A synapse which can switch from inhibitory to excitatory and back

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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 post-synaptic 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: Changing synapses

Co-release of transmitters have been observed at periferal and central synapse ter-

minals [4, 7, 11, 14] and can even be a combination of transmitters exerting an excitatory and an inhibitory effect such as glutamate and GABA [11, 14]. 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 [17, 18]. These neocortical synapses display a depression down to some 50% of their initial peak amplitude if preceded by a conditioning of the postsynaptic cell producing backpropagating dendritic action potentials. This depolarization activates Ca-currents leading to a Ca-influx, which in turn leads to release of a transmitter from the dendrite. This transmitter binds presynaptically and reduces the 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, thus a synapse which can switch from inhibitory to excitatory.

Experimental indications for the possibility of a change of polarization of a synapse comes from studies of $GABA_A$ synapses *e.g.* [13, 8] showing a change from hyperpolarizing to depolarizing action, and have been modeled by Szalisznyo and Erdi [15]. In these studies a change of reversal potential of the GABA-ergic synapse takes place due to changes in extracellular potassium or pH. The experiments, which commonly are

performed on tissue in an early developmental stage, usually involve a high frequency tetanus for the change to take place. It is important to note that the change in reversal potential is from below resting to above resting potential. GABA-ergic synapses are in this sense becoming depolarizing, but importantly it is not a change surpassing the spike threshold. This type of synapse is therefore not excitatory in the strict sense of unequivocally increasing likelihood of spiking.

In this work, a semi-stable switch from inhibitory to excitatory action can however result from the following: Consider a neuron A which has a synaptic contact to neuron B, and assume B is excitatory. Then if the synapse has co-release 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 presynaptic 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 thus opposing conditioning, 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 [10] for the kinetics of ion channels. Ion channel

conductances were tuned to replicate basic electrophysiological characteristics [12, 17]. 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 decrease 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 decay time constants is fairly large, but is considerably smaller for the rise time constants. Therefore, to constrain our parameter study two different rise time constants, 1ms (standard [2, 3]) or 4ms (slow case) were tested for both the inhibitory and the excitatory components. For the decay time constants, a value of 6ms (standard [2, 3]) or 18ms (slow case) were used for one of the components while the other was varied over an interval.

The conditioning induced short-term synaptic depression of the inhibitory synapse component was modeled according to Zilberter [17] and Kaiser *et al.* [9]. The conditioning depression model 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 [17] and as modeled in [5]. The same type of model formalism was used as in Varela *et al.* [16]. 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 constitutes the remainder.

The effect of a synaptic event was measured as the soma membrane potential difference just before the PSP and 1.5 (or 3) decay time constants after the peak of the synaptic event. The two potential differences, before and after conditioning, were summed with the requirement that only cases were included where the first difference was negative and the second difference was positive, indicating a switch from inhibitory to excitatory effect had taken place.

3. Results: Synaptic change from inhibition to excitation

Whether a switch takes place and the magnitude of this change depends on the kinetics of the two synaptic components AMPA and $GABA_A$. In this work we have studied quantitatively how large the effect is on the soma membrane potential of the postsynaptic cell under a variety of values of the rise and decay time constants. More importantly, we have also studied how large the parameter interval is over which a switching from inhibition to excitation occurs.

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 >

Figure 2 shows results from simulations with a variation in the time constant of the

decay of the inhibitory and of the excitatory component. As can be seen the synapse displays switching over an extended interval of parameter values.

< insert figure 2 around here >

Figure 3 shows a summary of several different cases. In A, B and C the soma membrane time constant is 7ms corresponding to a cell under *i.e.* synaptic input in an "*in vivo*-like" situation. In D and E the membrane time constant is 20ms corresponding more to an *in vitro* type situation. For A, B and D the decay time constant that is not changed is 6ms and in C and E it is increased to a slow case of 18ms. As can be seen the synapse displays switching over an extended interval of parameter values in all these cases.

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5. Discussion

We argue that a synapse displaying both co-release and conditioning suppression, a combination yet to be experimentally described, would exert a basic inhibitory action, and could on a short-term basis be modulated to be excitatory.

