1c. Modeling brain plasticity: *Biophysical models of synaptic plasticity*

Oct 24th, 2014

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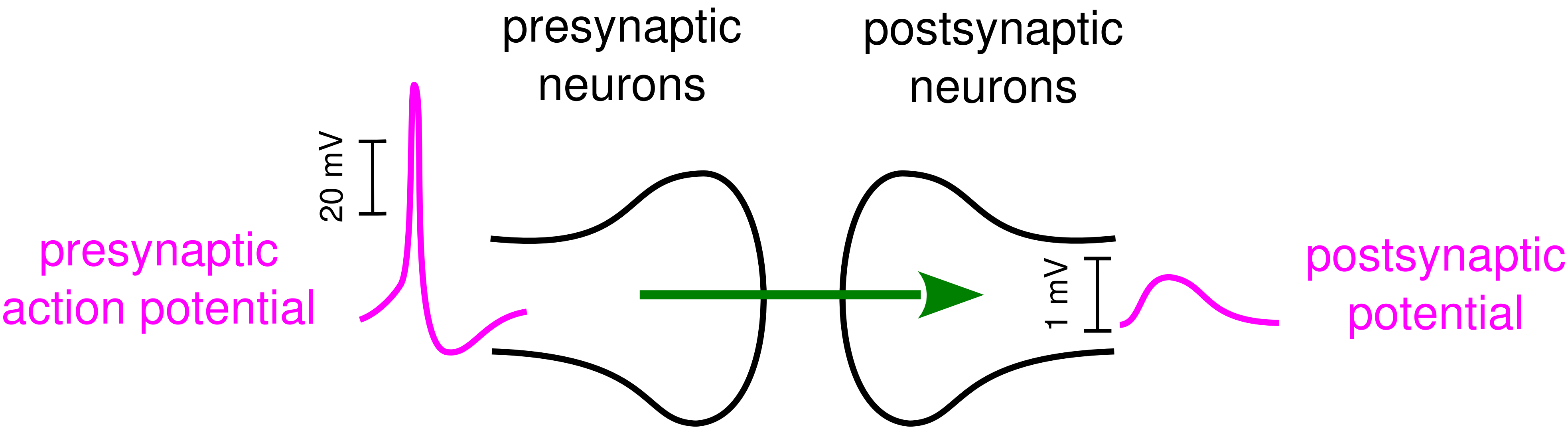
http://www.biomedicale.univ-paris5.fr/~mgraupe/brain_plasticity/

Outline

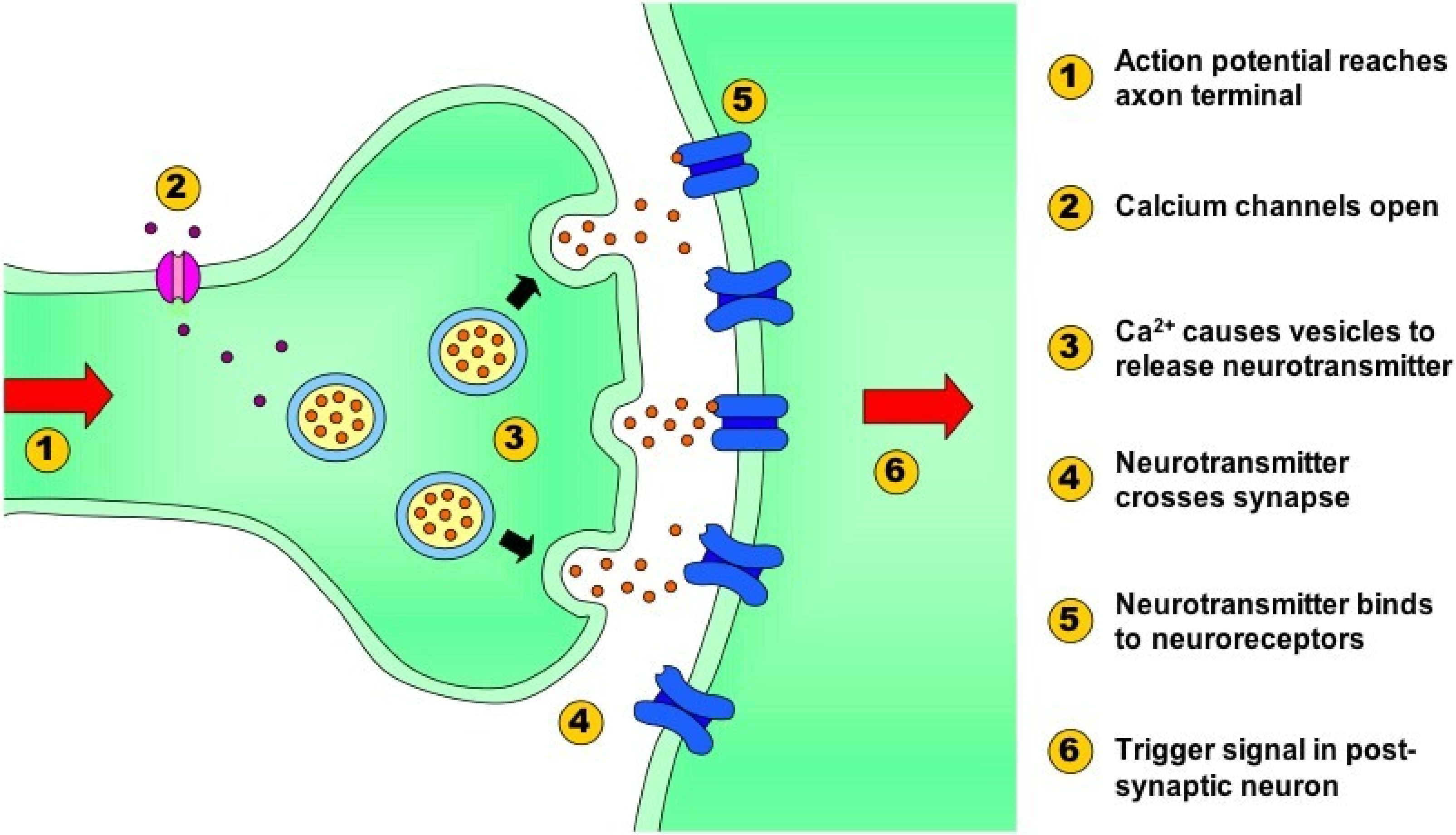
Chemical synapse : transmits electrical signals



electrical signal → chemical signal → electrical signal

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

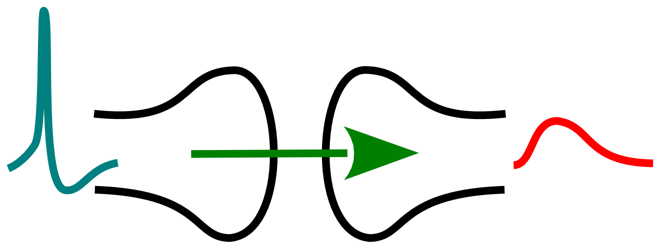
Chemical synapse : underlying biological machinery



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

Chemical synapse : excitatory or inhibitory

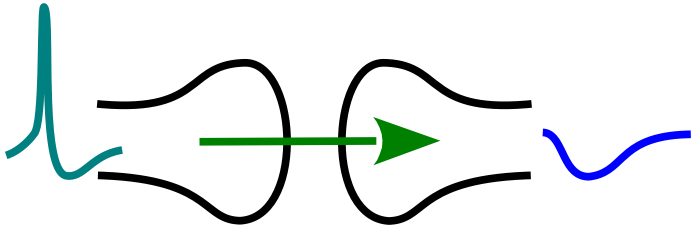
Excitatory synapse



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

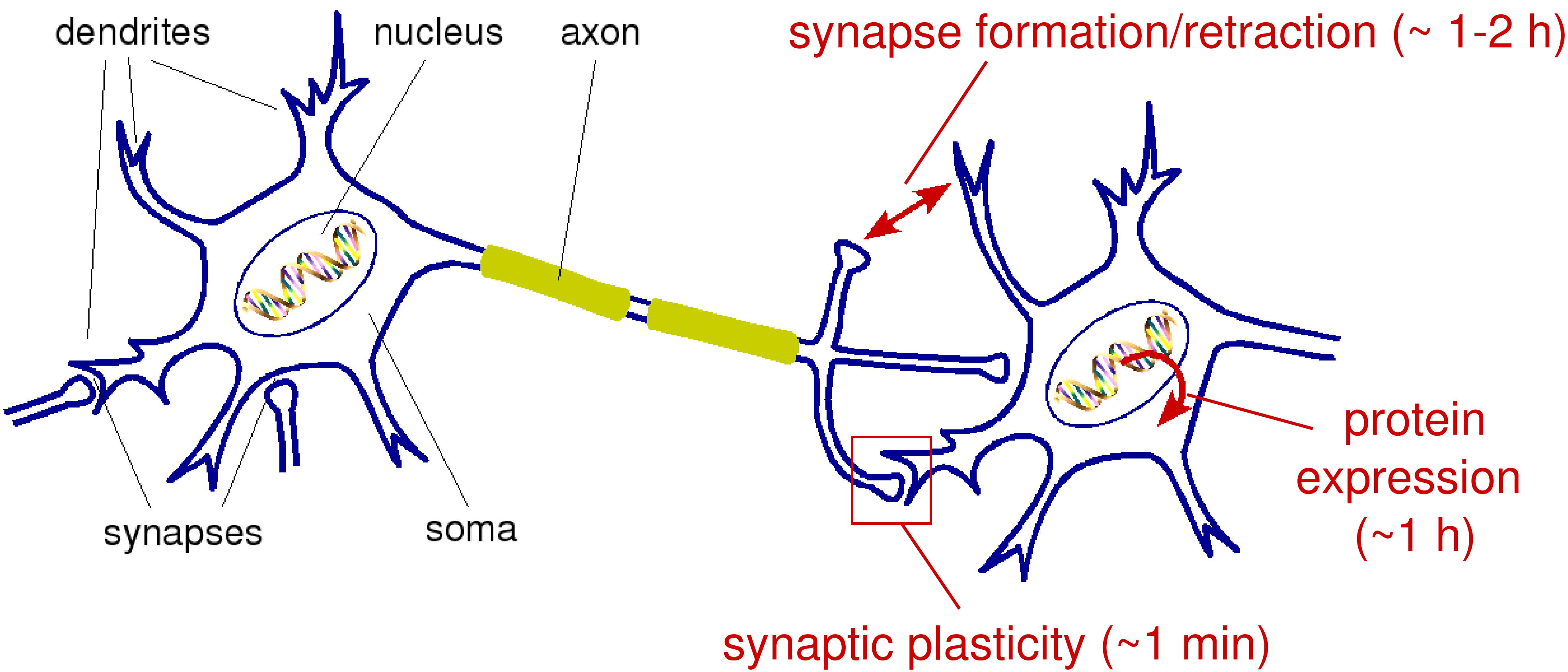


hyperpolarization:
Inhibitory postsynaptic potential (IPSP)

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

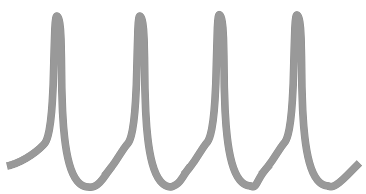
Different forms of plasticity

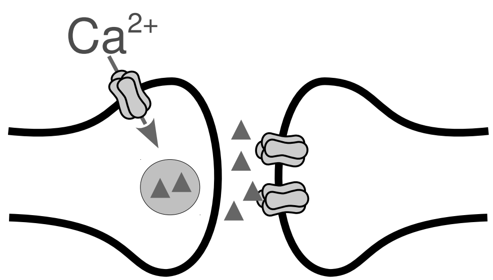
structure of neurons **changes related to neural activity**

