Neurocomputing 175 (2016) 300–309

Contents lists available at ScienceDirect

Neurocomputing

journal homepage: www.elsevier.com/locate/neucom

Computational simulation of dentate gyrus granule cell—The role of metaplasticity

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ARTICLE INFO

Article history:
Received 10 October 2014
Received in revised form
6 October 2015
Accepted 19 October 2015
Communicated by J. Torres
Available online 30 October 2015

Keywords:
Synaptic plasticity
Metaplasticity
STDP
BCM

ABSTRACT

After several decades of study, the dynamics of synaptic plasticity in neurons still remains somewhat a mystery. By conducting a series of simulations on a simulated version of an *in-vivo* experiment on the rat dentate gyrus granule cell, using the Izhikevich spiking neuron model, we compare and contrast several potential synaptic plasticity rules' applicability to the same experiment. Our simulations reveal that spike timing dependent plasticity (STDP), a more recent theory of synaptic plasticity, is insufficient to replicate the heterosynaptic LTD shown in the experiment without including aspects of the significantly older Bienenstock–Cooper–Munro (BCM) theory. The STDP rule modified by including the history of postsynaptic spiking seems most likely to be an accurate candidate for reproducing the heterosynaptic plasticity dynamics.

1. Introduction

Current understanding of the mechanisms of learning and long-term memory storage in the brain implies a key role for changes in synaptic weights induced by coincident pre- and postsynaptic activity [2]. In many regions of the brain, long-term potentiation (LTP), a prolonged increase in the synaptic efficacy of excitatory synapses, is produced by high-frequency stimulation (HFS) of presynaptic axons [3]. LTP in the rat can be either short- (1–3 h), intermediate- or long-lasting (>24 h), depending on the HFS protocol administered to the presynaptic inputs [4]. On the other hand, low-frequency stimulation (LFS) can yield long-term depression of synaptic weights [5], but often yields no change [6], and recently even a LFS induced LTP has been documented [7]. In order to reconcile numerous counter-intuitive results of frequency-dependent synaptic plasticity, Bienenstock, Cooper and Munro (BCM) proposed an influential theory of synaptic plasticity to explain plasticity in the developing visual cortex [8], which was later shown to hold in the adult somatosensory cortex too [10]. The crucial notion in the BCM theory is the existence of a so-called sliding LTD/LTP threshold. The LTD/LTP threshold corresponds to a value of the frequency of presynaptic stimulation, below which the stimulation induces LTD and above which the stimulation induces LTP. In addition, the position of the LTD/LTP threshold is not fixed but instead moves (slides) in proportion to the average postsynaptic activity. When the neuron is more active on average, the LTD/LTP threshold slides to higher values and it is more difficult to get LTP and easier to get LTD. The opposite is true when the average postsynaptic activity is low. In the BCM models, neurons received not only the patterned stimulation but also the noise corresponding to an ongoing *spontaneous activity* in the neural circuits [30,10]. In fact, this noise was "responsible" for weakening synapses that did not receive the patterned activity [9]. Later, many experimental studies demonstrated that prior history of pre- and postsynaptic neural activity controls the subsequent induction of LTP and LTD. This phenomenon is known as *metaplasticity* [11]. Metaplasticity thus refers to the prior history of pre- and/or postsynaptic neural activity controlling the occurrence and magnitude of subsequent induction of synaptic plasticity.

In addition, there are numerous experimental studies showing that both LTP and LTD depend not only on the frequency of the presynaptic stimulation but also on the precise timing of pre- and postsynaptic spikes. This property is called spike-timing-dependent plasticity or STDP for short [13]. Presynaptic spikes that precede postsynaptic spikes within a certain time window produce LTP, whereas presynaptic spikes that follow postsynaptic spikes within a certain time window produce LTD of synapses. Experimentally observed positive and negative changes in synaptic weight w are best fitted with exponential relationships, i.e.

$$\Delta w_+ = A_+ \exp(-\Delta t/\tau_+) \quad \text{if } \Delta t > 0 \tag{1}$$

$$\Delta w_- = A_- \exp(-\Delta t/\tau_-) \quad \text{if } \Delta t < 0 \tag{2}$$

where $\Delta t = t_{post} - t_{pre}$ is the time difference between the post- and presynaptic spikes. Amplitudes A_+, A_- and decay time constants

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http://dx.doi.org/10.1016/j.neucom.2015.10.063
0925-2312/

τ_+, τ_- for synaptic potentiation and depression, respectively, are different for different species, brain areas, and other conditions of experiment. We will refer to Eqs. (1) and (2) as the STDP rule. The final synaptic change can be additive (i.e. positive and negative changes add over time) or multiplicative (i.e. positive and negative changes multiply over time). There are also different options as to how many and which pre- and postsynaptic spikes contribute to the final change [23].

