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NEUROCOMPUTING

Neurocomputing 70 (2007) 2035–2040

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Modeling L-LTP based on changes in concentration of pCREB transcription factor

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Available online 15 November 2006

Abstract

We simulate the induction and maintenance of late long-term potentiation (L-LTP) in the hippocampal dentate gyrus by means of a new synaptic plasticity rule that is the result of combination of the spike-timing-dependent plasticity (STDP) and the moving LTD/LTP threshold θ_M from the Bienenstock, Cooper and Munro (BCM) theory of synaptic plasticity. We propose the activity-dependent functional equation for θ_M to be based on two processes: (1) fast process that depends on average postsynaptic spike count and (2) slow process that is a function of concentration of phosphorylated CREB (cAMP-responsive element binding) transcription factor, activation of which induces gene expression to maintain L-LTP. In the end, we propose a new, more general form of synaptic plasticity rule, which is applicable to any form of activity-dependent synaptic plasticity.

Keywords: L-LTP; STDP; BCM; pCREB

1. Introduction

Current understanding of the mechanisms of learning and memory storage in the brain implies a key role for changes in synaptic efficacy induced by coincident pre- and post-synaptic activity [7]. In many regions of the brain, long-term potentiation (LTP), a prolonged increase in synaptic efficacy of excitatory synapses, is produced by high-frequency stimulation (HFS) of pre-synaptic afferents [10,24]. LTP in the mouse can be either short (1−3 h), intermediate or long lasting (>24 h), depending on the HFS protocol administered to presynaptic inputs [21]. However, in all cases, the induction of LTP requires Ca^{2+} influx through the *N*-methyl-D-aspartate (NMDA) glutamate receptors. The short lasting or early form of LTP (E-LTP) requires the participation of a Ca^{2+}/calmodulin-depenendent protein kinase II (CaMKII). The long lasting or late form of LTP (L-LTP) requires the activation of the cyclic adenosine monophosphate (cAMP) signaling pathway, leading to gene transcription via CREB transcription factor [21]. CREB is the main transcription factor linking synaptic stimulation with gene expression [21]. CREB is activated by phosphorylation. Phosphorylated CREB (pCREB) induces specific immediate-response genes via cAMP-responsive element (CRE) in their promoter regions. Many immediate–early genes encode transcription factors that control expression of downstream or late-response genes, whose products are believed to bring about long-term plastic changes at stimulated synapses [15,25]. Sustained but not transient elevation of nuclear CREB phosphorylation is required for efficient stimulus–transcription coupling, for instance, by prolongation of synaptic input on the time scale of minutes [9]. Correlation between the duration of LTP and CREB phosphorylation was tested by quantifying changes in CREB phosphorylation throughout the induction and maintenance of L-LTP in freely moving rats [26]. L-LTP was evoked in hippocampal dentate gyrus and accompanying phosphorylation of CREB was measured by immunocytochemistry. Phosphorylation of CREB occurred in a biphasic manner, with a first short-lasting peak at 30 min, almost a zero minimum at 1 h, and a second long-lasting peak beginning 2 h after tetanic stimulation and lasting for at least 24 h (see Fig. 1). Biphasic course of [pCREB] elevation during

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0925-2312/$ - see front matter
doi:10.1016/j.neucom.2006.10.133

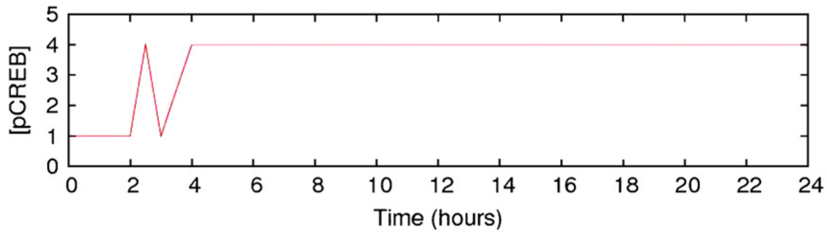

Fig. 1. Biphasic course of [pCREB(t)] with two four-fold peaks that accompanies the induction and maintenance of L-LTP in the hippocampal dentate gyrus as measured in [26].

L-LTP is in accordance with the discovery that different protein kinases, all activated by calcium, phosphorylate CREB with different temporal courses [28]. In [26], only HFS that generated nondecremental L-LTP promoted a sustained phosphorylation of CREB but not stimulation that produced decremental (early) E-LTP. For E-LTP, however, there is no quantitative analysis of the time course of CREB phosphorylation presented in [26]; therefore, we investigate only L-LTP.

We simulate the development of L-LTP in the hippocampal dentate gyrus by means of a new synaptic plasticity rule that is the result of combination of the STDP and the moving LTD/LTP threshold from the BCM theory of synaptic plasticity [8]. In STDP, the sign and degree of synaptic change depend on the relative timing of pre- and post-synaptic spikes [7]. For the moving LTD/LTP threshold, we propose its activity-dependent equation to be comprised of two temporal processes: a fast activity-integration relation that depends on average post-synaptic spike count and a slow-temporal relation that is related to the changes in concentration of pCREB transcription factor as they were measured in the real experiment [26]. In discussion, we propose a more general rule of synaptic plasticity.

2. Methods

In order to reproduce experimental data from Schulz et al. [26], we construct a simple spiking model of a hippocampal dentate granule cell, in which we consider only the excitatory inputs from ipsilateral and contralateral entorhinal cortex (EC). Thus, a model cell has three excitatory inputs, two of them representing ipsilateral medial and ipsilateral lateral perforant paths, mpp and lpp, respectively, and the third excitatory input representing the input from the contralateral EC (cEC) [3]. Mpp and lpp are two separate input pathways coming from the ipsilateral EC and terminating on separate, but adjacent distal dendritic zones of the hippocampal dentate granule cells [22]. They, together form an ipsilateral perforant pathway input (pp). Input from cEC terminates on the proximal part of the granule cell dendritic tree [3]. As a neuron model, we employ the simple model of spiking neuron introduced by Izhikevich [16], with the parameters values corresponding to a regularly spiking cell. Let the dimensionless variable v represent the membrane potential of the neuron and u represent a membrane recovery variable, which accounts for the activation of K^+ ionic currents and inactivation of Na^+ ionic currents and thus, provides a negative feedback to v. The dynamics of these two variables is described by the following set of ordinary differential equations:

$$\dot{v} = 0.04v^2 + 5v + 140 - u + I, \tag{1}$$

$$\dot{u} = a(bv - u). \tag{2}$$

Synaptic inputs are delivered via the variable I. After the spike reaches its apex ($\mathrm{AP} = 55\,\mathrm{mV}$), the membrane voltage and the recovery variable are reset according to the equation:

$$\text{if } v \geqslant \mathrm{AP}, \quad \text{then} \begin{cases} v \leftarrow c, \\ u \leftarrow u + d. \end{cases} \tag{3}$$

Parameter values correspond to a regularly spiking cell, i.e. $a = 0.02$, $b = 0.2$, $c = -69\,\mathrm{mV}$, $d = 2$ and the firing threshold is equal to $24\,\mathrm{mV}$ [23]. The model is simulated with the time step of 1 ms, since it does not cause stability problems. We assume the spike width being equal to 1 ms. Total synaptic input corresponding to variable I reads

$$I = hw_{\mathrm{mpp}}\,\mathrm{Im}_{\mathrm{pp}} + hw_{\mathrm{lpp}} I_{\mathrm{lpp}} + hw_{\mathrm{cEC}} I_{\mathrm{cEC}}, \tag{4}$$

where $h = 1$ or 0 when a presynaptic spike is present or absent at a given input, respectively, w_{mpp} (w_{lpp}, w_{cEC}) is the weight of the mpp (lpp, cEC) input, and I_{mpp} (I_{lpp}, I_{cEC}) is the intensity of electric stimulus delivered to mpp (lpp, cEC), respectively. Intensity of electric stimulus is understood as the number of input fibers that are engaged within a stimulated pathway and thus, is dimensionless. Intensities of stimulation were equal for all pathways, i.e. $I_{\mathrm{mpp}} = I_{\mathrm{lpp}} = I_{\mathrm{cEC}} = 100$. Initial values of all synaptic weights were chosen to be equal to 0.5 so, when at least two out of the three input pathways were stimulated simultaneously or in a close temporal succession, a post-synaptic spike followed.

