Systems Biology Across Scales: A Personal View
IX. Landscapes

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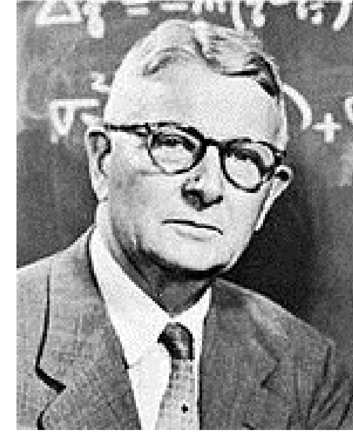
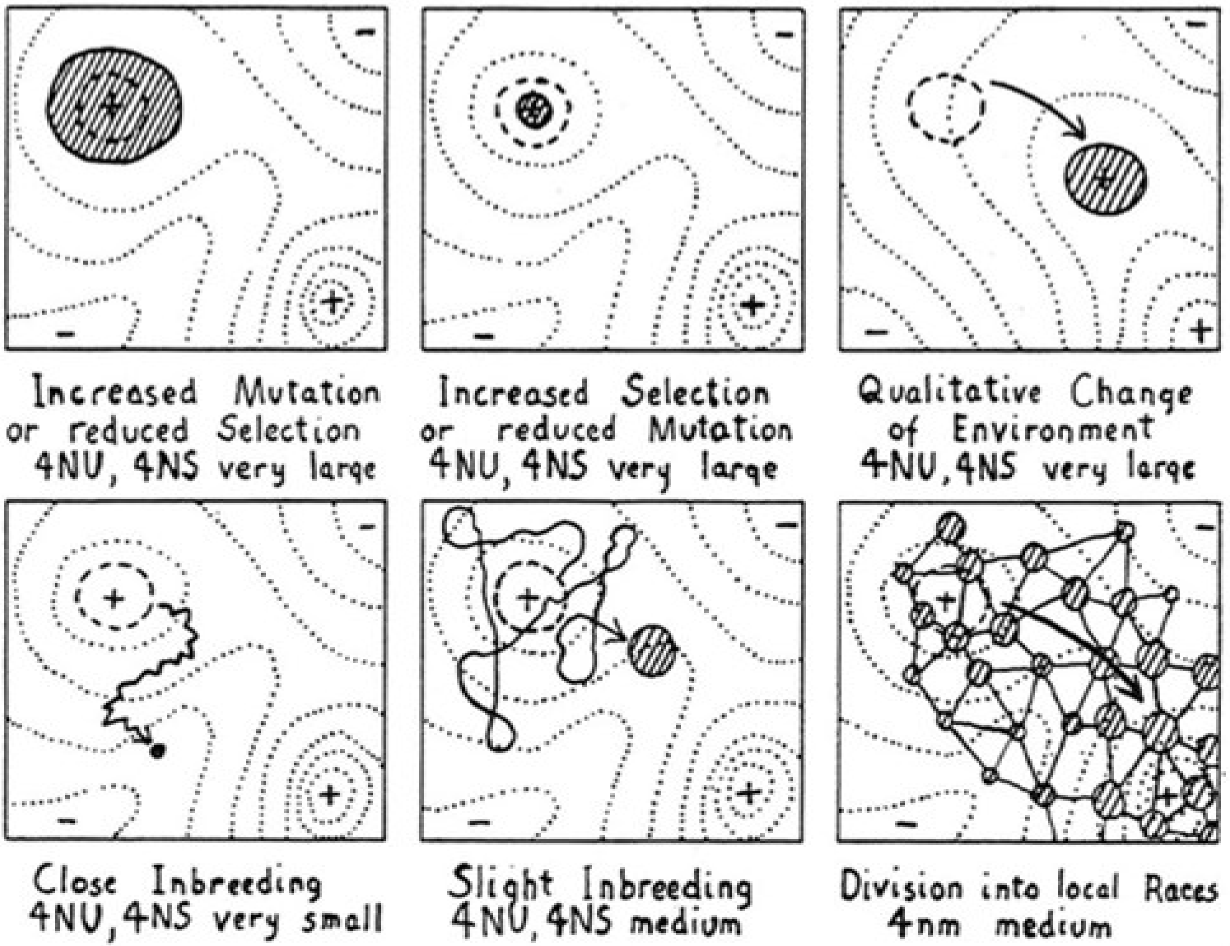
Fitness Landscapes



Sewall G. Wright
(1889 –1988)

Sewall Wright pioneered the description of how genotype or phenotypic fitness are related in terms of a fitness landscape (an imaginary surface in genotype space, each genotype next to others differing by a single mutation and assigned a fitness, on which trajectories due to evolutionary dynamics can be visualized)



Mean population fitness of a genotype is represented by height of the surface.

Natural selection would lead to a population climbing the nearest peak in the fitness landscape, while genetic drift causes random wandering

Image from Sewall Wright, "The Role of Mutation, Inbreeding, Crossbreeding, and Selection in Evolution," *6th Int Congress of Genetics*, Brooklyn, NY(1932).

Networks: a better description

+ …….. wild type
a ………. alternative allele
on locus A
:
:
:
abcde … alternative alleles
on all five loci