In 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 operating on a slower time scale than single spikes, the synapse can store temporarily a correlation which has existed in a time window. This could therefore be one correlate of the intermediate memory for temporary bindings often discussed in learning theories. Further, the usefulness of changes in polarization of a synapse in associative memory formation has been demonstrated in modeling studies [15]. Fi-

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

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References

[1] P Bush and T Sejnowski. Reduced compartmental models of neocortical pyramidal cells. *J. Neurosci. Methods*, 46:159–166, 1993.

[2] A Destexhe, ZF Mainen, and TJ Sejnowski. An efficient method for computing synaptic conductances based on a kinetic model of receptor binding. *Neur. Comput.*, 6:14–18, 1994.

[3] A Destexhe, ZF Mainen, and TJ Sejnowski. Synthesis of models for excitable membranes, synaptic transmission and neuromodulation using a common kinetic formalism. *J. Comput. Neurosci.*, 1:195–230, 1994.

[4] M Docherty, HF Bradford, and JY Wu. Co-release of glutamate and aspartate from cholinergic and GABAergic synaptosomes. *Nature*, 330:64–66, 1987.

[5] D Eriksson, E Fransén, Y Zilberter, and A Lansner. Effects of short-term synaptic plasticity in a local microcircu it on cell firing. *Neurocomputing*, 52–54:7–12, 2003.

[6] M Hines, N Carnevale, J Moore, and G Shepherd. Using the NEURON simulation environment. Society for Neuroscience meeting satellite symposium, 1999.

[7] P Jonas, J Bischofberger, and J Sandkühler. Corelease of two fast neurotransmitters at a central synapse. *Science*, 281:419–424, 1998.

[8] K Kaila, K Lamsa, S Smirnov, T Taira, and J Voipio. Long-lasting GABA-mediated depolarization evoked by high-frequency stimulation in pyramidal neurons of rat hippocampal slice is attributable to a network-driven, bicarbonate-dependent K+ transient. *J Neurosci.*, 17:7662–72, 1997.

[9] K Kaiser, Y Zilberter, and B Sakmann. Back-propagating action potentials mediate calcium signalling in dendrites of bitufted interneurons in layer 2/3 of rat somatosensory cortex. *J. Physiol.*, 535.1:17–31, 2001.

[10] W Lytton and T Sejnowski. Simulations of cortical pyramidal neurons synchronized by inhibitory interneurons. *J. Neurophysiol.*, 65:1059–1079, 1991.

[11] ID Manns, L Mainville, and BE Jones. Evidence for glutamate, in addition to acetylcholine and GABA, neurotransmitter synthesis in basal forebrain neurons projecting to the entorhinal cortex. *Neuroscience*, 107:249–263, 2001.

[12] A Mason and A Larkman. Correlations between morphology and electrophysiology of pyramidal neurons in slices of rat visual cortex. II Electrophysiology. *J. Neurosci.*, 10:1415–1428, 1990.

[13] HB Michelson and RK Wong. Excitatory synaptic responses mediated by $GABA_A$ receptors in the hippocampus. *Science*, 253:1420–3, 1991.

[14] R Sandler and AD Smith. Coexistence of GABA and glutamate in mossy fiber terminals of the primate hippocampus: An ultrastructural study. *J. Comp. Neurol.*, 303:177–192, 1991.

[15] K Szalisznyo and P Erdi. Depolarizing/hyperpolarizing effects of the GABA(A) synapse have a beneficial role in synaptic weight resetting in the hippocampus. *Neuroreport*, 11:3559–6, 2000.

[16] J Varela, K Sen, J Gibson, J Fost, L Abbott, and S Nelson. A quantitative description of short-term plasticity at excitatory synapses in layer 2/3 of rat primary visual cortex. *J. Neurosci.*, 17:7926–7940, 1997.

[17] Y Zilberter. Dendritic release of glutamate suppresses synaptic inhibition of pyramidal neurons in rat neocortex. *J. Physiol.*, 528.3:489–496, 2000.

