Synaptic Plasticity :
Spike-timing dependent plasticity (STDP)

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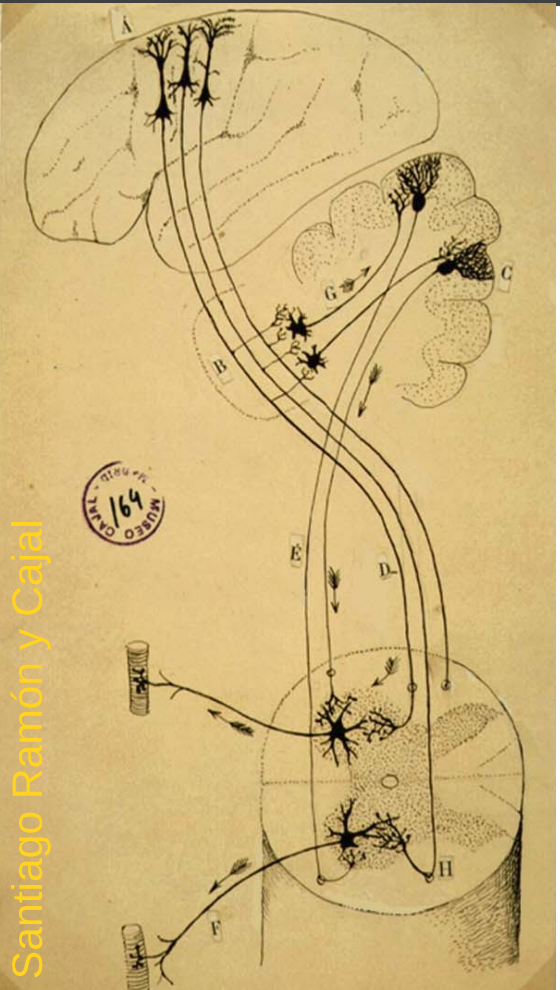
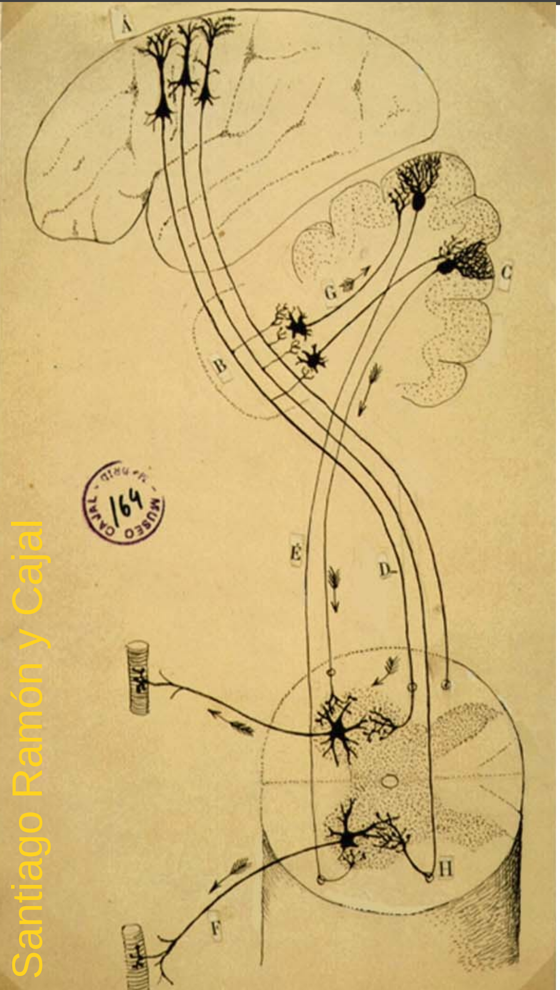
slides on : https://www.biomedicale.parisdescartes.fr/~mgraupe/teaching.php

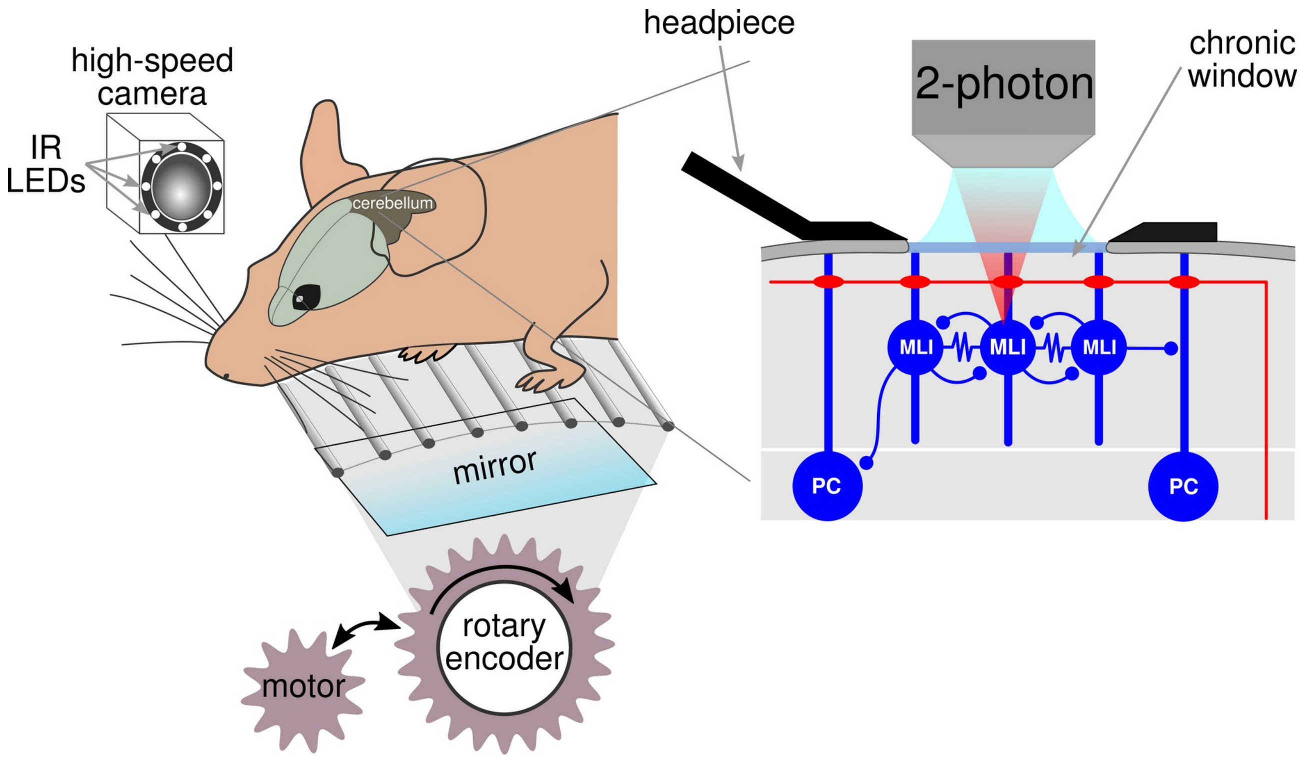
Cerebellum and locomotion



Cerebellum ensures that movements are well timed and highly coordinated.

Cerebellum and locomotion





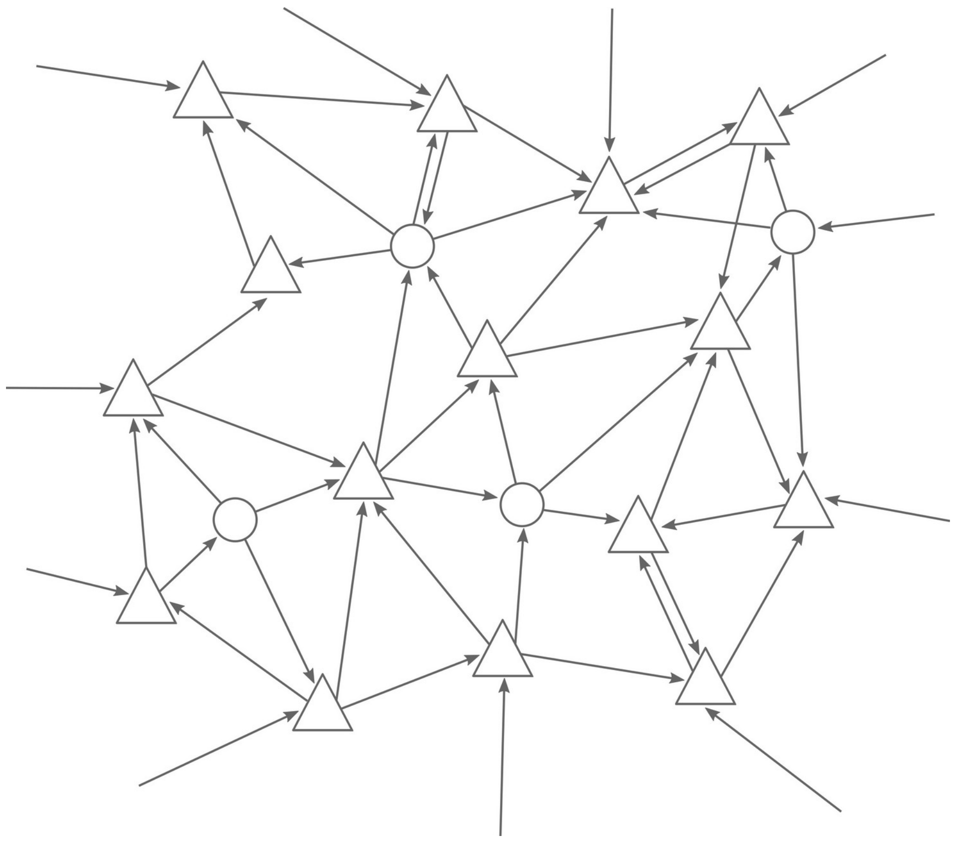
Students are welcome !

At which university am I working ?

At which university am I working ?

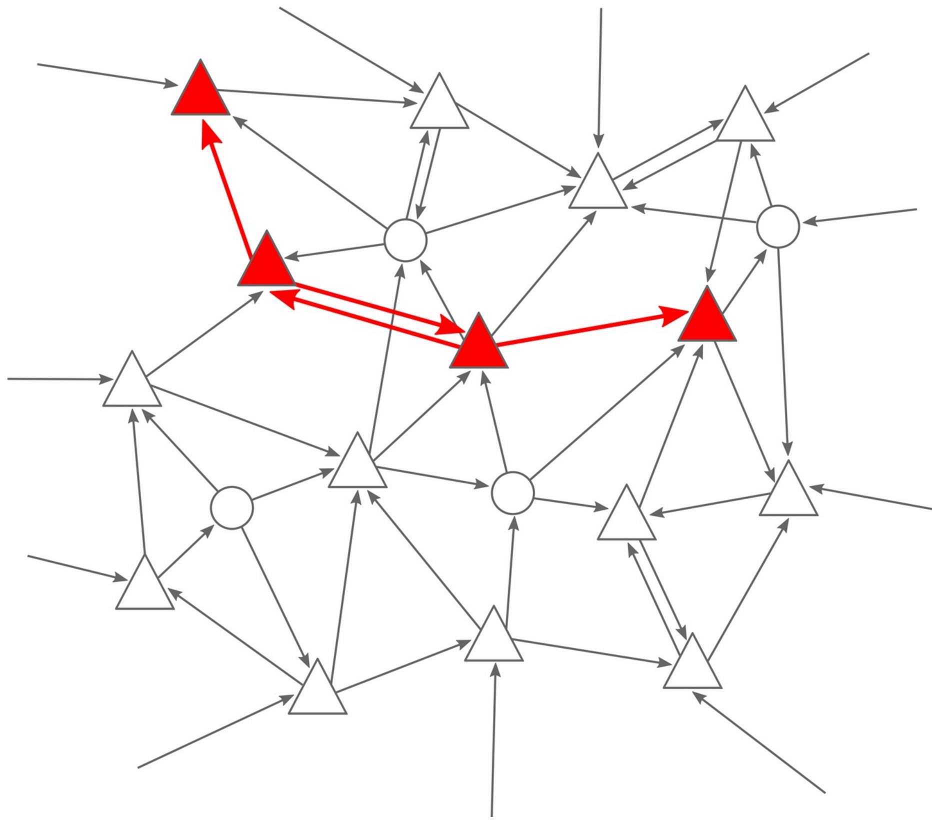
→ What happens in your brain when you learn ?

Learning on the neuronal network level

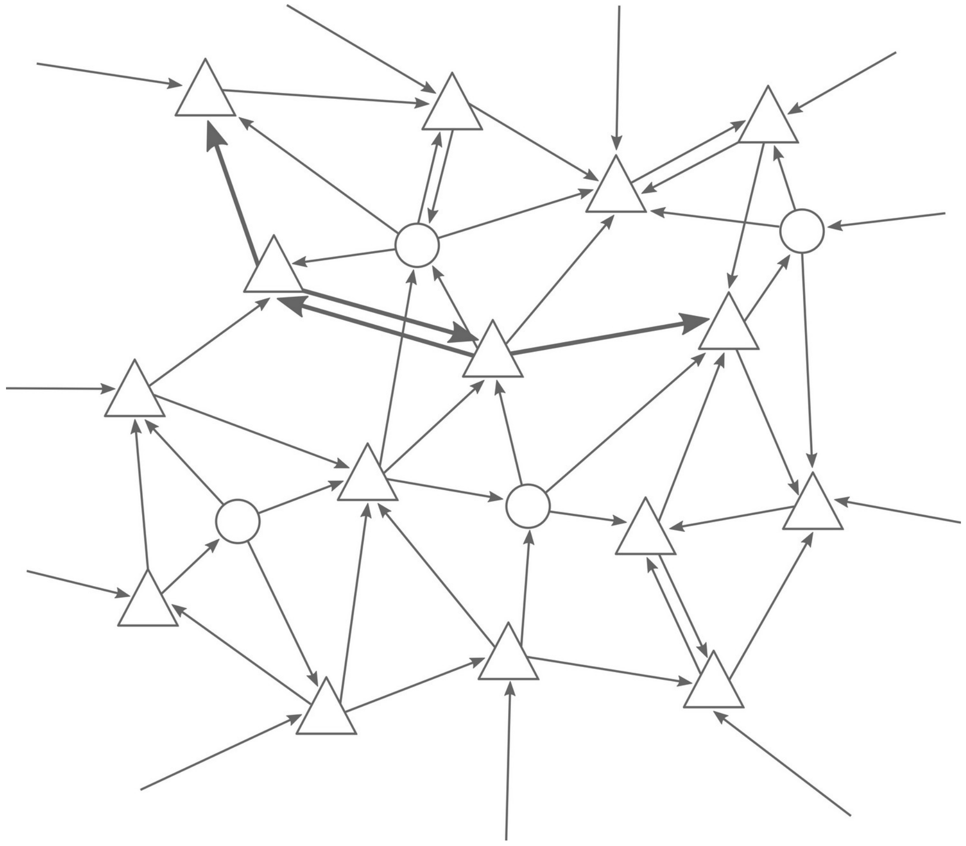


Learning on the neuronal network level

Stimulus / Experience



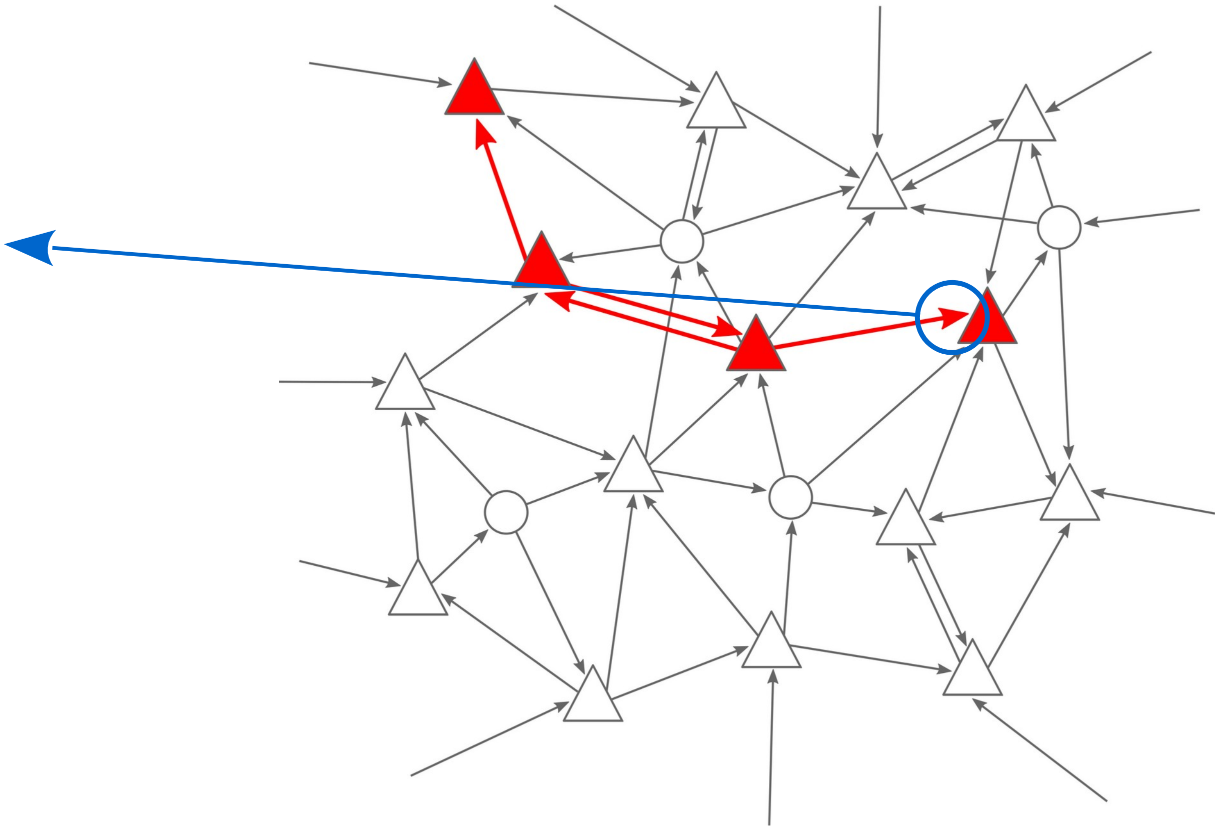
Learning on the neuronal network level



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 ?

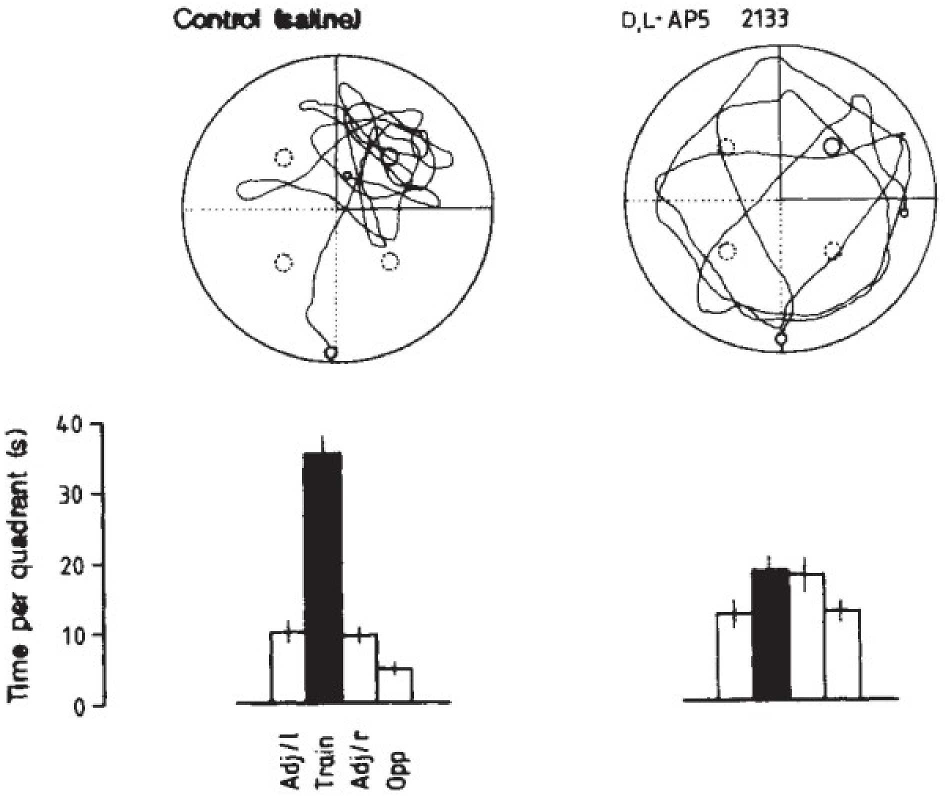


Experimental evidence : synaptic plasticity <-> memory

Morris water maze

[Morris *et al.*, 1986]

Relation between LTP and learning/memory



- NMDA receptor required to learn platform location [Morris *et al.*, 1986]

- NMDA receptor required to form spatial memories (place fields)

[McHugh *et al.* 1996]

Outline : STDP ... spike-timing dependent plasiticity

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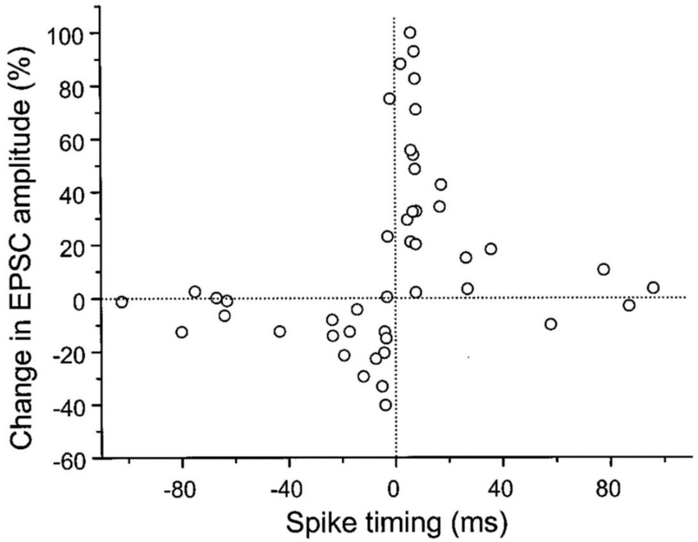
2. Phenomenology of STDP
3. Induction mechanisms
4. Biophysical models of STDP
5. STDP *in vivo*



[Bi & Poo 1998]

