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ORIGINAL ARTICLE

Activity-dependent competition regulated by nonlinear interspike interaction in STDP: a model for visual cortical plasticity

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Abstract The development of visual cortical circuits is strongly influenced by the sensory experience during a restricted critical period, as demonstrated by the loss of neural responses to the eye that has been briefly deprived of vision. It has been suggested that, to reflect the sensory experience into the synaptic pattern, the competition between different groups of correlated inputs to a post-synaptic cell is essential and that spike-timing-dependent plasticity (STDP) may provide the basis of this type of activity-dependent competition. To predict the consequences of competition by STDP in natural physiological conditions, I here investigate the effects of nonlinear interspike interactions in STDP which are experimentally observed in the visual cortical cells. The simulations using a biophysical STDP model show that the interspike interaction can prevent the induction of competition and counteract the effect of activity-dependent feedback (ADFB) modulation of STDP that facilitates competition. However, once the competition occurs, the level of competition is not affected by the interspike interaction. These results may suggest that the interspike interaction in STDP leads to a delay in the induction of experience-dependent plasticity through suppressing synaptic competition, thereby causing a delay in the onset of critical period in the visual cortex.

Keywords Critical period · Visual cortex · STDP · Activity-dependent feedback

1 Introduction

Synaptic circuits are developed through reflecting sensory experience during a critical period in postnatal development [1]. A representative example of the experience-dependent synaptic modification is the ocular dominance plasticity observed in visual cortical cells [1–3]. Physiological experiments have shown that if either one eye is briefly deprived of vision within a critical period, the response of many visual cortical neurons is dominated by the non-deprived eye following deprivation; in contrast, the monocular deprivation before or after the critical period does not significantly affect the cell responses [1–3].

Both experimental and theoretical findings have suggested that the ocular dominance plasticity may involve the competition between different groups of inputs that originate from each eye and are correlated within each group [1, 4–6]. In the presence of the correlation-based competition, the strengthening of the inputs from one eye leads to the weakening of those from the other eye. Therefore, the neural response can be dominated by one eye and which group becomes dominant depends on earlier sensory experience, thereby introducing experience-dependent plasticity [4]. Furthermore, recent modeling studies have shown that spike-timing-dependent plasticity (STDP), wherein the magnitude and direction of synaptic weight changes depend on the precise timing of pre- and post-synaptic spikes, may provide a physiological mechanism that underlies the correlation-based competition [4, 7].

To investigate the consequences of the activity-dependent competition by STDP in natural physiological conditions,

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I examine in this study the effects of nonlinear interspike interactions in STDP, which are experimentally observed in the visual cortex [8], on the dynamics of synaptic population. The interspike interaction in STDP has been suggested to exert a suppressive effect on synaptic modifications such that the occurrence of a spike weakens the level of plasticity produced by a successive spike in the same neuron. The decay process of the suppressive influence of a spike on the subsequent spike is described as an exponential function of the time interval between the two spikes, with the time constants of 28 and 88 ms for the pre- and postsynaptic cells, respectively, implying that the interspike interaction can strongly and nonlinearly modulate STDP in a physiological range of firing activity [8]. In this study, a conductance-based pyramidal neuron is constructed that receives many random inputs from synapses following STDP, as in in vivo conditions. The simulations demonstrate that the interspike suppression tends to significantly prevent the occurrence of competition between two groups of correlated inputs. This may suggest that the interspike interaction can inhibit the ability of neurons to embed the input correlation structure to synaptic weights and can delay the onset of the critical period of ocular dominance plasticity in early development.

2 Methods

2.1 Conductance-based neuron model

A two-compartment conductance-based pyramidal neuron, which comprises a soma and a dendrite, was constructed. The neuron model is described by the following equation [4]:

$$C_{\mathrm{m}}\frac{\mathrm{d}V_{\mathrm{s}}}{\mathrm{d}t} = -I_{\mathrm{leak}} - I_{\mathrm{Na}} - I_{\mathrm{K}} + \frac{g_{\mathrm{c}}}{p}(V_{\mathrm{d}} - V_{\mathrm{s}}), \tag{1}$$

$$C_{\mathrm{m}}\frac{\mathrm{d}V_{\mathrm{d}}}{\mathrm{d}t} = -I_{\mathrm{leak}} - I_{\mathrm{Na}} - I_{\mathrm{K}} - I_{\mathrm{Ca,V}} - I_{\mathrm{AHP}} + \frac{g_{\mathrm{c}}}{1-p}(V_{\mathrm{s}} - V_{\mathrm{d}}) - I_{\mathrm{syn}}. \tag{2}$$

Here, V_{s} and V_{d} are the membrane potentials of the somatic and dendritic compartments, respectively. Both the compartments contain leak (I_{leak}) and voltage-dependent Na^+/K^+ currents ($I_{\mathrm{Na}}/I_{\mathrm{K}}$). The voltage-dependent calcium currents ($I_{\mathrm{Ca,V}}$) and calcium-dependent K^+ currents (I_{AHP}) are included in the dendrite to reproduce spike frequency adaptation observed in pyramidal cells [9]. g_{c} is a coupling conductance between the two compartments, and I_{syn} is the synaptic current.

2.2 Synaptic inputs

The dendritic compartment receives random inputs, which are activated by Poisson processes, from 4000 excitatory (mediated by AMPA and NMDA receptors) and 800 inhibitory (GABAergic) synapses [10]. To explore the predicted effects of input correlation, I divided excitatory inputs into two equally sized groups and introduced the same magnitude of correlation into each input group [11]. Any two inputs that belong to different groups are uncorrelated. All the inhibitory inputs are uncorrelated and activated by random homogeneous Poisson processes. Mean input frequencies are set to 3 Hz for all the synapses. Taking into account the low success rate (around 10 %) of synaptic transmission observed in central synapses [12], the input frequency of 3 Hz corresponds to the presynaptic firing rate of 30 Hz. This firing rate can be considered physiologically relevant as the sensory-evoked response of neocortical cells [9]. To quantify the level of competition between the two groups of excitatory inputs, I introduced synaptic competition index (SCI) defined as $|\bar{w}_1 - \bar{w}_2|/(\bar{w}_1 + \bar{w}_2)$ with the average weight $\bar{w}_i$ for group i [4]. SCI of 0 means that the two groups have the same average weight, whereas SCI of 1 means that the synaptic weights of either one group converge to 0 and only one group contributes to the postsynaptic activity.

2.3 Biophysical STDP model

A biophysical STDP model [13] was applied to all the excitatory synapses. In this model, the change in the synaptic weights induced by each pre- and postsynaptic spike pair is determined using an STDP map $\Delta w(\Delta t, \tau_{\mathrm{NMDA}}, g_{\mathrm{NMDA}})$, which was constructed using an in vitro pairing protocol simulation based on intracellular Ca^{2+}-dependent plasticity [10]. In this STDP map, the magnitude of plasticity Δw is given as a function of an interspike interval between pre- and postsynaptic spikes Δt, NMDA receptor (NMDAR) peak conductance g_{NMDA}, and NMDAR decay time constant τ_{NMDA} [13]. Theoretical studies suggest that an approximate balance between LTP and LTD is required to activate the competitive function of STDP [4, 7, 14]. To attain the balanced state automatically, I introduced the activity-dependent feedback (ADFB) mechanism, in which the NMDAR peak conductance and its decay time constant are dynamically regulated as a function of the postsynaptic firing rate f_{post} [13]:

$$\tau_{\mathrm{NMDA}} = (1-\rho)\tau_1 + \rho\tau_2 - k_1\rho f_{\mathrm{post}}, \tag{3}$$

$$g_{\mathrm{NMDA}} = g^0_{\mathrm{NMDA}} - k_2\rho f_{\mathrm{post}}. \tag{4}$$

Here, ρ represents a parameter associated with the expression level of NR2A subunits in NMDARs, which considerably increases during early development [14–16]. In this model, the increase in ρ values functions to strengthen the ADFB mechanism: $\rho = 0$ corresponds to a state where the ADFB modulation is absent because of

very low level of NR2A subunits, whereas $\rho = 1$ corresponds to a state where the ADFB modulation is sufficiently strong due to a large number of NR2A-containing NMDARs. The first two terms in the right-hand side of Eq. 3 describe the alteration in the decay kinetics of single NMDAR currents by the change in the number of NR2A-containing receptors [17, 18]. The ADFB model in Eqs. 3 and 4 is to describe the effects of activity- and subunit-dependent desensitization of NMDARs on STDP [19, 20], which leads to the facilitation of the correlation-based competition [4, 13].

