Biophysical model of a single synaptic connection: transmission properties are determined by the cooperation of pre- and postsynaptic mechanisms

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Abstract

A stochastic model of synaptic transmission has been designed on the basis of electrophysiological experiments. The model includes presynaptic mechanisms of recruitment and calcium related release of vesicles, transmitter dynamics in the cleft and postsynaptic receptor kinetics. Monte Carlo simulations of a single synaptic connection are performed and demonstrate that synapses depress during repetitive presynaptic stimulation due to depletion of presynaptic vesicles as well as receptor desensitization. Only for stimulation frequencies below 40 Hz depression is caused solely presynaptically by depletion of vesicles. It is shown that specific physiological conditions determine the frequency dependence of steady state depression currents and set limits on the range of possibly rate-coded transmission.

1 Introduction

We study the dependence of excitatory postsynaptic currents (EPSCs) on the frequency of incoming presynaptic action potentials. Our motivation is twofold: First, several experiments have observed short term depression of synaptic transmission. The steady state amplitude of the depressed current was found to exhibit a characteristic frequency dependence. Our model allows to study the underlying physiological mechanisms responsible for depression. Second, concerning the rate-coding of information it is of interest to find out under what physiological conditions frequencies of incoming presynaptic spike trains can be transmitted towards the postsynaptic side. Although phenomenological models are able to describe experiments on short term plasticity and make predictions about the limits of frequency coding [7,12,16], these models do not yield insight into the underlying physiological mechanisms.

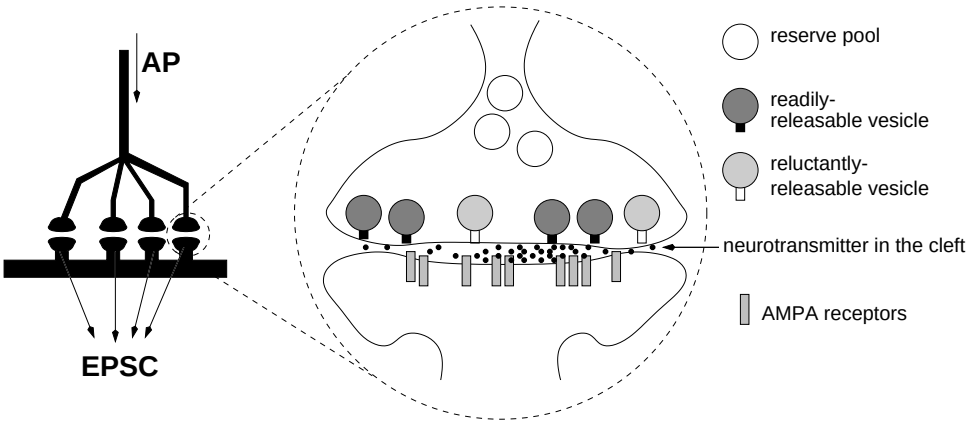

Figure 1: Cascade of physiological processes during synaptic transmission.

2 Model and Methods

Based on electrophysiological experiments we have designed a stochastic model of synaptic transmission that allows to study the effects of pre- and postsynaptic mechanisms on the transmission properties of individual synaptic connections. We consider a synaptic scenario as displayed in Fig. 1: The axonal exit of the presynaptic neuron branches into a few collaterals at some distance from the cell forming individual synaptic connections with the postsynaptic side. These single synaptic boutons are activated by the same presynaptic stimulus and act as independent synaptic entities. Each synaptic bouton exhibits a single active zone, which contains a small number of releasable vesicles. Currents from individual boutons add linearly and yield the total number of open channels, which we interpret as the theoretical analogue of the postsynaptic current (EPSC).

Successive modeling steps comprise presynaptic vesicle dynamics, transmitter motion in the cleft and postsynaptic receptor kinetics as described in the following:

1. *Presynaptic model of vesicle release and recruitment:*

   The model of presynaptic vesicle dynamics has been designed on the basis of experimentally observed patterns of synaptic depression (and facilitation) at the Calyx of Held synapse in the mammalian auditory pathway [11,17,18], but may also hold for hippocampal synapses where heterogeneous release-probabilities have been reported [4,8,10]. Our approach comprises *two types of vesicles* (Fig. 2): *readily-releasable vesicles* and in addition *reluctantly-releasable vesicles* . Empty release sites are first refilled with reluctantly-releasable vesicles which slowly turn into readily-releasable vesicles. Facilitation of release due to previous synaptic activity is included in the model as a consequence of changes in the global residual calcium accumulating during repetitive activity (for details see [15]).

