Synapses and synaptic plasticity

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Lecture 8

How neurons communicate

How do we learn and remember

Centre for Cognitive Science
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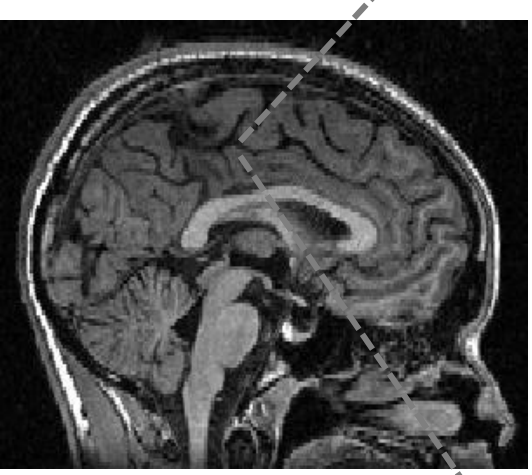
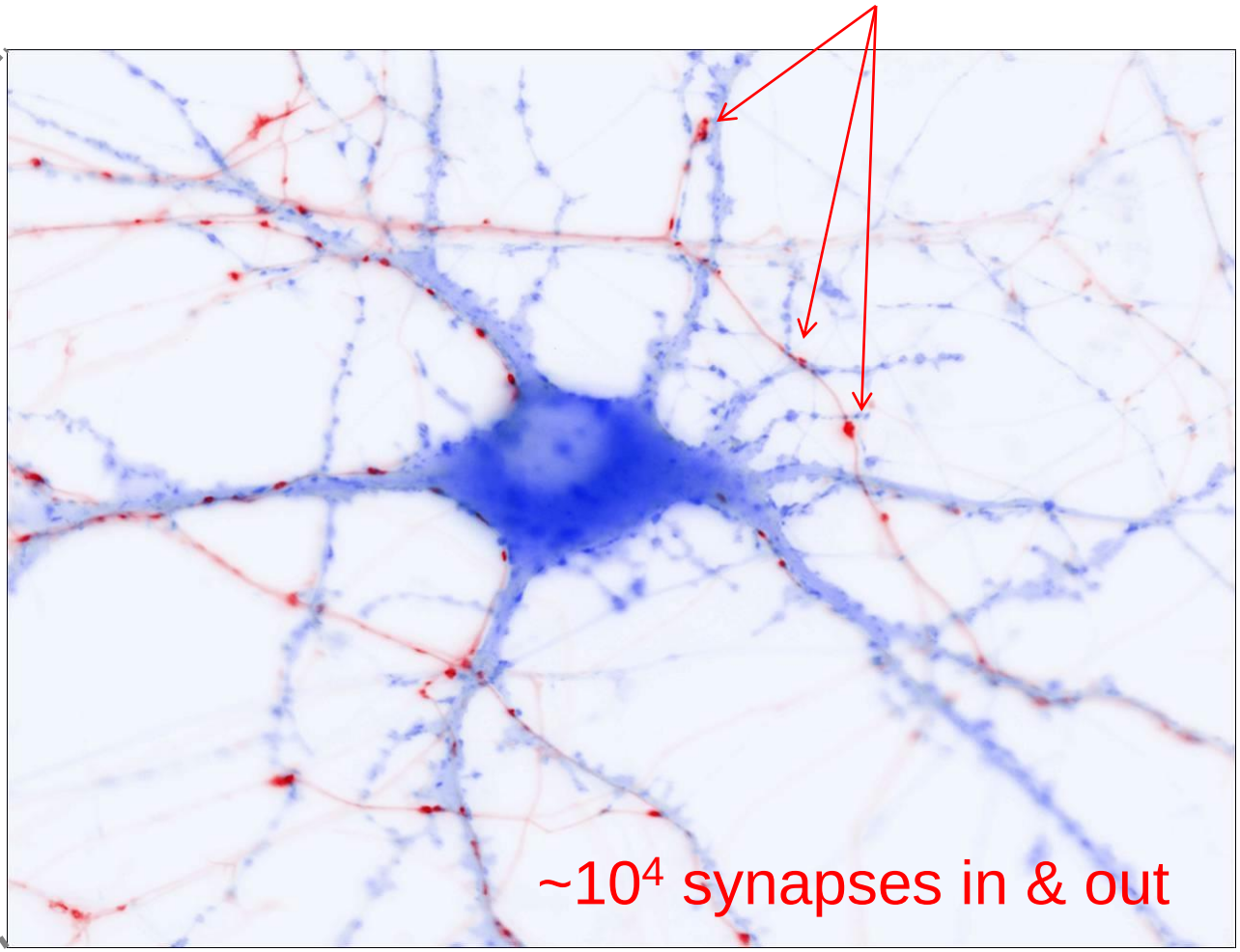
MEi:CogSci

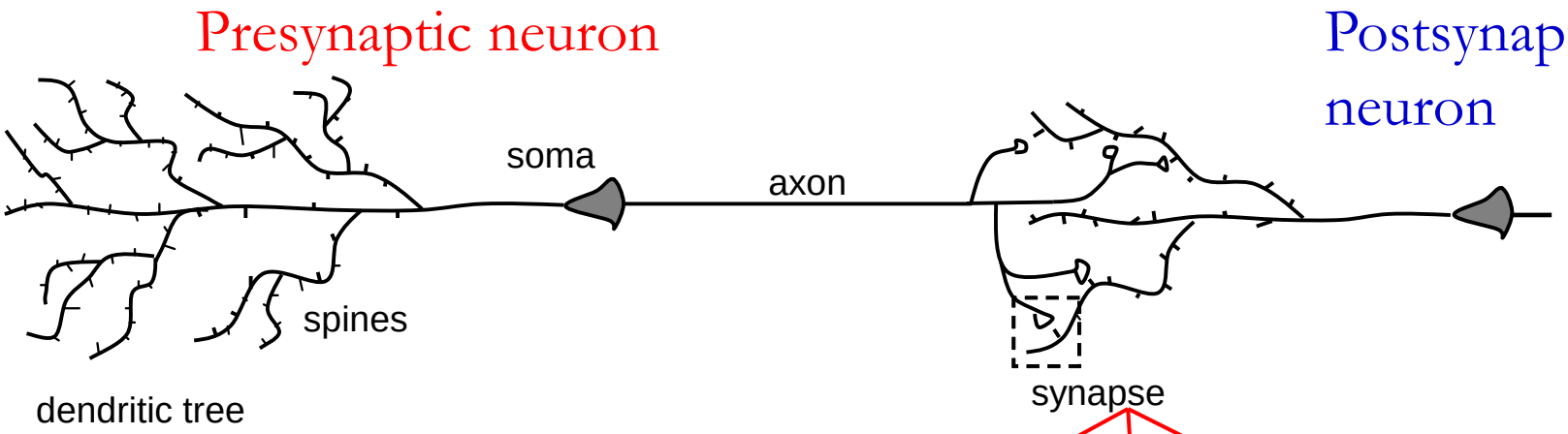
Brain: huge networks of neurons connected via synapses



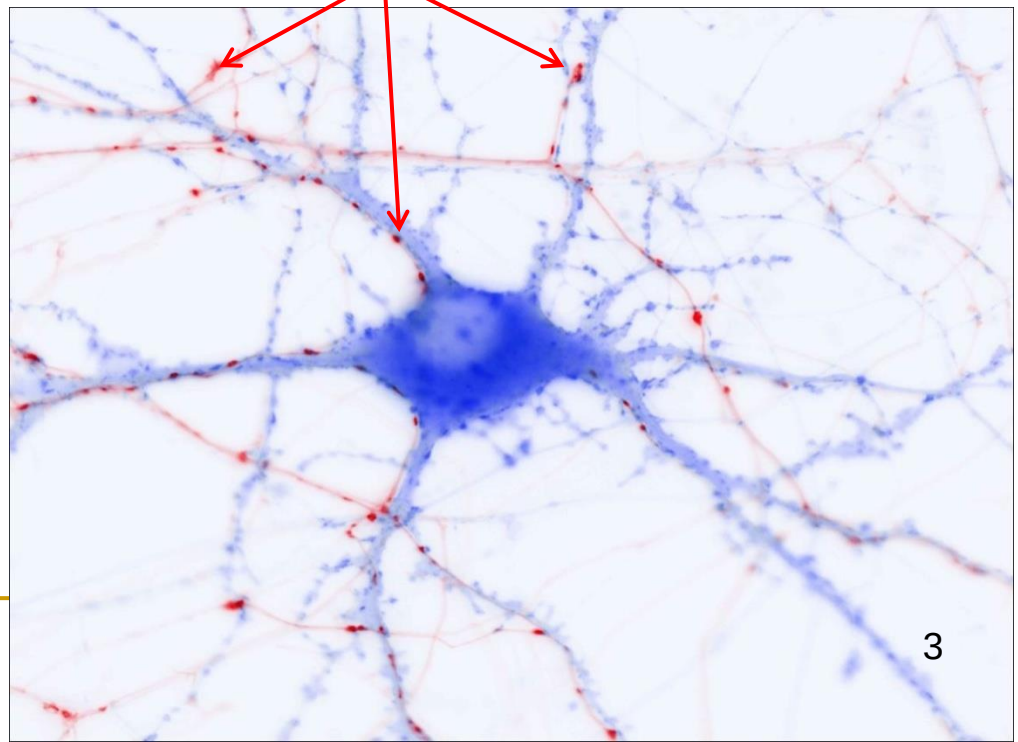
86×10^9 neurons



Presynaptic and postsynaptic neurons

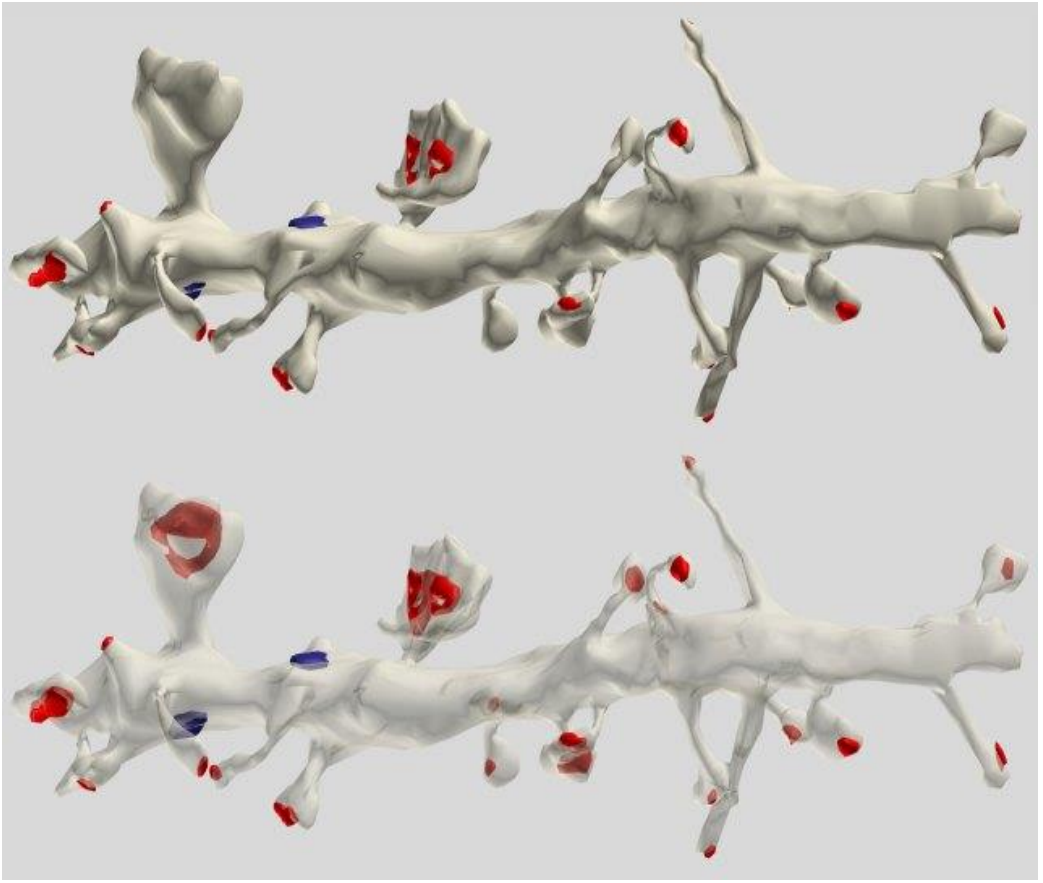


Axons of presynaptic neurons make synapses (little blobs) on the soma and dendrites of the postsynaptic neuron(s).



Spines

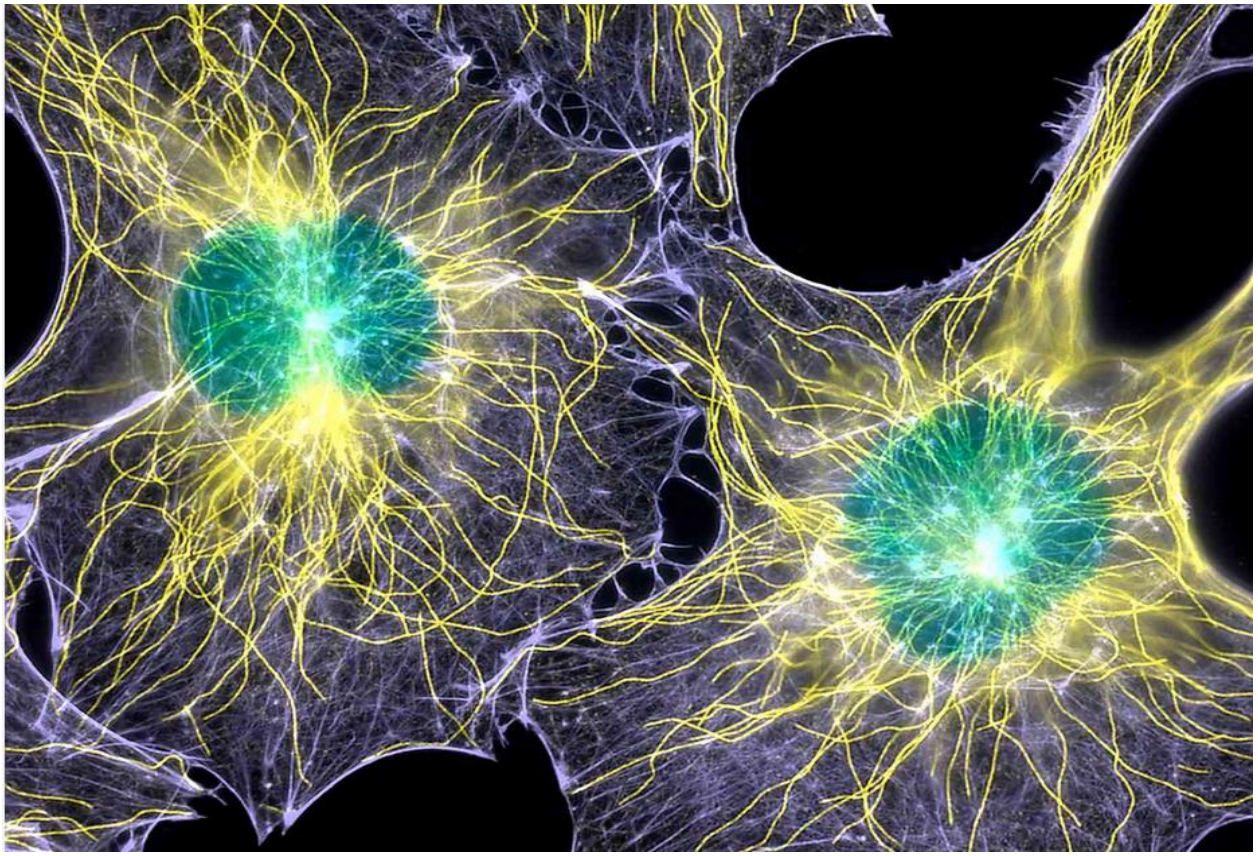
- Postsynaptic spines are numerous small protrusions on dendrites.
- 90% of excitatory synapses in the cortex are on spines, the rest of excitatory and all inhibitory synapses are on dendritic shafts and soma.
- Red area(s) on spines are PSD – postsynaptic density, where the postsynaptic receptors and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



http://synapses.clm.utexas.edu/anatomy/compare/compare.stm

Microtubules

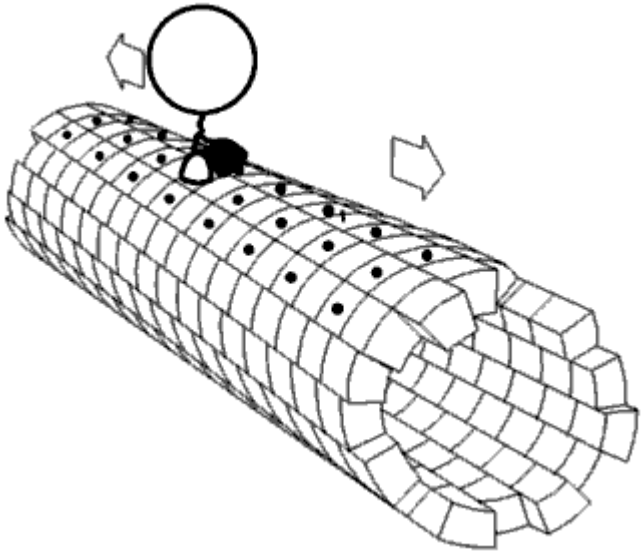
- Microtubules are fibrous, hollow tubes that function primarily as a cell **skeleton** to support the shape of a cell. They also function as **routes** along which organelles and vesicles can move throughout the cytoplasm.