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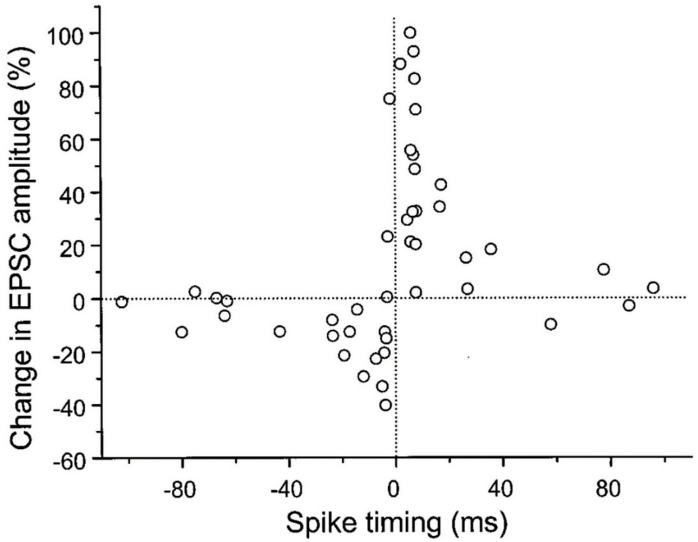
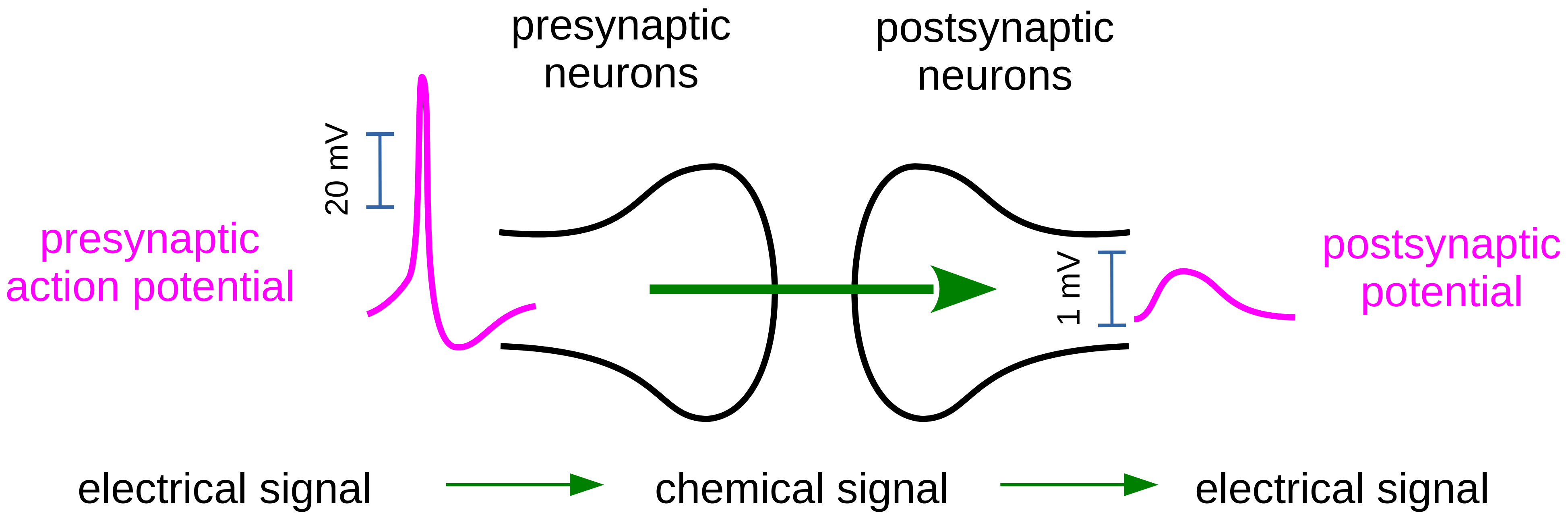


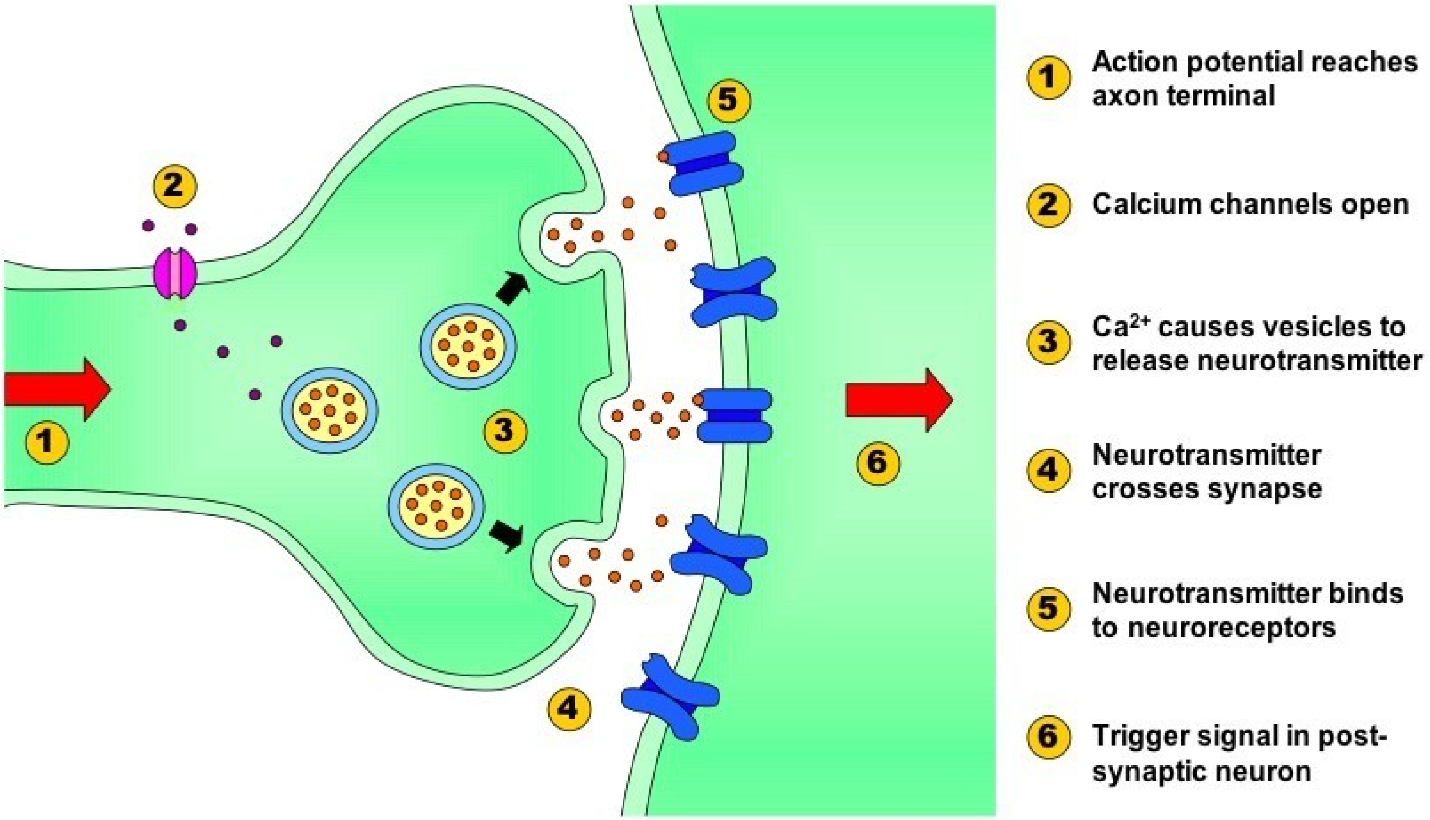
[Bi & Poo 1998]

Chemical synapse : transmits electrical signals



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

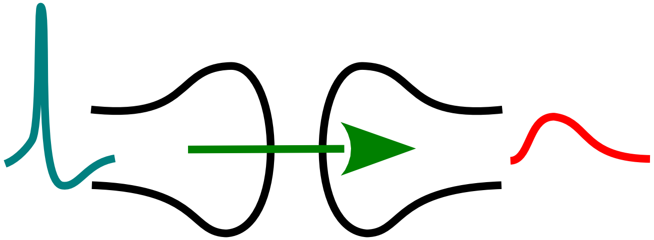
Chemical synapse : underlying biological machinery



http://outreach.mcb.harvard.edu/animations/synaptic.swf

Chemical synapse : excitatory or inhibitory

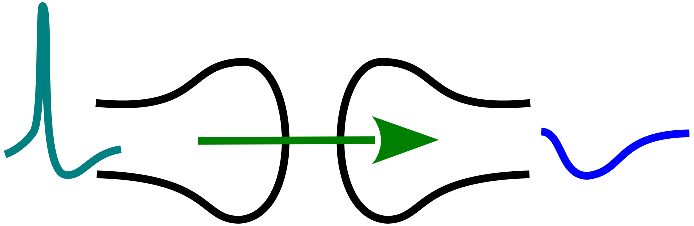
Excitatory synapse



depolarization:
excitatory postsynaptic potential (EPSP)

neurotransmitter	receptor
glutamate	AMPA, NMDA
acetylcholine	nAChR, mACHR
catecholamines	G-protein-coupled receptors
serotonin	$5\text{-}HT_3$, ...
histamine	G-protein-coupled receptors

Inhibitory synapse



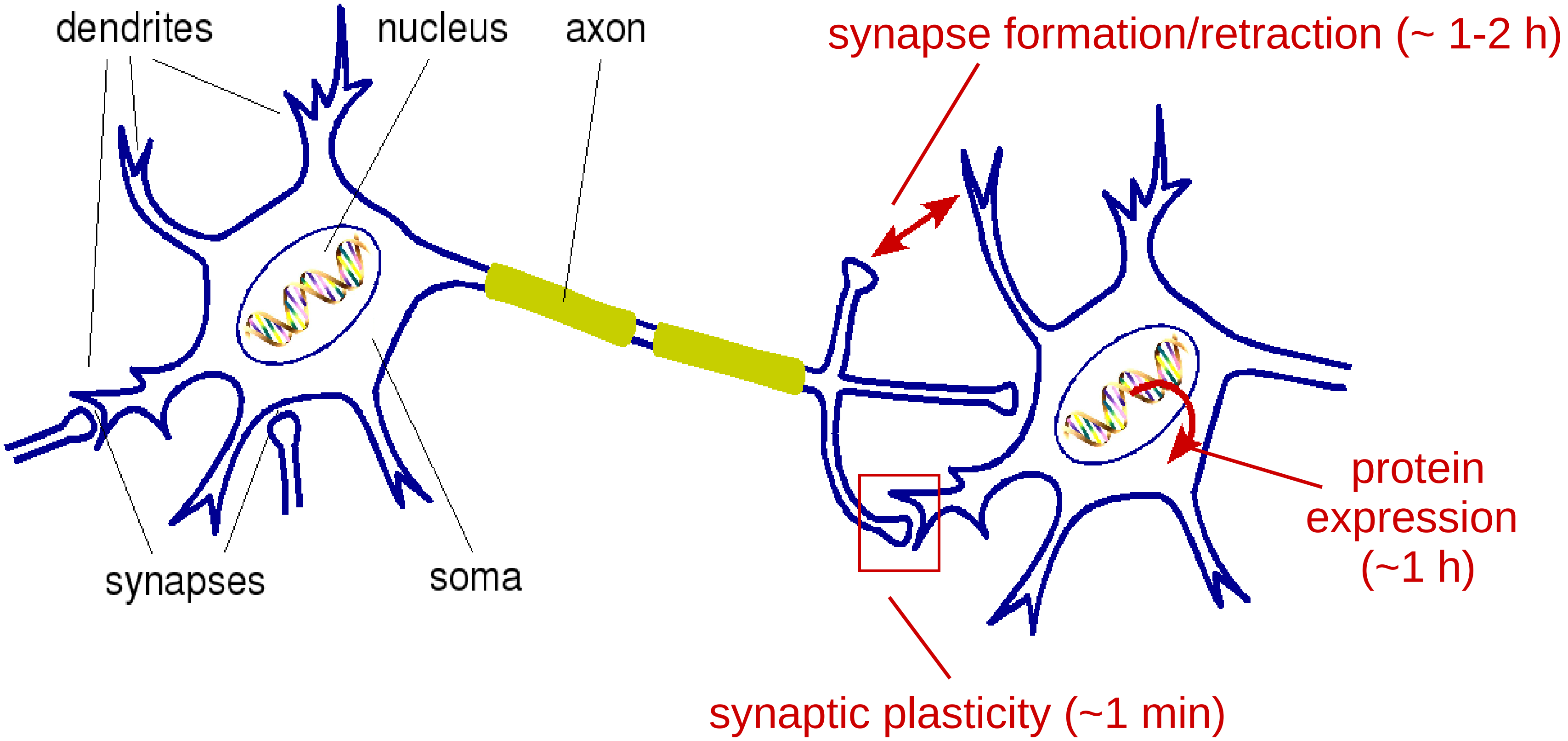
hyperpolarization:
Inhibitory postsynaptic potential (IPSP)

