Extracting information from the power spectrum of voltage noise

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Abstract

We outline an approximation for obtaining an analytic expression of the power spectral density (PSD) of the membrane potential (V_m) in neurons subject to synaptic noise. In high-conductance states, models show a remarkable agreement between this approximation and the PSD computed from V_m activity. This analytic expression can be used to predict how the PSD depends on the exact kinetic model for synaptic currents, as well as on the values of the rate constants. This approach can therefore yield methods to estimate the characteristics of the kinetics of individual synaptic conductances from the analysis of the V_m activity in intracellular recordings *in vivo*.

Key words: cerebral cortex, subthreshold activity, synaptic noise

1 Introduction

Neocortical neurons during active states *in vivo* display intense and irregular subthreshold synaptic activity ("synaptic noise") which may strongly affect their integrative properties [1]. It is possible to characterize synaptic background activity using voltage-clamp methods applied *in vivo* [2] or *in vitro* [3]. However, most experiments, in particular *in vivo* recordings, are performed in current-clamp mode, in which the membrane potential activity is recorded. One therefore needs methods to extract the characteristics of the synaptic inputs under current-clamp by analyzing the voltage fluctuations, which is our goal in the present paper.

2 Methods

To simulate synaptic noise, we used a single-compartment model described by the passive membrane equation

$$C_m \frac{dV}{dt} \;=\; -g_{leak}\,(V - E_{leak}) \;-\; \sum_j g_j(t)\,[V(t) - E_j]\,, \tag{1}$$

where V is the membrane potential, $C_m = 1\ \mu F/cm^2$ is the specific membrane capacitance, $g_{leak} = 0.1\ mS/cm^2$ and $E_{leak} = -70\ mV$ are the leak conductance and reversal potential, respectively. The last term represents a large number of conductance-based synaptic inputs, where, for each synapse j, g_j denotes the conductance and E_j is the reversal potential. g_j can be expressed as $g_j = \bar{g}_j\, r_j$ where $\bar{g}_j$ is the maximal conductance and $r_j(t)$ is the fraction of postsynaptic receptors in the open state. r_j was described by 2-state or 3-states kinetic models [4] (see below). Excitatory and inhibitory synapses were modeled by α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic (AMPA) and γ-aminobutyric acid (GABA) postsynaptic receptors, respectively. To simulate synaptic background activity, all synapses were activated randomly according to Poisson processes with mean rate λ. All simulations were performed under NEURON [5].

3 Results

We start by providing a general expression for the power spectral density (PSD) of the membrane potential (V_m), then consider the expression for two particular kinetic models.

Taking the Fourier transform of the membrane equation (Eq. 1) yields:

$$i\omega\, C_m\, V(\omega) \;=\; -g_{leak}\,[V(\omega) - E_{leak}\delta(\omega)] \;-\; \sum_j g_j(\omega) * [V(\omega) - E_j]\,, \tag{2}$$

where $*$ is the convolution operator. This equation is not solvable, precisely because of this convolution, which is a consequence of the multiplicative aspect of conductances.

To solve this equation, we make the following approximation. In high-conductance states, the total membrane conductance is always about 2 orders of magnitude larger than any isolated conductance input [6]. In this case, the voltage deflection due to isolated inputs is small compared to the distance to reversal potential, and we can consider the driving force as approximately constant. However, we must take into account the high-conductance state of the membrane, which can be done by using an "effective leak conductance", which is the average of the sum of all conductances in the membrane. The membrane equation then becomes:

$$C_m \frac{dV}{dt} \;=\; -g_T\,(V-\bar{V}) \;-\; \sum_j g_j\,(\bar{V}-E_j)\;, \tag{3}$$

where g_T is the total average membrane conductance, and $\bar{V}$ is the average membrane potential. Note that the driving force $(\bar{V}-E_j)$ is now constant, which is therefore equivalent to approximate conductance-based inputs as current-based inputs, but arising on top of a large overall membrane conductance.

Taking now the Fourier transform, one obtains:

$$i\omega\, C_m\, V(\omega) \;=\; -g_T\,[V(\omega)-\bar{V}\;\delta(\omega)] \;-\; \sum_j g_j(\omega)\,(\bar{V}-E_j)\;. \tag{4}$$

For $\omega > 0$, we have:

$$V(\omega) \;=\; \frac{\sum_j\; g_j(\omega)\;(E_j-\bar{V})}{i\omega\, C_m + g_T}\;. \tag{5}$$

The PSD is then given by:

$$|V(\omega)|^2 \;=\; \frac{\left[\sum_j\; g_j(\omega)\;(E_j-\bar{V})\right]^2}{\omega^2\, C_m^2 + g_T^2}\;. \tag{6}$$

If all synaptic inputs are based on the same quantal events, then $g_j(\omega) = g(\omega)$, and incorporating the "effective" membrane time constant $\bar{\tau}_m = C_m/g_T$, we can write:

$$|V(\omega)|^2 \;=\; \frac{C\;|g(\omega)|^2}{1+\omega^2\;\bar{\tau}_m^2}\;, \tag{7}$$

where C is a constant.

Thus, the PSD of the membrane potential is here expressed as a "filtered" version of the PSDs of synaptic conductances $|g(\omega)|^2$, where the filter is given by the RC circuit of the membrane in the high-conductance state.

We consider this equation for two particular kinetic models of synaptic conductances. We first use the simple two-state kinetic model [4] (Fig. 1A, left):

$$\frac{dr}{dt} \;=\; \alpha\, T\;(1-r) \;-\; \beta\, r\;, \tag{8}$$

where r is the fraction of open receptors, α and β are the forward and backward rate constants, and T is the concentration of neurotransmitter.

We also consider the three-state scheme [4] (Fig. 1A, right):

$$\frac{dc}{dt} = \alpha\,(1-c-r)\,\sum_j \delta(t-t_j)\; - \;(\beta+\gamma)\,c \tag{9}$$

$$\frac{dr}{dt} = \gamma\,c\; - \;\varepsilon\,r\,, \tag{10}$$

where c is the fraction of receptors in an intermediate state, and α, β, γ, ε are voltage-independent rate constants.

Assuming that the transmitter time course is described by a Dirac delta function $T = \delta(t-t_j)$, one can solve these two models analytically and their PSD is given by:

$$|r(\omega)|^2 \;=\; \frac{\alpha^2\,\sum_j\,[1-c(t_j)]^2}{\beta^2+\omega^2} \tag{11}$$

for the two-state kinetic scheme, and

$$|r(\omega)|^2 \;=\; \frac{\alpha^2\gamma^2\,\sum_j\,[1-c(t_j)-r(t_j)]^2}{[(\beta+\gamma)^2+\omega^2]\;[\varepsilon^2+\omega^2]} \tag{12}$$

for the three-state kinetic scheme.

Using these two expressions, the PSD of the membrane potential for synaptic conductances described by two-state kinetics is given by:

$$|V(\omega)|^2 \;=\; \frac{C'}{(1+\omega^2\,\tau_{syn}^2)\;(1+\omega^2\,\tilde{\tau}_m^2)}\,, \tag{13}$$

where $\tau_{syn} = 1/\beta$. In the case of three-state kinetic models (Eqs. 9-10), the PSD is given by:

$$|V(\omega)|^2 \;=\; \frac{C''}{(1+\omega^2\,\tau_1^2)\;(1+\omega^2\,\tau_2^2)\;(1+\omega^2\,\tilde{\tau}_m^2)}\,, \tag{14}$$

where $\tau_1 = 1/(\beta+\gamma)$ and $\tau_2 = 1/\varepsilon$ are the time constants associated with the three-state kinetic model. Simulations of random synaptic inputs using these two models yielded only slightly different voltage fluctuations (Fig. 1B). This difference was also apparent in the PSD calculated from the membrane potential of both models

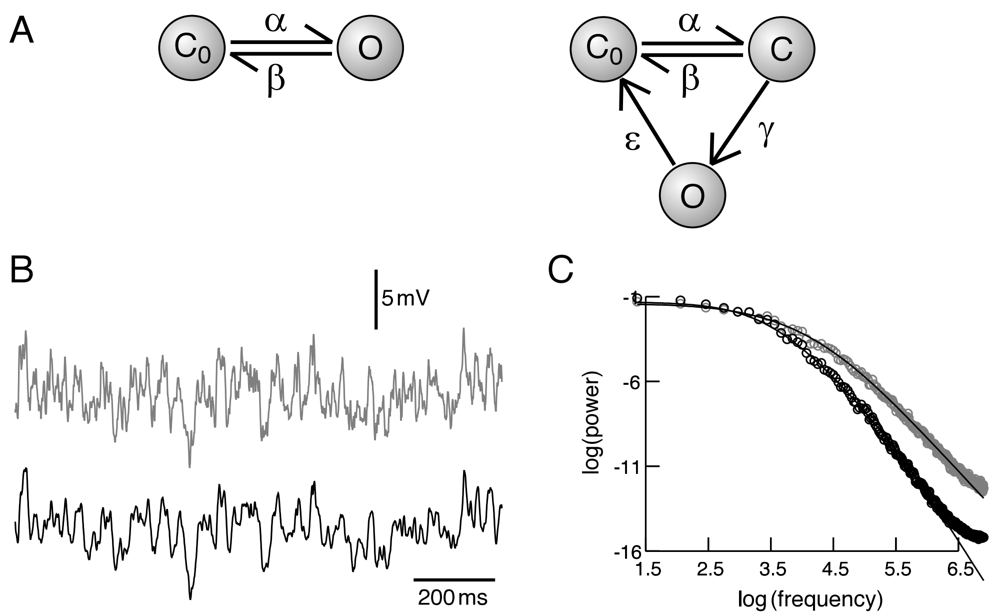

Fig. 1. Power spectral estimates of the membrane potential for two different kinetic models of synaptic inputs. A. Two-state (left) and three-state (right) kinetic models of postsynaptic receptors used in the simulations. B. Simulation of a single-compartment neuron receiving a large number of randomly-releasing synapses, according to the two kinetic models in A (gray: two-state kinetic model; black: three-state kinetic model). In both cases, we used 4470 AMPA-mediated and 3800 $GABA_A$-mediated synapses releasing according to independent Poisson processes with average rates of 2.2 and 2.4 Hz, respectively (same random numbers used in the two simulations). C. Power spectral density (PSD) calculated for numerical simulations (gray circles: two-state model; black circles: three-state model). The continuous curves show the theoretical predictions from Eq. 13 (gray) and Eq. 14 (black).

(Fig. 1C, circles). The analytic estimates of the PSD (Eq. 14) yielded a remarkable agreement with the PSD obtained numerically from the conductance-based model (Fig. 1C, continuous lines).

4 Conclusions

We showed that, under some approximations, one can derive an analytic expression for the PSD of the V_m for neurons subject to synaptic noise. This analytic expression can be used to yield two types of information about synaptic conductances. The first type of information is qualitative and concerns the kinetic model underlying synaptic conductances. The exact type of model will affect the scaling of the PSD at high frequencies. This scaling is determined by the number of exponential modes in the decay of synaptic conductances, which itself depends on number of states in the kinetic model. The second type of information is quantitative and is related to the value of the decay time constant for each mode. These values will determine the frequency at which the PSD starts to scale as a negative power of frequency and should be accessible by standard curve fitting.

This analytic expression, however, is only valid for high-conductance states, in which the V_m deflection of quantal synaptic events is small. It may not be valid for low-conductance situations, such as miniature synaptic events. Another approximation was that the maximal conductance of each synapse was considered uniform, but non-uniform conductances should not affect the frequency-dependence of the PSD. A third approximation was that all synapses were at equal electrotonic distance. In real neurons, synapses are subject to a differential dendritic filtering, which may have consequences on the PSD of the V_m (presumably recorded in the soma). This contribution should be investigated by future work.

Using this approach, our goal is to yield methods to analyze intracellular recordings *in vivo*. V_m activity could be collected in active cortical states (high-conductance states), and the fitting of the PSD should yield estimates of the kinetics of synaptic conductances. This type of analysis is complicated by the fact that several types of synaptic receptors contribute (such as AMPA and $GABA_A$ in Fig. 1). In such a case, PSDs could be computed at different V_m (different levels of constant current injection), yielding different relative weights of these contributions. These relative weights could be exploited to attempt to disambiguate the different inputs.

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