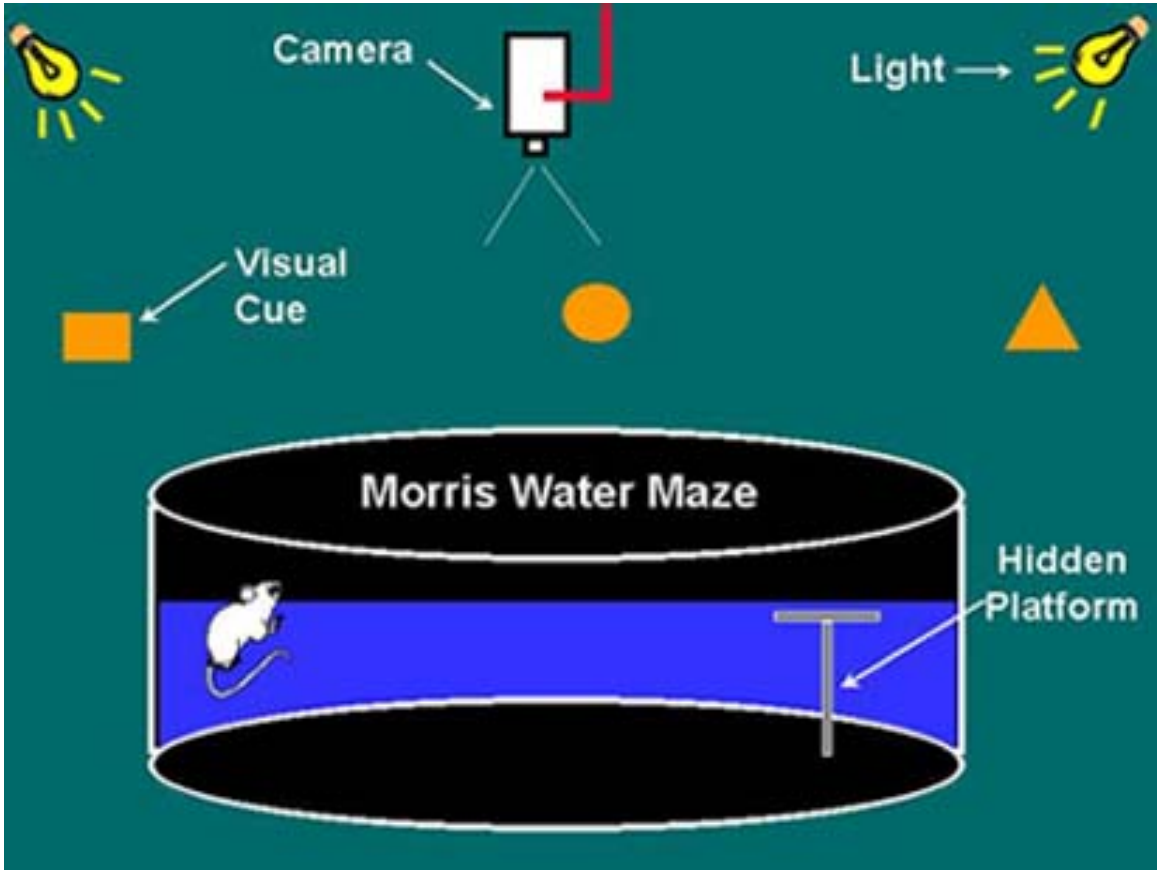
Biophysical models of synaptic plasticity

Oct 30th, 2015

Michael Graupner

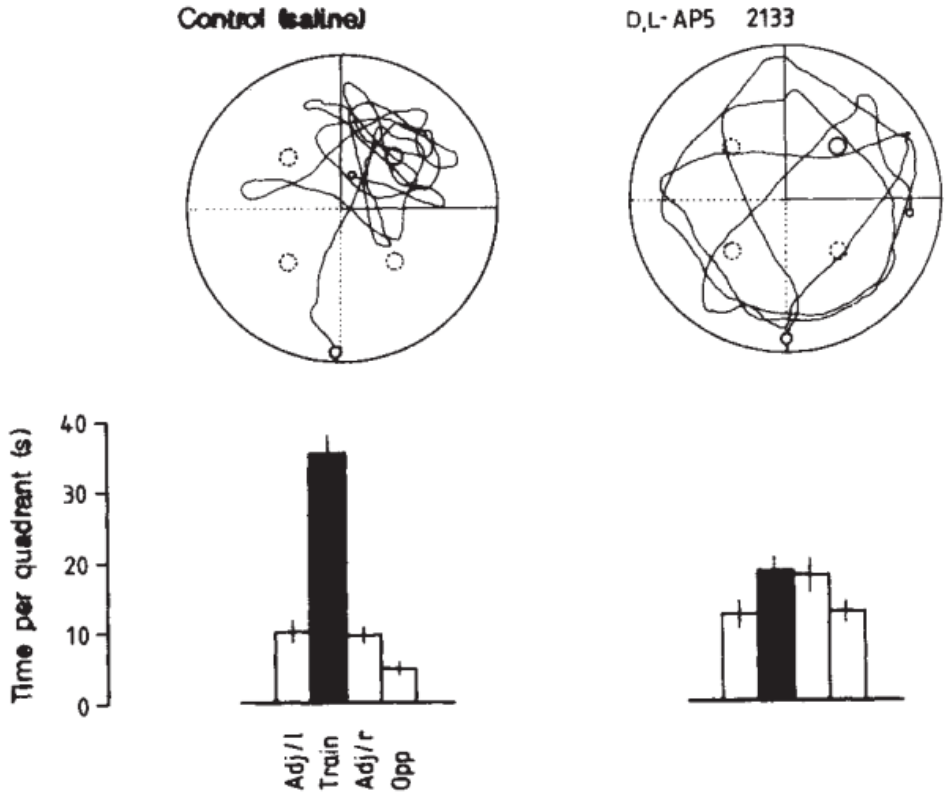
michael.graupner@parisdescartes.fr
http://www.biomedicale.univ-paris5.fr/~mgraupe/

Why are we interested in synaptic plasticity ?



[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]

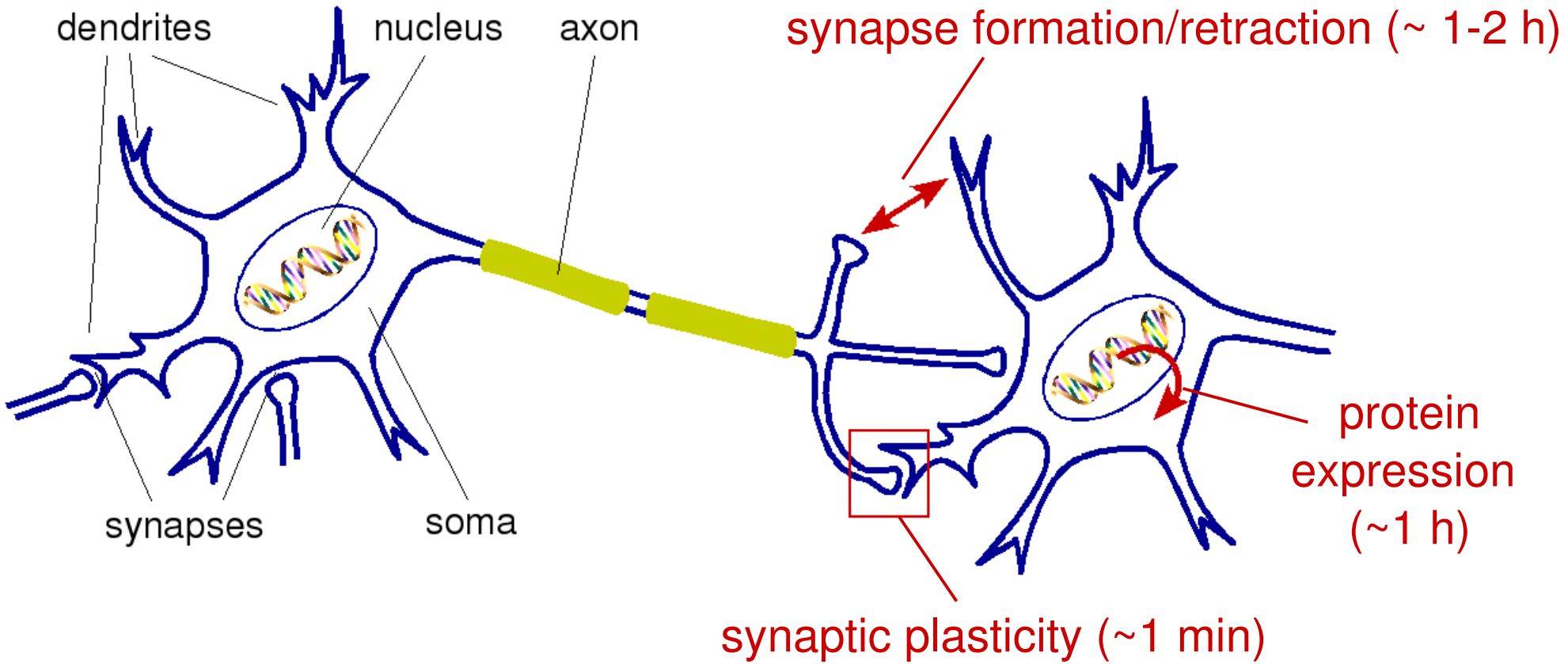
Outline

Outline

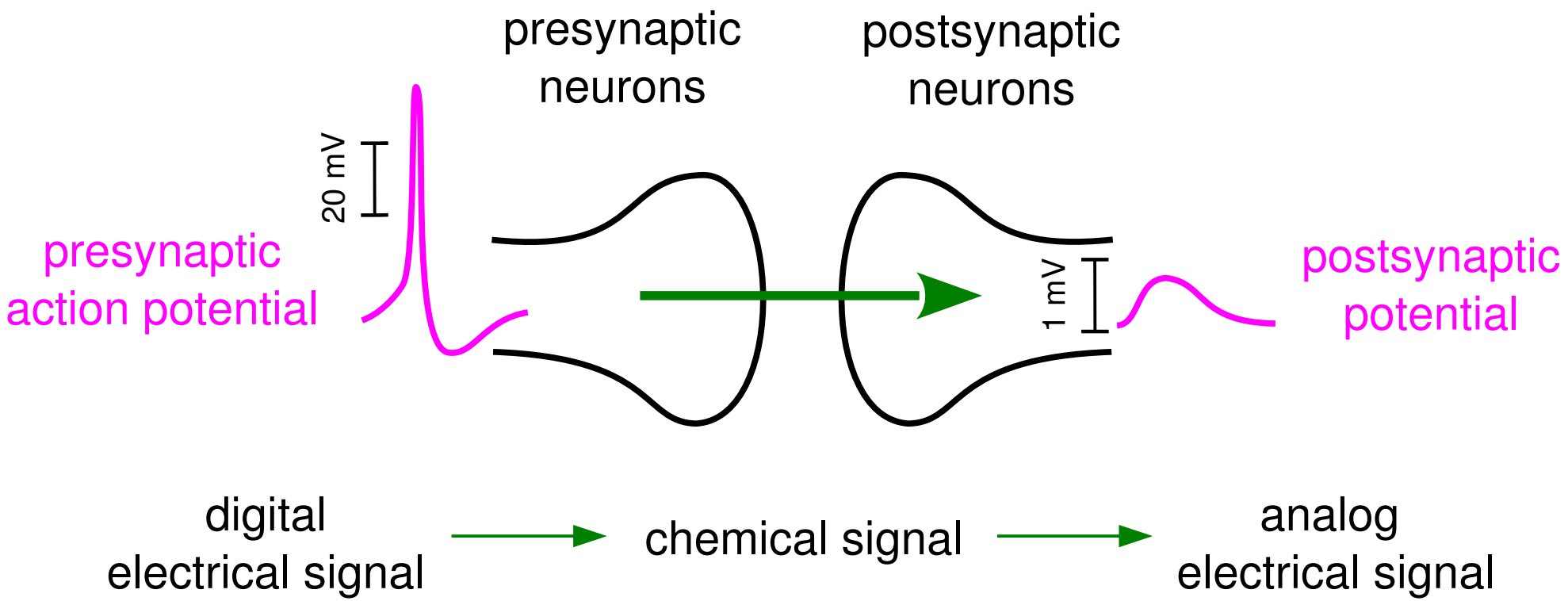
Different forms of plasticity

structure of neurons

changes related to neural activity

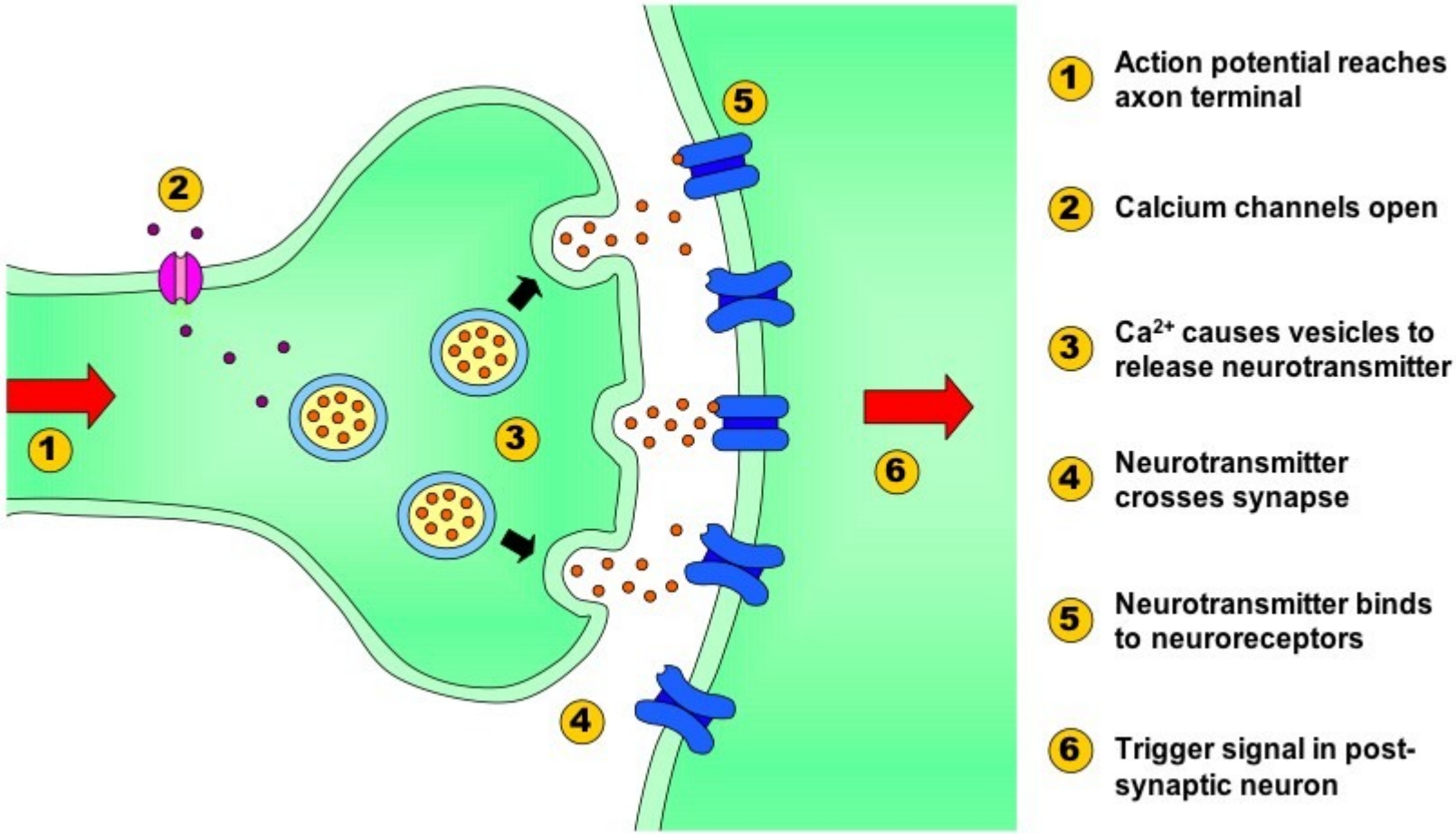


Chemical synapse : transmits electrical signals



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

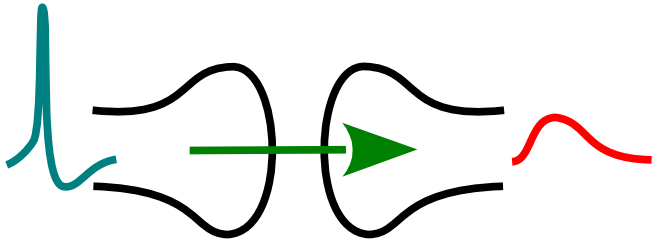
Chemical synapse : underlying biological machinery



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

Chemical synapse : excitatory or inhibitory

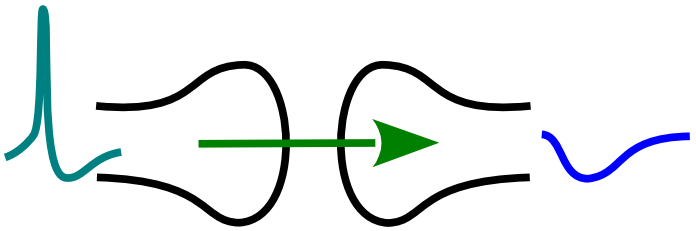
Excitatory synapse



depolarization:
excitatory postsynaptic potential (EPSP)