neurotransmitter	receptor
GABA	$GABA_A$, $GABA_B$
glycine	GlyR

Different forms of plasticity

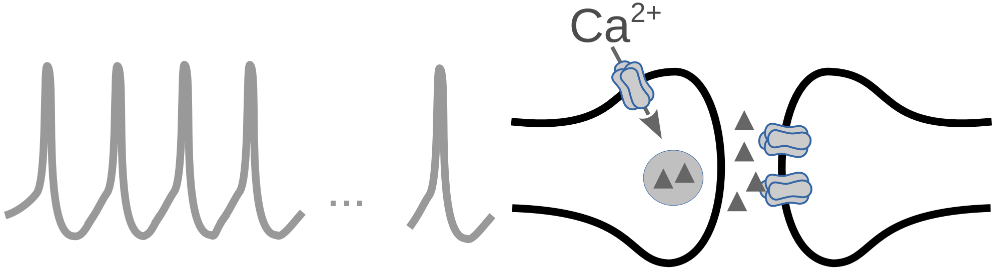
structure of neurons

changes related to neural activity



Short-term synaptic plasticity

train of presynaptic action potentials

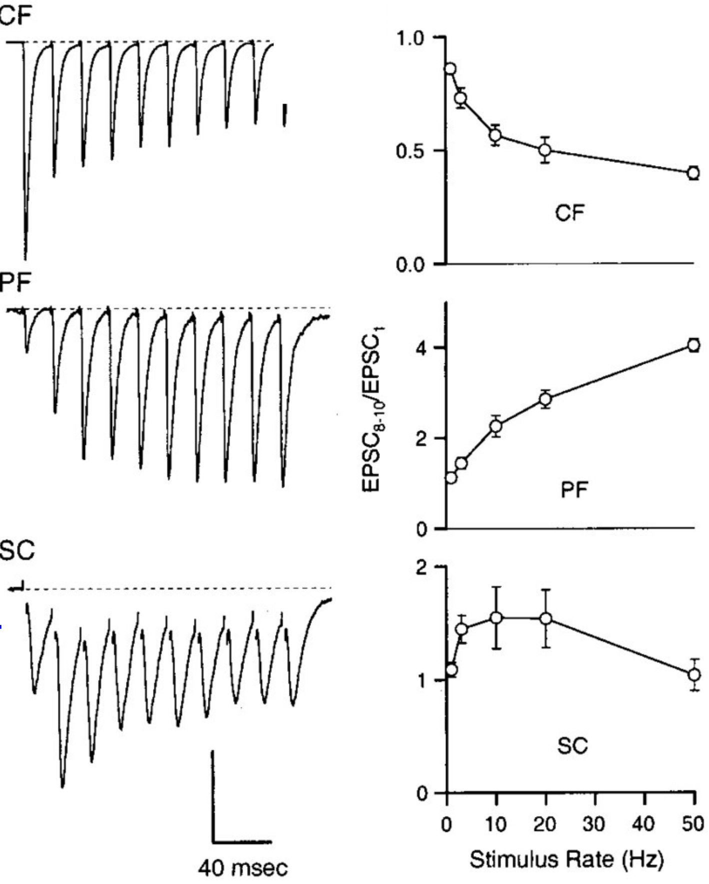


- transient change in transmission efficacy
- time scale of changes ~1 sec

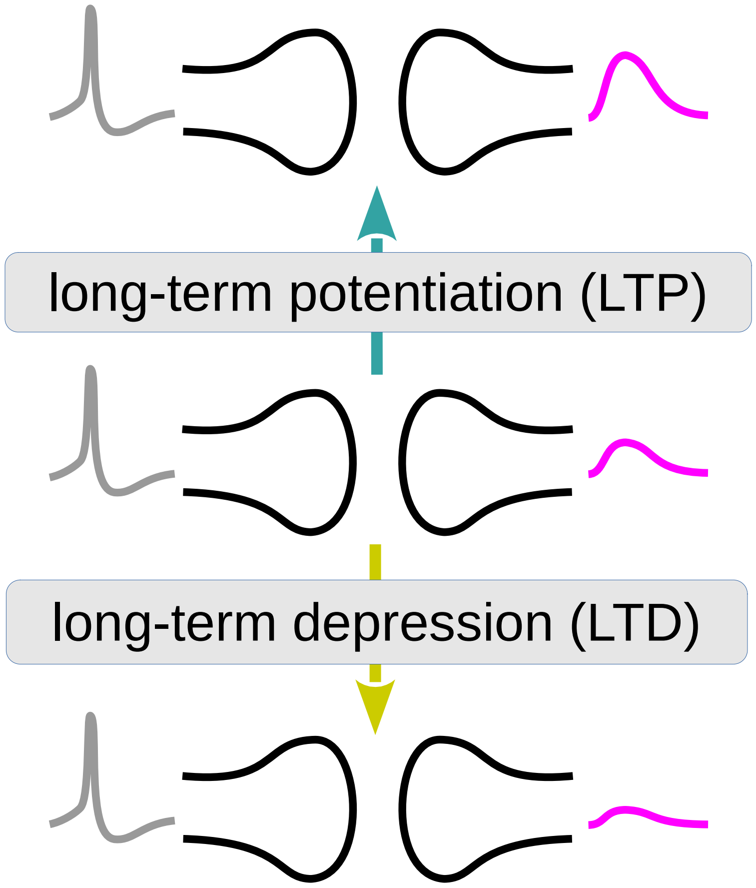
facilitation

depression

facilitation+ depression

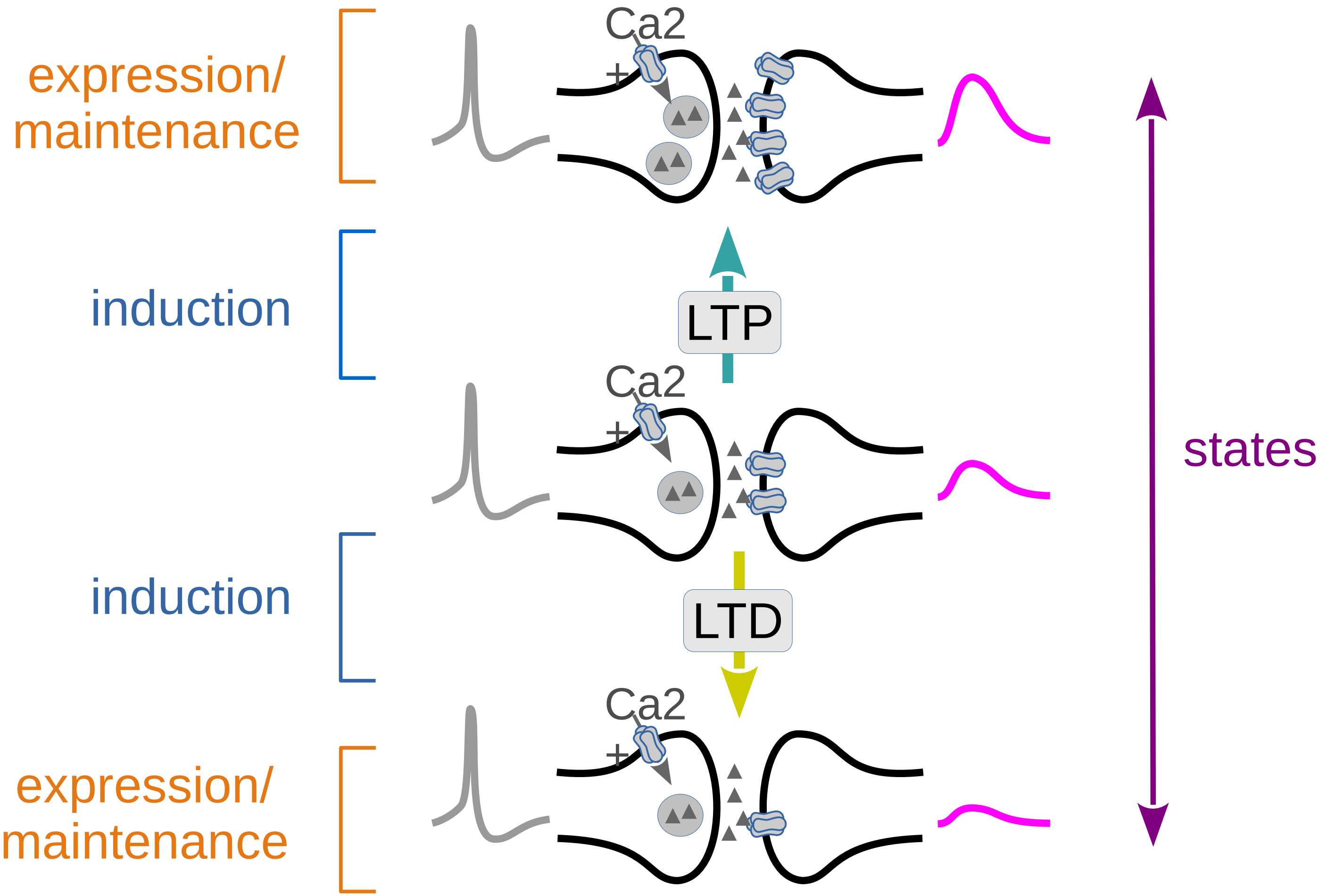


Long-term synaptic plasticity

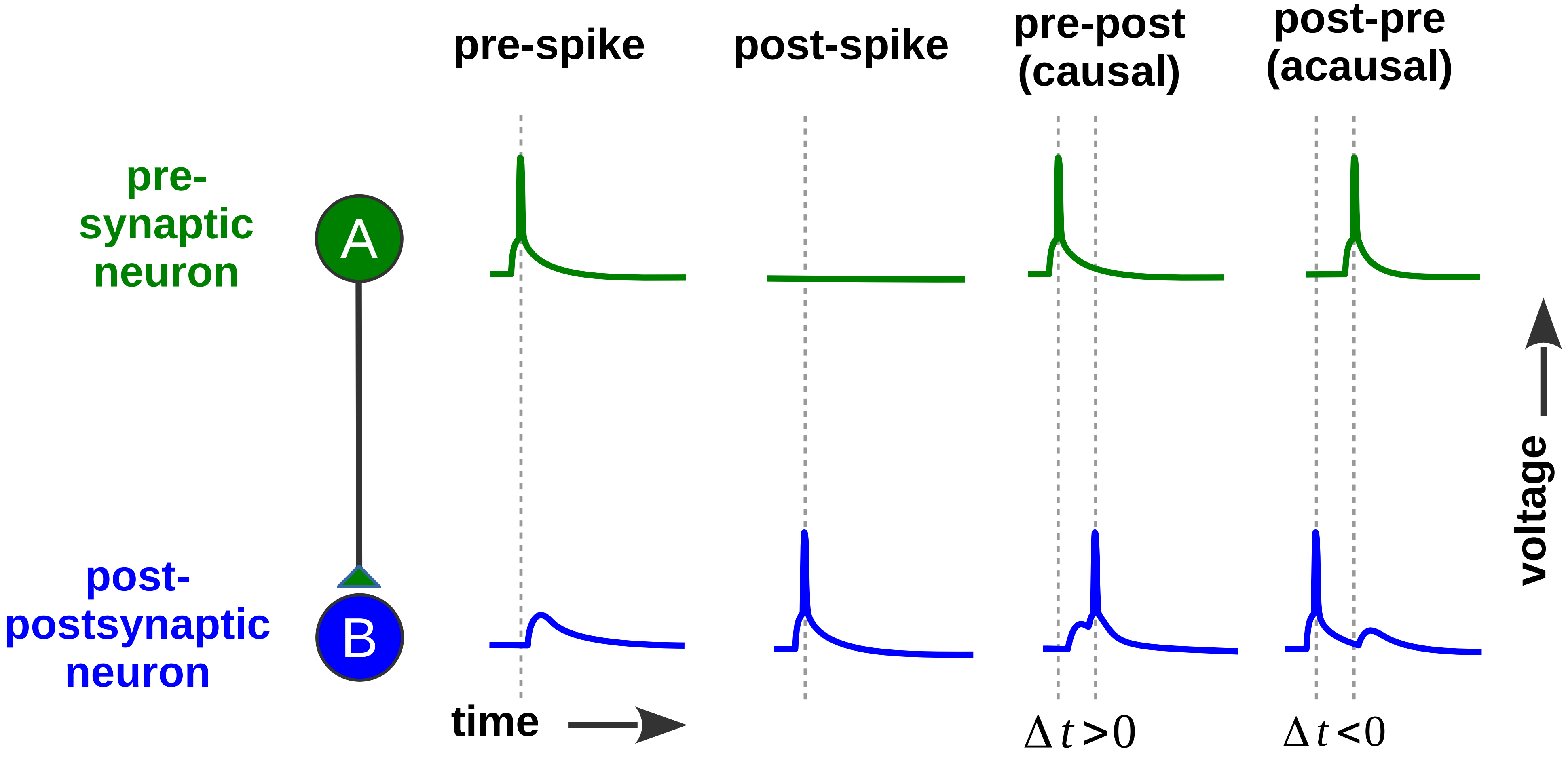


- long-lasting change (>60 min) in transmission efficacy
- time scale of induction ~ 1 min

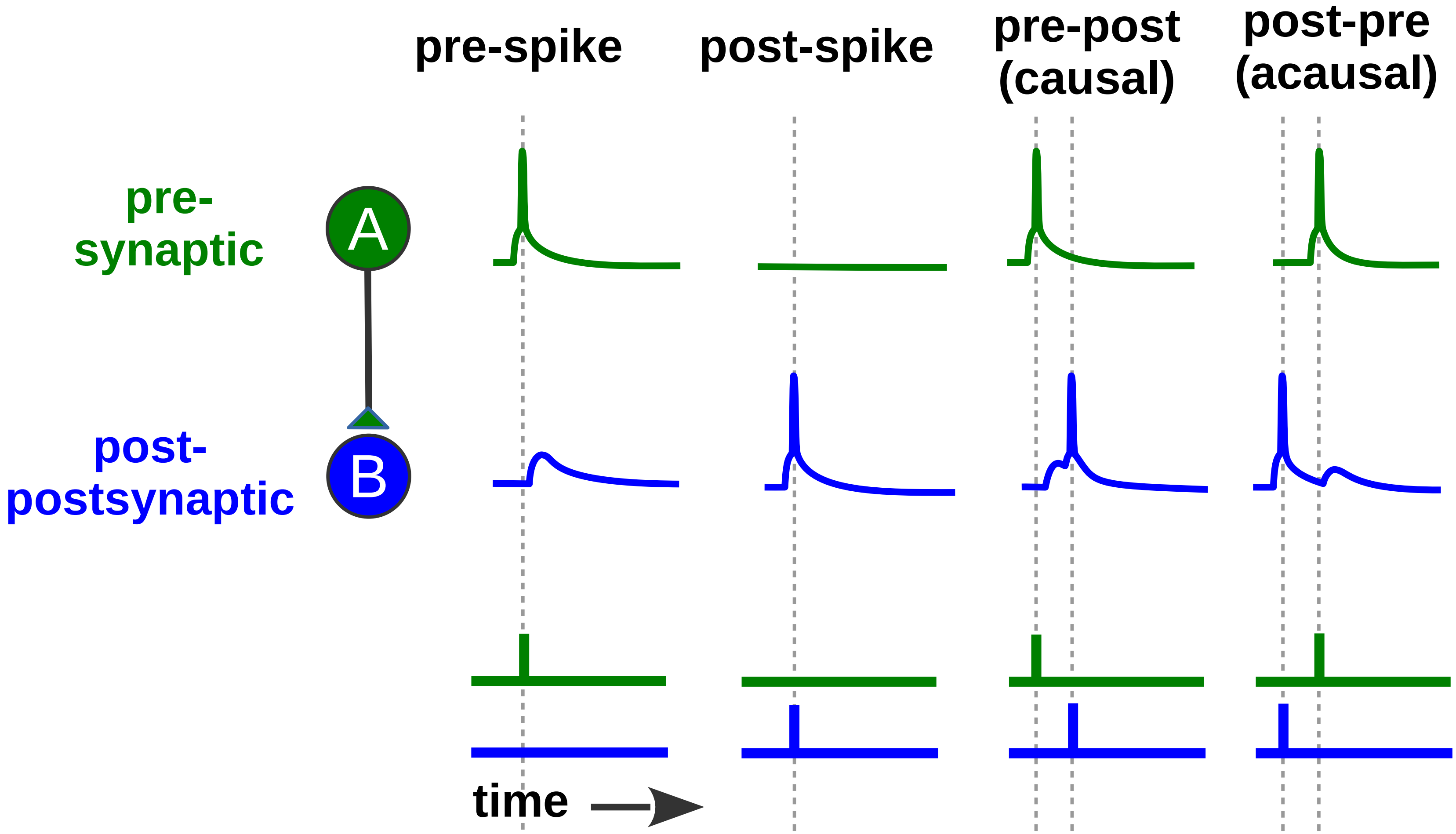
Synaptic plasticity: induction, maintenance & states



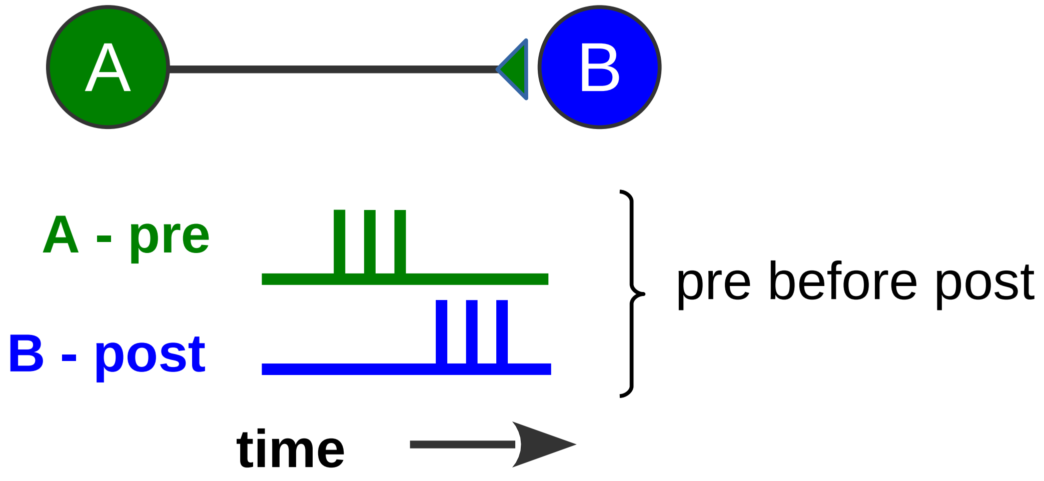
Spike timing : nomenclature



Spike timing : nomenclature



LTP induction: early conceptual work

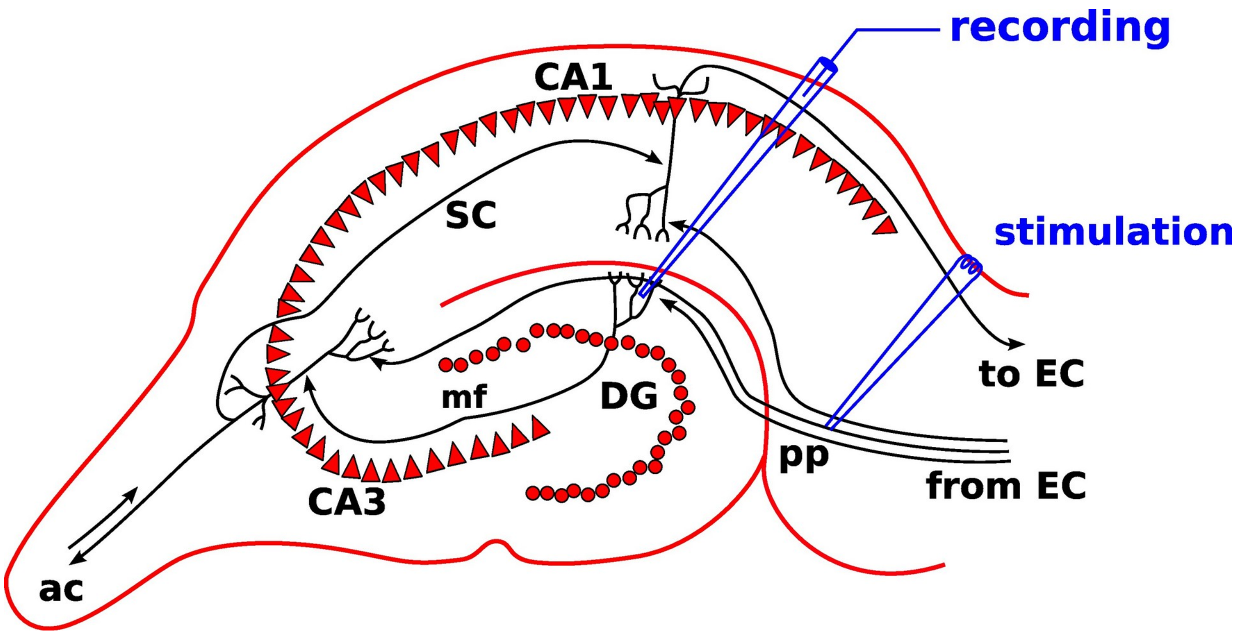


“When an axon of cell A is near enough to excite a cell B and *repeatedly* and *persistently* takes part in firing it, some growth or metabolic changes take place in one or both cells such that A’s efficiency, as one of the cells firing B, is *increased.*”

[Hebb 1949;
see also Konorski 1948]

Induction: first experimental work in hippocampus

hippocampus

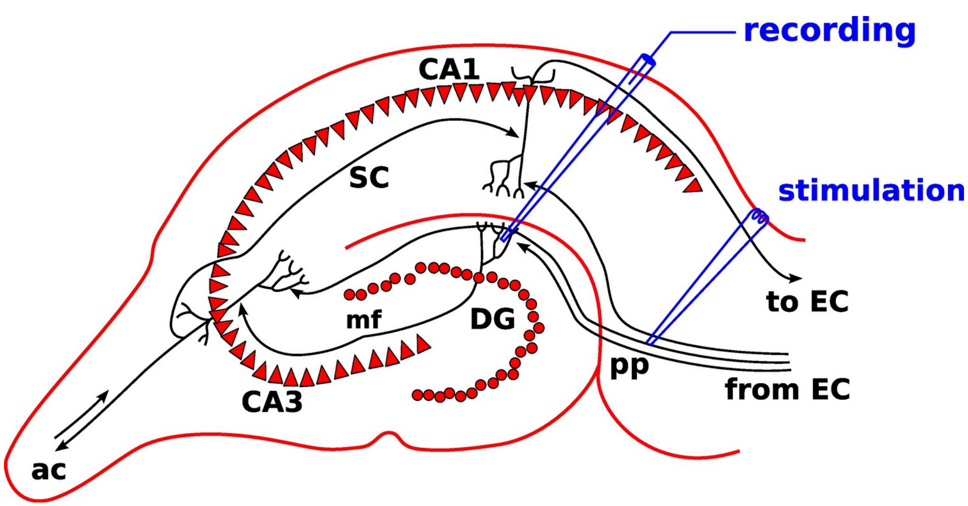


EC ... enthorhinal cortex
DG ... dentate gyrus
CA3/1 ... cornu ammonis 3/1

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

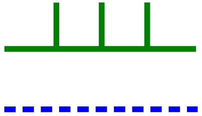
Induction: LTP through high frequency stimulation

hippocampus (*in vivo*)

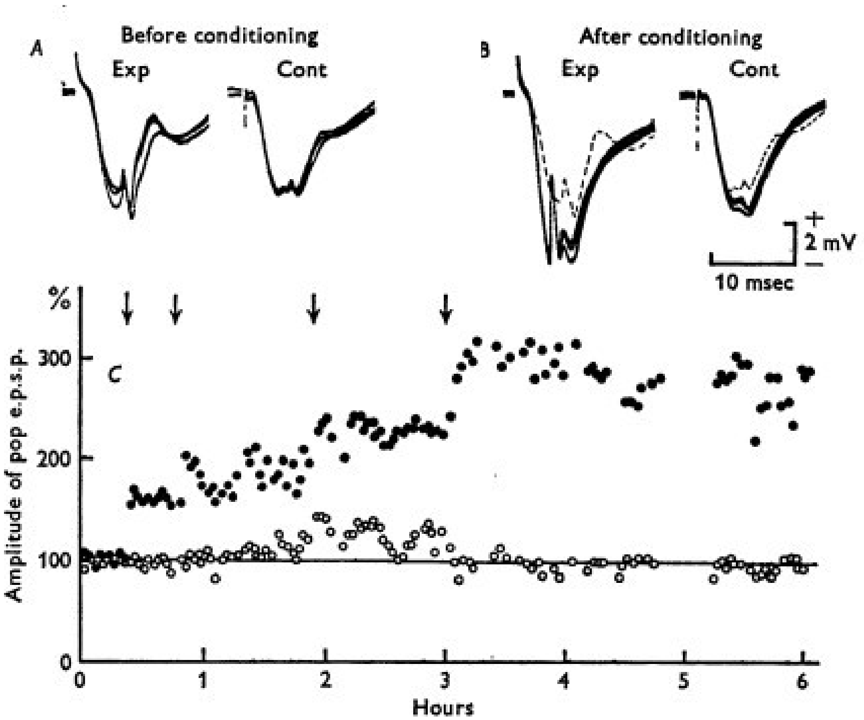


pre

post

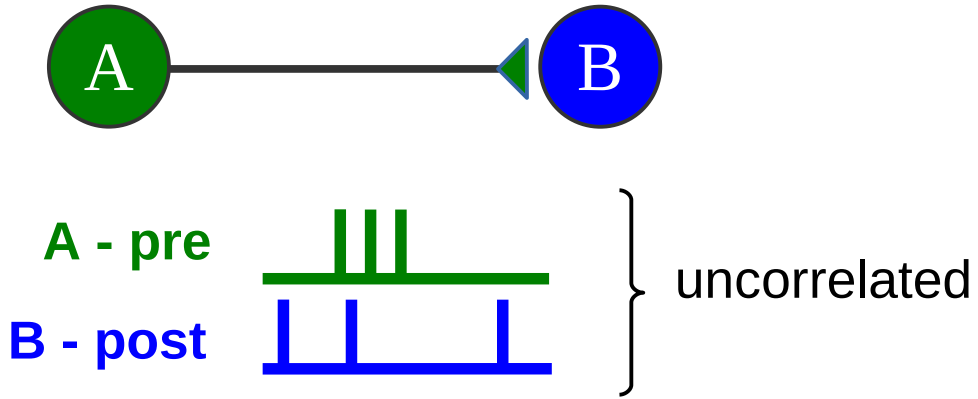


10-20 Hz for 10-15 sec
or 100 Hz for 3-4 sec



[Bliss and Lømo 1973]

LTD induction: postulate of Stent

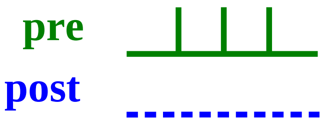


"When the presynaptic axon of cell A *repeatedly* and *persistently* fails to excite the postsynaptic cell B while cell B is firing under the influence of other presynaptic axons, metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is *decreased*."

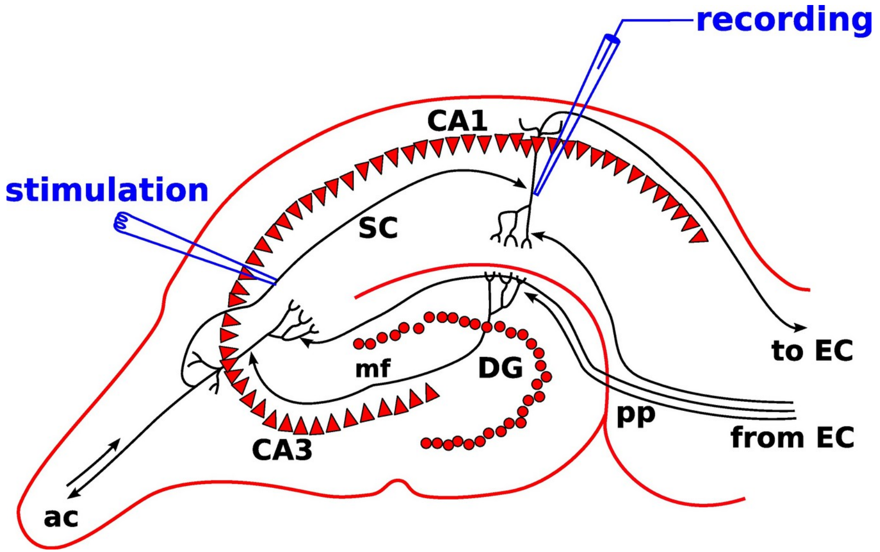
[G. Stent 1973;
see also Sejnowski 1977, von der Malsburg 1973, Bienenstock et al. 1982]

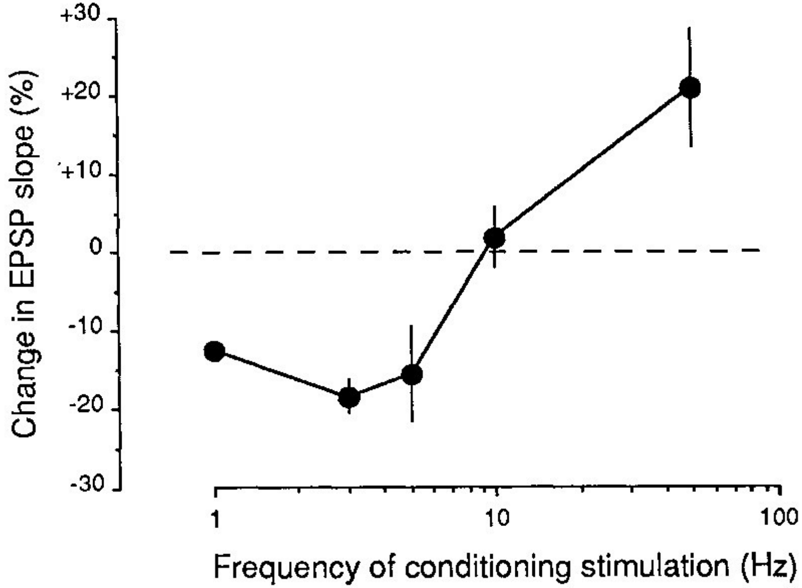
Plasticity induction: LTD obtained at low frequencies

hippocampus (slices)



900 pulses at 1-50 Hz

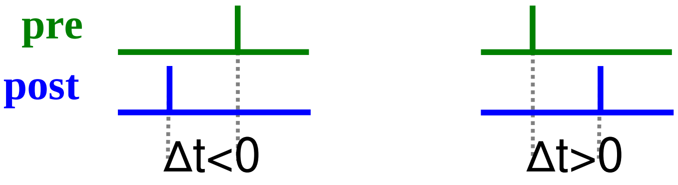




[Dudek and Bear 1992;
Dunwiddie and Lynch 1978]

