Systems Biology Across Scales: A Personal View
XV. Brain: a network of neurons

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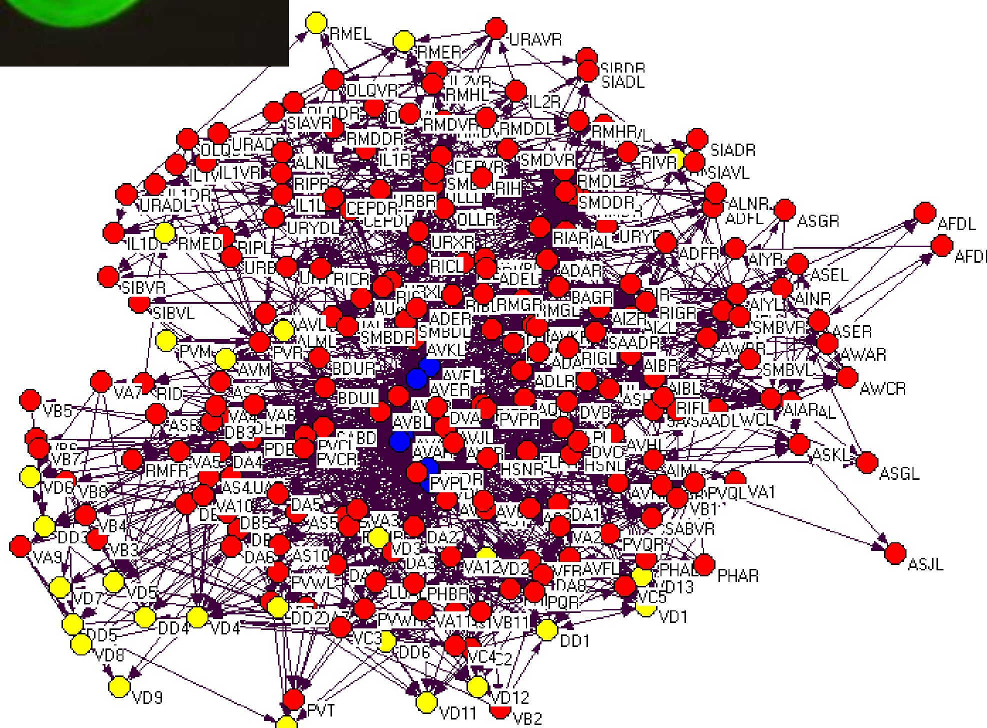
The brain as a network of neurons

Caenorhabditis elegans nematode nervous system
- neurons ~ 300
- connections ~ 3000

(synaptic ~ 2500, gap junctions ~ 500)

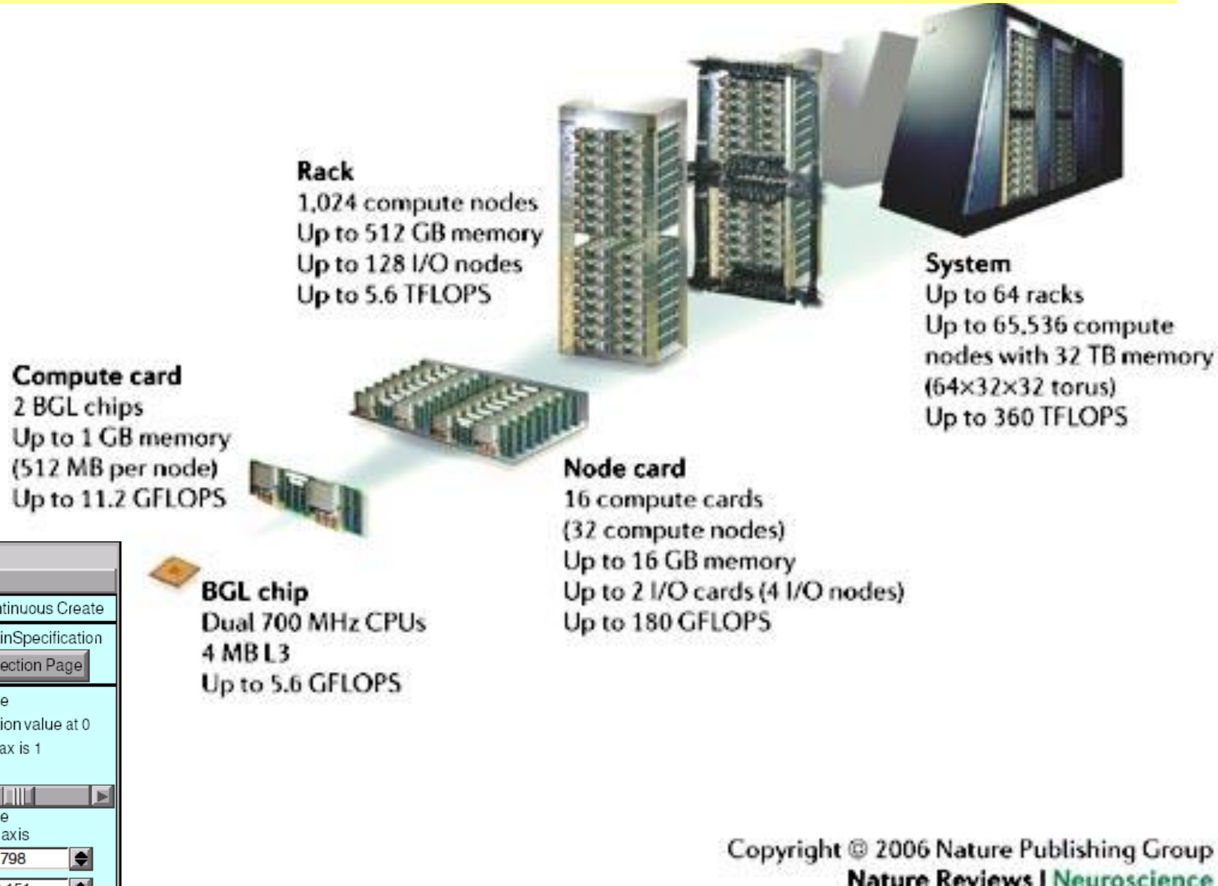


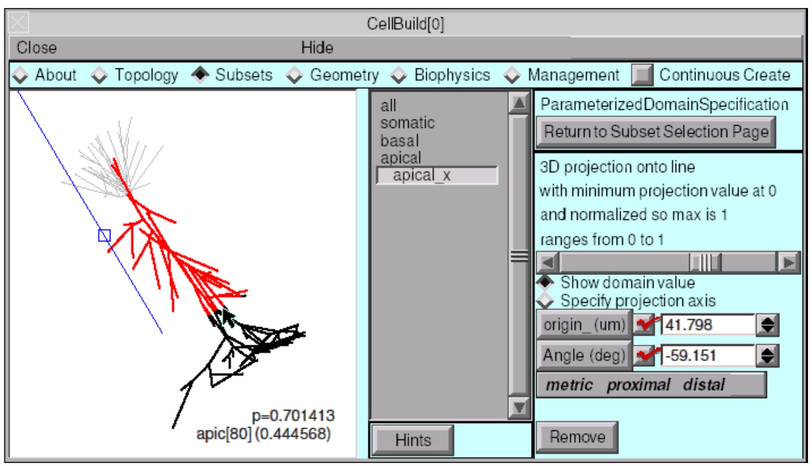
The human brain

- neurons ~ 10^{11}
- connections ~ 10^{14}

Can we understand its workings by treating the mammalian brain as a very large network of neurons ?

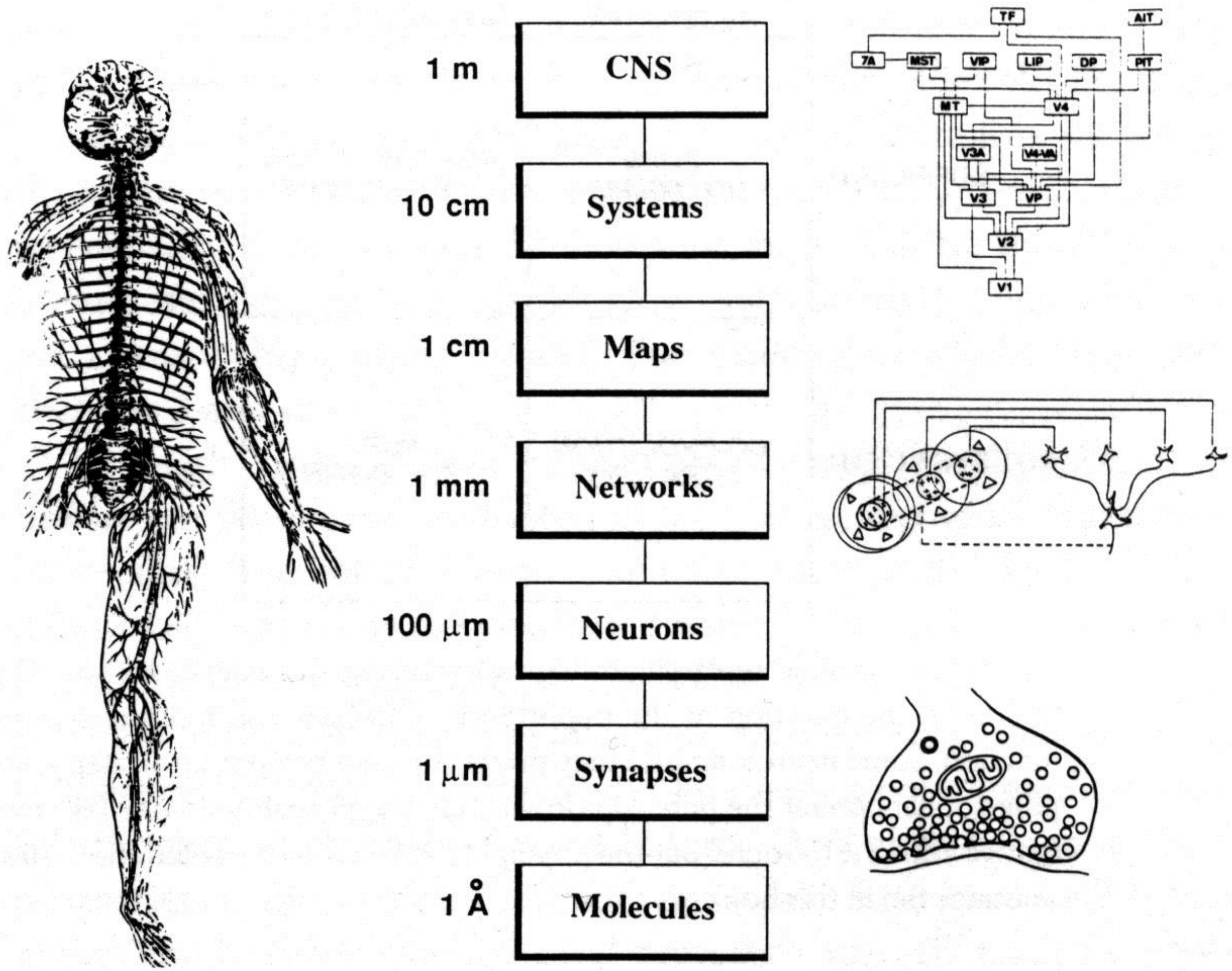
Blue Brain Project



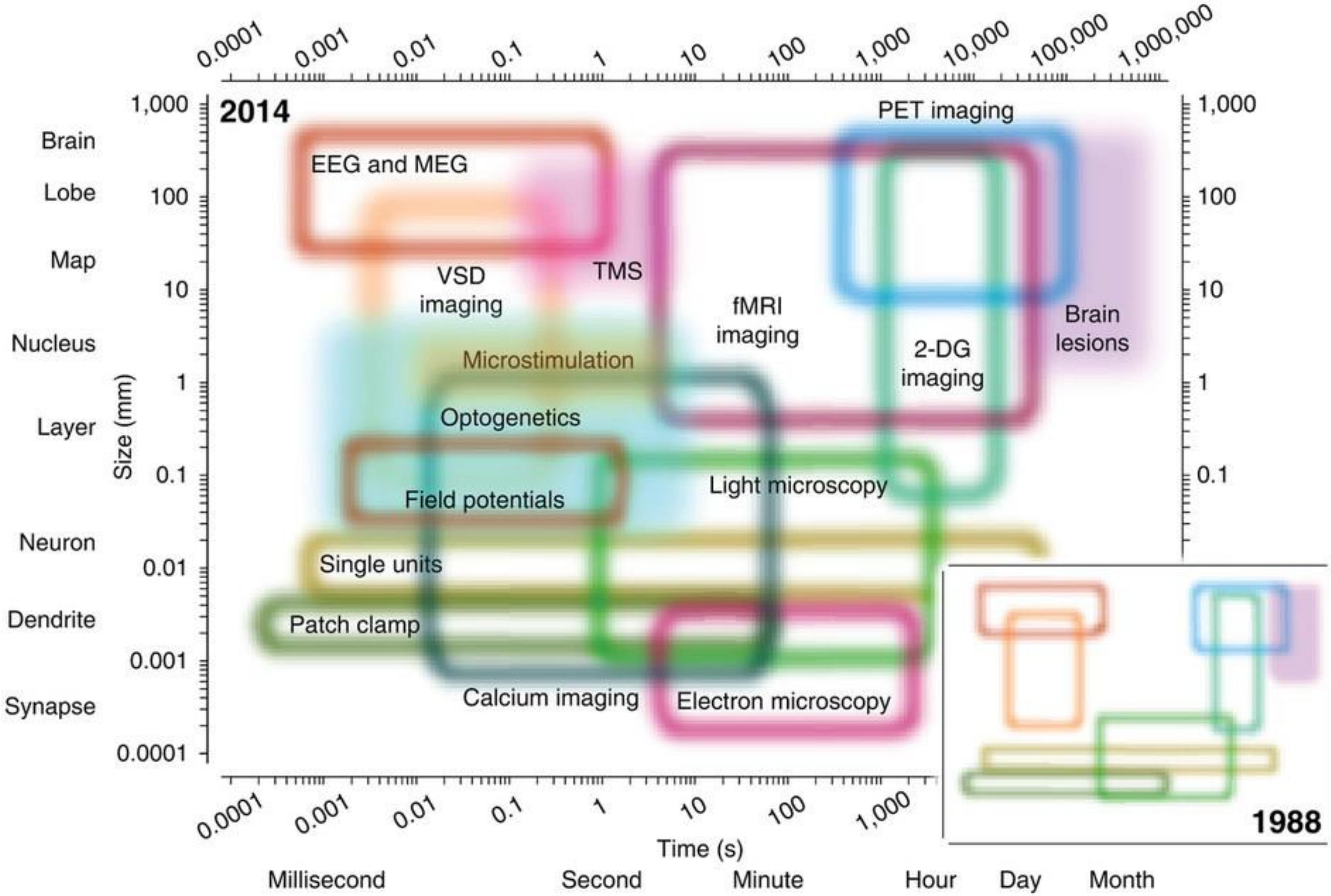


H Markram *Nature Rev Neurosci* (2006)