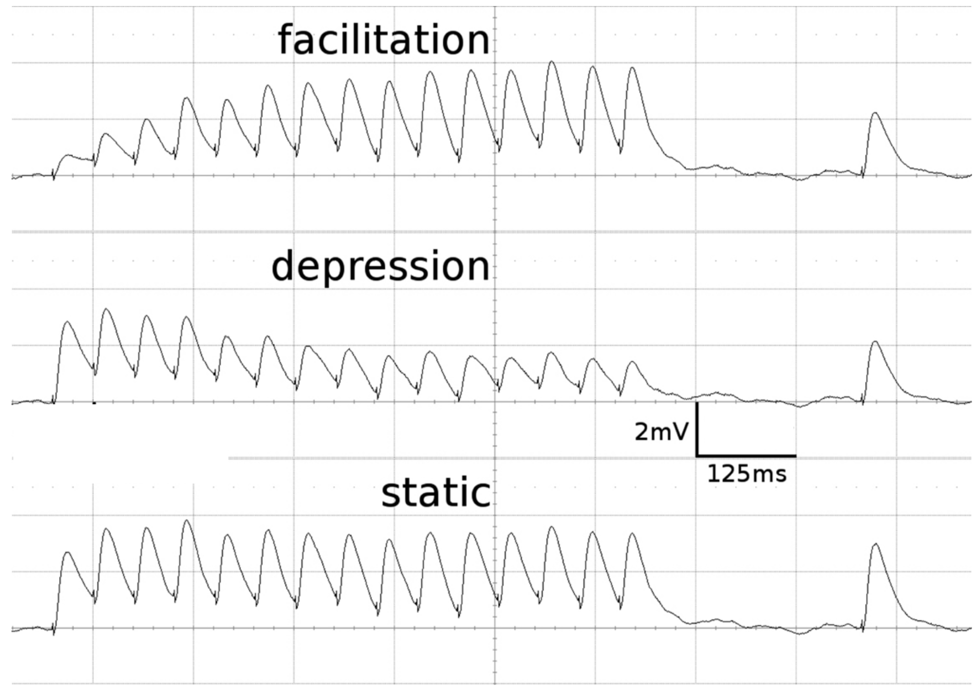


Short-term synaptic plasticity

train of presynaptic action potentials

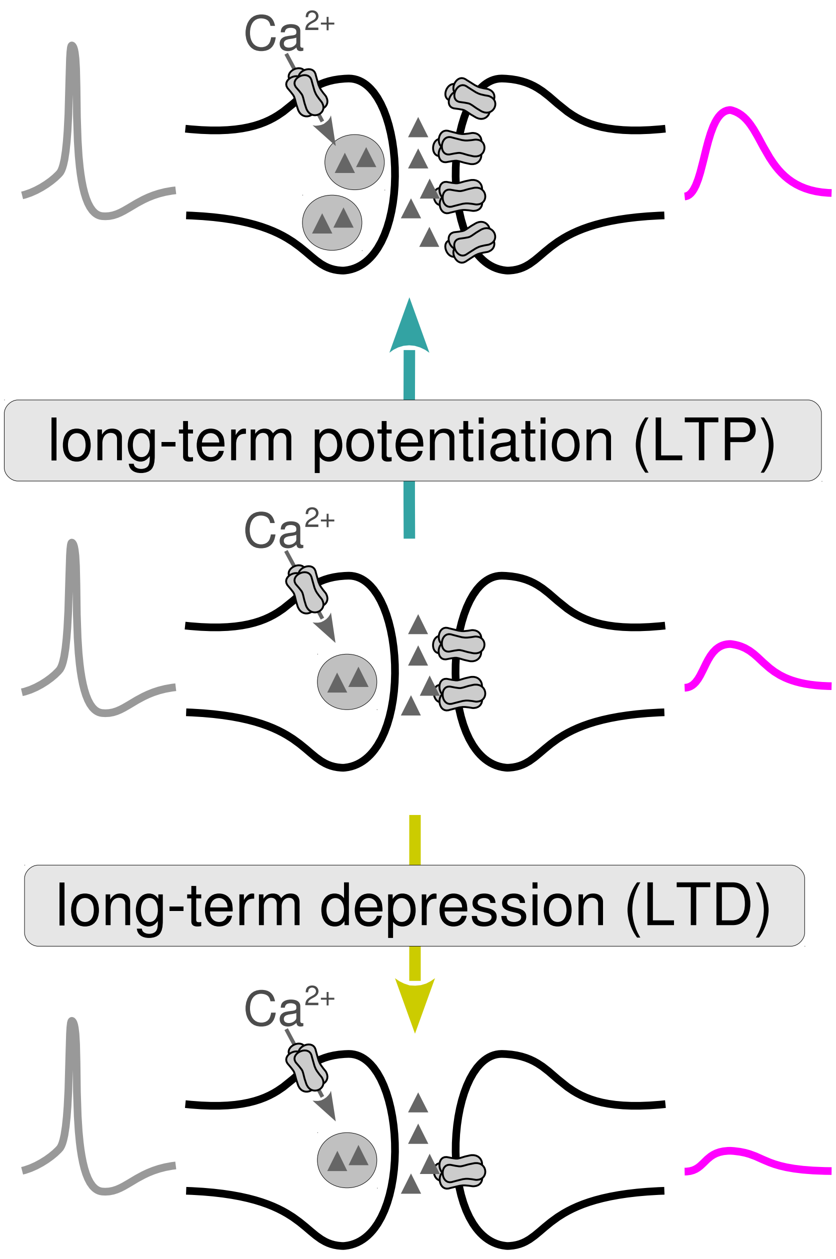






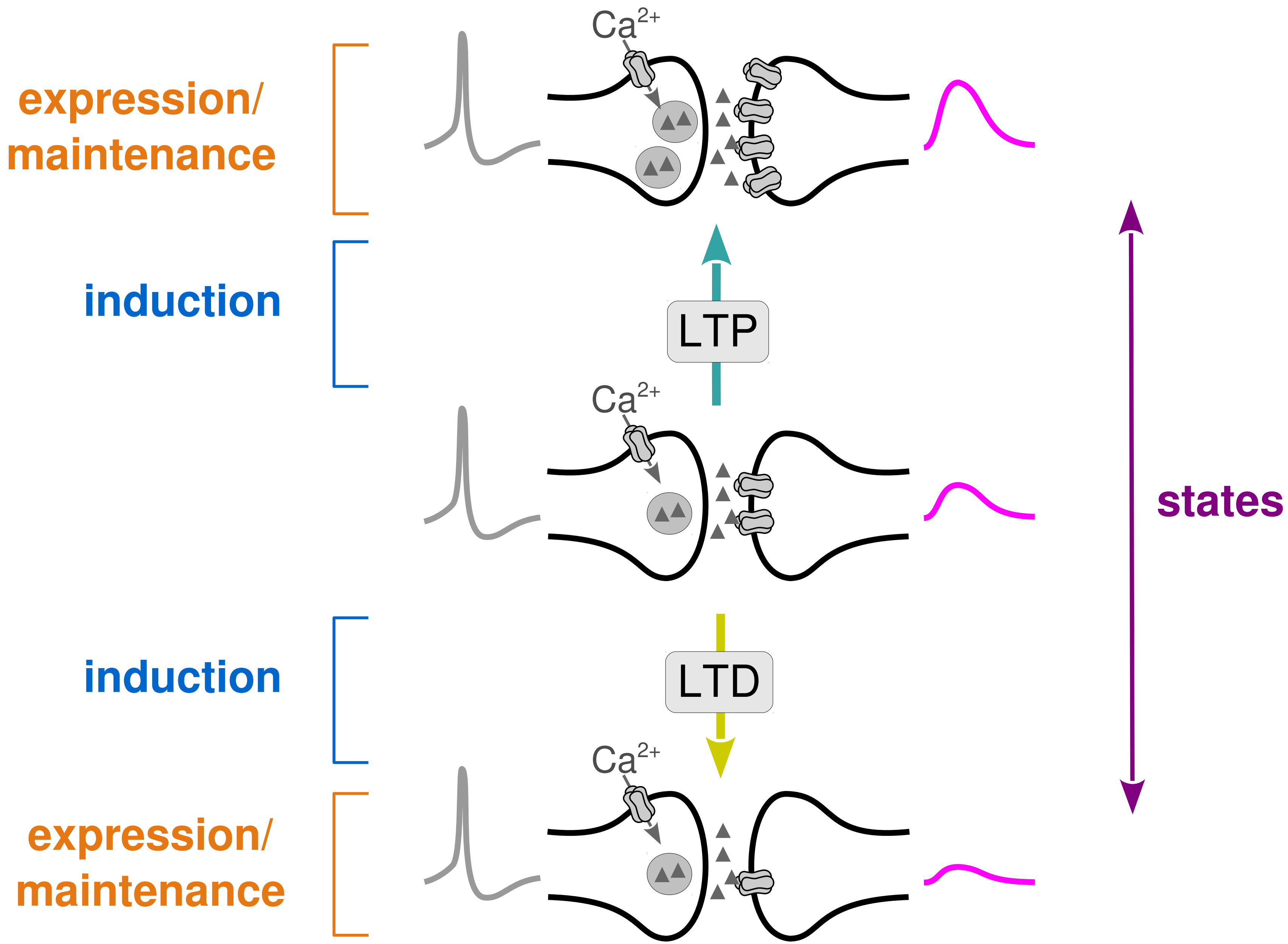
- transient change in transmission efficacy
- time scale of changes ~1 sec

Long-term synaptic plasticity



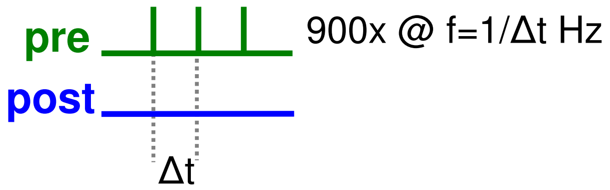
- long-lasting change (>60 min) in transmission efficacy
- time scale of induction ~ 1 min

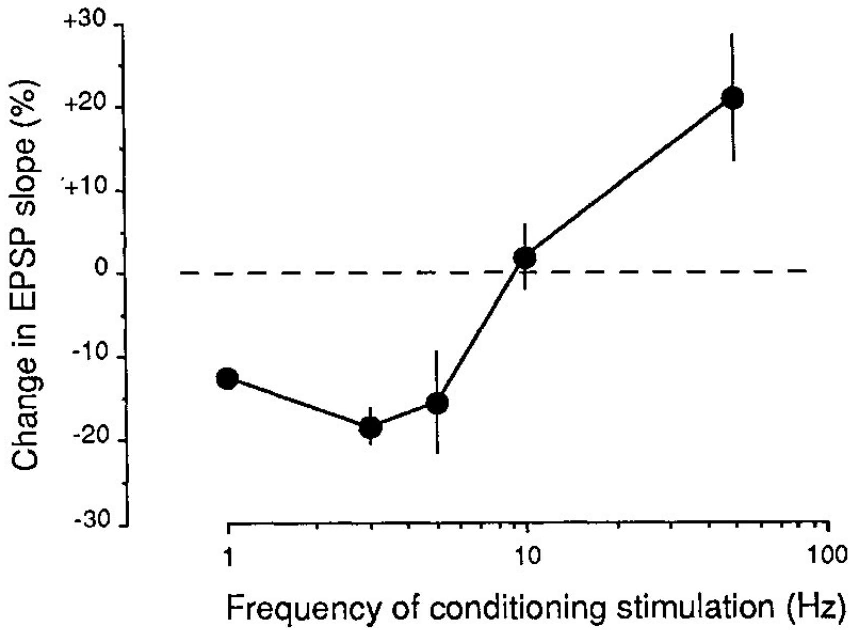
Synaptic plasticity: induction, maintenance & states



Induction: Stimulation protocols evoking LTP/LTD

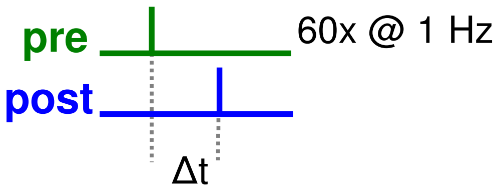
spike-frequency

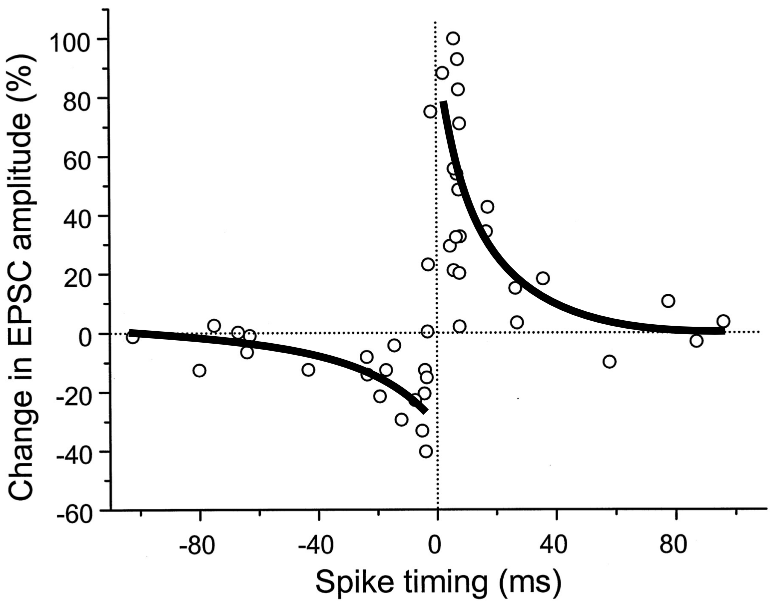




[Dudek *et al.*, 1992]

spike-timing

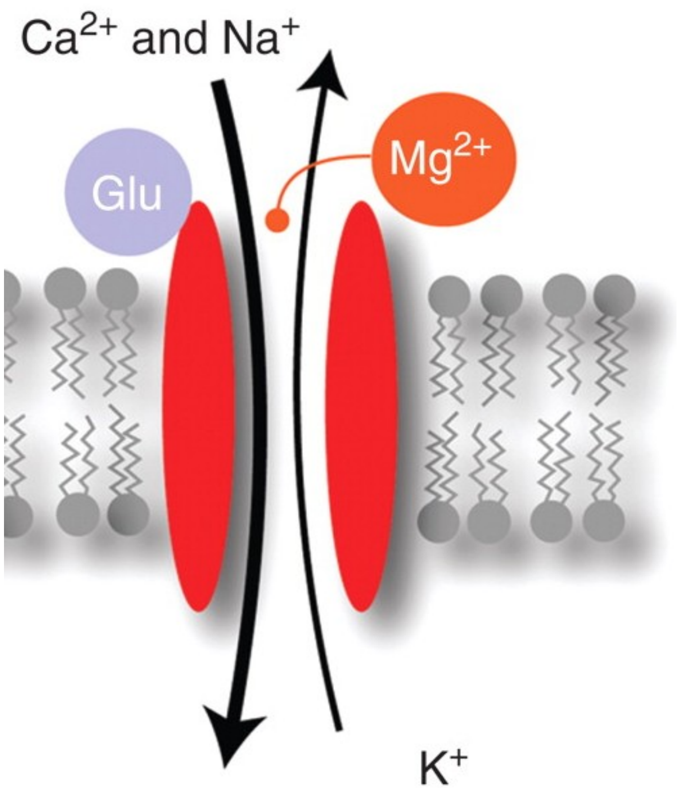




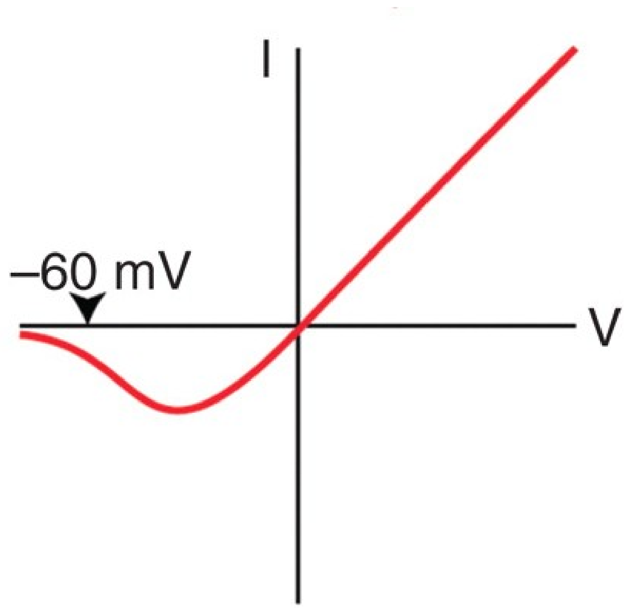
[Bi & Poo, 1998]

Induction: postsynaptic NMDA receptor activation required

NMDA receptor



current-voltage relationship



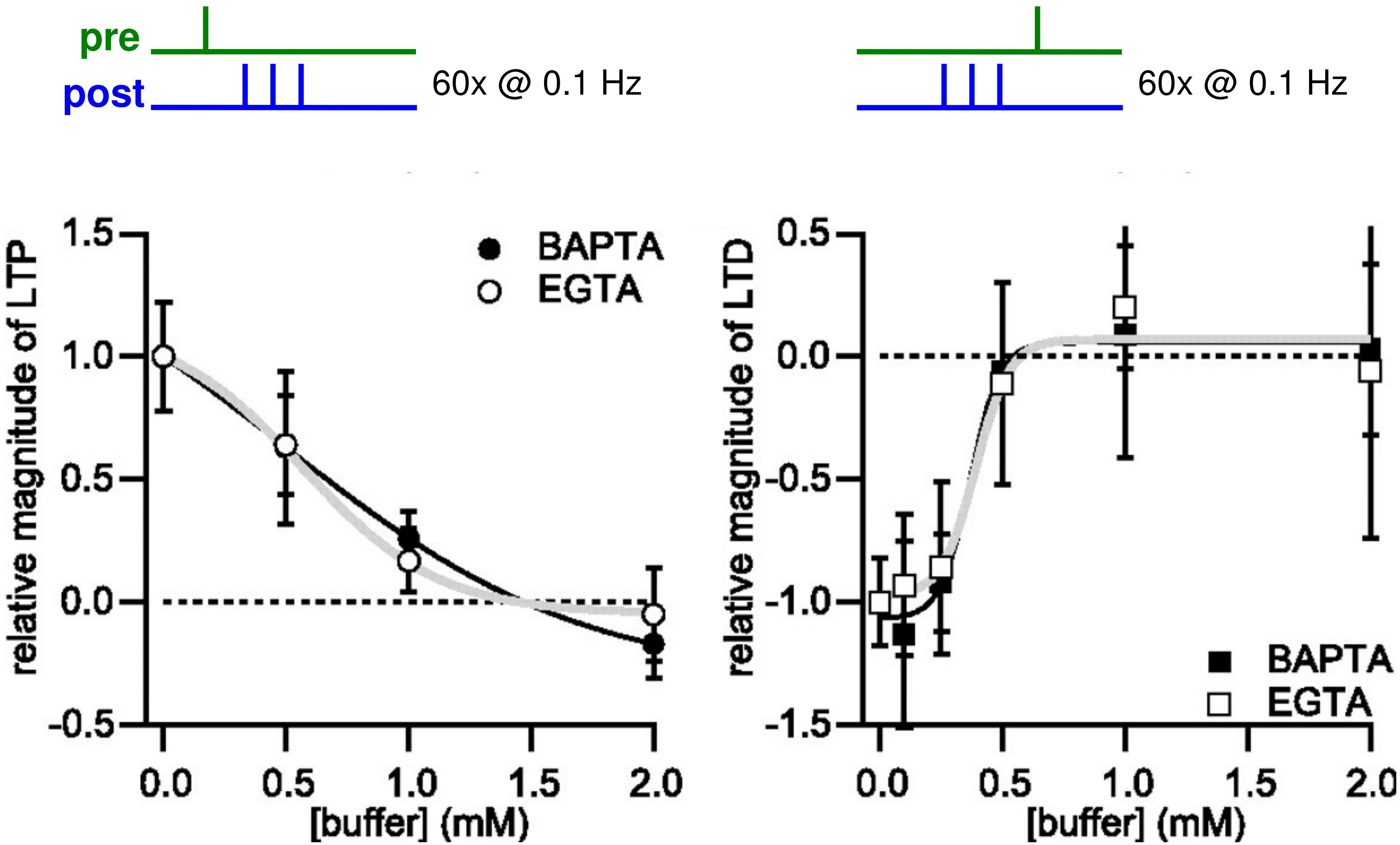
- coincidence detector :

  presynaptic action potential → glutamate (Glu)

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

- calcium permeable

Postsynaptic calcium *required* for plasticity

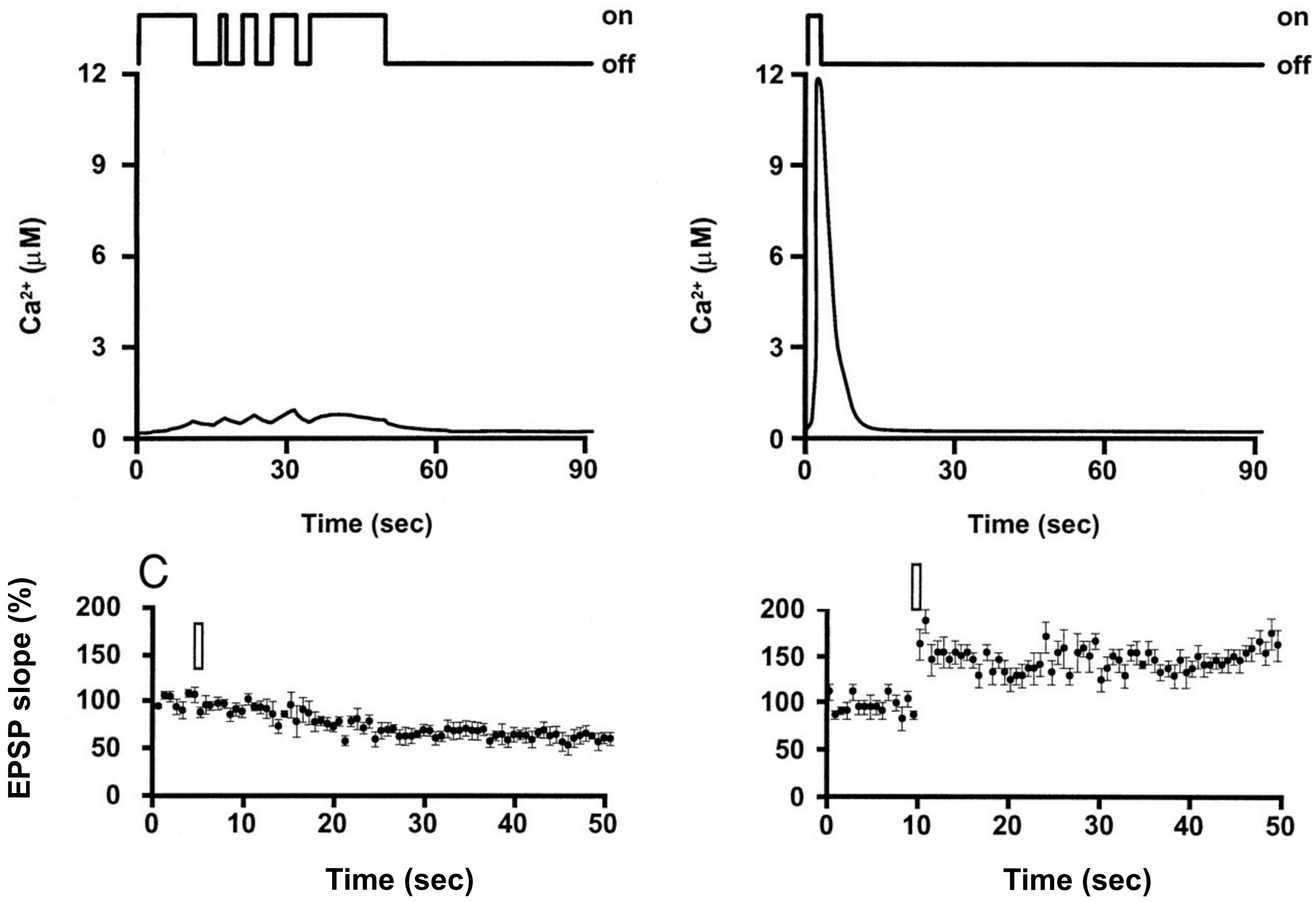


[Nevian & Sakmann *et al.*, 2006]