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

Inhibitory synapse

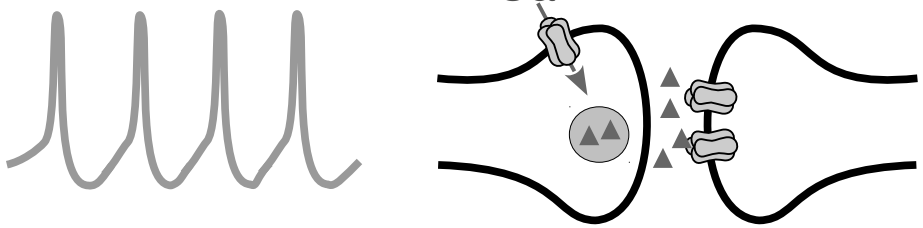


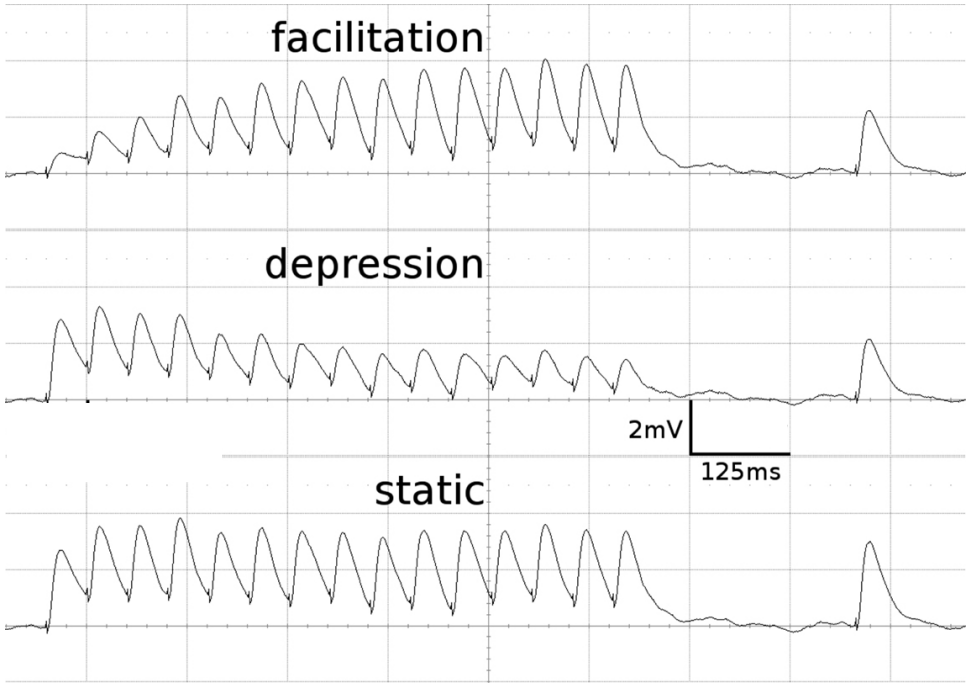
hyperpolarization:
Inhibitory postsynaptic potential (IPSP)

neurotransmitter	receptor
GABA	GABA_A, GABA_B
glycine	GlyR

Short-term synaptic plasticity

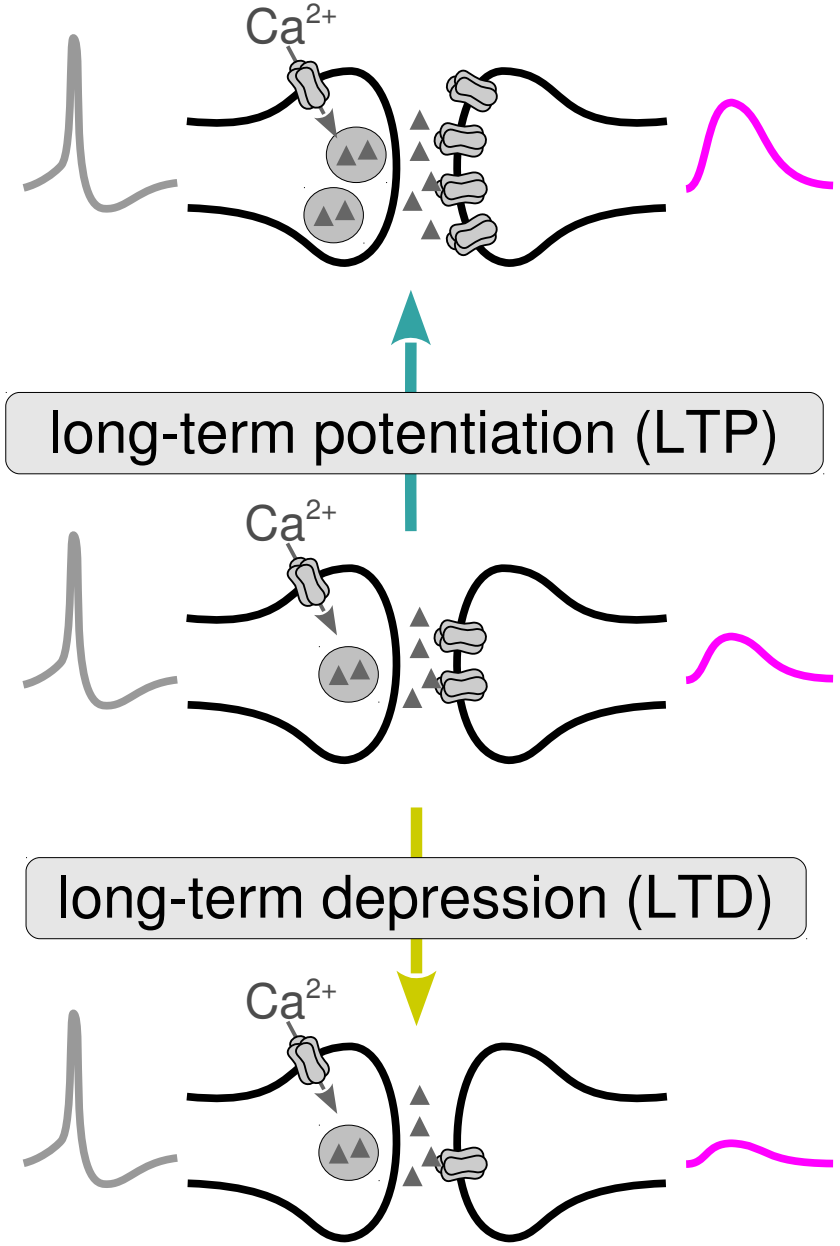
train of presynaptic action potentials





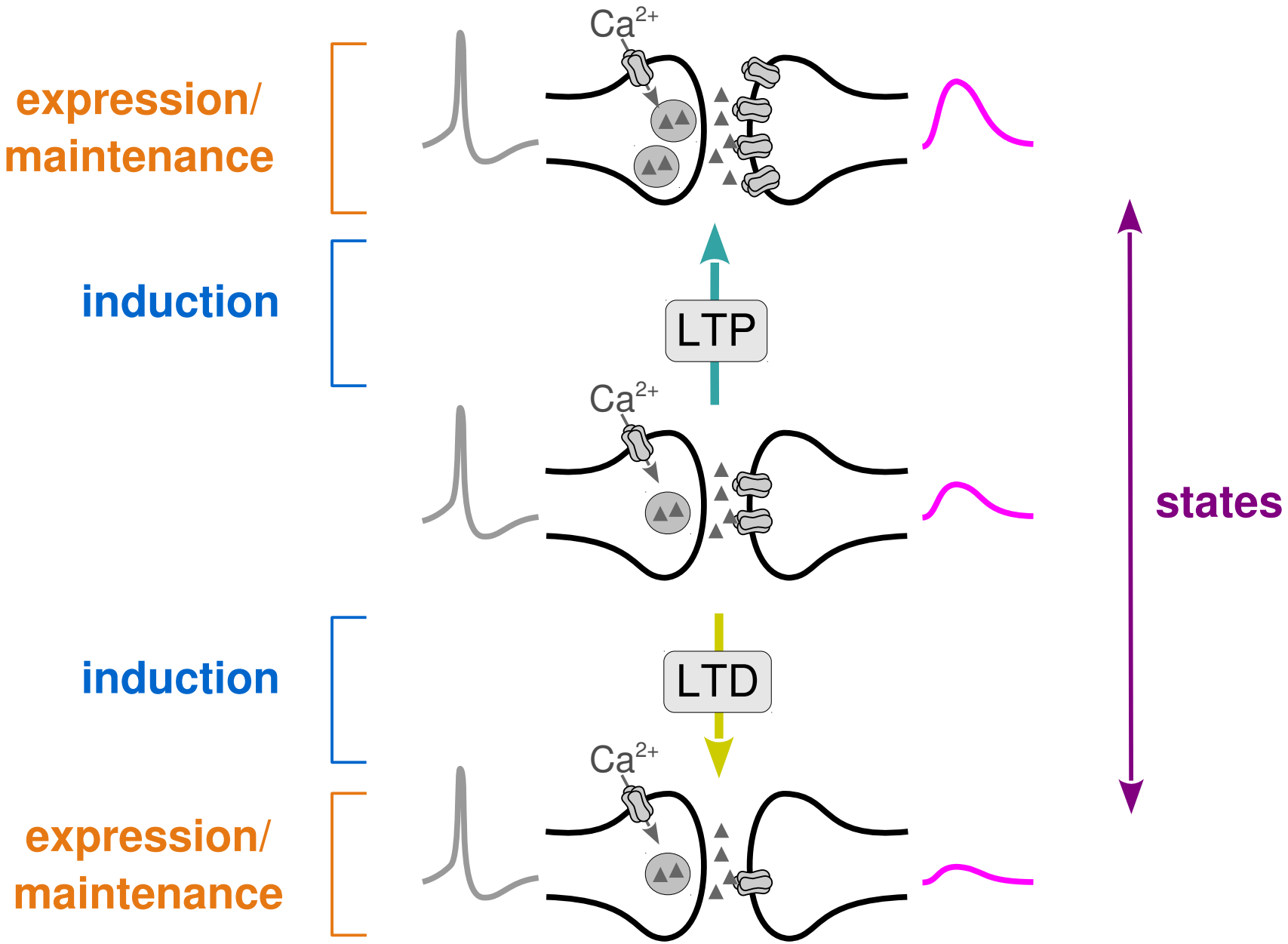
- transient change in transmission efficacy
- time scale of changes ~1 sec

Long-term synaptic plasticity



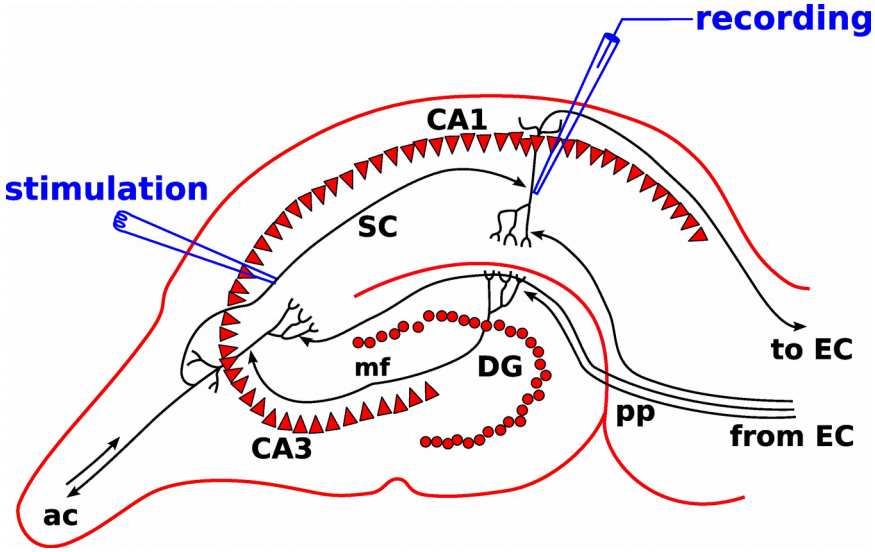
- long-lasting change (>60 min) in transmission efficacy
- time scale of induction ~ 1 min

Synaptic plasticity: induction, maintenance & states

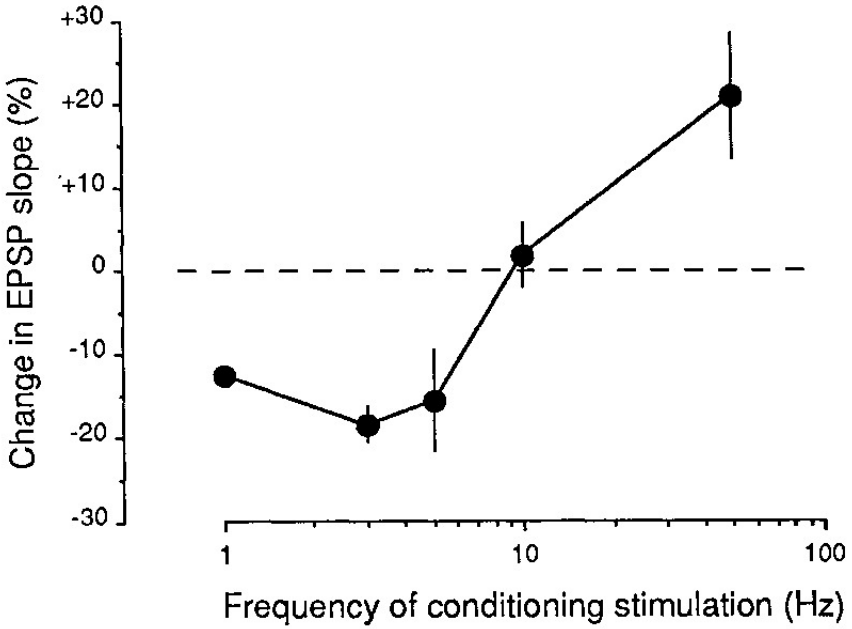


Plasticity induction: spike-frequency stimulation

hippocampus (slices)



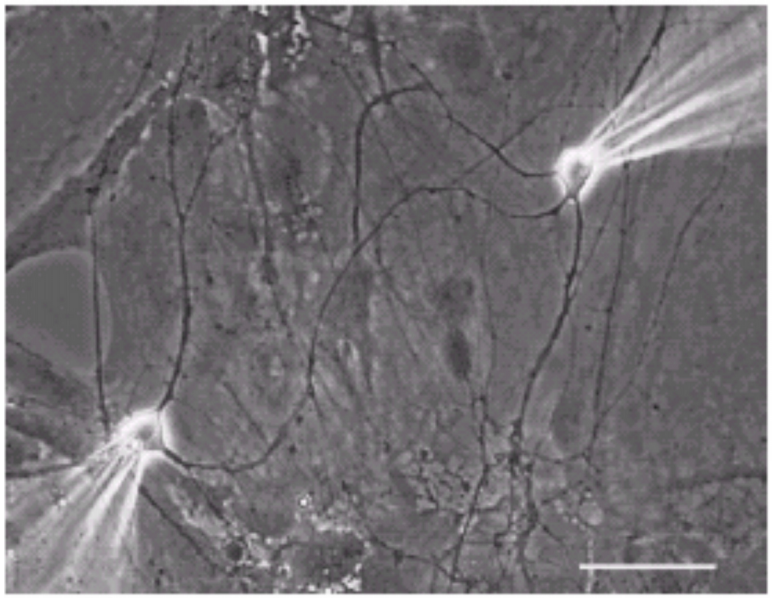
900 pulses at 1-50 Hz



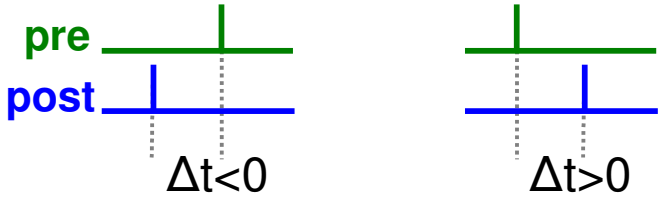
[Bliss and Lømo 1973; Dudek and Bear 1992; Dunwiddie and Lynch 1978]

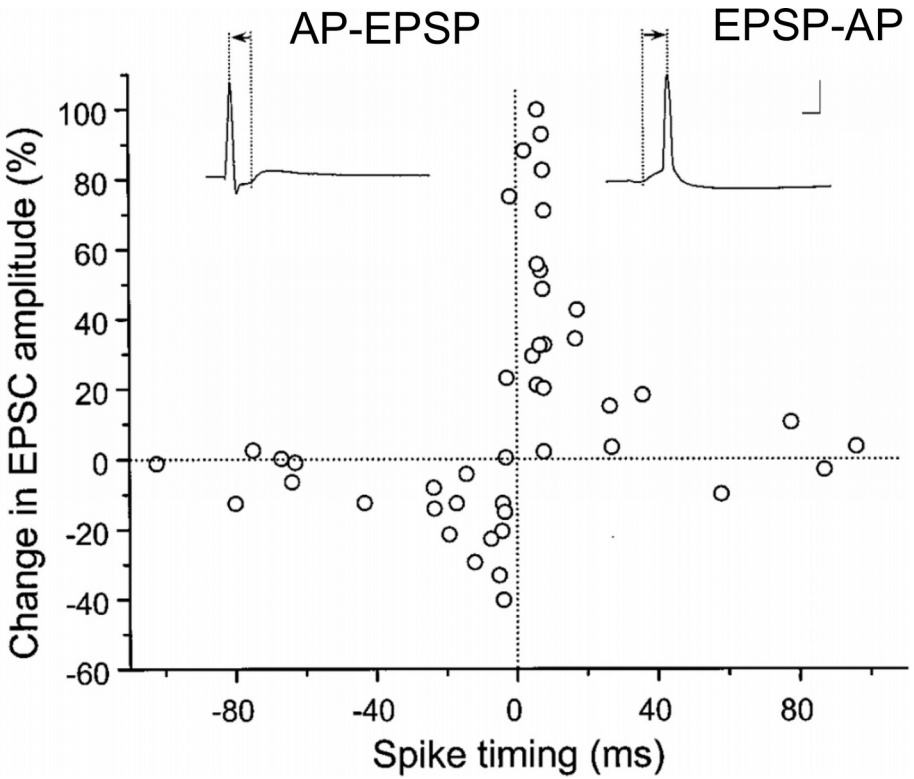
Plasticity induction : spike-pair stimulation

hippocampal cultures



60 pairings @ 1 Hz



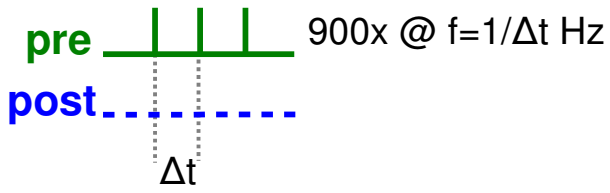


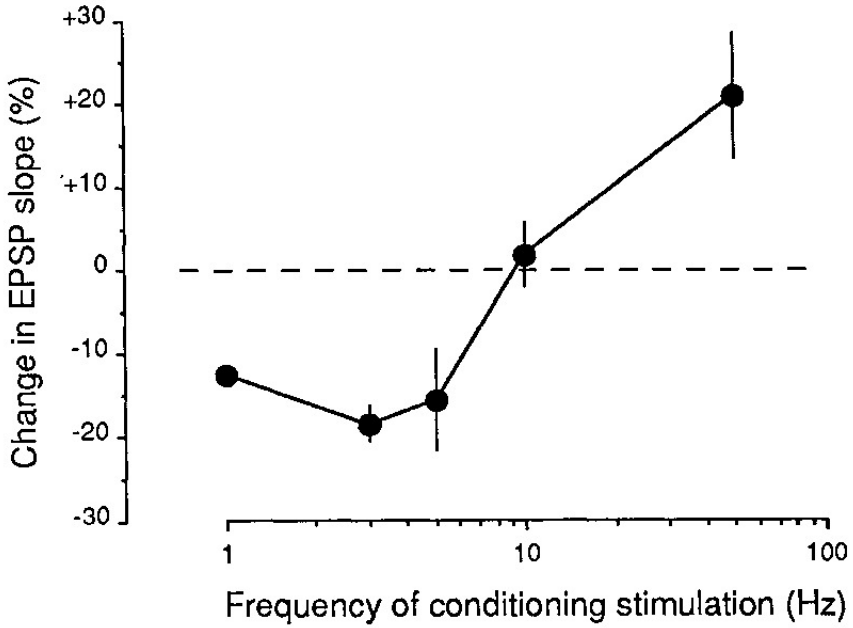
[Bi & Poo, J Neurosci 1998]

