A CA^{2+} Dynamics Model of the STDP Symmetry-to-Asymmetry Transition in the CA1 Pyramidal Cell of the Hippocampus

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Abstract. Recent experimental evidence has reported that the profiles of spike-timing-dependent plasticity (STDP) in the CA1 pyramidal neuron can be classified into two types depending on the location along the stratum radiatum (SR) dendrite: (1) A symmetric STDP profile centered at 0 ms (largest LTP value) with two distinct LTD windows at about ±20ms in the proximal SR dendrite, and (2) an asymmetric one in the distal SR dendrite. Bicuculline application revealed that GABAA is responsible for the symmetry of the STDP curve. We investigate via computer simulations the STDP symmetry-to-asymmetry transition in the proximal SR dendrite. Our findings indicate the transition from symmetry-to-asymmetry is indeed due to decrease of GABAA, but the simulated symmetrical STDP profile is centered at +10ms (and not at 0ms) with two distinct LTD tails at -10ms and +40ms (and not at ±20ms). The simulated LTD tails are strongly dependent on the GABAA conductance.

Keywords: Hippocampus, CA1 pyramidal neuron, computer model, STDP, GABA, LTP, LTD, calcium.

1 Introduction

In 1949, Hebb [1] postulated that a synapse is strengthened only if the pre- and postsynaptic neurons are activated simultaneously. Recently, Hebb's law has been refined ever further with STDP, where the precise timing of presynaptic and postsynaptic action potentials (spikes) determines the sign and magnitude of synaptic modifications [5]. Bi and Poo [7] showed that the profile of the STDP curve in the in-vitro hippocampal network has an asymmetrical shape with the largest LTP/LTD value at $\Delta\tau = t_{post} - t_{pre} = \pm 10$ms, respectively.

Recently, a study by Nishiyama and colleagues [4] reported that "the profile of STDP induced in the hippocampal CA1 network with inhibitory interneurons

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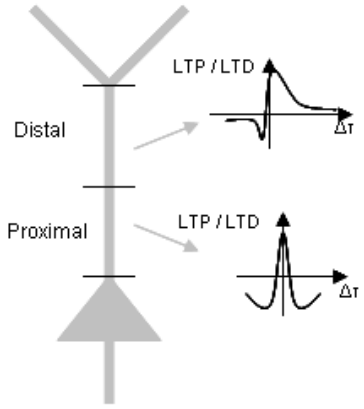

Fig. 1. Pyramidal cell. Asymmetric STDP learning curve at distal dendrite. Symmetric STDP learning curve at proximal dendrite.

is *symmetrical* for the relative timing of pre- and post-synaptic activation". Two long-term depression (LTD) windows at ±20ms and a central long-term potentiation (LTP) peak at 0 ms have been observed (see figure 1) [4]. Further optical imaging studies revealed that the shape of the STDP profile depended on the location on the SR dendrite. A symmetric STDP profile was observed in the proximal SR dendrite and an asymmetric STDP profile in the distal one [2], [3]. It was reported that the transition from symmetry-to-asymmetry is due to the presence of GABAA inhibition in the proximal SR dendrites.

In this study, we investigate via computer simulations the validity of the reported GABAA effects on the symmetry-to-asymmetry transition. To do so, we employed and extended a well established Ca^{2+} dynamics model of the CA1 pyramidal neuron [6] by incorporating the effects of inhibitory interneurons in the SR dendrites. In support of the experimentally observed evidence, we report that the symmetry-to-asymmetry transition is indeed due to GABAA depletion. However, in the model, the simulated symmetrical STDP curve is centered at +10ms ($\Delta\tau$ = t_{post} - $t_{pre} > 0$) and not at 0ms [2],[3]. Two distinct LTD tails are present at -10ms and +40ms and not at ±20ms [2],[3]. Finally, the presence/absence of LTD tails strongly depends on the conductance value of GABAA, with high GABAA conductance ($g_{GABA} = 0.5$) leading to the lift-off of both LTD tails (and not only the positive LTD tail [2],[3]) towards the LTP region.

