



**SPPIN** SAINTS-PERES  
Paris Institute for  
the Neurosciences



# Synaptic Plasticity : Spike-timing dependent plasticity (STDP)

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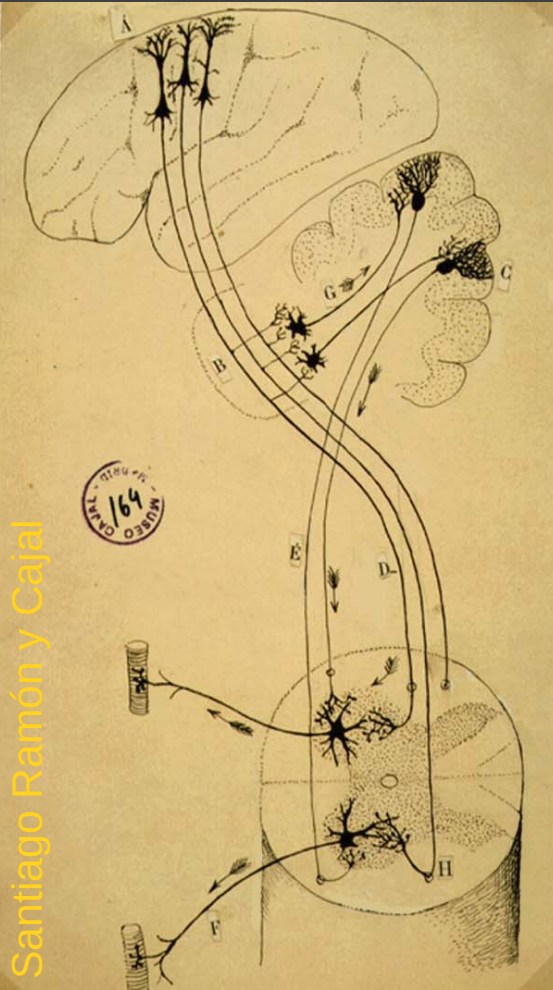
*Saints-Pères Paris Institute for the Neurosciences*

*CNRS UMR 8003, Université de Paris*

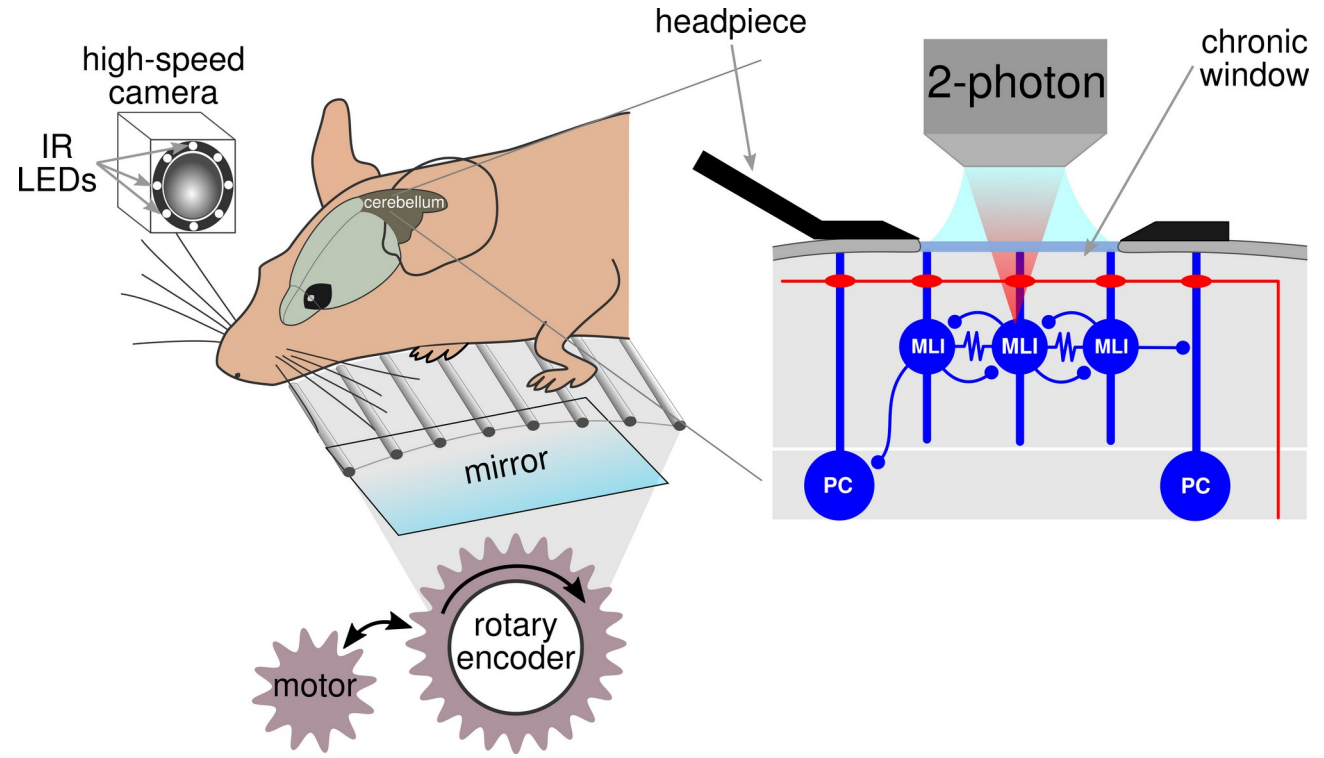
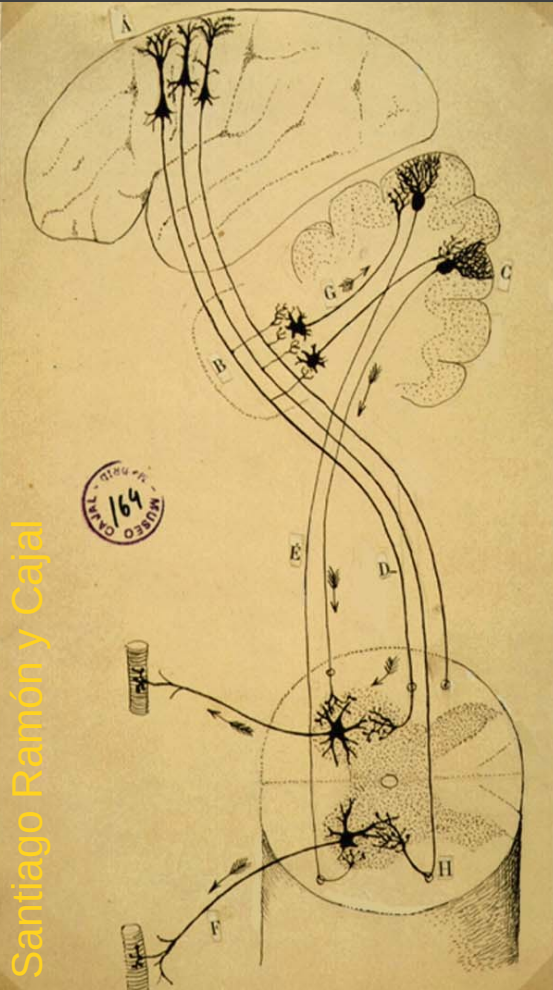
slides on : <https://www.biomedicale.parisdescartes.fr/~mgraupe/teaching.php>

# Cerebellum and locomotion

Cerebellum ensures that movements are well timed and highly coordinated.



# Cerebellum and locomotion



Students are welcome !

A white line-art illustration of a human brain, showing the intricate folds and grooves of the cerebral cortex. The brain is centered on a solid blue background. A semi-transparent blue horizontal bar is overlaid across the middle of the brain, containing the text.

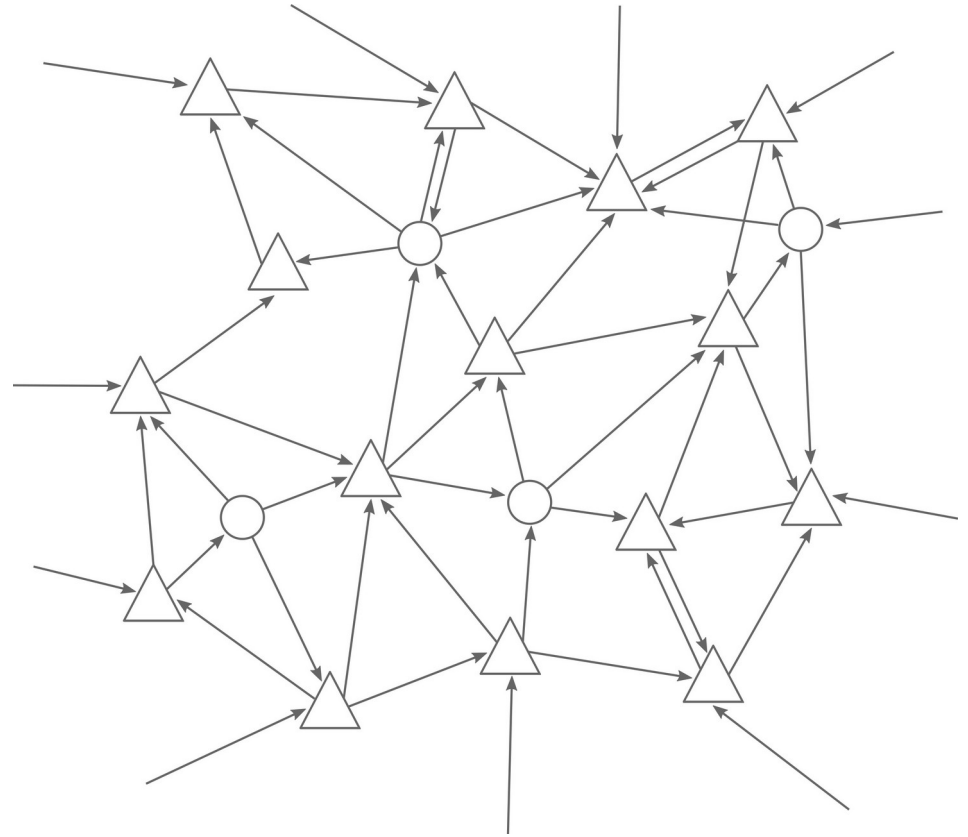
**At which university am I working ?**

A white outline of a human brain, showing the complex folds and gyri of the cerebral cortex. The brain is centered on a solid blue background. A semi-transparent light blue rectangular area is overlaid on the brain, containing text.

**At which university am I working ?**

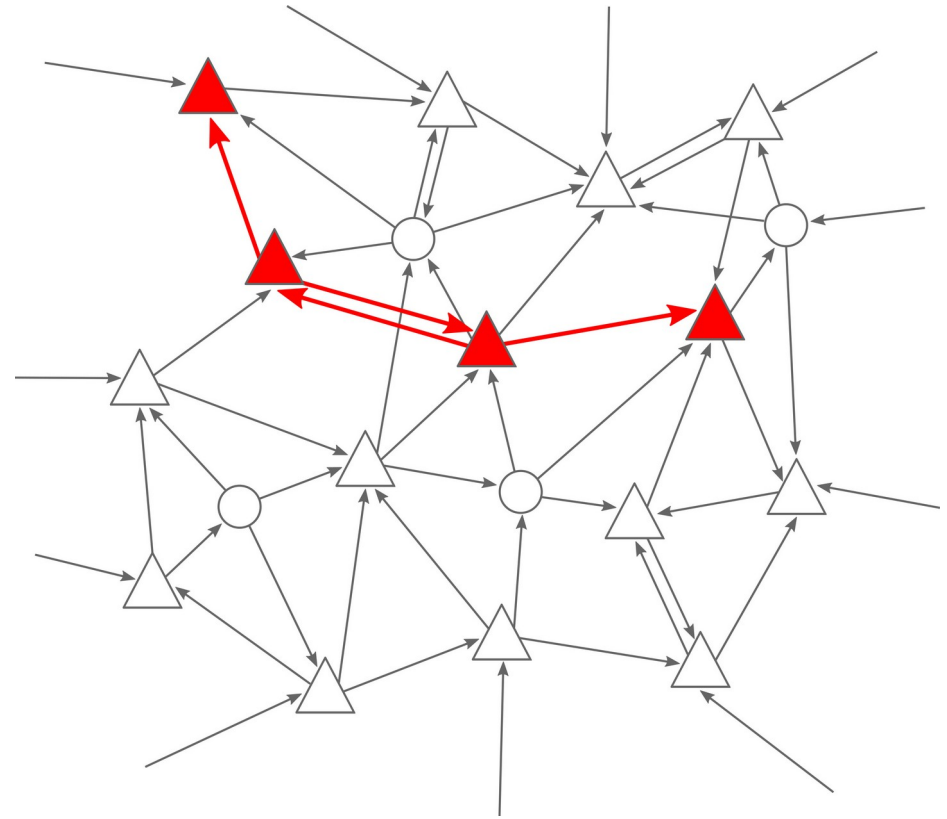
**→ What happens in your brain when you learn ?**

# Learning on the neuronal network level

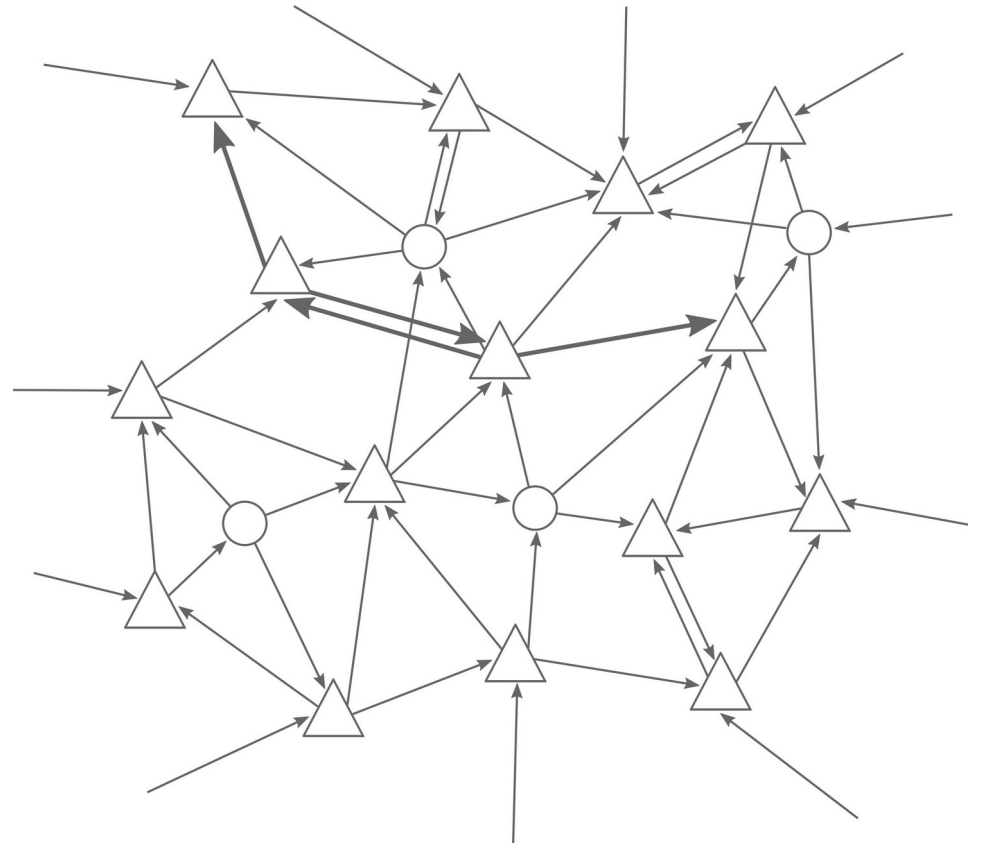


# Learning on the neuronal network level

Stimulus / Experience



# Learning on the neuronal network level

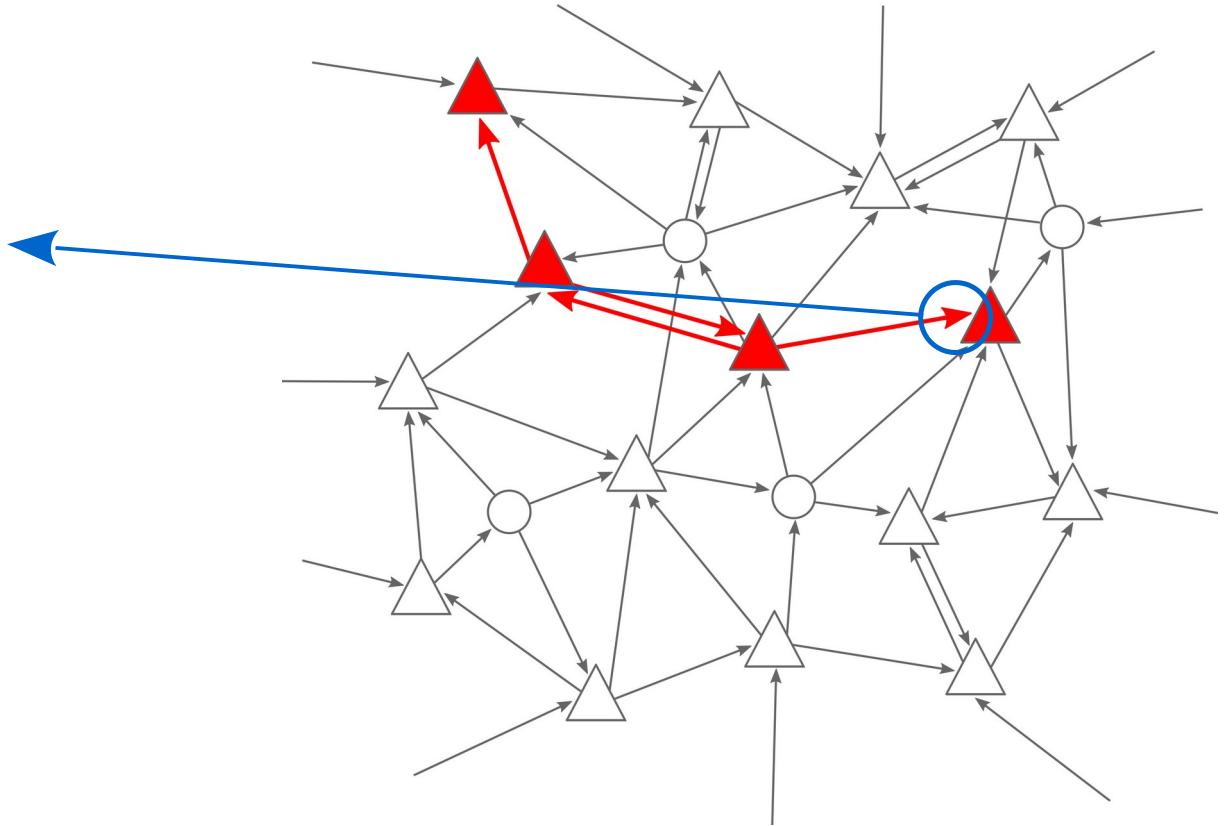




# Focus of today's lecture

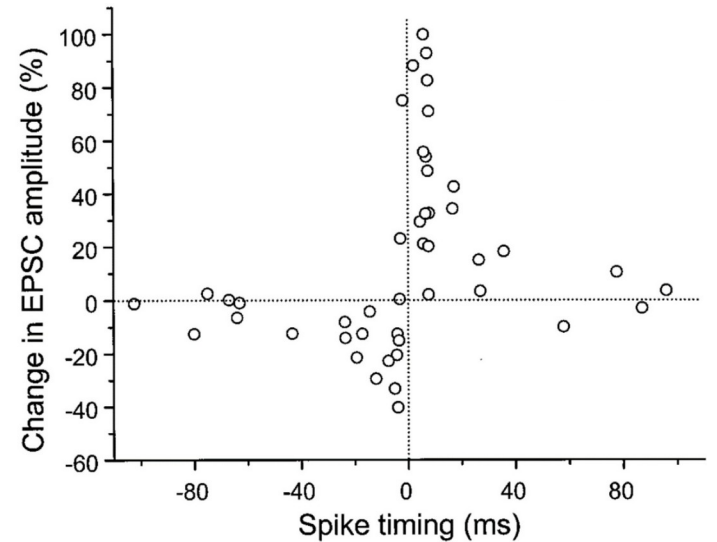
Which activity pattern leads to a change in the connection between the neurons ?

Which role does the timing of pre- and postsynaptic action potentials play ?



