(Boring) overview of phenomenological rules for synaptic plasticity

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Outline

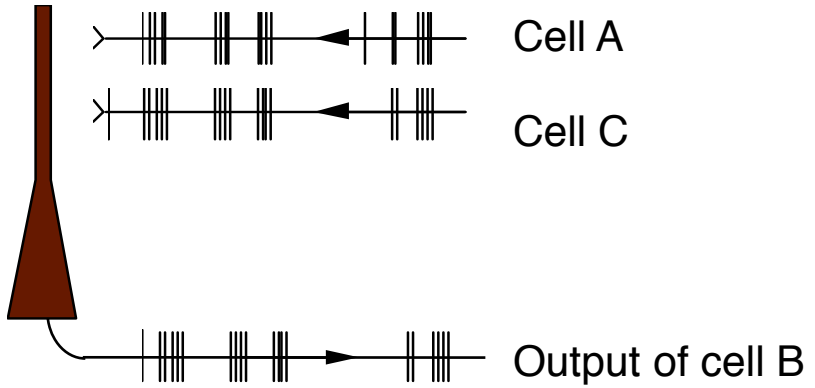
- This talk will be about the so-called **phenomenological rules** of synaptic plasticity (= rules of changes of synaptic weights) in biological neurons.

- Phenomenological rules attempt to capture the phenomenon of synaptic plasticity on a higher level without going into details about molecular and biophysical processes that underlie these changes in synapses (albeit trying to have these in mind as much as possible).

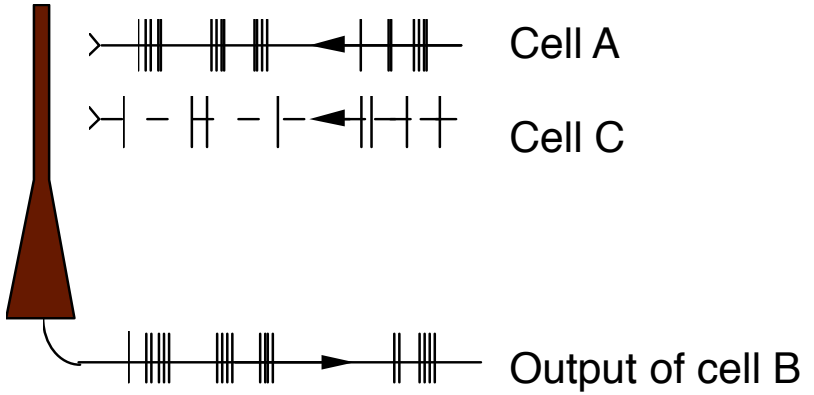
- The relationship between phenomenological rules of synaptic plasticity and more detailed biophysical and biochemical models is similar to the relationship between thermodynamic equations and equations of statistical physics.

Hebb rule (1949)

- When an axon of cell A is near enough to excite a cell B and **repeatedly or persistently** takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased."



Neurons that fire together wire together.



Neurons that fire out of sync lose their link.

Hebb rule: mathematical formulas

$$\dot{w}_j = \eta \, x_j \, y \qquad\qquad y = \sum_j w_j \, x_j$$

- The problem with weights growing to infinity has been solved by modifications like
  - Adding various forms of a decay term (e.g. Oja's rule) or
  - Weigth re-normalization after each update or
  - Setting up the maximal value of the weight.

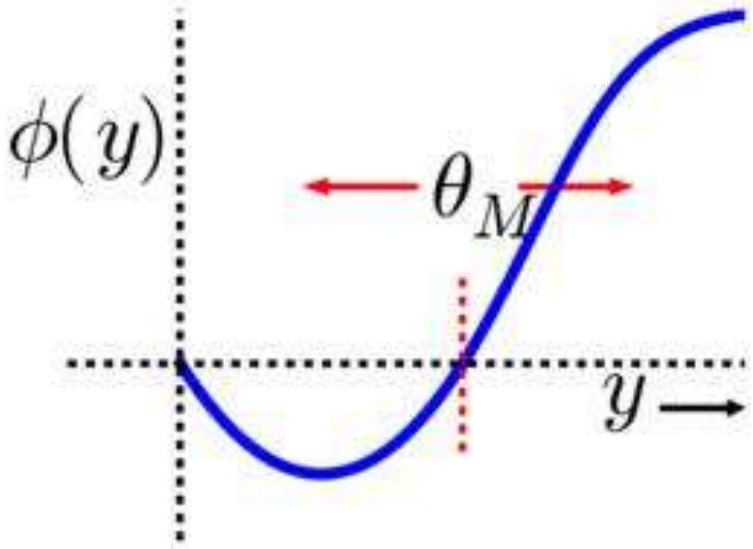
- However, numerous neurobiological experiments have brought results that were in contradiction with the basic Hebb postulate. Therefore a new insight was needed.

Bienenstock, Cooper, Munro (BCM, 1982)

$$y = \sum_j w_j \, x_j$$

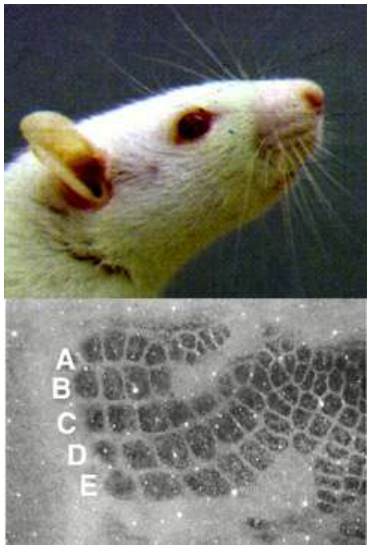
$$\dot{w}_j = \eta \, x_j \, \phi(y, \theta_M)$$

$$\phi(y, \theta_M) = y(y - \theta_M)$$

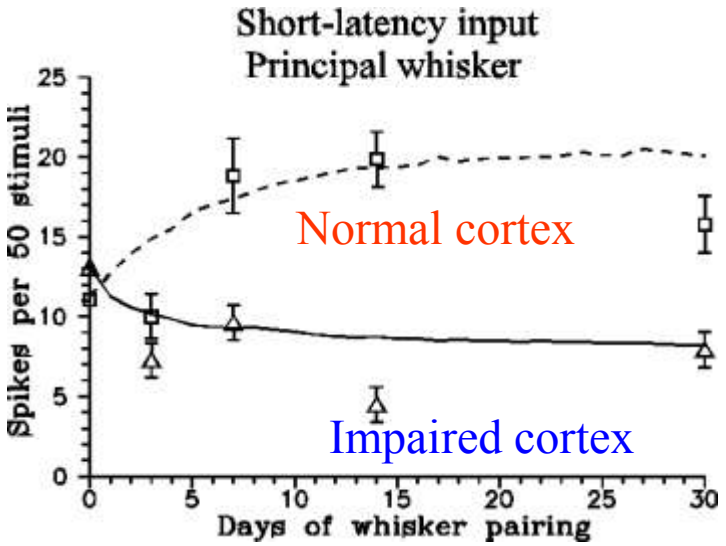


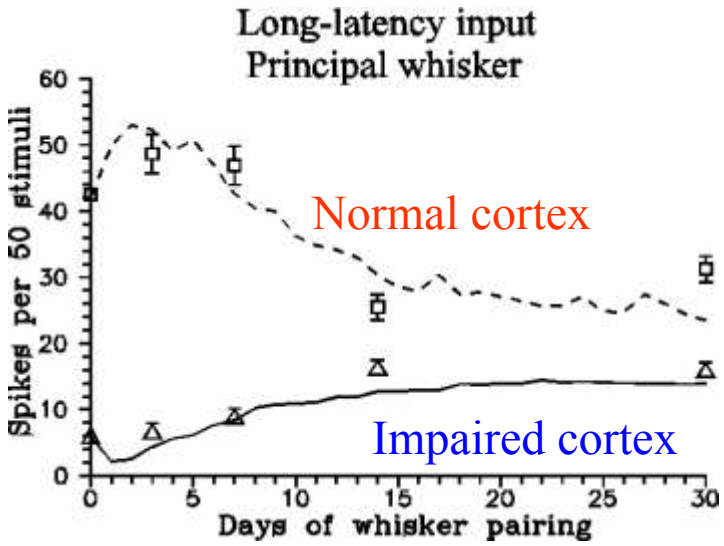
$$\theta_M(t) = E\left[y^2\right] = \left\langle y^2 \right\rangle_\tau = \theta_0 \, \frac{1}{\tau} \int_{-\infty}^{t} y^2(t') e^{-(t-t')/\tau} dt'$$

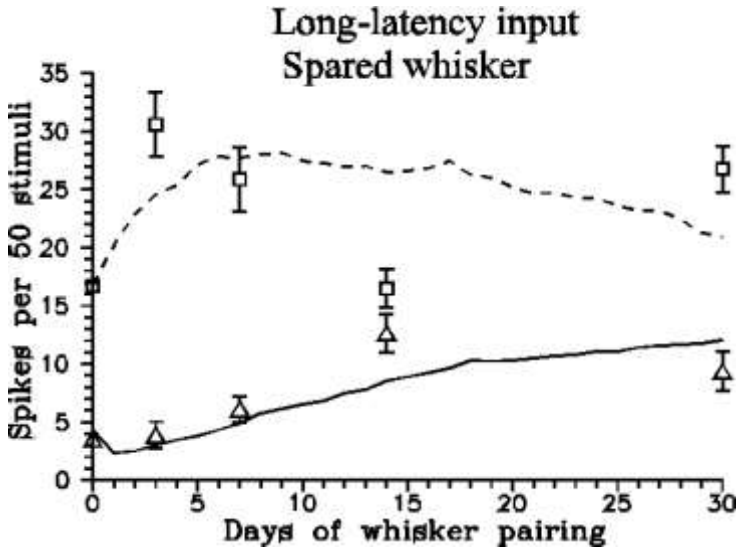
Results for somatosensory cortex of rats



