Long Term Plasticity, Biophysical Models

Computational Neuroscience Encyclopedia

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1 Definition

Connections between neurons are called *synapses*. Their *strength* is defined as the voltage amplitude, or slope, of a postsynpatic neuron response to a presynaptic action potential. The synapses can change in strength, i.e., they are *plastic*, and these changes can operate on different time scales. *Long-term plasticity* denotes the synaptic changes that last more than 20-30 minutes (see Fig. 1). This is opposed to short-term plasticity that lasts hundreds of milliseconds.

Models of synaptic plasticity describe mathematically how synapses change under which factors. They are often formulated as differential equations. *Biophysical models* describe how biophysical quantities, such as spike timing, voltage, calcium, Ca2+/calmodulin-dependent protein kinases (CaMKII) influence changes in synaptic strength. These latter models can also be called *bottom-up*. If the variables of the model are only a few biophysical quantities (for example only spike-timing) or are abstract quantities, they are called *phenomenological* models (although there is no sharp distinction). Biophysical models are opposed to optimal or top-down models, designed to optimally fulfill a function (see Fig. 2).

2 Detailed description

This article is first describing the basic mechanism of synaptic plasticity, and presenting the different experimental evidence of long-term plasticity, before describing the different models of long-term plasticity, from the most simple ones to the most detailed ones.

2.1 Synaptic plasticity

Two neurons can be connected via chemical and/or electrical (gap junction) synapses. A chemical synapse is placed between the axon of a presynaptic neuron and a dendrite of the postsynaptic neuron forming a unidirectional connection. The classical view of the synaptic communication mechanism is as follows: When a presynaptic spike arrives at the presynaptic terminal, neurotransmitters, typically glutamate for excitatory synapses,

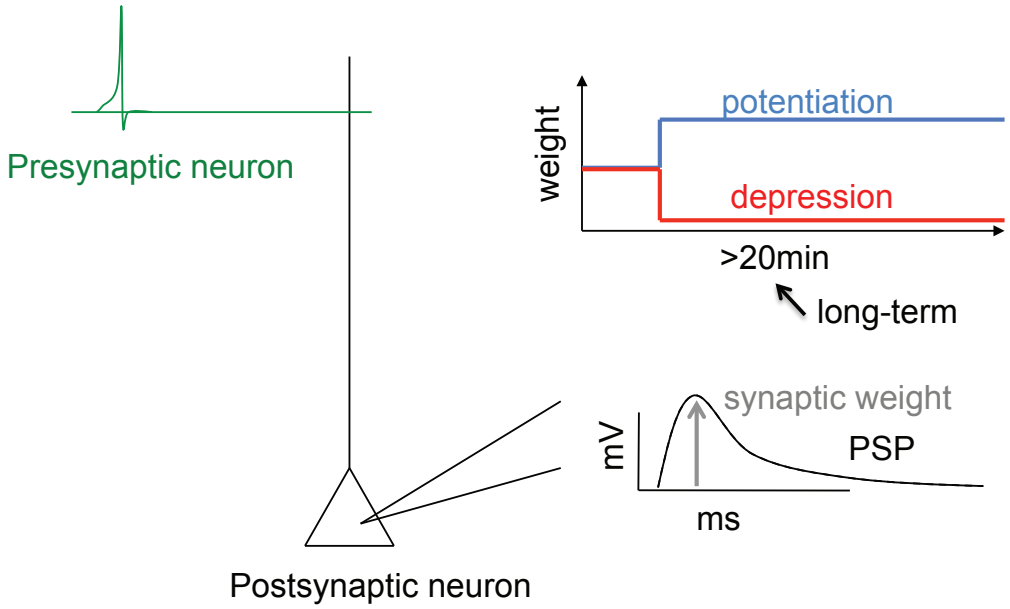

Figure 1: *Cartoon of long-term plasticity.* The synaptic stregth is defined as the height, or the slope, of the postsynaptic voltage response (post-synaptic potential (PSP)) to a presynaptic spike. If the weight is increased, it is called potentiation, and if it is decreased, it is called depression. Long-term plasticity denotes the changes that last more than 20 min.

