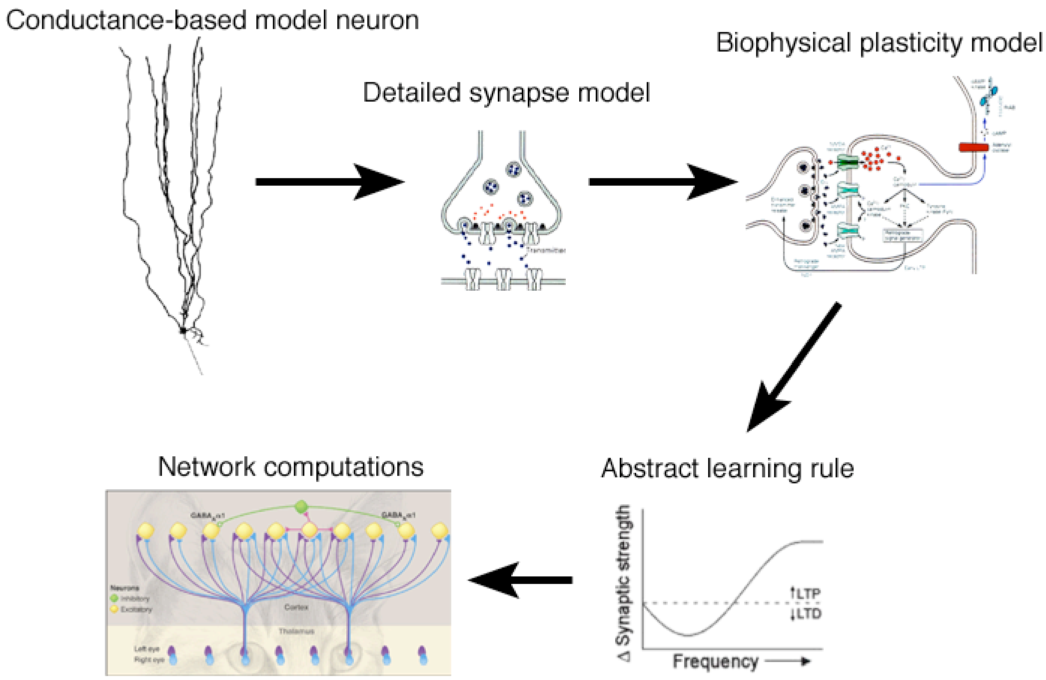
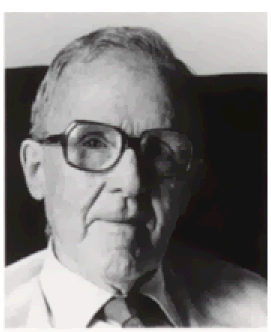
Biophysical models of synaptic plasticity



Course website: http://www.bme.ogi.edu/BME665/

00_title.psd

Long-term Synaptic Plasticity



Donald O. Hebb
(1904–1985)

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.

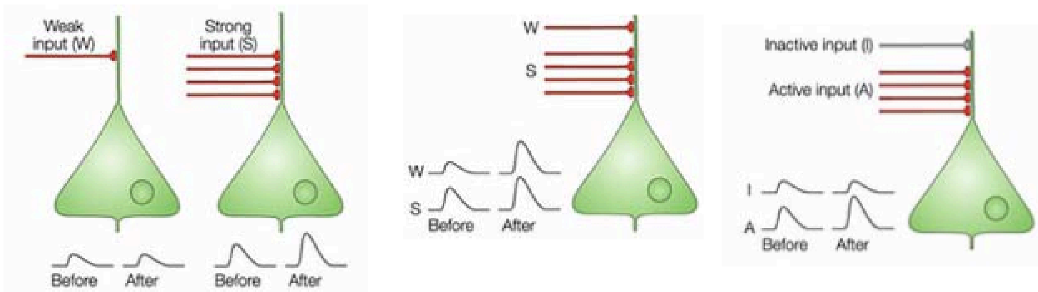
— Donald O. Hebb, 1949

Long-term potentiation (LTP) is a long-term results of A causing B to fire.

