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**Review**

# Messages in Spike Timing-Dependent Plasticity: Pros and Cons

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## Abstract

**Spike-timing dependent plasticity (STDP), a synaptic modification depending on a relative timing of presynaptic and postsynaptic spikes, has fascinated researchers in the fields of neurophysiology and computational neuroscience, because it is not only conceptually simple or biologically reasonable but is also versatile in neural network simulations. The STDP rule may be valid only under specific conditions, however. We propose herein a method that could find more natural and potent rules of synaptic plasticity.**

**Key Words: synaptic plasticity, hippocampus, neocortex**

## Rules and Mechanisms of Spike-Timing Dependent Plasticity (STDP)

The ability of neurons to modulate their synaptic connectivity and excitability underlies behavioral adaptation and memory. After Hebb's postulate, the so-called "cells that fire together, wire together" theorem, one of the most accepted learning rules is spike-timing-dependent plasticity (STDP), in which synaptic weights change along the relative timings of pre- and postsynaptic action potentials (4, 27, 33, 38, 46; for review see 1, 5, 7, 8). In general, in order to induce long-term potentiation (LTP), postsynaptic spikes must occur within a time window of tens of milliseconds after presynaptic spikes, whereas the reversal order of presynaptic and postsynaptic spikes leads to long-term depression (LTD) (Fig. 1).

The cellular mechanisms of STDP have been addressed mainly in *in vitro* preparations. In primary hippocampal neuron cultures (4) and acute neocortical slices (27), repeated "pre → post" pairings of single spikes (*e.g.*, 60 pair pulses at 1 Hz) lead to spike timing-dependent LTP (tLTP). In contrast, pairings of single spikes at a negative interval result in spike timing-dependent LTD (tLTD). These synaptic modifications require NMDA receptor activation (4).

The pairing stimuli also cause a rapid and persistent enhancement (14) or reduction (24) of excitability of the presynaptic neuron. This form of plasticity also depends on NMDA receptor activation and $Ca^{2+}$ influx to the postsynaptic neurons (14). As for the presynaptic neurons, protein kinase C (PKC) is required for the increase in excitability (14), and protein kinases A (PKA) and C are both required for the decrease in excitability (24). Interestingly, the changes in excitability are not necessarily associated with the changes in synaptic strength, because presynaptic blockage of PKC and/or PKA abolished the excitability changes with little effect on synaptic modifications.

## Locally Modified STDP Rule

The STDP rule varies depending on the synapse location along dendrites. At the intermediate-distal part of the apical dendrite (100~150 μm from the soma) of layer 2/3 pyramidal cells in visual cortical slices (12), the magnitude of tLTP is smaller, and the

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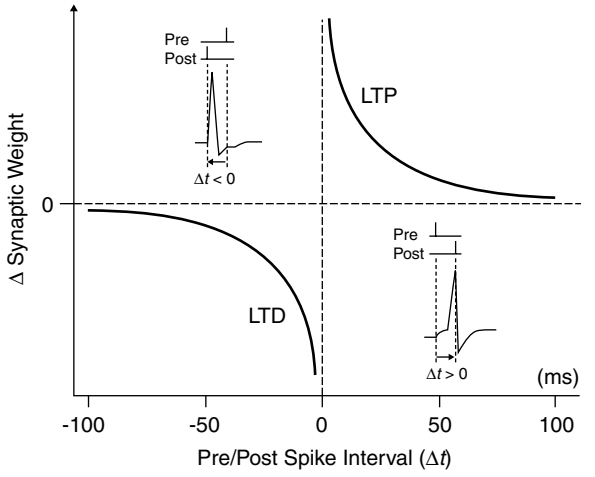


Fig. 1. Temporal window for STDP induction. Presynaptic spikes preceding postsynaptic spikes ($\Delta t > 0$) cause long-term potentiation (LTP), whereas postsynaptic spikes preceding presynaptic spikes ($\Delta t < 0$) cause long-term depression (LTD). Thus, synapses are considered as "rewarded" when inputs actively contribute to the spiking of a cell, otherwise they are "punished".

temporal window for tLTD is broader than at the proximal dendrite, which may attribute to the attenuation of back-propagating action potentials at the distal dendrite, because action potentials may not reach the distal tip of the dendrite or because the basal and oblique dendrites of pyramidal neurons might receive more synaptic inputs. At distal synapses between layer 2/3 and layer 5 pyramidal neurons in somatosensory cortex, preceding presynaptic spikes leads to a distance-dependent shift toward tLTD, which can be converted to tLTP at more proximal sites by dendritic depolarizations with backpropagation activated calcium firing (23). Thus, synapse location within the dendritic tree is a crucial determinant of STDP.

STDP also alters the dendritic interaction among synaptic input. Wang *et al*. (44) examined the changes in spatial summation between two input pathways in hippocampal CA1 neurons. Induction of tLTP in one pathway resulted in an increase in the linearity of spatial summation of the two pathways, whereas tLTD produced the opposite effect. These changes depend on NMDA receptor activation and may be mediated by persistent modulation of $I_h$ channels. It is possible, therefore, that the STDP rule itself is modified after STDP-induced changes in the dendritic properties.

