Experimental data on the induction of LTP and LTD

Previously, the induction of LTP and LTD has been thought to depend on the rate of stimulation, number of afferents stimulated and the degree of depolarization obtained in the postsynaptic neuron. For example, in many preparations, electrical stimulation of the presynaptic axons at 100 Hz induces LTP (an increase of synaptic strength on an excitatory synapses) and stimulation at 20 Hz induces LTD (a decrease of synaptic strength of an excitatory synapses). This is thought to be due to the fact that high levels of calcium enter the cell after high frequency stimulation and that low levels of calcium enter the cell after low frequency stimulation. At very low frequencies, neither LTP or LTD are induced.
Many formal descriptions of LTP translate these data into simple equations of the form:

$$\Delta w_{ij} = \mu \cdot x_j \cdot (v_i - \phi),$$

where $x_j$ is the output (action potentials) of the presynaptic neuron $j$ and $v_i$ is the membrane potential of the postsynaptic neuron and $w_{ij}$ is the synaptic strength (weight, efficacy) of the synapses from neuron $j$ to neuron $i$. One can see that if the presynaptic neuron were to fire at 100 Hz, the postsynaptic depolarization would rapidly exceed the threshold for LTP induction ($f$); however, if the presynaptic neuron were to fire at 20 Hz, the postsynaptic depolarization would stay below the threshold $p$ and the synaptic weight would be decreased. At very low presynaptic firing rates, the postsynaptic depolarization would always return to rest before the occurrence of the next postsynaptic action potential and no changes in synaptic weight would occur.
In real life, neurons rarely fire at 100 Hz. One should rather imagine that any individual neuron is receiving inputs from many presynaptic neurons at the same time.

In contrast to many previous studies, more recent studies find that the strengthening and weakening of synapses depends on the precise temporal relationship between the presynaptic and the postsynaptic action potentials.
Two pyramidal neurons in a cortical brain slice preparation are simultaneously impaled with intracellular electrodes. Both neurons can have current injected individually in such a way as to trigger an action potential. Pre. Im: presynaptic current injection; Pre. APs: presynaptic action potential; Post. Im: presynaptic current injection; Post. APs: presynaptic action potential;

When both neurons are activated to fire at approximately 20 Hz, and the postsynaptic neuron fires 5ms after the presynaptic neuron (is phase locked), then an increase of the synaptic strength between the pre- and postsynaptic neurons can be observed.
Pre and post AP’s separated by 5 ms

The EPSP amplitude or rising slope is measured before the experimental manipulation, this baseline or control amplitude is reported as 100%. Subsequently, the experimental manipulation, which consists in firing the pre- and postsynaptic neurons at 20 Hz, with the postsynaptic neuron firing 5 ms after the presynaptic neuron is executed for several minutes. The EPSP amplitude is then recorded again by firing only the presynaptic neuron at a low (1 Hz) frequency and recording the EPSP in the postsynaptic neuron. When only the pre- or postsynaptic neuron are fired at 20 Hz (pre-only and post-only), no change in EPSP amplitude is observed. When both are fired at 20 Hz with the postsynaptic neuron firing 5 ms after the presynaptic neuron, an increase in EPSP amplitude can be measured.


The observed increase in EPSP amplitude depends on the frequency of stimulation. In this experiment, no increase was observed at stimulation rates < 20 Hz and the EPSP increase was correlated with stimulation frequency.

Subsequently, these researcher analyzed how the timing of action potentials in the pre- and postsynaptic neurons affects the observed changes in EPSP amplitude. They did an experiment in which they triggered bursts of action potentials in connected pyramidal cells at various delays. Briefly, they impaled pairs of pyramidal cells until they found a pair which was reciprocally connected. Then, they were able to inject current into each of those cells and to record the resulting EPSPs in the second cell. Since both cells are connected, changes in evoked EPSPs (which is a measure for synaptic strength) could be observed in both cells.

In this experiment, Markram et al. looked at how the temporal relationship between evoked EPSPs (due to presynaptic spiking) and action potentials in the postsynaptic cell affects the strength of the synapse (measured as the amplitude of the evoked EPSP). Because of the setup, each cell can be regarded as pre- or postsynaptic, since both are reciprocally connected with each other.
(1) Let's assume a burst of action potentials is first evoked in cell 1. This burst of action potentials will evoke an EPSP in cell 2.

(2) Subsequently a burst of action potentials is evoked in cell 2, which will evoke an EPSP in cell 1.

In the example shown here, (1) and (2) are separated by 100 ms. Because the cells are reciprocally connected, in each cell, the burst of action potentials and evoked EPSPs are separated by 100 ms. In cell 1, the burst of action potentials precedes the EPSP by 100 ms and in cell 2, the EPSP precedes the action potentials by 100 ms.

In this experiment, they found that the degree of change in synaptic strength depended on the temporal relationship between the postsynaptic EPSP and the postsynaptic action potential.

**Strengthening** of synaptic strength was obtained when the postsynaptic cell fired 10 ms after its EPSP.

**Weakening** of synaptic strength was obtained when the postsynaptic cell fired 10 ms before its EPSP.

No change in synaptic strength was obtained when the postsynaptic EPSP and AP were separated by 100 ms in either direction.

Bursts of AP triggered 10 ms apart
Research by other groups using different types of preparations have confirmed that the degree to which synapses are weakened or strengthened depends on the time elapsed between the evoked EPSP and the action potential in the postsynaptic cell.

The change in EPSC (excitatory postsynaptic current) is plotted as a function of the time elapsed between the postsynaptic action potential and the postsynaptic EPSP during simultaneous stimulation of pre- and postsynaptic cells.

