Calcium dynamics as a signal for spike-timing dependent plasticity

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1 Summary

Recent experiments have shown that the modification of synaptic strengths in many systems depends on the precise timing of pre- and post-synaptic spikes (reviewed e.g. in [6]). In this spike-timing dependent plasticity (STDP), if a pre-synaptic spike precedes a post-synaptic spike within a window of tens of milliseconds, then the corresponding synapse potentiates. If a pre-synaptic spike arrives after a post-synaptic spike within a similar window, then the synapse depresses. The details of the signaling mechanism that the synapse uses to detect the timing of pre- and post-synaptic spikes are still unknown.

Computational efforts to assess the implications of STDP at synapses have generally taken one of two approaches. In a large number of studies, STDP has been treated as an abstract mathematical rule to be applied to adjust synaptic weights with each pre- and post-synaptic spike pair that occurs, depending only on the timing of that pair (e.g., implications of such a treatment in certain networks are discussed in [30, 22, 23]). The timing of spikes may be supplied to the system or may be computed dynamically by the evolution of differential equations [1, 13].

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Either way, effects of subsequent spike pairs are summed linearly. Recent experimental findings on the plasticity outcomes from multiple spikes are not conistent with those predicted by repeated application of pair-based rules, however [27, 8, 31].

A second computational approach is to model and track the post-synaptic calcium concentration as a determinant of STDP. Calcium has long been suggested as a signaling agent for long-term potentiation (LTP) and depression (LTD) and more recently for STDP. In particular, calcium can enter dendrites through NMDA channels if the magnesium block has been sufficiently lifted by incoming EPSPs or back-propagating somatic or axonal action potentials (BPAPs), while BPAPs can also induce dendritic calcium entry via local voltage-gated calcium channels (VGCCs). Recent modeling work has considered post-synaptic calcium *levels* as the signal to trigger STDP [14, 26, 2]. In these models, high post-synaptic calcium levels lead to LTP and lower levels lead to LTD. Models using this hypothesis can capture certain of the phenomena of STDP and/or classical LTP/LTD. They predict, however, that when a pre-synaptic spike precedes a post-synaptic spike by a sufficiently long time interval, calcium levels drop low enough so that the synapse depresses. While one lab reports such a result [19], most see no such effect, and there is evidence that the observed pre-post depression may arise from feedforward inhibition in the native circuitry [3, 28].

In this work, we use simulations of post-synaptic calcium dynamics to show that for any deterministic signaling system based only on calcium levels, this pre-before-post depression is unavoidable. Further, we demonstrate that the results from calcium level detection necessarily conflict with new experimental findings on STDP from triplets of pre-and post-synaptic spikes. As an alternative, we present a model based on calcium *time course* that can reproduce a full range of STDP outcomes for spike pairs and triplets in hippocampal preparations, as well as classical LTP and LTD results (see e.g. Figure 1). In this model, LTD depends on the width of the calcium signal, namely the durations and relative timings of periods that the calcium signal spends above certain thresholds, interacting nonlinearly. Plasticity outcomes are determined dynamically, through the evolution of differential equations that are driven by changes in calcium concentration. To our knowledge, this is the first computational model for STDP to truly utilize the calcium time course, as suggested by various experimental findings [32, 33, 24, 10, 25]. In particular, while Abarbanel et al. [2] do state that calcium time course is important for arriving at experimental STDP results, their model is still based on different levels of calcium that arise through differences in pre- and post-synaptic spike timings.

2 Model Details

Our simulations capture the post-synaptic effects of pre- and post-synaptic suprathreshold stimulation. Our post-synaptic cell model starts with a two-compartment reduction of the experimentally-calibrated multi-compartment CA1 pyramidal cell developed by Poirazi et al. [21]. Two compartments, one somatic and one dendritic, allow for consideration of BPAPs initiated by stimulation in the soma; we have obtained similar results with additional compartments, but they are not necessary for theoretical analysis. We have adjusted calcium dynamics in the dendritic compartment, using equations developed by Traub et al. [29], to match calcium profiles reported experimentally [15, 18, 25]. The dendritic compartment includes AMPA and NMDA synaptic currents, including magnesium block of NMDA [11, 12], modeled to fit experimental data [20, 4].

Within this conductance-based model post-synaptic CA1 cell, we include a novel calcium time course detection system. Three detector agents A, B, C respond to the instantaneous calcium level in the dendritic compartment. The interactions of these three agents, together with two others D, E, act to detect the calcium time course. More specifically, different calcium time courses lead to different time courses of A and D, which compete to influence a plasticity variable W. This term W encodes the sign and magnitude of synaptic strength changes from baseline. Note that this scheme is significantly different from a detection of peak calcium levels, in which the change in W would be determined by how large spine calcium becomes during an appropriate set of spikes.

