Spike-timing dependent plasticity

Order of pre- and post-synaptic spiking (left) determines if potentiation or depression occurs (right); measured in cultured hippocampal neurons [Poo98].

Plasticity depends on relative timing of pre- and post-synaptic spikes:
- Potentiation occurs if pre proceeds post repeatedly
- Depression occurs if post proceeds pre repeatedly
- Is firing order detected by one or two coincidence-detectors?
Synapses between Layer 5 pyramidal neurons potentiate for pre-before-post pairings (+10ms; open squares in C) and depress for post-before-pre pairings (-10ms; solid squares in C). Longer delays are ineffective (+/- 100ms; open and closed circles in C) [Markram97].

Changes in synaptic efficacy, which rarely exceed a factor of two, persists for over half an hour—this criteria must be met to receive the moniker long-term potentiation or depression (LTP/D).
TEMPORAL CONTIGUITY REQUIREMENTS FOR LONG-TERM ASSOCIATIVE POTENTIATION/DEPRESSION IN THE HIPPOCAMPUS

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Initial discovery of spike-timing dependent plasticity in synapses from entorhinal cortex to dentate gyrus (hippocampus) [Levy83].

Glutaminergic synapses have two types of receptors

Excitatory synapses express two types of glutamate receptors: AMPA and NMDA [Barth06].

Excitatory synapses use the neurotransmitter glutamate, which binds to two types of receptors: NMDA and AMPA.

Newborn synapses, which have only NMDARs, are essentially silent. Because, whereas AMPARs pass current whenever they bind glutamate, NMDA receptors require the membrane to be depolarized first (releases a Mg block).
Potentiation inserts AMPARs

When a synapse is potentiated (Spd), its AMPA-to-NMDA ratio increases [Barth06].

Efficacy of AMPA and NMDA receptors was determined by taking advantage of NMDA’s voltage dependence.

Voltage-clamping the cell to -70 or +40 mV resulted in a fast-inward (AMPA) or a slow-outward current (NMDA), respectively.

One coincidence-detector
Change "Dendrite" to "spine".

Calcium triggers potentiation and depression through kinase and phosphatase pathways [Lisman89].

As NMDARs pass calcium as well as sodium when open, coincident pre- and postsynaptic activity elevates the intracellular calcium concentration.

Large increases in calcium activate the kinase pathway (CaMKII), which promotes potentiation.

Moderate increases in calcium activate the phosphatase pathway (PP1), which promotes depression.

Or two coincidence-detectors

Voltage-controlled Ca-channels (VCCC) and metabotropic glutamate receptors (mGluR) detect post-pre pairing [Sakmann06].

Calcium comes in through voltage-controlled Ca-channels (VCCC) when dendrite is depolarized.

Subsequent binding of glutamate to metabotropic receptors (mGluR) triggers LTD.
Imaging Ca in single spines

Ca-signal, imaged with green dye, is normalized by spine size, imaged with red [Sakmann06].

In this imaging experiment, the change relative to baseline of a Ca-sensitive green fluorescent dye ($\Delta G$) was normalized by a Ca-insensitive red fluorescent dye (R) to account for differences in spine volume.
No difference in Ca thresholds

Voltage-controlled Ca-channels (VCCC) and metabotropic glutamate receptors (mGluR) detect post-pre pairing [Sakmann06].

The peak [Ca] level in dendritic spines of pyramidal cells (L2/3, somatosensory cortex) does not predict the occurrence of LTP or LTD.

Blocking mGluR caused turned LTD into LTP.

Two coincidence-detector model

Pre Glu NMDA CaMK LTP

Post Glu CaVC mGluR V_th LTD
Spikes trigger and sample decay profiles, feeding samples to leaky integrators.

**Potentiation pathway**

When a presynaptic spike occurs, a decay element is activated (Glu).

When a subsequent postsynaptic spike occurs, it samples the decay-element's output (NMDA).

These samples are fed to a leaky integrator, where they accumulate (CaMK).

If the integrator reaches a threshold, the synapse potentiates.

**Depression pathway**

Works similarly, except that the roles of pre- and postsynaptic spikes are reversed (with \( \text{Ca}_{\text{VC}} \), mGluR, and PL playing the roles of Glu, NMDA and CaMK).

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**Model waveforms**

Pre-spike triggers as decaying profile that is sampled by post-spike, and vise versa.

Potentiation and depression time-windows are determined by decay elements.
LTP and LTD in model

Each dot represents a pre-post (left) or post-pre (right) pairing.

The state of the model synapse (potentiated or depressed) is remembered by a state-holding element (flip-flop). It's output determines whether or not AMPARs are inserted.

Model's equations: Pairing's efficacy

If we drive the synapse periodically at $T_s$ with a constant pre-post pairing $t_{pair}$, the LTP integrator's output after $n$ pairings is

$$ P = nS[t_{pair}] - (n - 1)L[T_s] $$

where $S(t_{pair})$ is the sampled decaying profile and $L(T_s)$ is the integrator's leakage. Thus, the number of pairings required to reach threshold ($P_{th}$) is

$$ n_{th} = \frac{P_{th} - L[T_s]}{S[t_{pair}] - L[T_s]} $$

or

$$ \frac{1}{n_{th}} = \frac{S[t_{pair}] - L[T_s]}{P_{th} - L[T_s]} $$

is the efficacy of each pairing.
Model's equations: Linear decay profile

If the profile decays linearly from 1 to zero in $t_p$ seconds, then

$$S[t_{\text{pair}}] = 1 - \frac{t_{\text{pair}}}{t_p}, \quad t_{\text{pair}} < t_p$$

And if the integrator's output decays by 1 every $\tau_p$ seconds, then

$$L[T_s] = \frac{T_s}{\tau_p}$$

Thus, we have

$$\frac{1}{n_{\text{th}}} = \frac{S[t_{\text{pair}}] - L[T_s]}{p_{\text{th}} - L[T_s]} = \frac{1 - \frac{t_{\text{pair}}}{t_p} - \frac{T_s}{\tau_p}}{p_{\text{th}} - \frac{T_s}{\tau_p}}$$

The equation for depression is similar—with $t_D$ and $\tau_D$ playing the roles of $t_p$ and $\tau_p$—except that $t_{\text{pair}}$'s sign is flipped.
Pre-post pairings result in LTP and post-pre pairings result in LTD.