How Bursts Shape the STDP Curve in the Presence/Absence of GABAergic Inhibition

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Abstract. It has been known for some time that the synapses of the CA1 pyramidal cells are surprisingly unreliable at signalling the arrival of single spikes to the postsynaptic neuron [2]. On the other hand, bursts of spikes are reliably signalled, because transmitter release is facilitated. In the hippocampus, a single burst can produce long-term synaptic modifications. Bursts of spikes in addition to increasing reliability of synaptic transmission [3], they have been shown to provide effective mechanisms for selective communication between neurons in a network [4]. We investigate via computer simulations how the profile of spike-timing-dependent plasticity (STDP) in the CA1 pyramidal cell synapses is affected when an excitatory burst of spikes applied to dendrites is paired with an excitatory single spike applied to the soma in the absence and presence of a 100Hz GABAergic inhibitory spike train applied to the dendrites. We report that the shape of the STDP curve strongly depends on the burst interspike interval in the presence/absence of $GABA_A$ when a presynaptic burst and a postsynaptic spike are paired together.

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

1 Introduction

Hebb's law states a synapse is strengthened only if the pre- and postsynaptic neurons are activated simultaneously [1]. STDP is a refinement of Hebb's law, which states that the precise timing of presynaptic and postsynaptic action potentials is actually the one that determines the sign and magnitude of synaptic modifications [7]. Bi and Poo 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 +/-10ms, respectively [7].

A recent study reported that the shape of the STDP profile depends on the location on the stratum radiatum (SR) dendrite [5]. A symmetric STDP profile is observed in the proximal SR dendrite, whereas an asymmetric one is observed

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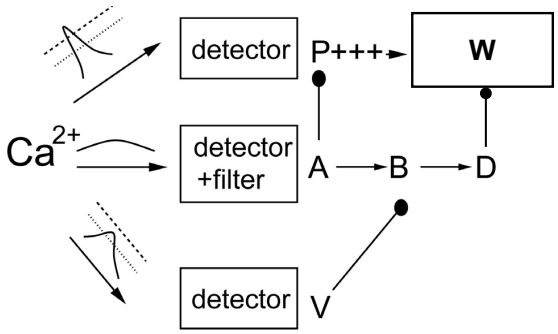

Fig. 1. Model calcium detection system [8], [11]. P detector: potentiation detector; D detector: depression detector; V detector: veto detector; W: synaptic weight.

in the distal one [6]. A symmetric STDP profile with short temporal window may serve as a coincidence detector between the incoming input and the output of the CA1 pyramidal cell, whereas an asymmetric profile with a broad temporal window may play a role in chunking of items in sequence learning. Recent computational works from our group predicted that the switching between operational modes (asymmetry-to-symmetry) is strongly dependent on the frequency band (theta vs. gamma) of the $GABA_A$ inhibition, the conductance value of $GABA_A$ inhibition and the relative timing between the GABAergic spike train and the pre- and post-synaptic excitation [8], [10]. A long-term potentiation (LTP) peak and two distinct long-term depression (LTD) tails of the symmetrical STDP curve were shown to be centered at +10 ms, +40 ms and -10 ms, respectively [8], [10]. The largest LTP value and the two distinct LTD tails were inversely proportional to the increase of $GABA_A$ conductance [8], [10].

In this study we continue to investigate the asymmetry-to-symmetry transition in the CA1-SR synapses in the presence of complex inputs, such as bursts. We examine how the STDP profile in the CA1-SR pyramidal cell synapse is affected when a burst of excitatory spikes applied to the SR synapses is paired with a single excitatory spike applied to the soma in the absence and presence of a 100Hz GABAergic inhibitory spike train applied to the SR dendrites as a function of $GABA_A$ conductance and burst interspike interval.

2 The Model

We used a Ca^{2+} dynamics model for the CA1 pyramidal cell [8], [11]. The 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 protocol. The mechanism for plasticity had a modular structure consisting of three biochemical detectors, which responded to the instantaneous calcium level in the SR dendrite. The detection system (see