01_hebb.psd

LTP properties

A. cooperativity B. associativity C. Synapse specificity

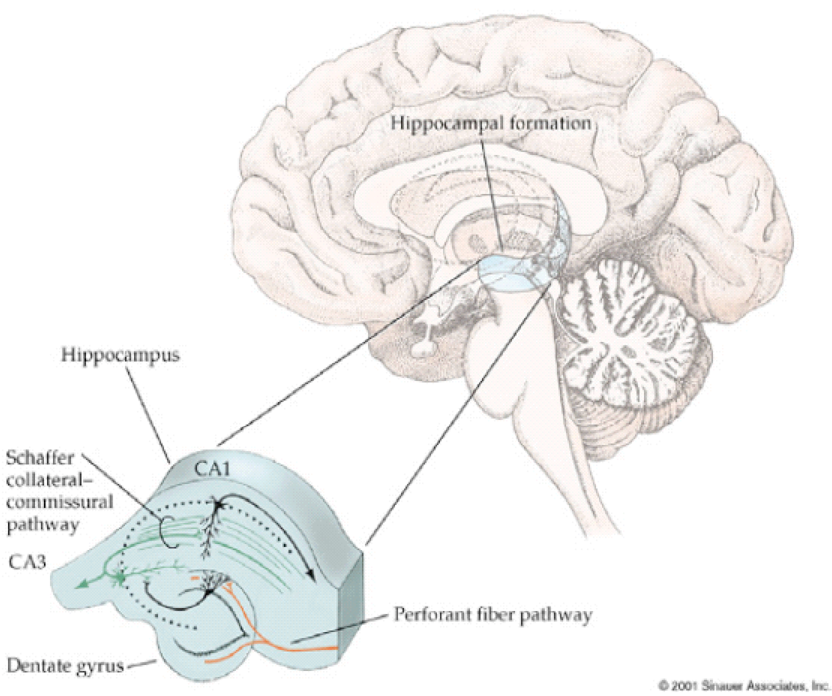


Voltage-dependence of NMDAR

Localization of glutamate and calcium

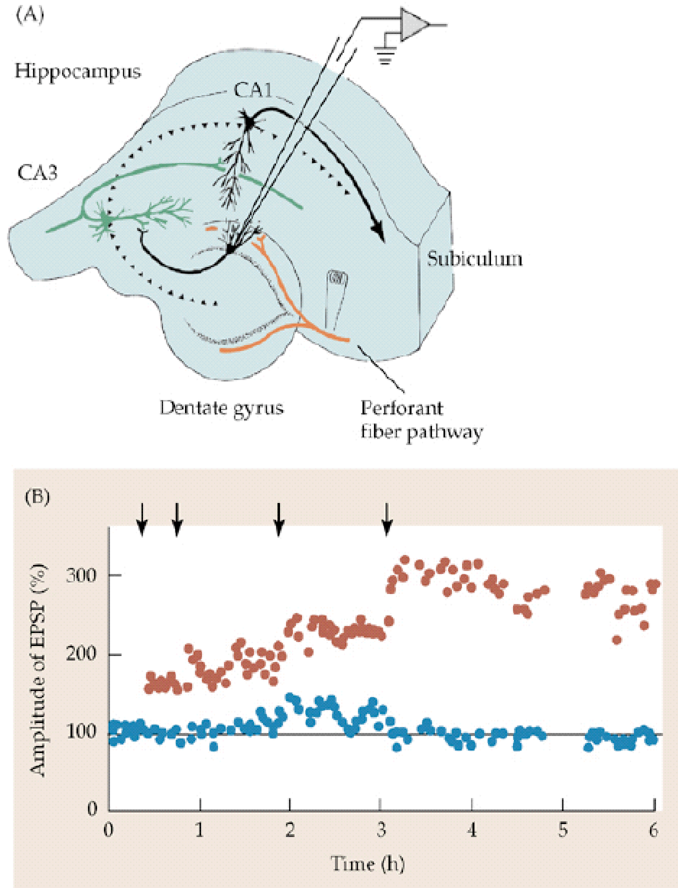
02_ltp_props.pdf

LTP was discovered in the hippocampal formation



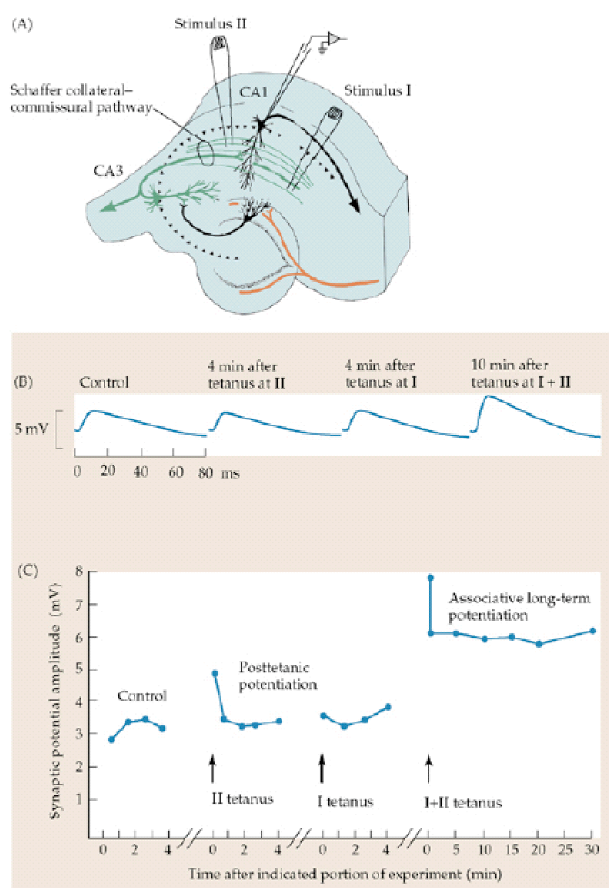
03_hippoLTP.pdf

Homosynaptic LTP in the perforant pathway



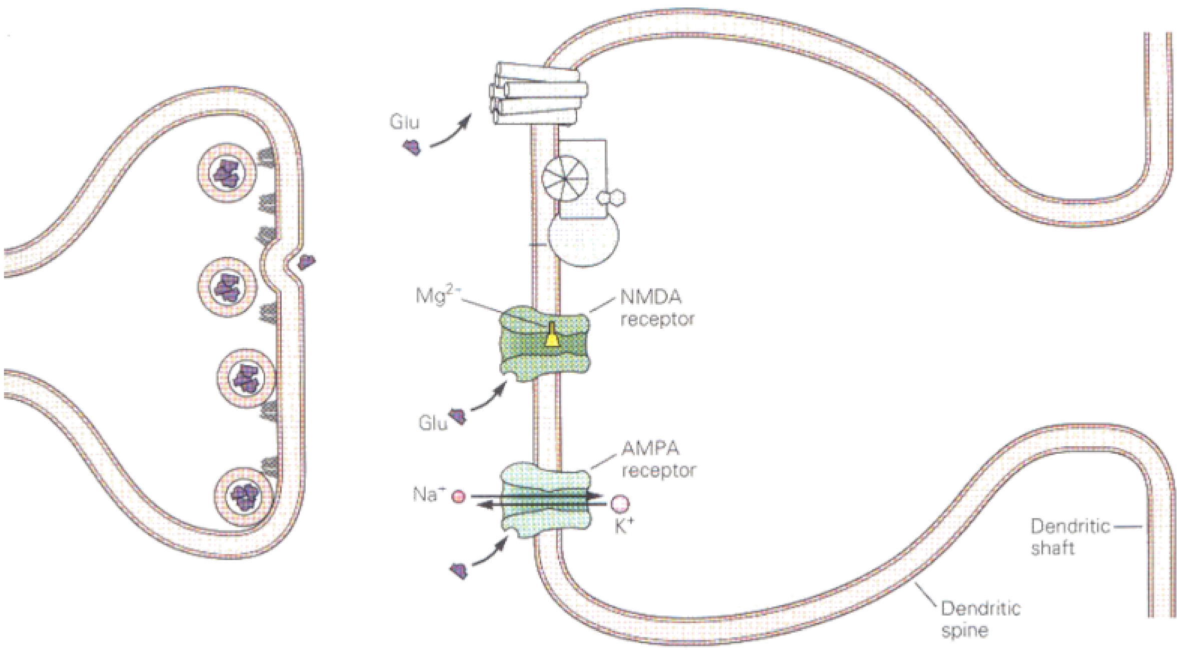
04_hippoLTP2.pdf

Associative LTP in the Schaffer collateral pathway



05_hippoLTP3.pdf

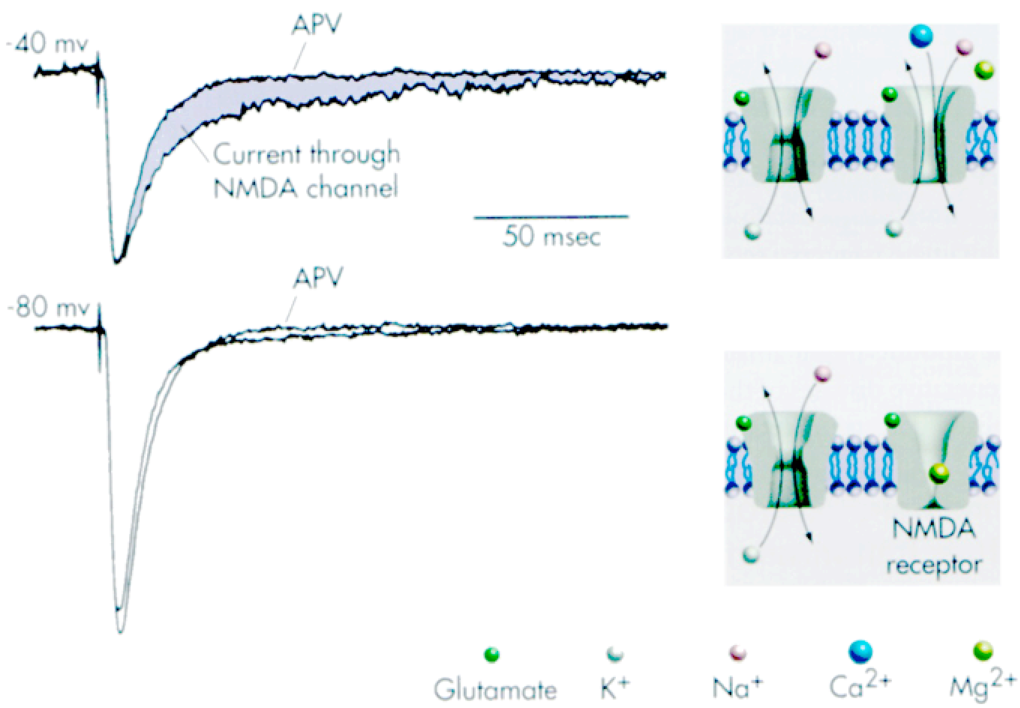
Receptor types: Ionotropic and Metabotropic



Kandel, Schwartz, and Jessell (2000)

07_receptorTypes.psd

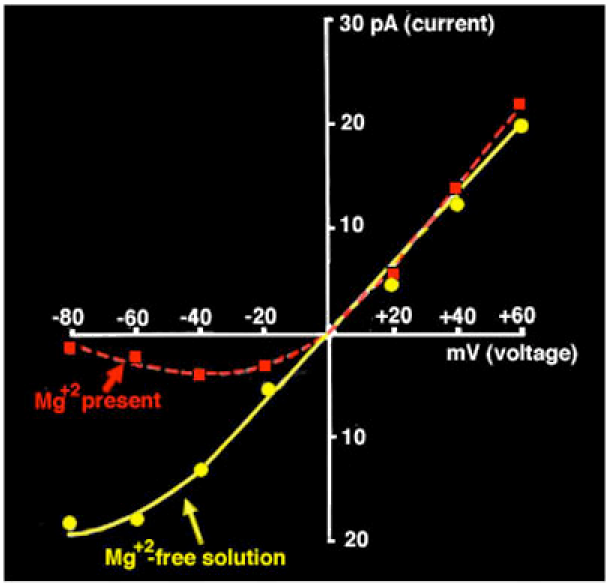
NMDA Receptor: Voltage-gated, Ionotropic Receptor



The Human Brain: An Introduction to Its Functional Anatomy (1999) John Nolte

08_nmdar.psd

Current-Voltage Relation Shows Mg-block



Mg^{+2} ions block NMDA receptor channels in a voltage-dependent manner. In Mg^{+2}-free solutions, the I-V curve is linear. When Mg^{+2} is present, current amplitude is reduced at negative potentials (from Nowak et al., 1984, Fig. 1).

09_i_vs_vNMDAR.psd

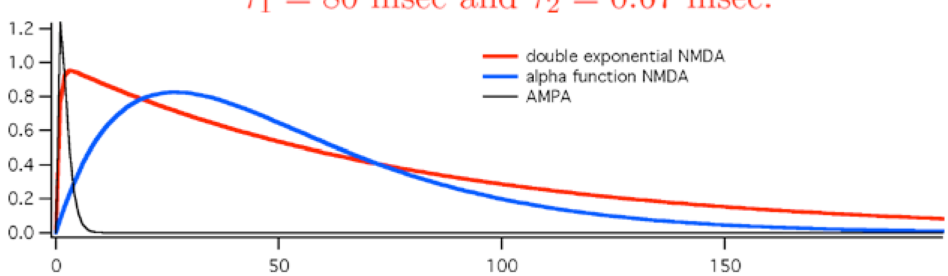
NMDA Receptor Current Equation

$$I_{nmda} = g_{nmda}(t)B(V)(V - E_{Ca})$$

The conductance decay is slow:

$$g_{nmda}(t) = \bar{g}_{nmda}\ (e^{-t/\tau_1} - e^{-t/\tau_2})$$

$$\tau_1 = 80 \text{ msec and } \tau_2 = 0.67 \text{ msec.}$$



The Mg^{2+} block is dependent on the membrane potential and Mg^{2+} concentration:

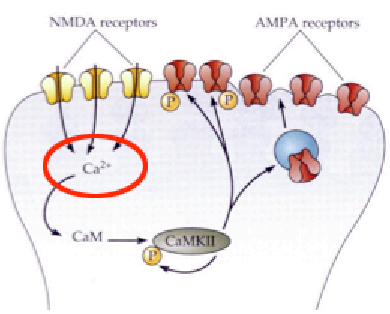
$$B(V) = \frac{1}{1 + 0.33e^{-0.06V}[Mg^{2+}]_o}$$