STDP : plasticity from single spike-pairs

60 pairings @ 1 Hz



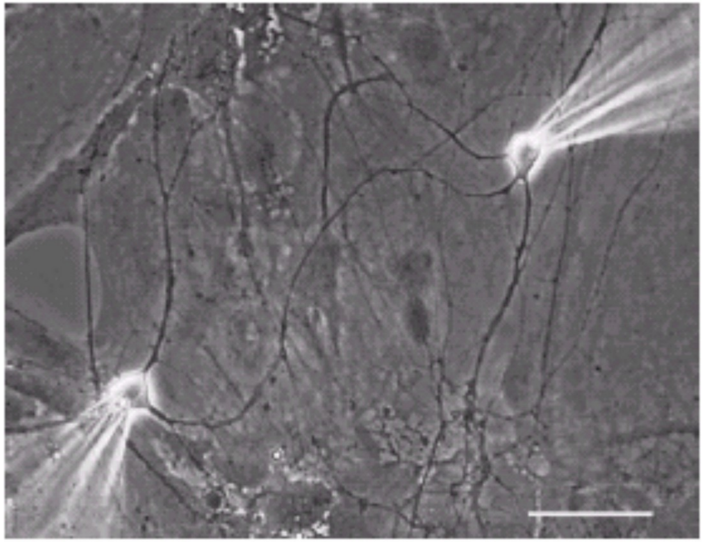
Δt<0

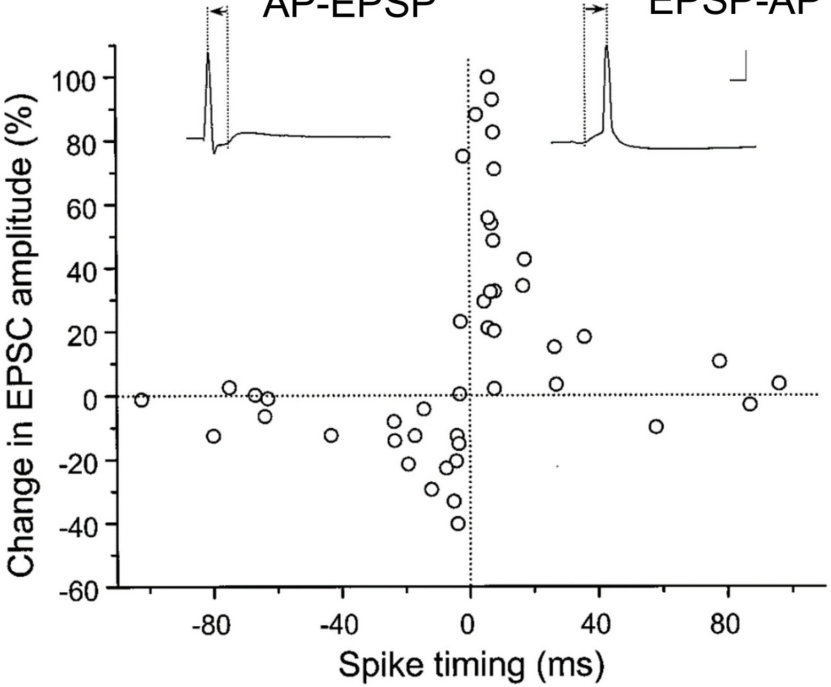
AP-EPSP

Δt>0

EPSP-AP

hippocampal cultures





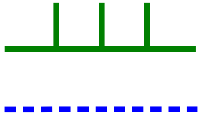
[Bi & Poo, J Neurosci 1998]

[Magee & Johnston 1997;
Zhang et al. 1998;
Markram et al. 1997;
Sjöström et al. 2001;
Feldman 200]

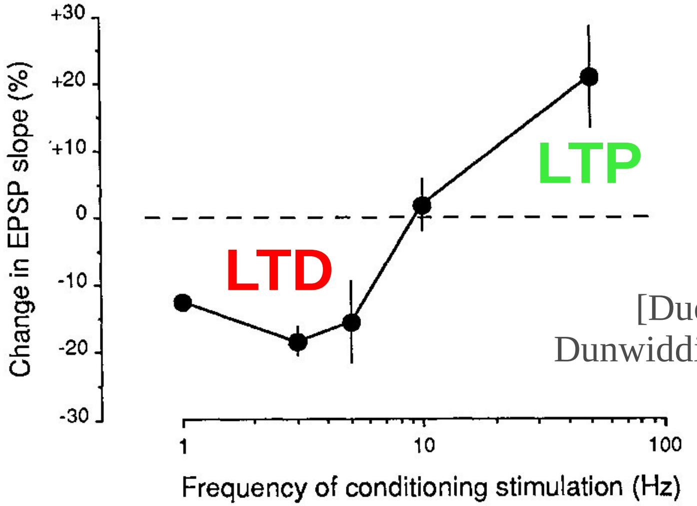
Frequency-dependent plasticity and STDP

frequency-dependent plasticity

pre
post



900 pulses at 1-100 Hz

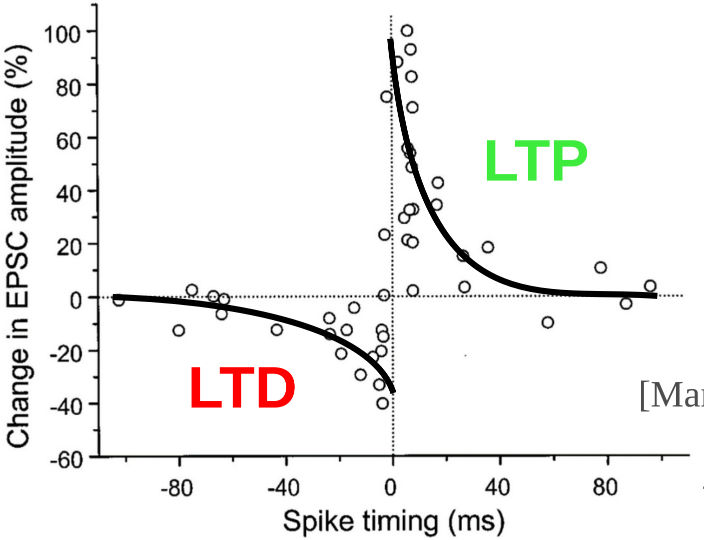


[Dudek and Bear 1992;
Dunwiddie and Lynch 1978]

spike timing-dependent plasticity

pre
post

60 pairings @ 1 Hz



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

Outline : STDP ... spike-timing dependent plasiticity

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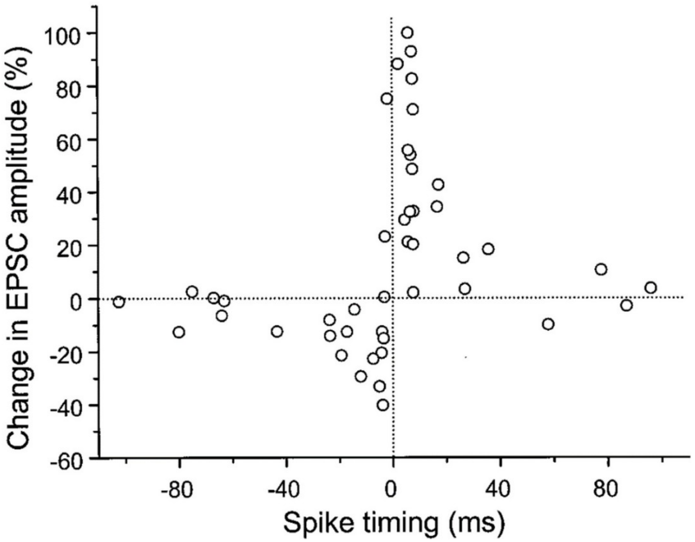
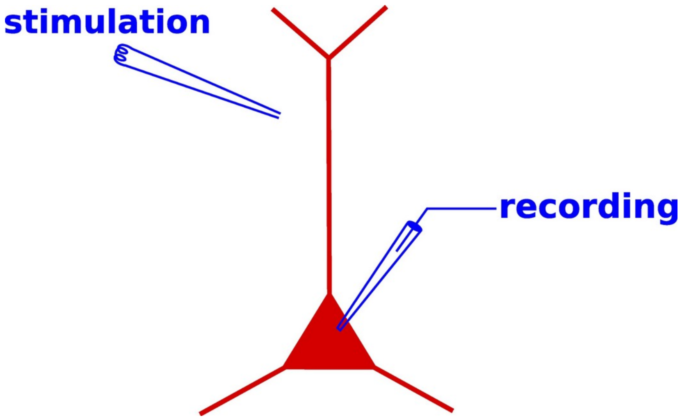
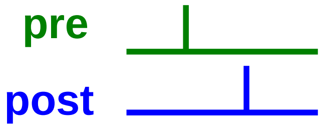


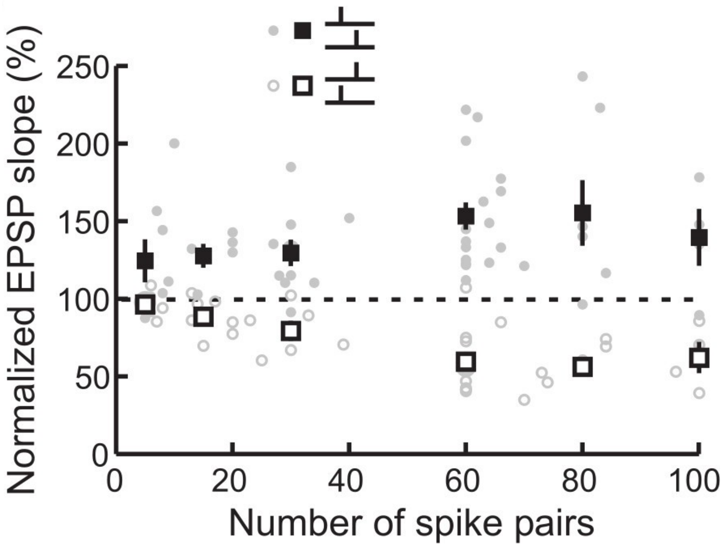
[Bi & Poo 1998]

Number of pairings





XX pairings @ 0.2 Hz

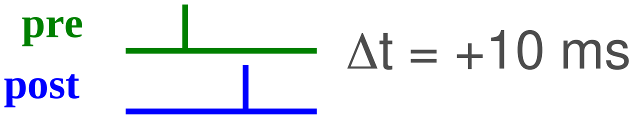


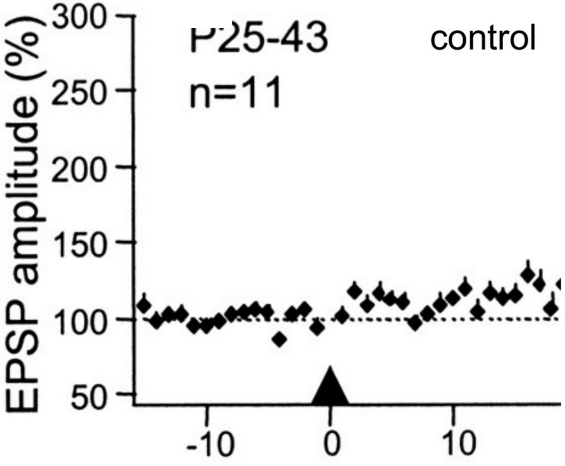
- generally : plasticity induction with spike-pairs requires the *repeated* presentation of the pre-post pair
- LTP induced with a few pairs
- LTD requires the presentation of ~20 stimulation pairs

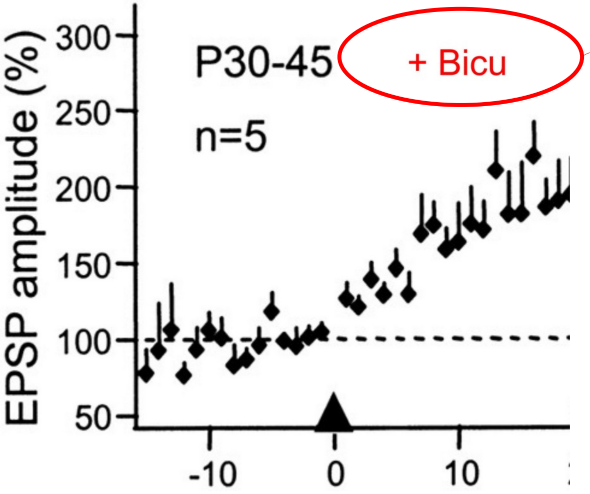
Role of synaptic inhibition

control
→ no plasticity

inhibition blocked
→ LTP





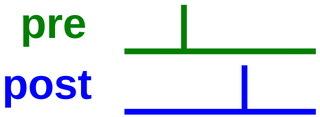


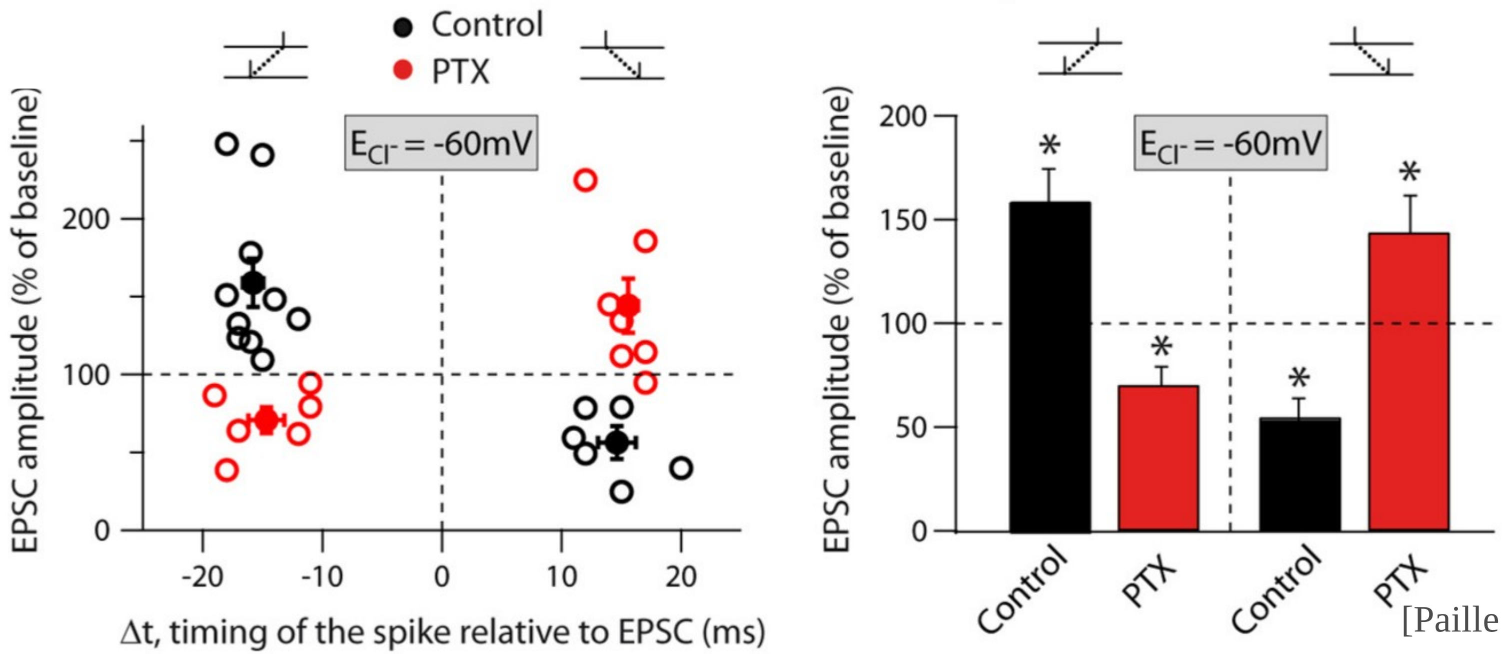
[Mederith et al. *J Neuroci* 2003]

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

Bicuculline is a competitive anta-gonist of $GABA_A$ receptors.

Role of synaptic inhibition

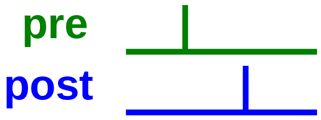




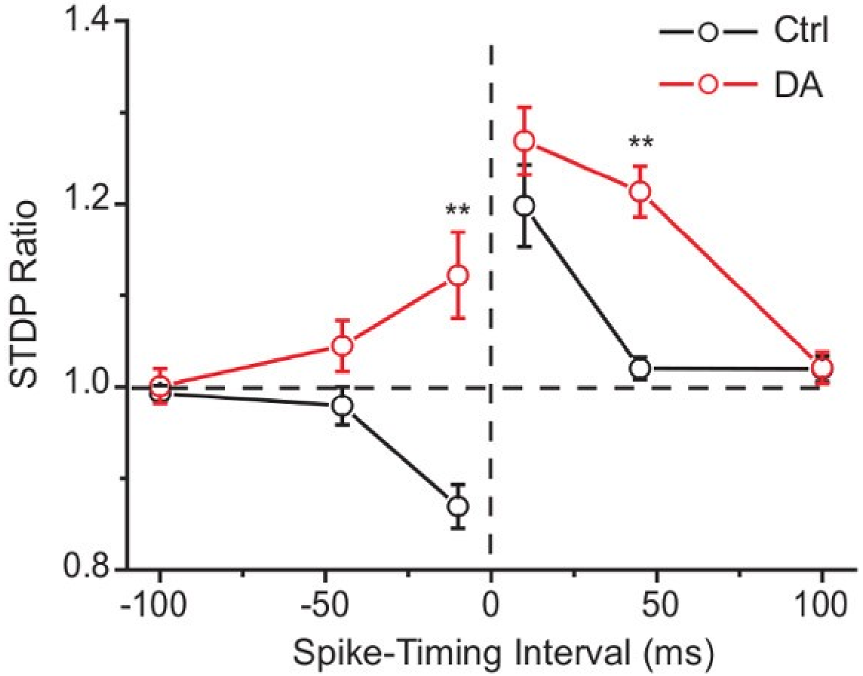
[Paille et al. *J Neurosci* 2013]

- at the corticostriatal synapse : inhibition inverts the STDP curve

Role of neuromodulation - Dopamine



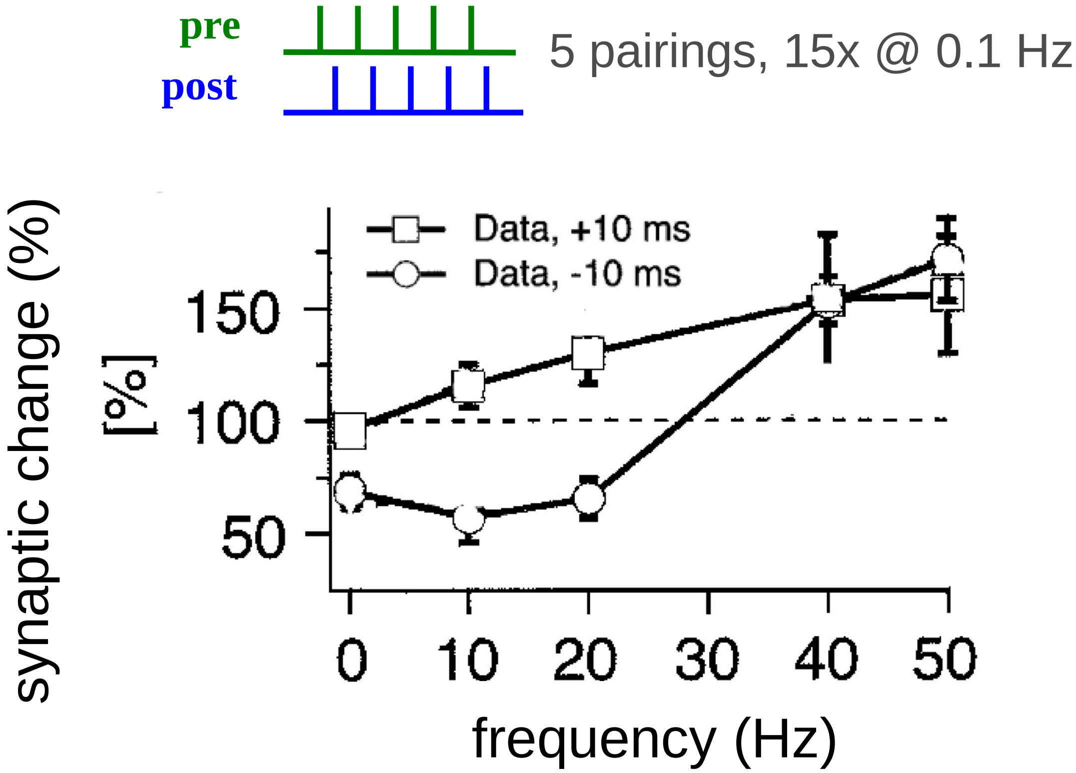
60 pairings @ 1 Hz



[Zhang et al. *PNAS* 2009]

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

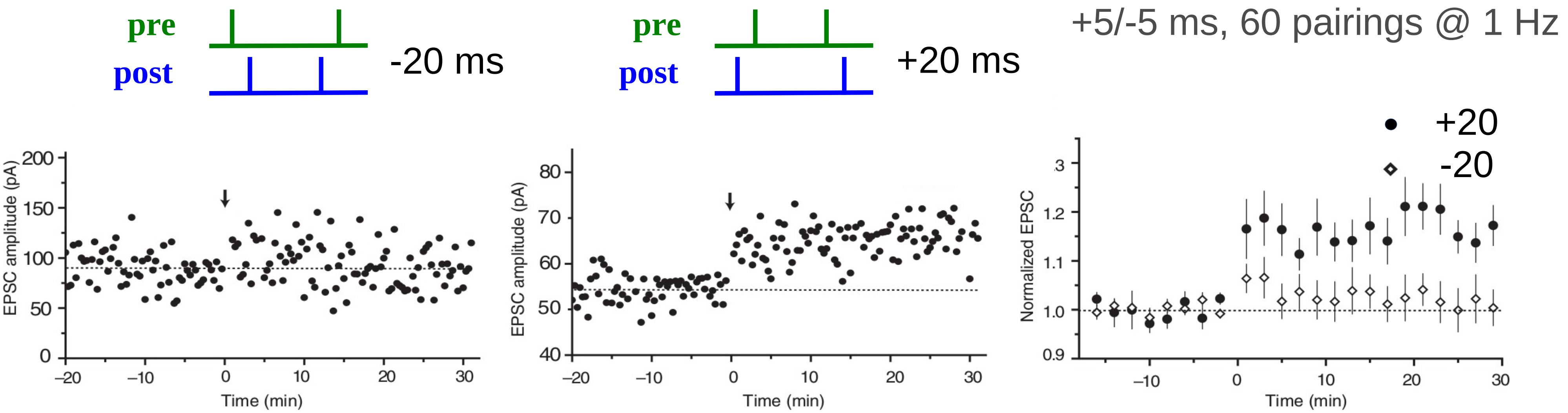
STDP depends on frequency of spike-pairs



- 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

[Sjöström et al. *Neuron* 2001]

