A biophysical basis for the inter-spike interaction of Spike-Timing-Dependent Plasticity

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Abstract: Experiments involving Spike-Timing Dependent Plasticity (STDP) are often performed under artificial conditions, where one pre- and one postsynaptic spike is delivered systematically at fixed time lags, and the corresponding change in synaptic strength is mapped onto a learning curve. However, the manner in which STDP generalizes for more complex temporal patterns of spikes is unknown. It has been shown that the effects of STDP from different spike pairs are not independent and therefore do not add linearly. Here, we show that the previously proposed Calcium-Dependent Plasticity Model can reproduce this result if short-term depression and spike adaptation are taken into account. This suggests that for realistic spike-trains the canonical form of STDP is insufficient to account for the observed plasticity and that complex cellular and synaptic biophysics must be considered.

Keywords: synaptic plasticity, Hebbian learning, STDP, calcium, NMDA, short-term plasticity.

In the spike-timing dependent form of synaptic plasticity, the temporal order between pre- and postsynaptic action potentials determines the direction and magnitude of synaptic changes: LTP is elicited if pre-spikes arrive before post-spikes within tens of milliseconds, and LTD is elicited if pre-spikes occur after post-spikes (Markram et al., 1997; Bi and Poo, 1998). When multiple spikes arrive in close succession to the synapse of a neuron that is itself firing, many possible pre-post spike pair combinations exist. Recent work on visual cortical slices has strongly indicated that the contributions of these spike pairs to the dynamics of the synaptic weight are not independent from each other (Froemke and Dan, 2002). For example, consider a STDP curve that gives 50% potentiation at a given time lag Δt, and 50% depression at a time lag $-\Delta t$. Three spikes in succession with intervals Δt and $-\Delta t$ respectively would be in the sequence “pre-post-pre”. Summing the effects of STDP linearly, one would expect a 50% potentiation from the first pair (“pre-post”) and a 50% depression from the second pair (“post-pre”), resulting in a net

depression of 25%. However, it has been shown experimentally that, in such a spike triplet condition, the contribution of the first pair dominates over that of the second pair.

This result has been described by the phenomenological “Suppression Model” (Froemke and Dan, 2002; Senn, 2002) (Figure 1). In this model, each spike is assigned an “efficacy”, which is suppressed by the preceding spike in the same spike train. The spike efficacy is reduced to zero immediately after the preceding action potential, and recovers exponentially towards. The exact form and the biological origins of the inter-dependence of these spike pairs, however, are not yet elucidated.

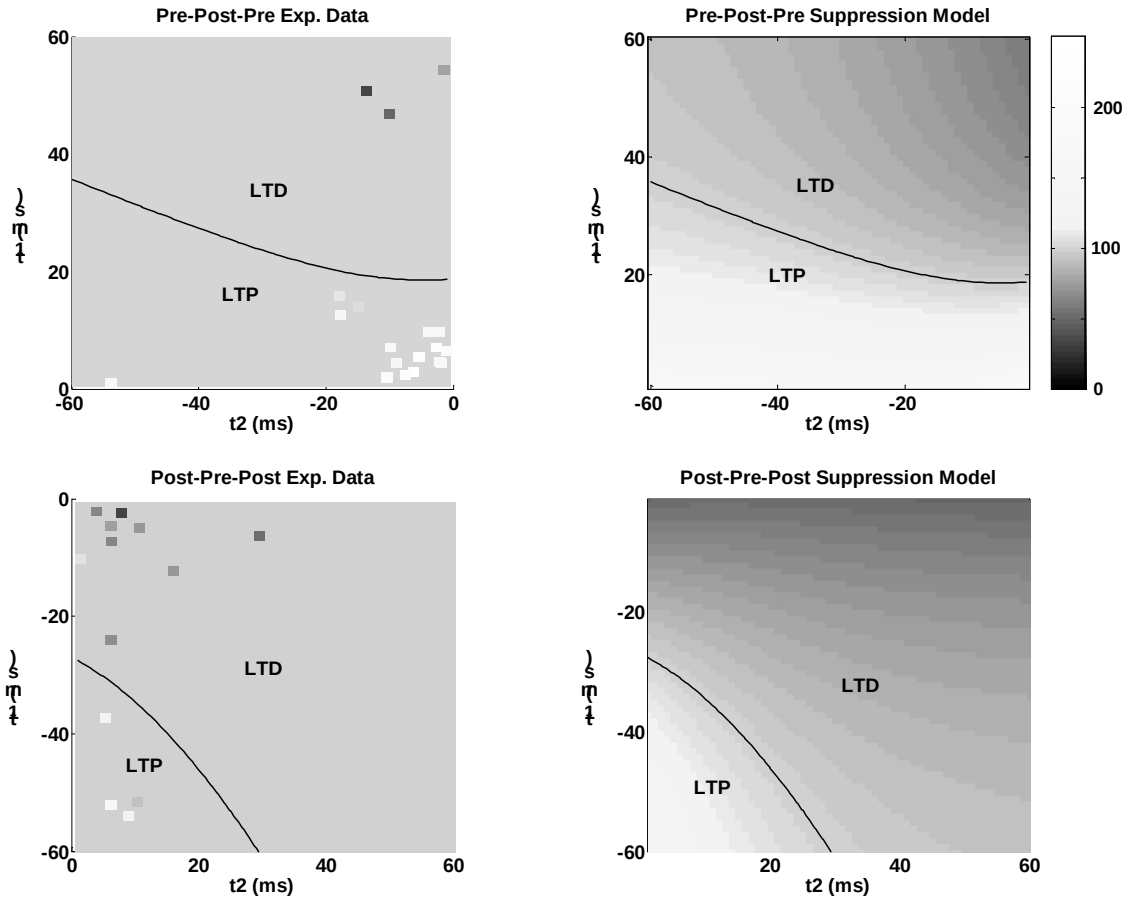

Figure 1: Comparison between the experimental data (left column) and the Suppression Model (right column) for the pre-post-pre condition (top row) and the post-pre-post condition (bottom row) for various time-intervals. t1 corresponds to the first interval and t2 to the second interval. Data points are shown in percentage of initial weights.

A recently proposed biophysical model of plasticity can shed light onto the mechanisms inducing interspike suppression. This model, denoted Calcium-Dependent Plasticity (CaDP), has provided a possible cellular basis for STDP and other forms of synaptic plasticity (Shouval et al., 2001). It is based on the assumption that the degree of synaptic modification depends on the intracellular level of NMDAR-mediated calcium. This dependence is U-shaped: low levels of calcium induce no synaptic change, while intermediate levels of calcium lead to depression, and high levels of calcium, to potentiation. Further, it assumes that the postsynaptic action potential propagates back into the dendrites, and that the waveform of this back-propagating action-potential (BPAP) is that of an exponential with a fast and a slow decaying time constants. Coincident pre and post spiking is detected because glutamate binds to NMDAR (after pre-spike) at the same time as a massive depolarization invades the dendrite (after post-spike), relieving the magnesium block of the NMDAR, and allowing calcium influx. The spike-timing information is thus kept track of by the NMDAR closing rate (fast and slow time constants = 50 and 100 ms) and by the BPAP decay (fast and slow time constants = 3 and 30 ms).

A direct implementation of the CaDP in the triplet's condition yields unrealistic results: a pre-post-pre in close succession leads to exceedingly high potentiation, because the second pre-spike induces cumulative glutamate release during the tail of the BPAP-induced depolarization. A post-pre-post condition also leads to high potentiation, because the second post-spike generates strong magnesium-relieving depolarization before the NMDAR have completely closed.

Two factors have to be considered to correctly describe the suppression results using CaDP. First, it is observed that neocortical excitatory synapses exhibit significant paired-pulse depression (Tsodyks and Markram, 1997; Varela et al. 1997; Philpot et al., 2001), which may be explained by the depletion of neurotransmitters in the presynaptic terminal or by the saturation of postsynaptic receptors. Second, BPAP amplitudes also experience attenuation with repeated activation, which may be due to calcium-dependent conductances (Stuart and Sakmann, 1994) or to activity-dependent inactivation of sodium channels (Colbert et al, 1997).

We model the presynaptic form of short-term depression by a dynamic probability of glutamate release with parameters that closely fit the experimental data of Philpot et al., 2001. After a presynaptic spike, the release probability is instantaneously zero, recovering to a maximum probability of 0.304 with a time constant of 141 ms. In addition, postsynaptic attenuation is modeled in terms of the direct dependence of

BPAP magnitude on a fixed number of “resources” (these resources could, for example, be the number of active Na channels). It is clear from the experimental data that these resources are greatly reduced following a post-spike but then are quickly recovered with a time constant of approximately 50 ms.

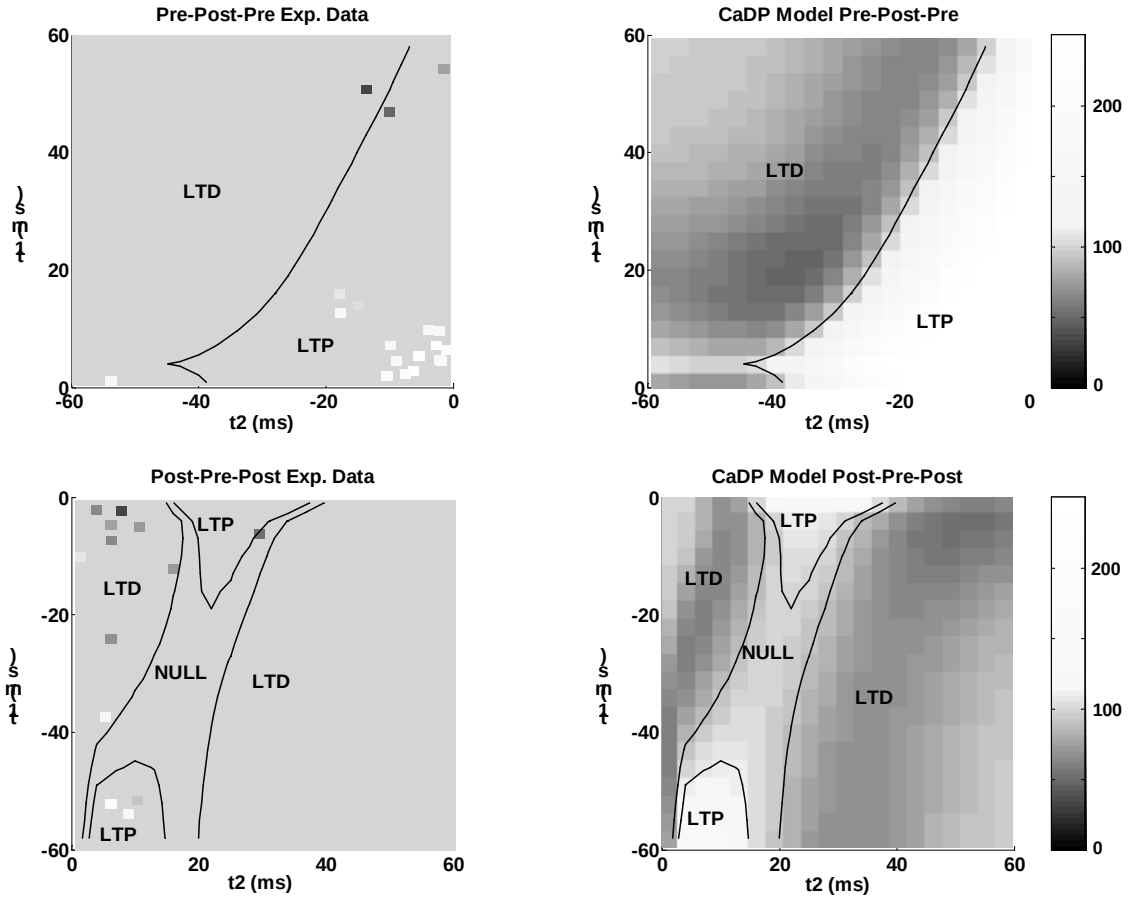

Figure 2: Comparison between the experimental data (left column) and the CaDP (right column) for the pre-post-pre condition (top row) and the post-pre-post condition (bottom row) for various time intervals. t1 corresponds to the first interval and t2 to the second interval. Data points are shown in percentage of initial weights.

In the spike triplet analysis, the analog of the one-pre-one-post STDP learning curve is a STDP map, as depicted in figure 1, where the axes are the two time intervals between the three spikes. Simulation of the above short-term depression models, combined with CaDP, yields results comparable to experimental data points (Figure 2). The full extent of the STDP map, nevertheless, has significant qualitative differences with the Suppression Model. One key difference between the two models is that with increasing time intervals, the Suppression Model predicts increased modification as spike efficacy is

recovered, whereas the CaDP predicts less modification as calcium influx is reduced. An additional reason for these differences is that CaDP predicts a region of pre-before-post depression, which is contrary to traditional STDP models. As a result, these models have different LTP/LTD borders as well as opposite gradients of modification. Unfortunately, the existing data is limited, and does not cover the entire area of the STDP map. The application of CaDP to these cases of spike triplets indicates that more experiments need to be performed in order to verify the hypothesis underlying our formalism, particularly in areas where there are discrepancies between CaDP and the Suppression Model.

Current efforts are devoted to extending the concept of short-term depression-modulated STDP to more general situations. There exist data demonstrating that the Suppression Model can account for experimental results involving four spikes (two pre and two post) (Froemke and Dan, 2002). In addition, recent experiments in hippocampal slices show that, while the traditional STDP results hold across different systems, the triplets experiments yield very different consequences in different areas of the brain. In these experiments, a pre-post-pre and a post-pre-post condition elicit, respectively, no plasticity and LTP (Wang and Bi, 2003). This indicates that complex spike trains have effects that are target-specific. Whether all of these processes can be explained under the same theoretical framework remains to be investigated.

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