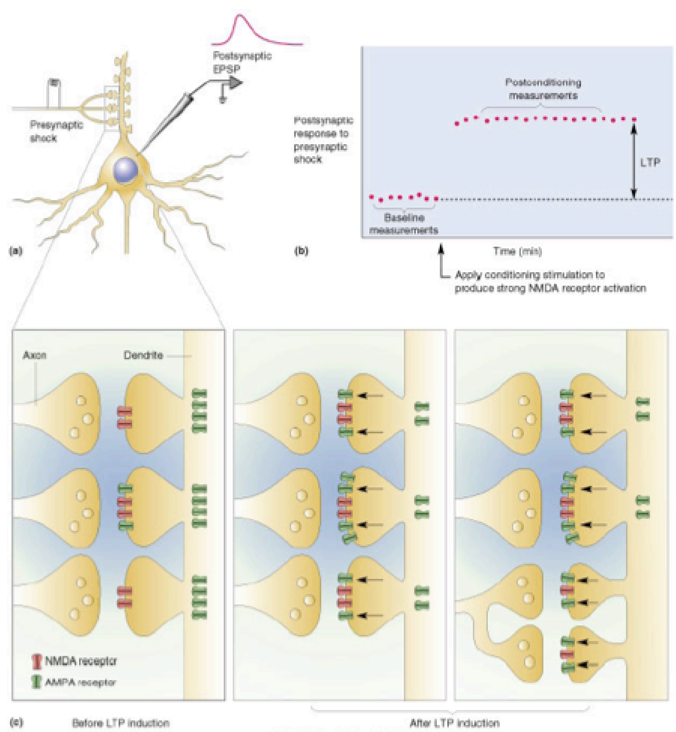
10_nmdaCurrent.psd

11_alphaSimul.psd

LTP Induction Hypothesis

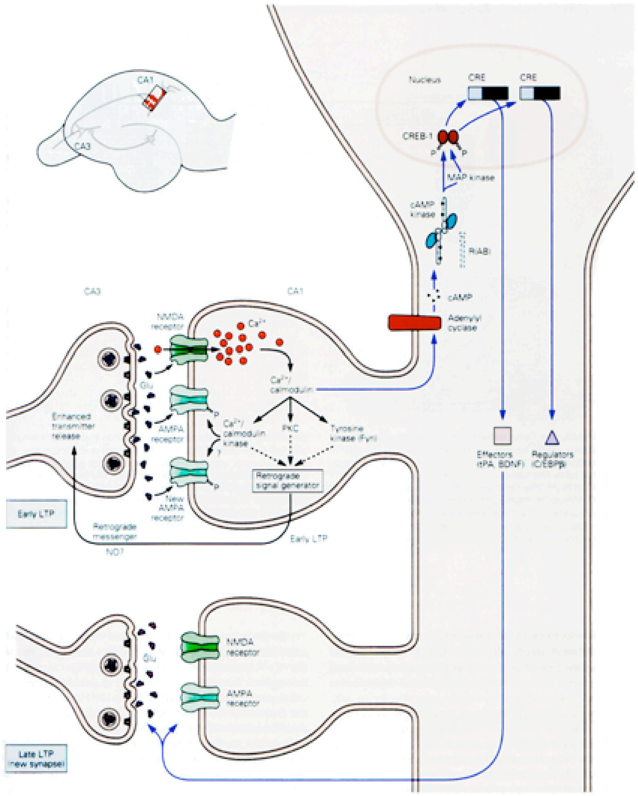
High calcium concentration initiates processes that lead to synaptic potentiation.





12_LTP_induct.psd

Ca2+ Influx via NMDA Receptors Signals Synaptic Change

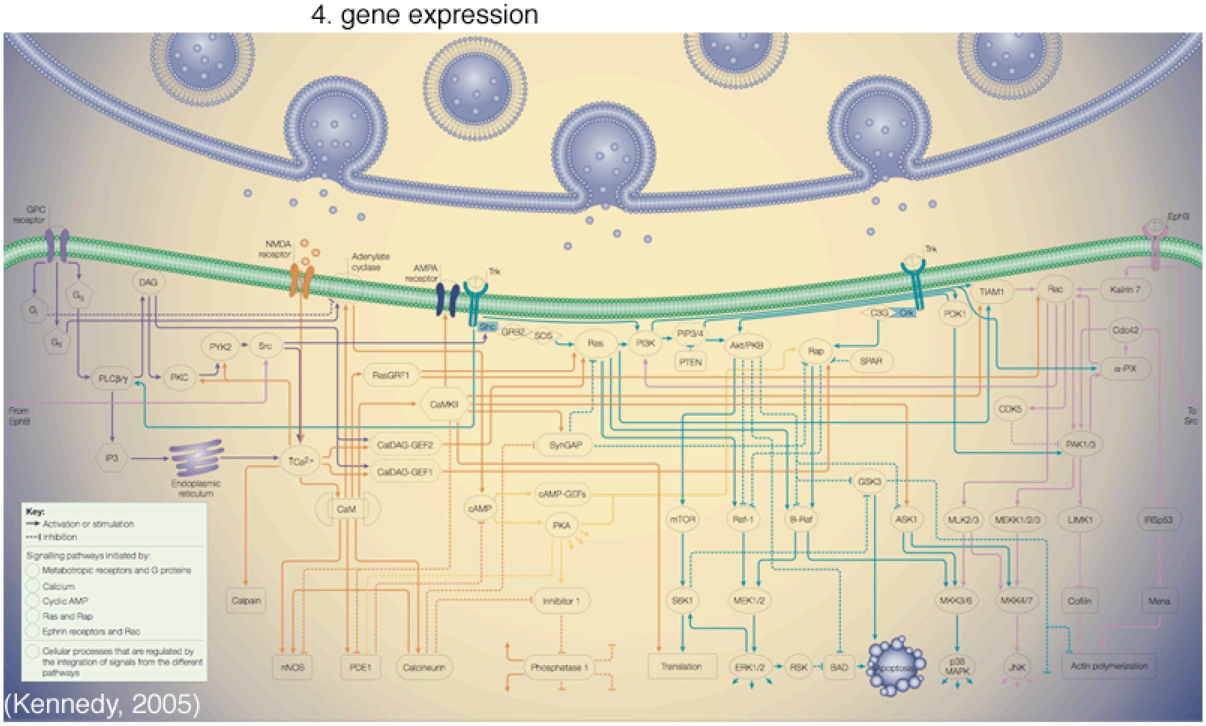


Kandel, Schwartz, and Jessell (2000)

13_nmdaLTP.psd

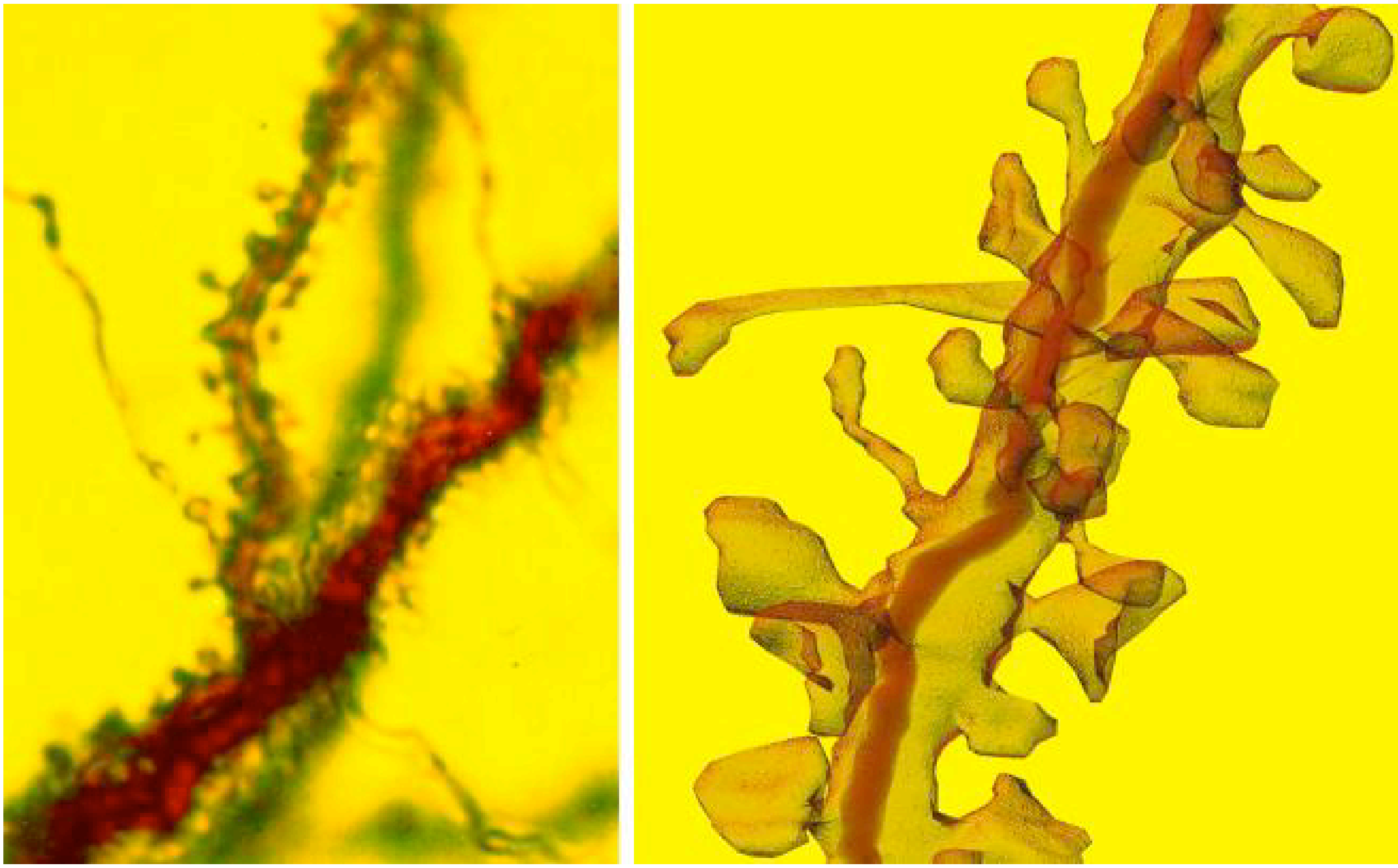
Pathways that control four postsynaptic physiological processes that are crucial for synaptic plasticity:

1. regulation of AMPA- type glutamate receptors
2. polymerization of the actin cytoskeleton
3. local protein synthesis
4. gene expression

