COMPUTATIONAL MODELING OF LONG-TERM DEPRESSION OF SYNAPTIC WEIGHTS: INSIGHTS FROM STDP, METAPLASTICITY AND SPONTANEOUS ACTIVITY

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Abstract: Using the STDP rule with metaplasticity, we show that to evoke long-term depression (LTD) or depotentiation of synaptic weights in the spiking model of granule cell is not easy. This is in accordance with a number of experimental studies. On the other hand, heterosynaptic LTD which accompanies homosynaptic long-term potentiation (LTP) is induced readily both in the model as well as in experiments. We offer possible explanation of these phenomena from STDP, metaplasticity and spontaneous activity. We suggest conditions under which it would be possible to induce homosynaptic LTD and depotentiation.

Key words: *LTP, LTD, STDP, metaplasticity, spontaneous activity*

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1. Introduction

Our current understanding of mechanisms of learning and explicit memory storage in the brain implies a key role for changes in synaptic weights in the hippocampus and cerebral cortex. These changes are induced by coincident pre- and postsynaptic activity (Bi and Poo, 2001; Abraham and Robins, 2005). In this paper, we focus on long-lasting changes of synaptic weights, the so-called long-term potentiation (LTP) and long-term depression (LTD), respectively. These changes can last for hours even days and weeks and thus are considered to be the neural correlate of long-term memory. Different stimulation protocols lead to LTP and

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LTD. It has been shown that high-frequency stimulation (HFS) induces LTP at all major excitatory synaptic pathways in the hippocampus (Heynen et al., 1996; Doyère et al., 1997; Abraham et al., 2001). There are, however, mixed reports on ability of low-frequency stimulation (LFS) to induce LTD on naive synapses and depotentiation of previously potentiated ones. In this study, we will concentrate on granule cells in the dentate gyrus, which is the input part of the hippocampus (http://en.wikipedia.org/wiki/Hippocampus). The entorhinal cortex projects monosynaptically to the granule cells in the dentate gyrus via the lateral and medial perforant paths. Medial perforant path (MPP) and lateral perforant path (LPP) are two separate inputs terminating on separate but adjacent distal dendritic zones of the hippocampal dentate granule cells. They together form an ipsilateral perforant path input (PP) (McNaughton et al., 1981; Förster et al., 2006). We choose granule cells in the hippocampal dentate gyrus for two main reasons. Firstly, there are many studies reporting failure to induce homosynaptic LTD and depotentiation of the perforant path *in vivo* in both awake and anesthetized rats of all ages (Errington et al., 1995; Abraham et al., 1996; Martin, 1998; but see also Manahan-Vaughan and Braunewell, 1999). Still, some studies found that depotentiation can be achieved under certain timing conditions between HFS and LFS (Martin, 1998; Kulla et al., 1999; Straube and Frey, 2003). Also, *in vitro* in acute slices, depotentiation of the previously potentiated pathway is possible (Lin et al., 2006). Secondly, it has been shown *in vivo* that heterosynaptic LTD can be reliably induced in the lateral perforant pathway, when the medial perforant pathway receives HFS (Abraham et al., 2001) or vice versa, the heterosynaptic LTD is induced in the medial perforant path when the lateral perforant path receives HFS (Doyère et al., 1997). Thus, there are some puzzling data on LTD in the dentate gyrus, namely why it would be difficult to elicit homosynaptic LTD, if the same input readily expresses heterosynaptic LTD when the neighboring input pathway is tetanized by HFS? The latter is called heterosynaptic plasticity and means that HFS of one set of synapses leads to synaptic plasticity in a neighboring non-tetanized set of synapses.

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 (Levy and Steward, 1983). This property is called the spike-timing-dependent plasticity or STDP in short (Markram et al., 1997; Bi and Poo, 2001; Sjöström et al., 2008; Markram et al., 2011). 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, respectively. In 2006, Lin et al. (2006) published results of the study of the STDP in granule cells in hippocampal slices. They used the pairs of presynaptic stimuli and the postsynaptic antidromic spikes delivered to granule cells in different orders (pre-post and post-pre) and with different delays to succesfully 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. (2006) showed the interaction of STDP and frequency-dependent plasticity at one synaptic path, thus suggesting they may actually share the same mechanisms.

It has been long known that differential elevations of postsynaptic Ca^{2+} concentrations are crucial for the development of both LTP and LTD (Mayford and

Kandel, 1999; Bi and Poo, 2001). Medium elevation in $[Ca^{2+}]$ leads to LTD and high elevation of $[Ca^{2+}]$ leads to LTP through activation of two distinct chains of intracellular enzymes. Since most of the Ca^{2+} enters through the NMDA receptors, several detailed phenomenological and biophysical models of calcium-dependent and/or NMDAR-dependent synaptic plasticity have been proposed (Abarbanel et al., 2002; Karmarkar and Buonomano, 2002; Shouval et al., 2002a; 20002b; Yeung et al., 2004; Graupner and Brunel, 2012). Some of these biophysical models account also for the relationship between STDP and the BCM theory (Shouval et al., 2002a; 20002b; Yeung et al., 2004). The BCM or Bienenstock, Cooper and Munro theory of synaptic plasticity was proposed in 1982 to explain plasticity in the developing visual cortex (Bienenstock et al. 1982; Cooper et al. 2004). The crucial notion in this theory is the existence of the so-called sliding or moving BCM threshold. The BCM 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 this 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, then the 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 fact, many experimental studies demonstrated that prior history of pre- and postsynaptic neural activity controls the subsequent induction of LTP and LTD. This phenomenon was named *metaplasticity* (Abraham and Bear, 1996; Abraham, 2008) and was linked to the BCM theory (Jedlička, 2002).