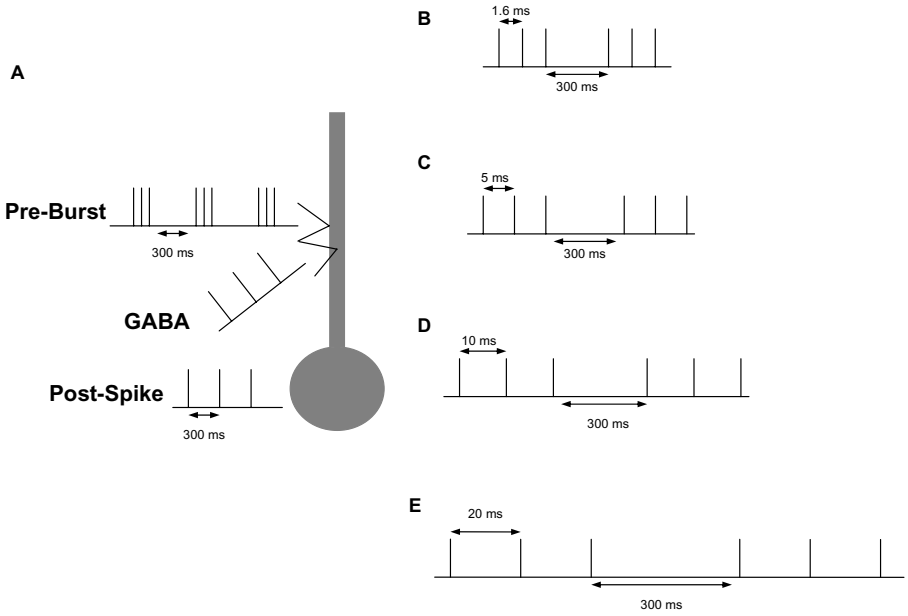

Fig. 2. (A) Our model CA1 neuron with its three transient inputs to the soma and SR dendrite. In all experimental paradigms, pairing takes place between an excitatory burst of spikes with T ms burst interspike interval, where T is a free parameter and an excitatory single spike (not shown) in the absence and presence of a 100Hz GABAergic spike train applied between the excitatory pair interval (not shown). (B) Experimental paradigm 1: burst interspike interval, T, is 1.6 ms (C) Experimental paradigm 2: burst interspike interval, T, is 5 ms (D) Experimental paradigm 3: burst interspike interval, T, is 10 ms (E) Experimental paradigm 4: burst interspike interval, T, is 20 ms.

fig. 1) consisted of: (1) a potentiation detector which detected calcium levels above a high-threshold (e.g. 4 M) and triggered LTP, (2) a depression detector which detected calcium levels exceeding a low threshold level (e.g. 0.6 M) 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 (e.g. 2 M) and triggered a veto of the model's depression components. More details on the Ca^{2+} detectors system can be found in [8] and [10].

In this study we investigate how the pairing of a repeating excitatory burst applied to the SR dendrite and a repeating excitatory single spike applied to the soma affect the STDP curve in the presence and/or absence of a 100 Hz $GABA_A$ inhibitory transient input to the SR dendrite.

3 Experiments

To investigate how the STDP curve is affected by the pairing of excitatory bursts and excitatory single spikes in the presence/absence of GABAergic inhibition,

we designed the following experimental protocol: Excitatory burst of spikes with T ms burst interspike interval and single spikes, which were repeatedly applied to the SR dendrite and soma, respectively, for 2 s (7 times at about 3 Hz) were paired in the absence and presence of a 100 Hz GABAergic inhibitory spike train applied between the excitatory pair interval $\Delta\tau$. Based on this protocol, we designed the following four physiological experiments (see figure 2), where the burst interspike interval, T, was allowed to vary:

- T = 1.6 ms
- T = 5 ms
- T = 10 ms
- T = 20 ms

During all experimental paradigms, we varied the conductance of $GABA_A$ 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 Pairing of an SR Burst and a Somatic Spike in the Absence of $GABA_A$ as a Function of Burst Interspike Interval

Figure 3 depicts the saturated synaptic weight values (W_∞) as a function of the interstimulus interval, $\Delta\tau = t_{post}$ - t_{pre}. $\Delta\tau$ is the interstimulus interval between the first presynaptic spike of the burst (a presynaptic burst is composed of three spikes with varying interspike interval) and the postsynaptic spike. Simulations were performed with $\Delta\tau$ ranging from -100 to 100 in increments of 10 ms. When the burst interspike interval is 1.6 ms, a symmetric STDP profile is evident. The largest LTP value is at 10 ms. The duration of the temporal window for learning is 30 ms, where beyond that only forgetting (i.e LTD) is taking place. When the burst interspike interval is increased to 5 ms, an asymmetric STDP profile appears. The largest LTP and LTD values are at 20 ms and -10 ms, respectively. At 10 ms burst interspike interval the asymmetric STDP profile is maintained and all W_∞ values are positive and larger than 0.1. This means that only LTP (i.e. learning) is possible when a CA3 Schaffer collateral burst and a CA1 output spike are paired in the absence of GABA, but how strong learning is depends on $\Delta\tau$. As 20 ms burst interspike interval, another symmetric curve appeards with the largest LTP value at 60 ms.

4.2 Pairing of an SR Burst and a Somatic Spike in the Presence of a 100Hz GABA Spike Train in the $\Delta\tau$ Interval

Figure 4 is a composite figure of four graphs of W_∞ vs $\Delta\tau$ as a function of burst interspike interval and GABA conductance. It is clear from all four graphs that at GABA presence and as the conductance of GABA increases a symmetric

STDP profile appears. Particularly interesting is the case of 20 ms burst interspike interval, where when GABA is present, even at low conductance values, "catastrophic forgettting" (i.e. LTD for all $\Delta\tau$ values) is present.

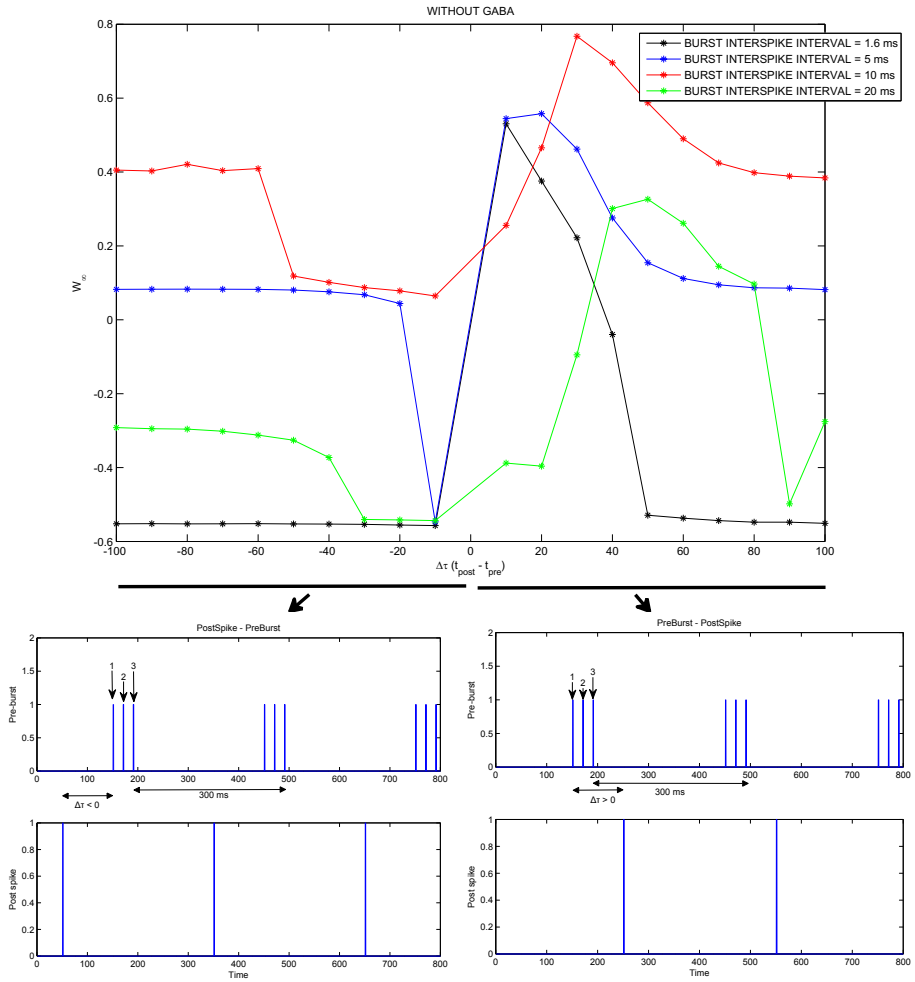

Fig. 3. (Top) Simulated asymmetric STDP profile as a function of burst interspike intervals in the absence of $GABA_A$. $\Delta\tau$ (t_{post} - t_{pre}) is the interstimulus interval between the first presynaptic spike of the burst and the postsynaptic spike. $\Delta\tau$ ranges from -100 to 100 in increments of 10 ms. Solid lines with arrows point to the bottom two figures, which depict the relative timing between the presynaptic burst and the postsynaptic spike. (Bottom-left) PostSpike - PreBurst scenario, where postsynaptic single spike preceeds the presynaptic burst, comprised of three spikes, by $\Delta\tau$. $\Delta\tau$ takes values from -10 ms to -100 ms. The pairing repeats every 300 ms. (Bottom-right) PreBurst - PostSpike scenario, where a presynaptic burst preceeds the postsynaptic spike by $\Delta\tau$. $\Delta\tau$ takes values from +10 ms to +100 ms. The pairing repeats every 300 ms.