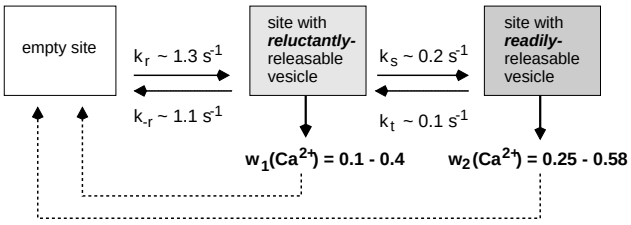

Figure 2: Model of release and recruitment of presynaptic vesicles

2. *Transmitter dynamics in the cleft:*

   As pre- and postsynaptic terminal stick together closely in central synapses, the geometry of the synaptic cleft is described by a flat cylinder. Neuronal and glial transmitter uptake is modeled by an absorbing boundary for the diffusion field. Its location at radius r_{abs} is chosen outside the postsynaptic density (PSD), which contains the postsynaptic receptors and here exhibits a radius of $r_{\text{PSD}} = 150$ nm. The absorbing boundary is set at $r_{\text{abs}} = 500$ nm, comparable to the typical distance between neighboring synapses. An absorbing boundary at larger distances has the same effect as less efficient uptake mechanisms (see [13] for details). The content of a single vesicle is released at once from a point source chosen randomly within the PSD. Individual transmitter molecules diffuse with an effective diffusion coefficient of $D_{\text{net}} = 40\ \text{nm}^2/\mu\text{s}$.

3. *Postsynaptic receptor kinetics:*

   Individual postsynaptic glutamate activated AMPA-receptors are described by the kinetic three-state model (1), comprising a *closed unbound*, *double bound open*, and *desensitized* state:

$$\text{desensitized} \underset{k_d\, f([\text{glu}])}{\overset{k_r}{\rightleftarrows}} \text{closed} \underset{k_c}{\overset{k_o\, f([\text{glu}])}{\rightleftarrows}} \text{open} \,. \tag{1}$$

   Transitions into the open and desensitized state depend on the transmitter concentration [glu]. Binding of transmitter is rapid, such that $f([\text{glu}])$ comprises the binding of two glutamate molecules necessary for channel opening and desensitization:

$$f([\text{glu}]) = [\text{glu}]^2/([\text{glu}]^2 + K_B)$$

   with the transition rates $k_o = 6\ \text{ms}^{-1}$, $k_d = 1.1\ \text{ms}^{-1}$, $k_c = 1.25\ \text{ms}^{-1}$, $k_r = 0.02\ \text{ms}^{-1}$ and $K_B = 450\ \mu\text{M}$ [14].

Monte Carlo simulations are performed to generate individual postsynaptic responses of a single synaptic connection: For a given stimulus protocol the change in presynaptic calcium is

