Computational model of CA1 pyramidal cell with meta-STDP stabilizes under ongoing spontaneous activity as *in vivo*

Matúš Tomko, Ľubica Beňušková
Centre for Cognitive Science, DAI FMPI UK, Mlynská dolina, 84248 Bratislava, Slovakia
matus.tomko@fmph.uniba.sk; lubica@ii.fmph.uniba.sk

Peter Jedlička
Institute of Medical Informatics, Faculty of Medicine, Justus-Liebig-University, Rudolf-Buchheim-Str. 6, D-35392 Giessen, Germany
peter.jedlicka@informatik.med.uni-giessen.de

Abstract

Synaptic plasticity is the basic mechanism of learning and memory. It is the ability of neurons to change efficacies of synaptic weights in response to stimuli. There is no general agreement on which synaptic plasticity rule(s) hold in the brain, although some general principles have been agreed upon. Thus, we implemented the Spike-Timing Dependent Plasticity rule with metaplasticity (meta-STDP) in a biophysically realistic computational model of hippocampal CA1 pyramidal cell in order to model synaptic plasticity in alive hippocampus. Characteristic feature of the brain in vivo is an ongoing spontaneous or background activity in neural circuits. Neurons should not change their weights as a result of this background activity, only when a statistically different pattern of input activity appears. As a first step in our research, we subjected our CA1 model to realistically simulated input activity and we have achieved realistic output spontaneous activity and stabilization of synaptic weights after a short time.

1 Introduction

Synaptic plasticity is ability of synapses to change their strength or efficacy of the synaptic transmission according to input/output activity (Hughes, 1958). It is considered as a critical neural mechanism for learning and memory. In the field of hippocampus, the research is focused primarily on long-term synaptic changes lasting minutes, hours, or months. They are called long-term potentiation (LTP) and long-term depression (LTD) of synaptic efficacy.

Several models of synaptic plasticity have been proposed (Mayr and Partzsch, 2010). Meta-STDP rule (Benuskova and Abraham, 2007) is a synaptic rule that combines classical STDP (spike-timing dependent plasticity; Markram et al., 1997) and metaplasticity (Abraham, 2008). The main idea of metaplasticity is that previous presynaptic and postsynaptic activity affects the sign and size of synaptic plasticity at the stimulated synapses (Abraham, 2008). Benuskova and Abraham (2007) used this approach to modify classical STDP rule. Magnitudes of LTP / LTD in the meta-STDP are dynamically changed as a function of a previous average postsynaptic activity (Benuskova and Abraham, 2007). Computational models of the granule cell endowed with this rule were able to reproduce experimental results of synaptic plasticity occurring in the dentate gyrus, provided the model exhibited ongoing spontaneous activity (Benuskova and Abraham, 2007; Jedlička et al., 2015). Based on computer simulations, the authors concluded that ongoing spontaneous activity is the key factor that determines the degree of long-term potentiation and long-term depression. The role of spontaneous activity in the induction of heterosynaptic LTD has been experimentally confirmed by Abraham et al. (2007). As predicted by the model, procaine infusion into the lateral path fibers, sufficient to transiently block neural activity in this pathway, prevented the induction of LTD in the lateral path following medial path high-frequency stimulation. Similar conclusions have been reached by Dong et al. (2008) who concluded that coincident activity of afferent pathways in the CA1 region can induce either LTP only or LTP/LTD depending on the experimental stimulation protocol and the state of hippocampal activity. The hippocampal EEG power was higher in urethane-anaesthetized rats and much higher in awake rats, which was correlated to the magnitude of LTD in following commissural pathway but not to that of LTP in preceding Schaffer pathway (Dong et al., 2008).

CA1 pyramidal cells are principal excitatory cells in the hippocampal CA1 region. Ovoid cell bodies are located in the stratum pyramidale. A surface area of the pyramidal cells body is 465 ± 50 μm^2 and a diameter is ~15 μm. CA1 pyramidal cell dendrites are classified into nine categories according to location,

diameter, length and spine density. Basal dendritic tree is formed of primary dendrites (3 − 5) located in the stratum oriens. Proximal dendrites (close to the soma) are thick with few or no dendritic spines. Thin distal dendrites are densely covered with spines. CA1 pyramidal cells express typically one thick apical trunk. In the stratum radiatum, the apical dendrite giving off from 9 to 30 oblique side thin branches. After reaching the stratum lacunosum-moleculare they end with the bifurcation and form the dendritic tuft in this layer. Dendrite spines increase the dendritic surface area. They are the main target of excitatory synaptic connection. The total number of excitatory synapses was estimated on over 30 000. Their relative representation on individual parts of the dendritic tree is as follows: 38.3% on the stratum oriens distal dendrites, 0.8% on the stratum oriens proximal dendrites, 0.9% on the stratum radiatum thick medial dendrites, 7.1% on the stratum radiatum thick distal dendrites, 47.1% on the stratum radiatum thin dendrites, 1.6% on the stratum lacunosum-moleculare thick dendrites, 1.4% on the stratum lacunosum-moleculare medial dendrites, and 2.8% on the stratum lacunosum-moleculare thin dendrites (Megiás et al., 2001).

The entorhinal-hippocampal system is characterized by occurrence of different types of oscillations. Dominant are theta (~6–10 Hz) and gamma (~30–150 Hz) oscillations that are often correlated with spatial navigation and memory. Timing and strength of inputs from EC and CA3 have significant role on the activity of the CA1 pyramidal cells (Buzsáki, 2002; Schomburg et al., 2014). The mean firing rates of individual CA1 pyramidal cells are in range from 0.001 Hz to 10 Hz in different brain states. Distribution of firing rates is strongly skewed and the most of CA1 neurons fires at frequency ~1–2 Hz (Mizuseki and Buzsáki, 2013).

In this work we apply the meta-STDP synaptic plasticity rule to the compartmental model of CA1 and subject the model to the simulated ongoing spontaneous activity. The goal is to optimize the values of parameters in order to achieve dynamically stable synaptic weights.

2 Methods

2.1 Compartmental model of the CA1 cell

NEURON simulation environment (Hines and Carnevale, 1997), version 7.6.5, and Python, version 3.6, running on PC under Windows 7 or Windows 10 were used to create and simulate the model. The model was previously published by Cutsuridis et al. (2009). Source code of the model is available from the ModelDB database at https://senselab.med.yale.edu/modeldb/, accession No. 123815. The CA1 pyramidal cell compartmental model is comprised 15 distinct sections, i.e. soma, axon, 4 stratum oriens (SO) dendritic sections, 3 stratum radiatum (SR) dendritic sections, and 6 stratum lacunosum-moleculare (SLM) dendritic sections (Cutsuridis et al., 2009).

Each section contains a calcium pump and buffering mechanism, a calcium activated slow afterhyperpolarization (AHP) potassium current, a medium AHP potassium current, a high voltage activated (HVA) L-type calcium current, an HVA R-type calcium current, a low voltage activated (LVA) T-type calcium current, an h current, a fast sodium current, a delayed rectifier potassium current, a slowly inactivating M-type potassium current and a fast inactivating A-type potassium current. Active and passive properties were taken from Poirazzi et al. (2003a, 2003b).

2.2 Model inputs

The NEURON built-in class *Exp2Syn* is used to model all excitatory synapses. This class models synaptic conductivity g as a two-state kinetic scheme described by two exponential functions:

$$g(t) = w\left(e^{-\frac{t}{\tau_2}} - e^{-\frac{t}{\tau_1}}\right) \quad (1)$$

where w is synaptic weight, $\tau_1 = 0.5$ ms is the rise time constant, and $\tau_2 = 3$ ms is the decay time constant. The peak conductance represents synaptic weight and is modified according to the plasticity rule (see below).

A total number of excitatory synapses was set at 98 (see Fig. 1). The distribution of synapses on the dendritic tree was determined according to experimental data (Megiás et al., 2001). The number of synapses in the stratum oriens distal sections was 40, representing 40.81% of all model synapses. Apical branches in the stratum radiatum were modelled by tree connected sections with total number of 52 excitatory synapses, representing 53.06% of all model synapses. The total number of excitatory synapses in the stratum lacunosum-moleculare sections was 6, representing 6.12% of all model synapses.

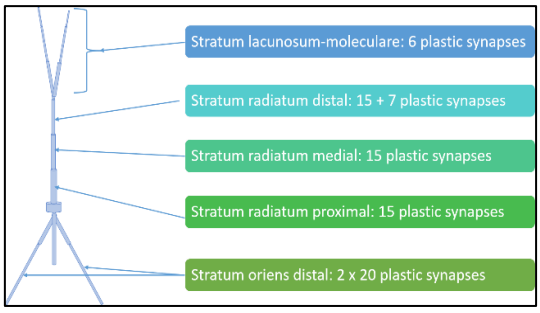

Fig. 1: Compartmental model of CA1 pyramidal cell with position and number of synapses (schematic).

There are two main excitatory synaptic inputs into the CA1 cell, i.e. Schaffer and commissural pathways, which make synapses in all layers except soma and stratum lacunosum-moleculare. In the latter, synapses originate from the perforant path. Based on experimental data from Shinohara et al. (2012), we divided synapses as follows: for stratum oriens 2 x 20 synapses (12 commissural and 8 Schaffer) and for stratum radiatum 17 commissural and 35 Schaffer synapses.

Each synapse received a train of presynaptic spikes that were generated by independent spikes generators. In NEURON it is taken care of by the built-in process *NetStim*. Presynaptic spikes sequence delivered to one synapse consisted of a combination of random and periodic spike trains. We have chosen this strategy because we can thus simulate the theta activity that is a prominent state of the hippocampal network (Buzsáki, 2002), plus the background random spikes.

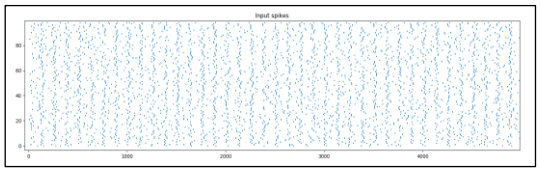

Fig. 2: Ongoing input spontaneous activity over the period of 5s. In this graph the x-axis is the time in ms, and y-axis is the order number of a synapse.

2.3 Synaptic plasticity

Meta-STDP rule was employed to model synaptic plasticity. Implementation of the rule was the same as for the granule cell model in Jedlička et al. (2015). We too have used the presynaptic centered pairing scheme because it is biologically relevant and compatible with the Bienenstock-Cooper-Munro (BCM) theory. In this scheme, for each presynaptic spike, only one last and one next postsynaptic spike is considered. The weight change is calculated as:

$$\mathrm{w}(\mathrm{t}+\Delta\mathrm{t}) = \mathrm{w}(\mathrm{t})\left(1+\Delta\mathrm{w}_\mathrm{p}-\Delta\mathrm{w}_\mathrm{d}\right) \quad (2)$$

where Δw_p is positive weight change and Δw_d is negative weight change.

On the one hand, the positive weight change (potentiation) occurs when presynaptic spike precedes postsynaptic spike. On the other hand, weakening of the weight (depression) occurs when postsynaptic spike precedes postsynaptic spike. It is formulated as:

$$\Delta w_p(\Delta t) = A_p exp\left(-\frac{\Delta t}{\tau_p}\right)\Delta t > 0 \quad (3)$$

$$\Delta w_d(\Delta t) = A_d exp\left(\frac{\Delta t}{\tau_d}\right)\ if\ \Delta t < 0 \quad (4)$$

where $\Delta t = t_{post} - t_{pre}$, A_p and A_d are amplitudes, τ_p and τ_d are decay constants for the time windows over which synaptic change can occur. Parameter t_{post} represents the instant of time at which the voltage on the postsynaptic dendrite, where a synapse is located, exceeds the threshold of −37 mV. It is experimentally estimated threshold for induction of LTD/LTP (Lisman and Spruston, 2005).

Amplitudes of LTP / LTD in the meta-STDP are dynamically changed as a function of a previous temporal average of soma spiking ϑ_S:

$$\mathrm{A_p(t)} = \mathrm{A_p(0)}\left(\frac{1}{\theta_S(t)}\right) \quad (5)$$

$$A_d(t) = A_d(0)\theta_S(t) \quad (6)$$

$$\theta_S(t) = \alpha\langle c\rangle_\tau = \frac{\alpha}{\tau}\int_{-\infty}^{t} c(t')exp\left(\frac{-(t-t')}{\tau}\right)dt' \quad (07)$$

where $A_p(t)$ and $A_d(t)$ are amplitudes for potentiation and depression at time t, and α is a scaling constant. $A_p(0)$ and $A_d(0)$ are initial values at time *0*. The term $\langle c\rangle_\tau$ expresses the weighted temporal average of the postsynaptic spike count, with the most recent spikes entering the sum with bigger weight than the previous ones (Benuskova and Abraham, 2007).

In our simulations, we used already existing .mod files developed by Jedlička et al. (2015) (https://senselab.med.yale.edu/modeldb/ShowModel.cshtml?model=185350) to model plastic synapses according to the meta-STDP synaptic plasticity rule. We joined these files with the files of the compartmental CA1 model into a one synaptically plastic CA1 model.

3 Results

The first step was to optimize our model parameters to mimic firing as in *in vivo* conditions. We performed it in two phases: the model with fixed weights (without synaptic plasticity rule) and the model with plastic weights (with the synaptic plasticity rule described above).

In experiments with the model with fixed weights we manipulated the values of initial weights and parameter *start* of *Netstim*. The model output firing frequency corresponded to *in vivo* CA1 pyramidal cell behavior when the weights were randomly initiated to values from interval [0.0002, 0.0003) and parameter *start* of *Netstim* to random values from interval [0, 46). Average input frequency from 10 runs was 7.27 (standard deviation 0.03) and average output frequency was 2.56 (standard deviation 0.76), see Fig. 3.

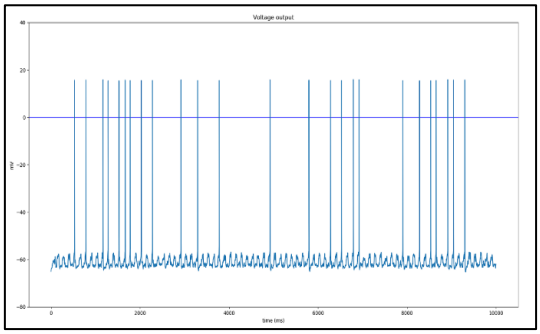

Fig. 3: The CA1 pyramidal cell model firing at frequency 2.56 Hz without synaptic plasticity over 10s. The x-axis is the time in ms, and y-axis is the somatic voltage in mV.

The model with plastic synapses had more parameters that were optimized. Each simulation run covered about 5 minutes of real time. Parameters were considered as optimal when the model output firing frequency was about 2.0 Hz, and weights, average weights and amplitudes A_p and A_d were dynamically stable. This has been accomplished using the following parameter values: *NetStim* parameter *start* from interval [0, 40), initial random weights from interval [0.0002, 0.0006)[0.0002,0.0006). Initial amplitudes were set to $A_p(0)$ = 0.004 for potentiation and $A_d(0)$ = 0.002 for depression. Scaling constant α was set to 3000. Decay time constant for potentiation and depression was τ_p = τ_d =15 ms, and averaging time constant τ for postsynaptic spike count was 50000 ms.

The following figures show the results of individual weights (Fig. 4), average weights (Fig. 5), potentiation and depression amplitudes (Fig. 6) and integrated spike count ϑ_S (Fig. 7) for one typical simulation. The next figure shows the evolution of individual synaptic weights in all the layers i.e. oriens distal, radiatum proximal, radiatum medial, radiatum distal and lacunosum-moleculare, over the first 5 minutes of time.

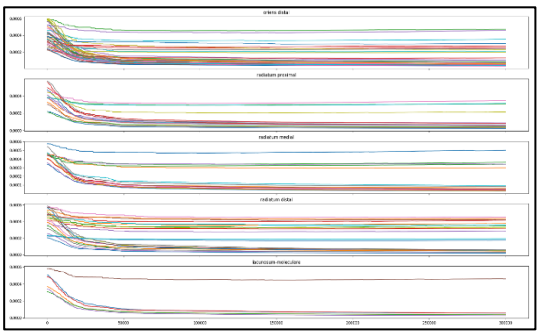

Fig. 4: The CA1 pyramidal cell model weights were stabilized with employed meta-STDP rule after a short transitory period. The x-axis denotes time in ms and the y-axis denotes values of synaptic weights. Output firing frequency 1.78 Hz.

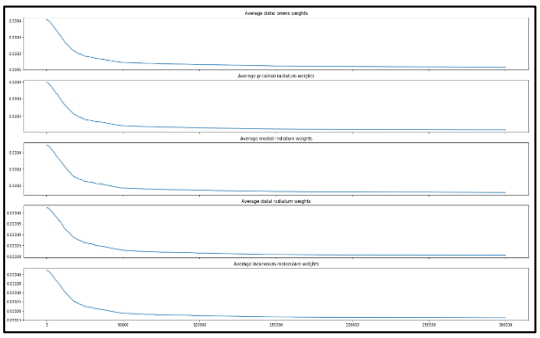

Fig. 5: The CA1 pyramidal cell model average weights in all the layers were stabilized with employed meta-STDP rule. Output firing frequency 1.78 Hz.

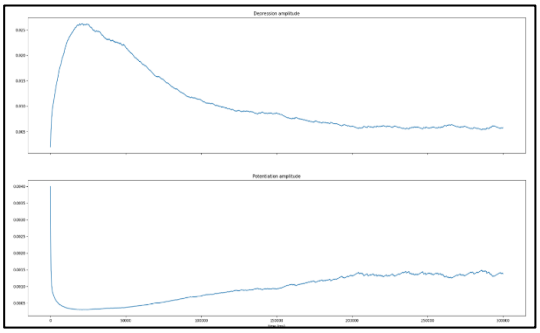

Fig. 6: The CA1 pyramidal cell model depression and potentiation amplitudes were stabilized with employed meta-STDP rule. Output firing frequency 1.78 Hz.

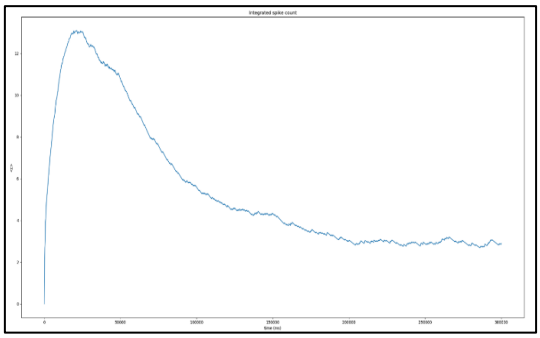

Fig. 7: The CA1 pyramidal cell model integrated spike count was stabilized with employed meta-STDP rule. Output firing frequency 1.78 Hz.

4 Discussion

A detailed biophysically realistic compartmental model of the CA1 pyramidal cell endowed with the meta-STDP synaptic plasticity rule has been introduced. In this study we optimized the model parameters to mimic *in vivo* firing under realistically simulated ongoing spontaneous activity as recorded in neuronal circuits (Buzsáki, 2002). Each synapse received an independent spike train input consisting of periodic spikes corresponding to theta activity and random spikes corresponding to random background activity. Average frequency of spikes in the one spike train was ~8 Hz. We also found that only random spikes are not sufficient to generate action potential at the soma. On the other side, fully synchronized inputs have caused a very high output firing frequency.

In our model we used the same synaptic plasticity mechanism as in the granule cell model in which ongoing spontaneous activity was a key determinant of degree of LTP and LTD (Jedlička et al., 2015). The meta-STDP rule consists two components. Each synapse has implemented paired-centered voltage-based STDP. For each presynaptic event are considered two postsynaptic events, one occurred before and one occurred after presynaptic event. The presynaptic event is a delivery of spike at the synapse. The postsynaptic event is registered when voltage at the synapse reaches threshold −37 mV (Lisman and Spruston, 2005). This is due to propagation of excitatory postsynaptic potentials from other synapses, and to back-propagation of action potentials from the soma. The second component of the meta-STDP rule is the BCM-like metaplasticity. It calculates current depression and potentiation amplitudes based on average soma output firing activity ϑ_S. Higher average output activity decreases potentiation amplitude and increases depression amplitude, lower output activity decreases depression amplitude and increases potentiation amplitude to maintain homeostasis. STDP at the synapses uses these amplitudes for weights modification. This synaptic plasticity rule is in accord with other recent implementations of metaplastic synaptic plasticity rules like in Clopath et al. (2010) and Zenke et al. (2013).

5 Conclusion

We have modified existing compartmental model of the CA1 pyramidal cell by adding synapses and by implementing synaptic plasticity rule, namely meta-STDP rule. Our model exhibits realistic input-output spontaneous activity as neurons *in vivo*. During ongoing spontaneous activity, synapses should not change their weights. This has been achieved after manual optimization of model parameters. Next, we will implement *in vivo* synaptic plasticity protocols as described in Dong et al. (2008).

References

Abraham, W.C. (2008). Metaplasticity: tuning synapses and networks for plasticity. *Nat. Rev. Neurosci*. 9(5): 387-399.

Abraham, W.C., Logan, B., Wolff, A. and Benuskova, L. (2007). "Heterosynaptic" LTD in the dentate gyrus of anesthesized rat requires homosynaptic activity. *J. Neurophysiol*. 98: 1048–1051.

Benuskova, L. and Abraham, W.C. (2007). STDP rule endowed with the BCM sliding threshold accounts for hippocampal heterosynaptic plasticity. *Journal of Computational Neuroscience* 22(2): 129-133.

Buzsáki, G. (2002). Theta oscillations in the hippocampus. *Neuron* 33(3): 325-340.

Clopath, C., Büsing, L., Vasilaki, E., Gerstner, W. (2010). Connectivity reflects coding: a model of voltage-based STDP with homeostasis. *Nature Neurosci*. 13: 344–352.

Cutsuridis, V., S. Cobb and Graham, B. P. (2009). Encoding and retrieval in a model of the hippocampal CA1 microcircuit. *Hippocampus* 20(3): 423-446.

Dong, Z. et al. (2008). Coincident activity of converging pathways enables simultaneous long-term potentiation and long-term

depression in hippocampal CA1 network *in vivo*. *PLoS ONE*. 3(8): e2848.

Hines, M. L. and Carnevale, N. T. (1997) The NEURON Simulation environment. *Neural Computation*. 9(6): 1179-1209.

Hughes, J. R. (1958). Post-tetanic potentiation. *Physiological Reviews*. 38(1): 91-113.

Jedlicka, P., Benuskova, L. and Abraham, W. C. (2015). A voltage-based STDP rule combined with fast BCM-like metaplasticity accounts for LTP and concurrent "heterosynaptic" LTD in the Dentate Gyrus *in vivo*. *PLOS Computational Biology*. 11(11): 1-24.

Lisman, J. and Spruston, N. (2005). Postsynaptic depolarization requirements for LTP and LTD: a critique of spike timing dependent plasticity. *Nat. Neurosci.* 8: 839–841.

Markram, H., Lübke, J., Frotscher, M., Sakmann, B. (1997). Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. *Science*. 275(5297): 213-225.

Mayr, C.G. and Partzsch, J. (2010). Rate and pulse based plasticity governed by local synaptic state variables. *Front. Syn. Neurosci*. doi: 10.3389/fnsyn.2010.00033

Megías, M. et al. (2001). Total number and distribution of inhibitory and excitatory synapses on hippocampal CA1 pyramidal cells. *Neuroscience*. 102(3): 527-540.

Mizuseki, K. and Buzsáki, G. (2013). Preconfigured, skewed distribution of firing rates in the hippocampus and entorhinal cortex. *Cell Reports*. 4(5): 1010-1021.

Poirazzi, P., Brannon, T. and Mel, B. W. (2003a). Arithmetic of subthreshold synaptic summation in a model CA1 pyramidal cell. *Neuron*. 37(6): 977-987.

Poirazzi, P., Brannon, T. and Mel, B. W. (2003b) Pyramidal neuron as a 2-layer neural network. *Neuron*. 37: 989–999.

Shinohara, Y. et al. (2012) Hippocampal CA3 and CA2 have distinct bilateral innervation patterns to CA1 in rodents. *European Journal of Neuroscience*. 35(5): 702-710.

Schomburg, E. W. et al. (2014). Theta phase segregation of input-specific gamma patterns in entorhinal-hippocampal networks. *Neuron*. 84(2): 470-485.

Zenke, F., Hennequin, G. and Gerstner, W. (2013). Synaptic plasticity in neural networks needs homeostasis with a fast rate detector. *PLoS Comput Biol* 9(11): e1003330. pmid:24244138