Effects of short-term synaptic plasticity in a local microcircuit on cell firing

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Abstract

Effects of short-term synaptic plasticity on cell firing properties in a microcircuit formed by a reciprocally connected pyramidal cell and FSN interneuron in layer 2/3 of neocortex were analyzed in a biophysical model. Induction of synaptic depression by backpropagating dendritic action potentials was replicated, as well as the resulting time dependent depression of IPSP amplitudes. Results indicate that the effect of the depression becomes significant above 30 Hz input frequency. The magnitude of the effect depends on the time constant of the dendritic calcium regulating the depression. The frequency range depends on the time constant of the IPSP.

1 Introduction

External excitatory input to a pyramidal cell can cause the cell to fire. In the case the pyramidal cell is reciprocally connected to an inhibitory interneuron, the local negative feed-back may however prevent sustained firing. Pyramidal cell spike frequency adaptation may further reduce the likelihood of prolonged firing. We study how short-term synaptic depression, dependent on spike activity of the post synaptic cell, may affect the firing of the pyramidal cell in a cortical microcircuit.

2 Experimental background

Dual whole-cell recordings were made in layer 2/3 of the rat neocortex in synaptically connected pyramidal cells and fast-spiking non-accommodating (FSN) interneurons. In 75% of cell pairs (n=80), the cells formed reciprocal synaptic connections. Trains of backpropagating action potentials (APs) in pyramidal cells induced Ca^{2+} transients in dendrites followed by inhibition of unitary IPSPs [7], see Fig.1a. In 16 cell pairs, the mean IPSPs decreased during conditioning to 68% of control. The onset time of synaptic depression was within one second and transmission recovered during one minute. Synaptic depression was dependent on a rise in dendritic Ca^{2+} with a threshold at about 40 nM $[Ca^{2+}]$i , and saturating at about 1 μM $[Ca^{2+}]$i . Depression was prevented by loading pyramidal cells with exogenous Ca^{2+} buffers, 5 mM BAPTA or EGTA. Paired-pulse depression of IPSPs decreased significantly following the AP bursts suggesting the presynaptic expression of depression. IPSP depression was mimicked by the metabotropic glutamate receptor (mGluR) agonist ACPD and was prevented by a mixture of the mGluR antagonists CPCCOEt and EGLU, indicating that activation of mGluRs underlies this form of synaptic modulation. We concluded that presynaptic mGluRs are activated by a retrograde messenger, presumably glutamate, released from pyramidal cell dendrites following backpropagating APs. Glutamate activates presynaptically located mGluRs receptors that results in inhibition of FSN terminal Ca^{2+} channels via a G-protein dependent pathway leading to a reduction in GABA release.

3 Modeling methods

Biophysical multicompartmental neuronal simulations were performed using the NEURON simulation package [2].

The layer 2/3 neocortical pyramidal cell was modeled according to Bush and Sejnowski [1] for the passive compartmental representation, and according to Lytton and Sejnowski [4] for the kinetics of ion channels.

Ion channel conductances were tuned to replicate basic electrophysiological characteristics [7, 5]. For the FSN interneuron the same set of parameters were used, except that the Ca-current and the Ca-dependent K-current were omitted yielding a non-adapting cell, and with a change of the conductance of the leakage K-current, yielding a cell with shorter soma membrane time constant and higher input resistance. Pair-pulse depression at the connections between the FSN and the pyramidal cell were modeled according to Varela *et.al* [6].

As described above, the pyramidal cell and the interneuron were reciprocally connected. When present, the pyramidal to pyramidal connection is very weak, 0.2 mV EPSP amplitude (Zilberter, unpublished observations) and was therefore omitted. FSN to FSN connections appears absent (Zilberter, unpublished observations), and were also omitted.

The fast component of the conditioning induced short-term synaptic depression of the inhibitory synapse was modeled according to Zilberter [7] and Kaiser *et.al* [3]. The same type of model formalism was used as in Varela *et.al* [6]. It should be noted that the fast component only corresponds to about 20% of the total decrease in amplitude. The total decrease of the IPSP is about 50% for the conditioning protocol of 10 APs at 50 Hz used here. Thus, including also the slower time constant would increase the effects of the depression reported here.

4 Results

Induction of synaptic depression by backpropagating dendritic action potentials leading to elevated Ca-levels followed by release of a retrograde messenger were replicated, as well as the resulting time dependent depression of IPSP amplitudes, see Fig. 2.

In the microcircuit simulations, the cells were driven by a constant stimulation frequency that was varied between simulations. Preliminary results indicate that at low input frequencies, up to around 30 Hz the effect of the depression is rather small, but increase thereafter, see Fig 3.

The input frequency at which the influence changes from small to substantial depends on the magnitude of the inhibitory synaptic conductance, see Fig. 4a. Conceptually, this can be understood in terms of how EPSPs and IPSPs sum up to potentially reach the spiking threshold, and subsequently how spike mediated AHPs sum up and potential prevent spiking, see Fig 1b. In this tug-of-war the depression may lower the inhibition and allow spikes to occur due to EPSPs that otherwise would not have reached threshold. The magnitude of the effect depends on the time constant of the dendritic calcium that regulates the depression.

The magnitude of the effect also depends on the time constant of the spike frequency adaptation as well as on the time constant of the cell membrane (data not shown).

There is a time window for the effects of the plasticity. Due to the relative slow kinetics of the induction of the depression, short lasting inputs will be relatively unaffected by the depressio and be subject to the full level of inhibitory IPSP amplitudes. It takes on the order of 10 spikes before the depression has started to build up, see Fig. 4b. Inputs lasting long enough for depression of IPSPs to develop, will however be less attenuated. Excitability and firing frequencies will therefore be higher thereafter.

5 Discussion

Microcircuit interactions play a crucial role in determining the response of a pyramidal cell to afferent input. We show here how a conditioning induced short-term synaptic depression affects the interplay between a pyramidal cell and an interneuron which are reciprocally connected, essentially modulating the gain in the negative feed-back from the interneuron to the pyramidal cell. The result is a frequency dependent "restoration" of action potentials that in the case of intact inhibition would have been lost.

References

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Fig. 1

a Synaptic plasticity. Backpropagating action potential depolarization activates Ca-currents leading to Ca-influx. Subsequently, glutamate is released which activates presynaptic metabotropic glutamate receptors, which ultimately leads to a reduction in the GABA release.

b Summation of EPSPs, IPSPs and AHPs. Depending on the current activation of AHP-related currents, as well as preceding IPSCs, incoming EPSPs may or may not reach spike threshold.

Fig. 2

Stimulation protocol. The effect of postsynaptic cell conditioning with 10 APs at 50 Hz (c), leading to elevated levels of [Ca] (d), is shown as a decrease in IPSP amplitude between second and third IPSP (b). Double pulses before and after conditioning show existence of pair-pulse depression as well (b). (a), (c) presynaptic and postsynaptic cell membrane potential respectively. (b) IPSP amplitude, baseline subtracted. (d) Dendritic [Ca] (arbitrary units).

Fig. 3

Restoration of spikes. Below some 30 Hz the synaptic plasticity does not contribute to the spike restoration. Above some 40 Hz the synaptic depression of inhibition allows more spikes to be produced, *i.e.* spike restoration.

Fig. 4

a Window where depression restores spikes. Darker color indicates larger number of restored spikes. At stimulation frequencies above some 35 Hz and between inhibitory synaptic conductances of about 0.07 to 0.23 μS, more spikes are generated due to suppression of IPSPs. Color range from light gray to black: $\leq$-1, 0, 1, 2, $\geq$3 restored spikes.

b Temporal development of suppression. Due to the kinetics of the suppression, full suppression is not reached until some 15 spikes have passed. A 10 Hz difference corresponds to 20% change from steady-state. Abscissa: inter-spike interval, ordinate: frequency difference between the case with the synaptic plasticity included and the case without plasticity.

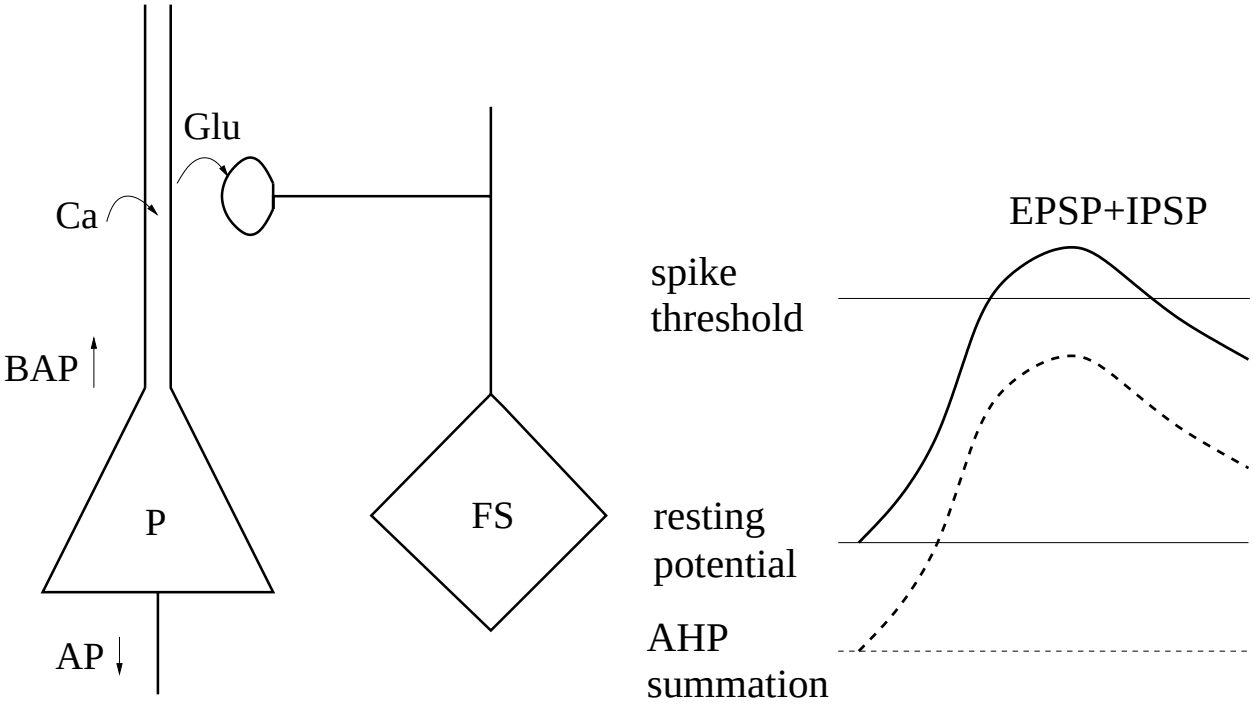


Figure 1: a (left), b (right)

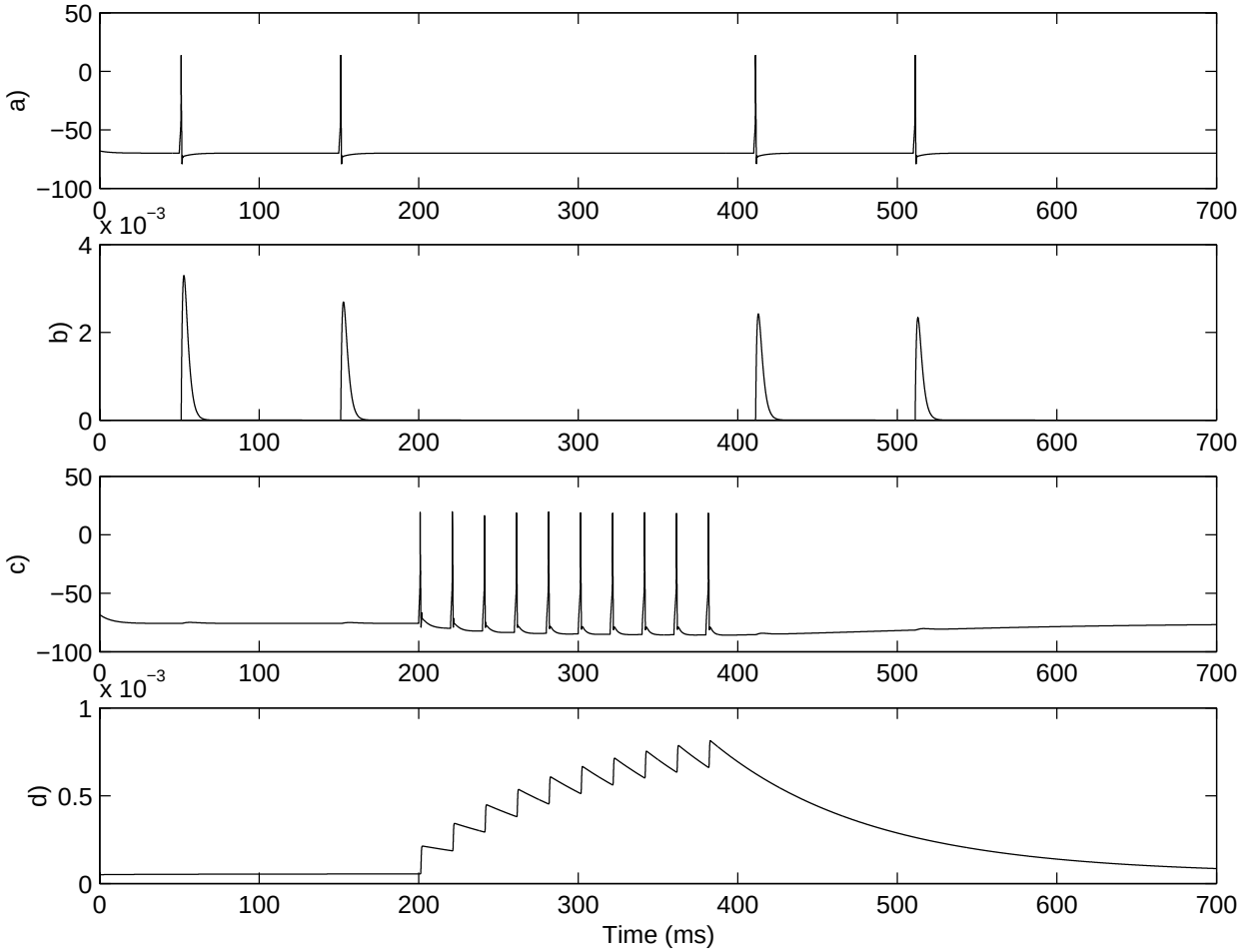


Figure 2:

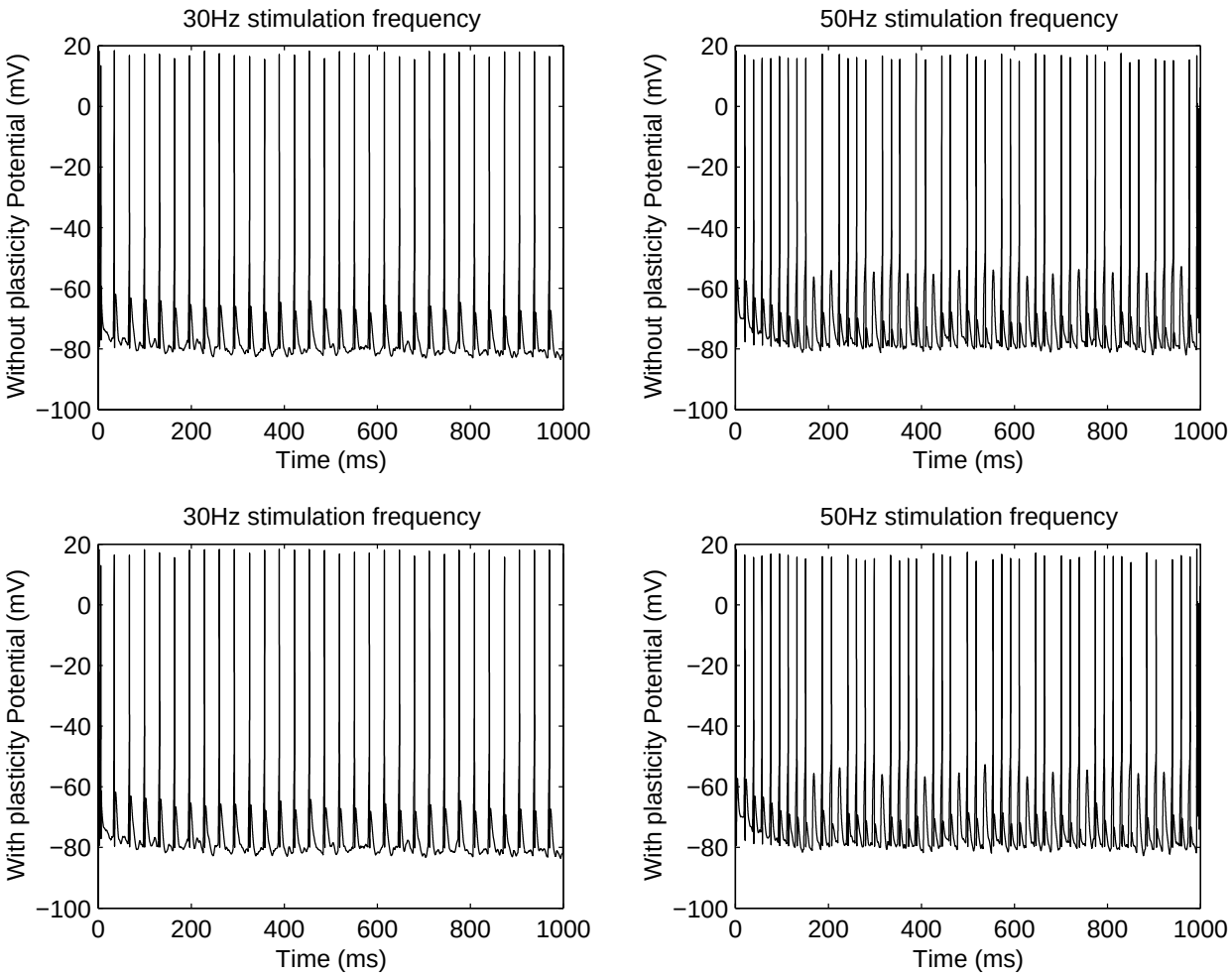
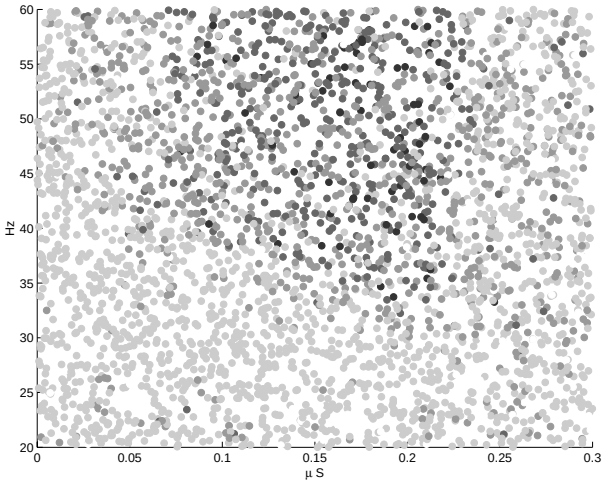

30Hz stimulation frequency
50Hz stimulation frequency
Without plasticity Potential (mV)
With plasticity Potential (mV)
Time (ms)
20
0
−20
−40
−60
−80
−100
0
200
400
600
800
1000

Figure 3:



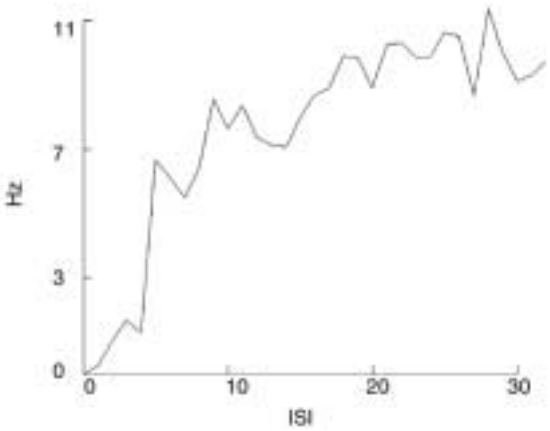


Figure 4: a (left), b (right)