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

Induction: Stimulation protocols evoking LTP/LTD

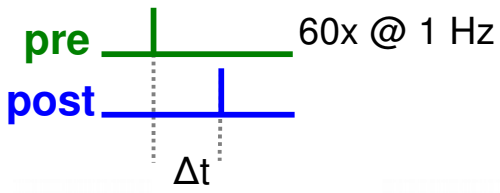
spike-frequency

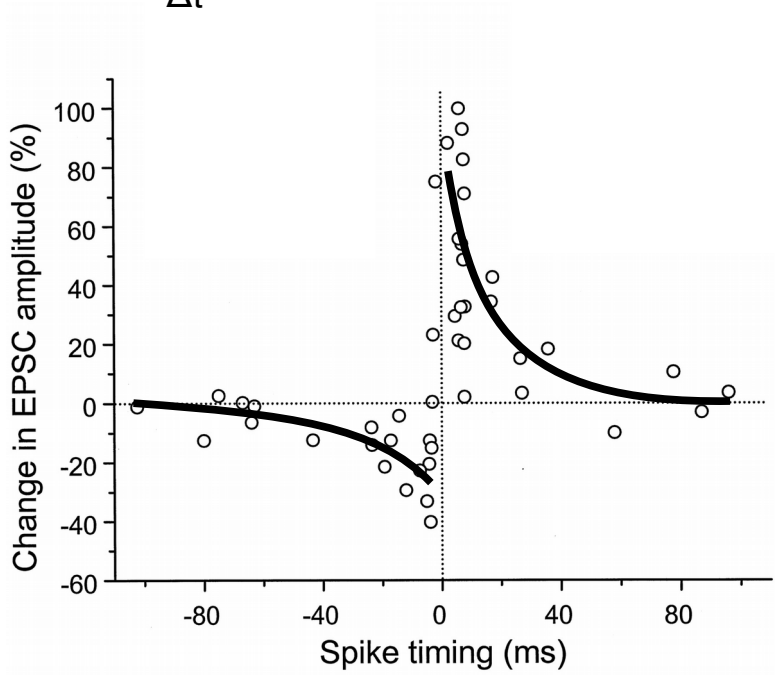




[Dudek *et al.*, 1992]

spike-timing





[Bi & Poo, 1998]

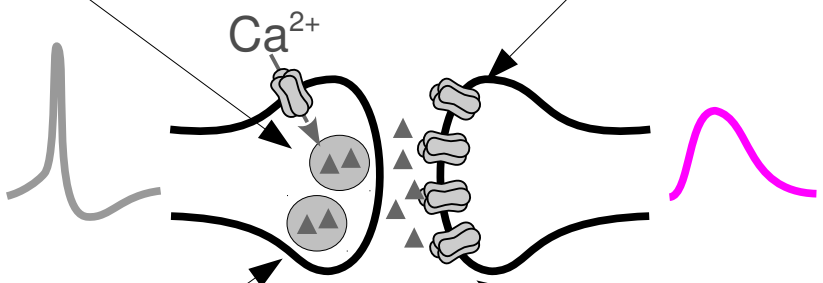
Expression of long-term changes

presynaptic

postsynaptic

neurotransmitter vesicle number

number of AMPA receptors



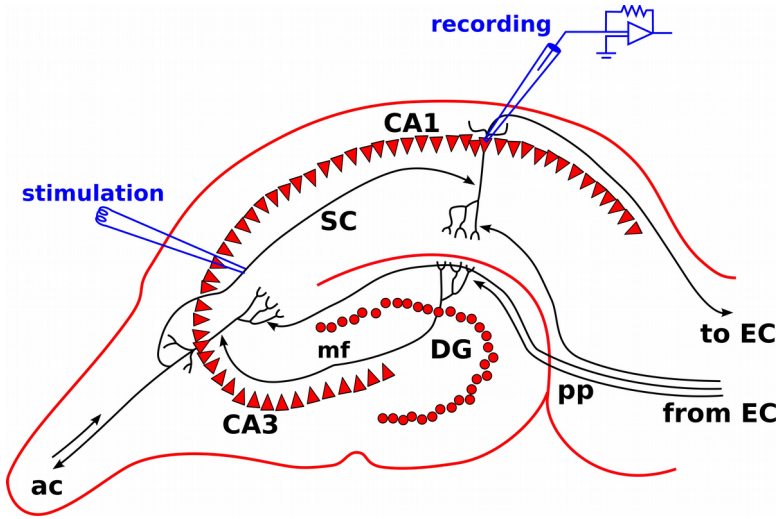
probability of vesicle release

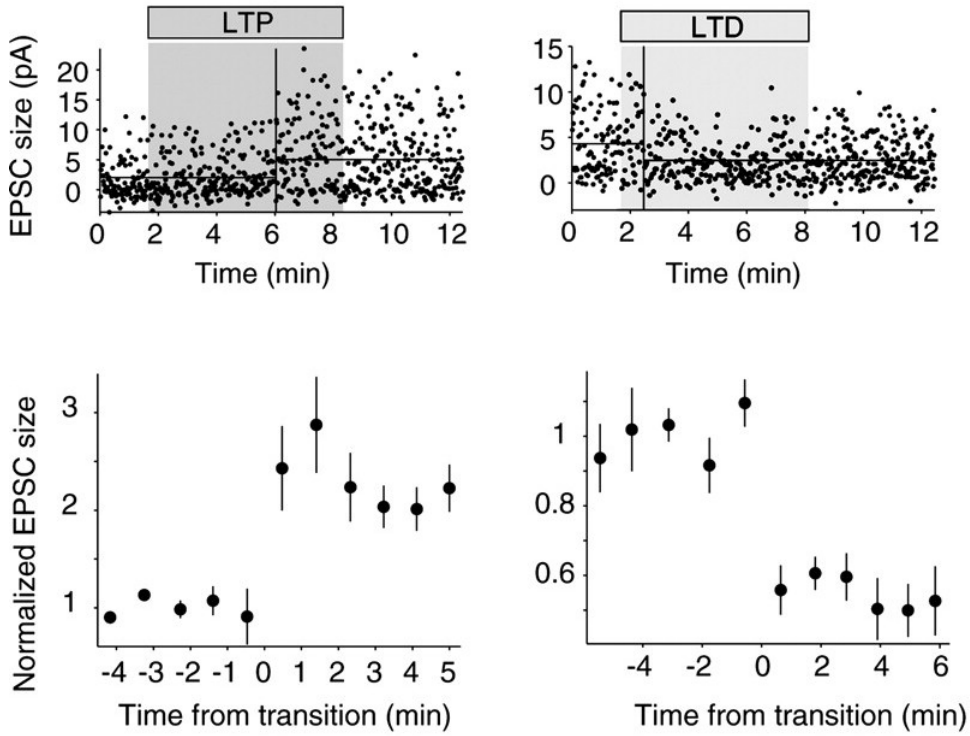
conductance of AMPA receptors

States of a synapse : analog or digital?

- most experiments involved multiple synaptic contacts
- Petersen *et al.* 1998, O'Connor *et al.* 2005 investigate single synapse

→ suggest binary synapse



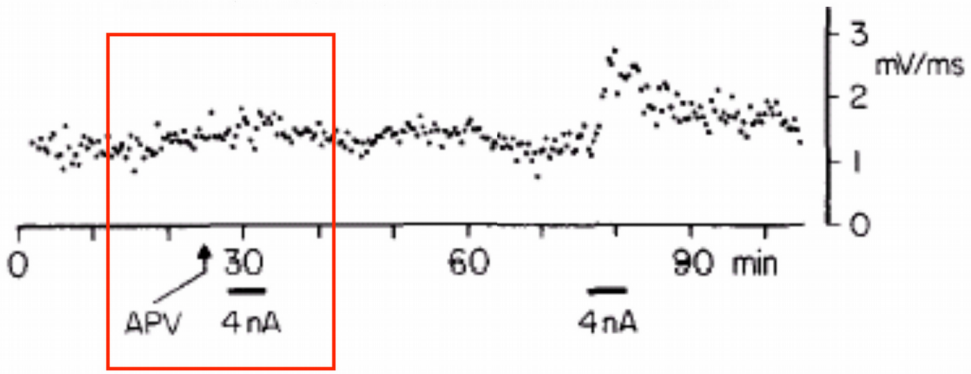


[O'Connor *et al.*, 2005]

Outline

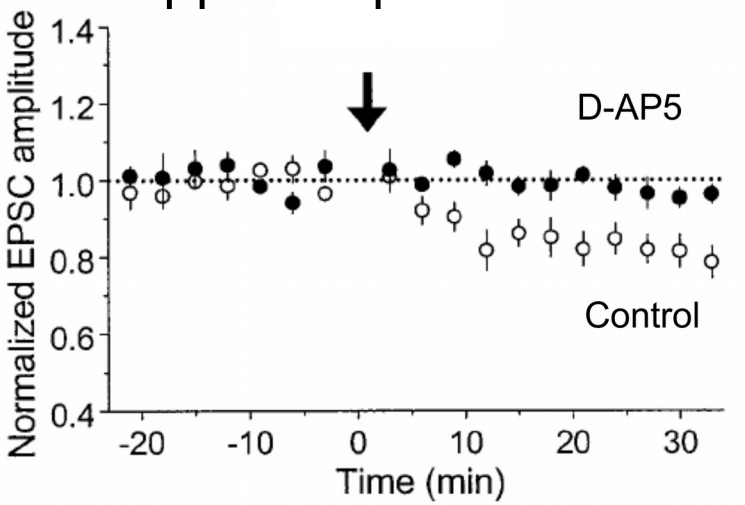
Plasticity requires NMDA receptor activation

hippocampal slices



[Gustafsson et al. *J Neurosci* 1987]

hippocampal cultures

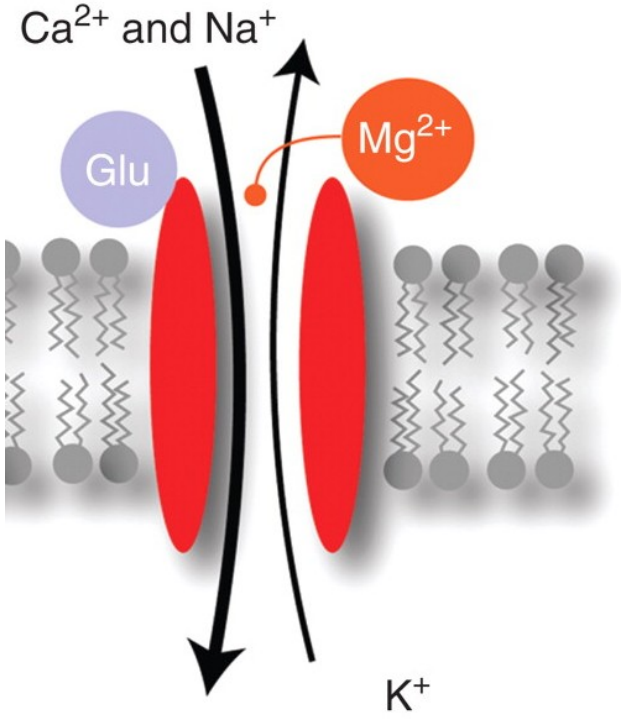


[Bi & Poo *J Neurosci* 1998]

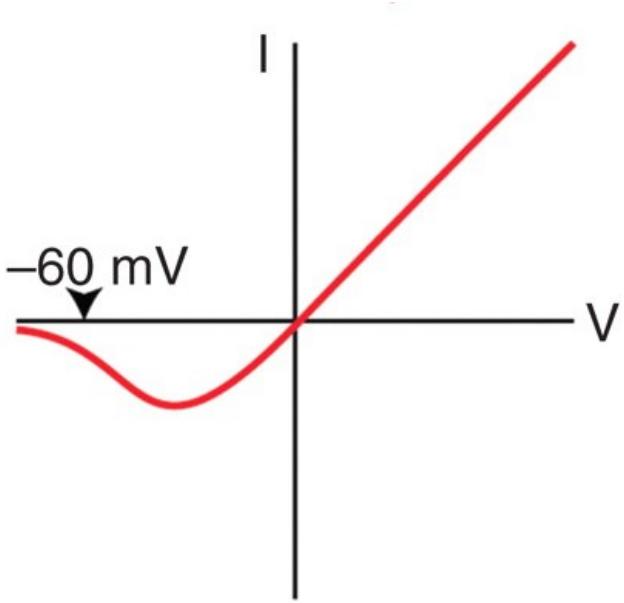
NMDAR antagonist blocks LTP/LTD induction

- CA3-CA1 pyramidal cell synapse
- CA3-CA3 pyramidal cell synapse
- Layer V – layer V synapse
- Layer II/III
- Layer IV stellate cell synapse
- Dorsal cochlear neurons (brainstem)
- Retino-tectal synapse

Induction: postsynaptic NMDA receptor activation required



current-voltage relationship



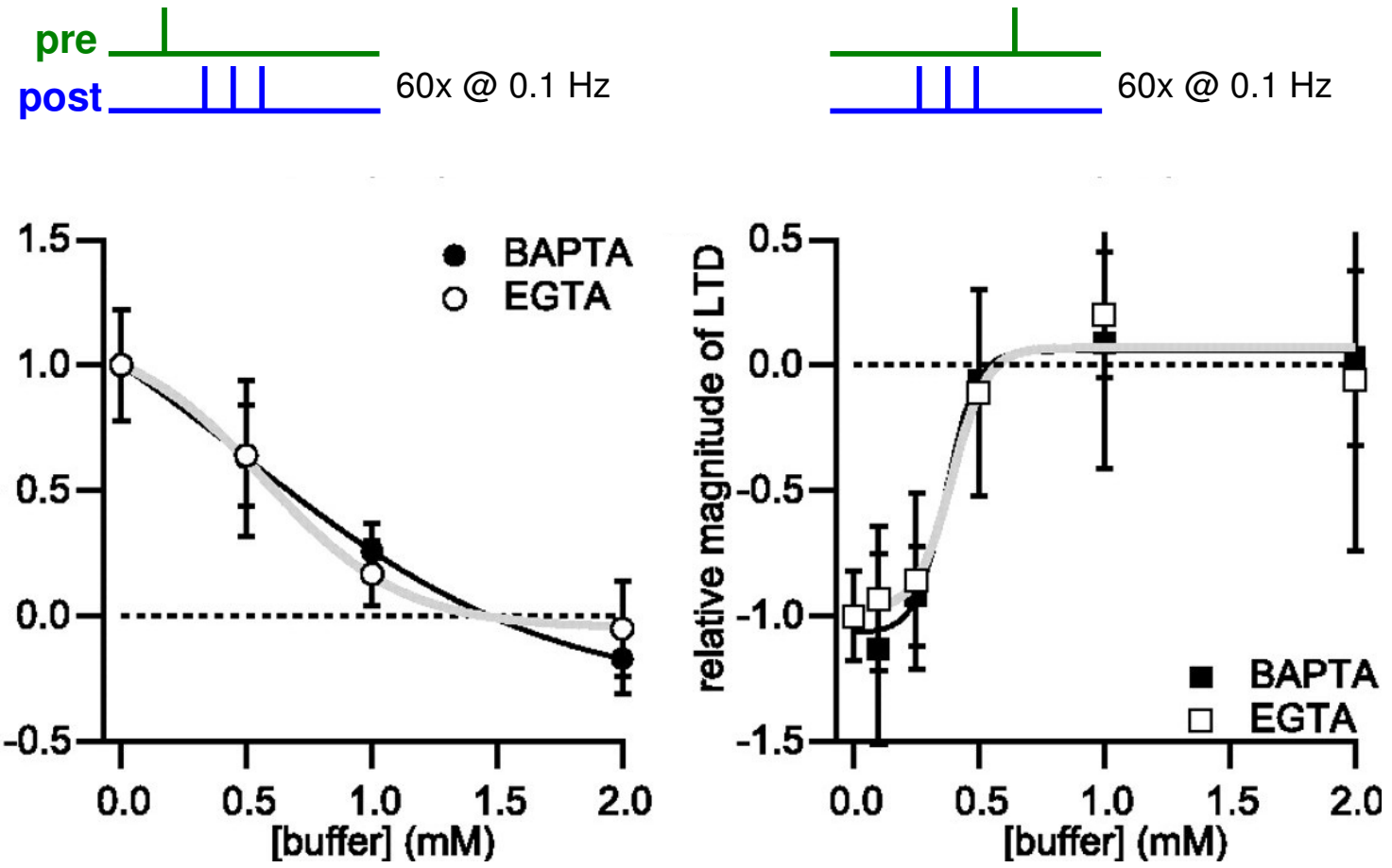
- coincidence detector :

  presynaptic action potential → glutamate (Glu)