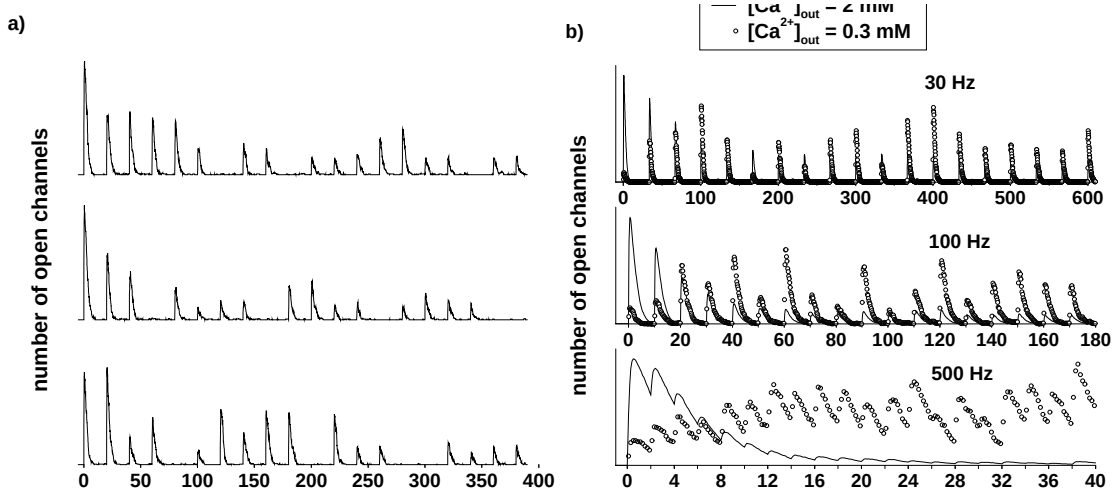

Figure 3: Simulated postsynaptic responses during repetitive stimulation for physiological conditions as found in the hippocampus. a) Three individual simulation runs for stimulation with 50 Hz. b) Averaged synaptic responses (mean over 50 simulations runs each).

calculated, vesicles are released (considering a calcium dependent release-machinery) and the activation of postsynaptic receptors due to the exocytosis of neurotransmitter is computed. Currents of five individual, independently acting synaptic boutons which are activated by the same presynaptic stimulus yield the overall postsynaptic response, the EPSC or total number of open channels, respectively (see Fig. 3a for exemplary simulation results).
The computer simulations and numerical routines were written in C language, compiled and run on Pentium PCs. Random numbers were generated using the ran2 routine [9]. The parameters employed [1] correspond to the synaptic scenario at hippocampal synapses and have been taken from the literature [1,2,4,5,8,10].

3 Results

In order to study synaptic depression as a function of physiological mechanisms and input-frequency the total number of open channels as a function of time is studied for varying physiological conditions under repetitive stimulation with constant frequency. A typical pattern of synaptic-depression is displayed in Fig. 3 (black line). Depression is due to, first, depletion of presynaptic vesicles and, second, postsynaptic receptor desensitization. In contrast to these two mechanisms which exhaust synaptic resources, the facilitation of release-probability following

[1]Number of synaptic boutons: 5; release site per bouton: 10; occupancy of release sites at rest: 78 %; kinetic rate constants for vesicle dynamics and release probabilities: see Fig. 2; AMPA receptors per bouton: 70; receptor kinetics: see scheme 1; molecules per vesicle: 2000; diffusion coefficient in the cleft: 40 nm^2/mus.

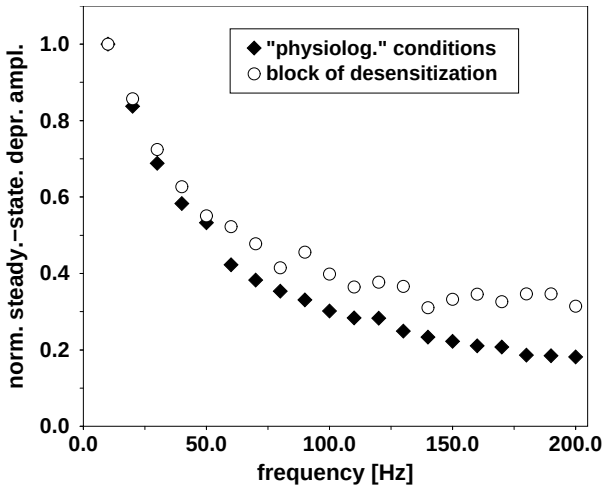

Figure 4: Averaged EPSC amplitude during steady state depression (normalized by steady state amplitude at 10 Hz).

previous synaptic activity may potentiate synaptic currents – if the overall release-probability, i.e. the depletion of vesicles, is strongly reduced. As shown in Fig. 3b (white circles) alterations in release probability may turn a depressing synapse into a facilitating connection: The synaptic connection depresses under physiological (hippocampal) conditions, but exhibits a facilitating behavior if the release probability is lowered.

Synaptic depression is shaped by release-probability and receptor desensitization

To further elucidate pre- and postsynaptic contributions to short-term depression, simulations under normal physiological control conditions are compared to simulations under *block of receptor desensitization*, i.e. setting the rate k_d in scheme 1 to zero: As displayed in Fig. 4 EPSC amplitudes during steady state depression do not differ from control conditions for stimulation frequencies below 40 Hz if receptor desensitization is blocked. This suggests that depression in this frequency range is solely due to presynaptic depletion of vesicles. For stimulation frequencies above 40 Hz steady state depression currents are considerably larger under block of desensitization. For instance the steady state depression current reaches $\sim$ 134 % of the value under control conditions if desensitization is blocked. This demonstrates that pre- *and* postsynaptic mechanisms affect synaptic depression for high stimulation frequencies.

Hippocampal synapses do not exhibit a 1/f-behavior

It has been predicted that beyond a limiting frequency f_{lim} steady state depression currents decay according to 1/f, if f denotes the stimulation frequency [12]. This finding indicates that for

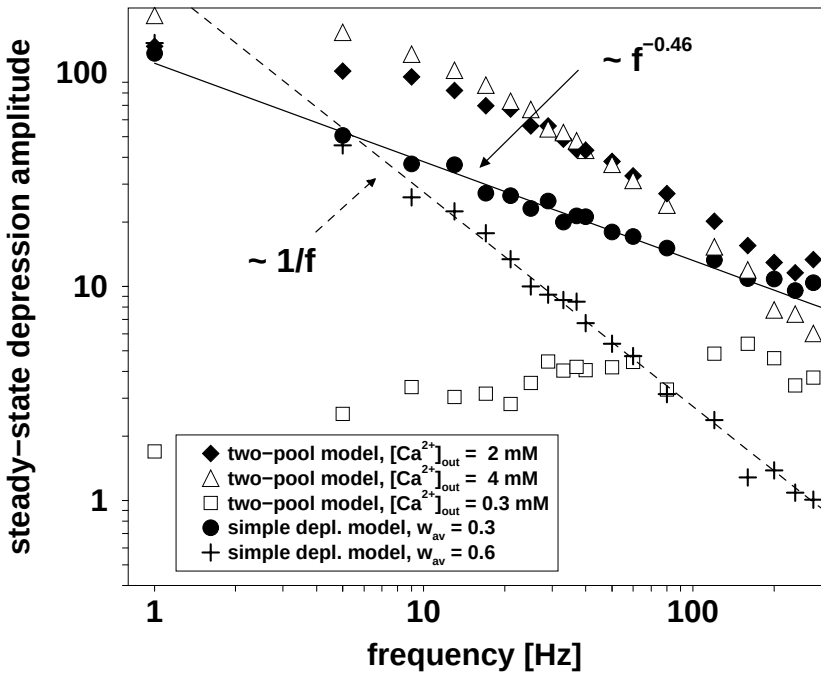

Figure 5: Averaged number of open channels during steady state depression for different concentrations of extracellular calcium, i.e. varying release probabilities, and for two different models of presynaptic release and recruitment.

frequencies larger than $f_{\lim}$, the amount of charge transferred across the postsynaptic membrane within a certain time window will not change with increasing frequency rendering rate-coding for f $> f_{\lim}$ impossible.

Our simulations show that it depends crucially on the physiological properties of the individual neuronal connection whether synaptic transmission exhibits a 1/f-behavior of the steady state amplitude. As displayed in Fig. 5 (black diamonds) the steady state depression current does not decay according to 1/f for hippocampal synapses. For alterations in release-probability (by variations in extracellular calcium concentration) the predicted 1/f-behavior occurs only for higher presynaptic release-probabilities of approximately 0.6, which have been reported from neocortical pyramidal cells [12]. Under physiological hippocampal conditions, however, the predicted 1/f-behavior is not apparent in our simulations and points towards an unlimited range of frequencies that can be transmitted in a rate-coded manner.

To further study how presynaptic mechanisms contribute to the observed frequency dependence, we compare our approach of modeling presynaptic processes of release and replenishment of vesicles with the commonly used simple depletion model [6], which fails to explain electrophysiological experiments on short-term depression (reviews by [3,19]). As displayed in Fig. 5 depression is stronger for the simple-depletion model, but again does not exhibit a 1/f-behavior

of the depression amplitude for physiological conditions at hippocampal synapses: the steady state current decays according to an exponent of -0.46 (Fig. 5, $[Ca^{++}] = 2$ mM).
We conclude that the specific combination of release-probability, receptor desensitization and presynaptic release-machinery determines whether synaptic connections facilitate or depress and sets the range of input-rates, i.e. frequencies $f < f_{\mathrm{lim}}$ that can be transmitted via rate-coding towards the postsynaptic side.

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