One of the first attempts to connect the frequency- and timing-dependent synaptic plasticity in a single phenomenological model was made by Sjöström et al. [18]. Later, more variations of the STDP rule accounting for the frequency-dependent synaptic plasticity were proposed (see, e.g. [14]). One of such modifications of the original rule (Eqs. (1) and (2)) is the STDP rule with metaplasticity introduced by Benuskova and Abraham in 2007 [15]. The authors have brought STDP, frequency-dependent plasticity and metaplasticity into a unified theoretical framework and provided putative explanation of heterosynaptic plasticity phenomena in the hippocampal dentate gyrus of freely moving rats as reported in [16]. Heterosynaptic plasticity means that high-frequency stimulation (HFS) of one set of synapses leads to synaptic plasticity not only of the stimulated synapses but also in a neighbouring set of synapses that were not subject to HFS [16]. This heterosynaptic plasticity is still a puzzling matter. The reasoning behind their modification of the STDP rule was based on the paper of Izhikevich and Desai [17], in which the authors showed mathematically for uncorrelated and weakly correlated Poisson spike trains that the STDP, Eqs. (1) and (2), actually lead to the emergence of a fixed LTD/LTP frequency threshold, but only when we consider the nearest-neighbour spike interactions. To include the sliding property of the LTD/LTP threshold as a function of previous postsynaptic activity, Benuskova and Abraham suggested that amplitudes, A_+, A_-, of LTP and LTD, respectively, are not constant but instead depend metaplastically on the average postsynaptic spiking activity [15]. They used this new STDP with metaplasticity to explain the frequency-dependent homosynaptic LTP and heterosynaptic LTD demonstrated in the dentate gyrus of the hippocampus of live rats [16]. Thus, they assumed that STDP can underlie also the frequency-dependent synaptic plasticity. This assumption is corroborated by the experimental study of Lin et al. [19], who published experimental results on STDP in granule cells in hippocampal slices. Lin et al. used pairs of presynaptic stimuli and postsynaptic antidromic spikes delivered to granule cells in different orders (pre–post and post–pre) and with different delays to successfully induce STDP. Stimulated synapses exhibited STDP with two windows, one for LTP for the pre–post sequence and the other one for LTD for the post–pre sequence. In addition, Lin et al. [19] showed the interaction of STDP and frequency-dependent plasticity at one synaptic path, thus suggesting that they may actually share the same biological mechanisms.

In order to investigate the role of metaplasticity in explaining the heterosynaptic plasticity phenomenon, we have implemented and simulated the spiking model of the granule cell in the hippocampal dentate gyrus. We aim to reproduce the homosynaptic long-term potentiation of the tetanised input and heterosynaptic long-term depression of the untetanised input, as observed in real experiments after applying HFS to the MPP input [16] with a selection of STDP-inspired models of synaptic plasticity. We use the Benuskova & Abraham rule [15] as a baseline, to which the other rules are compared. The other rules we have implemented are the original, unmodified STDP rule (hereafter referred to as conventional STDP), the Froemke et al. suppression model [20], Pfister & Gerstner's triplet STDP model [21], and the Clopath et al. voltage-dependent model [22]. The latter model allows for metaplastic modification of the LTD amplitude only, and we will test Pfister & Gerstner's model alongside a modified version of itself allowing for metaplastic modification of both STDP amplitudes. Our results show that all of the STDP-like plasticity rules conformed closest to experiment feature at least some level of BCM-like metaplasticity.

2. Methods

2.1. Spiking neuron model

In this study, we simulated a spiking model of excitatory granule cells (GCs) in the dentate gyrus. The dentate gyrus is the input part of the hippocampus [25]. Granule cells in the dentate gyrus receive excitatory input from outside of the hippocampus via the lateral and medial perforant paths. The medial and lateral perforant paths (MPP and LPP respectively) are two separate inputs terminating on separate but adjacent dendritic zones of the hippocampal dentate granule cells. The MPP and LPP are the major excitatory inputs to the GC as their synapses occur at more than 80% of the GC dendritic tree [24]. In turn, granule cells project their axons to the pyramidal cells in the CA3 area of the hippocampus, thus relaying the spatial and associational information for further processing in hippocampal circuitry.

We used a simple model of a representative dentate granule cell (GC), in which we ignored the effects of local inhibitory as well as local and contralateral excitatory neurons. Thus, the model neuron has only two inputs representing the medial and lateral perforant paths. In the real GC, the MPP synapses are closer to the soma as they are localised on the medial part of the dendritic tree while LPP synapses are localised on the most distal part [25]. As a result, there is a delay in propagation of PSPs and backpropagtion of action potentials (bAPs) in the dendritic tree. However, GCs are small compact cells in comparison with, for instance, pyramidal cells. Modelling studies using the multicompartmental model of the GC dendritic tree show that the delay between bAPs reaching MPP and LPP synapses is about 1–2 ms (see e.g., Fig. 3B in [12]). Thus, we have neglected this small delay in the model of the spiking neuron and in implementations of all STDP rules below.

For the neuron model we employed the simple model of a spiking neuron introduced by Izhikevich [26]. The neuron model is described by two dimensionless variables $v(t)$ and $u(t)$ obeying these two ordinary differential equations:

$$\frac{dv}{dt} = 0.04v^2 + 5v + 140 - u + I \tag{3}$$

$$\frac{du}{dt} = a(bv - u) \tag{4}$$

Variable v corresponds to membrane voltage and u is the so-called recovery variable. After the value of variable v reaches spike apex (e.g., AP = 55 mV), the membrane voltage and the recovery variable are reset according to the formula:

$$\text{If } v \geq AP \text{ then } \begin{cases} v \leftarrow c \\ u \leftarrow u + d \end{cases} \tag{5}$$

Different firing characteristics of neurons (i.e. regular spiking, chattering, and bursting) are achieved with different values of dimensionless parameters *a, b, c* and *d*. We have employed the parameter values corresponding to a regularly spiking excitatory cell, because this is appropriate for granule cells, i.e. $a = 0.02$, $b = 0.2, c = -69$ mV, $d = 2$. Synaptic inputs are delivered via variable I, which is determined in the same way for spontaneous and evoked input activity, i.e.

$$I = s_{MPP} w_{MPP} N_{MPP} + s_{LPP} w_{LPP} N_{LPP} \tag{6}$$

We update the neuron model every 1 ms. That is, we numerically calculate/evaluate Eqs. (3)–(6) for every millisecond of real