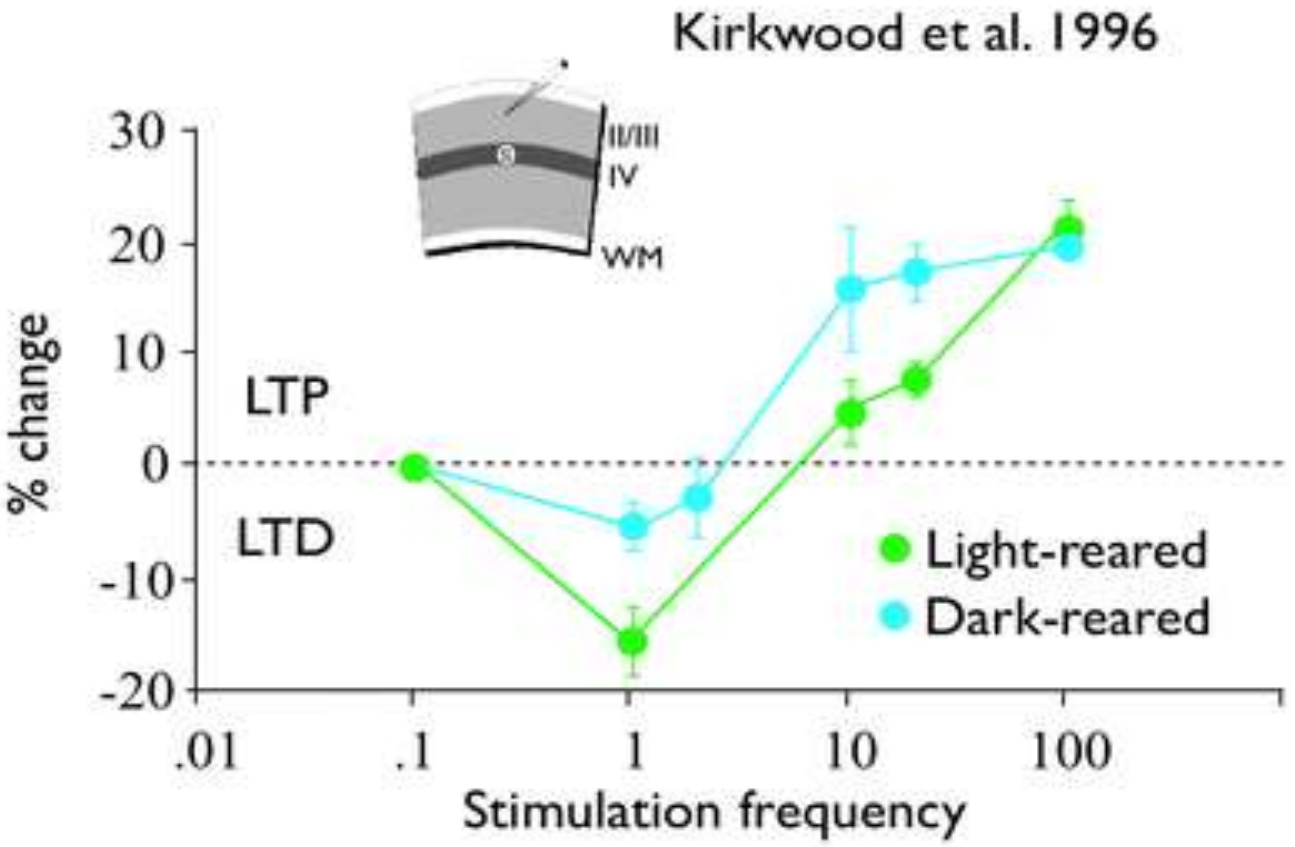
[Benuskova et al., PNAS 1994, 2001]







Experimental evidence for sliding θ_M



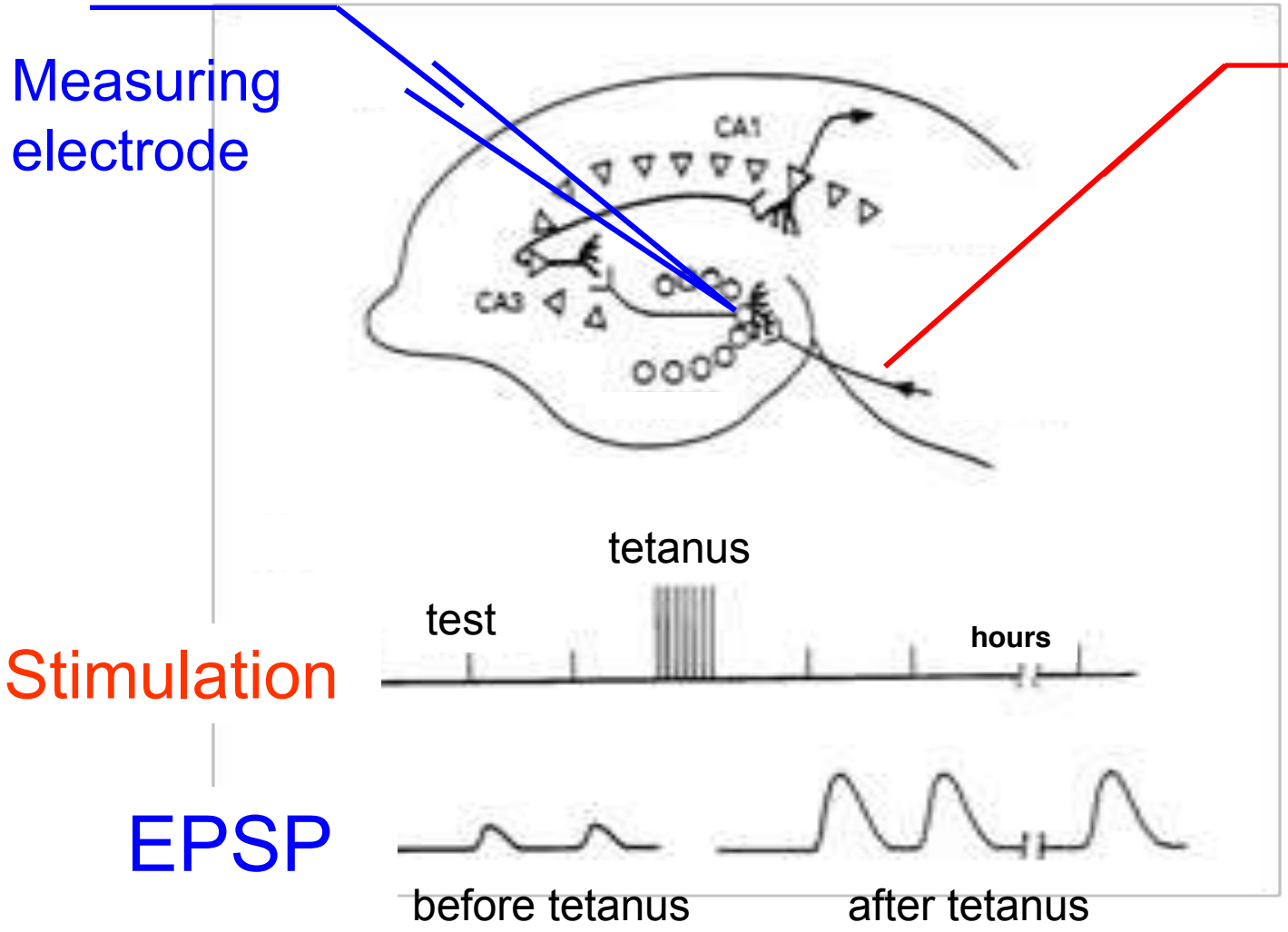
METAPLASTICITY: Position of θ_M depends on the neuron's past activity

(Term coined by Cliff Abraham and Mark Bear, TINS, 1996)

LTP/LTD = long-term potentiation/depression

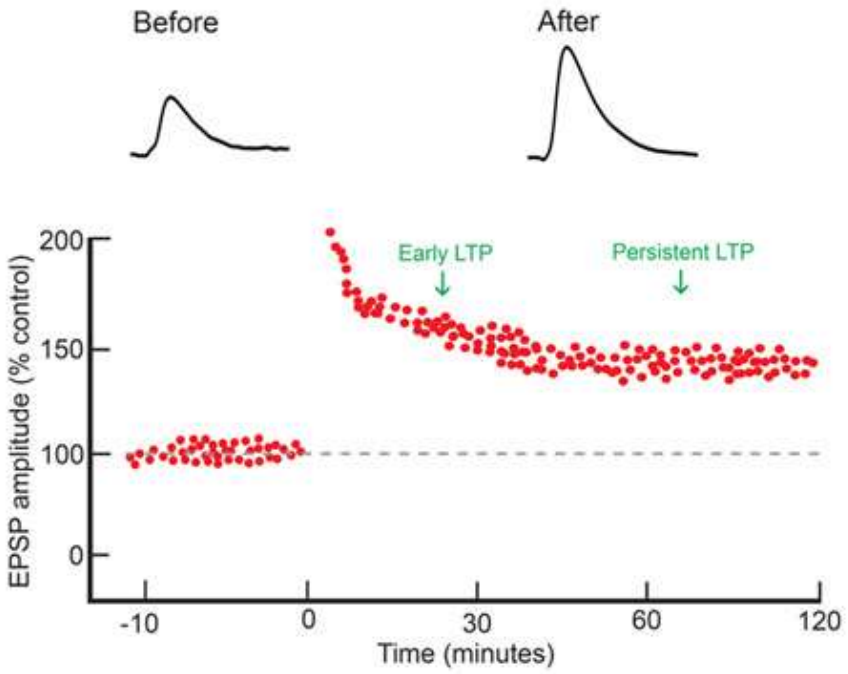
- LTP/LTD are the gold standard synaptic models for mammalian memory mechanisms for 4 decades;
- LTP/LTD occur in hippocampus and in neocortex, which are brain regions involved in formation of long-term memories;
- LTP/LTD are long-lasting synaptic changes; can last for hours, days, weeks even months;
- LTP/LTD are synaptic activity-dependent.
- There is a moving LTD/LTP threshold that depends on the average of postsynaptic activity