## *In Vivo* STDP

An increasing number of *in vivo* studies have begun to address the functional consequences of STDP. These studies are divided into three types, based on how spike timing is experimentally controlled. First, postsynaptic spiking is evoked by electrical stimulation, while presynaptic activation is induced by either sensory or electrical stimulation (31, 42, 46). The pairing of visually evoked presynaptic spikes and postsynaptic spikes leads to potentiation or depression, just like *in vitro* STDP, and the temporal window is also similar to that of *in vitro* STDP.

Second, all spike timings are manipulated by sensory stimuli, without use of artificial electrical stimulation. In anesthetized adult cats, repetitive presentation of gratings at a pair of orientations induces a shift in the orientation tuning of individual V1 neurons. The direction of the shift depends on the temporal order of the two orientations (45). In a parallel set of experiments, repeated visual stimulation in two adjacent retinal regions induces a shift in V1 receptive fields, with a similar dependence on the stimulus order (13). In both cases, significant changes in the cortical response properties occur at intervals within ± 40 msec. In the Xenopus tadpole, repeated presentation of a moving bar in a given direction selectively potentiates the response to the conditioned direction, resulting in the emergence of direction sensitivity in the activated tectal neurons (10). Another study was carried out using both sequentially flashed bars and moving bars in the induction of direction selectivity (31) and revealed that the magnitude and polarity of changes in light-evoked excitatory synaptic responses in tectal neurons exhibit a temporal specificity consistent with *in vitro* STDP.

Finally, STDP is applied to natural patterns of sensory stimuli in order to predict experience-dependent plasticity. Mehta *et al*. (29) show that repeated locomotion of rats along a linear track induces an asymmetric expansion of hippocampal place fields, which seems to be consistent with the STDP rule. This form of place field plasticity may underlie sequence learning during spatial navigation. A theoretical study predicts that the efficacy of STDP can bridge the discrepancy between synaptic and behavioral timescale (9).

These studies provide compelling evidence that the STDP is indeed elicited by sensory stimuli, but it should be noted that all these reports, except for Mehta *et al*. (29), used very unnatural sensory stimulation, such as repetitive presentation (or movement) of a light bar and repetitive flash light. Furthermore, all experiments, again except for Mehta *et al*. (29), were conducted with anesthetized animals.

## STDP Rule Collapsing

After all, there is no evidence that STDP occurs in the brain, despite its rule appears biologically

simple and intuitively reasonable. Under physiological conditions, importantly, neurons usually emit spikes at high frequencies. Several *in vitro* studies have shown that the rule of STDP easily breaks down under the "bursty" conditions in which neighboring spikes occur at very close intervals (36). In visual cortical slices (11) and hippocampal slice cultures (43), spike "triplets" (pre → post → pre) or (post → pre → post) and "quadruplets" (pre → post → post → pre) or (post → pre → pre → post) were tested. In both studies, it turns out that the interaction between multiple spikes is nonlinear and cannot be extrapolated by the "pairwise" STDP rule. What is even worse is that the form of nonlinearity is different between brain regions. In the visual cortex, the nonlinear interactions could be fit to a suppression model in which the magnitude of the latter spike is reduced by preceding spikes. In the hippocampus, the "pre → post → pre" triplets induce no synaptic change, which suggests that tLTP and tLTD cancel out each other, but the "post → pre → post" triplets induce tLTP, which suggests that tLTP "wins over" tLTD. To make things more complicated, STDP can be modulated by inhibitory inputs and neuromodulators, such as acetylcholine (6) and dopamine (32).

We now should go back to the basics; STDP was originally found in *in vitro* experiments, in which making use of very simple protocols (pairwise neuron stimulation) was a key to discover the rule of STDP (4, 27). These patterns of stimulation, *i.e.*, stereotypic repetition of defined presynaptic and postsynaptic timings, however, are extremely non-physiologic, because spike timings highly fluctuate in the brain (35). Therefore, care must be paid for interpretation and application of those data, although such induction protocols might be experimentally optimal and versatile.

Moreover, we have to know that only few studies have indeed depicted the asymmetry curve of the STDP rule (4, 11, 20, 36, 46). In most of other STDP studies, only two different stimulation timings, *e.g.*, $\Delta t = \pm 20$ ms, were used to evaluate the inducibility of tLTP and tLTD, so that the actual rule of STDP is uncertain for the entire $\Delta t$ range. Even in those studies somehow showing the STDP curve, individual data vary considerably from experiment to experiment, to a degree that the true STDP curve function cannot be estimated (for example, see the famous Fig. 7 in ref. 4). In addition, STDP has been studied so far in relatively limited preparations. To our knowledge, surprisingly, no report shows the existence of STDP in acute hippocampal slices, using dual patch-clamp recordings from hippocampal pyramidal neurons. More critically, Sjöström *et al*. (37) found that in neocortical layer 5 pyramidal connections, tLTD can be induced by pairing presynaptic firing with subthreshold postsynaptic depolarization alone, that is, postsynaptic spikes are not indispensable for tLTD. Therefore, the classical rule of STDP is no longer validated.

To evaluate the consequence of STDP-driven learning, we computer-simulated a realistic neural network with the STDP rule. When a neural network in which STDP was the only learning rule was allowed to spontaneously self-organize, the network activity inevitably became divergent and stopped further learning at certain time points, that is, all neurons were urged into either epileptiform synchronization or zero activity (unpublished data). The weights of individual synapses were extremely bisected into winning or losing, and the projection patterns were asymmetric. In the real neocortical network, the synaptic weights are more widely distributed, and the distribution has a bell shape in a lognormal plot (39). Moreover, neurons are more likely to be reciprocally (*i.e.*, symmetrically) connected (39). This cannot be accounted for by the temporally asymmetric STDP rule. These facts suggest that there exists another plasticity rule, rather than STDP.

## Search of New Synaptic Plasticity Rules

Under natural situations, the brain spontaneously self-organizes through intrinsically emitting neuronal activity. Some reports have shown spontaneously occurring synaptic plasticity during ongoing activity. With patch-clamp recordings from single CA3 pyramidal neurons, we showed that ongoing activity causes complex reorganization of synaptic connectivity without any artificial stimuli, indicating that active hippocampal networks continuously and intrinsically remodel their internal connectivity through ongoing plasticity (40). This may underlie spontaneous network state drifting (34, 41). With multiple patch-clamp recordings from pyramidal cells in rat neocortical slices, Le Be and Markram (21) demonstrated that synaptic connectivity displays spontaneous rewiring over hours, indicating that pyramidal neurons autonomously connect and disconnect each other. Other pieces of physiological, morphological and biochemical evidence are accumulating that spontaneously active networks undergo spontaneous and rapid changes in the functional strength, shapes, and molecular markers of synapses (2, 3, 16, 18, 19, 30, 47).

It is noteworthy that spontaneously occurring neuronal activity is non-randomly organized in space and time (17, 25, 26). We thus expect that plasticity rules can be extracted from spontaneous activity patterns (Fig. 2). In our current trials, synaptically connected cortical neurons are dual whole-cell patched, and their synaptic strength is compared

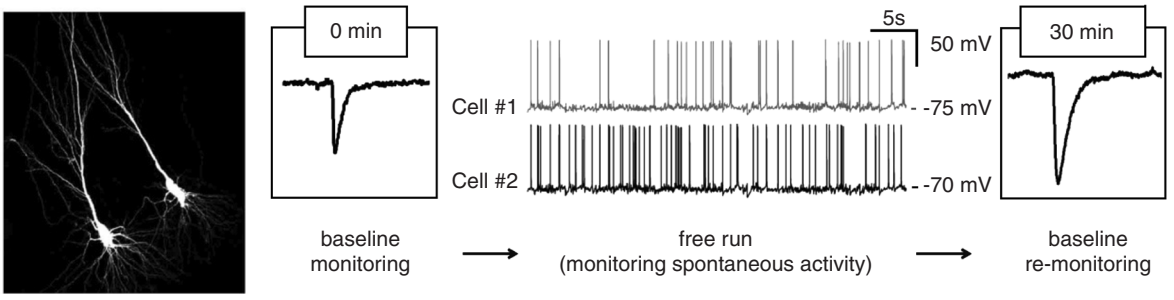


Fig. 2. Monitoring of ongoing plasticity. Synaptically connected neurons are patch-clamp recorded (left photo), and their connection strength is compared before and after a "free-run" period during which the network is allowed to emit spontaneous activity. Then, the 'real' rule of synaptic plasticity is extracted from the pattern of the spontaneous activity and the resultant synaptic plasticity.

before and after a 30-min "free-run" period during which the network is freely allowed to emit spontaneous activity. We already found that this experimental design successfully captures spontaneous synaptic modification. Thus, the 'natural' rule of synaptic plasticity is expected to be obtained by solving the inverse problem between the spontaneous activity pattern and the resultant synaptic plasticity (*i.e.*, its direction, magnitude, and persistency).

To this end, the selection of preparations is critical. Natural spontaneous activity is more likely to be replicable in the *en bloc* cortex and *in toto* hippocampus (15), rather than slice or culture preparations. Patch-clamp recording techniques from free-moving mice have recently been established (22), which will promisingly allow monitoring more psychophysiologically relevant activity during exploring and learning. In complex networks, mice that express channelrhodopsin 2 in cell-specific manner may help to find synaptically connected neuron pairs in the interested region (28). We hope that revealing the yet-unknown rules, in addition to STDP, could open the way toward better understandings of network plasticity.

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