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

Postsynaptic calcium *sufficient* for plasticity

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



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

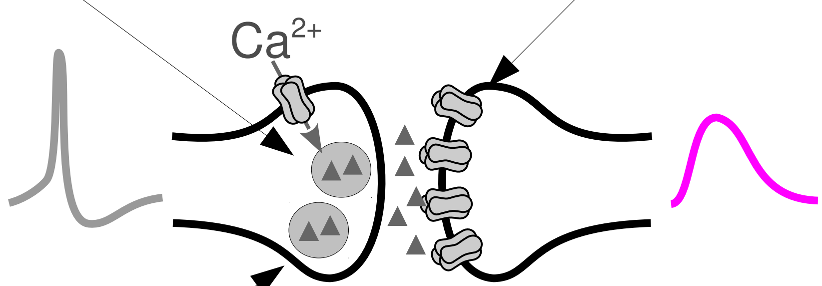
Expression of long-term changes

presynaptic

postsynaptic

neurotransmitter vesicle number

number of AMPA receptors



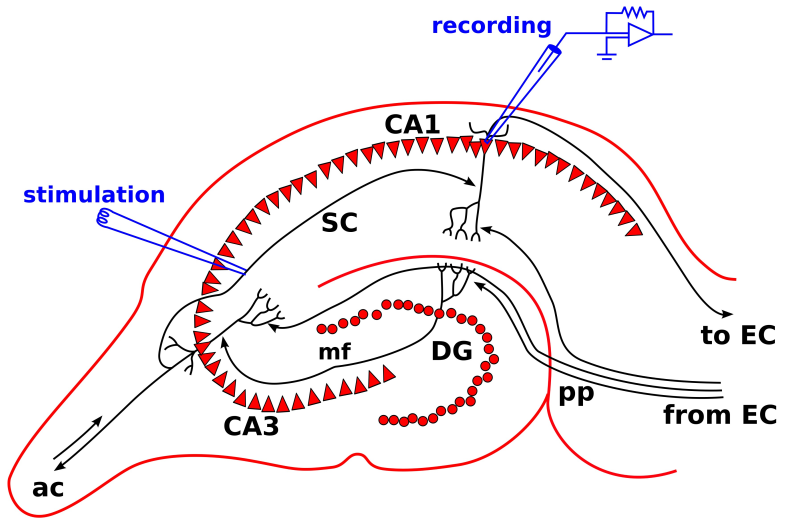
probability of vesicle release

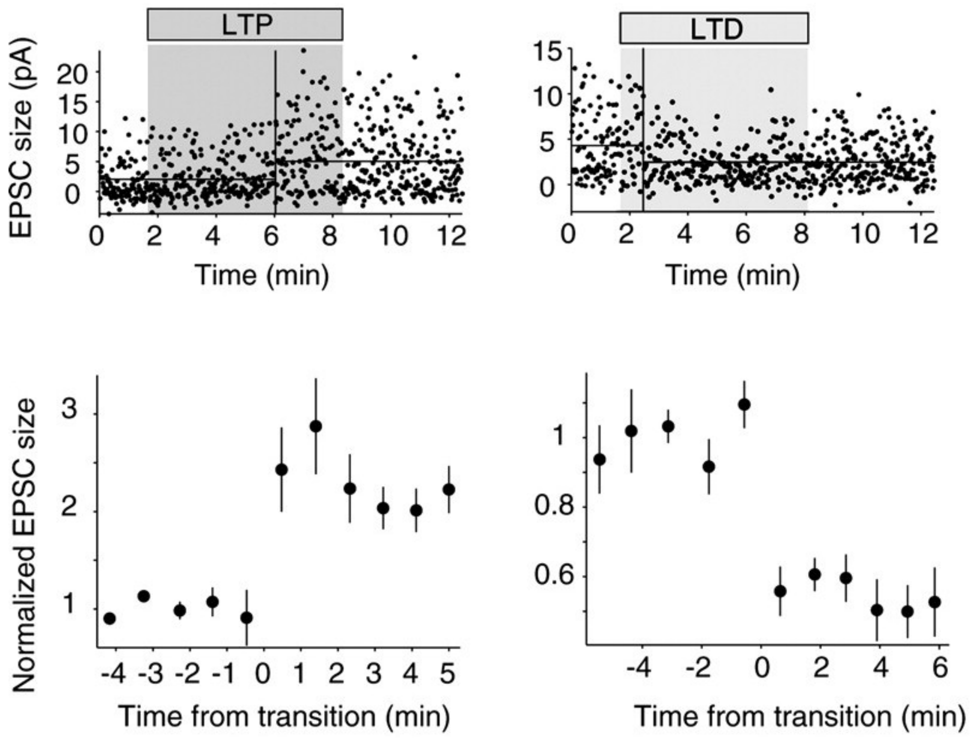
conductance of AMPA receptors

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



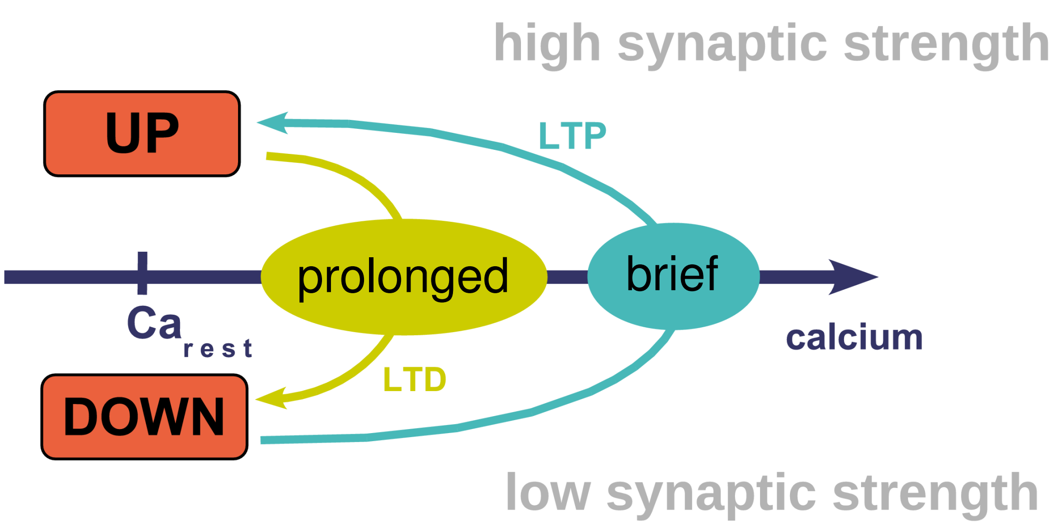


[O'Connor *et al.*, 2005]

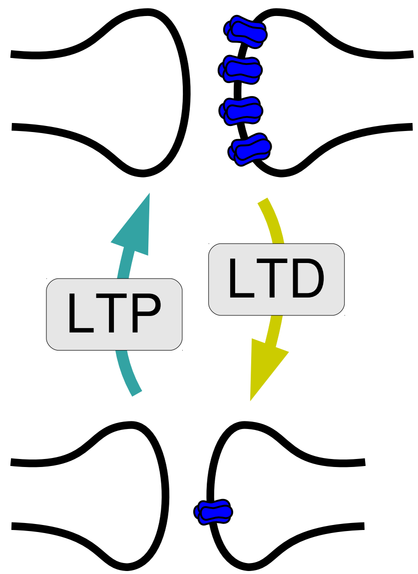
Scheme of single synapse (Hippocampus : SC→CA1)

- **states :** two stable states
- **signal inducing transitions** : intracellular calcium concentration [Malenka *et al.*, 1988; Yang *et al.*, 1999]
- **expression** : number or conductance of AMPA receptors [Bliss *et al.*, 2003; Lisman, 2003]

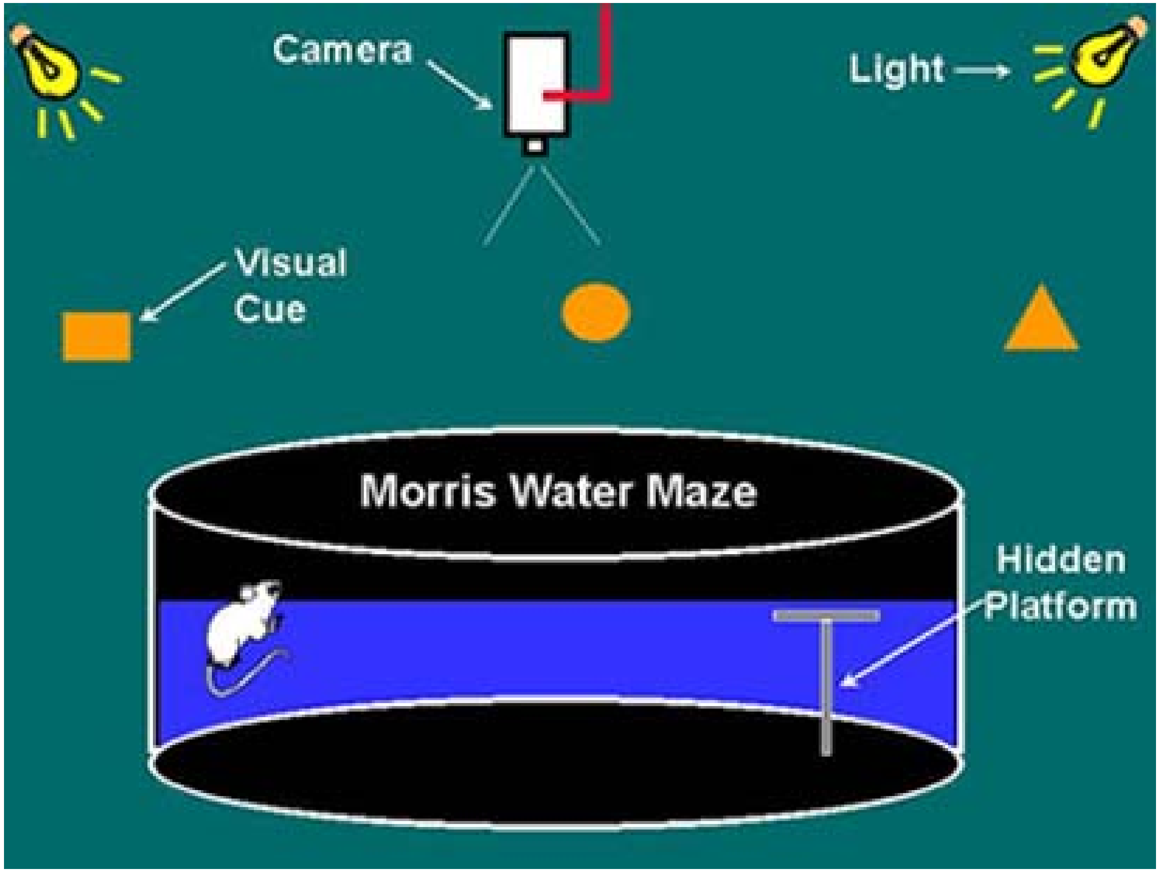
states and transitions



postsynaptic expression

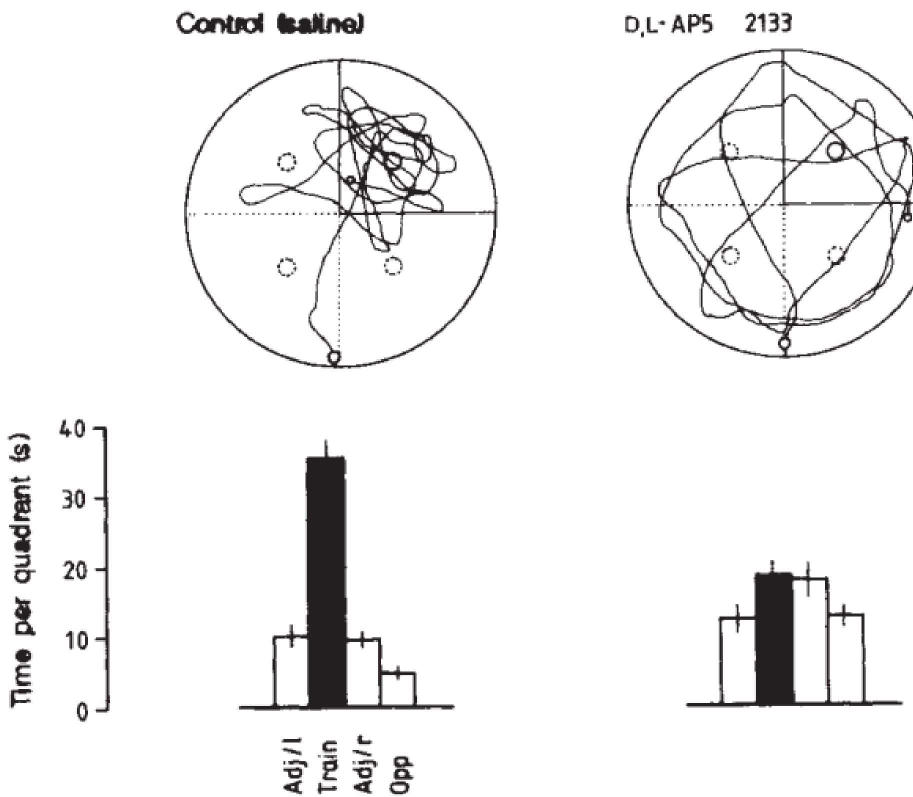


Relation between LTP and learning/memory



[Morris *et al.*, 1986]

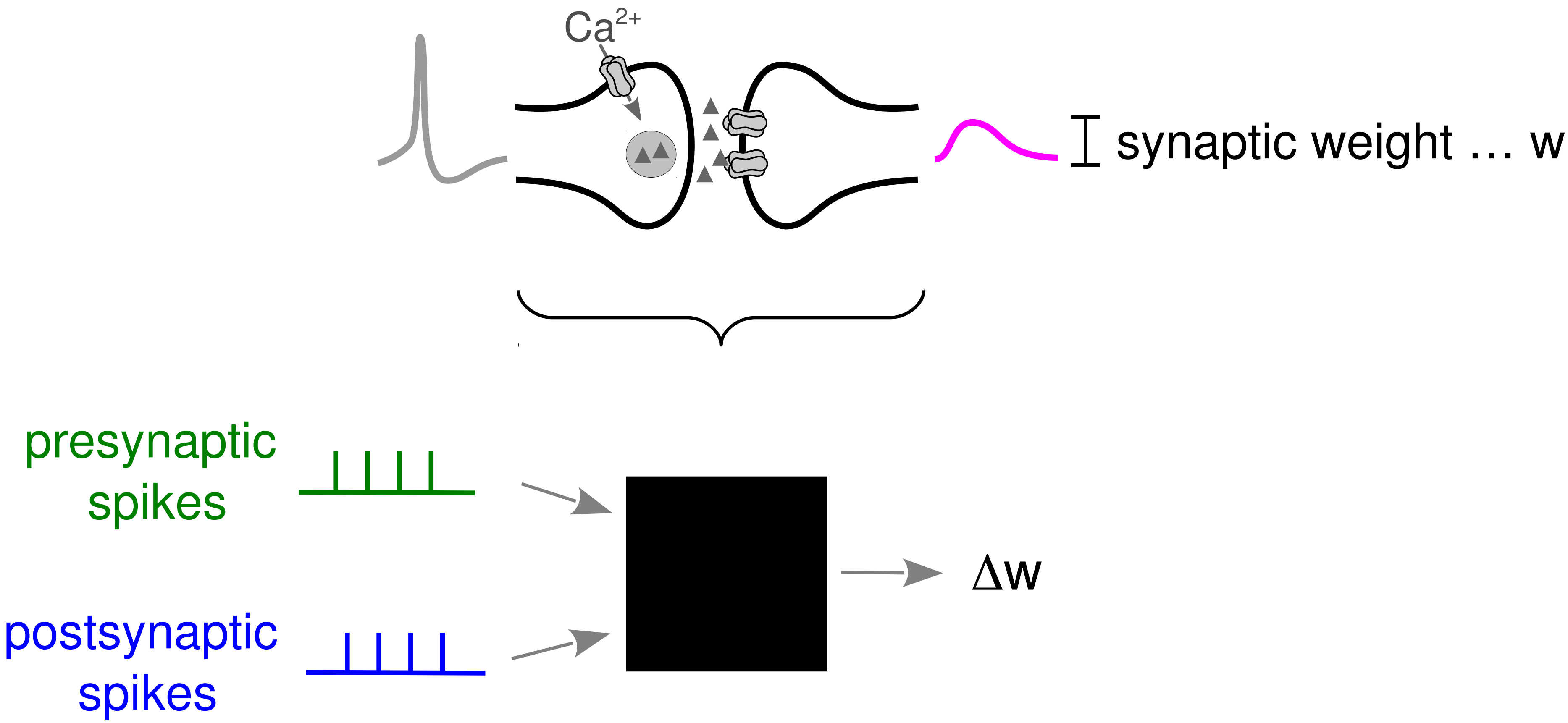
Relation between LTP and learning/memory