We are interested in developing a more abstract phenomenological model of synaptic plasticity that is computationally much less expensive than the more detailed models, and yet still biologically accurate. The breakthrough came in the paper of Izhikevich and Desai (2003), in which they showed that the phenomenological equations for STDP when we consider only nearest neighbors pairings actually lead to the emergence of LTD/LTP frequency threshold. To include the sliding property of the LTD/LTP threshold as a function of previous postsynaptic activity, we suggested that amplitudes of LTP and LTD are not constant but instead depend metaplastically on the average postsynaptic activity (Benuskova and Abraham, 2007). We used this new phenomenological computational model of STDP to explain the frequency-dependent homosynaptic LTP and heterosynaptic LTD in the dentate gyrus. In our model, synapses of MPP and LPP modify according to the pair-based STDP rule, in which the amplitudes of LTP and LTD are not constant but instead depend metaplastically on the postsynaptic spike count averaged over some recent past. In this way, we have linked the STDP rule to the sliding property of LTD/LTP threshold in the BCM theory. In this new formulation of the STDP rule, the relative size of LTP is larger and LTD smaller when the average postsynaptic activity is low, thus favoring LTP, whereas the magnitude of LTP is smaller and LTD larger when the average postsynaptic activity is high, thus favoring LTD. Additional assumption in our study was that of an ongoing spontaneous spiking activity along the MPP and LPP inputs *in vivo*. This is a crucial feature of our model. We predicted that heterosynaptic LTD is in fact a homosynaptic phenomenon that requires an ongoing spontanepous presynaptic spiking activity to occur. This prediction was experimentally tested and confirmed by Abraham et

al. (2007). The ongoing spontaneous spiking activity was blocked by injecting the anesthetic procaine to the LPP, and then the MPP was tetanized. This protocol induced homosynaptic LTP in tetanized MPP but no heterosynaptic LTD in LPP with no spontaneous activity.

In the present paper, we concentrate on the phenomenon of long-term depression LTD *in vivo*. In our model, we assume that classical pair-based STDP (Markram et al., 1997; Sjöström et al., 2008) underlies all frequency-evoked synaptic plasticity, although dependence on more spikes was recently suggested (Pfister and Gerstner, 2006). Based on this simple assumption, we offer novel insights into the LTD phenomena using spiking model of granule cell. Its inputs modify according to recently suggested modification of the STDP equation with metaplasticity that can account for homosynaptic LTP and heterosynaptic LTD in the dentate gyrus *in vivo* (Benuskova and Abraham, 2007). In this paper, we simulate several published experiments and suggest testable conditions under which LTD and depotentiation can and cannot be evoked by LFS. Preliminary results were accepted as a conference contribution (Benuskova, 2012).

2. Methods

2.1 Neuron model

Recently, several publications compared different simple spiking models in their ability to predict spiking times of biological neurons (Jolivet et al., 2008; Kobayashi et al., 2009). Although Izhikevich model neuron was not used in these comparisons, it is very similar to the adaptive exponential integrate-and-fire model (aEIF) of Brette and Gerstner (2005) with the difference the latter contains an exponential rather than a quadratic nonlinearity in the calculation of membrane potential. This exponential model performed the best in the benchmark test of Jolivet et al. (2008). Izhikevich performed his own succesful testing of the ability of his simple spiking model to predict spiking times of a real neuron in (Izhikevich, 2007). We have chosen Izhikevich simple spiking model that has fewer parameters to fit than aEIF and these values have been already provided in (Izhikevich, 2003; 2007). It is also very fast to simulate. In the Discussion, we show that in fact our explanation of the observed phenomena does not depend on the neuron model but only on the STDP and stimulation protocol.

Thus, to model a granule cell we employ the simple model of spiking neuron introduced by Izhikevich (Izhikevich, 2003), which can simulate the wide range of spiking behaviors by varying the values of just four parameters a, b, c, d (Izhikevich, 2003; 2007). In this simple spiking model, the dimensionless variable v represent the membrane potential of the neuron and u represent a membrane recovery variable, which provides a negative feedback to v. The dynamics of v and u is described by the following set of ordinary differential equations:

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

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

Synaptic inputs are delivered via the variable $Input$. We use a simple spiking model of a hippocampal dentate granule cell, in which we consider only excitatory inputs.

Thus, a model cell has $N = 3$ excitatory inputs, two of them representing ipsilateral medial and ipsilateral lateral perforant paths, MPP and LPP, respectively, and the third excitatory input representing the commissural/associational input. The commissural/associational fibres originate from the mossy cells in the contralateral and ipsilateral hilar region and terminate in the proximal dendritic zone of the granule cell dendritic tree (Förster et al., 2006). Thus, the total synaptic input corresponding to variable $Input$ reads:

$$Input = \sum_{k=1}^{N} s_k w_k I_k, \tag{3}$$

where k = MPP, LPP, ComAs; $s_k = 1$ or 0 when a presynaptic spike is present or absent at a given input, respectively; w_k is the weight of the given input synapse, and I_k is the intensity of electric stimulus delivered to the given pathway. Intensity of electric stimulus is understood as the number of input fibers/synapses that are engaged within a stimulated pathway, and thus is dimensionless. The stimulus intensity variable was introduced because in some simulated experiments, experimenters might use different intensities for conditioning and for testing stimulation.

The firing threshold of granule cells is equal to 24 mV (McNaughton et al., 1981). When v crosses the firing threshold from below, the granule cell fires a postsynaptic spike. After the postsynaptic spike is fired, after 1 ms, in the next iteration, the membrane voltage v and the recovery variable u are reset as follows:

$$v \leftarrow c, \quad u \leftarrow u + d, \tag{4}$$

The model neuron cannot fire again for a few miliseconds, thus effectively simulating the refractory period. Since granule cells are regularly spiking cells, we simulate the simple spiking model with the values of parameters a, b, c, d corresponding to a regularly spiking cell, i.e. $a = 0.02$, $b = 0.2$, $c = –69$ mV, $d = 2$ (Izhikevich, 2003; 2007). The model is simulated in real time with the time step of 1 ms, but with the integration step of 0.5 ms for numerical stability as in the code in (Izhikevich, 2003).

2.2 Simulated spontaneous spiking

Because the simulated experiments were done in live animals, our model granule cell was subject to simulated ongoing spontaneous input activity that is present in biological neurons *in vivo*. All the spontaneous input spiking was generated randomly as Poisson spike trains. The Poisson process is the simplest model of neuronal firing and is often found in recordings of the spontaneous activity of biological neurons *in vivo* (Rudolph and Destexhe, 2003). Simulated ongoing spontaneous input spiking had two components. The first component were the correlated spontaneous spikes in MPP and LPP and commissural/associational input. By correlated we mean that the spikes occurred at the same time in all three inputs. Superimposed on this correlated spiking was uncorrelated random activity occuring at different times in all three inputs. The average frequency of all spontaneous input spiking at each of the three inputs was 8 Hz to simulate the theta rhythm modulation observed experimentally at the output from entorhinal cortex in live rats (Gloveli

et al., 1997; Frank et al., 2005). Out of this 8 Hz, we tried different proportions of correlated versus uncorrelated components, e.g. correlated spikes with average frequency of 7 Hz accompanied with uncorrelated spikes at frequency of 1 Hz or correlated spikes with average frequency of 1 Hz accompanied with uncorrelated spikes at frequency of 7 Hz, and all the options in between these two extremes. The simulated spontaneous activities, as described above, have lead to a postsynaptic spontaneous spiking activity of the simulated granule cell of ∼1 Hz, which is in accordance with the data (Kimura and Pavlides, 2000). All described scenarios of presynaptic spontaneous spiking activity lead to the same results, as described in the Results section below.

In addition, all types of input-output spiking activity, i.e. spontaneous or evoked by various protocols (see below), were accompanied by the STDP with metaplasticity as described in the next subsection.

2.3 Synaptic plasticity rule

In our model, we assume that classical pair-based STDP underlies all frequency-evoked synaptic plasticity, although dependence of STDP on more pre- and postsynaptic spikes was recently suggested (Pfister and Gerstner, 2006). However, Lin et al. (2006) used the two spike-pairing paradigm in the dentate gyrus to evoke STDP and identified two exponential windows, one for LTP and the other one for LTD. Because we have no evidence about interactions of more than two spikes in granule cells, each excitatory synaptic weight modifies according to the additive nearest neighbors STDP rule using the standard exponential relationships as in (Izhikevich and Desai, 2003):

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

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

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

where $\delta t = 1$ ms is the time step of weight updating. This implementaion corresponds to the presynaptic centered interpretation according to Morrison et al. (2008, Fig. 7B). The reason for the nearest neighbors implementation of STDP is that Izhikevich and Desai (2006) showed that this particular implementation of STDP leads to the BCM-like LTD/LTP threshold value for the frequency of presynaptic stimulation.

Previously we showed that in order to account for synaptic plasticity in the dentate gyrus when the spontaneous activity is going on, it is necessary to introduce

metaplasticity into the STDP rule (Benuskova and Abraham, 2007). We proposed that the amplitudes of positive and negative synaptic changes, A_+ and A_-, are not fixed, but instead they depend on the average of the postsynaptic spiking activity over some recent past $\langle c \rangle_\tau$, calculated as an integral:

$$\langle c(t) \rangle_\tau = \frac{c_0}{\tau} \int_{-\infty}^{t} c(t') \exp\Big(-(t-t')/\tau\Big) dt' \tag{7}$$

with $c(t) = 1$ or 0 if the postsynaptic spike is present or absent at time t, respectively, τ is the integration period, and c_0 is the scaling constant. The integral can be replaced with a discrete sum, but we actually numerically calculated the above integral in our code. The rationale for using the spike count for equation (7) comes from experiments of Abraham et al. (2001), in which antidromic spikes (with NMDA receptors blocked) were sufficient to increase the threshold for subsequent LTP induction by HFS. In this calculation of the average of the past spike count of the postsynaptic cell, the most recent spikes have the largest weight and this influence decays exponentially into the past. This relationship was inspired by the calculation of the dynamic position of the LTD/LTP threshold in the plasticity model of the visual (Clothiaux et al., 1991) and somatosensory cortices (Benuskova et al., 2001). Thus, the amplitudes of potentiation and depression windows for the STDP equations metaplastically expand or shrink as a function of previous postsynaptic activity like this:

$$A_+(t) = \frac{A_+(0)}{\langle c \rangle_\tau} \quad \text{and} \quad A_-(t) = A_-(0) \langle c \rangle_\tau. \tag{8}$$

Positive constants $A_+(0)$ and $A_-(0)$ are initial amplitude values for synaptic potentiation and depression, respectively, used in the simulations. If $\langle c(t) \rangle_\tau = 0$, then $A_+(t) = A_+(0)$ and $A_-(t) = A_-(0)$. Equations (8) simply mean the amplitude for LTP gets smaller and the LTD amplitude gets larger when the average postsynaptic activity is high. The opposite is true for a low average postsynaptic activity. Then, it is easier to potentiate the synapses than to weaken them due to an expanded amplitude for LTP and shrunken amplitude for LTD. The new values of $A_+(t)$ and $A_-(t)$ are updated at each iteration based on the actual value of the recent average activity $\langle c(t) \rangle_\tau$.

Values of model parameters used in the following computer simulations were: $A_+(0) = 0.001$, $A_-(0) = 0.01$, $\tau_+ = 20$ ms, $\tau_- = 100$ ms, $\tau = 60$ sec, $c_0 = 1000$. Unless stated otherwise, intensities of evoked and spontaneous presynaptic spikes were equal for all pathways, i.e. $I_{\mathrm{MPP}} = I_{\mathrm{LPP}} = I_{\mathrm{ComAs}} = 150$. Initial values of synaptic weights were chosen to be $w_{\mathrm{MPP}}(0) = w_{\mathrm{LPP}}(0) = w_{\mathrm{ComAs}}(0) = 0.033$, so when the three input pathways were spiking simultaneously or in a close temporal succession, a postsynaptic spike followed after 2–3 ms, which corresponds to the delay in real granule cells between their synaptic stimulation and natural postsynaptic spiking. The same results were obtained with stimulus intensity = 100 and initial weights = 0.05, or stimulus intensity = 200 and initial weights = 0.025, and so on.

It is notable that in our simulations we used no lower nor upper bound on synaptic weights, no renormalization, no decay term, etc. It is only the dynamics of changing LTD and LTP amplitudes that prevents the weight values to grow to infinity.

3. Results

First, we simulated the granule cell just in the condition of an ongoing spontaneous presynaptic activity, as described in Subsection 2.2. The first 30 min in each of the following figures shows a dynamically stable trace achieved for the model granule cell for the spontaneous input activity and the choice of the cell and synaptic plasticity parameters given in Section 2. Parameter values were optimized by hand to give the model cell stability in the spontaneous activity condition and to achieve the best match with the experimental data. We do not show the S.D. for clarity of the pictures, just the averages of 10 runs. S.D. for each weight at each time instant was never larger than 8% of the initial weight value, i.e. it was 0.0024 at maximum, while the initial weight value of single input was 0.033. That was the case for all simulated experiments.

Previously we simulated experiments of Abraham et al. (2001) of heterosynaptic plasticity in the dentate gyrus with the model like above having only two inputs, i.e. MPP and LPP (Benuskova and Abraham, 2007). Heterosynaptic plasticity involved homosynaptic LTP of the MPP and heterosynaptic LTD of LPP following the HFS applied to MPP only. First, we reproduce this result with the 3-input model as it is relevant for the simulation and explanation of absence of homosynaptic LTD and depotentiation.

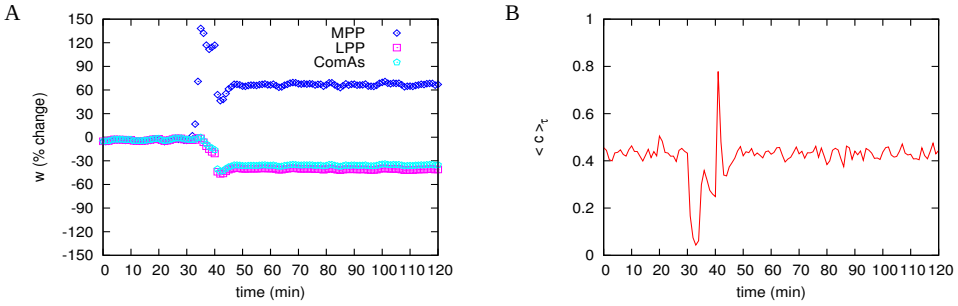

Fig. 1 *(A) Evolution of weights of the three inputs to model granule cell before, during and after MPP HFS. HFS to MPP commenced at 30 min and lasted till 40 min of time. (B) Corresponding evolution of the average postsynaptic spike count over time. All traces are average of 10 runs.*

Our model granule cell was subject to realistically simulated spontaneous input activity. Spontaneous input spiking activity had two components: uncorrelated random activity with frequency $\leq$ 1 Hz generated randomly (Poisson spike

train) with superimposed correlated spontaneous spikes from EC and commissural/assocciational input with an average frequency of 8 Hz to simulate the theta rhythm modulation (Frank et al., 2001). Such a spontaneous input activity has lead to a postsynaptic spontaneous spiking activity of a simulated granule cell of ∼1 Hz, which is in accordance with data (Kimura and Pavlides, 2000). Superimposed upon the ongoing spontaneous input were the test spikes delivered alternately to MPP and LPP at 10-s intervals 30 min before and 90 min after HFS of MPP (Abraham et al., 2001). In the real experiment as well as in model described above, HFS consisted of 50 trains of ten pulses at 400 Hz delivered to MPP. HFS was delivered in bursts of 5 trains at 1-s intervals, with 60 s between bursts. Intensity of spontaneous and test stimulation was = 150 and intensity of HFS pulses was = 250, thus reflecting the ratio of stimulus intensities used in experiment (Abraham et al., 2001). Ongoing spontaneous input occurred on all three inputs all the time as *in vivo* experiments were simulated. During the trains of HFS, however, there was an ongoing 8 Hz-spontaneous input activity on non-tetanized inputs 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 HFS or LFS, were accompanied by STDP with metaplasticity. Fig. 1A shows temporal evolution of weights of three types of inputs to the model granule cell following HFS applied to MPP.

In Fig. 1A, we can see that HFS of MPP causes LTP of MPP, and there is a heterosynaptic LTD of LPP and ComAs. The latter two inputs receive only the spontanoeus presynaptic activity during the MPP HFS. The model reproduces the findings of homosynaptic LTP of MPP and heterosynaptic LTD of LPP (Abraham et al., 2001). The commissural/associational (ComAs) input pathway was not assessed in this experiment, thus the heterosynaptic LTD of the commissural/associational pathway is a prediction of the model.

We have demonstrated that heterosynaptic LTD *in vivo* can be accounted for by:

(1) The STDP rule is allowed to dynamically change the sizes of potentiation and depression amplitudes according to the previous mean spike count of the postsynaptic neuron. The LTP size expands when the average activity drops below the previous resting average (see Fig. 1B).

(2) Drop in the average postsynaptic activity during HFS is a result of the decorrelated spontaneous activity in LPP and ComAs with the HFS stimulation of MPP during the trains and of the decorrelation of spontaneous activity in all inputs during the interburst episodes (assumption of the model). Drop in $\langle c \rangle_\tau$ enables MPP to potentiate as HFS presynaptic spikes are correlated with postsynaptic spikes they evoke.

(3) During HFS, high-frequency presynaptic spikes in MPP cause granule cell to spike and, therefore, lead to LTP of MPP according to STDP. Spontaneous presynaptic spikes of LPP and ComAs occur randomly and are not causally related to postsynaptic spikes, therefore LTD of these inputs follows.

Our model explains heterosynaptic LTD as a homosynaptic phenomenon due to ongoing spontaneous presynaptic activity. Thus, a prediction from the model is

this: if STDP underlies all synaptic plasticity, then if the spontaneous activity is blocked, so is the heterosynaptic LTD. Fig. 2 shows the results of simulation of our present 3-input model when presynaptic spontaneous activity of LPP pathway is blocked.