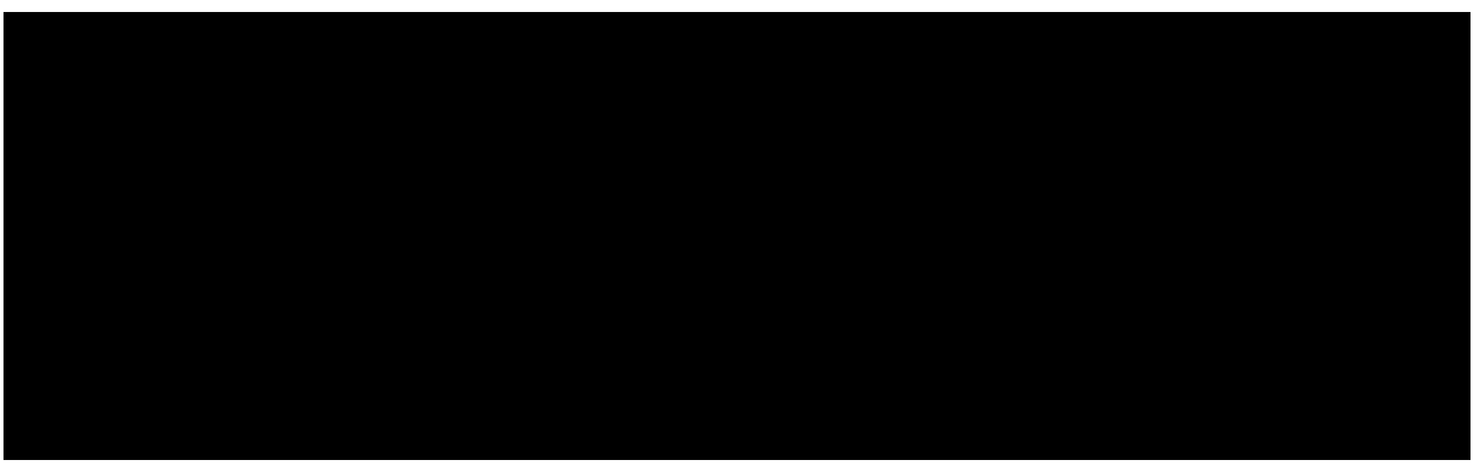


(Kennedy, 2005)

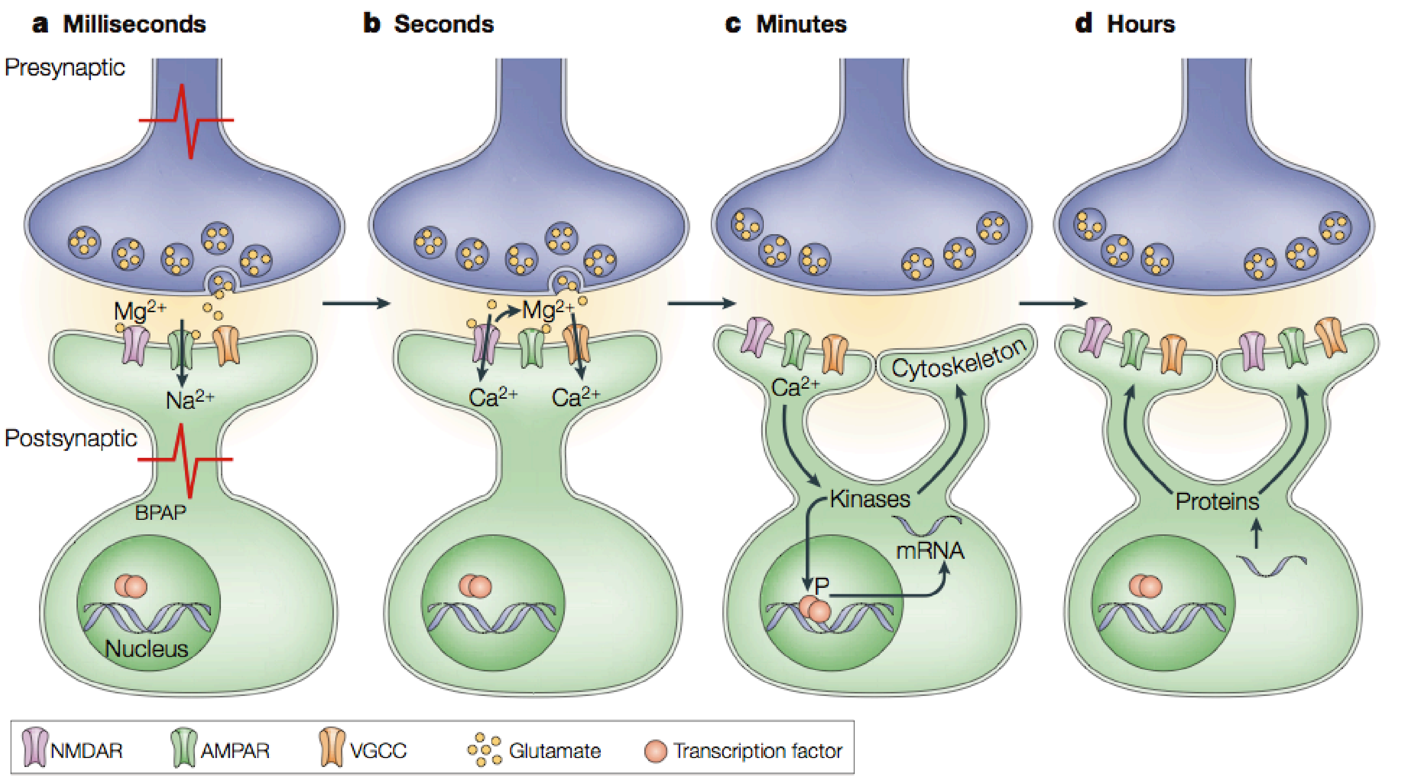
14_pathways.psd



15_spiny.jpg



15b_SPINE3.mov



Molecular mechanisms involved in the initiation and maintenance of synaptic plasticity. (Lamprecht, 2004)

16_Lamprecht04Fig1.png

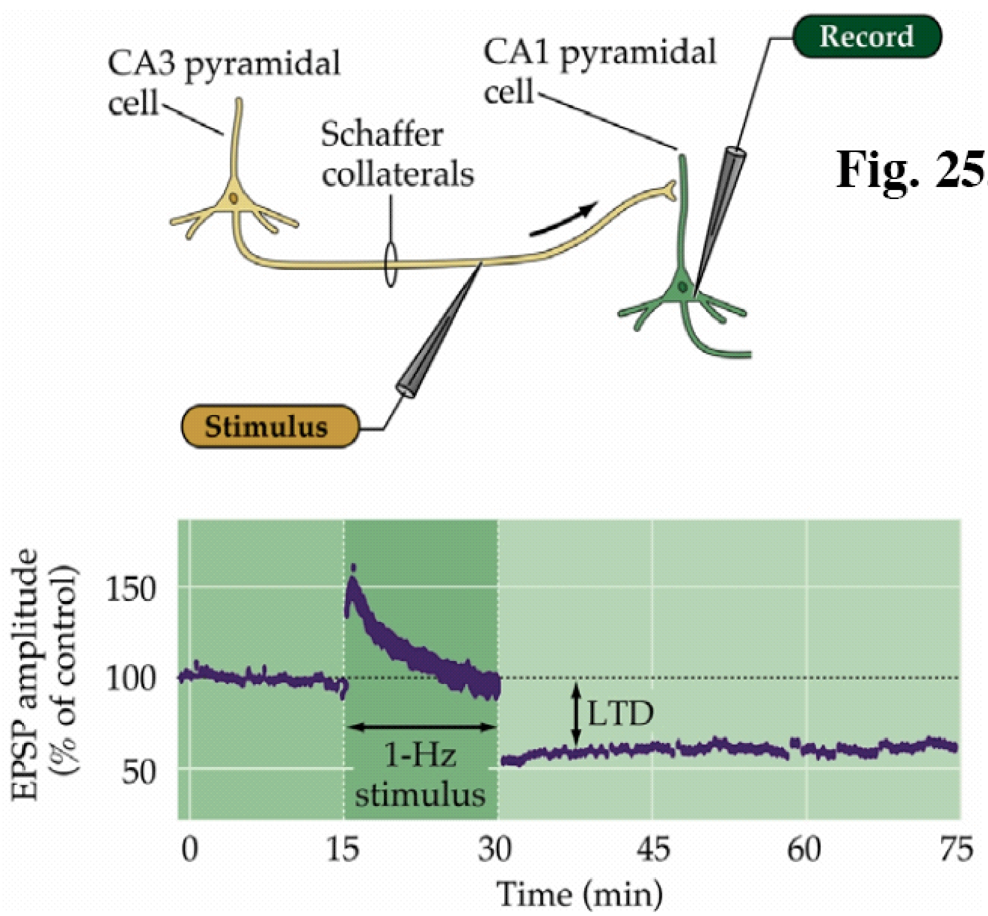
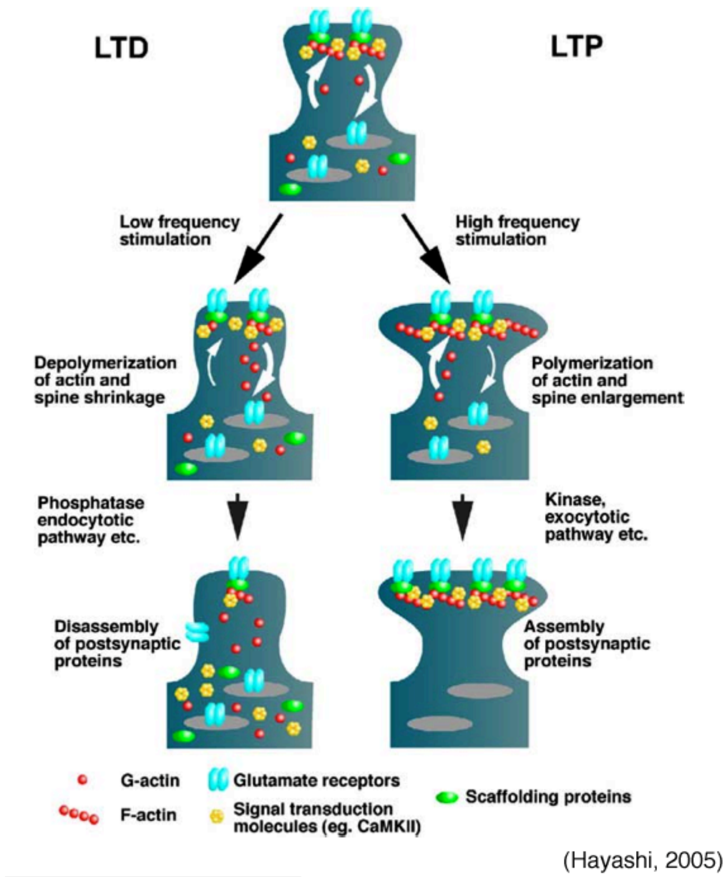


Fig. 25.12

16b_LTDInduct.pdf



17_Hayashi05Fig2.png

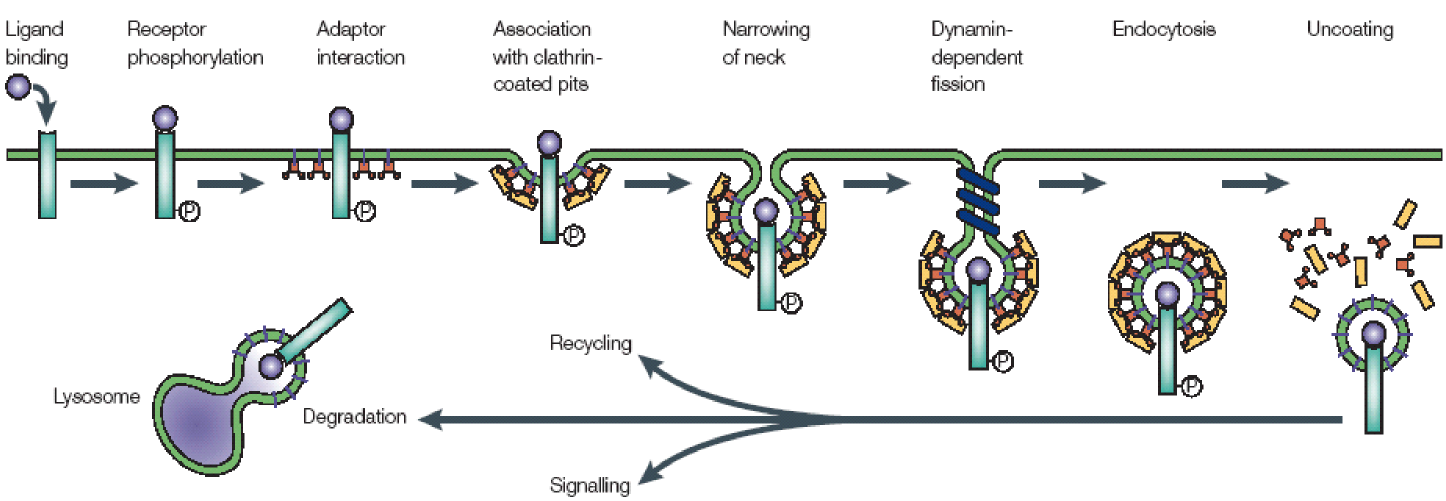
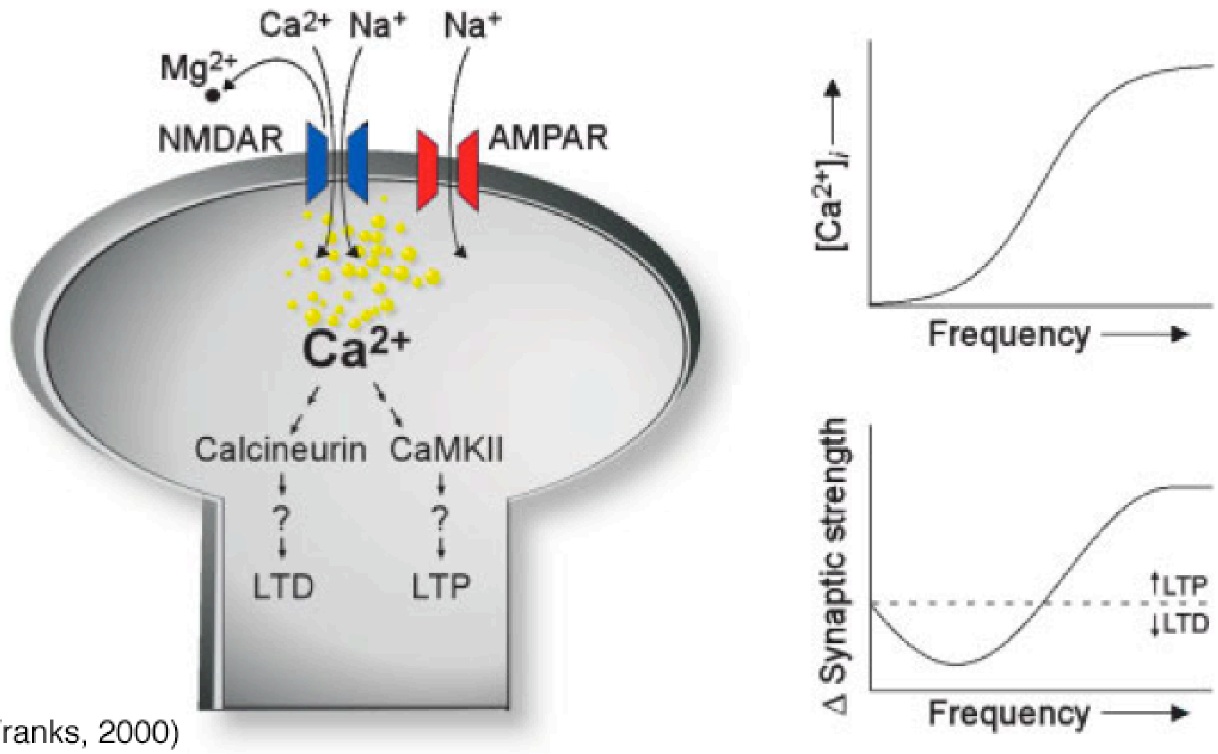


Figure 1 | **Endocytosis of cell-surface signalling receptors.** Several basic steps have been identified in the regulated endocytosis of a number of membrane signalling receptors. Following binding of the receptor by ligand, activation of downstream signalling pathways results in the phosphorylation of the receptor. This modification allows for the interaction of the receptor with adaptor proteins that couple it to the clathrin endocytic machinery. Clathrin-coated pits that contain the receptor subsequently invaginate and bud off from the cell surface. Dynamin is believed to be involved in the fission of the invaginated pits. After endocytosis, the receptors can recycle back to the plasma membrane, be targeted for degradation in lysosomes or continue to serve some signalling function. Many receptor tyrosine kinases dimerize and autophosphorylate as a result of ligand binding.

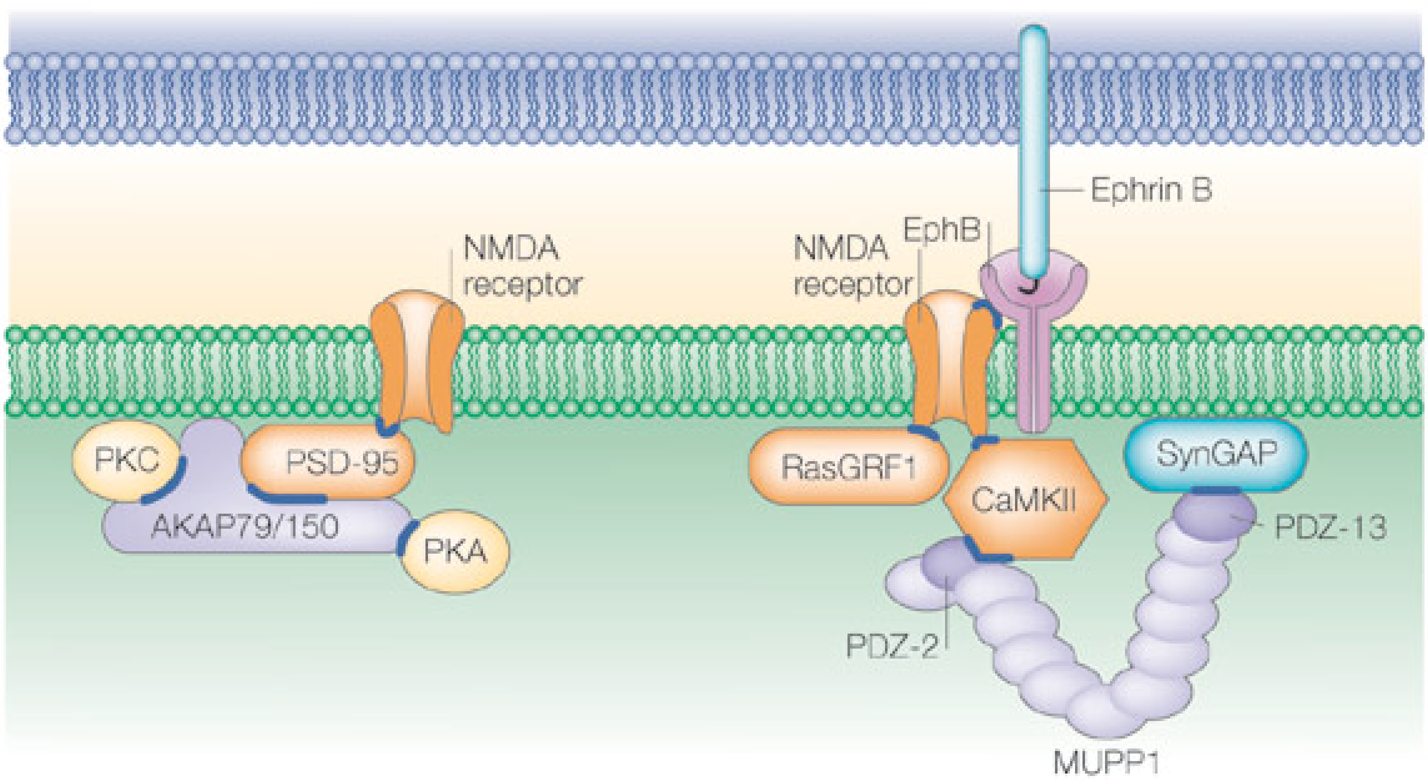
17b_endocyto_Carroll01f1.pdf

Simple, schematic model of frequency-selective, Ca-dependent induction of LTP and LTD



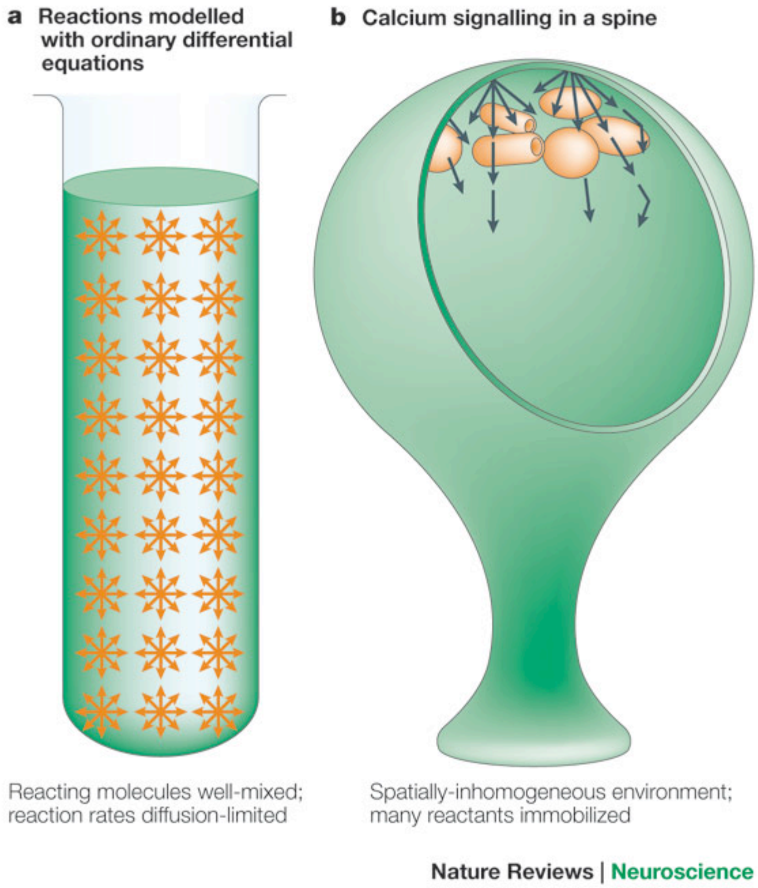
(Franks, 2000)

18_CaInduction.psd



Nature Reviews | Neuroscience

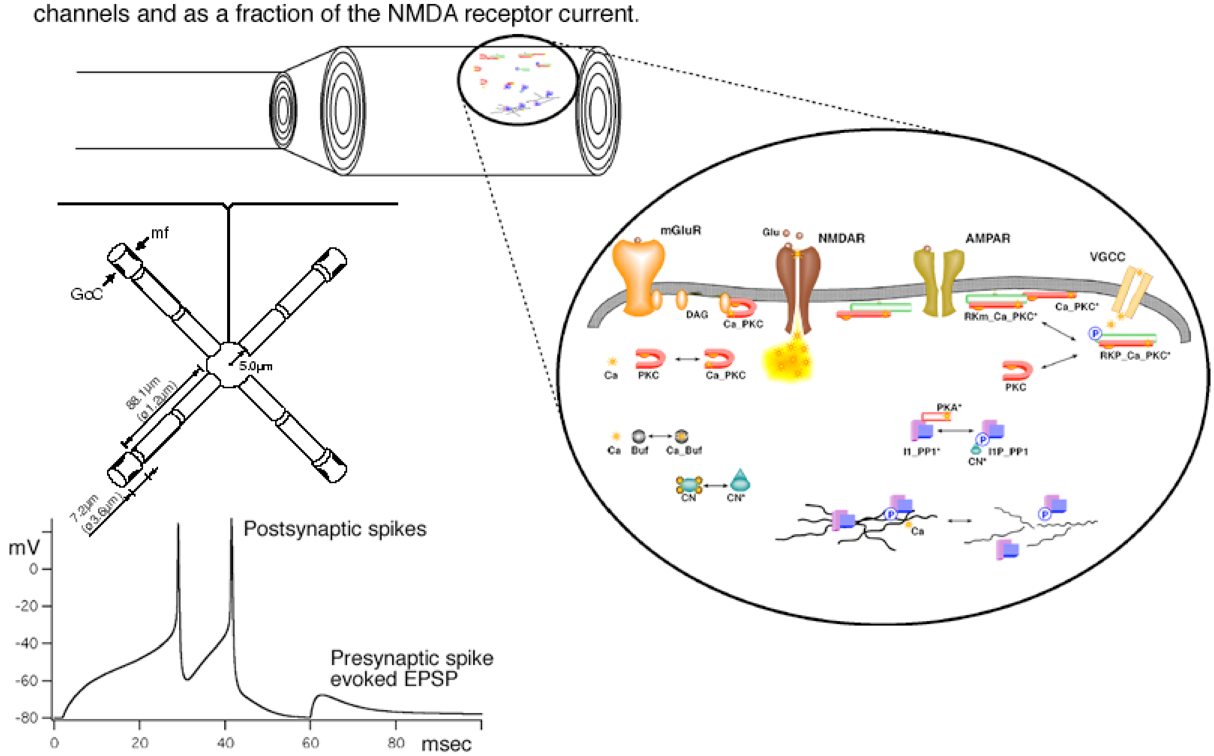
19_Kennedy05Fig2.jpg



20_Kennedy05Box1.jpg

Model of LTP Induction in Cerebellar Granule Cells

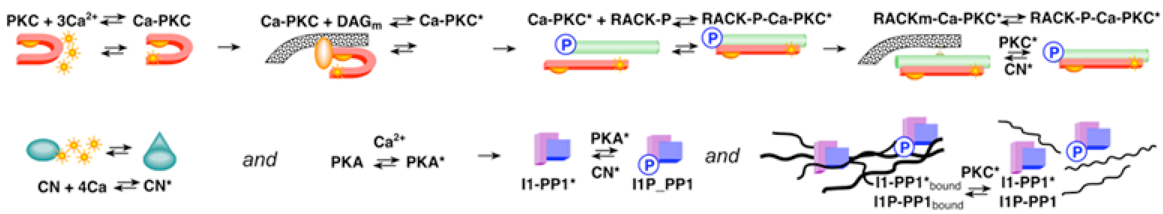
Enzyme kinetics were calculated in a compartment coupled electrotonically to a dendrite, effectively voltage clamped to the electrical cell. In this "chemical compartment" Ca^{2+} influx occures via high threshold Ca^{2+} channels and as a fraction of the NMDA receptor current.



21compartModel.psd

Chemical Reactions are Represented by Differential Equations

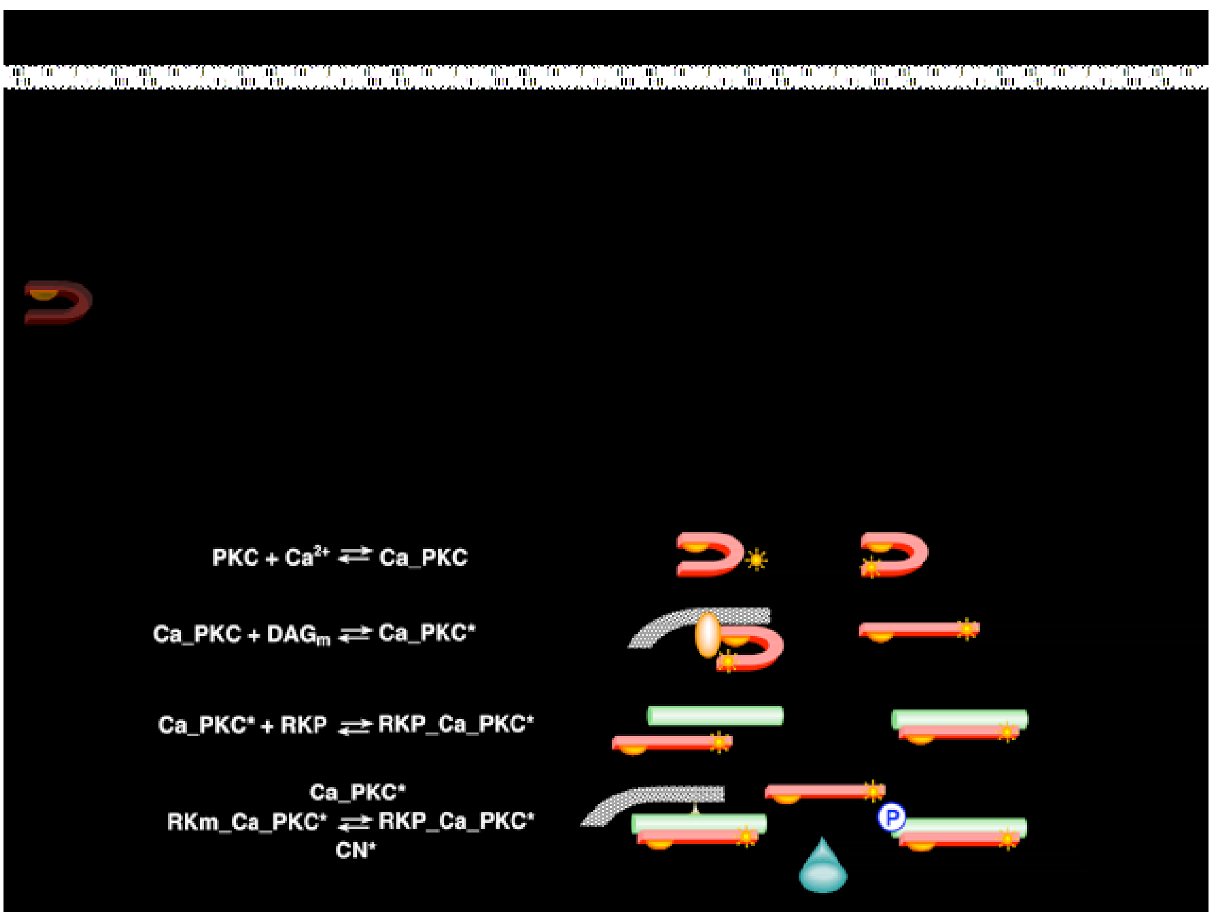
To compute the changes in chemical concentrations that lead to synaptic plasticity, we converted the kinetic reactions into differential equations that we could numerically integrate.



