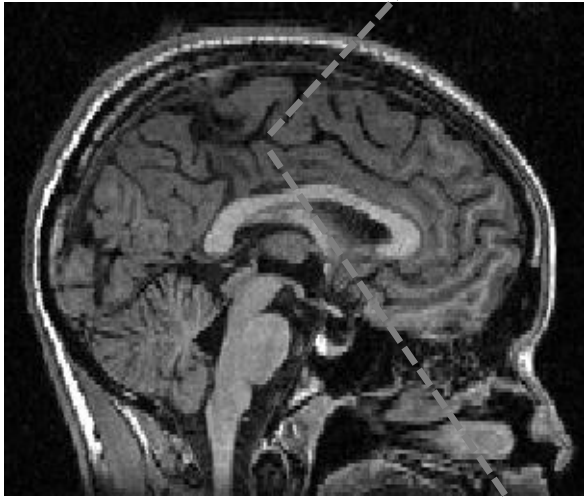

Synapses and synaptic plasticity

COSC422 – lecture 8

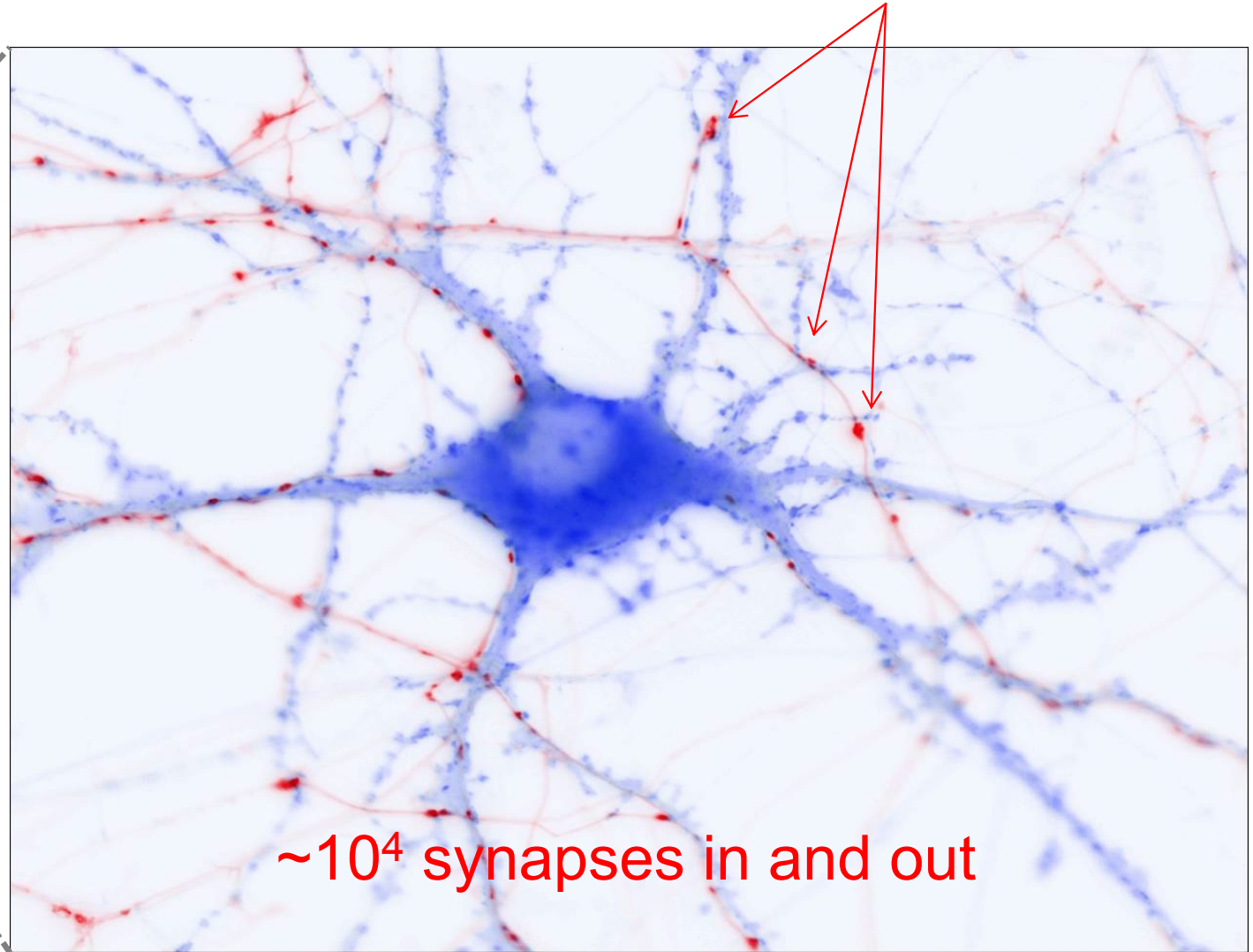
How neurons communicate

How do we learn and remember

Brain is comprised of networks of neurons connected and communicating via synapses

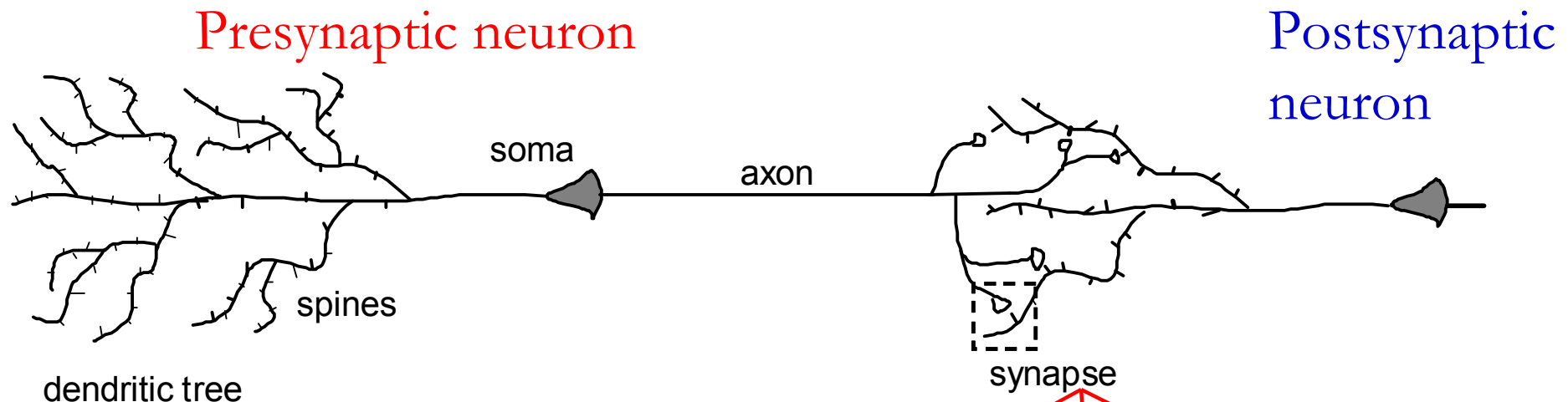


$\sim 10^{12}$ neurons

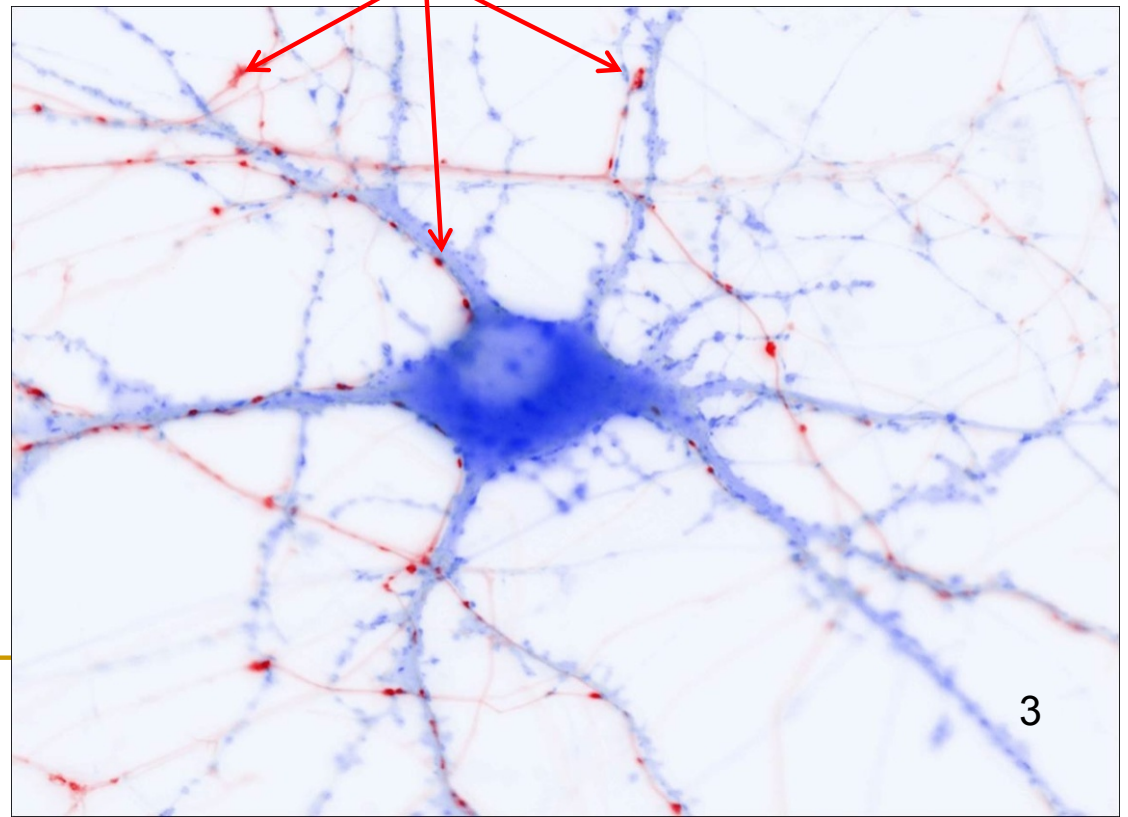


$\sim 10^4$ synapses in and out

Presynaptic and postsynaptic neurons

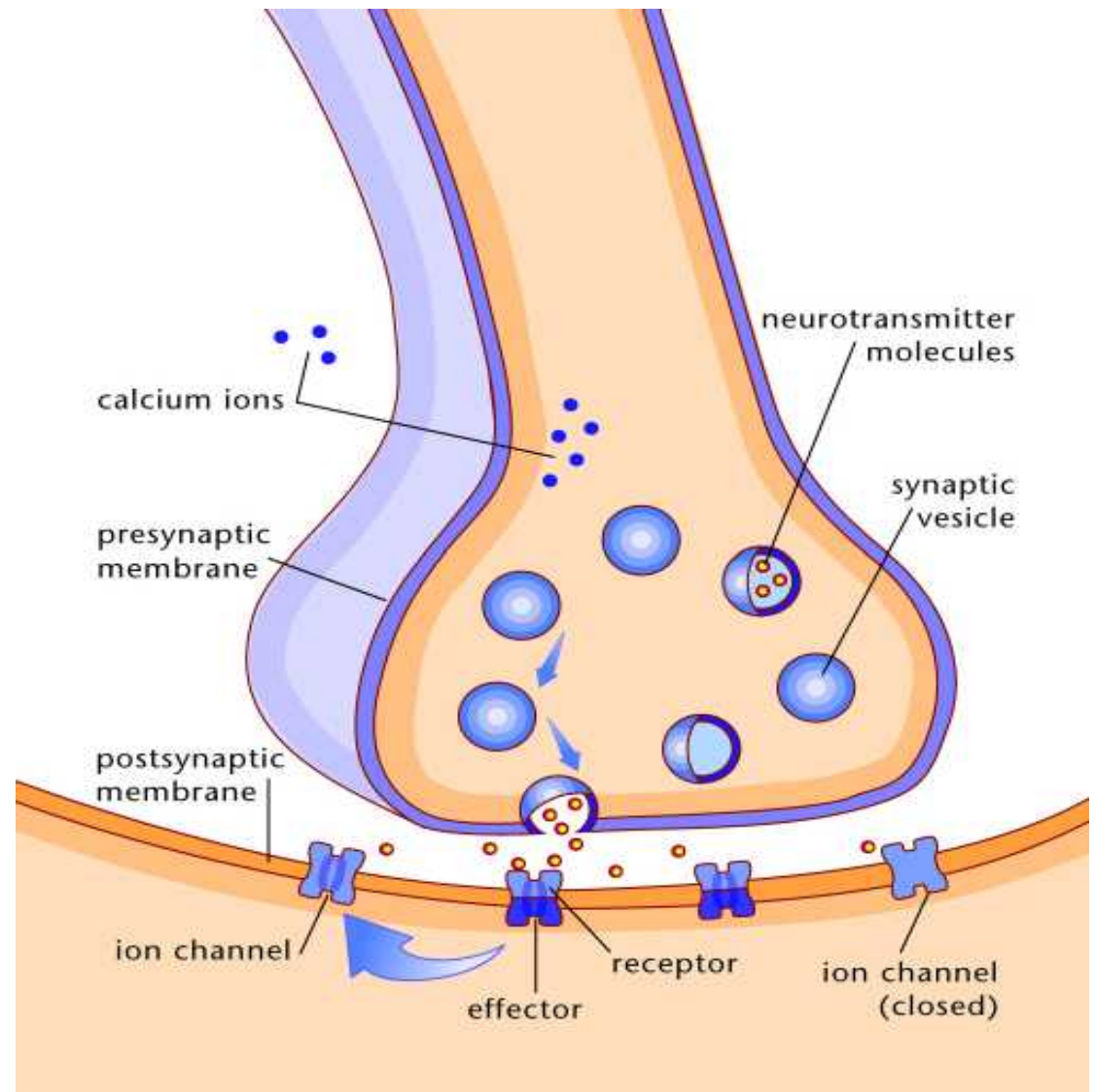


Axons of **presynaptic** neurons make synapses (little blobs) on the soma and dendrites of the **postsynaptic** neuron(s).



Synapse: from Greek “sunapsis”, point of contact

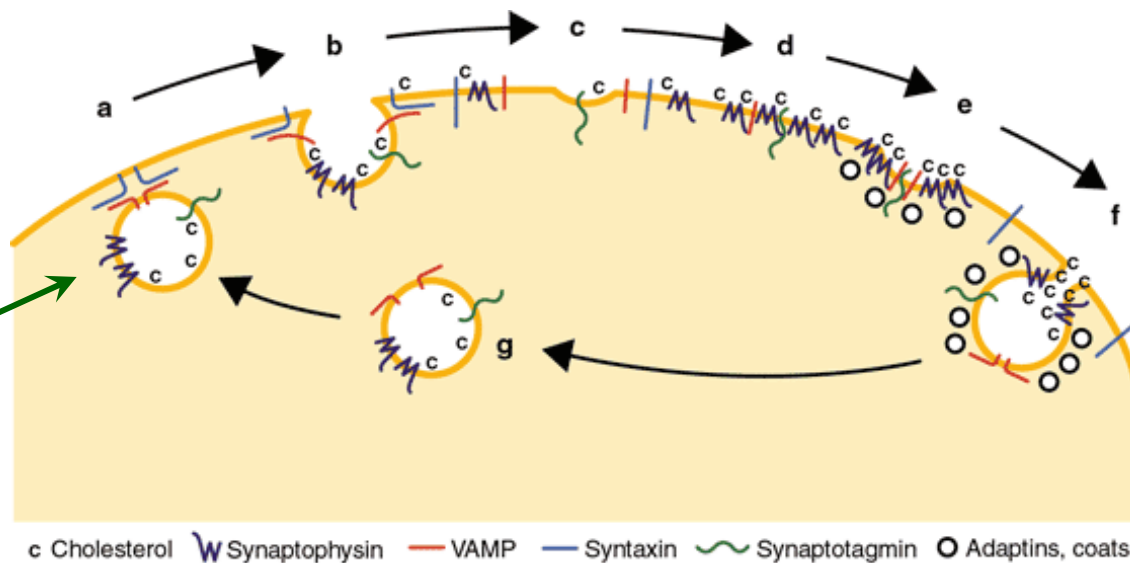
- Synapse consists of 3 parts:
 - Presynaptic terminal – contains vesicles filled with **neurotransmitter**.
 - Synaptic cleft – filled with tiny filaments that attach terminal to the postsynaptic neuron (they r not shown).
 - Postsynaptic membrane contains – **receptors** associated with **various effectors**, passive and voltage-gated ion channels.



Role of calcium in release of presynaptic vesicles

- When presynaptic spike (action potential, AP) arrives at the presynaptic terminal, voltage-gated ion channels for calcium in the terminal's membrane open and let ions of Ca^{2+} enter to the terminal.
- Calcium triggers a chain of processes that lead to the fusion of vesicles with the membrane and release of their content into the synaptic cleft.

Influx of calcium triggers fusion (exocytosis)



Vesicles are “recycled” while re-uptaking the neurotransmitter from the cleft (note: molecules of neurotransmitter are not shown here)

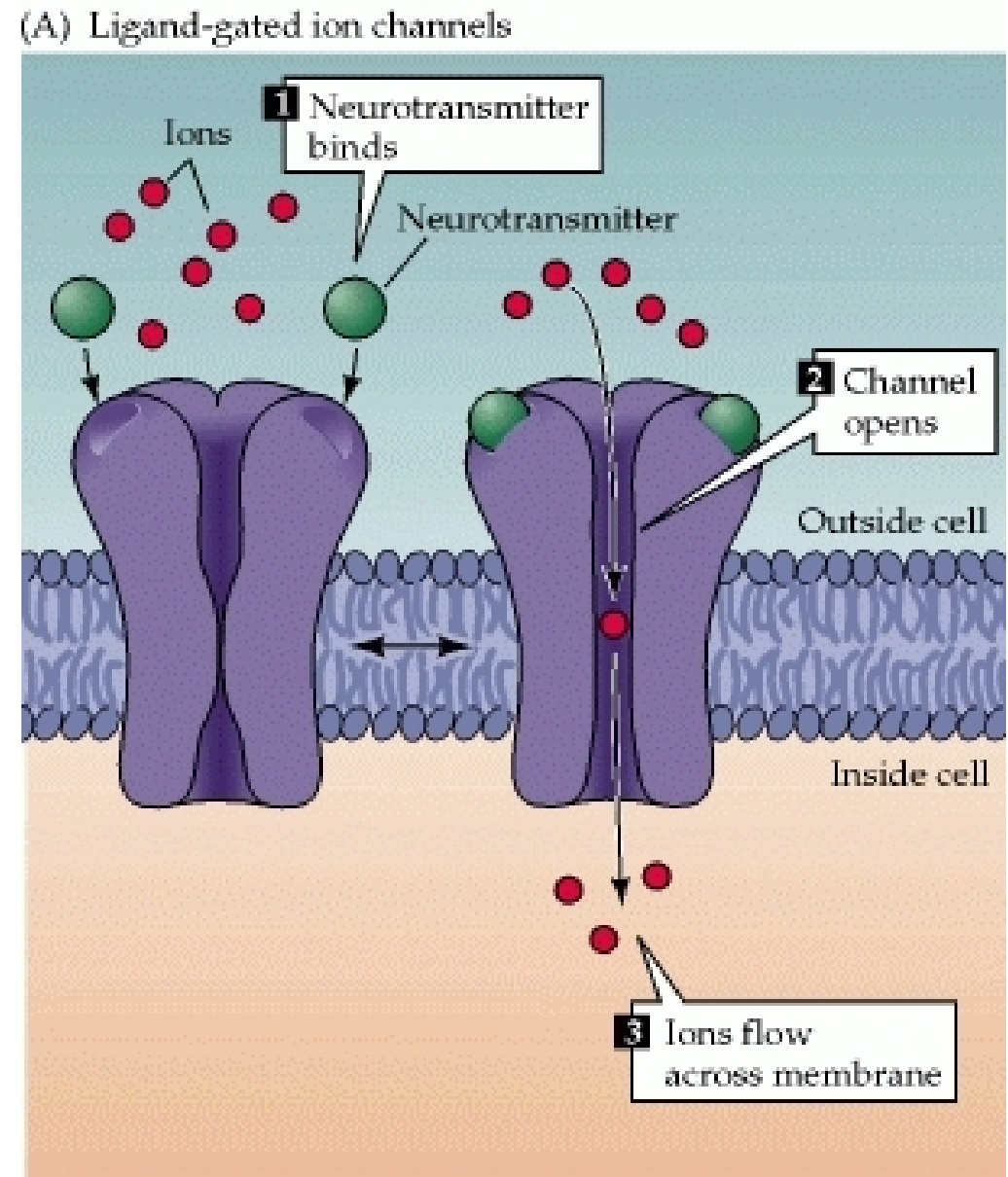
Presynaptic release of vesicles is probabilistic

- One vesicles contains around 10^4 molecules of neurotransmitter. We consider the content of one vesicle to be one “quantum” of neurotransmitter.
- When presynaptic spike (action potential, AP) arrives at the presynaptic terminal, x number of vesicles release their content.
- When we denote by m the average (mean) number of vesicles released per one AP, then the probability that one arriving AP causes release of x vesicles is Poissonian, i.e.

$$P(x) = \frac{m^x}{x!} e^{-m}$$

Neurotransmitter binds to postsynaptic receptors

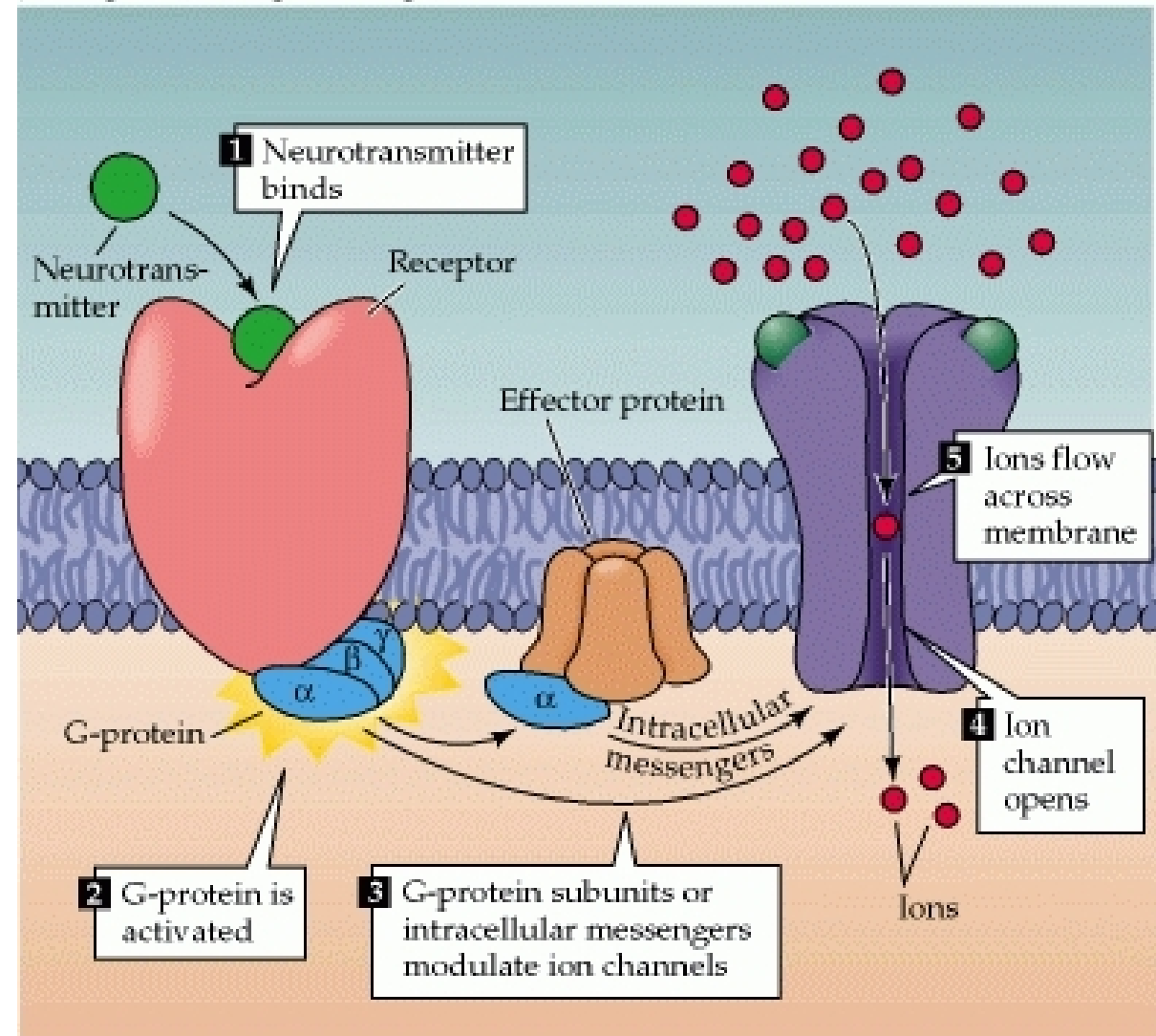
- Postsynaptic receptors are associated with ion channels, in fact they form one big molecule.
- When neurotransmitter (ligand) binds to the receptor part, that opens the ion channel.
- Receptors are specific for given neurotransmitter and ion channels are specific for concrete ions.
- Ions that are allowed to move through the channel then flow in or out (according to electro-chemical gradient).



G-protein coupled receptors

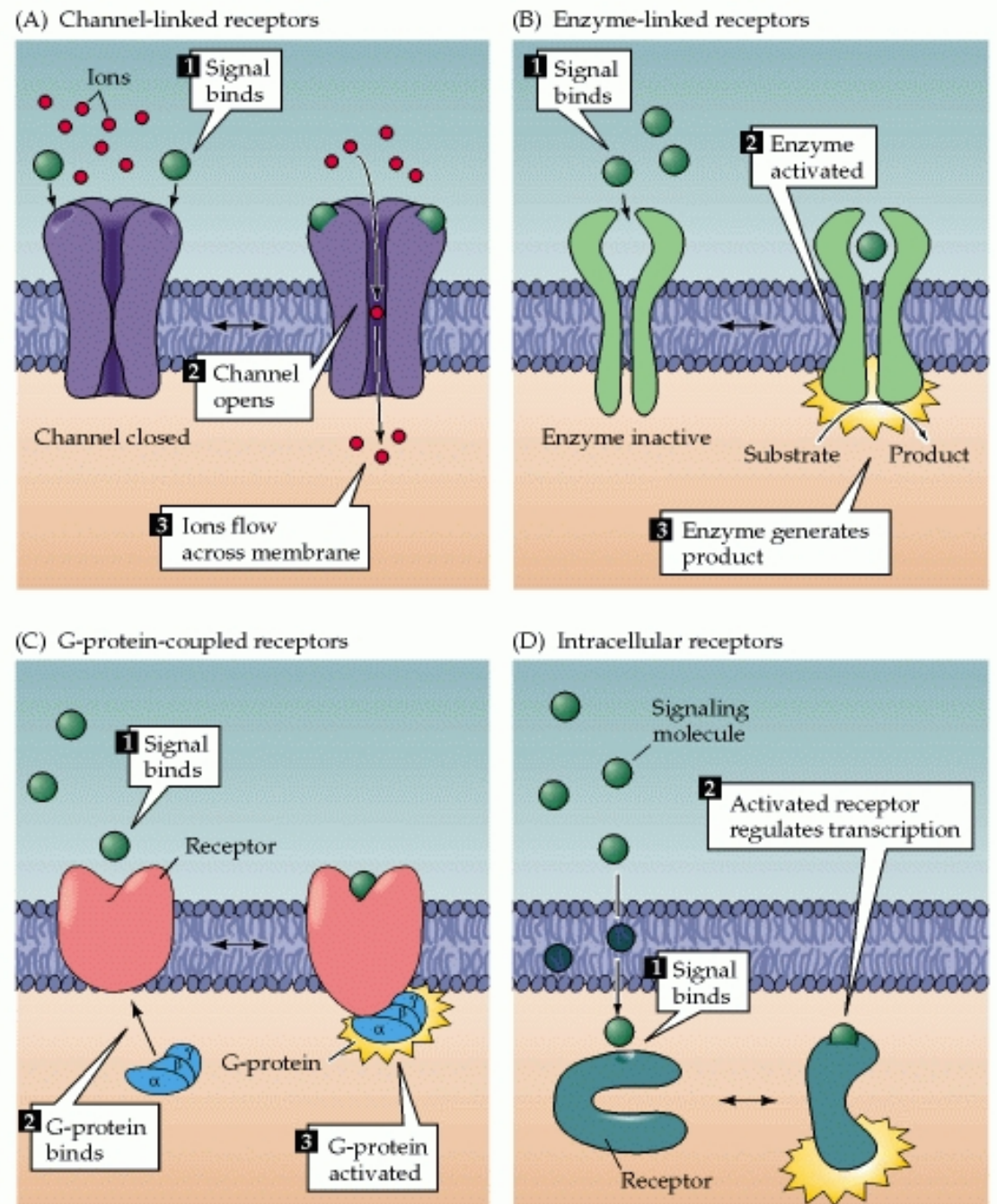
- Many types of receptors are not associated with ion channels.
- Instead they are associated with the so-called G-protein.
- G-protein activates various messengers that in turn modify the permeability of the nearby ion channels.

(B) G-protein-coupled receptors



Neurotransmitters

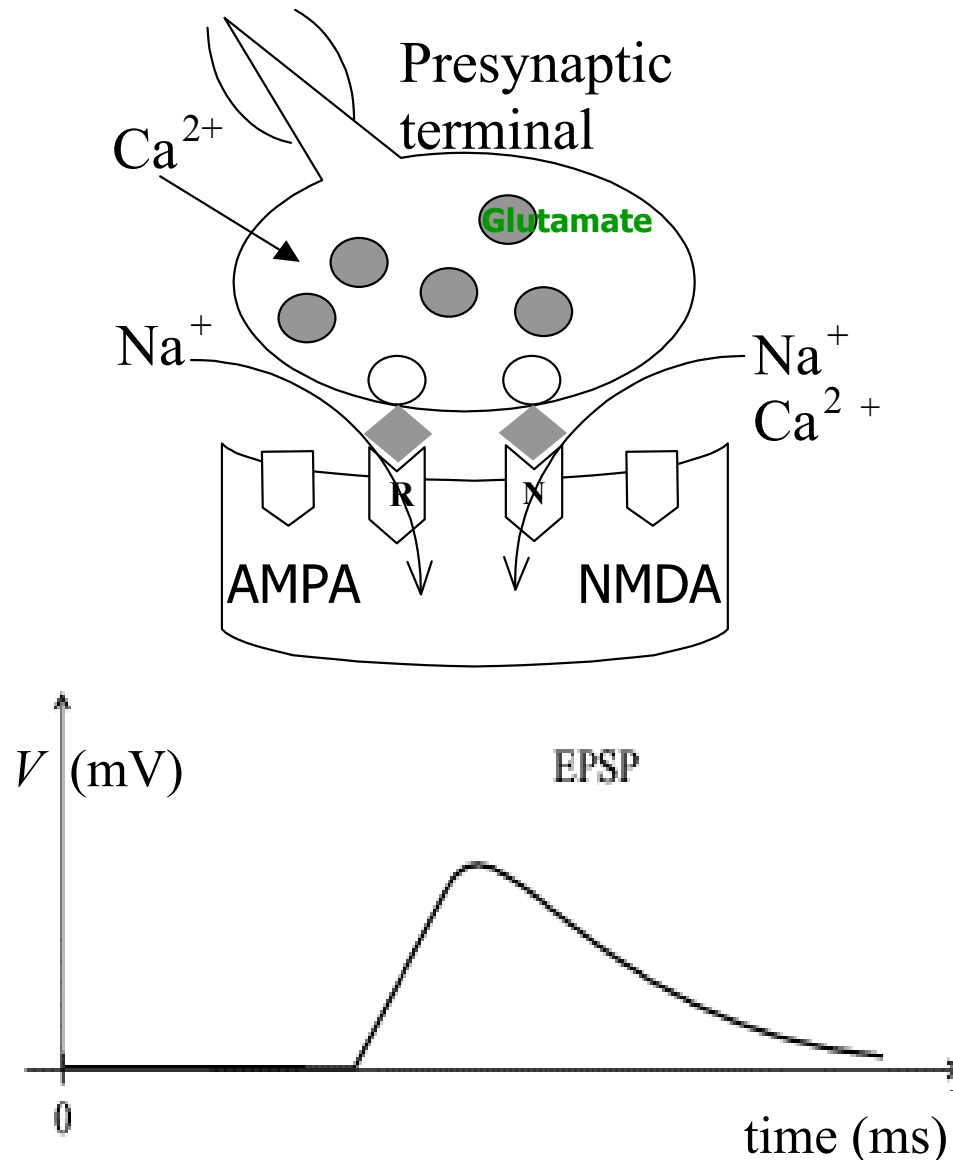
- There are about 50 different neurotransmitters in the brain.
- They act through the receptors associated with ion channels and also receptors associated with messengers, thus influencing neurotransmission of the same or other neurotransmitter(s).
- There can be several types of receptors in the PSP membrane for one neurotransmitter.



Receptor/ion channels: excitation versus inhibition

- When nothing is happening postsynaptic membrane is polarized at $V_0 \cong -65$ mV (the resting potential).
- If the neurotransmitter interacts with receptor/ion channels that cause **depolarization** of the postsynaptic membrane towards positive values – then we speak about **excitation**.
 - Major excitatory neurotransmitter in the brain is **glutamate (Glu)**.
- If the neurotransmitter interacts with receptor/ion channels that cause **hyper-polarization** of the postsynaptic membrane towards more negative values – then we speak about **inhibition**.
 - The major inhibitory neurotransmitter in the brain is γ -aminobutyric acid (**GABA**).

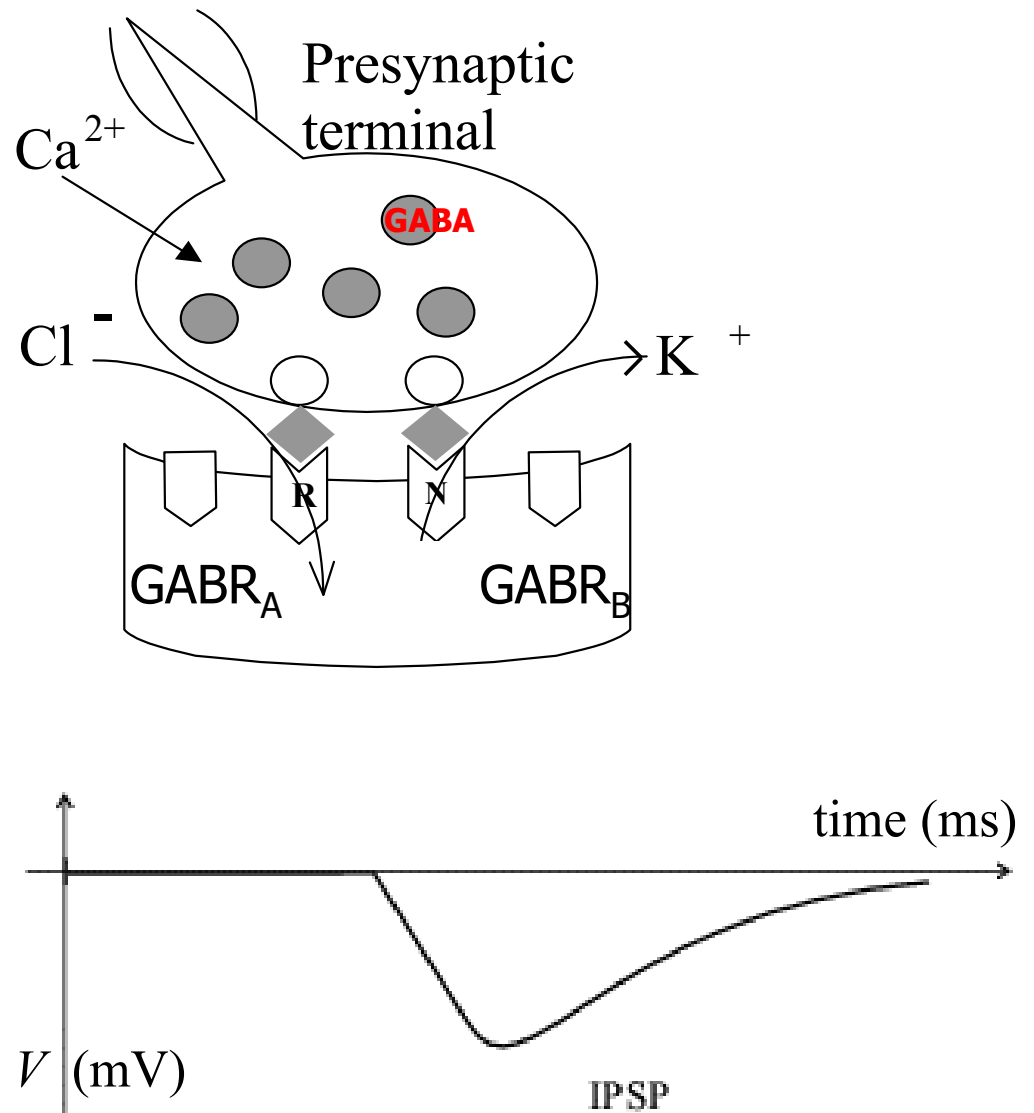
Excitatory synapses



- Neurotransmitter: **glutamate**.
- Postsynaptic receptors associated with ion channels are called AMPAR and NMDAR, (there are also metabotropic receptors there that are not associated with ion channel).
- When we measure the electric potential at the postsynaptic membrane, we see a positive deviation from the resting potential, which is called **excitatory postsynaptic potential (EPSP)**.

Inhibitory synapses

- Neurotransmitter: **GABA**
- Postsynaptic receptors **GABRA** and **GABRB**, ion channels for K^+ and Cl^-
- When we measure the electric potential at the postsynaptic site, we see a negative deviation from the resting potential, which is called **inhibitory postsynaptic potential (IPSP)**.



Postsynaptic potential (PSP)

- PSP (either EPSP or IPSP) is the result of electric current I that flows through the receptor-fated ion channels and obeys the equation:

$$I_{syn}(t) = g_{syn}(t)(V(t) - E_{syn})$$

- Where the effect of neurotransmitter binding to and opening the postsynaptic receptors/ion channels is a conductance change, g_{syn} , in the postsynaptic membrane.
- V is the current (momentary) value of transmembrane potential,
- E_{syn} is the reversal potential of those ion channels (Na, K, Cl, Ca) that mediate the synaptic current in the postsynaptic membrane.

Model functions for postsynaptic potential (PSP)

- To model the time course of postsynaptic conductance change for the time t after arrival of presynaptic spike t_s , we use these waveforms:

- Single exponential decay:
$$g_{syn}(t) = g_{max} \exp\left(-\frac{t-t_s}{\tau}\right)$$

- Alpha function (Rall, 1967):
$$g_{syn}(t) = g_{max} \frac{t-t_s}{\tau} \exp\left(-\frac{t-t_s}{\tau}\right)$$

- Dual (double) exponential function:

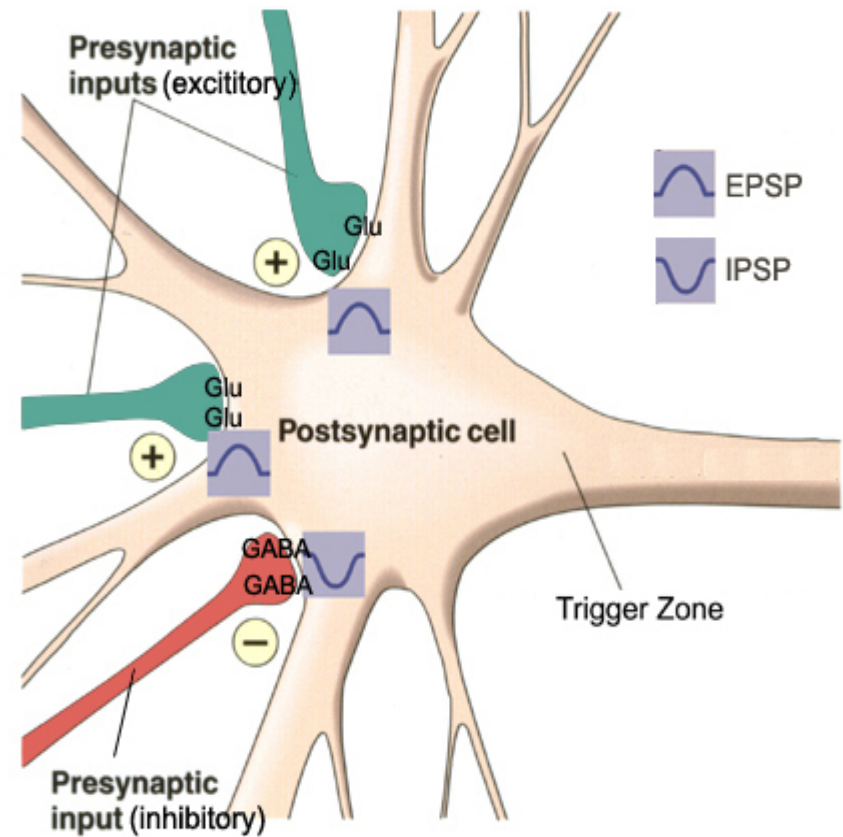
$$g_{syn}(t) = g_{max} \frac{\tau_1 \tau_2}{\tau_1 - \tau_2} \left[\exp\left(-\frac{t-t_s}{\tau_1}\right) - \exp\left(-\frac{t-t_s}{\tau_2}\right) \right]$$

Summation of EPSPs and IPSPs in space

- Let's have only the synapses on the soma. The total synaptic conductance change is the sum of individual waveforms, i.e.:

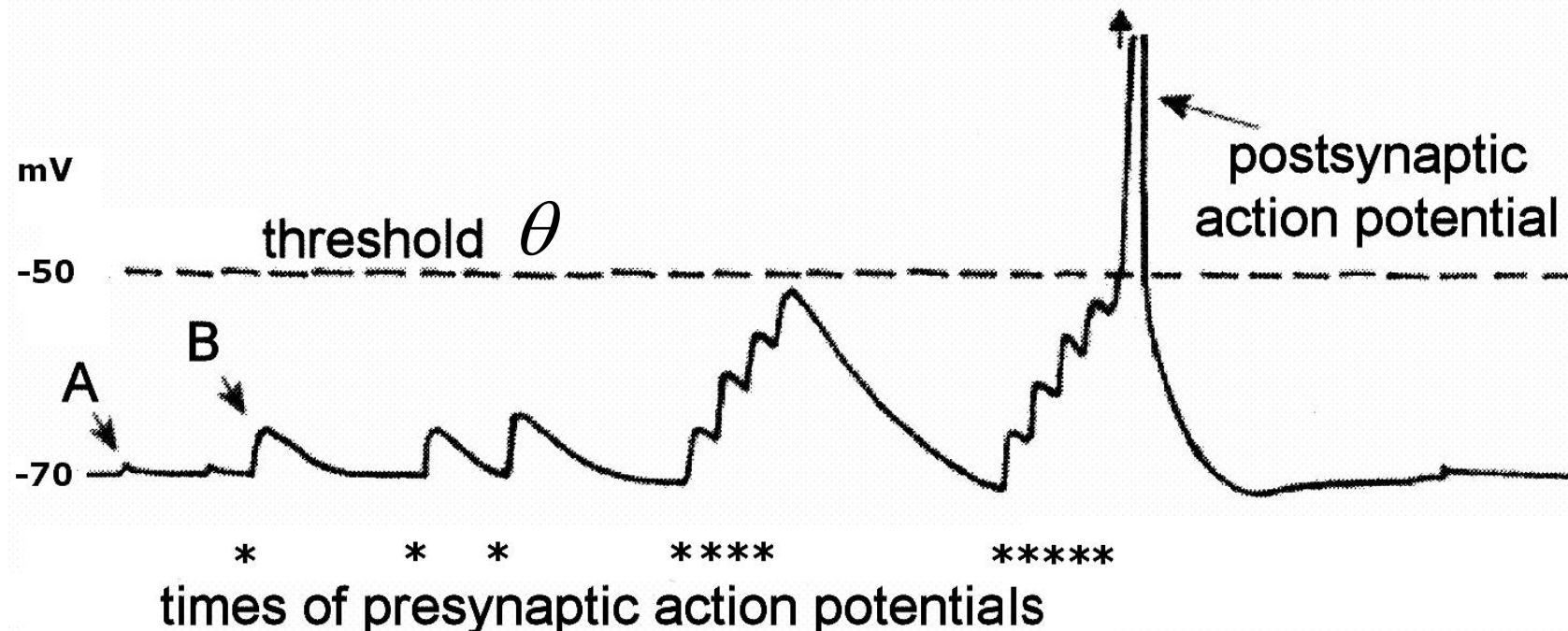
$$g_{syn}^{soma}(t) = \sum_{i=1}^n g_{syn,i}$$

- All the EPSPs and IPSPs add up instantly (soma is equipotential).
- If $PSP_{total} = EPSP_{total} - IPSP_{total} > \text{firing threshold } \theta$, then an action potential is generated in the trigger zone between soma and axon (axonal hillock).



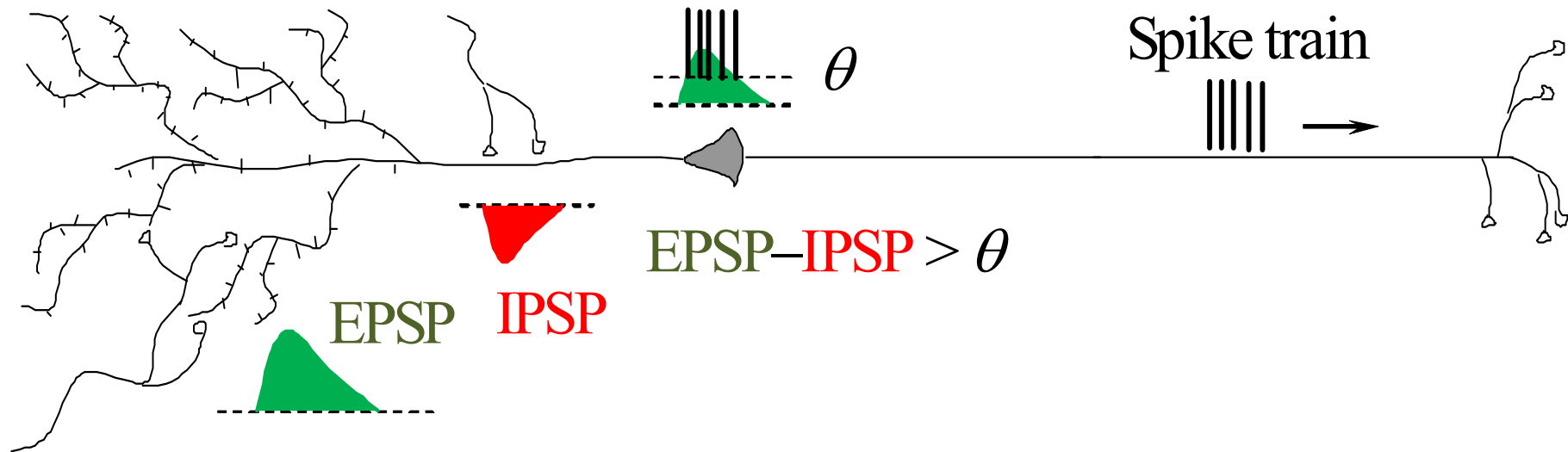
Summation of EPSPs in time

- Each presynaptic spike causes an EPSP at the postsynaptic site ('B'). On arrival of many presynaptic spikes in close succession, these EPSPs sum on top of each other and if the cumulative sum crosses the firing threshold θ , neuron generates an output spike (action potential).



Note: Symbol 'A' denotes a miniature postsynaptic voltage.

Neurons are analog-digital convertors



- Postsynaptic potentials from synapses spread towards soma where they sum up. If the total somatic PSP $> \theta$, then the neuron fires.
- Output of a neuron is usually a series of spikes: the number and frequency (rate) of spikes within the output spike train is proportional to the magnitude and duration of the total PSP = EPSP-IPSP at the soma.

The role of synapses

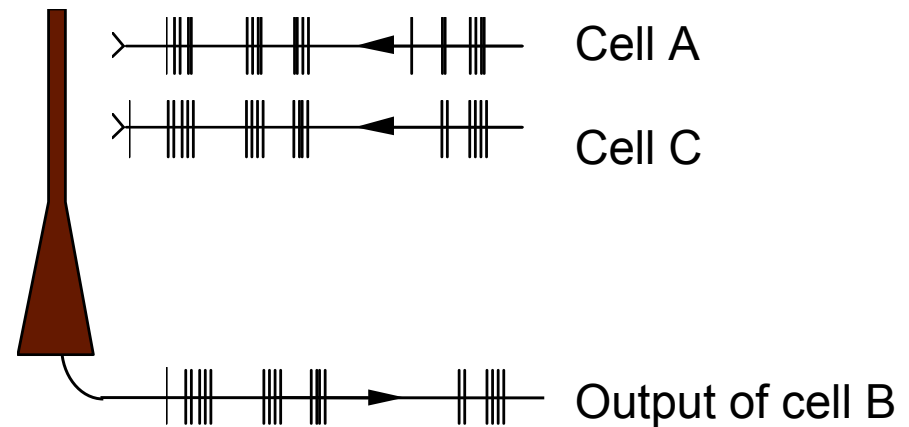
- Each synapse has a measurable strength or weight (function of number of PSP receptors, spine shape, distance from soma, etc.) that reflects its impact upon firing the neuron.
- Synapses essentially direct information traffic, influencing which neural circuits will be activated.
- Increase or decrease in the strength of a synapse can change the directions of the flow of information in neural circuits.



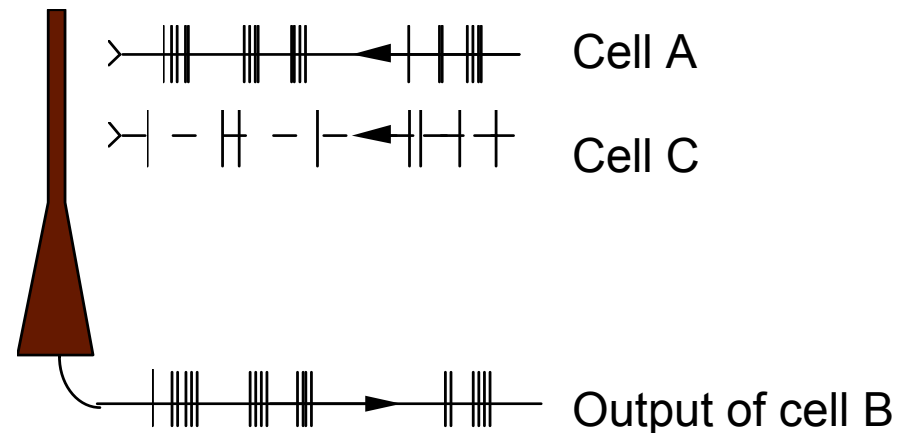
Hebb rule of synaptic plasticity (1949)

- When an axon of cell A is near enough to excite a cell B and **repeatedly or persistently** takes part 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.”

- Consequences ----->



Neurons that fire together wire together.

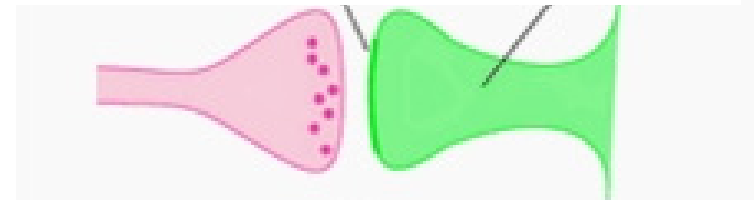


Neurons that fire out of sync lose their link.

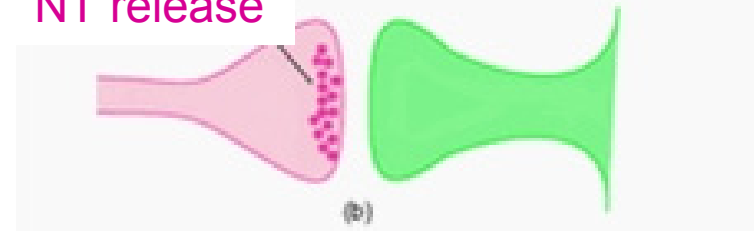
Synaptic plasticity

- Definition: synaptic plasticity is the ability of the synapse to change its strength (weight).
- Various mechanisms:
 - ❑ change in number/functionality of postsynaptic receptors,
 - ❑ change in the amount of released neurotransmitter (short-term),
 - ❑ morphological changes like axonal sprouting and spine size changes (long-term).

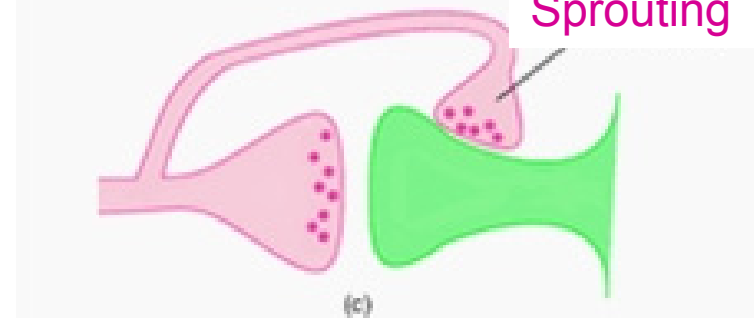
Change in number or function of postsynaptic receptors spine



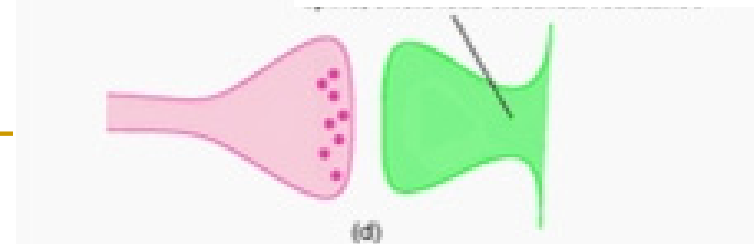
Change in NT release



Sprouting

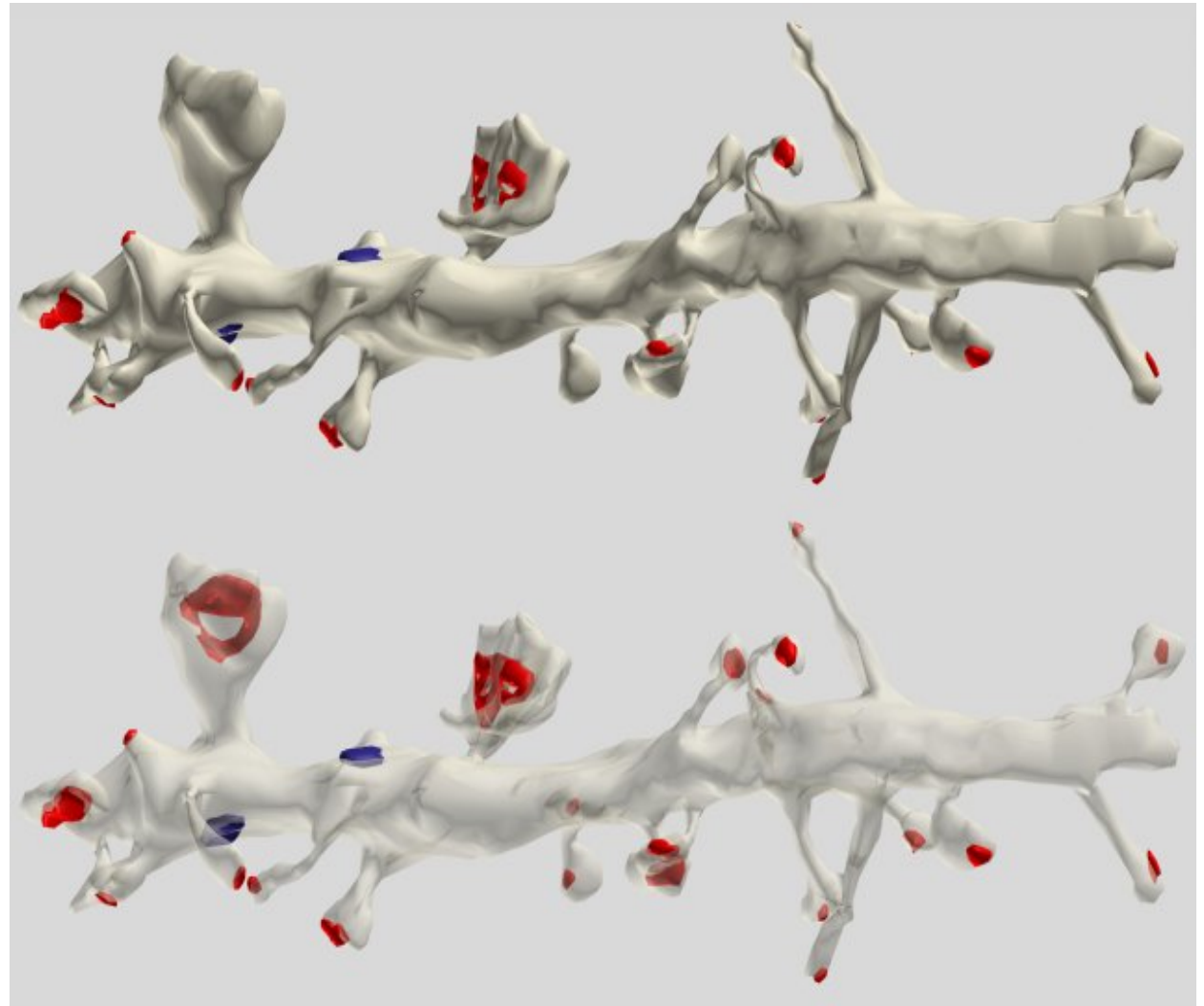


Change in spine geometry



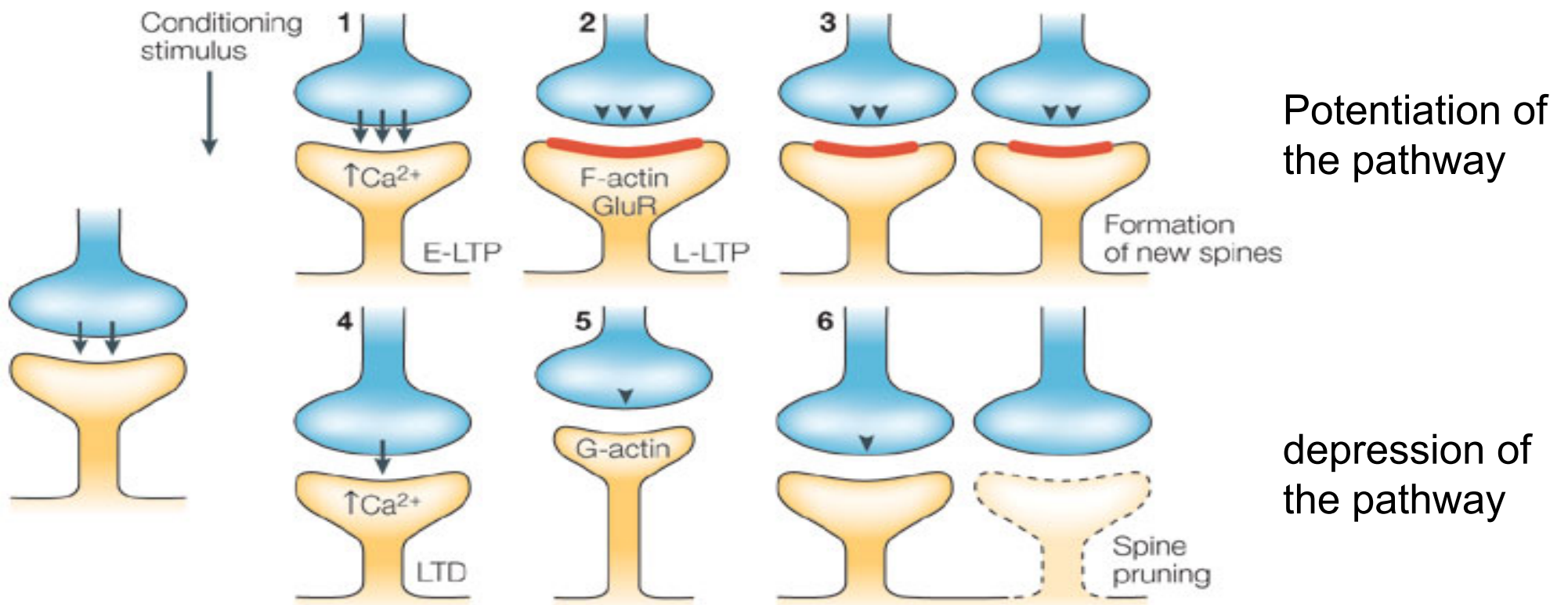
Spines: what's their role?

- Postsynaptic spines are numerous small protrusions on dendrites.
- 90% of excitatory synapses in the cortex are on spines, the rest of excitatory and all inhibitory synapses are on dendritic shafts and soma.
- Red area(s) on spines are the PSD – postsynaptic density, where the postsynaptic receptors and their supporting molecules are.



Spines can change their shape & numbers

- Long-term synaptic plasticity is accompanied with increase and decrease in numbers of spines and thus in numbers of synapses.

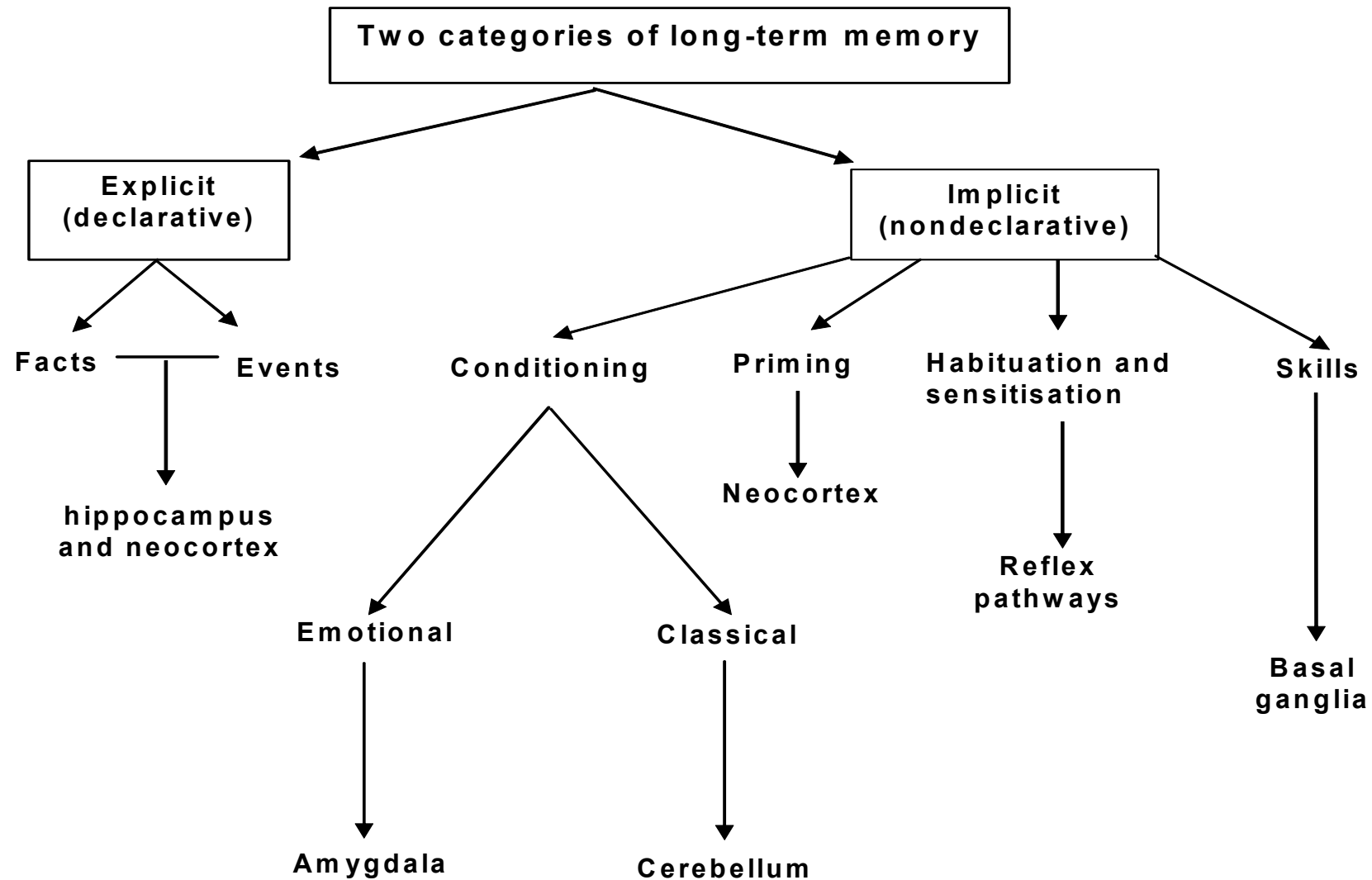


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Learning and brain plasticity

- **Synaptic plasticity** underlies the brain plasticity, which is a lifelong ability of the brain to reorganize neural circuits based on new experience.
- Organism's ability to store, retain, and subsequently recall information is called *memory*.
- The process of acquisition of memories is called *learning*.
- Synaptic plasticity is a cellular mechanism of learning and memory formation.
- We distinguish short-term and long-term memory.

Long-term memory: types and localisation



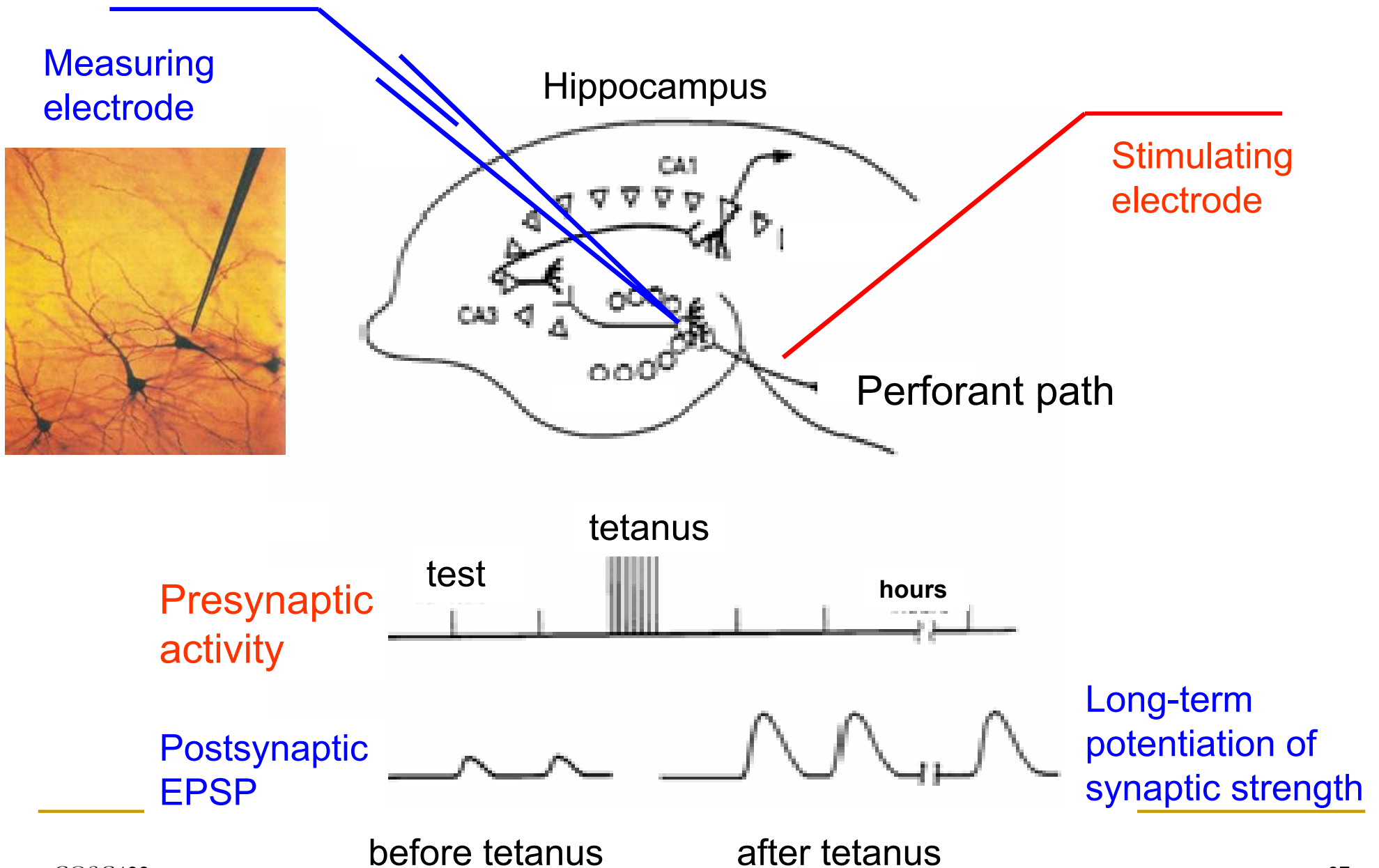
“We are what we can remember”

- We have several types of memory (short-term, long-term, explicit, implicit, working, etc).
- It is widely accepted that long-term memories of all kinds are stored in the brain in the patterns of synaptic weights in the relevant brain areas (i.e. cortex, cerebellum, etc.).
- Big scientific questions:
 - ❑ How neural activity causes changes in synaptic weights?
 - ❑ How long can these changes of synaptic weights last?
 - ❑ How many memories we can store in one neural network?
 - ❑ What is forgetting and how it happens?

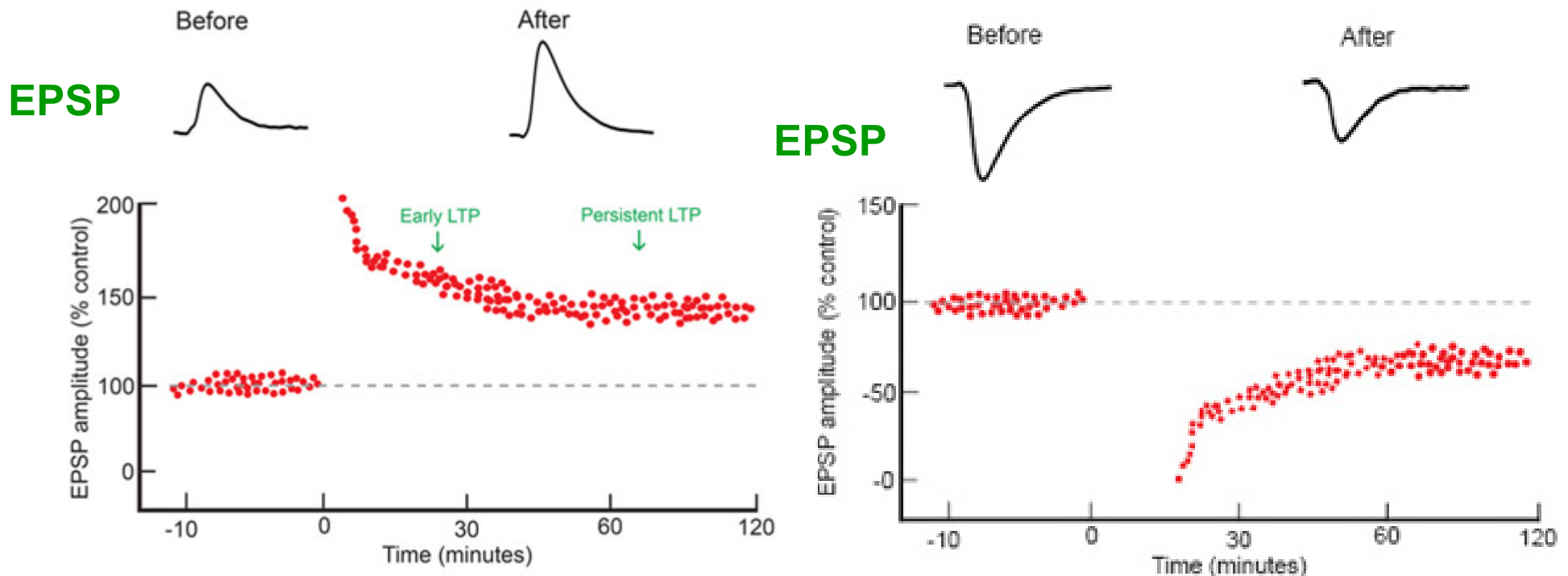
LTP/LTD = long-term potentiation/depression of efficacy of synaptic transmission

- LTP/LTD are the gold standard synaptic models for mammalian long-term memory mechanisms for 3 decades;
- LTP/LTD occur in hippocampus and in neocortex, which are brain regions involved in formation of long-term memories;
- LTP/LTD are long-lasting synaptic changes; can last for hours, days even weeks and months;
- LTP/LTD are synaptic activity-dependent, either in a homo- or heterosynaptic fashion.