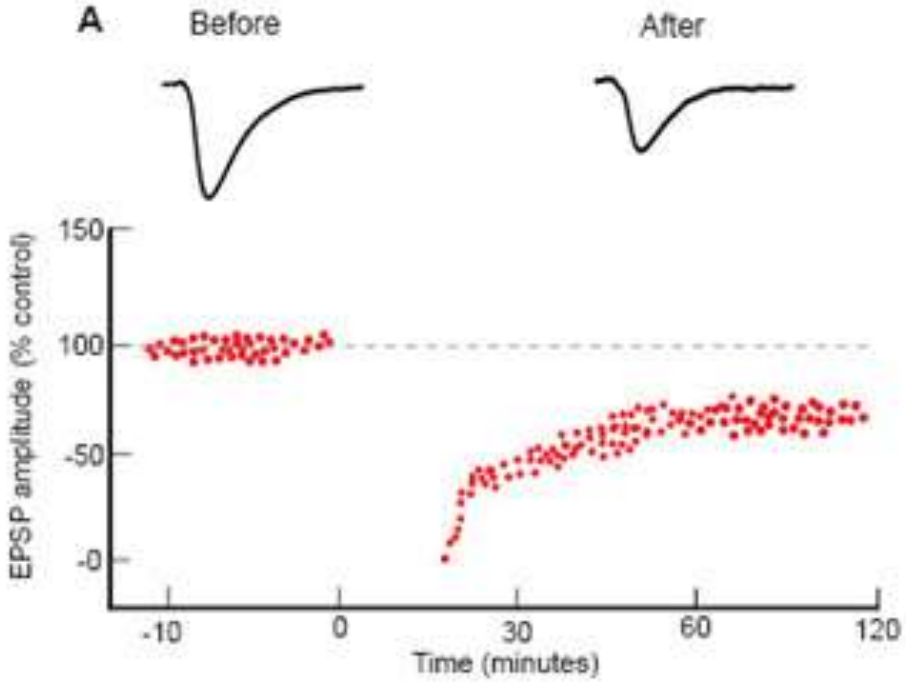
Protocol for induction of LTP



LTP and LTD depends on frequency of tetanus

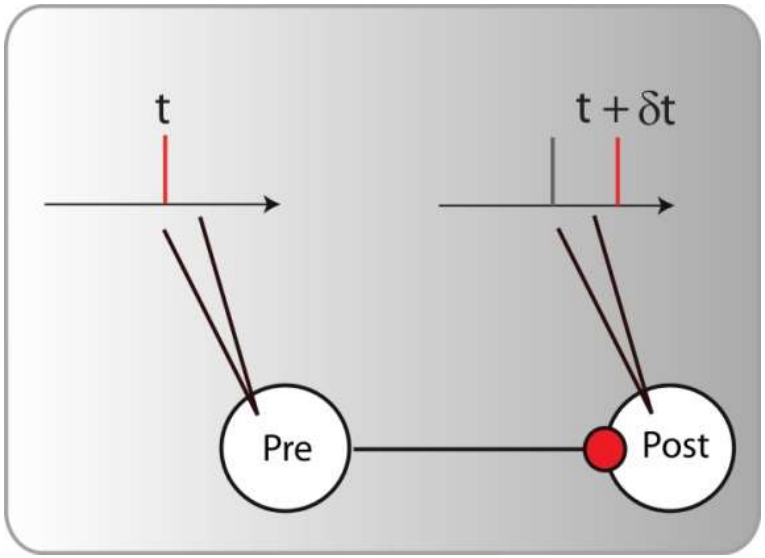
- The same synapse can become potentiated or depressed based on frequency of tetanus:
  - high frequencies ~ 100 Hz induce LTP and
  - low frequencies ~ 1–10 Hz induce LTD





Timing (Markram et al., Science, 1997)

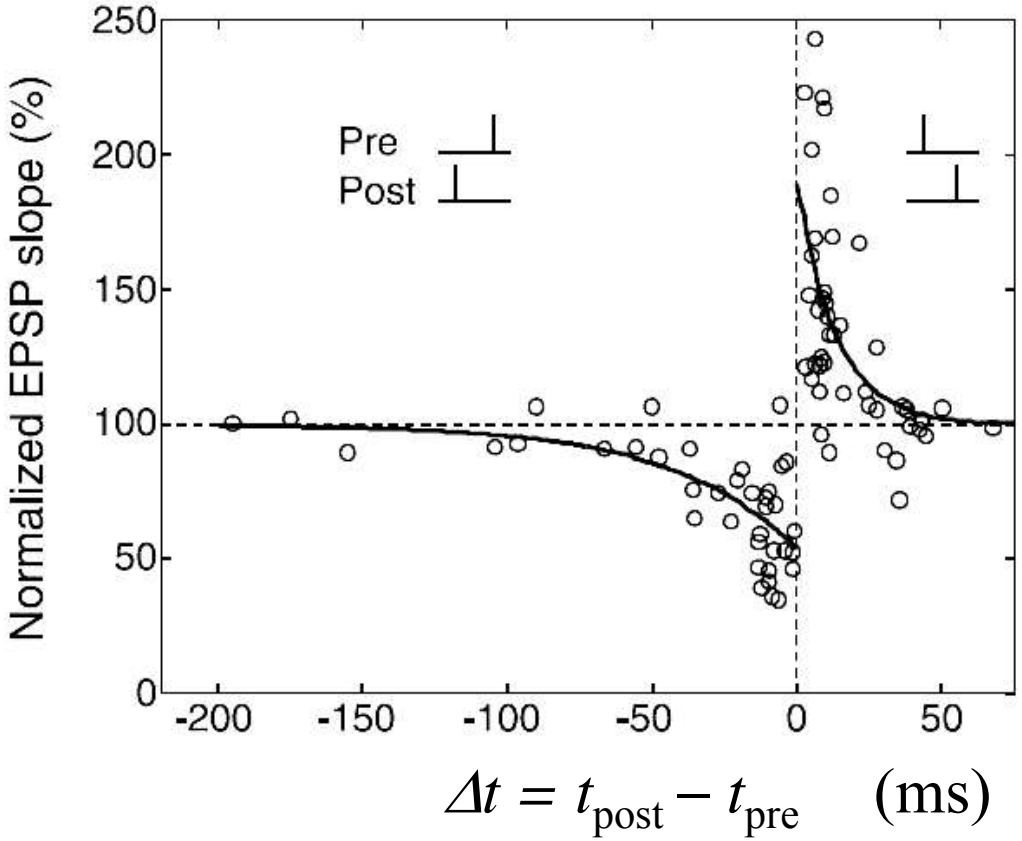
- In 1997, a new phenomenon was discovered – that the sign and magnitude of synaptic weight change depend also on the relative timing of pre- and postsynaptic spikes.



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

STDP: spike-timing dependent plasticity

- Depending on the precise time difference Δt between pre- and post-synaptic spike, the synaptic weight can be either depressed or potentiated and the magnitude of change depends on Δt.



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

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

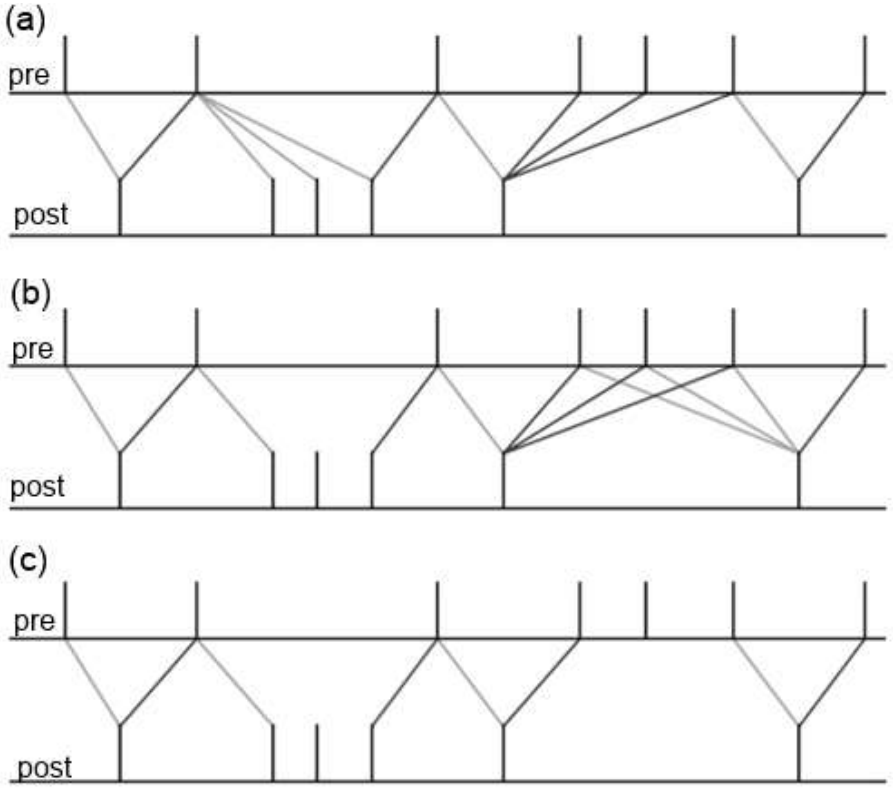
But which spike pairings contribute?