$$\mathrm{A} + m\mathrm{B} \underset{k_2}{\overset{k_1}{\rightleftarrows}} \mathrm{C},$$

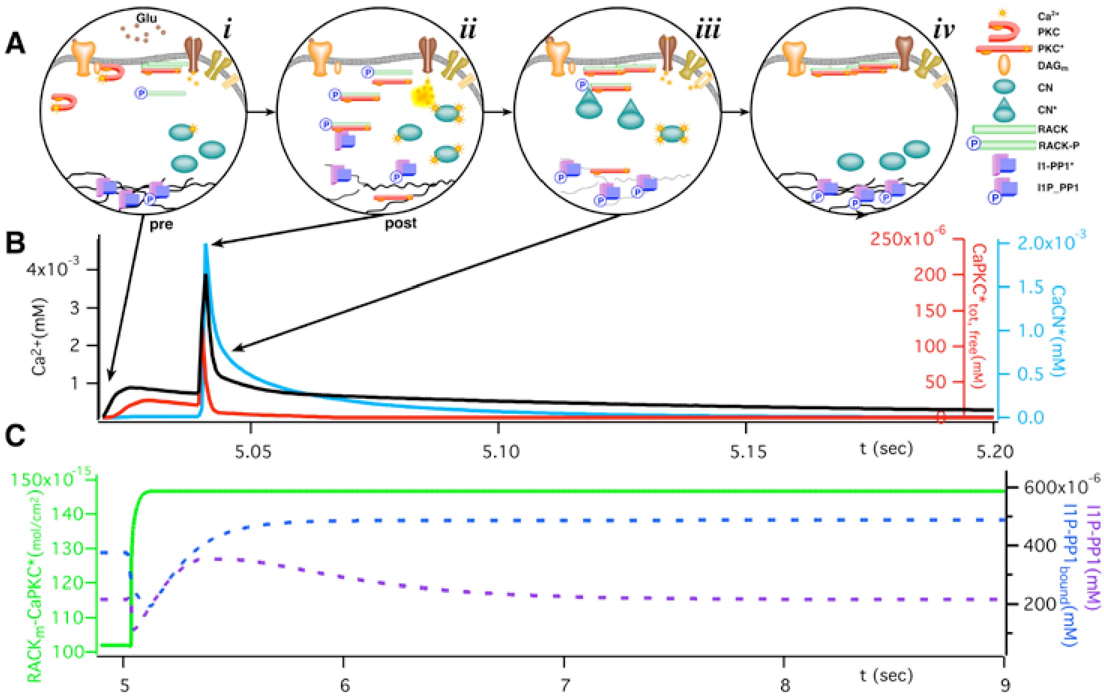
$$\begin{aligned}
\frac{d}{dt}A(t,x) &= k_2 C(t,x) - k_1 A(t,x)\cdot B(t,x)^m \\
\frac{d}{dt}B(t,x) &= m k_2 C(t,x) - m k_1 A(t,x)\cdot B(t,x)^m \\
\frac{d}{dt}C(t,x) &= -k_2 C(t,x) + k_1 A(t,x)\cdot B(t,x)^m
\end{aligned}$$

22_chemEq.psd



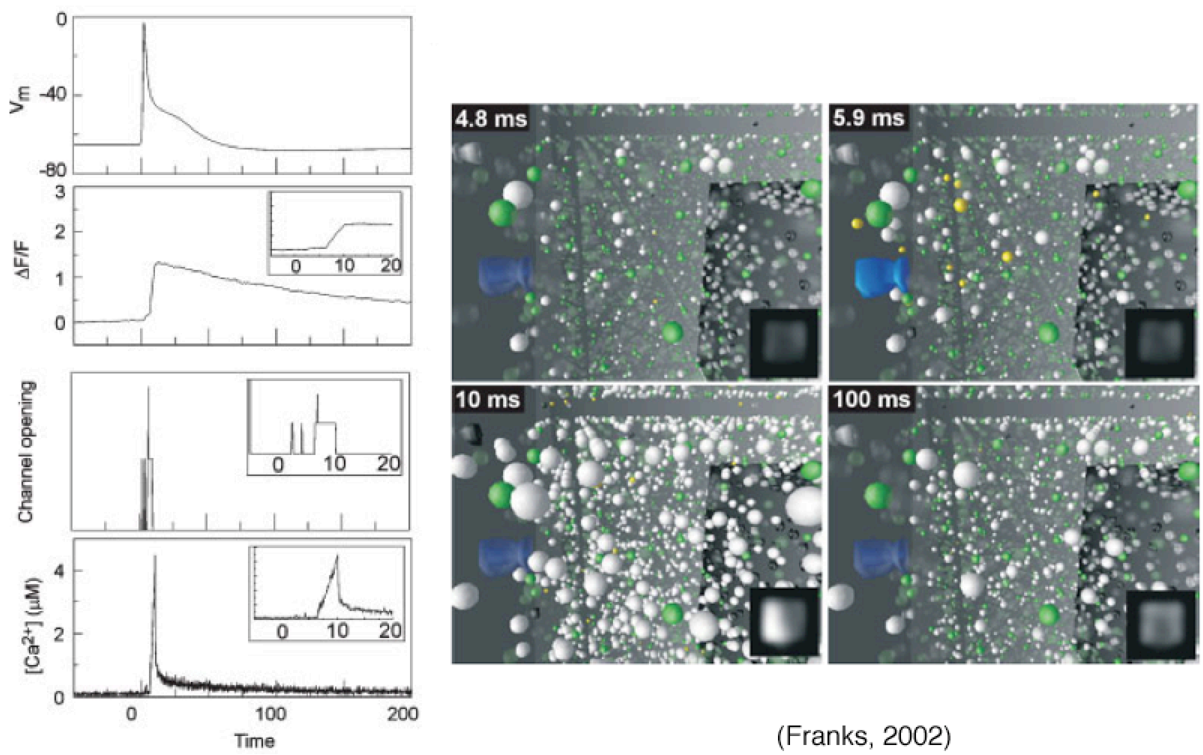
23_pkc_magnus.mov

Induction mechanism for LTP
and simulated concentration transients of critical metabolites



24_modelLTP.psd

Monte Carlo Simulation Provides Extreme Detail



(Franks, 2002)

25_mcSyn.psd

Glutamate spillout from cleft

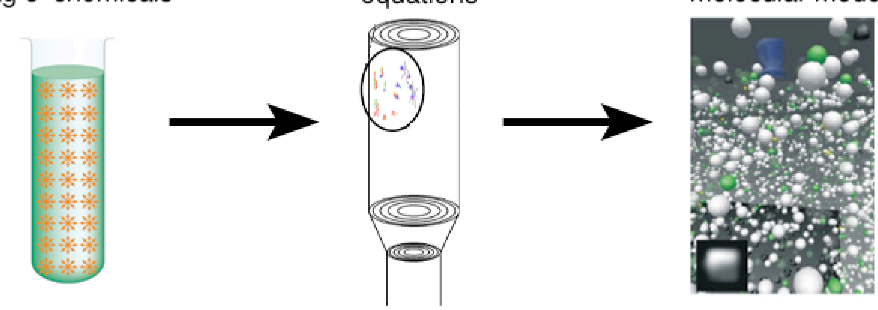
Full uptake

Kevin M. Franks
Thomas M. Bartol Jr.
Terrence J. Sejnowski

26_mcellGlu.mov

Biophysical models of synaptic plasticity

Well-mixed bag o' chemicals	Compartmental, differential equations	Monte Carlo molecular model

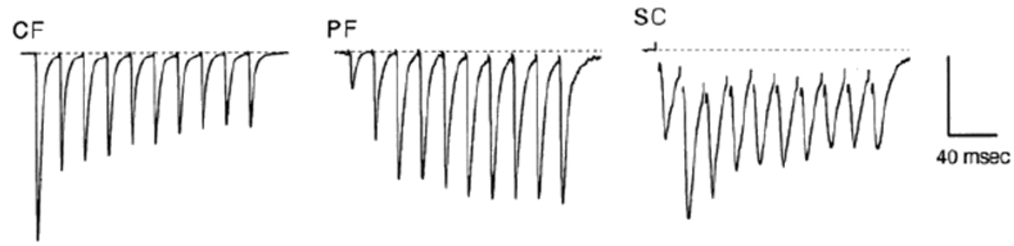


Computationally efficient	Computationally sluggish	Computationally expensive
No structure	Some structure	Exact structure

Course website: http://www.bme.ogi.edu/BME665/

30_summary.psd

Short-term Synaptic Plasticity:
A time-dependent change in synaptic strength

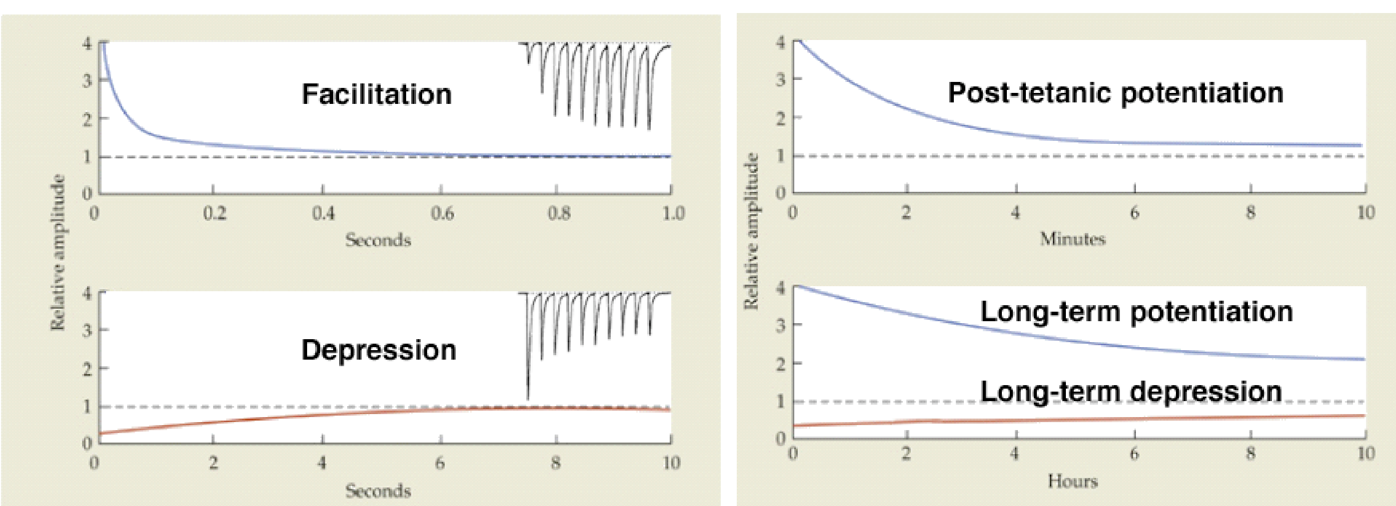


(*CF*) Climbing fiber to Purkinje cell EPSCs
(*PF*) parallel fiber to Purkinje cell EPSCs
(*SC*) CA3 to CA1 Schaffer collateral EPSCs

Dittman et al., *J Neuroscience*, 2000, 20(4):1374-1385

36_synPlast_def.psd

Types of Synaptic Plasticity

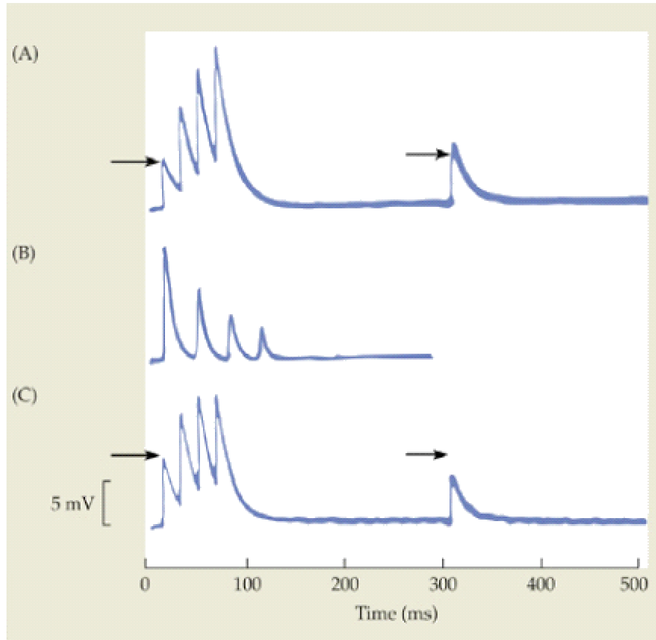


37_types_of_plast.psd

Facilitation and Depression are Dependent on Presynaptic Calcium Ion Level.

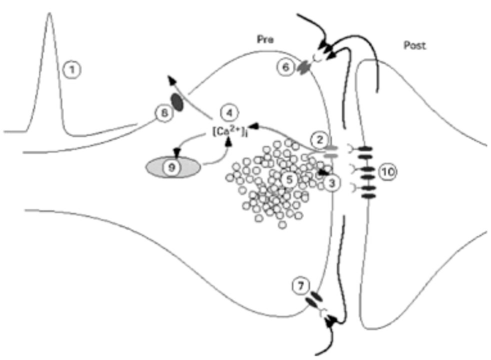
(A) Low Ca^{2+}
(B) High Ca^{2+}
(C) Normal Ca^{2+}

One possible mechanism for facilitation and depression is changes in release probability of the presynaptic terminal.

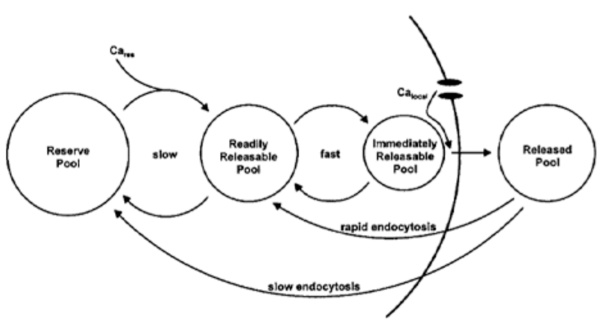


38_fascilDepres.psd

Sites of regulation of short-term synaptic plasticity



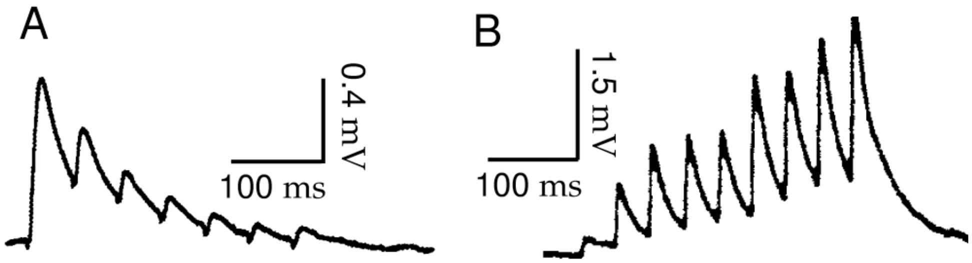
(1) AP waveform
(2) Ca2+ channel activation
(3) facilitation trigger and the readily releasable pool
(4) residual [Ca2+]i
(5) reserve pool
(6) metabotropic autoreceptors
(7) ionotropic autore- ceptors
(8) Ca2+-ATPase, regulating residual [Ca2+]i in augmentation
(9) mitochon- drial regulation of residual [Ca2+]i in PTP
(10) postsynaptic receptor desensitization.



(Zucker, 2002)

38b_mechs.psd

Probability of transmitter release and synaptic transmission:



Depression (D) and facilitation (F)
of excitory intercortical synapses

$$\tau_P \frac{dP_{rel}}{dt} = P_0 - P_{rel}$$

$$P_{rel} \rightarrow P_{rel} + f_F(1 - P_{rel})$$

$$P_{rel} \rightarrow f_D P_{rel}$$

with P_0 the release probability after a long period of silence

39_stp_std.pdf

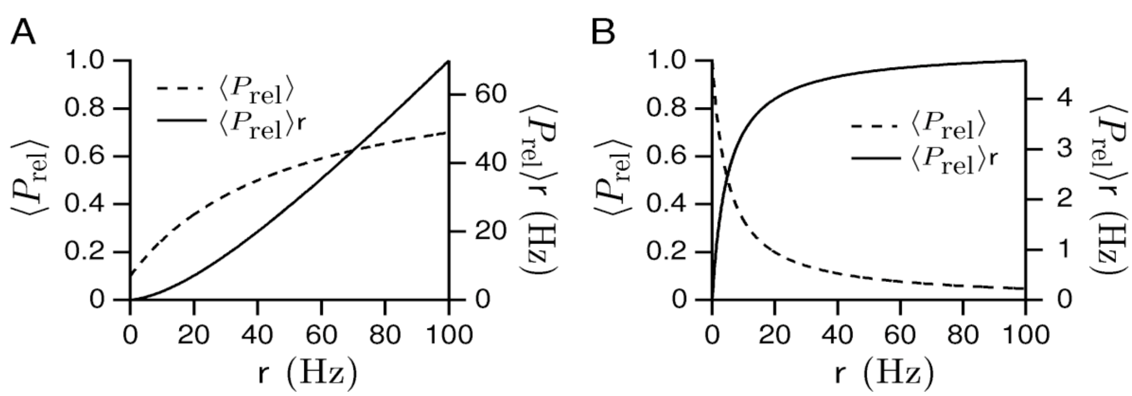
Steady-state release probability for a presynaptic Poisson spike-train:

$$\langle P_{rel} \rangle = \frac{P_0 + f_F r \tau_p}{1 + f_F r \tau_p}$$

$$\langle P_{rel} \rangle = \frac{P_0}{1 + (1 - f_D) r \tau_p}$$

Facilitating synapse

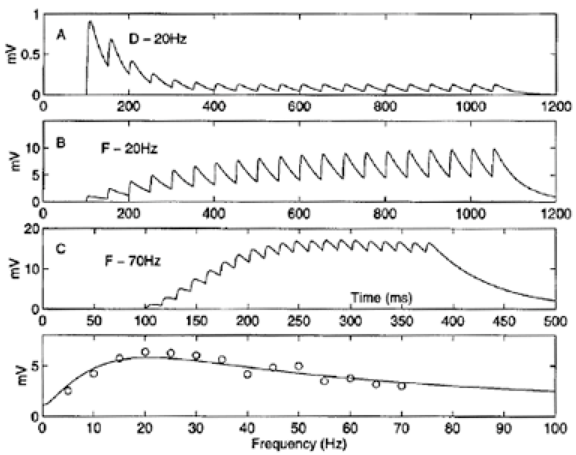
Depressing synapse

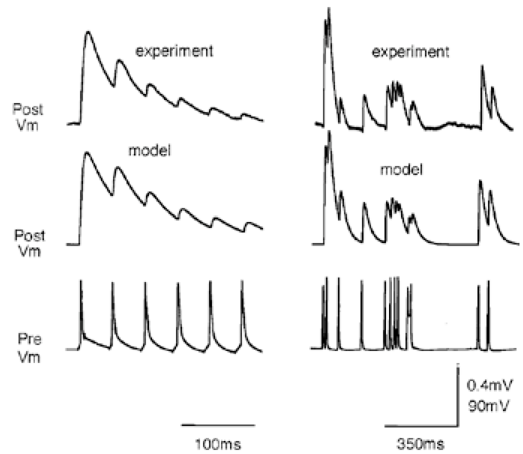


$r\langle P_{rel} \rangle$: Synaptic transmission

40_stp_vs_freq.pdf

Combination of Facilitation and Depression Yields Temporal-Pattern Selective Neurons





Tsodyks, Pawelzik, and Markram (1998)
Neural Computation, 10(4): p821

Tsodyks and Markram (1997)
PNAS **94**(2): 719-723.

41_tsydoksPattern.psd