  postsynaptic depolarization → Mg^{2+} block is expelled

- calcium permeable

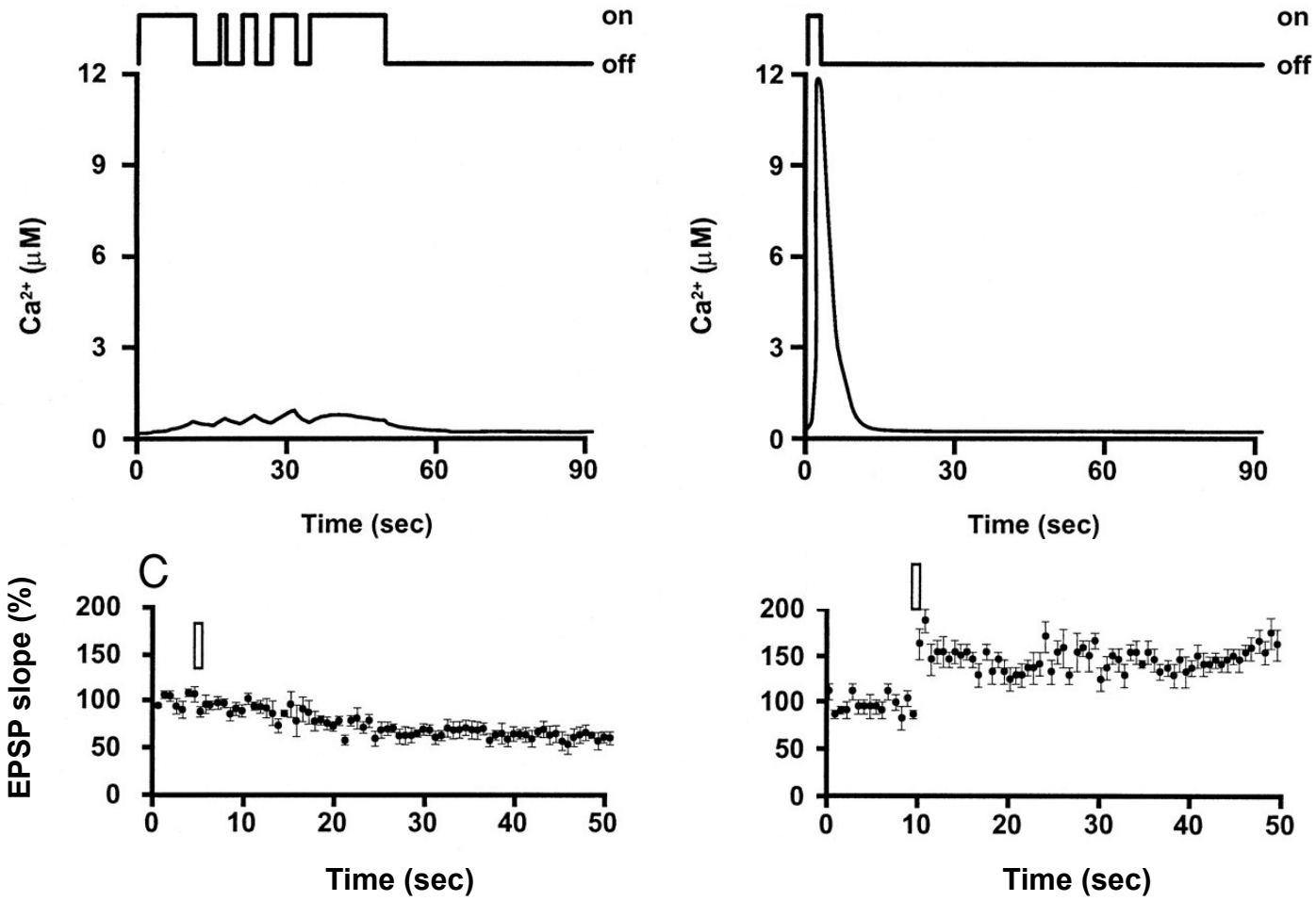
Postsynaptic calcium *required* for plasticity



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

[Lynch et al., 1983; Malenka et al., 1988; Neveu and Zucker, 1996; Yang et al., 1999; Zucker, 1999; Mizuno et al., 2001; Ismailov et al., 2004]

Postsynaptic calcium *sufficient* for plasticity

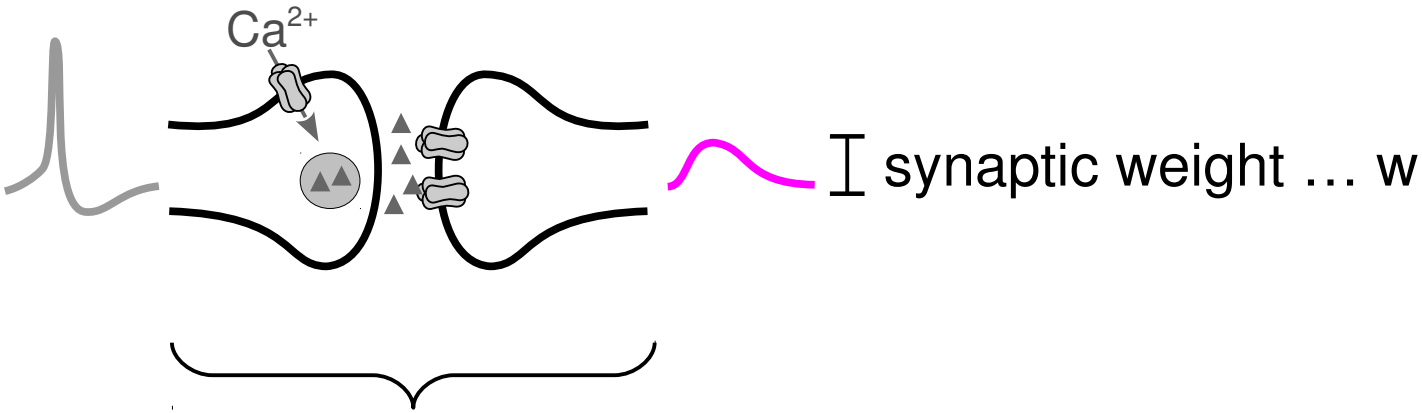


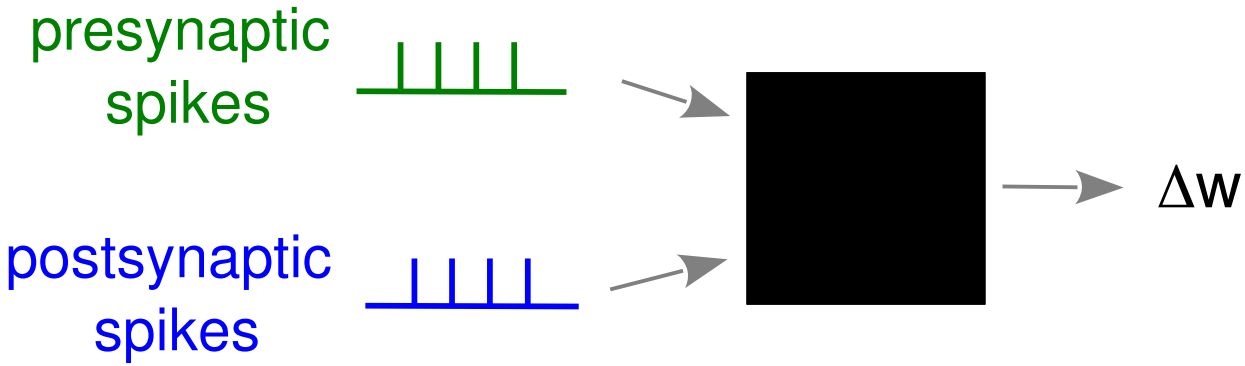
[Yang *et al.*, 1999]

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

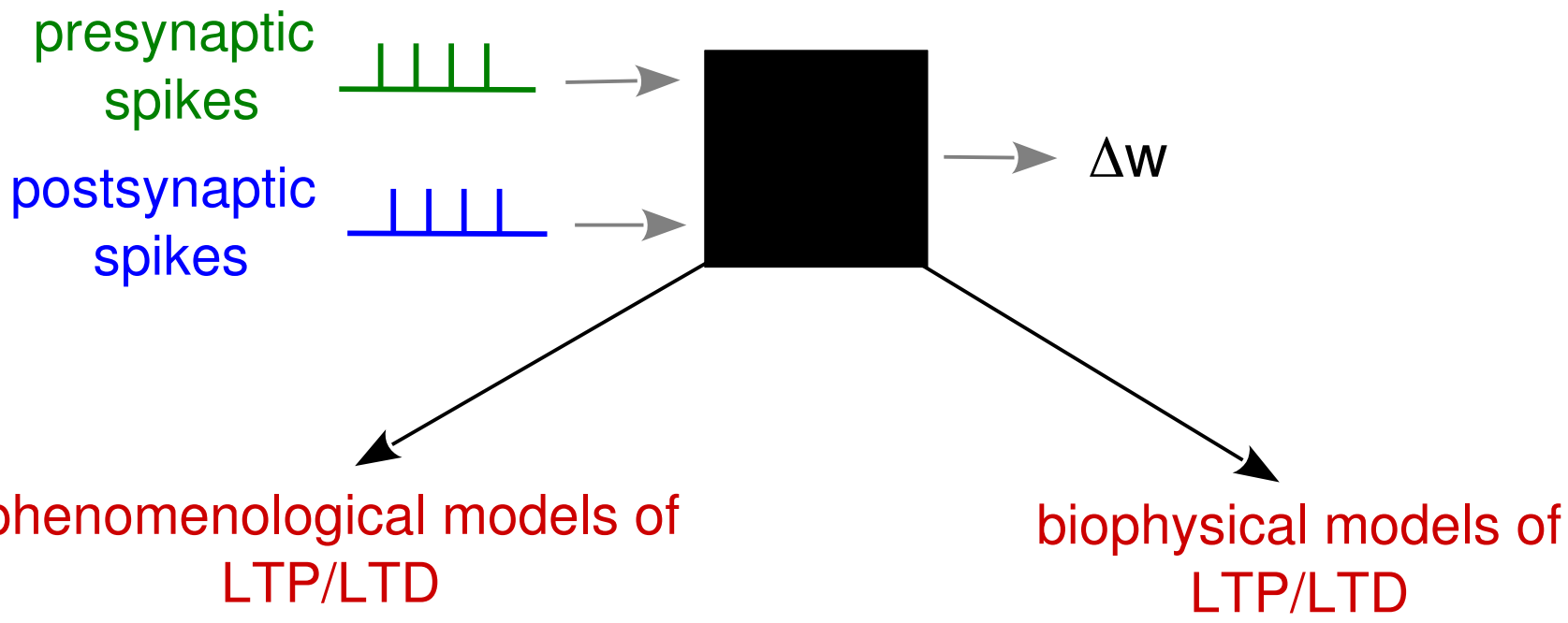
Outline

Plasticity models link activity to synaptic change





Modeling approaches : phenomenological vs. biophysical



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

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

Modeling studies : phenomenological vs. biophysical

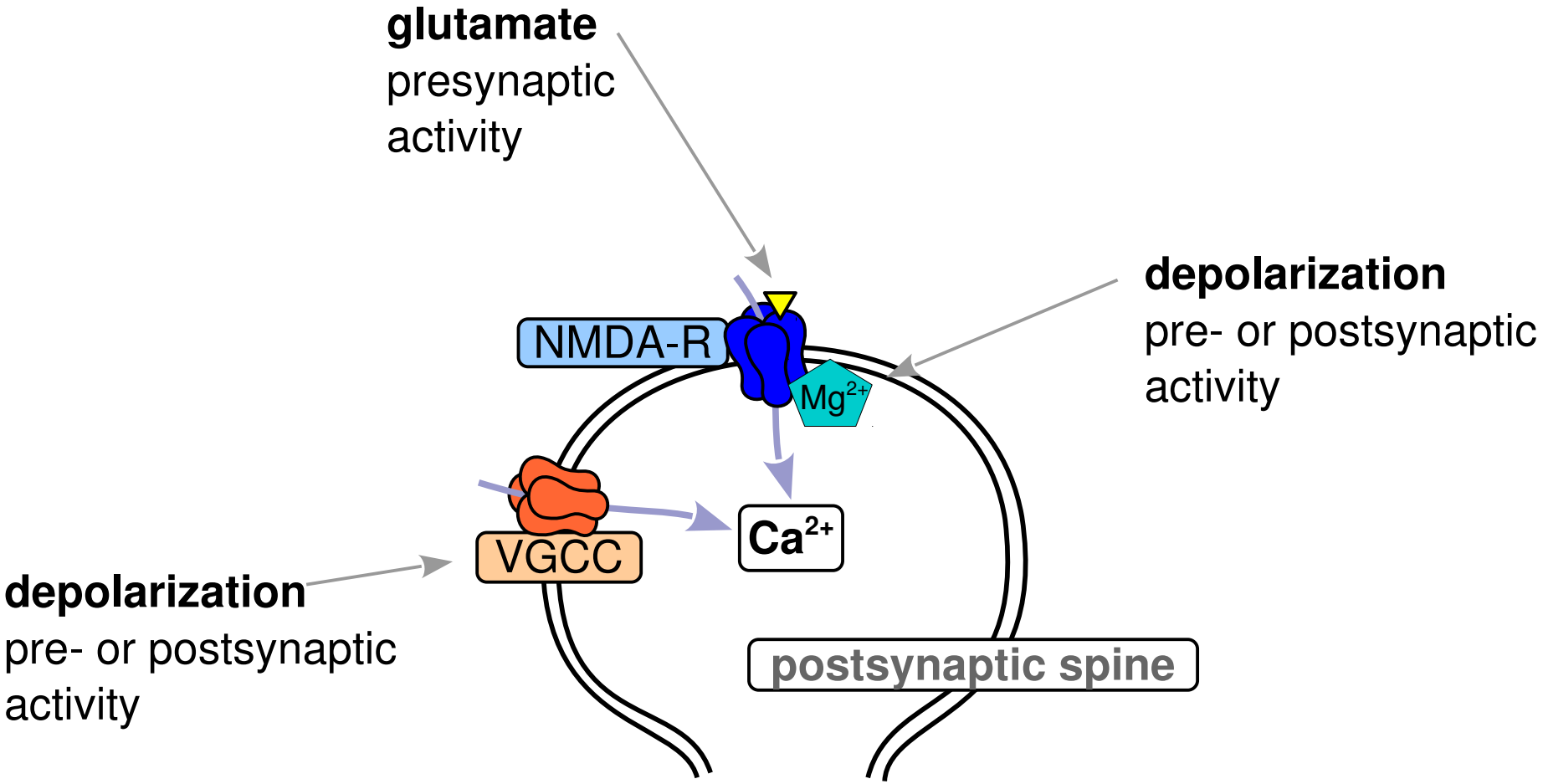
phenomenological models of LTP/LTD

- 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]

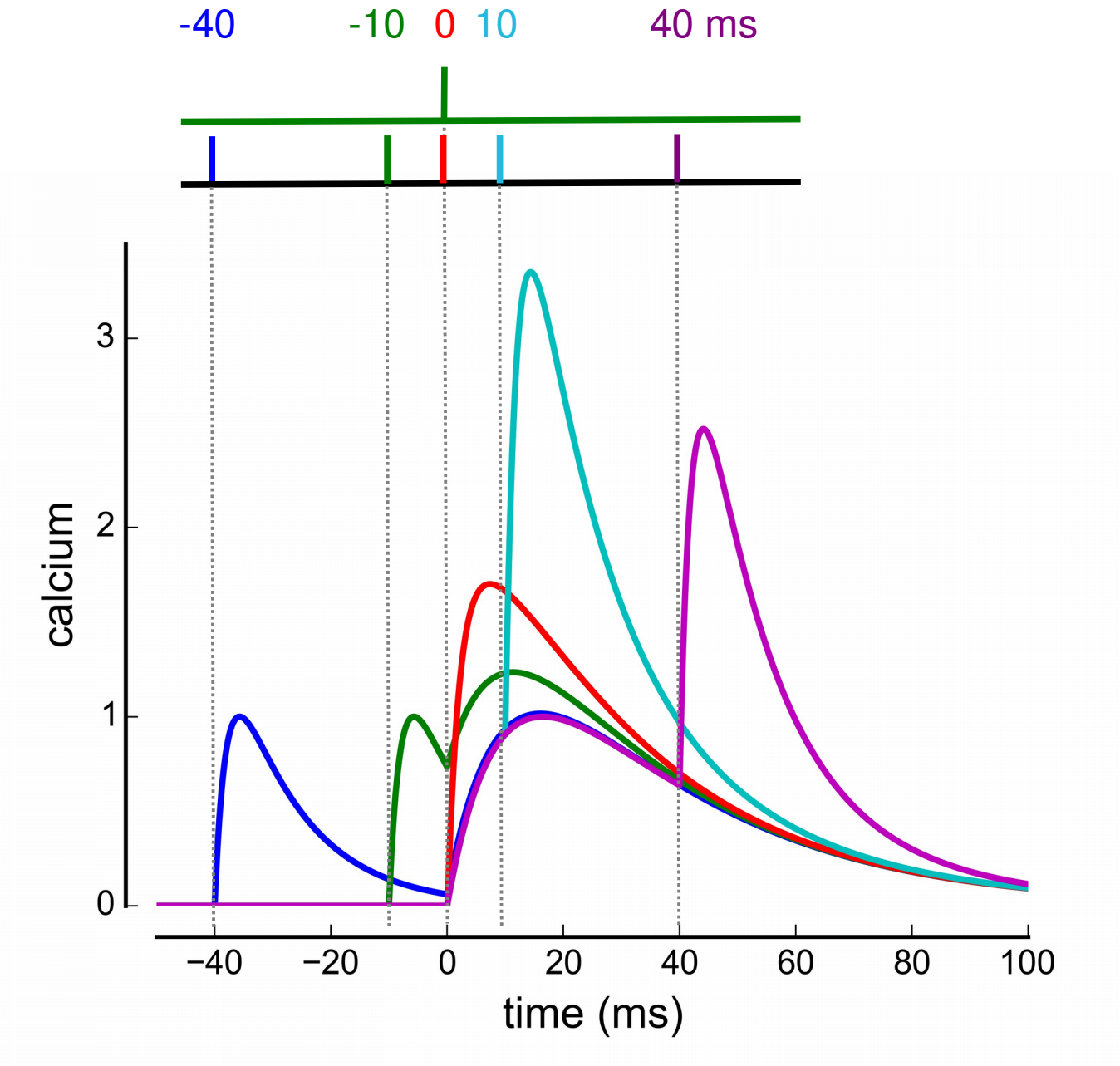
biophysical models of LTP/LTD

- Voltage-based models
  [Clopath *et al.* 2010]
- Ca^{2+} – dynamics based models
  [Karmarkar *et al.*, 2002; Shouval *et al.*, 2002; Rubin *et al.*, 2005; Graupner *et al.* 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]

