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Inferring presynaptic population spiking from single-trial membrane potential recordings

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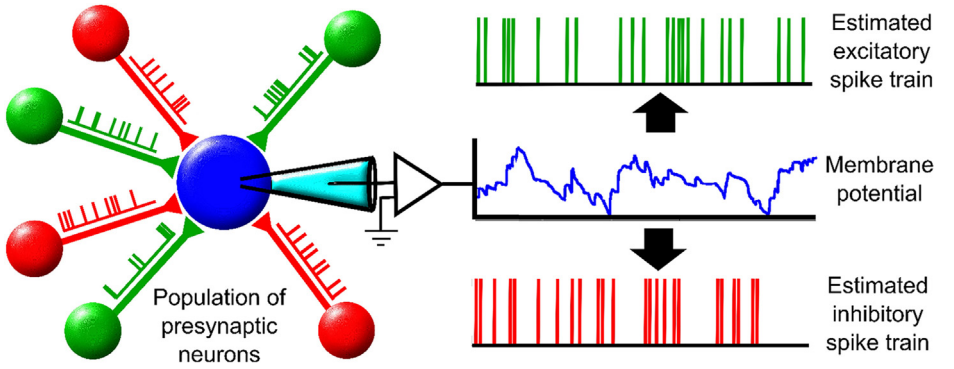
HIGHLIGHTS

- Method to extract the time course of synaptic inputs to a neuron.
- Tested on a model neuron under varying conditions.
- Demonstrated on cortical neurons of mouse and turtle.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: The time-varying membrane potential of a cortical neuron contains important information about the network activity. Extracting this information requires separating excitatory and inhibitory synaptic inputs from single-trial membrane potential recordings without averaging across trials.
New method: We propose a method to extract the time course of excitatory and inhibitory synaptic inputs to a neuron from a single-trial membrane potential recording. The method takes advantage of the differences in the time constants and the reversal potentials of the excitatory and inhibitory synaptic currents, which allows the untangling of the two conductance types.
Results: We evaluate the applicability of the method on a leaky integrate-and-fire model neuron and find high quality of estimation of excitatory synaptic conductance changes and presynaptic population spikes. Application of the method to a real cortical neuron with known synaptic inputs in a brain slice returns high-quality estimation of the time course of the excitatory synaptic conductance. Application of the method to membrane potential recordings from a cortical pyramidal neuron of an intact brain reveals complex network activity.
Comparison with existing methods: Existing methods are based on repeated trials and thus are limited to estimating the *statistical* features of synaptic conductance changes, or, when based on single trials, are limited to special cases, have low temporal resolution, or are impractically complicated.
Conclusions: We propose and test an efficient method for estimating the full time course of excitatory and inhibitory synaptic conductances from single-trial membrane potential recordings. The method is sufficiently simple to ensure widespread use in neuroscience.

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1. Introduction

A cortical neuron in vivo resides in a high conductance state as it receives excitatory and inhibitory presynaptic inputs from numerous other cortical neurons (Azouz and Gray, 1999; Pare et al., 1998; Rancz et al., 2011). Each presynaptic input creates a change in the excitatory or inhibitory conductance of the cell membrane, and these changes result in a membrane potential fluctuation of the postsynaptic neuron. Information about the presynaptic population activity thus could be obtained by analyzing a single-trial intracellular whole-cell recording of that neuron (Fig. 1). The main difficulty of this problem results from the fact that both excitatory and inhibitory conductance traces, two unknowns, need to be extracted from one channel of information: the single membrane potential time series. Several studies have attempted to address this important problem by taking different approaches. For example, one technique involves using multiple membrane potential recordings from the neuron to estimate the activity of the presynaptic population (Lankarany et al., 2013; Paninski et al., 2012; Pospischil et al., 2009), whereas others depend on the continuous measurements of the membrane time constant (Berg and Ditlevsen, 2013), or a so-called "oversampling" method (Bédard et al., 2012).

The goal of this study is to extract the presynaptic population spike train from the single-trial membrane potential recordings of a postsynaptic neuron via the estimation of the time course of the excitatory and inhibitory synaptic conductances; the primary objective being the extraction of the excitatory presynaptic spike train. We perform the estimation of the synaptic conductances by a novel method that is fundamentally based on the biophysical principles of synaptic conductances. We test the method in two ways: first on simulated membrane potentials subject to known inputs, and then on the membrane potentials of neurons recorded in slice, subject to experimenter-determined current waveforms. We then use the method to infer network synaptic inputs to individual cortical neurons using ex vivo patch clamp recordings.