Our model granule cell was subject to realistically simulated spontaneous input activity. Spontaneous input spiking activity had two components: uncorrelated-random activity with frequency <1 Hz generated randomly (Poisson spike train) with superimposed correlated-spontaneous spikes from EC (ipsilateral and contralateral) with an average frequency of 8 Hz to simulate the theta rhythm modulation [13]. Spontaneous input activity has lead to a post-synaptic spontaneous spiking activity of the model granule cells of $\sim$1 Hz [19]. This type of spontaneous input occurred before and after HFS. During the trains of HFS at pp, there was an ongoing 8 Hz spontaneous input activity of cEC input only. Between the HFS trains, all inputs received uncorrelated spikes, generated with an average frequency of 8 Hz. All types of input–output spiking activity, be it spontaneous or evoked by pp HFS, were accompanied by the STDP as described below.

Each excitatory synaptic weight modifies according to the additive nearest neighbor STDP rule using the standard exponential relationships as in [17]

$$\Delta w_+ = A_+ \exp(-\Delta t/\tau_+) \quad \text{for } \Delta t > 0,$$
$$\Delta w_- = A_- \exp(-\Delta t/\tau_-) \quad \text{for } \Delta t < 0, \tag{5}$$

where $\Delta t = t_{\text{post}} - t_{\text{pre}}$ is the time difference between the post- and pre-synaptic spikes, τ_+ and τ_- are modification windows for synaptic potentiation and depression, respectively. Synaptic change is comprised of contributions from only two nearest spikes, i.e., for each pre-synaptic spike, only two post-synaptic spikes are considered: the one that occurs right before and the one that occurs right after the given pre-synaptic spike, respectively, i.e.,

$$w(t + \delta t) = w(t)(1 + \Delta w_+ - \Delta w_-), \tag{6}$$

where $\delta t = 1$ ms is the time step of weight updating. To merge the BCM theory with the STDP rule in [4], we proposed that the amplitudes of positive and negative synaptic changes, A_+ and A_-, respectively, are not constant anymore, but instead they depend on the dynamic LTD/LTP threshold θ_M in the following way:

$$A_+(t) = \frac{A_+(0)}{\theta_M(t)} \quad \text{and} \quad A_-(t) = A_-(0)\theta_M(t). \tag{7}$$

Constants $A_+(0)$ and $A_-(0)$ are initial amplitude values for synaptic potentiation and depression, respectively. This relationship is motivated by the function of the LTD/LTP threshold θ_M to determine the easiness of LTP induction. θ_M is not fixed, but instead, is a function of post-synaptic activity [8]. In such a way, the easiness of LTP induction depends on the previous activity of a neuron. In this paper, we propose a new rule for moving LTD/LTP threshold that now reads

$$\theta_M = \alpha F1(t)F2(t), \tag{8}$$

where α is the scaling constant. $F1(t)$ reflects some fast-activity integration process, which depends on the average post-synaptic spike count that can be calculated as in Ref. [6] by numeric integration of the following integral:

$$F1(t) = \frac{1}{\tau_M}\int_{-\infty}^{t} c(t')\exp(-(t-t')/\tau_M)\,dt' \tag{9}$$

with $c(t) = 1$ or 0 if the post-synaptic spike is present or absent at time t, respectively. Integration period τ_M is on the order of tens of seconds to minutes [6].

$F2(t)$ depends on the slowly changing level of [pCREB]. Since the value of LTD/LTP threshold determines the easiness of LTP induction, function $F2(t)$ will be the inverse of the pCREB formation curve, i.e.

$$F2(t) = \frac{1}{[\text{pCREB}(t)]}, \tag{10}$$

where [pCREB(t)] is the concentration of pCREB in the post-synaptic neuron. For $F2$(t), we used the concentration values and temporal course measured in Ref. [26] and depicted in Fig. 1.

3. Results

With this model, we simulated the experiments of Schultz et al. [26], in which, to induce L-LTP in dentate gyrus, HFS was delivered to the perforant pathway (pp), which is the mixture of lpp and mpp fibers. L-LTP was induced by stimulating pp with 20 trains of pulses. Each train consisted of 15 pulses with the frequency 200 Hz. The distance between trains was 5 s. In addition, at 5 (8, 15) min, and 1 (2, 6, 24) h post-HFS, the rats were tested. Test stimulation consisted of eight impulses at frequency of 0.2 Hz. This testing stimulation was also simulated in the model. Values of model parameters were: $A_+(0) = 0.02$, $A_-(0) = 0.01$, $\tau_+ = 20$ ms, $\tau_- = 100$ ms, $\tau_M = 30$ s and scaling constant $\alpha = 3000$. These values were tuned to fit the experimental data [26]. Magnitude and duration of fEPSP change (i.e. 24 h) in our computer simulation of L-LTP match the experimental data of Schulz et al. [26] (see Fig. 2). In the model, change in the field EPSP (fEPSP) in response to test stimulation of pp, that is the mixture of mpp and lpp, was calculated as a linear sum of mpp and lpp weight changes in percents, i.e., $\Delta\text{fEPSP}_{\text{pp}}\% = \Delta w_{\text{mpp}}\% + \Delta w_{\text{lpp}}\%$, and the change in the fEPSP evoked by simulated stimulation of the contralateral pathway cEC, $\Delta\text{fEPSP}_{\text{cEC}}\% = \Delta w_{\text{cEC}}\%$. In all graphs presented in this section, each point is an average of six runs. Similarly, like in the experimental study, 3–6 animals were analyzed for each time point and treatment condition [26].

To demonstrate the need for the link of STDP with the long-term function, we show the results of simulation of the model in which synapses modify according to the classical STDP rules. To simulate the plain STDP, we employed Eqs. (5) and (6) with a synaptic decay term, i.e., $w(t+1) = w(t)(1+\Delta w_+(t) - \Delta w_-(t)) - \lambda \text{w}(t)$ or $+\lambda w(t)$,

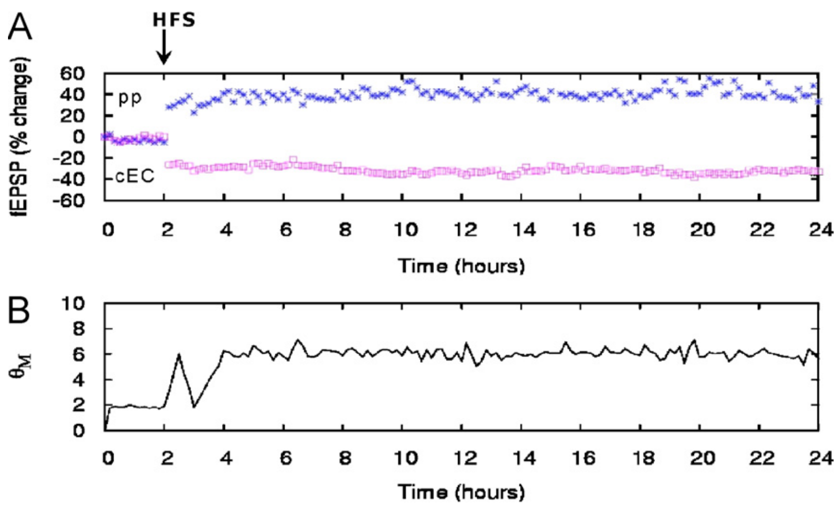

Fig. 2. (A) Temporal evolution of the fEPSP change in our computer simulation of L-LTP. Nondecremental L-LTP continues to last for 24 h of simulation. An arrow indicates the beginning of pp HFS (20 trains). (B) Evolution of the modification threshold θ_{M}.

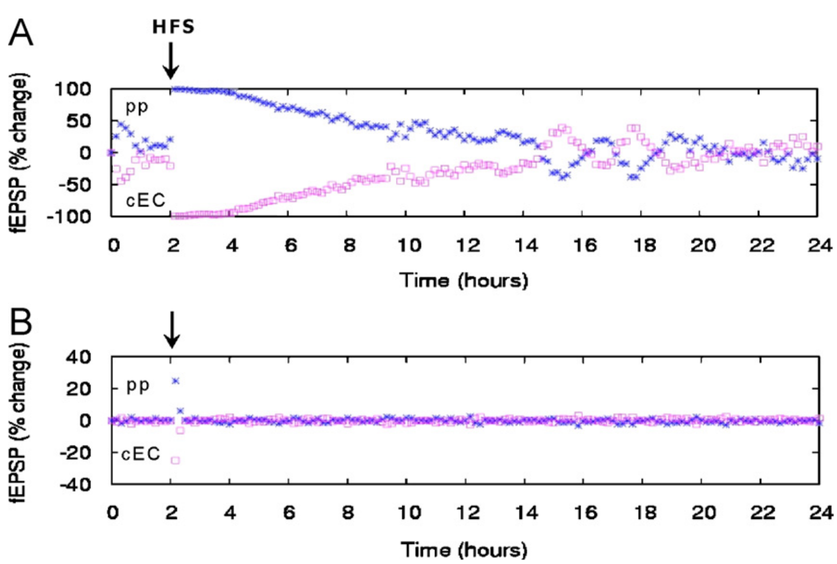

Fig. 3. (A) Temporal evolution of the fEPSP change with the classical additive STDP. (B) Temporal evolution of the fEPSP change with the multiplicative STDP.

depending on whether the weight increased in value or decreased, respectively, with $\lambda = 0.05$. The amplitudes A_+ and A_- were constant and equal to $A_+(0)$ and $A_-(0)$, respectively. The second STDP implementation was the multiplicative STDP rule of the form used in Ref. [12], i.e., $A_+(t) = \eta(1.0 - w(t))$ and $A_-(t) = \eta w(t)$, with $\eta = 0.05$ and no synaptic decay term. Thus, these two STDP implementations correspond to the case of $\mu = 0$ and 1, respectively, according to Gütig et al. [14]. Both plain STDP rules were accompanied by weight renormalization. All other parameters, like temporal windows for potentiation and depression, had the same values for all STDP implementations and all STDP were nearest-neighbor implementations. Other parameter values did not yield results even close to the target results for both plain STDP rules.

Results of simulation of both rules are shown in Fig. 3. As we can see, neither of these classical rules can faithfully reproduce the data on L-LTP, which points to the necessity to consider some long-term function in the synaptic plasticity rule. Another result that came out of the simulations of our and additive STDP rules is the heterosynaptic long-term depression (LTD) of the nontetanized contralateral pathway, cEC that accompanies the homosynaptic LTP. This outcome of the model is in accordance with experimental data of Levy and Steward [20], in which the HFS of ipsilateral pp depressed the contralateral pathway when the latter was not receiving a concurrent HFS.

4. Discussion

Computational model of synaptic plasticity introduced in this paper, is an abstract phenomenological model, which is computationally effective and does not have many parameters to fit unlike the more detailed biophysical models of synaptic plasticity [1,27,29]. Therefore, it may be more suitable when modeling plasticity phenomena in large networks of spiking neurons.

The key to the successful simulation of L-LTP is the combination of STDP with the BCM moving LTD/LTP threshold, which depends on the post-synaptic spike count over the recent past and on temporal evolution of phosphorylation of CREB, which is the major transcription factor linking synaptic stimulation with gene expression known today. In our computational model, we incorporated temporal changes in the levels of pCREB to the dynamics of the BCM synaptic modification LTD/LTP threshold that determines the magnitude of synaptic potentiation and depression in STDP, which is our novel and original contribution. A fast activity-integration relation F1 in the equation for θ_{M} that depends on average post-synaptic spike count provides for the stability and fast changes in weights. Renormalization of weights is not necessary. A slow temporal relation F2 that is related to the changes in concentration of pCREB transcription factor provides for the long duration of synaptic changes. This leads us to a more general formulation of the proposed synaptic plasticity rule. In this respect, we want to recall the earlier proposal of Cooper [11], in which he proposed that the BCM synaptic modification function depends not only on the previous activity of a neuron but also on the so-called enabling factors or global variables, like the levels of neuromodulators. Thus, let the dynamic synaptic modification threshold be expressed as

$$\theta_{\mathrm{M}} = \alpha F1(t)F2(X, Y, Z, \ldots, t), \tag{11}$$

where X, Y, Z are global variables that are related to the so-called metaplasticity [2]. These global variables represent overall number and composition of NMDA receptors, levels of neuromodulators like acetylcholine, noradrenalin, etc., levels of second messengers, level of pCREB and other genetic factors that influence the easiness of LTD/LTP induction and maintenance. All these factors can influence the width of modification windows in the STDP rule with different time courses. Those factors that are constant at least during the time of the measurement can affect the value of the scaling constant α and those that change in time can be considered for the composite function of $F2$.

Thus, our model can also be considered to be the first step in the computational neurogenetic modeling (CNGM) of learning and memory, since it takes into account the role of pCREB in synaptic plasticity and shows the direction how to integrate genetic factors in the learning rule. The CNGM approach can go beyond the study of relationship between a single gene or transcription factor and a single neuronal function to model the interactions between several and many genes in the neuron and their implications on the functioning of neural ensembles in the brain [5,18]. We believe these integrated genetic and neuronal information processing models will be an important part of the theoretical and computational neuroscience of the future.

Acknowledgments

Supported by the NERF project AUTX0201 and by KEDRI AUT, Auckland, New Zealand (www.kedri.info).

References

[1] H.D.I. Abarbanel, R. Huerta, M.I. Rabinovich, Dynamical model of long-term synaptic plasticity, Proc. Natl. Acad. Sci. USA 99 (2002) 10132–10137.
[2] W.C. Abraham, M.F. Bear, Metaplasticity: the plasticity of synaptic plasticity., Trends Neurosci. 19 (1996) 126–130.
[3] D.G. Amaral, M.P. Witter, The three-dimensional organization of the hippocampal formation: a review of anatomical data, Neuroscience 31 (1989) 571–591.
[4] L. Benuskova, W. C. Abraham, STDP rule endowed with the BCM sliding threshold accounts for hippocampal heterosynaptic plasticity, J. Comp. Neurosci. (2006), doi:10.1007/s10827-006-0002-x.
[5] L. Benuskova, V. Jain, S.G. Wysoski, N. Kasabov, Computational neurogenetic modelling: a pathway to new discoveries in genetic neuroscience, Int. J. Neural Systems 16 (2006) 215–227.
[6] L. Benuskova, V. Rema, M. Armstrong-James, F.F. Ebner, Theory for normal and impaired experience-dependent plasticity in neocortex of adult rats, Proc. Natl. Acad. Sci. USA 98 (2001) 2797–2802.
[7] G.-Q. Bi, M.-M. Poo, Synaptic modification by correlated activity: Hebb's postulate revisited, Annu. Rev. Neurosci. 24 (2001) 139–166.
[8] E.L. Bienenstock, L.N. Cooper, P.W. Munro, Theory for the development of neuron selectivity: orientation specificity and binocular interaction in visual cortex, J. Neurosci. 2 (1982) 32–48.
[9] H. Bito, K. Deisseroth, R.W. Tsien, Ca^{2+}-dependent regulation in neuronal gene expression, Curr. Opin. Neurobiol. 7 (1997) 419–429.
[10] T.V. Bliss, T. Lomo, Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of perforant path, J. Physiol. 232 (1973) 331–356.
[11] L.N. Cooper, Cortical plasticity: theoretical analysis, experimental results, in: J.P. Rauschecker, P. Marler (Eds.), Imprinting and Cortical Plasticity, Wiley, New York, 1987, pp. 117–191.
[12] A. Delorme, L. Perrinet, S.J. Thorpe, Network of integrate-and-fire neurons using rank order coding B: spike timing dependent plasticity and emergence of orientation selectivity, Neurocomputing 38 (2001) 539–545.
[13] L.M. Frank, E.N. Brown, M.A. Wilson, A comparison of the firing properties of putative excitatory and inhibitory neurons from CA1 and the entorhinal cortex, J. Neurophysiol. 86 (2001) 2029–2049.
[14] R. Gütig, R. Aharonov, S. Rotter, H. Sompolinsky, Learning input correlations through nonlinear temporally asymmetric Hebbian plasticity, J. Neurosci. 23 (2003) 3697–3714.
[15] S.J. Hong, H. Li, K.G. Becker, V.L. Dawson, T.M. Dawson, Identification and analysis of plasticity-induced late-response genes, Proc. Natl. Acad. Sci. USA 101 (2004) 2145–2150.
[16] E.M. Izhikevich, Simple model of spiking neurons, IEEE Trans. Neural Networks 14 (2003) 1569–1572.
[17] E.M. Izhikevich, N.S. Desai, Relating STDP to BCM, Neural Comput. 15 (2003) 1511–1523.
[18] N. Kasabov, L. Benuskova, Computational neurogenetics, J. Comput. Theor. Nanosci. 1 (2004) 47–61.

[19] A. Kimura, C. Pavlides, Long-term potentiation/depotentiation are accompanied by complex changes in spontaneous unit activity in the hippocampus, J. Neurophysiol. 84 (2000) 1894–1906.
[20] W.B. Levy, O. Steward, Temporal contiguity requirements for long-term associative potentiation/depression in the hippocampus, Neuroscience 8 (1983) 791–797.
[21] M. Mayford, E.R. Kandel, Genetic approaches to memory storage, Trends Genet. 15 (1999) 463–470.
[22] B.L. McNaughton, C.A. Barnes, P. Andersen, Synaptic efficacy and EPSP summation in granule cells of rat fascia dentata, J. Neurophysiol. 46 (1981) 952–966.
[23] B.L. McNaughton, C.A. Barnes, P. Andersen, Synaptic efficacy and EPSP summation in granule cells of rat fascia dentata studied in vitro, J. Neurophysiol. 46 (1981) 952–966.
[24] D. Muller, I. Nikonenko, P. Jourdain, S. Alberi, LTP, memory and structural plasticity, Curr. Mol. Med. 2 (2000) 605–611.
[25] E. Nedivi, D. Hevroni, D. Naot, D. Israelei, Y. Citri, Numerous candidate plasticity-related genes revealed by differential cDNA cloning, Nature 363 (1993) 718–722.
[26] S. Schulz, H. Siemer, M. Krug, V. Hollt, Direct evidence for biphasic cAMP responsive element-binding protein phosporylation during long-term potentiation in the rat dentate gyrus in vivo, J. Neurosci. 19 (1999) 5683–5692.
[27] H.Z. Shouval, M.F. Bear, L.N. Cooper, A unified model of NMDA receptor-dependent bidirectional synaptic plasticity, Proc. Natl. Acad. Sci. USA 99 (2002) 10831–10836.
[28] G.-Y. Wu, K. Deisseroth, R.W. Tsien, Activity-dependent CREB phosphorylation: convergence of a fast, sensitive calmodulin kinase pathway and a slow, less sensitive mitogen-activated protein kinase activity, Proc. Natl. Acad. Sci. USA 98 (2001) 2808–2813.
[29] L.-C. Yeung, H.Z. Shouval, B.S. Blais, L.N. Cooper, Synaptic homeostasis and input selectivity follow from a calcium-dependent plasticity model, Proc. Natl. Acad. Sci. USA 101 (2004) 14943–14948.

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