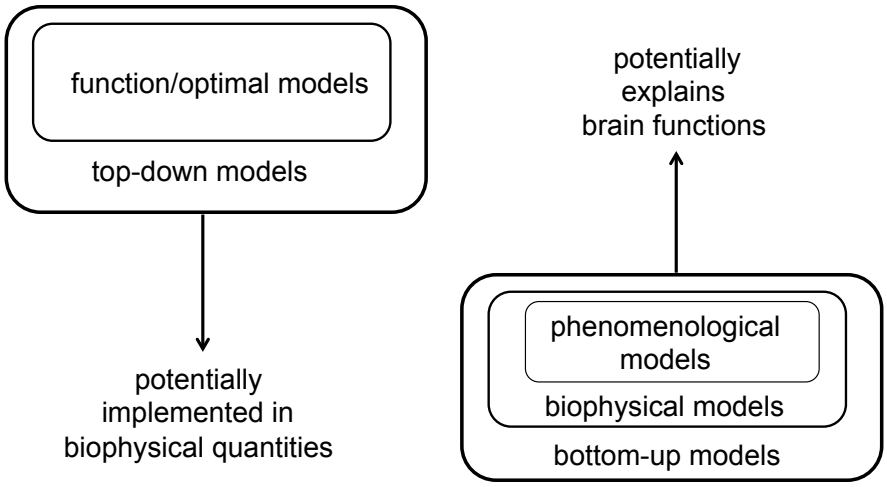

Figure 2: *Models of synaptic plasticity.* Biophysical models denote models that take into account biophysical quantities in order to explain synaptic plasticity. If the biophysical quantities are restricted or abstract, the models are called phenomenological. These models are also called bottom-up, since they are based on biophysical quantities but ultimately can be used to described brain functions ("bottom" for biophysical quantities and "up" for brain functions). This is opposed to functional or optimal models, designed to optimize a function. These models can then be related to biophysical qualities and are thus also called top-down models ("top" for function and "down" for biophysical implementation).

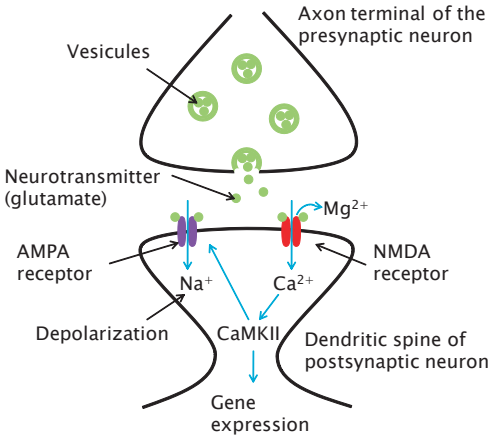

Figure 3: *Cartoon of a glutamatergic synapse.* When a presynaptic spike arrives at the synapse, neurotransmitters are released in the synaptic cleft. They can bind to the NMDA receptor, and if, at the same time the postsynaptic cell is depolarized, the channel opens. Calcium enters the cell, which induces a molecular cascade that phosphorylates the Ca2+/calmodulin-dependent protein kinases (CaMKII), which in turn acts on the AMPA receptor activation. Neurotransmitters can also directly bind to AMPA receptor, opening the channel, allowing sodium to enter, leading to a depolarization called excitatory postsynaptic potential (EPSP).

are released. They can bind on the postsynaptic side to receptors, such as N-methyl D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. AMPA receptors then open and let sodium ions flow into the cell, resulting in a depolarization of the postsynaptic membrane potential. The NMDA receptor opens only if at the same time (a) the glutamate binds to the receptors and (b) the postsynaptic cell is depolarized, freeing the magnesium block (see Fig. 3). This depolarization of the postsynaptic cell typically comes from back-propagating action potentials. The NMDA receptor is therefore seen as a *coincidence detector* between presynaptic and postsynaptic activities. The opening of these receptors allows calcium to enter the synapse. Despite the detailed description of the mechanisms that allow synaptic communication [73, 52], the mechanism that leads to changes in the synaptic strength is not completely clear. Calcium plays an important role for further cascade signaling, which acts on AMPA receptor activation through kinases and phosphatases [51]. Moreover retrograde messengers like endocannabinoids can influence plasticity, in particular for depression of the synapses [87, 70, 88, 61].

