

1 **Detailed dendritic excitatory/inhibitory balance through heterosynaptic**  
2 **spike-timing-dependent plasticity**

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11 **Competing interests**

12 The authors have declared that no competing interests exist.

13

14 **Acknowledgments**

15 The authors thank to Dr. Laurent Venance for kindly providing the experimental data. This work was  
16 partly supported by JSPS Doctorial Fellowship DC2 (NH), CREST JST, and KAKENHI No15H04265  
17 and No16H01289 (TF).

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19

20 **Abstract**

21 Balance between excitatory and inhibitory inputs is a key feature of cortical dynamics. Such balance  
22 is arguably preserved in dendritic branches, yet its underlying mechanism and functional roles  
23 remain unknown. Here, by considering computational models of heterosynaptic

24 spike-timing-dependent plasticity (STDP), we show that the detailed excitatory/inhibitory balance on  
25 dendritic branch is robustly achieved through heterosynaptic interaction between excitatory and  
26 inhibitory synapses. The model well reproduces experimental results on heterosynaptic STDP, and  
27 provides analytical insights. Furthermore, heterosynaptic STDP explains how maturation of inhibitory  
28 neurons modulates selectivity of excitatory neurons in critical period plasticity of binocular matching.  
29 Our results propose heterosynaptic STDP as a critical factor in synaptic organization and resultant  
30 dendritic computation.

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32

### 33 **Significance statement**

34 Recent experimental studies have revealed that relative spike timings among neighboring  
35 Glutamatergic and GABAergic synapses on a dendritic branch significantly influences changes in  
36 synaptic efficiency of these synapses. This heterosynaptic form of spike-timing-dependent plasticity  
37 (STDP) is potentially important for shaping the synaptic organization and computation of neurons,  
38 but its functional role remains elusive. Here, through computational modeling, we show that  
39 heterosynaptic plasticity causes the detailed balance between excitatory and inhibitory inputs on the  
40 dendrite, at the parameter regime where previous experimental results are well reproduced. Our  
41 result reveals a potential principle of GABA-driven neural circuit formation.

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43

### 44 **Introduction**

45 Activity dependent synaptic plasticity is essential for learning. Especially, spike time difference  
46 between presynaptic and postsynaptic neurons is a crucial factor for synaptic learning (Bi and Poo,

47 1998)(Caporale and Dan, 2008). Recent experimental results further revealed that the relative spike  
48 timings among neighboring synapses on a dendritic branch have significant influence on changes in  
49 synaptic efficiency of these synapses (Tsukada et al., 2005)(Hayama et al., 2013)(Paille et al.,  
50 2013)(Oh et al., 2015)(Bazelot et al., 2015). Especially, the timing of GABAergic input exerts a great  
51 impact on synaptic plasticity at nearby glutamatergic synapses. Similar phenomenon were also  
52 observed in biophysical simulations (Cutsuridis, 2011)(Bar-Ilan et al., 2013). This heterosynaptic  
53 form of spike-timing-dependent plasticity (h-STDP) is potentially important for synaptic organization  
54 on dendritic tree, and resultant dendritic computation (Mel and Schiller, 2004)(Branco et al., 2010).  
55 However, the functional role of h-STDP remains elusive, partly due to lack of simple analytical model.

56 In the understanding of homosynaptic STDP, simple mathematical formulation of plasticity  
57 has been playing important roles (Gerstner et al., 1996)(Song et al., 2000)(Vogels et al., 2011).  
58 Motivated by these studies, we constructed a mathematical model of h-STDP based on  
59 calcium-based synaptic plasticity models (Shouval et al., 2002)(Graupner and Brunel, 2012), and  
60 then considered potential functional merits of the plasticity. The model reproduces several effects of  
61 h-STDP observed in the hippocampal CA1 area and the striatum of rodents (Hayama et al.,  
62 2013)(Paille et al., 2013), and provides analytical insights for the underlying mechanism. The model  
63 further indicates that h-STDP causes the detailed balance between excitatory and inhibitory inputs  
64 on a dendritic branch owing to the inhibitory inputs that shunt long-term depression (LTD) at  
65 neighboring correlated excitatory synapses. This result suggests that not only the number and the  
66 total current of excitatory/inhibitory synapses are balanced at a branch (Liu, 2004)(Wilson et al.,  
67 2007), but temporal input structure is also balanced as observed in the soma (Dorrn et al.,  
68 2010)(Froemke, 2015). Moreover, by considering dendritic computation, we show that such detailed  
69 balance is beneficial for detecting changes in input activity. The model also reconciles with critical

70 period plasticity of binocular matching observed in V1 of mice (Wang et al., 2010)(Wang et al., 2013),  
71 and provides a candidate explanation on how GABA-maturation modulates the selectivity of  
72 excitatory neurons during development.

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74

## 75 **Methods**

76 In this study, we first constructed a model of dendritic spine, then based on that model, built models  
77 of a dendritic branch, and a dendritic neuron. We also created an analytically tractable model of a  
78 spine, by reducing the original spine model.

79

### 80 *Spine model: Calcium-based STDP model with current-based heterosynaptic interaction*

81 Let us first consider membrane dynamics of a dendritic spine. Membrane potential of a  
82 spine is mainly driven by presynaptic inputs through AMPA/NMDA receptors, backpropagation of  
83 postsynaptic spike, leaky currents, and current influx/outflux caused by excitatory/inhibitory synaptic  
84 inputs at nearby synapses. Hence, we modeled membrane dynamics of spine  $i$  with the following  
85 differential equation:

$$86 \frac{du_i(t)}{dt} = -\frac{u_i(t)}{\tau_m} + \gamma_A x_i^A(t) + \gamma_N g_N(u_i) x_i^N(t) + \gamma_{BP} x_i^{BP}(t) - \gamma_I \sum_{j \in \Omega_i^I} x_j^I(t - d_I) + \gamma_E \sum_{j \in \Omega_i^E} x_j^E(t - d_E), \quad (1)$$

87 where  $u_i$  is the membrane potential of the spine, and  $\tau_m$  is the membrane time constant(see **Table 1**  
88 for definitions of variables). Here, conductance changes were approximated by current changes. The  
89 resting potential was renormalized to zero for simplicity. In next terms,  $x_i^A$  and  $x_i^N$  are glutamate  
90 concentration on AMPA/NMDA receptors respectively. The function  $g_N(u_i) = \alpha_N u_i + \beta_N$  represents  
91 voltage dependence of current influx through NMDA receptors. This positive feedback is enhanced  
92 when additional current is provided through back-propagation. As a result, the model reproduces

93 large depolarization caused by coincident spikes between presynaptic and postsynaptic neurons.  
94 Although AMPA receptor also shows voltage dependence, here we neglected the dependence, as  
95 the relative change is small around the resting potential (Lüscher and Malenka, 2012).  $x_i^{BP}$  is the  
96 effect of backpropagation from soma, and the last two terms of the equation represents  
97 heterosynaptic current, which is given as the sum of inhibitory (excitatory) currents  $x_j^I$  ( $x_j^E$ ) at nearby  
98 synapses. We defined sets of nearby inhibitory/excitatory synapses as  $\Omega_i^I$  and  $\Omega_i^E$  respectively, and  
99 their delays were denoted as  $d_I$  and  $d_E$ . Each input  $x_i^Q$  ( $Q = A, N, BP, I, E$ ) is given as convoluted  
100 spikes:

$$101 \quad \frac{dx_i^Q(t)}{dt} = -\frac{x_i^Q(t)}{\tau_Q} + \sum_{s^k} \delta(t - s^k), \quad (2)$$

102 where  $s^k$  represents the spike timing of the  $k$ -th spike. In the simulation, although convolution is  
103 calculated at the heterosynaptic synapse, this does not influence results because exponential decay  
104 is linear.

105 We next consider calcium influx to a spine through NMDA receptors and VDCC. For a  
106 given membrane potential  $u_i$ , calcium concentration at spine  $i$  can be written as

$$107 \quad \frac{dc_i}{dt} = -\frac{c_i}{\tau_C} + g_N(u_i)x_i^N(t) + g_V(u_i), \quad (3)$$

108 where  $g_V(u_i) = \alpha_V u_i$  represents calcium influx through VDCC, and  $g_N(u_i)x_i^N(t)$  is the influx from NMDA.

109 Calcium concentration at spine is the major indicator of synaptic plasticity, and many  
110 results indicate that high  $Ca^{2+}$  concentration on a spine typically induces LTP, while low  
111 concentration often causes LTD (Lüscher and Malenka, 2012). Previous modeling studies revealed  
112 calcium-based synaptic plasticity model constructed on that principle well replicate various  
113 homosynaptic STDP time window observed in *in vitro* experiments (Shouval et al., 2002)(Graupner  
114 and Brunel, 2012). Hence, here we employed their framework for plasticity model. We additionally

115 introduced an intermediate variable to reflect all-or-none nature of synaptic weight change (Petersen  
116 et al., 1998). This variable approximately represents the concentration of plasticity related enzymes  
117 such as CaMKII or PP1 (Graupner and Brunel, 2007). In the proposed model the intermediate  $y_i$  and  
118 synaptic weight  $w_i$  follow

$$119 \quad \frac{dy_i(t)}{dt} = -\frac{y_i(t)}{\tau_y} + C_p [c_i - \theta_p]_+ - C_d [c_i - \theta_d]_+, \quad (4)$$

$$120 \quad \frac{dw_i(t)}{dt} = B_p [y_i - y_{th}]_+ - B_d [-(y_i + y_{th})]_+. \quad (5)$$

121  $[X]_+$  is a sign function which returns 1 if  $X \geq 0$ , returns 0 otherwise. Note that, in this model setting, as  
122 observed in recent experiments (Gambino et al., 2014), back-propagation is not necessary for LTP, if  
123 presynaptic inputs are given when the membrane potential at the spine is well depolarized.

124 In the simulation, we set common parameters as  $\tau_C=18.0\text{ms}$ ,  $\tau_M=3.0\text{ms}$ ,  $\tau_N=15.0\text{ms}$ ,  
125  $\tau_A=3.0\text{ms}$ ,  $\tau_{BP}=3.0\text{ms}$ ,  $\tau_I=3.0\text{ms}$ ,  $\tau_E=6.0\text{ms}$ ,  $\tau_Y=50\text{s}$ ,  $d_f=0.0\text{ms}$ ,  $\alpha_N=1.0$ ,  $\beta_N=0.0$ ,  $\alpha_V=2.0$ ,  $\gamma_A=1.0$ ,  
126  $\theta_p=70$ ,  $\theta_d=35$ ,  $C_d=1.0$ ,  $B_p=0.001$ ,  $B_d=0.0005$ . Note that due to positive feedback between equations  
127 (1) and (3), effective timescales of calcium dynamics and NMDA channel become longer than the  
128 given values. In the model of STDP at striatum, in addition, we used  $\gamma_N=0.05$ ,  $\gamma_{BP}=8.0$ ,  $\gamma_I=5.0$ ,  $C_p=2.3$ ,  
129  $y_{th}=250$ , while for the model of Schaffer collateral synapses, we used  $\gamma_N=0.2$ ,  $\gamma_{BP}=8.5$ ,  $\gamma_I=3.0$ ,  $C_p=2.2$ ,  
130  $y_{th}=750$ ,  $d_E=1.0$ ,  $\gamma_E=1.0$ . In the parameter search, decay time constants were chosen from  
131 biologically reasonable ranges (Koch, 1998),  $\alpha_N$ ,  $\gamma_A$ ,  $C_d$ ,  $B_d$  were fixed at unitary values, and other  
132 parameters were manually tuned. Subsequently, robustness of parameter choice was confirmed  
133 numerically (Fig. 3). Synaptic weight variables  $\{w\}$  were bounded to  $0 < w < 500$ , and initialized at  $w =$   
134 100. All other variables were initialized at zero in the simulation. Paired stimulation was given every 1  
135 second for 100 seconds, and synaptic weight changes were calculated from the values 400 seconds  
136 after the end of stimulation. In the cortico-striatal synapse model, the inhibitory spike was presented

137 at the same timing with the presynaptic spike, and for Schaffer collateral synapses, inhibitory spikes  
138 were given 10 milliseconds before pre (post) spikes in pre-post (post-pre) stimulation protocols. In  
139 calculation of intermediate variable  $y(t)$  in Figures 2B,D, we ignored the effect of exponential decay,  
140 because of the difference in timescale ( $\tau_y \gg 1$  seconds). We subtracted 7.5 milliseconds of axonal  
141 delay from the timing of presynaptic stimulation in the calculation of spike timing difference.

142

### 143 *Dendritic hotspot model*

144 Dendritic hotspot model was constructed based on the Schaffer collateral synapse model described  
145 above. For simplicity, we hypothesized that heterosynaptic current due to inhibitory spike arrives on  
146 excitatory spines at the same time, and also disregarded E-to-E interaction by setting  $\gamma_E=0.0$ .  
147 Correlated spikes were generated using hidden variables as in previous studies (Vogels et al.,  
148 2011)(Hiratani and Fukai, 2015). We generated five dynamic hidden variables, and updated them at  
149 each time step by  $s_\mu(t + \Delta t) = (\zeta - \frac{1}{2})(1 - \alpha_s) + s_\mu(t)\alpha_s$ , where  $\alpha_s = \exp[-\Delta t/\tau_s]$ ,  $\tau_s=10\text{ms}$ ,  
150  $\mu=0,1,\dots,4$ , and  $\zeta$  is a random variable uniformly chosen from  $[0,1)$ . In the simulation, the time step  
151 was set at  $\Delta t=0.1\text{ms}$ . Activities of presynaptic neurons were generated by rate-modulated Poisson  
152 process with  $r_i^E(t) = r_X^E + r_S^E s_\mu(t)$  for excitatory neuron  $i$  modulated by the hidden variable  $\mu$  (due to  
153 non-negative constraint on  $r_i^E(t)$ , we set  $r_i^E(t) = 0$  when  $r_X^E + r_S^E s_\mu(t) < 0$ ). Similarly, the  
154 presynaptic inhibitory neuron was described by a Poisson-model with  $r^I(t) = r_X^I + r_S^I s_0(t)$ . Activity of  
155 the postsynaptic neuron was given as a Poisson-model with a fixed rate  $r_{post}$ . We set parameters  $\{r_X^E,$   
156  $r_S^E, r_{post}\}$  in a way that all pre and postsynaptic excitatory neurons show the same average firing rate  
157 at 5Hz, to avoid the effect of firing-rate difference on synaptic plasticity.

158 For parameters, we used  $\gamma=1.2$ ,  $\beta_N=1.0$ ,  $\gamma_{BP}=8.0$ ,  $C_p=2.11$ ,  $y_{th}=250$  and other parameters  
159 were kept at the same value with the original Schaffer collateral model. Except for Figure 5D, the

160 delay of inhibitory spike was set as zero. Presynaptic activities were given by  $r_X^E=1.0\text{Hz}$ ,  $r_S^E=500.0$ ,  
 161  $r_X^I=2.0\text{Hz}$ ,  $r_S^I=1000.0$ , and postsynaptic firing rate was set as  $r_{post} = 5.0\text{Hz}$ . In Figure 5C, the  
 162 correlation was calculated between dendritic membrane potential  $g_b(u_b)$  and hidden variables  $\{s_\mu(t)\}$ ,  
 163 where  $u_b(t) \equiv \sum_{i=1}^{10} w_i u_i(t) / (w_o^E N_b^E)$ , and  $g_b(u)$  was defined as  $g_b(u)=u$  if  $u > u_b^o$ , otherwise  $g_b(u)=u_b^o$   
 164 with  $u_b^o=-5.0$ .

165

### 166 *Two-layered neuron model*

167 Previous studies suggest that complicated dendritic computation can be approximated by a  
 168 two-layered single cell model (Poirazi et al., 2003)(London and Häusser, 2005). Thus, we  
 169 constructed a single cell model by assuming that each hotspot works as a subunit of a two-layered  
 170 model. We defined the mean potential of a dendritic subunit  $k$  by  $u_b^k(t) \equiv \sum_{i=1}^{N_b^E} w_i^k u_i^k(t) / (w_o^E N_b^E)$ , and  
 171 calculated the somatic membrane potential by  $u_{soma}(t) \equiv \sum_{k=1}^K g_b(u_b^k(t))$ . Postsynaptic spikes were  
 172 given as a rate-modulated Poisson model with the rate  $u_{soma}(t)/I_{dv}(t)$ .  $I_{dv}(t)$  is the divisive inhibition  
 173 term introduced to keep the output firing rate at  $r_{post}$ . By using the mean somatic potential  
 174  $\frac{d\bar{u}_{soma}(t)}{dt} = -\frac{\bar{u}_{soma}(t) - u_{soma}(t)}{\tau_v}$ ,  $I_{dv}(t)$  was calculated as  $I_{dv}(t) \equiv \bar{u}_{soma}(t) / r_{post}$ .

175 In the simulations described in Figure 6, we used  $C_p=2.01$ ,  $\tau_v=1\text{s}$ ,  $K=100$ , and other  
 176 parameters were kept at the same values with the dendritic hotspot model. During the learning  
 177 depicted in Figure 6BC, we used the same input configuration with the dendritic hotspot model. In  
 178 Figure 6DE, The activity levels of hidden variables  $\{s_\mu(t)\}$  were kept at a constant value ( $s_\mu(t)=0.25$ )  
 179 during 500ms stimulation, and otherwise kept at zero. Additionally, inhibitory presynaptic activities  
 180 were set as  $r_X^I=10\text{Hz}$ ,  $r_S^I=2000$ . In Figure 6D, we modulated firing rates of both excitatory and  
 181 inhibitory presynaptic neurons, by changing the activity levels of hidden variables  $\{s_\mu(t)\}$  from 0.1 to



182 0.5. The ratio of change detecting spikes was defined as the ratio of spikes occurred within 50  
 183 milliseconds from the change to the total spike count.

184 For the model of critical period plasticity of binocular matching depicted in Figure 7, we also  
 185 used the two-layered single cell model. The neuron model has  $K=100$  dendritic branches, each  
 186 receives  $N_b^E=20$  excitatory inputs and 1 inhibitory input. At each branch, half of excitatory inputs are  
 187 from the contralateral eye, and the other half are from the ipsilateral eye. Each excitatory input  
 188 neuron have direction selectivity characterized with  $\theta_{k,i}^E$ , and shows rate-modulated Poisson firing  
 189 with

$$190 \quad r_{k,i} = r_x^E \exp\left[\beta_E \cos(\theta(t) - \theta_{k,i}^Q)\right] / I_0(\beta_E)$$

191 where  $\theta(t)$  is the direction of the visual stimulus at time  $t$ ,  $Q$  is either contra- or ipsilateral, and  $I_0(\beta_E)$  is  
 192 the modified Bessel function of order 0. Similarly, firing rate of an inhibitory neuron was given as

$$193 \quad r_k^I(t) = r_x^I \exp\left[\beta_I \cos(\theta(t) - \theta_k^I)\right] / I_0(\beta_I).$$

194 For each excitatory input neuron, mean direction selectivity  $\{\theta_{k,i}^Q\}$  was randomly chosen from a von Mises distribution  $\exp\left[\beta_S \cos(\theta_{k,i}^Q - \theta_Q)\right] / 2\pi I_0(\beta_S)$ , where

195  $Q=\{\text{contra, ipsi}\}$ . In the simulation, we used  $\theta_{\text{contra}}=-\pi/4$ ,  $\theta_{\text{ipsi}}=\pi/4$ . Correspondingly, mean direction

196 selectivity of a inhibitory neuron  $\{\theta_k^I\}$  was defined as the mean of its selectivity for ipsi- and

197 contralateral inputs (ie.  $\theta_k^I = (\theta_k^{I,\text{ipsi}} + \theta_k^{I,\text{contra}})/2$ ), where  $\theta_k^{I,\text{ipsi}}$  and  $\theta_k^{I,\text{contra}}$  were also randomly depicted

198 from  $\exp\left[\beta_S \cos(\theta_k^Q - \theta_Q)\right] / 2\pi I_0(\beta_S)$ . Direction of visual stimulus  $\theta(t)$  changes randomly with

199  $\theta(t + \Delta t) = \theta(t) + \sigma_{sr} \zeta_G$  where  $\zeta_G$  is a Gaussian random variable, and  $\Delta t$  is the time step of the

200 simulation. To mimic monocular deprivation, in the shadowed area of Figure 7E, we replaced

201 contra-driven input neuron activity with a Poisson spiking with constant firing rate  $r_{md}^E$ . In addition, to

202 simulate the lack of contra-driven inputs to inhibitory neurons, we replaced inhibitory activity with

203  $r'_k(t) = r'_{md} + (r'_x/2)\exp[\beta_l \cos(\theta(t) - \theta_k^{l,ipsi})]/I_0(\beta_l)$ . Similarly, in Figure 7C, we measured direction  
 204 selectivity by providing monocular inputs, while replacing the inputs from the other eye with a  
 205 homogeneous Poisson spikes with firing rate  $r_{md}^E$ .

206 To evaluate the development of binocular matching, we introduced three order parameters.  
 207 First, the difference between mean excitatory direction selectivity and inhibitory selectivity at a  
 208 branch  $k$  was evaluated by  $\theta_{b,k}^d = \left| \arg\left(\sum_i w_{k,i}^E e^{i(\theta_{k,i}^E - \theta_k^l)}\right) \right|$ . Similarly, the global direction selectivity  
 209 difference between inputs from the ipsi- and contralateral eyes were defined by

$$210 \quad \theta_G^d = \hat{d} \left[ \arg\left(\sum_{k=1}^K \sum_{i \in ipsi} w_{k,i}^E e^{i\theta_{k,i}^E}\right), \arg\left(\sum_{k=1}^K \sum_{i \in contra} w_{k,i}^E e^{i\theta_{k,i}^E}\right) \right], \quad (6)$$

211 where the function  $\hat{d}[\theta_1, \theta_2]$  calculates the phase difference between two angles. Finally, direction  
 212 selectivity index DSI for binocular input was calculated by

$$213 \quad DSI = \left| \frac{\sum_{k=1}^K \sum_{i=1}^{N_b^E} w_{k,i}^E e^{i\theta_{k,i}^E}}{\sum_{k=1}^K \sum_{i=1}^{N_b^E} w_{k,i}^E} \right|. \quad (7)$$

214 For the calculation of the monocular direction selectivity index, at each branch  $k$ , we took sum over  
 215  $N_b^E/2$  excitatory inputs corresponding to each eye instead of all  $N_b^E$  inputs.

216 In the simulation, we set  $\gamma_I=2.5$ ,  $C_p=1.85$ ,  $y_{th}=750.0$ ,  $u_b^o=0.0$ , and the rest of parameters  
 217 were kept at the values used in the dendritic hotspot model. Inputs parameters were set at  $\beta_E=4.0$ ,  
 218  $\beta_I=2.0$ ,  $\beta_S=1.0$ ,  $\theta_{contra}=-\pi/4$ ,  $\theta_{ipsi}=\pi/4$ ,  $r_X^E=5.0$ ,  $r_X^I=10.0$ ,  $r_{md}^E=1.0$ ,  $r_{md}^I=1.0$ , and  $\sigma_{sr} = 0.1\sqrt{\Delta t}$ .

219

## 220 *Reduced model*

221 If we shrink equations for membrane potential (eq. 1) and calcium concentration (eq. 3) into one, the  
 222 reduced equation would be written as,

$$\begin{aligned}
 223 \quad \frac{dC_i(t)}{dt} = & -\frac{C_i(t)}{\tau_C} + C_{pre} X_i(t) + C_{post} [1 + g_C(C_i(t - \Delta t))] X_{post}(t) \\
 & - C_I \sum_{j \in \Omega_I^I} X_j^I(t - d_I) + C_E \sum_{j \in \Omega_I^E} X_j^E(t - d_E),
 \end{aligned} \tag{8}$$

224 where  $g_c(X) = [X]_+ \eta X$  captures the nonlinear effect caused by pre-post coincidence (i.e.  $g_c(X)$  returns  
 225  $\eta X$  if  $X > 0$ , otherwise returns 0). All inputs  $X_i$ ,  $X_{post}$ ,  $X_j^I$ ,  $X_j^E$  were given as point processes, and  $d_I$ ,  $d_E$   
 226 are heterosynaptic delays.  $g_c$  was calculated from the value of  $C_i$  at  $t = t - \Delta t$  to avoid pathological  
 227 divergence due to the point processes. In the simulation, we simply used value of  $C_i$  one time step  
 228 before. For the intermediate  $y$ , we used the same equation as before. Note that above equation is  
 229 basically same with the one in (Graupner and Brunel, 2012) except for the nonlinear term  $g_c(C)$  and  
 230 the heterosynaptic terms.

231 Let us consider weight dynamics of an excitatory synapse that has only one inhibitory  
 232 synapse in its neighbor. For analytical tractability, we consider the case when presynaptic,  
 233 postsynaptic, and inhibitory neurons fire only one spikes at  $t = t_{pre}$ ,  $t_{post}$ ,  $t_I$  respectively. In case of the  
 234 CA1 experiment, because GABA uncaging was always performed before pre and postsynaptic spike,  
 235 the timing of inhibitory spike is given as  $t_I = \min(t_{pre}, t_{post}) - \bar{\delta}_I$  for  $\bar{\delta}_I > 0$ . In this setting, the change in  
 236 intermediate variable of the excitatory synapse is given as

$$237 \quad \Delta y = \begin{cases} G_1(C_1, t_{pre} - t_{post}) + G_2(C_{pre} + C_1 e^{-(t_{pre} - t_{post})/\tau_C}) & (\text{if } t_{post} < t_{pre}) \\ G_1(C_2, t_{post} - t_{pre}) + G_2(C_{post} [1 + g_C(C_2 e^{-(t_{post} - t_{pre})/\tau_C})] + C_2 e^{-(t_{post} - t_{pre})/\tau_C}) & (\text{otherwise}) \end{cases}$$

238 where,

$$239 \quad C_1 \equiv C_{post} - C_I e^{-(t_{post} - t_I)/\tau_C}, \quad C_2 \equiv C_{pre} - C_I e^{-(t_{pre} - t_I)/\tau_C}$$

$$\begin{aligned}
 240 \quad G_1(C, \Delta t) \equiv & B_p [C - \theta_p]_+ \left( \left[ \tau_C \log \frac{C}{\theta_p} - \Delta t \right]_+ \Delta t + \left[ \Delta t - \tau_C \log \frac{C}{\theta_p} \right]_+ \tau_C \log \frac{C}{\theta_p} \right) \\
 & - B_d [C - \theta_d]_+ \left( \left[ \tau_C \log \frac{C}{\theta_d} - \Delta t \right]_+ \Delta t + \left[ \Delta t - \tau_C \log \frac{C}{\theta_d} \right]_+ \tau_C \log \frac{C}{\theta_d} \right),
 \end{aligned}$$

241 
$$G_2(C) \equiv B_p [C - \theta_p]_+ \tau_C \log \frac{C}{\theta_p} - B_d [C - \theta_d]_+ \tau_C \log \frac{C}{\theta_d}.$$

242 Similarly, in case of the striatum experiment, by setting  $\eta=0$ , the change in the intermediate variable  
 243 is given as

244 
$$\Delta y = \begin{cases} G_1(C_{post}, t_{pre} - t_{post}) + G_1(C_3, t_I - t_{pre}) + G_2(-C_I + C_3 e^{-(t_I - t_{pre})/\tau_C}) & (\text{if } t_{post} < t_{pre} < t_I) \\ G_1(C_{pre}, t_I - t_{pre}) + G_1(C_4, t_{post} - t_I) + G_2(C_{post} + C_4 e^{-(t_{post} - t_I)/\tau_C}) & (\text{if } t_{pre} < t_I < t_{post}) \\ G_1(C_{pre}, t_{post} - t_{pre}) + G_1(C_5, t_I - t_{post}) + G_2(-C_I + C_5 e^{-(t_I - t_{post})/\tau_C}) & (\text{if } t_{pre} < t_{post} < t_I), \end{cases}$$

245 where

246 
$$C_3 \equiv C_{pre} + C_{post} e^{-(t_{pre} - t_{post})/\tau_C}, \quad C_4 \equiv -C_I + C_{pre} e^{-(t_I - t_{pre})/\tau_C}, \quad \text{and} \quad C_5 \equiv C_{post} + C_{pre} e^{-(t_{post} - t_{pre})/\tau_C}.$$

247 In the simulation, parameters were set at  $\tau_C=30\text{ms}$ ,  $C_{post}=2.0$ ,  $\theta_p=1.6$ ,  $\theta_d=1.0$ ,  $B_p=2.25$ ,  
 248  $B_d=1.0$ . Additionally, in the model of a Schaffer collateral synapse, we used  $\delta_f=1.0$ ,  $C_{pre}=1.0$ ,  $C_E=0.30$ ,  
 249  $\eta=2.0$ , and for the model of a cortico-striatal synapse, we employed  $\delta_f=5.0$ ,  $C_{pre}=0.75$ ,  $C_E=0.0$ ,  $\eta=0.0$ .  
 250 In Figures 3C and D, we used the parameter set for the model of Schaffer collateral synapse.

251 As depicted in Figure 3D, the model also provides an analytical insight to E-to-E interaction,  
 252 in addition to I-to-E interaction analyzed in the main result. In E-to-E interaction, neighboring  
 253 synapses receive small heterosynaptic calcium transient  $C_E$  instead of presynaptic input  $C_{pre}$ . Thus,  
 254 we can characterize the shapes of STDP time windows by the heterosynaptic excitatory effect  
 255 parameter  $C_E$ , and postsynaptic effect parameters  $C_{post}$  (Fig. 3D). When the postsynaptic effect  
 256 parameter  $C_{post}$  satisfies  $\theta_p < C_{post} < \theta_p + C_I e^{-\delta_I/\tau_C}$ , and the heterosynaptic effect parameter  $C_E$   
 257 fulfills  $C_I e^{-\delta_I/\tau_C} < C_E < \theta_p$ , STDP time window shows Hebbian-type timing dependency  
 258 (upper-middle orange-colored region in Fig. 3D). On the other hand, if  $C_E$  is smaller than  $C_I e^{-\delta_I/\tau_C}$   
 259 while satisfying  $\theta_p + C_I e^{-\delta_I/\tau_C} - C_{post} < C_E$ , then the STDP curve becomes LTD dominant (upper-left  
 260 green-colored region in Fig. 3D) as observed in experiments (Hayama et al., 2013)(Oh et al., 2015).

261 Excitatory heterosynaptic effect  $C_E$  is expectedly smaller than the inhibitory effect  $C_I$ , because the  
262 inhibitory potential is typically more localized (Gidon and Segev, 2012). Thus,  $C_E < C_I e^{-\delta_i/\tau_c}$  is also  
263 expected to hold for small  $\delta_i$ , suggesting robust heterosynaptic LTD at neighboring synapses.

264

265

## 266 **Results**

267 *Calcium-based synaptic plasticity model with current-based heterosynaptic interaction explains*  
268 *h-STDP.*

269 We constructed a model of a dendritic spine as shown in Figure 1A (see *Spine model* in *Methods* for  
270 details). In the model, the membrane potential of the spine  $u(t)$  is modulated by influx/outflux from  
271 AMPA/NMDA receptors ( $x^A$  and  $g_N(u)x^N$  in Fig. 1A), back-propagation ( $x^{BP}$ ), and heterosynaptic  
272 currents from nearby excitatory/inhibitory synapses ( $x^E$  and  $x^I$ ) (see **Table 1** for the definitions of  
273 variables). Calcium concentration in the spine  $c(t)$  is controlled through NMDA receptors and  
274 voltage-dependent calcium channels (VDCC)  $g_V(u)$  (Higley and Sabatini, 2012). Because both NMDA  
275 and VDCC are voltage-dependent (Lüscher and Malenka, 2012), the calcium level in the spine is  
276 indirectly controlled by pre, post, and heterosynaptic activities (Fig. 1B top and middle panels). For  
277 synaptic plasticity, we used calcium-based plasticity model, in which LTP/LTD are initiated if the  $\text{Ca}^{2+}$   
278 level is above LTP/LTD thresholds (orange and cyan lines in Fig. 1B middle). This plasticity model is  
279 known to well capture homosynaptic STDP (Shouval et al., 2002)(Graupner and Brunel, 2012). We  
280 introduced an intermediate variable  $y(t)$  to capture non-graded nature of synaptic weight change  
281 (Petersen et al., 1998). Thus, changes in  $\text{Ca}^{2+}$  level are first embodied in the intermediate  $y(t)$  (Fig.  
282 1B bottom), and then reflected to the synaptic weight  $w(t)$  upon accumulation. The intermediate  
283 variable  $y(t)$  is expected to correspond with concentration of plasticity related enzymes such as

284 CaMKII or PP1 (Graupner and Brunel, 2007).

285           We first consider the effect of inhibitory input to synaptic plasticity at nearby excitatory  
286 spines. A recent experimental result revealed that, in medium spiny neuron, synaptic connections  
287 from cortical excitatory neurons typically show anti-Hebbian type STDP under pairwise stimulation  
288 protocol, but if GABA-A receptor is blocked, STDP time window flips to Hebbian (Paille et al., 2013)  
289 (points in Fig. 2A). The proposed model can explain this phenomenon in the following way. Let us  
290 first consider the case when the presynaptic excitatory input arrives before the postsynaptic spike. If  
291 the GABAergic input is blocked, presynaptic and postsynaptic spikes jointly cause a large membrane  
292 depolarization at the excitatory spine. Subsequently, the calcium concentration rises up above the  
293 LTP threshold (red line in Fig 2B upper-right), hence inducing LTP after repetitive stimulation (red line  
294 in Fig 2B lower-right). In contrast, if the GABAergic input arrives coincidentally with the presynaptic  
295 input, depolarization at the excitatory spine is attenuated by negative current influx through the  
296 inhibitory synapse. As a result, calcium concentration cannot go up beyond the LTP threshold  
297 although it is still high enough to eventually cause LTD (black lines in Fig 2B right). Similarly when  
298 the postsynaptic spike arrives to the spine before the presynaptic spike does, without any GABAergic  
299 input, the presynaptic spike causes slow decay in the level of calcium concentration that may induce  
300 LTD (red lines in Fig 2B left). On the contrary, if the GABAergic input is provided simultaneously with  
301 the presynaptic input, slow decay in the calcium concentration is blocked because the inhibitory input  
302 causes hyperpolarization of the membrane potential at the excitatory spine. As a result, LTP is more  
303 likely achieved (black lines in Fig. 2B left). Therefore, when a GABAergic input arrives in coincidence  
304 with a presynaptic excitatory input, the STDP time window changes its sign in both pre-post and  
305 post-pre regimes (lines in Fig. 2A).

306           GABAergic effect on excitatory synaptic plasticity is also observed in CA1 (Hayama et al.,

2013). In this case, post-pre stimulation does not induce LTD unless GABA uncaging is conducted near the excitatory spine right before the postsynaptic spike arrives at the spine, whereas LTP is induced by pre-post stimulation regardless of GABA uncaging (blue and cyan points in Fig. 2C). The proposed model can also replicate these results. In pre-post stimulation, due to positive feedback through NMDA receptor, the membrane potential of the spine shows strong depolarization even if inhibitory current is delivered through GABA uncaging (solid and dotted blue lines in Fig. 2D upper-right). Thus, LTP is caused after repetitive stimulation (blue lines in Fig. 2D lower-right). By contrast, in post-pre protocol, LTP/LTD effects tend to cancel each other in the absence of GABAergic input, whereas LTD becomes dominant under the influence of GABAergic input (dotted and solid blue lines in Fig. 2D left, respectively).

In addition to inhibitory-to-excitatory effect, excitatory-to-excitatory (E-to-E) effect is also observed in case of CA1 (Hayama et al., 2013). If GABA uncaging is performed right before postsynaptic firing, LTD is also observed in neighboring excitatory spines (green point in Fig. 2C right). This E-to-E heterosynaptic effect is not observed in the absence of GABAergic input (green points in Fig 2C left). Correspondingly, in the model, excitatory current influx from a nearby synapse causes mild potentiation of calcium concentration in cooperation with inhibitory current influx, hence eventually induces LTD (green lines in Fig 2D left). Note that for this E-to-E effect, interaction at latter stage of synaptic plasticity may also play a dominant role (Hayama et al., 2013).

The obtained results are mostly robust against parameter change, as long as associated parameter values satisfy certain relationships (Fig. 3A). In addition, we found that the coefficient for heterosynaptic inhibitory effect should be larger for fitting the result from the striatum experiment, compared to CA1 (Fig. 3B top). This is consistent with strong inhibition observed in striatum (Mallet et al., 2005). We also found that for reproducing the result from the CA1 experiment, a high

330 NMDA/AMPA ratio is crucial, while the striatum model is rather robust against it, as long as calcium  
 331 influx/outflux is modulated by NMDA receptors (Fig. 3B bottom).

332

### 333 *Phase transitions underlying h-STDP*

334 In the previous section, we introduced a biophysical model to establish its relevance to the  
 335 corresponding biological processes and get insight into the underlying mechanism. However, not all  
 336 components of the model are necessary to reproduce the observed properties of h-STDP. Here, we  
 337 provide a simple analytically tractable model to investigate the generality of the proposed  
 338 mechanism.

339 To this end, we simplify the model to the one in which calcium level at a spine is directly  
 340 modulated by pre-, post-, and heterosynaptic activities as given below,

$$\begin{aligned}
 \frac{dC_i(t)}{dt} = & -\frac{C_i(t)}{\tau_C} + C_{pre} X_i(t) + C_{post} [1 + g_C(C_i(t - \Delta t))] X_{post}(t) \\
 & - C_I \sum_{j \in \Omega_i^I} X_j^I(t - d_j) + C_E \sum_{j \in \Omega_i^E} X_j^E(t - d_E).
 \end{aligned}
 \tag{9}$$

342 Here,  $C_i(t)$  represents  $Ca^{2+}$  concentration at spine  $i$ ,  $X_i$  and  $X_{post}$  represent presynaptic and  
 343 postsynaptic spikes respectively,  $d_I$  and  $d_E$  are heterosynaptic delays, and  $\Omega_i^I$  and  $\Omega_i^E$  are the sets of  
 344 neighboring inhibitory and excitatory synapses (see *Reduced model* in *Methods* for the details of the  
 345 model). Despite simplicity, the model can qualitatively reproduce heterosynaptic effects observed in  
 346 striatal and CA1 neurons, though the quantitative accuracy is degraded (Fig. 4A and B respectively).  
 347 Importantly, the reduced model provides further analytical insights into the phenomena.

348 Let us consider how the inhibitory effect parameter  $C_I$  controls I-to-E heterosynaptic effect  
 349 observed in the CA1 experiment. If we characterize the shape of STDP time windows by the total  
 350 number of its local minimum/maximum, the parameter space can be divided into several different



351 phases (Fig. 4C). If LTP threshold  $\theta_p$  satisfies  $C_{pre} < \theta_p < C_{post}$ , Hebbian type STDP time window  
352 appears when the strength of heterosynaptic inhibitory effect  $C_I$  satisfies  
353  $(C_{post} - \theta_p)e^{\delta_I/\tau_C} < C_I < C_{pre}e^{\delta_I/\tau_C}$  (upper orange-colored region in Fig. 4C; see *Methods* for the  
354 details of analysis). Here we defined  $\delta_I$  as the spike timing difference between inhibitory spike and  
355 presynaptic (postsynaptic) spikes in pre-post (post-pre) stimulation protocols. If  $C_I$  is larger than  
356  $C_{pre}e^{\delta_I/\tau_C}$ , a strong inhibitory effect causes LTD even in the pre-post regime (green-colored  
357 region in Fig. 4C), whereas LTD in the post-pre regime is suppressed when  $C_I$  is smaller than  
358  $(C_{pre} - \theta_p)e^{\delta_I/\tau_C}$  (gray-colored region in Fig. 4C). Thus, heterosynaptic LTD observed in Figure 2C  
359 can be understood as the phase shift from the gray-colored region to the orange-colored region in  
360 Figure 4C, due to change in the inhibitory effect  $C_I$ . This analysis further confirms that, for induction  
361 of heterosynaptic LTD, the heterosynaptic spike timing difference  $\delta_I$  should be smaller than the  
362 timescale of  $Ca^{2+}$  dynamics  $\tau_C$  (Hayama et al., 2013). This is because  $\delta_I < \tau_C \log\left(\frac{C_I}{C_{post} - \theta_p}\right)$  is  
363 necessary for a significant heterosynaptic LTD, and typically  $C_I$  is smaller than  $C_{post}$  and  $\theta_p$ . In  
364 addition, heterosynaptic suppression of pre-post LTP (green-colored region) is very unlikely to  
365 happen because  $C_I > C_{pre}e^{\delta_I/\tau_C}$  is necessary. This condition is difficult to satisfy even if  $\delta_I=0$ ,  
366 because the heterosynaptic effect on  $Ca^{2+}$  dynamics in the spine is expected to be smaller than the  
367 homosynaptic effect (i.e.  $C_I < C_{pre}$ ). A similar analysis is possible for E-to-E interaction although the  
368 phase diagram becomes complicated in this case (Fig. 4D; see *Methods* for details).

369 These analytical results revealed that the heterosynaptic effects are always observable if  
370 the parameters of calcium dynamics fall into a certain region in the parameter space, ensuring the  
371 robustness of h-STDP in our framework.

372

373 *h-STDP induces detailed dendritic E/I balance at dendritic hotspots*

374 Results so far suggest that the proposed model gives a good approximation of h-STDP. We next  
375 study how this h-STDP rule shapes synaptic organization on the dendrite of a simulated neuron to  
376 investigate its possible functions. To this end, we first consider a model of a dendritic hotspot (Jia et  
377 al., 2010) that receives 10 excitatory inputs and one inhibitory input (Fig. 5A), because  
378 heterosynaptic effect is typically confined within  $10\mu m$  from the synapse (Hayama et al., 2013).  
379 Excitatory inputs are organized into 5 pairs, and each pair of excitatory synapses receives correlated  
380 inputs (Fig. 5B; see *Dendritic hotspot model* in *Methods* for details). In addition, the inhibitory input is  
381 correlated with one excitatory pair (in Fig. 5A, blue ones). Here, we assumed that postsynaptic  
382 activity follows a Poisson process with a fixed rate, because the influence of a single hotspot to the  
383 soma is usually negligible. In addition, we neglected the effect of morphology and hypothesized that  
384 heterosynaptic interaction occurs instantaneously within the hotspot. In this configuration,  
385 surprisingly, excitatory synapses correlated with the inhibitory input are potentiated while other  
386 synapses experience minor depression (Fig. 5C top). As a result, the dendritic membrane potential  
387 becomes less correlated with all hidden signals, because strong negative correlation with the blue  
388 signal is cancelled by potentiated excitatory inputs, while weak positive correlation with other signals  
389 are diminished due to LTD at corresponding excitatory synapses (Fig. 5C bottom). This GABA-driven  
390 potentiation is only observable when inhibitory activity is tightly correlated with excitatory activities,  
391 and becomes larger when inhibitory spike precedes excitatory spikes compared to the opposite case  
392 (Fig. 5D). In addition, we found that when heterosynaptic inhibitory effect  $\gamma_I$  is large enough to causes  
393 strong hyperpolarization at nearby synapses, depression is observed at correlated excitatory  
394 synapses (blue area in Fig. 5E) instead of potentiation (red area in Fig. 5E). However, as we saw in  
395 Figures 3 and 4, such a large inhibitory effect does not reproduce STDP experiments, thus unlikely to

396 be observed in the actual brain. These results indicate that h-STDP induces dendrite-specific  
397 detailed E/I balance by potentiating excitatory synapses correlated with inhibitory synapses.

398 To reveal the underlying mechanism of this E/I balance generation, from the simulation  
399 data, we calculated the probability of calcium level being above the LTD/LTP thresholds after a  
400 presynaptic spike. The probability of LTP occurrence shows similar trajectories after a presynaptic  
401 spike, regardless of whether presynaptic activity is correlated with inhibitory input or not (blue and  
402 gray dotted lines in Fig. 5F, respectively). On the other hand, the maximum probability of LTD  
403 occurrence is significantly lower for spines correlated with inhibitory inputs (blue vs. gray solid line in  
404 Fig. 5F), although the probability goes up after the presynaptic spike in both cases. This asymmetry  
405 between LTP and LTD can be understood in the following way; LTD is mainly caused when the  
406 presynaptic neuron fires at a low firing rate and the postsynaptic neuron remains silent both in the  
407 experiment (Malenka and Bear, 2004) and in the model (gray line in Fig. 5G). However, if inhibitory  
408 input arrives at a nearby dendrite in coincidence, calcium boost caused by excitatory presynaptic  
409 input is attenuated by heterosynaptic inhibitory effect (black line in Fig. 5G). As a result, LTD is  
410 shunted by correlated inhibitory inputs. On the other hand, LTP is mainly caused by coincidence  
411 between pre and postsynaptic spikes, which induces a large increase in calcium level that  
412 overwhelms the attenuation by the heterosynaptic inhibitory effect. Thus, inhibitory activity at a  
413 nearby site does not prevent LTP at correlated excitatory synapses (Fig. 5H). Therefore, correlated  
414 spines experiences less depression, hence tend to be potentiated as a net sum.

415 To check the generality of the observed dendritic E/I balance, we extended the model to a  
416 two-layered single cell (Poirazi et al., 2003) by modeling each branch with one dendritic hotspot (Fig.  
417 6A; see *Two-layered neuron model* in *Methods* for details), and investigated the dendritic  
418 organization by h-STDP. Here, we introduced 10 ms delay between excitatory and inhibitory

419 stimulation(Froemke, 2015). Even in this case, when the postsynaptic neuron receives input from  
420 various neurons with different selectivity, each dendritic hotspot shapes its excitatory synaptic  
421 organization based on the selectivity of its inhibitory input (Fig. 6BC; the frame colors of Fig. 6B  
422 represent the inhibitory selectivities). As a result, excitatory synapses on the dendritic tree become  
423 clustered as observed in previous experiments (Kleindienst et al., 2011)(Takahashi et al., 2012).  
424 Note that, in our model, this clustering of excitatory synapses is caused by common inhibitory inputs  
425 instead of direct interaction among excitatory spines.

426 We further investigated the possible function of this synaptic organization in information  
427 processing. To this end, we consecutively presented the five stimuli to the two-layered neuron model  
428 (Fig. 6E). Before the learning, the neuron shows almost constant response to the stimulation with a  
429 small dip at the change points (Fig. 6E top). In contrast, after the learning, the neuron shows  
430 transient bursting activity immediately after the stimulus is changed to the next one, and rapidly  
431 returns to an almost silent state (Fig. 6E middle). Hence, by h-STDP, a neuron can acquire sensitivity  
432 toward abrupt changes in stimuli (Fig. 6D and 6E bottom).

433

#### 434 *h-STDP explains critical period plasticity of binocular matching*

435 Results so far indicate that h-STDP induces GABA-driven synaptic reorganization that enriches  
436 dendritic computation. To investigate its relationship with the developmental plasticity, we next  
437 consider a model of critical period plasticity in binocular matching (Wang et al., 2010)(Wang et al.,  
438 2013). In mice, one week after the eye opening, typically, binocular neurons in V1 still have different  
439 orientation selectivity for inputs from two eyes. Nevertheless, two more weeks after, selective  
440 orientations for both eyes get closer, and eventually they almost coincide with each other (Wang et  
441 al., 2010). Moreover, this binocular matching is disrupted by accelerating inhibitory maturation (Wang

442 et al., 2013). Thus, expectedly, activity of inhibitory neurons play a crucial role in binocular matching  
443 in addition to Hebbian plasticity at excitatory synapses.

444 We modeled this process with a two-layered single cell model introduced in Figure 6 (Fig.  
445 7A right; see *Two-layered neuron model* in *Methods* for details). Input spike trains were modeled as  
446 rate modulated Poisson processes driven by a circular variable  $\theta$ , which corresponds to the direction  
447 of moving visual stimuli. We assumed followings: (i) inputs from ipsi- and contralateral eyes already  
448 have some weak orientation selectivity at the eye opening (Wang et al., 2010)(Espinosa and Stryker,  
449 2012), (ii) Inhibitory cells are driven by both ipsi- and contralateral eyes (Yazaki-Sugiyama et al.,  
450 2009)(Kuhlman et al., 2011), (iii) The average selectivity of inhibitory inputs comes in between the  
451 selectivity for ipsilateral and contralateral excitatory inputs (Fig. 7A left). The last assumption has not  
452 yet been supported from experimental evidence, but if inhibition is provided from neighboring  
453 interneurons, these inhibitory neurons are likely to be driven by similar sets of feedforward excitatory  
454 inputs to those driving the output neuron. Here, we consider direction selectivity instead of orientation  
455 selectivity for mathematical convenience, but the same argument holds for the latter.

456 In the simulation, we first run the process without inhibition then introduced GABAergic  
457 inputs after a while (red lines in Fig. 7B,E represent the starting points of inhibitory inputs), because  
458 maturation of inhibitory neurons typically occurs in a later stage of the development (Hensch, 2005).  
459 Upon the introduction of inhibition, in each branch, the mean preferred direction of excitatory  
460 synapses converges to that of the local inhibition owing to heterosynaptic plasticity (Fig. 7B top; see  
461 *Methods* for details of evaluation methods), though synaptic weight development was biased toward  
462 the selectivity of the postsynaptic neuron (Fig. 7D; here, the bias is toward the right side). This  
463 dendritic E/I balancing shrinks the difference between ipsilateral and contralateral selectivity on  
464 average, because both of them get closer to the inhibitory selectivity (Fig. 7B middle). As a result,

465 binocular selectivity becomes stronger (Fig. 7B bottom), and the responses for monocular inputs  
466 approximately coincide with each other (Fig. 7C right). Deprivation of contralateral inputs  
467 immediately after the introduction of inhibition blocks binocular matching (Fig. 7E), as expected from  
468 the experiment (Wang et al., 2010).

469 In addition, precocious GABA maturation is known to disrupt binocular matching (Wang et  
470 al., 2013). Our model suggests that the disruption is possibly related to the violation of the third  
471 assumption in the model. When the direction of the mean inhibitory selectivity is far different from  
472 both ipsilateral and contralateral selectivity (in Fig. 7F, at the parameter regions outside of the area  
473 surrounded by purple and green lines), h-STDP does not work effectively (Fig. 7F top), and the  
474 difference between ipsi- and contralateral inputs is not reduced (Fig. 7F middle). As a result,  
475 binocular direction selectivity is not improved by learning (Fig. 7F bottom). These results indicate that  
476 GABA-maturation and resultant h-STDP are an important part of the underlying mechanisms of  
477 critical period plasticity in binocular matching.

478

479

## 480 **Discussion**

481 In this study, we first showed that a calcium-based plasticity model robustly captures several  
482 characteristics of plasticity-related interaction between neighboring synapses in millisecond  
483 timescale, by introducing heterosynaptic interaction terms (Fig. 2-4). Based on this proposed model,  
484 we next investigated the possible functions of h-STDP. Our study revealed that h-STDP causes the  
485 detailed dendritic E/I balance on dendritic hotspots (Fig. 5,6), which is beneficial for change detection  
486 (Fig. 6). Furthermore, we found that h-STDP can induce binocular matching upon GABA maturation,  
487 and support an accurate input estimation (Fig. 7).

488 *Experimental predictions*

489 Our study provides three experimental testable predictions: First, our results provide a  
490 hypothesis for synaptic organization on dendritic tree. It is known that excitatory synaptic inputs to a  
491 dendritic hotspot often show correlated activities (Kleindienst et al., 2011)(Takahashi et al., 2012).  
492 Our results indicate that an inhibitory input may also be correlated to excitatory inputs projecting to  
493 the nearby dendrite (Fig. 5,6), especially on a dendritic tree of an excitatory neuron that is sensitive  
494 to changes in the external environment (Fig. 6,7). Moreover, the model explains why feature  
495 selectivity of these spines only shows a weak similarity despite their correlations (Jia et al.,  
496 2010)(Chen et al., 2011). When a synaptic cluster is carved by the heterosynaptic effect of common  
497 inhibitory inputs, not by excitatory-to-excitatory interactions, variability of feature selectivity within the  
498 cluster tends to be large, because inhibitory neurons typically have a wider feature selectivity than  
499 excitatory neurons (Ma et al., 2010)(Moore and Wehr, 2013). In addition, it should also be noted that,  
500 E-to-E heterosynaptic LTP is typically induced as a meta-plasticity in the timescale of minutes  
501 (Harvey and Svoboda, 2007), which itself is not sufficient to create a correlation-based synaptic  
502 cluster.

503 Secondly, the results in Figure 5 indicate that LTD at an excitatory synapse is cancelled out  
504 by coincident inhibitory inputs to the nearby dendrite. Thus, LTD by low frequency stimuli (Malenka  
505 and Bear, 2004) can be attenuated by coincident GABA uncaging around the stimulated spine. Note  
506 that this result would not contradict with GABA-driven heterosynaptic LTD observed in paired  
507 stimulation, because in that experiment, the excitatory spine was presumably overexcited for  
508 inducing LTD in the absence of GABA (Hayama et al., 2013). Indeed, coincident GABAergic inputs  
509 may induce heterosynaptic LTD if combined with presynaptic stimulation at a moderately high  
510 frequency that itself does not cause LTD (Blaise and Bronzino, 2003).

511           The third implication of the model is about binocular matching. Our model indicates that  
512 GABA-maturation plays a critical role in binocular matching, and proposes a candidate mechanism  
513 for disruption of binocular matching by precocious GABA maturation (Wang et al., 2013)(Fig. 7).  
514 However, the phenomenon can also be explained by Hebbian plasticity plus some kind of  
515 meta-plasticity. If binocular matching is purely induced by Hebbian plasticity not through  
516 heterosynaptic mechanism, selective orientation after the matching should depend solely on the  
517 initial selectivity for monocular inputs, assuming that selectivity of presynaptic neurons remains the  
518 same. Especially when the contralateral input is larger than the ipsilateral input, the resultant  
519 selectivity should approximately coincide with the original contralateral selectivity. On the other hand,  
520 if the proposed mechanism takes part in the development, the consequent selectivity should also be  
521 influenced by the mean selectivity of inhibitory input neurons. Thus, long-term imaging of monocular  
522 selectivity at binocular neurons in V1 would reveal whether a covariance-based rule is sufficient  
523 enough to explain the phenomena, or some other mechanisms including the proposed one also play  
524 a major role in the shift.

525

### 526 *Carrier of heterosynaptic interaction*

527 Heterosynaptic plasticity has been observed in various spatial and temporal scales, and arguably  
528 underlying molecular mechanisms are different for different spatiotemporal scales (Nishiyama and  
529 Yasuda, 2015). In the case of milliseconds-order interaction, single-atomic ions are strong  
530 candidates, because poly-atomic ions such as  $IP_3$  are too big to move rapidly from spine to spine  
531 (Santamaria et al., 2006). Suppose that changes in  $Ca^{2+}$  concentration at an un-stimulated spine are  
532 crucial for heterosynaptic plasticity,  $Ca^{2+}$  influx/outflux from either intra or extracellular sources are  
533 necessary for induction of heterosynaptic plasticity. Because inhibitory synaptic inputs often change



534 the local  $\text{Ca}^{2+}$  concentration in the dendritic branch (Müllner et al., 2015), intracellular spreading of  
535  $\text{Ca}^{2+}$  may be a major source for  $\text{Ca}^{2+}$  changes in nearby un-stimulated spines. At the same time,  
536 because inhibitory inputs significantly modulate the membrane voltage of local dendrite (Gidon and  
537 Segev, 2012), a synaptic input should strongly drive  $\text{Ca}^{2+}$  influx/outflux through NMDA and VDCC  
538 from extracellular sources even at nearby un-stimulated spines. In addition, most of intracellular  
539 calcium-ions exist within calcium-buffer (Higley and Sabatini, 2012), and arguably they are also  
540 important for induction of synaptic plasticity. In our model, both current-based interaction (*Spine*  
541 *model*) and calcium-based interaction (*Reduced model*) replicate the experimental results (Fig. 2 and  
542 4, respectively). Nevertheless, our analytical study suggest that the heterosynaptic  $\text{Ca}^{2+}$  change  
543 typically needs to be comparable with the homosynaptic change in order to cause significant  
544 heterosynaptic plasticity through calcium-based interaction (Fig. 4C, D). Thus, our study implies  
545 possible importance of current-based interaction and spine specific influx/outflux of extracellular  $\text{Ca}^{2+}$   
546 for heterosynaptic plasticity.

547 Note that heterosynaptic interaction does not need to work in milliseconds order to interfere  
548 with STDP. For instance, E-to-E heterosynaptic LTD can be initiated by spreading of LTD-related  
549 molecules, not by messengers of neural activity (Hayama et al., 2013). In addition, for a shift in STDP  
550 time window, changes in the ratio between calcium influx through NMDA and the influx through  
551 VDCC possibly play a crucial role (Paille et al., 2013).

552

### 553 *Inhibitory cell types*

554 Somatostatin positive ( $\text{SOM}^+$ ) inhibitory neurons are typically projected to the apical dendrite, their  
555 IPSP curves is shorter than the timescales of NMDA or  $\text{Ca}^{2+}$  dynamics (Markram et al., 2004), and  
556 they often show strong feature selectivity compared to other inhibitory neuron types (Ma et al., 2010).

557 Thus, this inhibitory cell type is the likely candidate for heterosynaptic STDP. However, our results do  
558 not exclude parvalbumin positive (PV<sup>+</sup>) inhibitory neurons, which usually have projections to proximal  
559 dendrites, and also are typically fast spiking (Markram et al., 2004). In particular, h-STDP through  
560 PV<sup>+</sup> cell may play important roles in critical period plasticity (Takesian and Hensch, 2013).

561

#### 562 *Related theoretical studies*

563 Previous biophysical simulation studies revealed that synaptic plasticity at excitatory synapse  
564 critically depends on inhibitory inputs at nearby dendrite (Cutsuridis, 2011)(Bar-Ilan et al.,  
565 2013)(Jedlicka et al., 2015), but these studies did not reveal much of the functional roles of the  
566 heterosynaptic plasticity. On the other hands, network modeling studies found that heterosynaptic  
567 plasticity provides a homeostatic mechanism (Chen et al., 2013)(Zenke et al., 2015), but in these  
568 models, heterosynaptic plasticity was modeled as a global homeostatic plasticity without any branch  
569 specificity, and the advantage over other homeostatic mechanisms was unclear. In this study, by  
570 considering intermediate abstraction with analytical but biologically plausible models, we proposed  
571 candidate mechanisms for experimental results that have not been modeled before, and revealed  
572 potential functions of h-STDP in neural circuit formation.

573

574

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690

## 691 **Legends**

692 **Figure 1:** Schematic figure of the model of heterosynaptic spike-timing-dependent plasticity  
693 (h-STDP).

694 **A)** A schematic figure of the model. Two variables in the spine  $u(t)$  and  $c(t)$  represent the normalized

695 membrane potential and  $\text{Ca}^{2+}$  concentration respectively. Presynaptic action potentials modulate the  
696 membrane potential  $u(t)$  through AMPA ( $x^A$ ) and NMDA ( $g_N(u)x^N$ ) receptors. In addition,  $u(t)$  is  
697 modified by back-propagation ( $x^{BP}$ ), and heterosynaptic current caused by excitatory ( $x^E$ ) and  
698 inhibitory ( $x^I$ ) inputs. Calcium level  $c(t)$  is modulated by influx/outflux through NMDA ( $g_N(u)x^N$ ) and  
699 VDCC ( $g_V(u)$ ). Consequently,  $c(t)$  is indirectly controlled by  $u(t)$  because both NMDA and VDCC are  
700 voltage-dependent. **B)** An example of dynamics of the membrane potential variable  $u(t)$  (top),  $\text{Ca}^{2+}$   
701 concentration  $c(t)$  (middle), and the intermediate variable  $y(t)$  that controls the synaptic weight  
702  $w(t)$ (bottom). Change in the  $\text{Ca}^{2+}$  level roughly follows the membrane potential dynamics, and the  
703 intermediate variable  $y(t)$  is positively (negatively) modulated when  $\text{Ca}^{2+}$  level is above LTP(LTD)  
704 thresholds represented by orange(cyan) dotted lines. Based on the intermediate variable  $y(t)$ ,  
705 synaptic weight  $w(t)$  is updated in a slow timescale (see Figure 5C for example).

706

707 **Figure 2:** The model reproduces spike-timing-dependent heterosynaptic effects.

708 **A)** Spike timing window with/without a di-synaptic GABAergic input. Lines are simulation data, and  
709 points are experimental data taken from (Paille et al., 2013). Vertical dotted lines represent the  
710 spike-timing differences at which Panel **B** was calculated. **B)** Dynamics of calcium concentration  $c(t)$   
711 (top) and the intermediate variable  $y(t)$  (bottom) at the stimulated spine. Gray areas in the bottom  
712 figures represent the regions satisfying  $y(t) < y_{th}/K_{rep}$ , in which the change in the intermediate is not  
713 reflected into synaptic weight, where  $K_{rep}$  represents the number of paired stimulation given in the  
714 simulation for Panel **A**. **C)** Synaptic weight change with/without GABAergic inputs right before  
715 pre/post stimulation. Data points were taken from (Hayama et al., 2013). The cyan point is a result  
716 from muscimol application, not GABA uncaging. **D)** Dynamics of  $c(t)$  and  $y(t)$  at the stimulated spine  
717 (blue lines) and a neighboring spine (green lines). Solid lines represent the dynamics under GABA



718 uncaging, and dotted lines are the controls. Note that in the left panel, fractions of blue lines are  
719 hidden under green lines, because postsynaptic and inhibitory heterosynaptic inputs cause the same  
720 dynamics in both stimulated and neighboring spines.

721

722 **Figure 3:** Parametric robustness of h-STDP model.

723 **A)** Mean squared fitting errors for the model of the striatum experiment at various values of model  
724 parameters. In each panel, all other parameters were fixed, and the white mark represents the value  
725 used in Figure 2. See *Methods* for the definitions of parameters. **B)** Comparison of parametric  
726 dependence of models fitted for the results from the striatum and CA1 experiments. Vertical dotted  
727 lines represent the value used in Figure 2. NMDA/AMPA ratio in the bottom panel was calculated as  
728  $\gamma_N \tau_N / \gamma_A \tau_A$  at various values of  $\gamma_N$ . Note that the fluctuation in blue lines was caused by  
729 double-threshold dynamics of the model, not by noise.

730

731 **Figure 4:** Phase transitions on STDP time window in an analytical model of h-STDP.

732 **A, B)** STDP windows at various strength of heterosynaptic inhibitory effect  $C_I$ . Panel **A** corresponds  
733 to the striatum experiment, and Panel **B** corresponds to the CA1 experiment. Top and bottom figures  
734 in Panel **B** represent the stimulated and a neighbor spine, respectively. Note that values in Panel **B**  
735 were calculated by  $\tilde{y} = \text{sgn}(y) \cdot [|y| - 15]_+$  to reflect the effect of thresholding. **C)** Phase diagram of  
736 STDP time window calculated for inhibitory effect  $C_I$  and LTP threshold  $\theta_p$ . Colors show the number  
737 of local minimum/maximum, and lines are typical STDP time windows at each phase. Parameters  
738 written on the right side (top) of the panel represent the critical values of  $\theta_p$  ( $C_I$ ). **D)** Phase diagram  
739 calculated for heterosynaptic excitatory effect parameter  $C_E$  and postsynaptic effect parameters  $C_{post}$   
740 at a fixed inhibitory effect ( $C_I=0.5$ ). See *Reduced model* in *Methods* for details.

741 **Figure 5:** Emergence of detailed dendritic excitatory/inhibitory balance by h-STDP.

742 **A)** A schematic figure of a dendritic hotspot model. The shaft synapse represents an inhibitory input.

743 Colors represent spike correlation between synaptic inputs. **B)** Examples of correlated spike inputs.

744 Each Raster plot was calculated from 50 simulation trials. **C)** Changes in synaptic weight  $w$  (top) and

745 the correlation between the dendritic membrane potential and hidden signals (bottom) under h-STDP.

746 The blue lines represent dynamics of synapses correlated with the inhibitory input. **D)** Synaptic

747 weight change at the excitatory synapses correlated with the inhibitory inputs (blue) and at other

748 synapses (gray), at various inhibitory delays. Error bars in Panels **C** and **D** represent standard

749 deviations over 50 simulation trials. **E)** Relative weight changes  $w_R$  calculated at various parameters.

750 We defined  $w_R$  by  $\langle w_i^E \rangle_{i \in \text{corr}} - \langle w_i^E \rangle_{i \in \text{un-corr}}$ , where "corr" represents a set of excitatory synapses

751 correlated with the inhibitory synapse, and "un-corr" stands for uncorrelated ones. Here, weights

752 were calculated by taking average over 10 simulations. **F)** Probability of LTP/LTD occurrence after a

753 presynaptic spike calculated from a simulation. Lines represent the mean LTP/LTD probabilities at

754 excitatory synapses correlated with the inhibitory input (blue lines) and other synapses (gray lines),

755 respectively. **G, H)** Results in single-spike simulations. E/I coincidence prevents LTD effect due to

756 pre-spike (**G**), without affecting LTP effect due to pre-post coincidence (**H**). In Panel **G**, inhibitory

757 spikes were provided at  $t=0$  in the black line,  $t=-100\text{ms}$  in the gray line, and the excitatory presynaptic

758 spike was given at  $t=0$  in both lines. Similarly, in Panel **H**, postsynaptic spikes were provided at  $t=-75$

759 (light-gray), 0 (black),  $+75\text{ms}$  (dark-gray), and the presynaptic spike was given at  $t=0$  in all lines.

760

761 **Figure 6:** Detailed dendritic excitatory/inhibitory balance in a two-layered single cell model.

762 **A)** A schematic illustration of the single cell model. The actual model has 100 dendritic branches

763 each receiving 10 excitatory inputs and 1 inhibitory input. As in Figure 5A, inhibitory inputs are

764 represented by shaft synapses. **B)** Examples of synaptic weight change at each branch. The color of  
765 the frames represents the selectivity of the inhibitory input to the branch. Each row represents a  
766 different simulation trial. **C)** Mean synaptic weight dynamics of synapses correlated to the local  
767 inhibitory inputs, and other synapses. **D)** The ratio of change detecting spikes before and after  
768 learning. The ratio was defined as the fraction of spikes occurs within 50 milliseconds from a change  
769 in stimuli to the total. In the x-axis, in addition to the mean excitatory input firing rates, the mean  
770 inhibitory input firing rates were also modulated from 50 Hz to 210Hz correspondingly to keep the E/I  
771 balance of the input. **E)** Raster plots of output spikes before (top) and after (middle) learning, and  
772 their firing rate dynamics (bottom), averaged over 100 trials each for 10 simulated neurons. Colors of  
773 spikes in the Raster plots represent results from different simulation trials. Black vertical lines  
774 represent the change points of excitatory inputs, and horizontal colored bars at the top of the bottom  
775 panel corresponds to the colors of presynaptic neurons active in each period. We introduced 10  
776 milliseconds delay between excitatory and inhibitory stimulus both during learning (panel **B** and **C**)  
777 and in the change detecting task (panel **D** and **E**). The averages in panel **C** and **D** were taken over 10  
778 simulation trials.

779

780 **Figure 7:** h-STDP can trigger binocular matching.

781 **A)** (left): Direction selectivity of input neurons. In the model, as depicted by black vertical lines,  
782 majorities of excitatory input neurons from the contralateral (ipsilateral) eye are selective for  
783 directions around  $\theta = -\pi/4$  ( $\theta = \pi/4$ ), while inputs from the inhibitory neurons are weakly selective  
784 for  $\theta = 0$ . (right): A schematic figure of model configuration. Each dendritic branch receives inputs  
785 from both ipsi- and contralateral driven excitatory neurons and also from inhibitory neurons. **B)** (top):  
786 Difference between mean excitatory direction selectivity and inhibitory direction selectivity in each

787 branch. (middle): Difference between mean ipsi-driven excitatory direction selectivity and mean  
788 contra-driven excitatory direction selectivity over all synapses on the neuron. (bottom): Direction  
789 selectivity index (DSI) calculated for contralateral inputs (purple), ipsilateral inputs (light-green;  
790 hidden under the purple line), and binocular inputs (black). See *Neuron model* in *Methods* for the  
791 details of evaluation methods. Red vertical lines represent the timing for introduction of inhibitory  
792 inputs. Throughout Figure 7, error bars are standard deviations over 10 simulation trials. **C**) Firing  
793 responses of the neuron for monocular inputs, right after the initiation of inhibitory inputs (left;  
794  $t=30\text{min}$ ), and after the learning (right;  $t=60\text{min}$ ). **D**) Examples of direction selectivity of three  
795 representative branches before (gray lines;  $t=0\text{min}$ ) and after (purple/light-green lines;  $t=60\text{min}$ ) the  
796 learning. Black lines represent the selectivity of the inhibitory input to the branch. **E**) Behavior in  
797 monocular deprivation model. In shadowed areas, to mimic monocular deprivation, contra-driven  
798 inputs were replaced with rate-fixed Poisson inputs. Ordinates are the same with Panel **B**. **F**)  
799 Synaptic weights development at different mean inhibitory selectivity. Ordinates are the same with  
800 Panel **B**, and values were calculated at  $t=60\text{min}$ . Purple and green vertical dotted lines are mean  
801 selectivity of contra- and ipsilateral excitatory inputs, respectively.

802

803

804

805 **Table 1. Definitions of variables**

$u_i(t)$	Membrane potential at spine $i$	Eq. 1
$c_i(t)$	Calcium concentration at spine $i$	Eq. 3
$y_i(t)$	Intermediate factor (interim synaptic weight)	Eq. 4
$w_i(t)$	Synaptic weight of spine $i$	Eq. 5
$g_N(u)$	Voltage dependence of NMDA receptor	$g_N(u_i) = \alpha_N u_i + \beta_N$
$g_V(u)$	Voltage dependence of VDCC	$g_V(u_i) = \alpha_V u_i$
$x_i^A(t)$	Inputs through AMPA receptor	Eq. 2 (Q=A)
$x_i^N(t)$	Inputs through NMDA receptor	Eq. 2 (Q=N)
$x_i^{BP}(t)$	Back propagation	Eq. 2 (Q=BP)
$x_i^E(t)$	Excitatory heterosynaptic inputs	Eq. 2 (Q=E)
$x_i^I(t)$	Inhibitory heterosynaptic inputs	Eq. 2 (Q=I)
$u_b^k(t)$	Membrane potential at dendritic branch $k$	$u_b^k(t) = \sum_{i=1}^{N_b^E} w_i^k u_i^k(t) / (w_o^E N_b^E)$
$u_{soma}(t)$	Membrane potential at the soma	$u_{soma}(t) = \sum_k g_b(u_b^k(t))$
$g_b(u)$	Dendritic nonlinearity function	$g_b(u) = \begin{cases} u & (\text{if } u > u_b^o) \\ u_b^o & (\text{otherwise}) \end{cases}$

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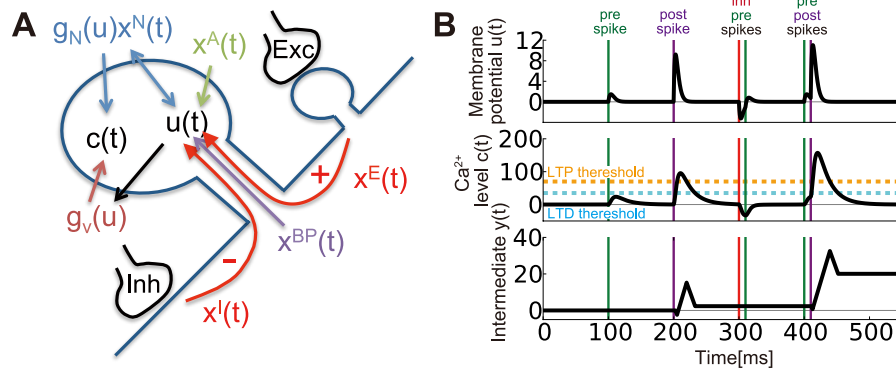


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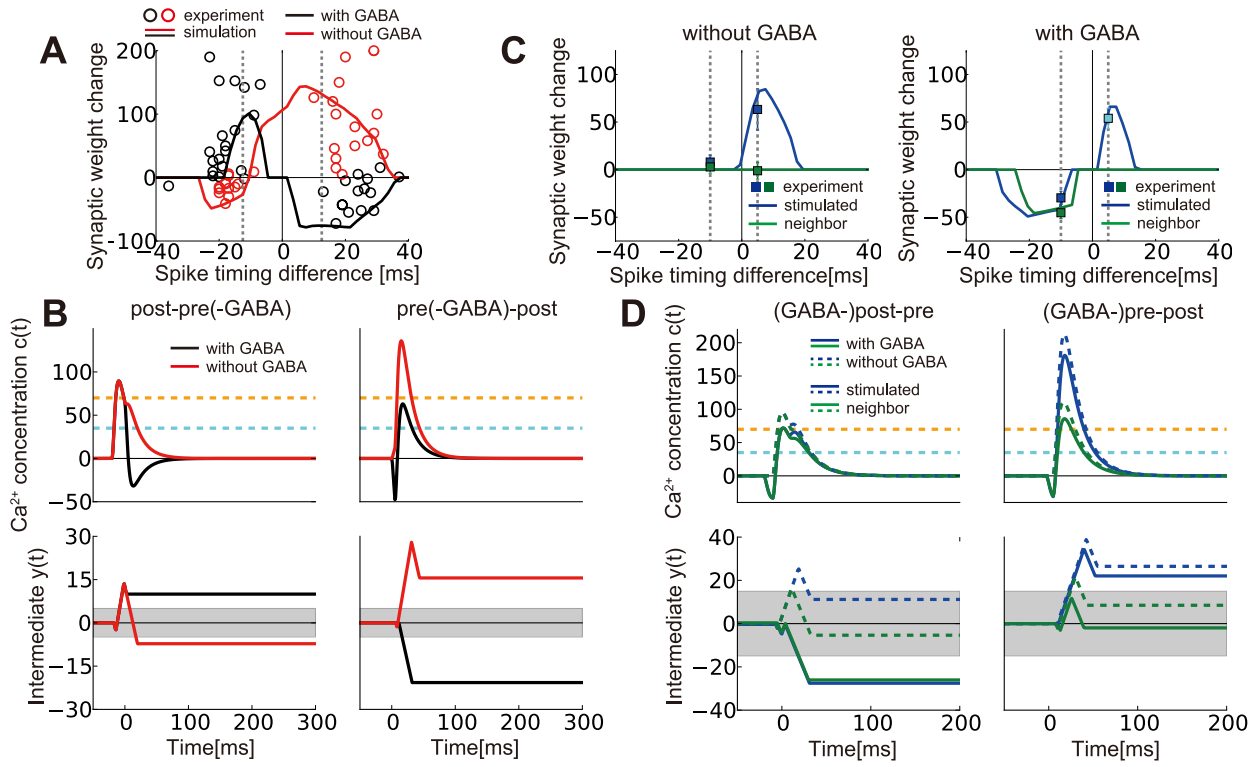


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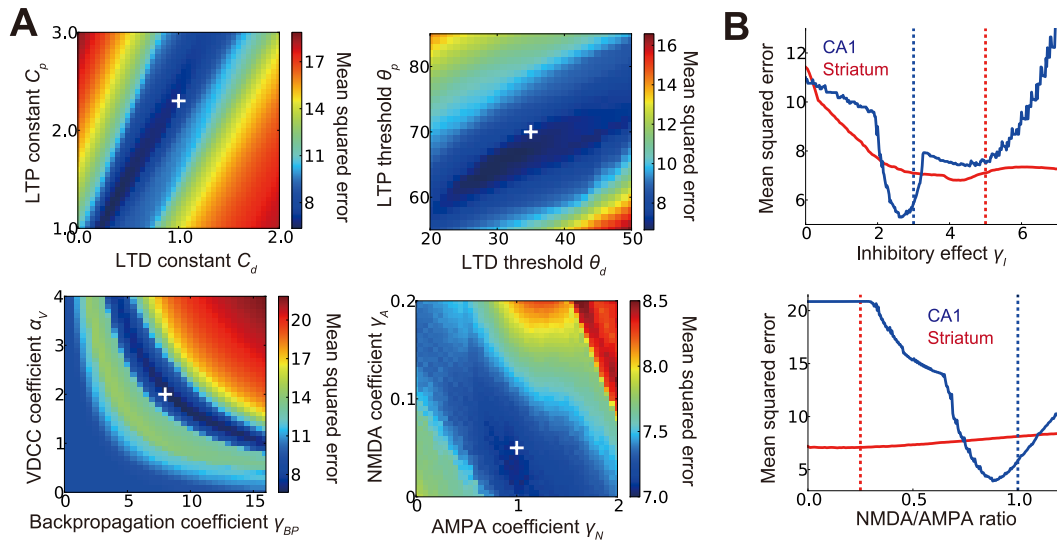


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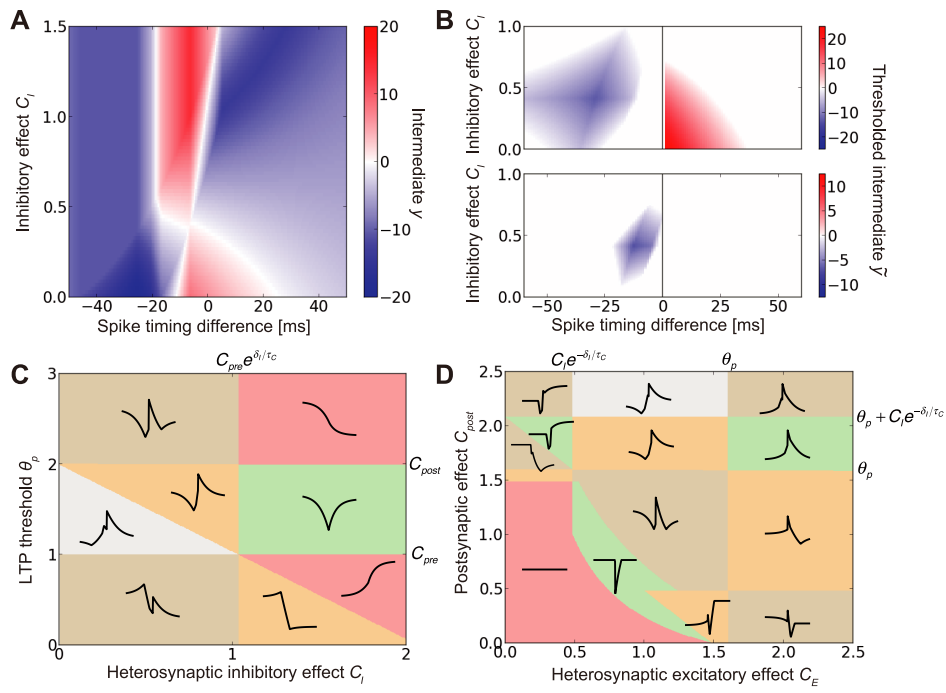


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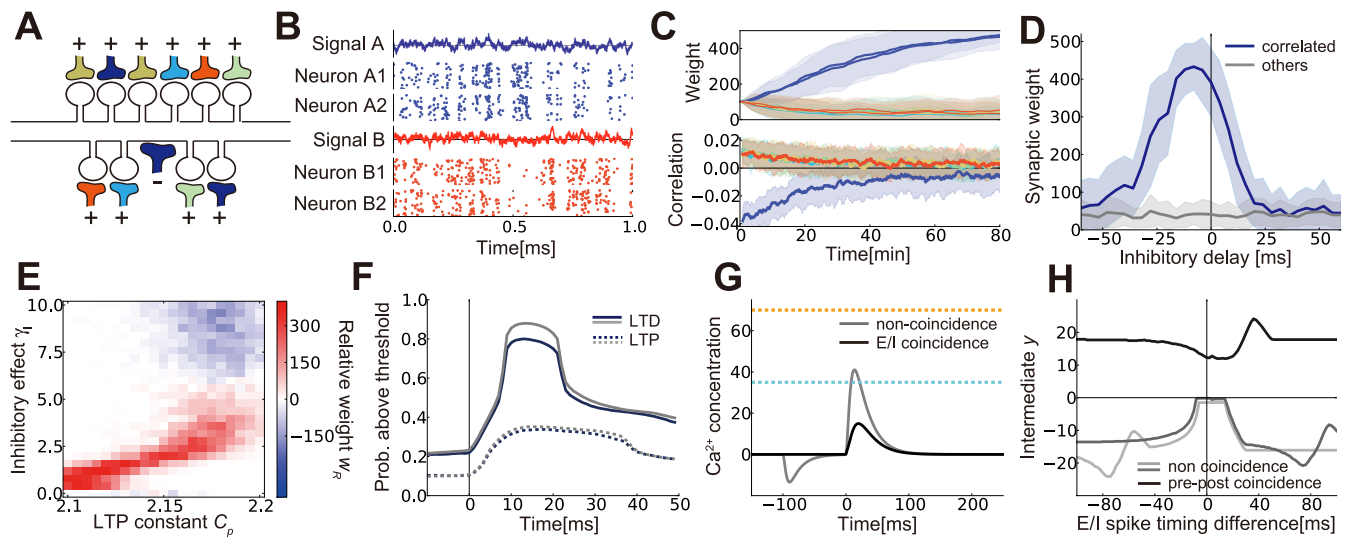


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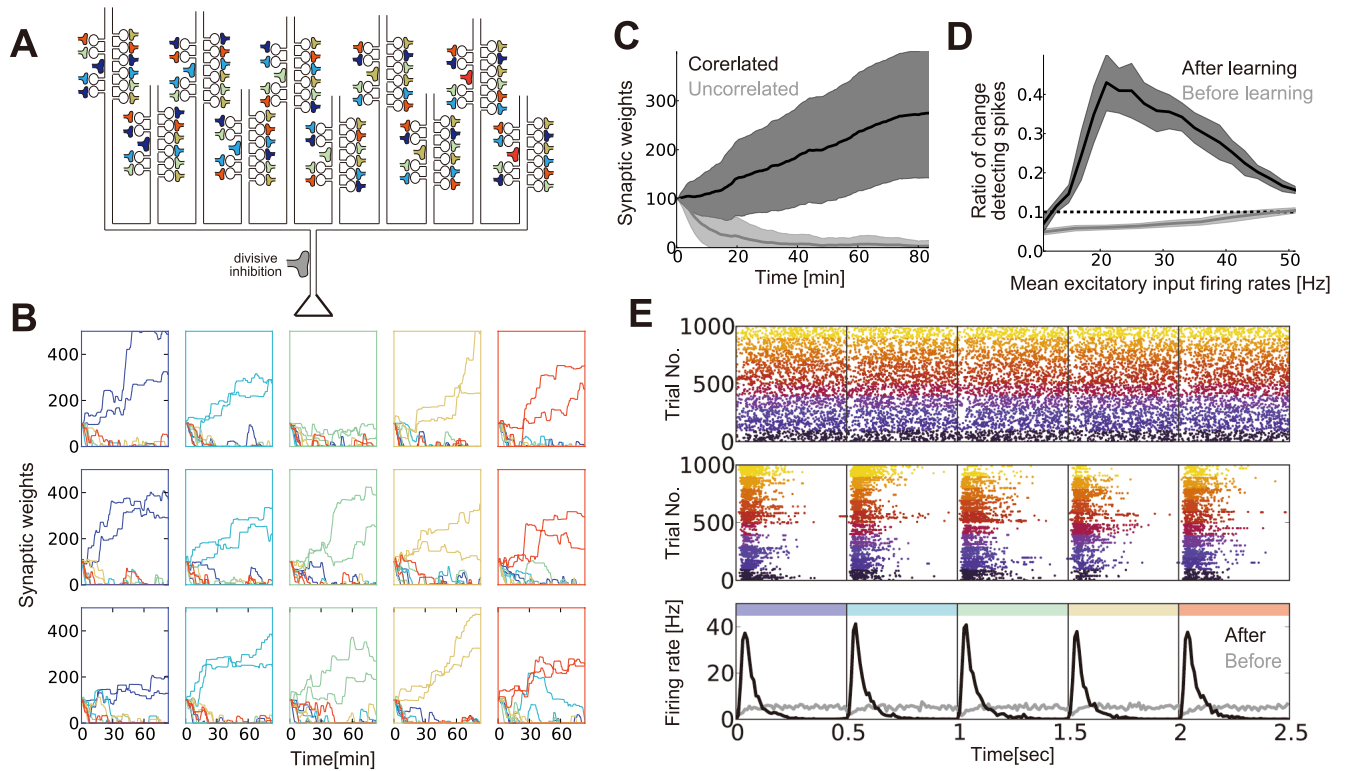


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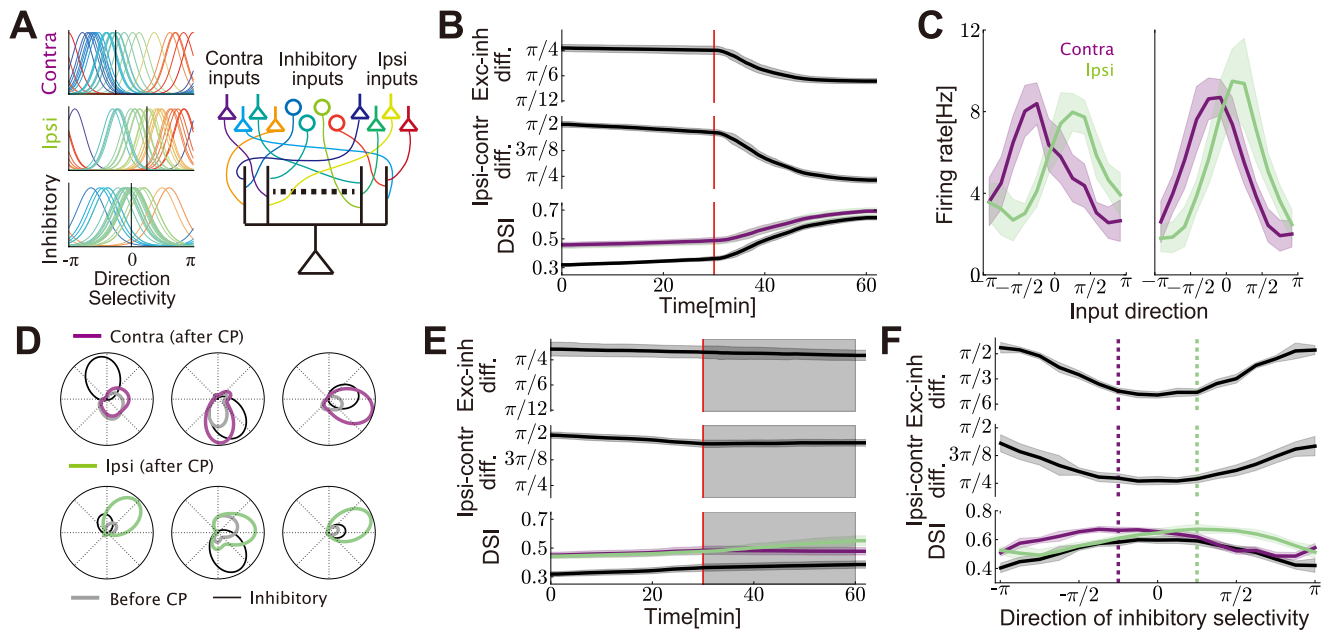


Figure 7: