

Variability of postsynaptic responses depends non-linearly on the number of synaptic inputs

Jutta Kretzberg^{a,*}, Terrence Sejnowski^a,
Anne-Kathrin Warzecha^b, Martin Egelhaaf^b

^a*Computational Neurobiology Laboratory, The Salk Institute, 10010 N. Torrey Pines Road,
La Jolla, CA 92037 USA*

^b*Lehrstuhl Neurobiologie, Universität Bielefeld, Postfach 100131, 33501 Bielefeld, Germany*

Abstract

A conductance-based model for synaptic transmission and postsynaptic integration reveals how postsynaptic responses and their variability depend on the number of synaptic inputs. With increasing number of balanced stochastic excitatory and inhibitory inputs, the postsynaptic responses and their variance first increase and then decrease again. This non-linearity can be attributed to an anti-correlation between the total excitatory and inhibitory currents. The anti-correlation, which occurs even though the conductances of the individual synapses vary independently of each other, is determined by the total synaptic conductance and grows with the number of inputs. As the number of inputs increases, the membrane potential comes increasingly closer to the resting level.

Keywords: Model; Graded synaptic transmission; Number of inputs; Synaptic conductances; Correlated synaptic currents

1. Introduction

A neuron that is synaptically contacted by N input neurons does not necessarily receive input from all those neurons simultaneously. The presynaptic neurons contributing to the response of an integrating neuron are mainly those that are stimulated. This is a plausible assumption, for instance, when a stimulus is moved across the receptive

* Corresponding author.

E-mail address: jutta@salk.edu (J. Kretzberg).

field of a visual interneuron. We analyze the effect of the number of active synaptic inputs on the variability of the postsynaptic responses with a conductance-based model that was fitted to experimentally determined data of fly motion-sensitive interneurons [3]. These cells receive an equal number of excitatory and inhibitory synaptic inputs, that, depending on the stimulus, can both be activated simultaneously. Here we model one special situation by assuming that both types of inputs have equal maximum conductance. We assume all presynaptic signals to be independent from each other. The number of pairs of excitatory and inhibitory inputs was varied in the range from 1 to 1000, corresponding to stimuli of different sizes, ranging from a tiny stimulus to one that covers the entire receptive field of the fly visual interneuron.

With this conductance-based, one-compartment model of synaptic transmission and postsynaptic integration we show that not only the average postsynaptic responses but also their variability depend non-linearly on the number of active synaptic inputs. This non-linear dependence is accompanied by an anti-correlation between total excitatory and inhibitory currents that occurs even though the individual presynaptic membrane potentials are uncorrelated.

2. The model

2.1. Model of synaptic transmission and postsynaptic integration

To analyze how postsynaptic responses depend on the number of synaptic inputs we use a conductance-based, one-compartment model for synaptic transmission and postsynaptic integration. Analogous to the graded information transfer between neurons in the retina or the olfactory bulb of vertebrates (review Ref. [4]) or between fly visual neurons, synaptic transmission is not restricted to presynaptic spikes. The graded de- and hyper-polarizations of the presynaptic membrane potential induce conductance changes of the postsynaptic membrane via a sigmoidal transfer function.

The resulting postsynaptic potentials contribute to the continuously varying signal $V(t)$ according to a one-compartment model of a passive membrane.

$$\begin{aligned} \frac{dV(t)}{dt} = & \frac{1}{C} \cdot (g_m \cdot (V_{\text{rest}} - V(t)) + \sum_k^{N_e} s_{e_k}(V_{\text{pre}_k}) \cdot g_e \cdot (E_e - V(t)) \\ & + \sum_l^{N_i} s_{i_l}(V_{\text{pre}_l}) \cdot g_i \cdot (E_i - V(t))), \end{aligned}$$

with postsynaptic membrane potential $V(t)$, membrane capacitance C , resting potential V_{rest} , leak conductance g_m , maximal synaptic conductances g_e and g_i , number of synaptic inputs N_e and N_i , reversal potentials E_e and E_i .

The maximum conductance of each individual synapse g_e or g_i is scaled at every time step with $s_{e_k}(V_{\text{pre}_k})$ or $s_{i_l}(V_{\text{pre}_l})$, a scaling factor depending on the presynaptic membrane potential V_{pre} . In the case of excitatory synapses the scaling factor s_e is

determined according to the equations

$$\frac{ds_e(V_{\text{pre}})}{dt} = \frac{1}{\tau_e} \cdot (\bar{s}_e(V_{\text{pre}}) - s_e),$$

$$\bar{s}_e(V_{\text{pre}}) = \frac{1}{1 + \exp((V_{h_e} - V_{\text{pre}})/\Delta_e)},$$

where τ_e ($=\tau_i$) denotes the synaptic time constant with which the steady state scaling factor \bar{s}_e (\bar{s}_i) for a given value of V_{pre} is reached. The steady state scaling factor \bar{s}_e (\bar{s}_i) is a sigmoidal function of V_{pre} . Δ_e ($=\Delta_i$) determines the slope of the transfer function. V_{h_e} ($=V_{h_i}$) is the value of V_{pre} for which the half maximum conductance is reached. Equivalent equations are used for inhibitory synapses.

Unless otherwise specified parameter values are $C = 4.2 \cdot 10^{-10}$ F, $V_{\text{rest}} = -50$ mV, $g_m = 2 \cdot 10^{-7}$ S, $g_e = g_i = 2 \cdot 10^{-9}$ S, $N_e = N_i = 1 \dots 1000$, $E_e = 0$ mV, $E_i = -100$ mV, $\tau_e = \tau_i = 0.1$ ms, $V_{h_e} = V_{h_i} = 1$ mV, $\Delta_e = \Delta_i = 0.5$ mV. The parameter values are chosen to be in the range experimentally determined for visual interneurons of the fly [1]. Identical model parameters for excitatory and inhibitory synapses are a good approximation for this system.

2.2. Model of spike generation

A simple model of spike generation that was used before to reproduce and explain experimental data of fly visual interneurons [3,5] transformed the postsynaptic membrane potential $V(t)$ into spikes. This model consists of a variable threshold $\theta(t)$ that is compared with the membrane potential $V(t)$. A spike is generated if $V(t) > \theta(t)$. The spike threshold is calculated for each time step according to the equation

$$\theta(t) = \begin{cases} \infty & \text{if } t - t^* \leq \gamma^{\text{ref}}, \\ \theta_0 + \eta(t - t^*) + \rho(t) & \text{if } t - t^* > \gamma^{\text{ref}} \end{cases}$$

with t^* being the time when the previous spike occurred and γ^{ref} the absolute refractory period. θ_0 is a constant basis threshold like in a standard integrate and fire neuron, $\eta(t - t^*) = \eta_0 / (t - (t^* + \gamma^{\text{ref}}))$ is the influence of the relative refractoriness with weight constant η_0 . $\rho(t) = -\rho_0 / T \cdot \sum_{j=1}^T 1/j \cdot (V(t_i) - V(t_{i-j}))$ is the influence of the membrane potential changes within the last T data points, with weight constant ρ_0 and actual membrane potential $V(t_i)$. Parameter values: $\theta_0 = 1$ mV, $\gamma^{\text{ref}} = 2$ ms, $\eta_0 = 20$ ms · mV, $\rho_0 = 3.75$, $T = 1$ ms [3].

2.3. Generation of input signals

The membrane potentials of the presynaptic neurons fluctuate stochastically and independently from each other. This membrane potential noise is modeled as Gaussian white noise that is low-pass filtered and has a variance of 2.5 mV^2 . It was adjusted to fit the variance and the power spectrum of intracellular recorded membrane potential noise in visual interneurons of the fly [3].

The duration of the input traces amounts to 1.32 s at a temporal resolution of 0.01 ms. This resolution was also used for all model simulations. All results shown here are averages over at least 100 simulations with different random inputs (see legends).

3. Results

3.1. The response of the integrating neuron with balanced excitation and inhibition depends non-linearly on the number of active synaptic inputs

First, the spike count increases steeply with increasing input number, then it reaches a maximum and decreases (Fig. 1A). Also the spike count variance (Fig. 1B) and the variance of the graded fluctuating postsynaptic potential that underly the spike responses

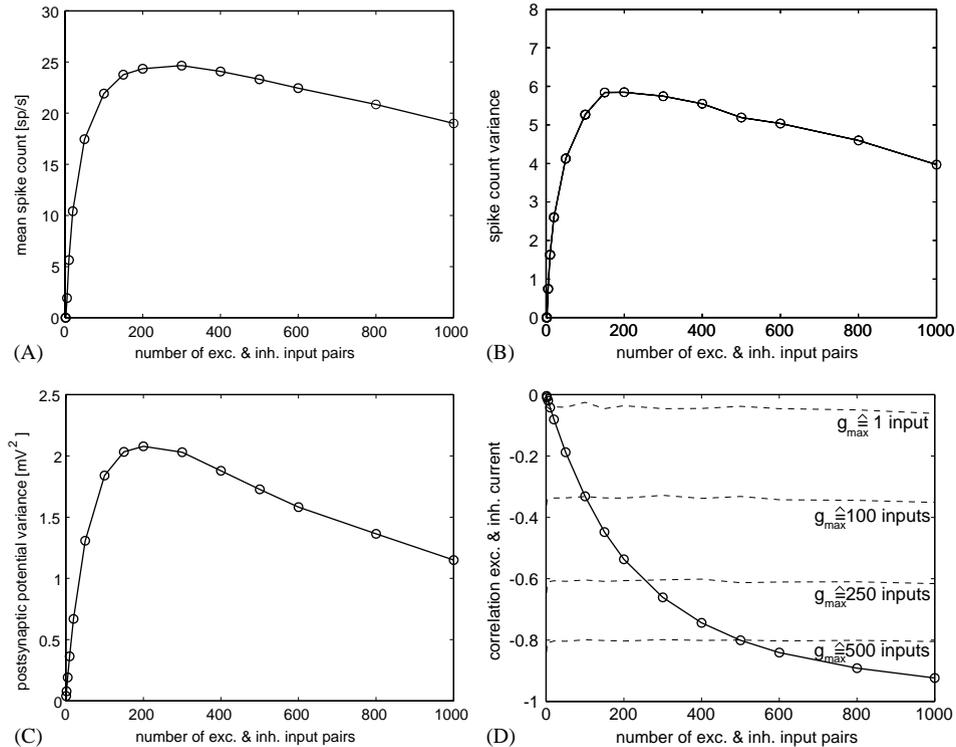


Fig. 1. The mean spike count (A), the spike count variance (B) and the variance of the postsynaptic potential (C) show a non-linear dependence on the number of active synaptic inputs. The anti-correlation between total excitatory and inhibitory currents assumes increasingly larger negative values with increasing number of inputs (D, solid line). When the total synaptic conductance is scaled by the number of inputs to keep it constant, the correlation between excitatory and inhibitory currents does not depend on the number of inputs (dashed lines). For the dashed lines 300 independent trials of 1.32 s duration were averaged, for the solid lines 3000 trials.

(Fig. 1C) depend in a non-linear way on the number of inputs. The similarity of Fig. 1C to Figs. 1A and B shows that the non-linear dependence is not due to the non-linearity of the spike threshold but is a property of the integration of synaptic inputs by a passive membrane.

3.2. Postsynaptic responses depend on the correlation of excitatory and inhibitory currents

The non-linear dependence of the postsynaptic responses on the number of inputs parallels the finding that the total excitatory and inhibitory currents are strongly anti-correlated for large numbers of synaptic inputs as is shown by the solid line in Fig. 1D. This anti-correlation occurs even though the membrane potentials of the individual presynaptic neurons are absolutely uncorrelated and the fluctuations of $V(t)$ are small compared to the distances to the reversal potentials. The reason for the anti-correlation between the total currents is the coupling of both excitatory and inhibitory currents to the postsynaptic membrane potential value. When the postsynaptic potential moves towards the excitatory reversal potential, the inhibitory driving force increases, leading to a large current opposing the excitatory current. This push-pull mechanism keeps the membrane potential close to the resting potential, resulting in fluctuations with a standard deviation as small as 1.5 mV.

The anti-correlation of the currents is determined by the maximum total synaptic conductance $g_{\max} = N_{\text{syn}} \cdot g_{\text{syn}}$ that can be reached when all N_{syn} synapses are maximally activated. The anti-correlation does not depend on the number of independent stochastic processes that are used as input signals. To obtain this result, the total maximum synaptic conductance g_{\max} was kept constant by scaling $g_{\text{syn}} = g_e = g_i$ with the increase of the number of synaptic inputs N_{syn} . In this case the correlation between the total excitatory and inhibitory currents is constant for varying numbers of independent inputs and depends only on the value of g_{\max} (dashed lines in Fig. 1D). The correlation function for the standard case (solid line in Fig. 1D) where g_{\max} increases linearly with the number of inputs intersects the correlation function for a given g_{\max} (dashed lines) exactly at the number of inputs that leads to the same maximum synaptic conductance.

3.3. Postsynaptic responses depend on the number of independent stochastic processes

Since the correlation between excitatory and inhibitory currents depends on the total maximum synaptic conductance it is not surprising that the postsynaptic potential variance depends quantitatively on the value chosen for the maximum conductance g_{syn} of one synapse. For a given number of synaptic inputs, the variance is larger for larger g_{syn} . Moreover, the maximum variance is reached at smaller numbers of inputs when g_{syn} is increased (Fig. 2A).

In contrast to the correlation of currents the membrane potential variance is not solely determined by the maximum total synaptic conductance $g_{\max} = N_{\text{syn}} \cdot g_{\text{syn}}$. The stars in Fig. 2A indicate two configurations with the same total synaptic conductance g_{\max} . The left star indicates a situation with half the number of independent synaptic

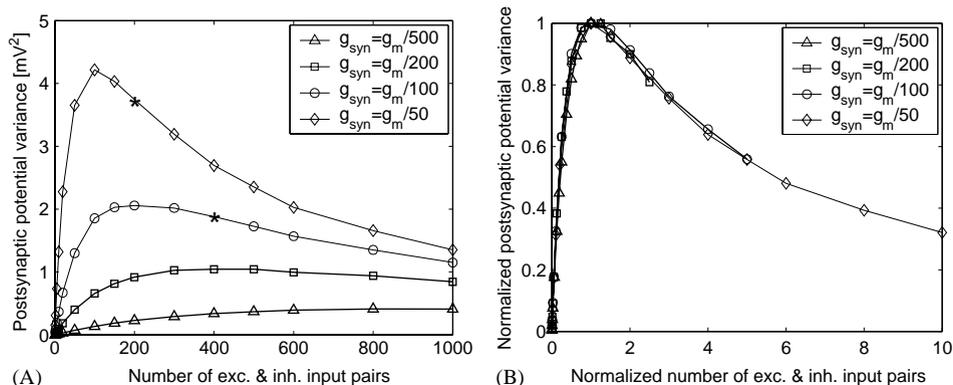


Fig. 2. (A) The variance of the postsynaptic potentials depends on the synaptic conductance. (B) When the curves shown in A are scaled in x - and y -direction by setting the maximum variance and the number of inputs at that maximum to 1, all curves have qualitatively the same shape. Between 100 and 300 independent trials of 1.32 s duration were averaged for each data point. Stars are explained in Section 3.3.

inputs N_{syn} and twice the conductance g_{syn} for each synapse as in the case indicated by the right star. The combination of stronger but less inputs leads to a dramatically higher postsynaptic variability than that of more but weaker synaptic inputs.

Despite the quantitative differences, qualitatively the variance curves do not differ for different values of g_{syn} . When the curves are scaled by setting both the maximum variance and the number of inputs at the maximum to one, all curves are similar (Fig. 2B).

The same analysis was done for the other model parameters. For all parameter combinations tested the postsynaptic response and its variance depends non-linearly on the number of inputs.

4. Discussion

We have shown that the strength and the variance of postsynaptic responses (membrane potential fluctuations as well as spike counts) depend in a non-linear way on the number of synaptic inputs. This non-linear dependence of postsynaptic spike responses on the number of synaptic inputs has recently been found experimentally in dynamic clamp stimulation of granule cells of the dentate gyrus in rats (S. Harney and M. Jones, “Temporally Precise Spiking in the Presence of Synaptic Noise”, CNS abstracts, Elsevier Preprint server). Similar results were reported in rat somatosensory cortex pyramidal neurons for the amplitude of sub-threshold membrane potential fluctuations [2]. Hence, this non-linear dependence on the number of synaptic inputs is a basic property of neurons. It is not induced by the spike non-linearity but by the anti-correlation of the total excitatory and inhibitory synaptic currents, which depends on the total synaptic conductance.

Acknowledgements

We thank Matthias Bethge and Jörn Anemüller for helpful discussions, Jean-Marc Fellous for comments on the manuscript, and Jens Lindemann for computer support. This work was supported by the Sloan Foundation, the Swartz Foundation and the Deutsche Forschungsgemeinschaft.

References

- [1] A. Borst, J. Haag, The intrinsic electrophysiological characteristics of fly lobula plate tangential cells: I. Passive membrane properties, *J. Computat. Neurosci.* 3 (1996) 313–336.
- [2] F.S. Chance, L.F. Abbott, A.D. Reyes, Gain modulation from background synaptic input, *Neuron* 35 (2002) 773–782.
- [3] J. Kretzberg, M. Egelhaaf, A.-K. Warzecha, Membrane potential fluctuations determine the precision of spike timing and synchronous activity: a model study, *J. Computat. Neurosci.* 10 (1) (2001) 79–97.
- [4] A. Roberts, B.M.H. Bush, *Neurons without Impulses*, Cambridge University Press, Cambridge, London, New York, 1981.
- [5] A.-K. Warzecha, J. Kretzberg, M. Egelhaaf, Reliability of a fly motion-sensitive neuron depends on stimulus parameters, *J. Neurosci.* 20 (23) (2000) 8886–8896.



Jutta Kretzberg studied 'applied computer science in the natural sciences' at the Department of Technology, University of Bielefeld, Germany, where she received a diploma in computer science in 1997. In her Ph.D. thesis she analyzed aspects of the reliability of spike responses, based on computer models for fly visual neurons. In 2001, she received a Ph.D. in biology from University of Bielefeld. J. Kretzberg currently is a Sloan-Swartz fellow at the Salk Institute for Biological Studies, La Jolla, CA, working in the groups of T. Sejnowski (Salk) and W. Kristan (UCSD). Her major research interests are the reliability of neuronal computations and the comparison of spiking and non-spiking neuronal information processing.



Terrence Sejnowski is an Investigator with Howard Hughes Medical Institute and a Professor at the Salk Institute for Biological Studies where he directs the Computational Neurobiology Laboratory. He is also Professor of Biology at the University of California, San Diego, where he is Director of the Institute for Neural Computation. Dr. Sejnowski received a B.S. in physics from the Case-Western Reserve University, a M.A. in physics from Princeton University, and a Ph.D. in physics from Princeton University in 1978. In 1988, Dr. Sejnowski founded Neural Computation, published by the MIT press. The long-range goal of Dr. Sejnowski's research is to build linking principles from brain to behavior using computational models.

Anne-Kathrin Warzecha received her diploma and doctoral degree in Biology from University of Tübingen, Germany in 1991 and 1994, respectively. During 1995 she held a postdoctoral position at the Centre for Visual Sciences, Australian National University, Canberra, Australia. Since then she has been working as a research fellow in the Dept. of Neurobiology at Bielefeld University, Germany. Major research interests of A.-K. Warzecha cover the reliability of neuronal computations, the mechanisms underlying motion vision and the visual control of behavior.

Martin Egelhaaf received his diploma and doctoral degree in Biology from Tübingen University (Germany) in 1980 and 1984, respectively. 1984-1993: research scientist at the Max-PlanckInstitute for Biological Cybernetics (Tübingen, Germany). 1994 - 1995: leader of a research group at the Centre of Visual Sciences (Australian National University, Canberra, Australia). Since 1995: Professor and head of the Department of Neurobiology at Bielefeld University (Bielefeld, Germany). Major research interest: visual information processing in biological systems.