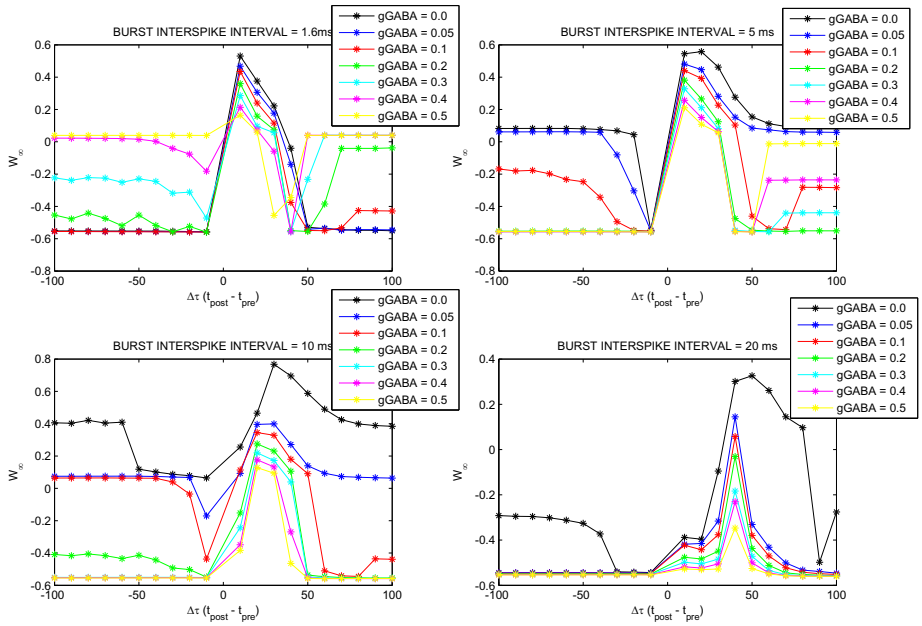

Fig. 4. STDP profiles from the pairing of a burst of spikes with T ms burst interspike interval, where T is a free parameter, applied to SR synapses and a single spike applied to the soma in the absence and presence of a 100 Hz GABA spike train as a function of $GABA_A$ conductance. $\Delta\tau$ (t_{post} - t_{pre}) ranges from -100 to 100 in increments of 10ms. (Top-left) Burst interspike interval, T, is 1.6 ms. (Bottom-left) Burst interspike interval, T, is 5 ms. (Top-right) Burst interspike interval, T, is 10 ms. (Bottom-right) Burst interspike interval, T, is 20 ms.

Figure 5 is a composite figure of the W_∞ vs $\Delta\tau$ graph as a function of a 5 ms burst interspike interval and increasing $GABA_A$ conductance (g_{GABA_A} = 0.0 mS/cm^2 and g_{GABA_A} = 0.1 mS/cm^2) and the [Ca^{2+}], P (i.e. potentiation) and LTD agents (V, A, B, and D) vs time graphs for B, C, D, E, F, G, H, and I W_∞ values of the W_∞ vs $\Delta\tau$ graph. In the paired protocol of a presynaptic burst stimulation followed by a postsynaptic single spike stimulation of 10 ms later (preBurst-10-postSpike) in the absence of $GABA_A$, we see a large influx of calcium through the NMDA channel due to removal of the magnesium block by the back propagating action potential (BPAP) (top figure 5B). In the preBurst-50-postSpike scenario, the influx of calcium is reduced because the arrival of the BPAP at the dendrite comes later. While the slow closing of the NMDA channels still allow calcium influx to be enhanced by this unblocking, the peak calcium level is lower in the preBurst-40-postSpike scenario than in the preBurst-10-postSpike (top figure 5C) because NMDA channels are more inactivated by the time the magnesium is removed. This leads to a large potentiation (i.e. P) spike (medium figure 5B) and small LTD agents' profiles (bottom figure 5B)

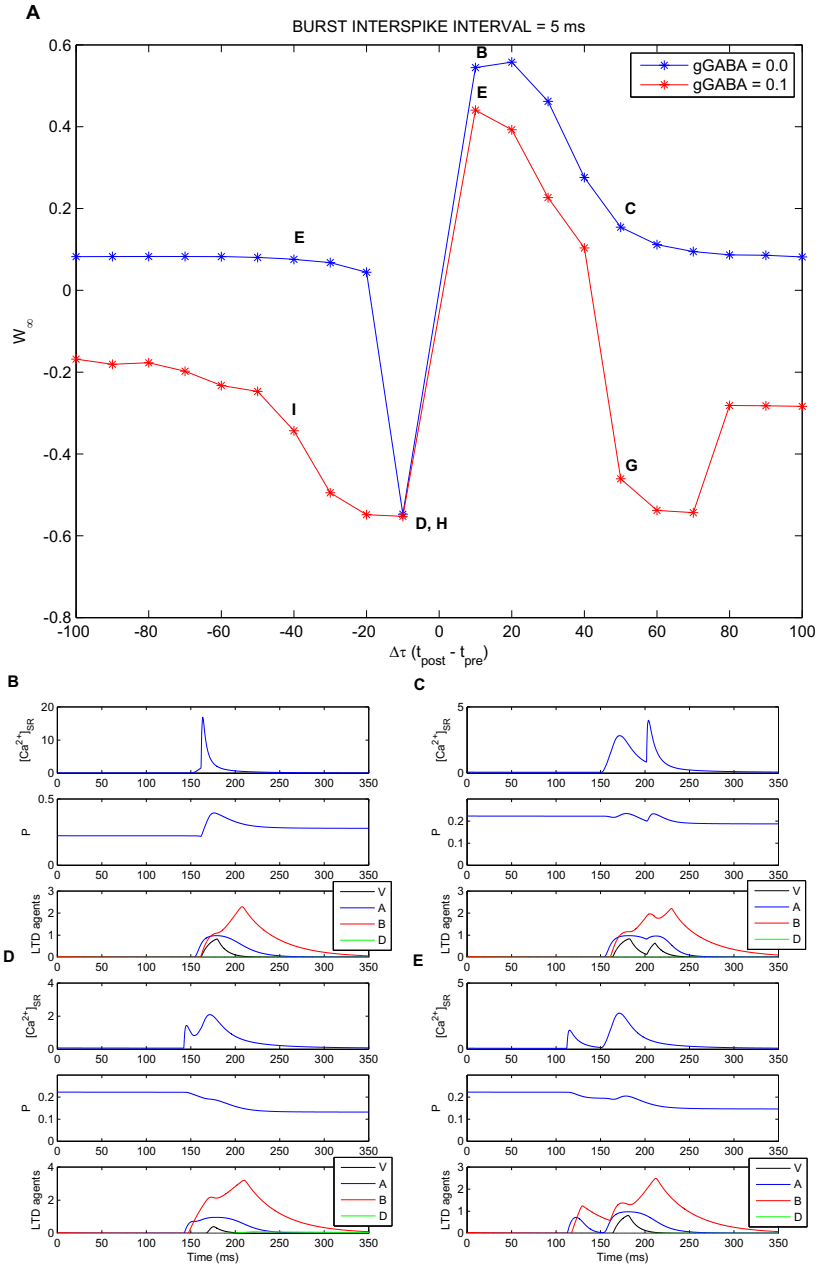

Fig. 5. (A) STDP profile from the pairing of a burst of spikes with 5 ms burst interspike interval applied to SR synapses and a single spike applied to the soma in the absence and presence of a 100 Hz $GABA_A$ spike train as a function of $GABA_A$ conductance. $\Delta\tau$ (t_{post} - t_{pre}) ranges from -100 to 100 in increments of 10 ms. (B-I) Composite figures corresponding to points B through I in figure 5A of [Ca^{2+}], P (potentiation) and LTD agents (V, A, B, and D) with respect to time.

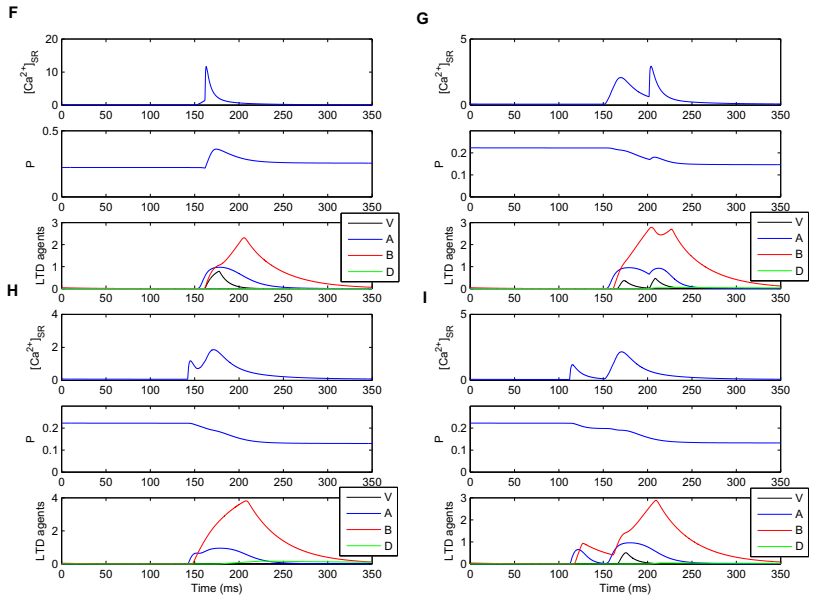

Fig. 5. (*continued*)

when compared with preBurst-50-postSpike case (medium and bottom figure 5C). The peak calcium level will continue to decrease as the preBurst-postSpike interstimulus interval is lengthened.

When $GABA_A$ inhibition is present the peak calcium level in the preBurst-10-postSpike (top figure 5F) is lower than in preBurst-10-postSpike case in the absence of $GABA_A$ (top figure 5B). In the preBurst-50-postSpike in the presence of $GABA_A$ scenario (top figure 5G), the effect of $GABA_A$ on W_∞ is more pronounced than in preBurst-10-postSpike without $GABA_A$ case. This is due to the increased number of $GABA_A$ spikes in the pre-post intersimulus interval (6 spikes in the 50 ms pre-post interstimulus interval vs 2 spikes in the 10 ms pre-post interstimulus interval).

In the postSpike-before-preBurst synaptic pairing with a 10 ms interval (postSpike-10-preBurst), a much smaller calcium enters the dendrite through the L-type voltage gated calcium channels (VGCCs) (top figure 5D). The effect of $GABA_A$ on calcium influx through the VGCCs is negligible and hence the LTD value of the W_∞ in the presence of $GABA_A$ (top figure 5H) is the same as in the absence of it (top figure 5D). The potentiation curves (medium figures 5D and 5H) are tonically decreasing. From the LTD agents (bottom figures 5D and 5H), the veto signal is low and hence its effect on the B curve is small. The tall B curve leads to a depression spike (i.e. D variable) and hence to LTD.

In the postSpike-40-preBurst without $GABA_A$ scenario, the calcium influx (top figure 5E) is greater than in the postSpike-10-preBurst (top figure 5D). Hence, a small but pronounced P spike is evident (medium figure 5E). A larger veto spike prevents the depression curve (D variable) from affecting the W_∞

value. In the postSpike-40-preBurst with $GABA_A$ scenario, the calcium influx (top figure 5I) is slightly greater than in the postSpike-10-preBurst (top figure 5H). Hence, a very small P spike is evident (medium figure 5I). A veto spike is present but not sufficient strong to prevent the depression curve (D variable) from affecting the W_∞, hence resulting to LTD.

5 Conclusion

A Ca^{2+} dynamics model of the CA1 pyramidal neuron with three calcium amplitude detectors was used to study the effects of GABAergic interneurons to the symmetry-to-asymmetry transition of the STDP profile in the proximal SR dendrite. In support of previous computational work from our group [8], [10], which predicted that the symmetry-to-asymmetry transition is strongly dependent on the frequency band (theta vs. gamma), the conductance value of $GABA_A$ inhibition and the relative timing between the GABAergic spike train and the pre-post interstimulus interval, the symmetry-to-asymmetry-back-to-symmetry transition is also depedent on the burst interspike interval in the presence/absence of $GABA_A$ when a presynaptic burst and a postsynaptic single spike are paired. In the future, we intend to investigate this transition even further for other pre-post burst and single spike pairings in the presence of different $GABA_A$ gamma frequency sub-bands and conductance values.

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