[18] Y Zilberter, KM Kaiser, and B Sakmann. Dendritic GABA release depresses excitatory transmission between layer 2/3 pyramidal and bitufted neurons in rat neocortex. *Neuron*, 24:979–988, 1999.

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Fig. 1

Synapse changing from inhibitory to excitatory after conditioning of the postsynaptic cell. Postsynaptic cell action potentials during conditioning are truncated. In this example, decay time constants of the excitatory and inhibitory synaptic components both are 6ms.

Fig. 2

Variation of synaptic decay time constant τ_d of the inhibitory component, (top) and of the excitatory component, (bottom). The figure shows the summed net difference before and after conditioning ΔV as described in the methods section. Note that outside these plotted intervals the synapse did not change from inhibitory to excitatory. Importantly, in both figures quite extended intervals of the decay time constant exists. The four different curves correspond to the different cases of rise time constant values tested, 14=inhibitory rise time constant = 1ms and excitatory rise time constant = 4ms, *etc.*

Fig. 3

Interval of decay time constant τ_d. The figure shows in A the result of the data from figure 2, and four more cases (B-E) studied. In these cases the voltage difference was measured 3 time constants from peak of the PSP to reflect better the membrane net effect of the PSC. B corresponds to the same case as A, decay time constant of the fixed variable is 6ms and soma membrane time constant is 7ms. In C the decay time constant held constant was raised to 18ms (slow case). In D the soma membrane time constant was raised to 20ms (*in vitro*), and in D both the decay time constant and the soma membrane time constant were raised. As can be seen in all cases there are extended intervals where a switch takes place. $\tau_r - cases$: In A

the lines correspond from left to right to the cases of inhibitory component varied using 1 and 1; 1 and 4; 4 and 1; 4 and 4 ms for the inhibitory and the excitatory rise time constants respectively, followed by the excitatory component varied with the same cases of rise time constants.