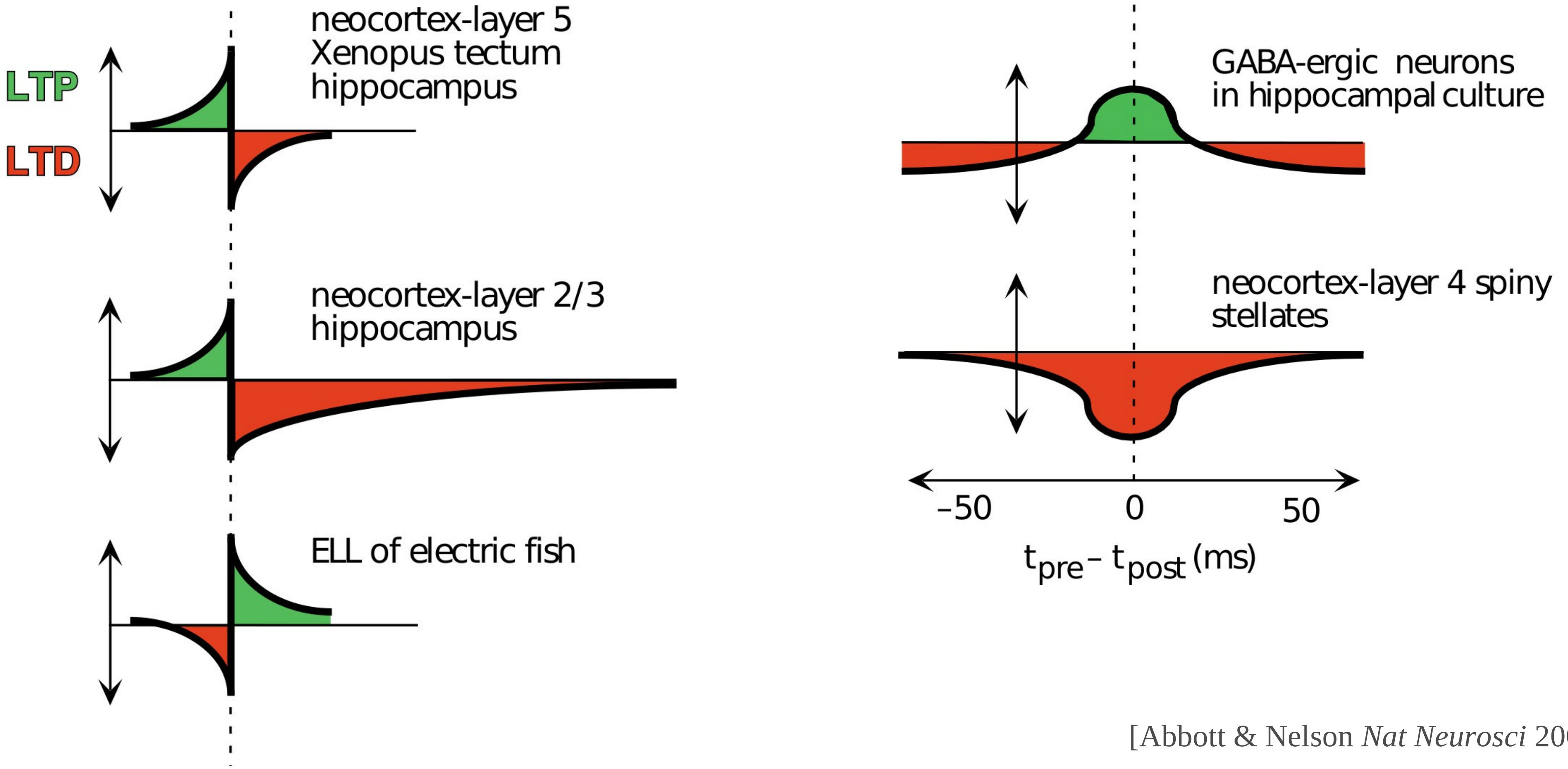
Non-linearity in STDP induction protocols



[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



[Abbott & Nelson *Nat Neurosci* 2000]

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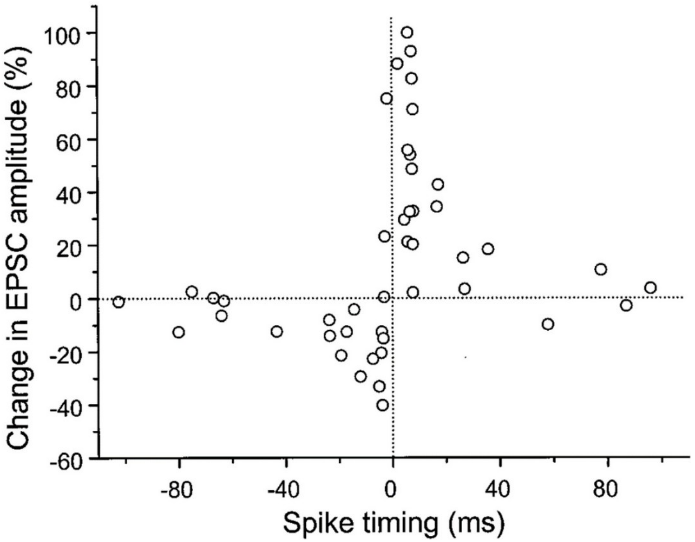


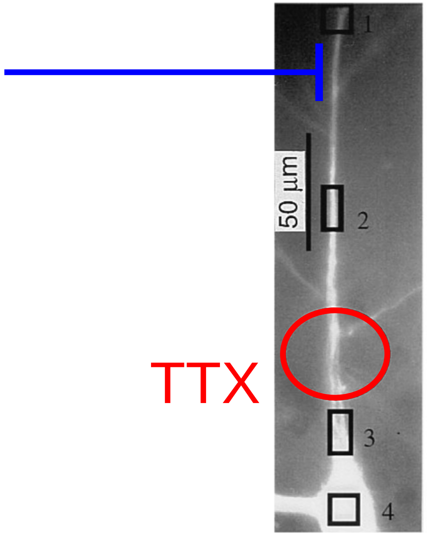
[Bi & Poo 1998]

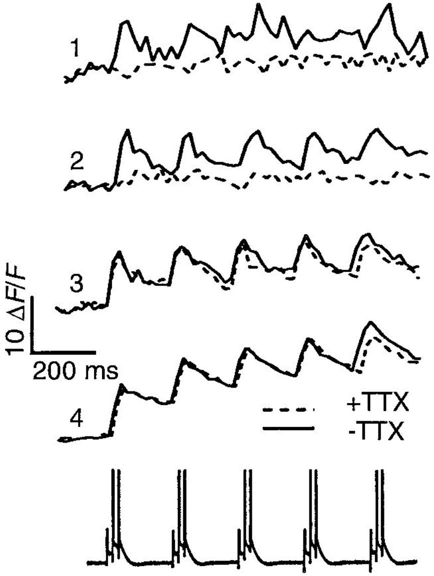
Backpropagating action potential required for STDP

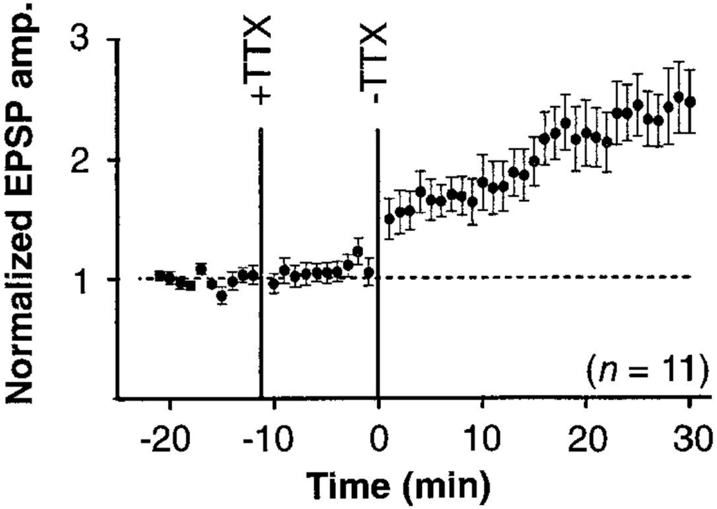
$[Ca^{2+}]$ imaging

stimulated synapse

TTX



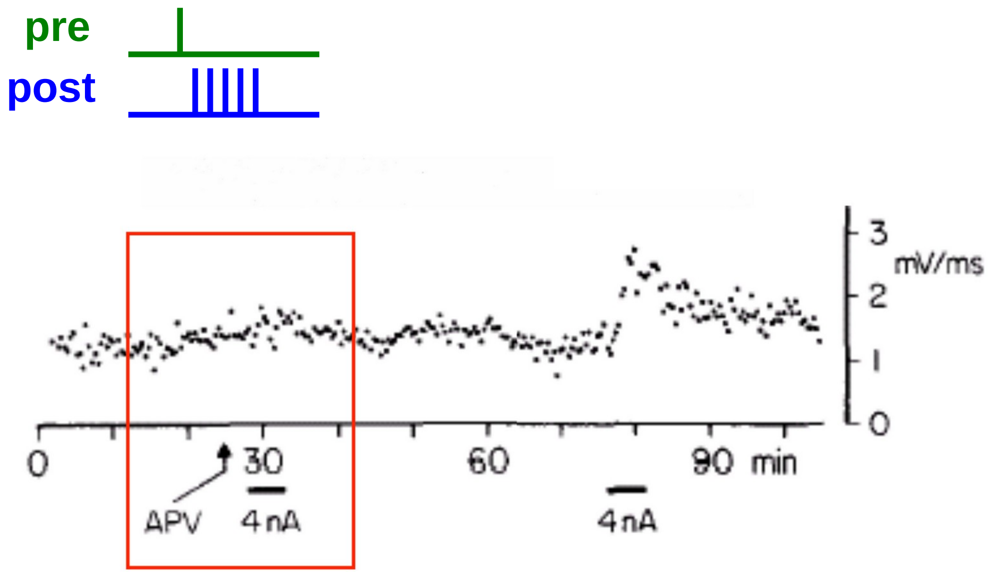




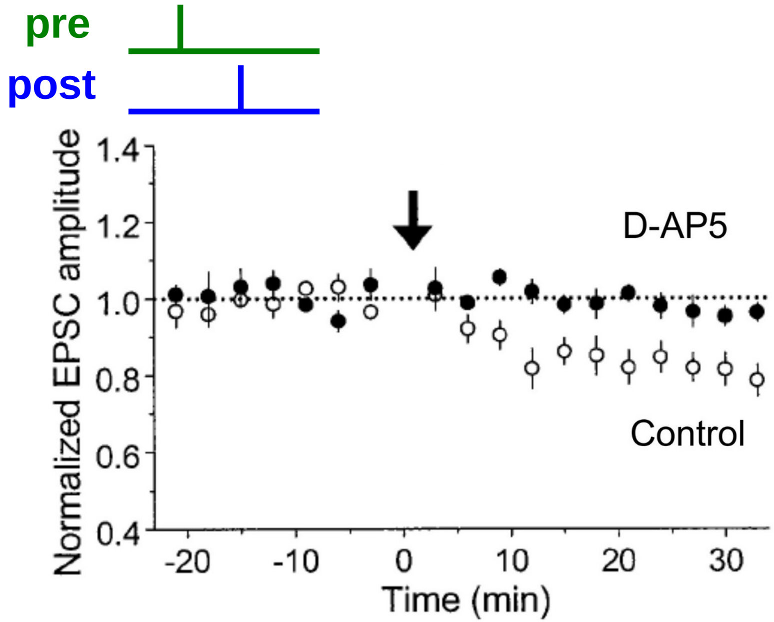
[Magee & Johnston *Science* 1997]

- Backpropagating action potential provides postsynaptic depolarization required for STDP

STDP requires NMDA receptor activation



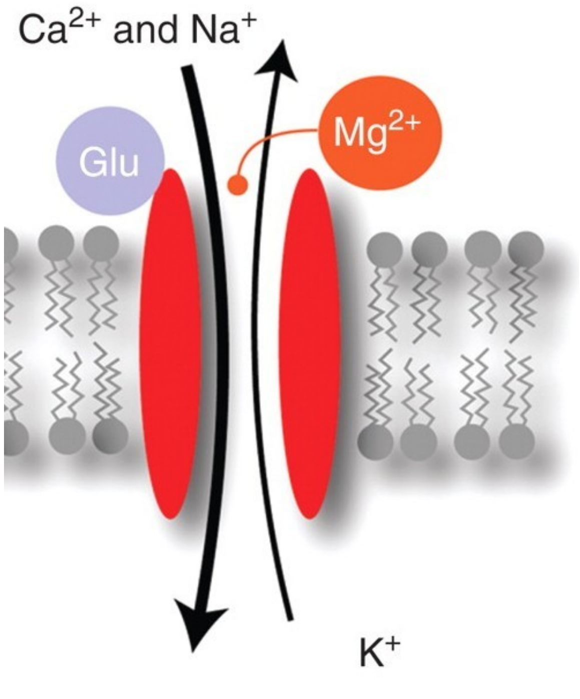
[Gustafsson et al. *J Neurosci* 1987]



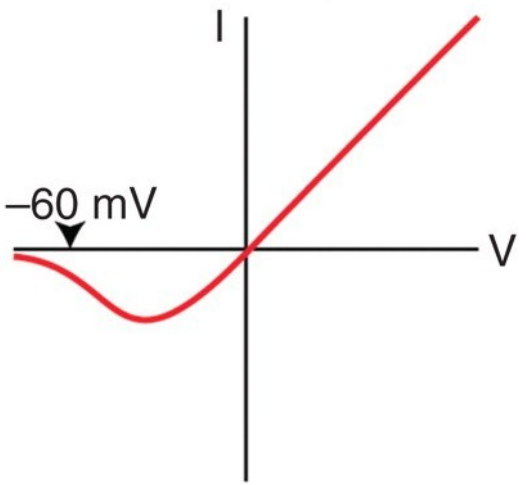
[Bi & Poo *J Neurosci* 1998]

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

Postsynaptic NMDA receptor



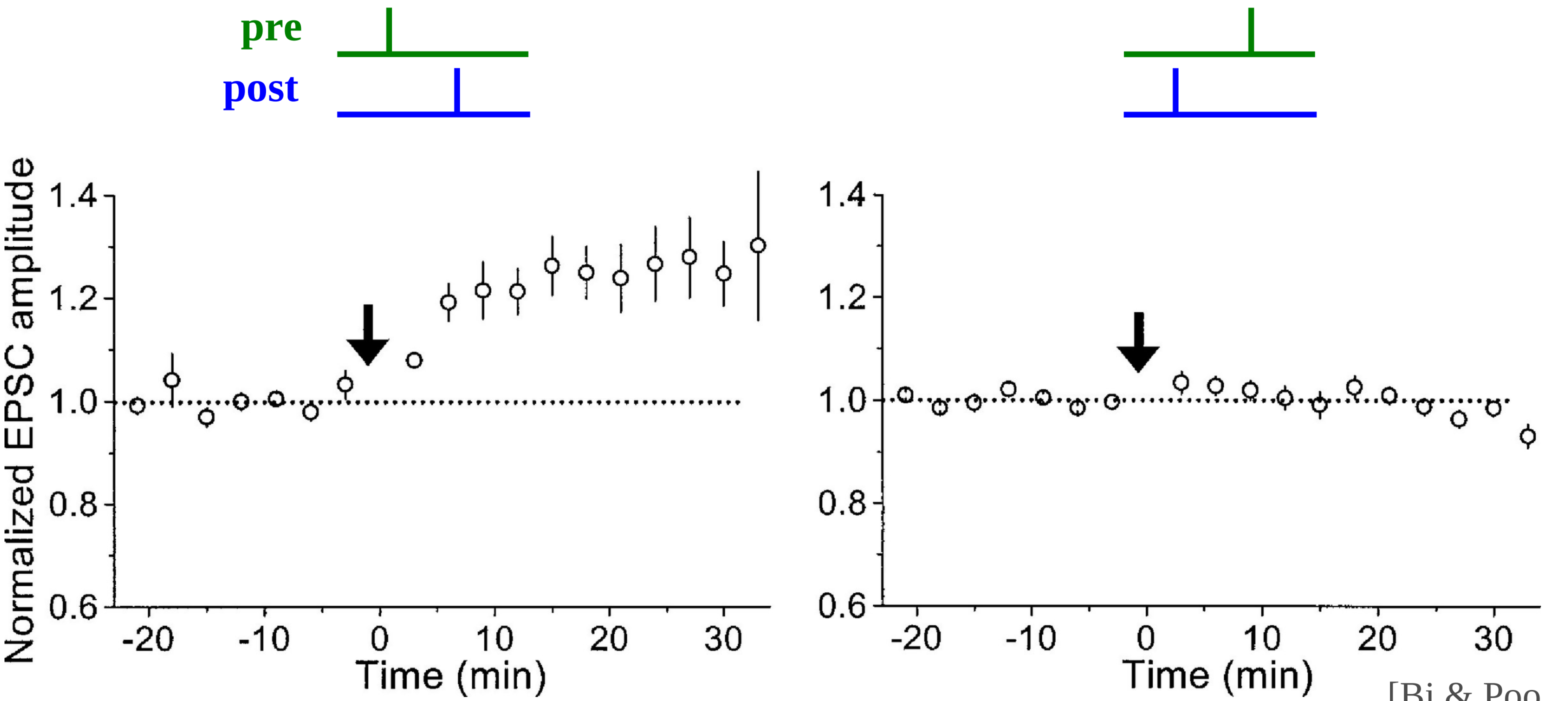
current-voltage relationship



- coincidence detector :
  presynaptic action potential → glutamate (Glu)
  postsynaptic depolarization → Mg^{2+} block is expelled
- calcium permeable

Voltage-dependent Ca channels required for LTD

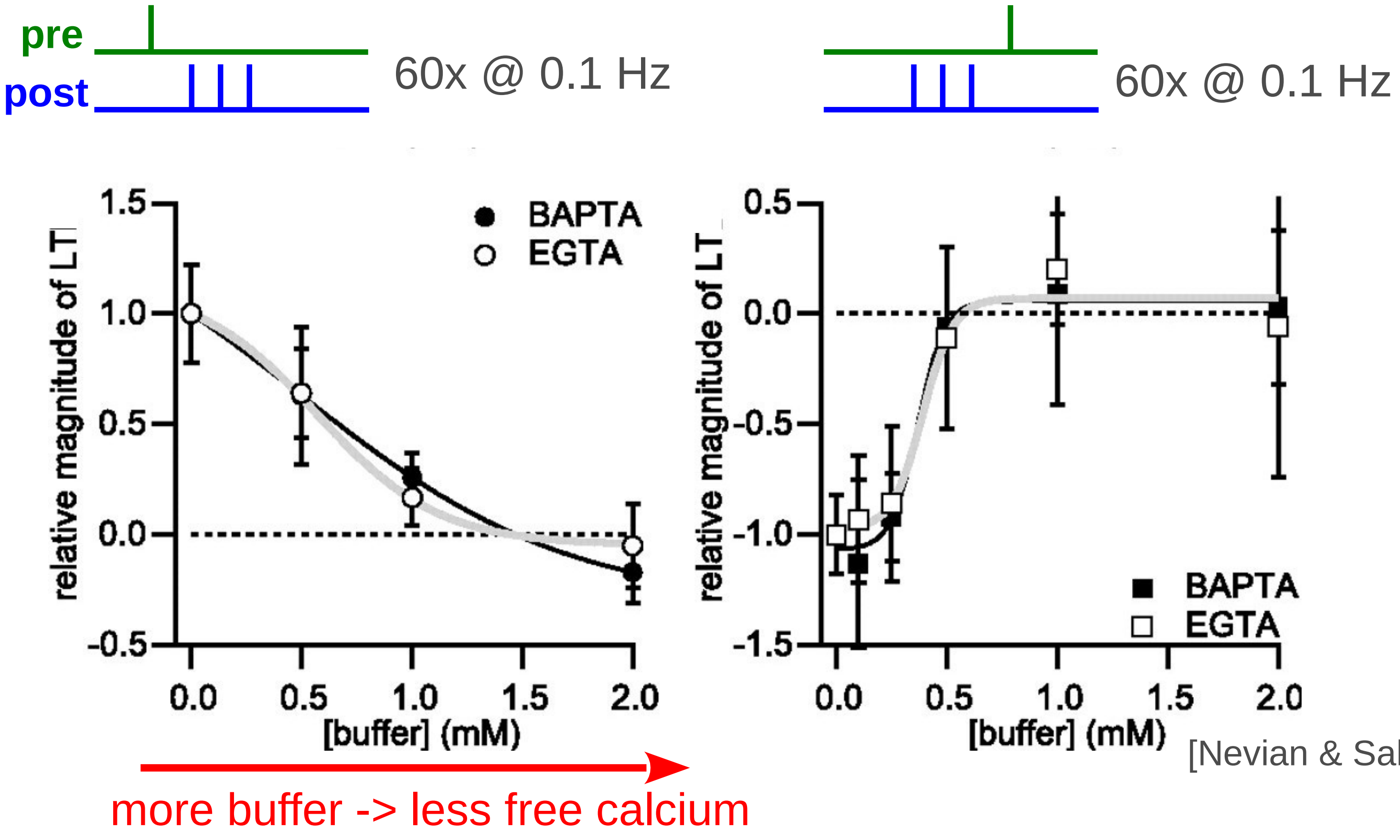
+ nimodipine (L-type calcium channel blocker)



[Bi & Poo *J Neurosci* 1998]