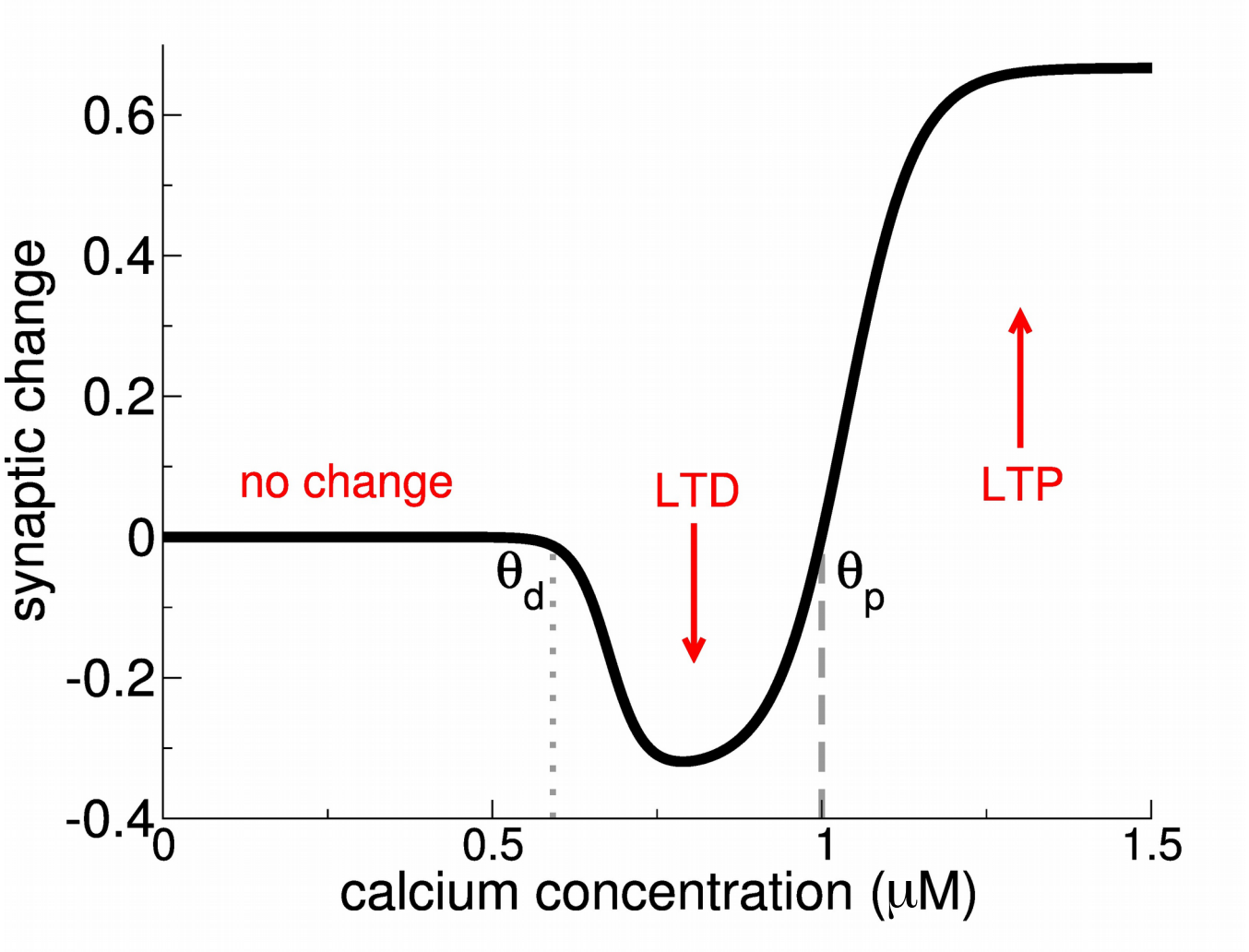
Calcium influx



Calcium transients from spike-pair stimulation

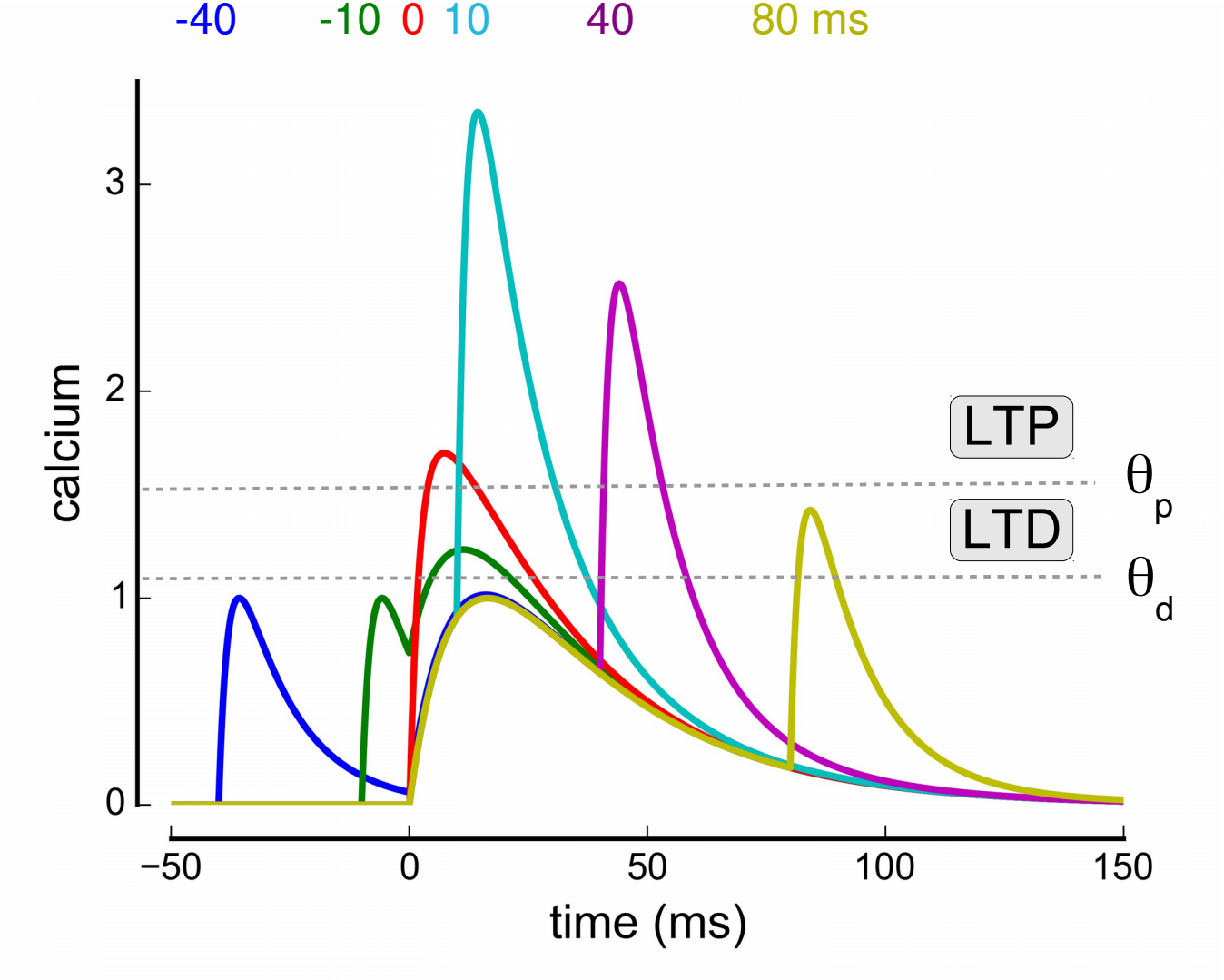


Calcium control hypothesis

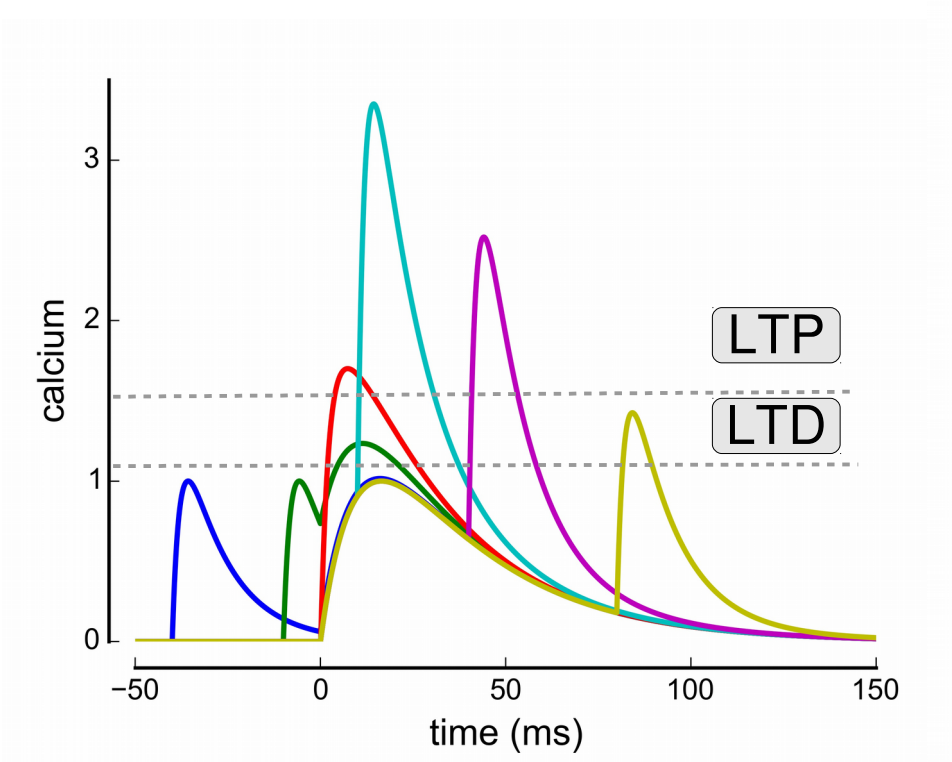


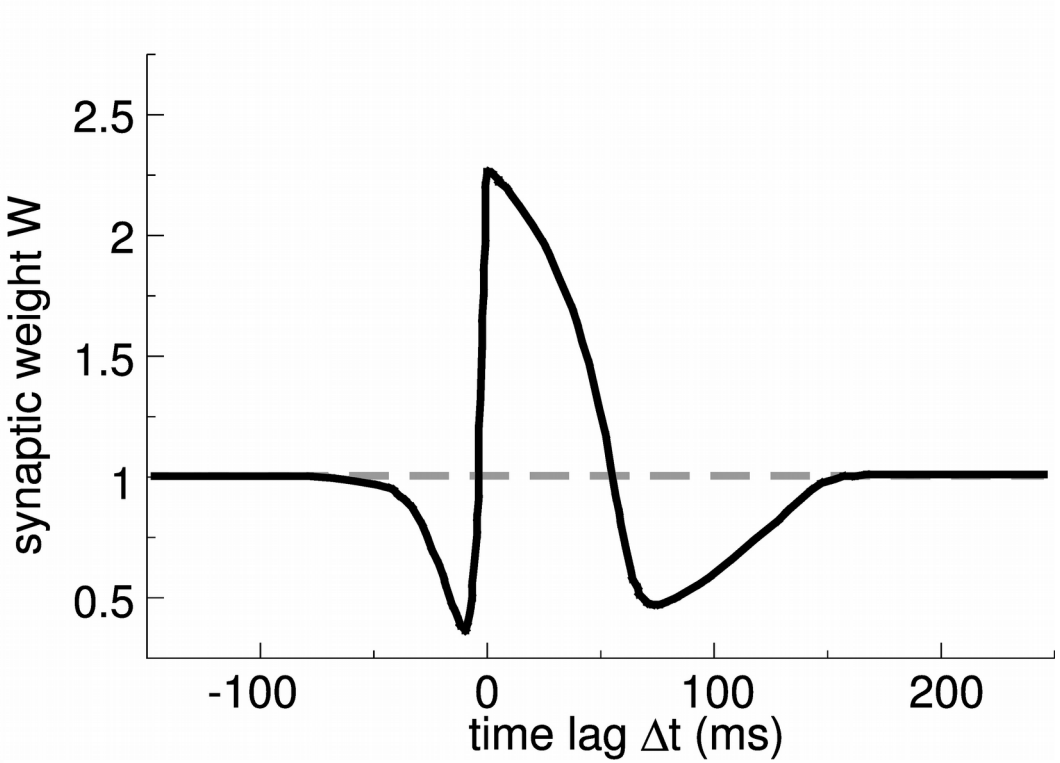
[Shouval *et al.*, 2002]

Calcium transients from spike-pair stimulation



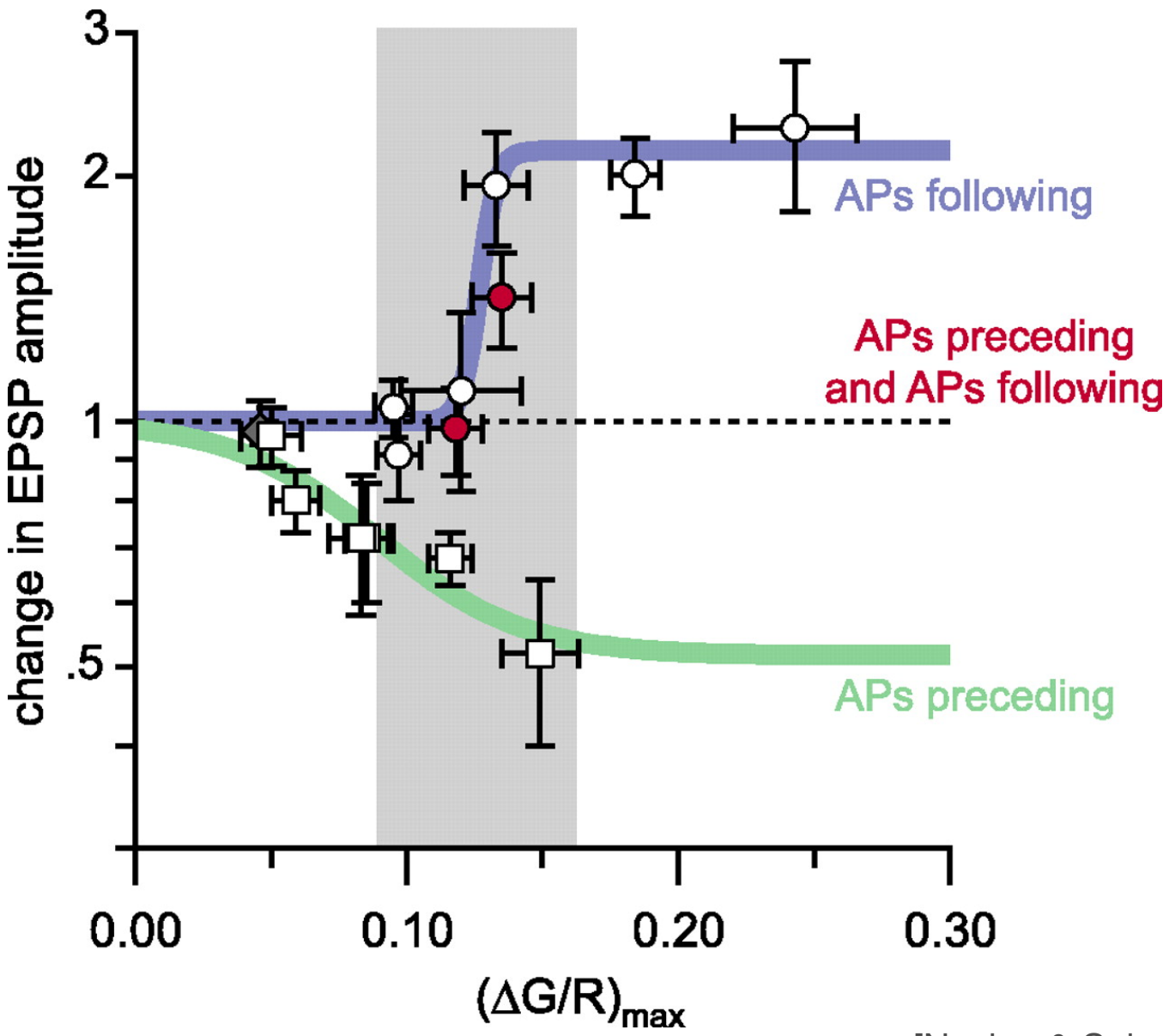
STDP curve





[Shouval *et al.*, 2002]

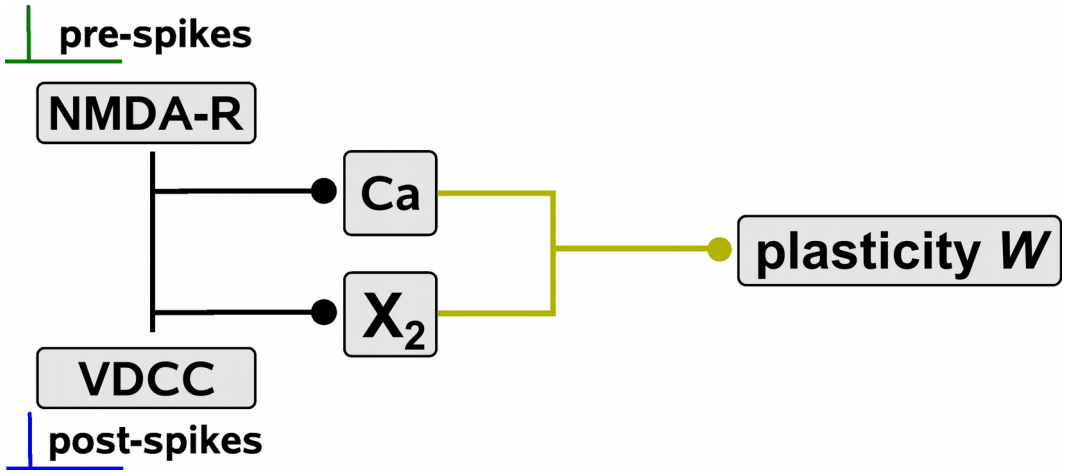
Peak Ca^{2+} amplitude does not predict LTP or LTD