Bailey, R. (2023) https://www.thoughtco.com/microtubules-373545

Axonal and dendritic transport

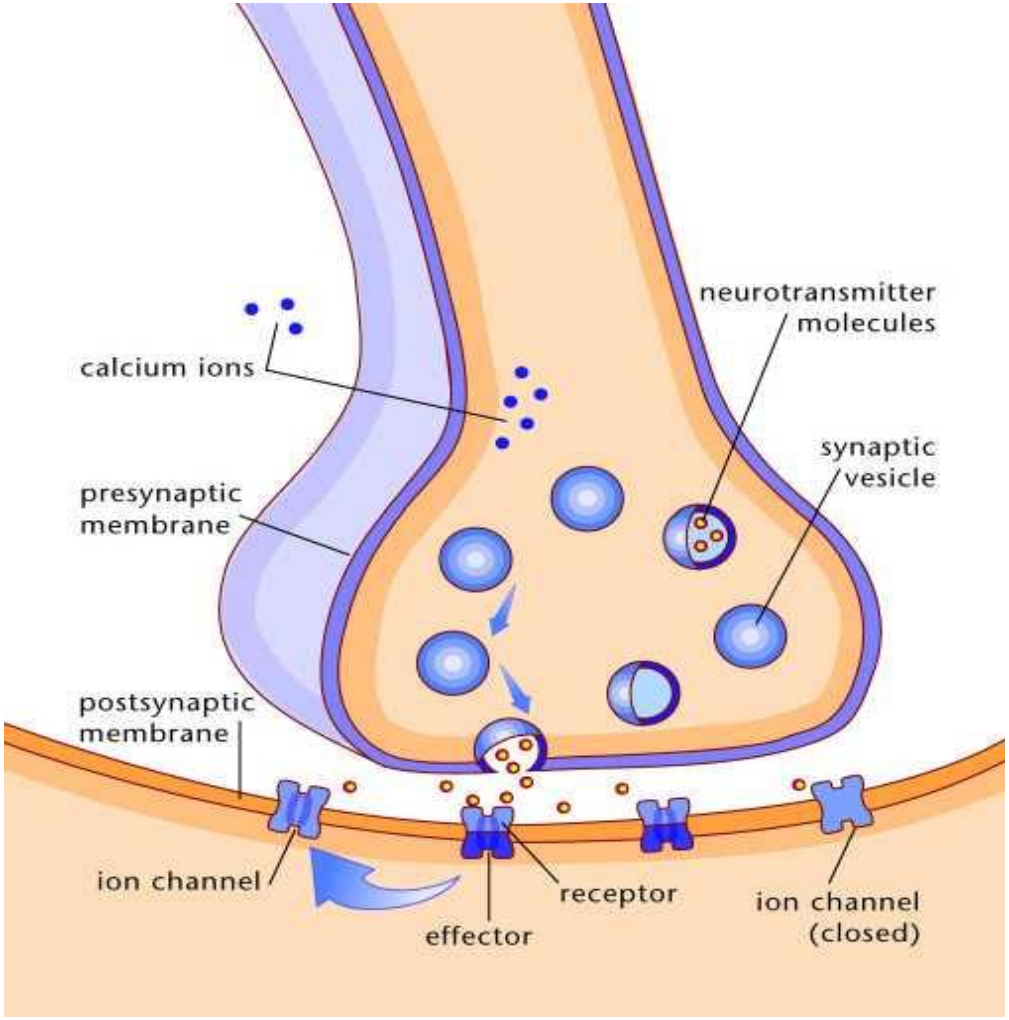
- The vast majority of proteins, including membrane proteins, are synthesized in the neuronal cell body and transported along axons and dendrites.
- Transport occurs throughout the life of a neuron and is essential to its growth and survival (life-time of proteins is hours to days).
- Kinesin and dynein are proteins that move cargoes in the anterograde (forwards from the soma) and retrograde (backwards to the soma) directions, respectively, with the speed of 50–400 nm/day.



https://en.wikipedia.org/wiki/Axonal_transport

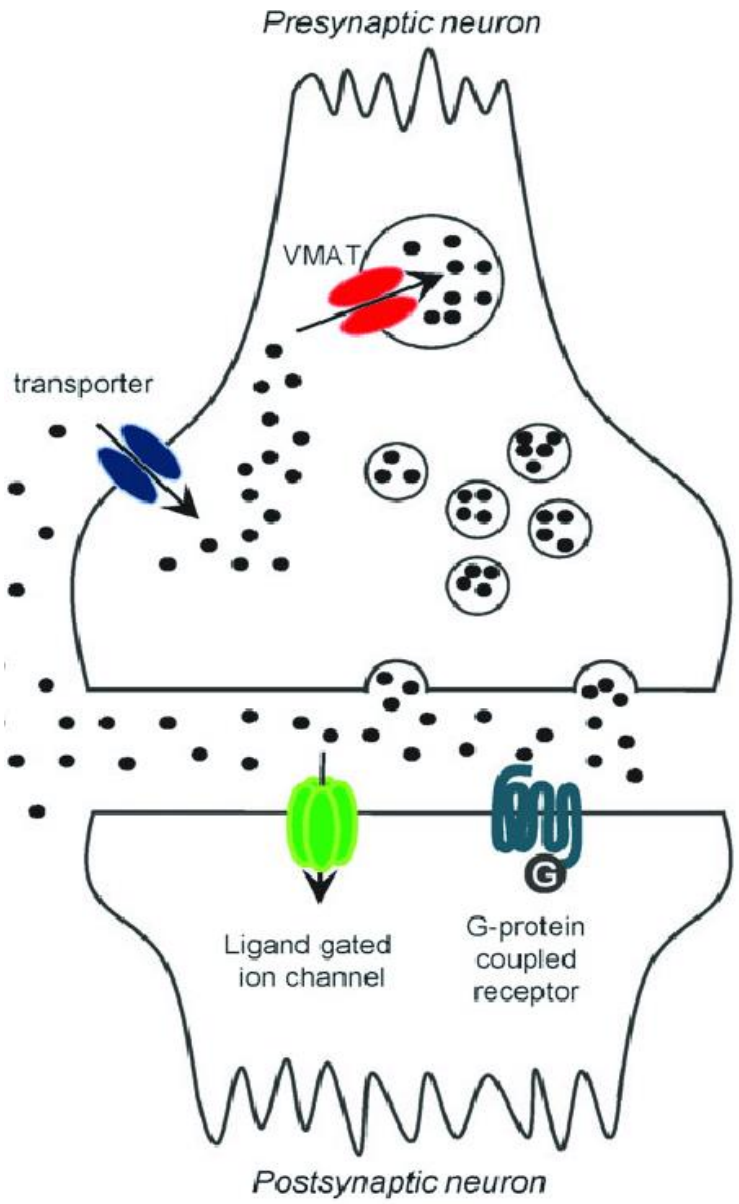
Synapse: from Greek "sunapsis", junction

- 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 or ion channels.



Reuptake of neurotrasmitters

- Re-uptake of neurotransmitter molecules is mediated by transporter.
- VMAT then mediate insertion of neurotransmitter into the vesicles.
- Psychoactive drugs like antidepressants block transporters of serotonin (SSRI) or both serotonin and norepinephrine (SNRI), thus increasing their levels.
- Mutation in genes coding synthesis of neurotransmitters and transporters are implicated in several mental disorders.

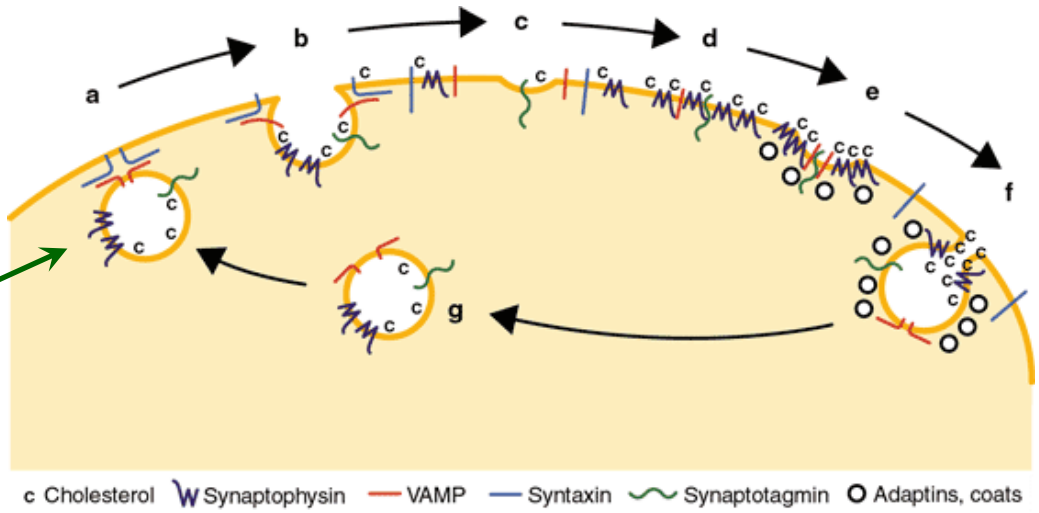


Role of calcium in release of presynaptic vesicles

- When a 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 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" (note: molecules of neurotransmitter are not shown here)

Source: T.F.J. Martin, Nature Cell Biology, doi:10.1038/71392

Presynaptic release of vesicles is probabilistic

- One vesicle 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) arrives at the presynaptic terminal, x number of vesicles release their content.

- When we denote by m the average number of vesicles released per one spike, then the probability that one arriving spike causes release of x vesicles obeys Poisson probability equation, i.e.

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

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, the ion channel opens.
- Receptors are specific for given neurotransmitter and ion channels are specific for concrete ions.
- Ions then flow in or out according to the membrane voltage and ion concentration.

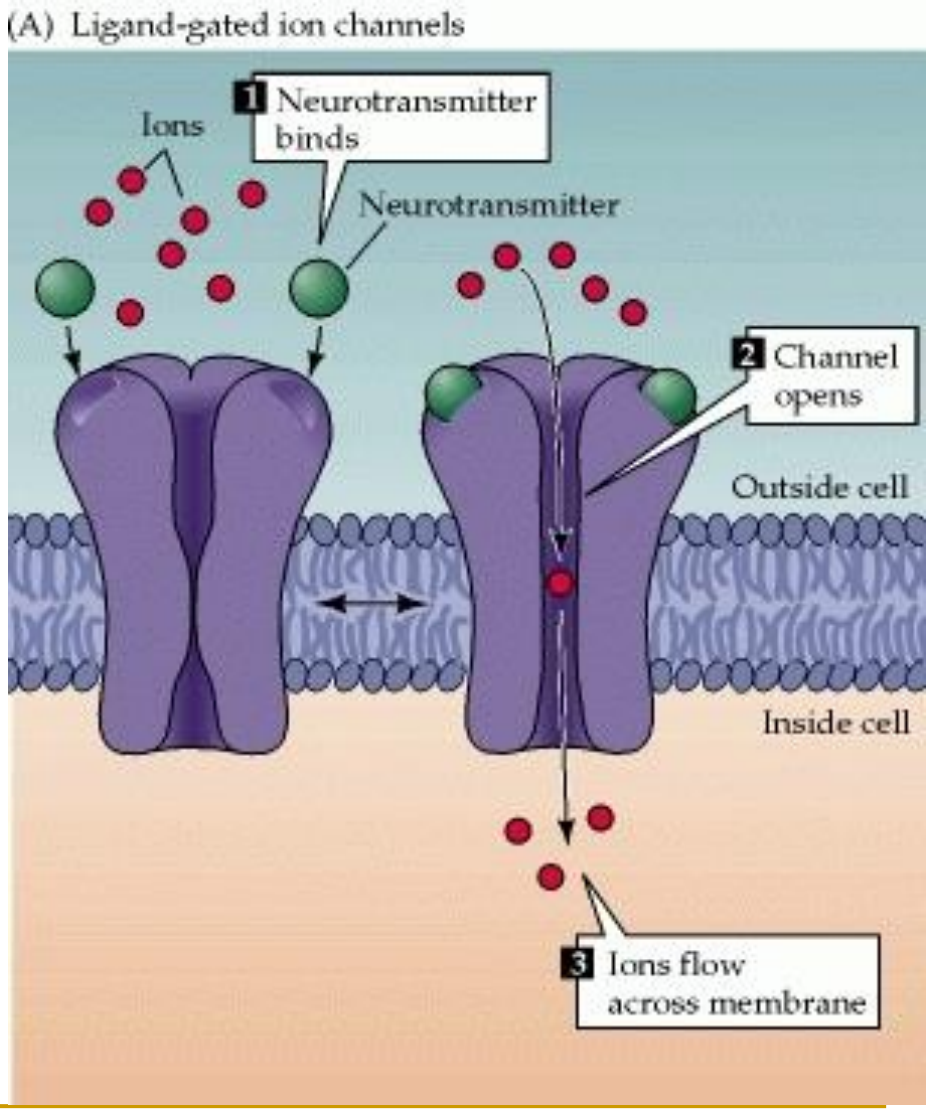


Image source: http://www.ncbi.nlm.nih.gov/books/NBK10855/

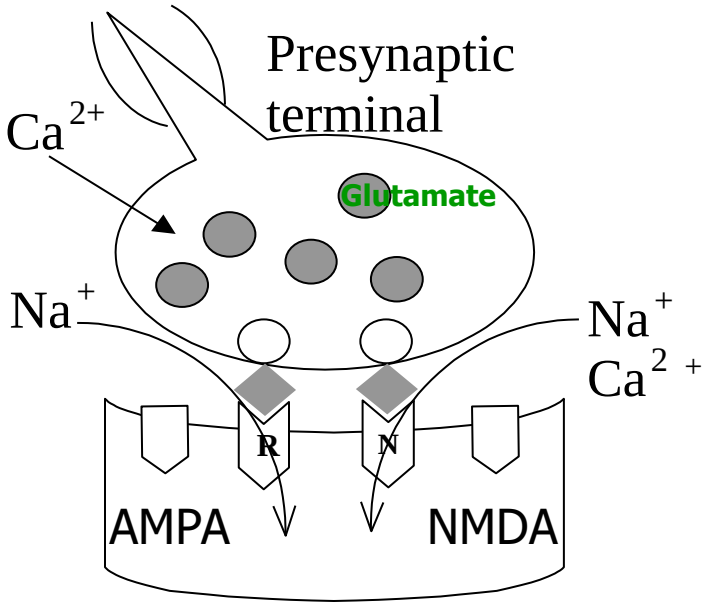
Receptor/ion channels: excitation versus inhibition

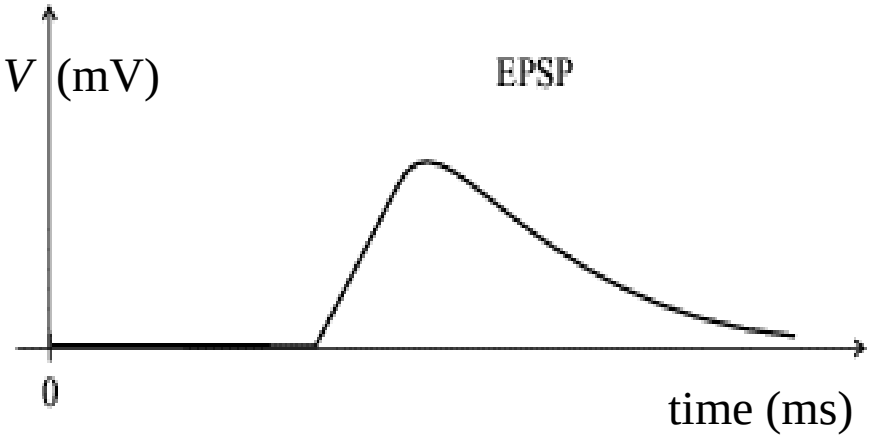
- When nothing is happening, the postsynaptic membrane is polarized at $V_0 \cong -65$ mV (the resting potential).

- If the neurotranmitter interacts with receptor/ion channels, which 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 neurotranmitter interacts with receptor/ion channels, which 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: glutamate



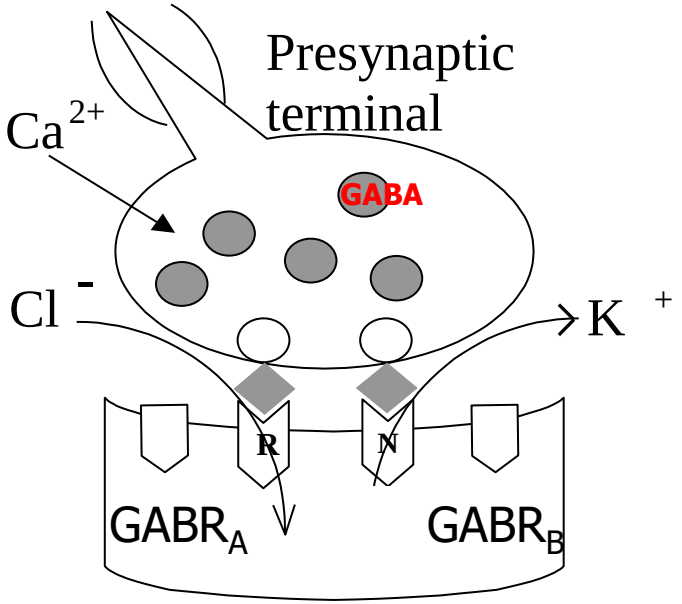


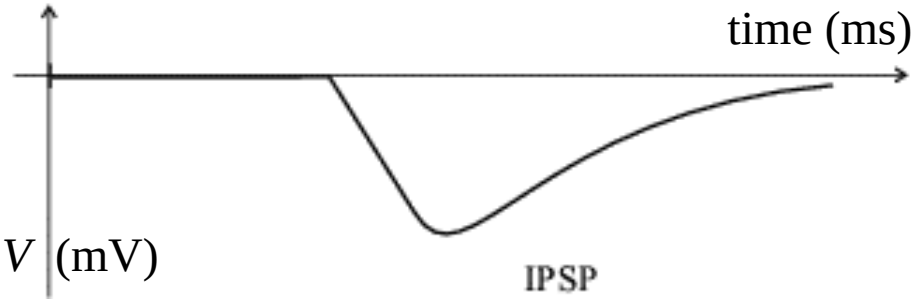
- Postsynaptic receptors called AMPA and NMDA are associated with ion channels for Na^+ or for Na^+ and Ca^{2+}, respectively.
- NMDAR channels open after AMPA caused depolarization removes the Mg^{2+} block.
- A positive deviation from the resting potential is called **excitatory postsynaptic potential (EPSP).**

Inhibitory synapses: GABA

- Postsynapstic receptors $GABR_A$ and $GABR_B$, ion channels for Cl^- and K^+, respectively.

- When we measure the electric potential at the postsynaptic site, we see a negative deviation – hyperpolarization from the resting potential, called **inhibitory postsynaptic potential (IPSP).**





Postsynaptic potential (PSP = I_{syn} R_m)

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

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

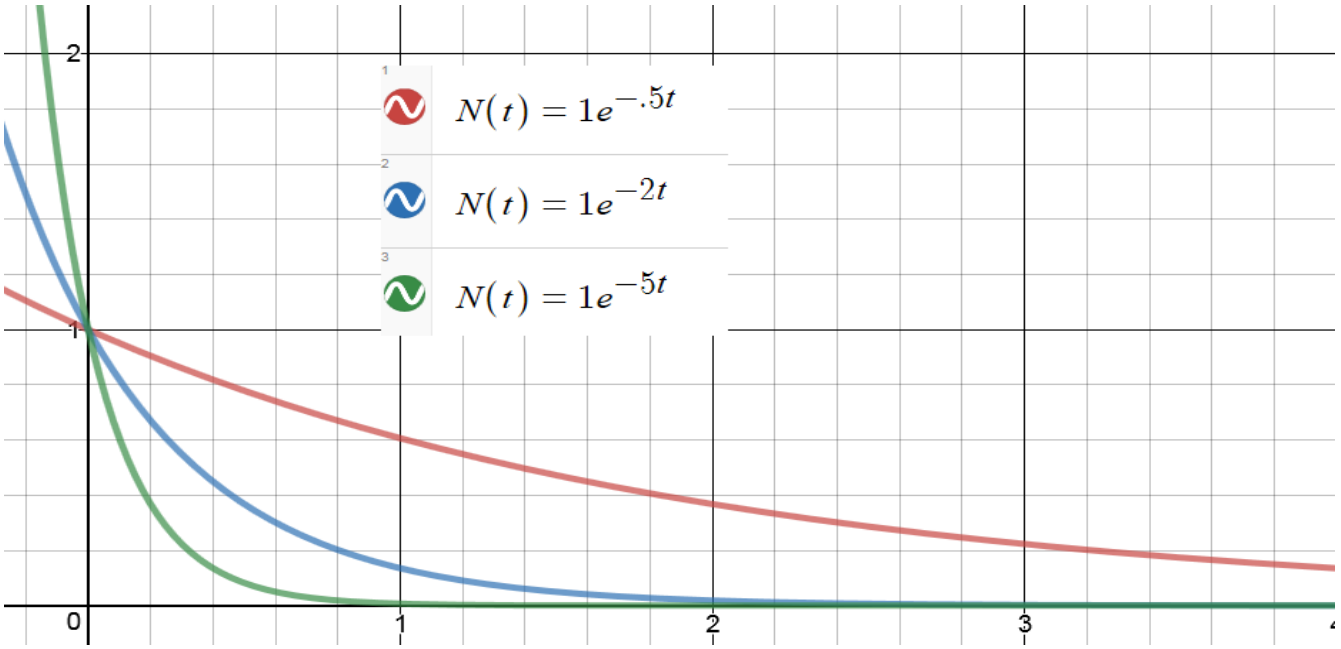
- Where the effect of neurotransmitter binding to and opening the postsynaptic receptors/ion channels is the conductance change g_{syn}.

- *V* is the actual (momentary) value of transmembrane potential.

- E_{syn} is the reversal potential of those ion channels (Na, K, Cl, Ca) that mediate a given synaptic current in the postsynaptic membrane.

Exponential model function for g_{syn}

- When the arrival of presynaptic spike is at t_s, then:
- Exponential decay (**ExpSyn**): $g_{syn}(t) = g_{\max} \exp\left(-\frac{t - t_s}{\tau}\right)$

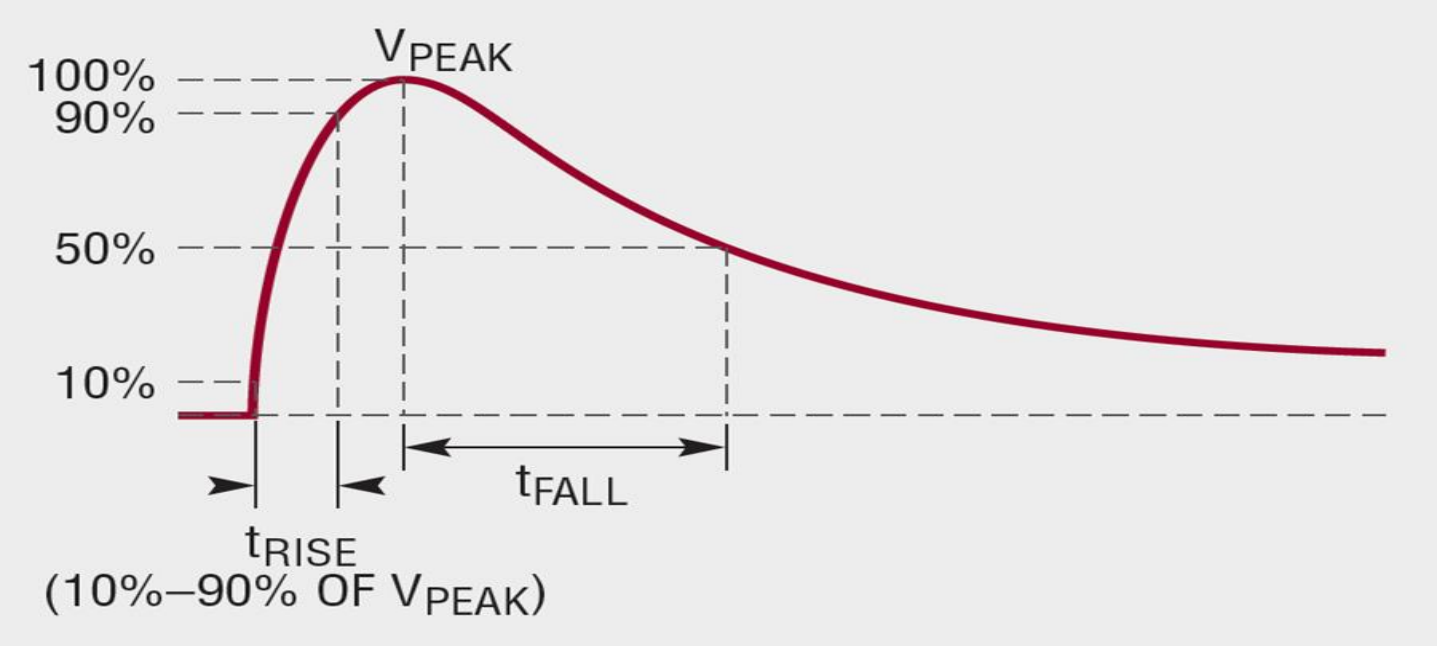


Source: https://advancedmathyoungstudents.com/blog/?p=797

Double exponential model function for g_{syn}

- Double (dual) exponential function (**Exp2Syn**):

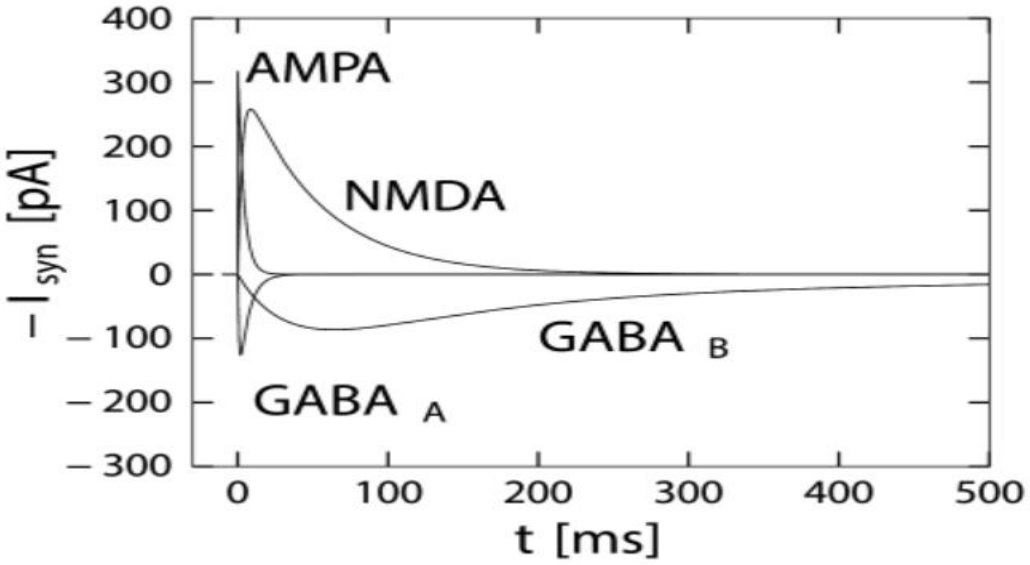
$$g_{syn}(t) = g_{\max} \frac{\tau_1 \tau_2}{\tau_1 - \tau_2} \left[\exp\left(-\frac{t - t_s}{\tau_1} \right) - \exp\left(-\frac{t - t_s}{\tau_2} \right) \right]$$



https://www.analog.com/en/technical-articles/ltspice-using-time-dependent-exponential-sources-to-model-transients.html

How do we model different synaptic currents?

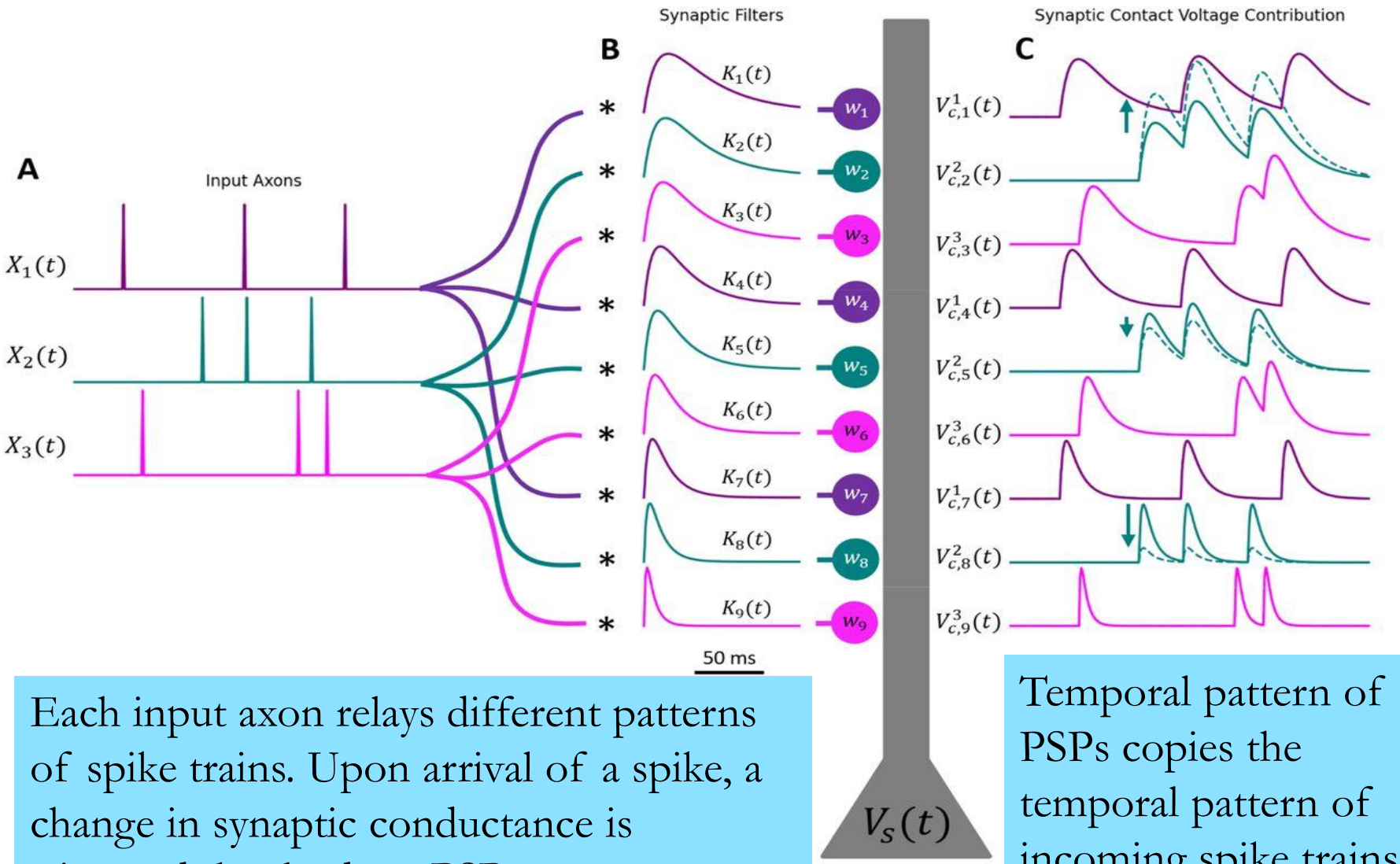
- Postsynaptic currents differ in maximal conductance g_{max} and τ:



- g_{max} is specified by the `weight` field of a `NetCon` object.
- Parameter τ is changed by command `syn.tau = 100` after the command `new ExpSyn`.
- For `Exp2Syn`, we can change `syn.tau1` and `syn.tau2`.

https://neuronaldynamics.epfl.ch/online/Ch3.S1.html

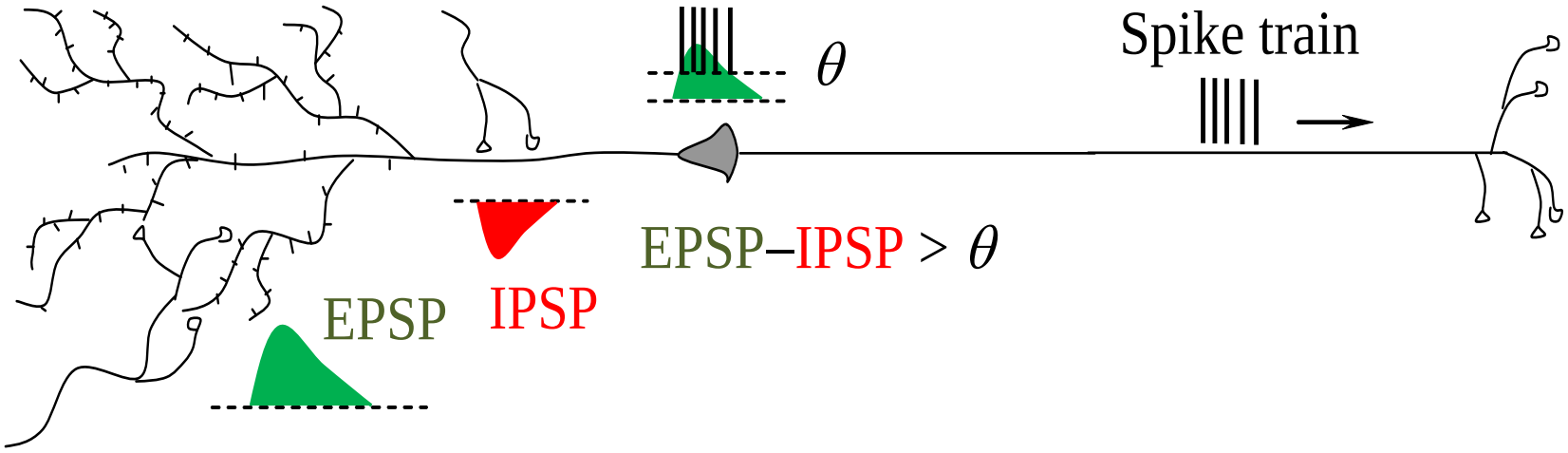
Temporal patterns of PSPs at individual synapses



Each input axon relays different patterns of spike trains. Upon arrival of a spike, a change in synaptic conductance is triggered that leads to PSP.