Churchland and Sejnowski's classic diagram of levels in the neurosciences

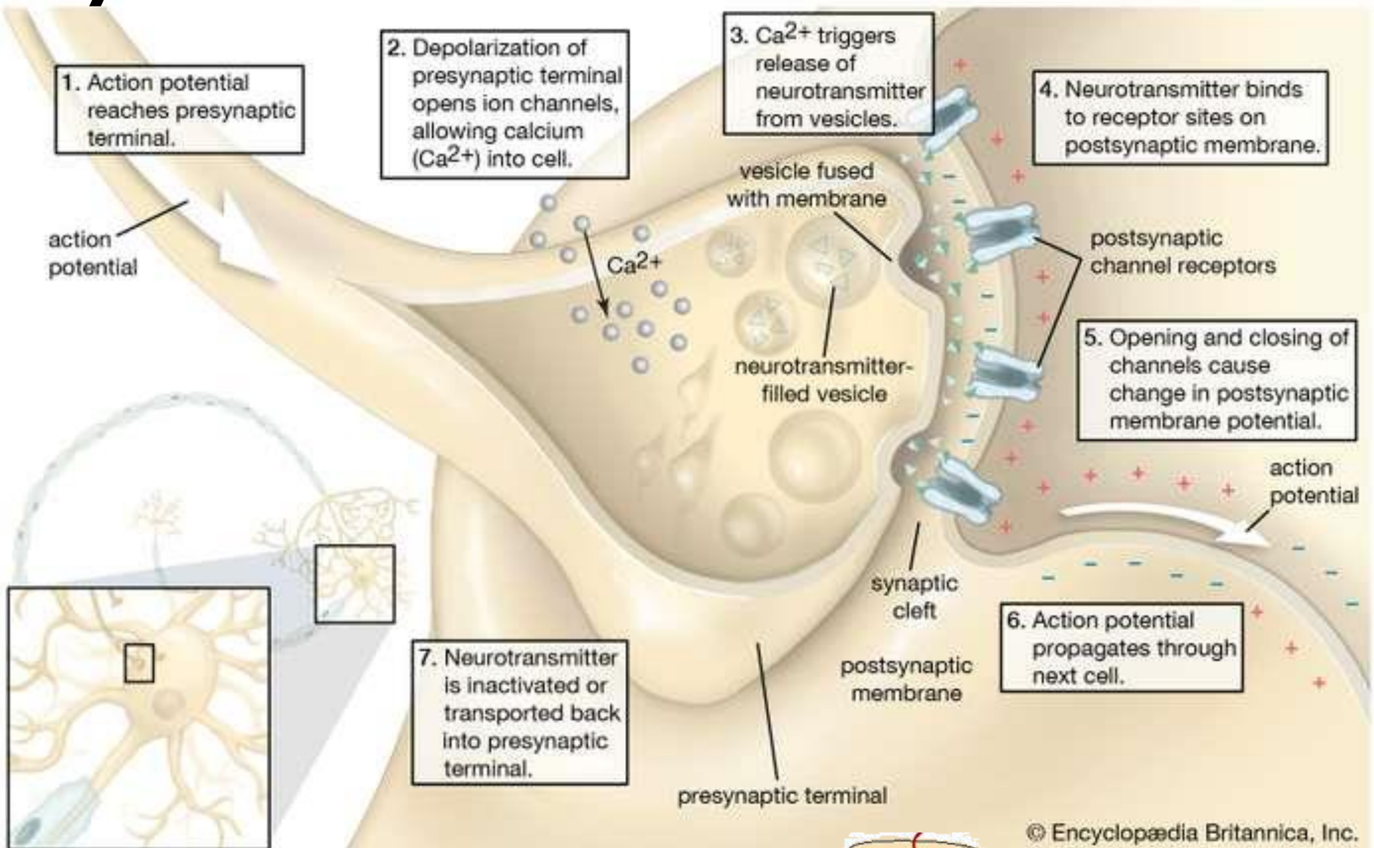


The spatiotemporal domain of neuroscience and of the main methods available for the study of the brain



Sejnowski, Churchland & Movshon, Nature (2014)

Dynamics on networks



Chemical communication: Synaptic (excitatory and inhibitory)

Electrical communication: gap junction

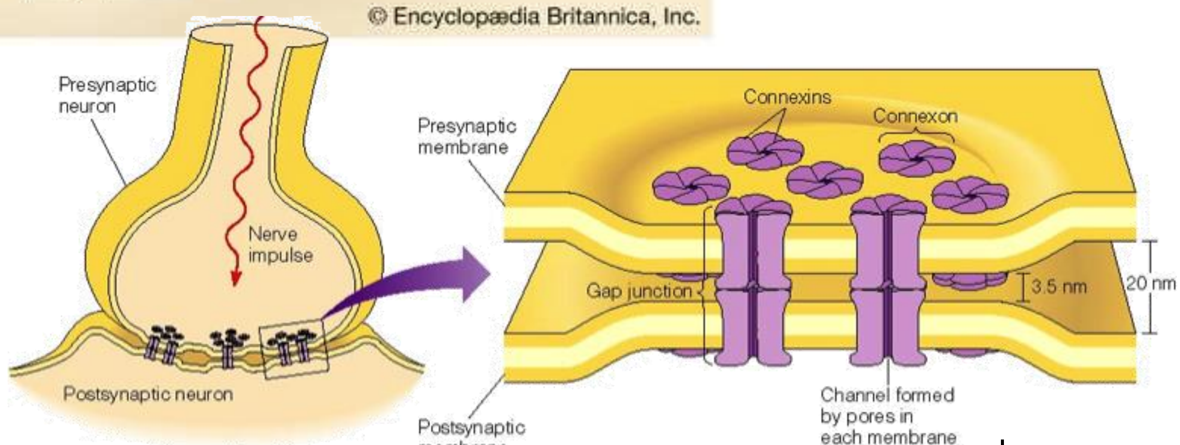


Image: quora.com

Lateral inhibition

Edge detection in vision

Network Motif implementing Center-Surround principle:

stimulation of cells in central region and those in surrounding regions having opposing responses to excitation of neurons downstream

Implements a "Mexican hat" function that can compute the smoothed Laplacian of the stimulus (e.g., an image)

Difference of Gaussians ("Mexican hat")

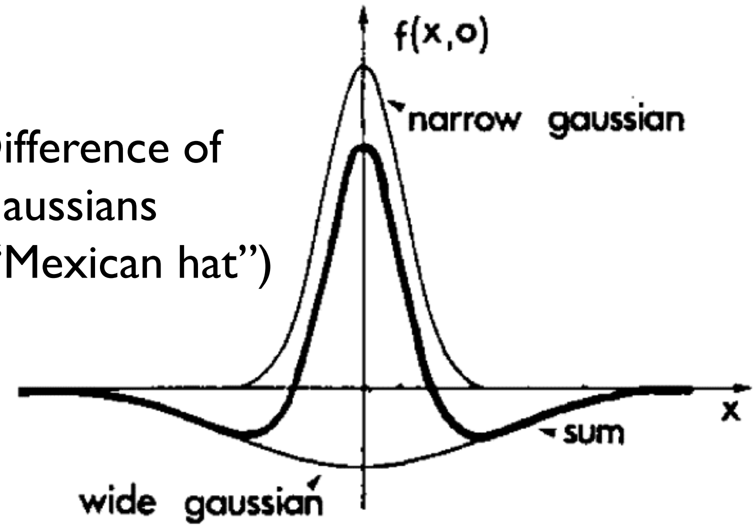


Image: Troy and Shou, Prog. Ret. Eye Res. **21** (2002)

Difference of Gaussians Filter

Image: Holger Winnemöller
doi:10.1145/2024676.2024700

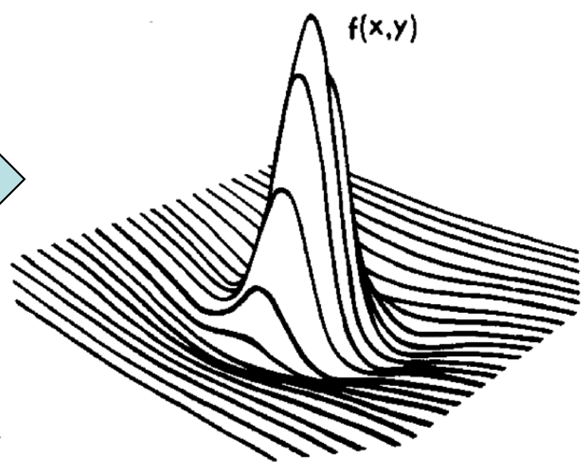


Image: Holger Winnemöller
doi:10.1145/2024676.2024700

Image: Troy and Shou, Prog. Ret. Eye Res. **21** (2002)

Receptive fields

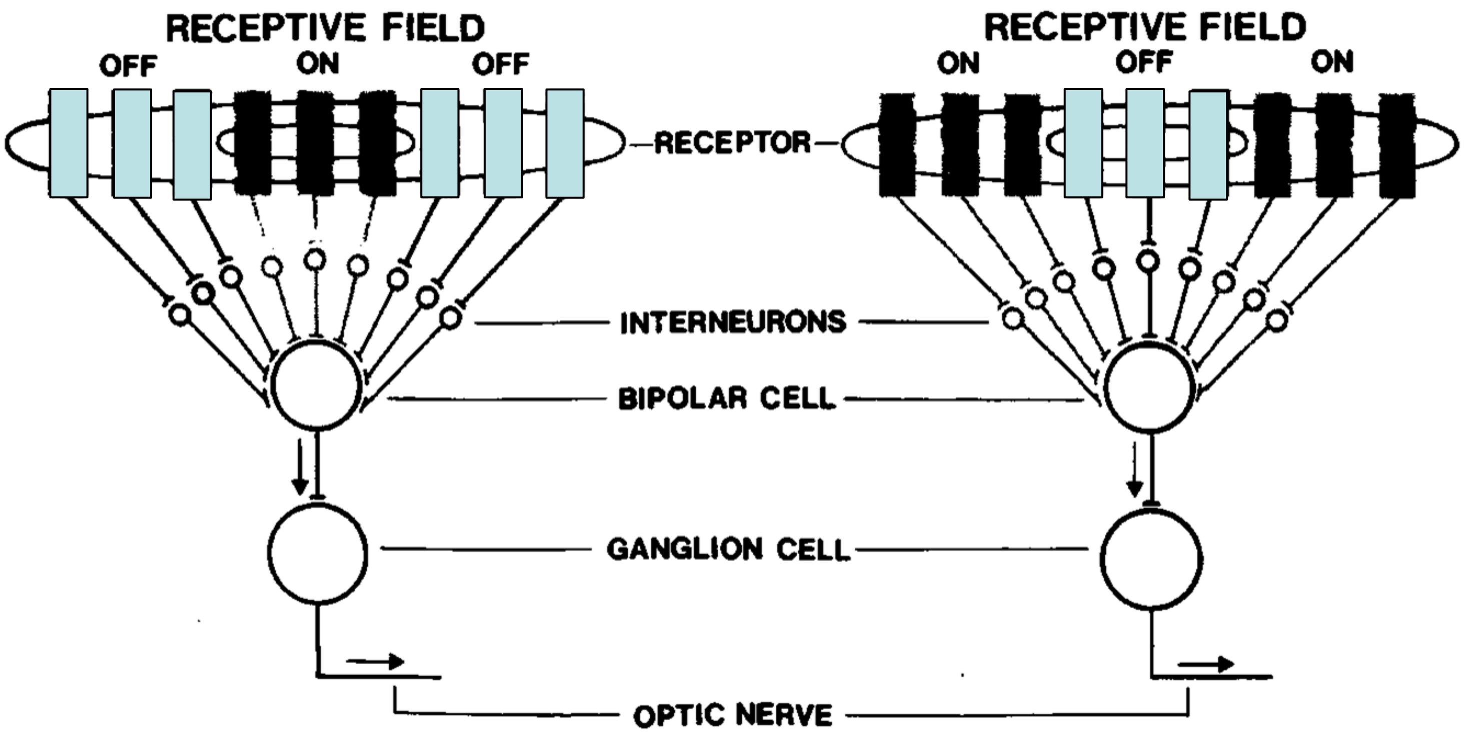


Image: David Ottoson, Physiology of the Nervous System (Oxford 1983)

synaptic arrangement underlying organization of receptive fields of the retina in ON and OFF regions.

ON-centre and OFF-centre cells

Image: David Ottoson, Physiology of the Nervous System (Oxford 1983)

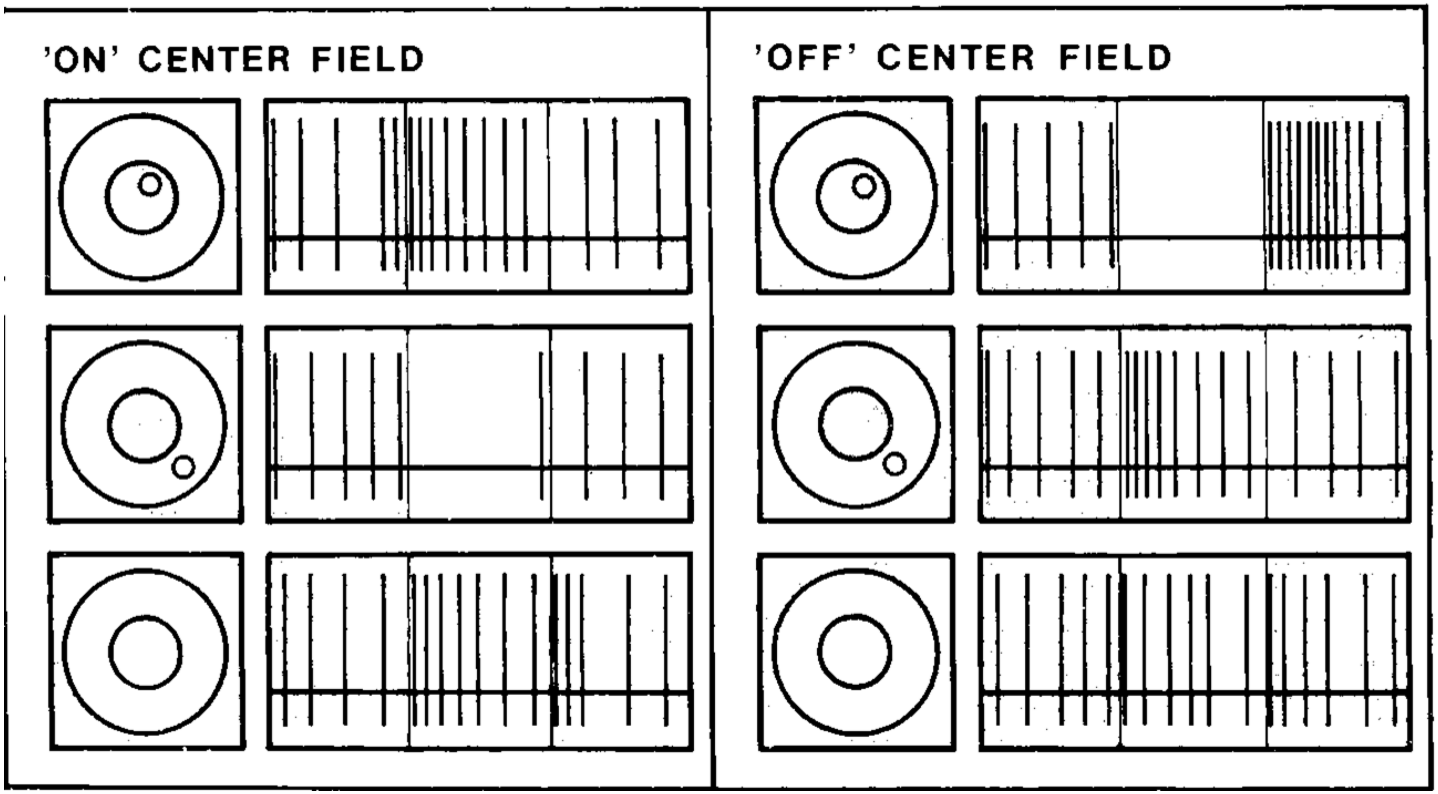


Image: royalsocietypublishing.org

Stephen W Kuffler
(1913-1980)

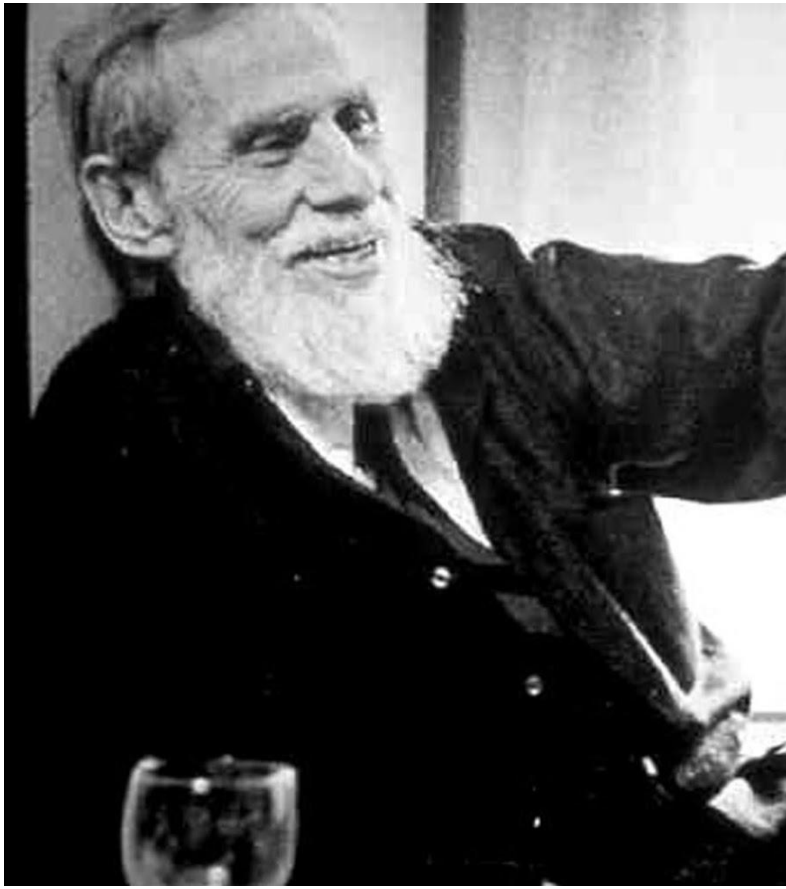
- responds to a spot of light in central part of receptive field
- inhibited by illumination of peripheral region of the field

- excited by a spot of light in peripheral part of receptive field
- inhibited by central illumination

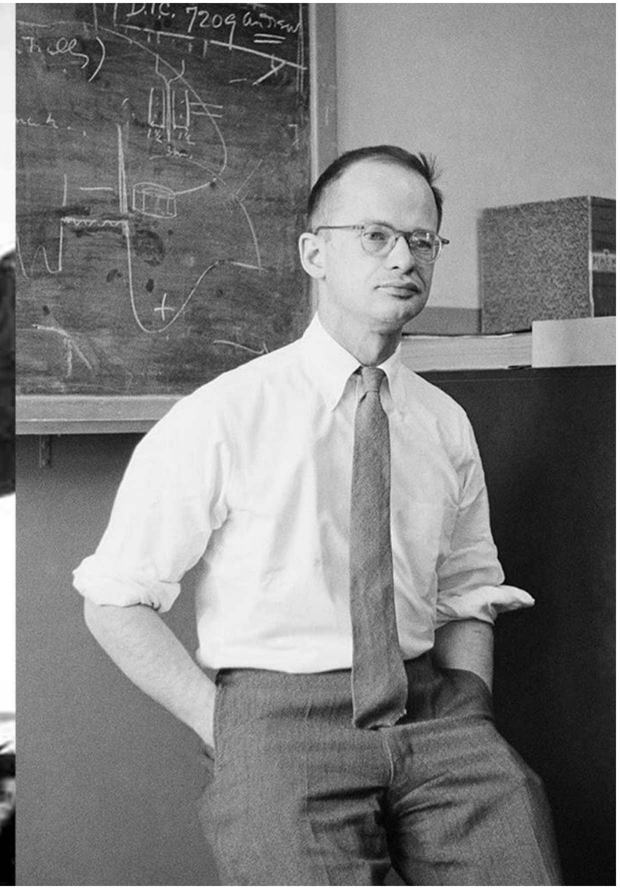
Illumination of the entire receptive field causes only slight increase in activity

The logical calculus of nervous activity

http://infonintelli.blogspot.com/2017/11/



Warren S. McCulloch (1898-1969)



Walter H Pitts (1923-1969)

“[They recognized that] the laws governing the embodiment of mind should be sought among the laws governing information rather than energy or matter.”

Seymour Papert

The alphabet of human thought

Reducing human reasoning to calculation

In the early 18th century, Leibniz provided an outline for a *characteristica universalis*
An artificial language in which each letter (a pictographic character) would represent a concept.
These could be then combined and manipulated according to a set of logical rules to compute all knowledge.

LEIBNIZ (1646 - 1716)

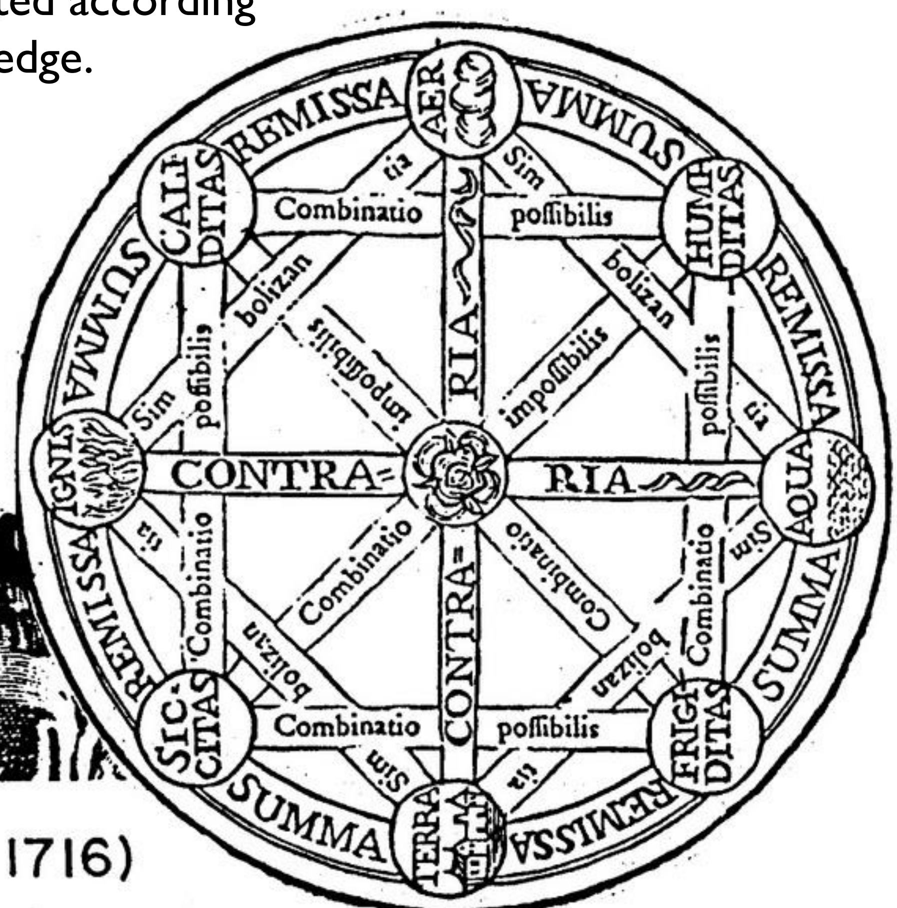


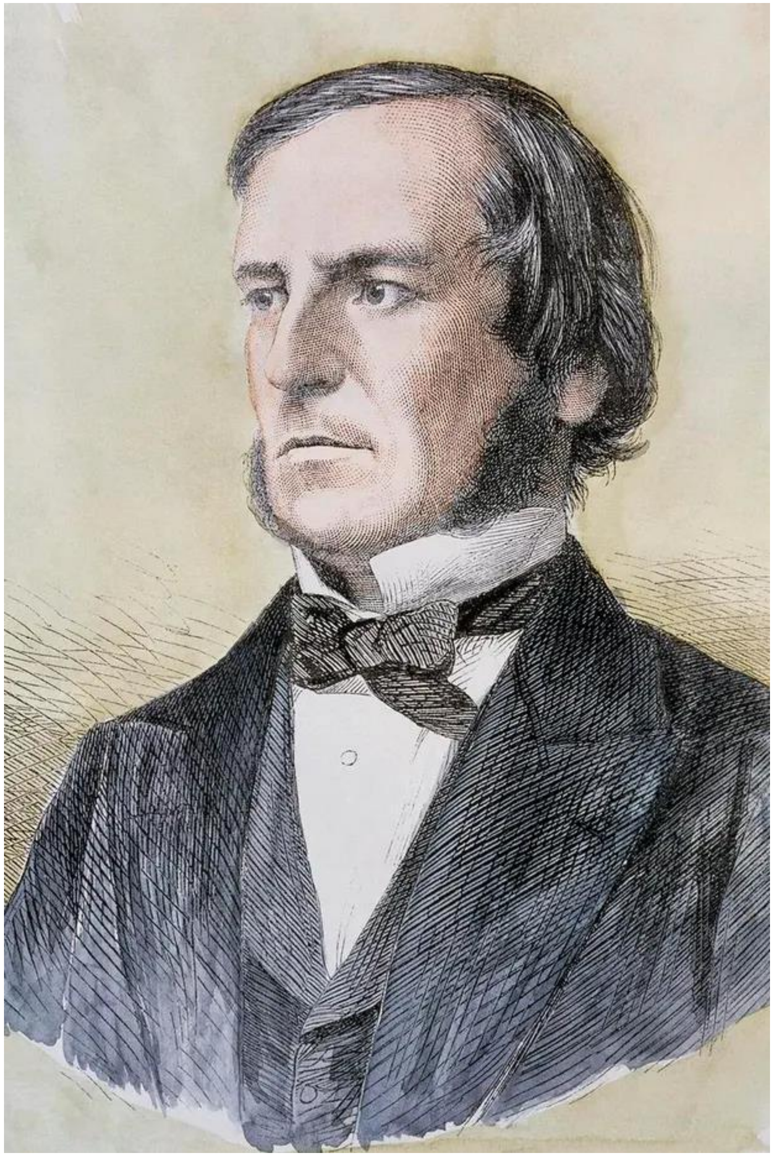
Image:quadriformisratio.files.wordpress.com/

The laws of thought

"…to investigate the fundamental laws of those operations of the mind by which reasoning is performed;
to give expression to them in the symbolical language of a Calculus, and upon this foundation to establish the science of Logic and construct its method …
… and, finally, to collect from the various elements of truth brought to view in the course of these inquiries some probable intimations concerning the nature and constitution of the human mind."

An Investigation of the Laws of Thought (1854)

George Boole
(1815-1864)



https://www.theguardian.com/

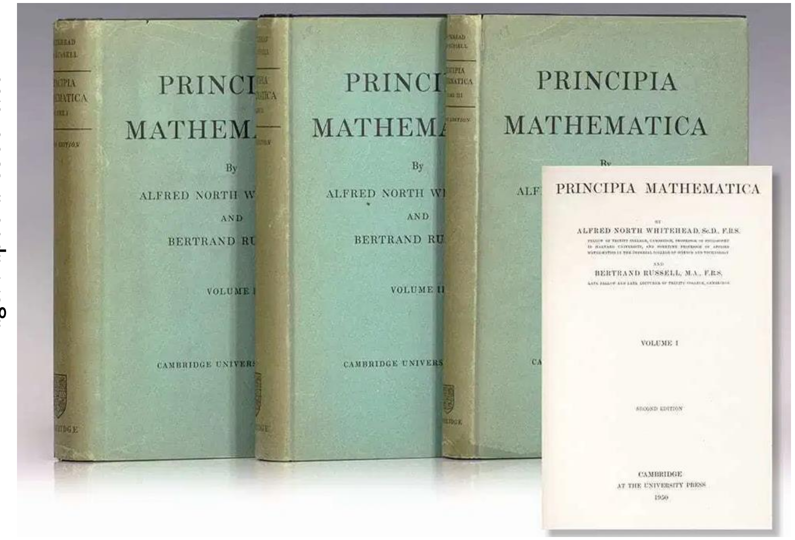
Logical calculus:
The automation of thought

Principia Mathematica (1910-1913) of Whitehead and Russell provided a model by attempting to derive the entire body of mathematical knowledge by using logical operations such as

- Conjunction (AND)
- Disjunction (OR)
- Negation (NOT)

on a set of simple propositions (either TRUE or FALSE)

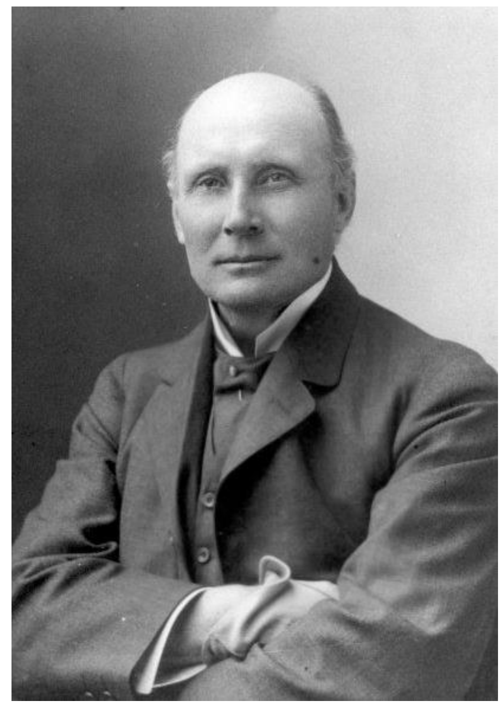
Image: .raptisrarebooks.com



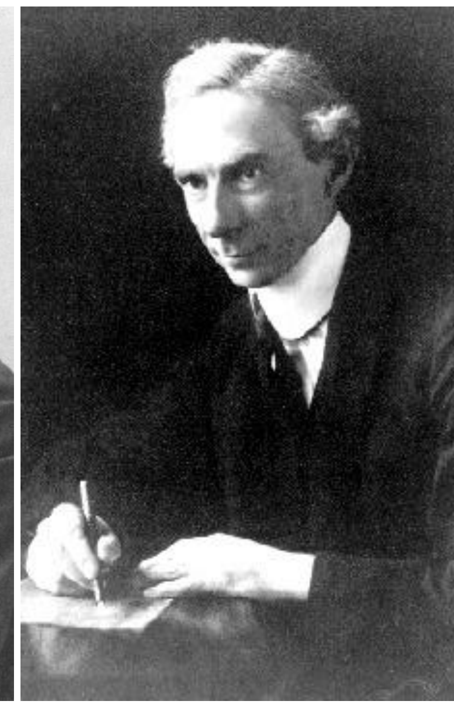
McCulloch

A neuron fires when the signals received from its neighboring cells exceed a threshold, else it is at rest $\Rightarrow$ binary state (ON/OFF $\equiv$ TRUE/FALSE)

- Signal: proposition
- Neurons: logic gates (e.g., AND)
- Varying threshold: Different logic gates



Alfred North Whitehead (1861-1947)
Image: pinterest.co.uk



Bertrand Russell (1872-1970)
Image: flickr.com

The McCulloch-Pitts neuron

Image: Current Biology

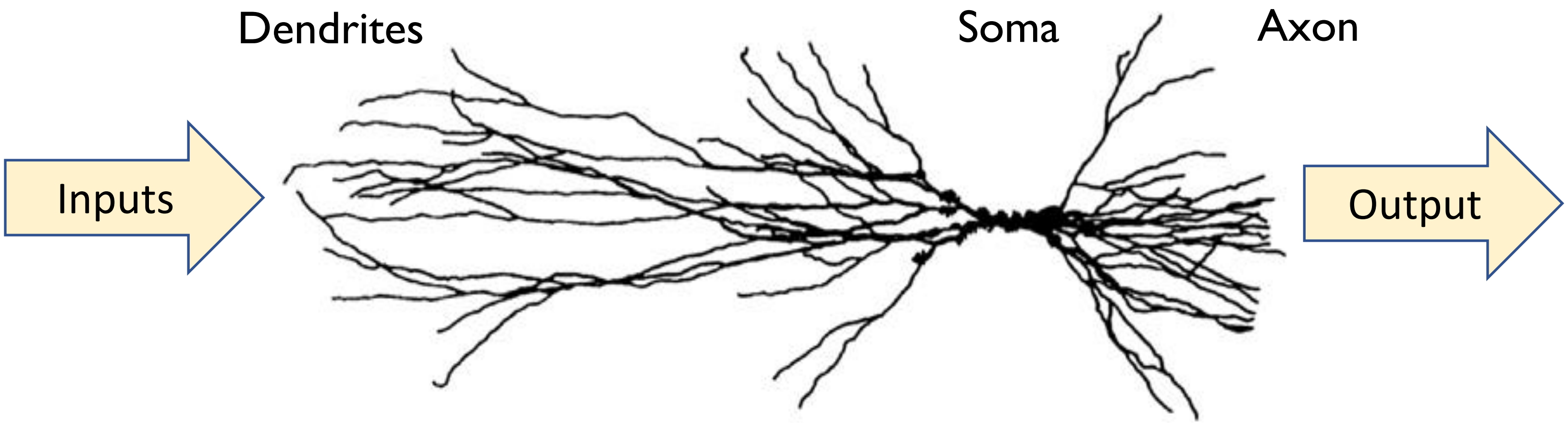
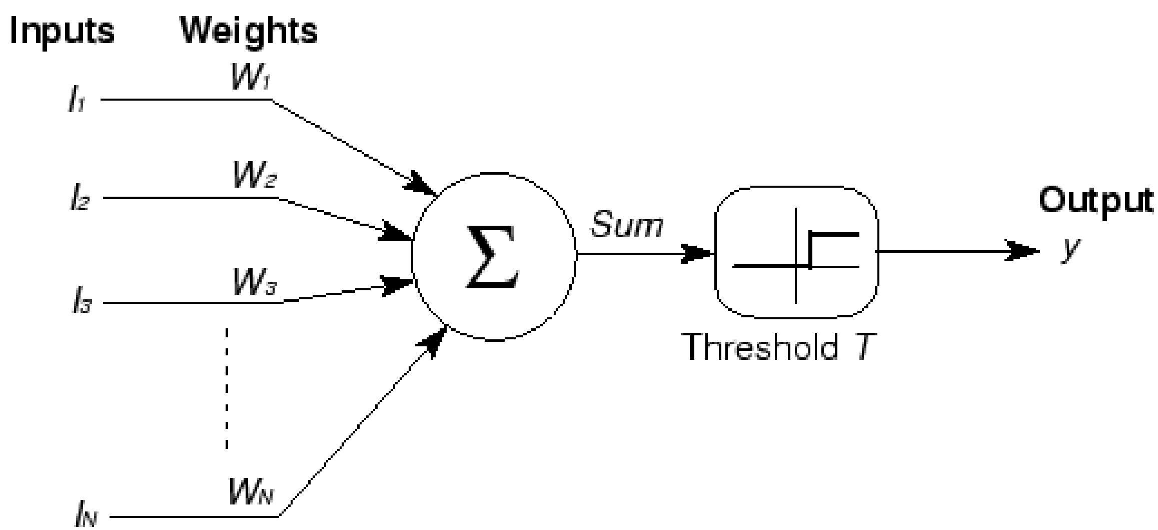


Image: chatbotslife.com/keras-in-a-single-mcculloch-pitts-neuron-317397cccd45



The McCulloch-Pitts network

Circuits implementing computational logic

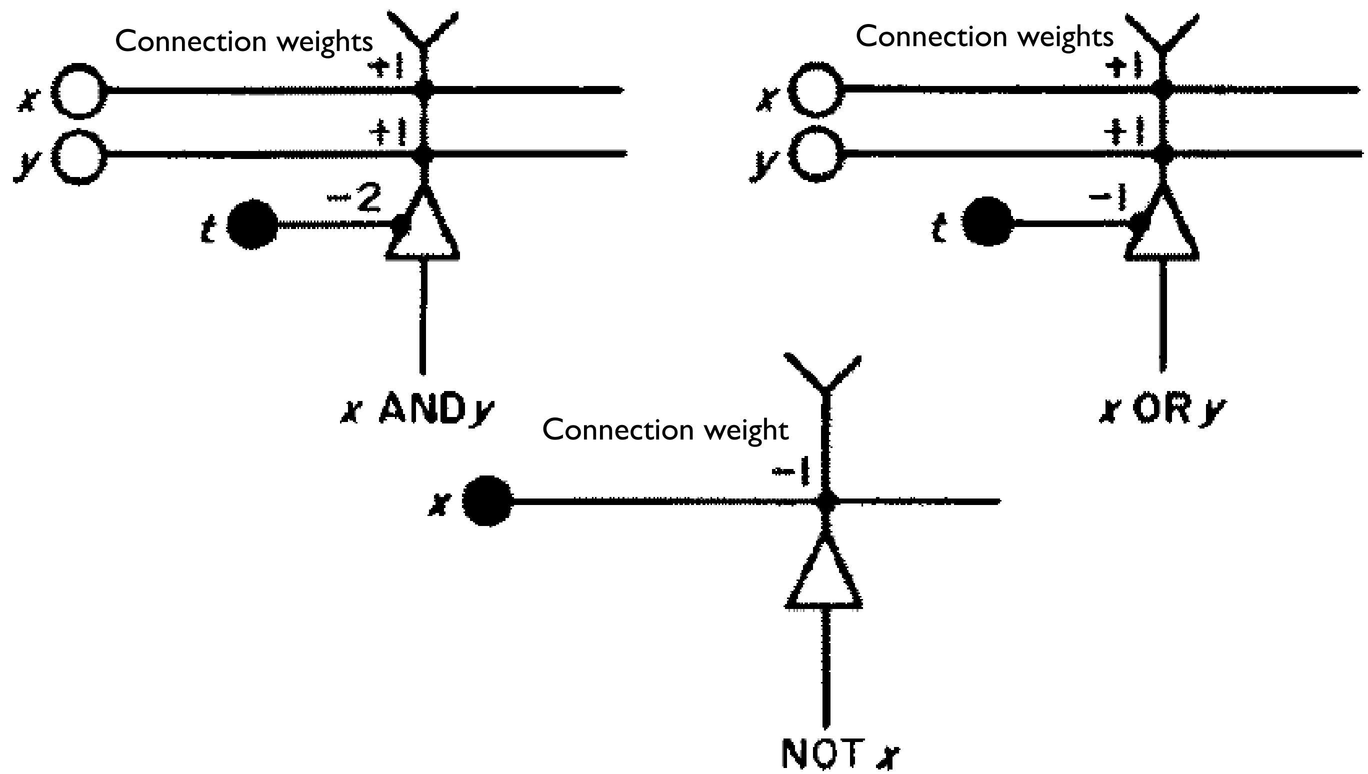


Figure: Cowan, Bull. Math. Biol. (1990)

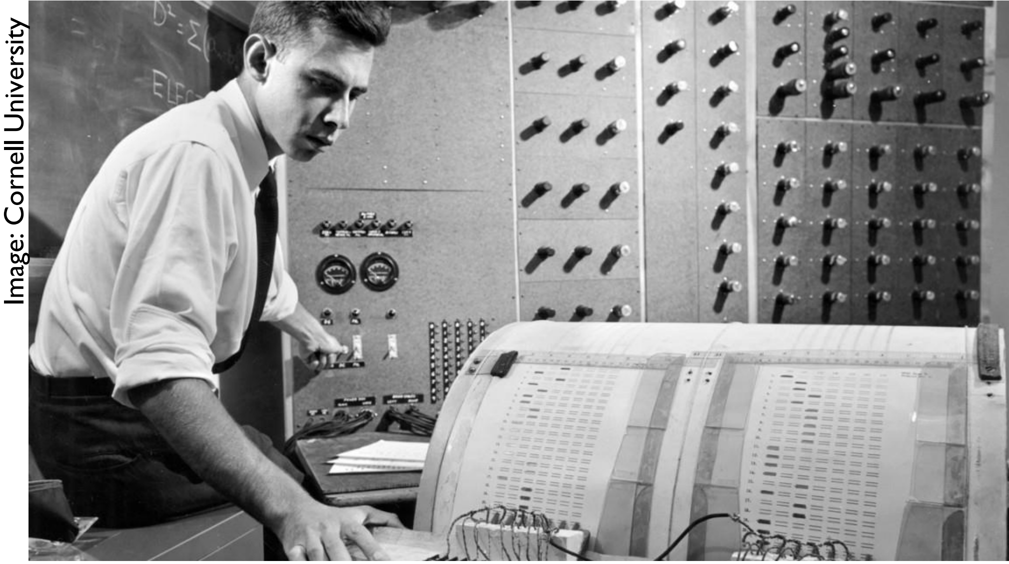
Each unit is activated iff its total excitation ≥ 0.
Positive weights: "excitatory"" synapses, negative weights: "inhibitory" synapses
open circles: excitatory neurons; filled circles: inhibitory neurons

Perceptron

The first neural network

McCulloch-Pitts network +
Learning to adapt the link weights
→ A binary classifier for patterns

Image: Cornell University



Frank Rosenblatt (1928 –1971)

FIG. 1 — Organization of a biological brain. (Red areas indicate active cells, responding to the letter X.)

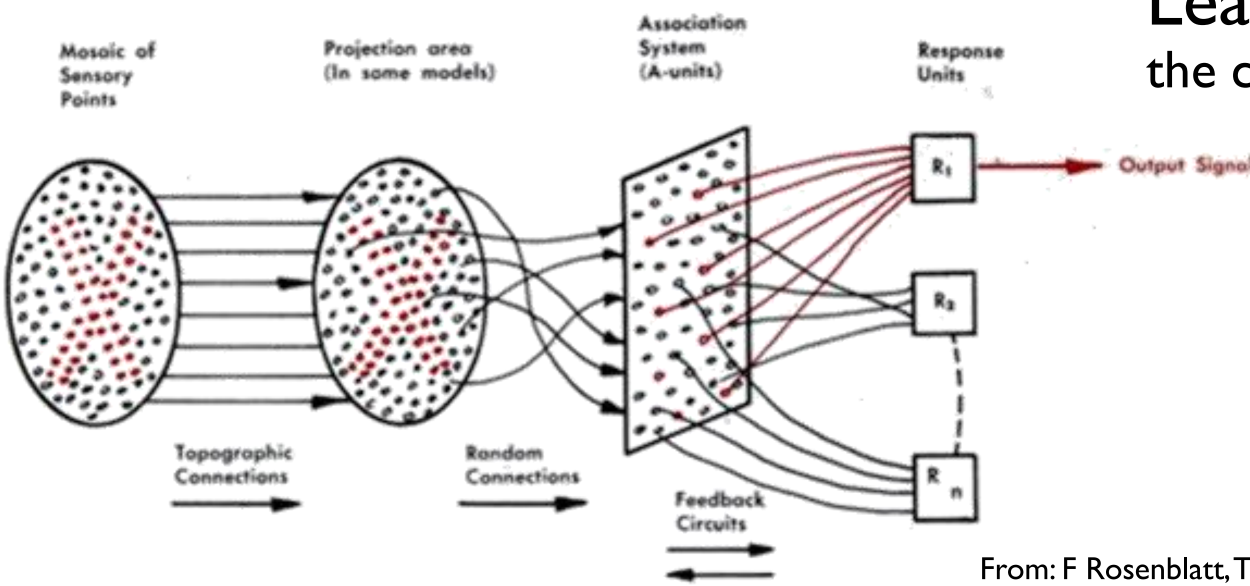
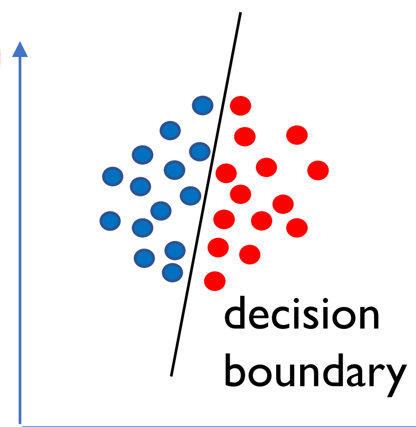


FIG. 2 — Organization of a perceptron.

Learning ≡ modifying the connection weights

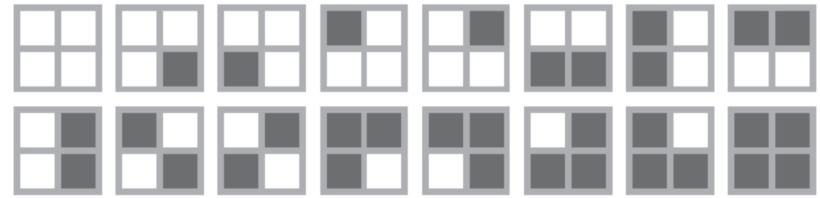


From: F Rosenblatt, The Design of an Intelligent Automaton (1958)
Image: Cornell University

A network for recognizing geometrical patterns

e.g., vertical stripes

All possible 2 × 2 patterns



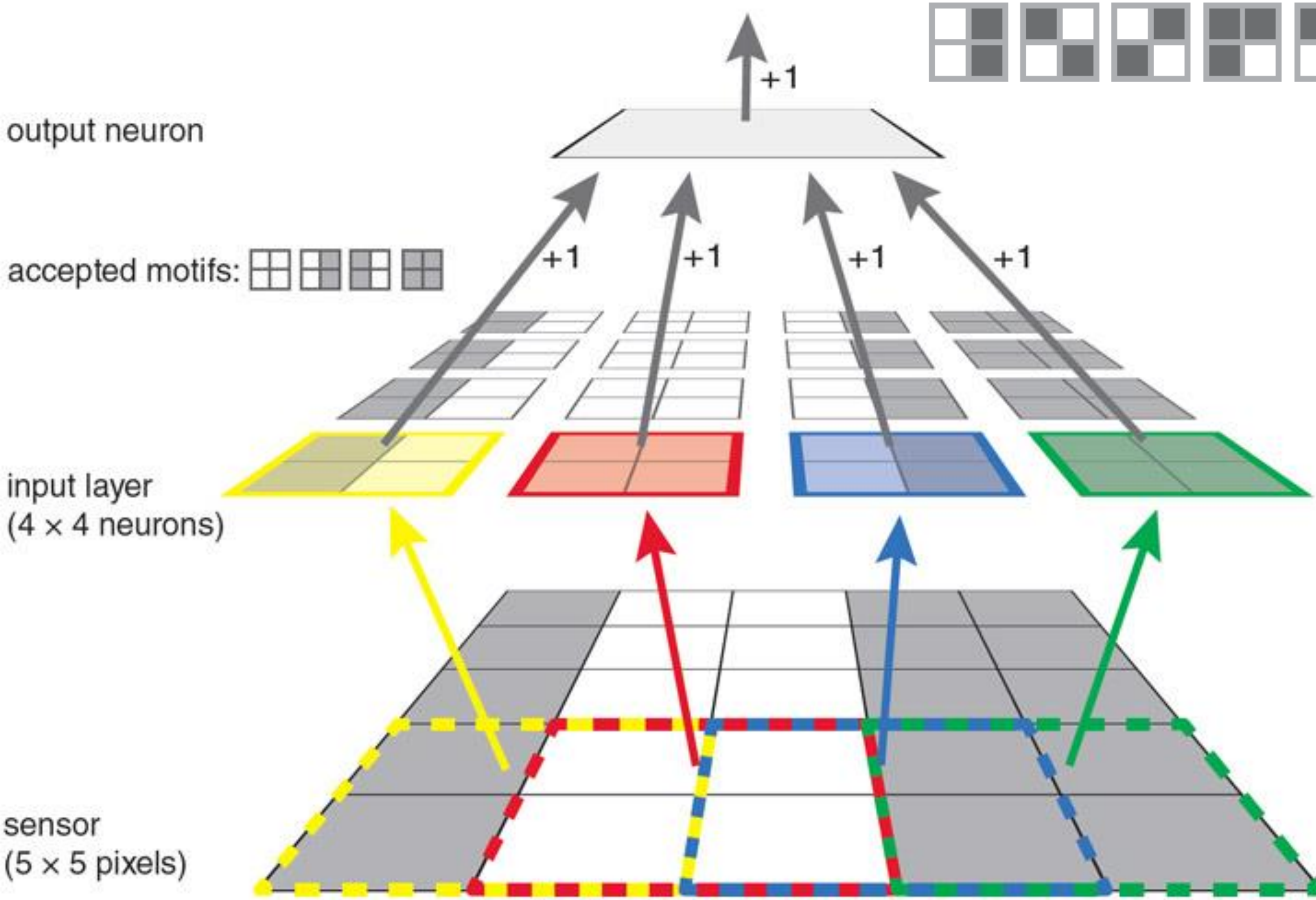


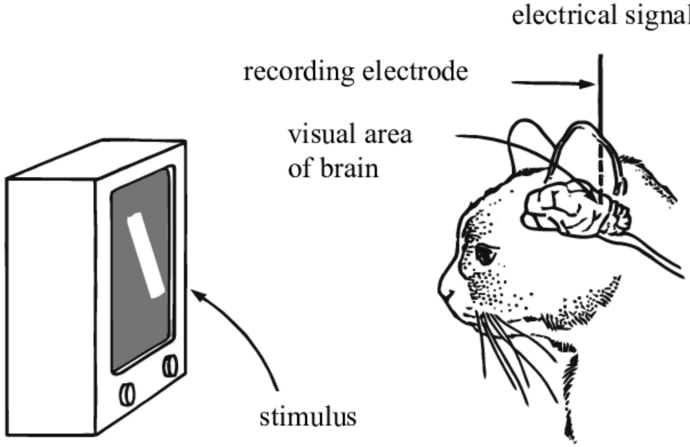
Figure: Brian Hayes, American Scientist (May-June 2014)

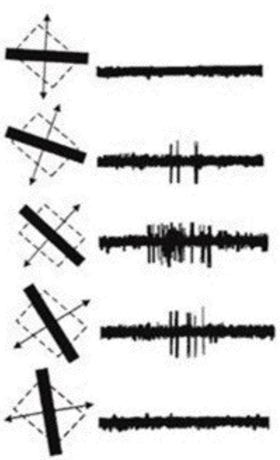
Orientation selective cells in Primary Visual Cortex

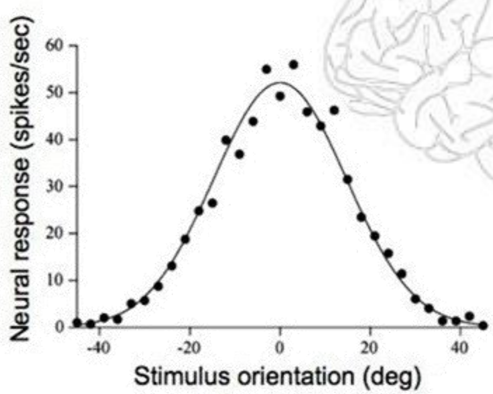
Image:braintour.harvard.edu

David Hubel and Torsten Wiesel
(1926-2013) (1924-)

Neurons responding to bright stripes against dark background or dark stripes against bright background oriented at specific angles







Hubel & Wiesel, 1968

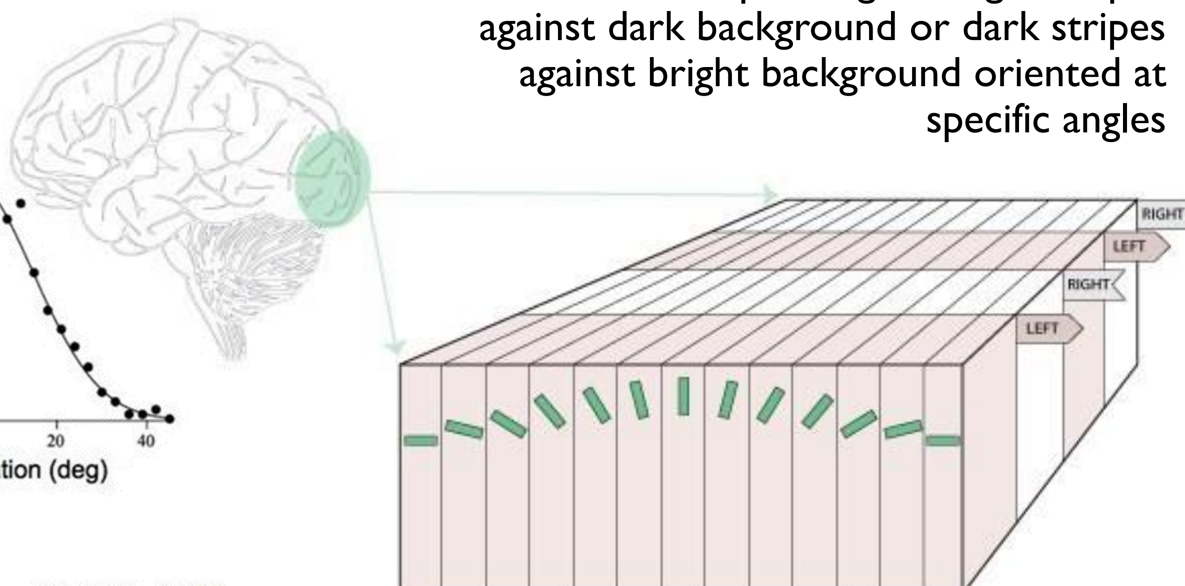
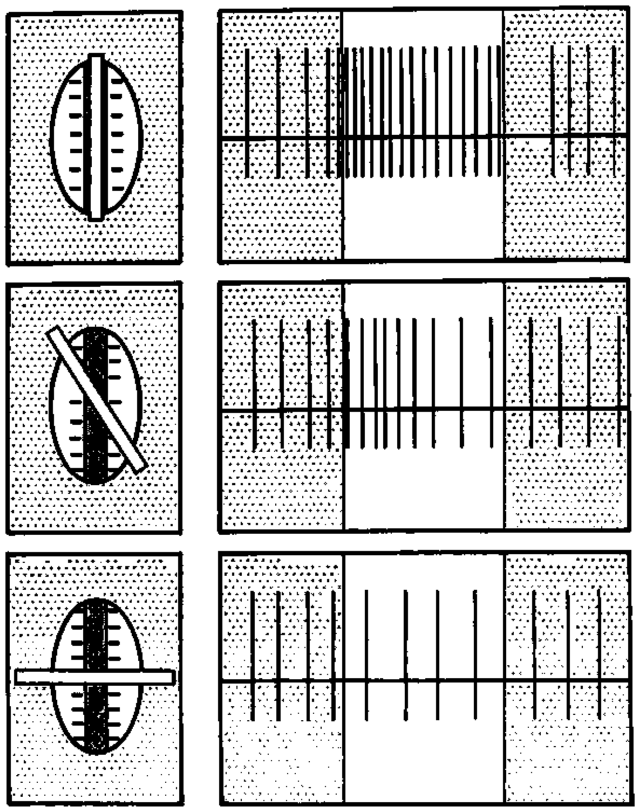


Image: www.researchgate.net/profile/Anh_Nguyen44/publication/335707980/figure/fig1/

Image: knowingneurons.com

Orientation selective cells in Primary Visual Cortex

Image: David Ottoson, Physiology of the Nervous System (Oxford 1983)



A vertical line detector in the visual cortex

The receptive field of a cortical cell with ON centre oriented along a line is generated from receiving excitatory inputs from several LGN ON center cells

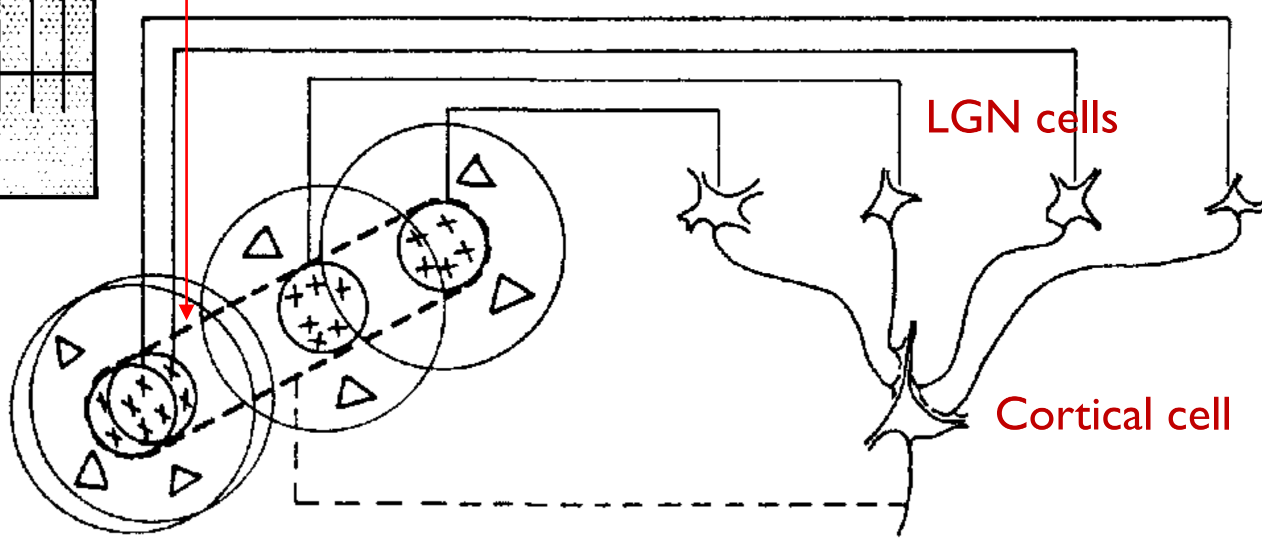


Image: Hubel and Wiesel, J. Physiol. **160** (1962), 160

Perceptron Learning Rule

$$w_i \leftarrow w_i + \Delta w_i$$

where

$$\Delta w_i = \eta(t - o)x_i$$

learning rate — target value — perceptron output — input value

https://dev.to/swyx/supervised-learning-neural-networks-mpo

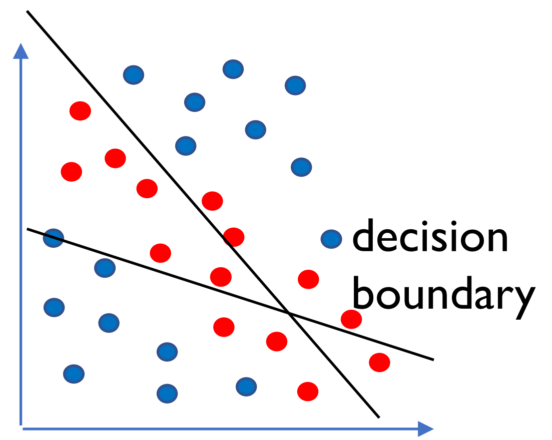
Image: MIT | Cynthia Solomon

Marvin Minsky (1927 –2016) & Seymour Papert (1928-2016)

… and the problem of XOR classification

In 1969, Minsky & Papert showed that the perceptron cannot be trained to function as a XOR gate

Only solved once a learning algorithm for multi-layer perceptrons (back-propagation algorithm) was developed in the 1980s



Multilayer Neural Networks & Deep Learning

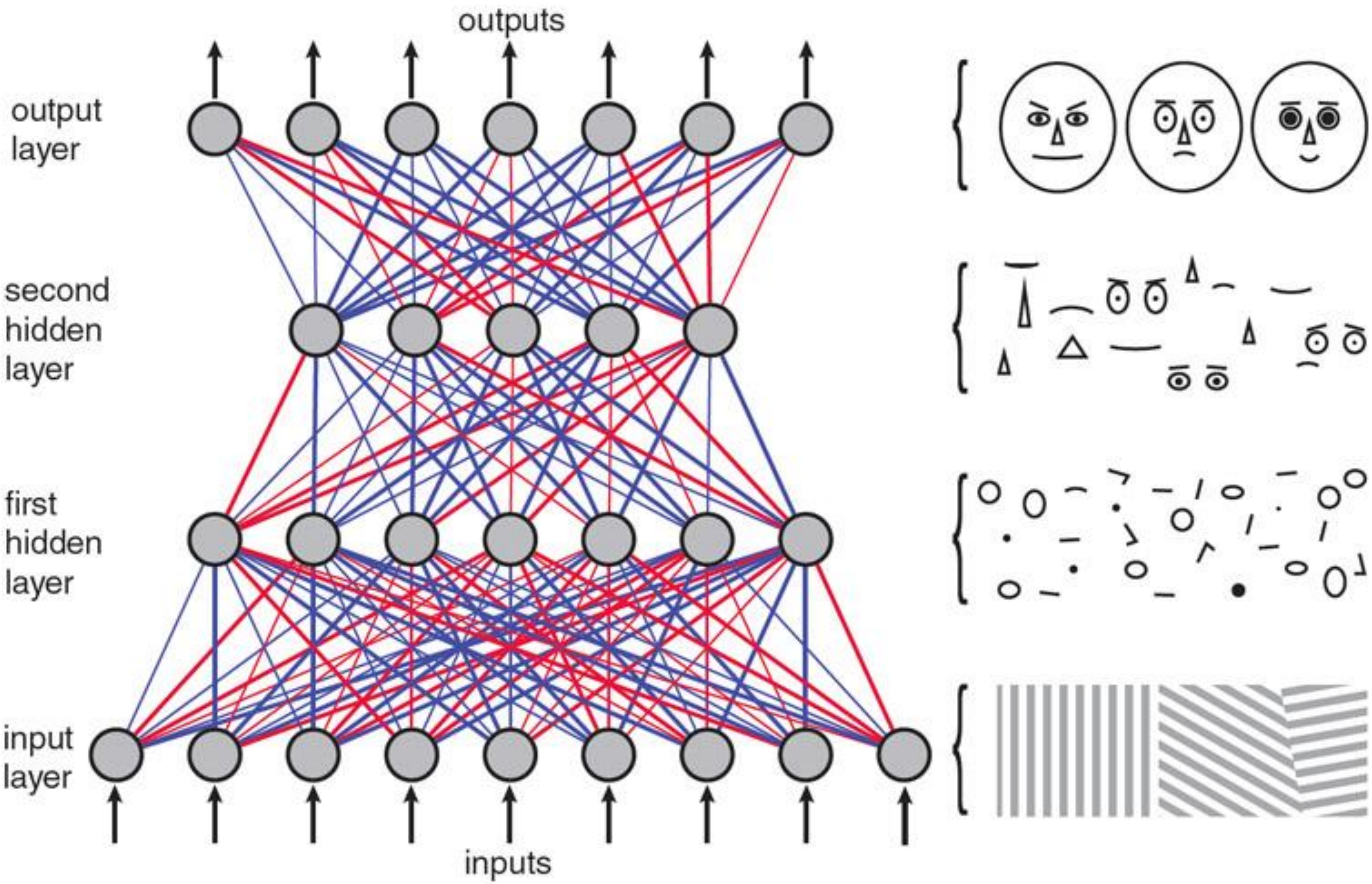
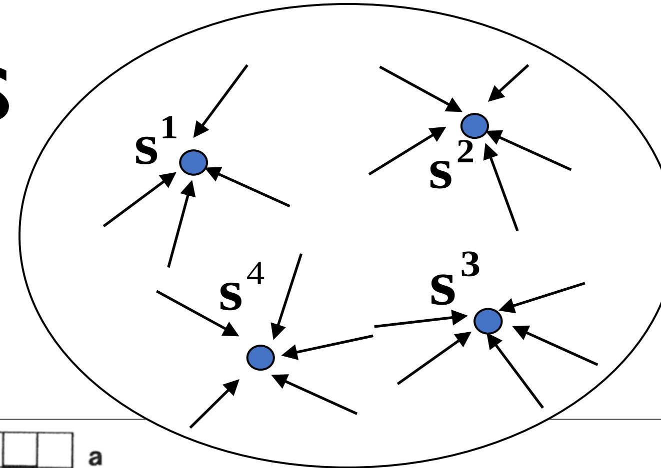


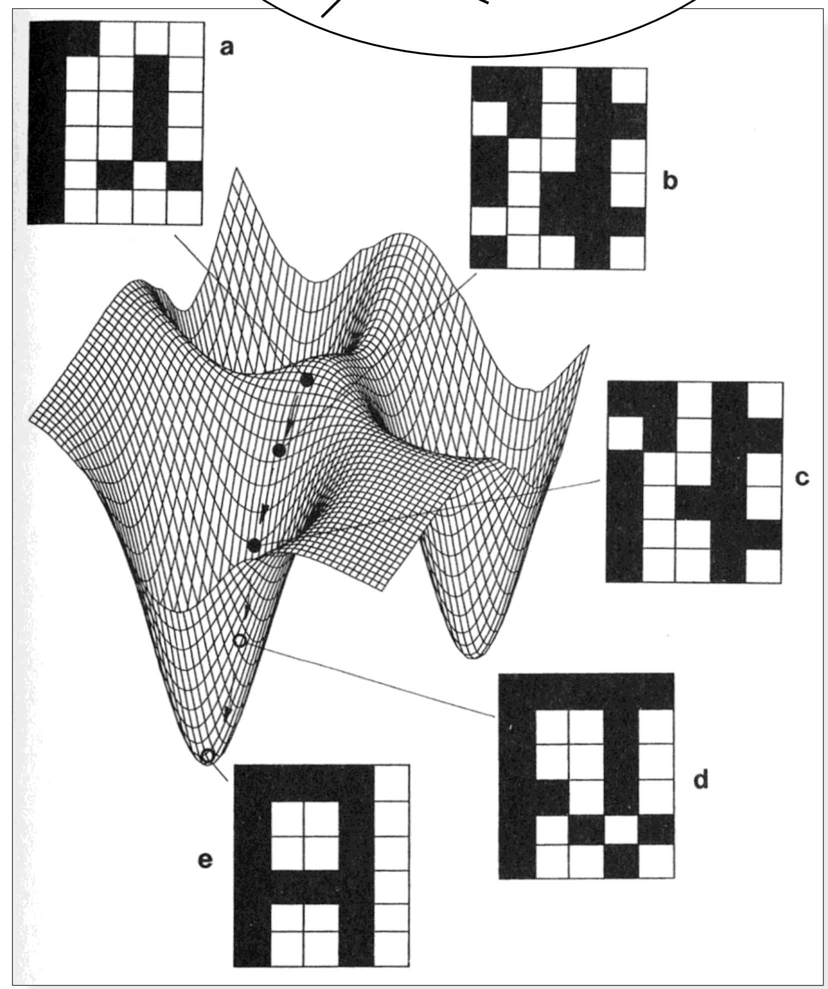
Figure: Brian Hayes, American Scientist (May-June 2014)

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).



Hopfield Model

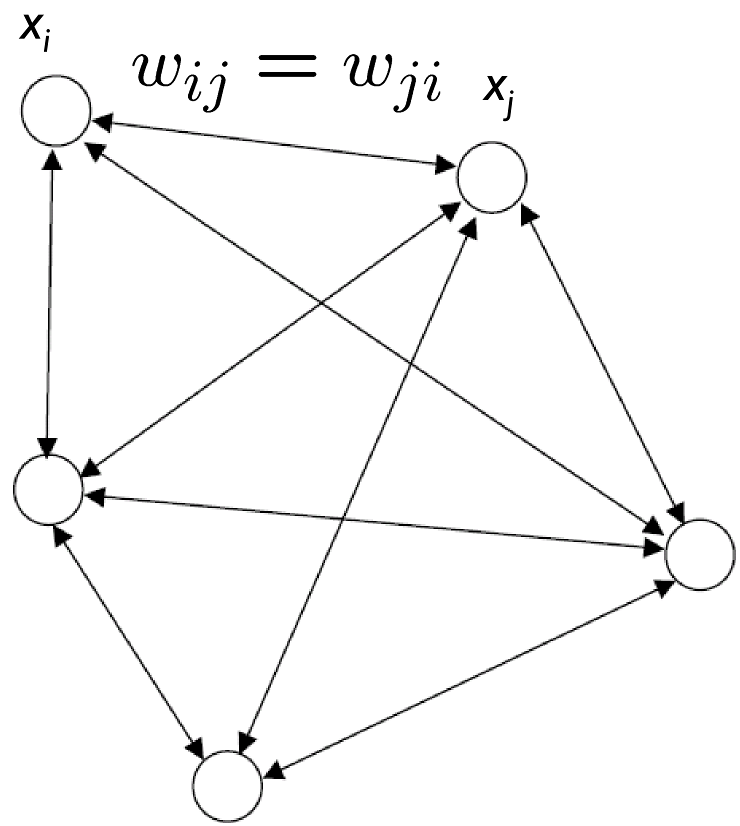
Attractor Network Model for Associative Memory

Image: bulletin.swarthmore.edu

John J Hopfield (1933-)

- ❑ Network of inter-connected binary state "neurons"
- ❑ $x_i = \{ -1$ or OFF, $+1$ or ON$\}$.
- ❑ Activation of the neurons are defined by $x_i = \text{sgn}(\sum_j w_{ij}\, x_j)$
  - ▪ sgn (q) = -1, if $q < 0$;
  - ▪ sgn (q) = $+1$, if $q > 0$

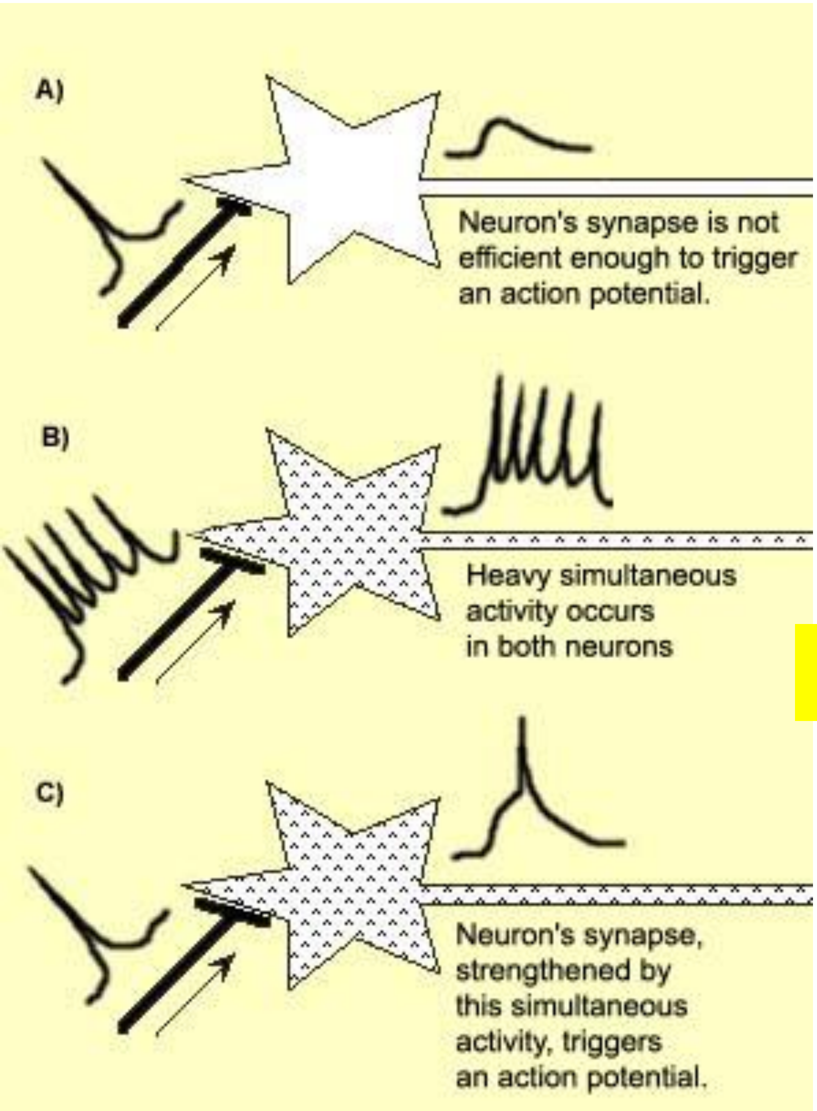
  T=0 or deterministic dynamics
- ❑ Symmetric connection weights,
  - ▪ i.e. $w_{ij} = w_{ji}$
- ❑ $w_{ii}=0$ (No self connections)



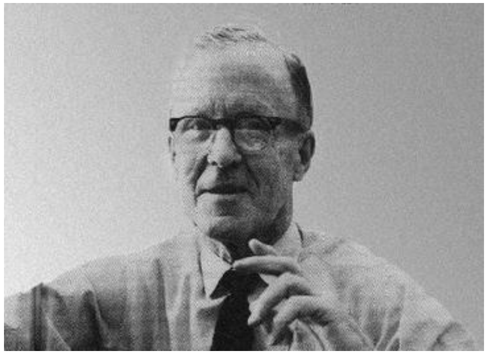
Learning

Modifying the synaptic weights

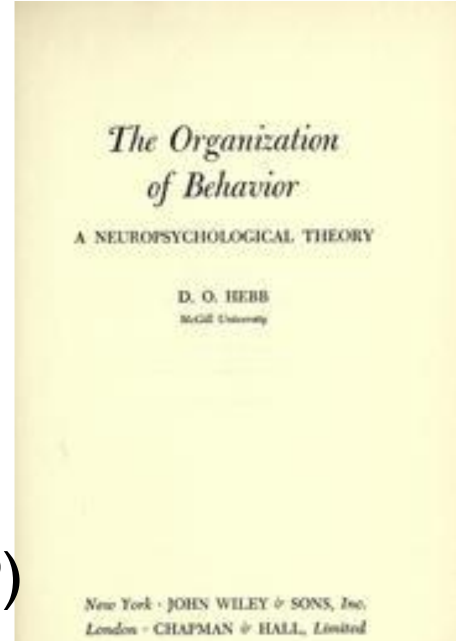
Dynamics of network affected by dynamics on networks



http://thebrain.mcgill.ca



Donald O Hebb (1904-85)



Hebb's hypothesis (1949)

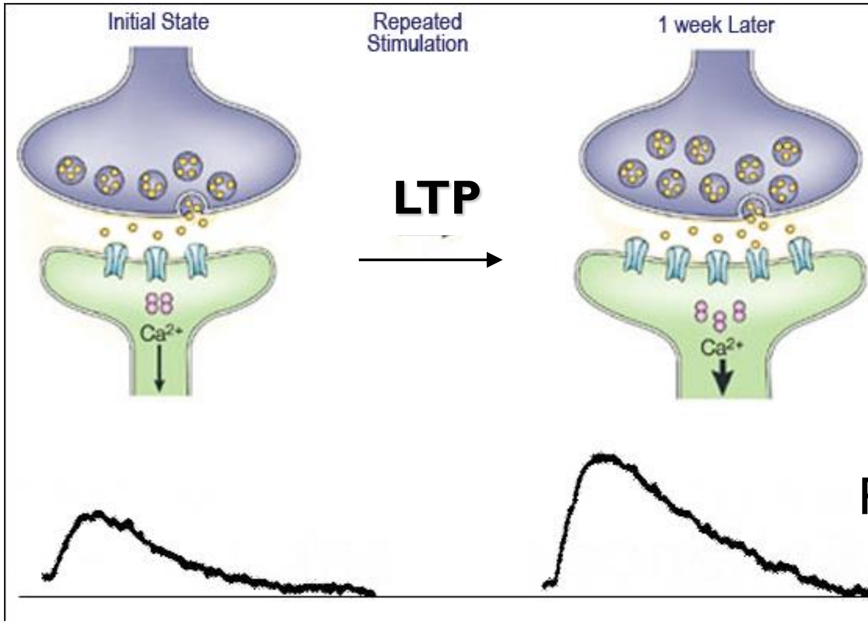
Neurons that fire together, wire together

"When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes place in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased."

Hebb Rule and Biology

Long-term potentiation

https://sites.google.com/site/mcauliffeneur493/home/synaptic-plasticity/Long-Term-Potentiation1.jpg?attredirects=0



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

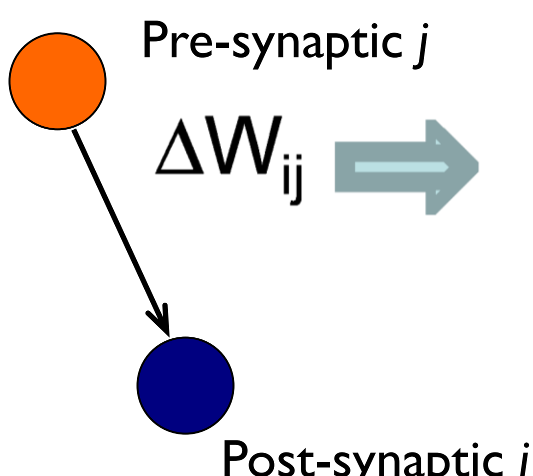
Persistent increase in synaptic strength after brief high-frequency stimulation of synapse

Spike-timing dependent plasticity

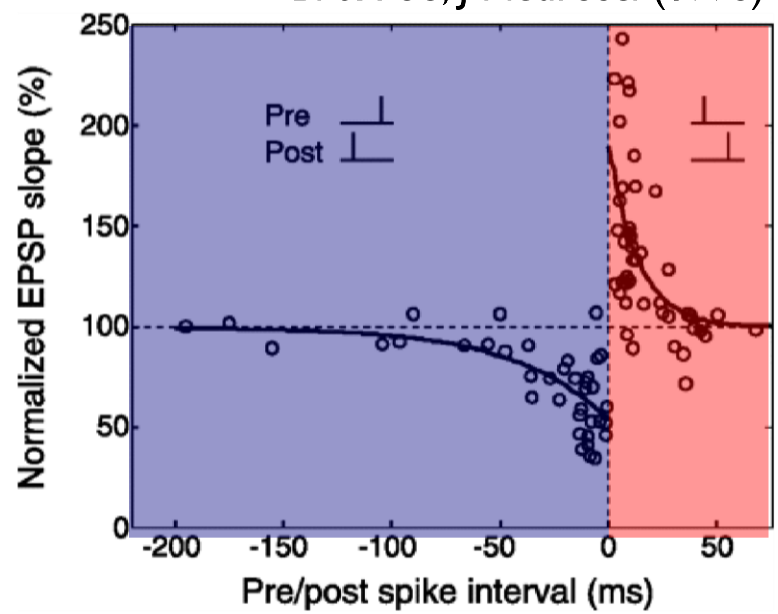
spike-based formulation of Hebb rule

(Markram, 1995)

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



Bi & Poo, J Neurosci (1998)



Learning in Hopfield Network

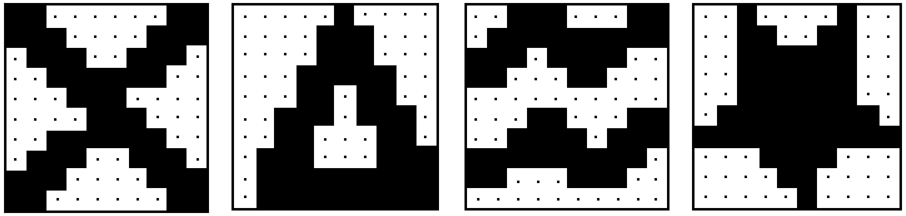
Implementing Hebb rule in synaptic weight determination

"One-shot" learning

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

ξ_i^p : state of i^{th} neuron in the p^{th} pattern

Four stored patterns in simulation

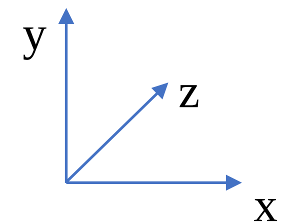


"■" i^{th} neuron is ON $\xi_i = +1$

"·" i^{th} neuron is OFF $\xi_i = -1$

Example of Hopfield Model: N=3, p=2

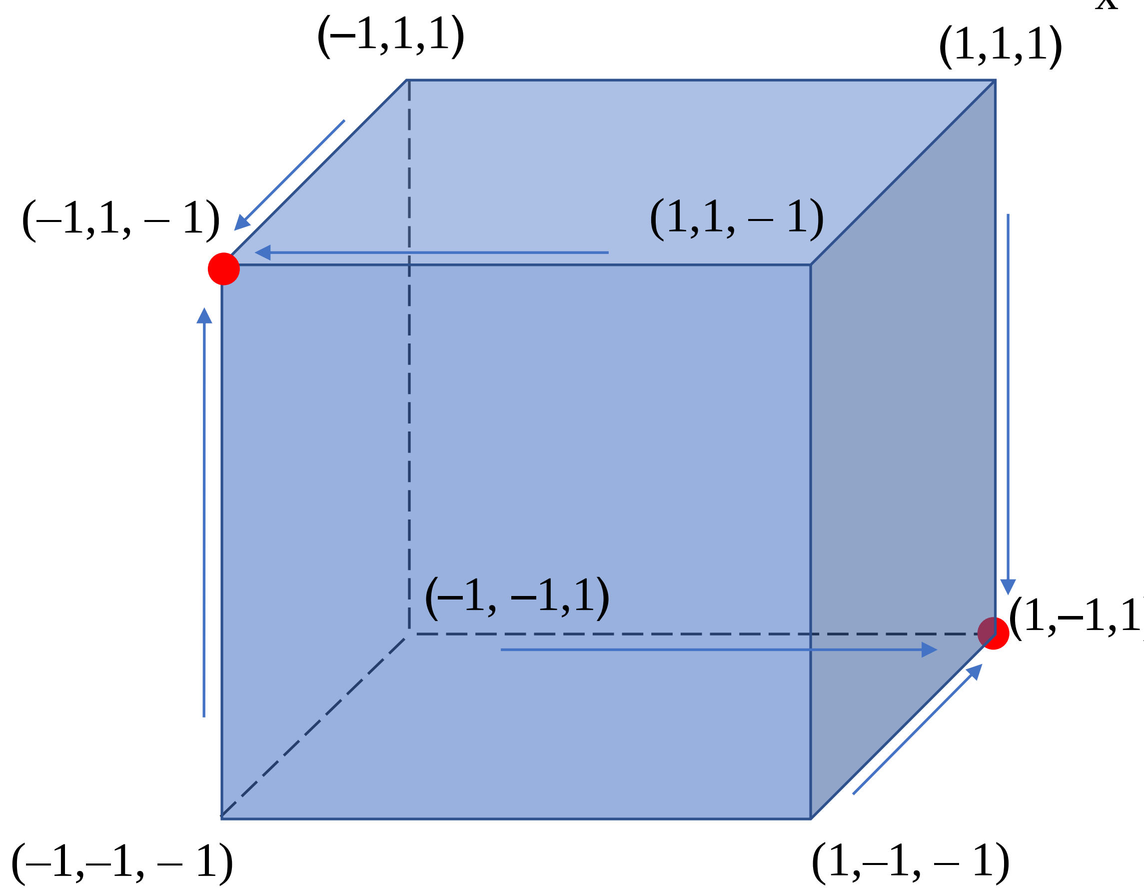
The strings $(1,-1,1)$ and $(-1,1,-1)$ are the stored patterns
Have to be made attractors of the dynamics



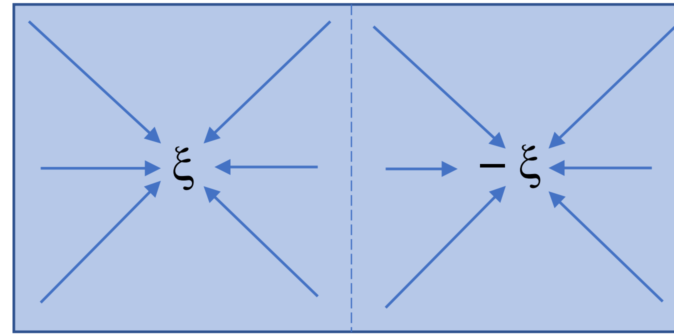
$$w_{ij} = \frac{1}{N}\sum_{p=1}^{M} \xi_i^p \xi_j^p$$

$$w_{ii} = 0$$

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



One pattern (p=1)



ξ_i : pattern memorized

For the pattern to be stable, $\mathrm{sgn}(\sum_j w_{ij}\, \xi_j) = \xi_i$ for all i

This is true if $w_{ij} \propto \xi_i\, \xi_j$ as $\xi_i^2 = 1$

(the proportionality constant being 1/N)

If M out of N components of the initial state S_i are wrong (opposite to ξ_i)

the input $h_i \equiv \mathrm{sgn}(\sum_j w_{ij}\, S_j) = \mathrm{sgn}(\underbrace{\sum_k w_{ik}\, \xi_k}_{\text{Same sign as } \xi} - \underbrace{\sum_m w_{im}\, \xi_m}_{\text{Opposite sign to } \xi})$

will converge to output same as the stored pattern ξ if $M < N/2$

$\Rightarrow$ Network will correct errors in the initial pattern and converge to ξ, the attractor of the recall dynamics

Many patterns (p>1)

ξ_i^μ (μ=1, …, p): patterns memorized

A natural extension is to make w_{ij} a superposition of terms – one for each pattern $w_{ij} \propto \sum_{\mu=1,p} \xi_i^\mu \xi_j^\mu$

For a particular pattern ξ_i^ν to be stable, $\mathrm{sgn}(\sum_j w_{ij} \xi_j^\nu) = \xi_i^\nu$ for all i

the input $h_i \equiv \sum_j w_{ij} \xi_j^\nu$

$$= (1/N)\sum_j\sum_\mu \xi_i^\mu\xi_j^\mu\xi_j^\nu = \underbrace{\xi_i^\nu}_{\text{Desired pattern}} + \underbrace{(1/N) \sum_j\sum_{\mu\neq\nu} \xi_i^\mu\xi_j^\mu\xi_j^\nu}_{\text{Crosstalk term}}$$

will converge to output same as the stored pattern if the magnitude of the crosstalk term < 1 (true for small p)

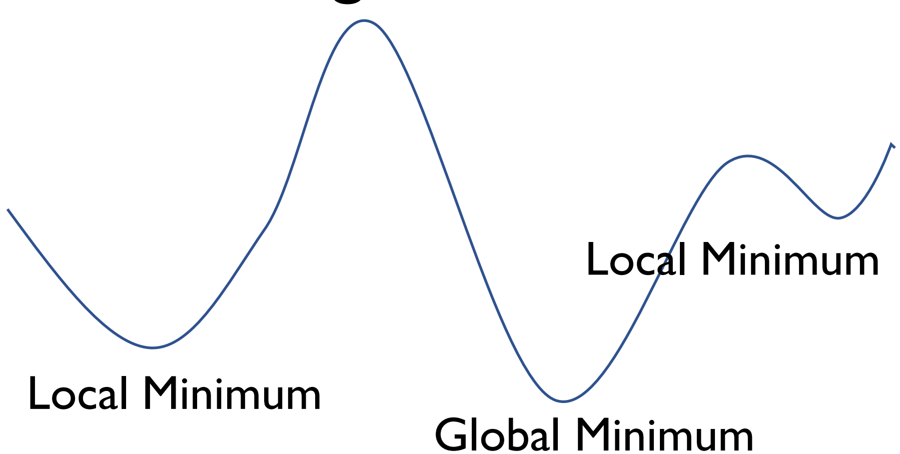
$\Rightarrow$ Network will correct errors in any initial pattern sufficiently close to any of the stored patterns ξ^μ (multiple attractors)

Memory Recall in 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 a local/global minimum of *E*



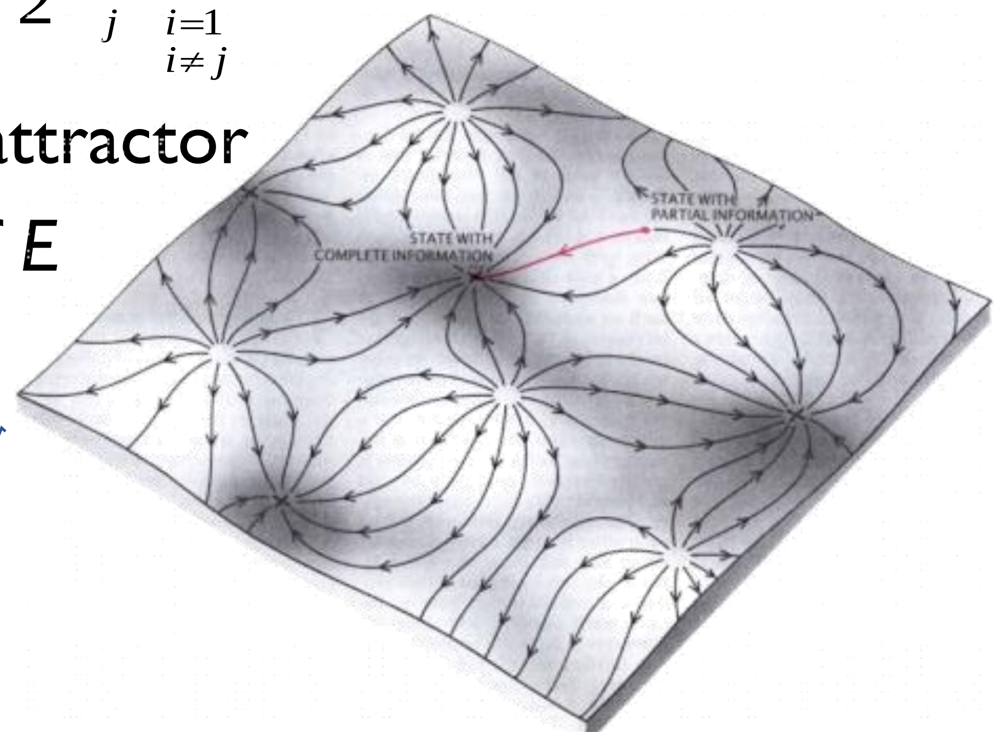


Image: Tank & Hopfield, Scientific American (1987)

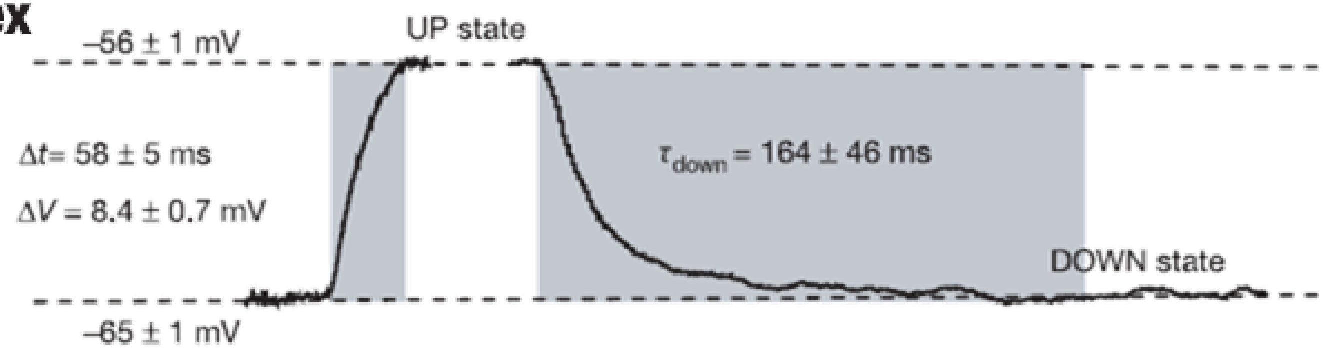
Attractor networks in the neocortex

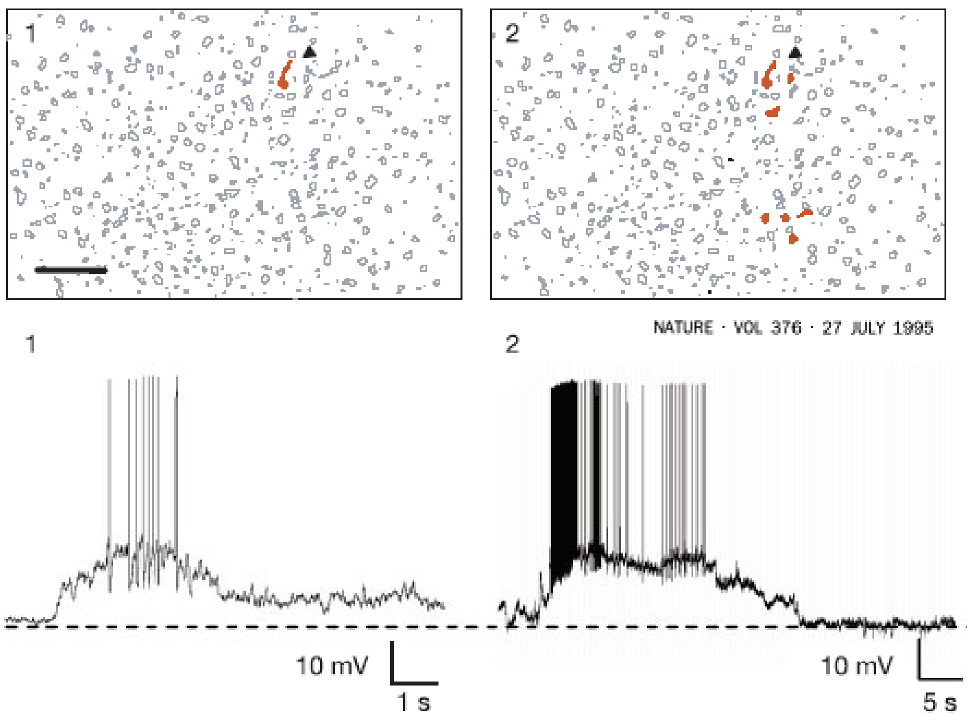
Attractor dynamics of network UP states in the neocortex

Rosa Cossart, Dmitriy Aronov & Rafael Yuste

NATURE | VOL 423 | 15 MAY 2003 |

Using two-photon calcium imaging reconstructed dynamics of spontaneous activity of ~1400 neurons in mouse visual cortex slices





NATURE · VOL 376 · 27 JULY 1995

"the membrane potential of cortical neurons fluctuates spontaneously between a resting (DOWN) and a depolarized (UP) state which may also be coordinated. The elevated firing rate in the UP state follows sensory stimulation and provides a substrate for persistent activity … that might mediate working memory."

"network UP states are circuit attractors …that could implement memory states or solutions to computational problems."

Storage capacity of the Hopfield Model

Paramagnetic: the state fluctuates all the time

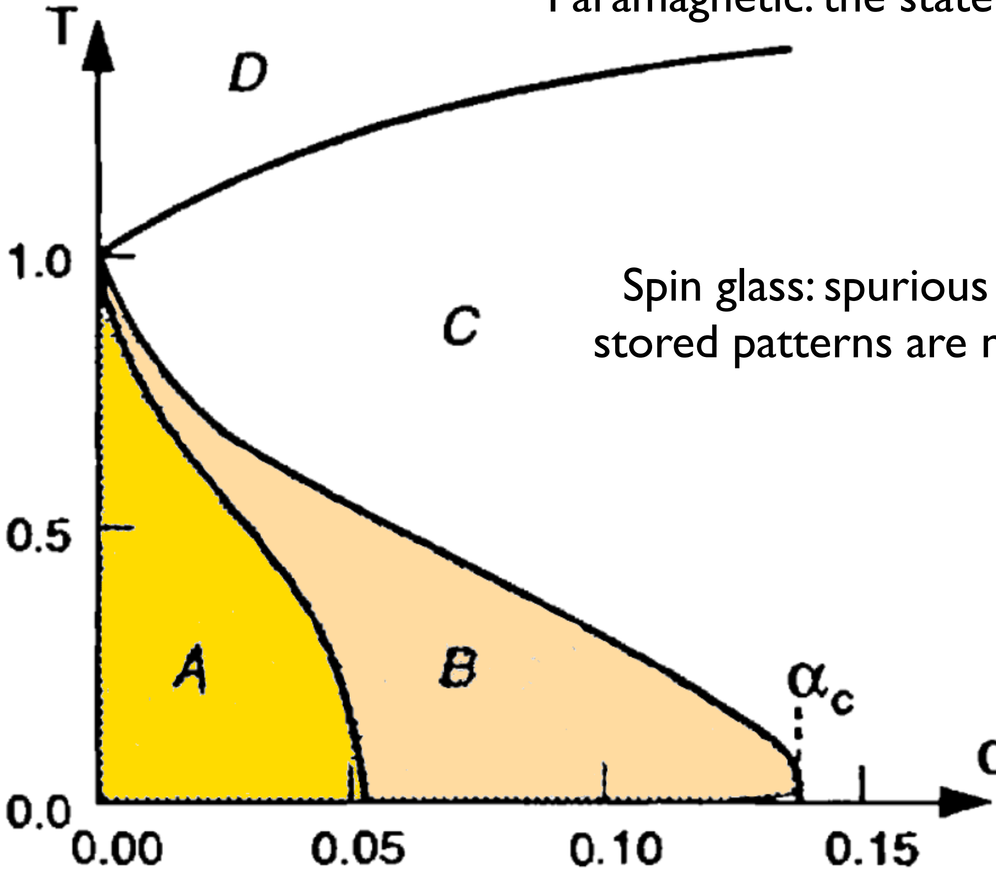
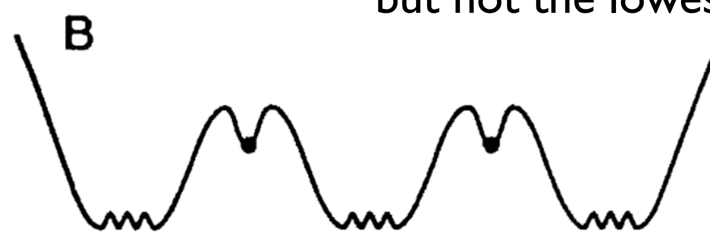


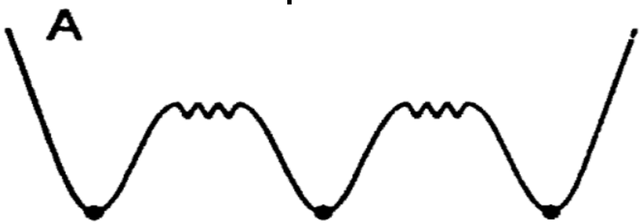
Image: Hertz, Krogh & Palmer, *Introduction to the Theory of Neural Computation*, 1990

Spin glass: spurious attractors;
stored patterns are not minima

Metastable : stored patterns are minima
but not the lowest



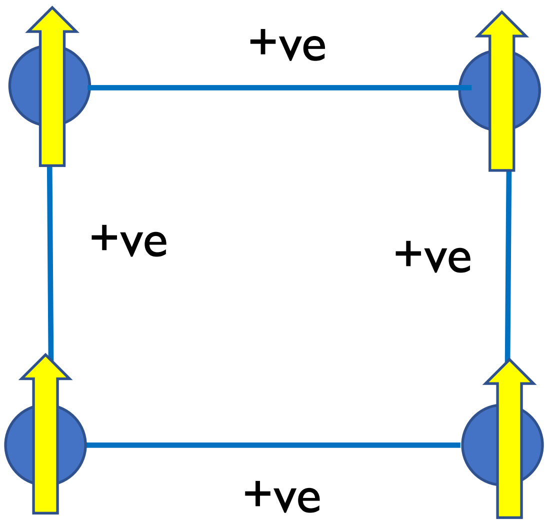
Recall : stored patterns are lowest minima

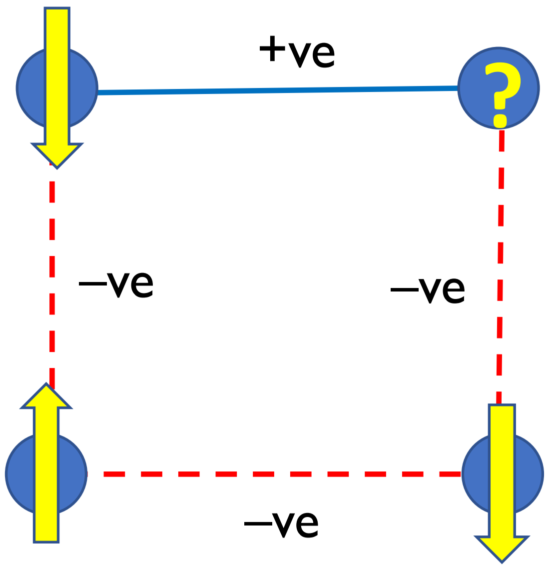


Frustration (Absence of structural balance)

Conflicting Constraints in Disordered Systems

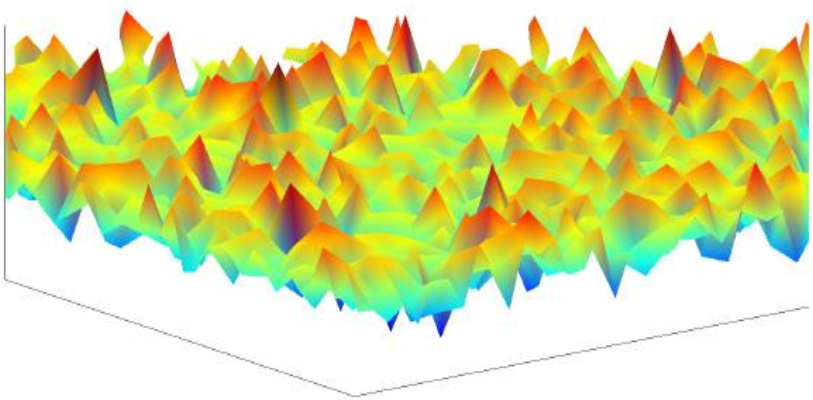
Spins in binary states $(+1/-1)$ having +/ – interactions at random



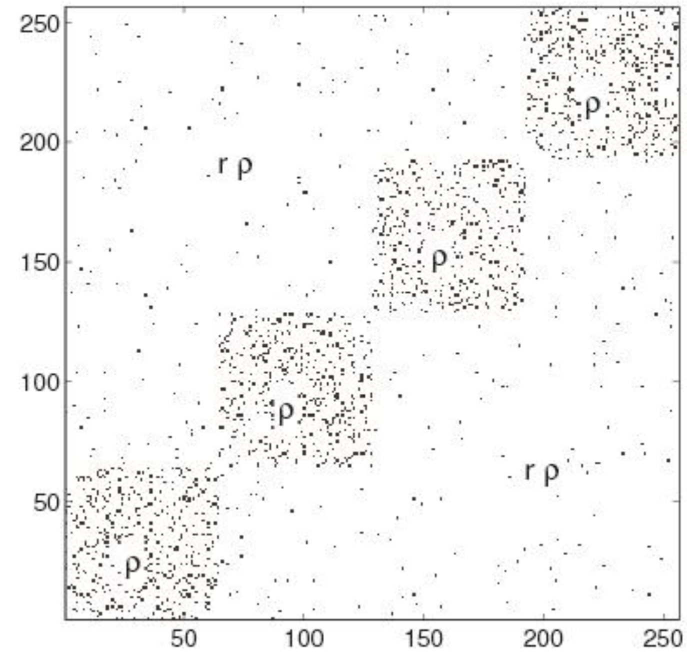


Frustration results in a rugged energy landscape, with the system trapped in any one of a large number of local minima (spin glass states)

Absence of frustration would correspond to a smooth energy landscape having a global minmum



Does mesoscopic network structure (in particular, modular organization) alter the dynamics of recall in an attractor network ?



Yes.

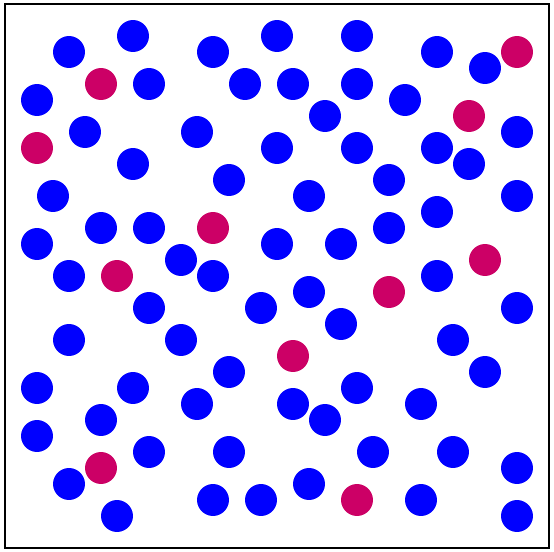
The convergence to an attractor corresponding to any of the stored patterns (recall) is most efficient when the network has an

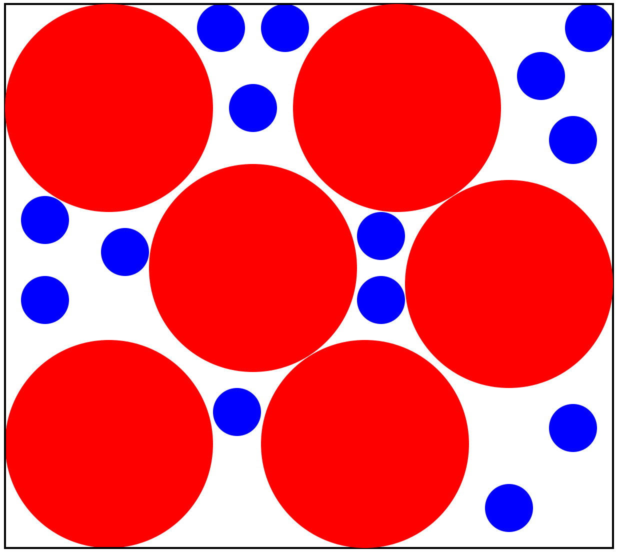
optimal modular structure ($r \approx r_c$)

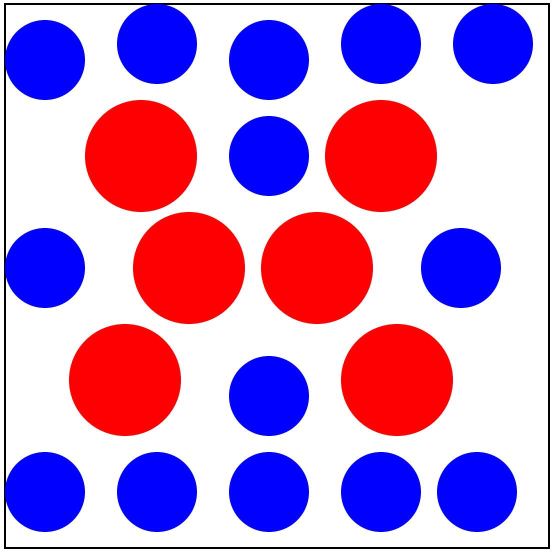
for storing multiple patterns in a network with *N* nodes and *L* links

The attractor landscape of the network changes with modularity

Isolated Modules	Modular	Homogeneous
$r << r_c$	$r \approx r_c$	$r = 1$
High-basin entropy	Low-basin entropy	High-basin entropy







Low *r*: "Chimera" attractors

In a network of isolated modules, randomly chosen initial states mostly converge to a *chimera* attractor state

Chimera attractor: a <u>stable</u> state comprising sub-parts of stored patterns belonging to different modules

Example: 2 stored patterns (colored blocks: modules)

$$\xi^1 = [\,1\ 1\ 1\ 1 \quad 1\ 1\ 1\ 1 \quad -1\ -1\ -1\ -1 \quad -1\ -1\ -1\ -1\,]$$
$$\xi^2 = [\,1\ 1\ 1\ 1 \quad -1\ -1\ -1\ -1 \quad 1\ 1\ 1\ 1 \quad -1\ -1\ -1\ -1\,]$$

A possible chimera state is

$$[\,1\ 1\ 1\ 1\ \ 1\ 1\ 1\ 1\ \ 1\ 1\ 1\ 1\ \ -1\ -1\ -1\ -1\,]$$

As *r* increases, these states become less likely via a percolation-like transition

High r : Mixed states

For more homogeneous networks, most attractors correspond to stored patterns or mixed states (mixture of the patterns)

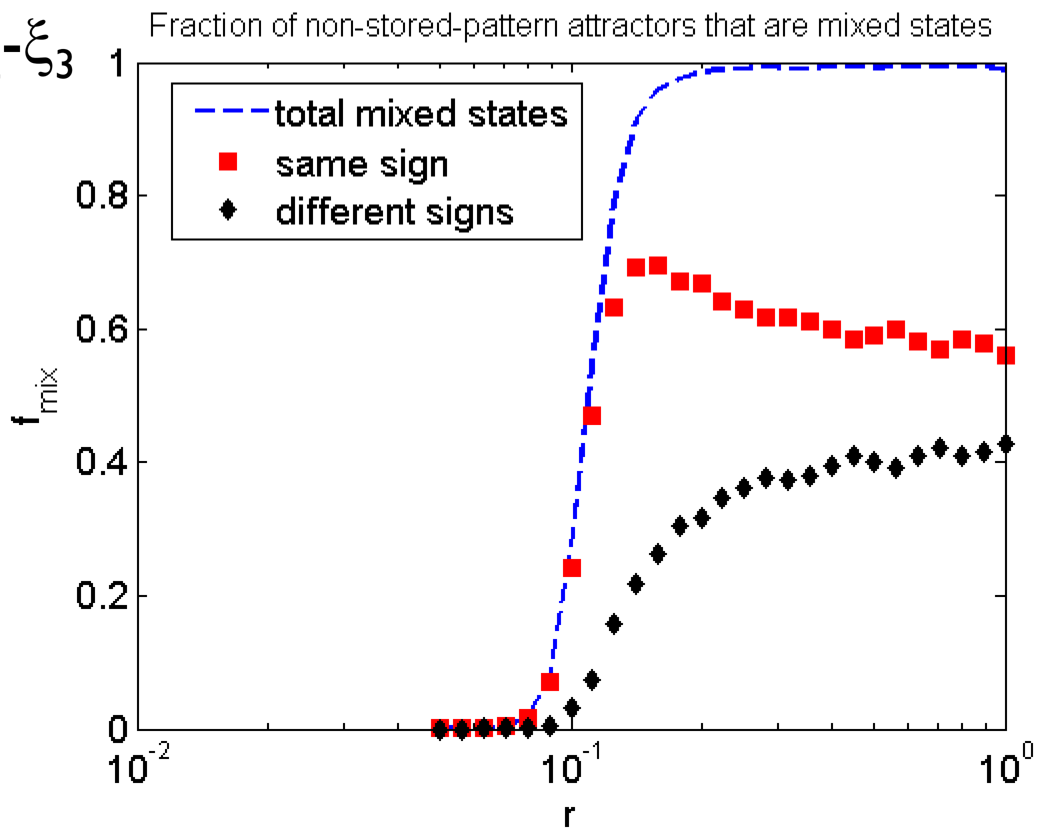
Mixed states can be linear combinations of

(A) same sign e.g. $\xi_1+\xi_2+\xi_3$

(B) different signs e.g. $\xi_1-\xi_2-\xi_3$

stored patterns, p = 4

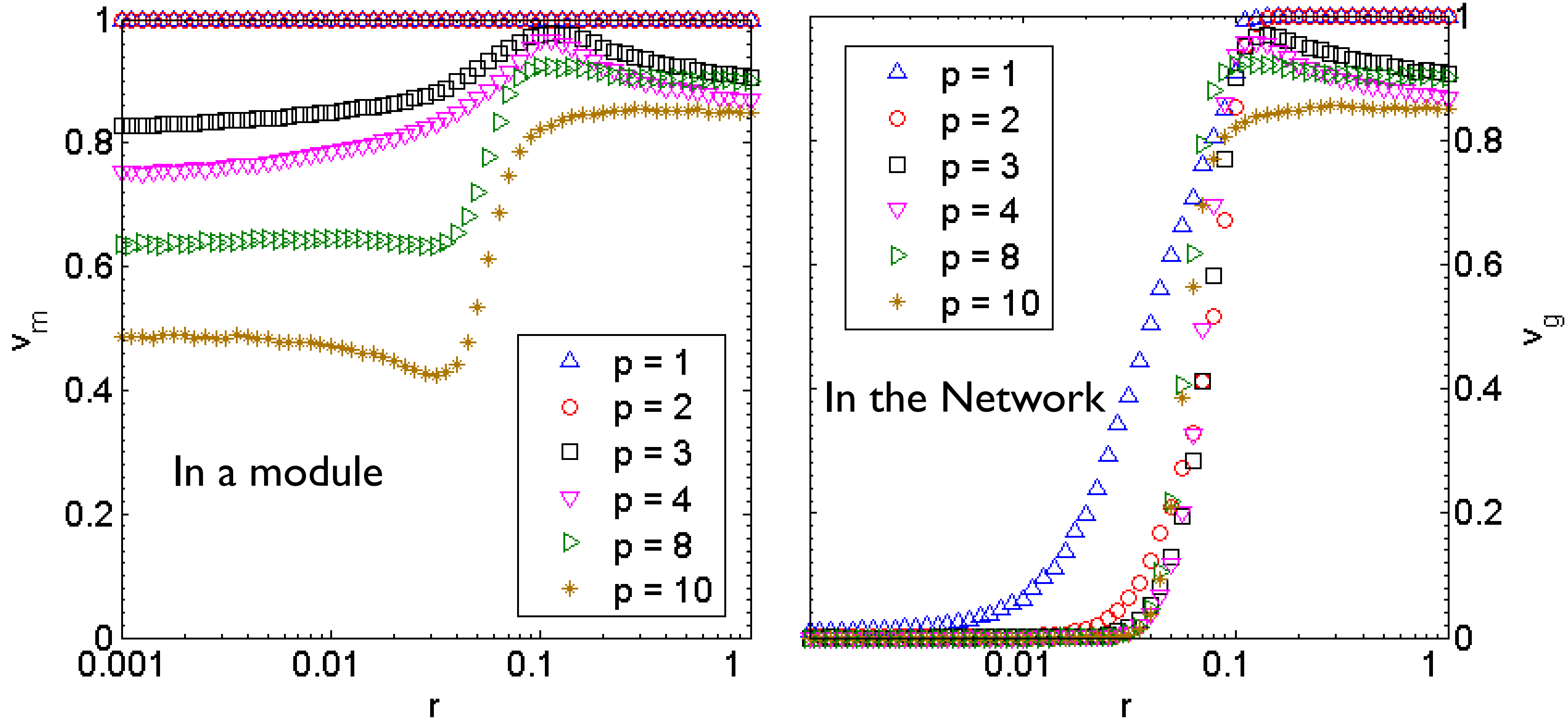
N=1024, n=128, <k> = 120



Basins of attraction of mixed states cover <u>smallest fraction</u> of phase space of network dynamics for *optimal value* of modularity r_c

Size of basins of attraction of stored patterns, *v*…

N=1024, n=128, <k> = 120

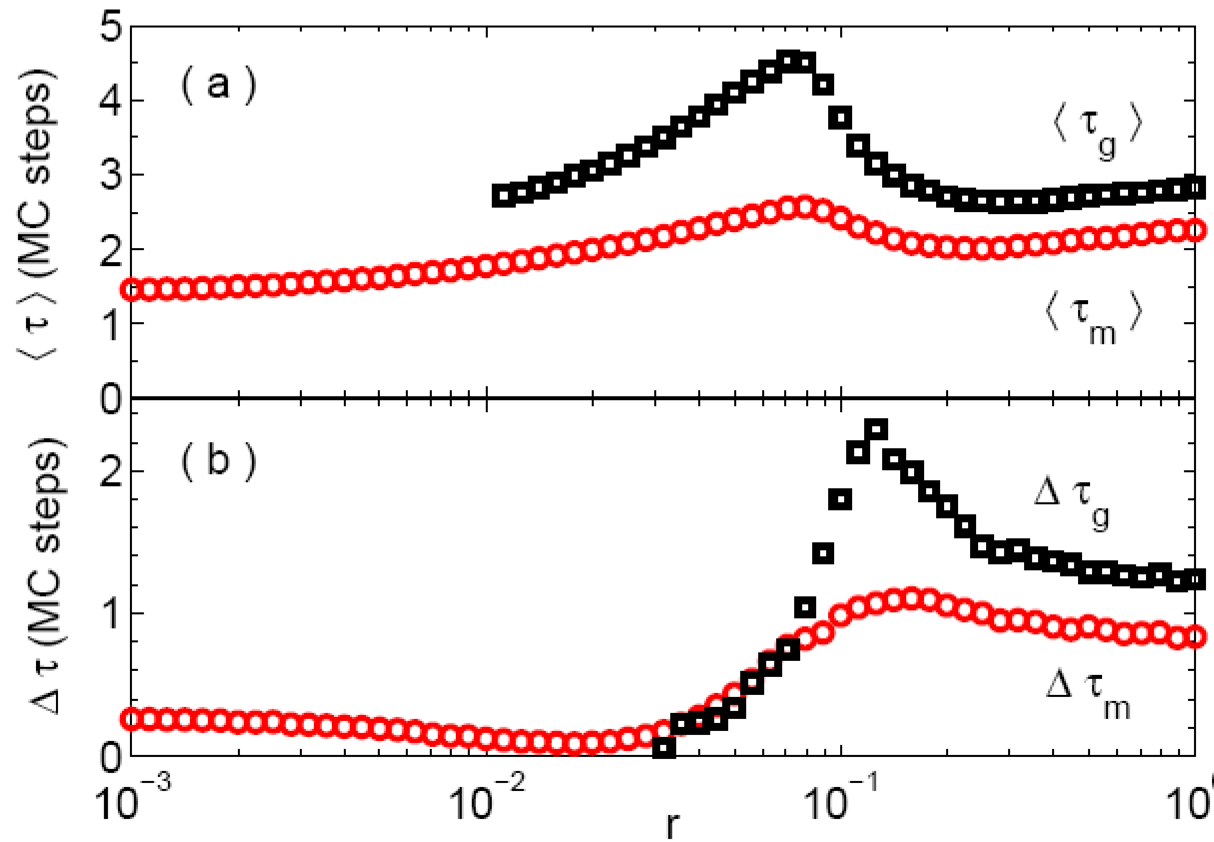


…exhibit <u>non-monotonic</u> variation with modularity parameter, *r*

Largest at optimal value $r_c \sim (n-1)/(N-n) \sim 0.14$

At optimal modularity, time of convergence to stored patterns faster than that to mixed states

# stored patterns, p = 4
N=1024, n=128, <k> = 120



Multiple time-scales in a modular network ⇒
Fast convergence to a stored sub-pattern within a module + slower convergence at network level