2. Methods

2.1. Model simulation

To test the ability of our algorithm to detect presynaptic spike trains, we implemented a single-compartment leaky integrate-and-fire model neuron in Python 2.7 (Fig. 2a). The model neuron had constant membrane capacitance $C = 0.5$ nF, leak conductance $g_l = 25$ nS (reversal potential $E_l = -74$ mV, McCormick et al., 1985), and time-varying excitatory ($g_e(t)$) and inhibitory ($g_i(t)$) synaptic conductances (with $E_e = 0$ mV, $E_i = -80$ mV). The equation of the membrane potential $V_m(t)$ for this model neuron is:

$$0 = C\frac{dV_m(t)}{dt} + g_l(V_m(t) - E_l) + g_e(t)(V_m(t) - E_e) + g_i(t)(V_m(t) - E_i) \quad (1)$$

The model neuron received inputs from 200 excitatory and 200 inhibitory presynaptic neurons. For each of these presynaptic neurons, an independent spike train was generated through the length of the computation time by using a homogeneous Poisson process. We varied the rates of these Poisson processes to yield different population input spike rates in different simulations. The individual excitatory and inhibitory spike trains were accumulated into one total excitatory and one total inhibitory spike train. Excitatory and inhibitory synaptic conductance changes were modeled by an alpha function (Rall, 1967). Thus, the synaptic conductance change for $t > t_0$ caused by a presynaptic spike at t_0 was $g_{max}\frac{t-t_0}{\tau}\exp\left(1-\frac{t-t_0}{\tau}\right)$, where g_{max} denotes the maximal synaptic conductance, and τ denotes the time at which the alpha function reaches its peak value. The values used for these parameters were $g_{max,e} = 1$ nS and $\tau_e = 2$ ms for the excitatory presynaptic inputs (Brunel and Wang, 2003; Hestrin et al., 1990; Spruston et al., 1995), and $g_{max,i} = 6$ nS and $\tau_i = 10$ ms for the inhibitory presynaptic inputs (Brunel and Wang, 2003; Salin and Prince, 1996). The parameters used for excitatory and inhibitory synapses correspond to the experimental values for AMPA and $GABA_A$ conductance,

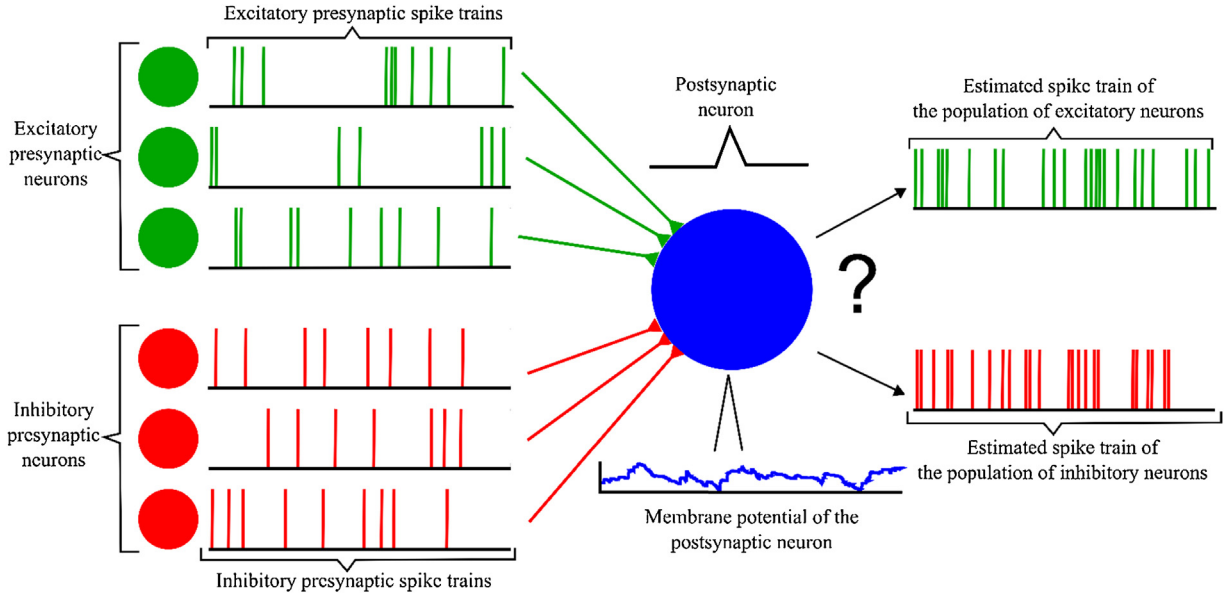

Fig. 1. Graphical representation of the presynaptic spike train estimation problem. A population of excitatory (green) and inhibitory (red) presynaptic neurons synapse onto the postsynaptic neuron (blue). For clarity, only three of each type of presynaptic neurons are shown. The input spikes result in fluctuations in the membrane potential (blue) of the postsynaptic neuron. We propose and test a method to estimate the spike trains of the populations of excitatory neurons from single-trial membrane potential recordings. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)