The data from these experiments have been used to formalize a new type of Hebbian Learning rule, commonly referred to as Spike timing dependent plasticity. This rule incorporates the timing differences between pre- and postsynaptic action potentials and has a means to increase or decrease the synaptic efficacy depending on the precise timing of these events. Note that synaptic efficacy is increased when the presynaptic spike occurs before the postsynaptic spike and remember: "...when neuron A takes part in firing neuron B ..."!

The major advantage of this learning rule is that one does not need separate rules for synaptic depression and potentiation and that a certain degree of normalization is built in.
(under certain conditions).

\[ \Delta t = \text{time}_{\text{pre}} - \text{time}_{\text{post}} \]

\[
F(\Delta t) = \begin{cases} 
A_e \exp(\Delta t / \tau_e) & \text{if } \Delta t < 0 \\
-A_i \exp(-\Delta t / \tau_i) & \text{if } \Delta t \geq 0 
\end{cases}
\]

Song, Miller and Abbott, Competitive Hebbian learning through spiketime-dependent synaptic plasticity.


Song et al. (Nat Neurosci 2000 Sep;3(9):919-26) used a large network of integrate and fire neurons to test the properties of such a learning rule.

\[
\tau_m \frac{dV}{dt} = V_{\text{rest}} - V + g_{\text{ex}}(t)(E_{\text{ex}} - V) + g_{\text{in}}(t)(E_{\text{in}} - V)
\]

with \( \tau_m = 20 \) ms, \( V_{\text{rest}} = -70 \) mV, \( E_{\text{ex}} = 0 \) mV, and \( E_{\text{in}} = -70 \) mV. In addition, when the membrane potential reached a threshold value of -54 mV, the neuron fired an action potential and the membrane potential was reset to -60 mV (resting potential). On arrival of a presynaptic action potential at excitatory synapse \( a, g_{\text{ex}}(t) \rightarrow g_{\text{ex}}(t) + g_a \), and when an action potential arrives at an inhibitory synapse, \( g_{\text{in}}(t) \rightarrow g_{\text{in}}(t) + g_{\text{in}} \), where \( g_a \) and \( g_{\text{in}} \) are the peak synaptic conductances. Otherwise, both excitatory and inhibitory synaptic conductances decay exponentially,

\[
\tau_{\text{ex}} \frac{dg_{\text{ex}}}{dt} = -g_{\text{ex}} \quad \text{and} \quad \tau_{\text{in}} \frac{dg_{\text{in}}}{dt} = -g_{\text{in}}.
\]
This results in the following:

\[ \tau_{ex} = \tau_{in} = 5 \text{ ms}, \quad \xi_{in} = 0.05, \quad \text{and} \quad 0 \leq \xi_{a} \leq \xi_{max} \text{ with } \xi_{max} = 0.015. \]  (For a 100 M\(\Omega\) input resistance, \(\xi_{max} = 0.015\) corresponds to a peak synaptic conductance of 150 pS.)

Synaptic modification was generated according to the following scheme:

\[
F(\Delta t) = \begin{cases} 
A_+ \exp(\Delta t / \tau) & \text{if } \Delta t < 0 \\
-A_- \exp(-\Delta t / \tau) & \text{if } \Delta t \geq 0 
\end{cases}
\]

with varying parameters for the function F.

What does this do? Synapses between simulated neurons are decreased or increased as a function of the time difference between the pre- and postsynaptic spikes.

The authors assume that on the average, synaptic depression should be more likely to occur than synaptic potentiation, as a consequence they choose \(A_- > A_+\).
The model examines how this learning rule acts on a model neuron receiving 1000 excitatory and 200 inhibitory synapses. The excitatory synapses are activated by various types of spike trains: uncorrelated (independent) Poisson processes at various rates and partially correlated spike trains. The inhibitory synapses fire at a fixed rate of 10 Hz (independent of each other), their strength is not varied!

What happens?

We set all synaptic weights to the same value (0.5) to start out (initial condition) in this case, equations similar to those described above and produce random presynaptic spike trains.

1) No learning rule: all synaptic weights stay at 0.5.
2) $A^+ > 0$ and $A^- = 0.0$; only weight increases happen. All synaptic weights grow (they are all limited to 1.0); if the simulation is run for a longer time, they will all saturate.
3) \( A^+ = 0.0 \) and \( A^- > 0 \); only weight decreases happen. After even a short simulation time, most weights are approaching their lower limit of 0.

4) If excitation and inhibition are balanced (\( A^+ = A^- \)), most of the synaptic weights stay around their initial value.
5) With excitation less likely than inhibition at higher presynaptic firing rates the distribution of synaptic weights becomes more diverse.

6) If some of the presynaptic spike trains are highly synchronized (correlated, non-independent), and only synchronized spikes can drive the postsynaptic neuron, then only those synapses driven by synchronized spikes are increased.
7) If inhibition is slightly larger than excitation, the synaptic weights from synchronous spike trains increase and other decrease.

The spike-timing dependent learning rule introduces a competition between presynaptic spike trains and favors synchronous spikes.
The temporal asymmetry of STDP has a number of important consequences. Consider two neurons, A and B, that tend to fire together in the sequence A followed by B. In a time-independent Hebbian model, excitatory synapses from A to B and from B to A would both be strengthened in this situation. STDP, on the other hand, strengthens the synapse from A to B while weakening the synapse from B to A. This allows neuron A to modify the selectivity of neuron B without itself being affected by the changes in B. In more general terms, STDP allows selective groups of neurons with correlated firing patterns to direct the development of nonselective neurons with more random firing patterns.

What can you do with it? We will discuss a few applications that have been proposed in future lectures.