The interactions between agents within our detector system are based qualitatively on the pathways influencing the regulation of calcium/calmodulin-dependent protein kinase II (CaMKII) (e.g. [5]). The detector equations are

$$\begin{aligned} A' &= (a_\sigma(\chi_{spine}) - c_p BA)/\tau_A \\ B' &= (b_\sigma(\chi_{spine}) - B)/\tau_B \\ C' &= (c_\sigma(\chi_{spine}) - C)/\tau_C \\ D' &= (d_\sigma(E) - D)/\tau_D \\ E' &= (e_\sigma(B) - E - c_d EC)/\tau_E \\ W' &= (\alpha_w/(1+\exp((A-a)/p_a) - \beta_w/(1+\exp((D-d)/p_d) - W)/\tau_W \end{aligned} \tag{1}$$

For biologically relevant calcium sensitivity in A, B, we use the Hill's equations

$$a_\sigma(x) = \frac{(x/CmHC)^{CmHN}}{1+(x/CmHC)^{CmHN}}$$

and

$$b_\sigma(x) = \frac{(x/CnHC)^{CnHN}}{1 + (x/CnHC)^{CnHN}},$$

with experimentally calculated Hill coefficients (with respect to Ca^{2+}) from previous modeling work on the activation, autophosphorylation, and dephosphorylation of CaMKII [9, 17]. We set

$$f_\sigma(x) = 1.0/(1.0 + \exp((x - \theta_f)/\sigma_f))$$

for $f \in \{c, d, e\}$. The relevant parameters appear in the following table:

parameter	value	parameter	value
$CmHC$	**4μM**	$CmHN$	**4**
$CnHC$	**0.7μM**	$CnHN$	**3**
θ_c	**2**	σ_c	**-0.05**
θ_d	**0.22**	σ_d	**-0.05**
θ_e	**0.6**	σ_e	**-0.01**
c_p	**0.6**	c_d	**25**
τ_A	**200 msec**	α_w	**0.8**
τ_B	**10 msec**	β_w	**2.0 (3.0)**
τ_C	**10 msec**	ξ	**100**
τ_D	**1000 msec**	a	**0.15**
τ_E	**100 msec**	d	**0.095 (0.1)**
τ_W	**500 msec**		

In the detector system (1), the variable A responds to high calcium levels. The B, E terms act as a calcium width detector. If enough E accumulates, then D is activated. Scenarios in which the calcium level rises due to both pre- and post-synaptic stimulation, but dips between the two, fail to activate D. Thus, the double filter system eliminates LTD from post-pre pairings with long interstimulus intervals, in a way that turns out to be well-suited for reproducing other experimental spike pair and triplet results. In the final equation of (1), A and D compete to increase and decrease W, respectively. Finally, the variable C responds to moderate calcium levels and acts as a veto on the accumulation of E, and thus on LTD. This veto is motivated by the inhibitory effect of protein kinase A on protein phosphatase 1, but it represents the integrated effect of many pathways, with an effective threshold set by our choice of $c_\sigma(\chi_{spine})$. The LTD block that the veto provides is relevant for pre-post spike pairings, for post-pre-post triplet experiments, and for classical LTP/LTD. In the latter case, the veto leads to the "no man's land" of no LTP or LTD for intermediate calcium levels [7, 16].

3 Conclusions

Our simulations of the calcium signals induced by different spike pair and triplet experiments imply that to reproduce the corresponding STDP results, any calcium detector should incorporate three features: 1) Calcium levels above a high threshold trigger potentiation; 2) Levels above a low threshold for a minimum continuous time trigger depression – that is, the width of the calcium signal must be accounted for; and 3) Levels exceeding a moderate threshold trigger a veto of the depression components of the model. We provide such a model detector system, inspired by the biomolecular pathways of protein phosphorylation and dephosphorylation, that captures experimental spike pair and triplet STDP results. Our findings suggest, however, that any model that aims to reconcile this data, using a calcium signal alone, will require fine-tuning. Consistency with classical LTP/LTD further constrains any model. This sensitivity suggets that plasticity induced by multi-spike patterns cannot be universal and consistent across all synapses and systems if changes in synaptic strengths are based exclusively on a calcium signal from NMDA channels and VGCCs. This conclusion may explain the disparate results of triplet STDP experiments performed in different systems [27, 8, 31].

