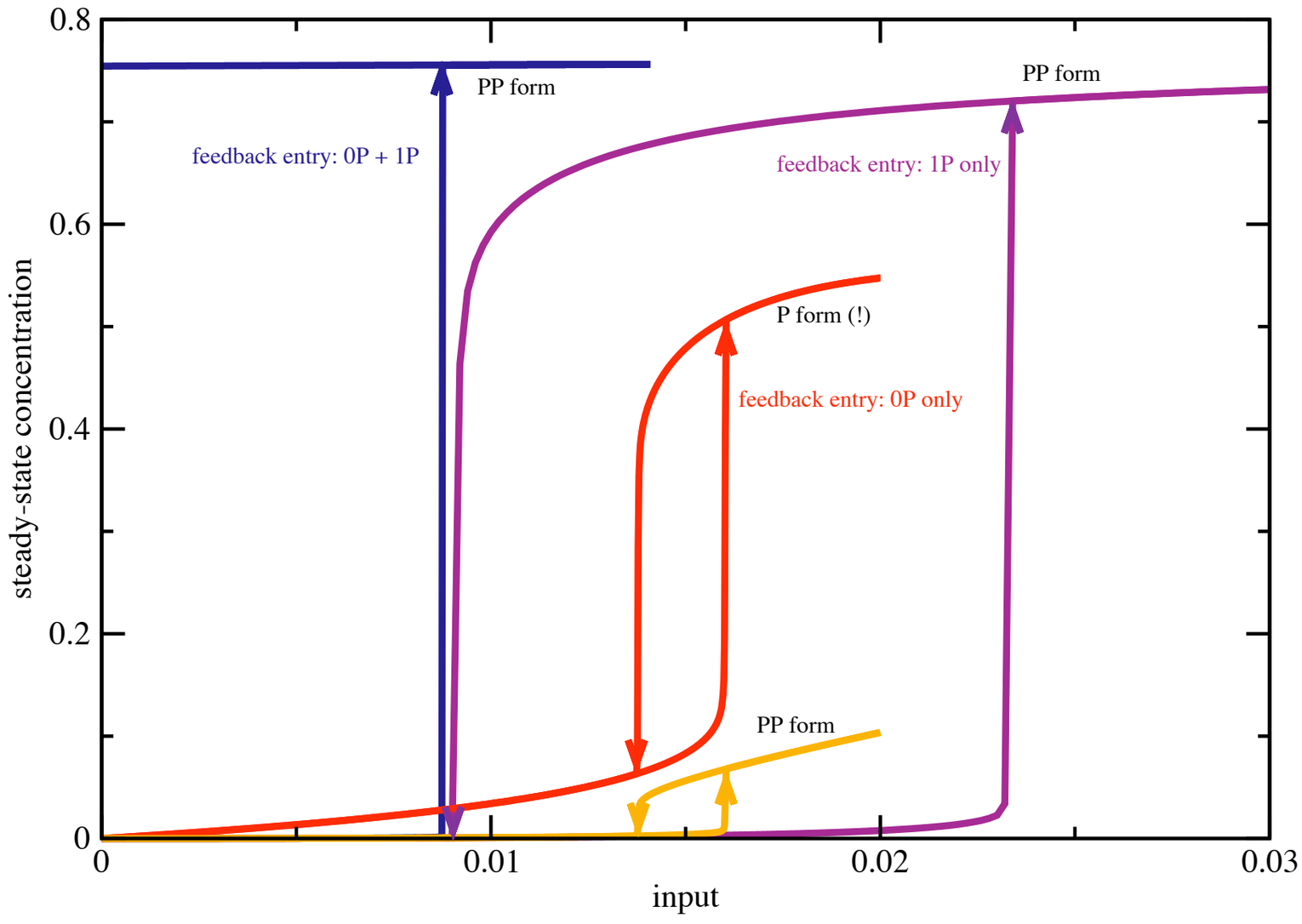
switch







1 level & 2 P-sites, various feedback entries



Communication

Persistent Protein Kinase Activation in the Maintenance Phase of Long-term Potentiation*

(Received for publication, September 12, 1991)

Eric Klann, Shu-Jen Chen, and J. David Sweatt

From the Division of Neuroscience, Baylor College of Medicine, Houston, Texas 77030

Long-term potentiation (LTP) of synaptic transmission in the hippocampus is a robust form of synaptic plasticity that may contribute to mammalian memory formation. A variety of pharmacological evidence suggests that persistent kinase activation contributes to the maintenance of LTP. To determine whether persistent activation of protein kinases was associated with the maintenance phase of LTP, protein kinase activity was measured in control and LTP samples using exogenous protein kinase substrates in an *in vitro* assay of homogenates of the CA1 region of rat hippocampal slices. After LTP, protein kinase activity was persistently increased, and the induction of this effect was blocked by the *N*-methyl-D-aspartate receptor antagonist DL-2-amino-5-phosphonovaleric acid. The increased protein kinase activity was found to be significantly attenuated by $PKC_{(19–36)}$, a selective peptide inhibitor of protein kinase C. Thus, LTP is associated with an *N*-methyl-D-aspartate receptor-mediated generation of a persistently activated form of protein kinase C. These data lend strong support to the model that persistent protein kinase activation contributes to the maintenance of LTP.

The Journal of Neuroscience, June 15, 2000, *20*(12):4497–4505

Presynaptic Protein Kinase Activity Supports Long-Term Potentiation at Synapses Between Individual Hippocampal Neurons

Paul Pavlidis, Johanna Montgomery, and Daniel V. Madison

Department of Molecular and Cellular Physiology, Stanford University School of Medicine, Stanford, California 94305-5345

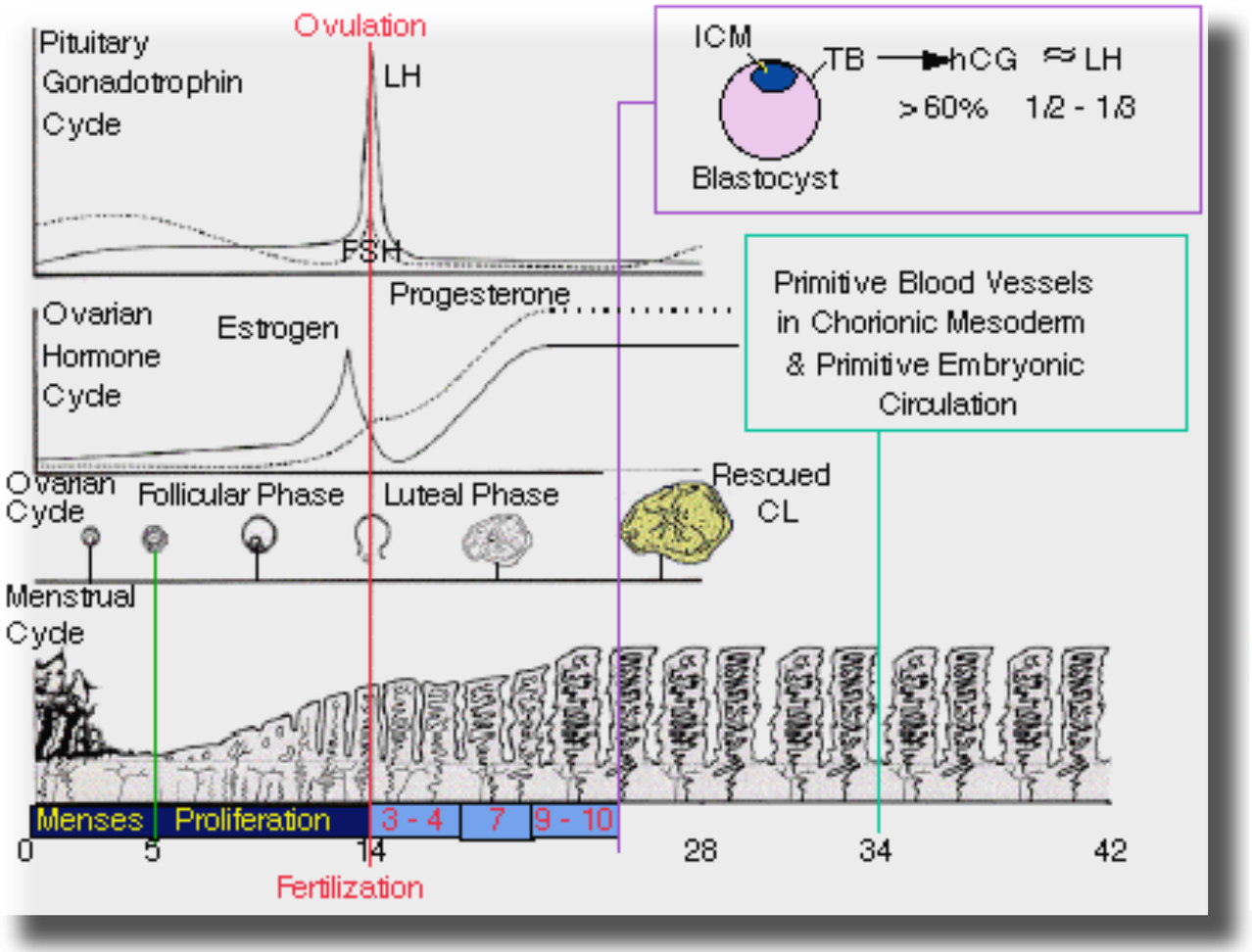
Simultaneous microelectrode recording from two individual synaptically connected neurons enables the direct analysis of synaptic transmission and plasticity at a minimal synaptic connection. We have recorded from pairs of CA3 pyramidal neurons in organotypic hippocampal slices to examine the properties of long-term potentiation (LTP) at such minimal connections. LTP in minimal connections was found to be identical to the NMDA-dependent LTP expressed by CA3–CA1 synapses, demonstrating this system provides a good model for the study of the mechanisms of LTP expression. The LTP at minimal synaptic connections does not behave as a simple increase in transmitter release probability, because the amplitude of unitary EPSCs can increase several-fold, unlike what is observed when release probability is increased by raising extracellular calcium. Taking advantage of the relatively short axon connecting neighboring CA3 neurons, we found it feasible to introduce pharmacological agents to the interior of presynaptic terminals by injection into the presynaptic soma and have used this technique to investigate presynaptic effects on basal transmission and LTP. Presynaptic injection of nicotinamide reduced basal transmission, but LTP in these pairs was essentially normal. In contrast, presynaptic injection of H-7 significantly depressed LTP but not basal transmission, indicating a specific role of presynaptic protein kinases in LTP. These results demonstrate that pharmacological agents can be directly introduced into the presynaptic cell and that a purely presynaptic perturbation can alter this plasticity.

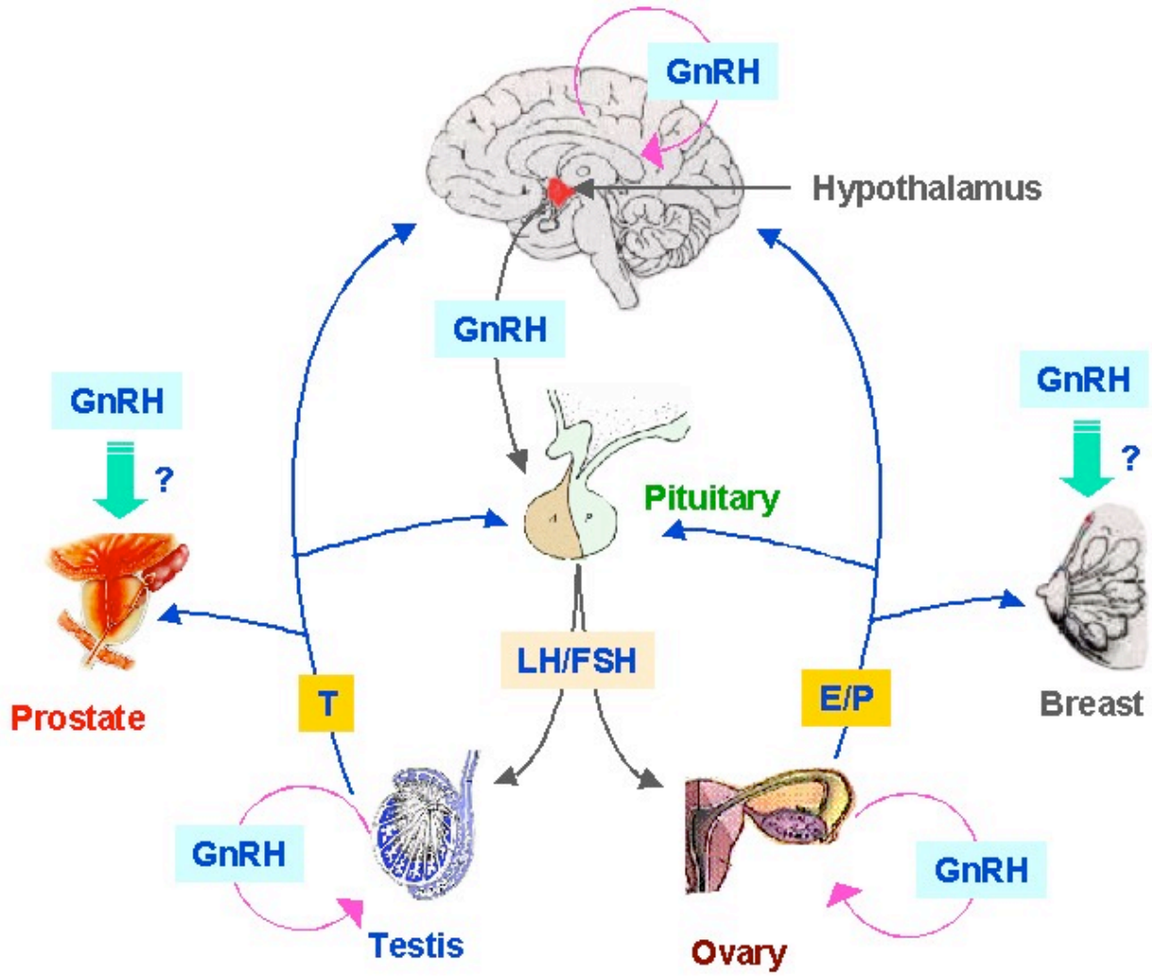
Key words: long-term potentiation; presynaptic; protein kinase; hippocampus; electrophysiology; synaptic transmission

Feature Detection

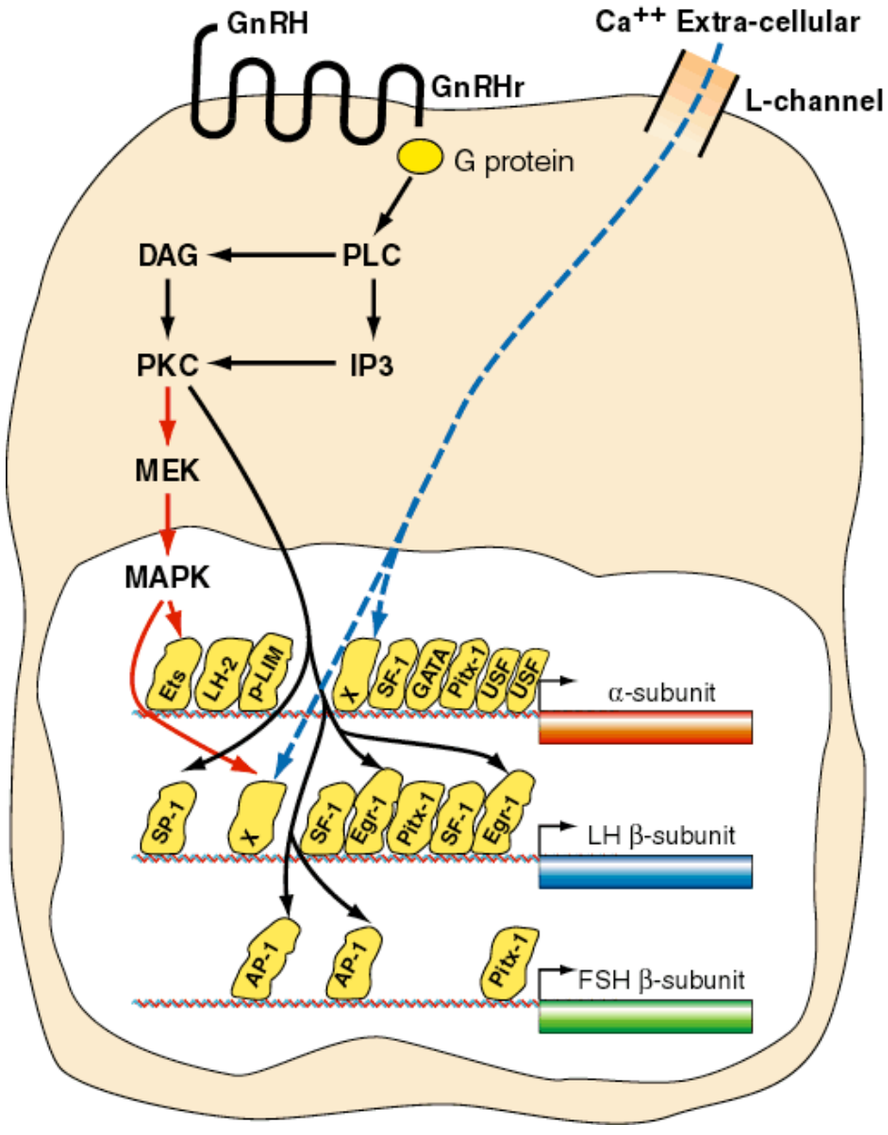
- Krakauer, D.C. & Page, K & Sealfon, S. Module dynamics of the GnRH signal transduction network. J. theor, Biol. 218, 457-470 (2002)

Reproductive Cycles





Reproductive Cycles



High Frequency: α

Med Frequency: LH β

Low Frequency: FSH β

$$\dot{b} = h'(a(t)) - pb \equiv f'(t) - pb, \tag{9}$$

$$\dot{c} = \begin{cases} kb(t-\sigma) - \delta' c, & a = 0, \\ -\delta' c, & a = a_0. \end{cases} \tag{10}$$

The activation of B only ensues in the presence of A, whereas the production of C only ensues in the presence of activated B. The choice of a piecewise function in our analysis reflects the total inhibition of the expression of C during the activation of A. Integrating eqn (9), analogously to the integration of eqn (1) to derive eqns (3) and (4), yields

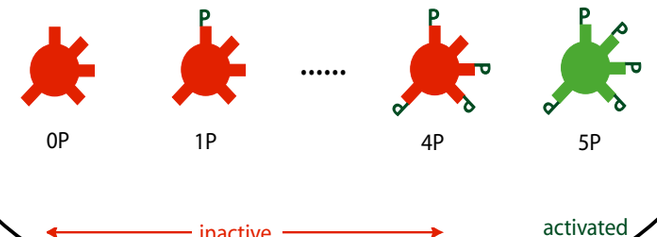
$$b(n\tau) = \frac{\mathrm{e}^{-pt}}{1 - \mathrm{e}^{-p\tau}} \int_0^\tau f(t)\mathrm{e}^{pt}\,\mathrm{d}t \quad \text{for } n \text{ large}, \tag{11}$$

$$b(n\tau + t_1) = \mathrm{e}^{-pt_1}\left[b(n\tau) + \int_0^{t_1} f(t)\mathrm{e}^{pt}\,\mathrm{d}t\right] \tag{12}$$