(a) Symmetric interaction – each presynaptic spike is paired with the last postsynaptic spike and each postsynaptic spike is paired with the last presynaptic spike.

(b) Presynaptic centred interaction – each presynaptic spike is paired with the last postsynaptic spike and the next postsynaptic spike.

(c) Reduced symmetric interaction – the same as in (a) but only the closest pairings are considered.

$$\Delta w = \Delta w_+ - \Delta w_-$$



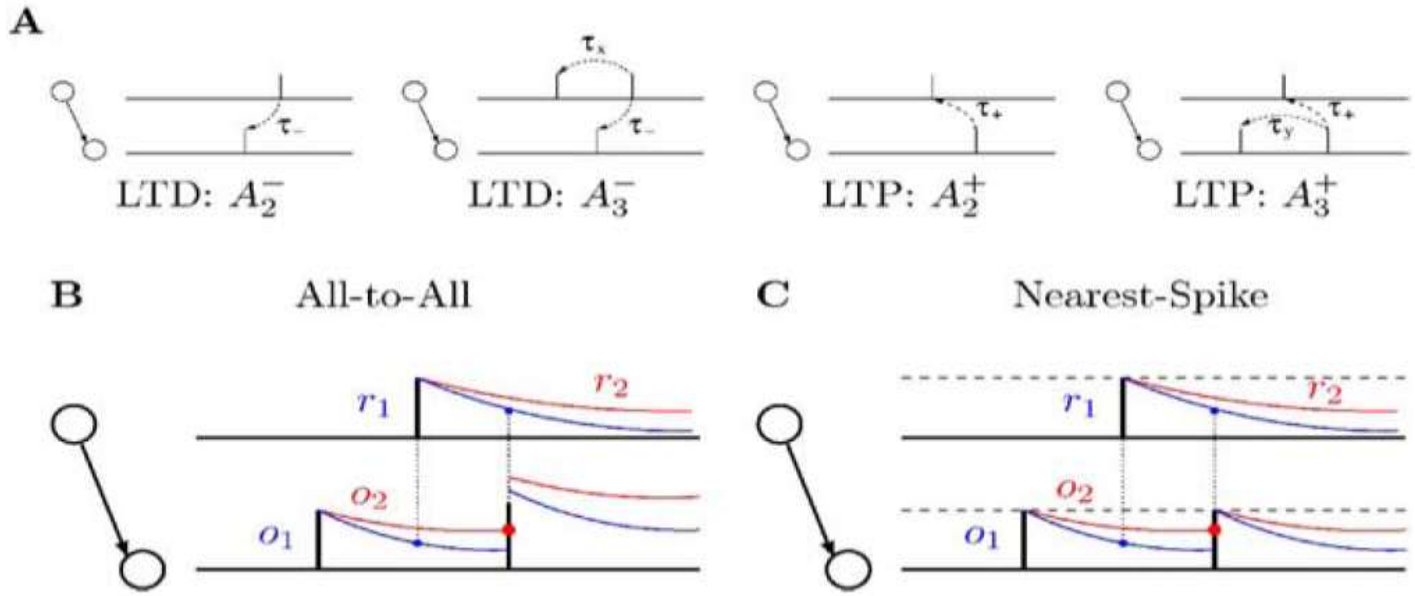
STDP fails

- It has soon become apparent that the STDP fails to account for a number of neurobiological experiments that involve frequency based protocols. (Assumption: if STDP is universal then it underlies all forms of synaptic plasticity.)

- Over last 10 yrs, about 50 modifications of the basic rule have been proposed (for a review see Christian G. Mayr and Johannes Partzsch, Frontiers in Synaptic Plasticity, doi: 10.3389/fnsyn.2010.00033).

- E.g., one of the recent modifications is the suppression model of Froemke et al. (2006), which proposes that $A+$ and $A-$ scale as a function of the complete history of the presynaptic spike train (what would be the biological mechanism for this is quite questionable).

Pfister & Gerstner's 3plet model w hidden variables ('06)



- Schemes of the triplet learning rules. ***A***, Schematic of the two terms contributing to LTD controlled by A^-_2 and A^-_3 and the LTP terms controlled by A^+_2 and A^+_3 . A presynaptic spike after a postsynaptic one (post→pre) induces LTD if the temporal difference is not much larger than τ_-. The presence of a previous presynaptic spike gives an additional contribution (2-pre-1-post triplet term, A^-_3) if the interval between the two presynaptic spikes is not much larger than τ_x. Similarly, the triplet term for LTP depends on one presynaptic spike but two postsynaptic spikes. The presynaptic spike must occur before the second postsynaptic one with a temporal difference not much larger than τ_+. ***B***, and ***C***, time courses of hidden variables *o* and *r*.

Pfister & Gerstner's 3plet model w hidden variables ('06)

- The weight decreases after presynaptic spike arrival by an amount that is proportional to the value of the (hidden) postsynaptic variable o_1 but depends also on the value of the presynaptic detector variable r_2. Hence, presynaptic spike arrival at time t^{pre} triggers a change

$$w(t) \to w(t) - o_1(t)\left[A_2^- + A_3^- r_2(t-\varepsilon)\right] \quad \text{if} \quad t = t^{pre}$$

- A postsynaptic spike at time t^{post} triggers a change that depends on the presynaptic variable r_1 and the second postsynaptic variable o_2 as follows:

$$w(t) \to w(t) - r_1(t)\left[A_2^+ + Ao_2(t-\varepsilon)\right] \quad \text{if} \quad t = t^{post}$$

- Here all *A*'s are constant amplitudes of change and variables o's and r's obey there own differential equations, and ε is a small positive constant.

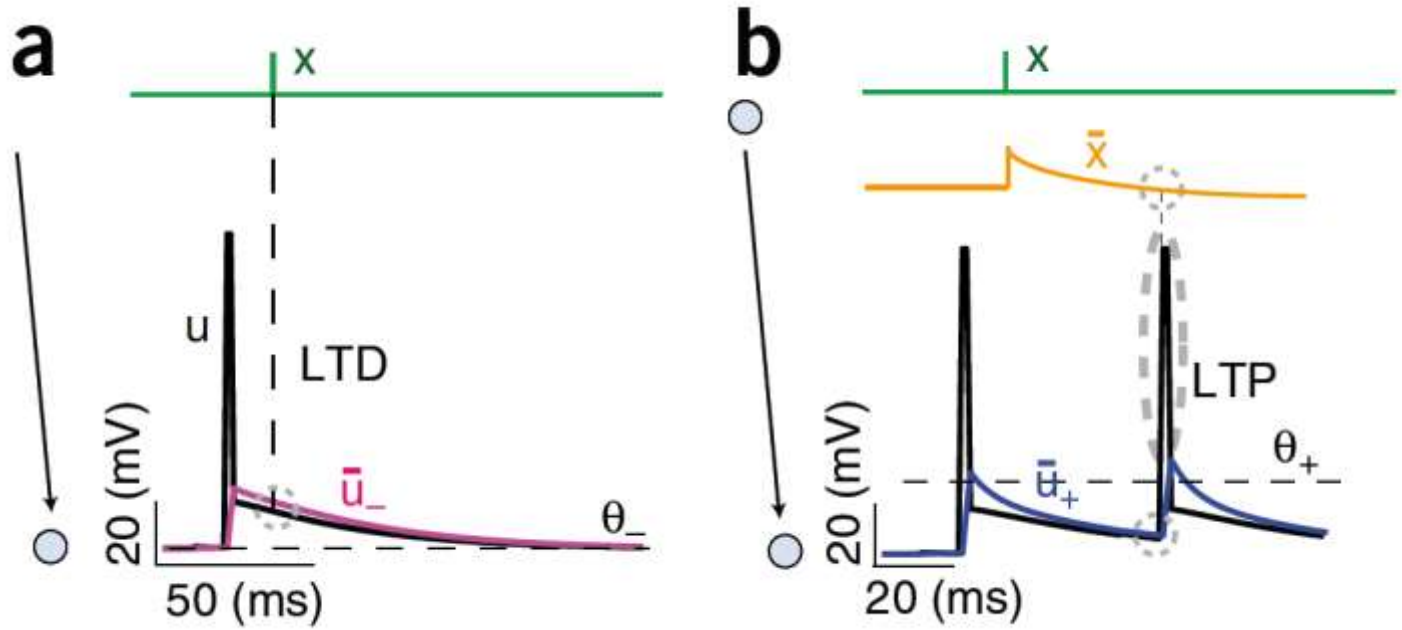
Critique of STDP as a unifying principle

- All these modifications of STDP explain results of different experimental protocols, different experimental conditions (in vitro vs. in vivo, etc), and experiments in different brain areas and sub-areas.

- Lisman, J., and Spruston, N. (2010). Front. Syn. Neurosci. doi: 10.3389/fnsyn.2010.00140, argued that postsynaptic depolarization rather than a spike is necessary and sufficient for the explanation of most experimental results that have usually been interpreted within the STDP framework.

- Direct evidence for STDP *in vivo* is **limited**. The studies use long-lasting large-amplitude postsynaptic potentials (PSP), and pairing usually involves multiple postsynaptic spikes or high repetition frequencies.

Clopath, Büsing, Vasilaki, Gerstner (Nat. Neurosci. 2010)



- (**a**) The synaptic weight is decreased if a presynaptic spike x (green) arrives when the low-pass-filtered value $\bar{u}_-$ (magenta) of the membrane potential is above θ_- (dashed horizontal line). (**b**) The synaptic weight is increased if the membrane potential u (black) is above a threshold θ_+ and the low-pass-filtered value of the membrane potential $\bar{u}_+$ (blue) is higher than a threshold θ_- and the presynaptic low-pass filter x (orange) is nonzero.

Voltage-based STDP with homeostasis

- The final weight change formula in combination with the hard bounds $w_{\min} \le w \le w_{\max}$ is

$$\dot{w} = -A_{LTD}(\langle u \rangle) X (\bar{u}_- - \theta_-)_+ + A_{LTP} \bar{x} (u - \theta_+)_+ (\bar{u}_+ - \theta_-)_+$$

- Where A_{LTP}, θ_- and θ_+ are constants, A_{LTD} is proportional to the average of a recent postsynaptic voltage, i.e. $A_{LTD} = A_0 \langle u \rangle$ (homeostasis), variable X is the series of presynaptic spikes occurring at times t_n, i.e.

$$X(t) = \sum_n \delta(t - t_n)$$

- And all other membrane voltage u variables obey exponential differential equations.

Our contribution to the chaos

- Us: Me, Cliff Abraham (Otago U) + Peter Jedlička (Goethe U) + our students (Azam Shirrafi Ardekani, Nick Hananeia)

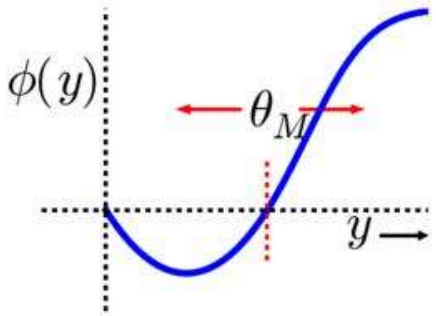
- Our strategy: Keep it simple as possible, but not any more simple.

STDP leads to BCM frequency threshold

- In 2003, Izhikevich and Desai showed the presynaptically centered (scheme b, slide 13) classical pair-wise STDP yields LTD / LTP threshold in the frequency domain:

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

$$= x\left(\frac{A_+}{\tau_+^{-1} + x} + \frac{A_-}{\tau_-^{-1} + x}\right) = 0 \quad \Rightarrow \quad \theta_M = -\frac{A_+/\tau_- + A_-/\tau_+}{A_+ + A_-}$$



- Amplitudes A's and decays τ's of potentiation and depression windows, are constants.
- However, in the original BCM theory, θ_M changes as a function of the average previous activity of a neuron.

STDP with "metaplasticity"

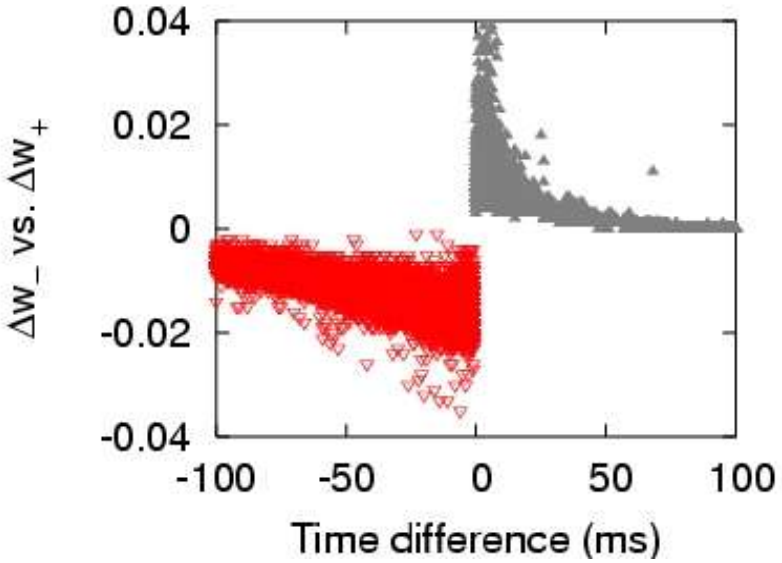
- Benuskova and Abraham (2007) introduced changing LTD/LTP amplitudes according to average postsynaptic activity:

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

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

$$A_+^t = A_+^0 \big/ \langle c \rangle_\tau$$

$$A_-^t = A_-^0 \; \langle c \rangle_\tau$$

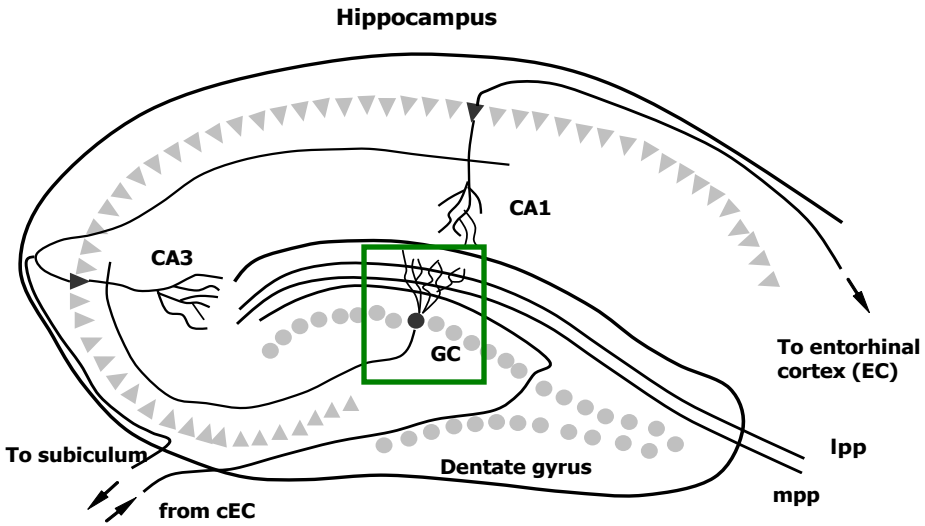


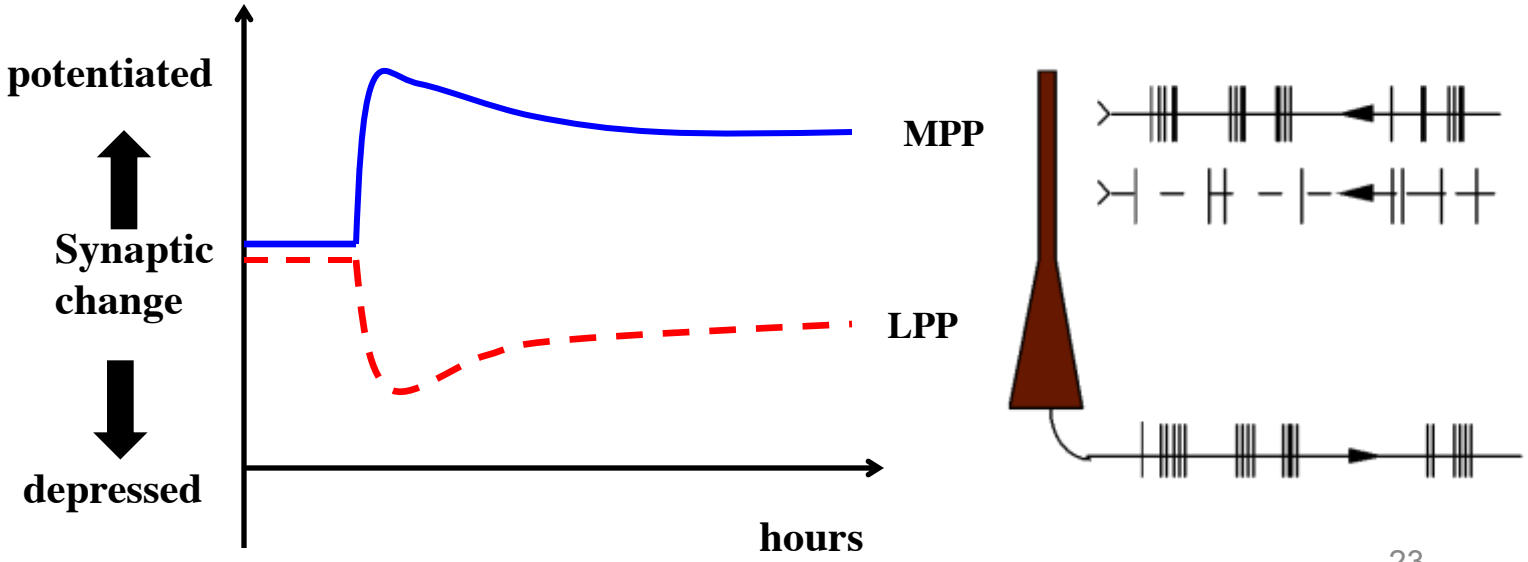
$$\langle c \rangle_\tau = \frac{c_0}{\tau} \int_{-\infty}^{t} c(t') \exp\left(\frac{-(t-t')}{\tau}\right) dt' \quad \text{where } c(t') = \begin{cases} 1 & \text{if there is a postsynaptic spike} \\ 0 & \text{if there is no postsynaptic spike} \end{cases}$$

* Works also when c is replaced with PSP !