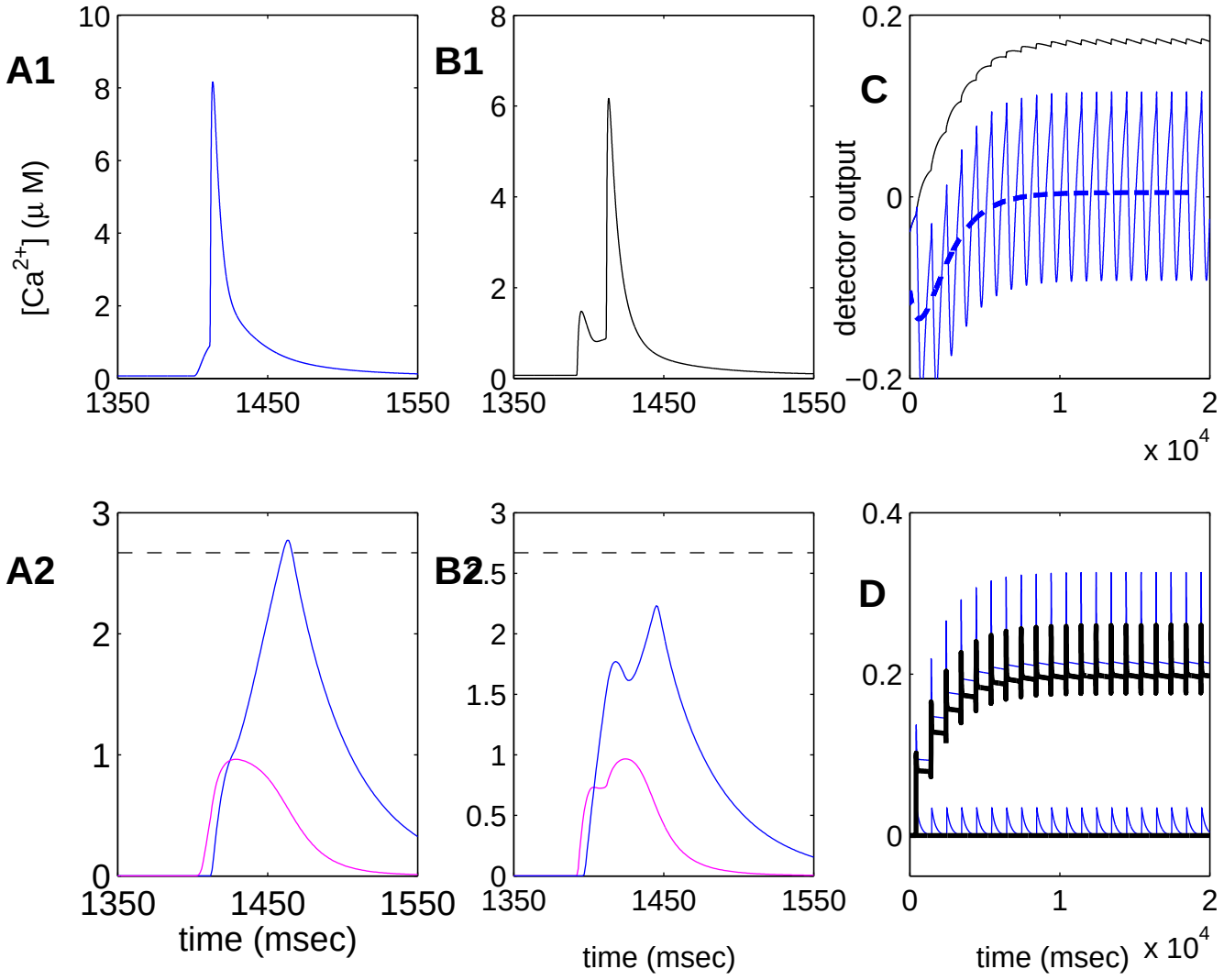

Figure 1: STDP from spike triplets in a computational model. **A**: Model response to pre-post-pre (with 10 ms separation between spike inductions). **1)** Calcium time course in a dendritic CA1 compartment in response to a single triplet. **2)** Response of detector elements B (magenta) and E (blue), from equations (1) below, to the same triplet; E crosses the threshold (dashed line) to activate D. **B**: Model response to post-pre-post (also with 10 ms spike separation). **1)** Calcium time course. **2)** Response of B and E, which does not cross threshold. **C**: Plasticity outcomes: pre-post-pre (blue curve) leads to oscillations of W in (1) but the net output is $W = 0$, corresponding to no synaptic change; post-pre-post (black curve) leads to $W > 0$, correponding to LTP. **D**: In pre-post-pre (blue curves), the LTP (upper curve) and LTD (lower curve) detectors (A, D respectively) are both activated, leading to the cancellation seen in **C**. In post-pre-post (black curves), there is less LTP detector activation (upper curve) than in pre-post-pre, but because there is no LTD detector activation (lower curve), there is net LTP.

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