Temporal pattern of PSPs copies the temporal pattern of incoming spike trains.

Neurons are analog-digital convertors



- Postsynaptic potentials from synapses spread towards soma where they sum up. If the total somatic PSP > θ, 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 weight of synapses

- Each synapse has a measurable **strength or weight** 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.

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

- LTP/LTD are **persistent** strengthening/weakening of synapses based on recent patterns of presynaptic spiking activity.
- LTP/LTD have been studied as long-term synaptic memory mechanisms for 50 years (Bliss and Lømo's, 1973).
- LTP/LTD occur in hippocampus, neocortex, amygdala, cerebellum and basal ganglia.
- LTP/LTD are **long-lasting synaptic changes**; can last for hours, days even weeks and months.

Different forms of LTP based on mechanism

- Different areas of the brain exhibit different forms of LTP.
- Hippocampal LTP depend on the NMDARs, others may depend upon the metabotropic glutamate receptor (mGluR), like LTD in the cerebellum.
- Activated intracellular messengers modify the permeability of the nearby ion channels. Some messengers can carry messages to the cell DNA.

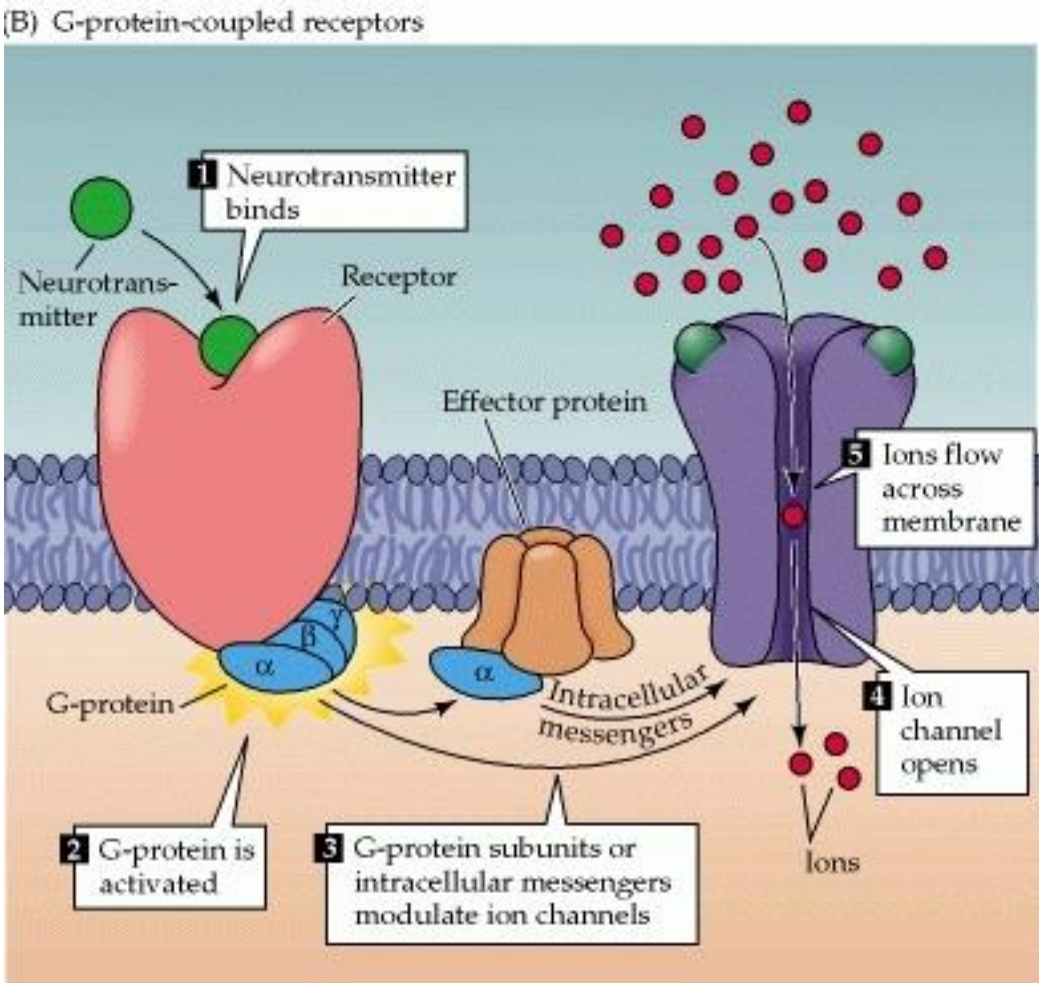
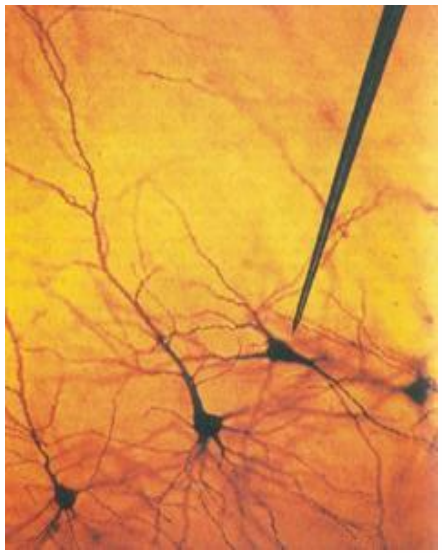


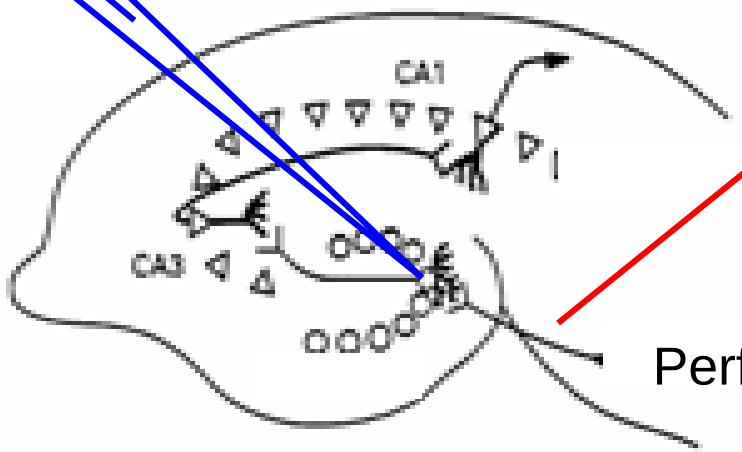
Image source: http://www.ncbi.nlm.nih.gov/books/NBK10855/

LTP induction

Measuring electrode



Hippocampus



Stimulating electrode

Perforant path

tetanus

test

hours

Presynaptic activity

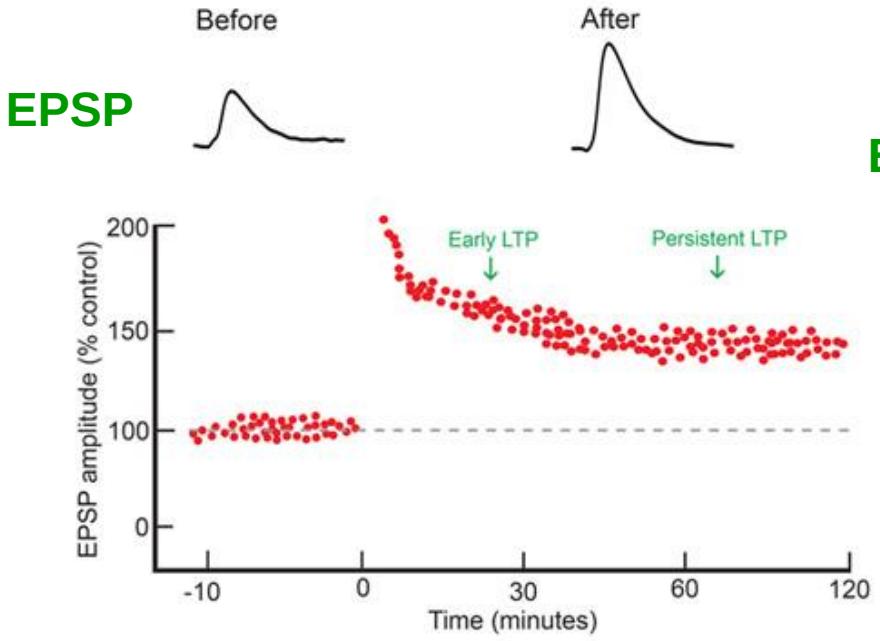
Postsynaptic EPSP

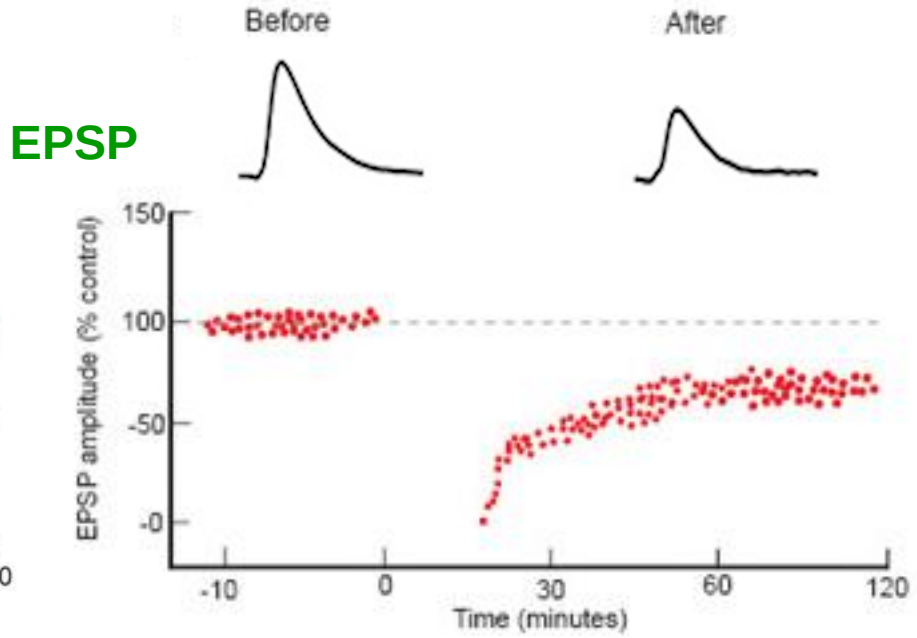
Long-term potentiation of synaptic strength

before tetanus

after tetanus

LTP / LTD: change in the peak of EPSP

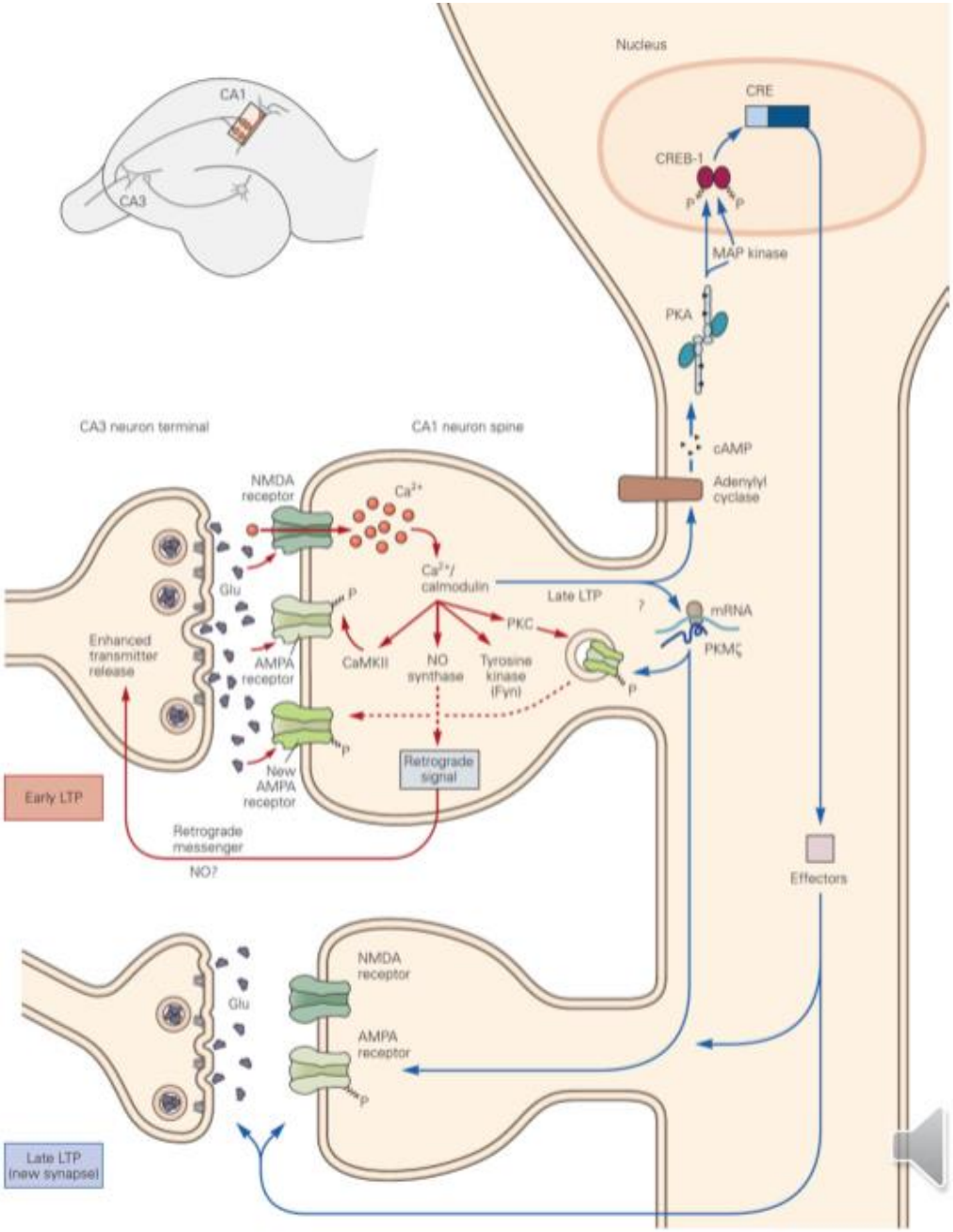




- The same synapse can become potentiated or depressed based on the frequency of tetanus:
  - f > 10 Hz (**high** frequency stimulation) for LTP
  - f < 10 Hz (**low** frequency stimulation) for LTD

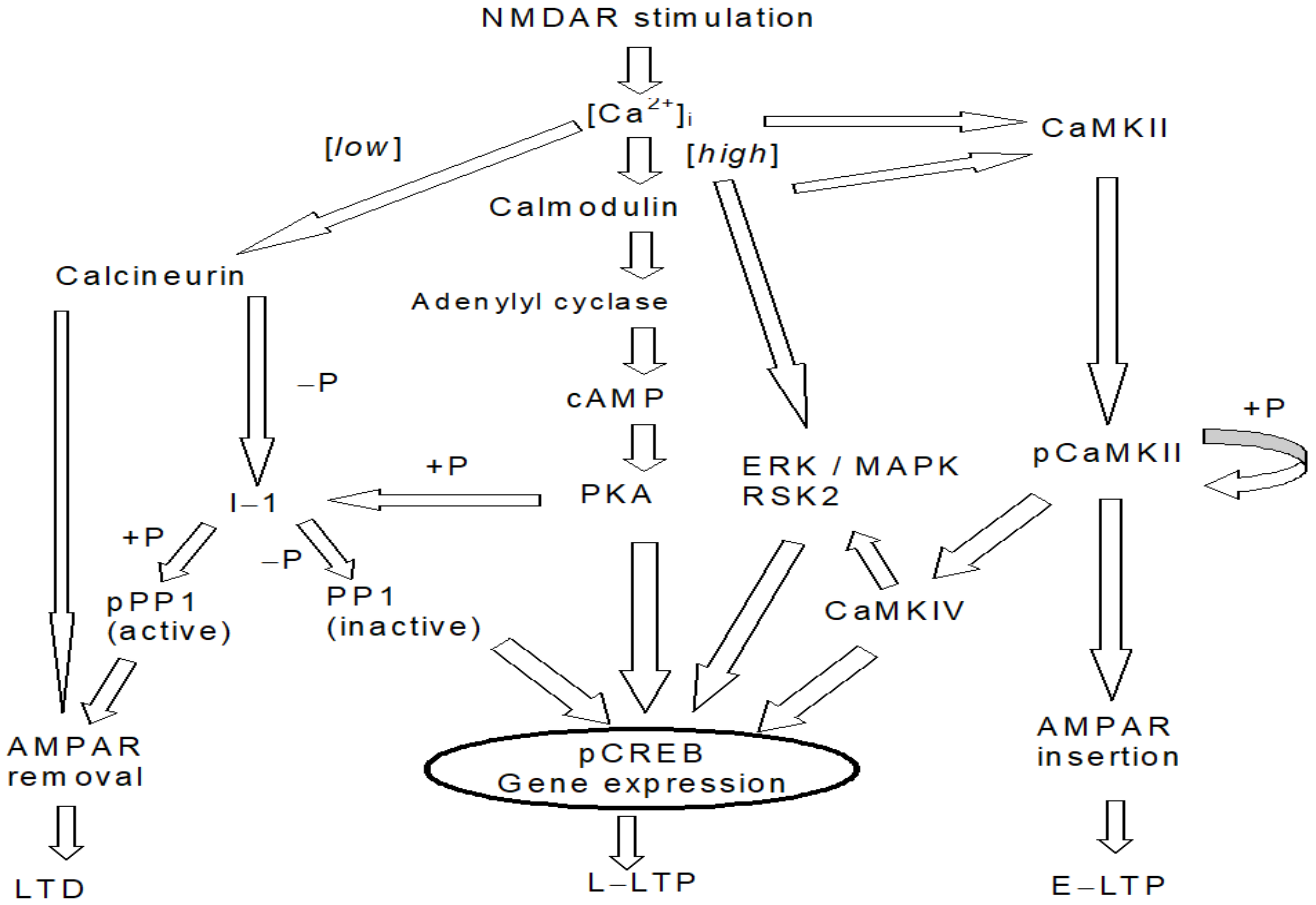
Stages of LTP

- Very early LTP: existing AMPARs phosphorylated via CaMKII.
- Early LTP: insertion of new AMPA receptors, mainly thanks to local protein synthesis.
- Late LTP: cAMP, MAPK, CREB and transcription of genes to create new synapses



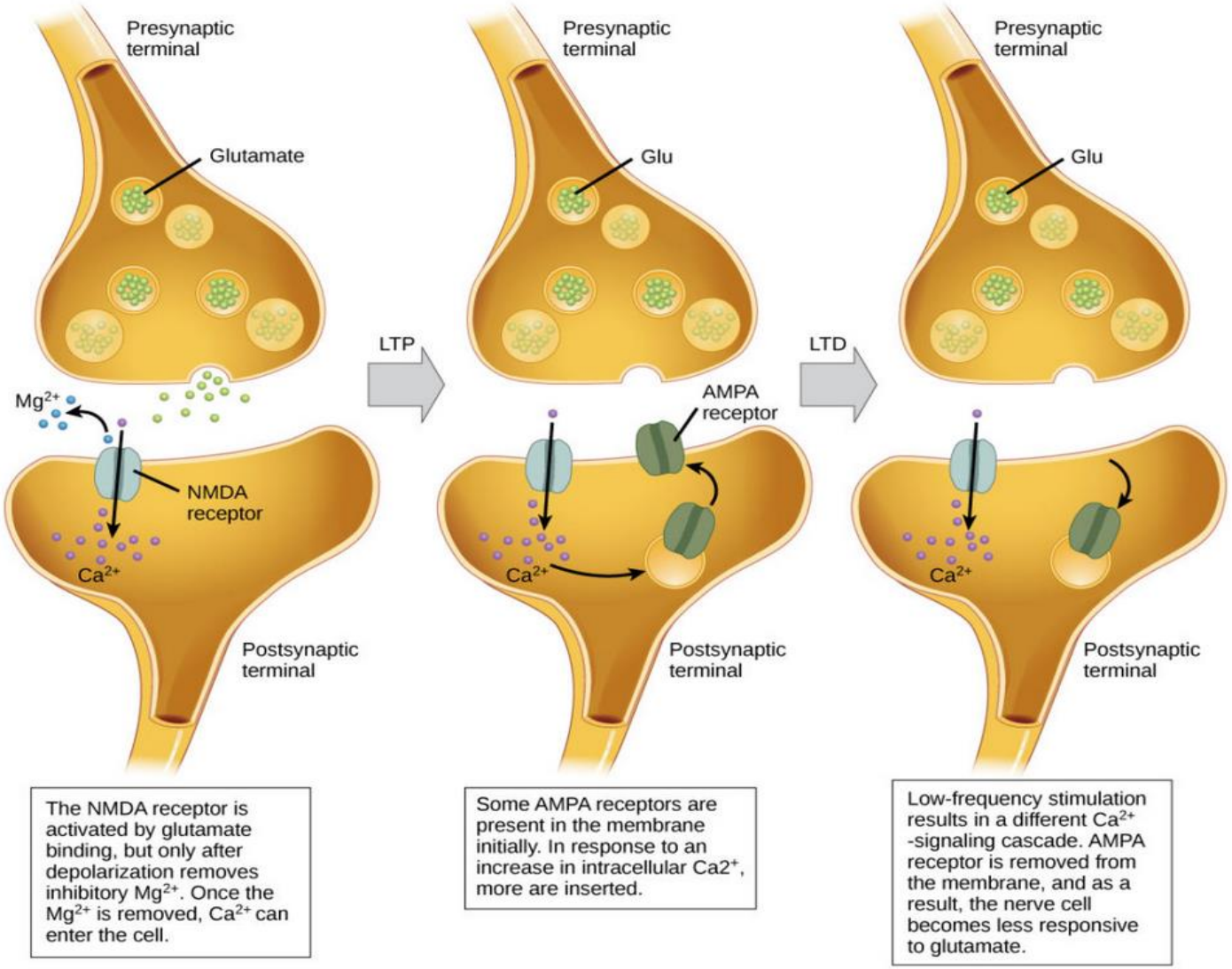
LTP and LTD: biochemical pathways

- Abbreviations: P = phosphorus, E-LTP = early LTP (1-3 hours), L-LTP = late LTP (> 24hrs), CaMK = Ca/Calmodulin dependent protein kinase, cAMP = cyclic adenosine monophosphate, PKA = cAMP-dependent protein kinase A, ERK/MAPK = extracellular signal-regulated protein kinase/ mitogen-activated protein kinase, RSK2 = ribosomal S6 kinase 2, CREB = cAMP-responsive transcription factor, PP1 = protein phosphatase 1, I-1 = inhibitor 1, +P = phosphorylation, -P = dephosphorylation.



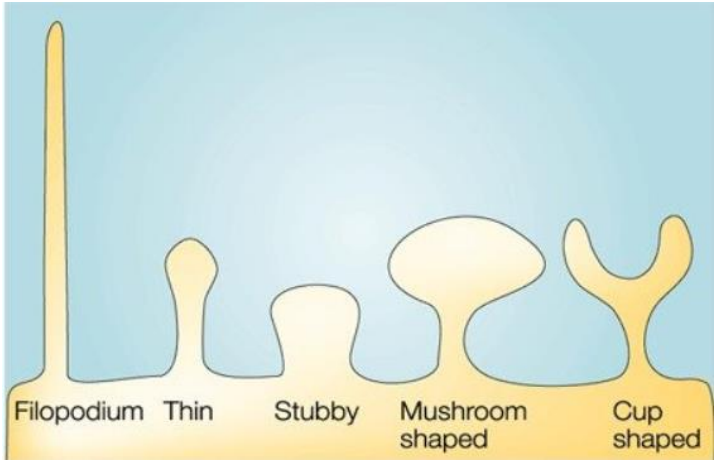
LTP and LTD: change in receptor number

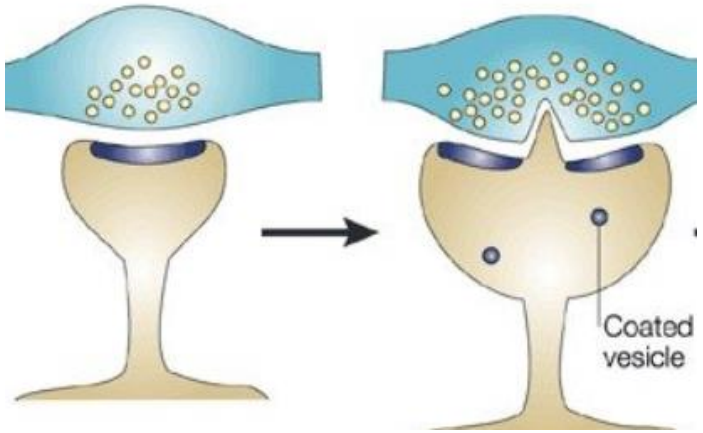
- https://courses.lumenlearning.com/wm-biology2/chapter/synaptic-plasticity/



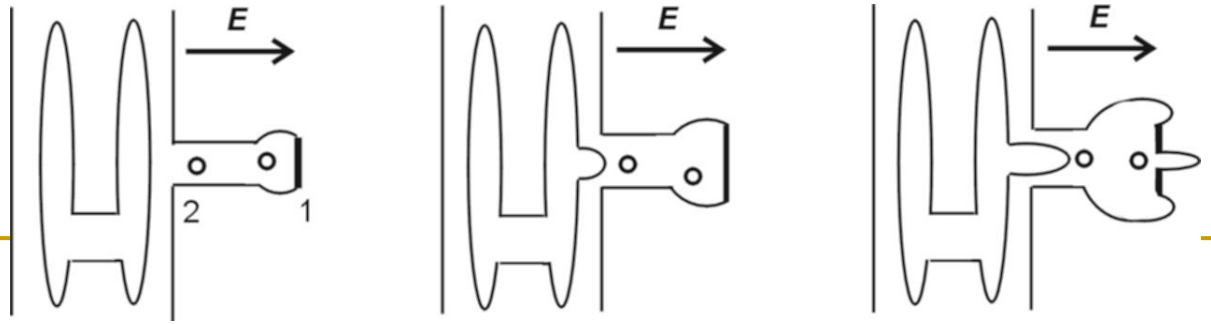
LTP: change of spine size and shape

- Spine shapes and change of spine size and shape during LTP (Hering and Sheng, 2001,https://www.nature.com/articles/35104061)



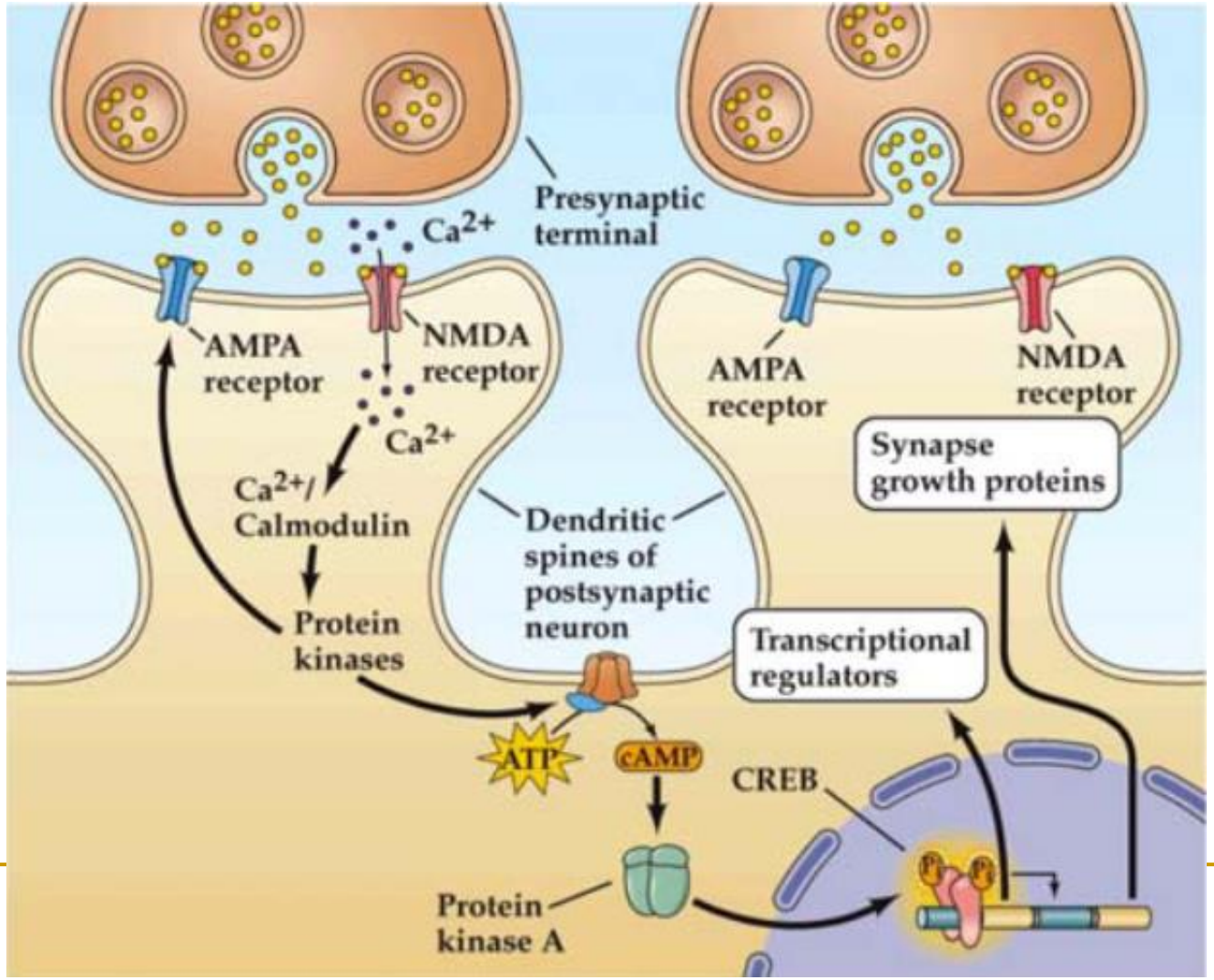


- Benuskova L (2000) The intra-spine electric force can drive vesicles for fusion: a theoretical model for long-term potentiation. Neuroscience Letters 280(1): 17-20.



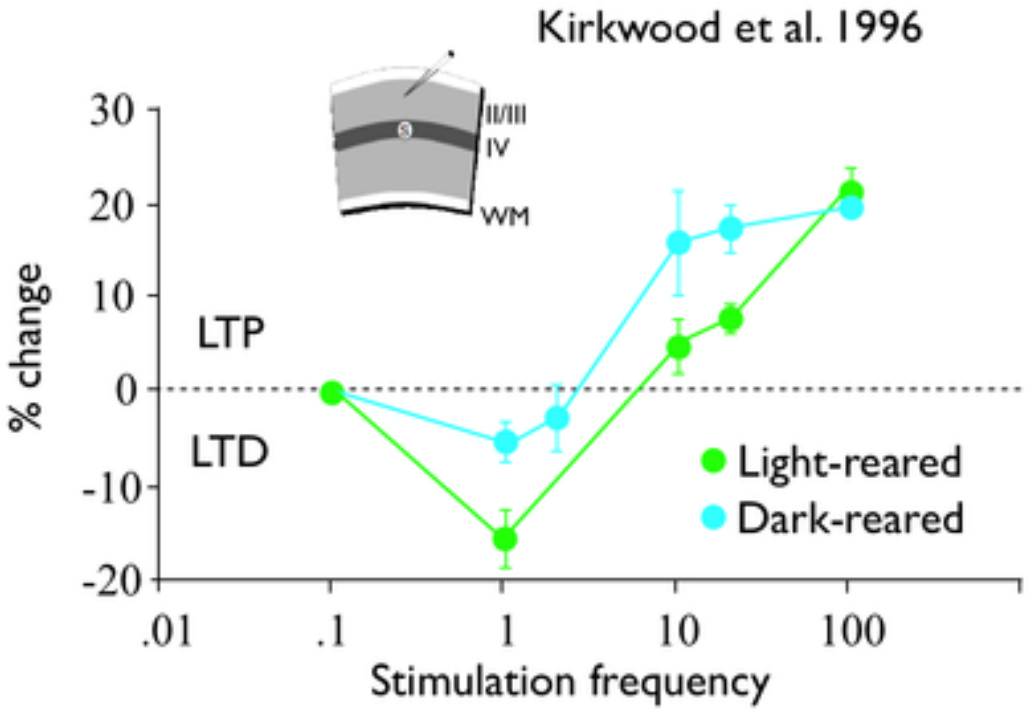
LTP: growth of new synapses

- Old synapse
- New synapse



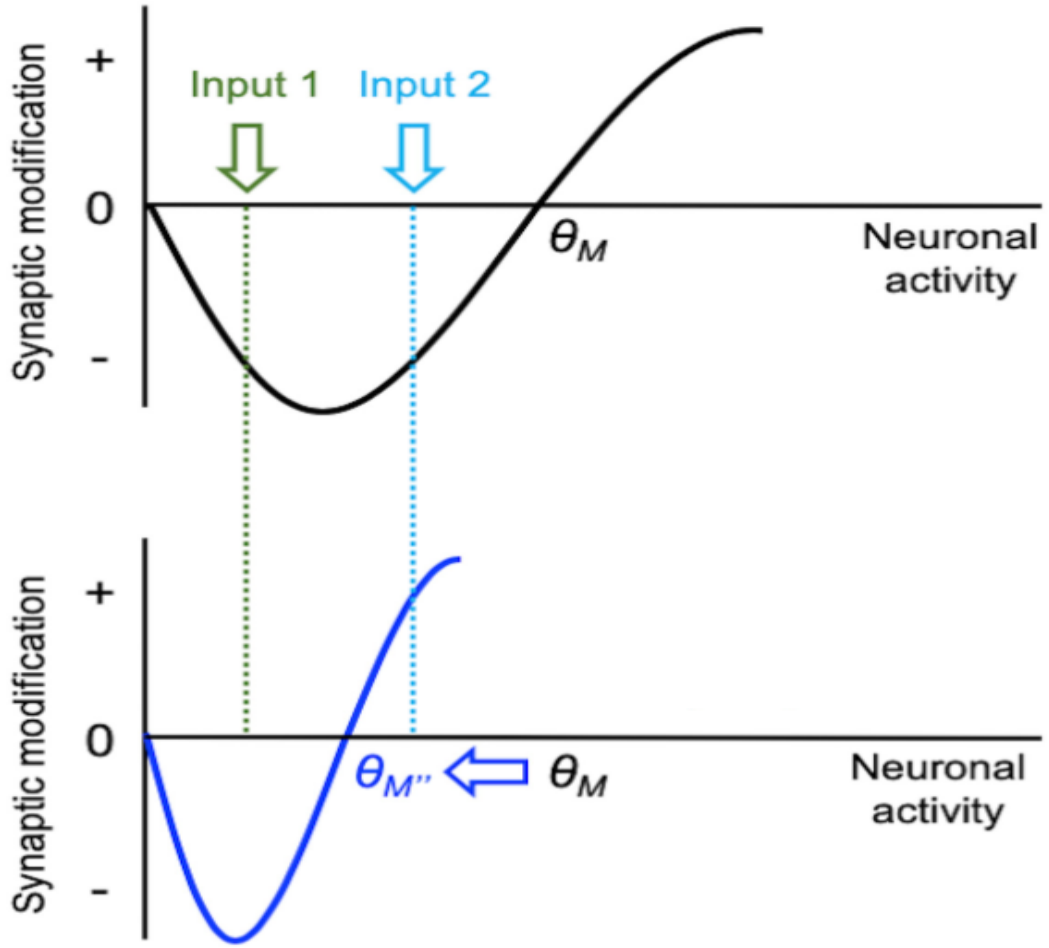
Dynamic LTP / LTD threshold

- 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 in Abraham, Nature Rev Neurosci (2008) 9: 387-399).

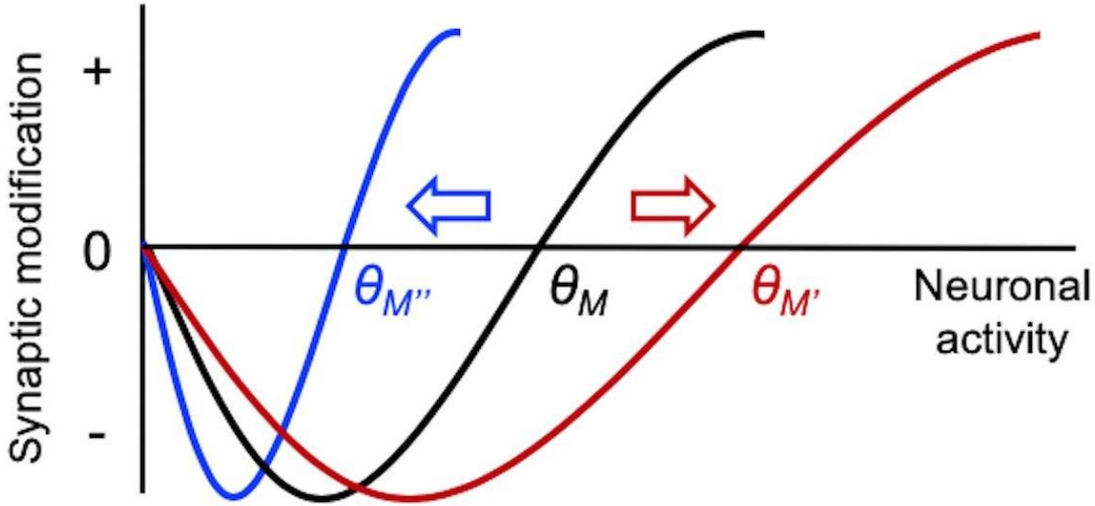
Dynamic LTP / LTD threshold predicted by Bienenstock, Cooper & Munro in their BCM theory (1982)



Source: https://www.frontiersin.org/articles/10.3389/fncel.2019.00520/full

Dynamic LTP / LTD threshold

- LTD / LTP threshold θ_M depends on the past overall postsynaptic cell activity and applies to all excitatory synapses on the postsynaptic cell thus, it is low for some of them and high for others.

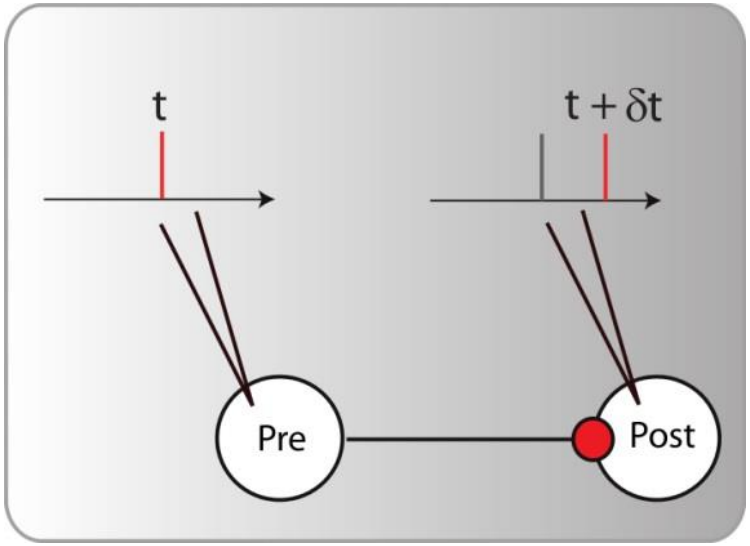


$$\langle y(t)\rangle_\tau = \frac{\alpha}{\tau}\int_{-\infty}^{t} y^2(t')\mathrm{e}^{\left(-\frac{(t-t')}{\tau}\right)}dt' \quad \text{where } y(t') = \begin{cases} 1 & \text{if there is a postsynaptic spike} \\ 0 & \text{if there is no postsynaptic spike} \end{cases}$$

Source: https://www.frontiersin.org/articles/10.3389/fncel.2019.00520/full

Timing (Markram et al., Science, 1997)

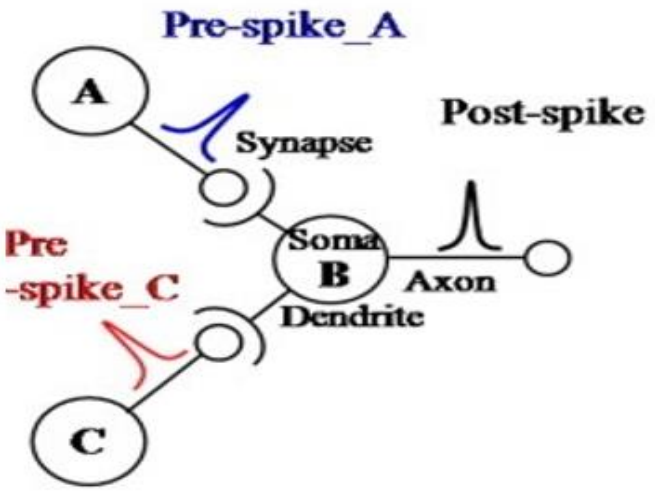
- In 1997, a new phenomenon was discovered – that the sign and magnitude of synaptic weight change depend also on the precise relative timing of pre- and postsynaptic spikes.



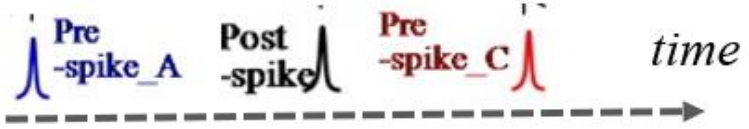
- Pre- and Post-synaptic neurons are forced to emit spikes with a pre-defined time difference, while the modification of the synaptic strength is monitored.

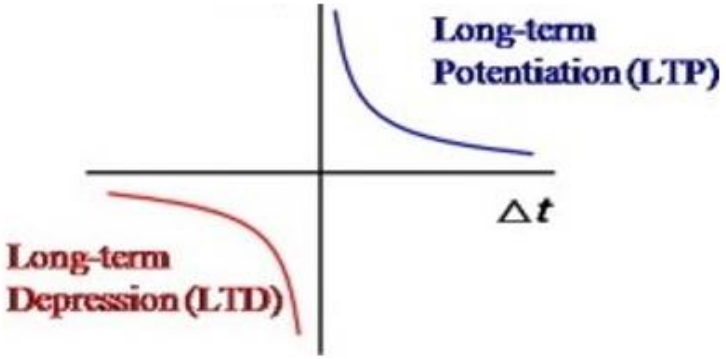
STDP: spike-timing dependent plasticity

- When presynaptic spike occurs before/after the postsynaptic spike, the synapse strength gets potentiated/depressed, respectively.



- The magnitude of weight change decreases exponentially with Δt.

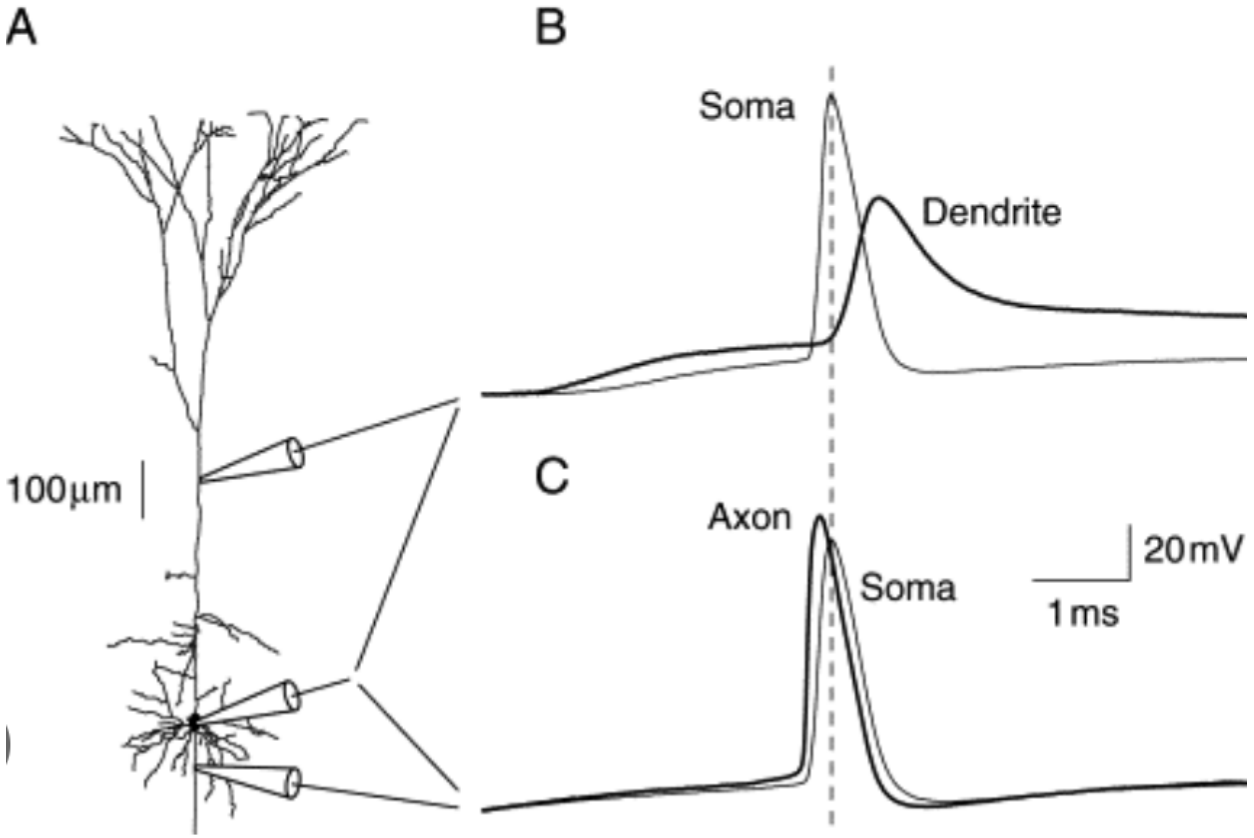




- Kang et al., 2015, https://doi.org/10.1016/j.neucom.2014.12.036

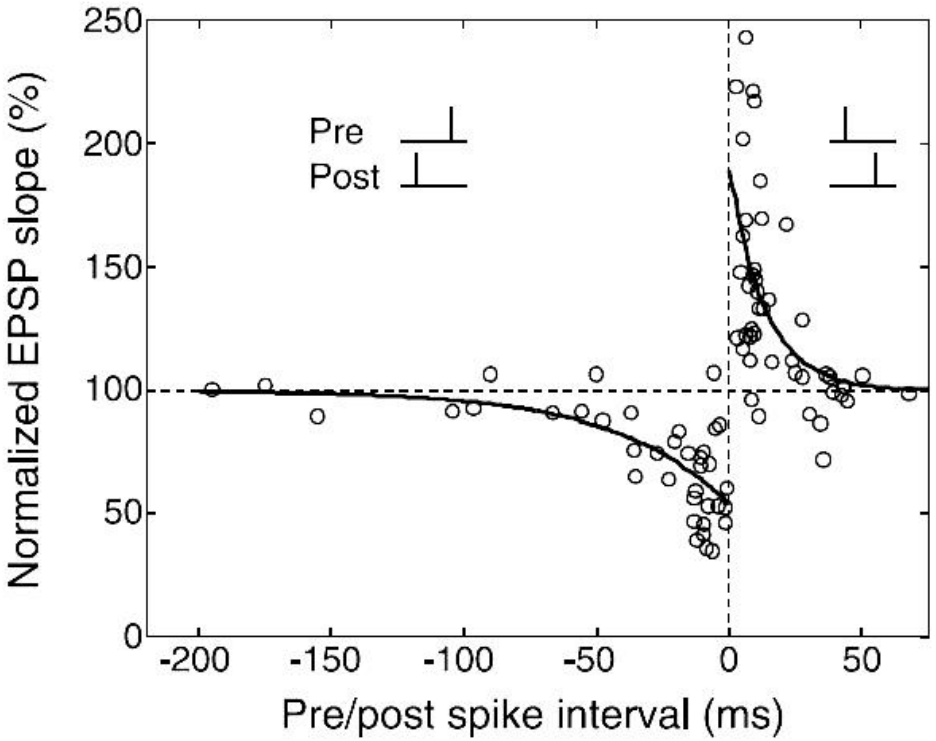
STDP: backpropagation of action potential (bAP)

- AP propagates not only along the axon but also back to the dendrites.
- Thus, lets synapses "know" when there is a postsynaptic spike.



STDP: formulas

- Parameters A_+, A_- are the amplitudes of synaptic change for $\Delta t = 0$.
- Parameters τ_+, τ_- are the so-called time decay constants of the exponential time window for potentiation/depression, respectively (Froemke et al., 2006).



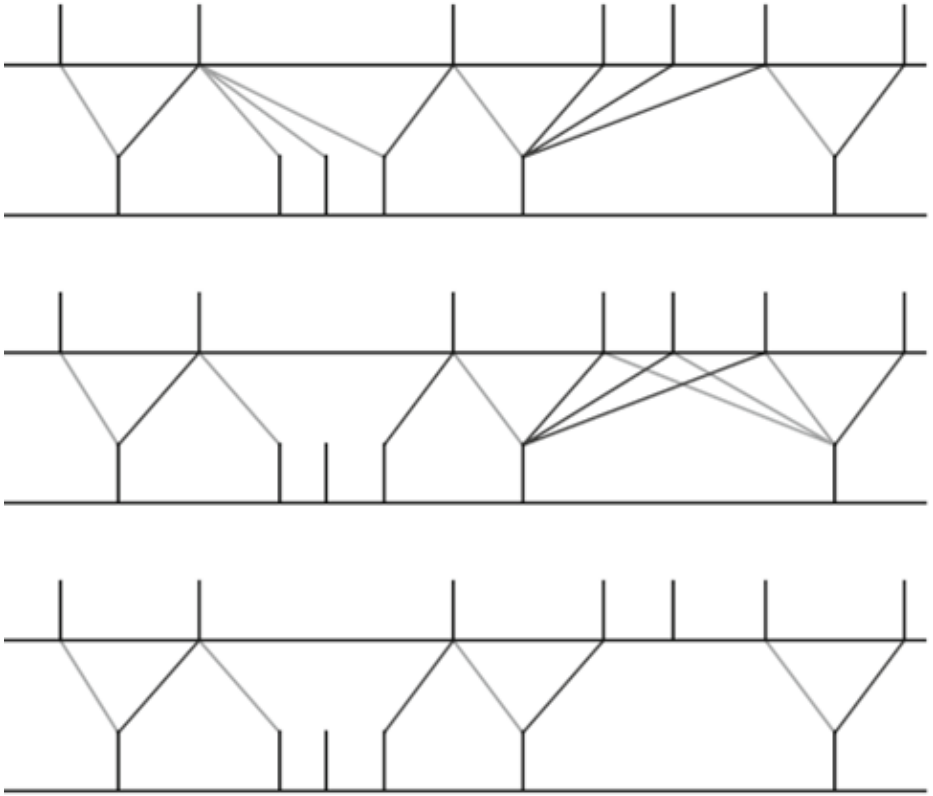
$$\Delta w_+ = A_+ \, e^{-\Delta t / \tau_+}$$

$$\Delta w_- = A_- \, e^{\Delta t / \tau_-}$$

$$\Delta t = t_{\text{post}} - t_{\text{pre}} \quad \text{(ms)}$$

STDP: nearest neighbours pairing schemes

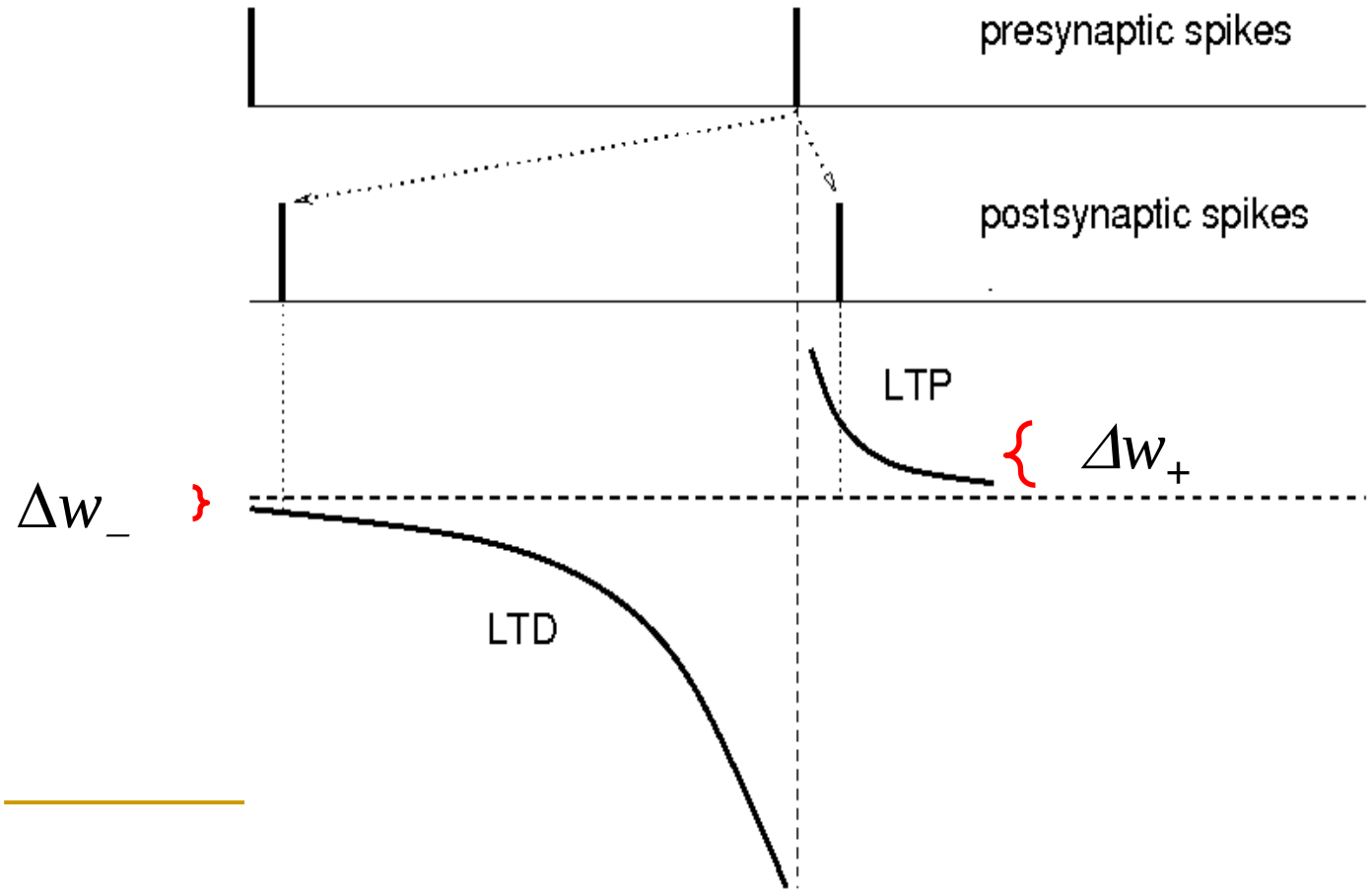
- **Symmetric:** each presynaptic spike is paired with the last postsynaptic spike and each postsynaptic spike is paired with the last presynaptic spike.
- **Presynaptic centred**: each presynaptic spike is paired with the last and next postsynaptic spike.
- **Reduced symmetric**: the same as in above,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



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

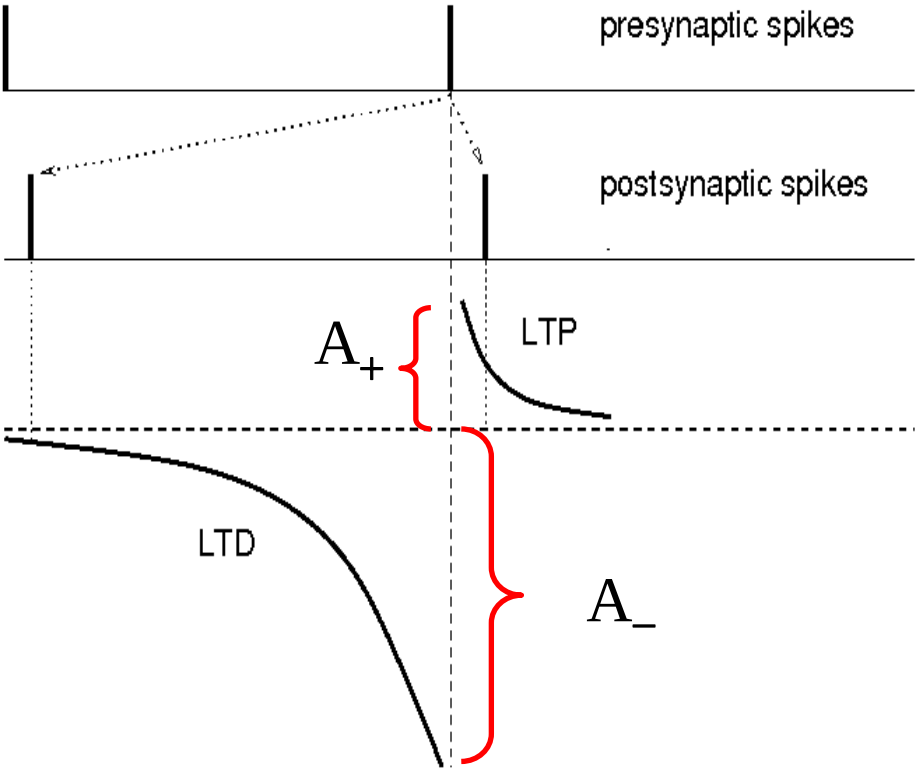
Presynaptic centred implementation of STDP

- The total change of synaptic weight: $\Delta w = \Delta w_+ + \Delta w_-$



STDP leads to the BCM threshold

- Izhikevich and Desai (2003) showed that STDP leads to BCM for the presynaptically centred pairing:



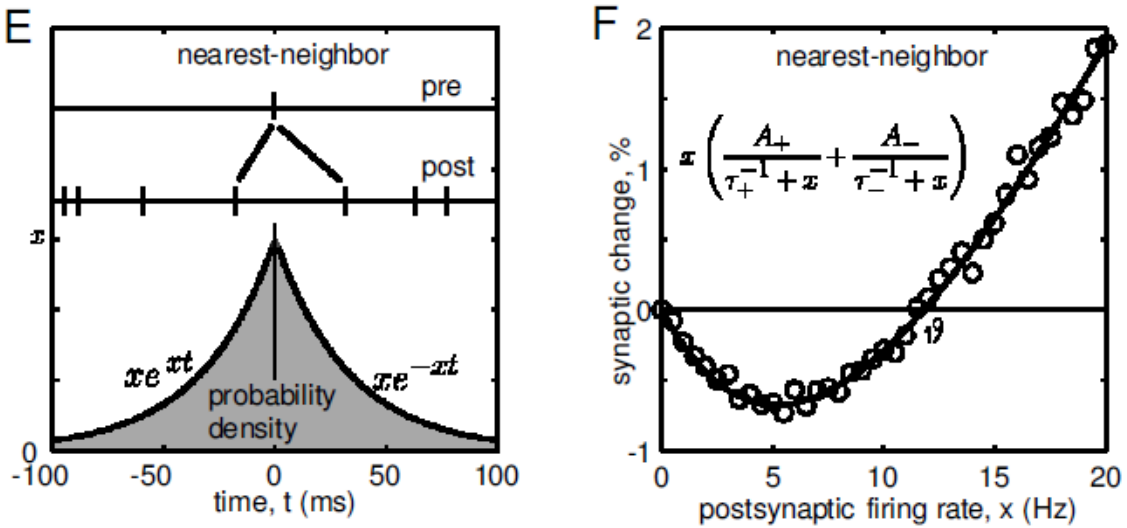
$$C(x) = \overbrace{\int_0^\infty A_+ \, e^{-t/\tau_+} \, x e^{-xt} \, dt}^{\text{average potentiation}} + \overbrace{\int_{-\infty}^0 A_- \, e^{t/\tau_-} \, x e^{xt} \, dt}^{\text{average depression}}$$

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

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

STDP leads to the BCM-like LTD/LTP threshold

- Izhikevich and Desai (2003) calculated the value of frequency of presynaptic spikes for which $\Delta w_+ = \Delta w_- = 0$

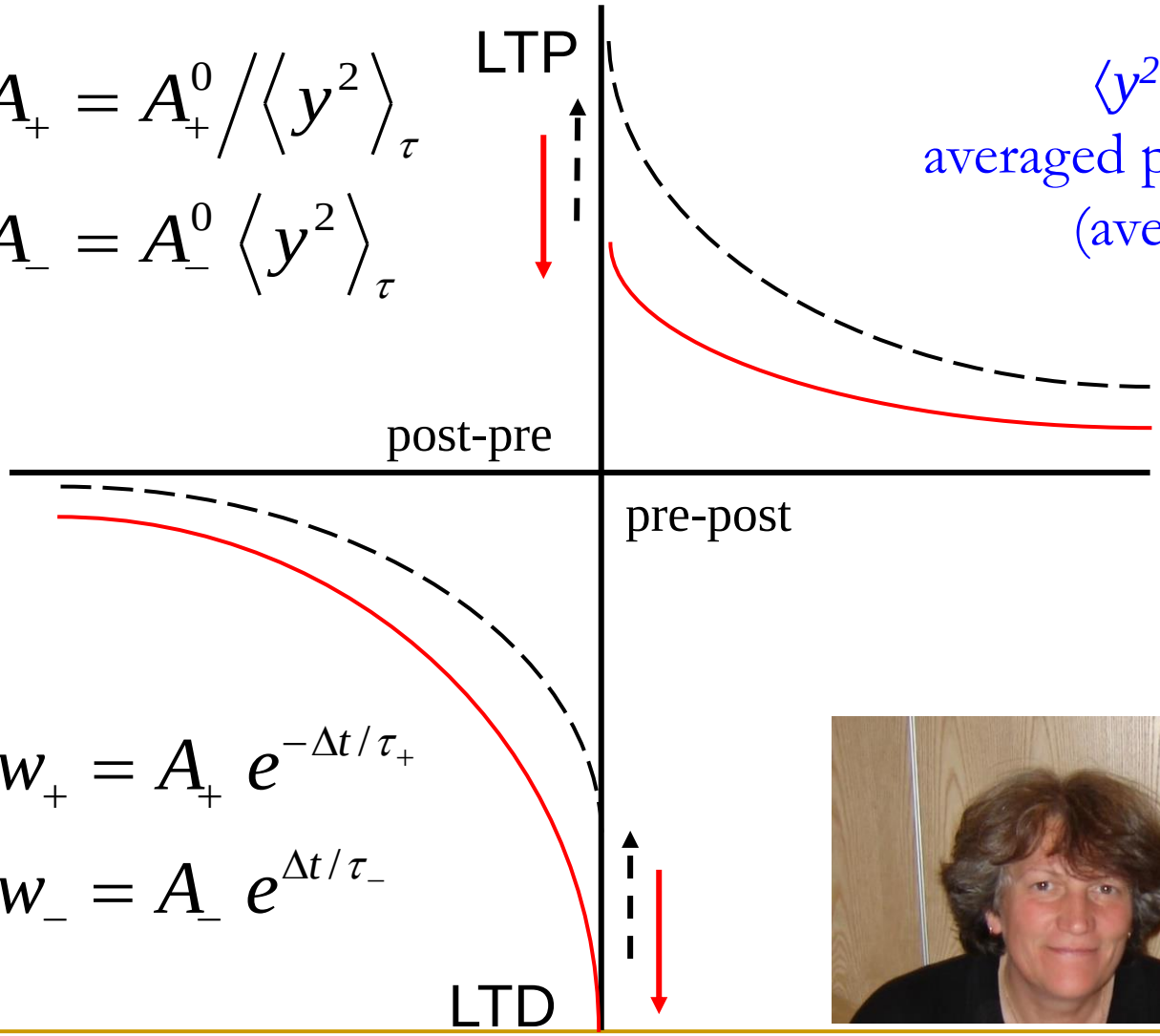


- This threshold corresponds to the BCM threshold and LTP/LTD curve has the shape of parabola as in the BCM theory.
- But, the LTD/LTP threshold is fixed, i.e. does not move.

metaSTDP (Benuskova & Abraham, 2007)

$$A_+ = A_+^0 \Big/ \left\langle y^2 \right\rangle_\tau$$

$$A_- = A_-^0 \left\langle y^2 \right\rangle_\tau$$

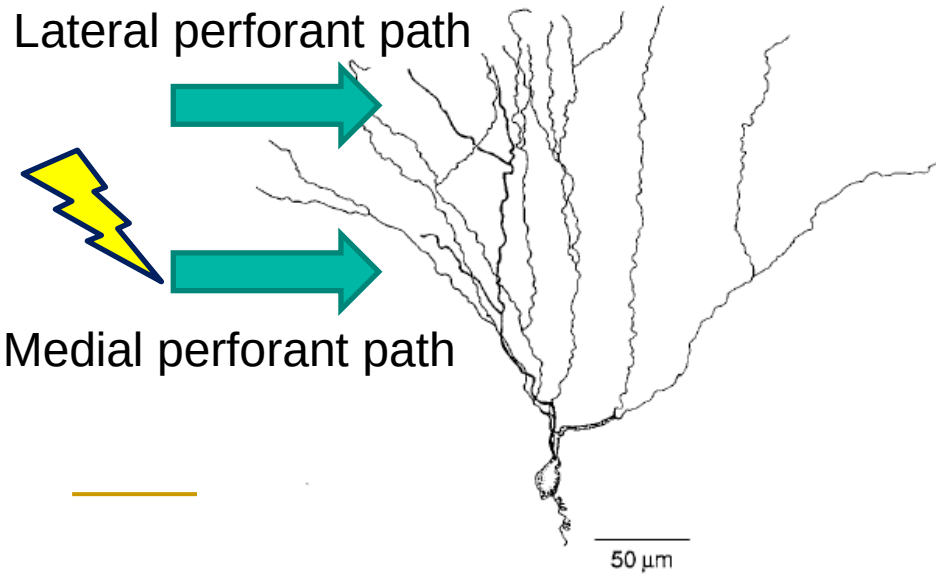


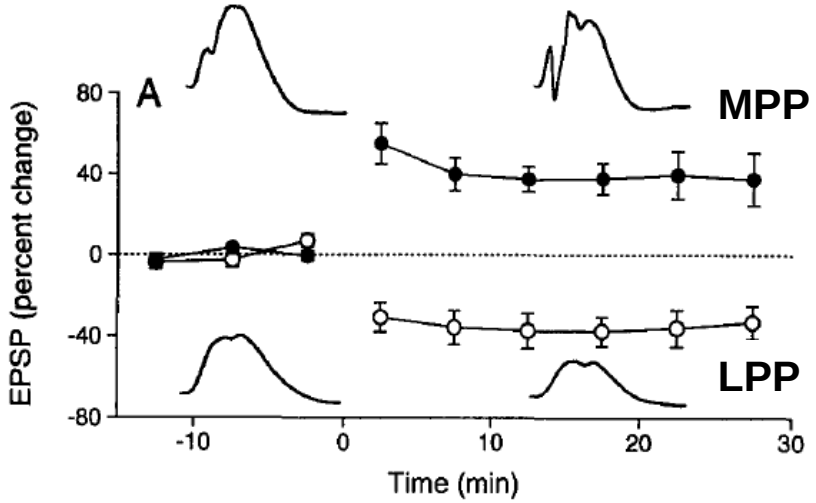
$$\Delta w_+ = A_+ \, e^{-\Delta t / \tau_+}$$

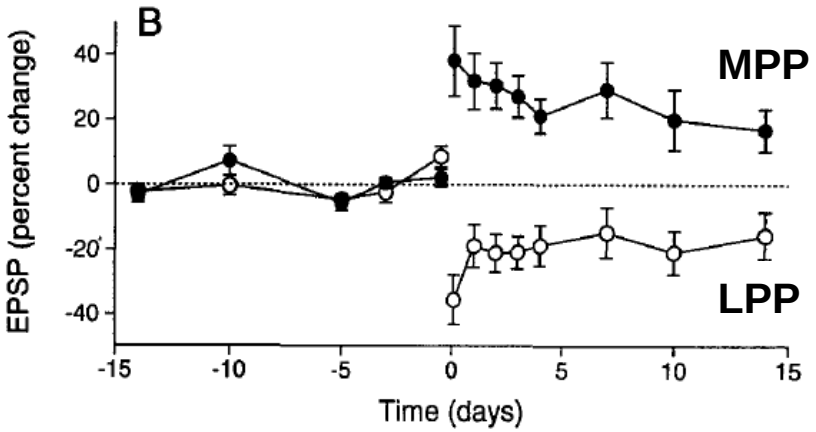
$$\Delta w_- = A_- \, e^{\Delta t / \tau_-}$$

$\langle y^2 \rangle_\tau$ is the *prior* time-averaged postsynaptic activity (average spike count or somatic voltage).

Heterosynaptic LTD

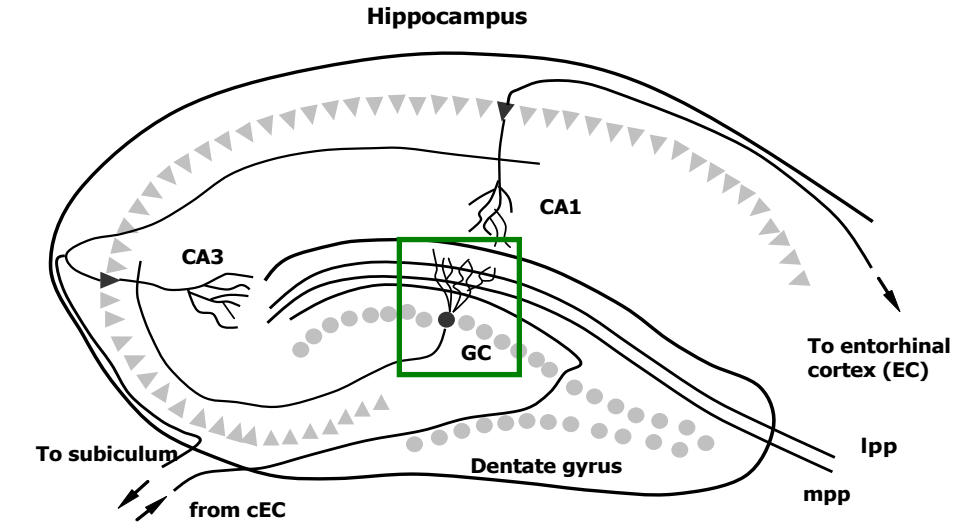


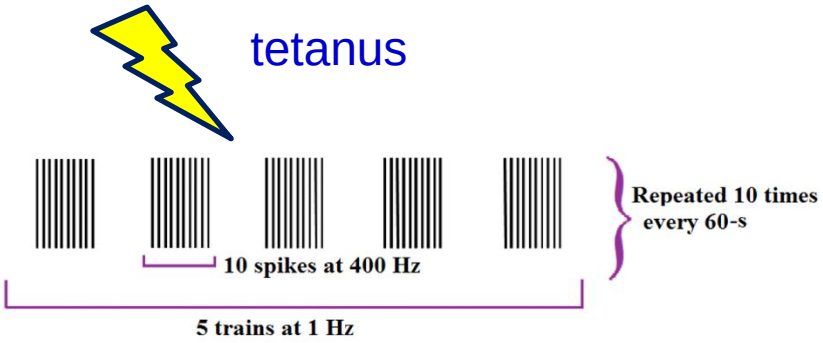


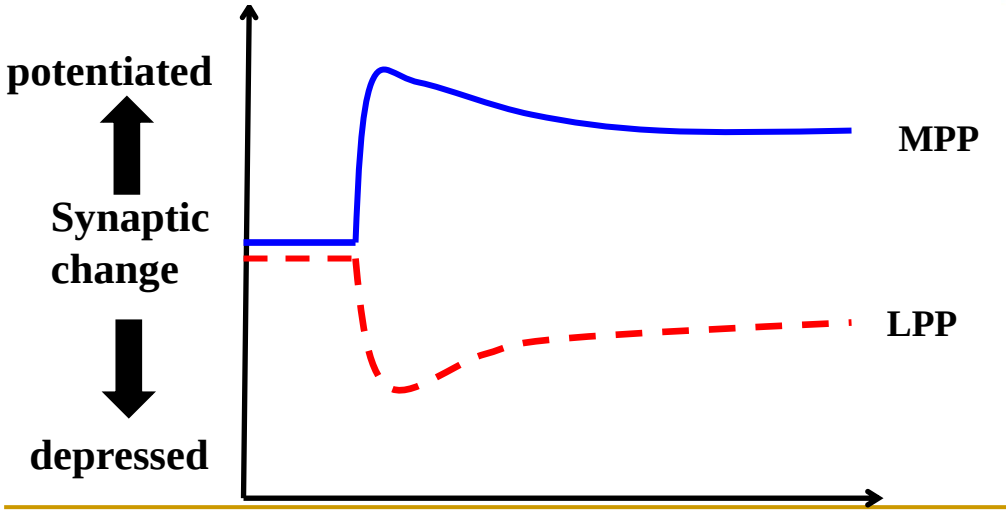


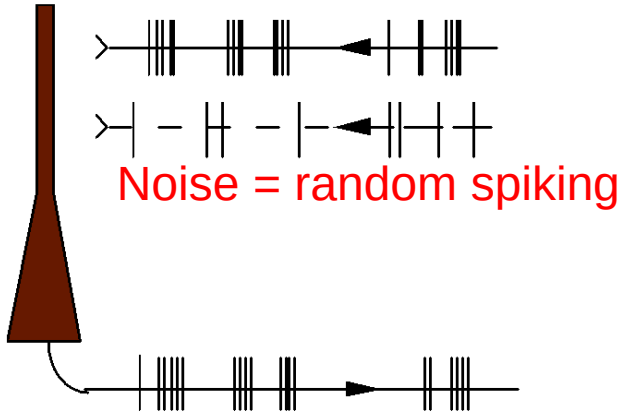
Abraham et al, *PNAS* 1994

Tetanus of MPP leads to homosynaptic potentiation of MPP and noise at LPP to **hetero**synaptic depression of LPP input

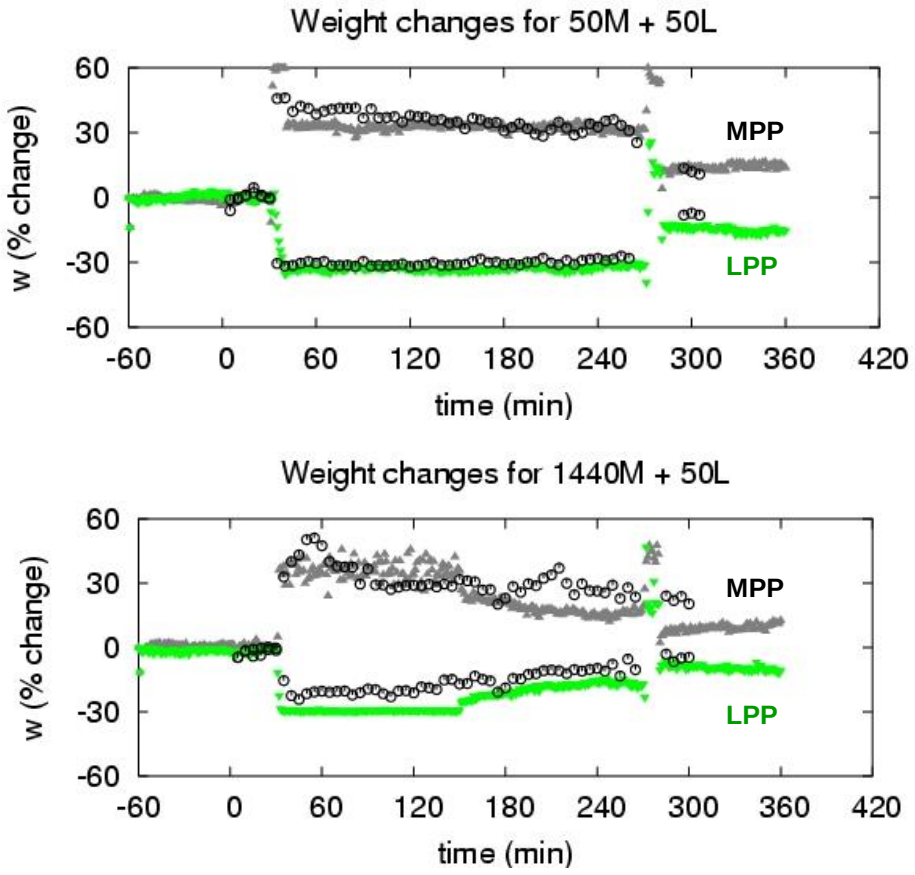








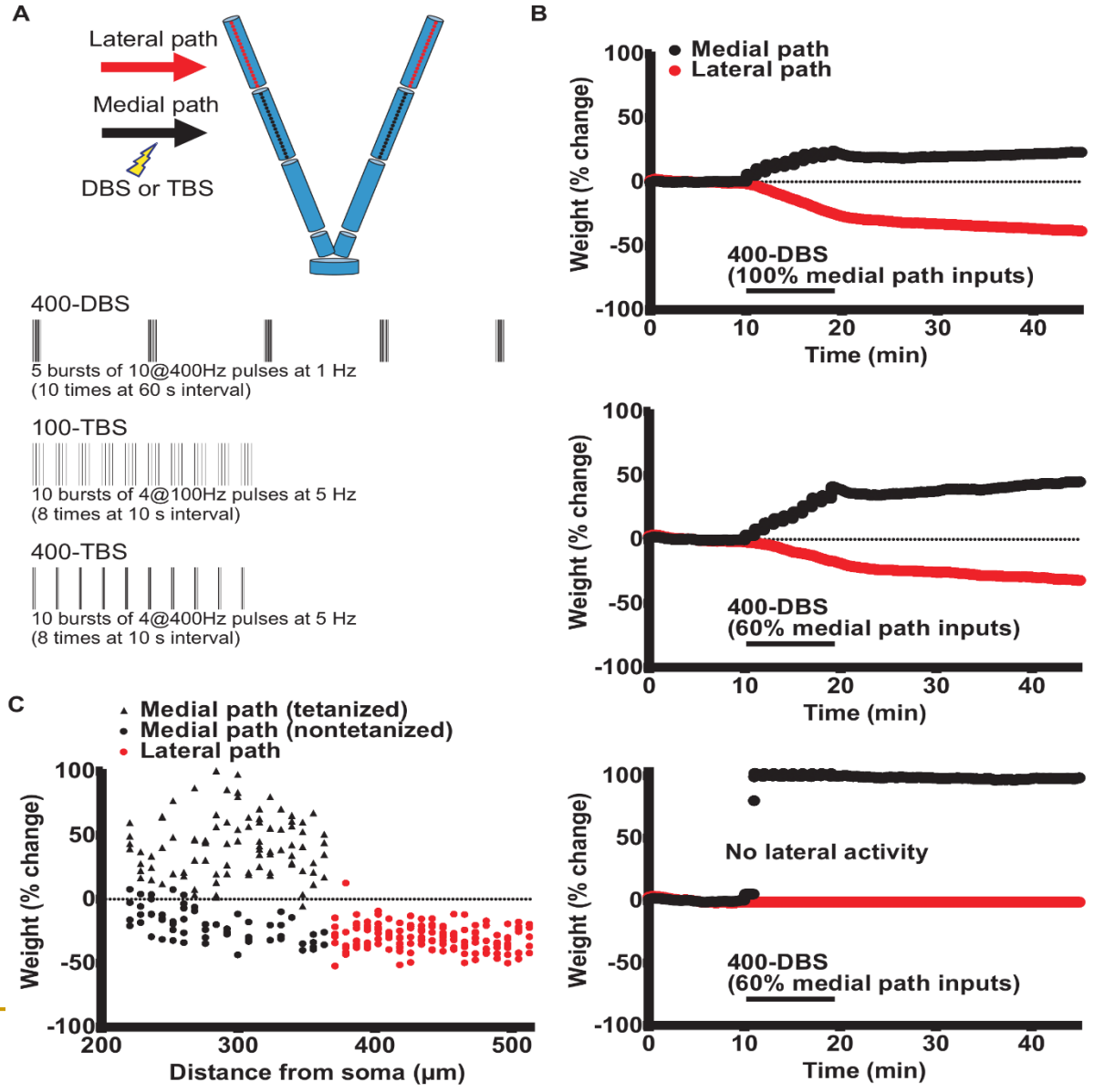
Results of metaSTDP



- Model: Izhikevich spiking neuron, initial weights adjusted so that the output spiking of the granule cell = 2Hz.
- Dynamic BCM threshold for LTD/LTP embedded in STDP (metaSTDP)
- Result: Frequency-dependent homo- and hetero-synaptic plasticity

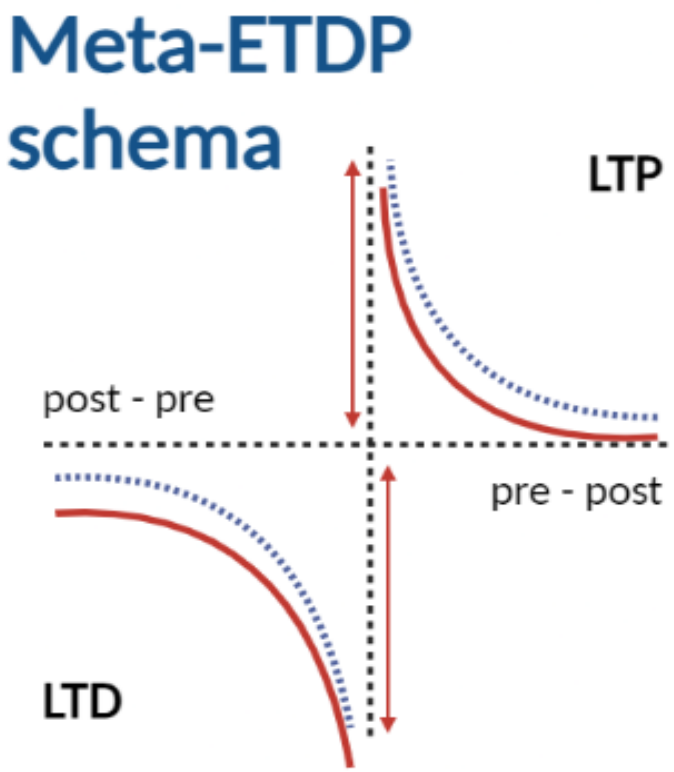
Source: Benuskova & Abraham, JCNS, 2007

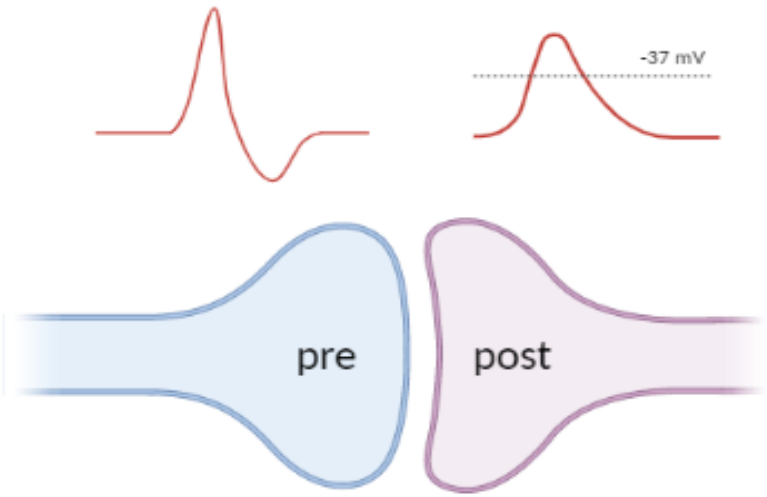
Multicompartmental model (Jedlicka, Benuskova, Abraham, 2015)



ETDP: event-timing dependent plasticity

- pre = time of presynaptic spike, post = time when PSP removes Mg block from NMDARs at the postsynaptic membrane.





Conclusion

- In the pre-post event-pairing timing (ETDP) rule, the presynaptic event is a presynaptic spike or release of glutamate, and the postsynaptic event is the local voltage crossing a given value.

- This local threshold is the same for LTD and LTP, and may correspond to a membrane voltage at which the Mg^{2+} block is removed from NMDARs. Local postsynaptic potential is the result of spatio-temporal summation of local potentials and bAP.

- Dynamic BCM threshold for LTD/LTP, embedded in the metaETDP is the same for all synapses and is calculated based on floating average of postsynaptic spiking over some recent time.