# Outline : STDP ... spike-timing dependent plasticity

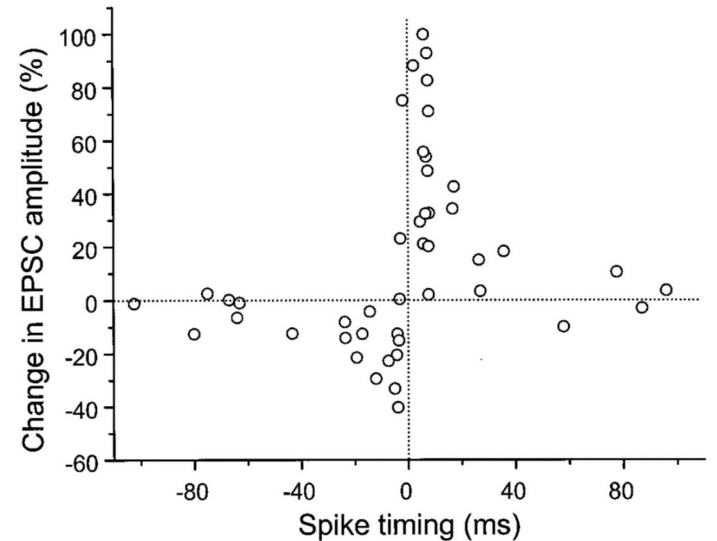
1. STDP : introduction and history
2. Phenomenology of STDP
3. Induction mechanisms
4. Biophysical models of STDP
5. STDP *in vivo*



[Bi & Poo 1998]

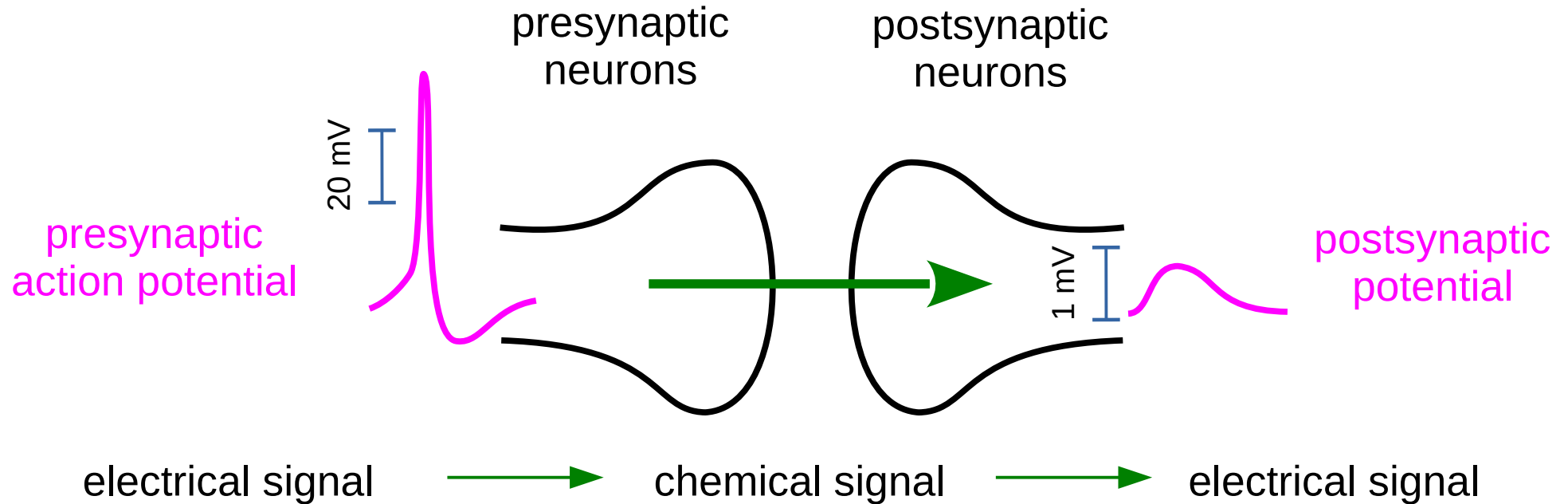
# Outline : STDP ... spike-timing dependent plasticity

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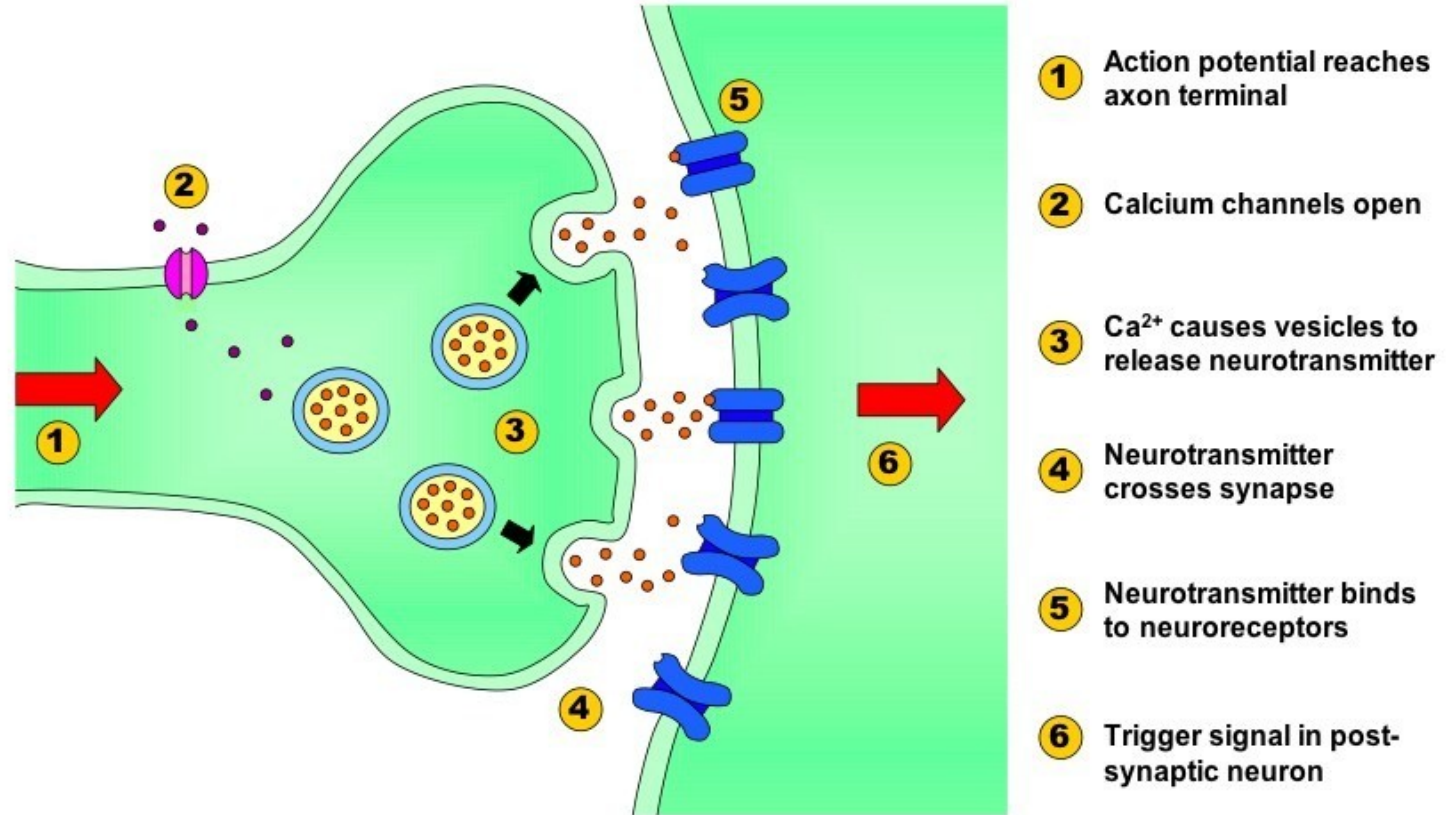
[Bi & Poo 1998]

# Chemical synapse : transmits electrical signals



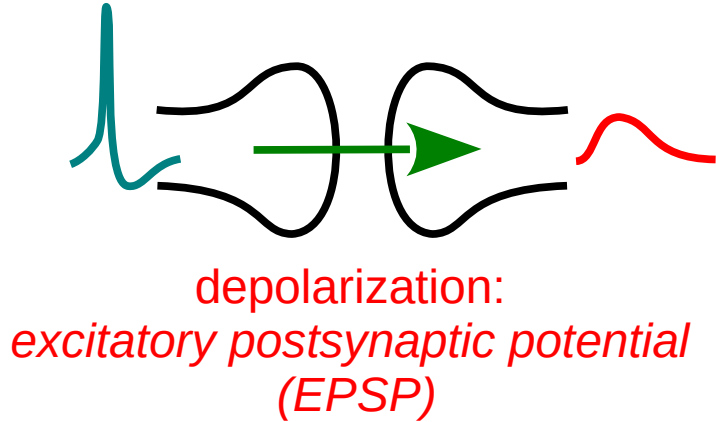
- directional transmission
- conversion of signals allows for flexibility/plasticity

# Chemical synapse : underlying biological machinery

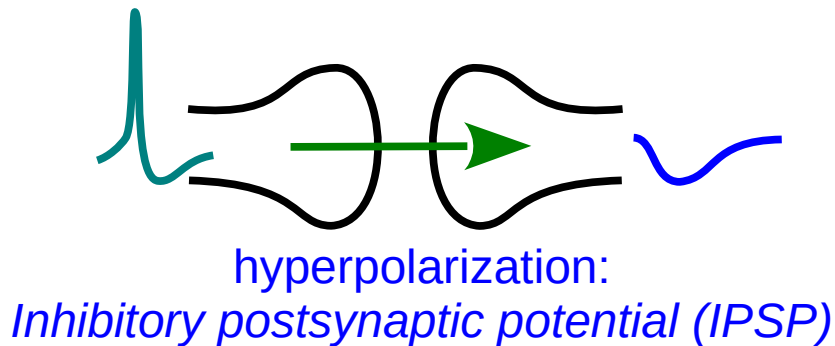


# Chemical synapse : excitatory or inhibitory

## Excitatory synapse



## Inhibitory synapse

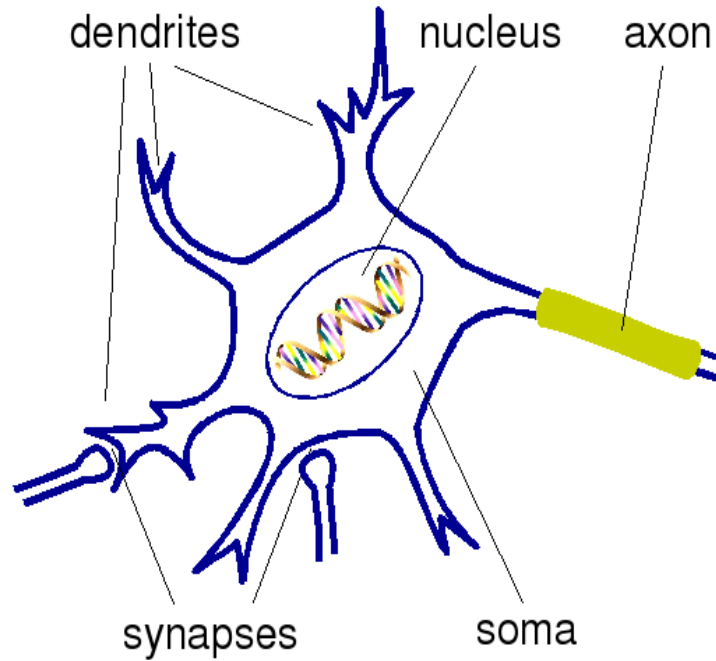


neurotransmitter	receptor
glutamate	AMPA, NMDA
acetylcholine	nAChR, mAChR
catecholamines	G-protein-coupled receptors
serotonin	5-HT <sub>3</sub> , ...
histamine	G-protein-coupled receptors

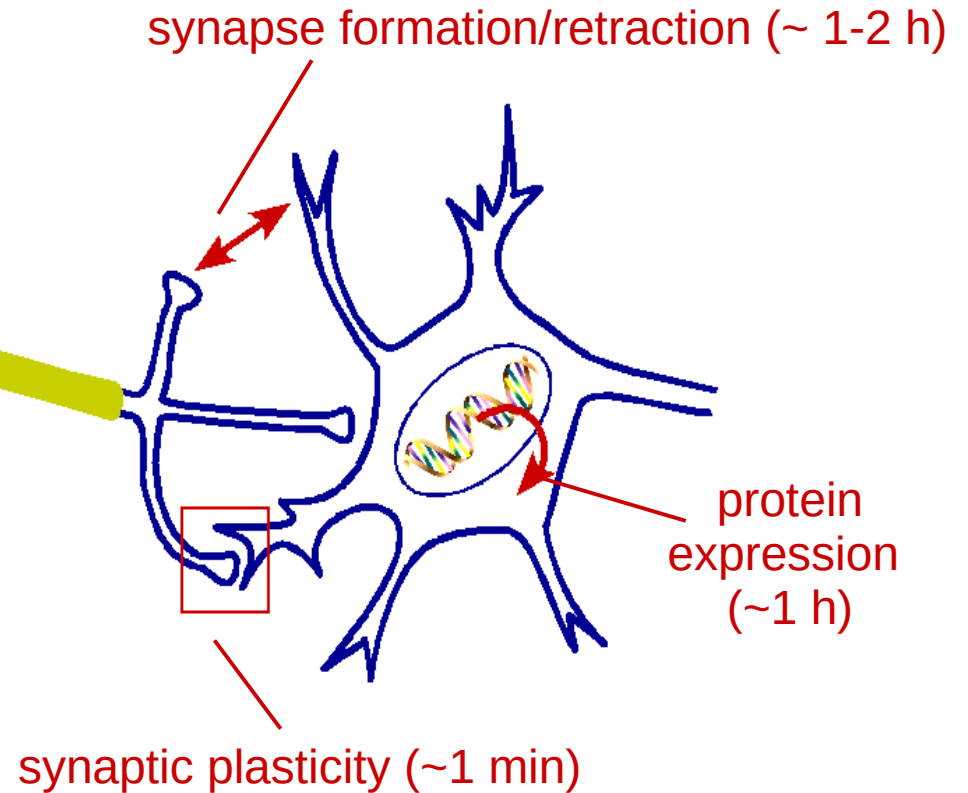
neurotransmitter	receptor
GABA	GABA <sub>A</sub> , GABA <sub>B</sub>
glycine	GlyR

# Different forms of plasticity

## structure of neurons

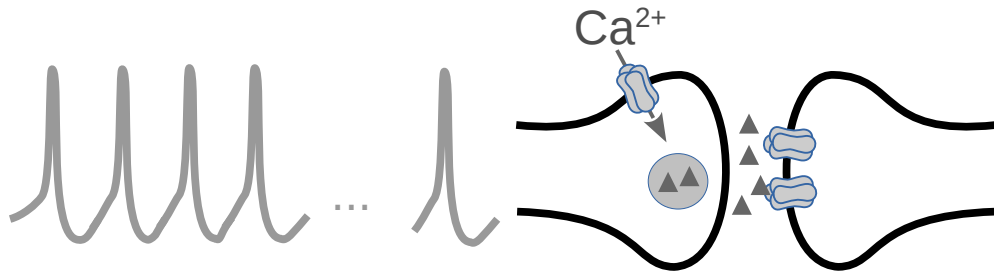


## changes related to neural activity

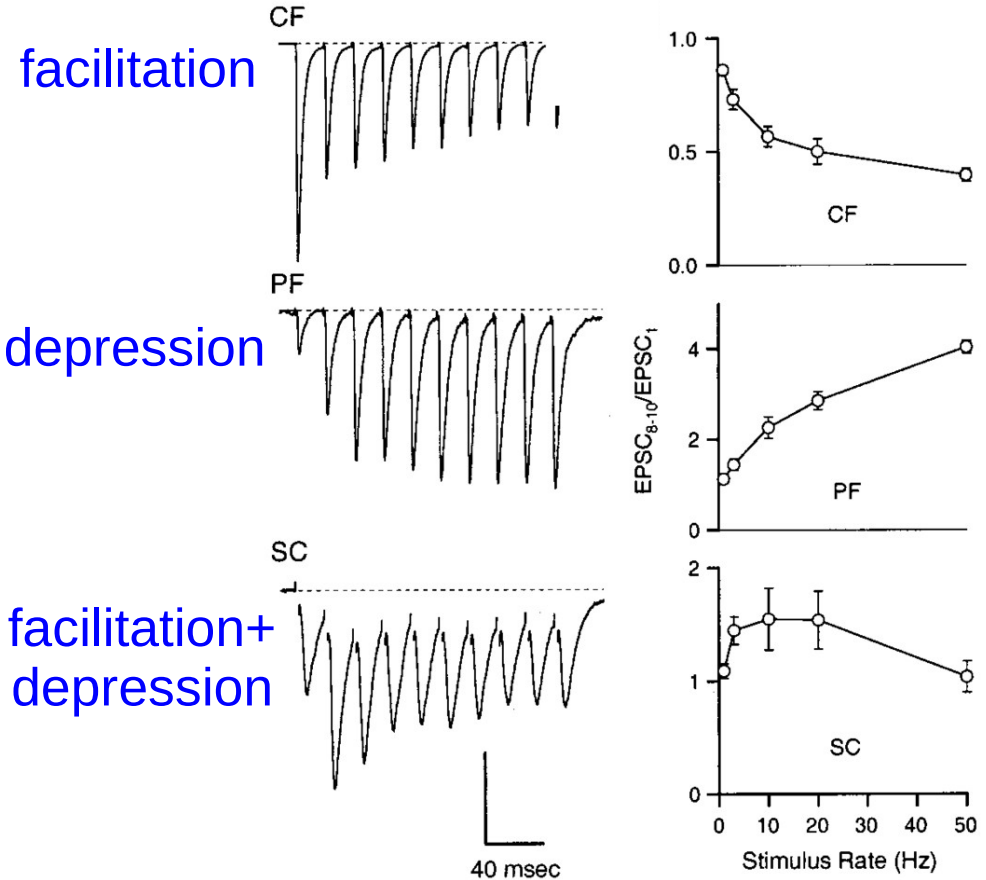


# Short-term synaptic plasticity

train of presynaptic action potentials

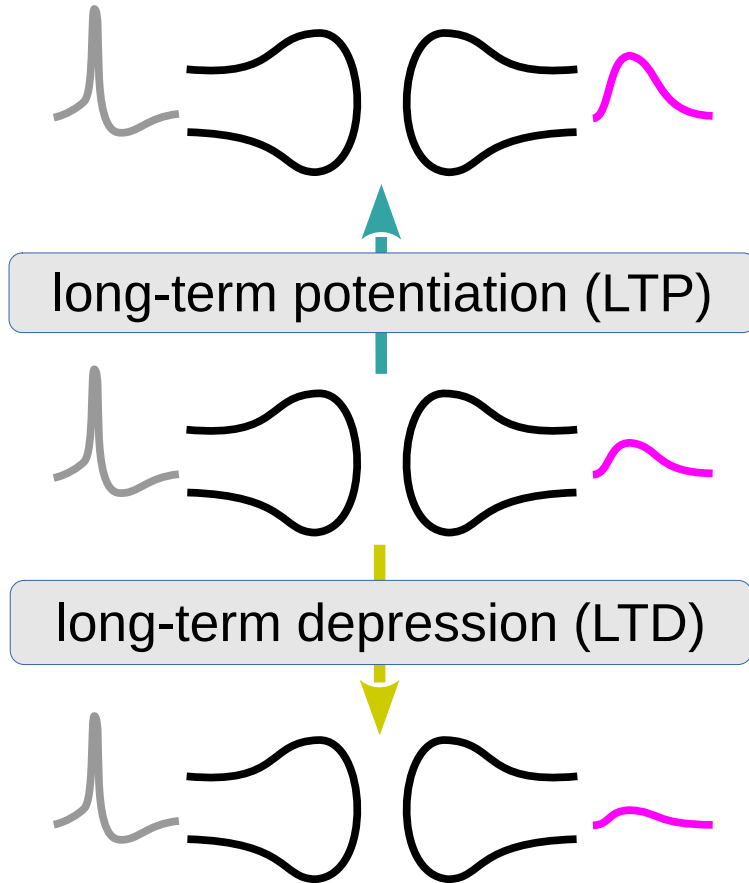


- transient change in transmission efficacy
- time scale of changes  $\sim 1$  sec



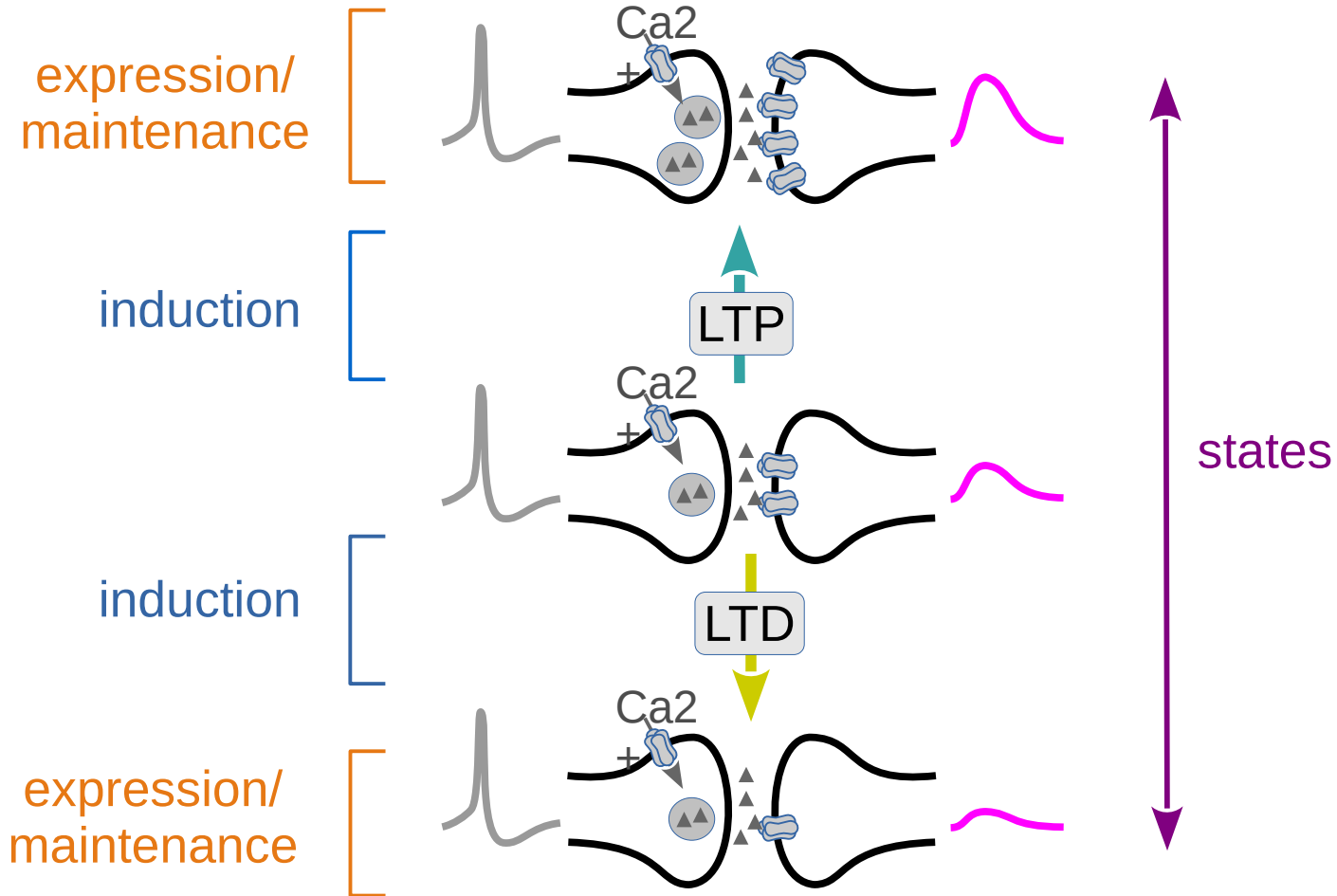


# Long-term synaptic plasticity

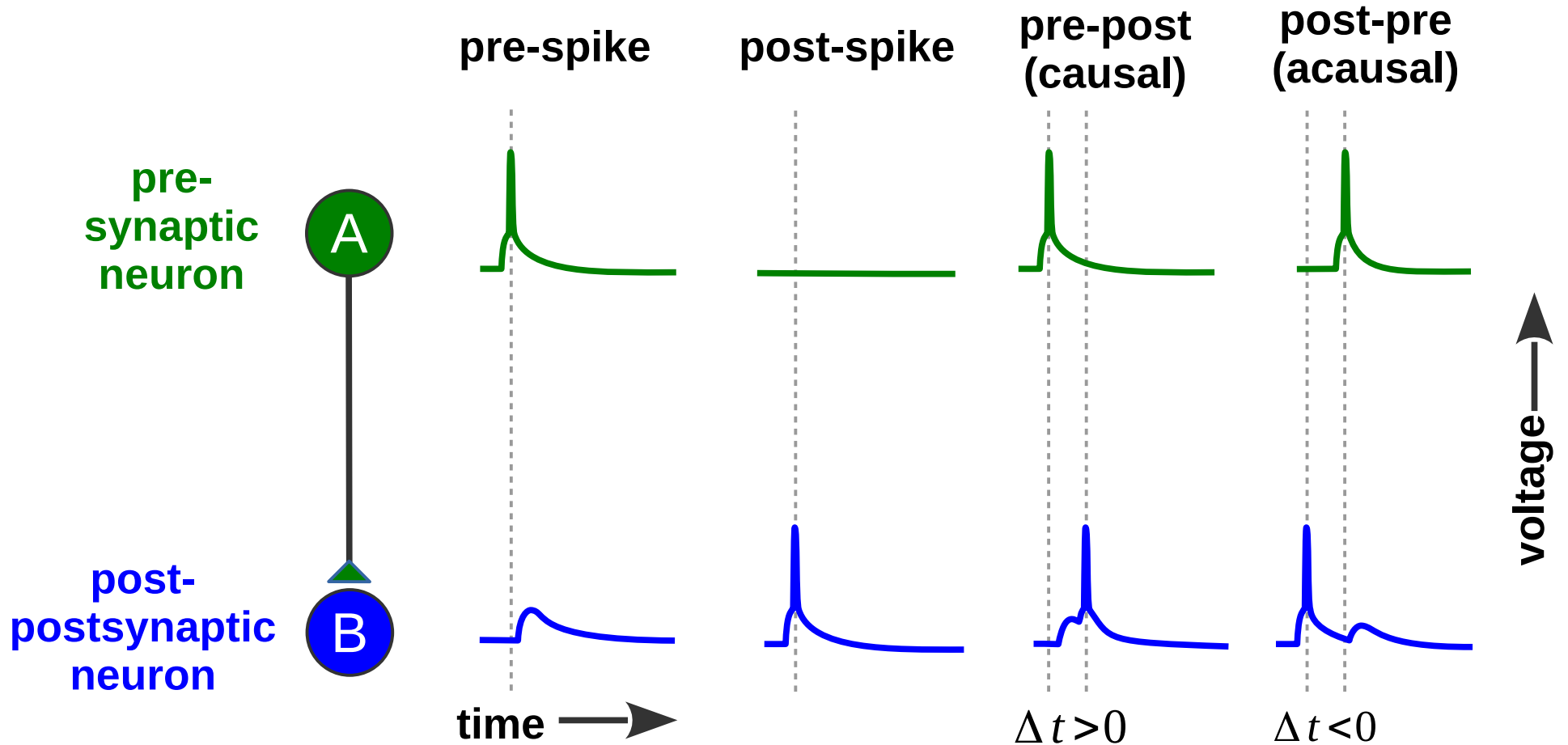


- long-lasting change (>60 min) in transmission efficacy
- time scale of induction ~ 1 min

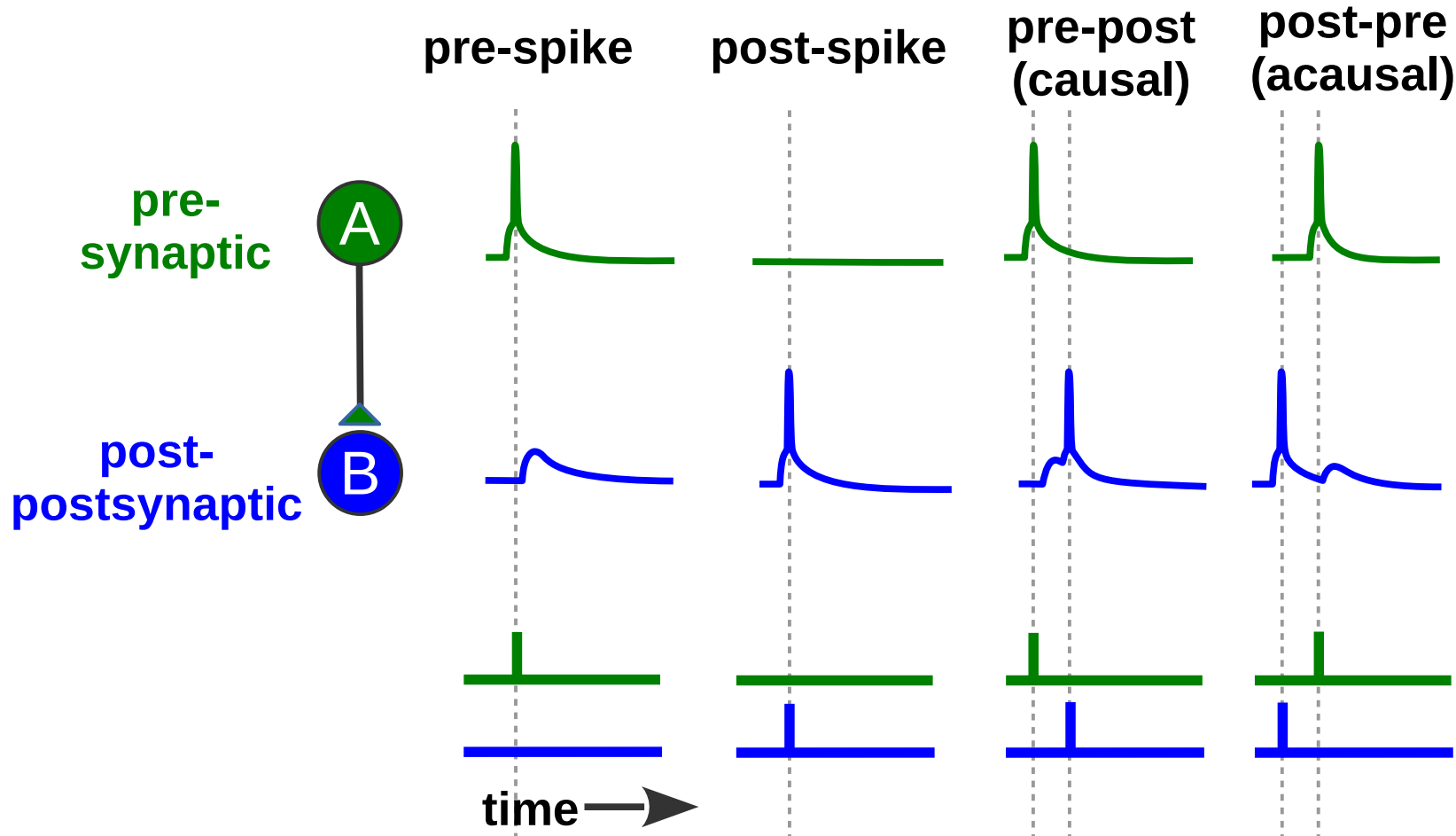
# Synaptic plasticity: induction, maintenance & states



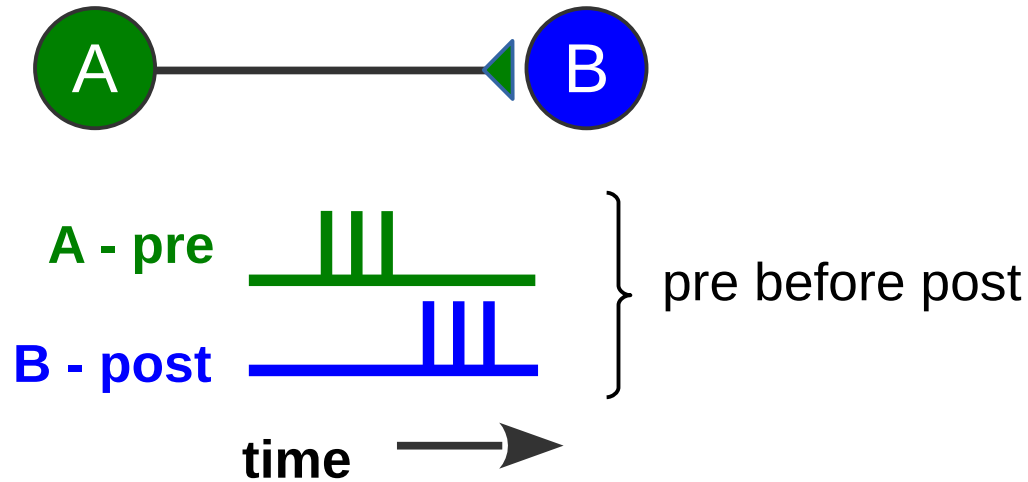
# Spike timing : nomenclature



# Spike timing : nomenclature



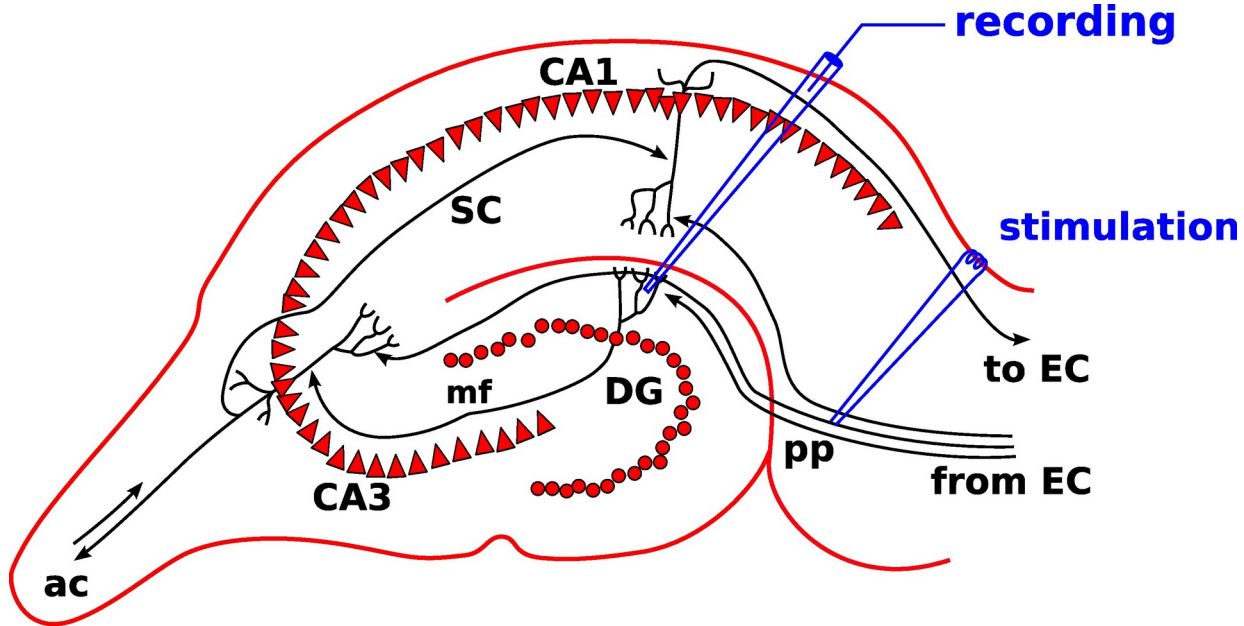
# LTP induction: early conceptual work



“When an axon of cell A is near enough to excite a cell B and *repeatedly* and *persistently* takes part in firing it, some growth or metabolic changes take place in one or both cells such that A’s efficiency, as one of the cells firing B, is *increased*.”

# Induction: first experimental work in hippocampus

hippocampus



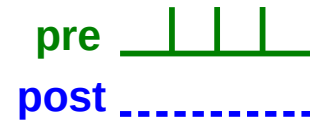
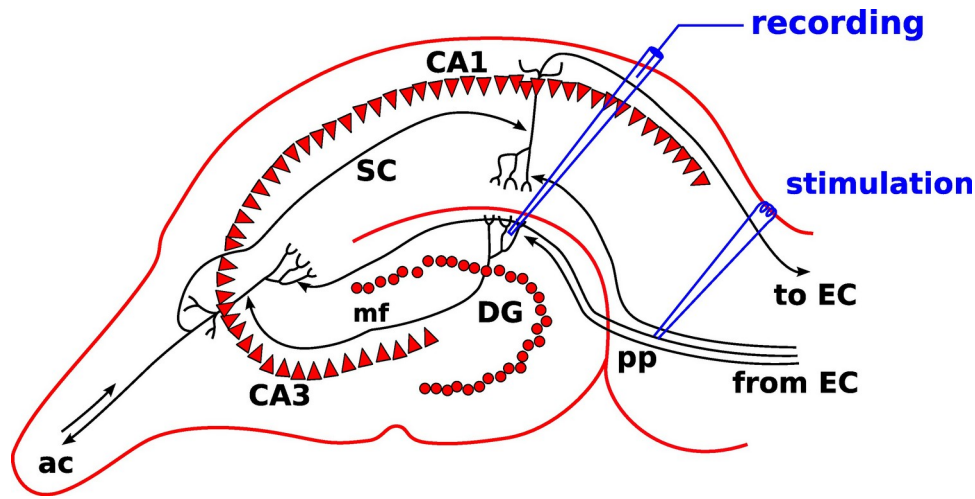
EC ... enthorhinal cortex  
DG ... dentate gyrus  
CA3/1 ... cornu ammonis 3/1

pp ... perforant path  
mf ... mossy fibres  
ac ... associational commissural path  
sc ... Schaffer collateral

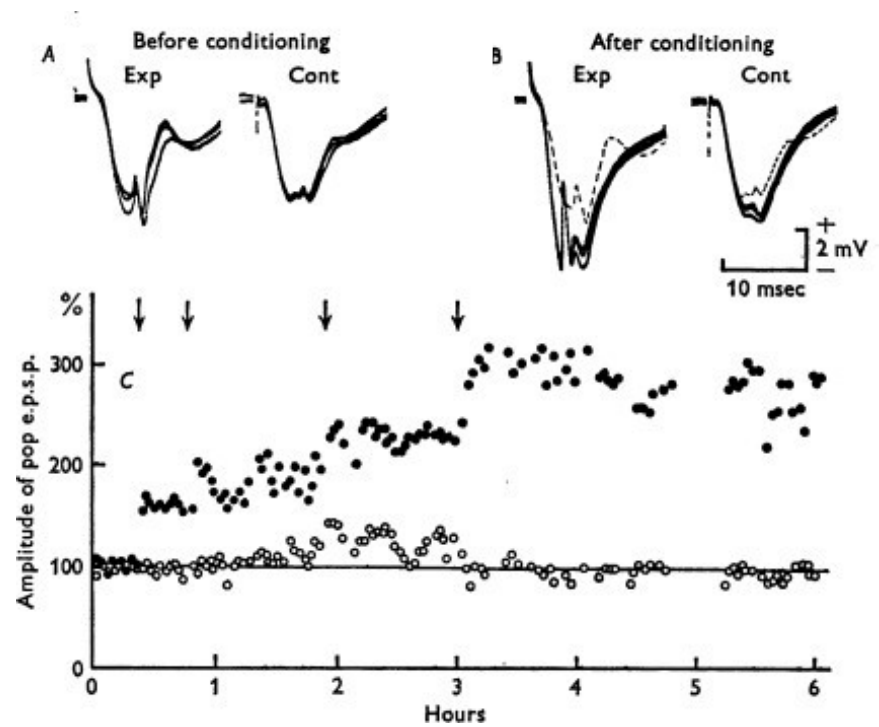
# 1. STDP : introduction and history

## Induction: LTP through high frequency stimulation

hippocampus (*in vivo*)

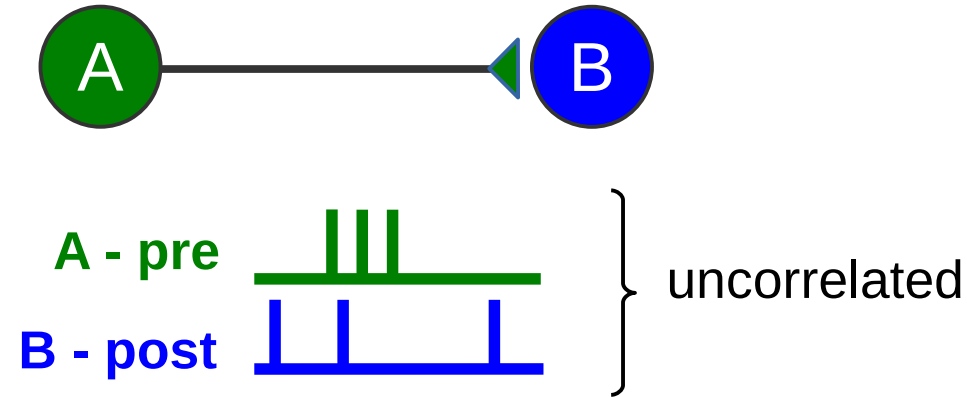


10-20 Hz for 10-15 sec  
or 100 Hz for 3-4 sec



[Bliss and Lømo 1973]

# LTD induction: postulate of Stent



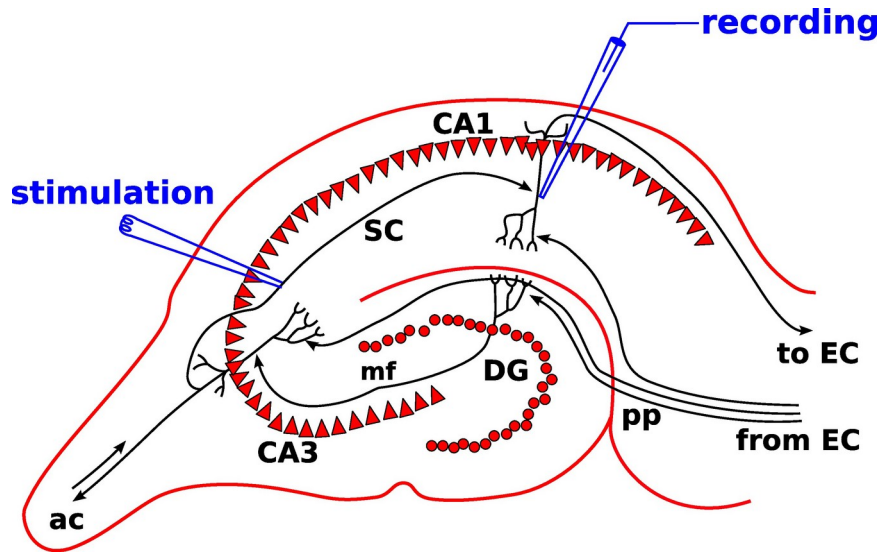
“When the presynaptic axon of cell *A* repeatedly and persistently fails to excite the postsynaptic cell *B* while cell *B* is firing under the influence of other presynaptic axons, metabolic change takes place in one or both cells such that *A*’s efficiency, as one of the cells firing *B*, is *decreased*.”

[G. Stent 1973;  
see also Sejnowski 1977, von der Malsburg 1973, Bienenstock et al. 1982]

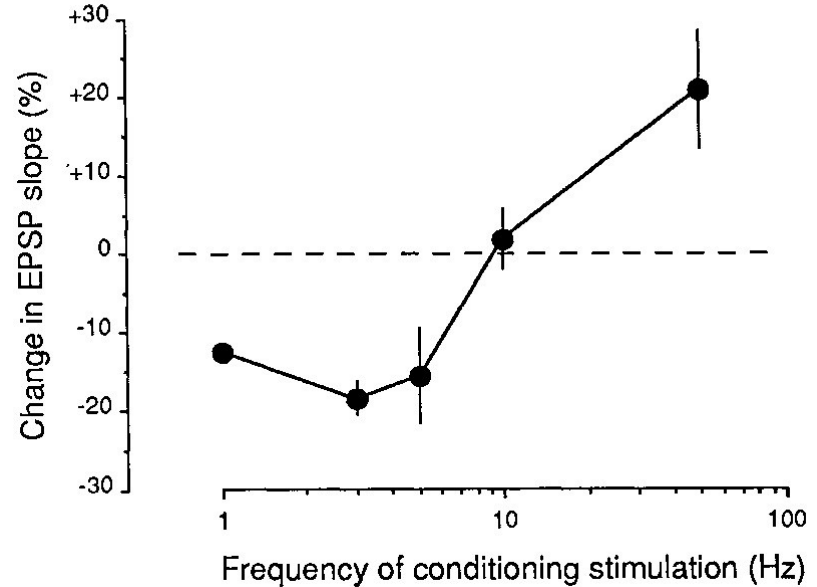


# Plasticity induction: LTD obtained at low frequencies

hippocampus (slices)



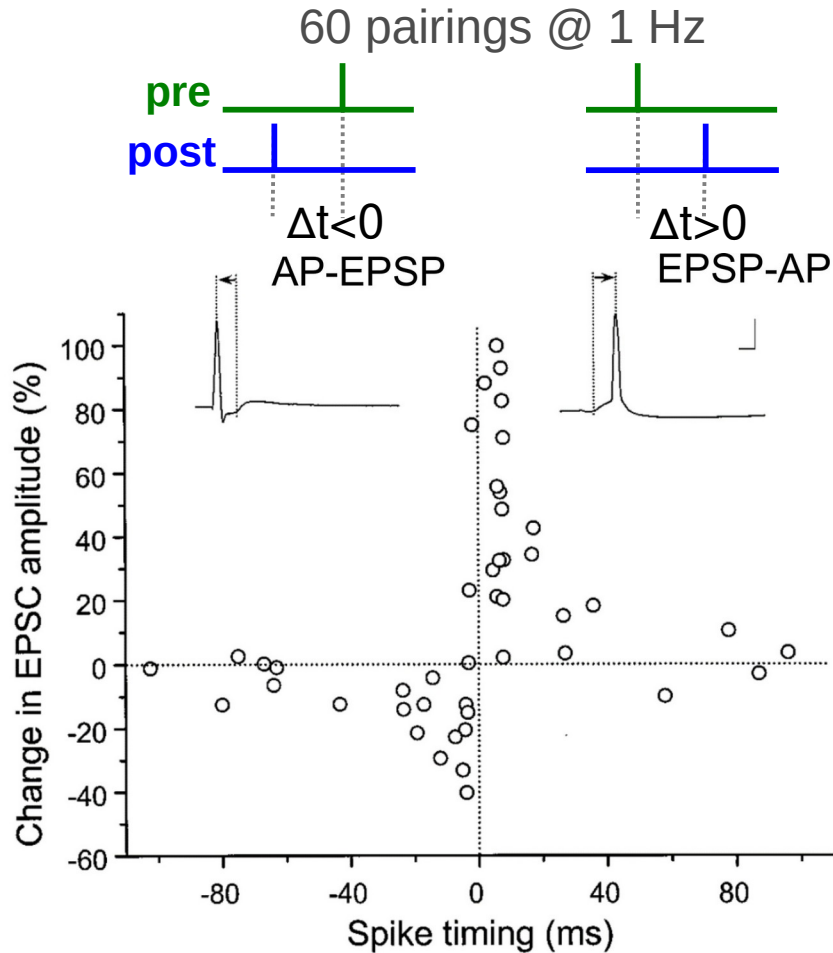
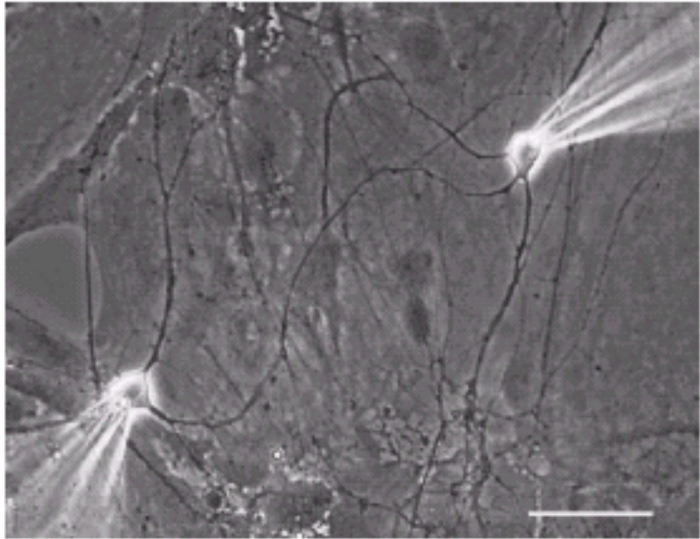
900 pulses at 1-50 Hz



[Dudek and Bear 1992;  
Dunwiddie and Lynch 1978]

# STDP : plasticity from single spike-pairs

hippocampal cultures

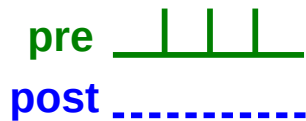


[Bi & Poo, J Neurosci 1998]

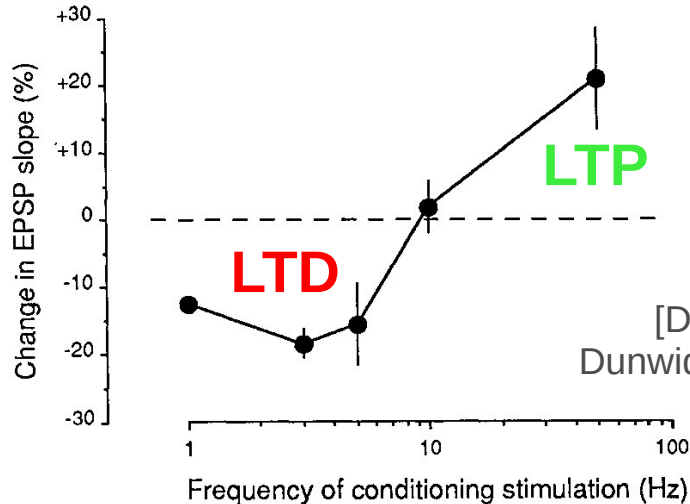
[Magee & Johnston 1997;  
Zhang et al. 1998;  
Markram et al. 1997;  
Sjöström et al. 2001;  
Feldman 2000]

# Frequency-dependent plasticity and STDP

## frequency-dependent plasticity



900 pulses at 1-100 Hz

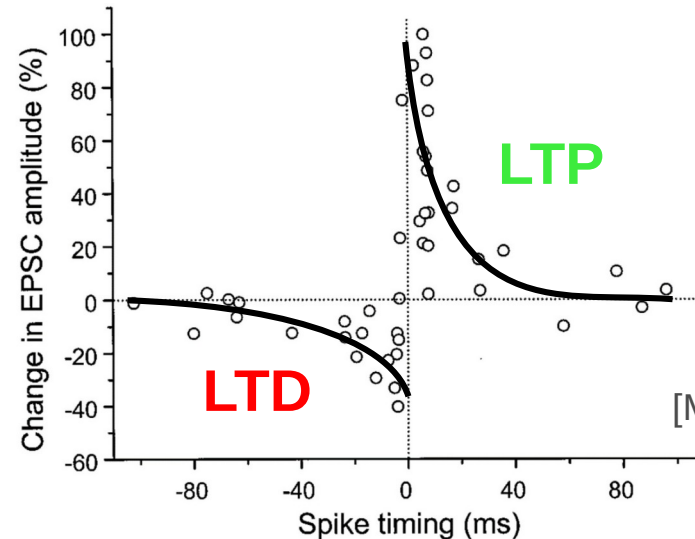


[Dudek and Bear 1992;  
Dunwiddie and Lynch 1978]

## spike timing-dependent plasticity



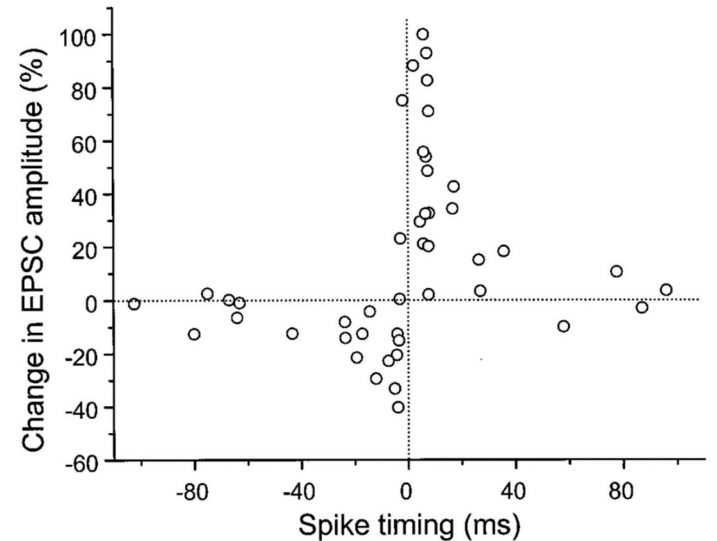
60 pairings @ 1 Hz



[Markram et al. 1997  
Bi & Poo 1998  
Zhang et al. 1998]

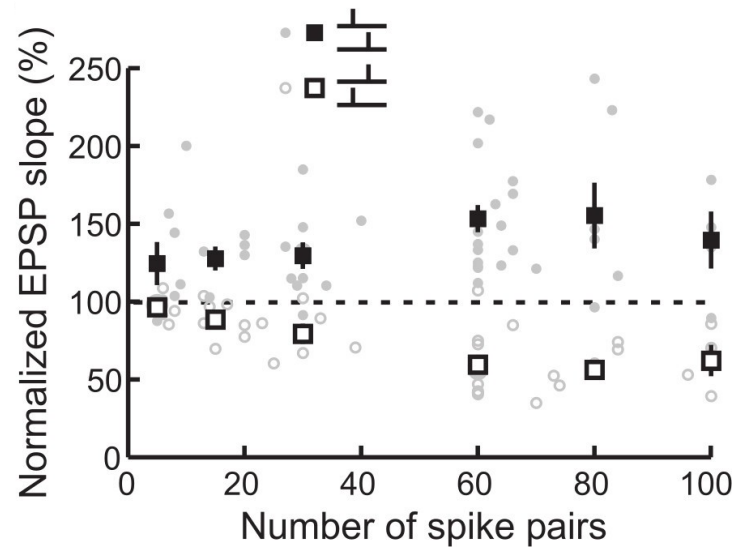
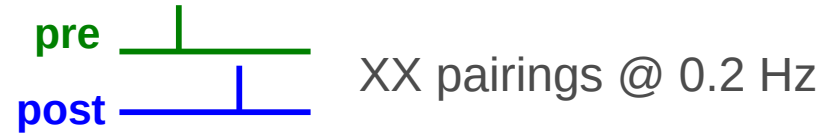
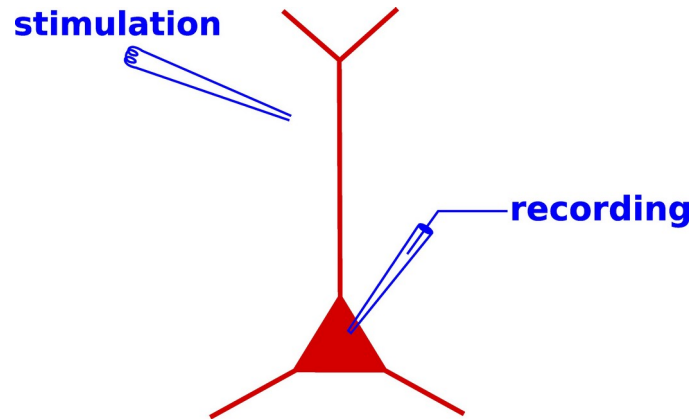
# Outline : STDP ... spike-timing dependent plasticity

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[Bi & Poo 1998]

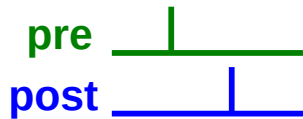
# Number of pairings



- generally : plasticity induction with spike-pairs requires the *repeated* presentation of the pre-post pair
- LTP induced with a few pairs
- LTD requires the presentation of ~20 stimulation pairs

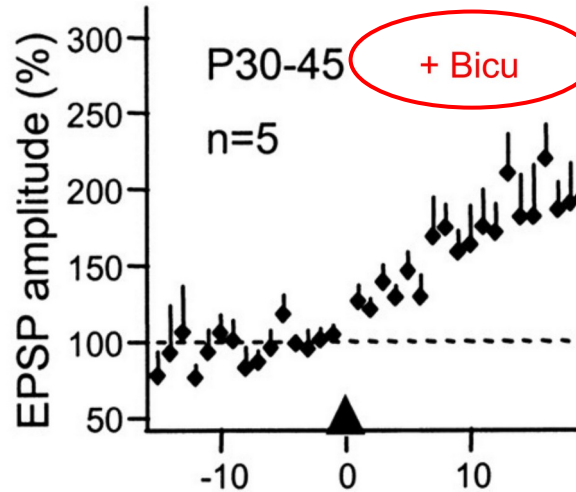
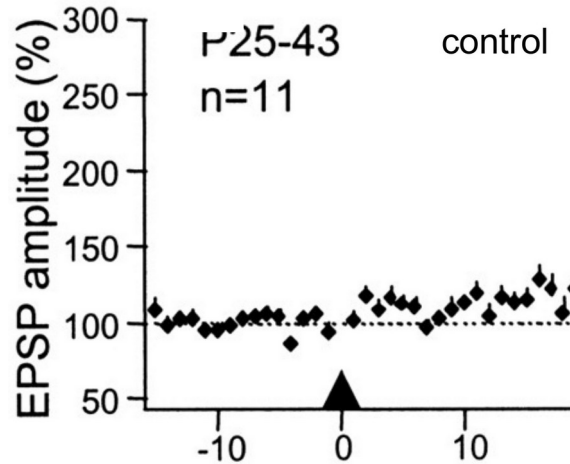
# Role of synaptic inhibition

**control**  
→ **no plasticity**



**inhibition blocked**  
→ **LTP**

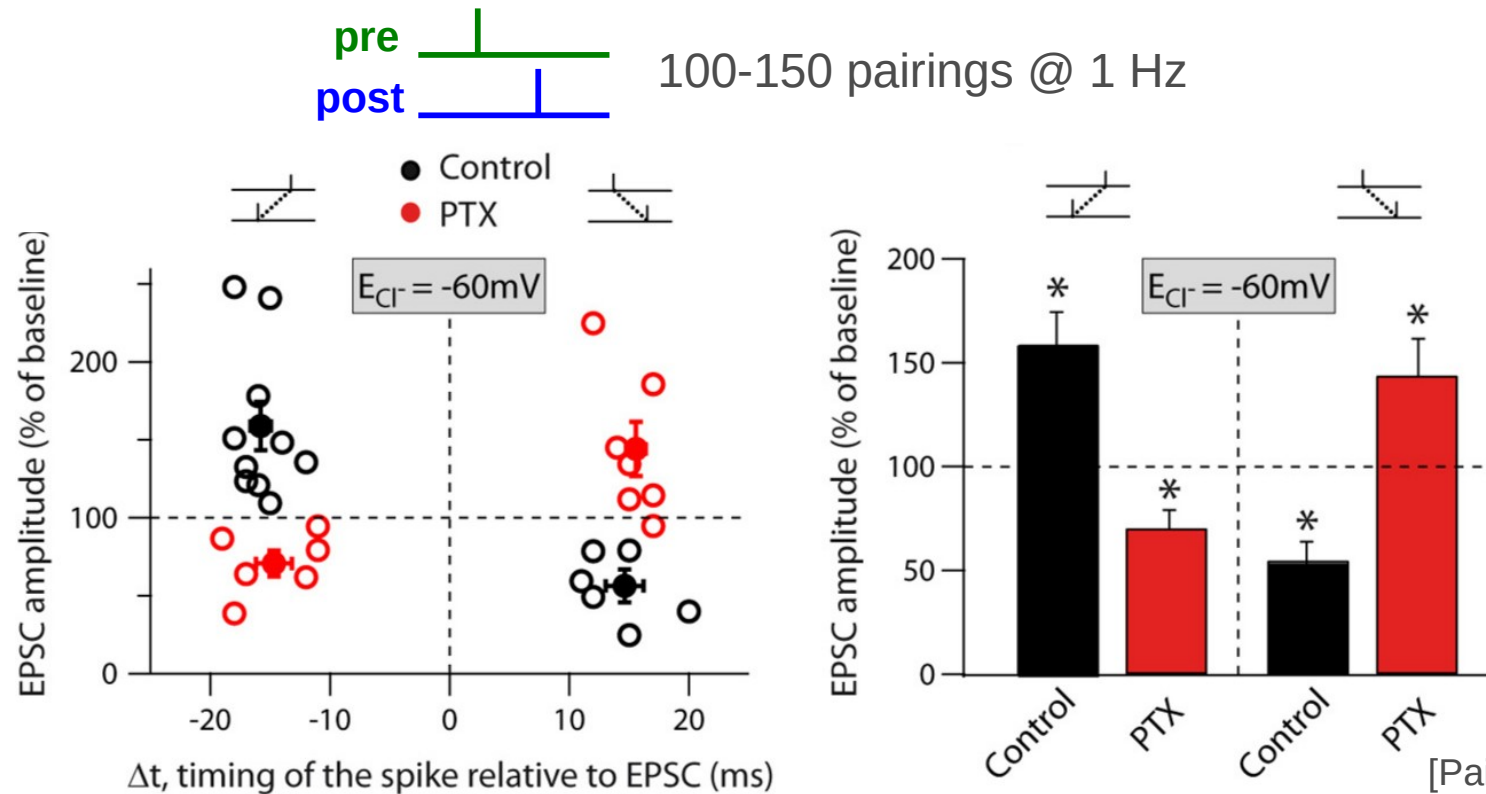
$\Delta t = +10 \text{ ms}$



- Attention : inhibition is blocked in many (in particular classical) plasticity studies
- synaptic inhibition can prevent plasticity induction



Bicuculline is a competitive antagonist of  $\text{GABA}_A$  receptors.

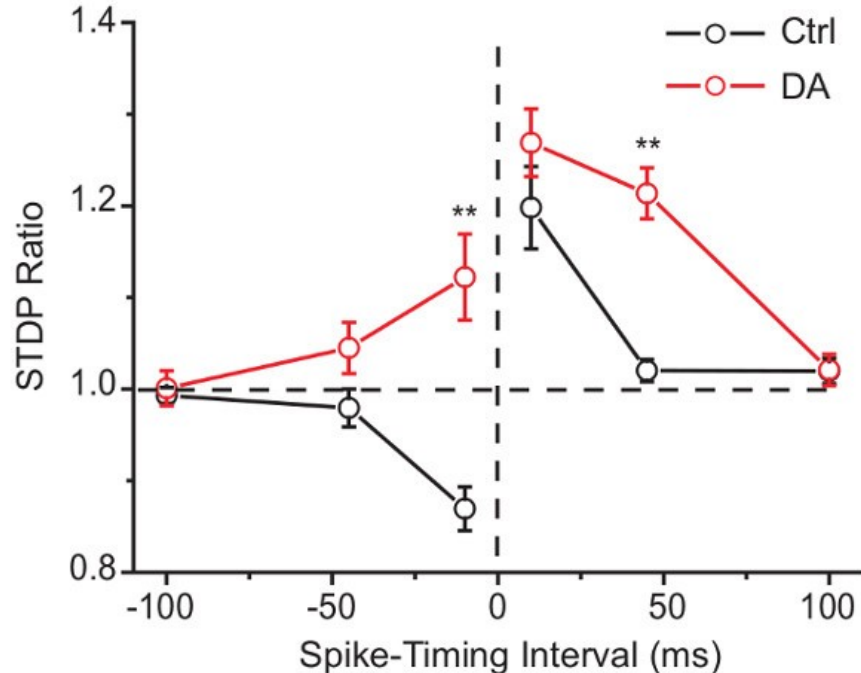
# Role of synaptic inhibition



- at the corticostriatal synapse : inhibition inverts the STDP curve

# Role of neuromodulation - Dopamine

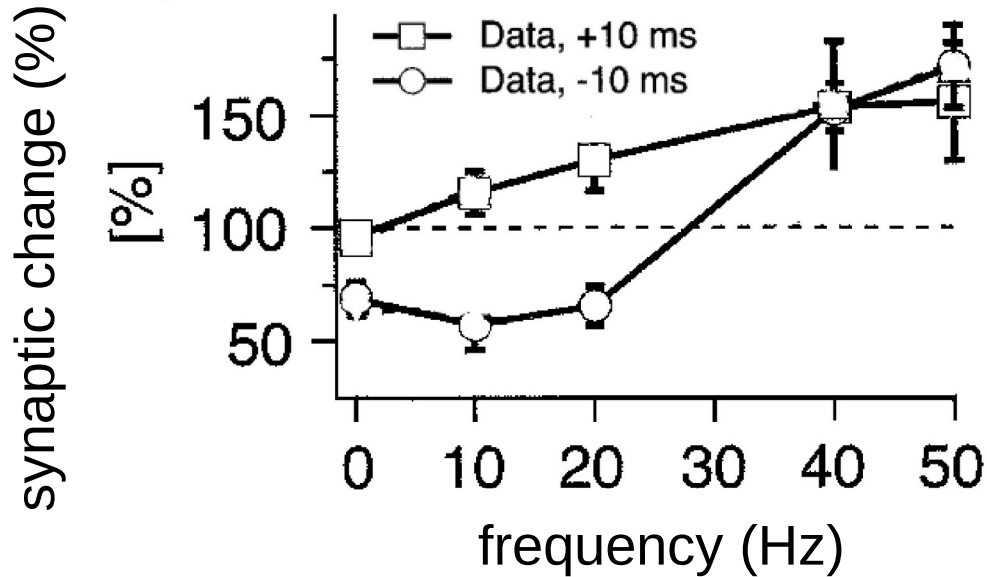
pre  60 pairings @ 1 Hz  
post 



- many neurotransmitter have been shown to shape synaptic plasticity
- e.g. : dopamine controls sign and magnitude of plasticity

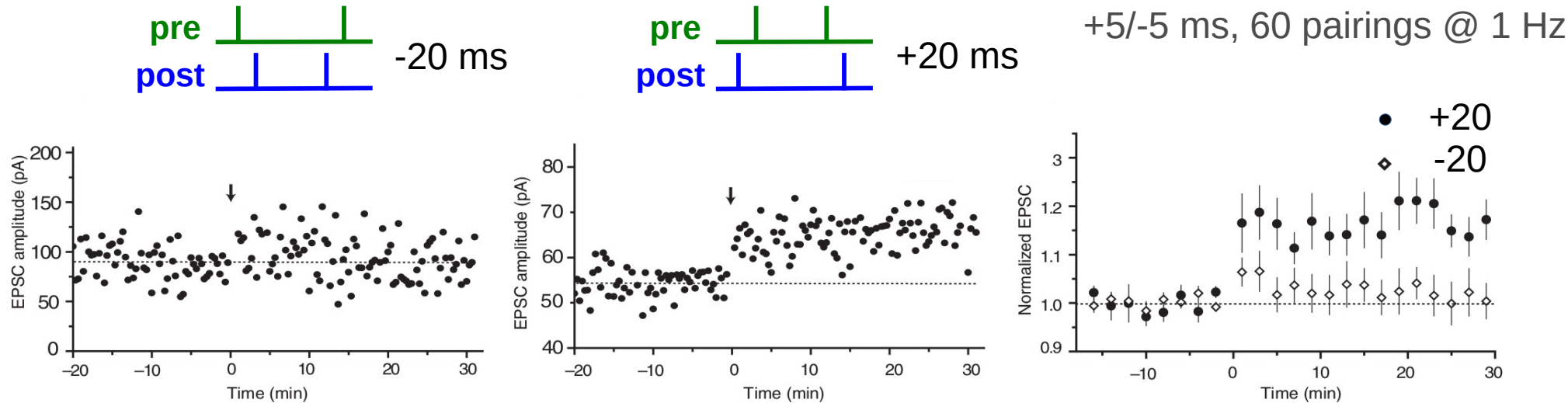


# STDP depends on frequency of spike-pairs



- in the first studies of STDP, spike-pairs were presented at low frequencies
- pre-post pairing induce no plasticity at low and LTP at high frequencies
- post-pre pairings induce LTD at low- and LTP at high frequencies

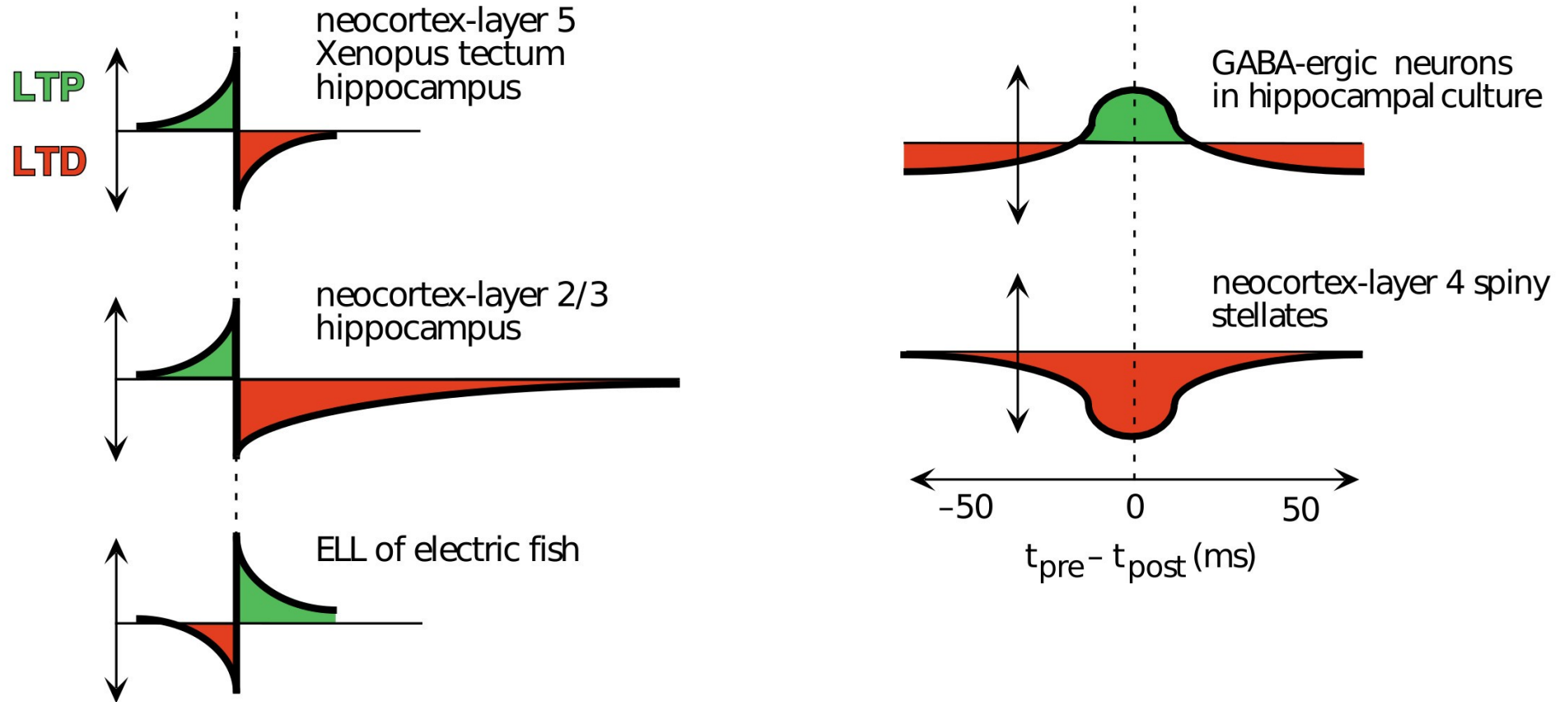
# Non-linearity in STDP induction protocols



[Wang et al. *Nat Neurosci* 2005]

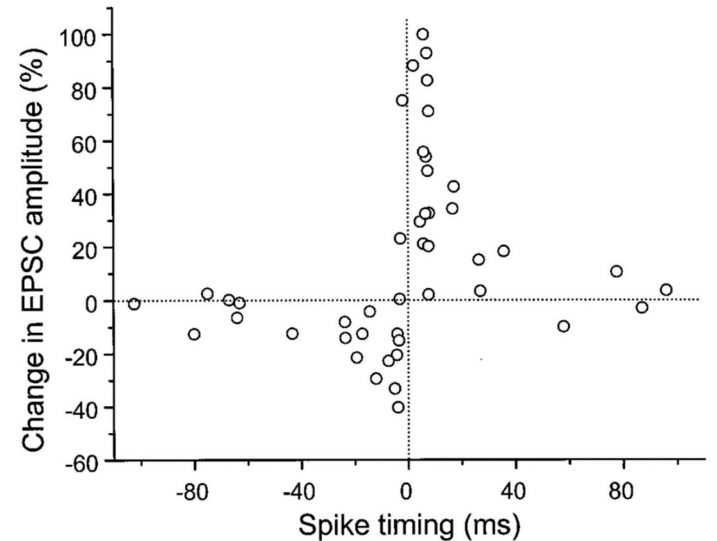
- order of pre-post, post-pre pairs in quadruplet stimulation determines plasticity outcome
  - pre-post post-pre quadruplet -> no plasticity
  - post-pre pre-post quadruplet -> LTP

# STDP windows depends on brain structure, synapse type



# Outline : STDP ... spike-timing dependent plasticity

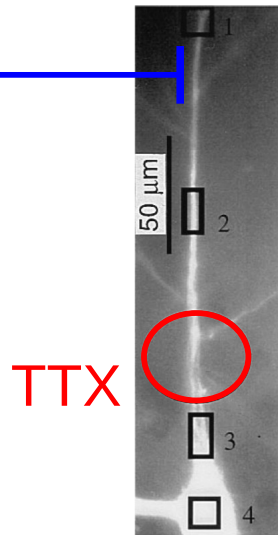
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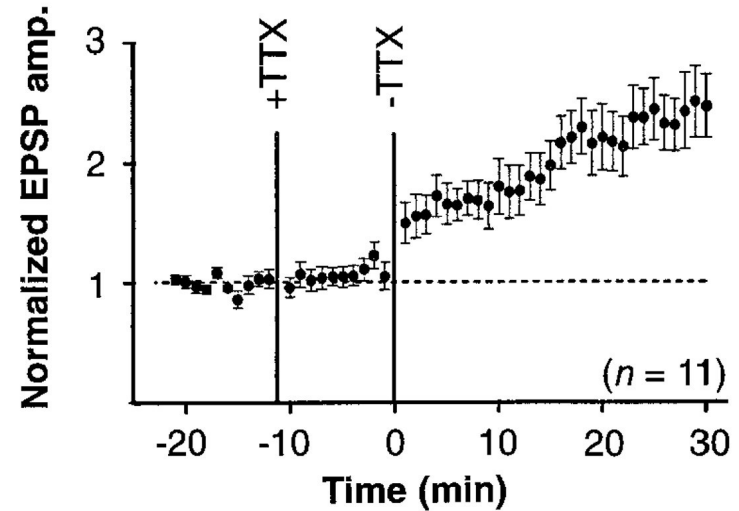
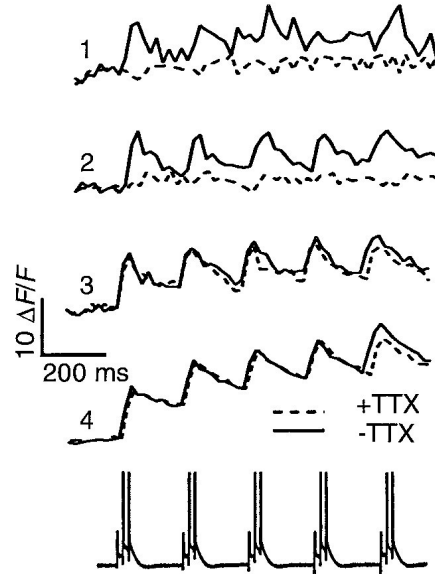
[Bi & Poo 1998]

# Backpropagating action potential required for STDP

stimulated synapse



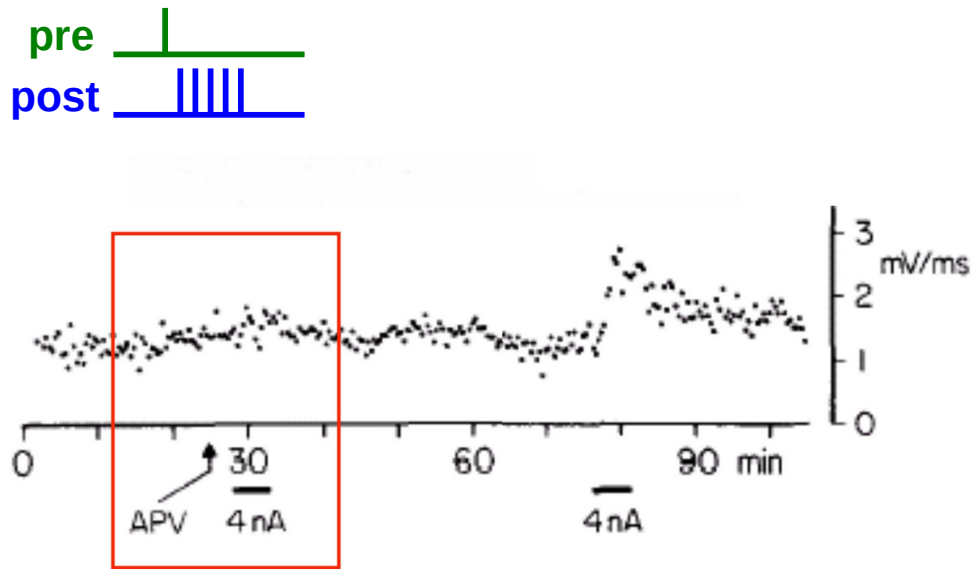
[Ca<sup>2+</sup>] imaging



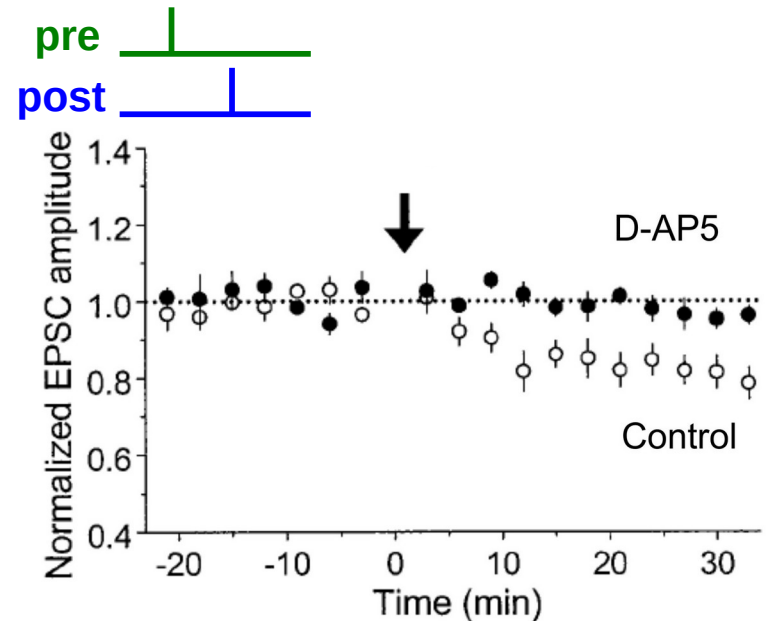
[Magee & Johnston *Science* 1997]

- Backpropagating action potential provides postsynaptic depolarization required for STDP

# STDP requires NMDA receptor activation



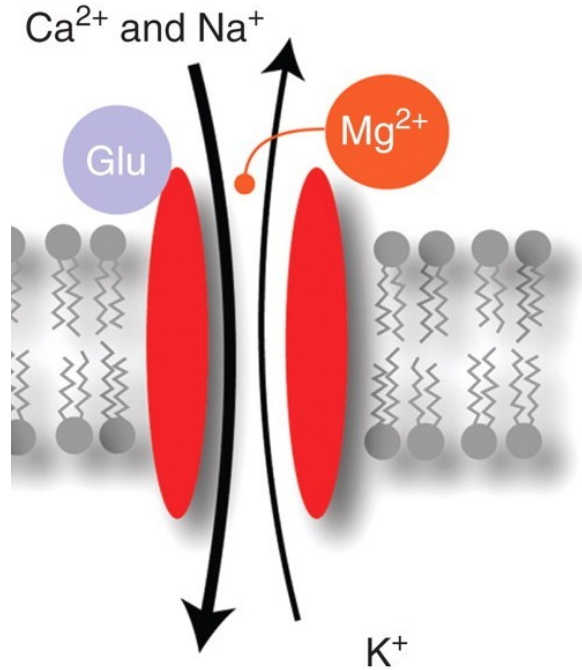
[Gustafsson et al. *J Neurosci* 1987]



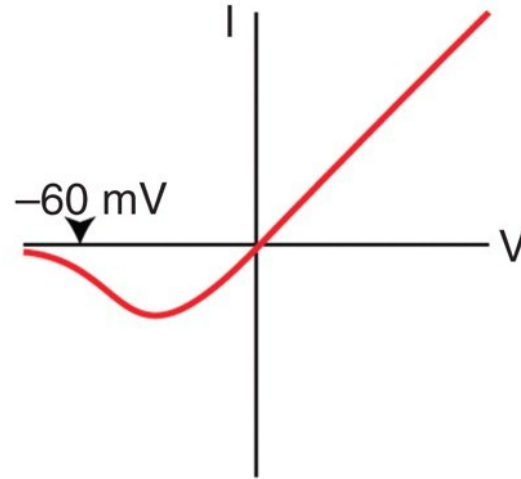
[Bi & Poo *J Neurosci* 1998]

- NMDAR antagonist blocks STDP induction (D-AP5 or APV is a selective NMDA receptor antagonist)

# Postsynaptic NMDA receptor

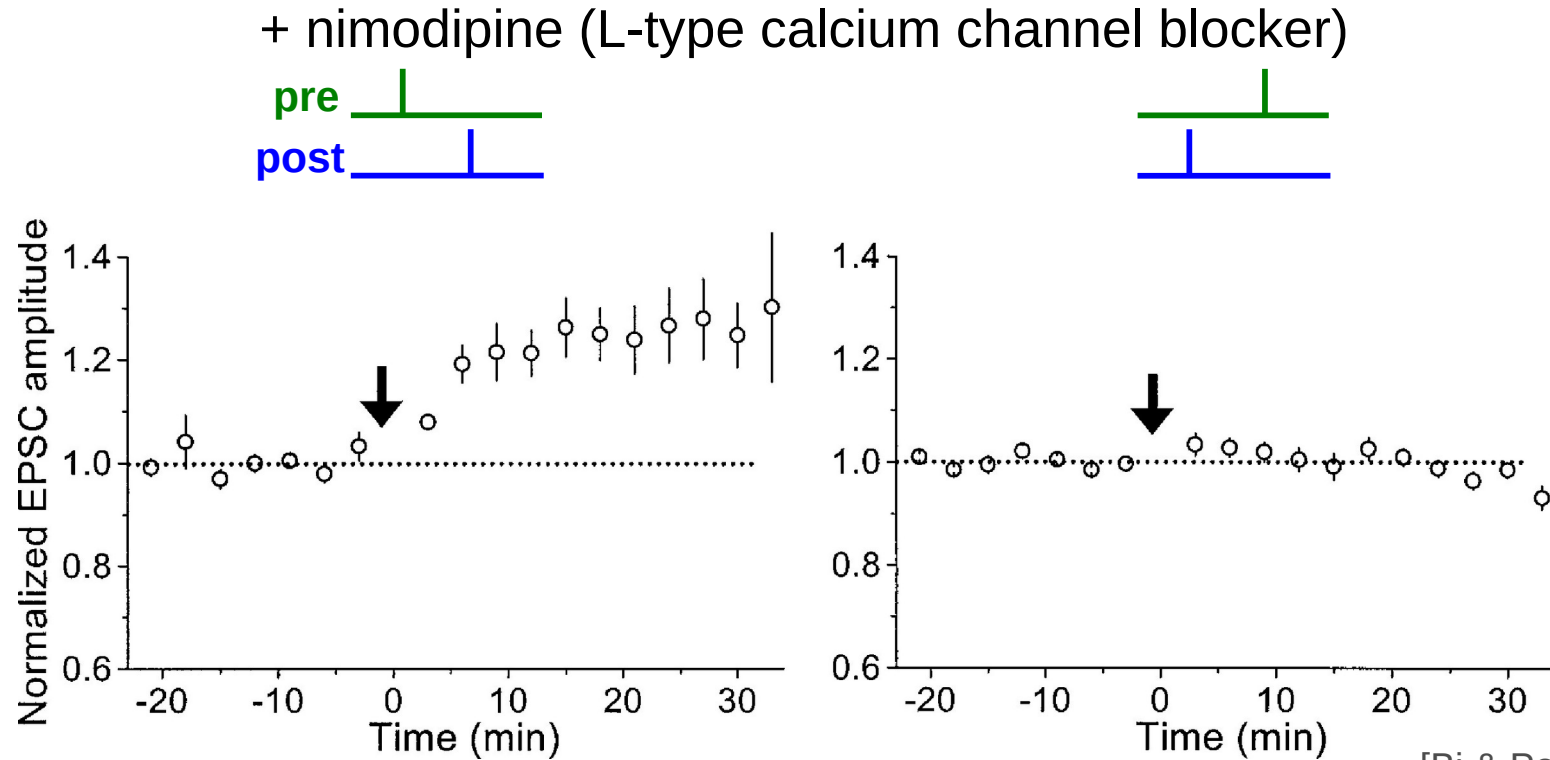


current-voltage relationship



- coincidence detector :
  - presynaptic action potential → glutamate (Glu)
  - postsynaptic depolarization → Mg<sup>2+</sup> block is expelled
- calcium permeable

# Voltage-dependent Ca channels required for LTD

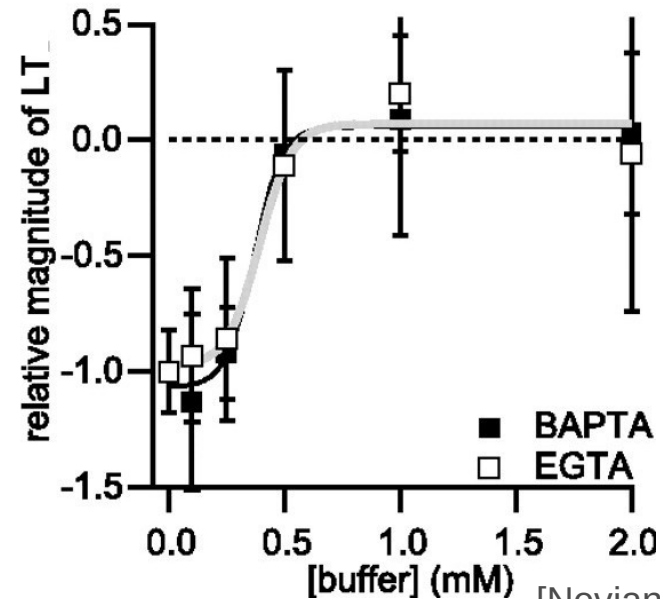
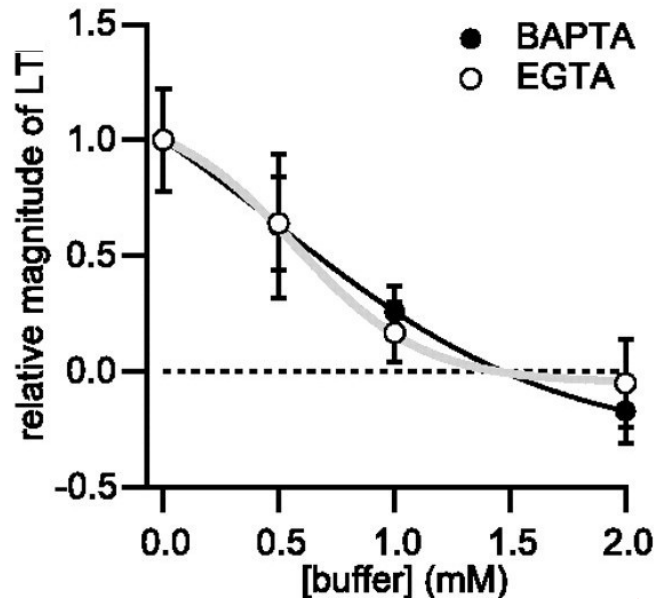
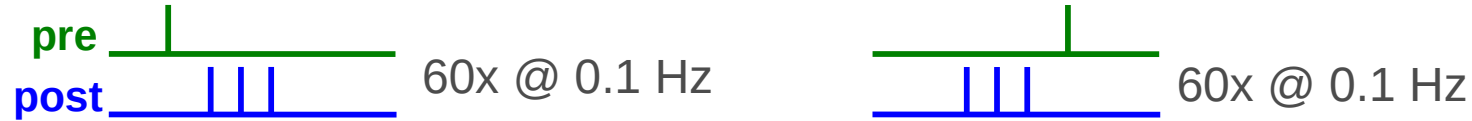


[Bi & Poo *J Neurosci* 1998]

- LTD but not LTP involves the activation of L-type calcium channels



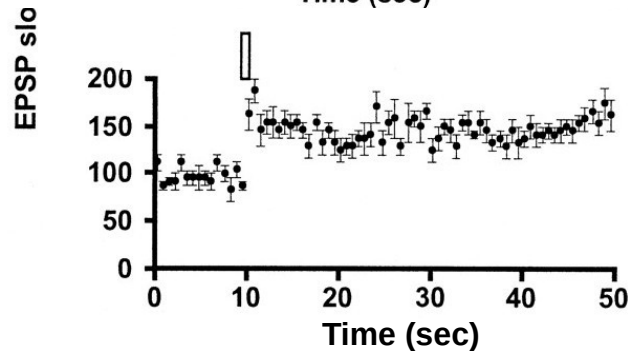
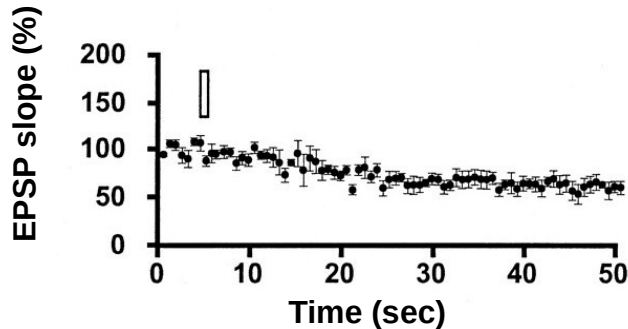
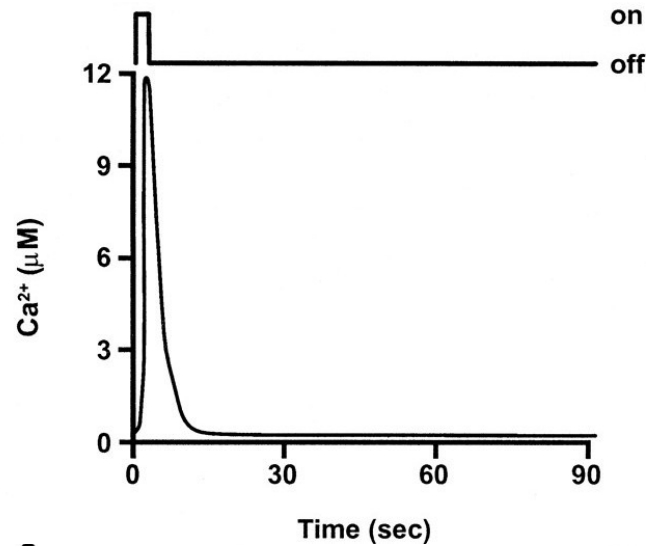
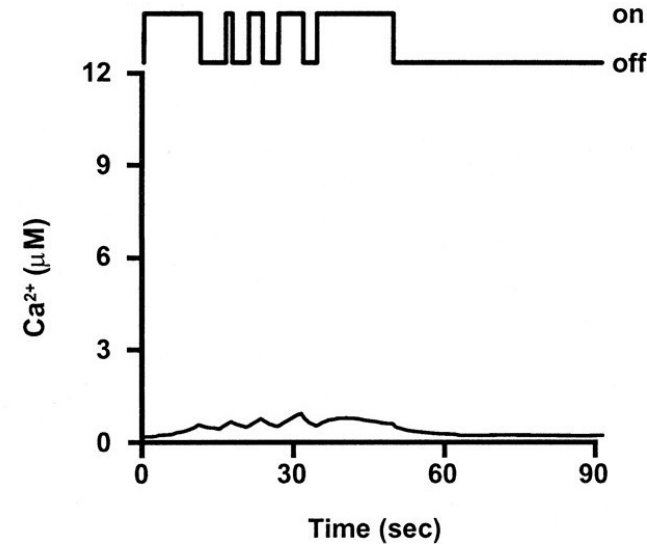
# Postsynaptic calcium *required* for plasticity

[Nevian & Sakmann *et al.*, 2006]

→  
more buffer -> less free calcium

- LTP/LTD equally sensitive to fast and slow  $[Ca^{2+}]$  buffers

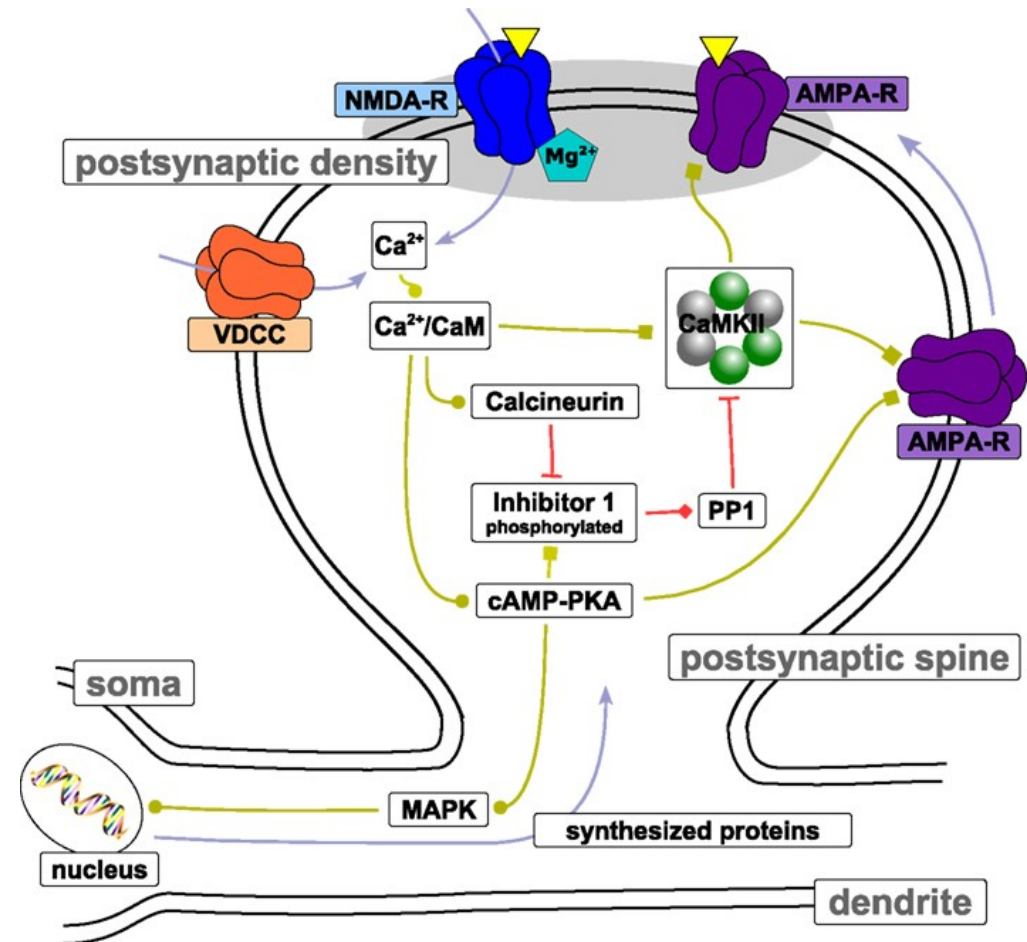
# Postsynaptic calcium *sufficient* for plasticity



- LTP induced by brief, large amplitude  $[Ca^{2+}]$  increases
- prolonged, modest rise in  $[Ca^{2+}]$  elicits LTD

[Malenka *et al.* *Science* 1988; Yang *et al.*, *J Neurophysiol* 1999]

# Signal pathways downstream of Calcium



# Expression of long-term changes

**presynaptic**

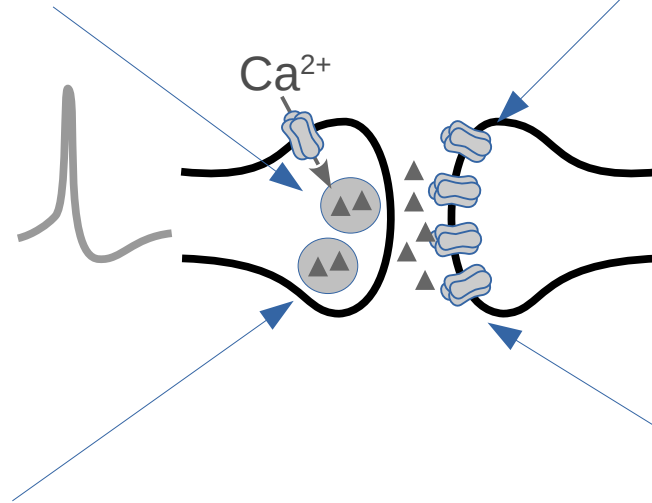
**postsynaptic**

neurotransmitter vesicle  
number

number of AMPA receptors

probability of vesicle  
release

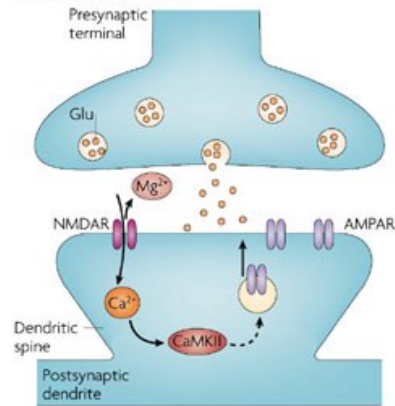
conductance of AMPA  
receptors



### 3. Induction mechanisms

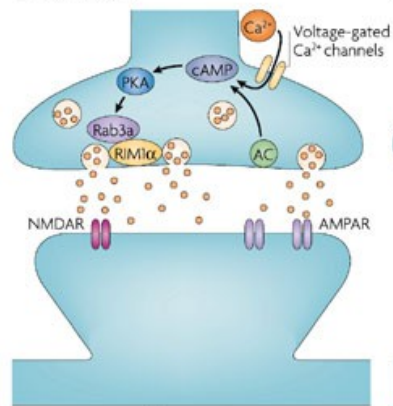
# Diversity of induction and expression pathways

**a NMDAR-dependent LTP**



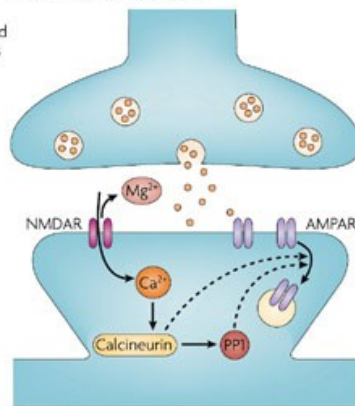
Expression: postsynaptic insertion of AMPARs

**b Presynaptic LTP**



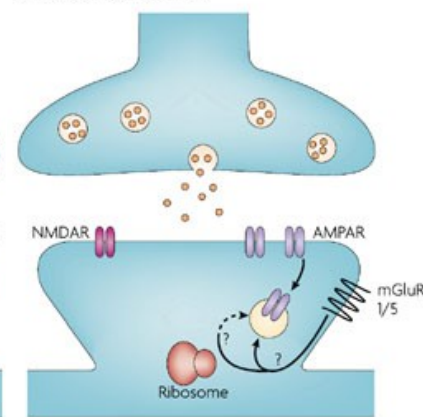
Expression: increased presynaptic neurotransmitter release

**c NMDAR-dependent LTD**



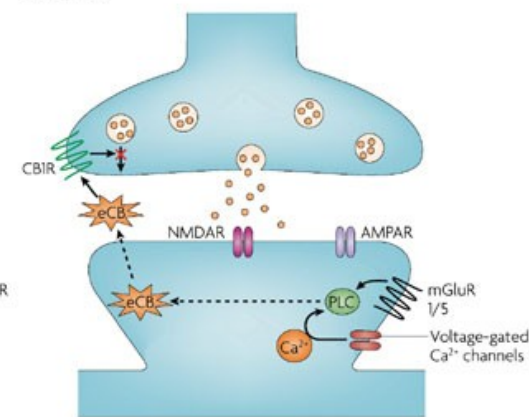
Expression: internalization of postsynaptic AMPARs

**d mGluR-dependent LTD**



Expression: internalization of postsynaptic AMPARs

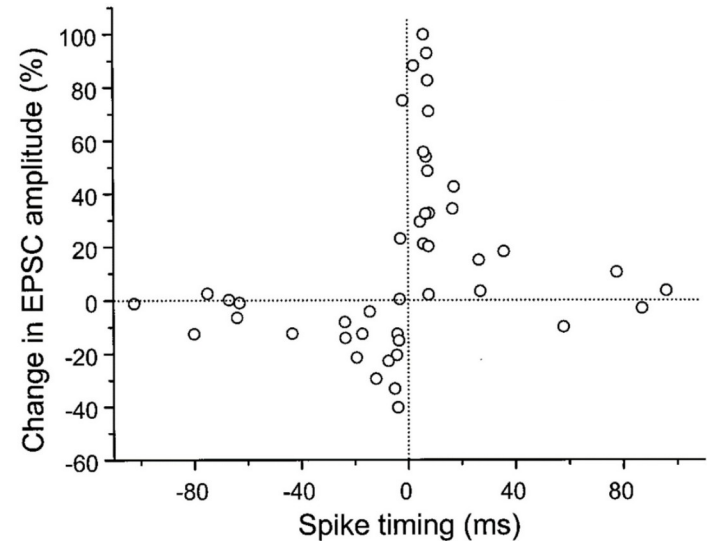
**e eCB-LTD**



Expression: decreased presynaptic neurotransmitter release

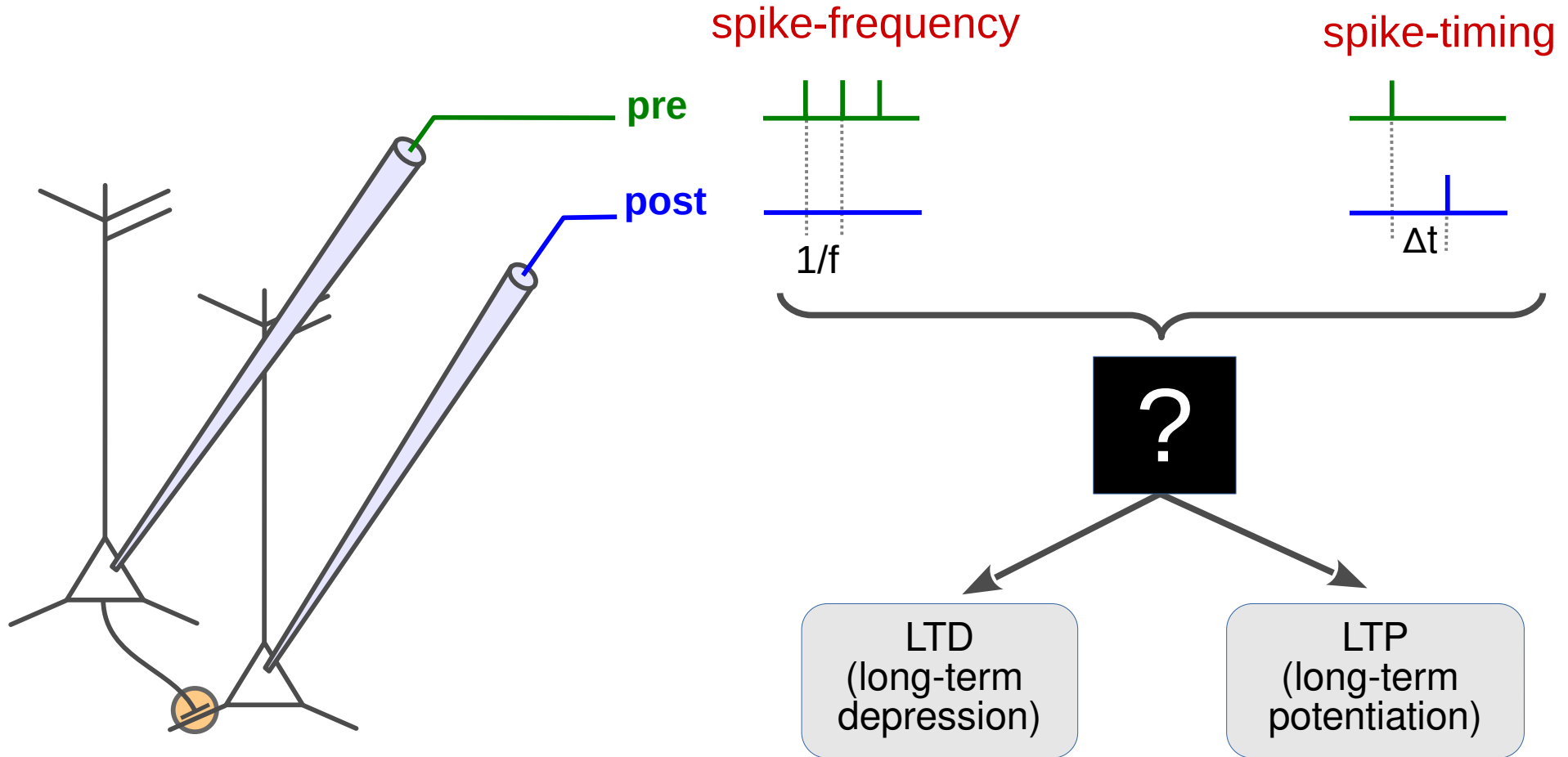
# Outline : STDP ... spike-timing dependent plasticity

1. STDP : introduction and history
2. Phenomenology of STDP
3. Induction mechanisms
4. Biophysical models of STDP
5. STDP *in vivo*

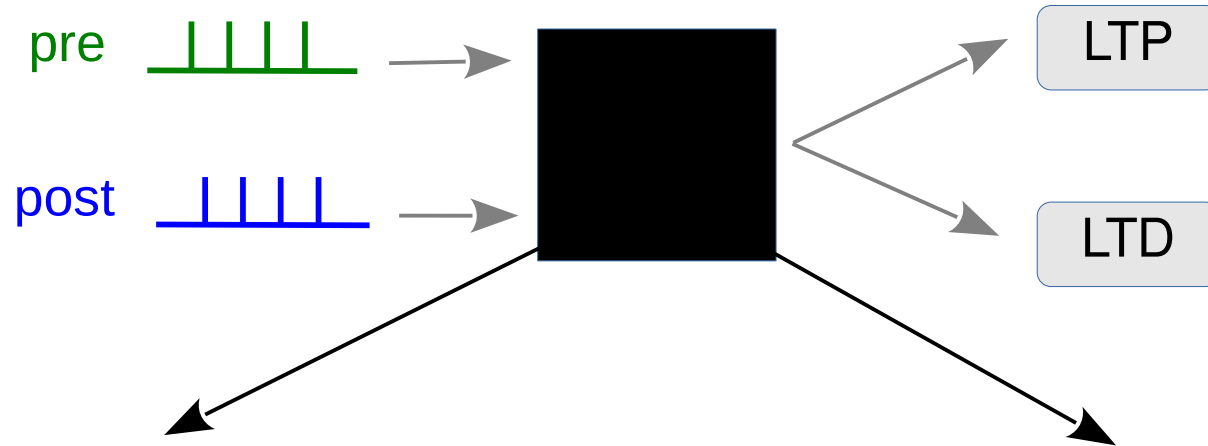


[Bi & Poo 1998]

# Modeling : translation from spikes to plasticity results



# Modeling approaches : phenomenological vs. biophysical



## phenomenological models of plasticity

- use pre- and postsynaptic spike times or rate to calculate change in synaptic strength
- conversion can involve arbitrarily complex mathematical models

## biophysical models of plasticity

- resolve *parts* of the underlying biological machinery involved in the induction of plasticity
- degree of biological detail varies largely



# Modeling approaches : phenomenological vs. biophysical

### phenomenological models of LTP/LTD

- **rate-based plasticity models**  
[Hebb, 1949; Bienenstock *et al.*, 1982; Oja, 1982]
- **spike-timing based models**  
[Gerstner *et al.*, 1996; van Rossum *et al.* 2000; Song, 2000; Pfister & Gerstner, 2006]

### biophysical models of LTP/LTD

- **Ca<sup>2+</sup> – dynamics based models**  
[Karmarkar *et al.*, 2002; Shouval *et al.*, 2002; Rubin *et al.*, 2005; Graupner & Brunel 2012]
- **CaMKII kinase-phosphatase system**  
[Crick 1984; Lisman, 1985; Okamoto & Ichikawa, 2000; Zhabotinsky, 2000; Graupner & Brunel, 2007; Urakubo *et al.*, 2008]
- **extensive protein networks**  
[Bhalla & Iyengar, 1999; Hayer & Bhalla, 2005]
- **local clustering of receptors**  
[Shouval, 2005]

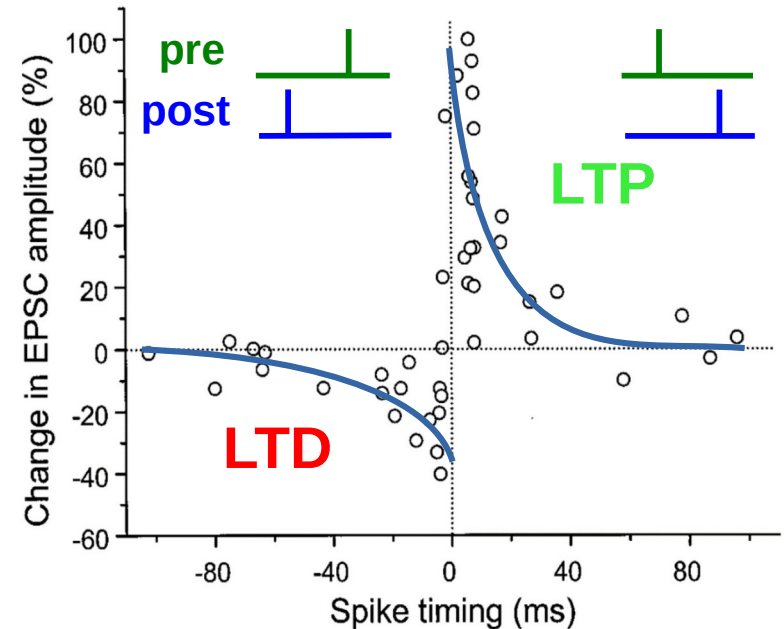
# “Standard” STDP model

- spike-timing based rules :  $\Delta w_{ij} = f(\{t_{ik}\}, \{t_{jk}\})$
- “standard” STDP :

$$f(\{t_{ik}\}, \{t_{jk}\}) = \sum_{k, k'} F(t_{ik} - t_{jk'})$$

$$F(\Delta t) = \begin{cases} A_+ \exp(-\Delta t / \tau_+) & \Delta t > 0 \\ A_- \exp(-\Delta t / \tau_-) & \Delta t < 0 \end{cases}$$

- Variations of the rule :
  - \* additive/multiplicative
  - \* All-to-all spike pairings / nearest neighbors

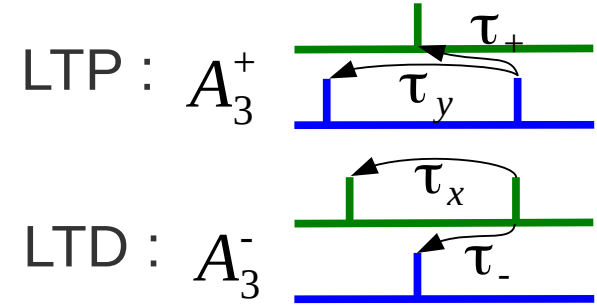
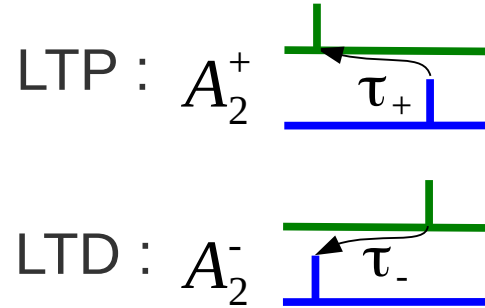


- **Problems** : does not depend on firing rate  
does not resolve the non-linearities of plasticity

# More recent plasticity models

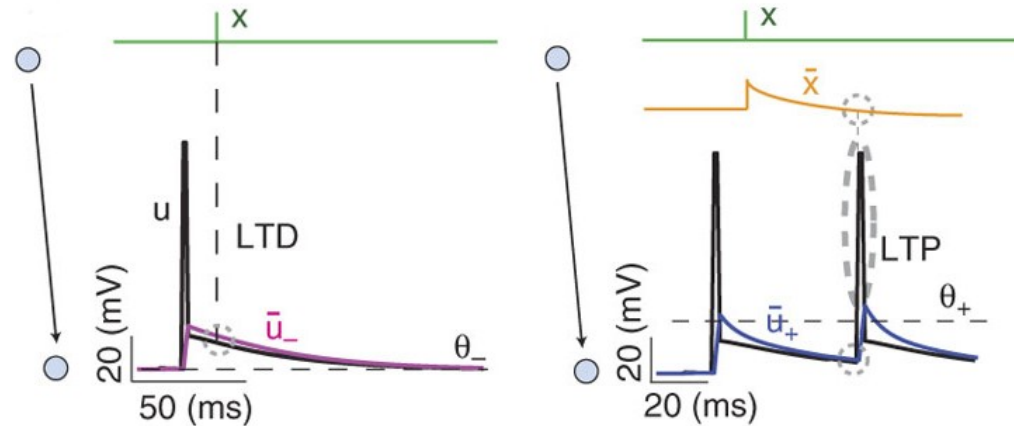
## Triplet-based model

[Pfister & Gerstner, 2006;  
Clopath et al., 2010]



## Model based on postsynaptic potential

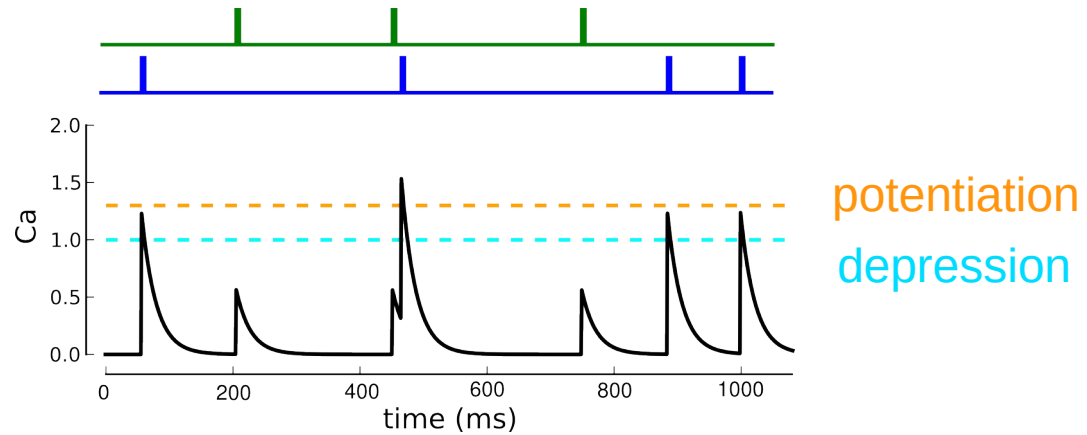
[Clopath et al., 2010]



# More recent plasticity models

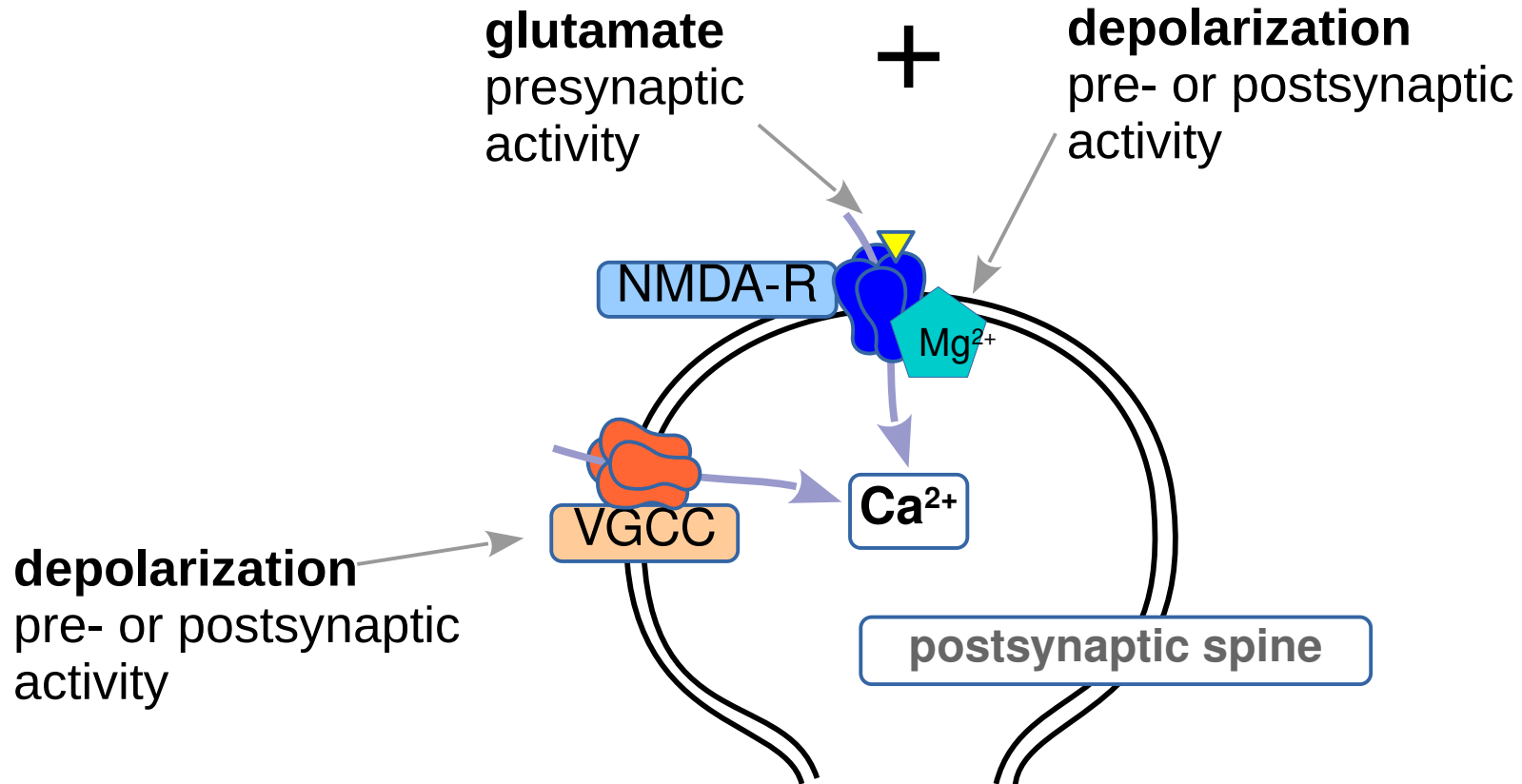
## Calcium-based model

[Shouval *et al.* 2002, Graupner & Brunel 2012]

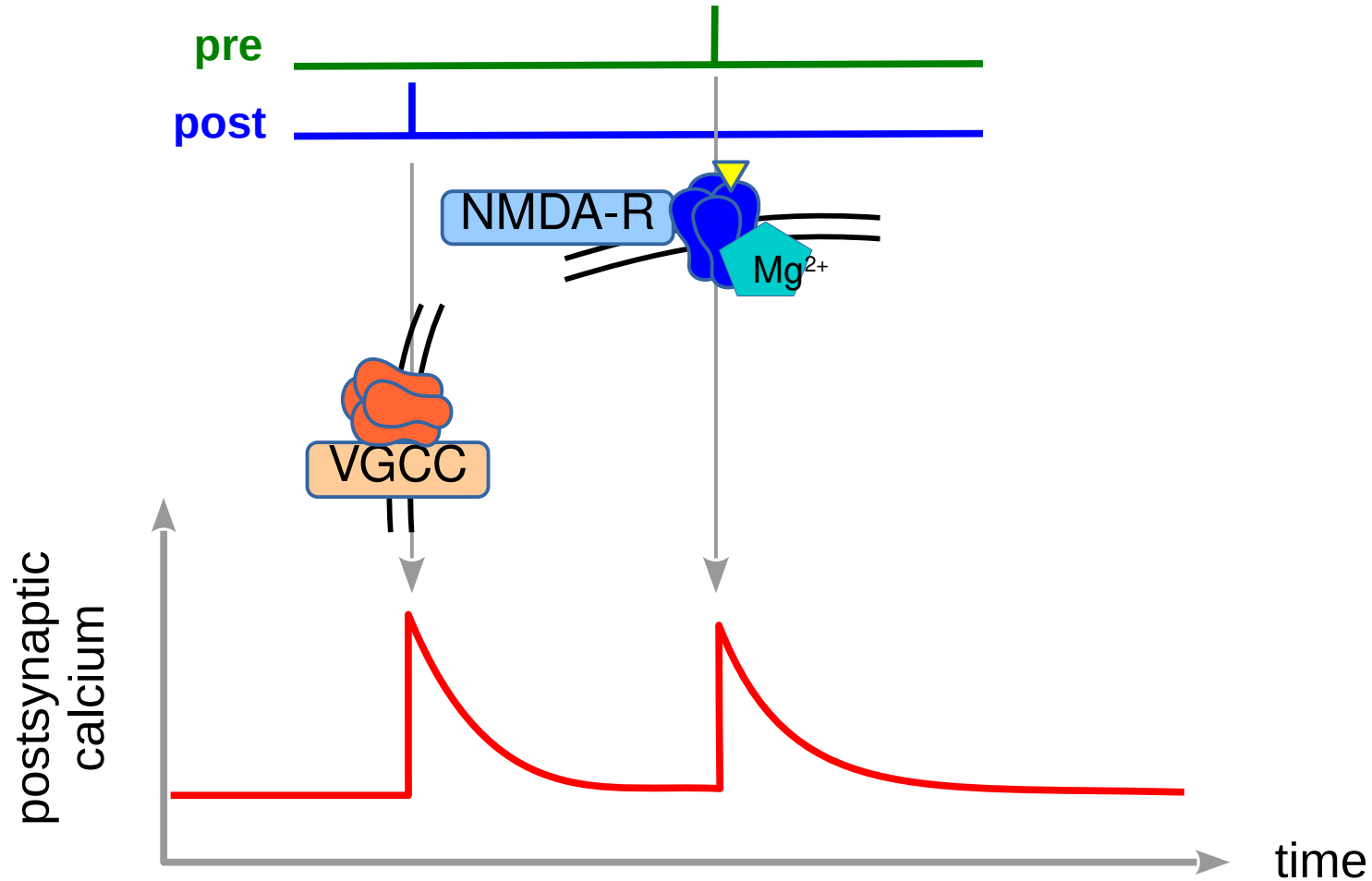


# Calcium influx

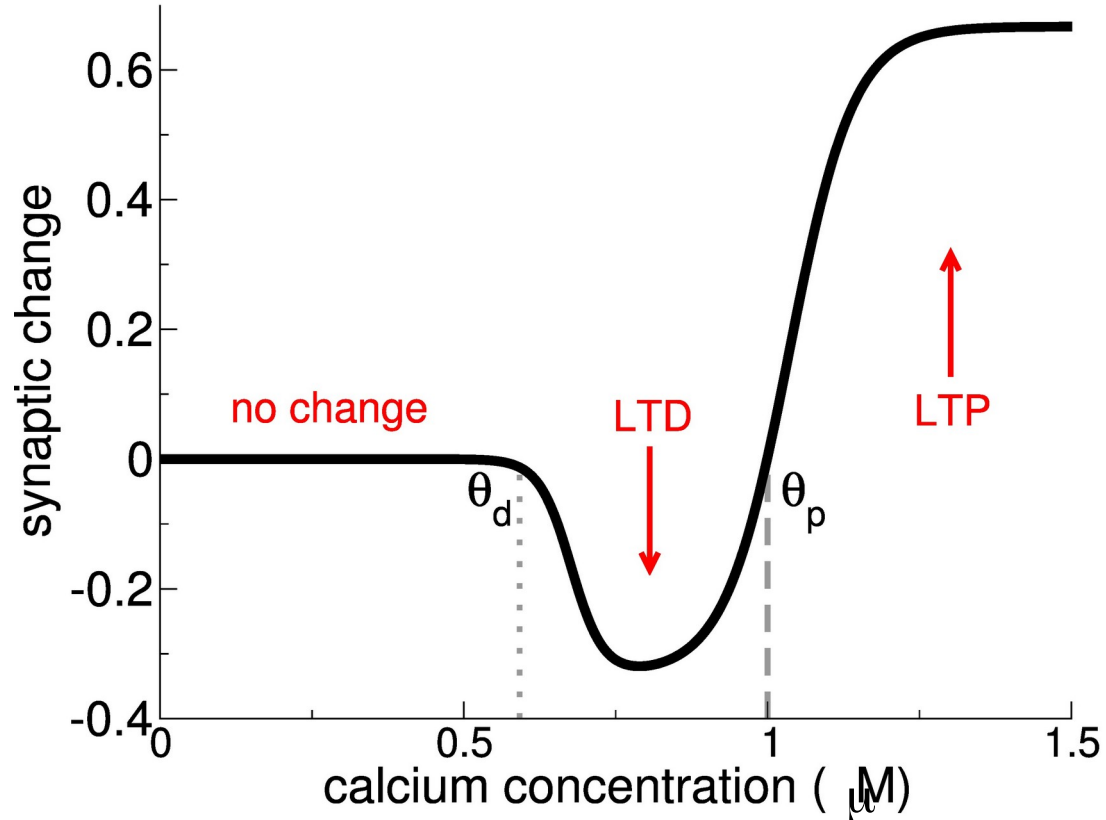
**coincidence detector :**



# Calcium transients from spike-pair stimulation

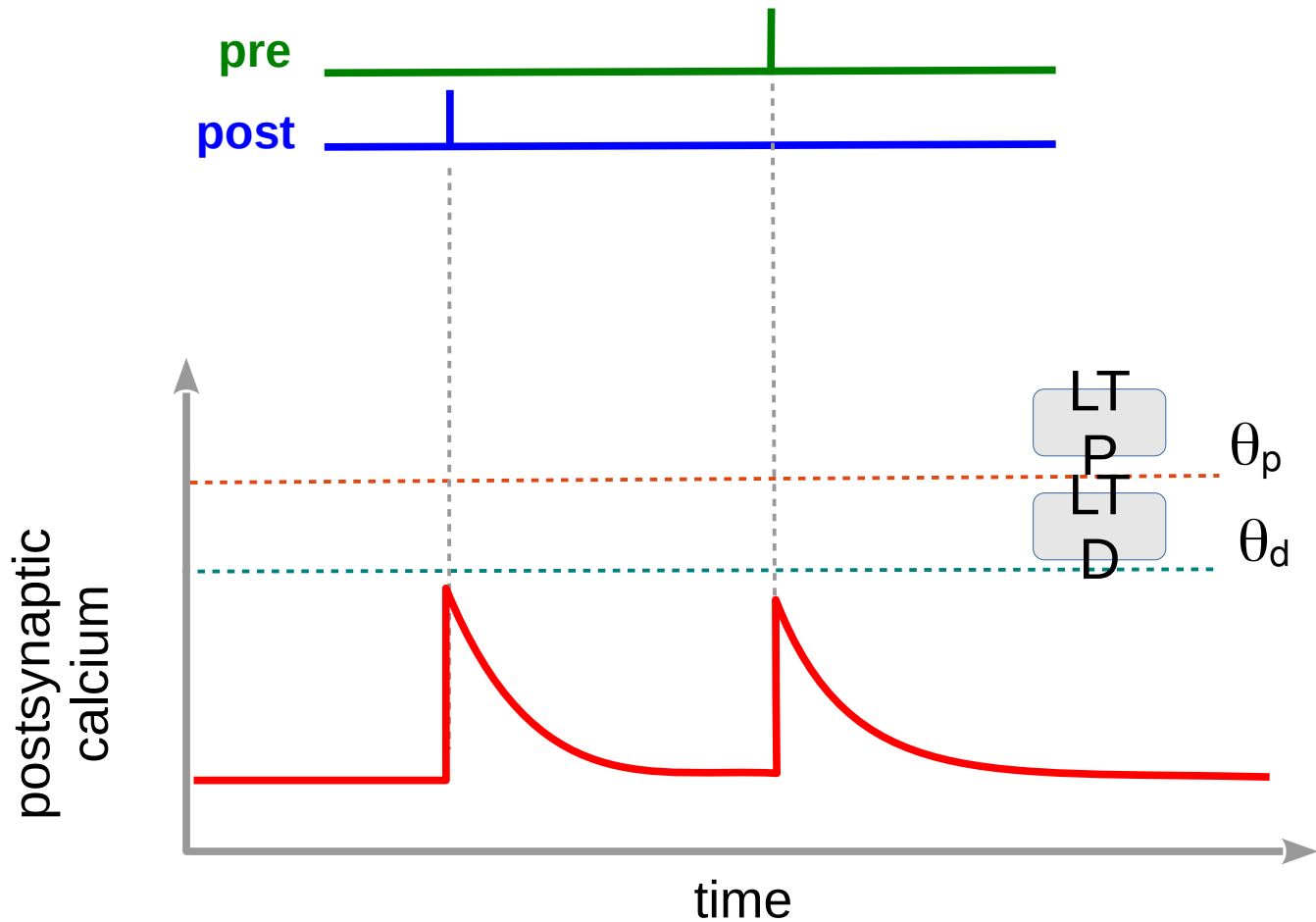


# Calcium transients from spike-pair stimulation



- the calcium control hypothesis posits that the level of postsynaptic calcium concentration controls amplitude and the sign of plasticity

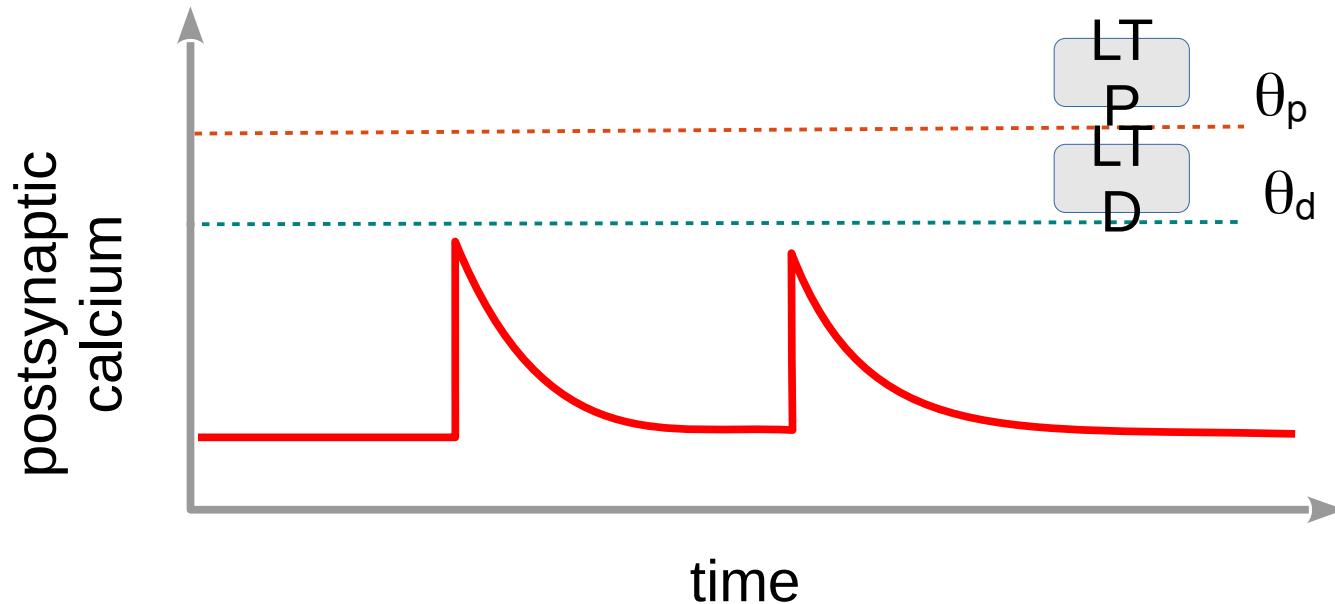
# Calcium control hypothesis introduces LTD/LTP thresholds





# Question : role of calcium in shaping STDP

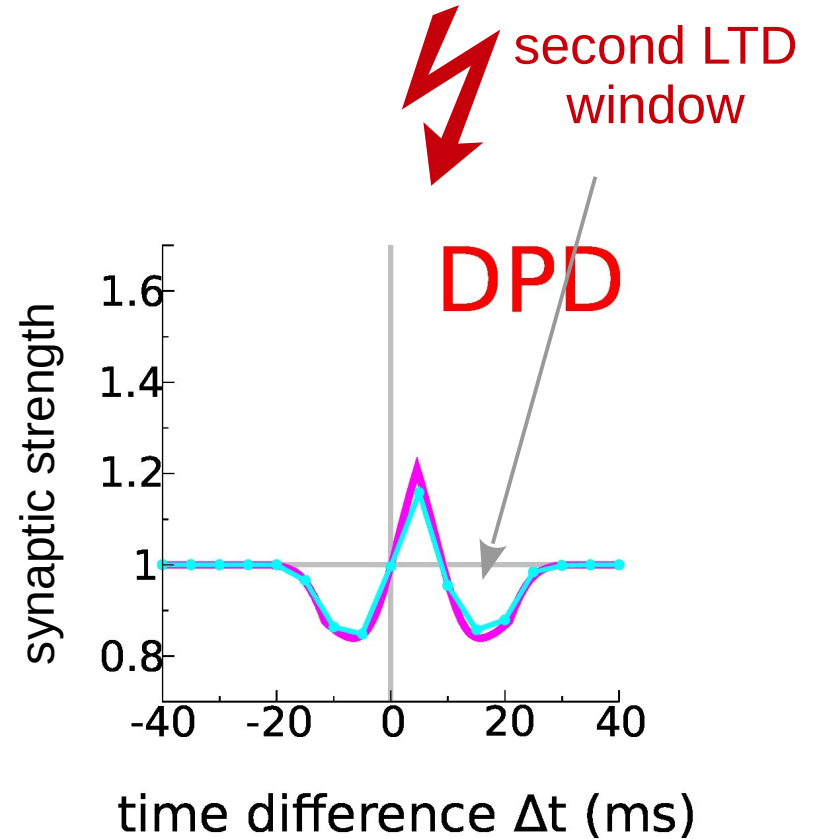
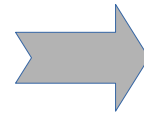
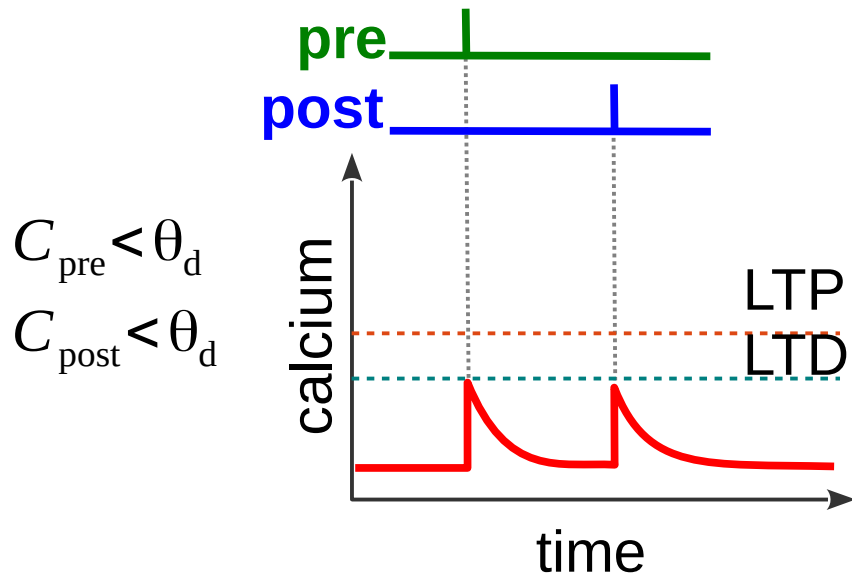
- I. Can the dynamics of the postsynaptic calcium account for synaptic plasticity induced by spike-pairs ?
- II. To which extent can the STDP phenomenology be explained by calcium ?



# Calcium amplitudes determine shape of STDP curve

simulation I

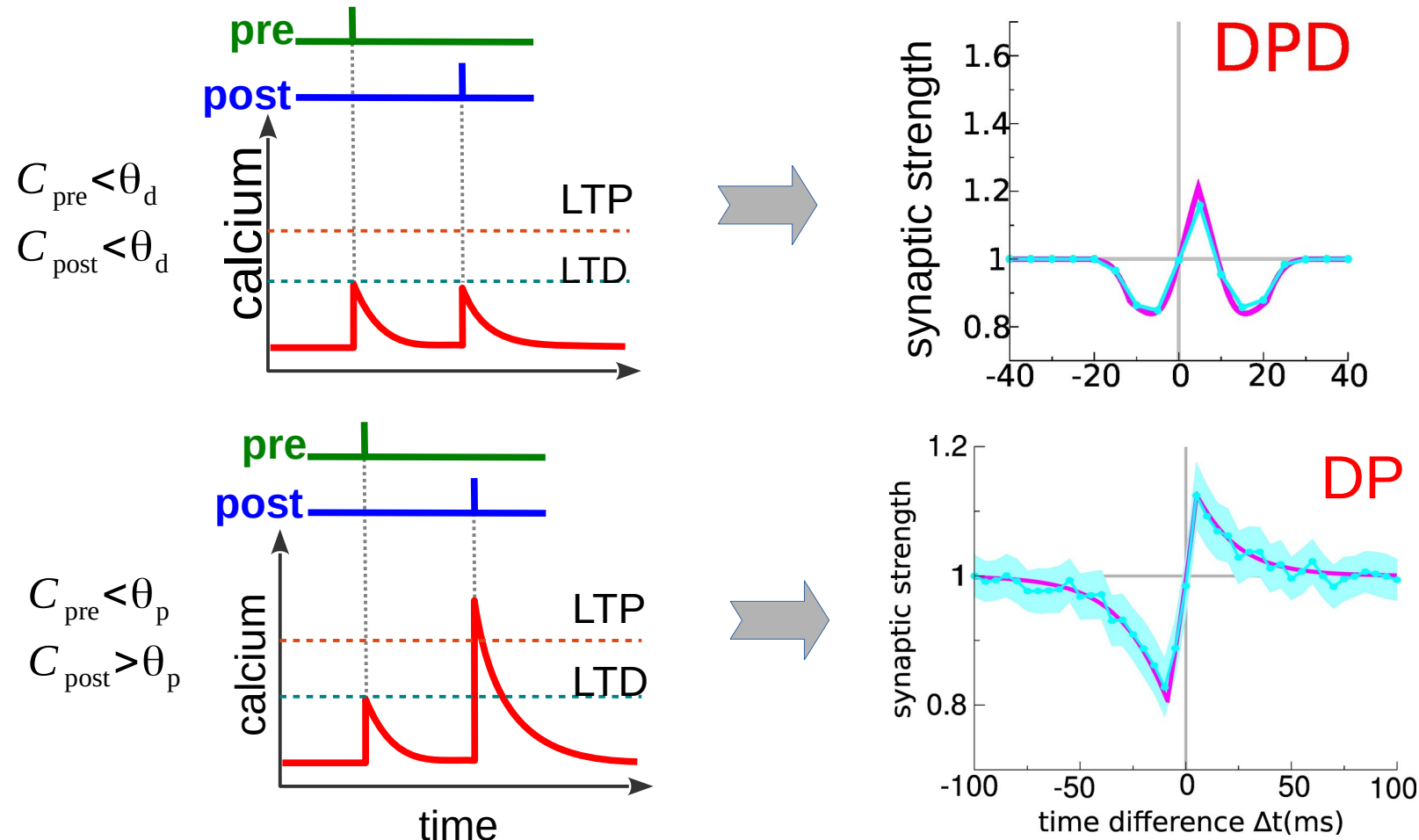
# Calcium amplitudes determine shape of STDP curve



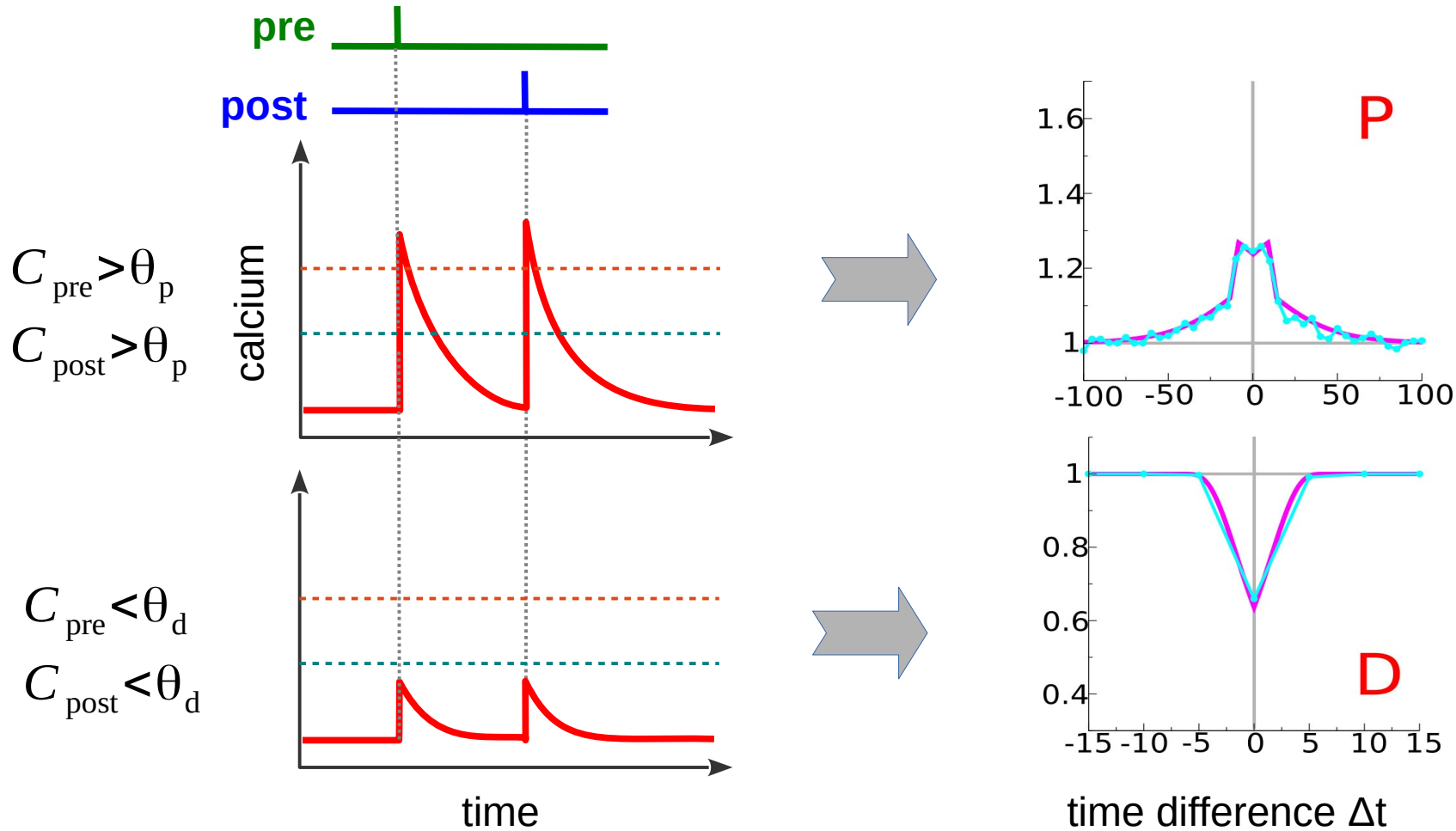
# Calcium amplitudes determine shape of STDP curve

simulation II

# Calcium amplitudes determine shape of STDP curve

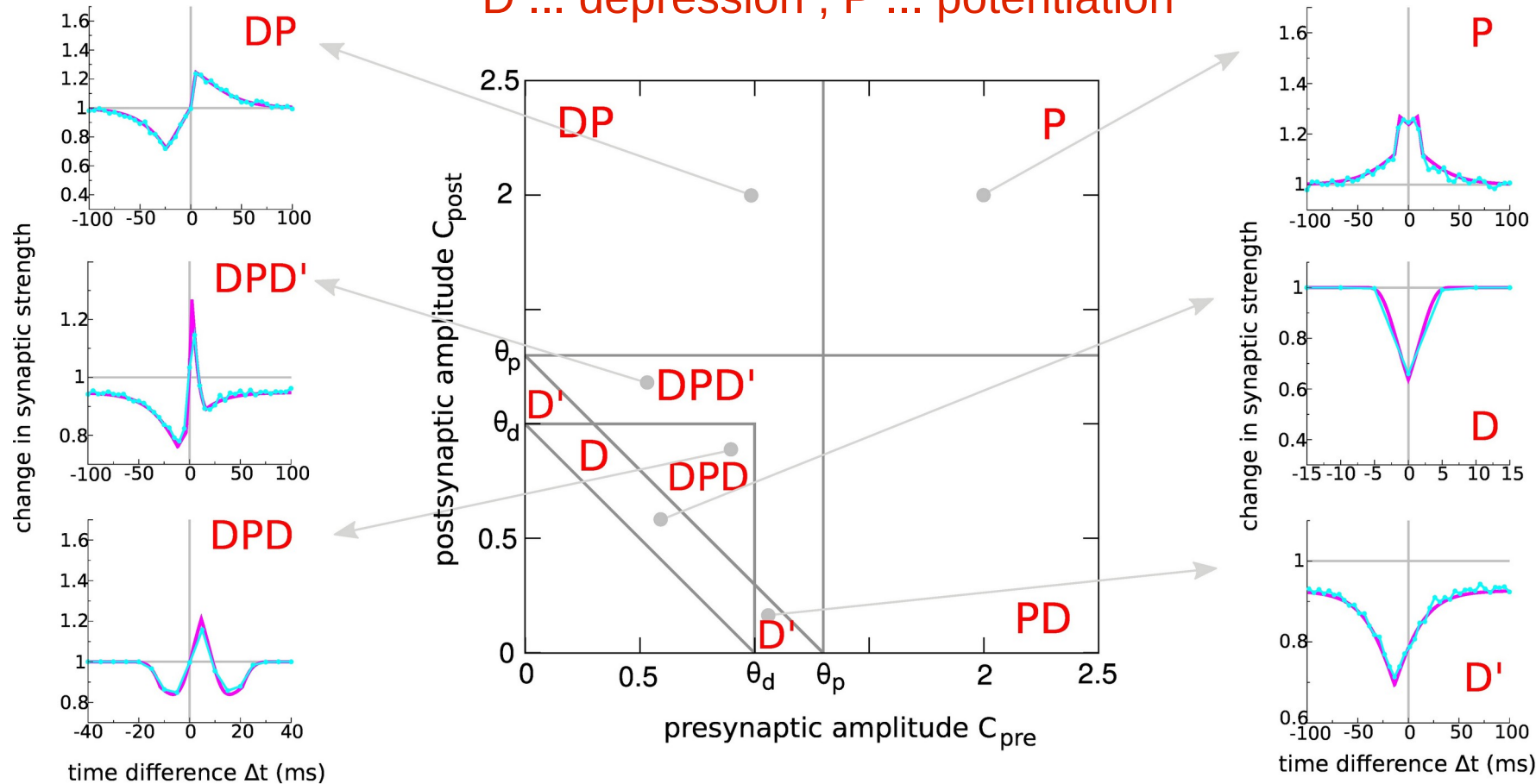


## Calcium amplitudes determine shape of STDP curve



# Diversity of STDP curves : spike-pair stimulation

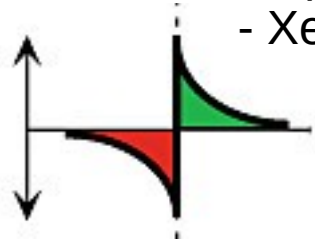
D ... depression , P ... potentiation



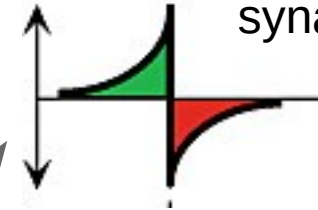
[Graupner & Brunel, *PNAS* 2012]

# Diversity of STDP curves : experimental results

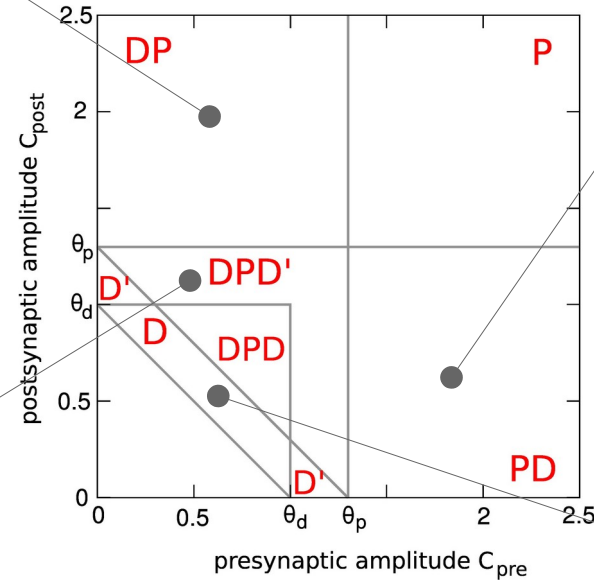
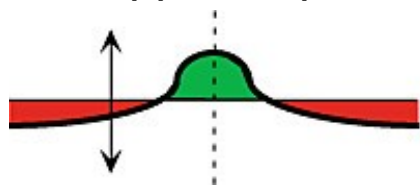
- neocortex-layer V
- hippocampus
- Xenopus tectum



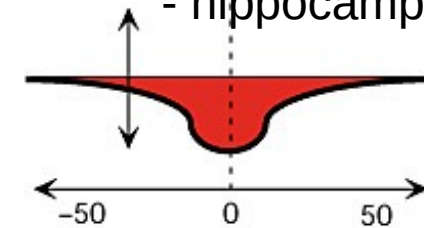
- ELL of electric fish
- corticostriatal synapse



- GABA-ergic neurons in hippocampal cultures



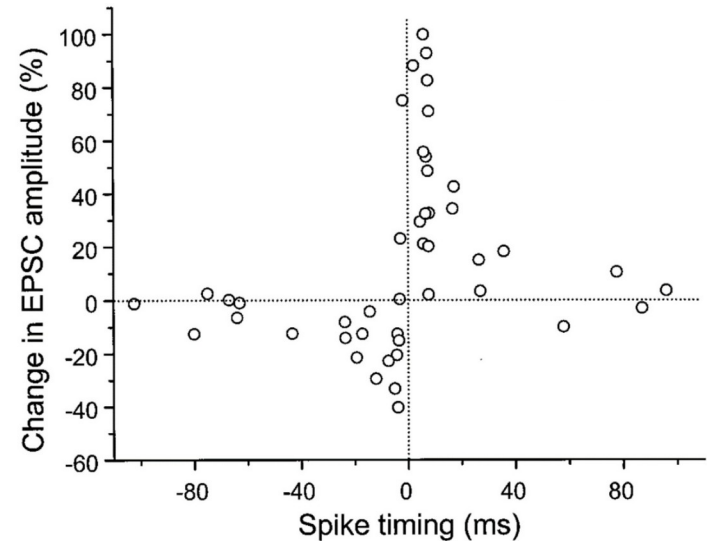
- neocortex-layer IV spiny stellates
- hippocampus





# Outline : STDP ... spike-timing dependent plasticity

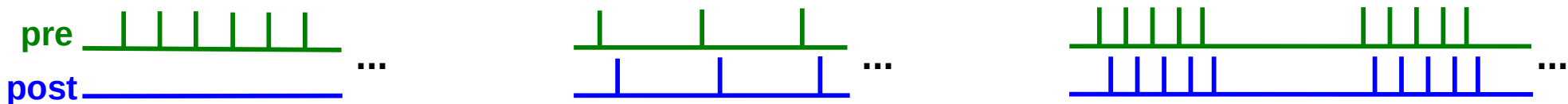
1. STDP : introduction and history
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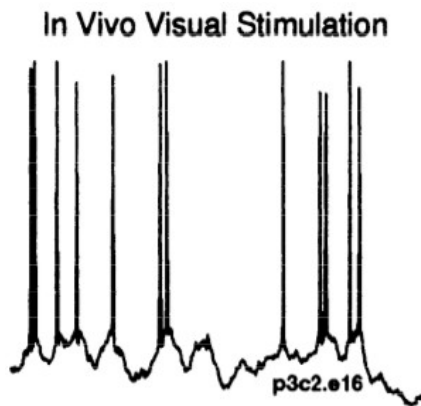
[Bi & Poo 1998]

# Firing patterns : Realistic firing is highly irregular

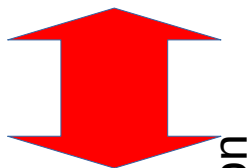
- stimulation protocols used to induce plasticity



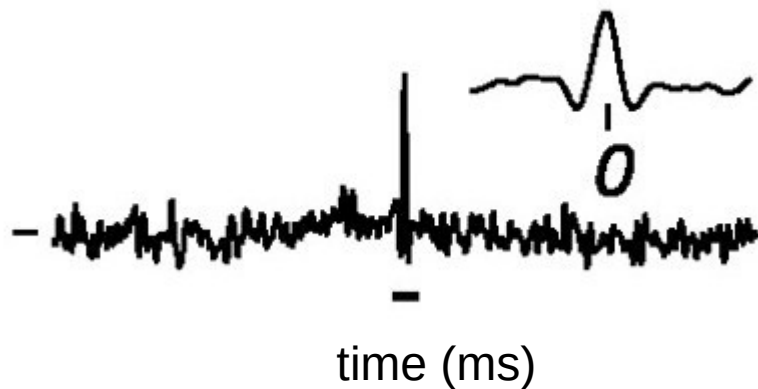
- *in vivo* firing patterns



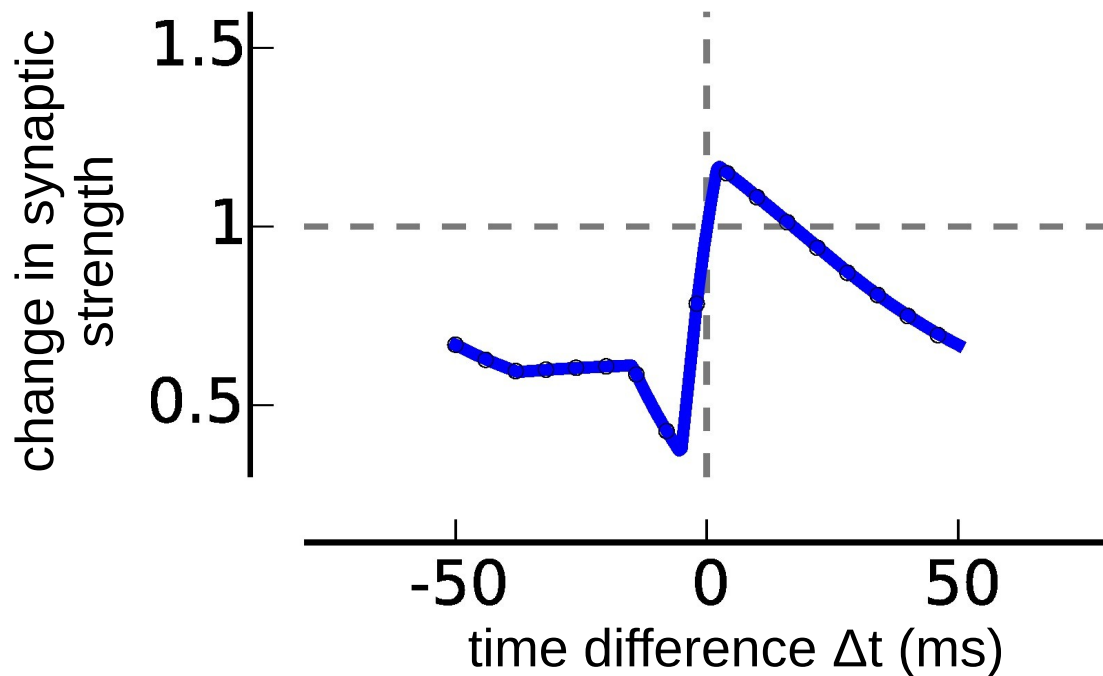
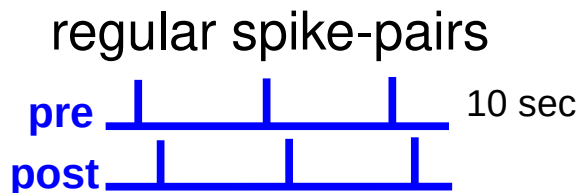
[Holt *et al.*, 1996]



cross-correlation

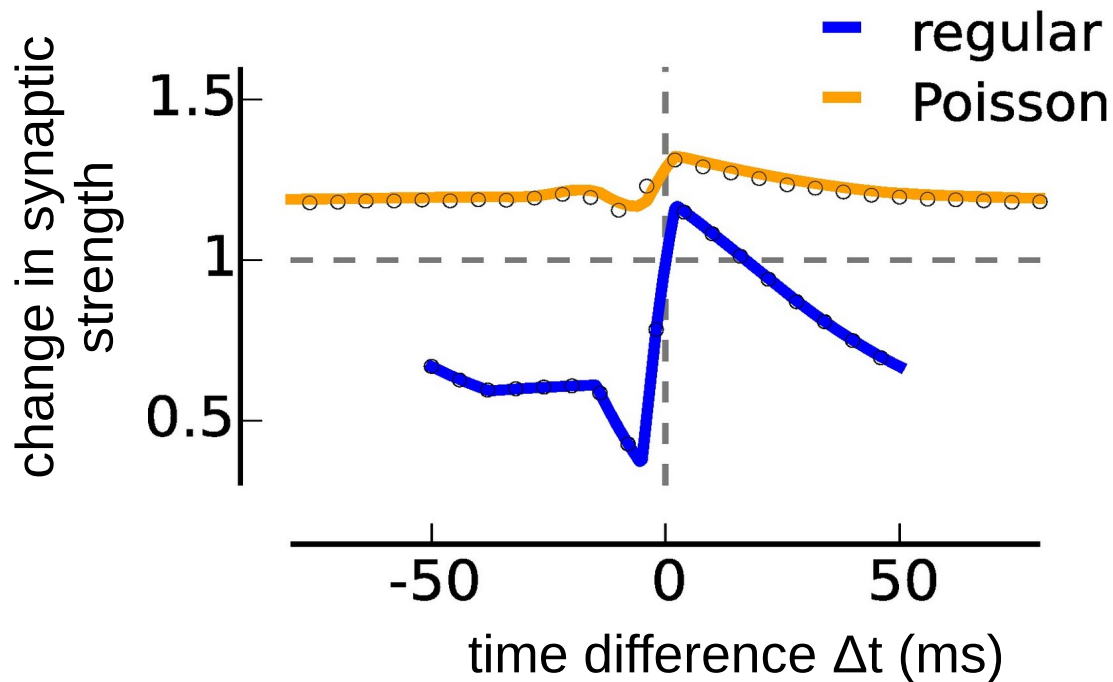
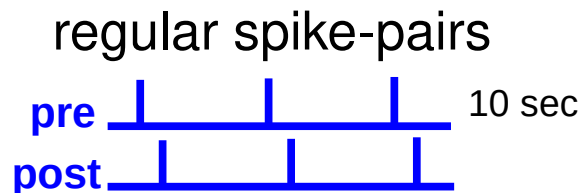


## Regular vs. irregular spike-pairs



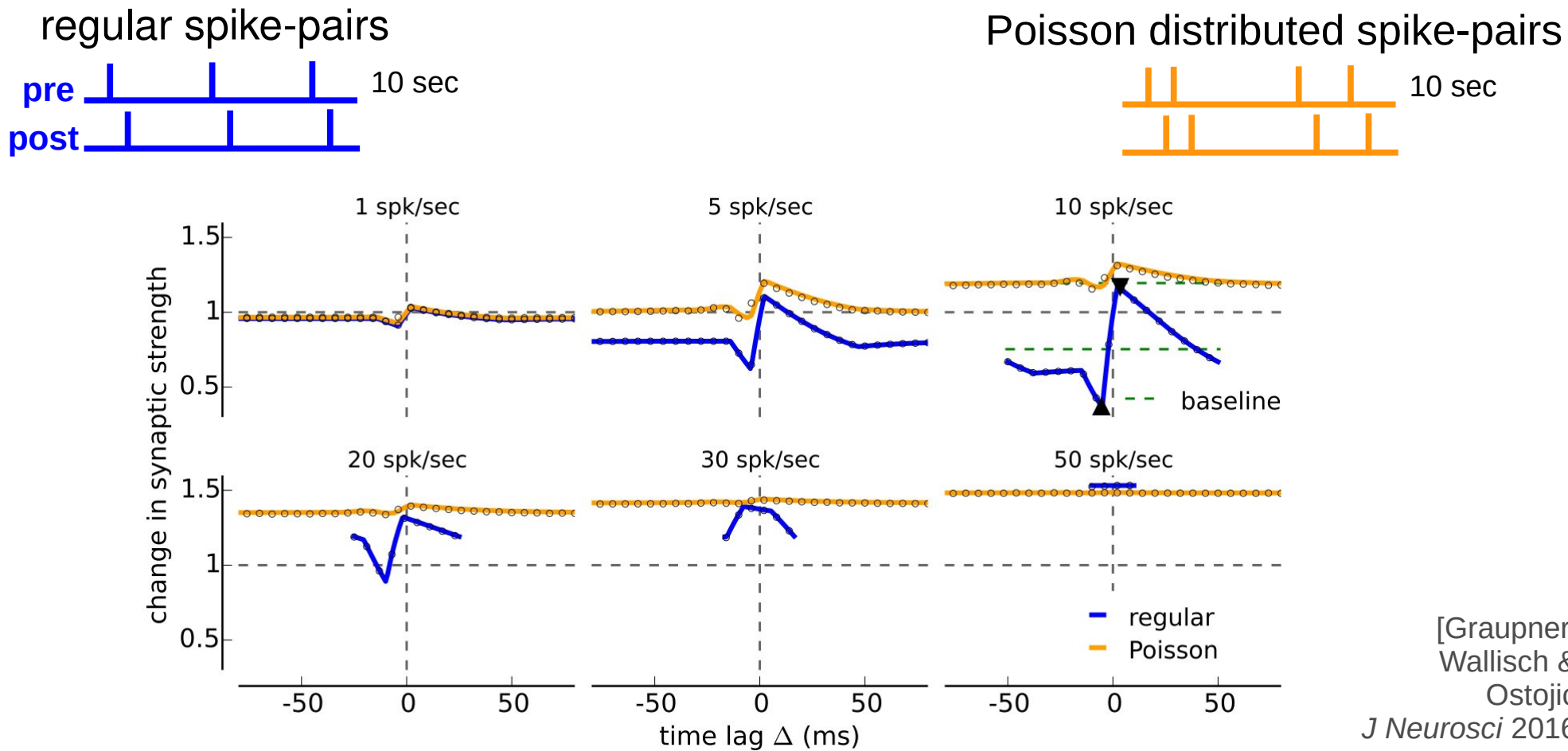
$$\nu_{\text{pre}} = \nu_{\text{post}} = 10 \text{ Hz}$$

## Regular vs. irregular spike-pairs



$$\nu_{\text{pre}} = \nu_{\text{post}} = 10 \text{ Hz}$$

## Regular vs. irregular spike-pairs



# Conclusions

- STDP : temporally asymmetric form of synaptic plasticity induced by tight temporal correlations between the spikes of pre- and postsynaptic neurons
- induction: coincident pre- and postsynaptic activity lead to calcium influx through NMDA receptors, triggering intracellular signaling cascades
- biophysical model resolve various aspects of the synaptic machinery involved in plasticity induction, most commonly the postsynaptic calcium dynamics
- the role of STDP for learning in the living animal remains elusive