2.4 Interspike interaction in STDP

I introduced the nonlinear interspike interaction in STDP observed in the visual cortex [8]. To incorporate this effect, each spike is assigned an efficacy, which is determined as a function of the time that has elapsed after a preceding spike in an identical neuron:

$$\varepsilon_K^f = 1 - \exp[-(t_K^f - t_K^{f-1})/\tau_K], \quad (K = \text{ pre or post}) \qquad (5)$$

where the subscript K denotes the pre- or postsynaptic activity, ε_K^f is the efficacy assigned to the fth spike, t_K^f and t_K^{f-1} are the fth and $(f-1)$th spike timing of the K neuron, $\tau_{\text{pre}} = 28$ ms and $\tau_{\text{post}} = 88$ ms are the time constants by which the influence of a prior spike decays exponentially for the pre- and postsynaptic cells, respectively [8]. The change in the synaptic weights induced by the pair of the fth presynaptic spike and f'th postsynaptic spike is described as $\varepsilon_K^f \varepsilon_K^{f'} \Delta w(\Delta t, \tau_{\text{NMDA}}, g_{\text{NMDA}})$ using the STDP map. The weight updating rule is assumed to be additive [21] and the effects of all the spike pairs on STDP are taken into account.

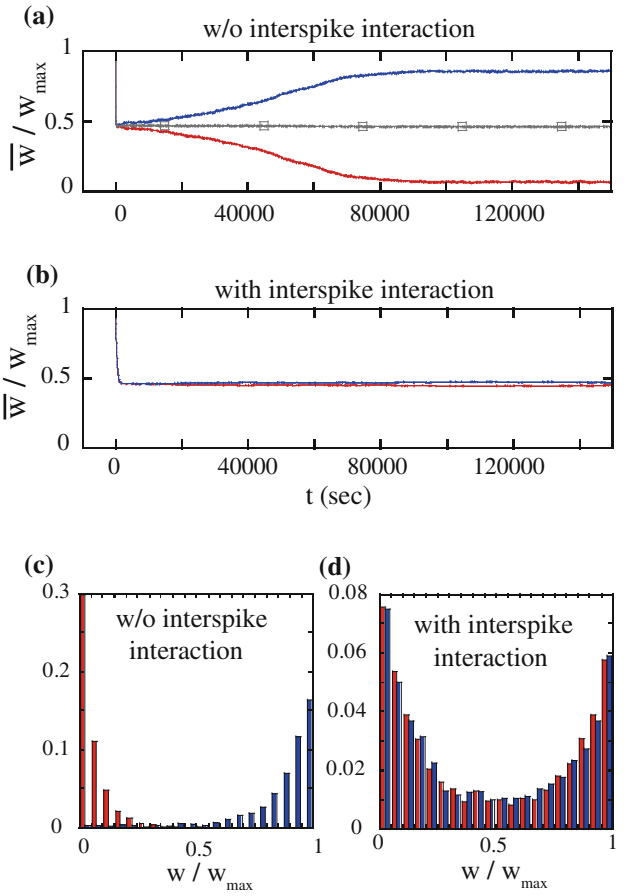

Fig. 1 The predicted effects of the nonlinear interspike interaction in STDP on the correlation-based competition. **a**, **b** The time courses of weight averages for the two groups are shown by *red* and *blue lines*. The *gray line* in **a** denotes the average weight of all the inputs. **a** and **b** show the cases without and with the interspike interaction, respectively. **c**, **d** The final weight distributions of the two input groups are depicted by *red* and *blue bars* for the cases without (**c**) and with (**d**) the interspike interaction. (Parameter $\rho = 0.8$) (color figure online)

3 Results

To explore the influences of the interspike interaction in STDP on the competitive property, I examined the dynamics of synaptic population when a neuron receives correlated inputs from two groups of STDP synapses. As shown in the previous study [4], in the absence of interspike interaction, STDP elicited strong competition where one group dominates over the other in the equilibrium state (Fig. 1a). However, in the presence of the interspike interaction, the between-group competition disappeared and the two input groups converged to the same average weights (Fig. 1b). The interspike interaction did not significantly alter the average weight of all the synapses (Fig. 1a (gray), b).

This result was clarified by examining the weight distribution at the equilibrium state of STDP (Fig. 1c, d). The figures show that without the interspike interaction, the weight distribution differs between the two input groups such that the synaptic weights of one group accumulate near 0, whereas those of the other group tends to be pushed toward the upper limit (Fig. 1c). However, in the presence of the nonlinear interaction, the weight distribution is nearly the same for the two groups (Fig. 1d), implying the lack of activity-dependent competition.

To examine a physiological significance of the interspike interaction, I calculated the weight averages of the two input groups with changing ρ, a parameter associated with the level of NR2A subunit expression in NMDAR channels. The results showed that the interspike interaction significantly increases a threshold value of ρ, above which the between-group competition takes place and the value of SCI becomes positive (Fig. 2a, b). Interestingly, once the competition occurs for sufficiently larger ρ values, the level of competition is nearly the same independent of whether

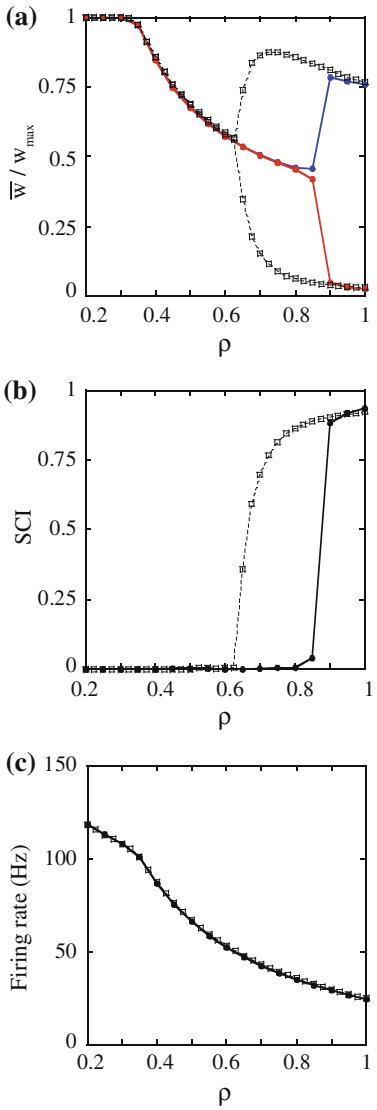

Fig. 2 The weight averages of the two groups (**a**), synaptic competition index (SCI) (**b**), and the postsynaptic firing rate (**c**) as a function of the strength of ADFB modulation ρ. In **a**–**c**, the *solid lines* show the cases of introducing nonlinear interspike interaction in STDP, whereas the *dashed lines* show the cases of not incorporating interspike interaction. The firing rate for the two cases takes almost the same values in (**c**)

the interspike interaction is incorporated. Given that the activity-dependent competition is highly involved in visual cortical plasticity [1, 4–6], the interspike interaction in STDP in the visual cortex may contribute to controlling the induction of competition and the resulting occurrence of critical period plasticity such that the nonlinear suppression would delay the timing of the critical period, but would not affect the level of plasticity once it has occurred.

To explore the mechanism underlying the regulation of the competitive property by the interspike interaction, I have examined the correlation between pre- and postsynaptic activities [4]. The correlation function $C(\Delta t)$ between the pre- and postsynaptic spike trains is described as

$$C(\Delta t) = \frac{< S_{\mathrm{pre}}(t-\Delta t) S_{\mathrm{post}}(t) >_t}{< S_{\mathrm{pre}}(t) >_t < S_{\mathrm{post}}(t) >_t}, \tag{6}$$

where $S_{\mathrm{pre}}(t) = \sum_f \delta(t - t^f_{\mathrm{pre}})$ and $S_{\mathrm{post}}(t) = \sum_f \delta(t - t^f_{\mathrm{post}})$ represent the pre- and postsynaptic spike trains, respectively, and the angular brackets with subscript t represent the time average. I examined the correlation function at the equilibrium state for both the cases with and without the interspike suppression in STDP (Fig. 3a, thin solid and dashed lines, respectively). However, the correlation functions for the two cases were found to take the same values for all Δt. This result will be consistent with the fact that the interspike interaction has no significant effect on the postsynaptic firing rate (Fig. 2c), since the level of postsynaptic activity can considerably affect the firing statistics of neurons [22]. To clearly describe the influence of the interspike suppression on the firing statistics, I introduce a new function $C^*(\Delta t)$, which is a modification of the standard cross-correlation function $C(\Delta t)$:

$$C^*(\Delta t) = \frac{< S^*_{\mathrm{pre}}(t-\Delta t) S^*_{\mathrm{post}}(t) >_t}{< S^*_{\mathrm{pre}}(t) >_t < S^*_{\mathrm{post}}(t) >_t}. \tag{7}$$

Here, $S^*_{\mathrm{pre}}(t) = \sum_f \varepsilon^f_{\mathrm{pre}} \delta(t - t^f_{\mathrm{pre}})$ and $S^*_{post}(t) = \sum_f \varepsilon^f_{post} \delta(t - t^f_{post})$ are defined as the trains of pre- and postsynaptic action potentials that are weighted by the efficacies of spikes, $\varepsilon^f_{\mathrm{pre}}$ and $\varepsilon^f_{\mathrm{post}}$, on plasticity. Note that the function $C^*(\Delta t)$ exactly agrees with function $C(\Delta t)$ in the absence of interspike interaction (i.e., $\varepsilon^f_{\mathrm{pre}} = \varepsilon^f_{\mathrm{post}} = 1$). The modified correlation function $C^*(\Delta t)$ regulates the synaptic drift produced by STDP in the presence of nonlinear interspike interaction, in a similar manner as the standard correlation function $C(\Delta t)$ regulates it in a linear summation model (Appendix A). As shown in Fig. 3a, the values of $C^*(\Delta t)$ significantly decrease as compared to those of $C(\Delta t)$ in a wide range of positive Δt values ($2\ \mathrm{ms} < \Delta t < 35\ \mathrm{ms}$). The difference between $C(\Delta t)$ and $C^*(\Delta t)$ can be understood as follows. Let us consider a case where the activation of a given input, as well as the inputs correlated with it, generates more than one action potentials within a short period of time. Then, the efficacy $\varepsilon^f_{\mathrm{post}}$ for the postsynaptic spikes following the first one will be suppressed by the influence of the immediately preceding spike, decreasing $C^*(\Delta t)$ but not $C(\Delta t)$. The effect of the interspike interaction to decrease the values of the modified correlation function would be weakened for larger values of ρ, where the activity level significantly decreases by the enhancement of ADFB so

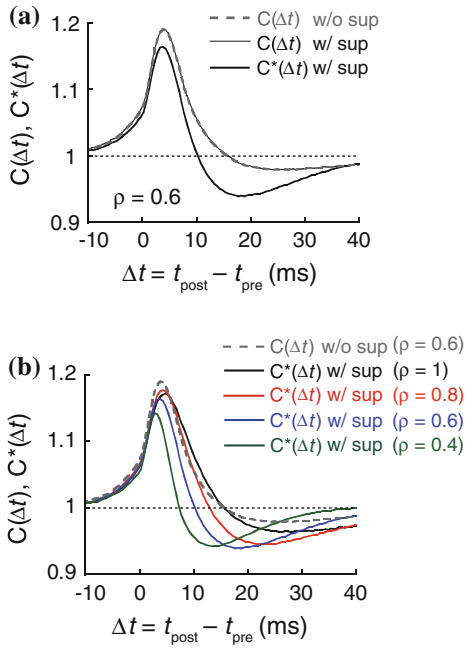

Fig. 3 The influences of the interspike interaction on the correlation between pre- and postsynaptic activities at the equilibrium state of STDP. **a** *Dashed line* The standard correlation function $C(\Delta t)$ obtained without the interspike suppression. *Solid lines* The standard correlation function $C(\Delta t)$ (*thin line*) and the modified correlation function $C^*(\Delta t)$ (*thick line*) for the cases using the interspike suppression model. The difference between the functions $C(\Delta t)$ with (*thin solid*) and without (*dashed*) the suppression model is invisible ($\rho = 0.6$). **b** The *solid lines* show $C^*(\Delta t)$ for four different values of ρ [$\rho = 0.4$ (*green*), 0.6 (*blue*), 0.8 (*red*), or 1 (*black*)]. The *dashed line* is the same as that in **a**, showing $C(\Delta t)$ at $\rho = 0.6$ for comparison. Note that, in **a**, the values of $C^*(\Delta t)$ (*thick solid line*) are considerably smaller than those of $C(\Delta t)$ (*dashed line*) in a wide range of Δt. However, such decrease in $C^*(\Delta t)$ via the nonlinear suppression can be compensated by the increased value of ρ in **b** (color figure online)

that the mean interval between the successive spikes becomes increased (Fig. 2c). Therefore, as shown in Fig. 3b, the decrease in the values of $C^*(\Delta t)$ via the interspike suppression can be compensated by the increased value of ρ. Furthermore, since the increase in the temporal width or the peak level of the input–output correlation can contribute to strengthening the ability of STDP to reflect the input correlation structure [4], one can understand that the change in the modified correlation function (Fig. 3b) will play a role in the recovery of the between-group competition through enhancing ADFB (Fig. 2a, b). In summary, the present results demonstrate that the interspike interaction in STDP may weaken the competition at higher firing activity, through decreasing the actual influence of input spikes on the output spiking, which contributes to STDP (Fig. 3a), but that the competition can be recovered by strengthening ADFB, which decreases the neuronal activity and enhances the effective correlation between inputs and output firing (Fig. 3b) [4].

4 Discussion

In this study, I have examined the effects of nonlinear interspike interaction in STDP on the competition between correlated input groups, using a biophysical Ca^{2+}-based STDP model [13]. I have found that the interspike interaction may prevent the emergence of the correlation-based competition but that the enhancement of ADFB mechanism can recover it. In addition, the interspike interaction has been shown to significantly weaken the actual impact of each input on the postsynaptic activity that can effectively contribute to plasticity, decreasing the ability of STDP to embed the correlation structure among inputs into synaptic weights [4]. Both experimental and theoretical studies have suggested that the activity-dependent competition between the input groups, originating from the two eyes, is highly required to initiate the critical period of visual cortical plasticity [1, 4–6]. Therefore, the present study suggests that the nonlinear interspike interaction may act to suppress the activation of competition and therefore may produce a delay in the onset of the critical period in early development. It has been suggested that the interspike suppression could result from the short-term depression of synapses or the weakening of the backpropagating action potentials caused by the occurrence of prior spikes [23]. Therefore, the coordinated action of such rapid feedback effects and slower feedback effects by the activity-dependent NMDAR desensitization [4], considered in this work, may contribute to modulating the timing of the critical period. Additional experiments would be required to sort out the influences of these feedback mechanisms on STDP and cortical experience-dependent plasticity.

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Appendix A Relationship between the modified correlation function $C^*(\Delta t)$ and the synaptic drift in the presence of interspike interaction

In this appendix, I simply consider the drift of synapses that follow STDP characterized by a time-invariant learning curve $f(\Delta t)$, as in many theoretical studies. Then, the weight change generated by STDP incorporating the interspike suppression, during time interval $[t_0,t_1]$, is

$$w(t_1) - w(t_0) = \sum_{t_0 < t^f_{\mathrm{pre}}, t^{f'}_{\mathrm{post}} < t_1} \varepsilon^f_{\mathrm{pre}} \varepsilon^{f'}_{\mathrm{post}} f(t^{f'}_{\mathrm{post}} - t^f_{\mathrm{pre}}) = \int_{t_0}^{t_1} \int_{t_0}^{t_1} f(t'' - t') S^*_{\mathrm{pre}}(t') S^*_{\mathrm{post}}(t'') \mathrm{d}t' \mathrm{d}t''. \quad \text{(A.1)}$$

Using the method similar to that of Kempter et al. [24], I can obtain from this equation the following relationship between the synaptic drift $\dot{w}$ and $C^*(\Delta t)$:

$$\dot{w} = r^*_{\mathrm{pre}} r^*_{\mathrm{post}} \int_{-\infty}^{\infty} f(\Delta t) C^*(\Delta t) \mathrm{d}\Delta t, \quad \text{(A.2)}$$

where $r^*_{\mathrm{pre}} = <S^*_{\mathrm{pre}}(t)>_t$ and $r^*_{\mathrm{post}} = <S^*_{\mathrm{post}}(t)>_t$. This implies that $C^*(\Delta t)$ regulates the direction (not magnitude) of synaptic drift in the STDP model including interspike suppression just as $C(\Delta t)$ regulates it in the absence of the interspike suppression [22, 24].

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