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

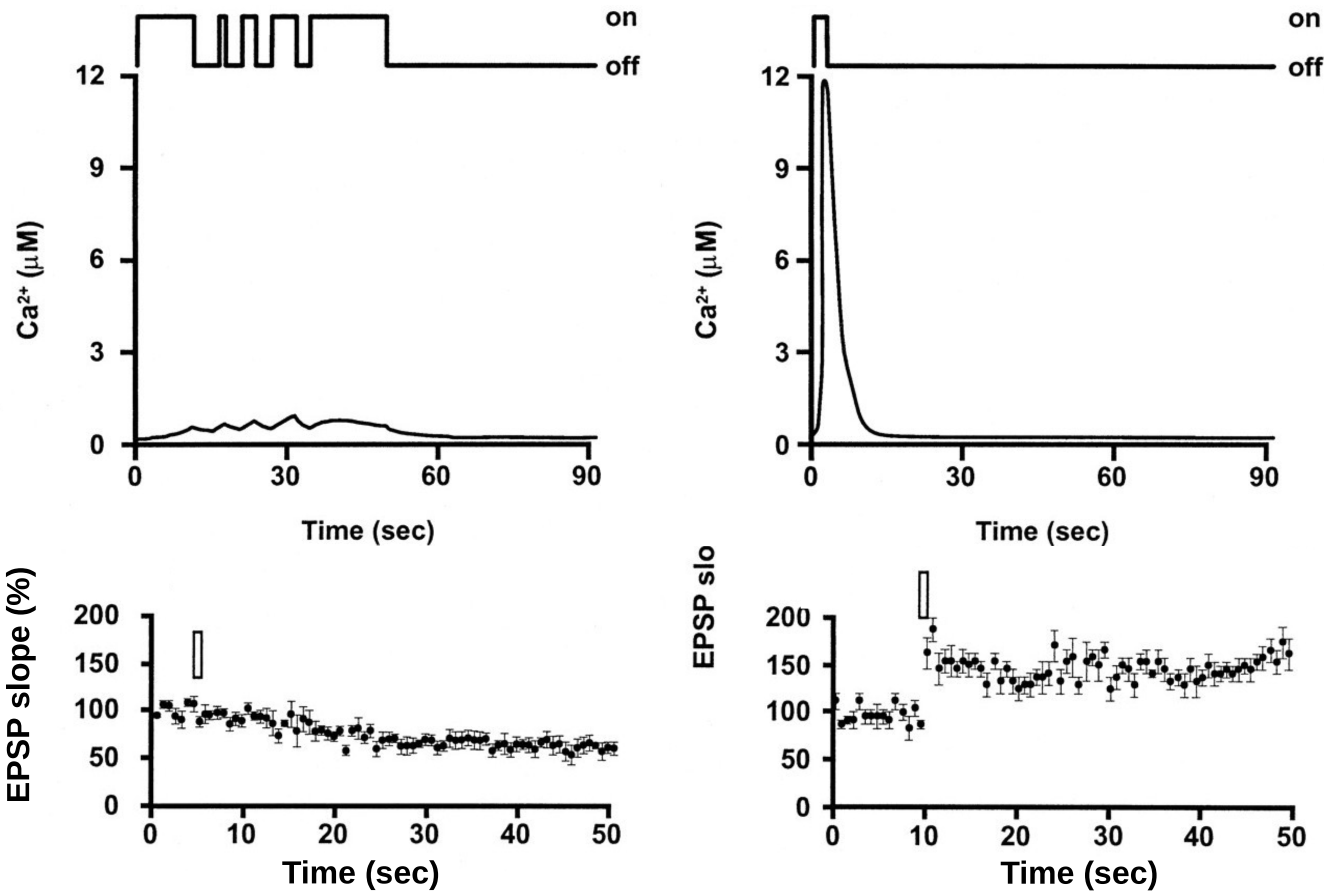
Postsynaptic calcium *required* for plasticity



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

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

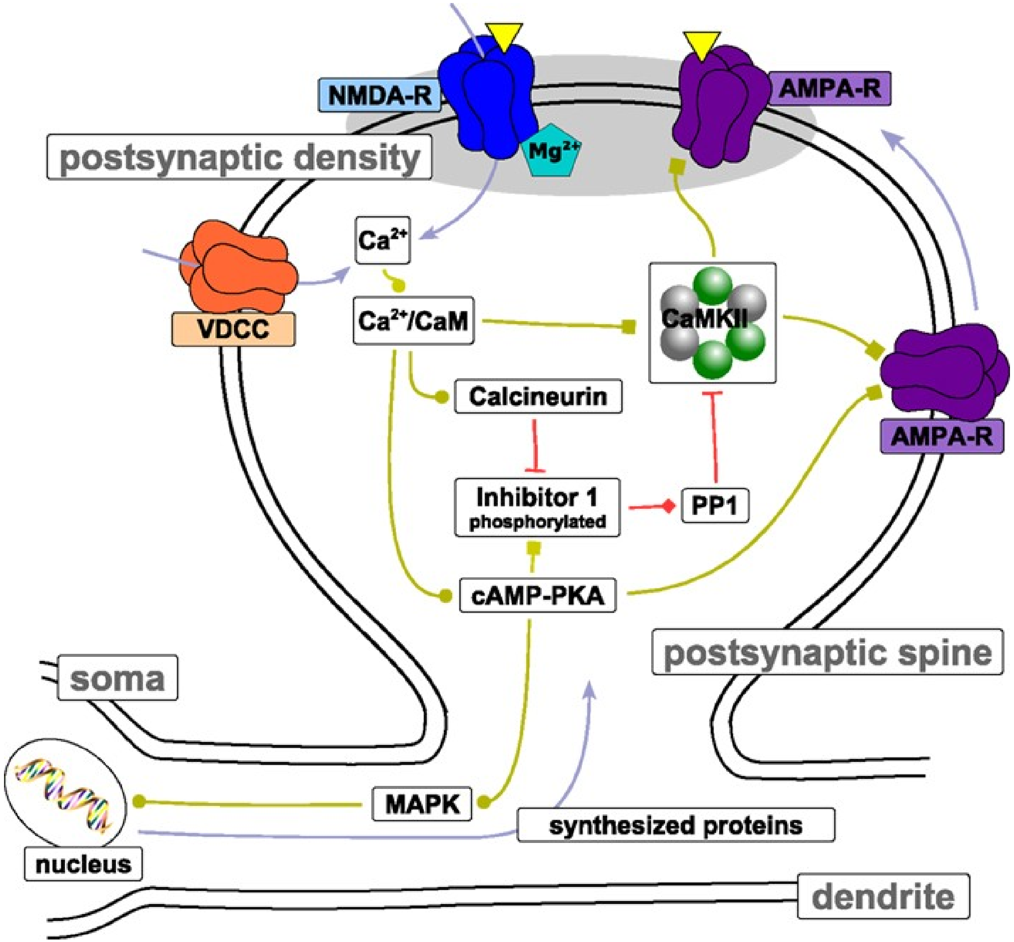
Postsynaptic calcium *sufficient* for plasticity



- 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

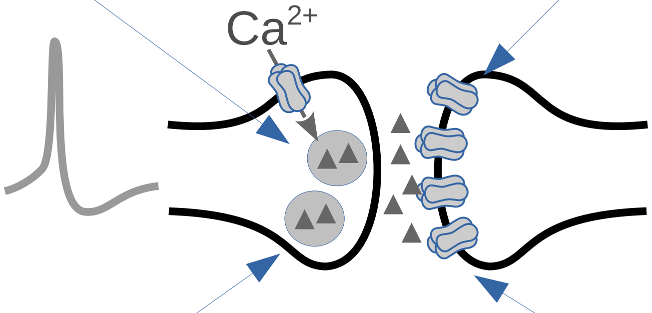
presynaptic | **postsynaptic**

neurotransmitter vesicle number

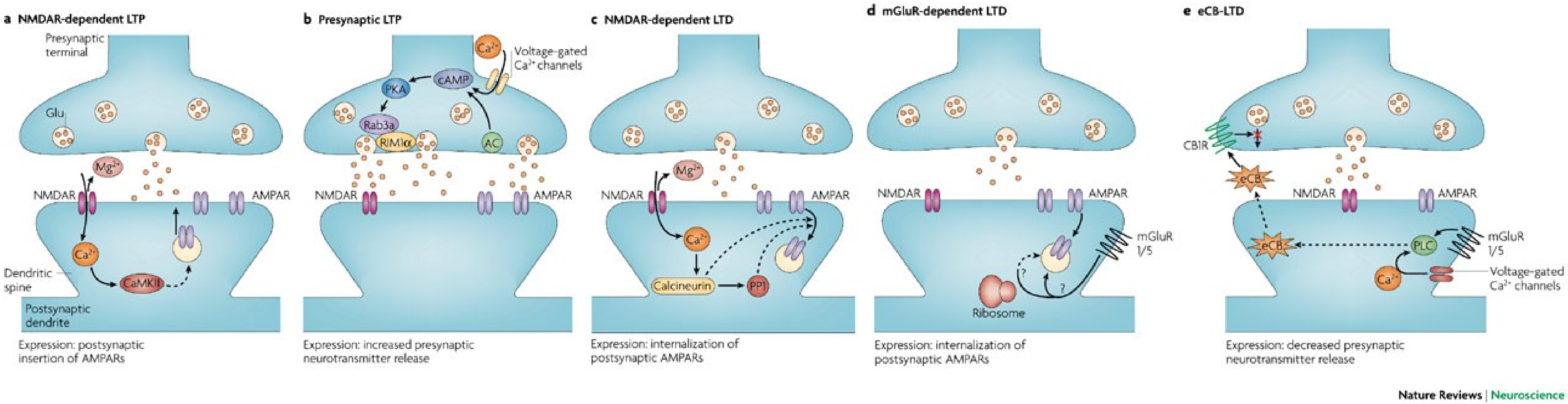
probability of vesicle release

number of AMPA receptors

conductance of AMPA receptors



Diversity of induction and expression pathways



[Kauer, Malenka. *Nat Rev Neurosci* 2007]

Outline : STDP ... spike-timing dependent plasiticity

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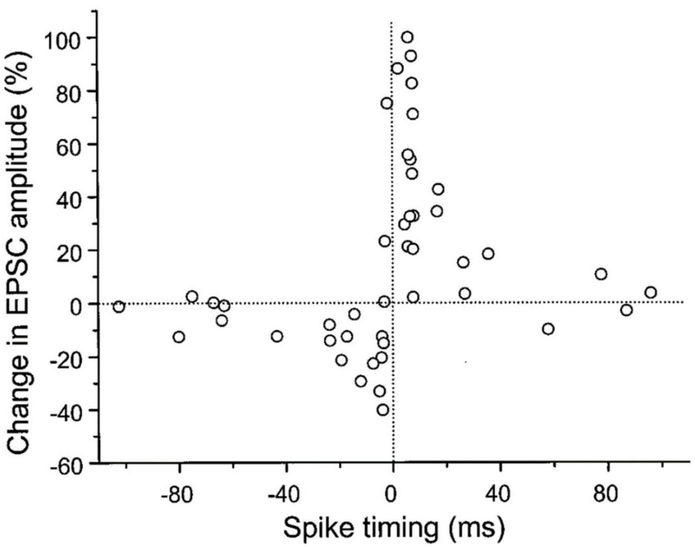
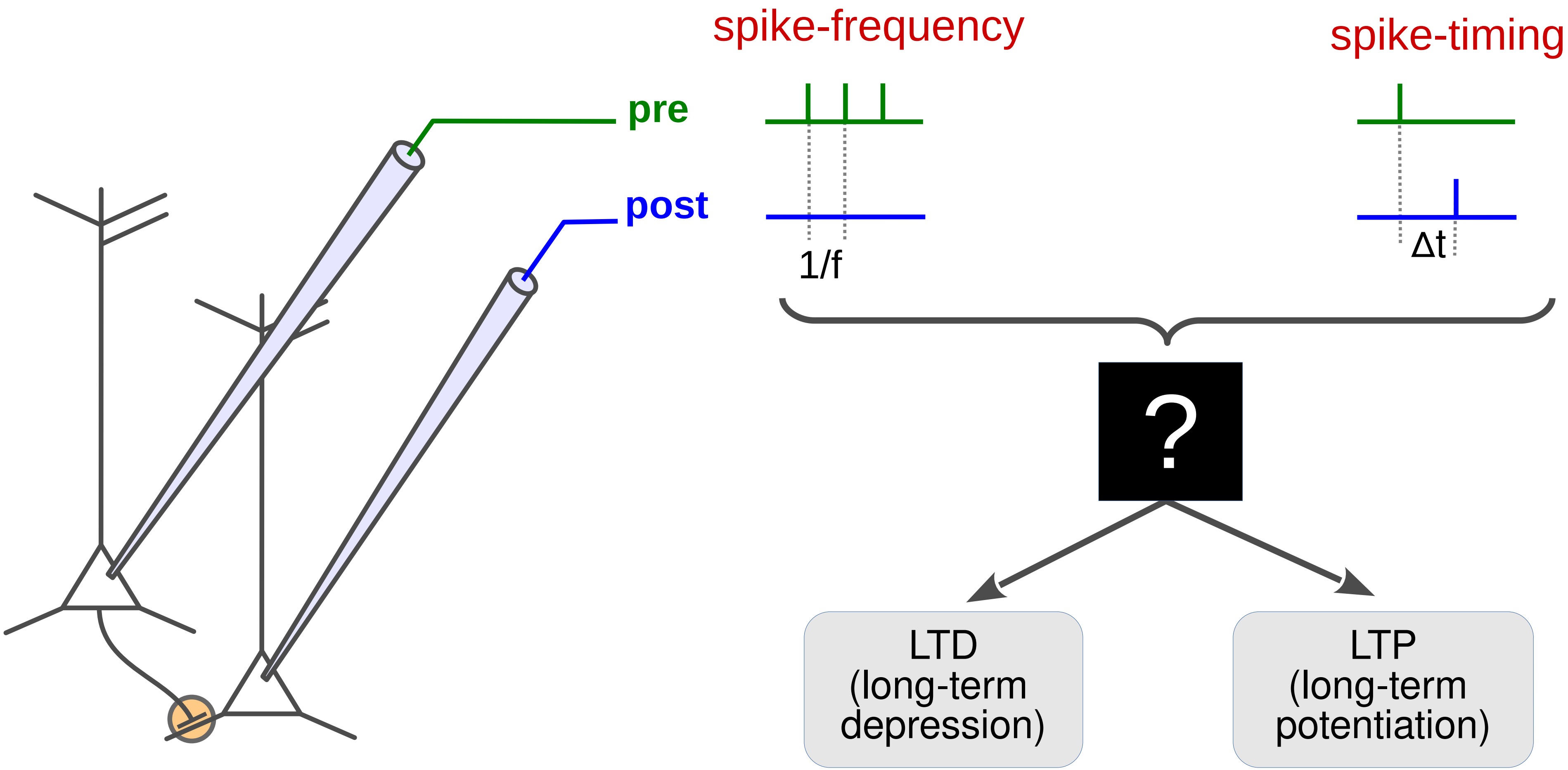
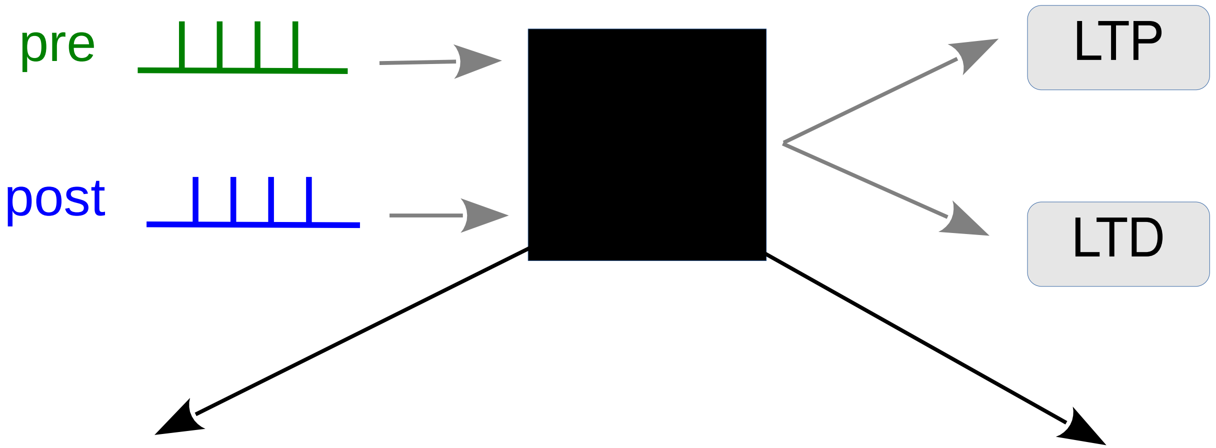


[Bi & Poo 1998]

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^{2+} – 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]

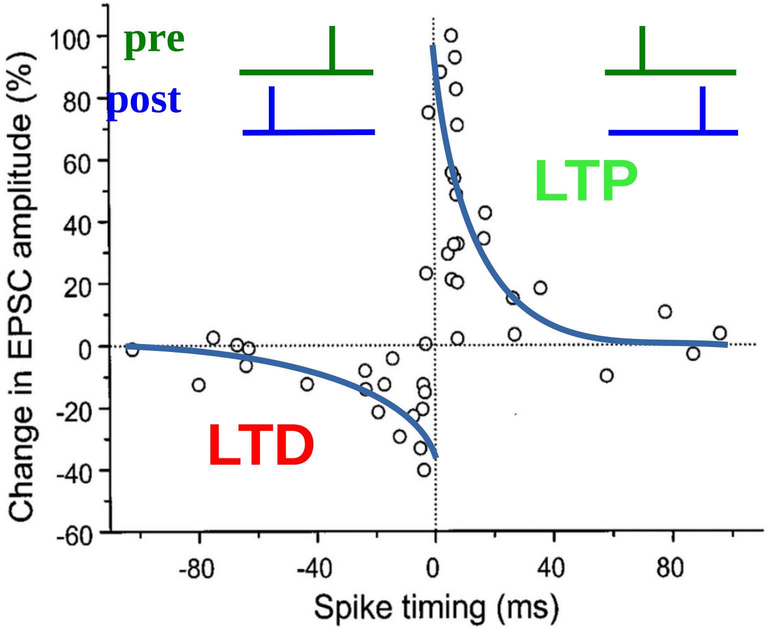
“Standard” STDP model

- 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

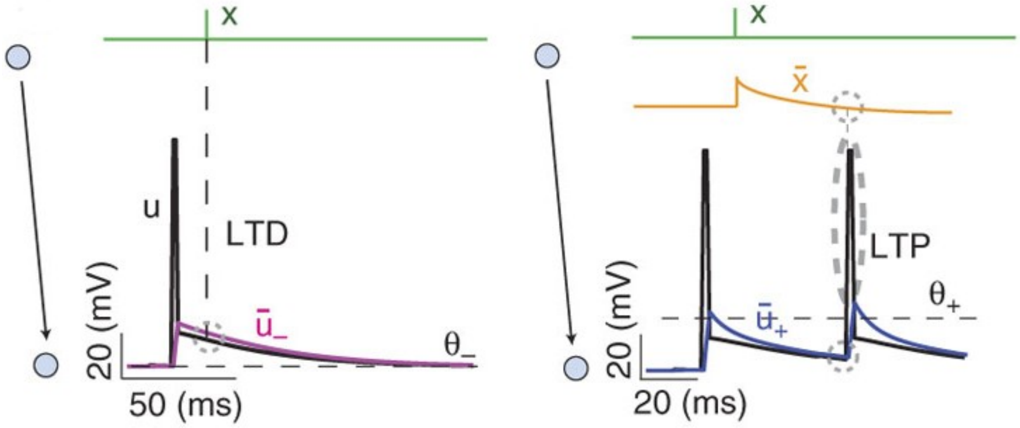
More recent plasticity models

Triplet-based model

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

Model based on postsynaptic potential

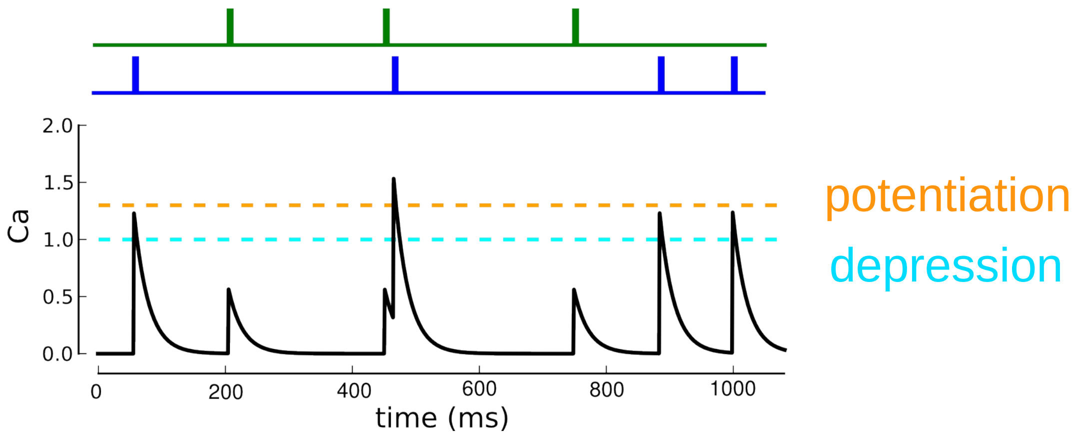
[Clopath *et al.*, 2010]



More recent plasticity models

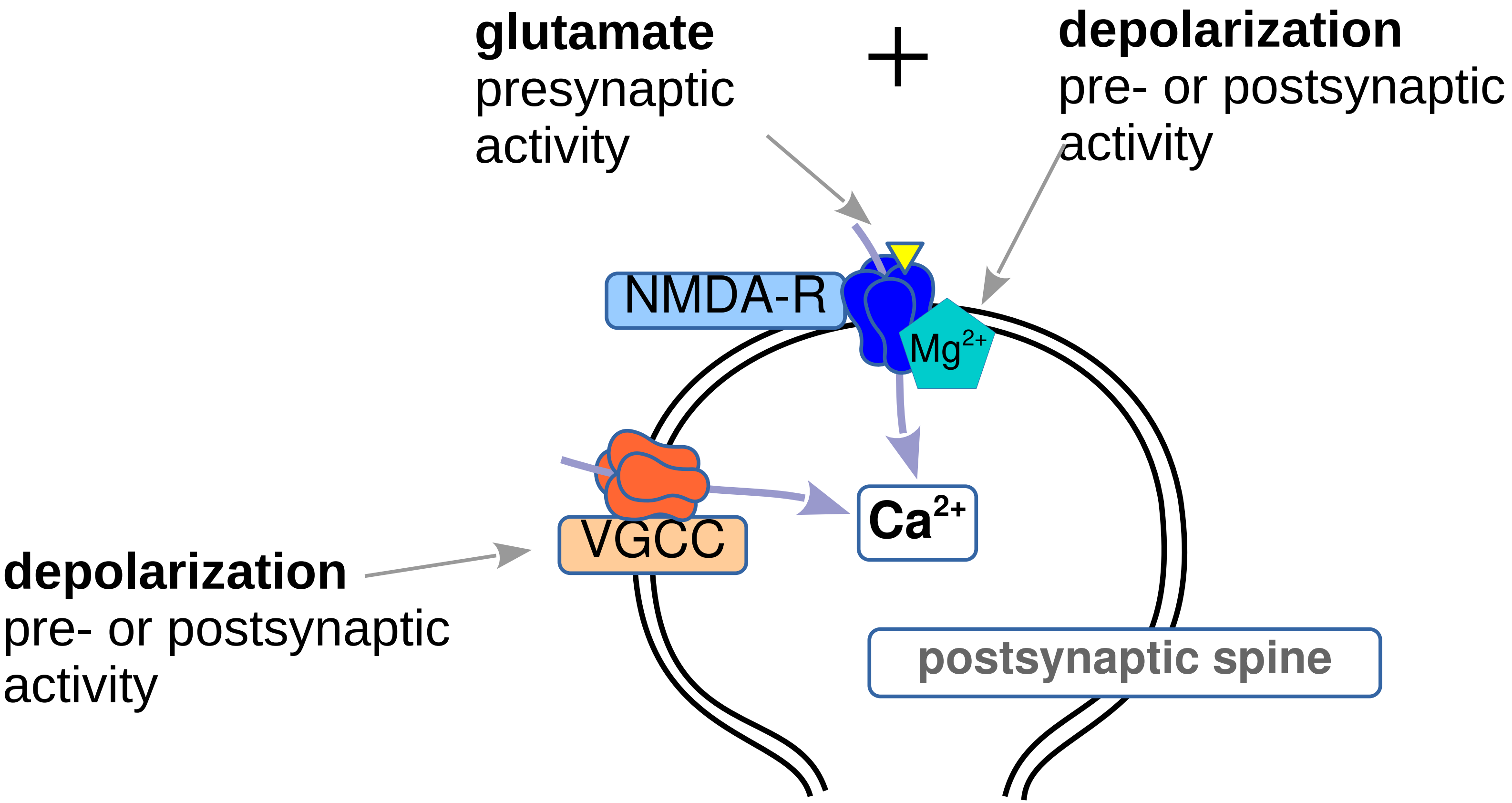
Calcium-based model

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

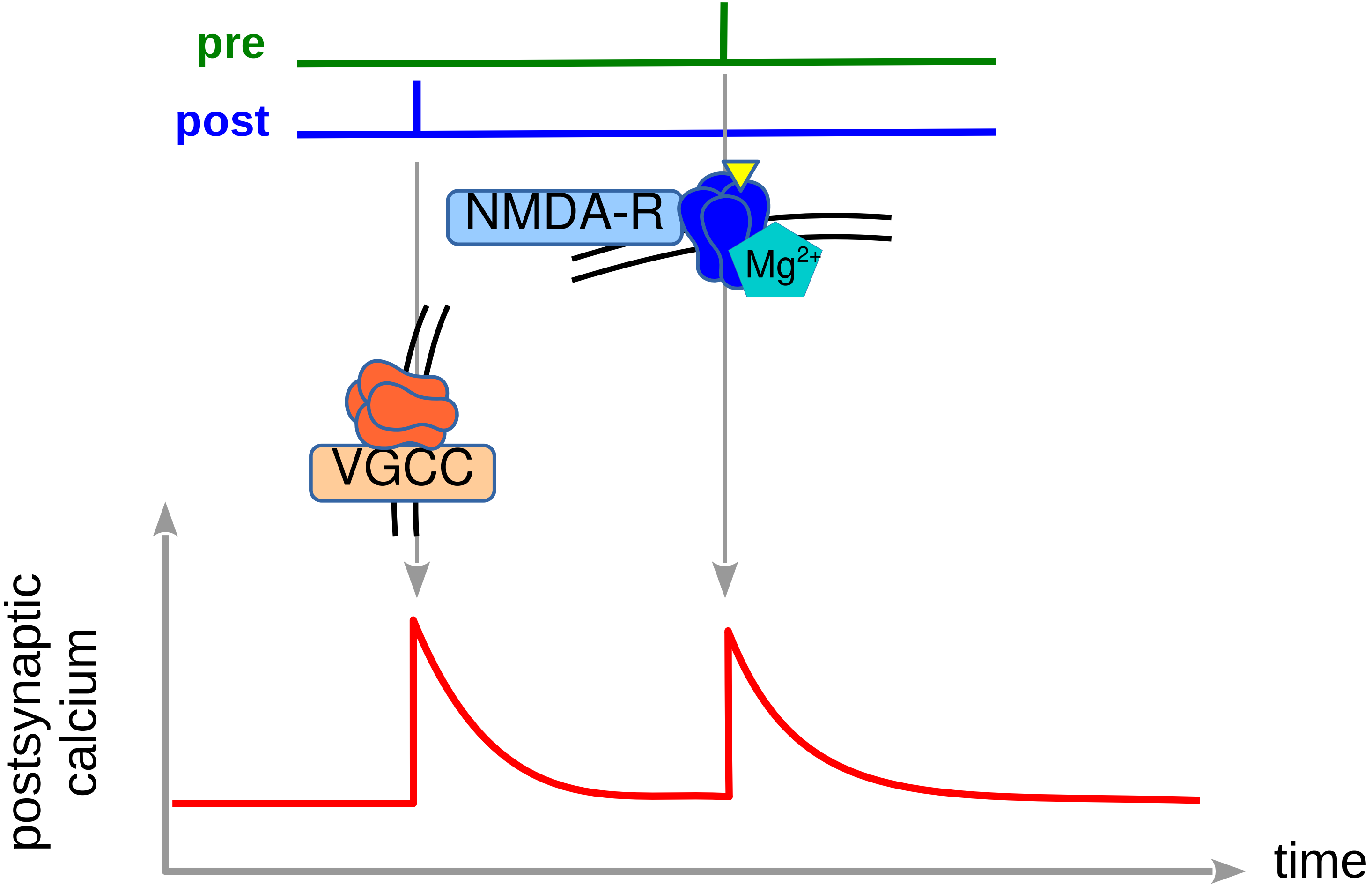


Calcium influx

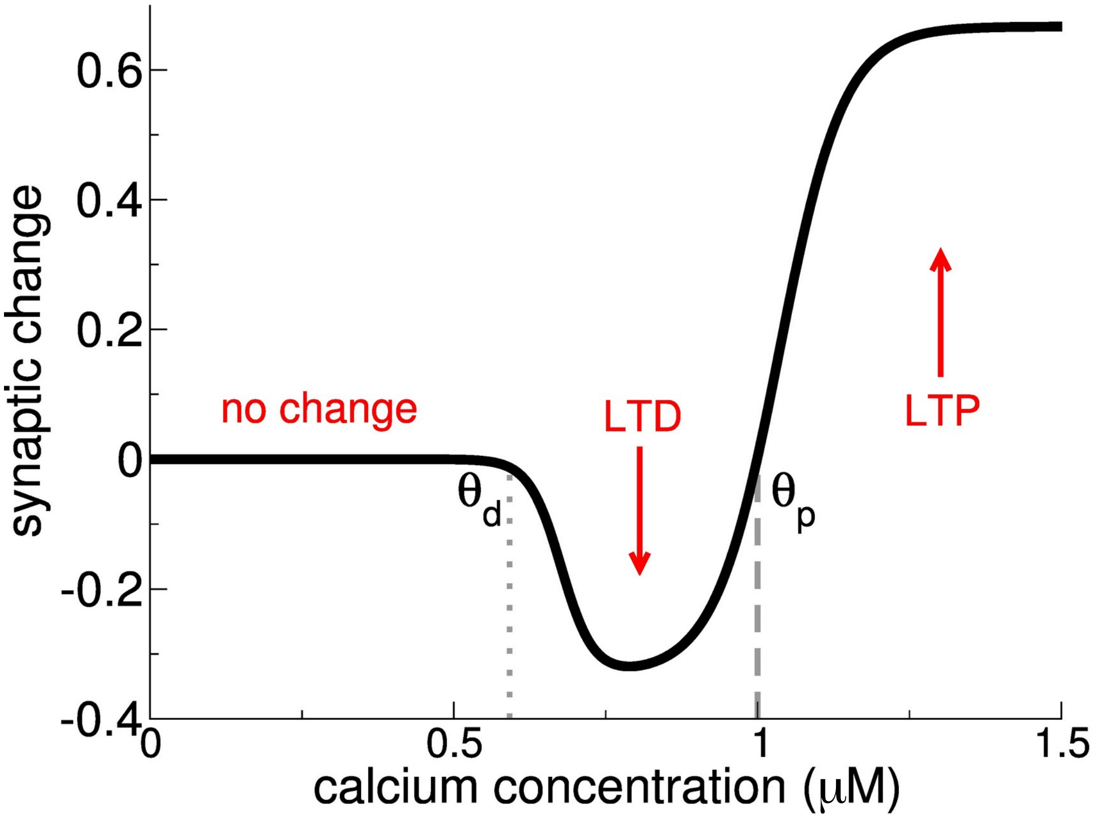
coincidence detector :



Calcium transients from spike-pair stimulation



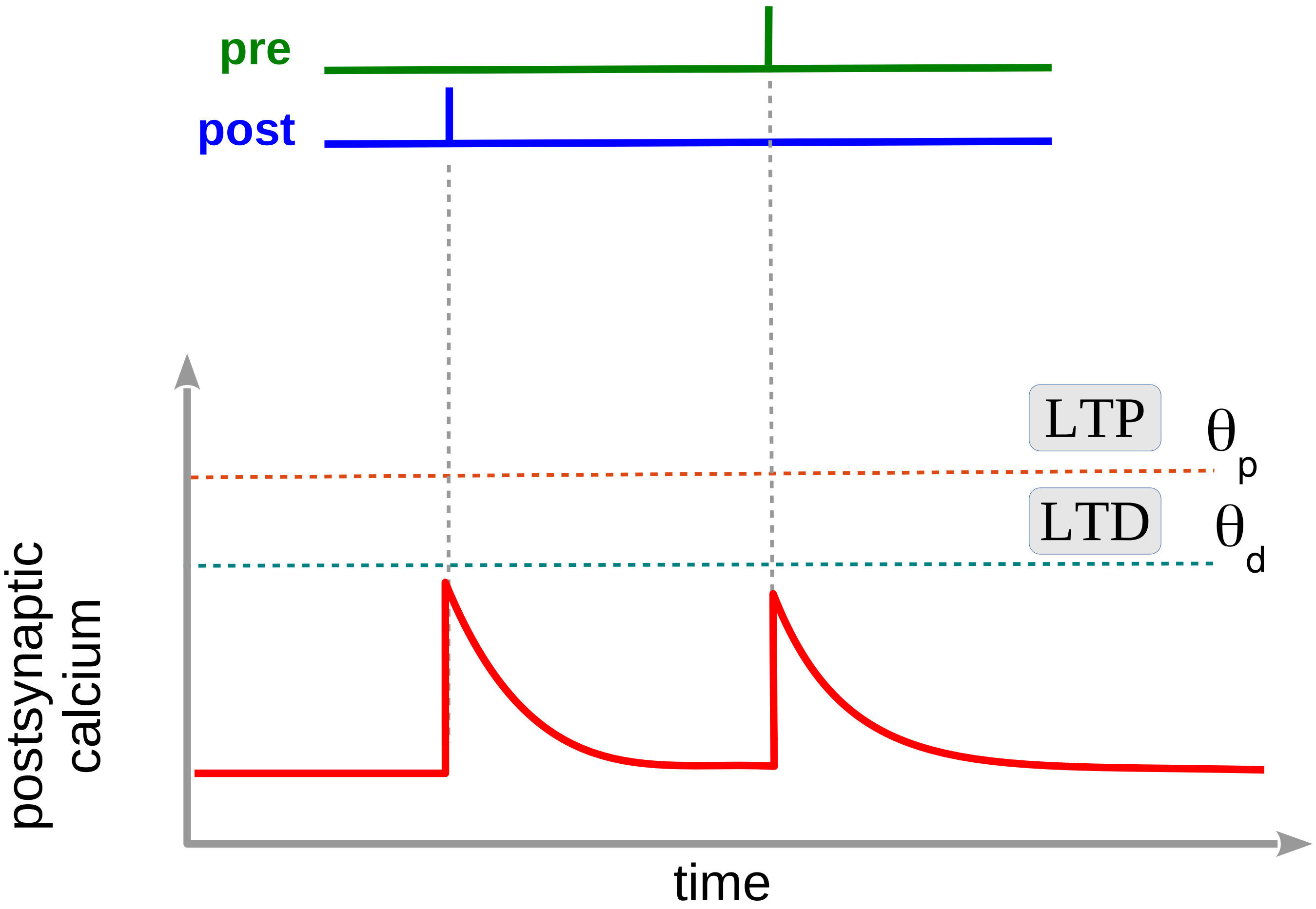
Calcium transients from spike-pair stimulation



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

[Shouval *et al.*, *PNAS* 2002]

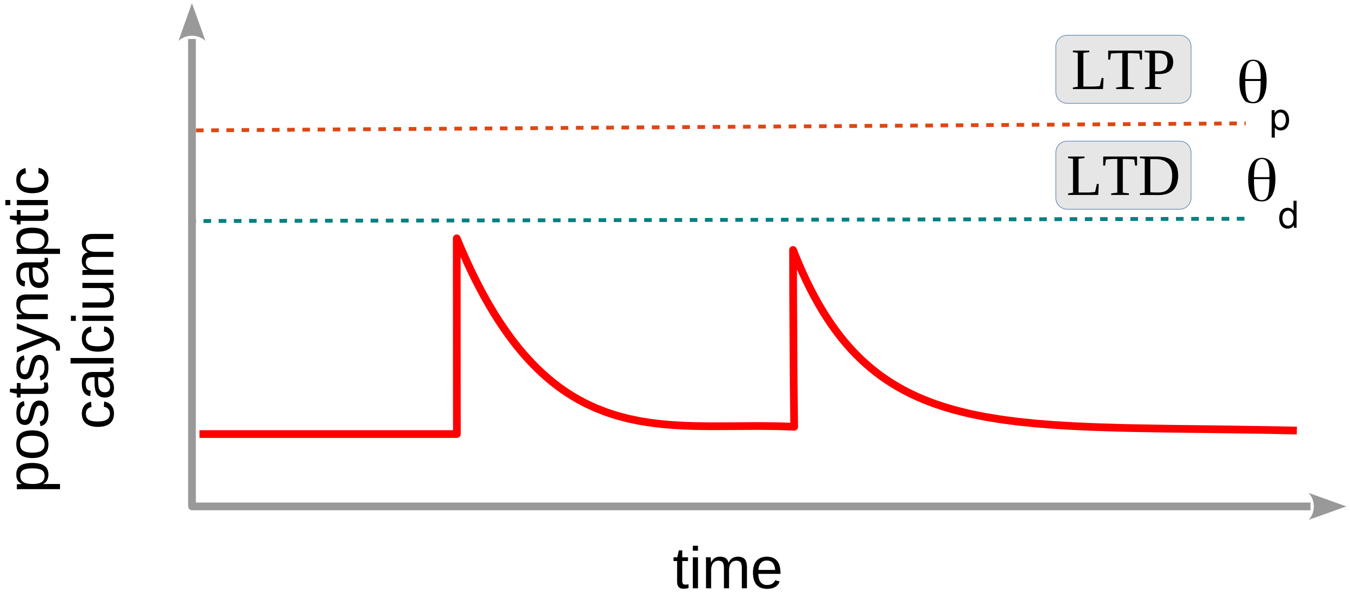
Calcium control hypothesis introduces LTD/LTP thresholds



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 ?



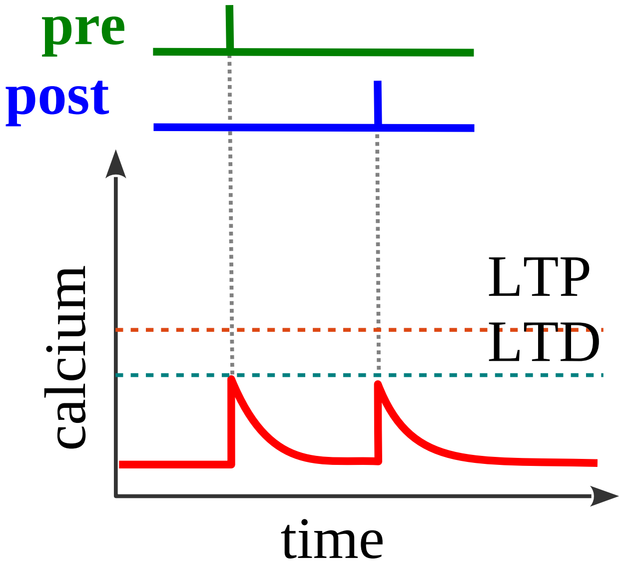
Calcium amplitudes determine shape of STDP curve

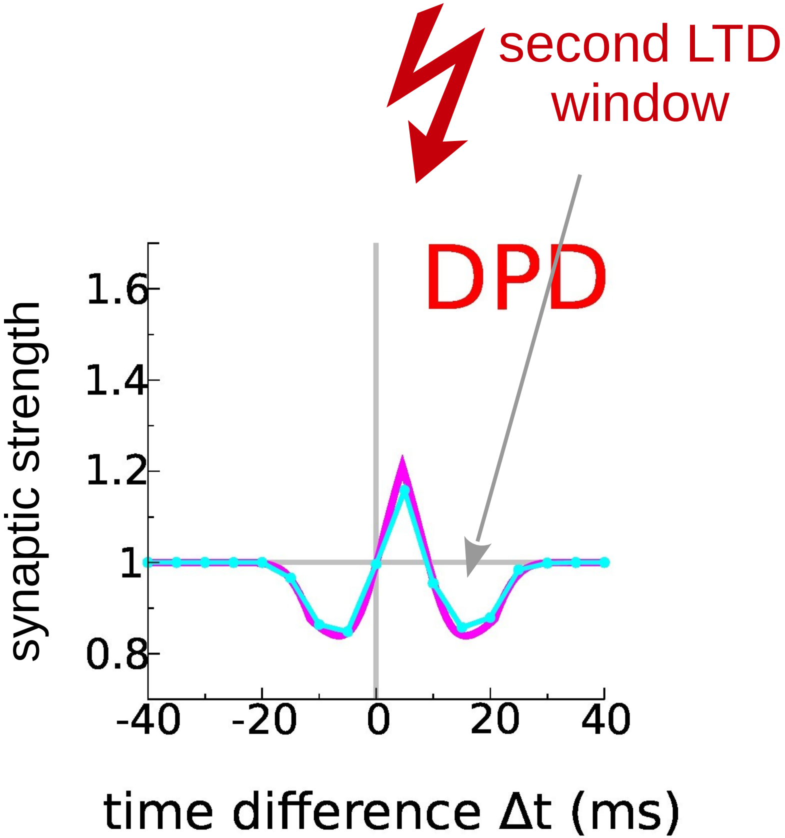
simulation I

Calcium amplitudes determine shape of STDP curve

$C_{pre} < \theta_d$

$C_{post} < \theta_d$



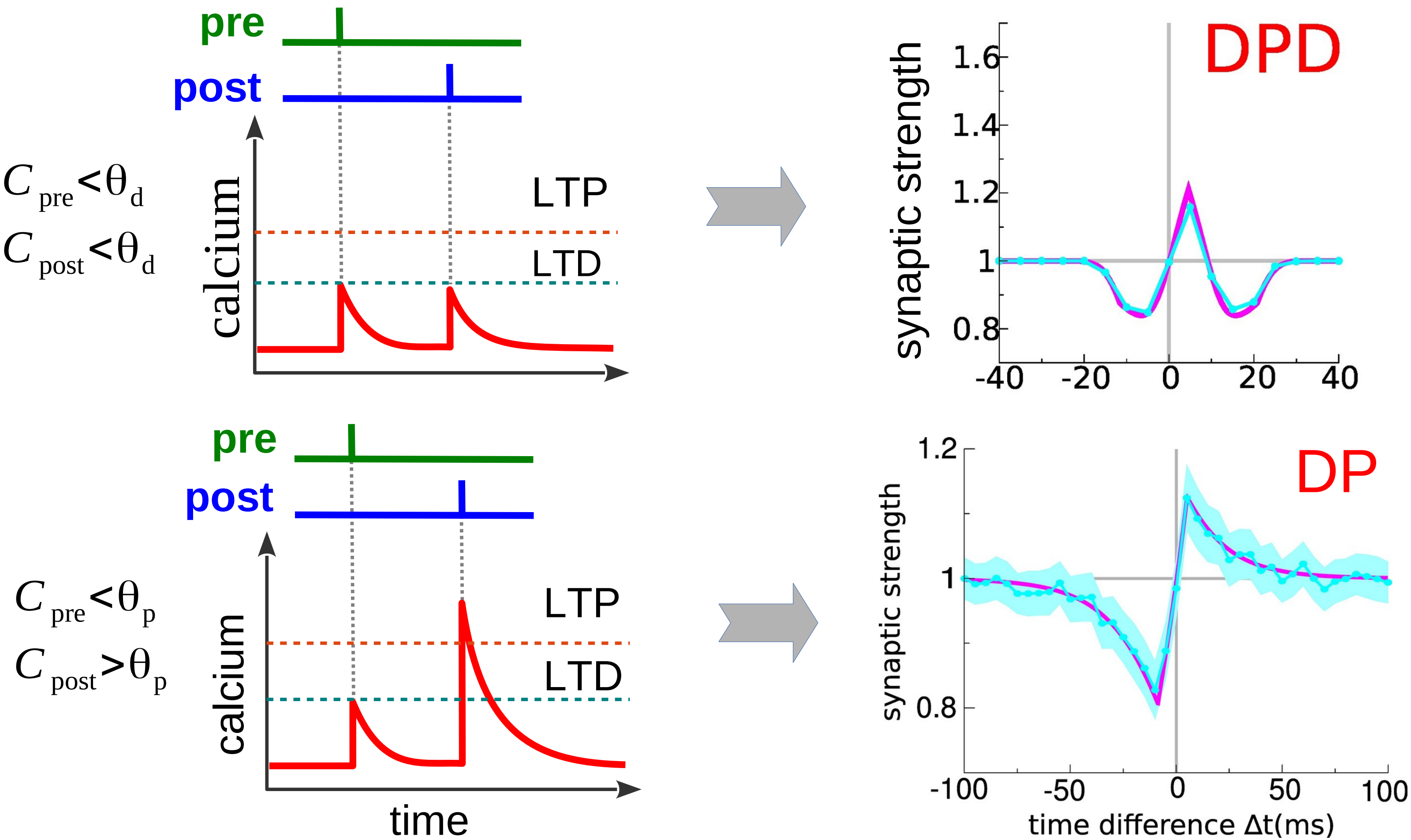


[Shouval *et al.*, 2002]