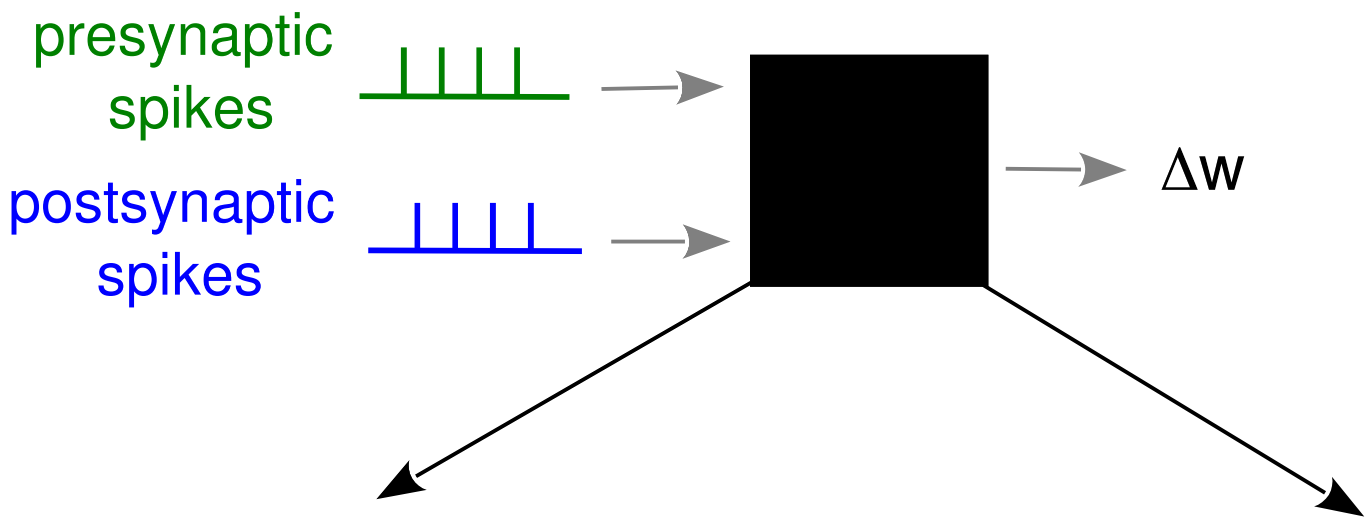
- NMDA receptor required to learn platform location [Morris *et al.*, 1986]
- NMDA receptor required to form spatial memories (place fields)

[McHugh *et al.* 1996]

2. Biophysical models of synaptic plasticity



Modeling approaches : phenomenological vs. biophysical



phenomenological models of LTP/LTD	**biophysical models of LTP/LTD**

phenomenological models of LTP/LTD

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

biophysical models of LTP/LTD

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

Modeling studies : phenomenological vs. biophysical

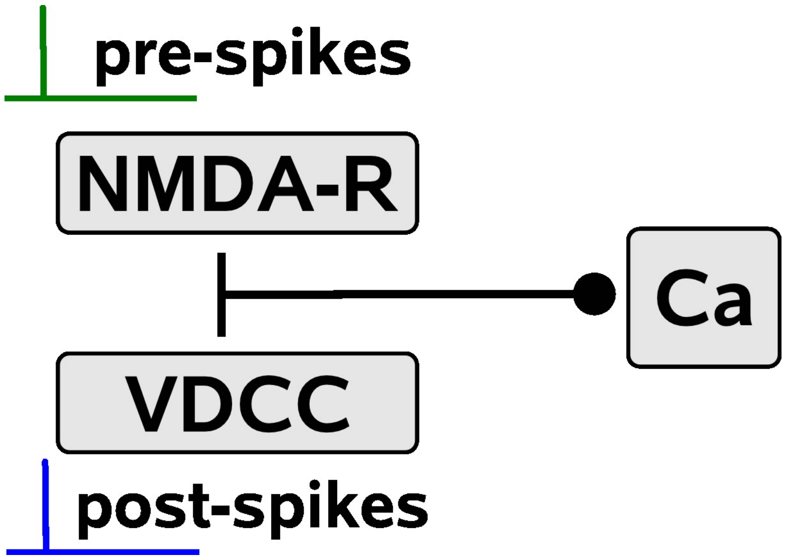
phenomenological models of LTP/LTD

- 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

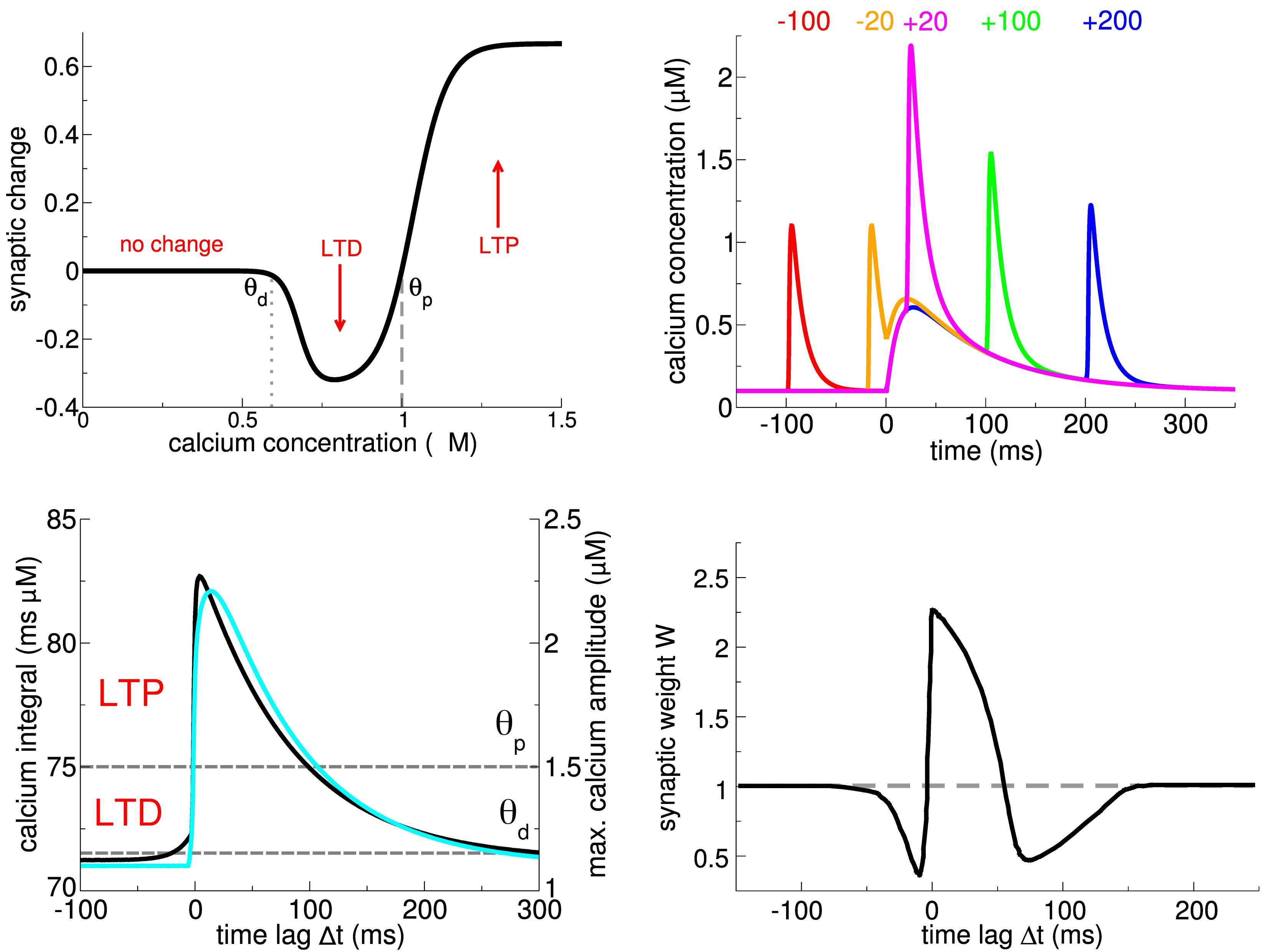
- Ca^{2+} – dynamics based models
  [Karmarkar *et al*., 2002; Shouval *et al*., 2002; Rubin *et al*., 2005]
- CaMKII kinase-phosphatase system
  [Crick 1984; Lisman, 1985; Okamoto & Ichikawa, 2000; Zhabotinsky, 2000; Graupner & Brunel, 2007; Urakubo *et al*., 2008]
- extensive protein networks
  [Bhalla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

Calcium influx



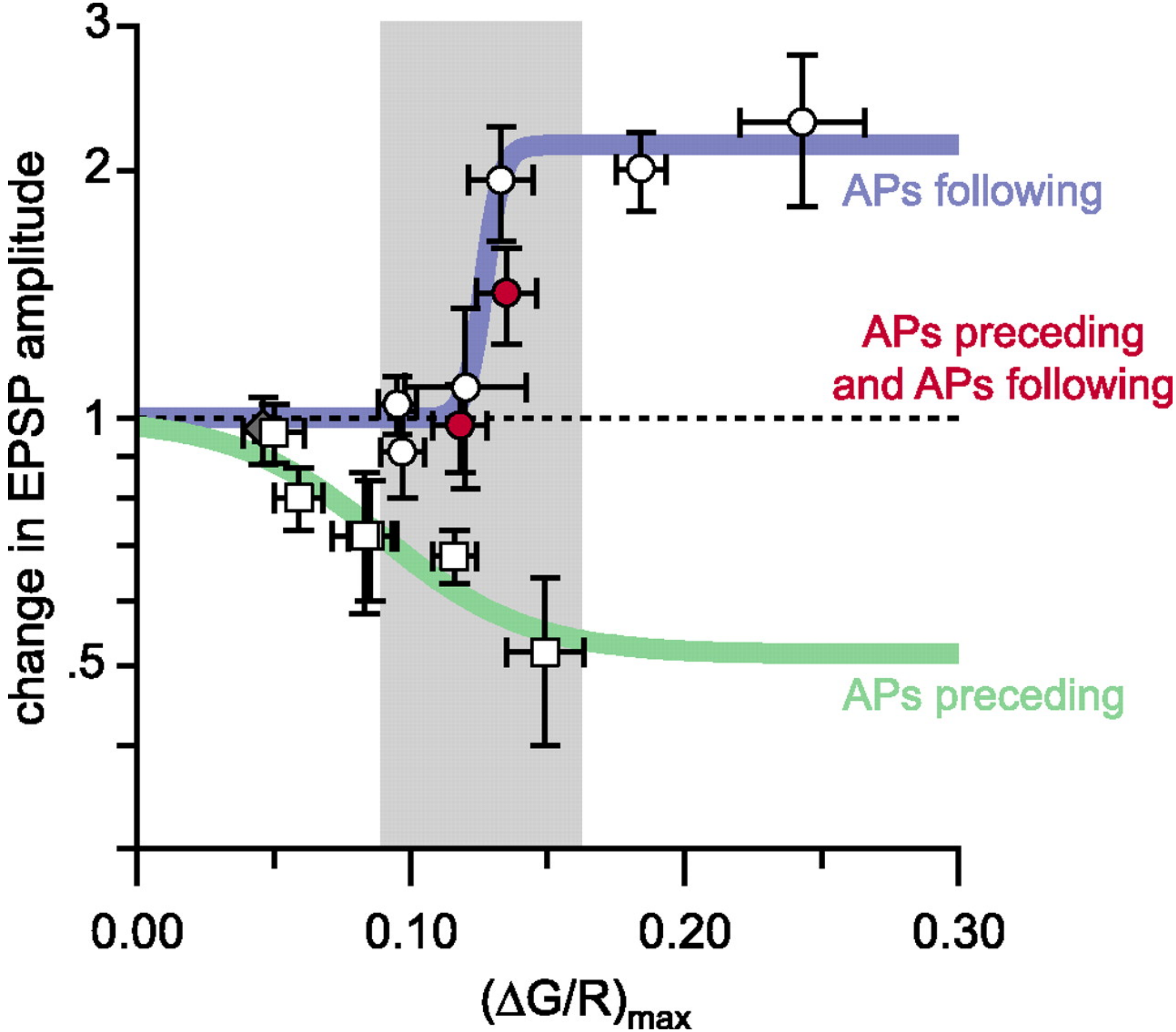
[Collingridge *et al.*, 1983; Markram *et al.*, 1997; Bi & Poo, 1998; Nevian & Sakmann 2006]

Calcium control hypothesis



[Shouval *et al.*, 2002]

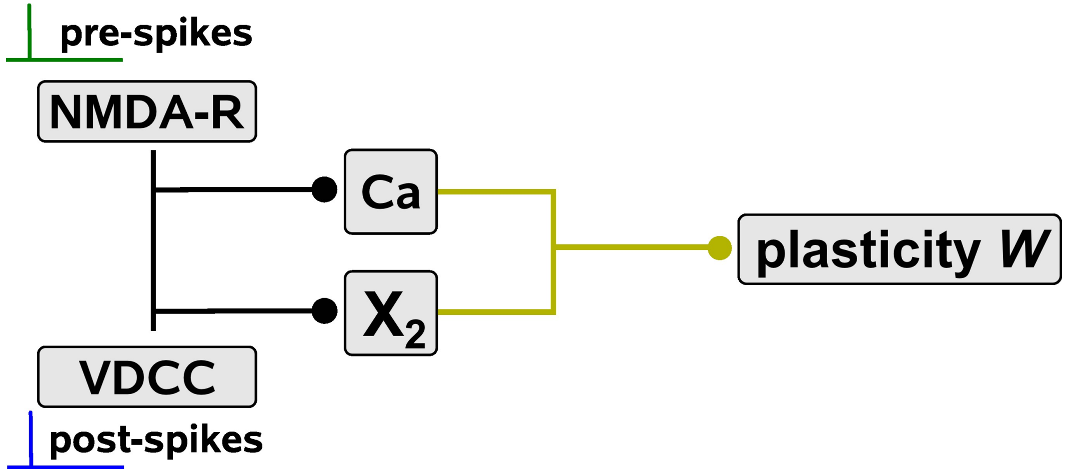
Peak Ca^{2+} amplitude does not predict LTP or LTD



[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]



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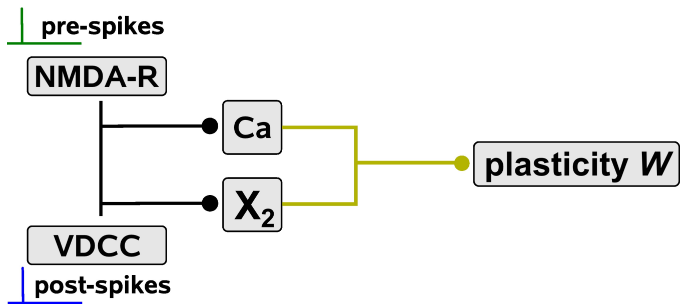
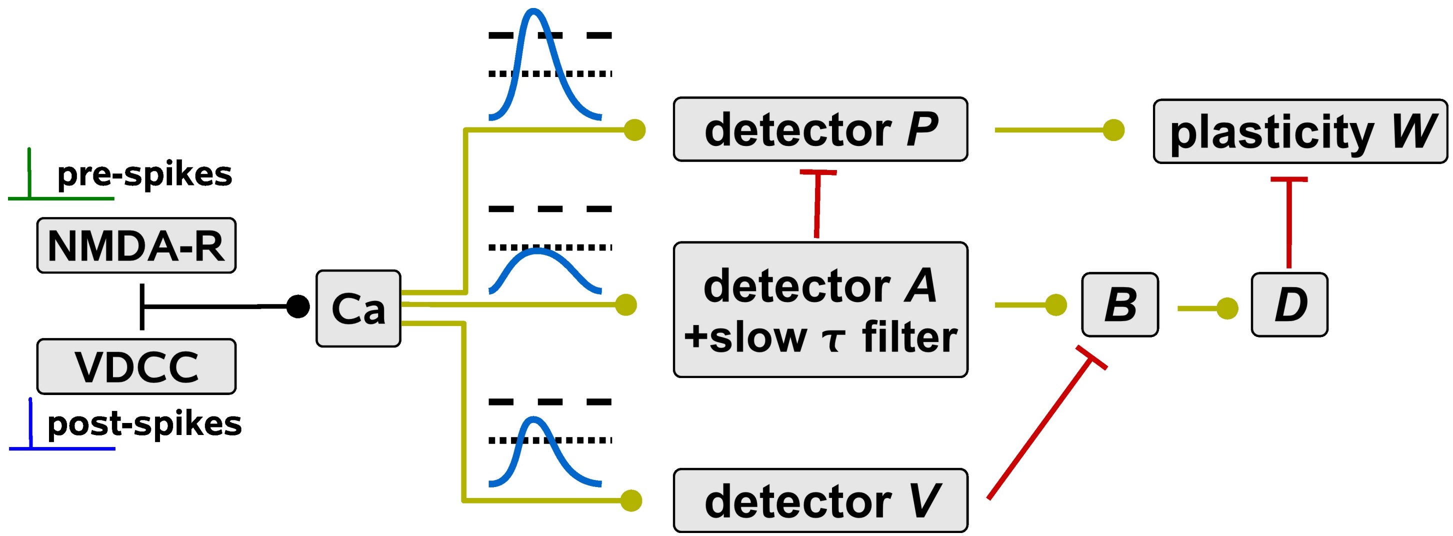


- phenomenological read-out of $[Ca^{2+}]$ [Rubin *et al.*, 2005]



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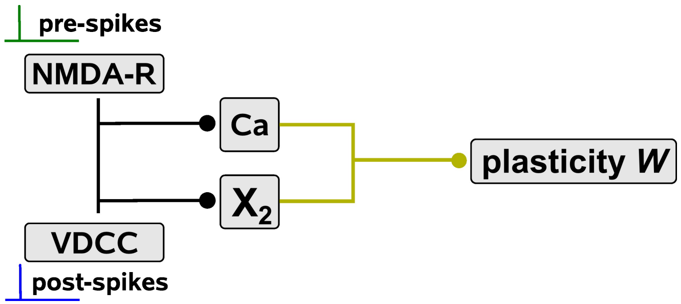