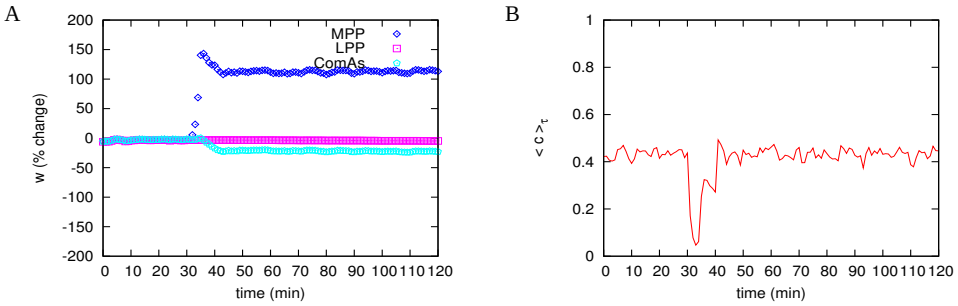

Fig. 2 *(A) Evolution of weights of the three inputs to model granule cell before, during and after MPP HFS when LPP ongoing spontaneous activity has been blocked. HFS to MPP commenced at 30 min and lasted till 40 min of time. From 30 min on, the LPP spontaneous activity was blocked, i.e. no presynaptic spikes occured. (B) Corresponding evolution of the average postsynaptic spike count over time. All traces are average of 10 runs.*

Fig. 2 shows that the block of ongoing spontaneous activity in LPP results in no plasticity of this input. This is a trivial consequnce of STDP, i.e. no presynaptic spikes, no synaptic plasticity. Abraham et al. (2007) tested and confirmed this prediction in rats anesthetized with urethane. The neurons in the entorhinal cortex that are the source of both the MPP and LPP input to the dentate gyrus still have spontaneous activity on the order of 2–8 Hz in the rats anesthetized with urethane (Dickson et al., 1994; Gloveli et al., 1997). As Abraham et al. (2007) showed, if they apply procaine selectively to LPP during MPP HFS, LPP pathway does not show heterosynaptic LTD. Thus, we have concluded that "heterosynaptic" LTD in the dentate gyrus requires ongoing spontaneous activity at the pathway to be depressed.

Now the question arises how is it with the true homosynaptic LTD, which is supposed to be evoked with low-frequency stimulation (LFS). To study the induction of LTD in our computer simulations of the model granule cell we used exactly the same protocols as in Abraham et al. (1996) who studied homosynaptic LTD and depotentiation in the rat dentate gyrus *in vivo*. First, they applied LFS to naive, i.e. unstimulated, perforant path, which is a mixture of MPP and LPP fibers. LFS in the real experiment and in our simulations consisted of 100 pulses of 1 Hz, and then of 900 pulses of 1 Hz or 900 pulses of 3 Hz. They also gave the test pulses (1/20 sec) for 10 min before and 20–30 min after LFS to monitor the amplitude of excitatory postsynapytic potentials before and after LFS. Intensity of test and LFS stimuli was the same. In our model, the LFS and test stimuli were administered with exactly the same timing as in the experiment, while the spon-

taneous presynaptic activity, as described in the previous Section 2.2, was present all the time. We also simulated the administration of test stimuli although we do not need them as we can monitor the weight changes directly. We also simulated the model without the test stimuli, and the results were the same. Thus, the test stimuli in the model do not make any difference, which should be the case.

The results for these three LFS protocols are shown in Fig. 3. As PP is the mixture of MPP and LPP, we consider $w_{\mathrm{PP}} = w_{\mathrm{MPP}} + w_{\mathrm{LPP}}$, and the pictures depict the percentual change against the initial weight value. We can see that the LFS induces only transient depression of PP input weights. Temporary depression of the PP weights lasts only for the period of LFS, then the weights return to the pre-LFS control values. The same magnitude and course of transient depression was observed in real experiment (Figs. 1B and 3A in Abraham et al. 1996). There was no change of the weight of the simulated commissural/associational input. These traces are not shown for the sake of Fig. 3A clarity. In Fig. 3b, we also monitored the evolution of $\langle c(t)\rangle_\tau$ as it affects the current size of potentiation and depression (see equation 8). We can see that when the synaptic weight goes down, there is a relatively more visible trough in $\langle c(t)\rangle_\tau$ too. This is caused by the fact that $\langle c(t)\rangle_\tau$ is calculated as the average of past postsynaptic spike count. When the input synapses are weakened, there are fewer postsynaptic spikes and thus $\langle c(t)\rangle_\tau$ decreases. This decrease is temporary, as it also means a decrease of further depression and increase in the potentiation size, so the balance is shifted towards potentiation and the weights return to control pre-LFS values, and so does the average postsynaptic spiking $\langle c(t)\rangle_\tau$.

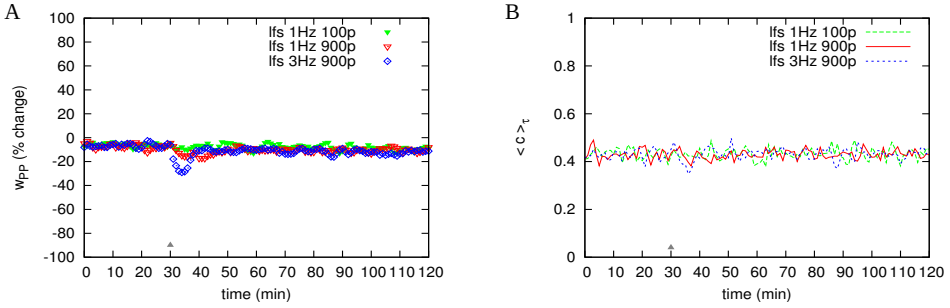

Fig. 3 *(A) Evolution of weights of the PP input to model granule cell before, during and after PP LFS. LFS to PP commenced at 30 min (arrowhead) and lasted till 45 min of time. (B) Corresponding evolution of the average postsynaptic spike count over time. All traces are average of 10 runs.*

In the next set of computer experiments, like in the real ones, HFS was applied to PP to induce homosynaptic LTP of PP to study depotentiation. HFS consisted of 50 trains of ten pulses at 400 Hz. HFS was delivered in bursts of 5 trains at 1-s intervals, with 60 s between bursts. LFS consisiting of 100 pulses of 1 Hz was delivered to PP at variable intervals after HFS completion, i.e. after 1 min, 15 min

and 60 min. The results of this series of simulations are shown in Fig. 4. We can see in Fig. 4A that HFS induces lasting LTP of the magnitude about 40% like in the real experiment (see Fig. 2A in Abraham et al., 1996). Subsequent LFS consisiting of 100 pulses of 1 Hz delivered to PP at variable intervals after HFS completion, i.e. after 1 min, 15 min and 60 min does not cause depotentiation, which is also the case in the real experiment (Fig. 2A in Abraham et al., 1996).

It is interesting to observe the dynamics of the average postsynaptic spike count in Fig. 4B. The average spike count actually decreases immediately after the start of HFS. This is due to the refractory period of the model neuron and one additional assumption of the model. This additional assumption states that during the HFS the spontaneous spiking at the three inputs gets decorrelated. The average frequency of the spontaneous spiking remains the same, i.e. 8 Hz, but the spikes never occur at the same time like they do before and after the HFS. We used the same assumption in modeling the heterosynaptic plasticity in the dentate gyrus (Benuskova and Abraham, 2007). This drop in $\langle c(t) \rangle_\tau$ enables the tetanized path to potentiate. The dynamics of $\langle c(t) \rangle_\tau$ also exhibits the stabilizing oscillations opposite to the direction of the synaptic change.

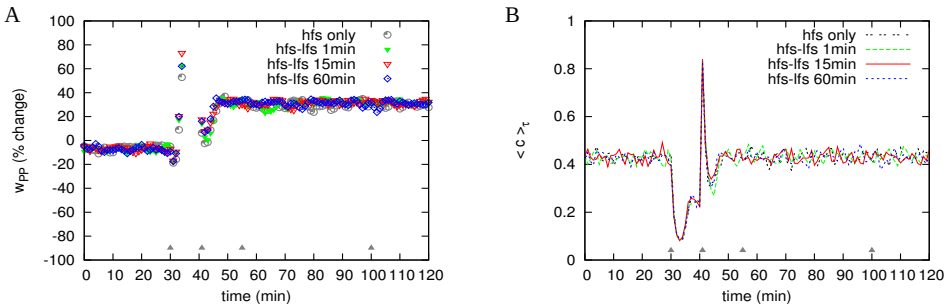

Fig. 4 *(A) Evolution of weights of the PP input to model granule cell before, during and after HFS followed by LFS. HFS of PP commenced at 30 min (first arrowhead) and lasted till 40 min of time. LFS of PP consisiting of 100 pulses of 1 Hz commenced 1 min, 15 min or 60 min after HFS (subsequent arrowheads). (B) Corresponding evolution of the average postsynaptic spike count over time. All traces are average of 10 runs.*

In another set of experiments, LFS was delivered 1 min after the end of HFS and consisted either of 100 pulses of 1 Hz or of 900 pulses of 1 Hz or 900 pulses of 3 Hz. The results are shown in Fig. 5A. None of these protocols caused depotentiation, which is consistent with data (Fig. 4A and 4B in Abraham et al., 1996). That is the case when the LFS did not cause the epileptic seizure-like activity of the granule cells, in which case Abraham notes there is an overall granule cell response depression, which manifests like an LTP reversal, but the next day the normal amplitude of LTP was observed (Fig. 4 in Abraham et al., 1996).

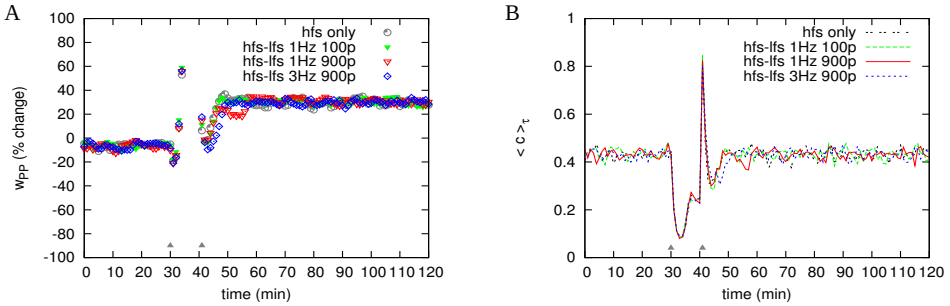

Fig. 5 *(A) Evolution of weights of the PP input to model granule cell before, during and after HFS followed by LFS. HFS to PP commenced at 30 min (first arrowhead) and lasted till 40 min of time. Subsequent LFS commenced 1 min after HFS (second arrowhead) and consisted either of 100 pulses at 1 Hz or 900 pulses of 1 Hz or 900 pulses at 3 Hz. (B) Corresponding evolution of the average postsynaptic spike count over time. All traces are average of 10 runs.*

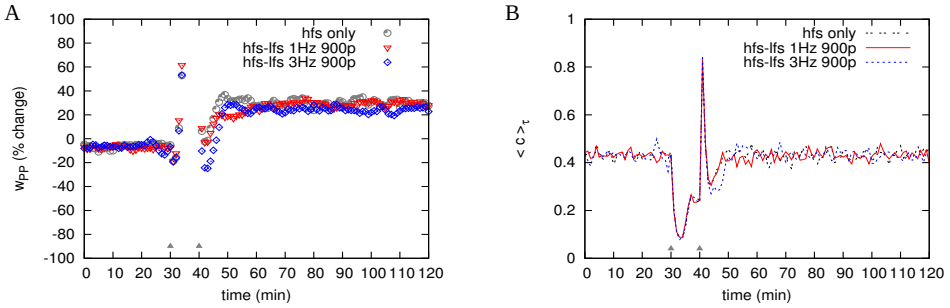

Fig. 6 *(A) Evolution of weights of the PP input to model granule cell before, during and after HFS followed by LFS. HFS to PP commenced at 30 min (first arrowhead) and lasted till 40 min of time. LFS commenced 10 s after HFS (second arrowhead) and consisted either of 900 pulses of 1 Hz or 900 pulses of 3 Hz. (B) Corresponding evolution of the average postsynaptic spike count over time. All traces are average of 10 runs.*

Martin (1998) showed that 10 min (3000 pulses) of 5 Hz cause depotentiation when applied less than 1 min after HFS, but he also notes that 5 Hz stimulation was always accompanied by seizure-like epileptiform activity of the granule cells. However, what he considered to be a depotentiation might as well have been the granule cell response depression, as documented by Abraham et al. in a similar stimulation paradigm (900 pulses of 3 Hz) (Abraham et al., 1996). Thus, we tried the 900 pulses of 1 and 3 Hz (Fig. 6), and also 3000 pulses of 5 Hz (not shown) commenced 10 s after the end of HFS too; but, without simulation of the

epileptiform postsynaptic activity because we would have to enhance our neuron model with some mechanism that causes its overall response deppresion when it goes into an epileptic mode of activity. Izhikevich and other simple spiking neuron models do not have such a mechanism, so this is something that needs to be taken into account in the future. We can see in Fig. 6A that the transient depotentiation lasted only while there was LFS, then the weights went back to the potentiated values. Our results are in accordance with Abraham et al. (1996) and also with Errington et al. (1995). Both these studies showed that various numbers of LFS pulses of the frequency 1–5 Hz do not cause depotentiation in the dentate gyrus.

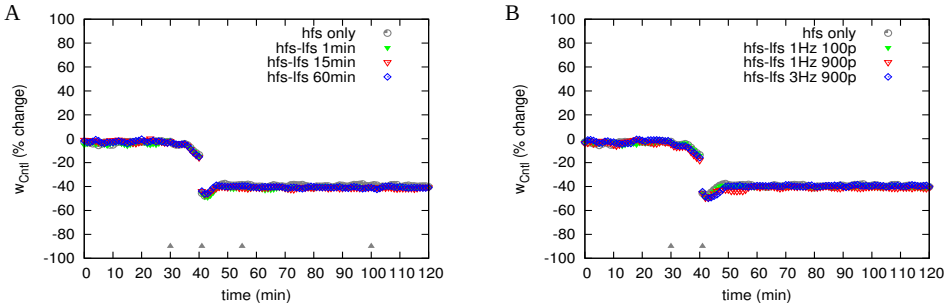

Fig. 7 *Evolution of weights of the commissural/associational input (ComAs) to model granule cell before, during and after HFS followed by LFS. HFS of PP commenced at 30 min (first arrowhead) and lasted till 40 min of time. (A) Subsequent LFS of PP consisting of 100 pulses of 1 Hz commenced 1 min, 15 min or 60 min after HFS (subsequent arrowheads). (B) Subsequent LFS commenced 1 min after HFS (second arrowhead) and consisted either of 900 pulses of 1 Hz or 900 pulses at 3 Hz. All traces are average of 10 runs.*

It is notable that all instances of homosynaptic LTP of the PP synapses are accompanied by the heterosynaptic LTD of the commissural/associational input as we can see in Fig. 7. This is exactly the same situation as the homosynaptic LTP of MPP being accompanied by the heterosynaptic LTD of LPP (Abraham et al., 2001; Benuskova and Abraham, 2007). As this commissural/associational input was not checked in the cited experiments of Abraham et al. (1996), Errington et al. (1995), Martin (1998), it is a testable prediction of the model for these protocols *in vivo*.

4. Discussion

Based on the pair-based STDP, we attempt to gain a novel insight into the homosynaptic LTD phenomenon using a spiking model of granule cell. Its inputs modify according to recently suggested STDP rule endowed with metaplasticity (based on BCM sliding threshold) that can account for homosynaptic LTP and heterosynaptic LTD in the dentate gyrus *in vivo* (Benuskova and Abraham, 2007). In our model,

we assume that classical pair-based STDP underlies also the frequency-evoked synaptic plasticity, although dependence on more spikes was recently suggested (Pfister and Gerstner, 2006). However, Lin et al. (2006) used the spike-pairing paradigm in the dentate gyrus to evoke STDP and so far we have no evidence about interactions of more than two spikes. Lin et al. (2006) estimated $\tau_+ = 26$ ms and $\tau_- = 36$ ms. With their parameter values, even the transient depression in Fig. 3A was almost absent. Thus, we have used bigger $\tau_- = 100$ ms to achieve quantitative match with the simulated experimental data. The reason for this differenece might be that Lin et al. (2006) used *in vitro* slices, whereas we modeled the *in vivo* experiments. The values of parameters may not be the same for *in vitro* and *in vivo* conditions.

Heterosynaptic LTD is induced very readily in our model when the other inputs are tetanized. This is not the case of the homosynaptic LTD, however, which ought to be evoked by LFS. The explanation lies in the STDP rule itself, which we assume is the basis of frequency-dependent synaptic plasticity, too. Let us use the following illustration of the concept, see Fig. 8. All the following reasoning holds for the nearest-neighbor implementation of the pair-based STDP, which we used in our simulations.

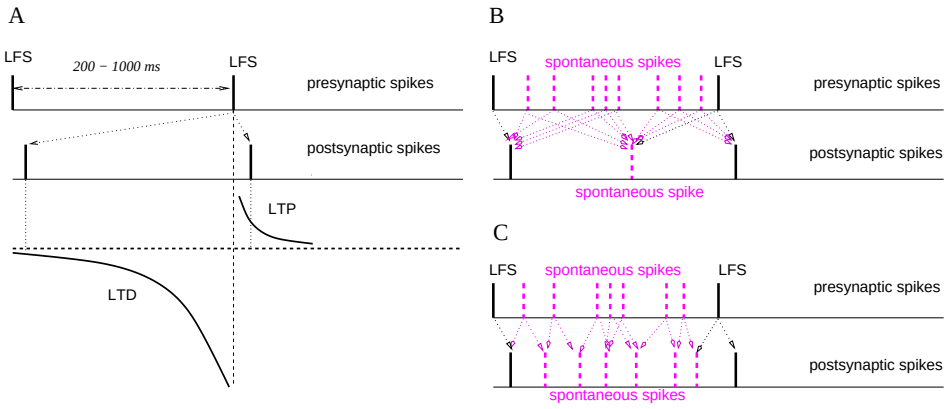

Fig. 8 *Illustration of the STDP rule and the timing relationships for the LTP and LTD windows during LFS. (A) Without spontaneous activity. (B) With spontaneous pre- and very few postsynaptic spikes like in the case of the granule cells. (C) With spontaneous pre- and many postsynaptic spikes like, for instance, in the case of the CA1 cell or perhaps also epileptic afterdischarges.*

Let us first exclude the spontanous activity and consider only LFS. The upper trace in Fig. 8A illustrates the succession of presynaptic spikes in LFS. The lower trace illustrates the series of postsynaptic spikes that are evoked by presynaptic spikes. Postsynaptic spike occurs within 2–3 ms after each presynaptic spike, if the former is strong enough to excite the postsynaptic cell. Since the frequency of LFS is between 1 Hz and 5 Hz, spacing between presynaptic spikes is from 1000 ms to 200 ms, respectively. Resulting size of LTD is much much smaller than the resulting size of LTP, and we hypothesize that even LTP may follow LFS.

What happens if we included spontaneous pre- and postsynaptic spiking? The average frequency of input spikes to granule cell is 8 Hz, while the average frequency of spontaneous spiking of granule cell itself is only around 1 Hz (Fig. 8B). Thus, in case of the granule cell there will be 8 spontaneous spikes between each two evoked presynaptic spikes (if the frequency of LFS was 1Hz). However, as for the postsynaptic spikes, there will be at most one spontaneous postsynaptic spike within this window. Thus, it seems that for the nearest neighbors pairwise STDP the mutual LTD/LTP interactions may as well annul themselves with zero overall synaptic change in this case.

It seems that it would be impossible to induce homosynaptic LTD at all, which is not the case, for example in the hippocampal area CA1 *in vivo* (Heynen et al., 1996). CA1 neurons have a higher spontaneous output activity than granule cells, on the order of 8 Hz (Frank et al., 2001). This spontaneous postsynaptic spiking would place more spikes between the two postsynaptic spikes evoked by LFS (Fig. 8C). If we consider the nearest-neighbors implementation of STDP, more postsynaptic spikes would actually help LTD because they are closer to the presynaptic spikes and, thus, the overall LTD size should be larger than for fewer postsynaptic spikes. This may be the intuitive explanation of why it is easier to evoke homosynaptic LTD in CA1 than in the granule cells, which have very low spontaneous spiking.

The situation for CA1 neurons can change, however, when the measurements are done under anesthesia. It is known that anesthetics like pentobarbital, propofol, ketamine, and ethanol inhibit spontaneous action potential firing in a concentration-dependent manner (Antkowiak, 1999). Urethane is a widely used anesthetic for animal experiments, and the simulated experiments were done either in awake rats or in rats anesthetized with urethane. Although urethane is thought to minimally interfere with neurophysiological processes and preserves synaptic signal transmission, it has also been reported that it may increase the interspike interval, in other words decrease the rate of spontaneous firing (Yutao et al., 2012). Thus, anesthesia may reduce the frequency of spontaneous spiking at both pre- and postsynaptic levels and scenario may look like in Fig. 8B or even 8A and, in fact, either no change or even potentiation may follow the LFS. Recently, indeed Habib and Dringerberg demonstrated that LFS evokes LTP in CA1 and CA3 area of hippocampus in urethane anesthetized rats (Habib and Dringenberg, 2009; Frausto et al., 2010).

The same reasoning as above would apply to depotentiation of a previously potentiated pathway. There are some reports, however, which report depotentiation of PP *in vivo* (Martin, 1998; Kulla et al., 1999; Straube and Frey, 2003). Martin (1998) but also Abraham et al. (1996) report that their LFS of 5 Hz or 3 Hz, respectively, always caused epileptic afterdischarges. In case of these afterdischarges, they could observe depotentiation. But to include epileptic afterdischarges would mean to include many spikes on the postsynaptic level, thus depression can be manifested because the interval between the presynaptic spike and the fast afterdischarge will be short enough for depression to dominate (see e.g. Fig. 8C).

Our future work will focus on extending the model to account for plasticity in the area CA1 and also on testing the robustness of the model with respect to variation of the rest of parameter values like, for instance, the number of input fibers/synapses belonging to each of the three pathways. Now the model cell has only 3 inputs, thus it would be interesting to experiment with hundreds of input

fibers, each having a different jitter. This extension is prepared for with the parameter $I_{\mathrm{MPP}} = I_{\mathrm{LPP}} = I_{\mathrm{ComAs}} = 150$, which represents the number of input fibers engaged in stimulation and which can be easily replaced with actual simulated fibers. We expect, however, that the general scenario outlined in Fig. 8 holds for any number of input fibers. Furthermore, in future computational analyses, it would be interesting to test the functional consequences of our STDP–BCM plasticity rule (e.g. the dependence of synaptic changes on dendritic location) in multicompartmental neuronal models with complex biophysics and morphology (cf. Jedlicka et al., 2011a; Vlachos et al., 2012). Since the STDP–BCM learning rule is computationally effective, its implementation in realistic dentate gyrus network models (Santhakumar et al., 2005; Morgan and Soltesz, 2008; Winkels, Jedlicka et al., 2009; Jedlicka et al., 2010; Jedlicka et al. 2011b) is feasible and might provide novel insights on effects of homeostatic synaptic plasticity on dentate network dynamics.

At this stage, the model generates four predictions that can be tested experimentally. First prediction is that there is a heterosynaptic LTD in the commissural/associational input accompanying the homosynaptic LTP of the whole ipsilateral perforant path. This follows directly from the simulations of three input pathways. Because this third input is, in fact, a combination of contra- and ipsilateral associational fibers, we have to be cautious about it. The ipsilateral associational part is activated by granule cells themselves (through intermediate mossy cells), which means it is not entirely independent of their activity. In fact, Kleschevnikov and Routtenberg (2003) observed that HFS of the perforant path induced not only homosynaptic potentiation of the perforant path but also heterosynaptic potentiation of the ipsilateral associational pathway. Thus, strictly speaking, our prediction concerns only the contralateral associational inputs. Second prediction is that the amplitudes of LTP and LTD depend on the average postsynaptic activity of a neuron over some recent past. This is the metaplasticity assumption of the model. It can be tested experimentally by artificially manipulating the postsynaptic spiking of a neuron. Third prediction is that in order to induce homosynaptic LTD one has to increase the frequency of stimulation so that the depression will actually dominate over potentiation (see Fig. 8A). From this follows the fourth prediction that LFS may, in some cases, lead to LTP. This has, indeed, been observed recently in the hippocampus by Habib and Dringenberg on CA1 neurons (2009) and by Frausto et al. (2011) on CA3 neurons.

To summarize, in this paper, we have offered some new insights on why it is difficult to induce homosynaptic LTD by LFS in granule cells in the dentate gyrus *in vivo*, while it is easy to induce the heterosynaptic LTD at the same synapses by applying HFS to the neighboring pathway. These insights follow from the nearest neighbors implementation of the pair-based STDP rule when we take into account also an ongoing spontaneous activity of neurons and metaplasticity. The main conclusion of the paper is that the ongoing input spiking activity is an important player in synaptic plasticity and that it should be included in theoretical and computational studies. We think that the stimulation protocol used for induction of plasticity plus the ongoing spontaneous activity and the phenomenon of metaplasticity are closely related and cannot be separated when studying synaptic plasticity.

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