Calcium amplitudes determine shape of STDP curve

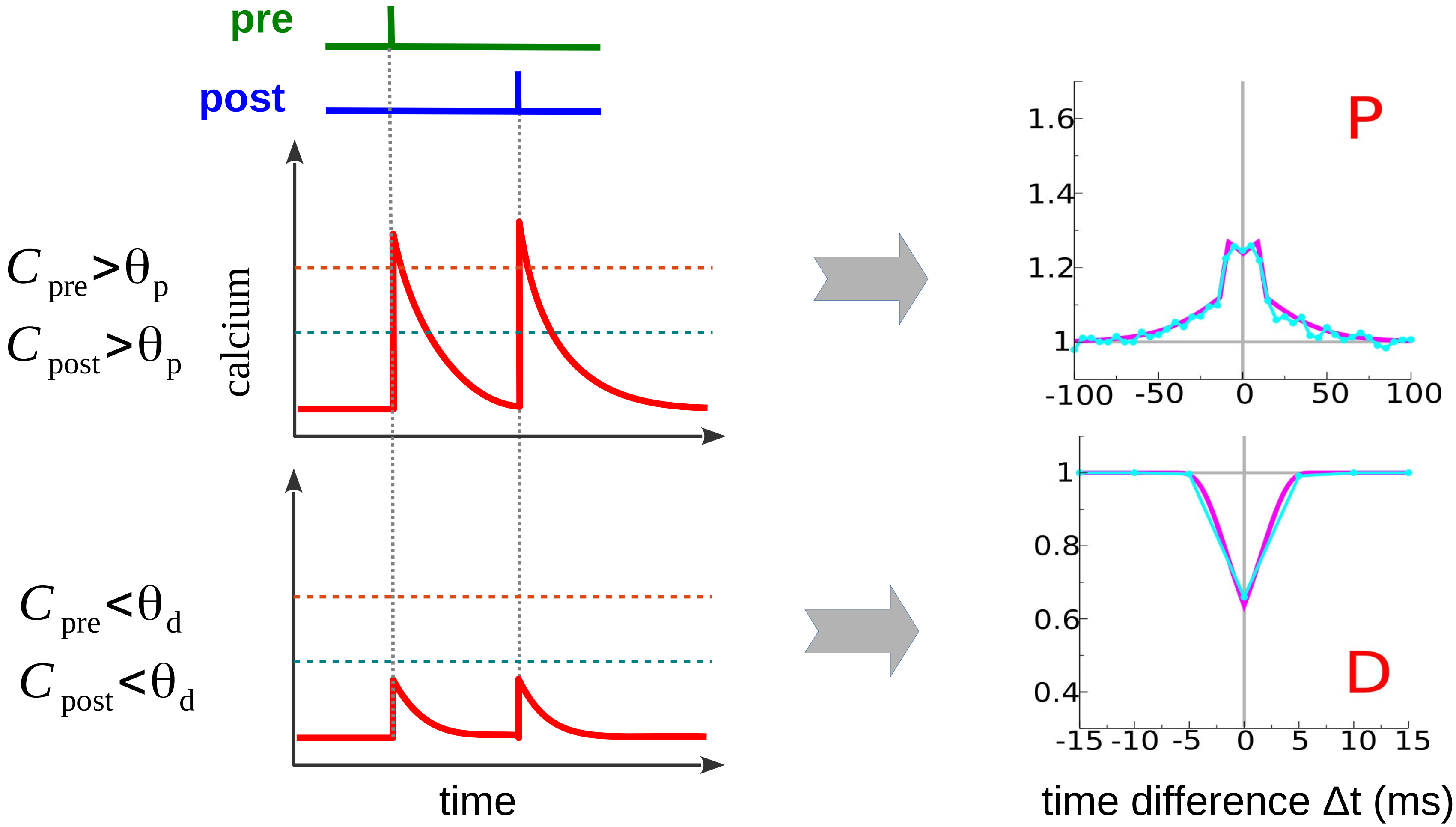
simulation II

Calcium amplitudes determine shape of STDP curve



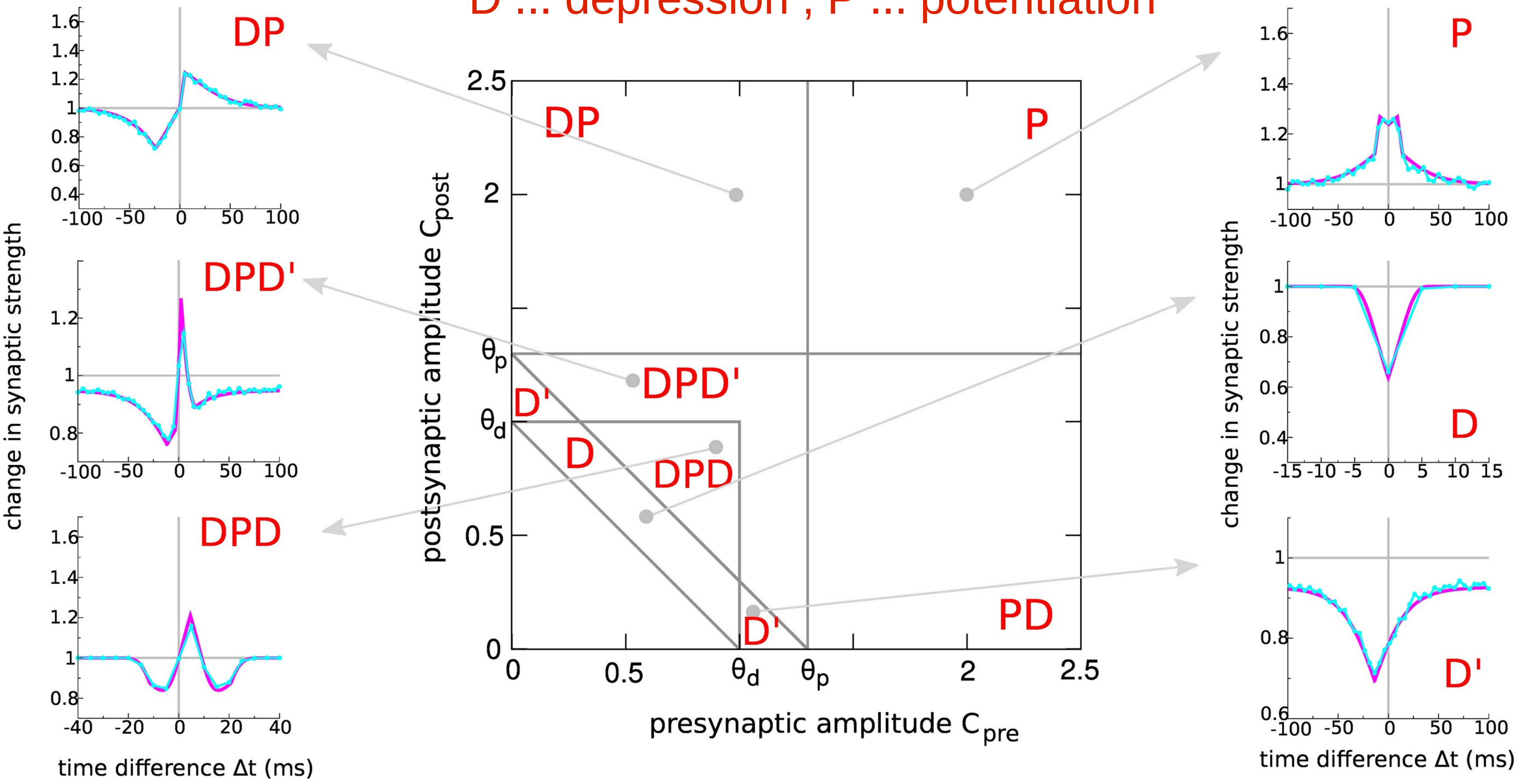
[Graupner & Brunel *PNAS* 2012]

Calcium amplitudes determine shape of STDP curve



Diversity of STDP curves : spike-pair stimulation

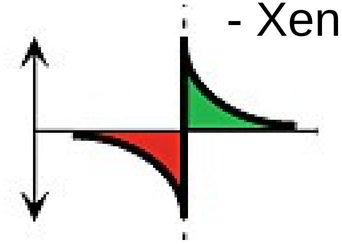
D ... depression , P ... potentiation



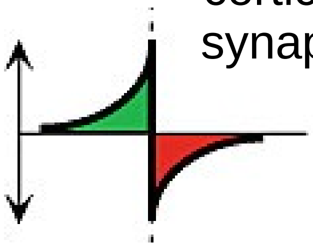
[Graupner & Brunel, *PNAS* 2012]

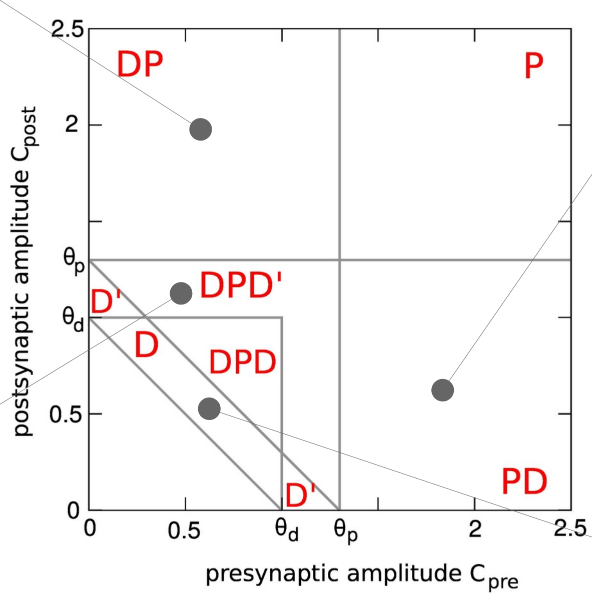
Diversity of STDP curves : experimental results

- neocortex-layer V
- hippocampus
- Xenopus tectum

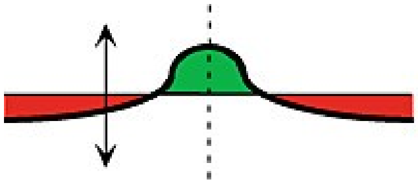


- ELL of electric fish
- corticostriatal synapse

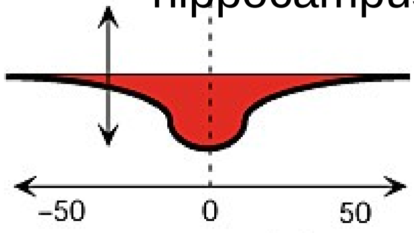




- GABA-ergic neurons in hippocampal cultures



- neocortex-layer IV spiny stellates
- hippocampus



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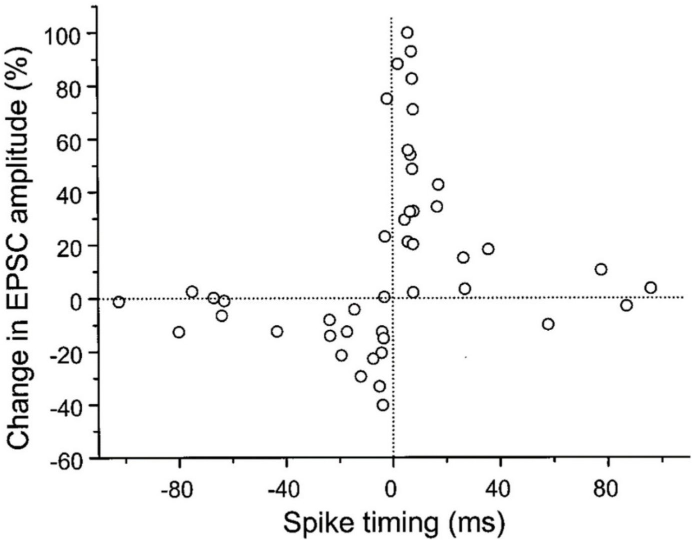
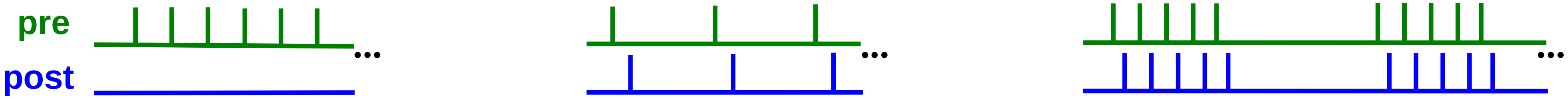


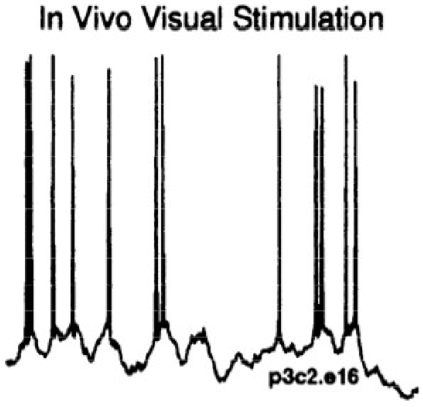
[Bi & Poo 1998]

Firing patterns : Realistic firing is highly irregular

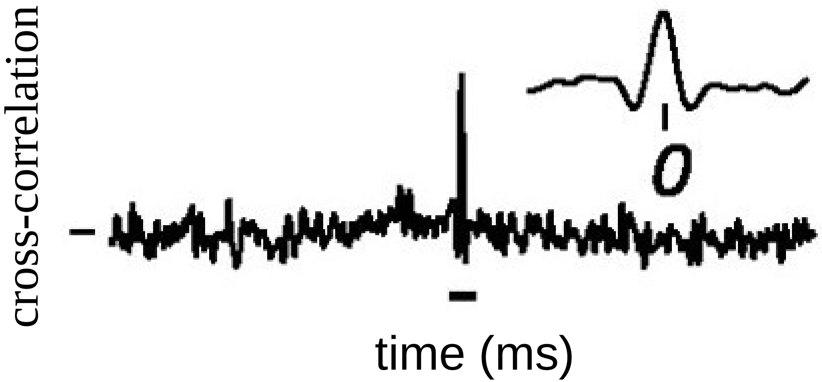
- stimulation protocols used to induce plasticity



- *in vivo* firing patterns



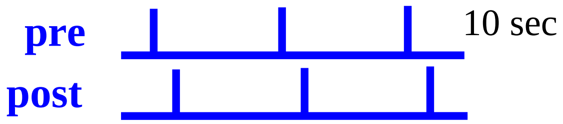
[Holt *et al.*, 1996]

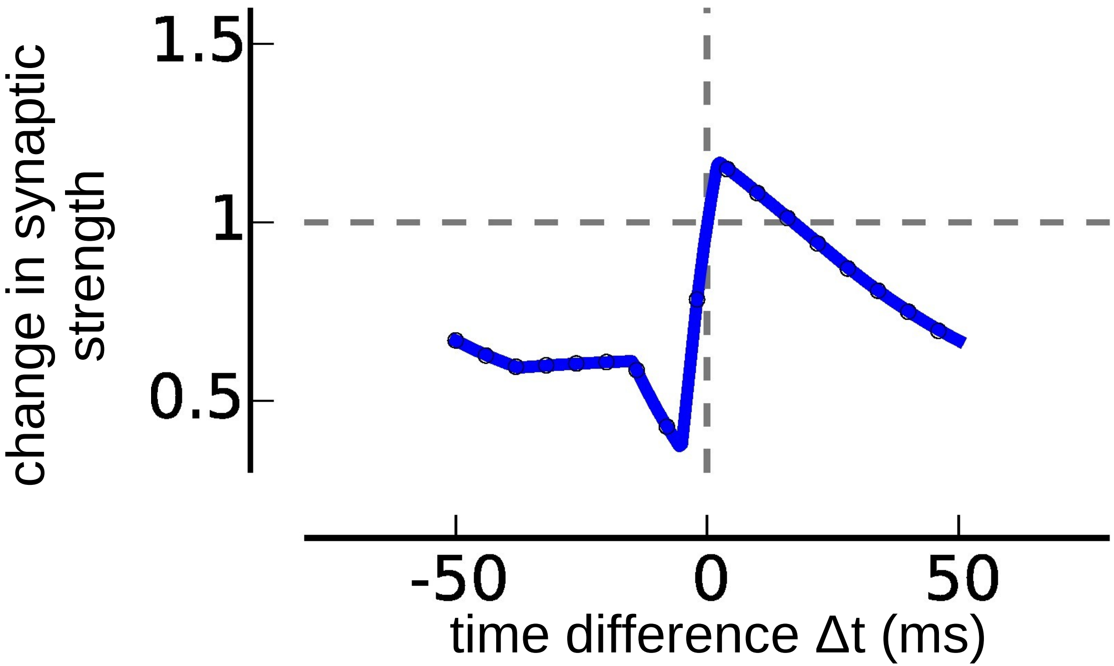


[Kohn and Smith, 2005]

Regular vs. irregular spike-pairs

regular spike-pairs



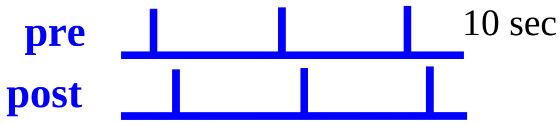


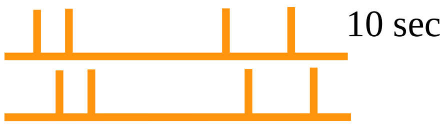
$\nu_{pre} = \nu_{post} = 10 \text{ Hz}$

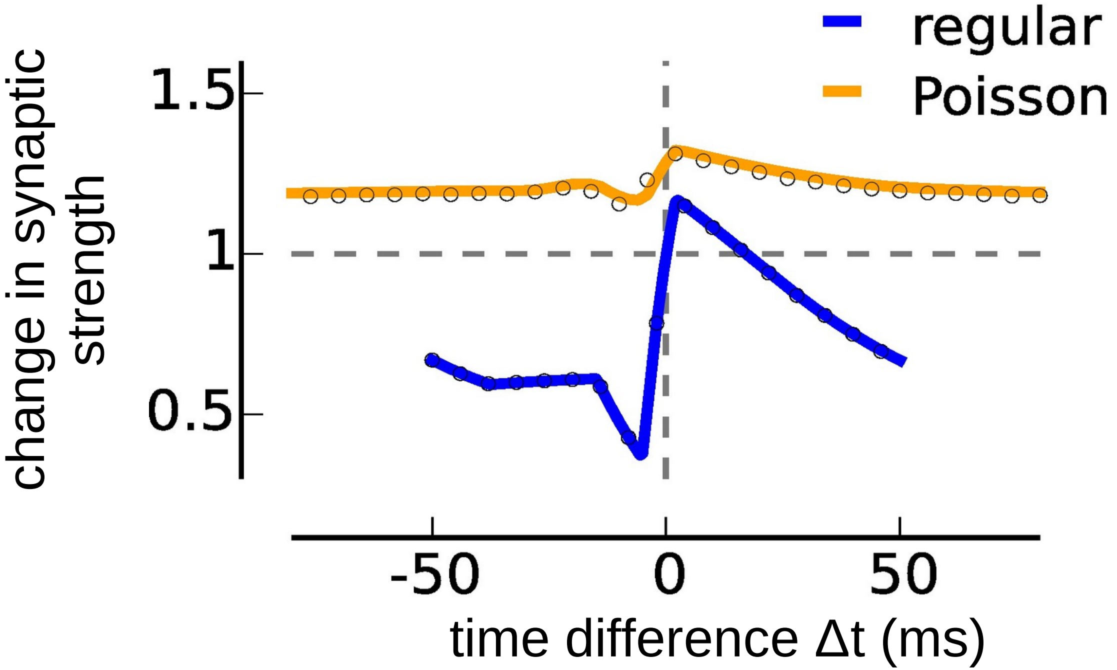
Regular vs. irregular spike-pairs

regular spike-pairs

Poisson distributed spike-pairs







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

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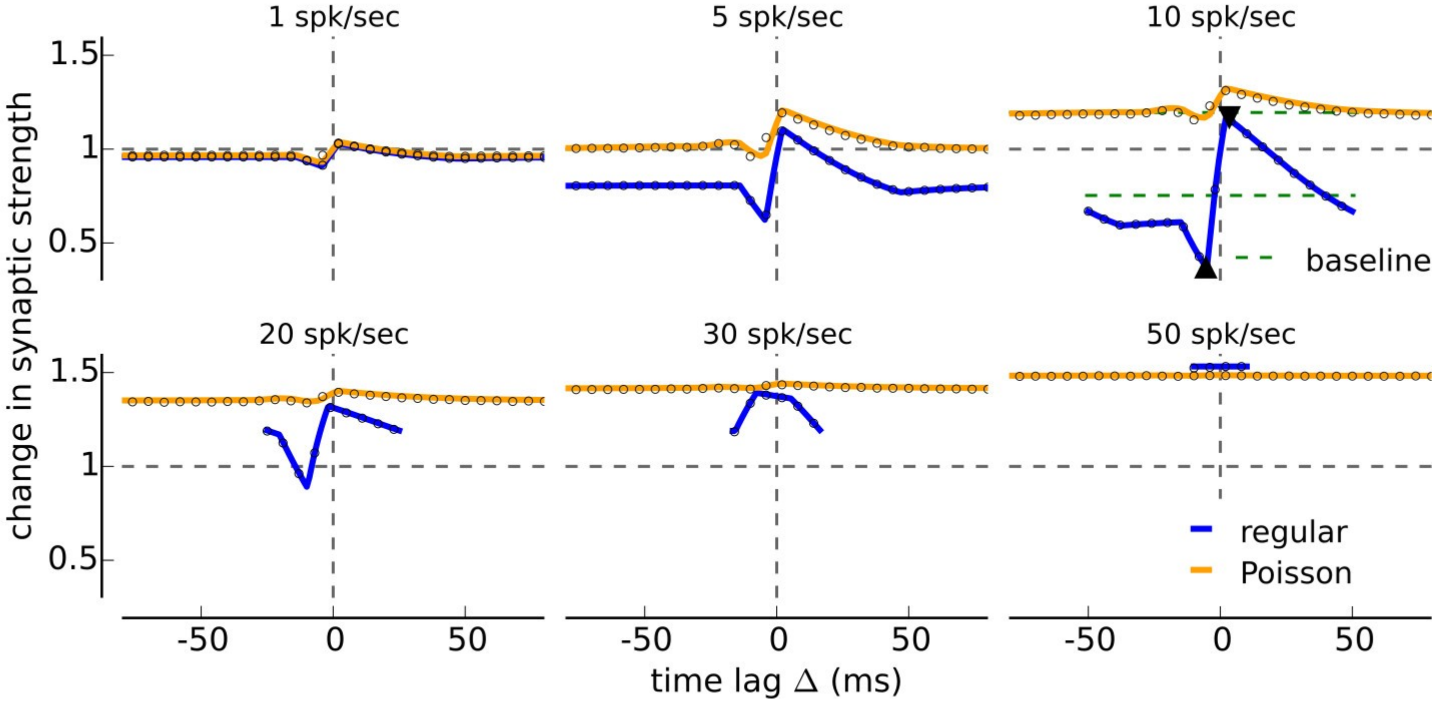

[Graupner, Wallisch & Ostojic. *J Neurosci* 2016]

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