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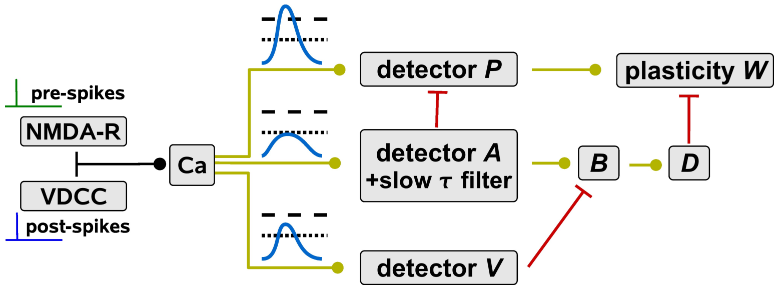
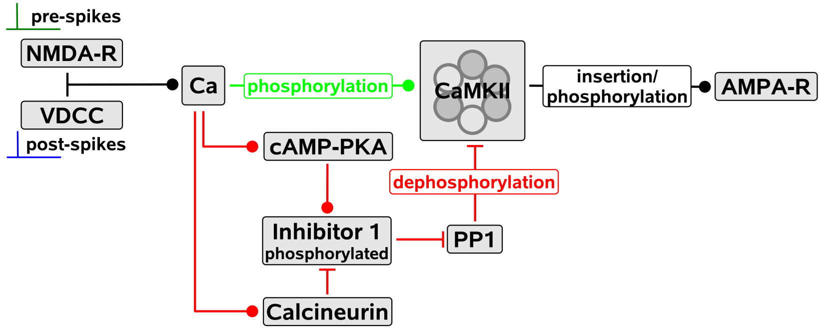
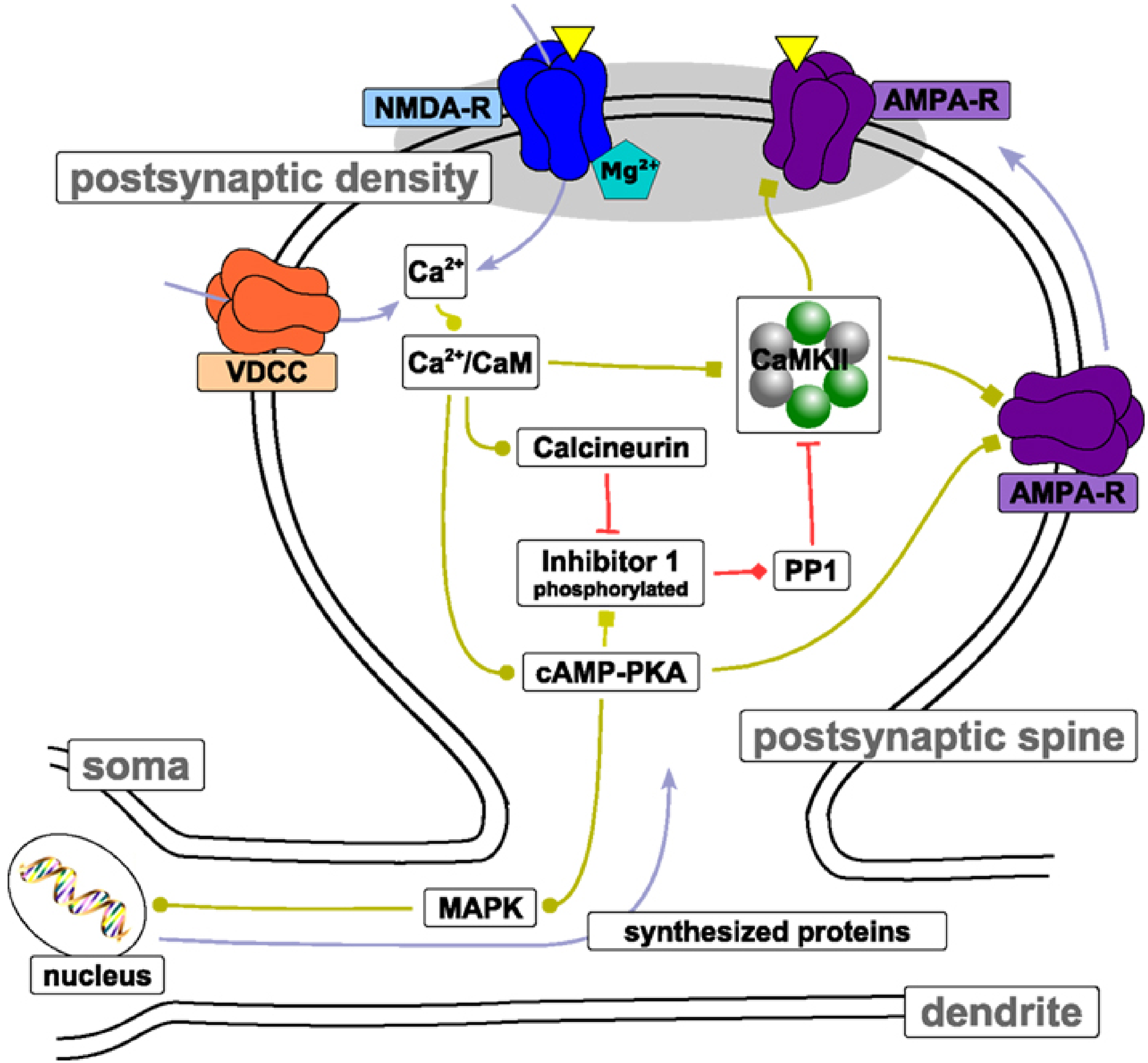


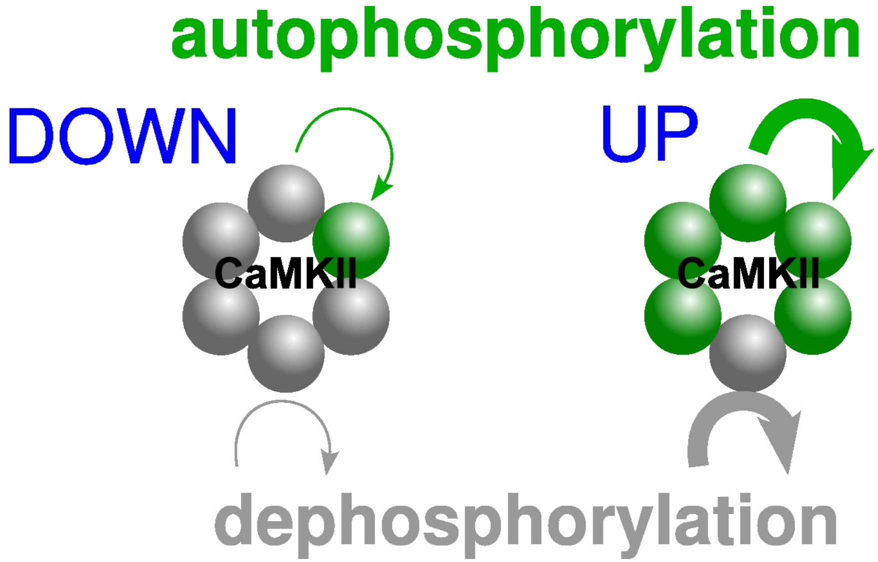
- protein signaling cascade activated by $[Ca^{2+}]$ [Graupner & Brunel, 2007; Urakubo *et al.*, 2008]



Protein signaling cascade involving CaMKII

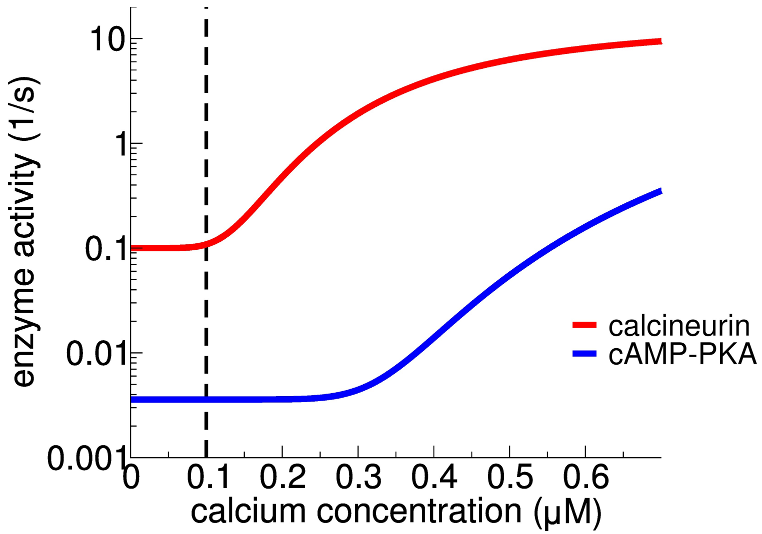


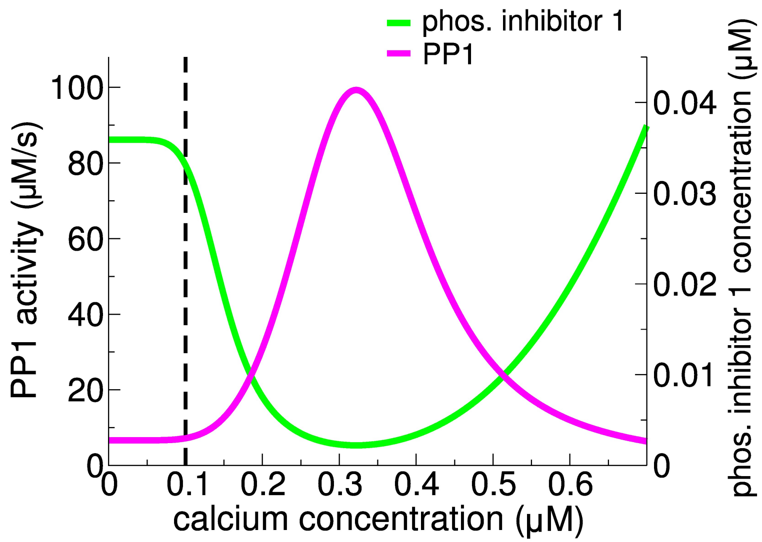
CaMKII : bistable phosphorylation level

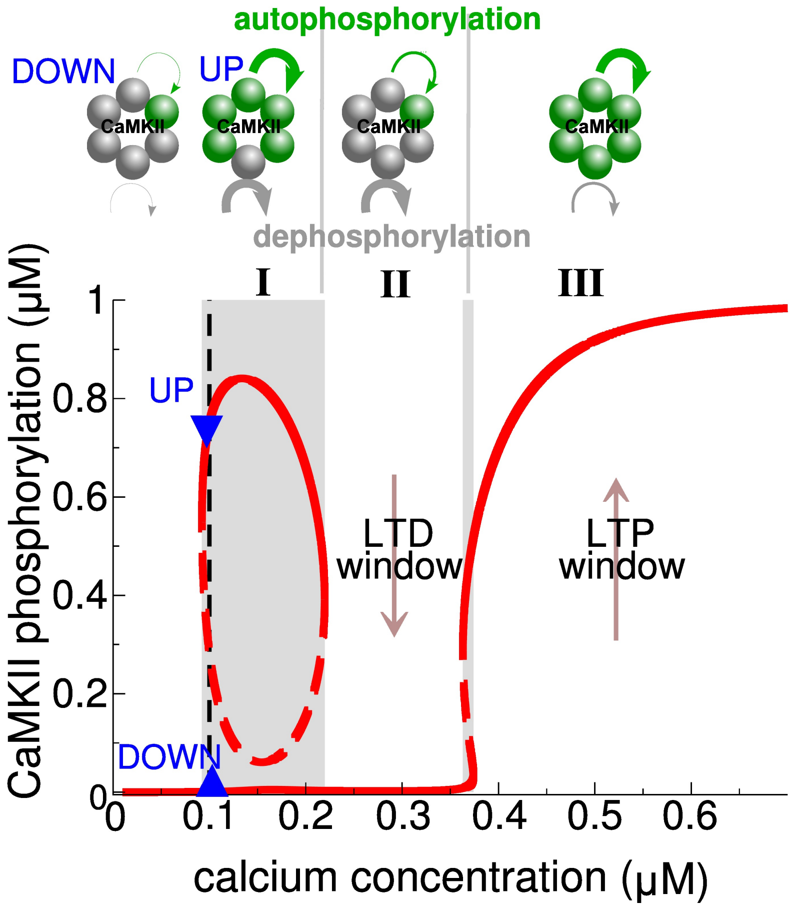


[Zhabotinsky, 2000]

Steady-state of the CaMKII phosphorylation level

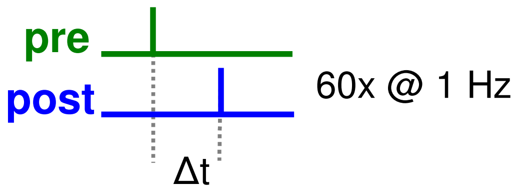


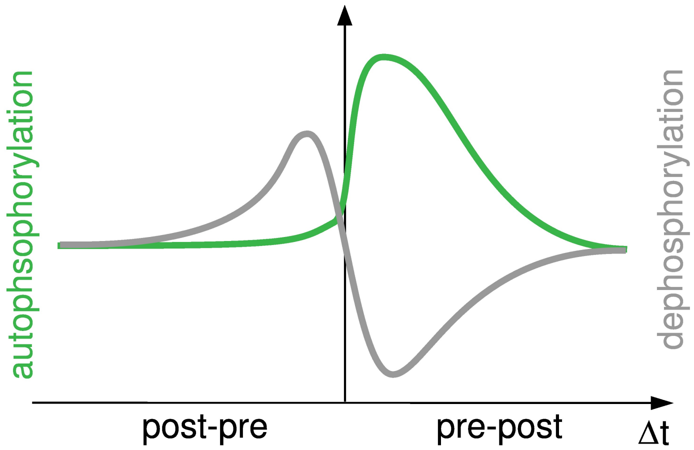


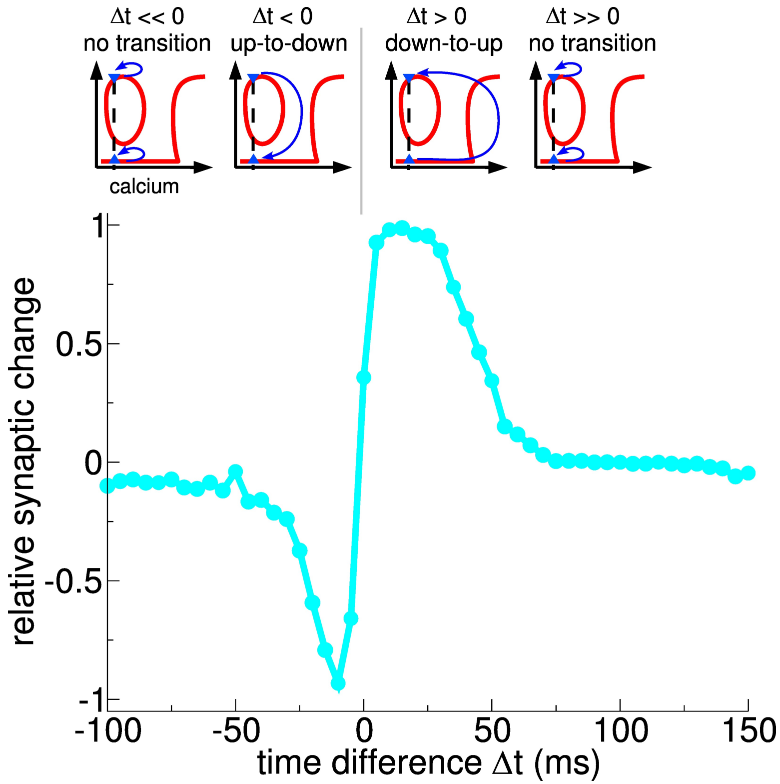


[Graupner & Brunel, 2007]

Transitions of CaMKII in response to spike-pairs







[Graupner & Brunel, 2007]

3. Applications for biophysical model of synaptic plasticity

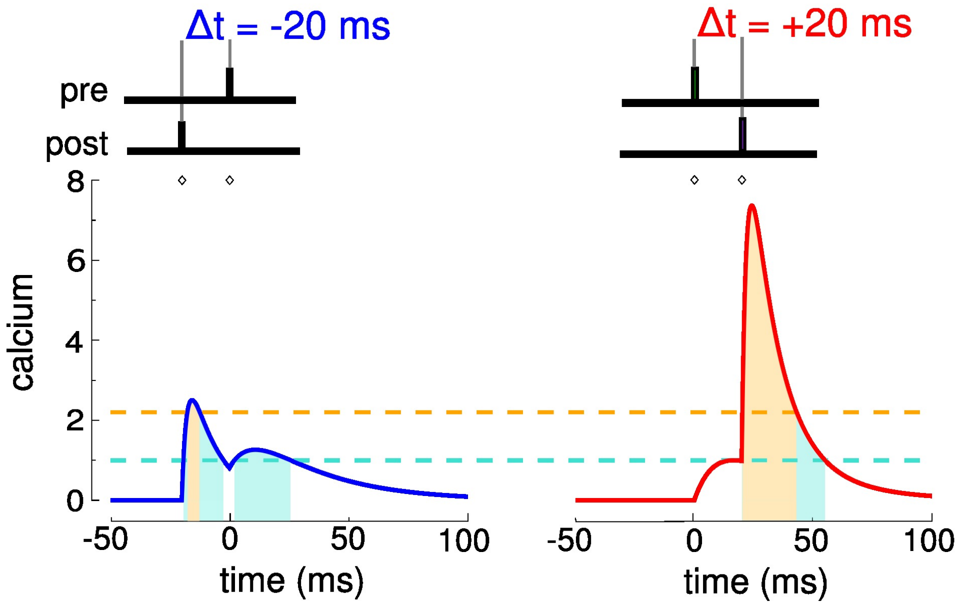
- explore/understand the diversity of plasticity results observed in different brain regions and under varying stimulation protocols
- explore synaptic plasticity for uncharted stimulation protocols
- understand the impact of pharmacological interventions :

  - study the effect of nootropic drugs

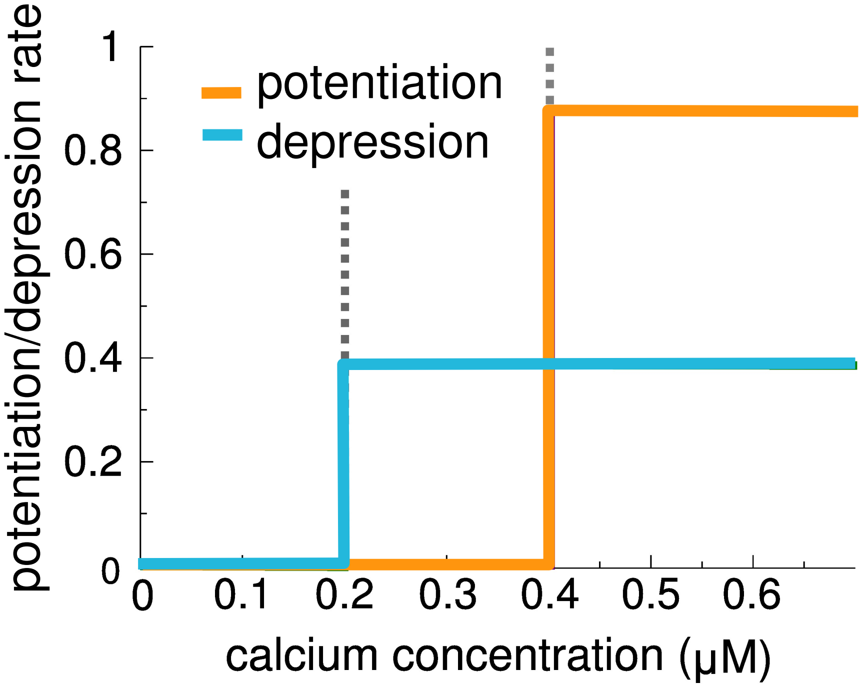
  - developing strategies for treating disorders of memory such as Alzheimer's disease and other forms of dementia

Simplified view on Ca^{2+}-based model

calcium transients

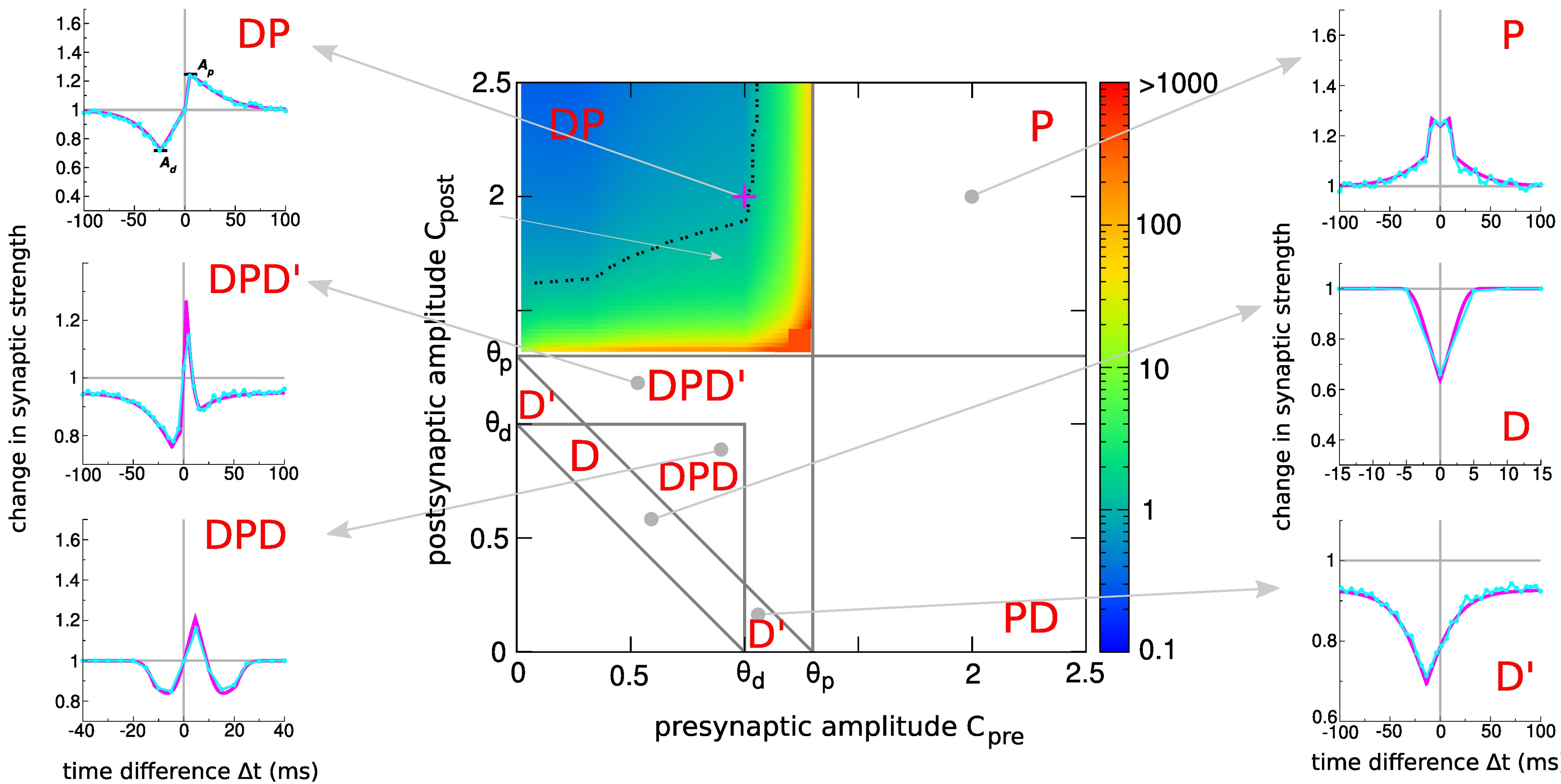


simplified view



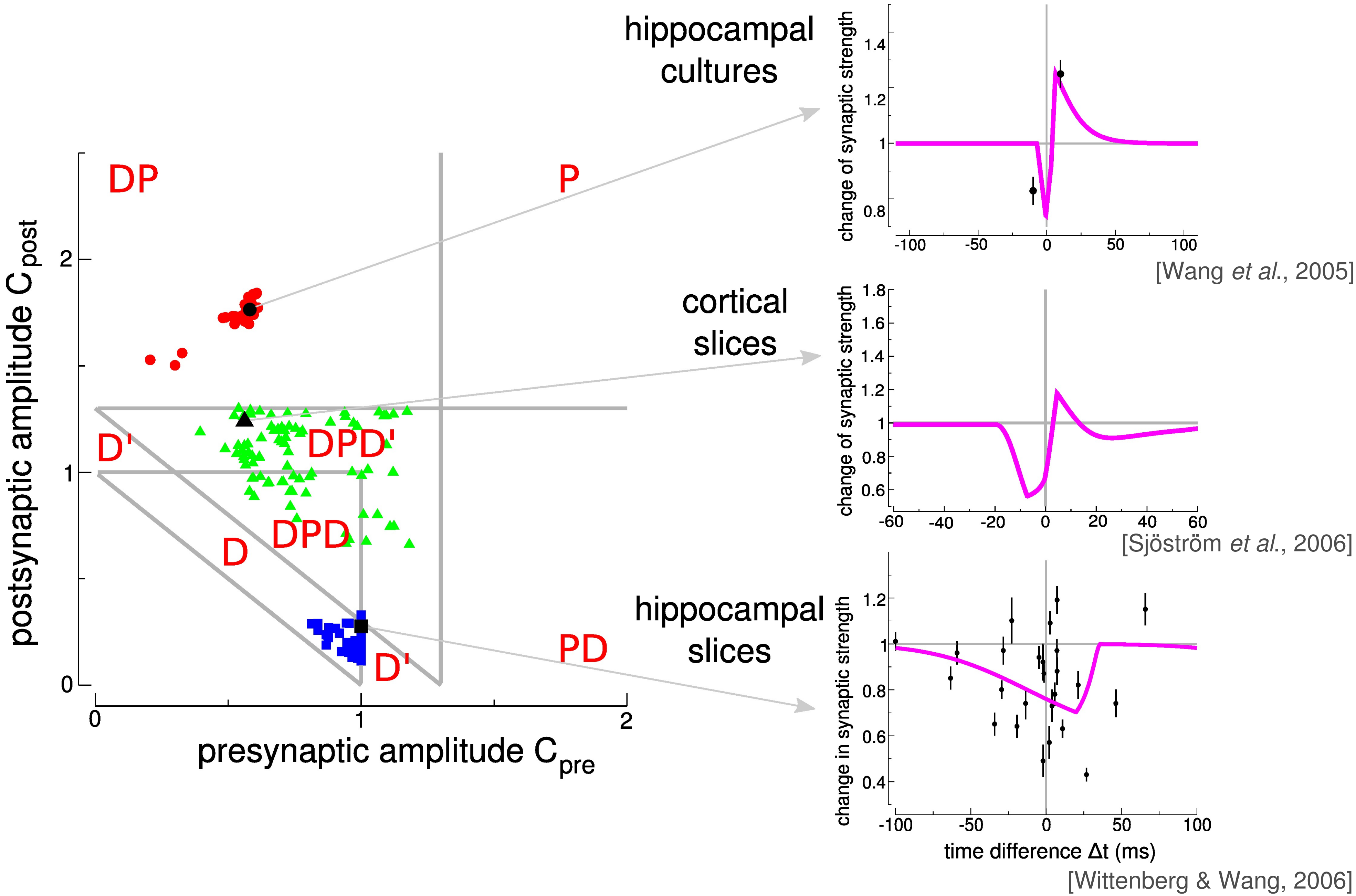
- two pathways controlled by Ca^{2+} having opposing influence on synaptic weight *w*
- depression pathway activated at intermediate Ca^{2+}-levels
- potentiation pathway activated at high Ca^{2+}-levels

Diversity of STDP curves : spike-pair stimulation

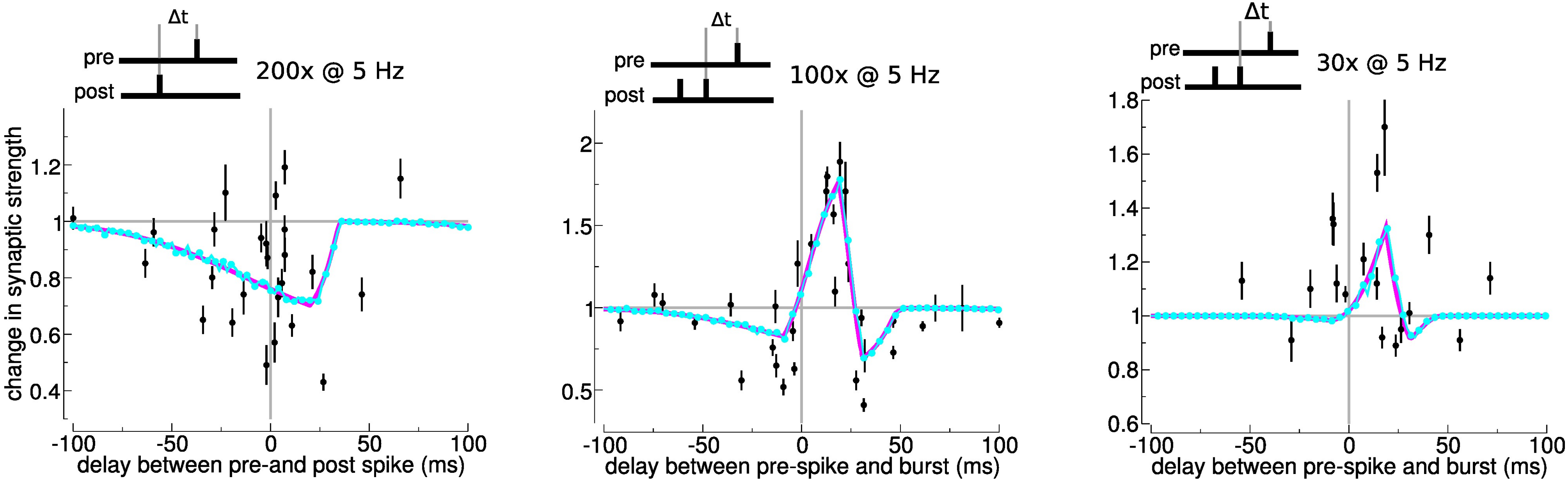


[Graupner & Brunel, 2012]

Experiments explained by different parameter sets

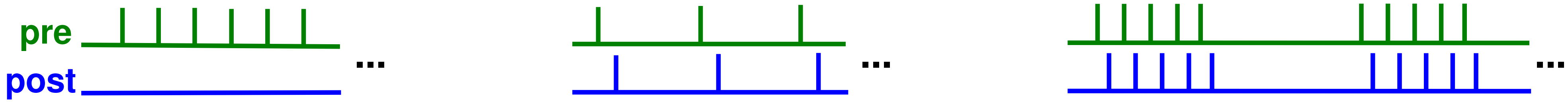


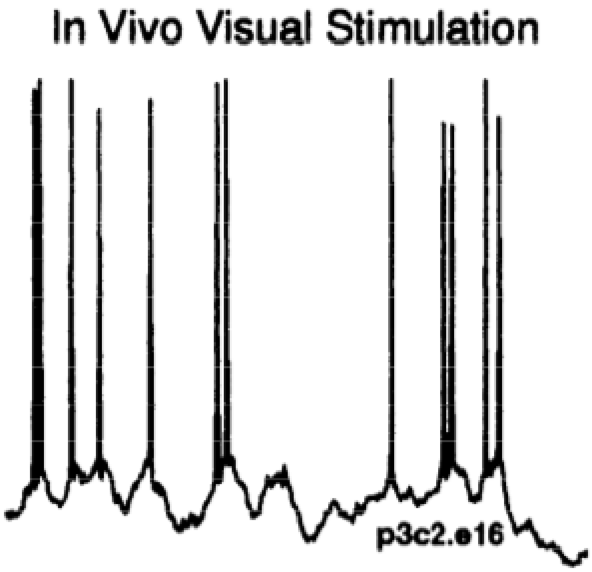
Malleability of hippocampal STDP explained by Ca^{2+}



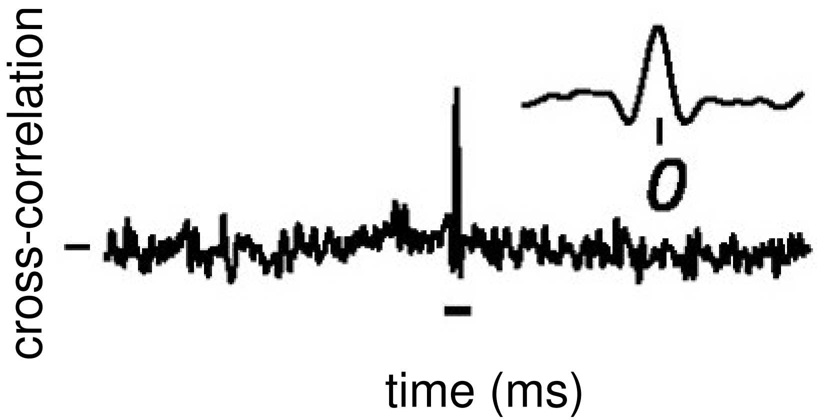
[Wittenberg & Wang, 2006]

Realistic firing is highly irregular



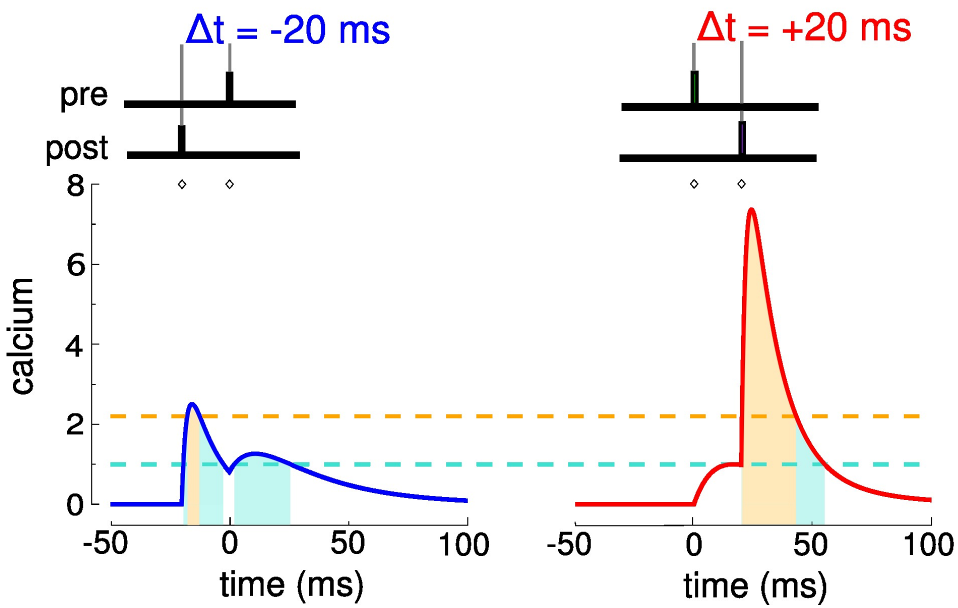


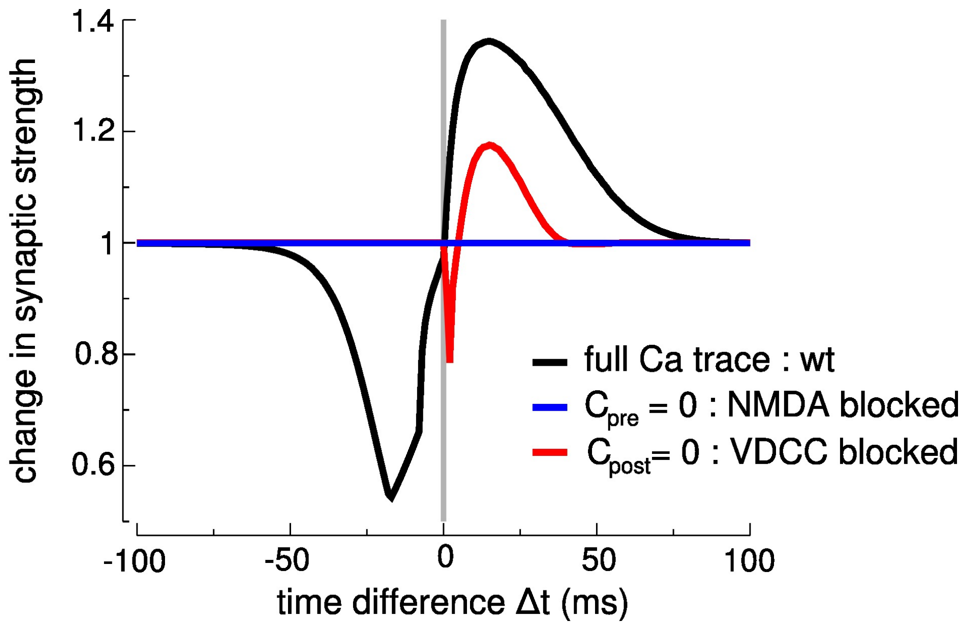
[Holt *et al.*, 1996]



[Kohn and Smith, 2005]

Pharmacological manipulations explained by Ca^{2+}

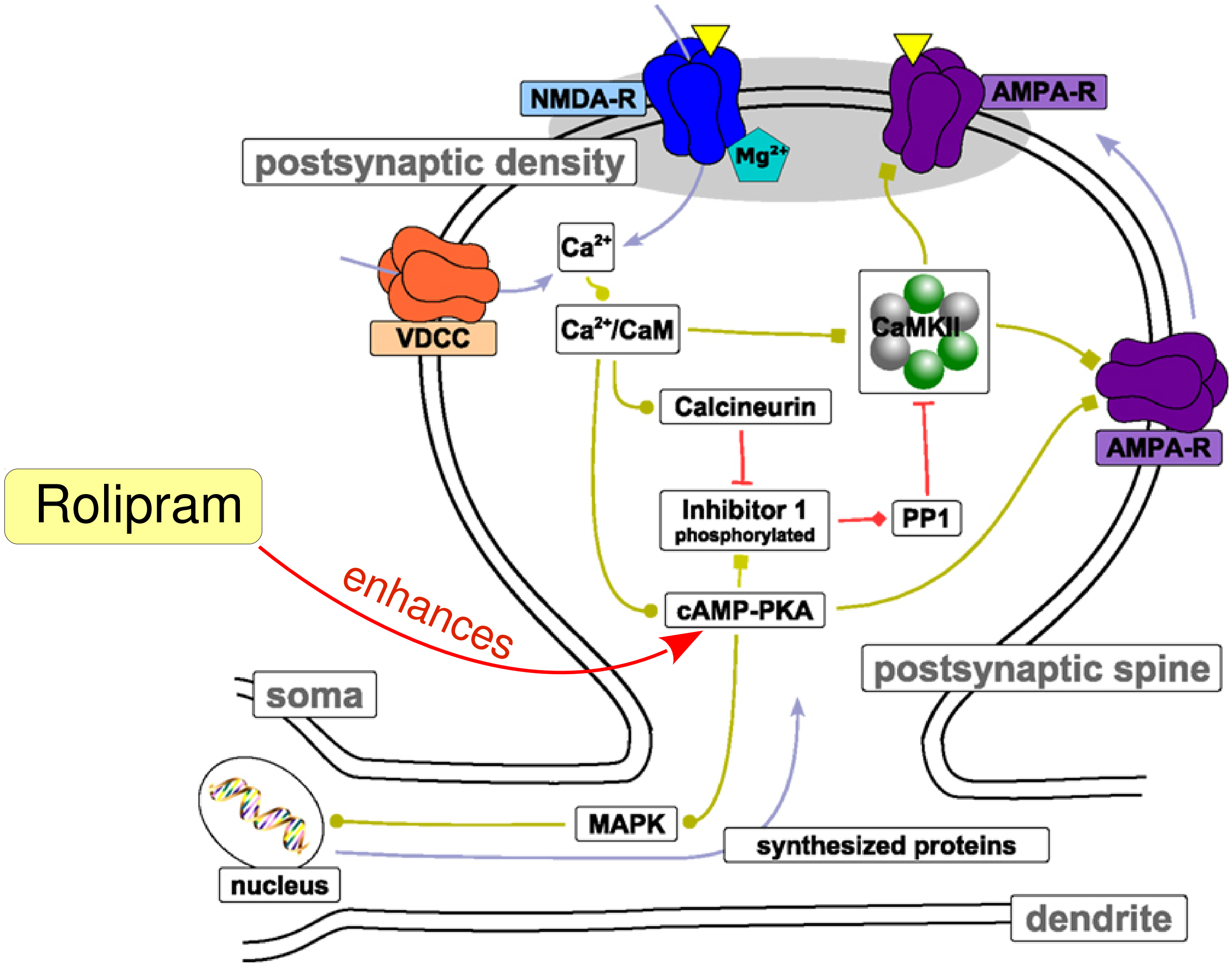




[Bi & Poo, 1998; Nevian & Sakmann, 2006]

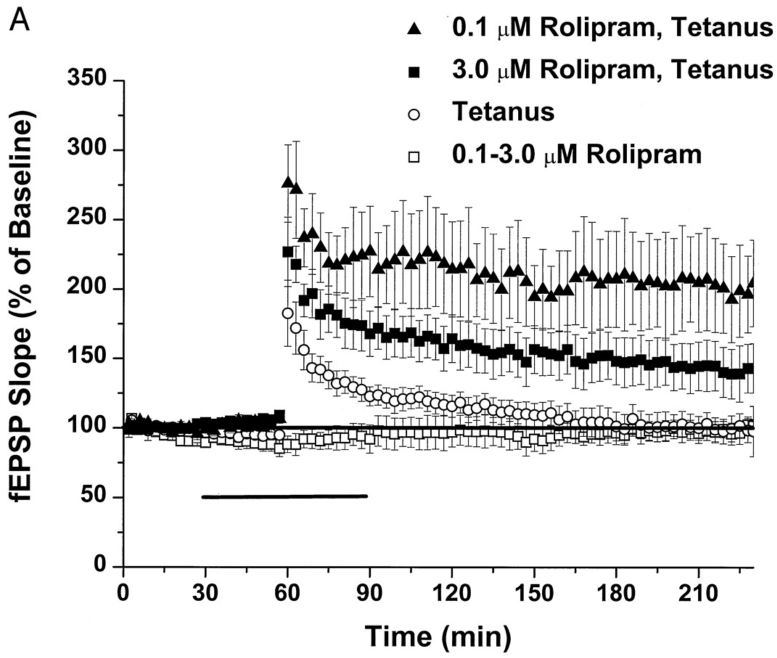
- nonlinear, finite rise time calcium transients necessary to reproduced pharmacological block experiments

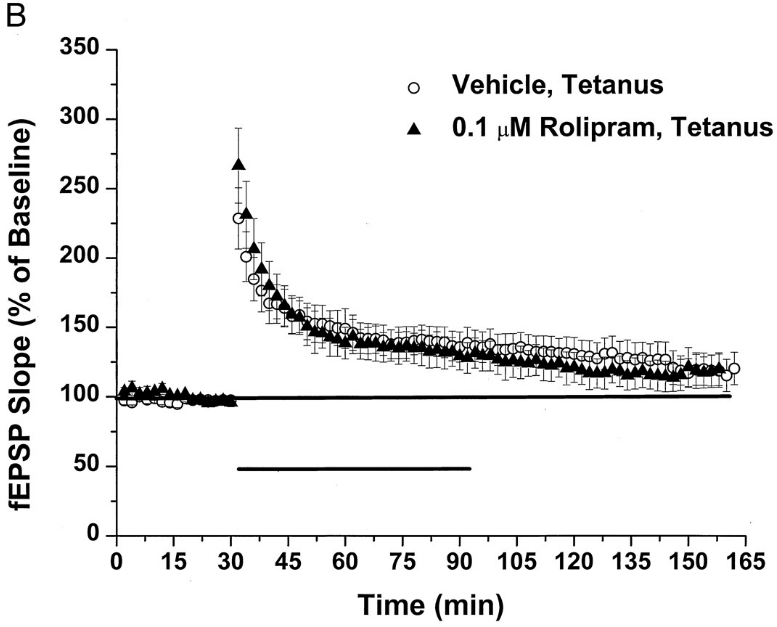
Study the effect of nootropic drugs (memory enhancer)



Rolipram … selective phosphodiesterase-4 inhibitor

Study the effect of nootropic drugs



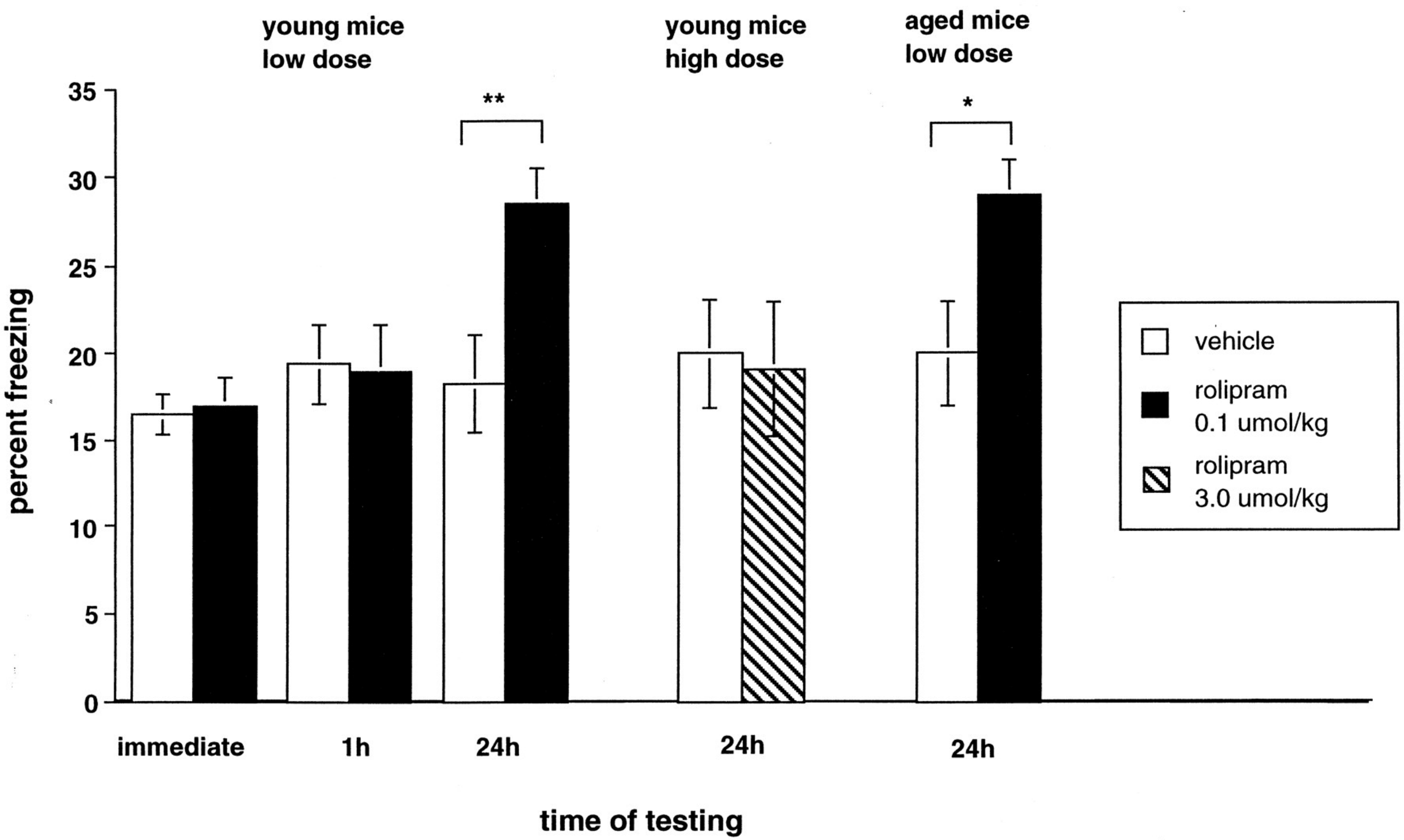


- boosting of cAMP *during* stimulation increases LTP

[Barath *et al.*, 1998]

Study the outcome of nootropic drugs

- Rolipram enhances memory



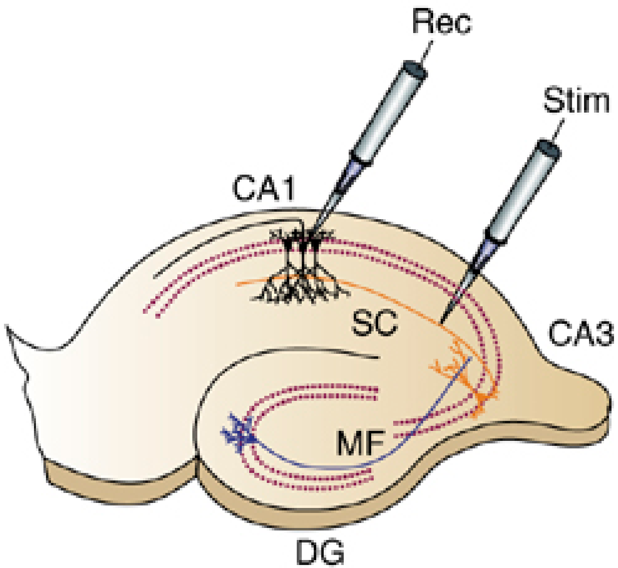
[Barath *et al.*, 1998]

Summary

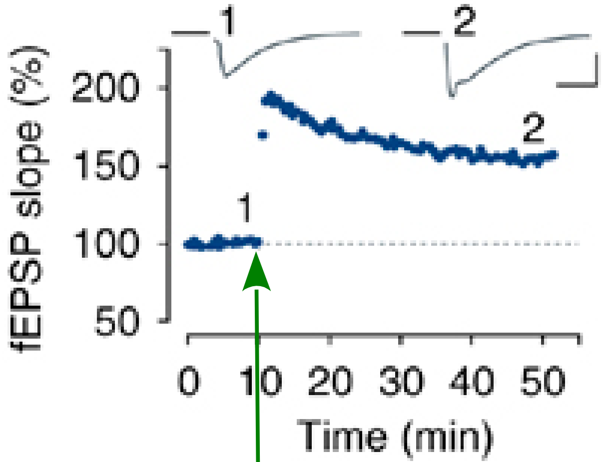
- synapses can change their transmission efficacy in an activity-dependent manner : long-term potentiation/depression
- induction: coincident pre- and postsynaptic activity lead to calcium influx through NMDA receptors, triggering intracellular signaling cascades
- biophysical model resolve various aspects of the synaptic machinery involved in plasticity induction, most commonly the postsynaptic calcium dynamics
- in turn, the biological nature of these models allows to get insights into plasticity processes, and study interactions drugs with the elements involved in plasticity

Nicolas Brunel, University of Chicago

Srdjan Ostojic, ENS Paris

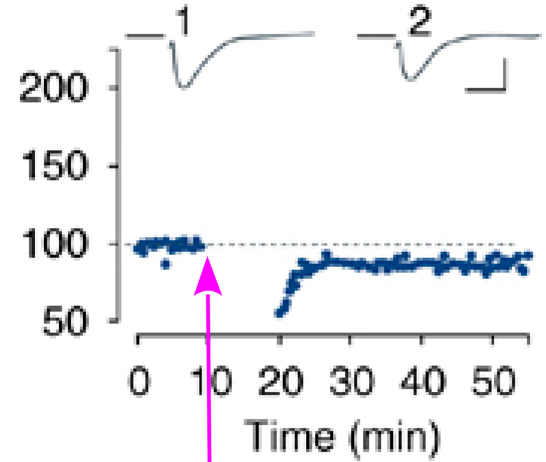


long-term potentiation LTP



100 Hz for 1 s

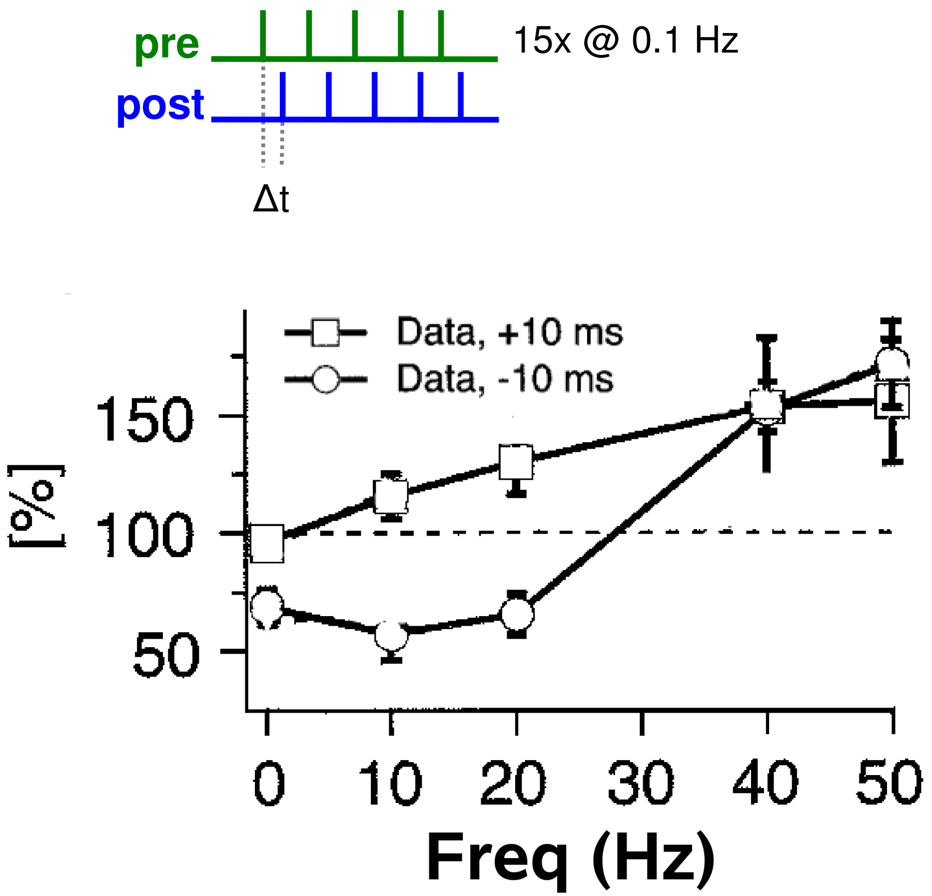
long-term depression LTD



2x 5 Hz for 3 min,
3 min interval

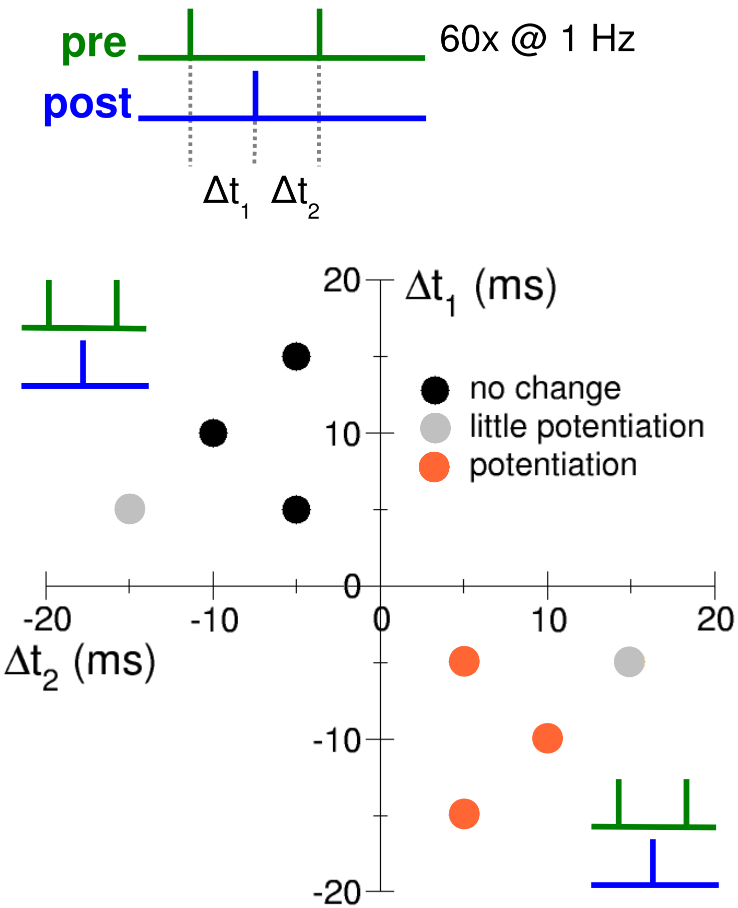
[Morishita *et al.*,2005]

spike-pair & frequency



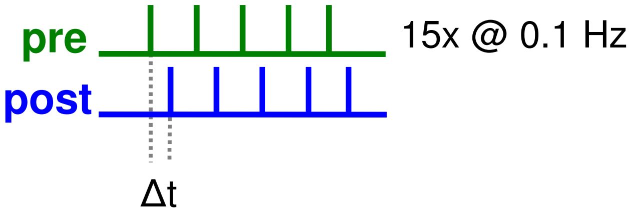
[Sjöström *et al.*, 2001]

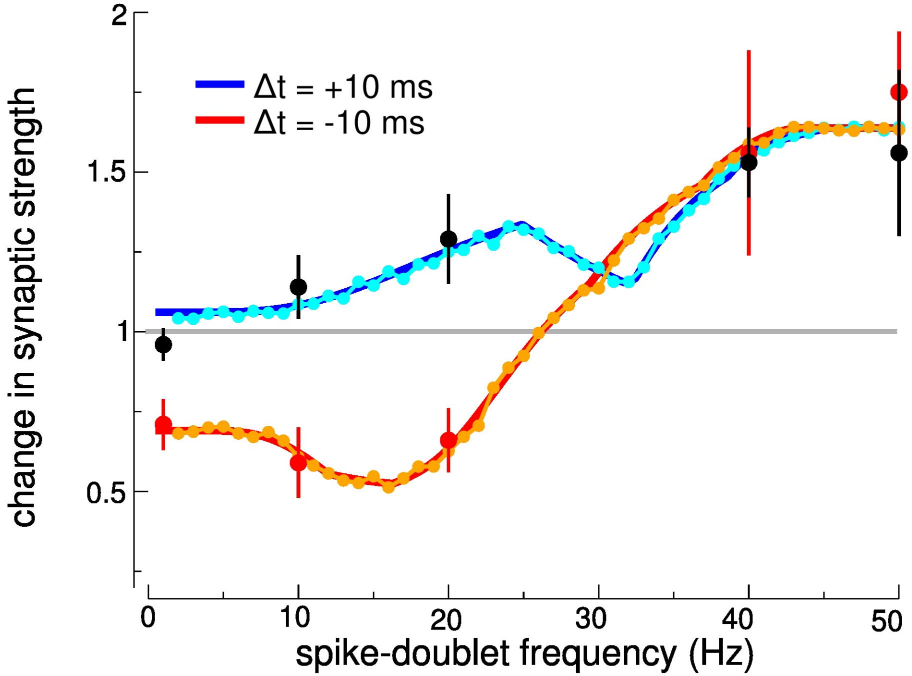
spike - triplets

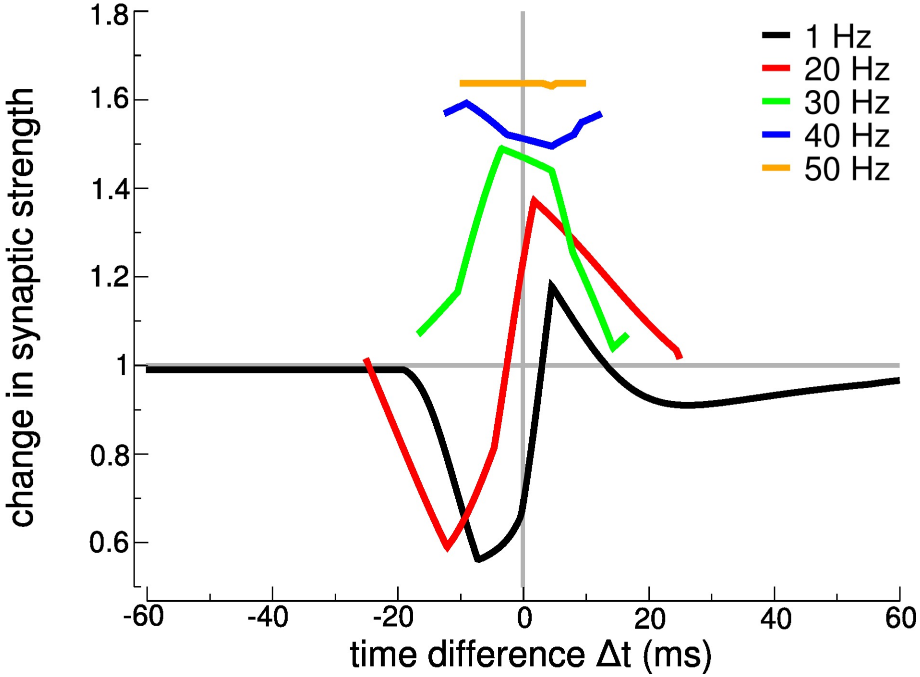


[Wang *et al.*, 2005]

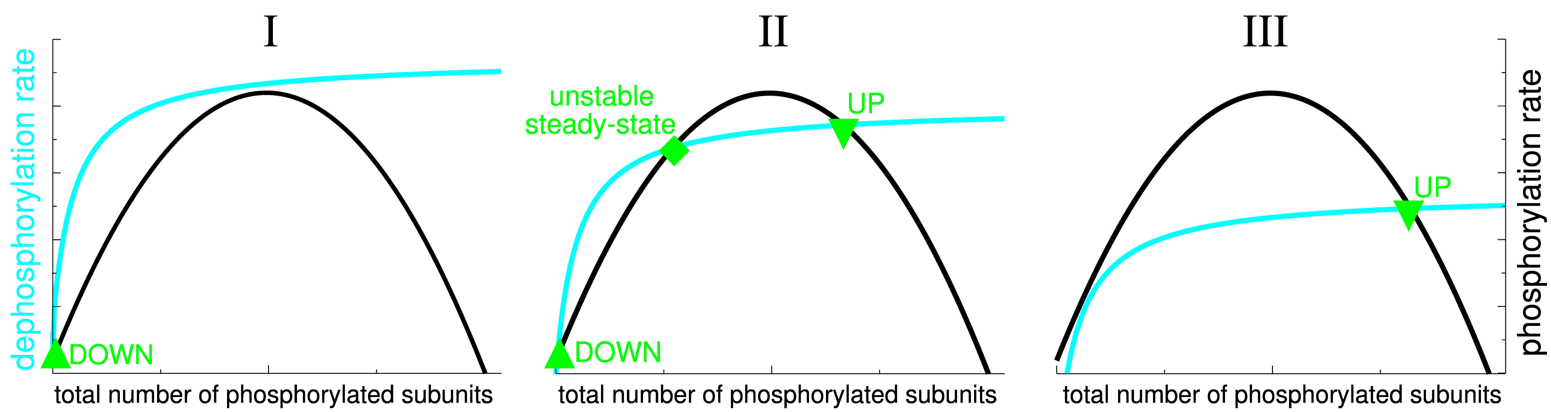
Firing rate dependence in cortical slices

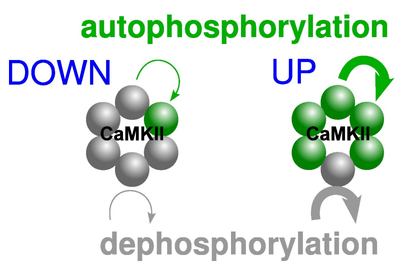


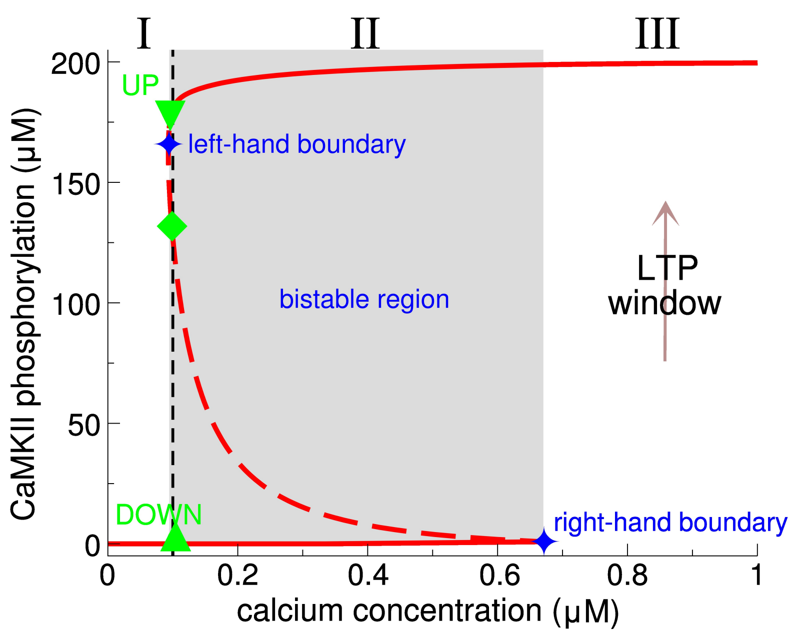




[Sjöström *et al.*, 2001]


I
II
III
dephosphorylation rate
phosphorylation rate
unstable
steady-state
UP
DOWN
total number of phosphorylated subunits


autophosphorylation
DOWN
UP
CaMKII
dephosphorylation


I
II
III
UP
left-hand boundary
bistable region
LTP
window
DOWN
right-hand boundary
CaMKII phosphorylation (μM)
calcium concentration (μM)
200
150
100
50
0
0.2
0.4
0.6
0.8
1

synaptic efficacy **ρ**

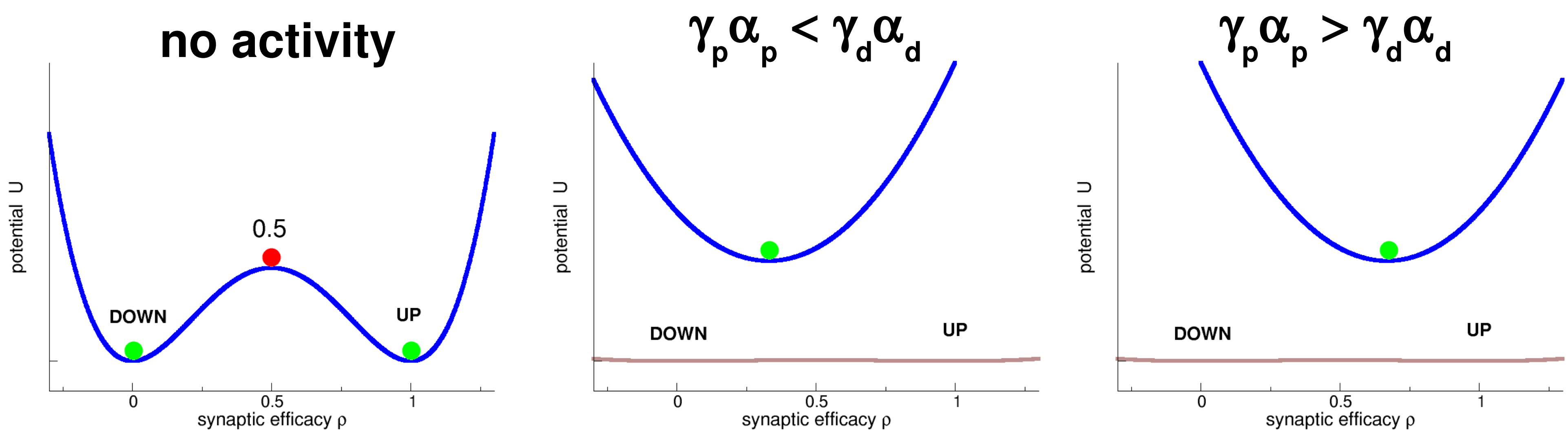
$$\tau\dot\rho = -\epsilon\rho(1-\rho)(1/2-\rho) + \gamma_p(1-\rho)\Theta(Ca(t)-\theta_p) - \gamma_d\rho\Theta(Ca(t)-\theta_d) + \sigma\sqrt{\tau}\Theta(Ca(t)-\theta_p)\Theta(Ca(t)-\theta_d)\eta(t)$$

time average over calcium transients

$$\tau\dot\rho = -\epsilon\rho(1-\rho)(1/2-\rho) + \gamma_p\alpha_p(1-\rho) - \gamma_d\alpha_d\rho + \sigma\sqrt{\tau}\sqrt{\alpha_p+\alpha_d}\,\eta(t)$$

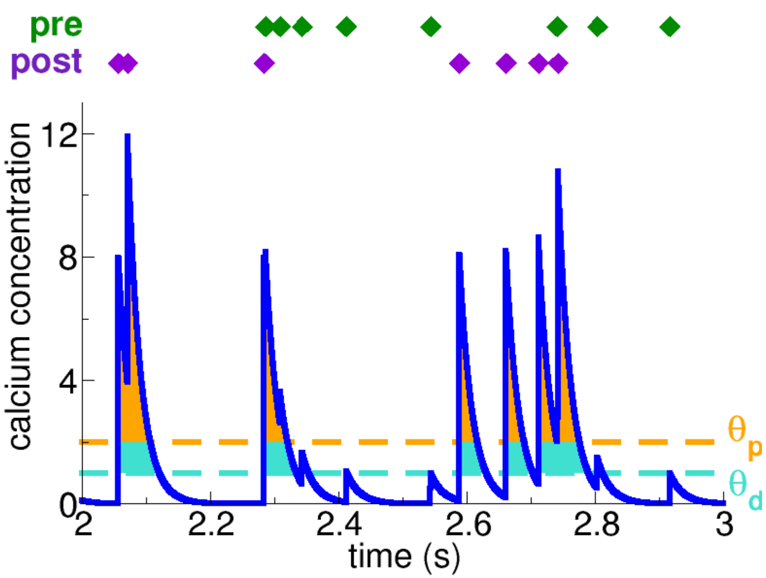
rewritten as Langevin equation

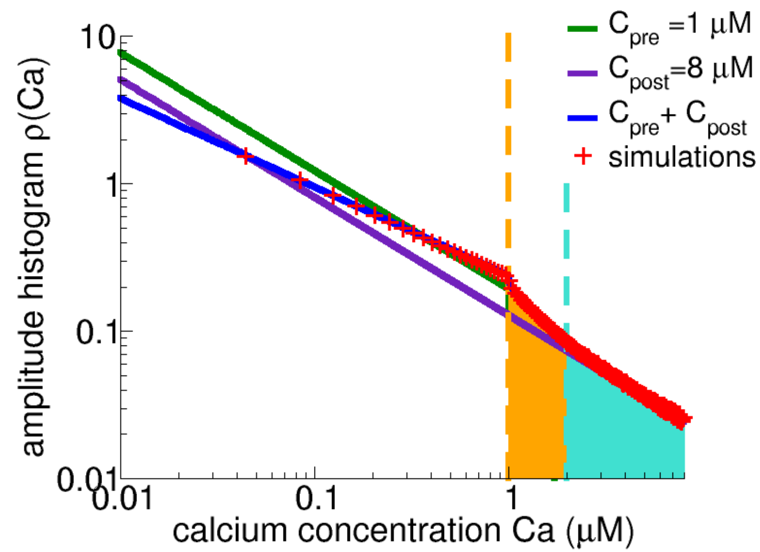
$$\tau\dot\rho = -\frac{\partial U}{\partial t} + \sigma\sqrt{\tau}\sqrt{\alpha_p+\alpha_d}\,\eta(t)$$



with $\varepsilon \ll 1$ → Ornstein-Uhlenbeck process : analytical solution for the PDF

$f_{pre} = f_{post} = 10$ Hz





[Gilbert *et al.*, 1960]