2.2 Experimental evidence of long-term plasticity

The typical measurement of synaptic strength is the amplitude or the slope of the excitatory postsynaptic potential (EPSP), i.e. the potential response to a single (or a group of coincident) presynaptic spike(s). Synaptic plasticity can be separated by two different time scales: short-term plasticity, where changes persist during a few hundred milliseconds, and long-term plasticity that lasts more than 20 minutes. Short-term plasticity is believed to be presynaptically expressed [57, 35] and is partly caused by the limited number of neurotransmitters at the synapse. It is well modeled by a reservoir that partially empties at the presynaptic spike time (with a certain probability), and recovers with a certain time constant [56, 3]. Here the focus is on long-term plasticity, which can be induced by different types of protocols.
(i) *Simultaneous voltage clamp and presynaptic stimulations* [62, 48] (Fig. 4A). If the cell is slightly depolarized while receiving presynaptic inputs, the synaptic weight is depressed, whereas if the cell is highly depolarized, the synapse is potentiated.
(ii) *Extracellular presynaptic stimulations at different frequencies* [44, 22, 63] (Fig. 4B). Low frequency stimulation leads to depression, whereas high frequency leads to potentiation.
(iii) *Pairing of presynaptic and postsynaptic spikes at different time lags* (Fig. 4C). In pyramidal cells pre-post pairing typically results in potentiation, whereas post-pre results in depression [55, 9](although it depends on the system [23, 53, 8, 92]).
(iv) *Pairing at different frequencies* [55, 86] (Fig. 4D). Pre-post pairing at low frequency does not change the synaptic weight, increasing the frequency leads to potentiation.
(v) *Induction of various spike patterns.* Synaptic plasticity can also be induced with different patterns, such as triplets of spikes [26], bursts [61, 36], quadruplets [95], or natural spike trains [26]. The resulting plasticity dependes on the protocol: in particular in depends if presynaptic stimulation is extracellular (many inputs at the same time, slices more active) [26] or intracellularly [86].
(vi) *Synaptic tagging experiments* [25]. These experiments provide evidence for another separation of time scales of long-term plasticity. The early phase of long-term plasticity lasts 2 to 3 hours and can be induced by tetanic stimulation for potentiation (Fig. 4E). The late phase, or consolidation phase, lasts more than 10 hours (i.e. the time of those experiments) and can be induced by a stronger extracellular tetanus that also stimulates dopaminergic fibers (Fig. 4F). Neuromodulation is therefore critical in the process of consolidation [71, 67].

2.3 Models

This section is describing the different models of long-term plasticity, from the most simple ones to the most detailed ones, starting from firing rate models all the way to detailed biophysical models.

2.3.1 Models based on firing rates

The first models of synaptic plasticity in line with Hebb's principle "Who fires together wires together") [40] depend on the correlation the pre- and postsynaptic firing rates. The subsequent models subtracted a baseline so that the weight can also be depressed (covariance rule [77]), added weight dependency (hard or soft bounds), and added normalization to induce competition between weights [58]. Multiplicative normalization was introduced

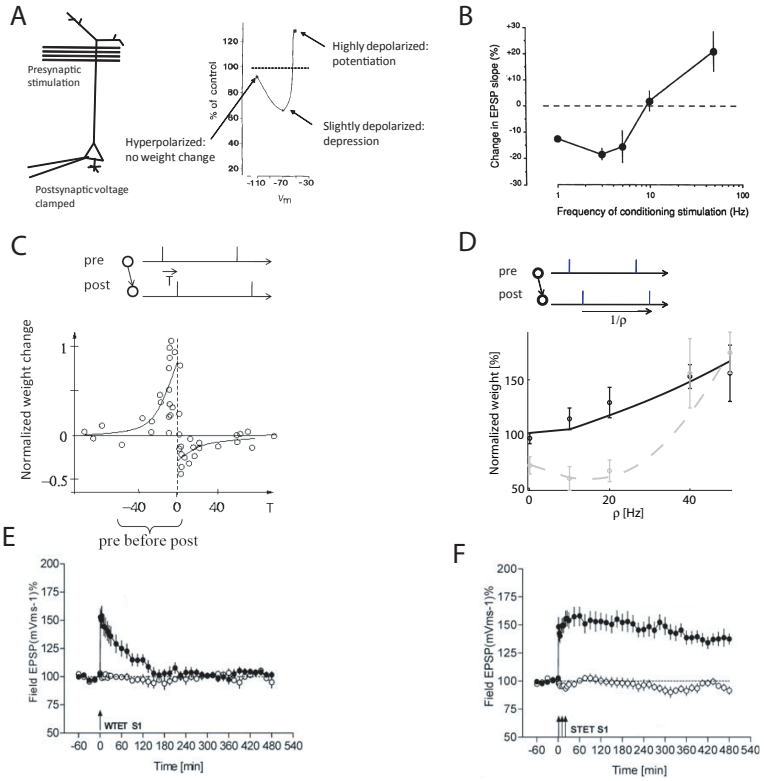

Figure 4: *Different experimental protocols.* A. *Voltage clamp experiment.* The postsynaptic voltage is clamped at the soma during extracellular presynaptic stimulation. If the voltage is hyperpolarized, no weight change is recorded; for slight depolarization, depression is observed; for strong depolarization, potentiation occurs. Figure redrawn from [5]. B. *Presynaptic frequency dependence.* Extracellular presynaptic spike trains at different frequencies are induced. Low frequency stimulation yields depression whereas high frequency stimulation results in potentiation. Figure redrawn from [22]. C. *STDP experiment.* Pairs of presynaptic and postsynaptic spikes are elicited, while the lag between the presynaptic spike and the postsynaptic spike varies. Pre-post pairing induces Long Term Potentiation (LTP) whereas post-pre leads to Long Term Depression (LTD). Figure redrawn from [9]. D. *Pairing frequency experiment.* Here the lag between the pre- and postsynaptic spike is constant (pre-post (black), post-pre (grey)) but the frequency of the pairings varies. Pre-post at low frequency does not lead to any weight change whereas increasing frequency allows for potentiation. Figure redrawn from [86]. E. *Weak tetanus stimulation.* Few extracellular high frequency trains stimulated presynaptically yield LTP that lasts 2 to 3 hours. F. *Strong tetanus stimulation.* If longer high frequency trains are induced, the potentiation is stable for longer than 10 hours. Figure redrawn from [74].

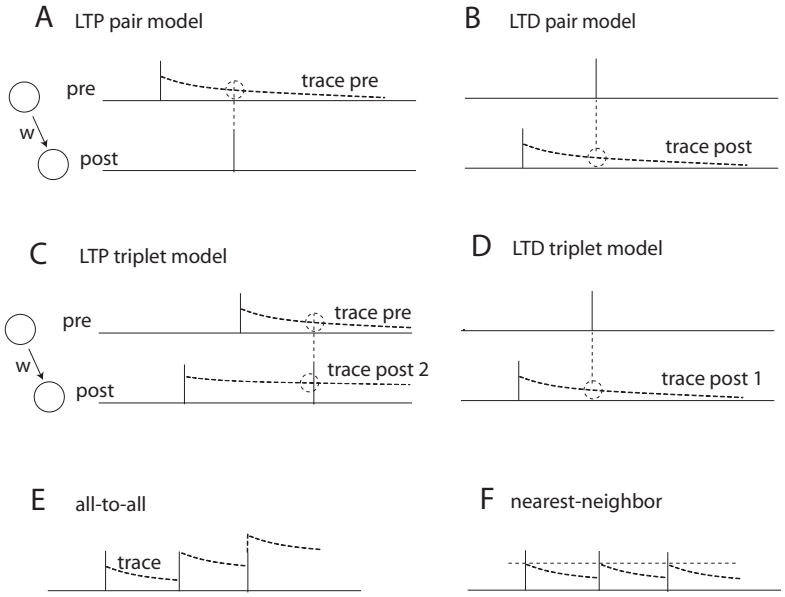

Figure 5: *Different types of models.* A. *LTP with standard STDP model.* The synaptic weight is potentiated at the time of the postsynaptic spike by an amount corresponding to the presynaptic trace. B. *LTD with standard STDP model.* The synaptic weight is depressed at the time of the presynaptic spike by an amount corresponding to the postsynaptic trace. C. *LTP with the minimal triplet rule [69].* The synaptic weight is potentiated at the time of the postsynaptic spike by an amount corresponding to the product of a presynaptic and a postsynaptic trace. D. *LTD with triplet rule.* Same as standard STDP model. E. *All-to-all interaction of spikes.* The trace jumps by a fixed amount when a spike occurs and decays otherwise, leading to cumulative effect from all the previous spikes. F. *Nearest-neighbor interaction of spikes.* The trace jumps to a fixed value when a spike occurs and decays otherwise. Only the last spike affects the trace.

in Oja's rule [64], which performs Principle Component Analysis (PCA). At the same time, the Bienenstock-Cooper-Munro (BCM) rule [10] was designed with a nonlinearity in the postsynaptic firing rate, and a sliding threshold, as a homeostatic mechanism. The BCM also model exhibits properties of selectivity in the inputs.

2.3.2 Models based on spike timing

Spike-Timing-Dependent Plasticity (STDP) models [30, 45, 78, 90, 94, 72, 37, 42] depend on the precise timing of the pre- and postsynaptic spike.

Standard pair-based models

For the LTD part, standard pair-based models assume that presynaptic spike arrival, at synapse i, induces depression of the synaptic weight w_i by an amount that is proportional

to $\bar{y}$, an exponential low-pass filtered version of the postsynaptic spike train $Y(t)$ with a time constant τ_- (see Fig. 5B, trace post):

$$\tau_- \frac{d}{dt}\overline{y}(t) = -\overline{y}(t) + Y(t),$$

where $Y(t)$ is expressed as the series of short pulses at time t^n, with n being a spike index, $Y(t) = \sum_n \delta(t - t^n)$. The variable $\bar{y}$ is an abstract variable which could, for instance, reflect the level of calcium concentration [50], the release of endocannabinoids [88], or the back-propagating action potential, although such an interpretation is not necessary for this type of phenomenological rules. Similarly, the presynaptic spike train is described as a series of short pulses at time t_i^n with i being the index of the synapse, $X_i(t) = \sum_n \delta(t - t_i^n)$. The depression is then modeled as the following equation (see Fig. 5B):

$$\frac{d}{dt}w_i^- = -A_{\text{LTD}}(w_i^-)\, X_i(t)\, \overline{y}(t), \tag{1}$$

where A_{LTD} is the amplitude for depression.

For the LTP part, the temporal evolution of the presynaptic low pass filter $\bar{x}_i(t)$ is described by (see Fig. 5A, trace pre):

$$\tau_+ \frac{d}{dt}\bar{x}_i(t) = -\bar{x}_i(t) + X_i(t),$$

where X_i is the spike train defined above. The quantity $\bar{x}_i(t)$ could for example represent the amount of glutamate bound to postsynaptic receptors [42, 69] or the number of NMDA receptors in an activated state [78]. The potentiation is then described by the following equation (see Fig. 5A):

$$\frac{d}{dt}w_i^+ = +A_{\text{LTP}}(w_i^+)\, Y(t)\, \bar{x}_i(t). \tag{2}$$

where A_{LTP} is the amplitude for potentiation.

There are several implementations of pair-based STDP models. For example, the pre- and postsynaptic traces can either consider all the spikes, i.e. all-to-all interactions (Fig. 5E) or only the nearest neighbor spike (Fig. 5F). Since the synaptic weight cannot grow indefinitely, STDP models add bounds. Additive STDP has hard bounds, i.e., there is a hard cut off at a minimal and maximal weight value. Multiplicative STDP has soft bounds and therefore the amount of plasticity depends on the actual synaptic strength [46, 94, 72, 38] (see experimental findings on weight dependence [9, 91]). Models of STDP also can take into account homeostasis [45, 94, 69, 19] (see [91] for experiments).

These types of models can reproduce the spike-timing-dependent learning window (see Fig. 4C), but not the pairing frequency dependence (see Fig. 4D), nor the voltage clamp experiment (see Fig. 4A)[55, 86]. Therefore non-linear models were developed to describe those experiments, where triplet interaction of spikes are considered [78, 69, 20, 19] (see below), or discount factors on the "efficacy" of successive spikes, similar to including a model of short-term plasticity ([26], model based on extracellular inductions of triplets of spikes).

Triplet model

The minimal triplet model [69] describes depression the same way as the standard pair-based models. However, potentiation takes into account triplet interactions of spike, two postsynaptic spikes and one presynaptic spike (see Fig. 5C). The model defines a second type of postsynaptic trace $\bar{y}_2$ that decays with a time constant τ_2, typically on the order of 100ms. This second trace might represent calcium concentration at the synapse. The synapse is potentiated at the postsynaptic spike time by an amount that is proportional to the product of the presynaptic spike trace $\bar{x}_i(t)$ (see Fig. 5C, trace pre) and the second postsynaptic spike trace $\bar{y}_2$ (see Fig. 5C, trace post 2). The potentiation is written:

$$\frac{d}{dt}w_i^+ = +A_{\text{LTP}}(w_i^+)\, Y(t)\, \bar{x}_i(t)\, \overline{y}_2(t), \tag{3}$$

where A_{LTP} is the amplitude for potentiation.