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

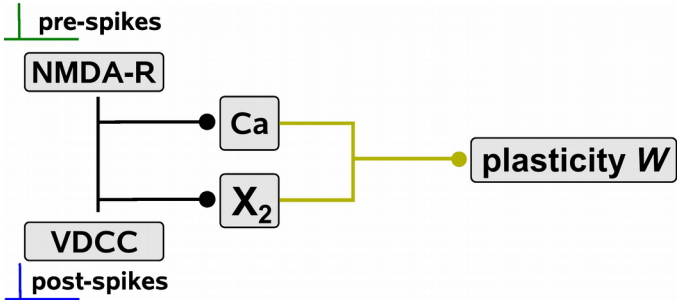
More complex read-out mechanisms of Ca^{2+} signal

- two distinct but converging dynamical variables [Karmarkar *et al.*, 2002; Badoual *et al.*, 2006]

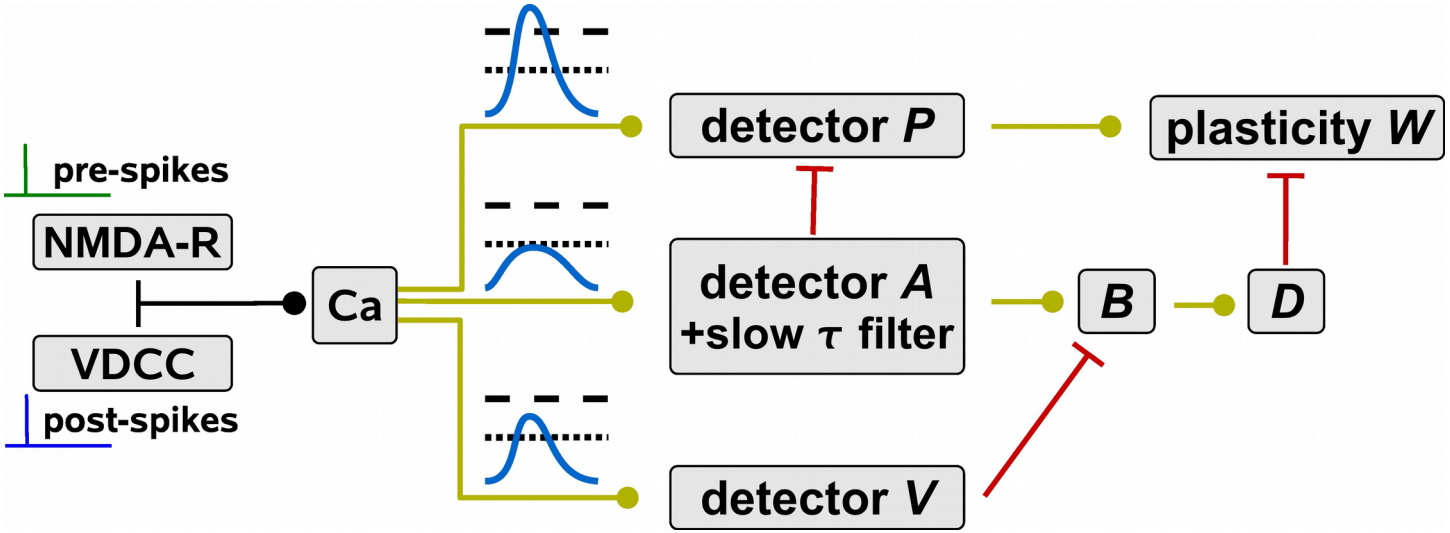


More complex read-out mechanisms of [Ca^{2+}] signal

- two distinct but converging dynamical variables [Karmarkar *et al.*, 2002; Badoual *et al.*, 2006]

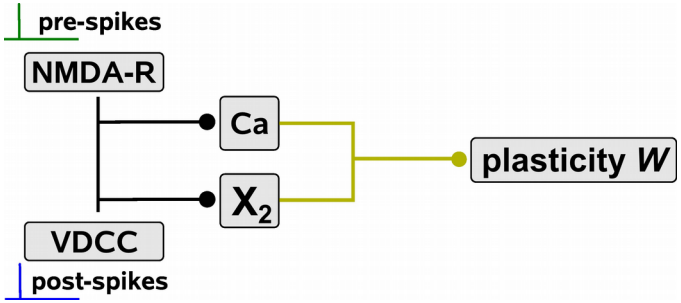


- phenomenological read-out of [Ca^{2+}] [Rubin *et al.*, 2005]

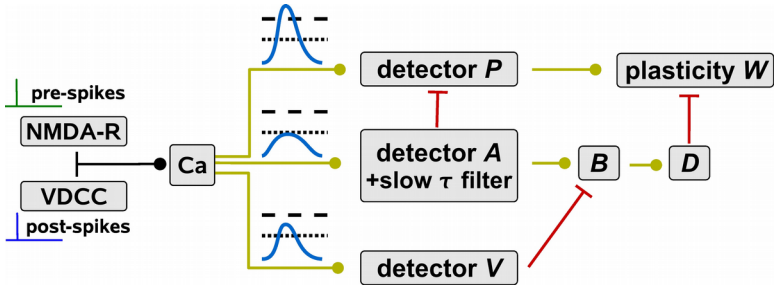


More complex read-out mechanisms of [Ca^{2+}] signal

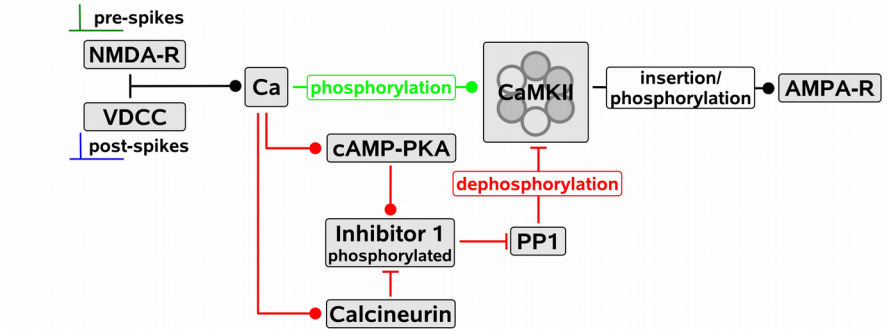
- two distinct but converging dynamical variables [Karmarkar *et al.*, 2002; Badoual *et al.*, 2006]



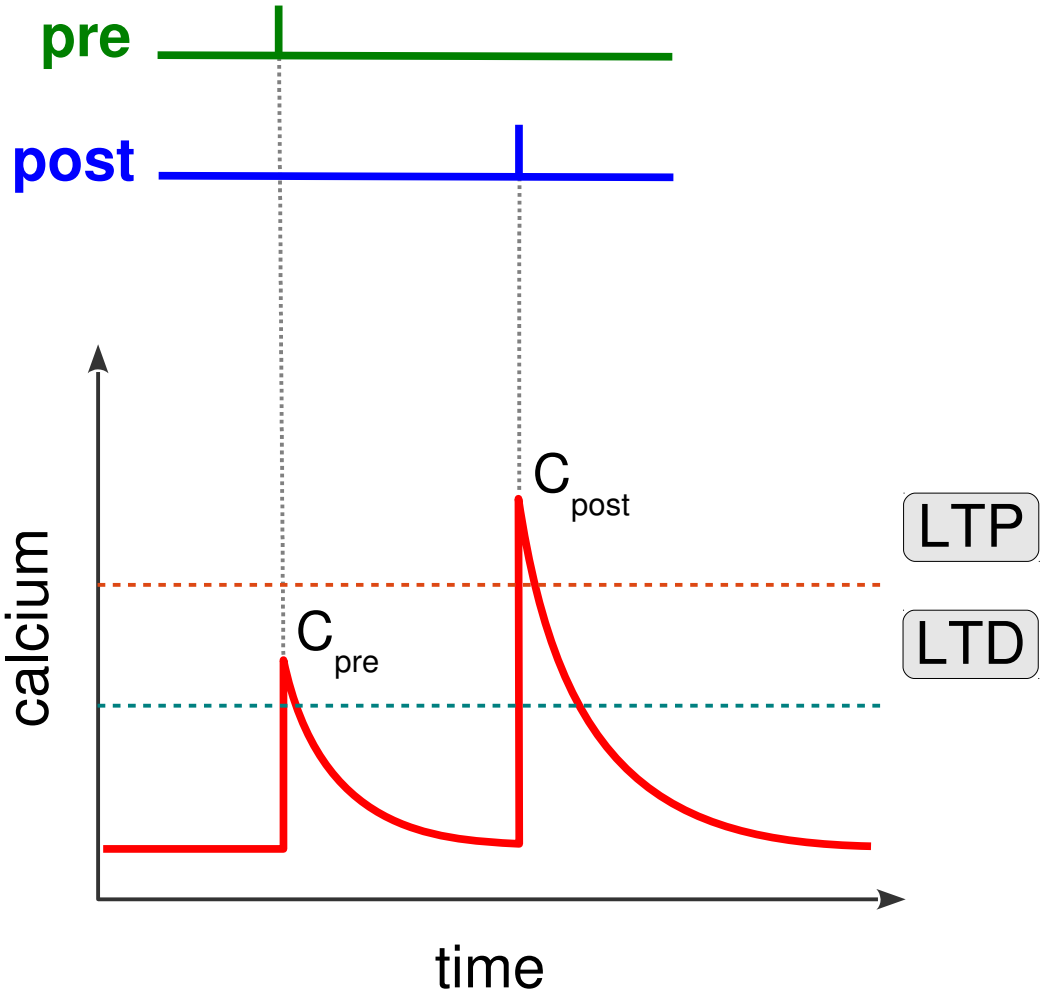
- phenomenological read-out of [Ca^{2+}] [Rubin *et al.*, 2005]



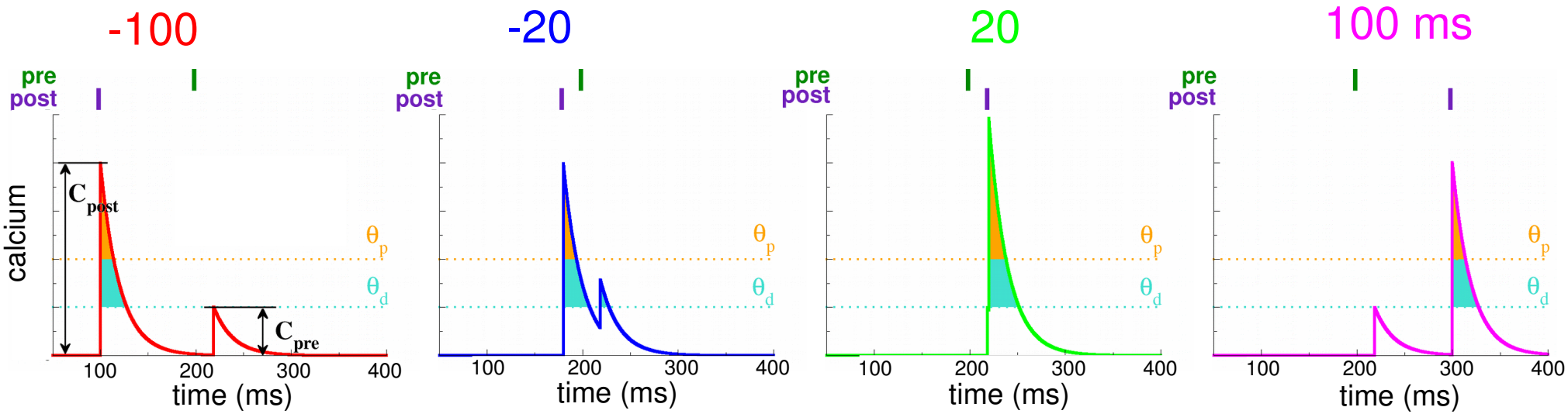
- protein signaling cascade activated by [Ca^{2+}] [Graupner & Brunel, 2007; Urakubo *et al.*, 2008]

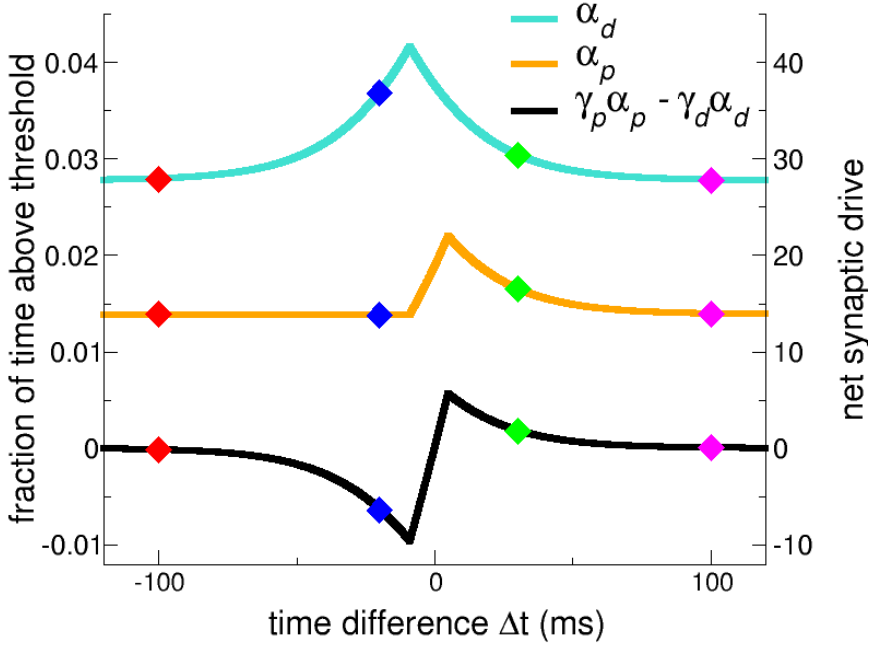


Simplified calcium model

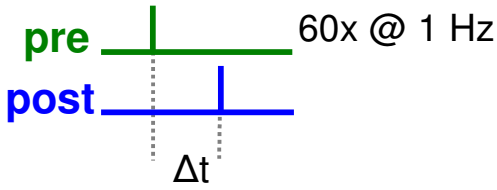


Calcium induced changes : spike-pair stimulation

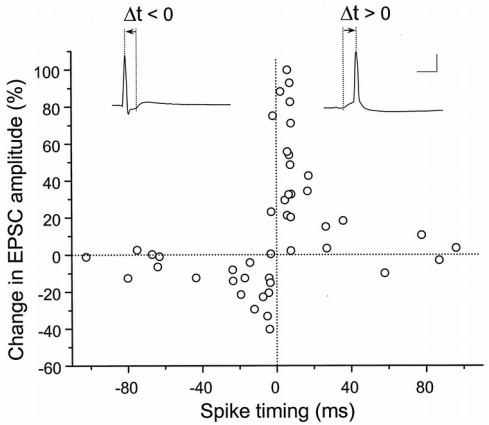


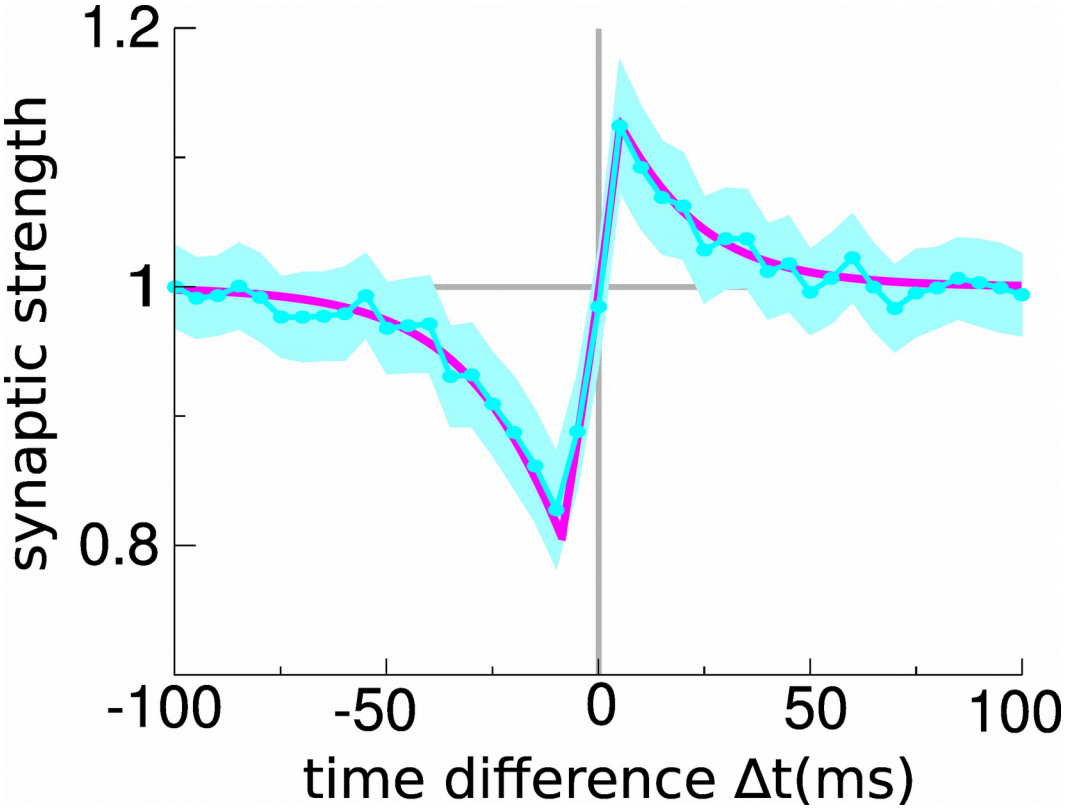


STDP curve in response to spike-pair stimulation



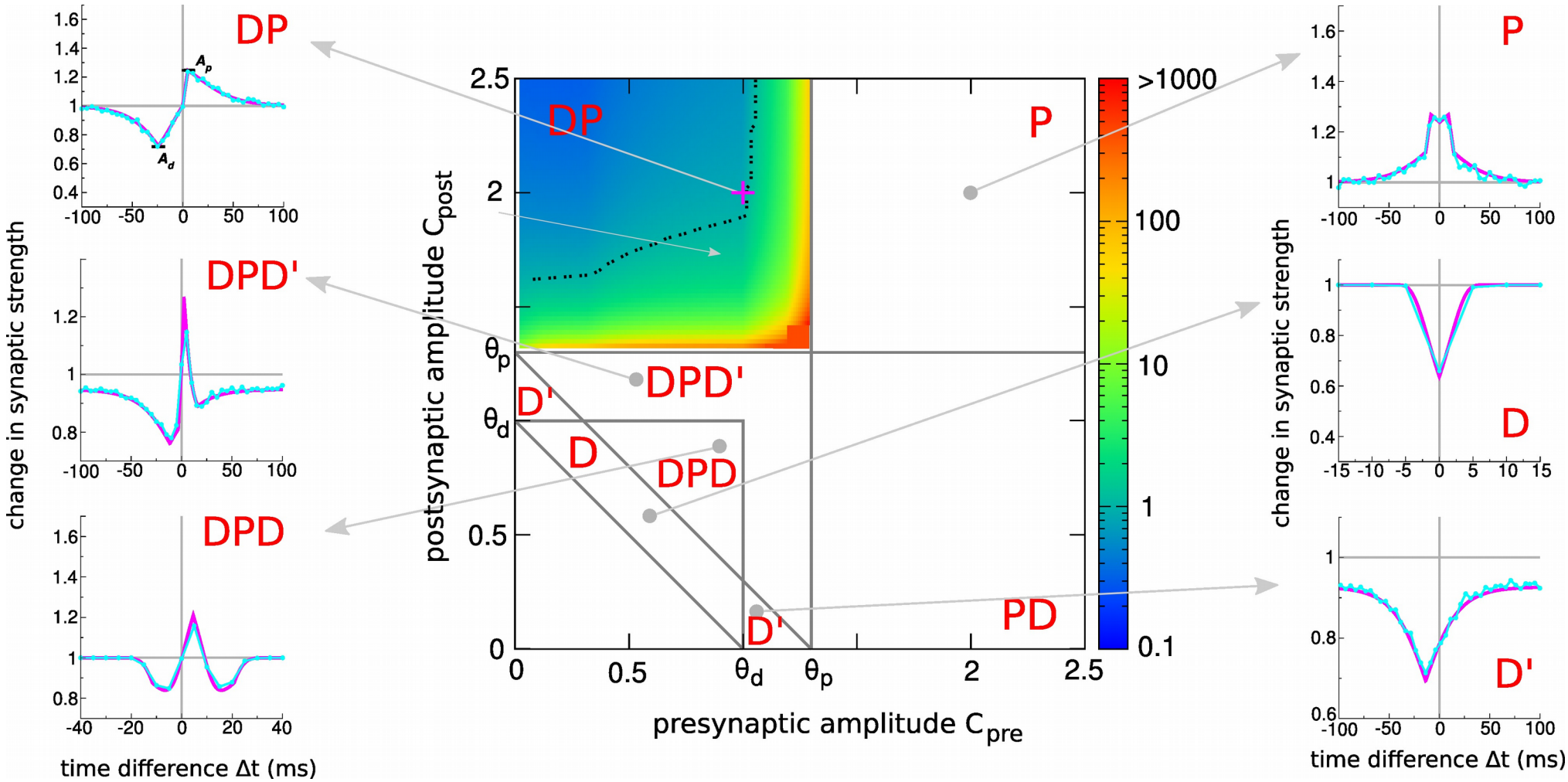
[Bi and Poo, 1998]





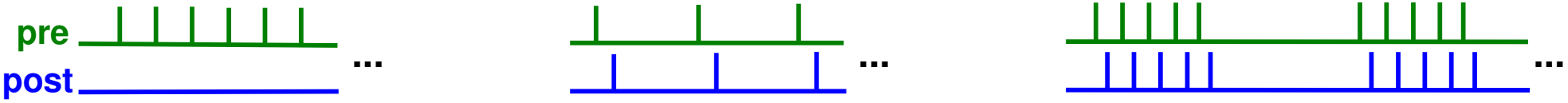
[Graupner & Brunel, 2012]

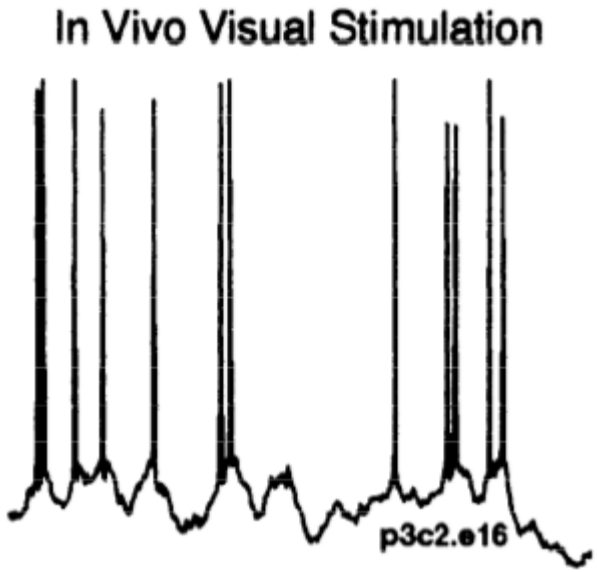
Diversity of STDP curves : spike-pair stimulation



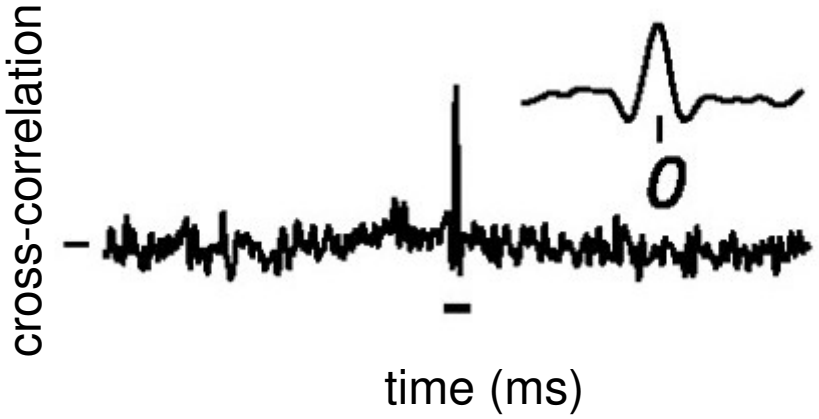
[Graupner & Brunel, 2012]

Plasticity *in vivo* : Realistic firing is highly irregular



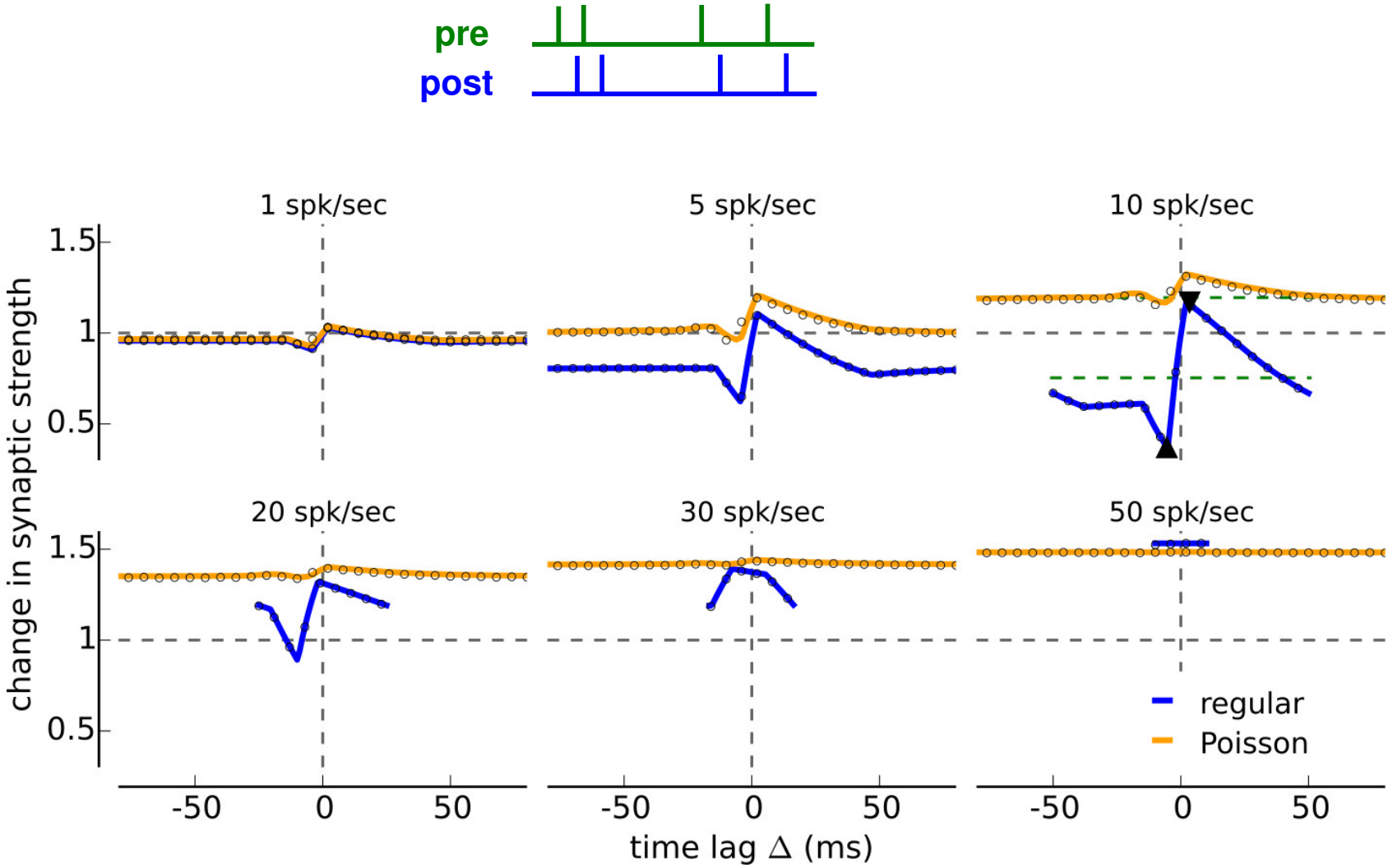


[Holt *et al.*, 1996]



[Kohn and Smith, 2005]

Irregular spike-pairs flatten STDP curve

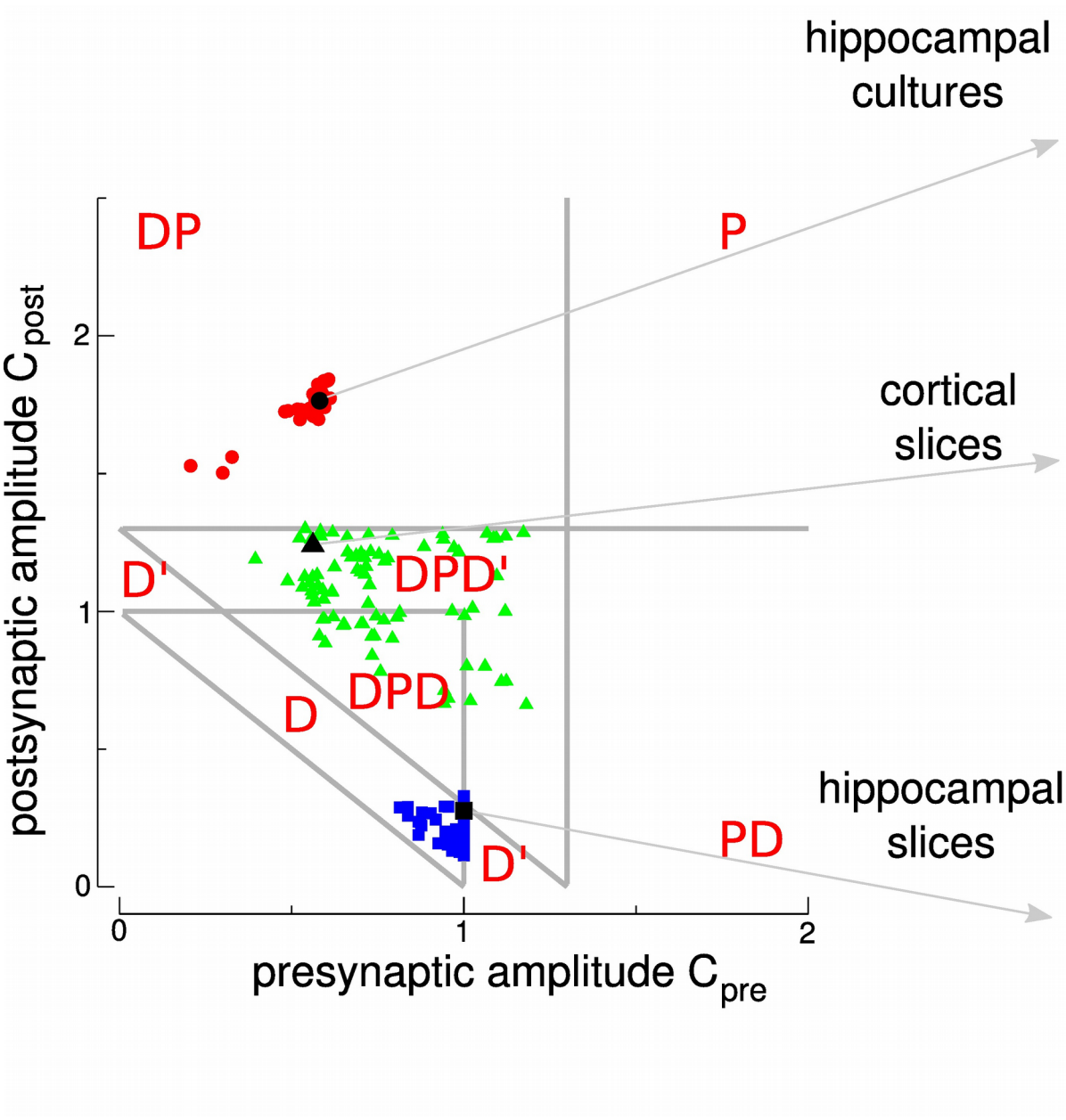


[Graupner et al. *unpublished*]

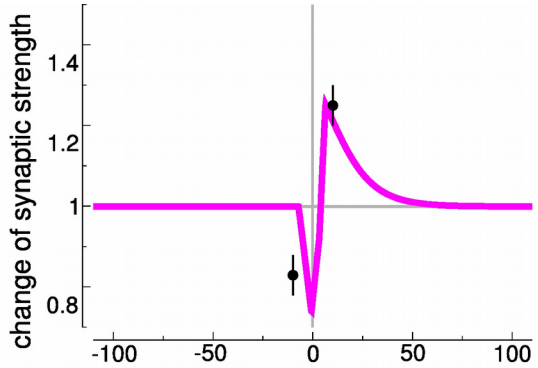
Summary

- synapses can change their transmission efficacy in an activity-dependent manner → LTP / LTD
- 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, *e.g.* the postsynaptic calcium dynamics
- calcium-based plasticity models can account for many aspects of the experimentally observed plasticity phenomenology.

Experiments explained by different parameter sets

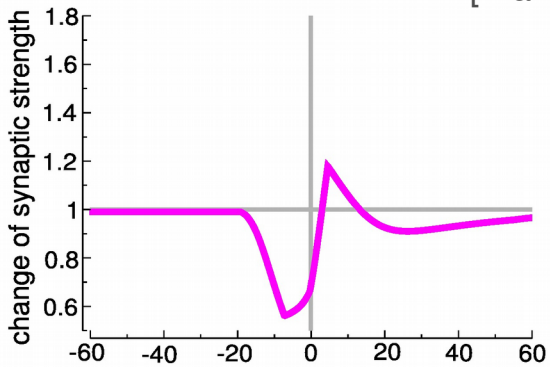


hippocampal cultures



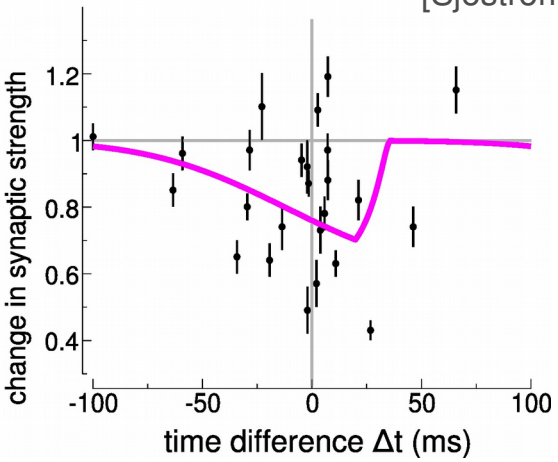
[Wang *et al.*, 2005]

cortical slices



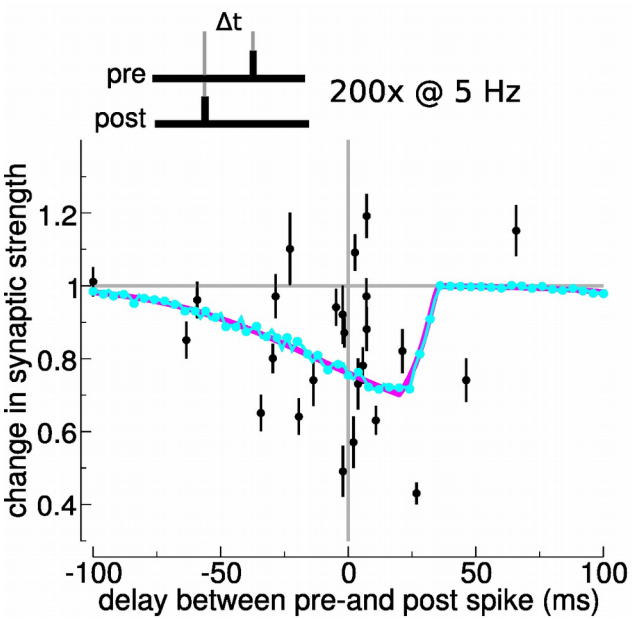
[Sjöström *et al.*, 2006]

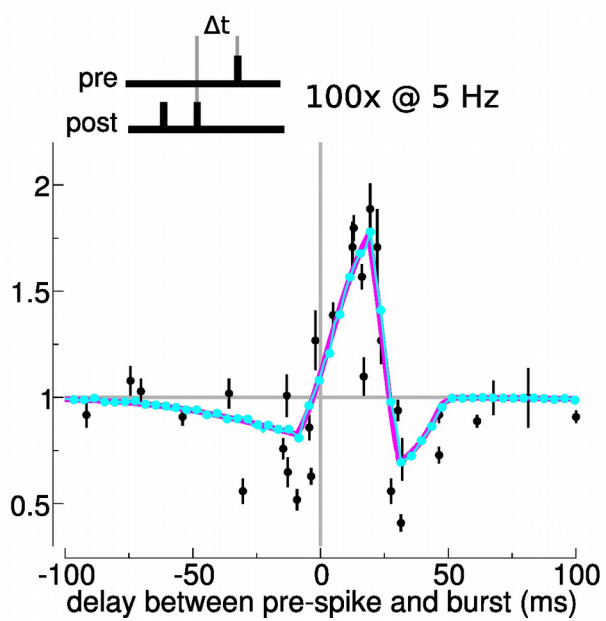
hippocampal slices

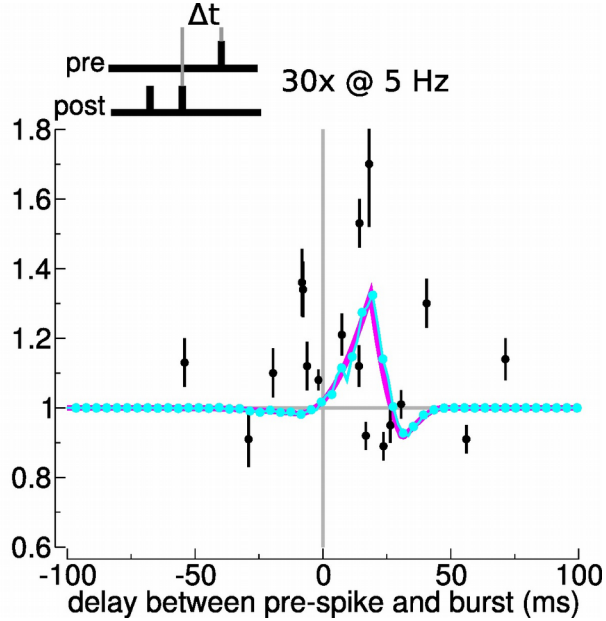


[Wittenberg & Wang, 2006]

Malleability of hippocampal STDP explained by Ca^{2+}

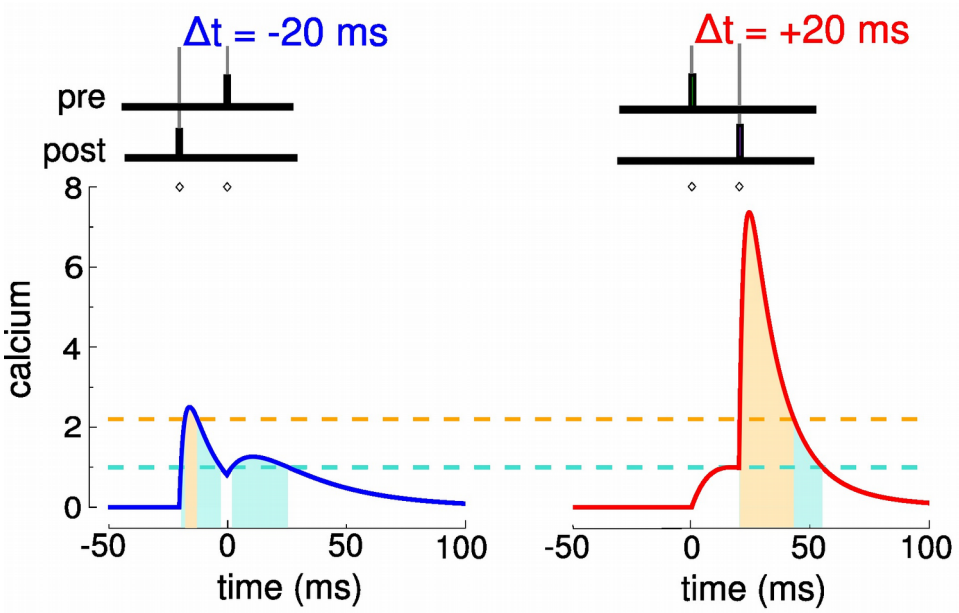


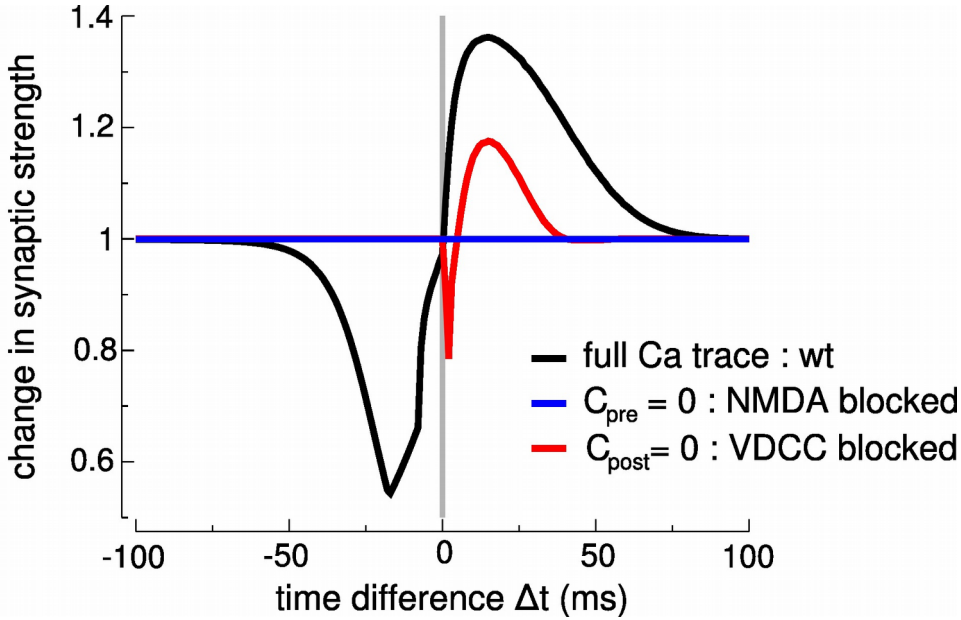




[Wittenberg & Wang, 2006]

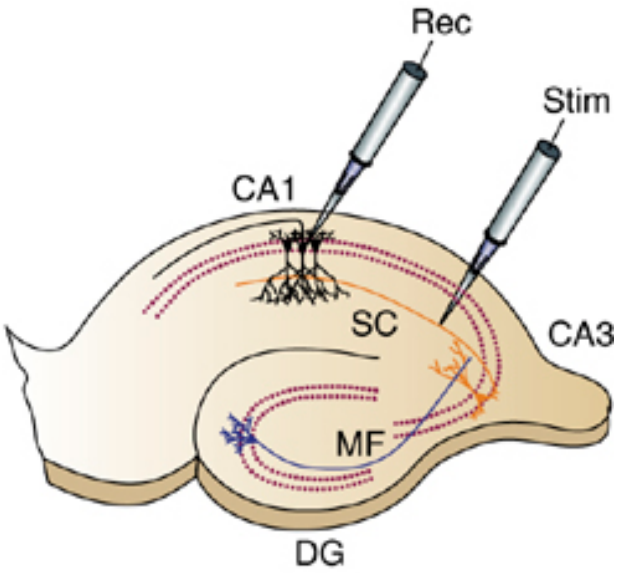
Pharmacological manipulations explained by Ca^{2+}



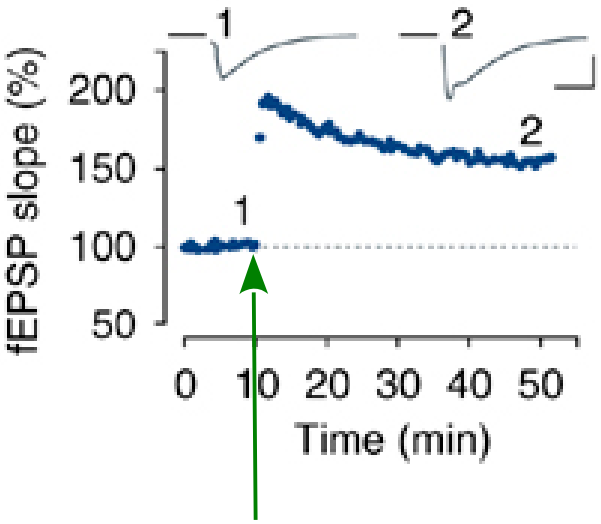


[Bi & Poo, 1998; Nevian & Sakmann, 2006]

- nonlinear, finite rise time calcium transients necessary to reproduced pharmacological block experiments

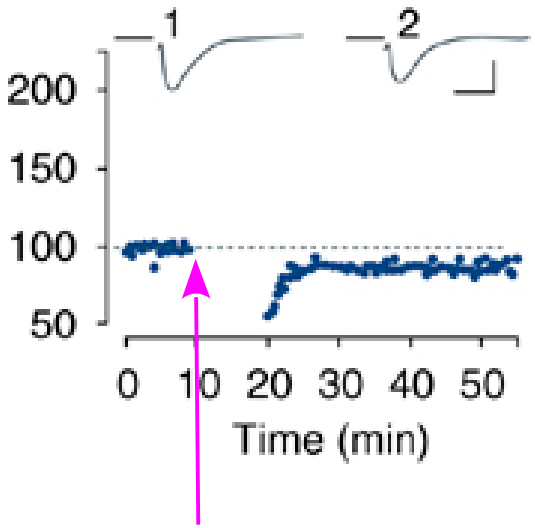


long-term potentiation
LTP



100 Hz for 1 s

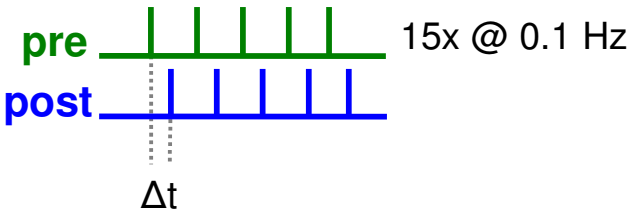
long-term depression
LTD

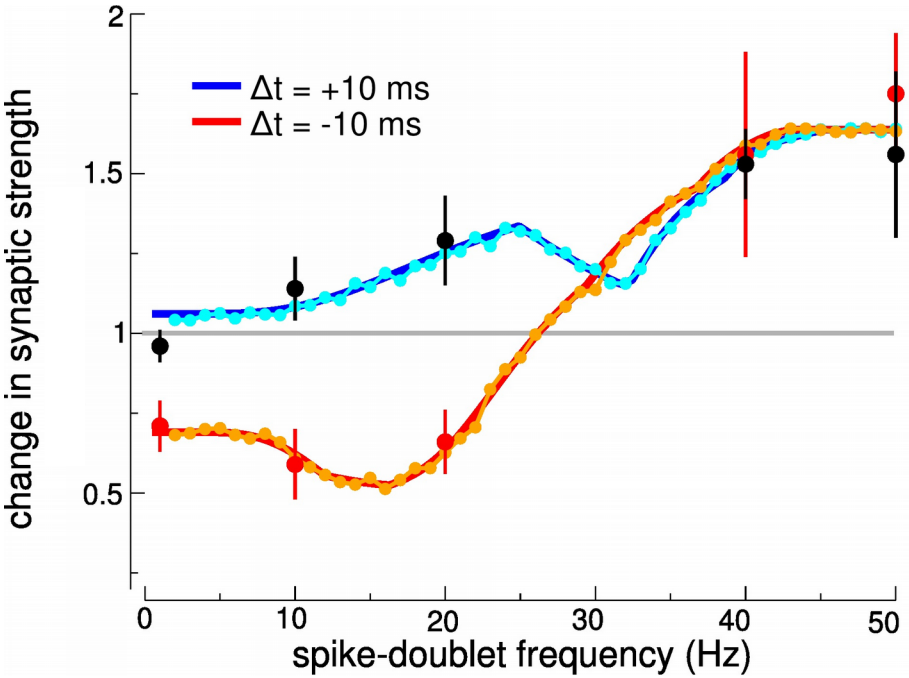


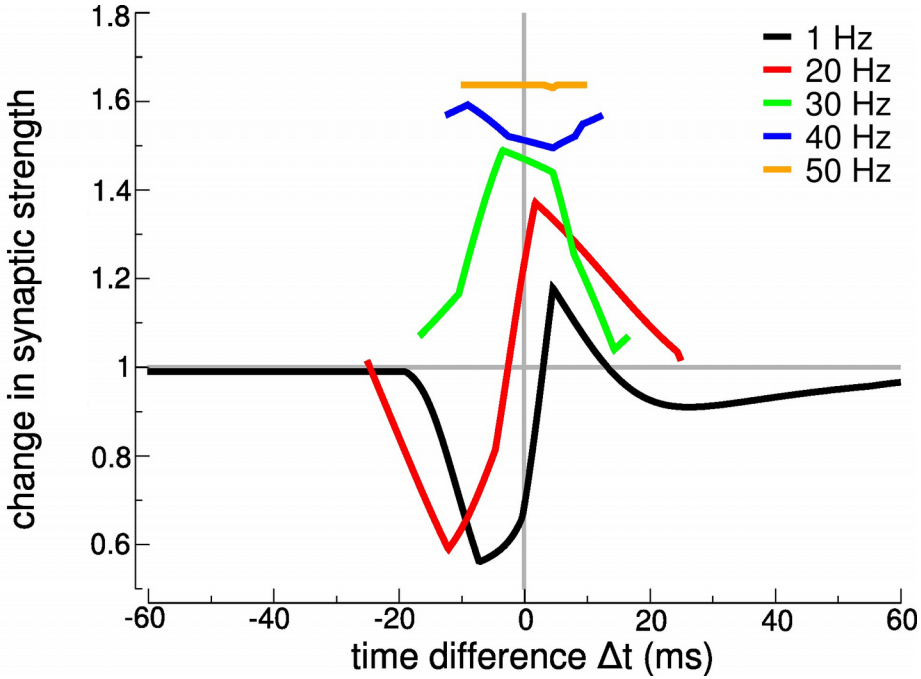
2x 5 Hz for 3 min,
3 min interval

[Morishita *et al.*,2005]

Firing rate dependence in cortical slices

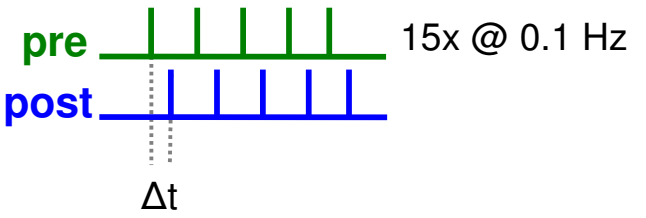


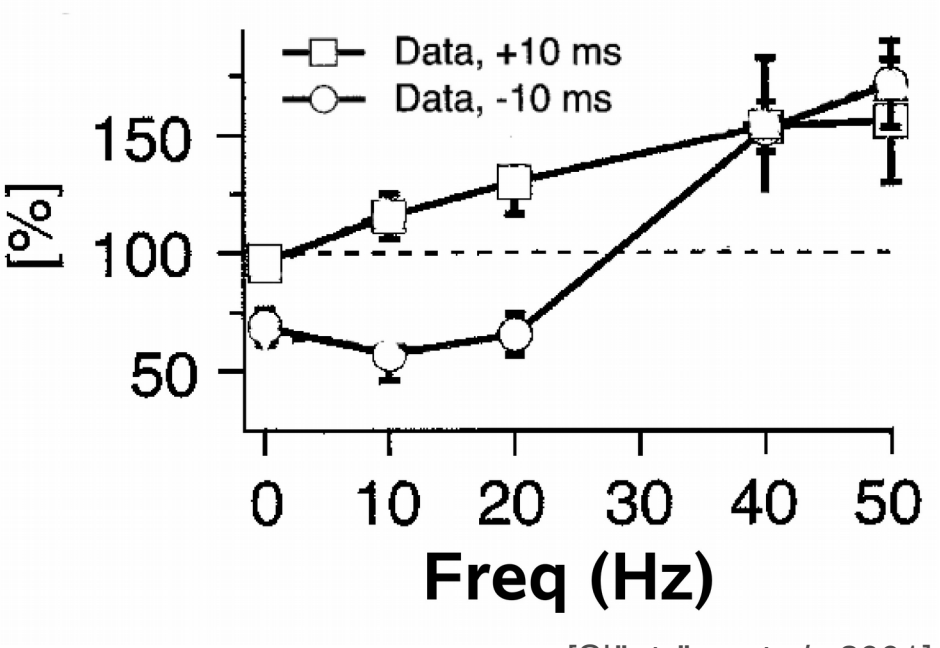




[Sjöström *et al.*, 2001]

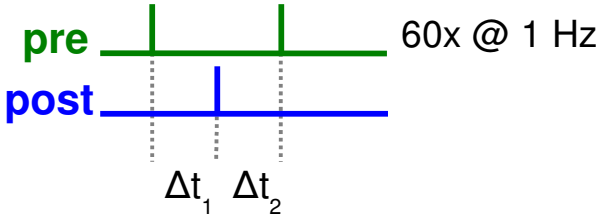
spike-pair & frequency

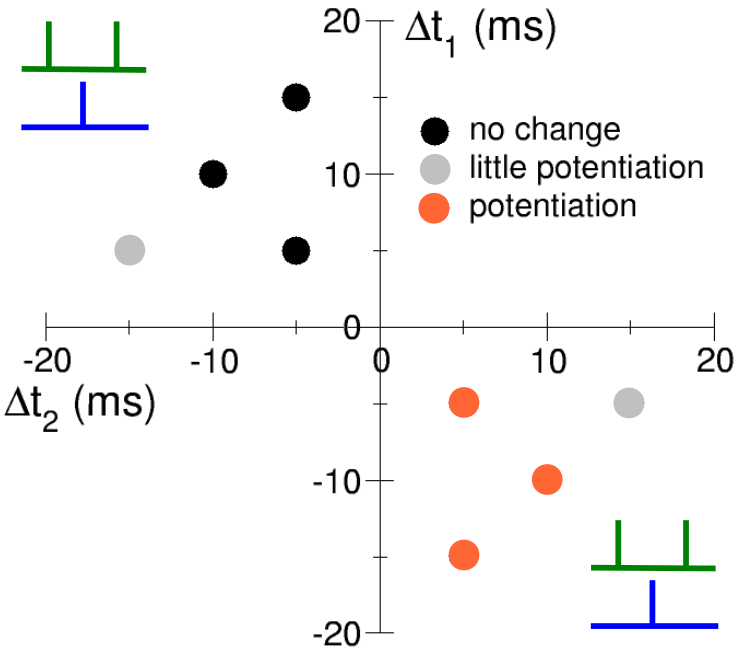




[Sjöström *et al.*, 2001]

spike - triplets





[Wang *et al.*, 2005]