LTP induction

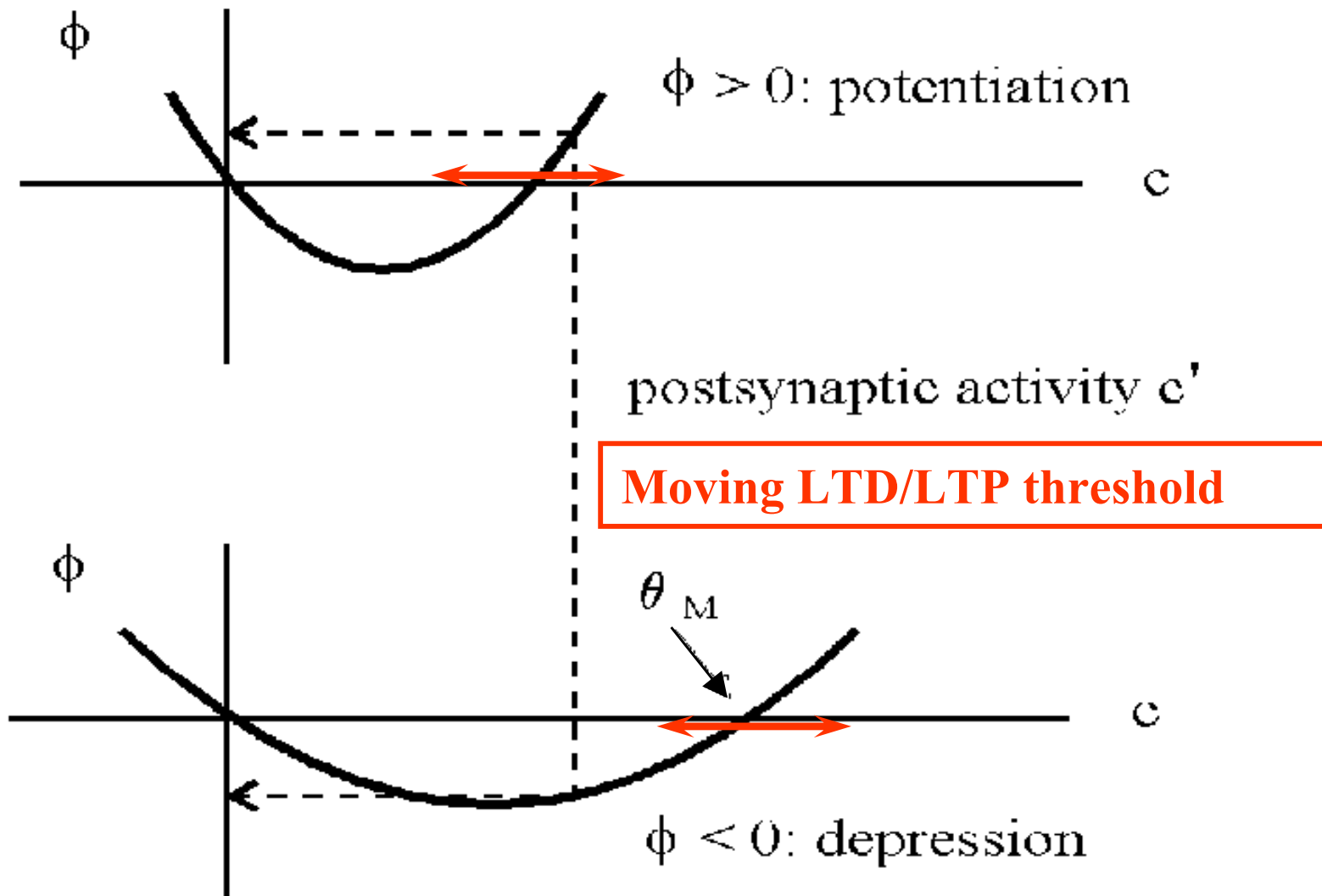


Properties of LTP / LTD: bidirectionality



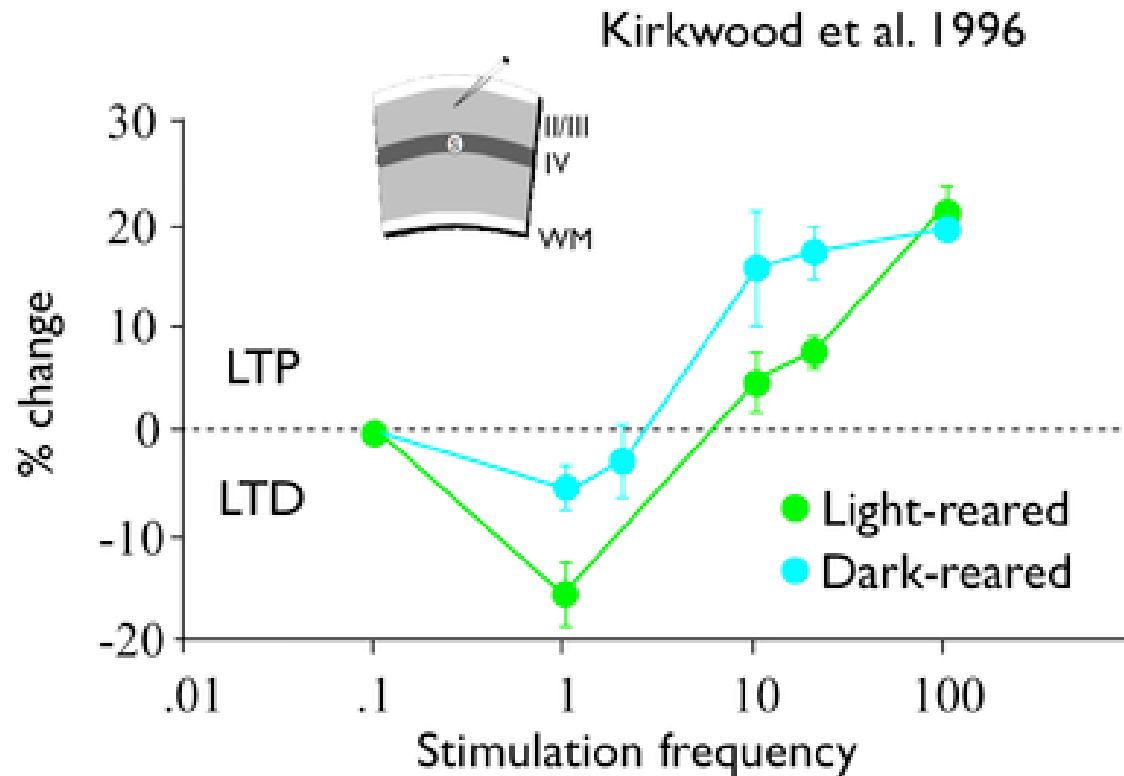
- The change is bidirectional, i.e. the same synapse can become potentiated or depressed based on frequency of tetanus:
 - ~ 100 Hz and more for LTP
 - ~ 1 Hz to 10 Hz for LTD

The Bienenstock-Cooper-Munro (BCM) rule of synaptic plasticity (1982)



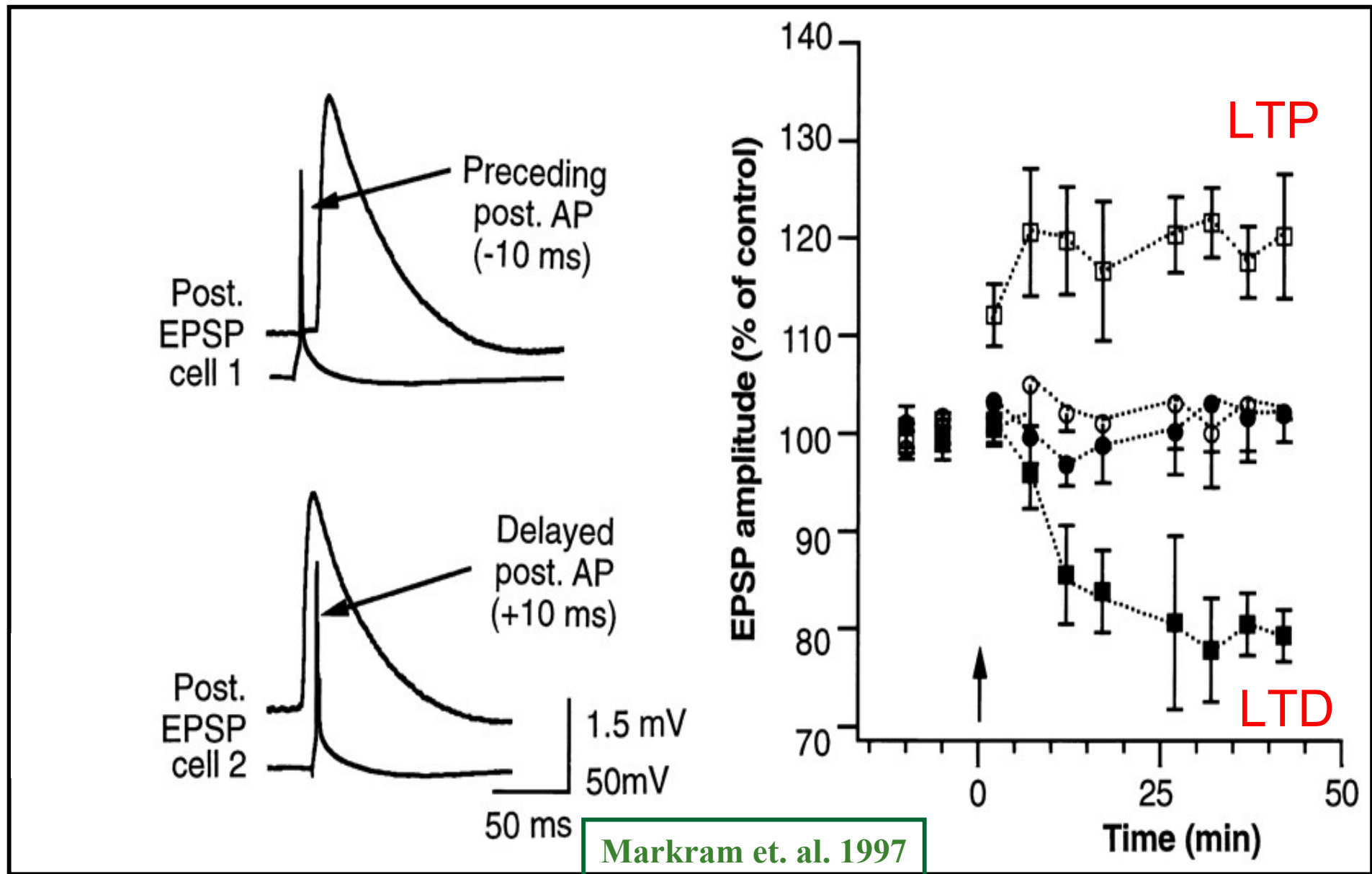
Sliding LTP / LTD threshold: metaplasticity

- Experiment: it is easier to obtain LTP in the visual cortex of dark-reared animals than in the light-reared ones.

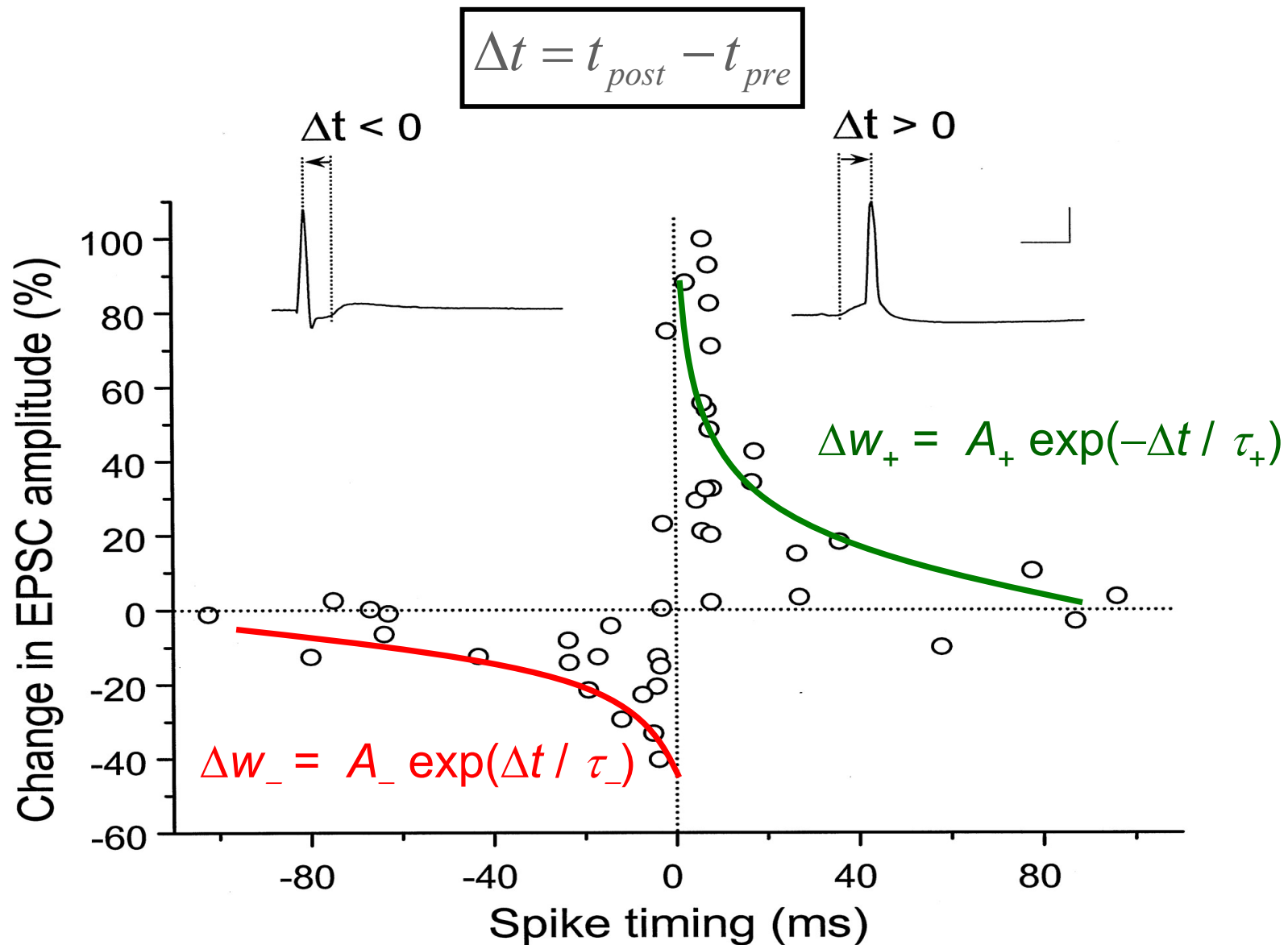


- **Metaplasticity:** LTD / LTP threshold depends on previous average activity (more see Abraham, Nature Rev Neurosci (2008) 9: 387-399).

LTP or LTD depends on precise timing of spikes

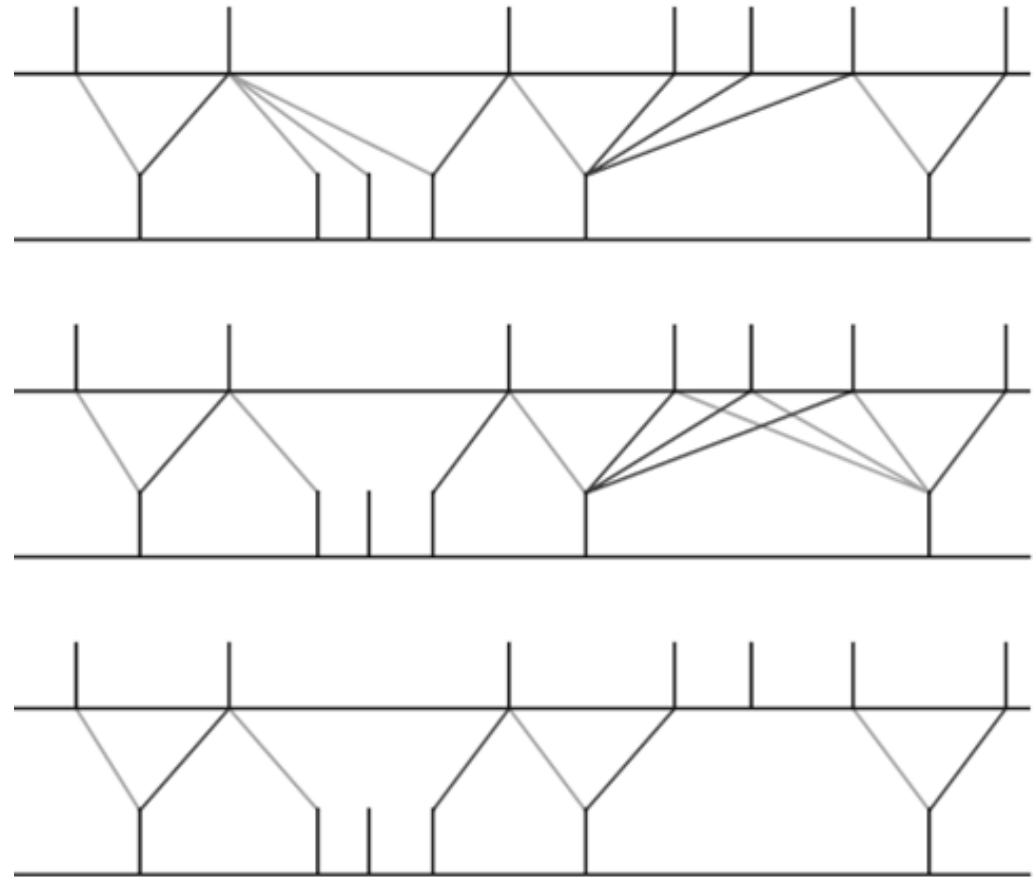


STDP: Spike Timing-Dependent Plasticity



STDP: nearest neighbours pairing schemes

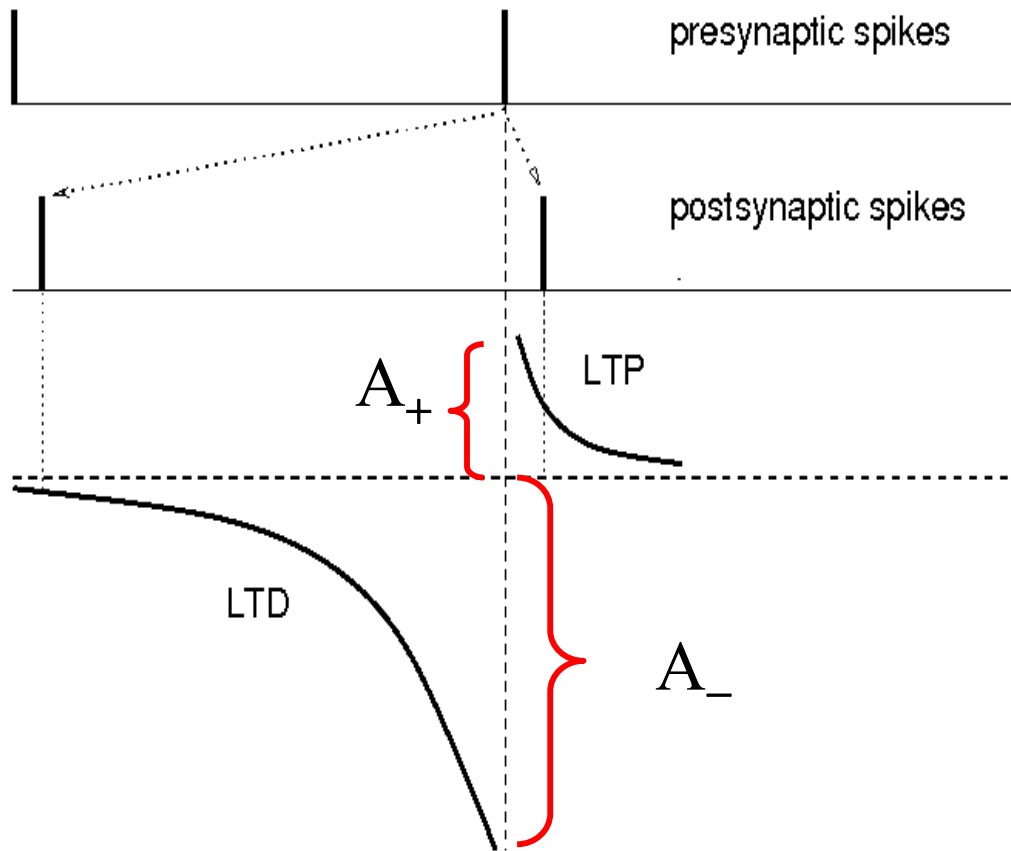
- **Symmetric:** each presynaptic spike is paired with the last postsynaptic spike and each postsynaptic spike is paired with the last presynaptic spike.
- **Presynaptic centered:** each presynaptic spike is paired with the last and next postsynaptic spike.
- **Reduced symmetric:** the same as in above, but only for the nearest pairings.



Source: Morrison, Diesmann, Gerstner: Biological Cybernetics (2008) 98: 459-478.

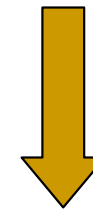
STDP leads to BCM threshold

- Izhikevich and Desai (2003) showed that STDP leads to BCM for the presynaptically centered pairing, when $w(t+1) = w(t) (1 + \Delta w_+ - \Delta w_-)$.



$$C(x) = \overbrace{\int_0^{\infty} A_+ e^{-t/\tau_+} x e^{-xt} dt}^{\text{average potentiation}} + \overbrace{\int_{-\infty}^0 A_- e^{t/\tau_-} x e^{xt} dt}^{\text{average depression}}$$

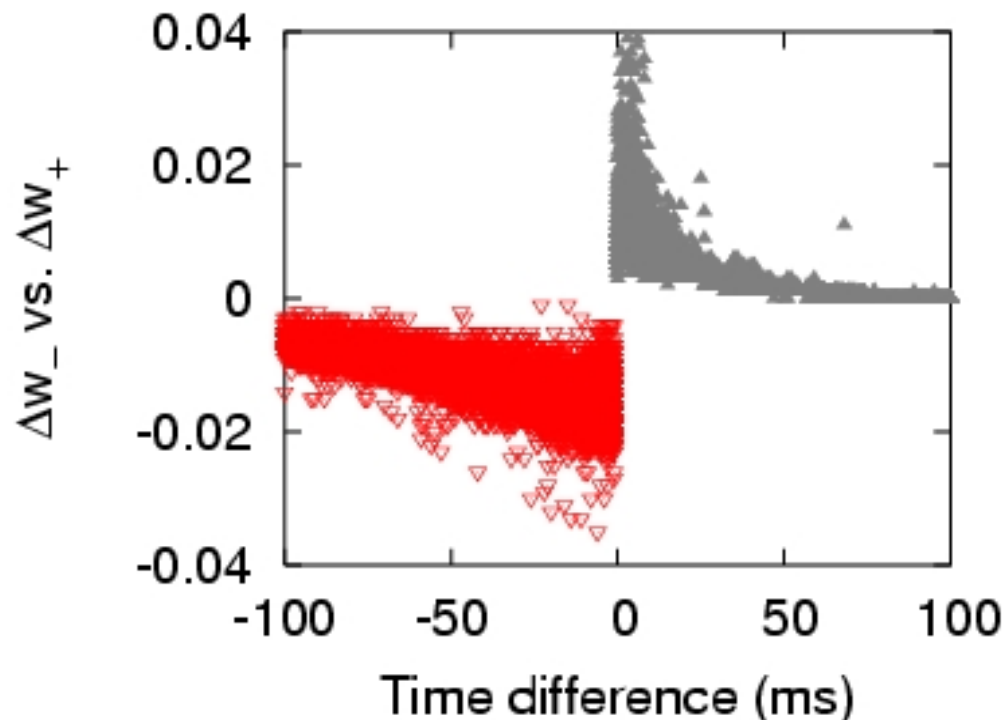
$$= x \left(\frac{A_+}{\tau_+^{-1} + x} + \frac{A_-}{\tau_-^{-1} + x} \right) = 0$$



$$\theta_M = - \frac{A_+/\tau_- + A_-/\tau_+}{A_+ + A_-}$$

STDP with metaplasticity

- The magnitudes of LTD and LTP depend on the previous average postsynaptic activity $\langle c \rangle$. If $\langle c \rangle$ is high, then it is more difficult to achieve LTP and if $\langle c \rangle$ is low, then it is easier to achieve LTP, and vice versa holds for LTD (Benuskova & Abraham, J Comp Neurosci (2007) 22: 129-133).



$$A_+^t = A_+^0 \frac{1}{\langle c \rangle}$$

$$A_-^t = A_-^0 \langle c \rangle$$

Hypothesis

- In our book, we suggested that the current position of LTP / LTD threshold depends also on many other factors:

$$A_+(t) = A_+(0) / (\phi(t) \langle c(t) \rangle_t)$$
$$A_-(t) = A_-(0) \phi(t) \langle c(t) \rangle_t$$

- Where the function ϕ , is the function of different biochemical factors, e.g. neuromodulators, hormones, transcription factors, genes, etc. The influence of each factor has different time course and scale, it can be minutes, hours, even days and years.