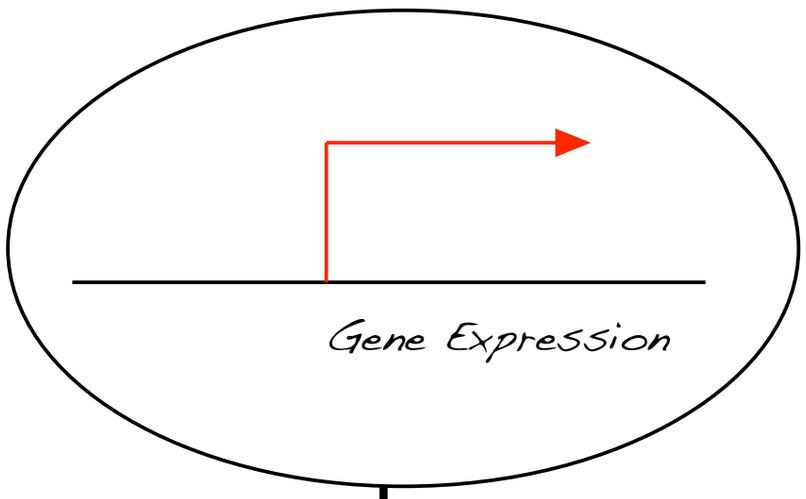
for $t_1 \in [0, \tau]$.

Extracellular Input

Signal Transduction



Fast Activation

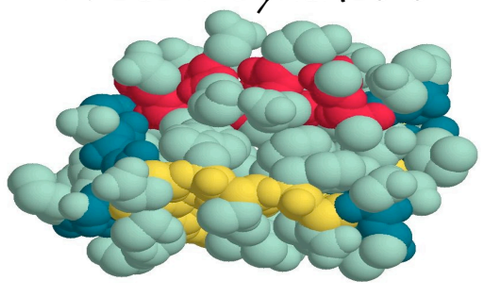


Fast Decay

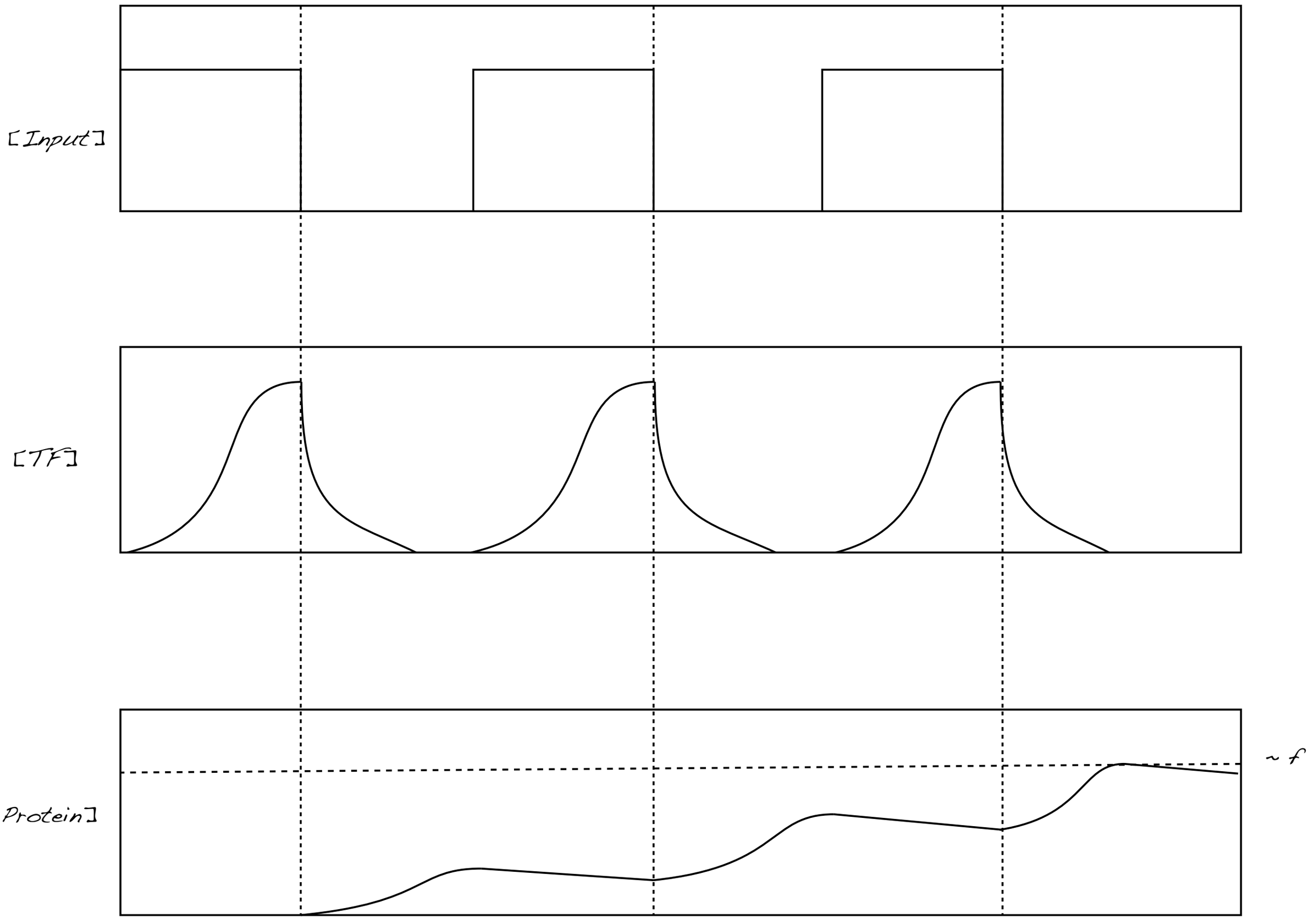
Fast Inhibition

Slow Production

Protein Synthesis



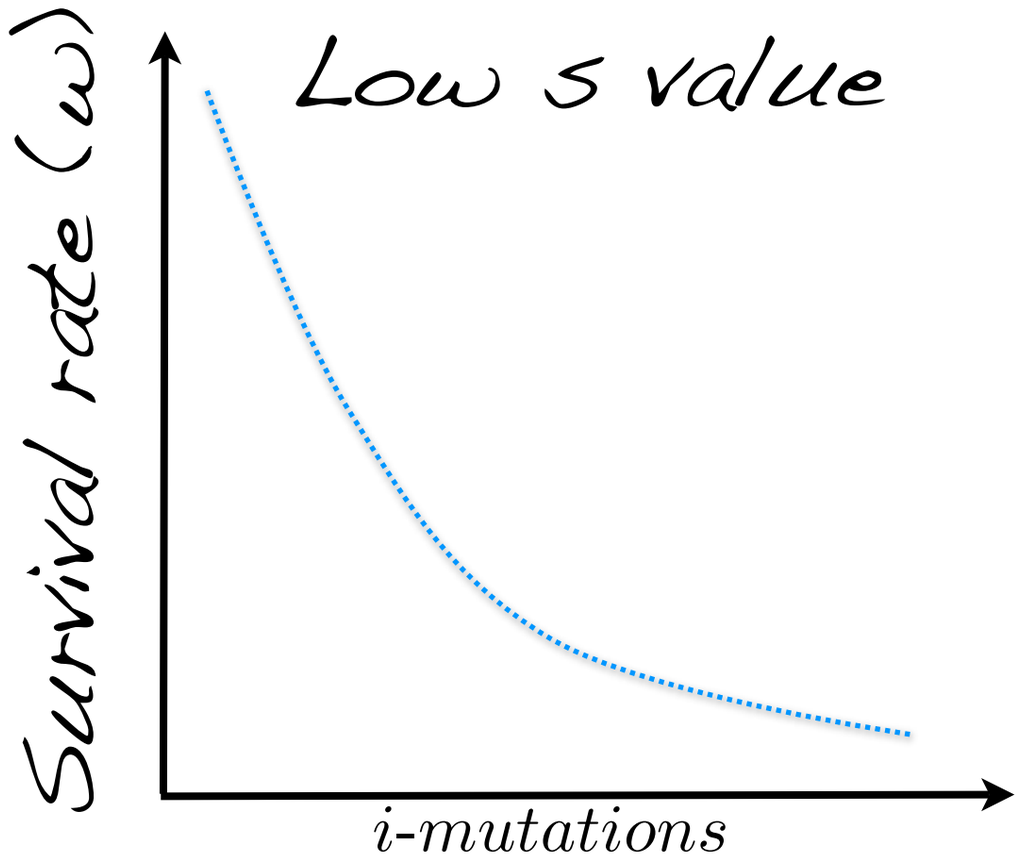
Slow Decay

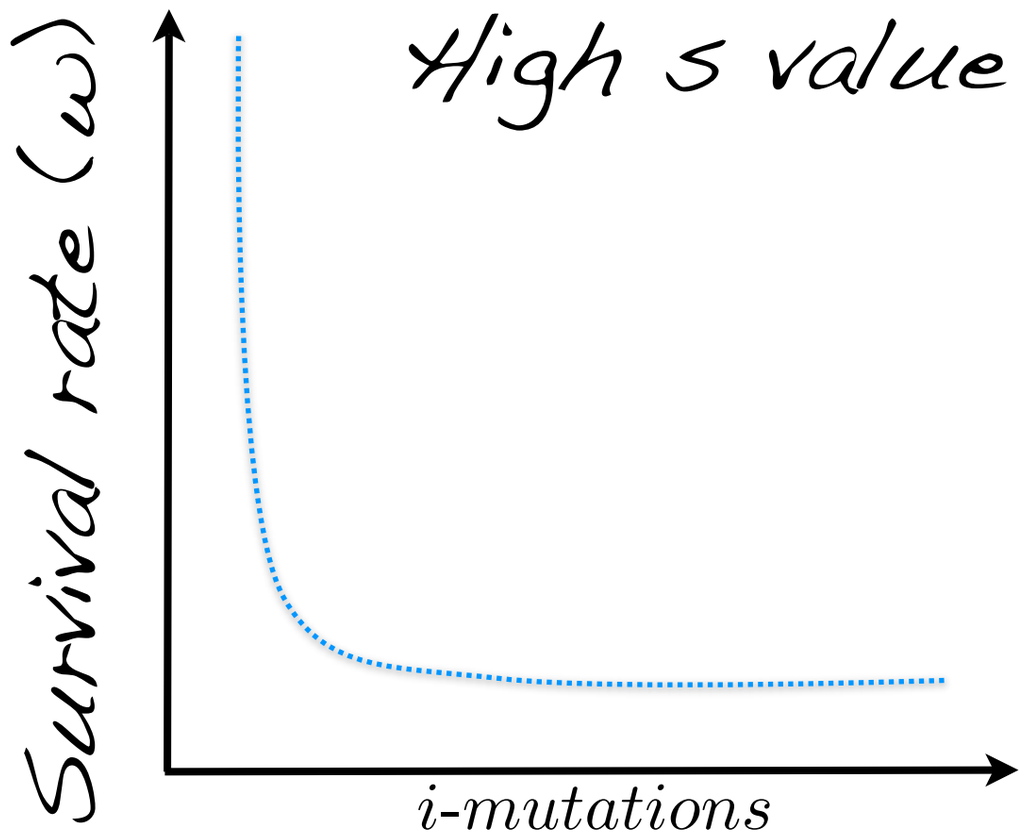

[Input]
[TF]
[Protein]
~ f

Robustness Issues:

Dichotomous approaches for Cells and Brains

- Krakauer, D.C. & Plotkin, J. Redundancy, antiredundancy and the robustness of genomes PNAS 99, 1405-1409 (2002)





More Robust Components ⟷ More Fragile Components

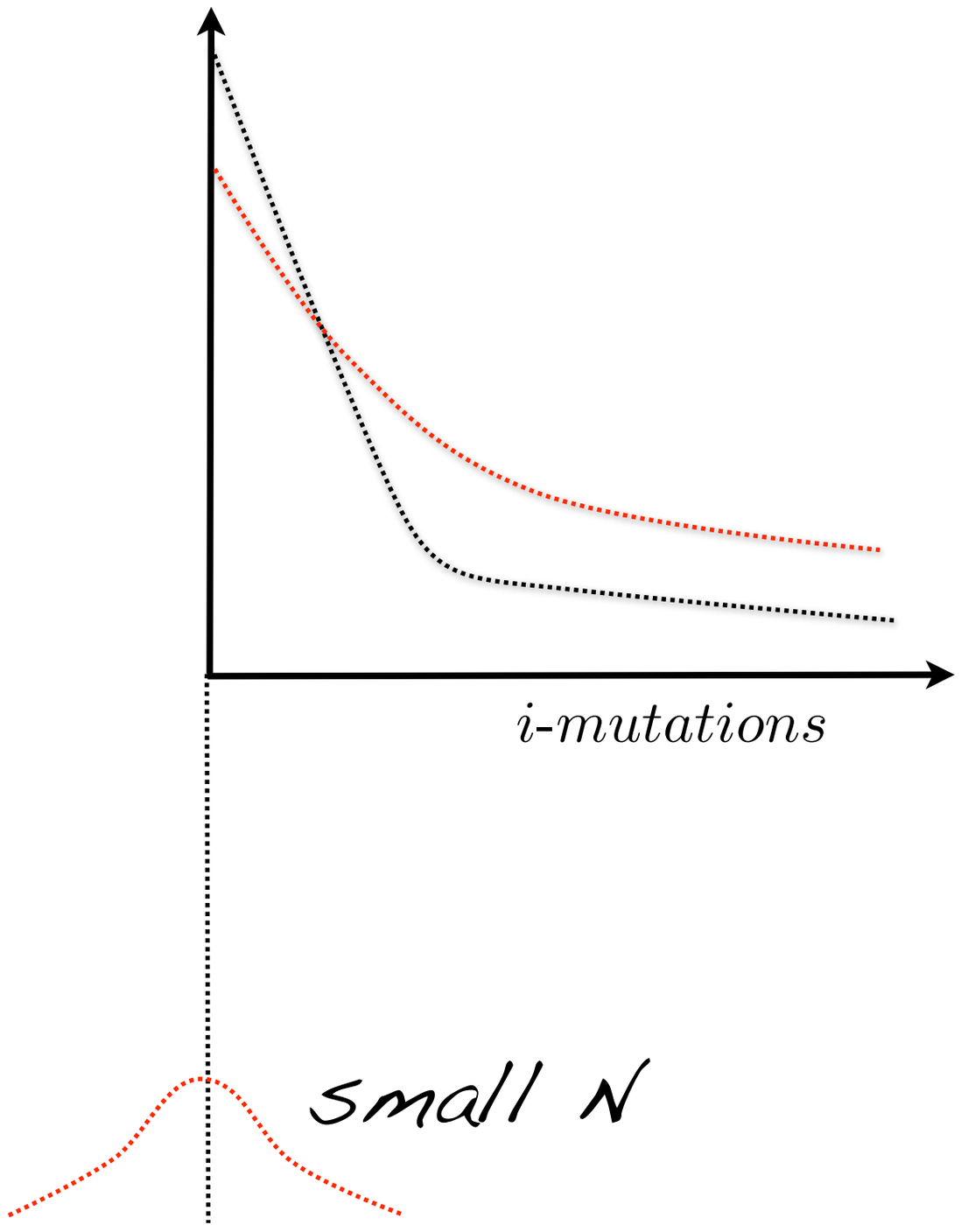
Survival rate

$$w_i = \frac{(1-s)^i}{\sum_{j=0}^{L}(1-s)^j}$$

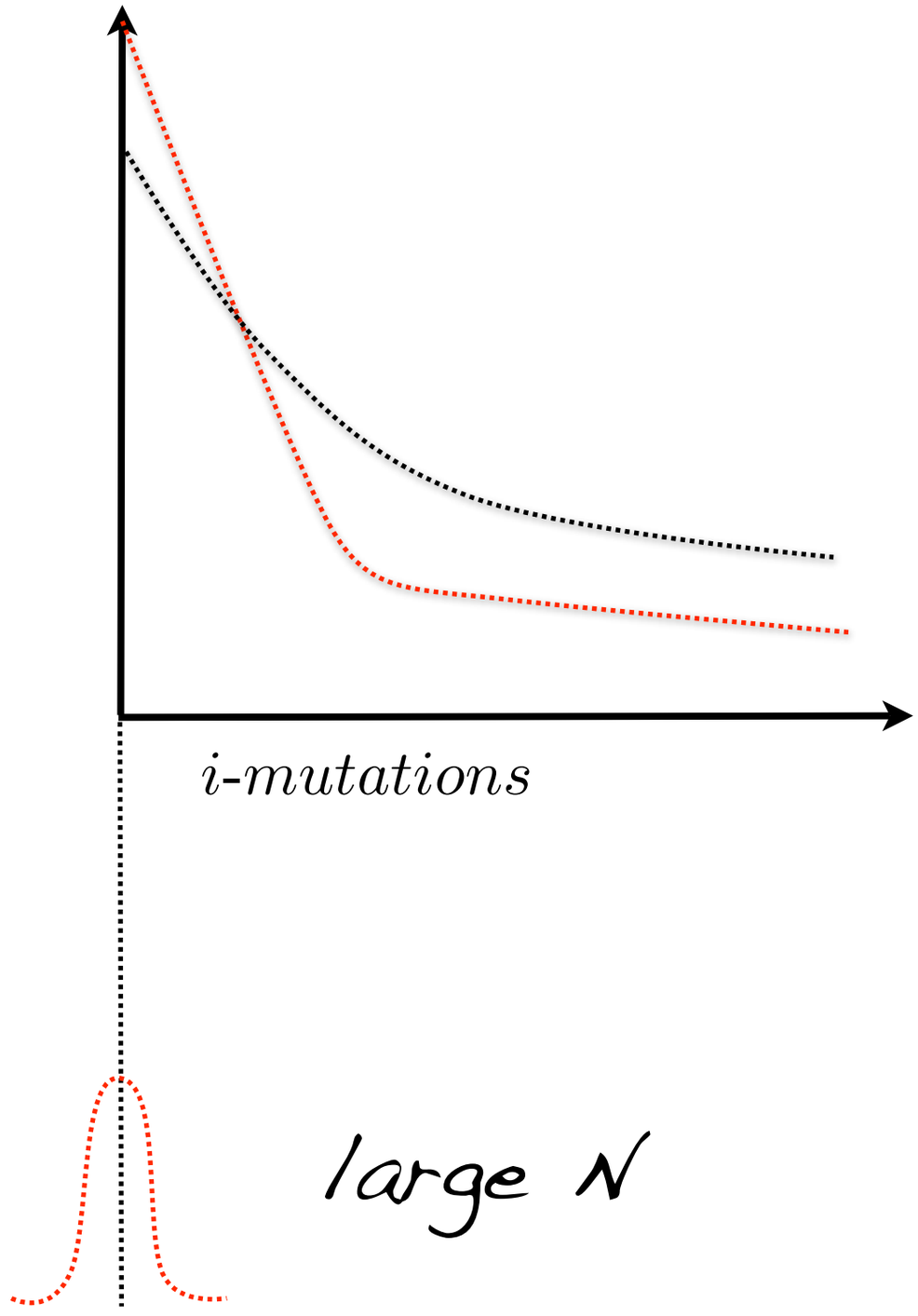
Competitiveness

$$\frac{dz}{dt} = \sum_{i=0}^{L} z_i w_i Q_{ki}$$

Low s value favored at small N



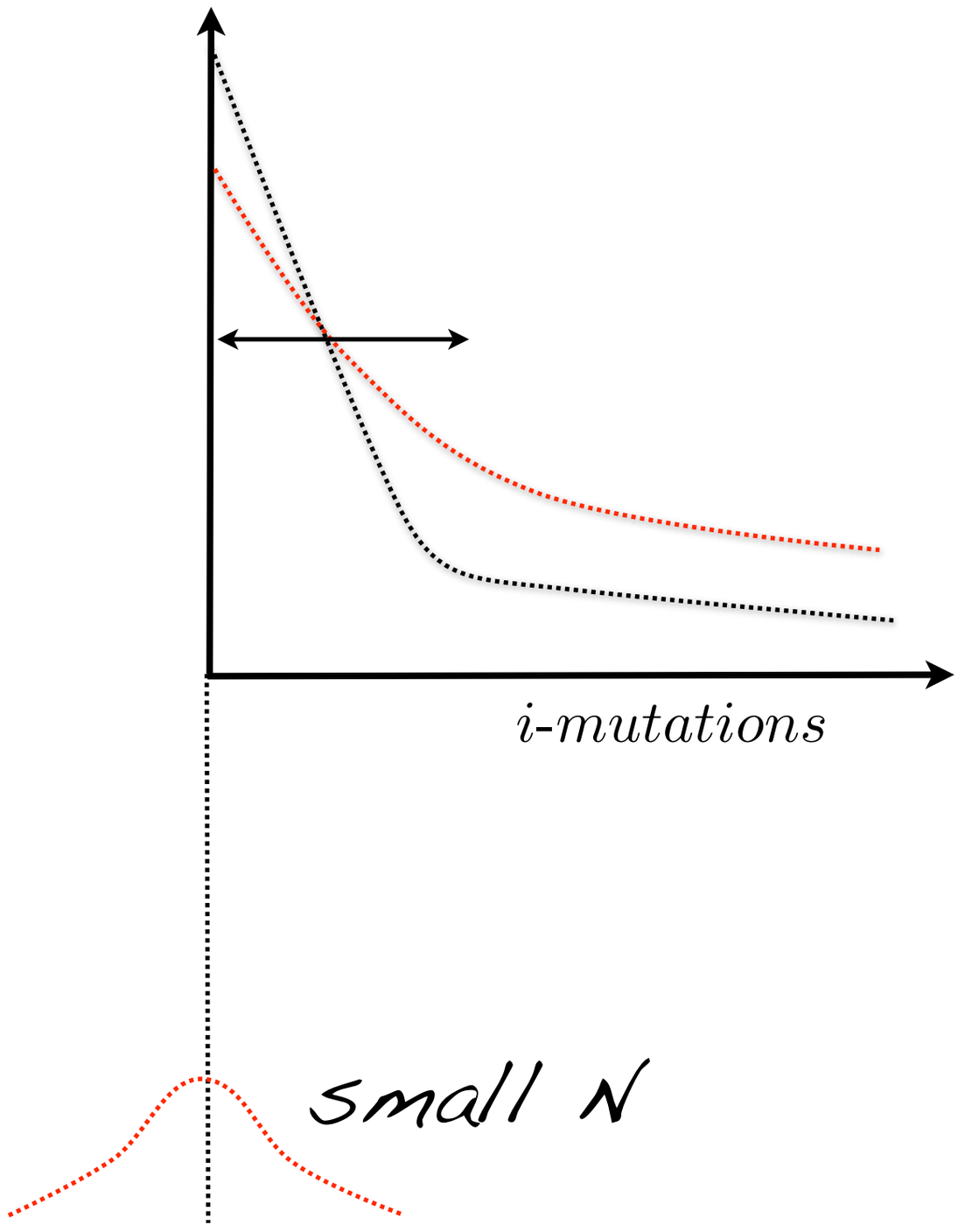
High s value favored at high N



$$\text{Low } C = \frac{L}{\sum_i^L H_i}$$

$$\text{High } C = \frac{L}{\sum_i^L H_i}$$

Low s value favored at small N



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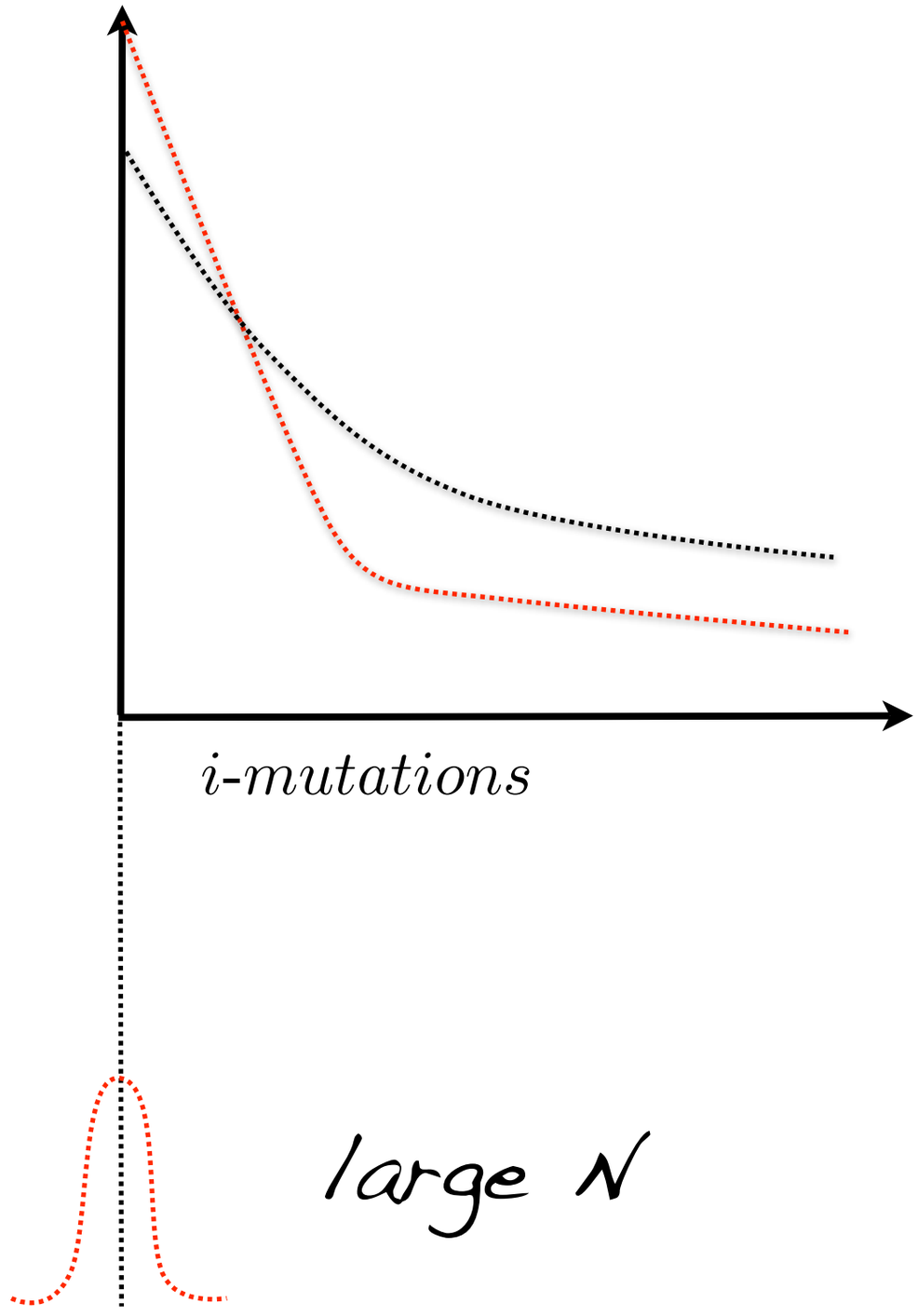

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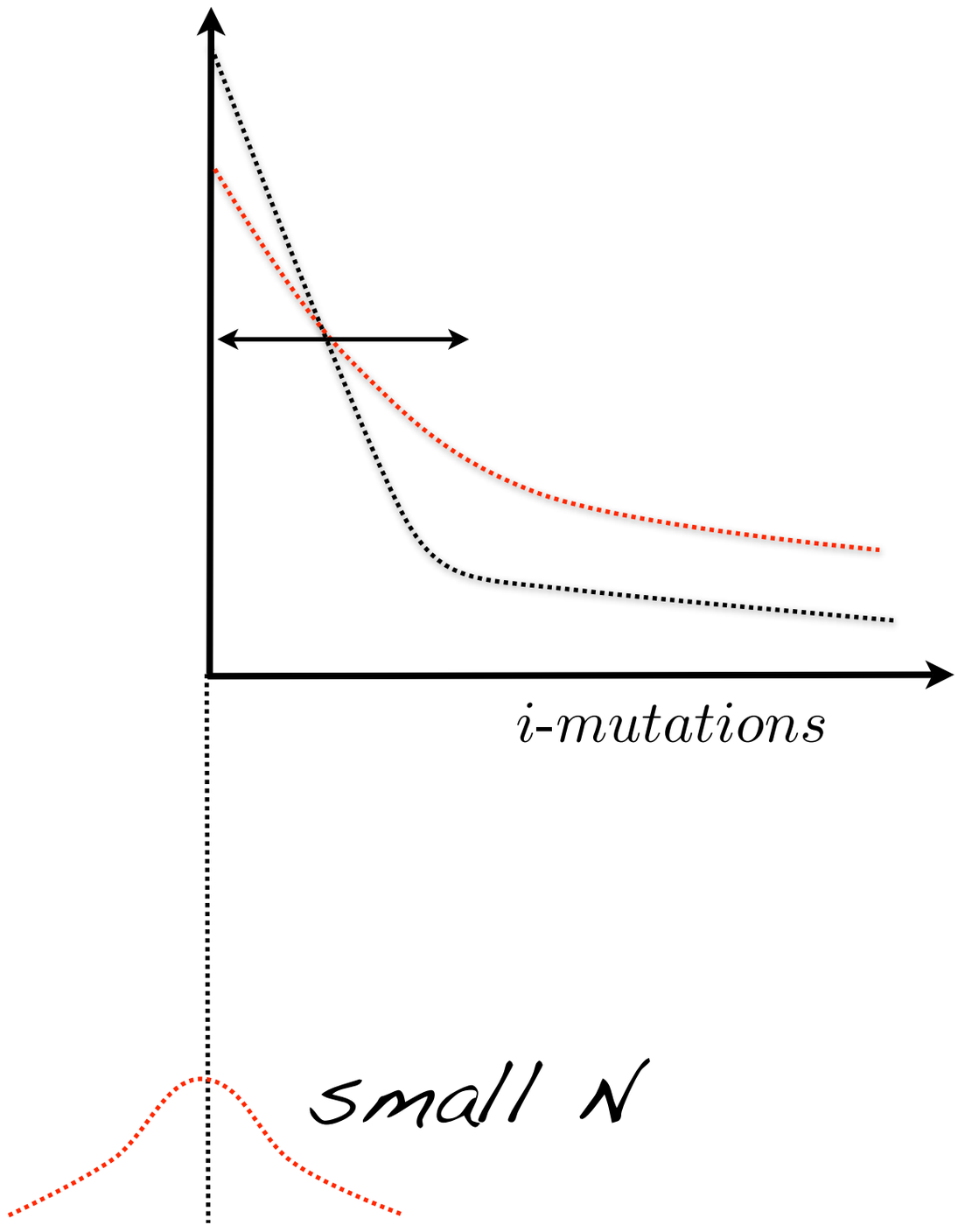

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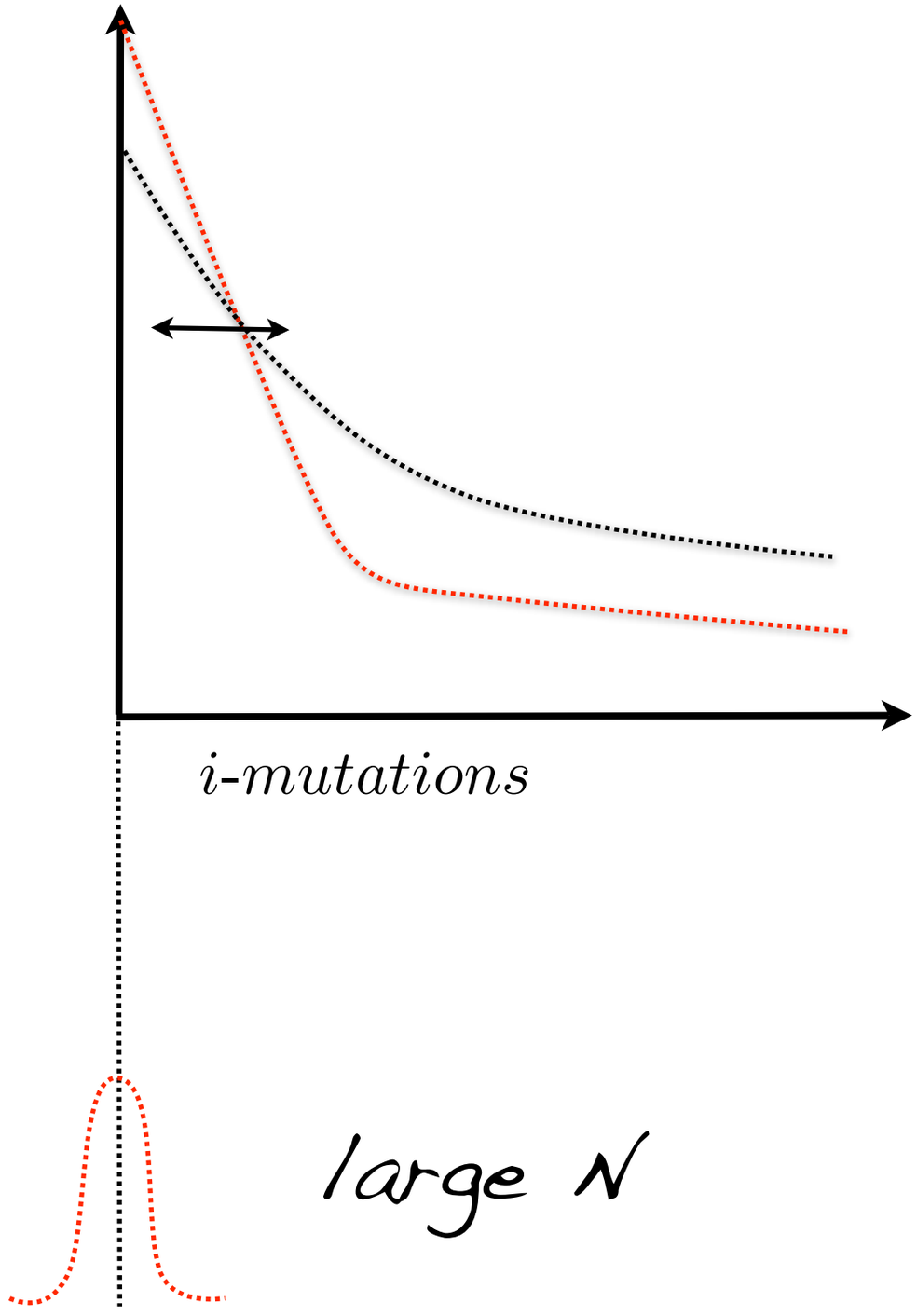

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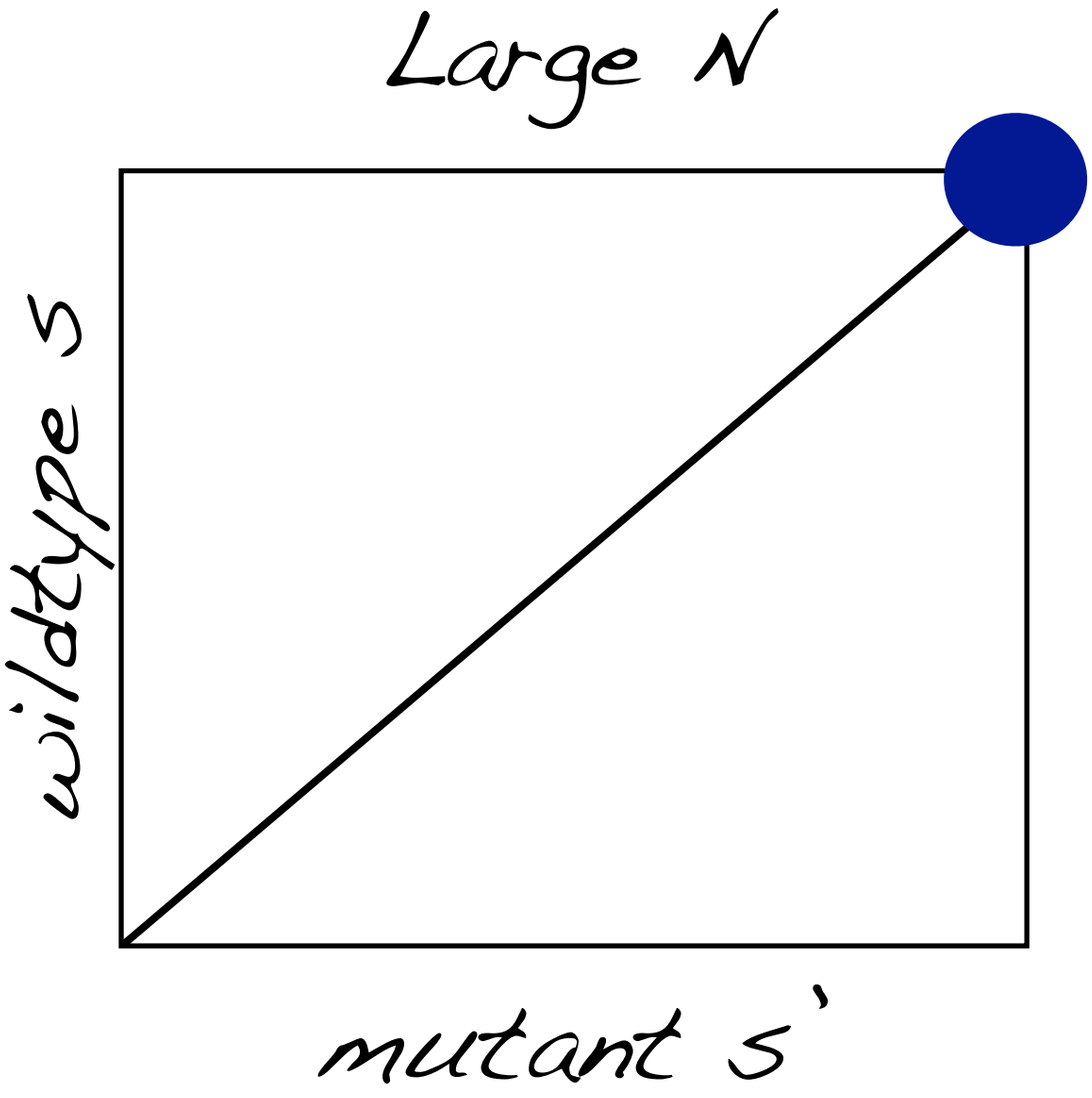
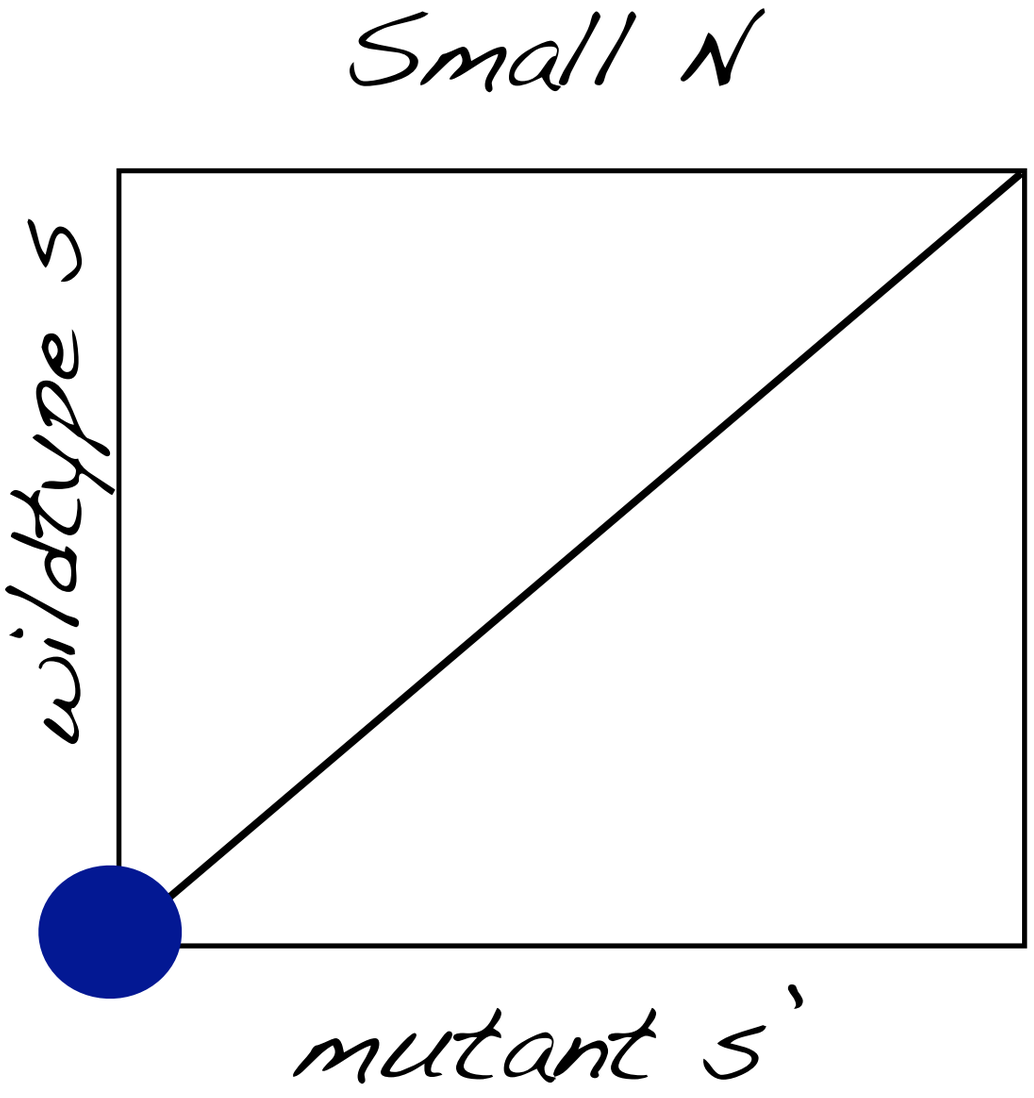
Pair-wise invasability plots





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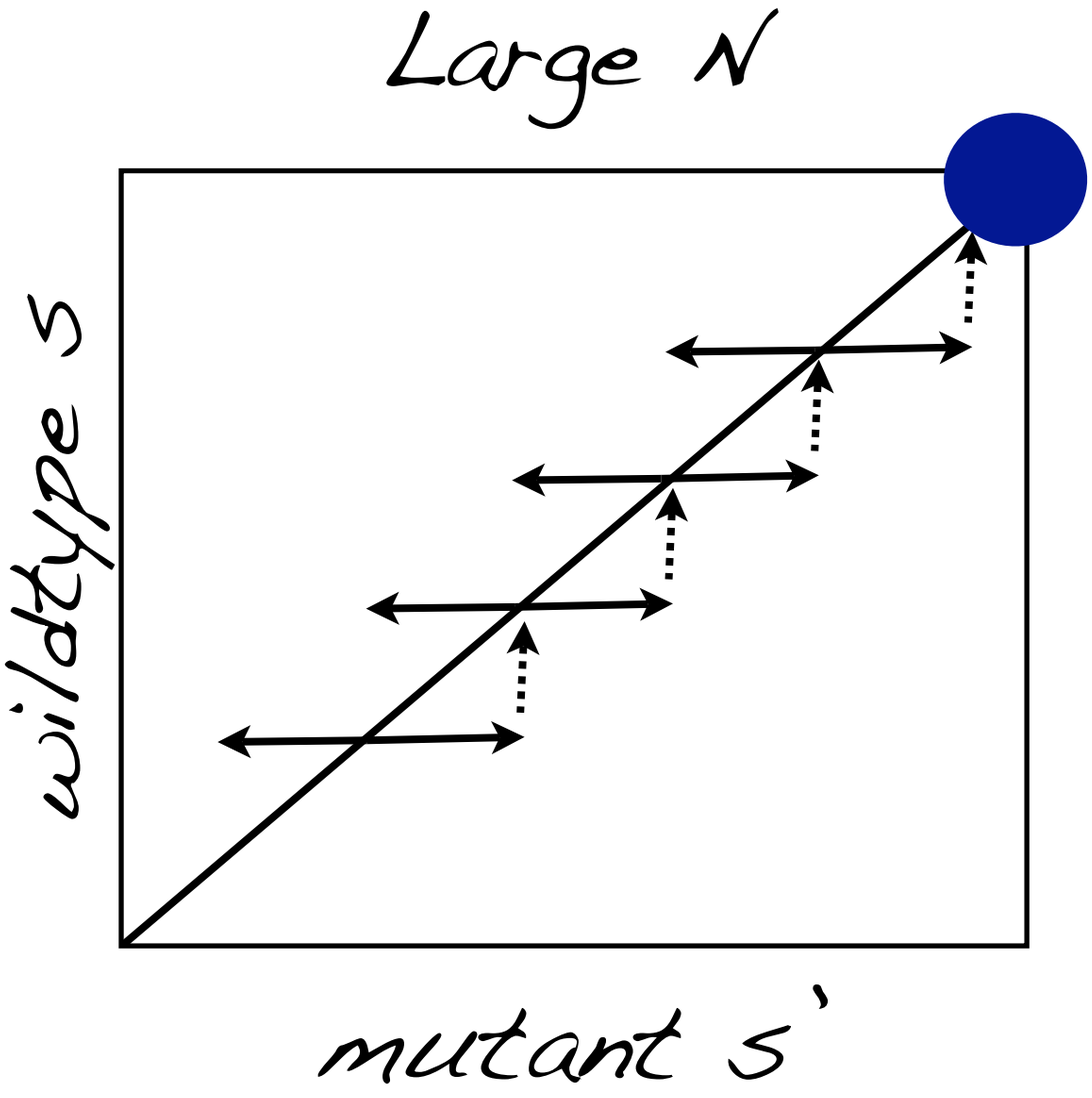

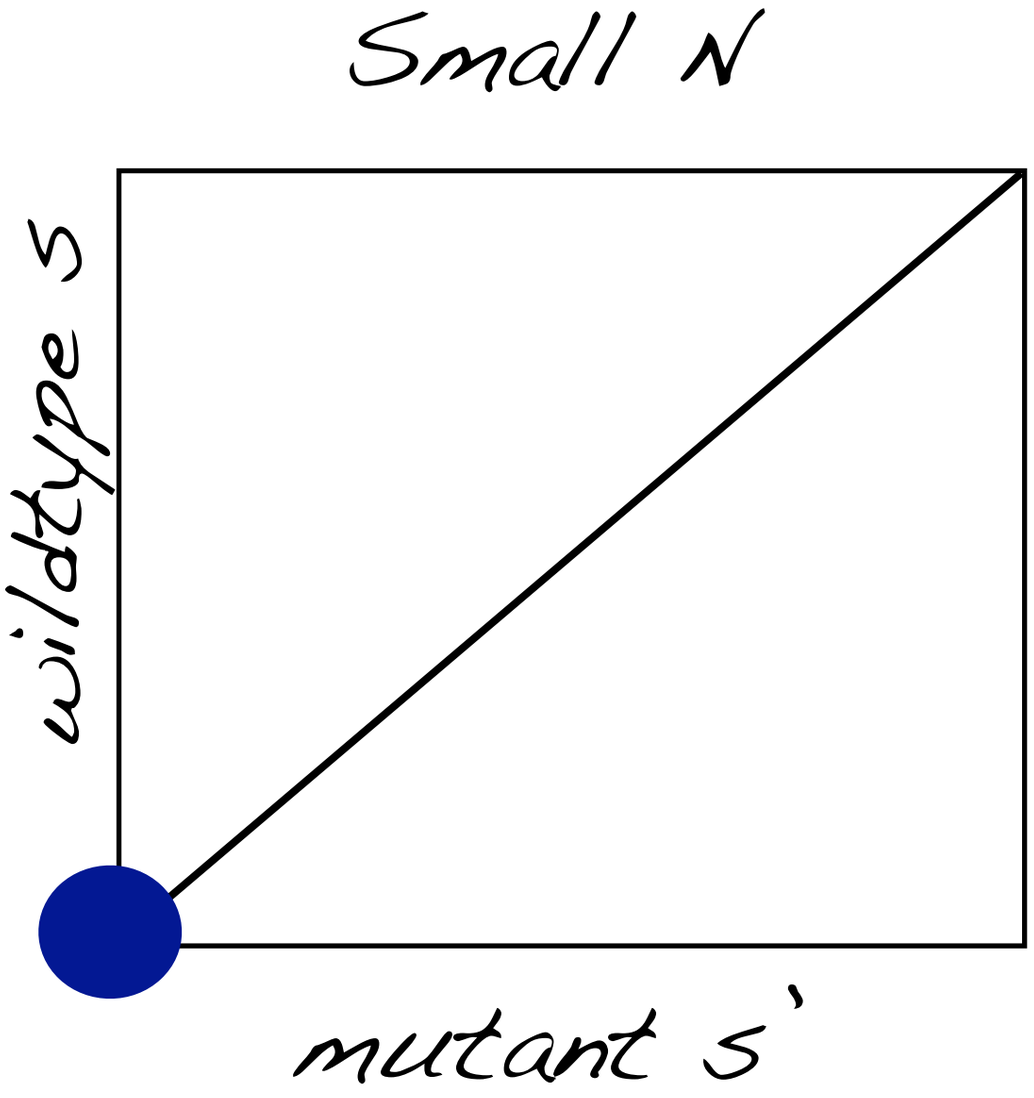

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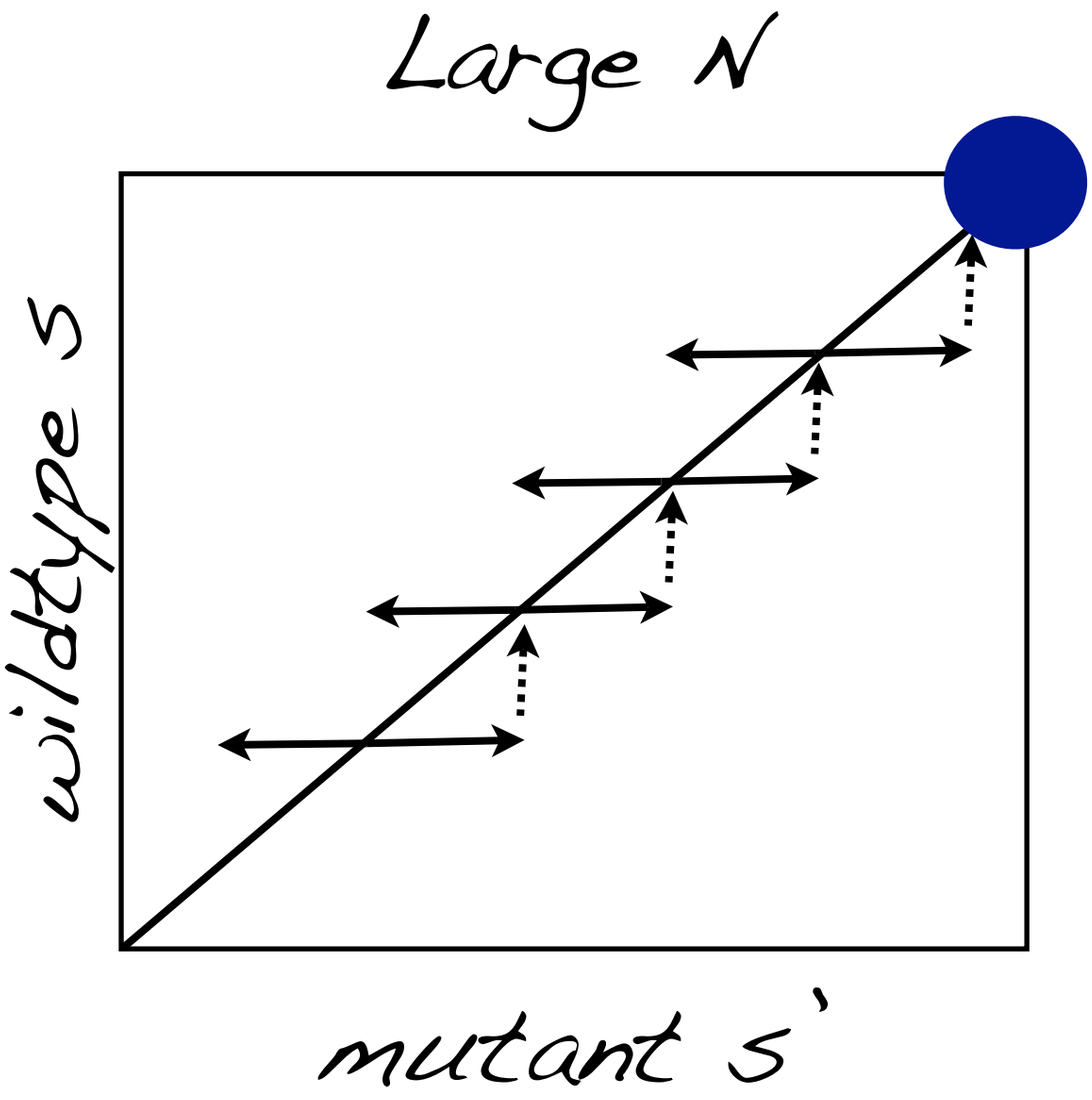

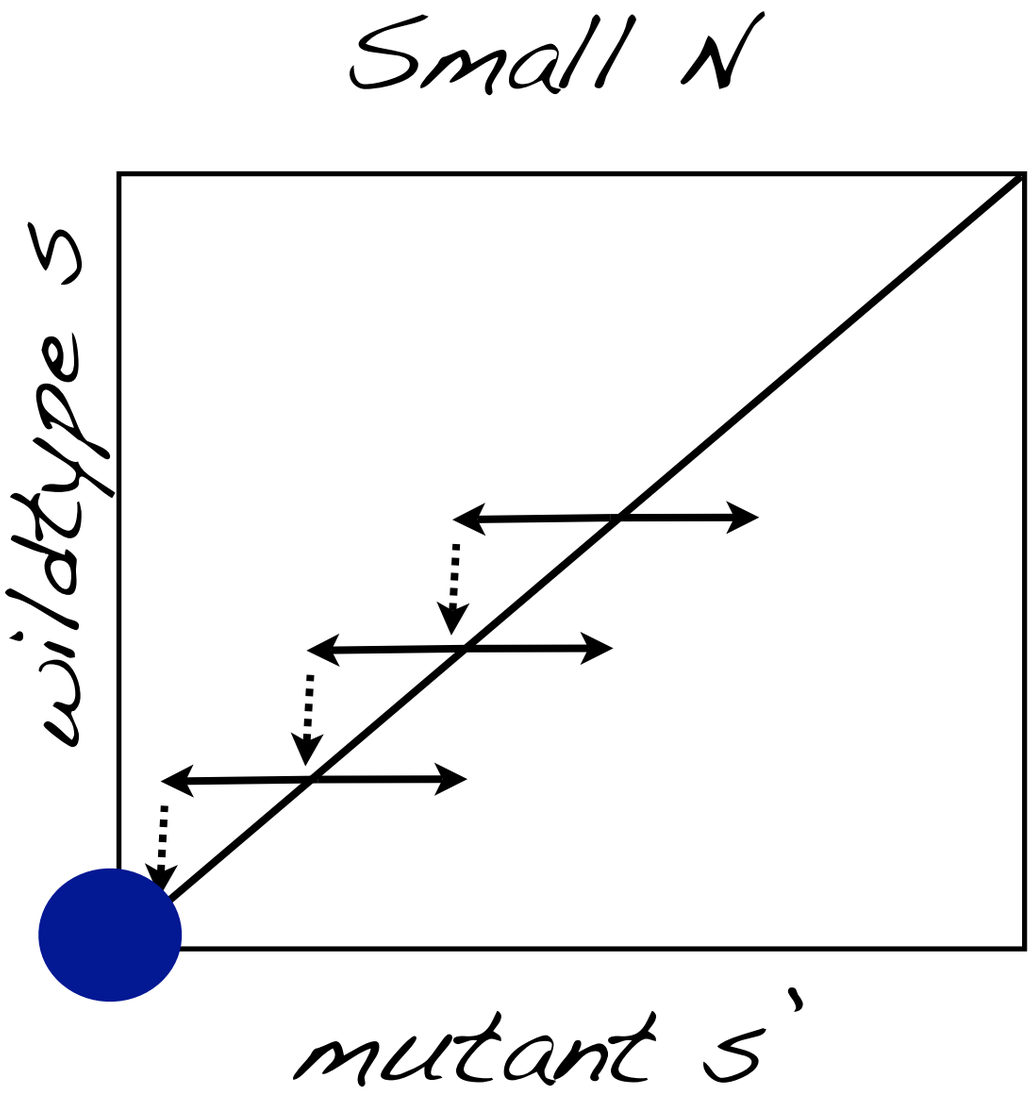

From Cells to Brains

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- Individual cells can only respond to stimuli of comparable space and time dimensions to their receptors - hence multi-cells required for larger features.

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- Long lived cells force the emergence of cell-population memory etc.

Selective Bibliography

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