Experimental data: tetanus of MPP leads to homosynaptic potentiation of MPP and **hetero**synaptic depression of LPP

[Abraham et al, PNAS 2001]



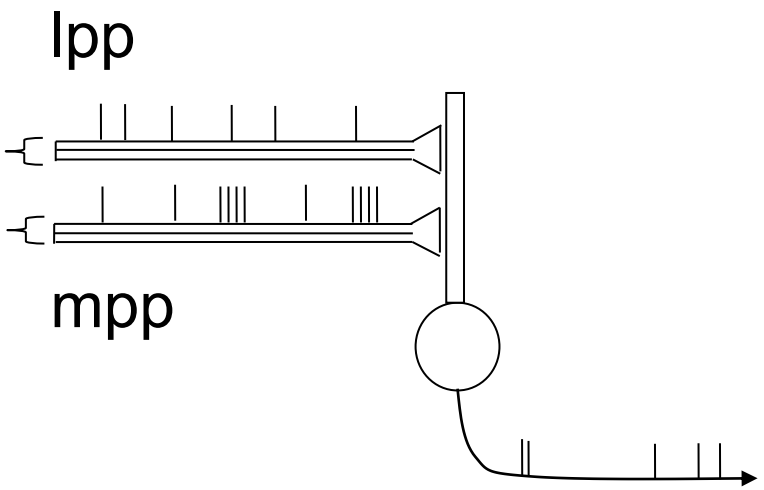


Izhikevich model of spiking neuron

$$\dot{v} = 0.04v^2 + 5v + 140 - u + I$$

$$\dot{u} = a(bv - u)$$

$$\text{if} \quad v \geq \text{AP}, \quad \text{then} \begin{cases} v \leftarrow c \\ u \leftarrow u + d \end{cases}$$



$$I = s_{\text{mpp}}\, w_{\text{mpp}}\, N_{\text{mpp}} + s_{\text{lpp}}\, w_{\text{lpp}}\, N_{\text{lpp}}$$

$$s_{\text{mpp/lpp}} = \begin{cases} 1 & \textit{if there is presynaptic spike} \\ 0 & \textit{otherwise} \end{cases}$$

Assumptions of the model

- The STDP rule is allowed to dynamically change the amplitudes of LTP and LTD according to the previous mean spike count of the postsynaptic neuron or the average of previous membrane voltage over short time ~ 1min (the results are the same).

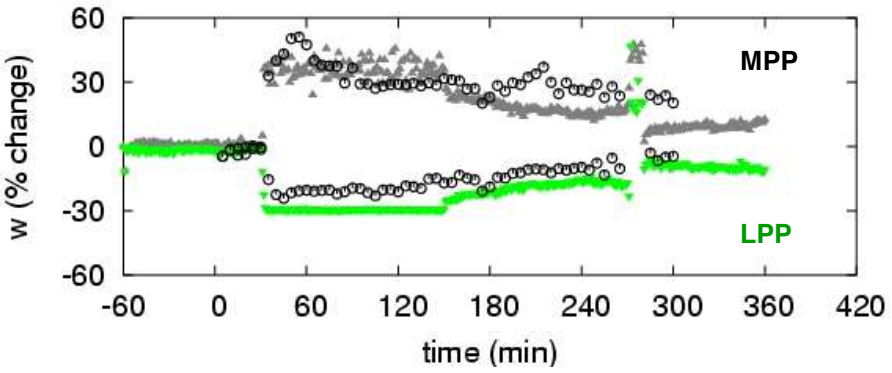
- We simulate the pre- and postsynaptic **spontaneous spiking** activity, which is random but correlated between LPP and MPP at the theta frequency because experiments were done *in vivo*.

- We temporarily de-correlate the spiking activity of MPP and LPP pathways during LTP induction (Benuskova & Abraham, *J. Comp. Neurosci.*, 2007).

Results of STDP with metaplasticity (homeostasis)

- Tetanus consisted of 1440, 50 or 10 trains of ten pulses at 400 Hz. It was delivered in bursts of 5–6 trains at 1-s intervals, with 30–120 s between bursts, depending on the protocol.

a



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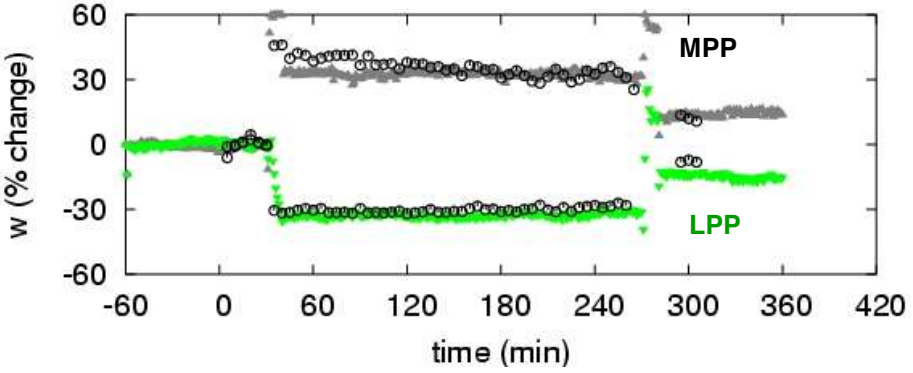

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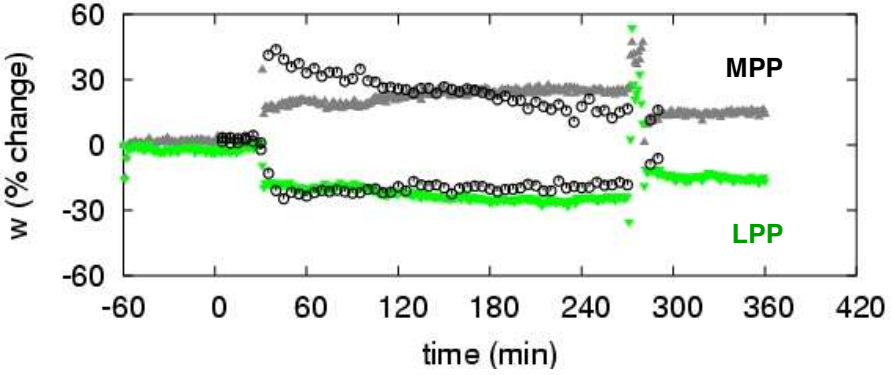

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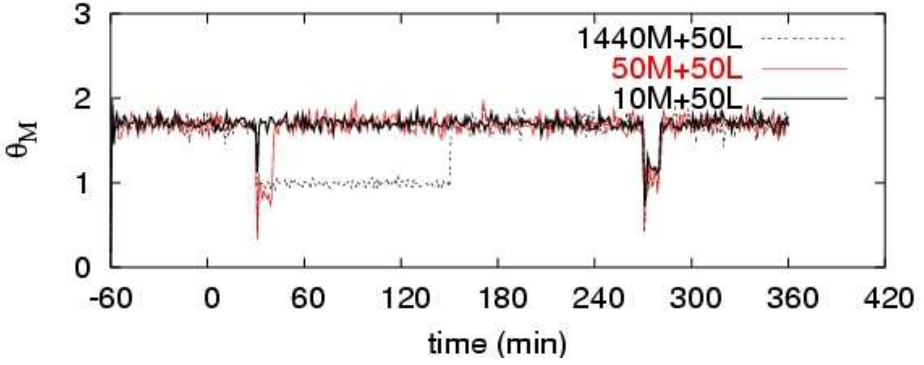
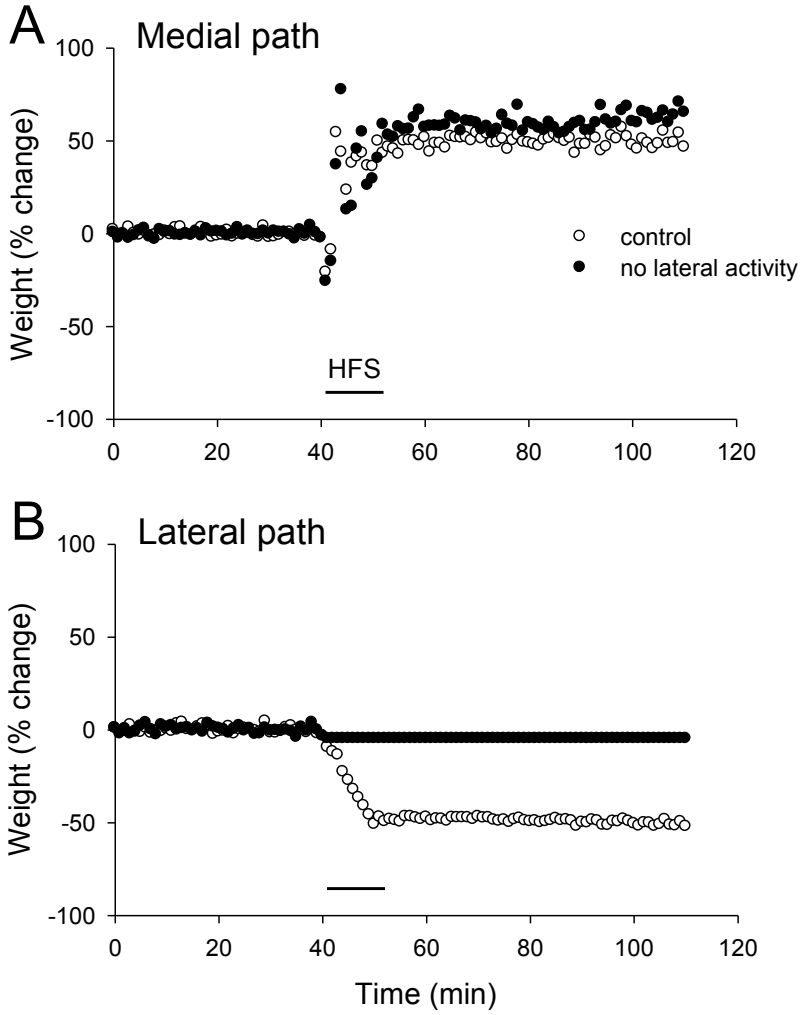


Prediction from this model: if the spontaneous activity (noise) is blocked so is the hetero-plasticity

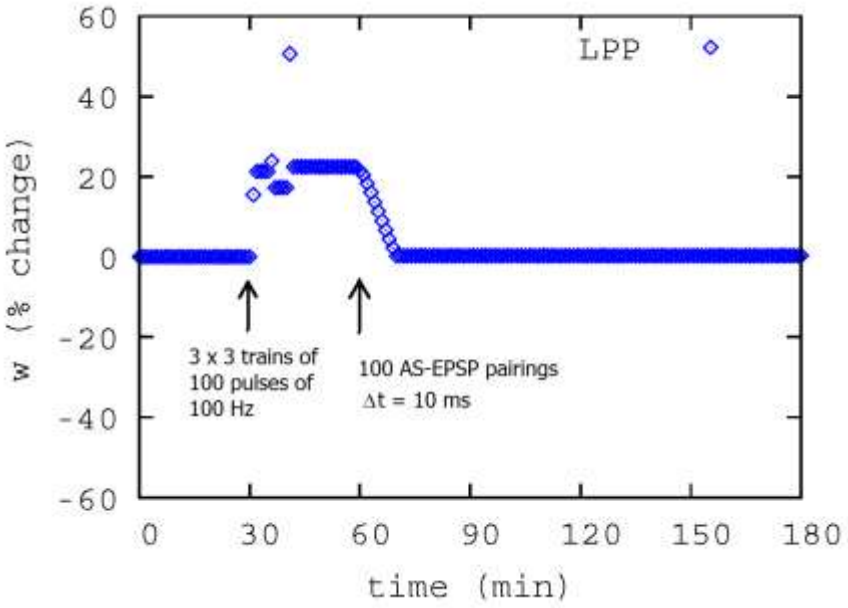


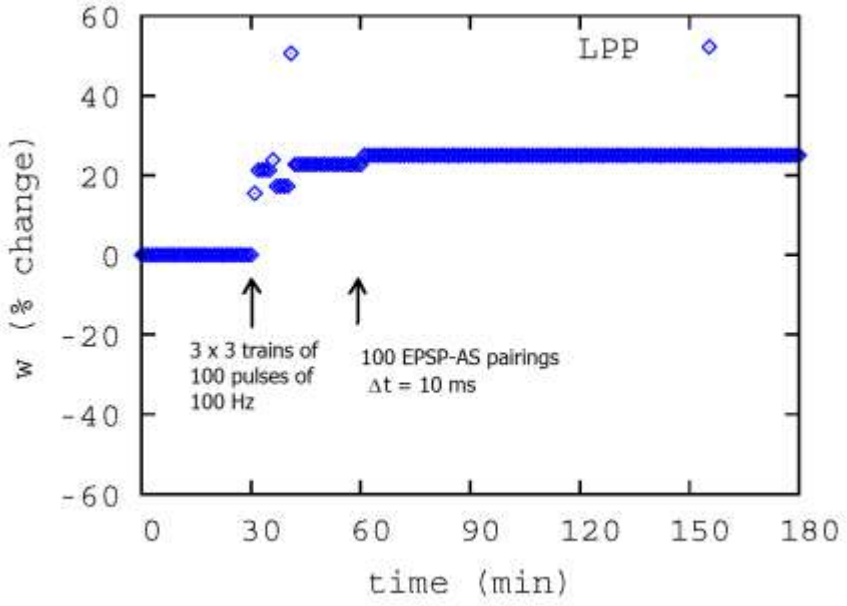
Abraham WC, Logan B, Wolff A, Benuskova L :

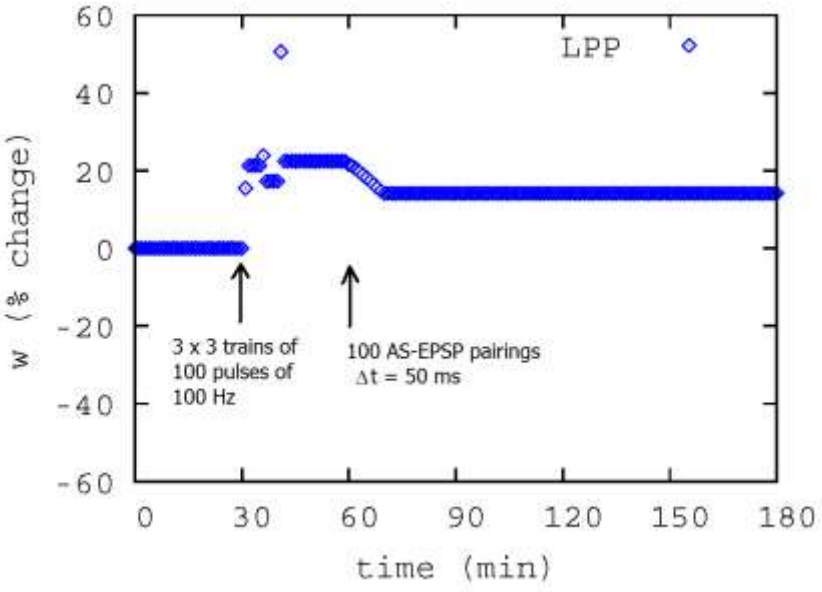
"Heterosynaptic" LTD in the dentate gyrus of anesthetized rat requires homosynaptic activity.

Journal of Neurophysiology, 98: 1048-1051, 2007.

Interplay between frequency and STDP



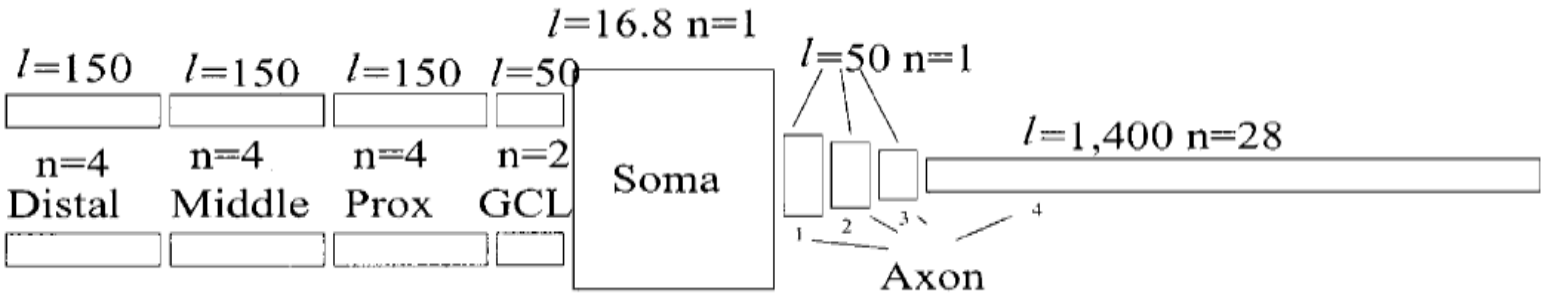




Simulations of *in vitro* results from Lin et al., J. Eur. Neuroscience, 2006.

Compartmental model of granule cell

- Aradi and Holmes (1999) developed a realistic compartmental model of the granule cell and Schmidt-Hieber implemented it in NEURON.



- In the reduced morphology model there are six regions of the DG cell having different distributions of voltage-activated channels—the soma, axon, granule cell layer dendrites, proximal, middle, and distal dendrites. Parameters l denotes the length in μm of a segment where channels are distributed uniformly, and n is the number of compartments.
- 150 MPP synapses are created at the middle parts of the dendrites and 150 LPP synapse are created at the distal parts of the dendrites.

Compartmental model of granule cell

- Differential equation for the membrane voltage reads:

$$
\begin{aligned}
C_{\mathrm{m},j}\frac{\mathrm{d}V_j}{\mathrm{d}t} &= g_{\mathrm{Na},j}m_j^3h_j(E_{\mathrm{Na}}-V_j)+g_{\mathrm{fKDR},j}n_{\mathrm{f},j}^4(E_{\mathrm{K}}-V_j)\\
&\quad+g_{\mathrm{sKDR},j}n_{\mathrm{s},j}^4(E_{\mathrm{K}}-V_j)+g_{\mathrm{KA},j}k_jl_j(E_{\mathrm{K}}-V_j)\\
&\quad+g_{\mathrm{TCa},j}a_j^2b_j(E_{\mathrm{Ca}}-V_j)+g_{\mathrm{NCa},j}c_j^2d_j(E_{\mathrm{Ca}}-V_j)\\
&\quad+g_{\mathrm{LCa},j}e_j^2(E_{\mathrm{Ca}}-V_j)+g_{\mathrm{BK},j}r_js_j^2(E_{\mathrm{K}}-V_j)\\
&\quad+g_{\mathrm{SK},j}q_j^2(E_{\mathrm{K}}-V_j)+g_L(E_L-V_j)+r_{j,j+1}(V_{j+1}-V_j)\\
&\quad+r_{j,j-1}(V_{j-1}-V_j)+I_{\mathrm{syn(e)}}^X \qquad (1)
\end{aligned}
$$

$$
\begin{aligned}
\frac{\mathrm{d}z_j}{\mathrm{d}t} &= \alpha_{z,j}-(\alpha_{z,j}+\beta_{z,j})z_j\\
&\quad (z_j : m_j, h_j, n_{f,j}, n_{s,j}, k_j, l_j, a_j, b_j, c_j, d_j, e_j, r_j, q_j), \qquad (2)
\end{aligned}
$$

$$
\frac{\mathrm{d}s_j}{\mathrm{d}t}=\frac{s_\infty-s_j}{\tau_s} \quad (s_\infty = 1/(1+4/[\mathrm{Ca}^{2+}]_j)), \qquad (3)
$$

$$
\frac{\mathrm{d}[\mathrm{Ca}^{2+}]_j}{\mathrm{d}t}=B_j(I_{\mathrm{TCa},j}+I_{\mathrm{NCa},j}+I_{\mathrm{LCa},j})-\frac{[\mathrm{Ca}^{2+}]_j-[\mathrm{Ca}^{2+}]_\infty}{\tau}. \qquad (4)
$$

Compartmental model of granule cell

- Equations for the excitatory synaptic current are as follows:

$$I^{X}_{syn(e)} = g^{X}_{syn(e)}(E_{syn(e)} - V_k)$$

$$g^{X}_{syn(e)} = w^{X}\left(\exp\left(-\frac{t}{\tau_{1,X}}\right) - \exp\left(-\frac{t}{\tau_{2,X}}\right)\right)$$

- Where X stands for MPP or LPP, E is the equilibrium potential for excitatory synapses, V_k is the membrane voltage at synapse k, g is membrane conductance, which obeys the double exponential equation with rise τ_2 and decay τ_1 constants.
- Parameter w is the synaptic weight that is updated according to our STDP rule with metaplasticity (implemented by Peter Jedlička).

STDP with "metaplasticity"

- Since now we have dendrites with passive membrane properties and spatio-temporal summation of PSPs, DT is calculated as

$$\Delta t = t_{\text{post}} - t_{\text{pre}}$$

- Where t_{post} = time when V_k > -37 mV. This can happen either as a result of backpropagating AP and/ or spatio-temporal summation of PSPs.

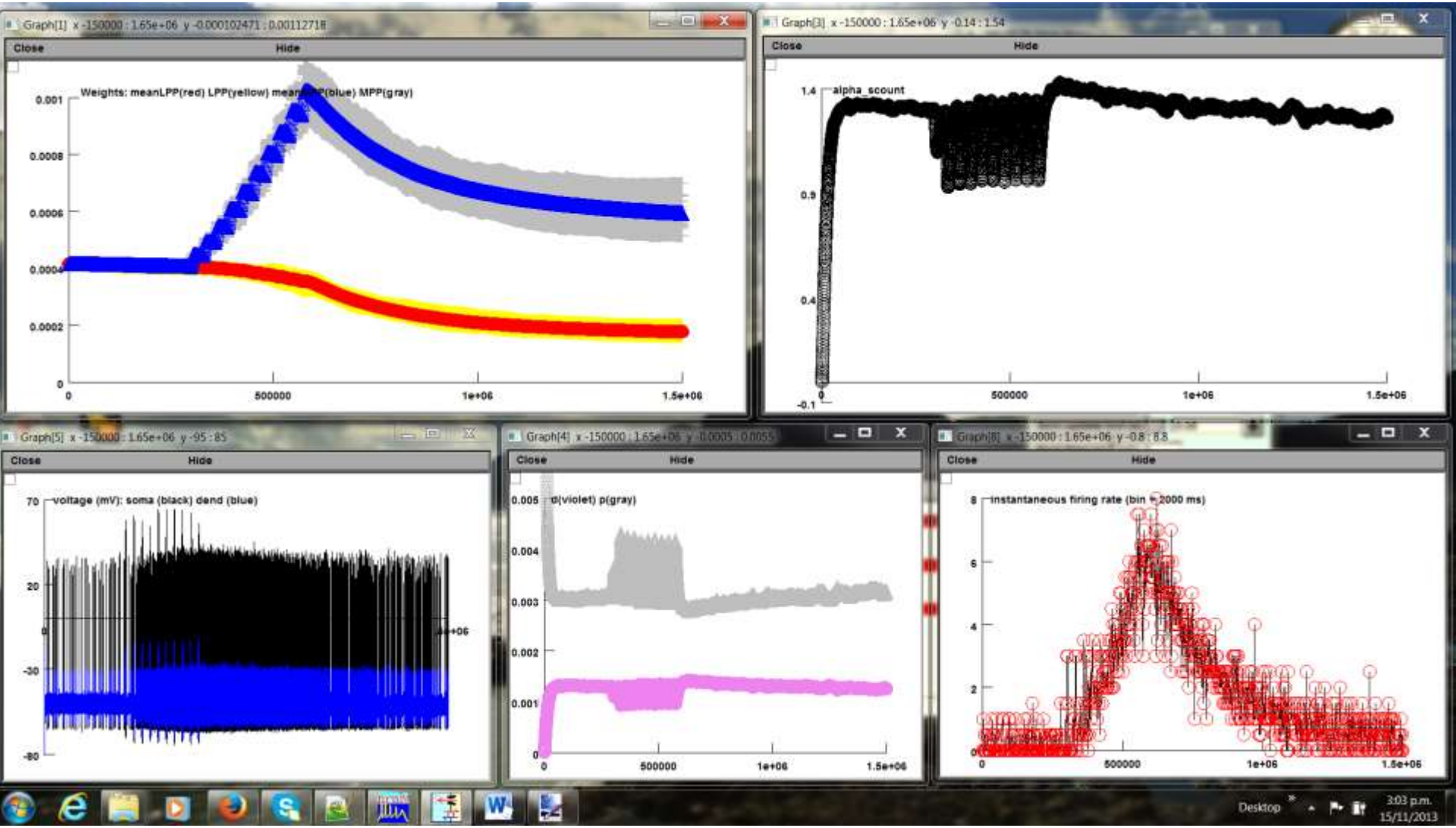
$$\Delta w_+ = A_+^t \, e^{-\Delta t/\tau_+} \qquad A_+^t = A_+^0 \big/ \langle c \rangle_\tau$$

$$\Delta w_- = A_-^t \, e^{\Delta t/\tau_-} \qquad A_-^t = A_-^0 \, \langle c \rangle_\tau$$

$$\langle c \rangle_\tau = \frac{c_0}{\tau} \int_{-\infty}^{t} c(t') \exp\left(\frac{-(t-t')}{\tau}\right) dt' \quad \text{where } c(t') = \begin{cases} 1 & \text{if there is a postsynaptic spike} \\ 0 & \text{if there is no postsynaptic spike} \end{cases}$$

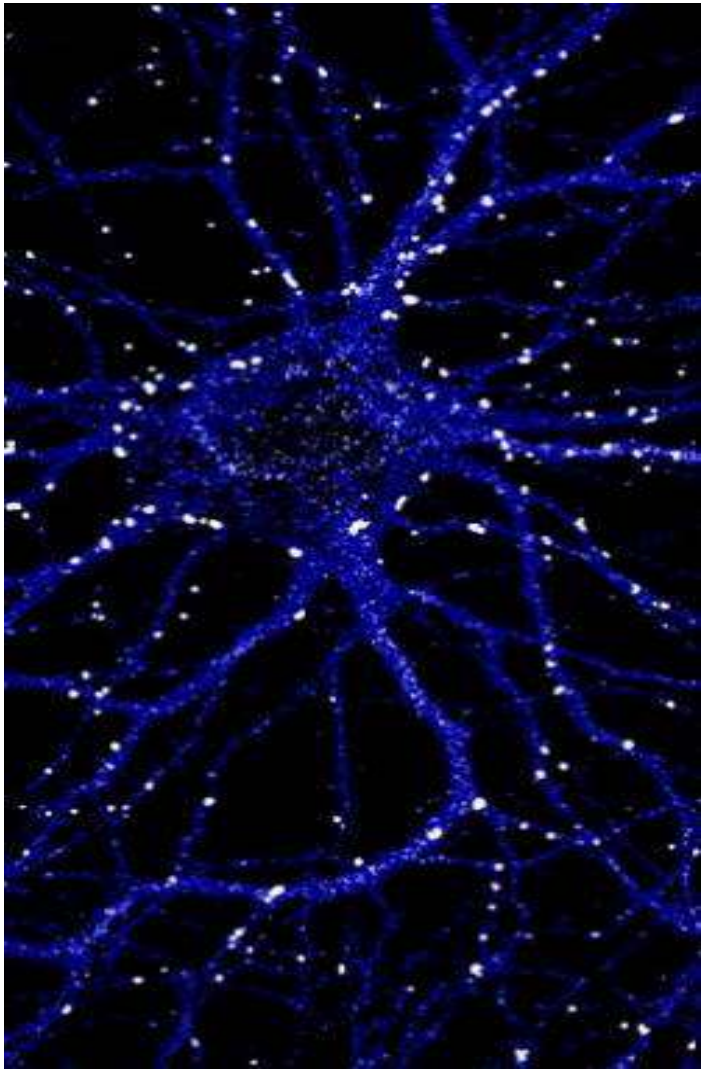
* Note: Works also when c is replaced with PSP.

Results


Graph[1]
Close
Hide
Weights: meanLPP(red) LPP(yellow) mean MPP(blue) MPP(gray)
0.001
0.0008
0.0006
0.0004
0.0002
0
0
500000
1e+06
1.5e+06
Graph[3]
Close
Hide
alpha_scount
1.4
0.9
0.4
-0.1
0
500000
1e+06
1.5e+06
Graph[5]
Close
Hide
voltage (mV): soma (black) dend (blue)
70
20
-30
-80
Graph[4]
Close
Hide
d(violet) p(gray)
0.005
0.004
0.003
0.002
0.001
0
0
500000
1e+06
1.5e+06
Graph[8]
Close
Hide
instantaneous firing rate (bin = 2000 ms)
8
6
4
2
0
0
500000
1e+06
1.5e+06
Desktop
3:03 p.m.
15/11/2013

Summary

- Hebbian rules
- BCM rule
- STDP rules
- Postsynaptic voltage-based rules
- What's next ???



Conclusion?

- "As far as the laws of mathematics refer to reality, they are not certain, and as far as they are certain, they do not refer to reality." (Albert Einstein)