2 The Model

Rubin and colleagues [6] have recently advanced a Ca^{2+} dynamics model for the CA1 pyramidal cell. Briefly, their model neuron had two compartments: a soma and a dendrite. The generation of action potentials was due to the interplay of a wealth of Na^+, K^+, Ca^{2+}-activated K^+ and Ca^{2+} currents as well as synaptic currents (AMPA and NMDA) [8],[9],[10]. Two excitatory transient inputs to the soma and SR dendrite were used to simulate the experimental STDP

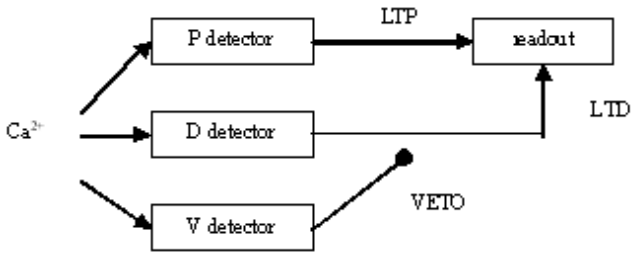

Fig. 2. Rubin and colleagues [6] calcium detection system. P detector: potentiation detector, D detector: depression detector, V detector: veto detector, LTP: long-term potentiation, LTD: long-term depression.

protocol. Their mechanism for plasticity had a modular structure consisting of three biochemical detectors, which responded to the instantaneous calcium level in the SR dendrite. More specifically, their detection system (see figure 2) consisted of: (1) a potentiation detector which detected calcium levels above a high-threshold (4 μM) and triggered LTP, (2) a depression detector which detected calcium levels that exceeded a low threshold level (0.6 μM) and remained above it for a minimum time period and triggered LTD, and (3) a veto detector which detected levels exceeding a mid-level threshold (2 μM) and triggered a veto of the model's depression components. Their detector system was inspired by the molecular pathways of protein phosphorylation and dephosphorylation. Their potentiation detector was an abstraction of the phosphorylation cascade of CaMKII, whereas the depression detector represented the kinetics of dephosphorylation agents such as PP1. The veto system represented the competition of kinases and phosphatases such as the inhibitory action of PKA.

We extended the Rubin et al. model [6] by incorporating the GABAA effects of inhibitory interneurons in the form of a second transient input to the SR dendrite.

3 Experiments

To investigate the transition of the STDP curve from symmetry to asymmetry in the SR dendrite, we designed the following experimental paradigms (figure 3):

1. Excitatory spike pairs repeatedly applied to the SR dendrite and soma for 2s (7 times at about 3 Hz) in the absence of GABA for various interspike intervals $\Delta\tau$.
2. Excitatory spike pairs repeatedly applied to the SR dendrite and soma for 2s (7 times at about 3 Hz) in the presence of a single pre-synaptic GABA spike slid between the interspike interval $\Delta\tau$.
3. Spike pairs repeatedly applied to the SR dendrite and soma for 2s (7 times at about 3 Hz) in the presence of a GABA inhibitory spike train presented at 100 Hz (gamma frequency) between the interspike interval $\Delta\tau$.

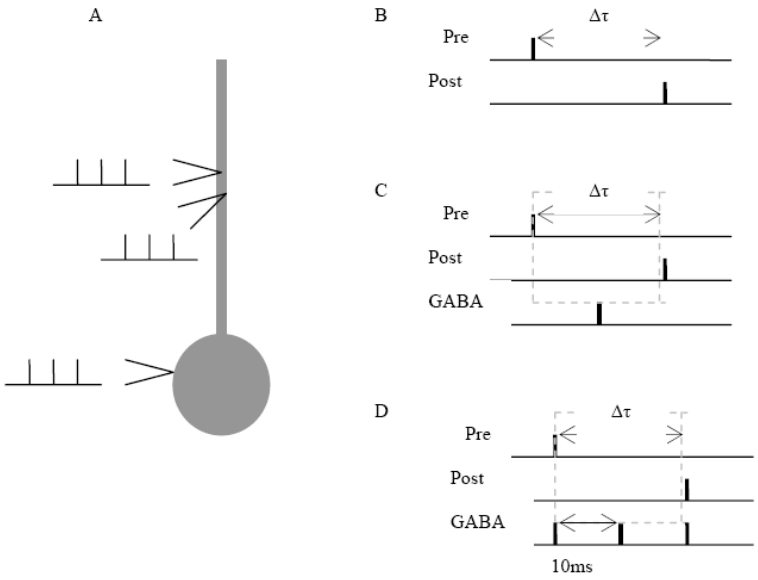

Fig. 3. (A) Our model CA1 neuron with its three transient inputs to the soma and SR dendrite. (B) Experimental paradigm 1: spike doublets in the absence of GABA. $\Delta\tau$ is the relative interval between the pre- and post-synaptic pairing. $\Delta\tau$ is positive (> 0) if pre-activation precedes the post-activation and negative (< 0) otherwise. (C) Experimental paradigm 2: spike doublets in the presence of a single GABA spike occurring during the interspike interval (gray dashed square). (D) Experimental paradigm 3: spike doublets in the presence of a GABA spike train at 100 Hz (individual spikes presented every 10ms) during the interspike interval (gray dashed square).

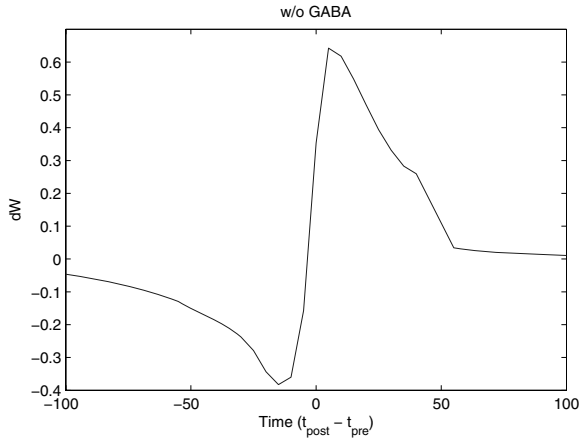

Fig. 4. Simulated asymmetric STDP profile in the absence of GABA. $\Delta\tau$ (t_{post} - t_{pre}) ranges from -100 to 100 in increments of 5ms.

During experimental paradigms 2 and 3, we varied the conductance of GABA and observed its effects on the amplitude of the proximal SR Ca^{2+} spike and the STDP curve. These results are reported in the next section.

4 Results

4.1 Spike Doublets in the Absence of GABA

Figure 4 depicts the saturated synaptic weight values (W_∞) as a function of the interspike interval, $\Delta\tau = t_{post}$ - t_{pre}. Simulations were performed with $\Delta\tau$ ranging from -100 to 100 in increments of 5ms. An asymmetrical STDP curve is shown with the largest LTP value at +10ms and the largest LTD value at -15ms [7].

4.2 Spike Doublets in the Presence of a Single GABA Event Introduced in the Interspike Interval

Figure 5 is a composite graph of W_∞ as a function of $\Delta\tau$ (figures 5A and 5D) and the time course of the calcium spike for different values of the GABA conductance ($g_{GABA} = 0.05$ mS/cm^2 and $g_{GABA} = 0.1$ mS/cm^2) (figures 5B, C, E and F) in the SR dendrite in the presence of a single GABA transient input spike occuring at different times in the interspike interval.

More specifically, figures 5A (GABA spike is introduced in the middle of the pre-post interval) and 5D (GABA spike is introduced at 15ms after the pre- activation) depict that as the conductance of GABA is increased, the STDP curve amplitude is reduced, but the asymmetry is preserved. As we further increased the conductance of GABA ($g_{GABA} = 0.2$ mS/cm^2 and $g_{GABA} = 1$ mS/cm^2), the STDP curve amplitude decreased even further (data not shown). The amplitude reduction is more pronounced with the GABA spike occurring 15ms after pre-activation, and also there is a shift in the peak LTP (LTD) changes to more positive (negative) time intervals.

Figures 5B, C, E and F show that even a single GABA spike has significant effects on the amplitude of the calcium spike. The effects are more pronounced for higher values of GABA as well as for shorter $\Delta\tau$ intervals and earlier GABA spike onset times (compare the [Ca^{2+}] values in figures 5B and 5C and in figures 5E and 5F).

4.3 Spike Doublets in the Presence of an 100Hz GABA Spike Train Introduced in the Inter-spike Interval

In this experimental paradigm, we tested the hypothesis of whether the frequency of GABA input presentation has any effect on the STDP profile. A GABA spike input train was presented at a frequency of 100Hz (i.e. a spike event every 10ms; see figure 3D). The GABA spike train was bounded by the onsets of the pre- and post-synaptic activations.

Direct comparison of figures 4 and 6A shows that the absence or presence of low conductance ($g_{GABA} = 0.05$ mS/cm^2) of GABA has no effect on the STDP

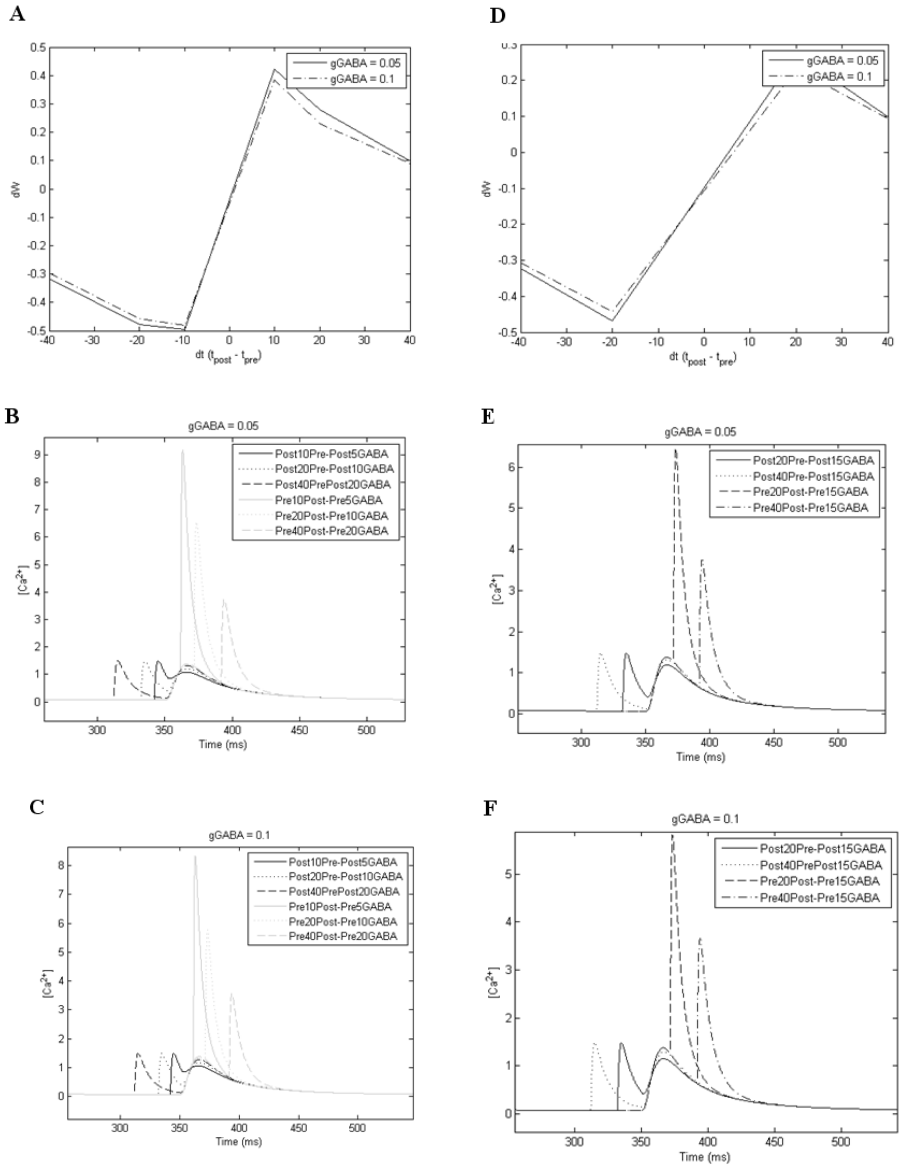

Fig. 5. Composite graph of the saturated synaptic weight values (W_∞) as a function of interspike interval, $\Delta\tau$ = t_{post} - t_{pre} (5A and 5D) and time course of the calcium spike in the SR dendrite (5B, C, E and F) when no GABA is present or a single GABA spike is introduced in the middle of the interspike interval $\Delta\tau$ (5A, B and C) and after 15ms from the pre-synaptic activation (5D, E and F) and for g_{GABA} = 0.05 mS/cm^2 (5B and E) and 0.1 mS/cm^2 (5C and F).

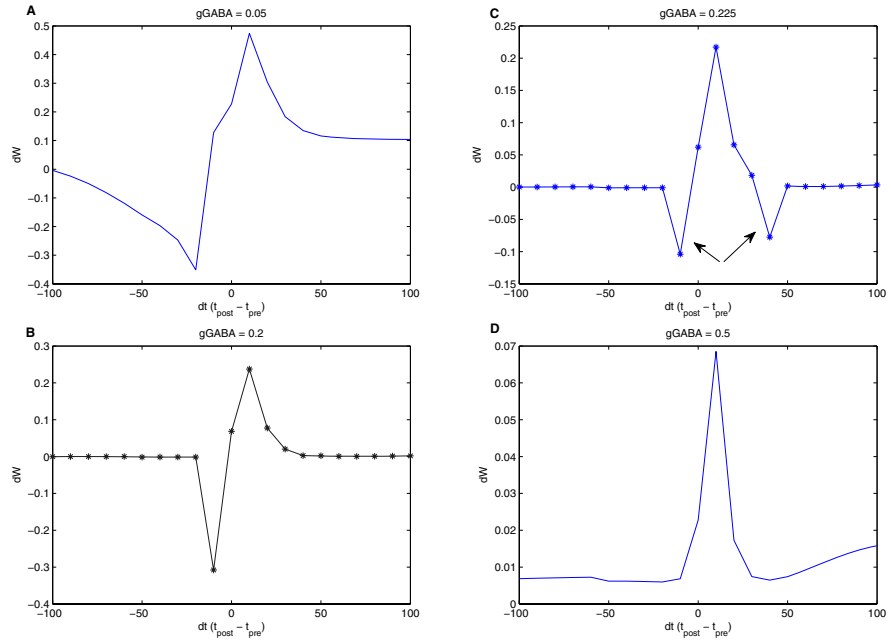

Fig. 6. Plot of the STDP profile in the presence of 100Hz GABAA input during the interspike interval, as a function of the interspike interval $\Delta\tau$ for different levels of GABAA conductance.

asymmetry. At $g_{GABA} = 0.2$ mS/cm^2, the width of the negative LTD window decreases considerably and it is present only at +10ms (compare Figs. 6A and 6B). At $g_{GABA} = 0.225$ mS/cm^2 ($0.2 < g_{GABA} \leq 0.3$), the asymmetrical STDP curve becomes symmetric centered at +10ms (and not at 0ms [2], [3]) with two distinct LTD windows. In contrast to experimental evidence [2], [3], which indicate the presence of two distinct LTD windows at ±20ms, our simulated negative LTD window is centered at -10ms, whereas the simulated positive one is centered at +40ms. At high GABAA conductance values (see fig. 6D), the two LTD windows are lifted-off towards the LTP regime. This finding supports and extends recent experimental evidence, which showed that in the presence of bicuculline, a GABA blocker, only the positive LTD tail is blocked [2], [3].

5 Conclusion

A well established Ca^{2+} dynamics model of the CA1 pyramidal neuron with three calcium amplitude detectors was extended by incorporating the effects of GABAergic interneurons to simulate the symmetry-to-asymmetry transition of the STDP profile in the proximal SR dendrite. In support of the experimental evidence [2], [3], [4], the transition was found to be due to the GABAA depletion. From our simulation results, we conclude that the transition is strongly

dependent on the conductance value of GABAA, where (1) at low GABAA conductance, the asymmetry is preserved, but the width of the negative LTD tail is reduced as GABAA is increased, (2) at intermediate conductance values, the symmetry appears with the positive LTP window centered at +10ms and two equal in height LTD tails at -10ms and +40ms, and (3) at high GABAA conductance values, the two distinct LTD tails disappear and a symmetrical LTP curve centered at +10ms becomes evident. Furthermore, an inverse relationship was found to exist between the Ca^{2+} spike amplitude in SR dendrite and the GABAA conductance. As the GABA conductance is increased, the amplitude of Ca^{2+} is decreased.

While GABA-A inhibition is sufficient to achieve a symmetric STDP curve, it does not provide the peak of LTP at 0ms, as found experimentally. So the question remains, is GABA-A inhibition sufficient, or is there another timing mechanism, perhaps outside the interspike interval, or another synaptic mechanism (e.g. GABA-B) that produces this shift? Several computational models [11], [12] have been published over the years that have modelled in detail the biochemical intracellular mechanisms of synaptic (meta)plasticity. To gain perhaps a better understanding of the symmetry-to-asymmetry transition in the CA1 SR dendrite, we need to incorporate some of this knowledge into our Ca^{2+} dynamics model.

Moreover, a more detailed compartmental model of the CA1 pyramidal neuron needs to be constructed to model the conditions under which the STDP asymmetry in the distal SR dendrites appears. Experimental evidence has shown that both distal and proximal SR dendrites receive excitatory inputs from CA3 cells as well as inhibitory inputs from local CA1 interneurons. An additional excitatory input drives the lacunosum-moleculare (LM) dendrites of the CA1 pyramidal neuron. Pairings of the SR and LM presynaptic excitatory and inhibitory inputs with the postsynaptic somatic activation will provide us with a more realistic picture of STDP in the SR dendrites.

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