This model is able to reproduce the frequency experiment (see Fig. 4D) but not the voltage clamp experiment (see Fig. 4A), since it only depends on the spike timing, and not on the postsynaptic membrane potential.

2.3.3 Models based on spike-timing and postsynaptic voltage

Voltage-based models [2, 19, 12] typically depend on the presynpatic spike time and on the postsynaptic voltage. We describe here one voltage-based model in more detail.

Voltage-triplet model

The voltage-based triplet model [20, 19, 18] is designed to reproduce the frequency experiment (see Fig. 4D), and the voltage clamp experiment (see Fig. 4A) [20]. The rule is written as

$$\frac{d}{dt}w_i = -A_{\text{LTD}}\, X_i(t)\, [\overline{u}_-(t) - \theta_-]_+ + A_{\text{LTP}}\, [u(t) - \theta_+]_+\, \bar{x}_i(t)\, [\overline{u}_+(t) - \theta_-]_+, \tag{4}$$

where u is the postsynaptic voltage, $\bar{u}_{+/-}$ are postsynaptic voltage low-pass filters with two different time constants, $\theta^{+/-}$ are thresholds, and $[x]_+$ is x when $x > 0$, and 0 otherwise. It was shown to reproduce a large part of the experimental literature on long-term plasticity [18], such as spike-timing pair, burst, triplet, quadruplet experiments [55, 9, 95, 61, 26], frequency dependence [21, 55, 86], voltage clamp experiments [5, 62] and dendritic dependency [85]. This model has very different functional implications in networks than pair-based rules [19].

2.3.4 Models based on receptors dynamics

Thoses models describes typically glutamate binding, AMPA receptors [76] or NMDA receptors [29, 97, 41, 78].

Senn-Tsodyks-Markram model

The Senn-Tsodyks-Markram (STM) model [78] takes into account the dynamics of the NMDA receptor. The receptors can be in 3 different states: rest, up or down. In absence of spikes, NMDA receptors are in the rest state, but they can be up-regulated

when a presynaptic spike occurs or down-regulated at the postsynaptic spike time. A notion of two types of second messengers is introduced in the model, so that when a postsynaptic spike occurs, second messengers type 1 can be up-regulated only if the NMDA receptors are in the up states already. Conversely, the second messengers type 2 can be down-regulated if there is a presynaptic spike and if the NMDA receptors are already in the down state. Finally LTP is elicited when there is a postsynaptic spike and the second messengers type 1 are in the up state, LTD occurs at the time of a presynaptic spike if the second messengers type 2 are down regulated. This model takes into account pair interaction of spikes and triplet interactions of spikes, i.e., 1 presynaptic spike, 2 postsynaptic ones for potentiation and 2 pre- and 1 postsynaptic spike for depression.
It reproduces frequency dependence experiment (see Fig. 4D), as well as STDP experiment (see Fig. 4C), but not the voltage clamp experiment (see Fig. 4A). It can be mapped to the BCM rule although the depression term in not linear in the presynaptic term.

2.3.5 Models based on calcium

There are several models depending on calcium concentration [50, 43, 42, 82, 1, 73, 27, 6, 14], two are described here in more detail.

Shouval model

The calcium model of Shouval et al. [82] takes the concentration of calcium in the postsynaptic cell as a measure for plasticity. Low calcium of concentration is not affecting the synapse, intermediate concentration leads to LTD, and high concentration leads to LTP. The model describes the calcium changes at the synapse: the calcium current flows through the NMDA receptors only if the presynaptic spike is paired with a back-propagating action potential.
It reproduces the voltage clamp experiment (see Fig. 4A), presynaptic stimulation frequency experiment (see Fig. 4B), and the STDP experiments (see Fig. 4C). However, it predicts a LTD part in the pre-post side of the STDP curve due to the shape of the back-propagating action potential. Refinements of this model are proposed in [83].

Graupner model

In the calcium model of Graupner et al. [34], potentiation and depression are activated by calcium thresholds, where presynaptic and postsynpatic action potentials elicit calcium transients. The synapses are considered to be bistable. The model gives rise to a multiple of learning curves and reproduces the frequency dependence (see Fig. 4D). This model is a simplified version of a more detailed biophysical model [31].

2.3.6 Models based on CaMKII

Bistable models

Bistable models [49] were introduced as a solution to the following paradox: Since the molecular turnover is fast, on the order of minutes to hours, how can the synapses keep their strength for much longer? The idea was that the CaMKII can switch between a phosphorilated and unphosphorilated state [49, 50, 98, 65]. Mathematical models of

CaMKII phosphorlisation and de-phosphorlisation show a bistability regime (see for example [98, 52, 59], although some don't find bistability mathematically [47] and in the experiments [13]). These models have a number of limitations concerning the number of molecules involved [59] and CaMKII trafficking [39]. Finally, although the importance of CaMKII for the induction of plasticity is clearly demonstrated, some experimental studies suggest that CaMKII is not involved for the maintenance of plasticity (late-phase, consolidation) [54, 66].

There are alternative models for the maintenance of plasticity, such as a bistability of translational switch [11], a cluster model of AMPA receptors [79], and memory reactivation model [96, 89]. For models of kinases and phosphates, refer to [15, 4, 1].

Bistable biophysical models and spike-timing

These models [32, 93] describe how precise spike timing induces a calcium transient. The resulting calcium concentration influences the CaMKII bistable system: at low concentration, up and down states are stable, at medium concentration only the down-state is stable, whereas at high calcium concentration, only the up-state is stable. The model reproduces the different spike-timing dependent plasticity experiments, and the bistable CaMKII system allows stable synapses.

2.3.7 Consolidation models

Synaptic tagging experiments [25] reveals two phases of long-term synaptic plasticity: the early phase, which induces a change that lasts 2 to 3 hours (Fig. 4E) and the late phase, which lasts more than 10 hours (Fig. 4F). Standard STDP models and detailed biophysical models don't discriminate, and only describe the induction of plasticity, assuming the changes to be long lasting. Below, models of synaptic consolidation are explained in detail.

Cascade model

The cascade model [28] is designed to optimize the memory life-time. It proposes a bistable synapse, that can either take a weak or a strong value. For each value, the synapse can be in different plastic states, called "meta-states". For example, if the synapse is already weak and undergoes a LTD protocol, it will keep the same weak value but will go to a lower metastate, where the synaptic weight is harder to change, i.e., less plastic.

Models of synaptic tagging

There are currently two models describing the late-phase of long-term plasticity.

The TagTriC model [20] is separated into three processes:

1) Tagging: The synapse strength is the sum of two parts, the weight of the early-phase and the weight of the late-phase. The early-weight is a stochastic three-states variable [68, 63], it can be in neutral state, high state or low state. If the early-weight is in the high or low state, it is automatically *tagged*. The state of the early-weight switches from neutral to high or low with a probability given by a Hebbian rule for the induction of plasticity [20, 19]. It decays back to neutral with a certain transition probability.

2) Trigger: If the number of tags exceeds a threshold, plasticity-related proteins are synthesized. The threshold depends on the dopamine level, such that if dopamine is high, the threshold is lowered. Extracellular stimulation also stimulates dopaminergic fibers, lowering the threshold.

3) Consolidation: The late-weight of the synapse is a continuous variable with two stable states. If plasticity-related proteins are available and if the synapse is tagged, the late-weight can switch to a different stable state, thus allowing for consolidation.

This model can reproduce the synaptic tagging experiment (Fig. 4EF), as well as several pharmacological experiments [25, 74].

The consolidation model of Barrett et al. [7] is very similar to TagTriC [20], with some differences in its implementation. A synapse has one of two states (weak or low) but each state additionally has one of three meta-states: early-phase, tagged or consolidated. As in TagTriC, synapses are stochastic and their synaptic weight is a compound of several synapses. The transitions between states are a function of the protocol (weak tetanus or strong tetanus). Thus, induction of plasticity is not modeled explicitly, nor is a mechanism of plasticity-related proteins synthesis designed, in contrast to the TagTriC model. However, the model dissociates the tag state from early-phase state, which is supported by the experiments where tags are reset [75], experiments that are not directly captured by the TagTriC model.

Sources and further readings

This text is based on the introduction of [16], and on [17]. For further readings, refer to the reviews on biophysical models [33] (and the chapter 2.7.2-4 of [31]), on phenomenological models of STDP [60], on models and experiments of STDP [24] and synaptic consolidation [17], as well as the Scholarpedia articles [84, 80, 81].

Acknowledgments

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