A synapse which can switch from inhibitory to excitatory and back

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Keywords: co-release, short-term synaptic plasticity, conditioning depression

Abstract

Co-release of transmitters have recently been observed at synapse terminals and can even be a combination such as glutamate and GABA.

A second recent experimental finding is a short-term synaptic plasticity which depends on postsynaptic depolarization releasing dendritic transmitter which affects presynaptic release probability.

In this work we are investigating the functional consequences for a synapse if it had both co-release and conditioning depression. If initially the GABA component is larger than the glutamate component, the synapse has an inhibitory net effect. However, if the postsynaptic cell is conditioned, the GABA component will be suppressed yielding an excitatory synapse.

1 Introduction

Co-release of transmitters have been observed at periferal and central synapse terminals [4] and can even be a combination of transmitters exerting an excitatory and an inhibitory effect such as glutamate and GABA [10, 12]. Presence of co-localization of functional receptors postsynaptically have been inferred from the corresponding currents for some of these cases [7], indicating that these synapses indeed are functional.

A second recent experimental finding is a short-term synaptic plasticity which depends on postsynaptic depolarization [14, 15]. These neocortical synapses display a depression down to some 50% of their initial peak amplitude if preceded by a conditioning of the postsynaptic cell comprised of backpropagating dendritic action potentials releasing dendritic transmitter which affects presynaptic release probability.

In this work, using computational modeling, we are investigating the functional consequences for a synapse if it had both co-release and conditioning depression. Assuming that initially the GABA component is larger than the glutamate component, the synapse has an inhibitory net effect. However, if the postsynaptic cell is conditioned thereby releasing glutamate, the GABA component will be suppressed and as a consequence the glutamatergic component may instead be larger, yielding an excitatory synapse.

A semi-stable switch from inhibitory to excitatory action can result from the following: Consider a neuron A which has a synaptic contact to neuron B, and assume this synapse has co-release. Then if neuron B is excitatory and displays short-term conditioning depression, this synapse may work like a bistable (semi-stable) switch. Supposing B is active and backpropagating Glu to the pre terminal of A, this will suppress the GABA component, and the synapse will switch from the initial net inhibitory action to an excitatory action. Subsequently, when A is active B will get excited and the situation is stable. If, instead B is not conditioned, then the GABA component is not suppressed and transmission from A will suppress B, also a stable situation.

2 Modeling methods

Biophysical multicompartmental neuronal simulations were performed using the NEURON simulation package [6]. The model was based on earlier work on conditioning depression [5]. In short, one 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 [9] for the kinetics of ion channels. Ion channel conductances were tuned to replicate basic electrophysiological characteristics [11, 14]. For the 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.

The interneuron is connected to the pyramidal cell with a synapse providing co-release of both glutamate and GABA. Postsynaptic receptors are assumed to be of the AMPA and $GABA_A$ types. Their kinetics of activation are the main parameters in this study as they together determine the net effect of the synapse. Variability in the literature on rise times are considerably smaller than on decay times, and to constrain our parameter study the rise time constant was set to 1ms for both components [2, 3].

The conditioning induced short-term synaptic depression of the inhibitory synapse component was modeled according to Zilberter [14] and Kaiser *et.al* [8]. The same type of model formalism was used as in Varela *et.al* [13]. The total decrease of the IPSP is here about 50% for the conditioning protocol of 10 APs at 50 Hz. It should be noted that in the data of Zilberter the decrease had a biphasic kinetics, with a faster component like the one used in this work amounting to some fifth of the decrease and a slower component for the rest. The conditioning depression works as follows: When the postsynaptic pyramidal cell fires action potentials, these back-propagate into the dendritic compartments and activate high-threshold Ca-channels. The amount of Ca in the dendrite compartment where the synapse is located controls the depression of the synaptic conductance, as described by Zilberter [14] and modeled in [5].

3 Results

Figure 1 shows a simulation where the first spike in the presynaptic neuron elicits a predominantly inhibitory effect on the postsynaptic cell. After a conditioning of the postsynaptic cell the depression has decreased the inhibitory component of the synapse so that the second spike in the presynaptic cell produces a net excitatory effect.

< insert figure 1 around here >

The magnitude of this effect depends on the kinetics of the two synapse components, and therefore the time constants of decay of the AMPA and $GABA_A$ components have been varied. In this ongoing work we want to study quantitatively how large the effect is using several different measures. One measure is the membrane potential shift that results from activation of the synapse. This constitutes the effect of the synapse on the excitability or spike probability of the postsynaptic cell in that repetitive activation of the synapse will by temporal summation lead to postsynaptic spiking or hyperpolarization. The difference in shift before and after conditioning was therefore used as a measure. Figure 2 shows a variation in the time

constant of the decay of the excitatory and of the inhibitory component. As can be seen the model works for an extended interval of parameter values.

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4 Discussion

We argue that a synapse may under assumptions of combined co-release and conditioning suppression except a basic inhibitory action, but can on a short-term basis be modulated to be excitatory.

This way a synaptic connection may store temporarily either a positive or negative weight depending on the activity of both the presynaptic and postsynaptic neurons. As the effect is working on a slower time scale than single spikes, the synapse can store temporarily a correlation which has existed in a time window. This could be one correlate of the intermediate memory for temporary bindings often discussed in learning theories.

Note, if instead the postsynaptic neuron is inhibitory, the synapse will not display switching as above, but negative feed-back and will be dynamically adjusting to produce a constant activity of the postsynaptic neuron. This synapse will thus display homeostatic effects as it tends to oppose changes in firing of the pre and postsynaptic cell.

5 Acknowledgments

This work was supported by the Swedish research council, VR 240-00023-061.

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Lars Zandén is an undergraduate in computer science at the Royal Institute of Technology in Stockholm. Material presented in this article is part of his Master Thesis.

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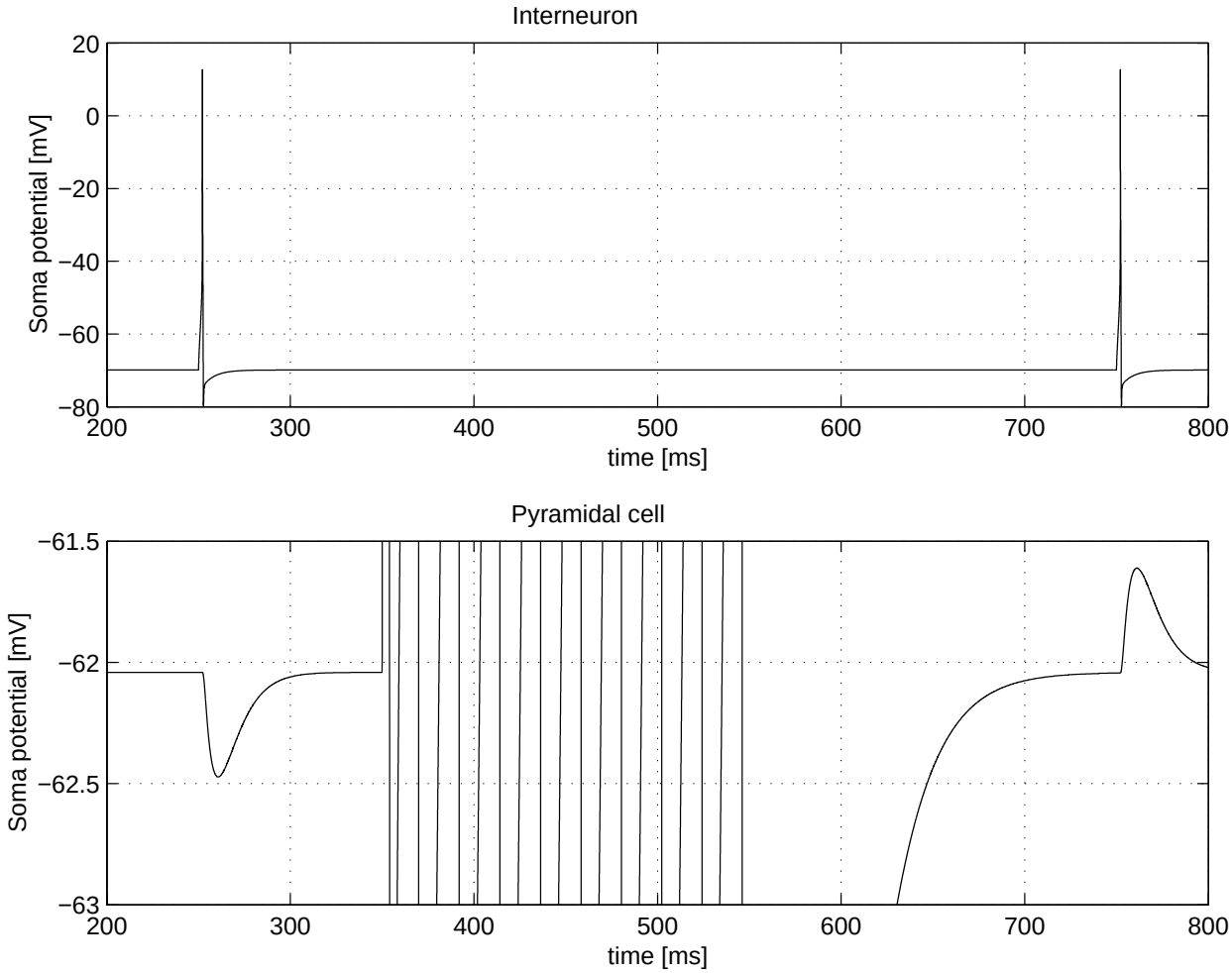
Interneuron
Soma potential [mV]
20
0
−20
−40
−60
−80
200
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400
500
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700
800
time [ms]
Pyramidal cell
Soma potential [mV]
−61.5
−62
−62.5
−63
200
300
400
500
600
700
800
time [ms]

Figure 1:

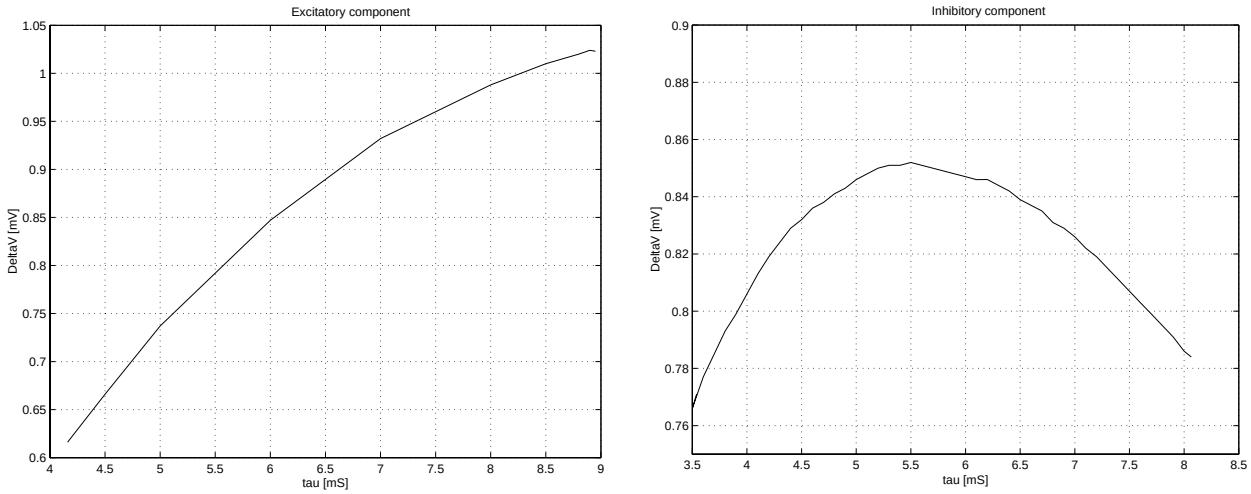

Figure 2: a (left), b (right)

Figure 1

Synapse changing from inhibitory to excitatory after conditioning of postsynaptic cell. Pyramidal cell action potentials during conditioning are truncated. Decay time constants of excitatory and inhibitory synaptic components are both 6ms [2, 3].

Figure 2

Variation of synaptic decay time constant. a (left) excitatory component, b (right) inhibitory component. The figures show the difference between the synaptic event before and after the conditioning, *i.e.* net depolarization from the second input - net hyperpolarization from the first input. The effect of a synaptic event was measured as the soma membrane potential difference before and 3 decay time constants after initiation of the synaptic event. Outside these curves the synapse did not change from inhibitory to excitatory.

Figure 3: Erik Fransén

Figure 4: Lars Zandén