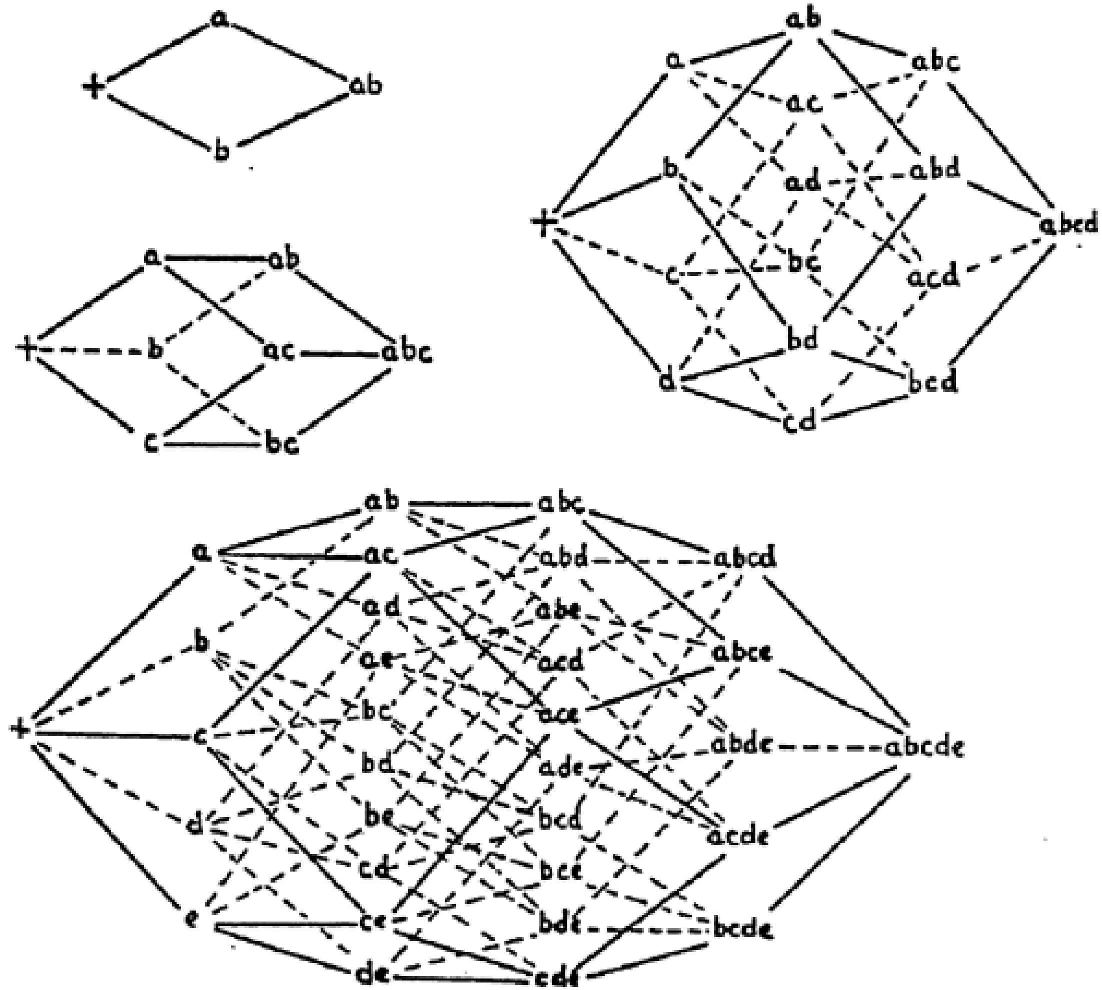
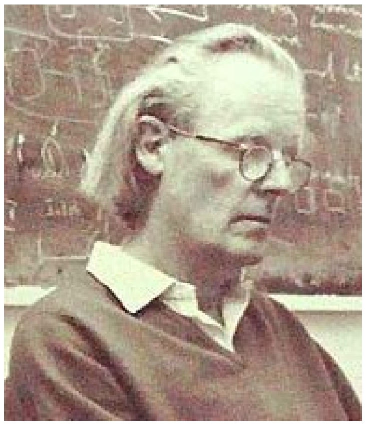


FIG. 1.—The combinations of from 2 to 5 paired allelomorphs.

Sewall Wright. "Surfaces of selective value revisited". *American Naturalist* **131** (1988) 115-123

Adaptive walks in Protein Space

Wright's genotype space concept was extended to that of proteins by Maynard Smith



J. Maynard Smith (1920 –2004)

Space of all proteins comprising N amino acids: 20^N vertices each having k=19N one-mutant neighbors.

Each protein assigned a "fitness" with respect to a specific property, e.g., binding to ligand.

Natural Selection and the Concept of a Protein Space

NATURE VOL. 225 FEBRUARY 7 1970

The model of protein evolution I want to discuss is best understood by analogy with a popular word game. The object of the game is to pass from one word to another of the same length by changing one letter at a time, with the requirement that all the intermediate words are meaningful in the same language. Thus WORD can be converted into GENE in the minimum number of steps, as follows:

WORD WORE GORE GONE GENE

This is an analogue of evolution, in which the words represent proteins; the letters represent amino-acids; the alteration of a single letter corresponds to the simplest evolutionary step, the substitution of one amino-acid for another; and the requirement of meaning corresponds to the requirement that each unit step in evolution should be from one functional protein to another. The reason for the last requirement is as follows: suppose that a protein A B C D . . . exists, and that a protein a b C D . . . would be favoured by selection if it arose. Suppose further that the intermediates a B C D . . . and A b C D . . . are non-functional. These forms would arise by mutation, but would usually be eliminated by selection before a second mutation could occur. The double step from a b C D . . . to A B C D would thus be very unlikely to occur. Such double steps with unfavourable intermediates may occasionally occur, but are probably too rare to be important in evolution.

Epistatic interactions

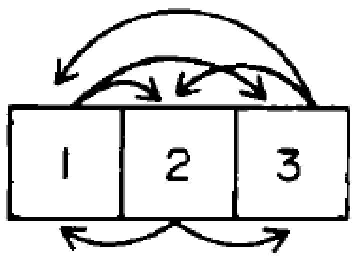
J. Arjan G.M. de Visser and Joachim Krug, *Nature Rev Genetics* (2014):
Wright's idea to explicitly consider the relationship between genotypic space and fitness came from his conviction that, different from Ronald Fisher's additive view of genetics, real fitness landscapes are likely to be complex owing to pervasive epistasis

Epistasis
Any kind of genetic interaction that leads to a dependence of mutational effects on the genetic background.