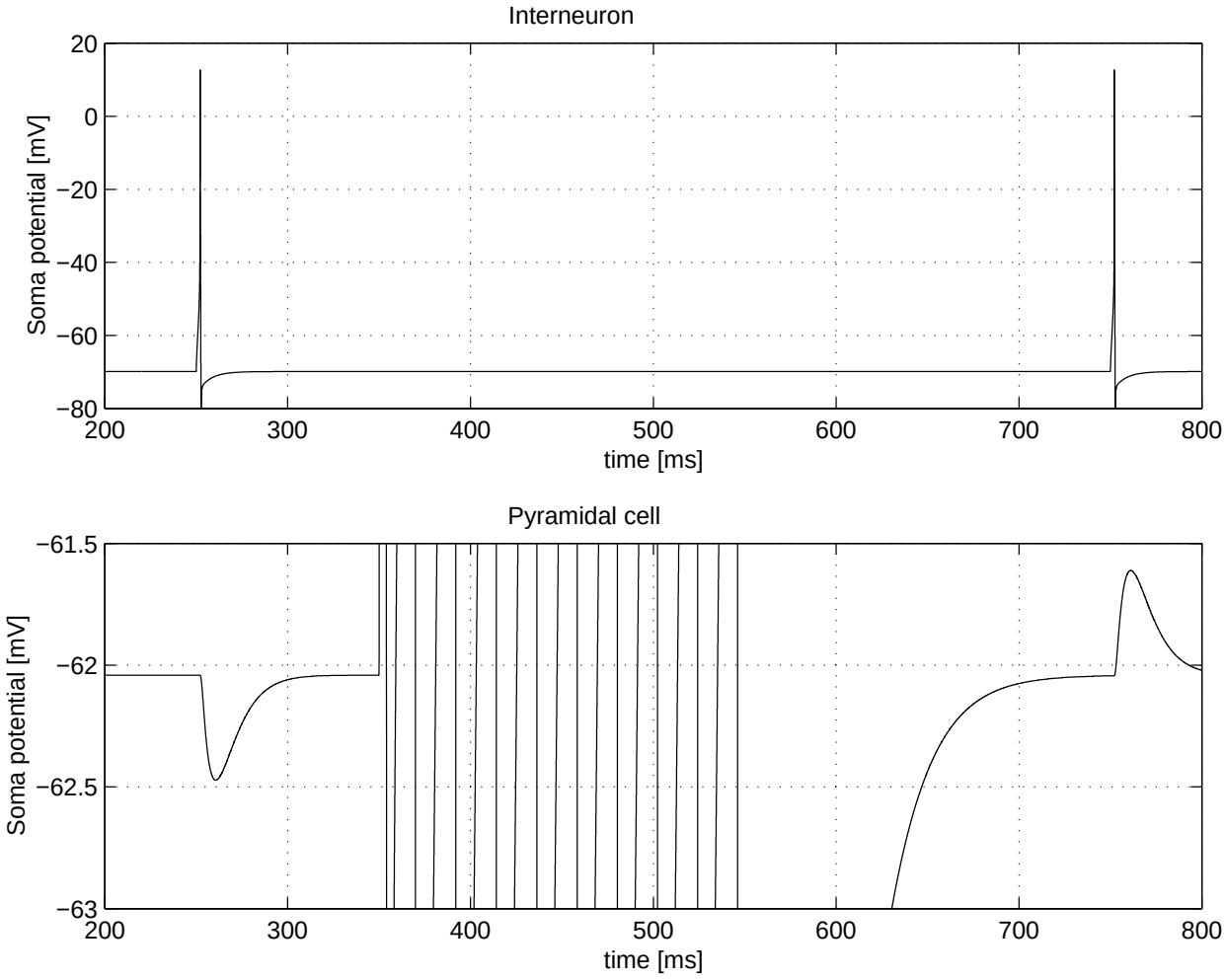
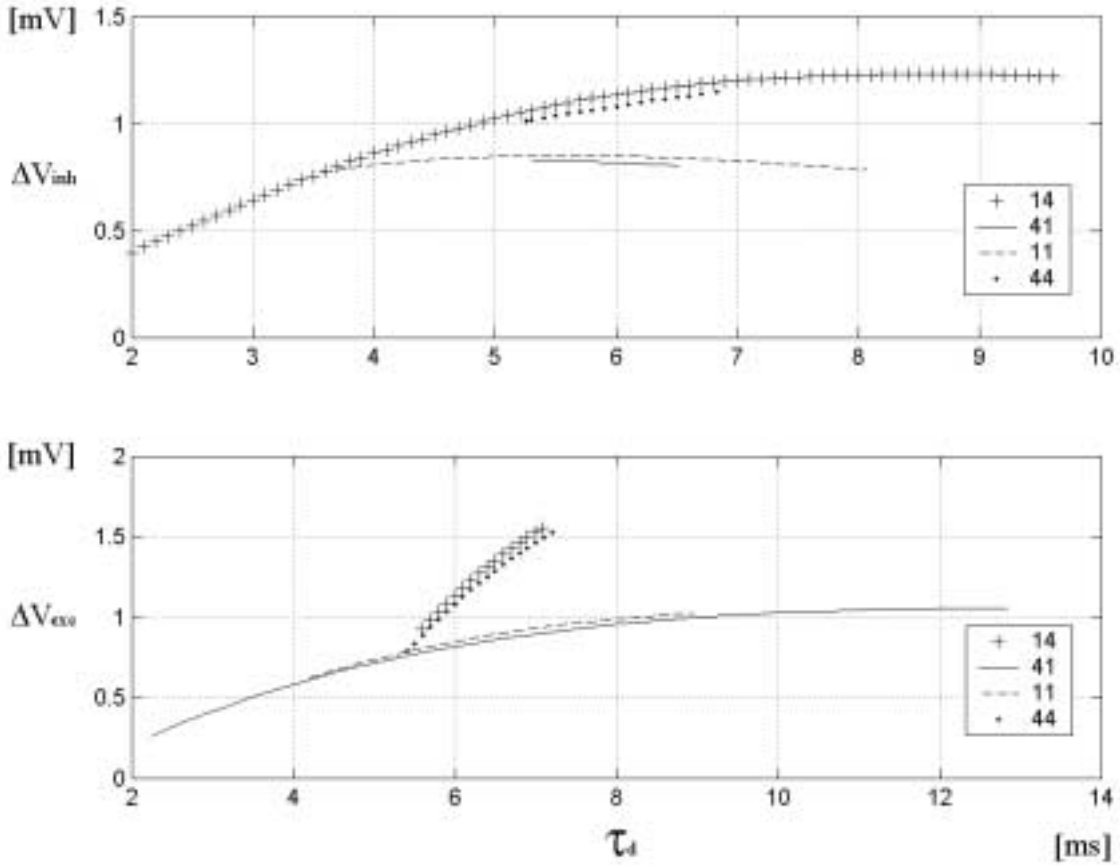

Interneuron
Soma potential [mV]
20
0
−20
−40
−60
−80
200
300
400
500
600
700
800
time [ms]
Pyramidal cell
Soma potential [mV]
−61.5
−62
−62.5
−63
200
300
400
500
600
700
800
time [ms]

Figure 1:


[mV]
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1
0.5
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ΔVinh
2
3
4
5
6
7
8
9
10
14
41
11
44
[mV]
2
1.5
1
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ΔVexc
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4
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τd
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41
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44

Figure 2:

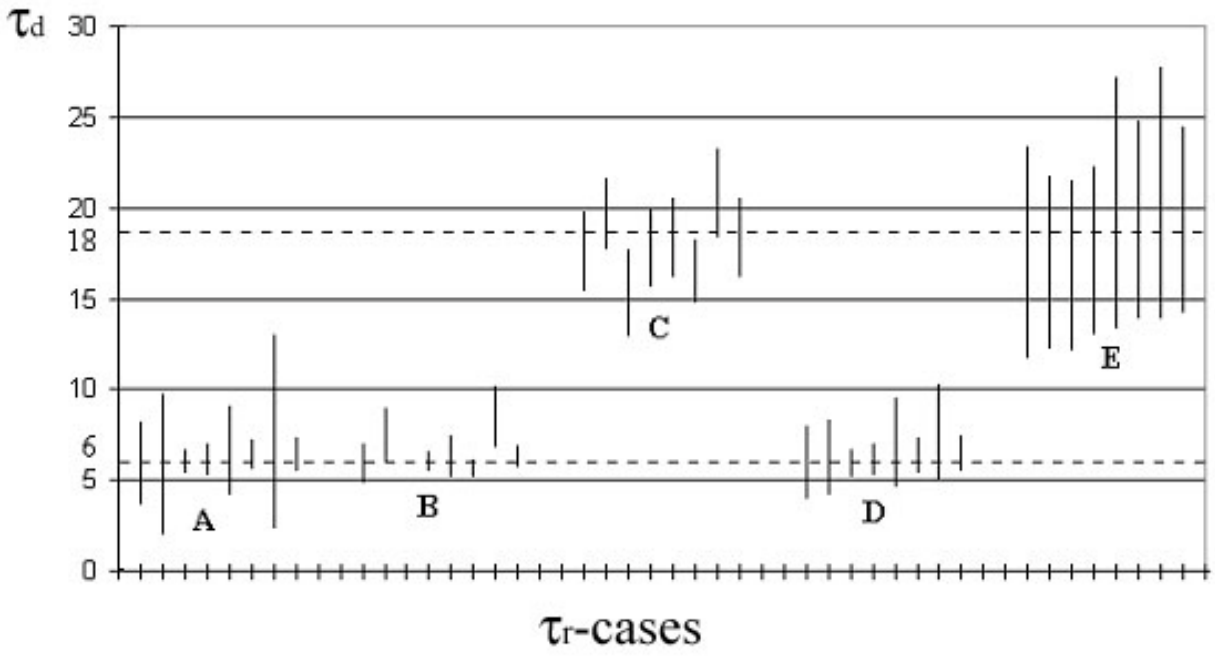

Figure 3: