Synaptic plasticity

A Citri, RC Malenka. Synaptic plasticity: multiple forms, functions, and mechanisms. *Neuropsychopharm* 33: 18–41, 2008.

D Feldman. The spike-timing dependence of plasticity. *Neuron* 75:556-571 (2012).

GQ Bi, MM Poo. Synaptic modifications in cultured hippocampal neurons: dependence on spike timing, synaptic strength, and postsynaptic cell type. *J. Neurosci.* 18, 10464–10472 (1998).

T Tzounopoulos, Y Kim, D Oertel, LO Trussell. Cell-specific, spike timing-dependent plasticities in the dorsal cochlear nucleus. *Nat. Neurosci.* 7:719-725 (2004).

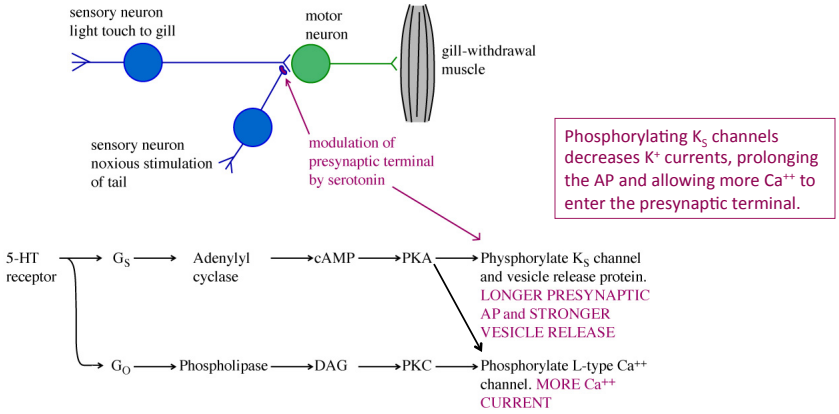
Types of synaptic plasticity, according to time scale:

1. Facilitation and depression of synaptic strength in a pulse pair or pulse train. Can be caused by accumulation of presynaptic Ca^{++} (facil.) or depletion of neurotransmitter (depress.).

2. Longer lasting facilitation and depression can be produced by neuromodulation, in which pre- or postsynaptic receptors change the properties of ion channels (and neural excitability) through a 2^{nd}-messenger system.

3. Long-term plasticity (long-term potentiation LTP or depression LTD) can change the strength of synapses for hours and is thought to underlie memory formation. It depends on changing the number of AMPA receptors in the postsynaptic membrane.

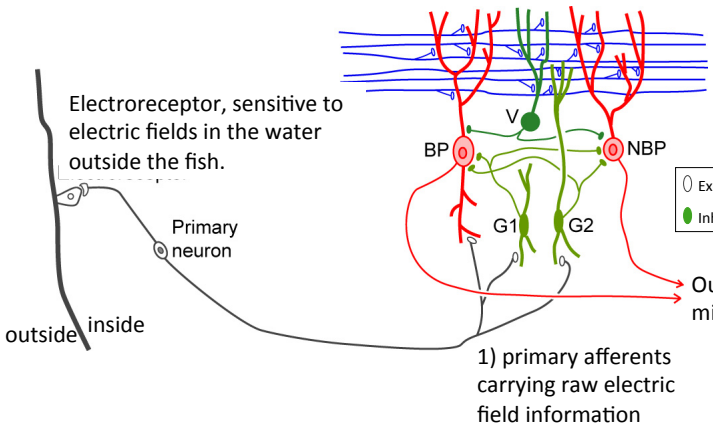
An example of neuromodulation, sensitization in the aplysia gill-withdrawal reflex. The reflex protects the gill from damage using the warning signal of strong stimulation of the tail. These effects can last for up to several days, if the stimulus is repeated enough times.



Phosphorylating K_S channels decreases K^+ currents, prolonging the AP and allowing more Ca^{++} to enter the presynaptic terminal.

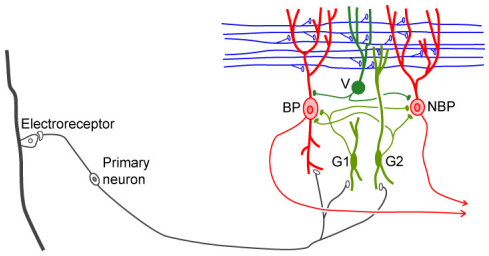
Kandel et al.

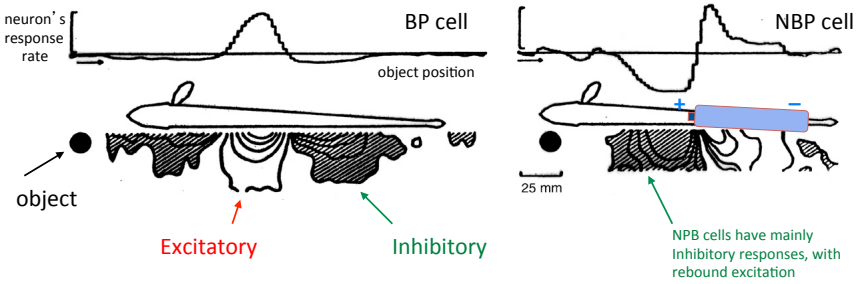
An example of the usefulness of moderate-term neural plasticity: the electrosensory lateral line lobe (ELLL) of weakly electric fish combines information from two sources to produce an image of objects in the water outside the fish.



2) Parallel fibers carrying information about the fish's movements, etc.

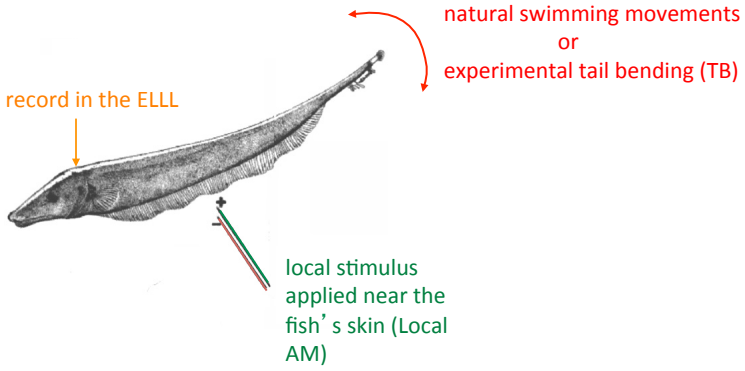
These fish have an electric organ in their tails (+ and - at right below) that produces an oscillating field in the water. Nearby objects disturb the field and electroreceptors in the fish's skin detect the disturbances. The plots below show the response fields of BP and NBP type cells as an object (the black circle) moves past the fish.





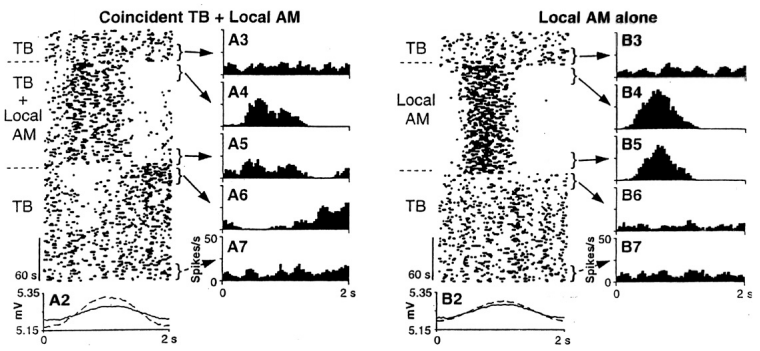
Bastian, 1986

A major problem for these fish is self-generated electric fields. Their breathing (gills) and their swimming movements produce electric fields as large as those from external objects. The ELLL removes these self-generated stimuli.



Bastian et al. 2002

Self-generated electric fields are cancelled at the output of the ELLL, presumably by learning associations between the movements of the tail and the electroreceptor inputs, and using the former to cancel the latter. This is an example of *plasticity* in a neural circuit.



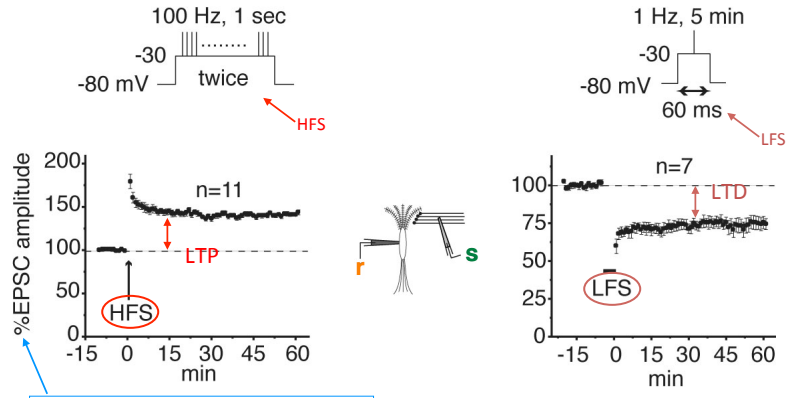
Note the decrease in response to AM applied with tail bending (A5 vs A4) and the negative image of the AM revealed when the AM is removed (A6)

Control: note that no plasticity occurs in the absence of pairing of tail bend and AM (B5 is the same as B4 and there is no negative afterimage in B6).

Bastian, 1996

Longer-term changes in the strength of a synapse occur due to correlation of synaptic activation and postsynaptic depolarization. Below are an example of long-term potentiation (LTP, left) and long-term depression (LTD, right). The stimulus protocol involves two components:

1. Stimulation of presynaptic fibers (**s**)
2. Depolarization of the postsynaptic cell through the recording electrode (**r**)



Amplitude of the post-synaptic current produced by stimulation of synaptic inputs.

Fujino and Oertel, 1999

Early studies showed that LTP displays the following properties:

Cooperativity – induced by co-incident activation of a number of synapses

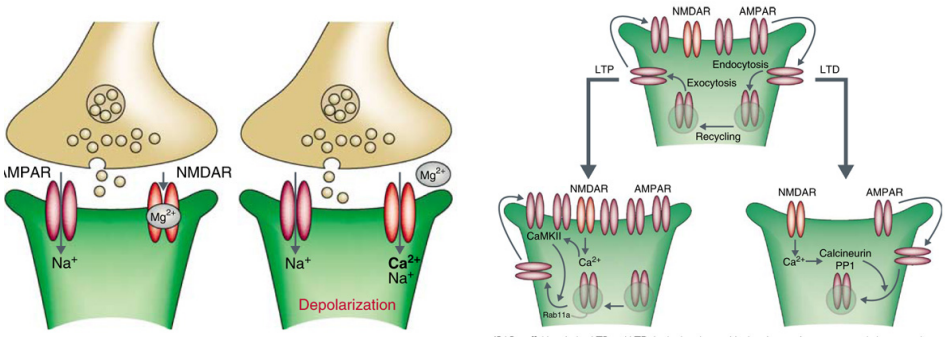
Associativity – a weak input can be strengthened if activated in association with a strong one

Input specificity – only the activated synapses are strengthened, not adjacent synapses.

Citri and Malenka 2008

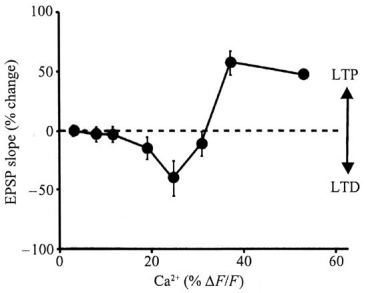
Induction of LTP requires activation of NMDA receptors, shown by blocking them with antagonists or by manipulating the Mg++ concentration. Ordinarily, the Mg block is relieved by postsynaptic depolarization. This requirement explains many properties of LTP. NMDA receptors admit Ca++, which is the intermediate signal for LTP or LTD.

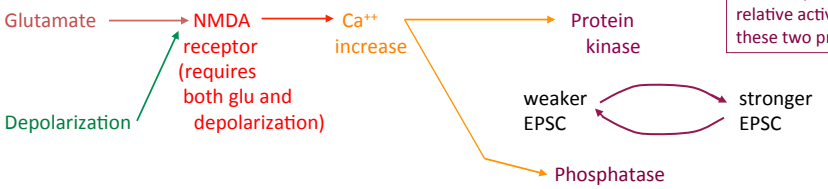
The best known mechanism for LTP and LTD is changing the number of AMPA receptors (and perhaps their conductance) in the postsynaptic terminal.



Citri and Malenka 2008

LTP and LTD can both occur at the same synapse, as in the previous example. The difference seems to depend on the strength of the Ca signal in the postsynaptic terminal. The sequence of events occurring in the postsynaptic cell is known partially and is described below.
A computational theory (BCM) supported by some evidence, requires this function to shift based on past activity levels.





Presumably the net effect depends on the relative activation of these two processes

Johnston et al. 2002

There are a large number of additional aspects of LTP and LTD, see the references for more details.

1. The discussion above is about initiation of LTP or LTD. Maintenance requires additional mechanisms, including gene expression.
2. Details about the signaling cascades involved in LTP and LTD.
3. Some LTP or LTD may occur presynaptically.
4. LTD can be produced based on signaling beginning with mGlu receptors.
5. Signaling can also occur by release of endocannabinoids in the postsynaptic terminal, which transiently inhibit neurotransmitter release via presynaptic CB1 receptors.

Citri and Malenka 2008

Synaptic plasticity is also analyzed in functional terms, as to whether it is Hebbian or anti-Hebbian.

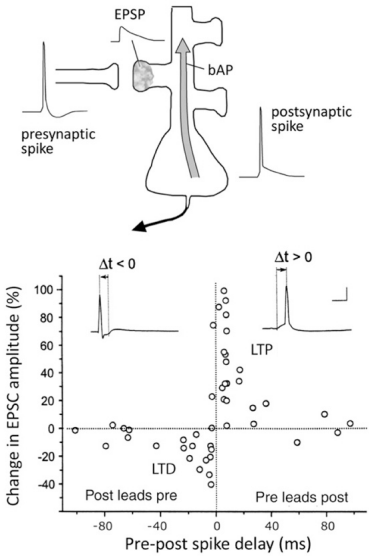
Hebb (1949) proposed that when cell A reliably contributes to spiking of postsynaptic cell B, the functional strength of the synapse from A to B is increased.

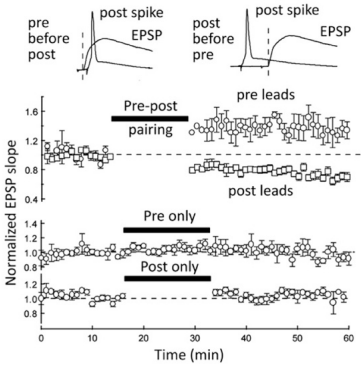
Others amended this idea to include weakening of ineffective synapses (Stent, 1973; von der Malsburg, 1973; Sejnowski, 1977; Bienenstock et al., 1982).

Note that LTP and LTD as discussed above is Hebbian.

Feldman 2012

Plasticity is time-dependent, meaning the timing of the presynaptic spike relative to the postsynaptic depolarization matters. Timing-sensitivity was revealed by study of spike-timing dependent plasticity (STDP).

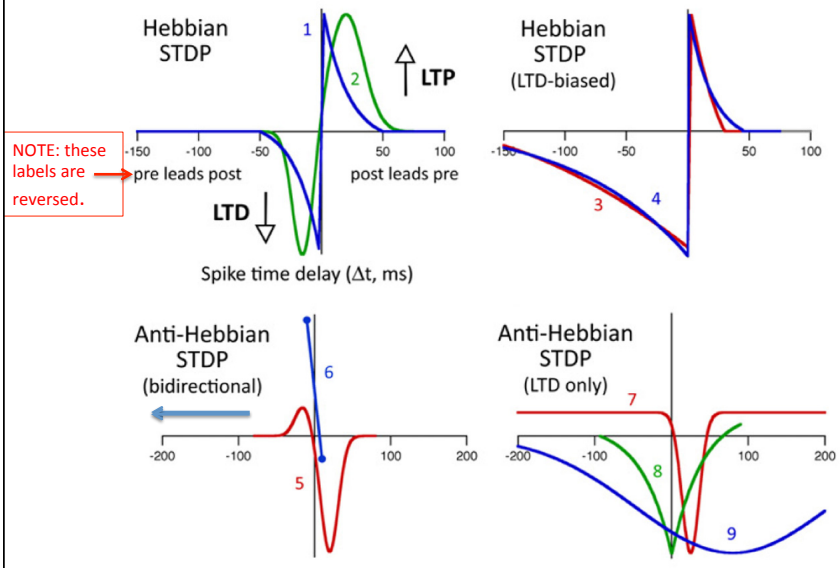




Note that with the polarity shown here, the STDP is Hebbian.

Bi and Poo 1998 via Feldman 2012

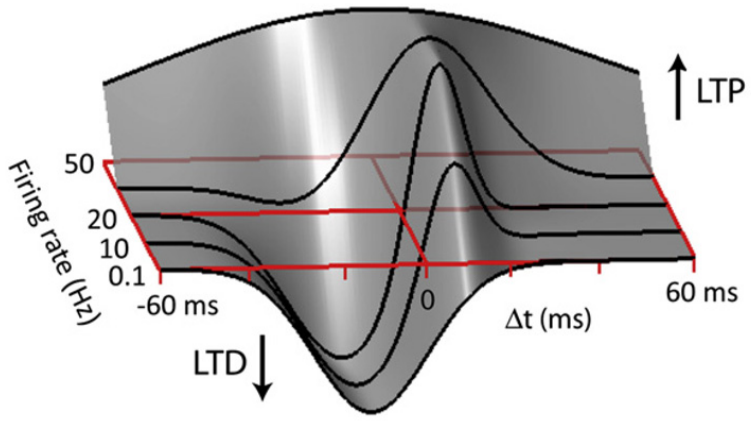
STDP can be either Hebbian or anti-Hebbian, with a range of balance between LTP and LTD.



NOTE: these labels are reversed.

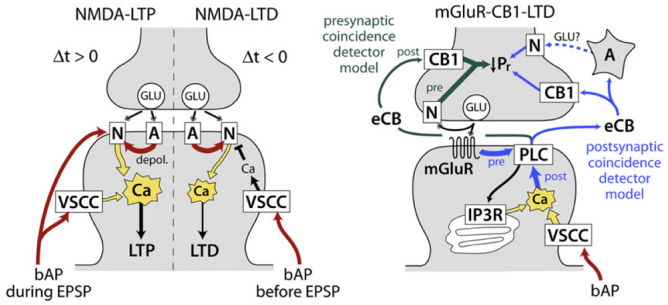
Feldman 2012

The nature of the STDP curve depends on the rate of stimulation during the pairing. Higher rates favor LTP, lower rates favor LTD. This seems to unify the two experimental methods (HFS/LFS versus STDP) of evoking long-term plasticity. Part of this story is that LTD often dominates STDP curves.



Feldman 2012

A summary of the mechanisms of Hebbian LTP and LTD (left) and Hebbian and anti-Hebbian presynaptic LTD (right).

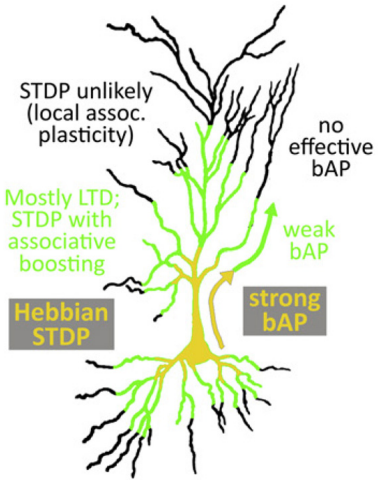


Feldman (2012) provides a summary of explanations for STDP in various parts of the brain using these systems.

Feldman 2012

It is likely that STDP varies in strength with position in the dendritic tree. Backpropagating APs are decremental, so produce less depolarization in the distal dendrites than in the proximal.

Thus, STDP should be strongest in proximal dendrites, should shade into LTD in intermediate dendrites, and may disappear in distal dendrites.



Feldman 2012

Some comments and reservations (see Feldman, 2012):

1. Backpropagating action potentials are only one source of postsynaptic depolarization and are very brief events. STDP is only part of the LTP/LTD story.
2. Insufficient consideration is given in STDP studies to the role of NMDA and dendritic Ca spikes.
3. In-vivo, spontaneous activity and inhibitory inputs make cells electrotonically larger, reducing the size of backpropagating spikes further.
4. The computational role of single-spike effects is unclear at present because of the vulnerability of stored synaptic strengths to erasure and information readout will modify the stored information.