Ruggedness of the fitness landscape arises through multi-dimensional epistasis

The NK model of fitness landscape

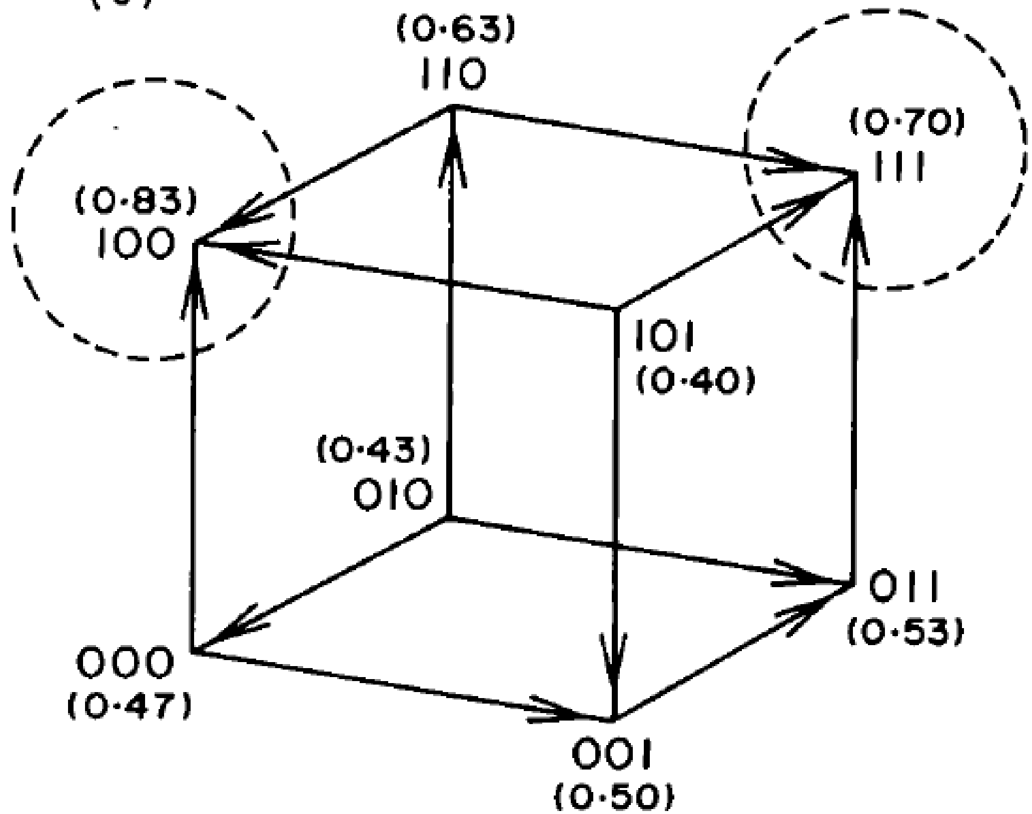
(a)



(b)

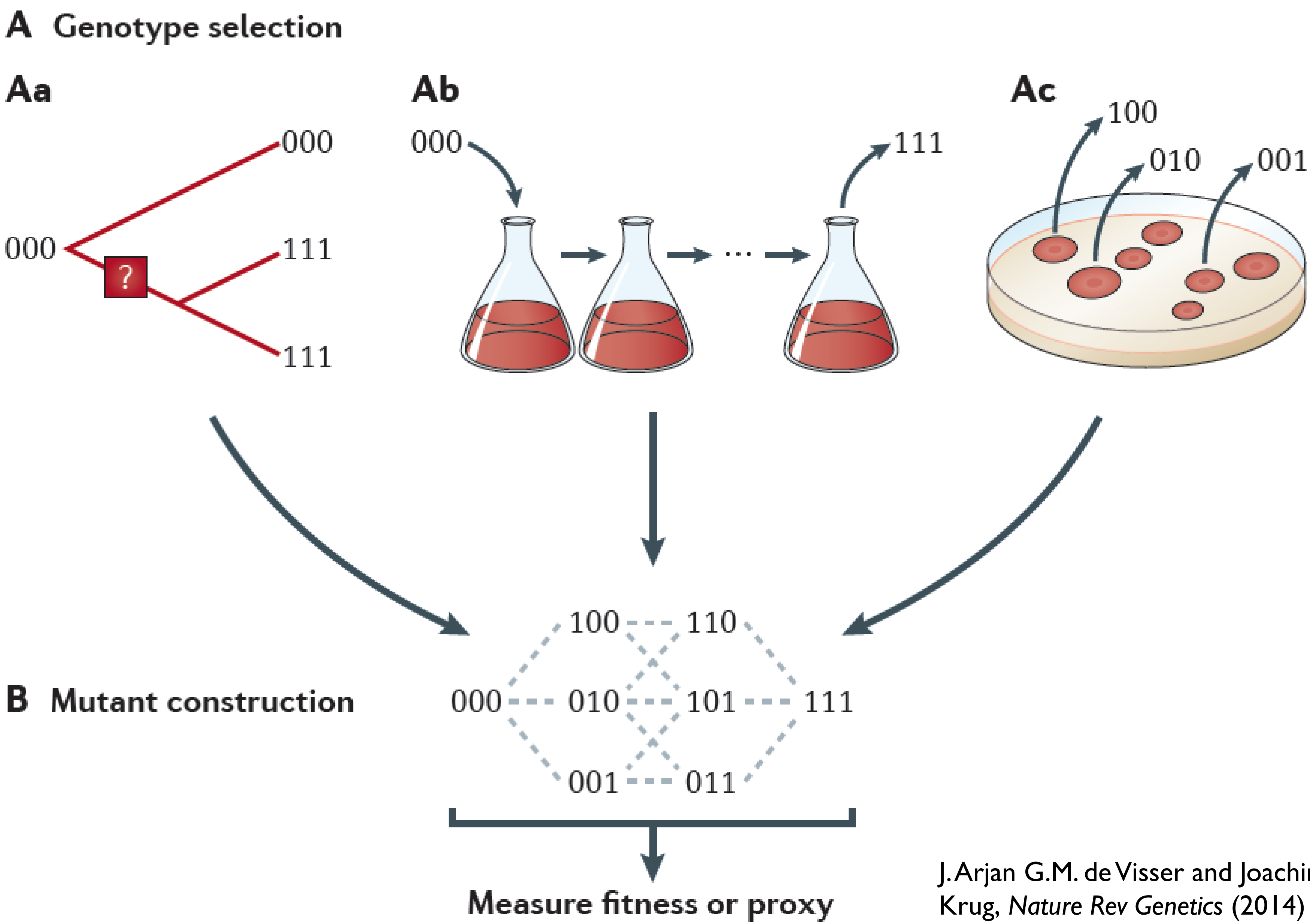
1 2 3	w_1	w_2	w_3	$W = \frac{1}{N}\sum_{i=1}^{N} w_i$
0 0 0	0·6	0·3	0·5	0·47
0 0 1	0·1	0·5	0·9	0·50
0 1 0	0·4	0·8	0·1	0·43
0 1 1	0·3	0·5	0·8	0·53
1 0 0	0·9	0·9	0·7	0·83
1 0 1	0·7	0·2	0·3	0·40
1 1 0	0·6	0·7	0·6	0·63
1 1 1	0·7	0·9	0·5	0·70

(c)



Kauffman & Weinberger, J Theo Biol (1989)

Empirical study of fitness landscapes

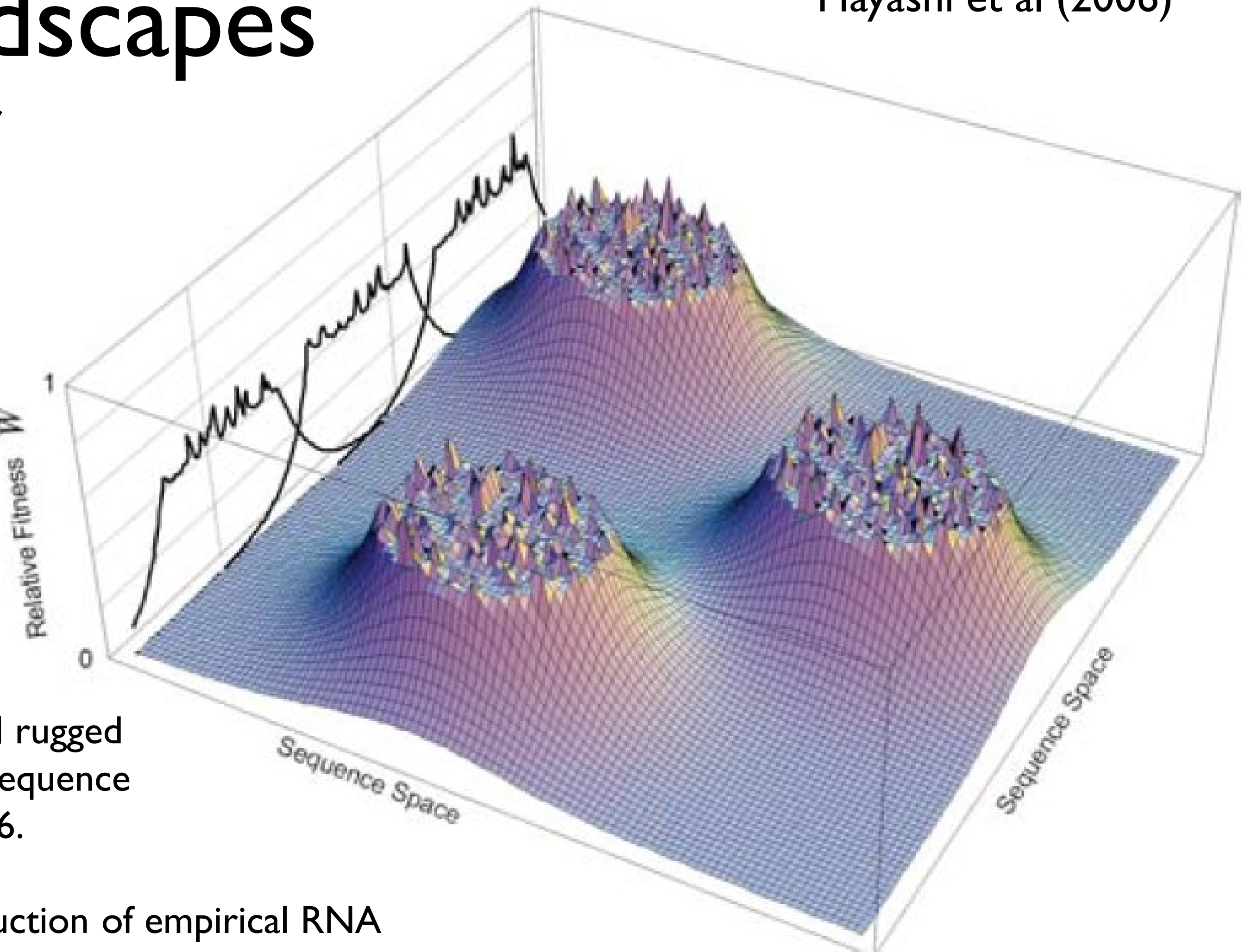


J. Arjan G.M. de Visser and Joachim Krug, *Nature Rev Genetics* (2014)

Experimentally accessible fitness landscapes

Hayashi et al (2006)

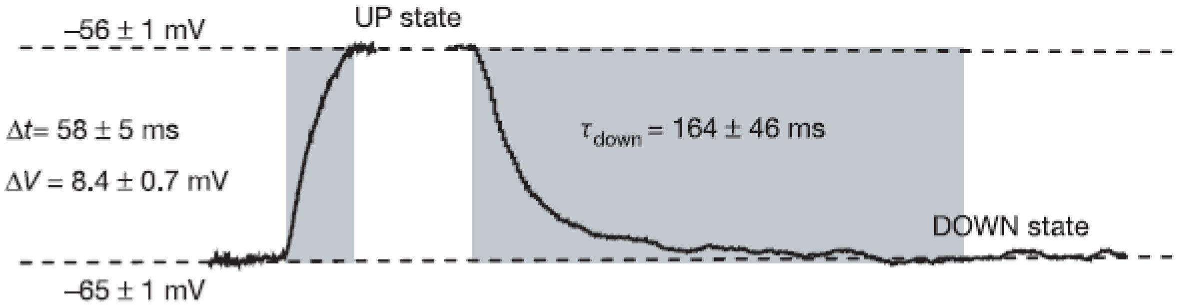
Result of *in vitro* molecular evolution beginning with a defective fd phage carrying a random polypeptide of 139 amino acids in place of the g3p minor coat protein D2 domain,
which is essential for phage infection.



Protein landscapes:
Y Hayashi et al. "Experimental rugged fitness landscape in protein sequence space" *PLoS One* **1** (2006) e96.
RNA landscapes:
D E Jason et al "Rapid construction of empirical RNA fitness landscapes" *Science* **330** (2010) 376-379.
Retroviruses:
R D Kouyos et al Exploring the complexity of the HIV-1 fitness landscape. *PLoS Genetics* **8** (2012) e1002551

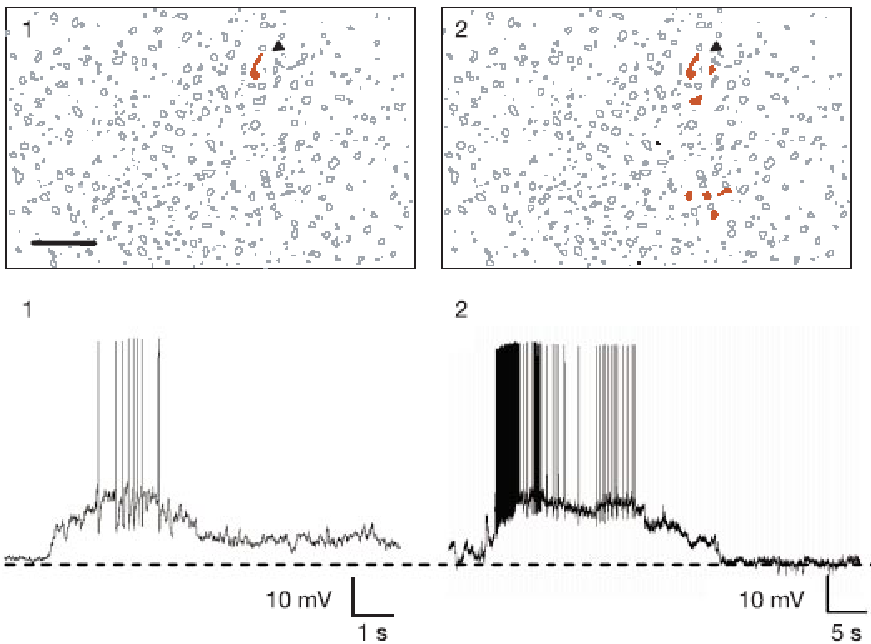
Attractor dynamics of network UP states in the neocortex

Rosa Cossart, Dmitriy Aronov & Rafael Yuste



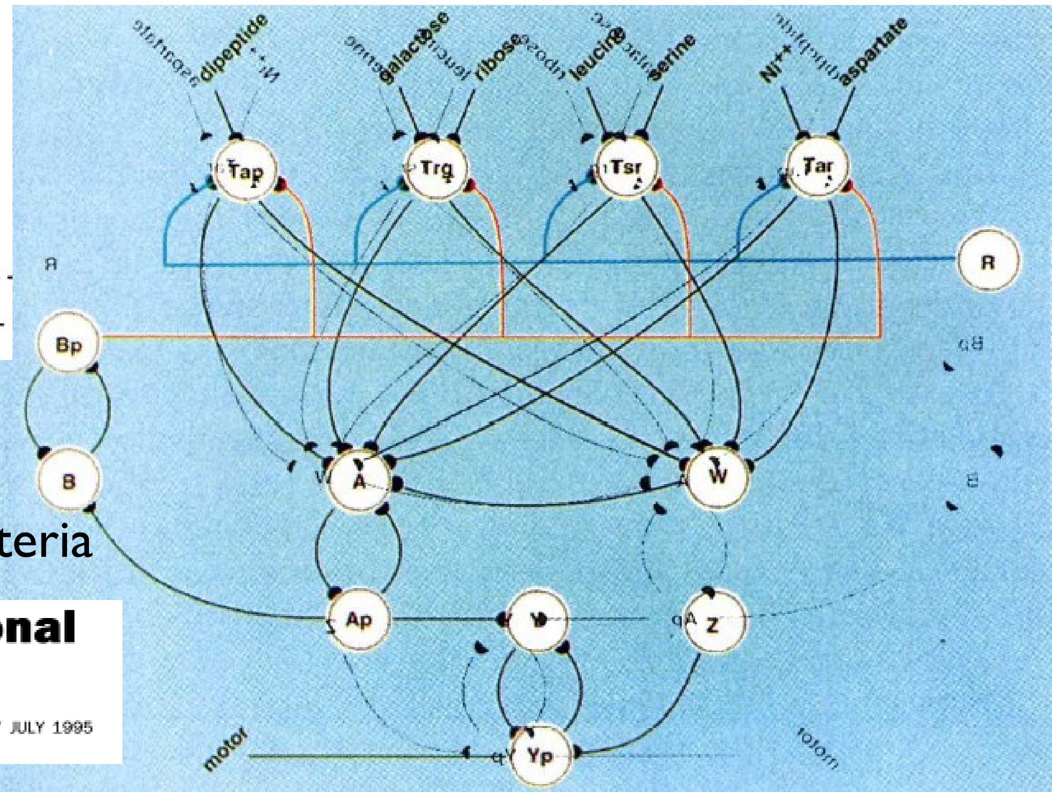
Attractor networks:

in the brain & inside the cell



Protein "circuit"

Chemotactic response of coliform bacteria



Protein molecules as computational elements in living cells

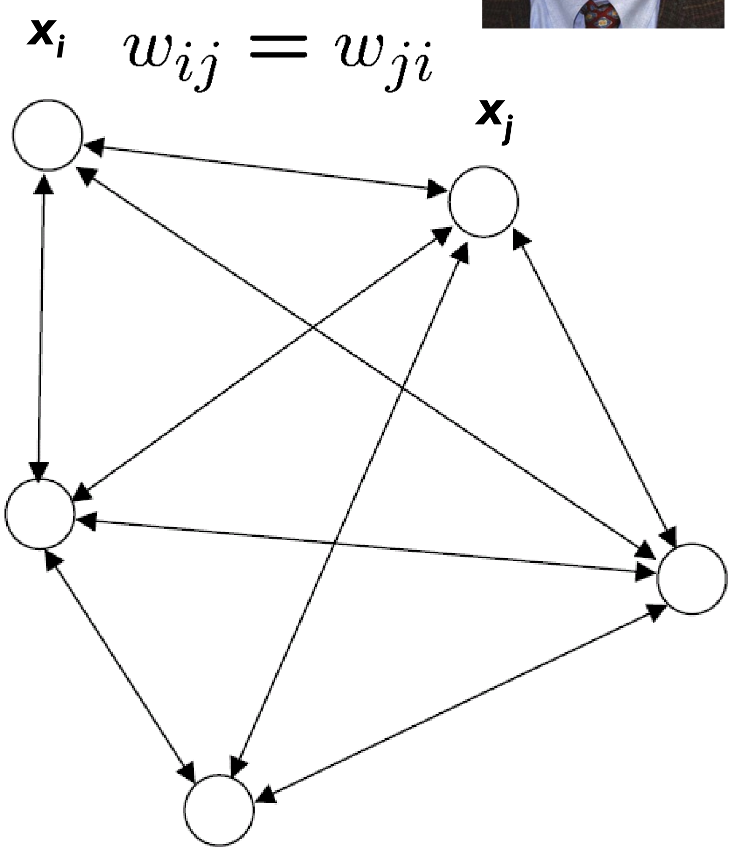
Dennis Bray

NATURE · VOL 376 · 27 JULY 1995

Hopfield Model: An Attractor Network Model for Associative Memory

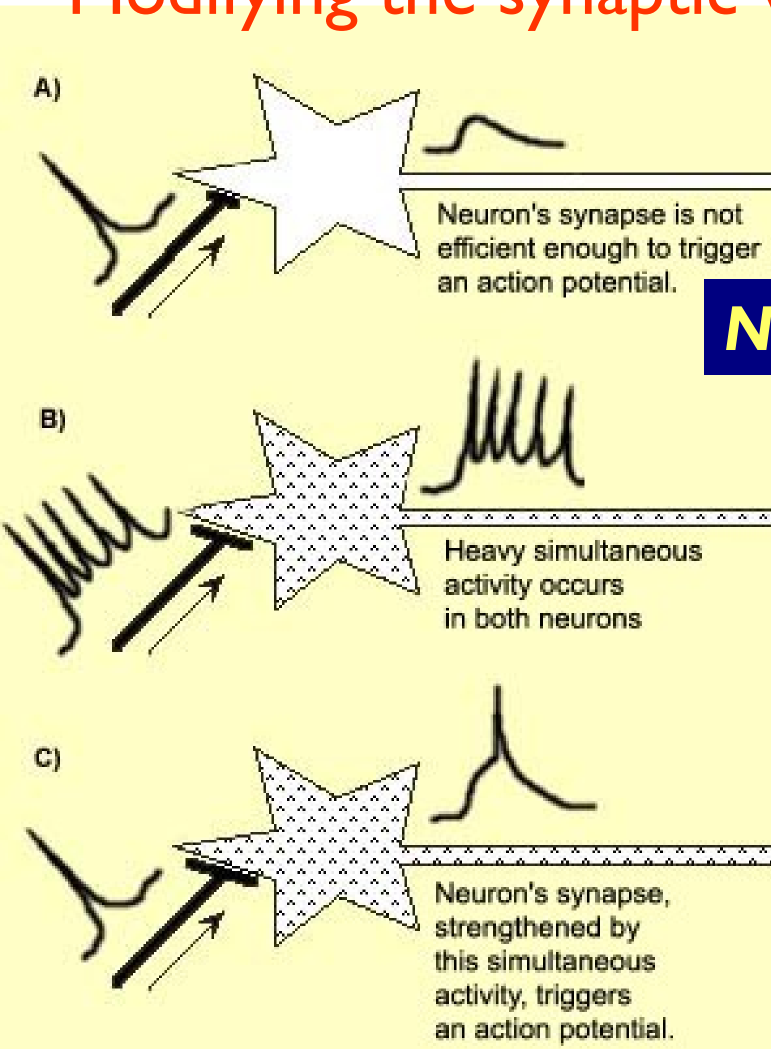
Hopfield and Tank, PNAS, 1982.

- Network of inter-connected binary state "neurons"
- x_i ={-1 or OFF,+1 or ON}.
- Activation of the neurons are defined by $x_i = \text{sgn}(\sum_j w_{ji} x_j)$
  - Sgn (q) = –1, if q < 0; = +1 otherwise
  - T=0 or deterministic dynamics
- Symmetric connection weights,
  - i.e. $w_{ij} = w_{ji}$
- w_{ii}=0 (No self connections)

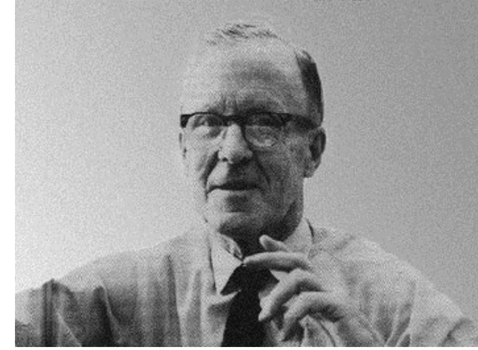


Learning

Modifying the synaptic weights by Hebb rule



http://thebrain.mcgill.ca



Donald O Hebb (1904-85)

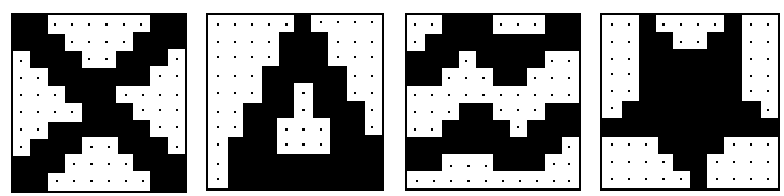
Hebb's hypothesis (1949)

Neurons that fire together, wire together

$$w_{ij} = \frac{1}{N} \sum_{p=1}^{M} \xi_i^p \xi_j^p$$

ξ_i^p: i^{th} component of the p^{th} binary pattern

Four stored patterns in simulation

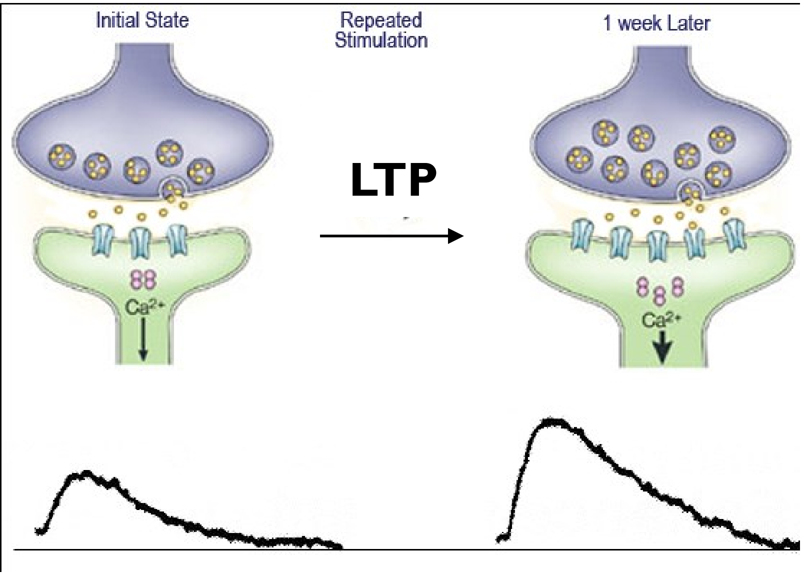


"■" i^{th} neuron is excited $x_i=1$

"." i^{th} neuron is resting $x_i=0$

Hebb Rule and Biology

Long-term potentiation



First empirical observation (Lomo, 1966) supporting Hebb's hypothesis

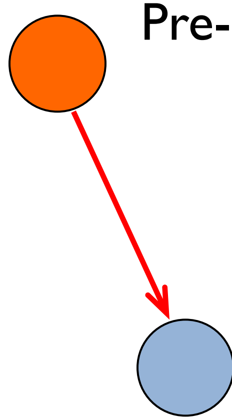
Persistent increase in synaptic strength after high-freq stimulation of synapse

Spike-timing dependent plasticity

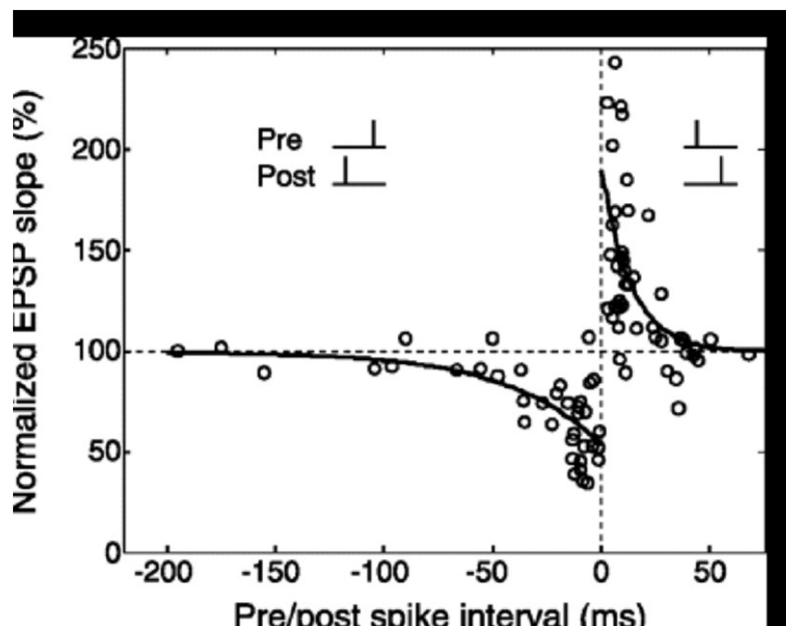
spike-based formulation of Hebb rule

(Markram, 1995)

synapse strengthened if presynaptic neuron "repeatedly or persistently takes part in firing" the postsynaptic one (Hebb 1949)



Bi & Poo, 1998



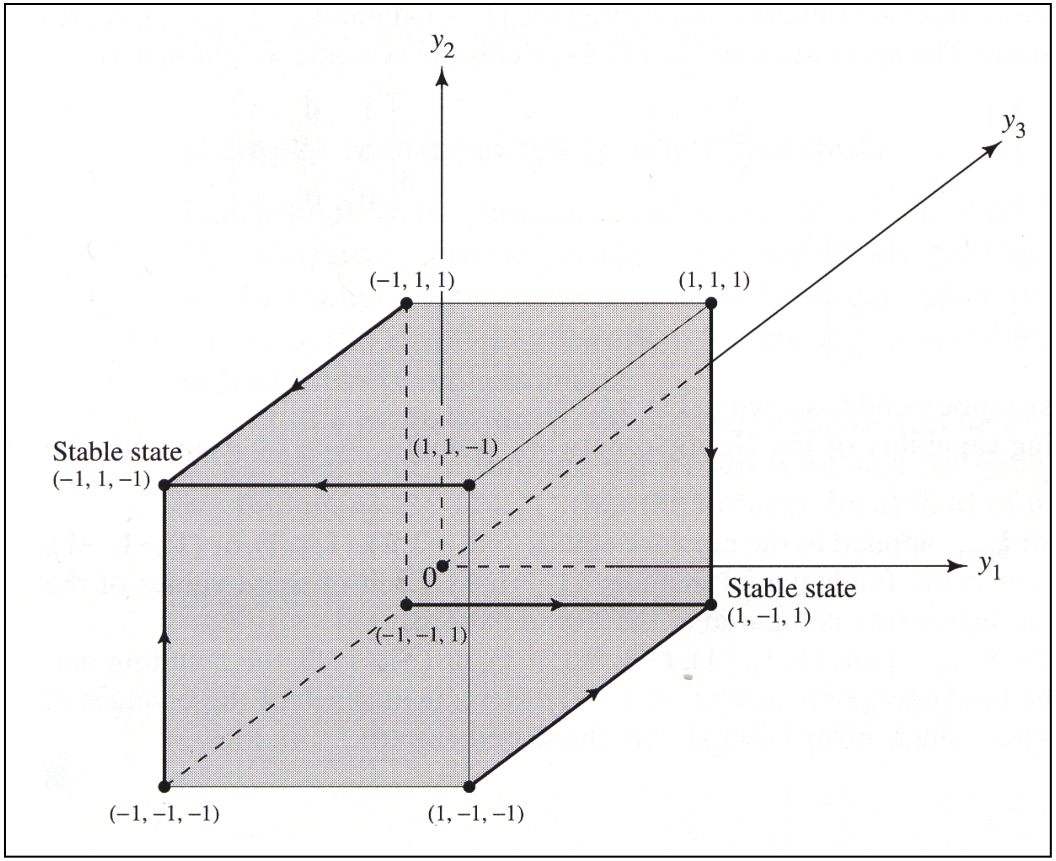
Example: A 3-node Hopfield model

p = 2: (1,-1,1) and (-1,1,-1) are the stored memories

$$w_{ij} = \frac{1}{N}\sum_{p=1}^{M} \xi_i^p \xi_j^p$$

$$w_{ii} = 0$$

$$W = \frac{1}{3}\begin{bmatrix} 0 & -2 & 2 \\ -2 & 0 & -2 \\ 2 & -2 & 0 \end{bmatrix}$$

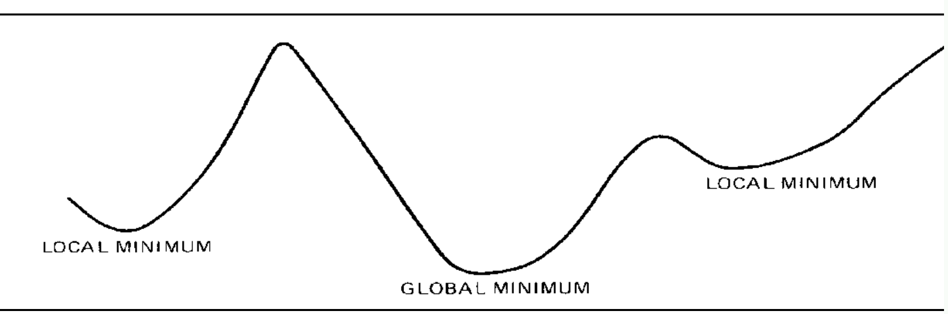


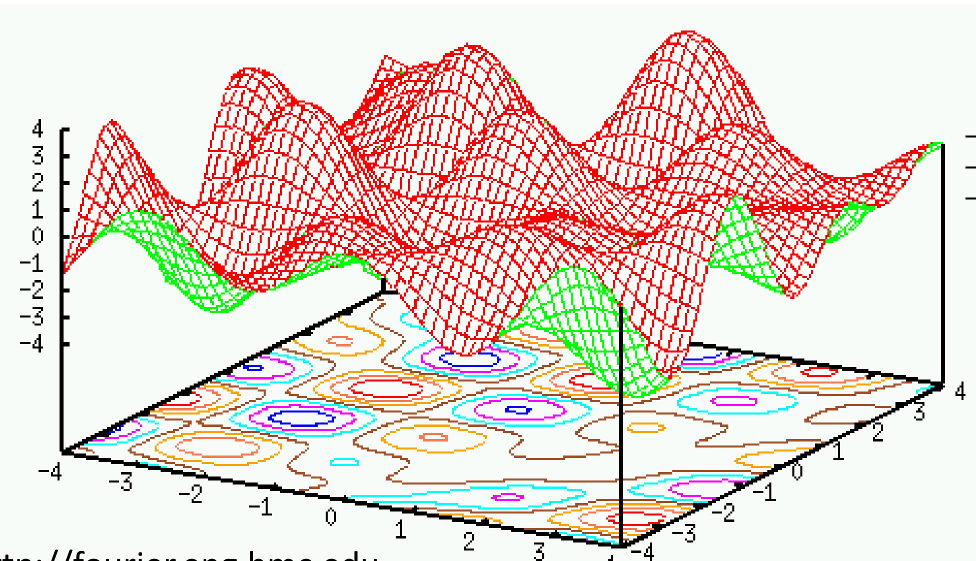
Recall dynamics of Hopfield Network

- Start from arbitrary initial configuration of {x}
- What final state does the network converge ?
- Evaluate an 'energy' value associated with the network state:

$$E = -\frac{1}{2}\sum_{j}\sum_{\substack{i=1 \\ i\neq j}}^{N} w_{j,i} x_i \, x_j$$

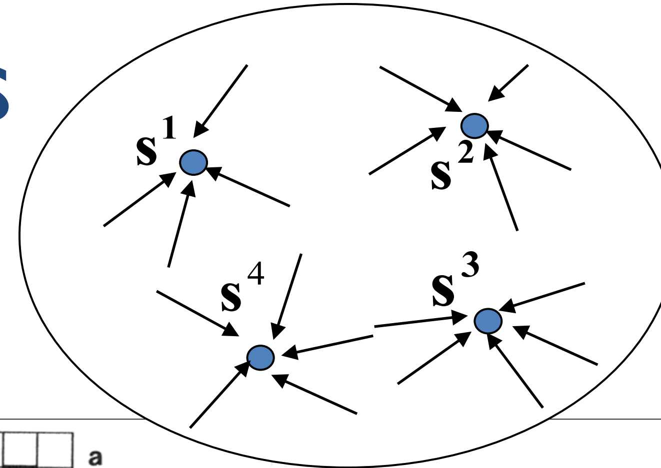
- System converges to an attractor which is a local/global minimum of *E*





http://fourier.eng.hmc.edu

Associative Memory as Attractor Network



Memories stored as attractors of network dynamics

When presented with a novel input, the network eventually converges to the stored pattern that is "closest" to it (i.e., to the pattern in whose *basin of attraction* the input lies).