An Autocatalytic Model of STDP Timing from Slow Calcium-Dependent Signals

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Abstract

Data of spike timing dependent plasticity (STDP) shows a sharp temporal transition between potentiation and depression despite a relatively slow time course of calcium concentration. We show how autocatalytic amplification of initial concentration differences can enable a high degree of temporal selectivity and produce the sharp STDP weight change curve despite having a relatively slow time constant. This simple model is robust to parameter changes, noise and details of the model. The model correctly predicts the location of the maximum and minimum for STDP at ±10 milliseconds from coincidence.

Key words: STDP, Autocatalysis, Calcium signal, Timing

1 Introduction: Achieving sharp temporal transitions using slow autocatalysis

How can relatively slow and stochastic Ca^{2+} signals and related processes in a synaptic spine achieve a reliable and sharp transition between LTP and LTD?

Spike timing dependent synaptic plasticity (STDP) [1–3] shows LTP or LTD effects depending on the time relation between pre- and postsynaptic signals at a synapse. While the temporal window of STDP is on the order of ≈ 40 ms, the temporal precision of the LTP-LTD transition is on the order of 10

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ms, short compared to the time constants involved in the postsynaptic Ca^{2+} dynamics [4] and subsequent Ca^{2+} dependent pathways leading to phosphorylation processes that regulate plastic change. Thus, even if the initial steps are very fast, e.g. NMDA voltage channel activation/blocking, it is not obvious how later slow steps can retain timing information.

Autocatalysis has been suggested as a key component of learning and memory on many timescales [5,6]. While a single feedback loop enables bistability with a suitable dose-response curve, competing feedback loops enables multistability and sensitivity to timing.

Our hypothesis is that a very small initial difference between the traces of pre- and post-synaptic stimuli is amplified by autocatalysis in a competitive manner. The autocatalysis is gated by the combined signals, producing associative learning, while competition between two autocatalytic loops produces temporal selectivity. This process may take a long time compared to the spike timing but will retain information about which trace arrived first. Thereby, it can amplify it beyond noise levels and can hence change the synaptic strength in a temporally sensitive manner without assuming very fast chemical processes.

2 Model: Plasticity with feedback

The Ca^{2+} signals after an incoming EPSP and a back-propagating action potential (BAP) produce two separate exponentially declining traces $T_{EPSP}(t)$ and $T_{BAP}(t)$ (see discussion for justification). $T_{EPSP}(t) = \exp(-(t-t_{prespike})/\tau_T)$ (similarly for $T_{BAP}(t)$), with $T_{EPSP}(t) = 0$ if the presynaptic spike has not yet occurred.

Assume that the weight change Δw is the result of integrating two competing factors $LTD(t)$ and $LTP(t)$: $\Delta w = \int (LTP(t) - LTD(t))dt$. The factors are enhanced through autocatalysis at a rate dependent on the summed strength of the synaptic traces and decay at a constant rate. The $LTP(t)$ factor is increased when $T_{EPSP}(t) > T_{BAP}(t)$ (before the BAP) and the $LTD(t)$ factor in the opposite case (after the BAP).

$$\tau LTP(t)' = k(T_{EPSP}(t) + T_{BAP}(t) - \theta)LTP(t) + \mu(T_{EPSP}(t) - T_{BAP}(t))$$

$$\tau LTD(t)' = k(T_{EPSP}(t) + T_{BAP}(t) - \theta)LTD(t) - \mu(T_{EPSP}(t) - T_{BAP}(t))$$

with a bound limiting both to positive or zero values.

The parameters of the model are: τ_T, the time constant of synaptic traces (set to 100 ms after [4]), τ, the time constant for $LTP(t)$ factor change, k, the

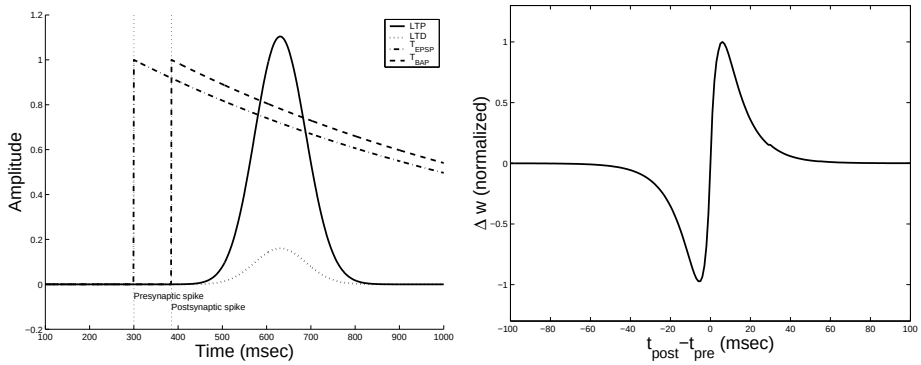

Fig. 1. Left: $LTP(t)$, $LTD(t)$, $T_{EPSP}(t)$ and $T_{BAP}(t)$ dynamics. Right: Δw for different $t_{posttime} - t_{pretime}$. The scale has been normalized so the maximum = 1. Timestep 1 ms, $k = 20$, $\theta = 1.5$, $\mu = 0.1$, $\tau = 1$, $\tau_T = 100$ ms.

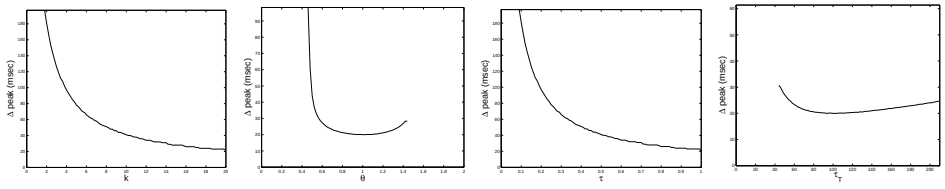

Fig. 2. Distance between the maximum and minimum of Δw for variations of k, θ, τ and τ_T.

strength of autocatalytic gain, θ, the threshold for enhancement and μ, the influence of trace difference on the factors. The scale of LTP,LTD and Δw is arbitrary.

3 Results: Sharp transitions with slow feedback

Before the EPSP and BAP signals have arrived both $LTP(t)$ and $LTD(t)$ approach 0 due to the lack of autocatalysis. When both arrive $T_{EPSP}(t) + T_{BAP}(t) > \theta$, making $LTP(t)$ and $LTD(t)$ begin to grow exponentially. This continues until the sum of the traces have decayed below the threshold (figure 1 left). Note that the peak of the $LTP(t)$ curve occurs several hundred ms after the initial coincidence, far from the temporal resolution of STDP. Despite this the integrated weight change Δw forms the familiar STDP weight change curve (figure 1 right) with a temporal resolution similar to experimental STDP.

The distance between the maximum and minimum of the integrated weight change curve is small ($\approx$ 20 ms) compared to the dynamic timescales of the variables (hundreds of ms). This shows that slow dynamics can efficiently detect small timescale phenomena and amplify them. We also note that the model correctly produces the peaks at $\pm$10 ms seen in experimental data.

Parameter Sensitivity: We have performed a number of variations of pa-

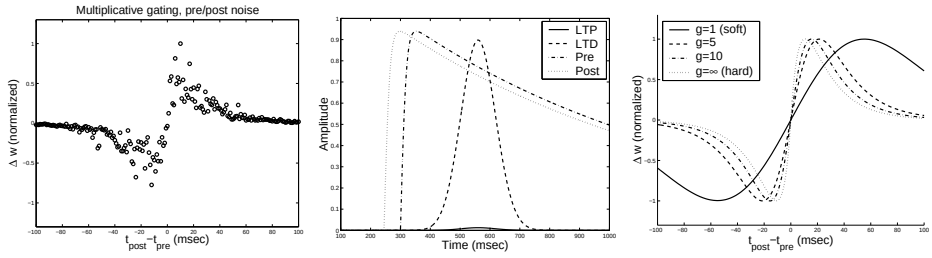

Fig. 3. Left: Effect of noise added to $T_{EPSP}(t)$ and $T_{BAP}(t)$ with multiplicative autocatalysis. Middle: tanh-softened synaptic traces, $g = 5$. Right: effect of softer synaptic traces, for $g = 1$, 5 and 10 (the size of $\int \Delta w dt$ was normalized to $[-1, 1]$).

rameter values, showing that the model is robust (figure 2). μ merely changes the weight scale. The transition between positive and negative weight change becomes sharper for increasing k. Faster τ can sharpen, while low values of τ_T gives a distorted curve showing LTP for the most positive values of $t_{postspike} - t_{prespike}$.

Mutual Inhibition: Adding mutual inhibition between $LTP(t)$ and $LTD(t)$ did not change the behavior qualitatively since they already compete in the Δw integral. The exponential growth ensures that one is far larger than the other. However, it was found that mutual inhibition reduced the effects of noise on the system slightly.

Multiplicative Autocatalysis: Instead of an autocatalytic gating based on the sum $T_{EPSP}(t) + T_{BAP}(t) - \theta$, a multiplicative term $T_{EPSP}(t) * T_{BAP}(t) - \theta$ can be used. For slightly shifted threshold values θ the response becomes practically identical to the additive case. Thus, it is enough that the gating is activated by the beginning of both signals.

Noise Sensitivity: Noise tolerance was good despite autocatalytic amplification. The transition between positive and negative synaptic change remained stable and sharp when $N(0, 0.1)$ noise was added either to the $T_{EPSP}(t)/T_{BAP}(t)$ traces or the $LTP'(t)/LTD'(t)$ values (figure 3 left). The transition was more resistant to trace noise than to noise in the $LTP(t)/LTD(t)$ values. The multiplicative autocatalytic model was somewhat more stable to noise in the traces while the additive model was more stable to noise in the $LTP(t)/LTD(t)$ values.

Trace shape: Making the shape of the synaptic traces softer by replacing $T(t) = \exp((t_{spike} - t)/\tau_T)$ with $T(t) = \tanh(g(t - t_{spike})) \exp((t_{spike} - t)/\tau_T)$ (figure 3 middle and right) or more slowly rising by adding a linear rise of length τ_r ms (not shown) did not change the qualitative behavior of the weight change but lowered the temporal precision slightly. Thus, a reasonably sharp increase in the traces improves temporal precision, and the autocatalysis further sharpens it.

4 Discussion

We have shown how a simple autocatalytic model can produce a high degree of temporal resolution despite having a slower internal timescale than the phenomenon it depends on. In a simple synaptic model it produces a STDP-like weight change with a sharp transition from LTP to LTD. We specifically note that the current model correctly produces the peaks at ± 10 ms seen in experimental data when the Ca^{2+} decay is of the same size as observed in synaptic spines [4].

We make the following prediction: there should exist an autocatalytic loop leading to stronger LTD just as the enhancement of calcium influx due to CaMKII phosphorylation produces a candidate autocatalytic loop leading to stronger LTP.

The assumption of separate $T_{EPSP}(t)$ and $T_{BAP}(t)$ traces is an assumption made mostly to clarify the essential components of the model. In biology they would correspond to different chemical species activated by the different Ca^{2+} activations of EPSP and BAP. It is plausible that proteins localized in nanodomains [7] near the ion channels opened by synaptic action and back-propagating action potentials, respectively, could act as detectors of different kinds of Ca^{2+} influx. Further, different pathways could also be activated depending on the overall concentration, especially since EPSPs and BAPs sum sub- and supralinearly depending on order [4] and calmodulin modulates P/Q-type Ca^{2+} channels differentially depending on number of bound ions [8]. The traces would then correspond to calmodulin with 2 or 4 bound Ca^{2+} .

BAP-Ca^{2+} dynamics may be faster than previously assumed [9] with $\tau \approx 15$ ms. But the Ca^{2+} related dynamics may still be relatively slow, especially when taking into account the subsequent delays in the kinase/phospatase pathways. In any case, the time course of EPSP Ca^{2+} influx is slow, making exact spike timing problematic.

Finally, our model shows that a sharp transition can be obtained in a system that does not contain an explicit threshold.

References

[1] W. Levy, O. Steward, Temporal contiguity requirements for long-term associative potentiation/depression in the hippocampus, Neuroscience 8 (1983) 791–797.

[2] H. Markram, J. Lubke, M. Frotscher, B. Sakmann, Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs, Science 245 (1997) 213–215.

[3] G.-Q. Bi, Spatiotemporal specificity of synaptic plasticity: cellular rules and mechanisms, Biological Cybernetics 87 (2002) 319–332.

[4] H. J. Koester, B. Sakmann, Calcium dynamics in single spines during coincident pre- and postsynaptic activity depend on relative timing of back-propagating action potentials and subthreshold excitatory postsynaptic potentials, PNAS 95 (16) (1998) 9596–9601.

[5] F. J. Lisman JE, What maintains memories?, Science 283 (5400) (1999) 339–340.

[6] Bhalla, U. S. Ravi Iyengar, Emergent properties of networks of biological signaling pathways, Science 283 (5400) (1999) 381–387.

[7] H. Kasai, Cytosolic Ca^{2+} gradients, Ca^{2+} binding proteins and synaptic plasticity, Neurosci. Res. 16 (1993) 1–7.

[8] C. DeMaria, T. Soong, B. Alseikhan, R. Alvania, D. Yue, Calmodulin bifurcates the local Ca^{2+} signal that modulates P/Q-type Ca^{2+} channels, Nature 411 (6836) (2001) 484–9.

[9] B. Sabatini, T. Oertner, K. Svoboda, The life cycle of ca^{2+} ions in dendritic spines, Neuron 33 (2002) 439–452.

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