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Characterizing the voltage fluctuations driven by a cluster of ligand-gated channels

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In this paper we present the properties of the voltage fluctuations driven by a cluster of ligand-gated channels. First, the second-order moment of the voltage is expressed in form of the integrated resistance and the random force. Then the power spectrum of the voltage noise is obtained analytically, and it is proved to have the $1/\omega^4$-form. Its mechanism lies in that the randomness of the voltage fluctuation is weaker than channel (conductance) noise, which can be approximately described by the Ornstein-Ulenbeck process.

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I. INTRODUCTION

The chemical synapse is the most common way of connections between neurons [1,2]. Though there are many kinds of synapses in the cental nervous system, their operating principles are similar. When an action potential reaches the end points of the upstream axon, the neurotransmitters will be released simultaneously, then these transmitters will bind to their receptors and open the latter. So the conductances of the postsynaptic membrane to specific ions are increased quickly, and the membrane potential will be changed in a short time. It is experimentally discovered that, even if the presynaptic stimulus are kept constant, there is variability in the postsynaptic response [3–5]. These phenomenon is called the synaptic variability [4]. Though the main source of the synaptic variability may originate from the randomness of the neurotransmitter releasing [4,5], the variability contained in the postsynaptic response is directly influenced by the (stochastic) gating of the synaptic-receptor channels: the fluctuation waves of the neurotransmitter densities must influence the gating of the channels first and then indirectly influence the postsynaptic response. Due to the discrete nature of the channels embedded in the membrane, there exists inevitably channel noise [6,7] accompanying the depolarizing or repolarizing of the membrane voltage.

In the past the noise components that are contained in the membrane noise have been identified separately [8]. Though there are several kinds of noises, such as capacitive noise [9], Johnson noise, shot noise, and excess noise [8], it is commonly recognized that the most significant one is channel noise [6] (or also called conductance noise since the conductances of the membrane to specific ions are directly determined by the gating of the channels). The roles of channel noise in several aspects of the action potential propagation are studied theoretically [10–14]. Many works have addressed how to correctly model channel noise in a compact form [7,15,16]. Through these works, the performance and effects of channel noise in nervous-system functions have been recognized more and more clearly [4,6]. But there still does not exist a universal theory on how to characterize channel noise. For example, it has been experimentally discovered that the voltage fluctuations in a cluster of K^+ channels has the $1/\omega^4$ power spectrum [17], but there is no theoretical explanation of the phenomenon.

In our opinion, in order to understanding channel noise, we need to separate the process of a given area of a membrane-channel system propagating the voltage signals into two parts. First, we need to know the intrinsic properties of the fluctuations of the membrane-channel system under constant environmental conditions. Second, by treating the chemical or the electrical pulses as the external stimuli, we need to know the responses of the membrane-channel system to such kinds of stimuli.

In this paper, we use the piecewise deterministic process [18] to describe the temporal evolving of the membrane voltage that is driven by the stochastic gating of a cluster of ligand-gated channels. We present the analytical expressions for the first- and second-order moments of the voltage. In particular, we present the analytical results for the power spectrum of the voltage fluctuations and prove that it has the $1/\omega^4$-form. So the voltage response is essentially different from the current response to the conductance noise since the voltage needs the relaxation process to its new reversal potentials when the conductance is changed. Yet the current is directly determined by the conductance under a clamped voltage. We believe that it is just the relaxation process of the voltage that makes the voltage fluctuation different from the conductance noise, which can be approximated by the Ornstein-Ulenbeck process.

The paper is organized as follows. In Sec. II we construct the stochastic process. In Sec. III we get the analytic expressions for the first- and second-order moments of the voltage. In Sec. IV we get the analytic expression for the power spectrum of the voltage fluctuation. In Sec. V we prove that the power spectral density has the form $1/\omega^4$. In the last section we present our understanding of the essential difference of the voltage noise from the conductance noise and the significance of the voltage noise in the realistic voltage signaling.

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II. THE MODEL THAT DESCRIBES THE VOLTAGE FLUCTUATIONS

Almost all kinds of ligand-gated channels are embedded in the postsynaptic membrane of their corresponding synapses. These tiny membrane-channel systems contain several necessary electric elements that constitute the resistor-capacitance circuit, which are illustrated in the following.

First, the lipid bilayer of the biological membrane is an extremely good insulator with the thickness of its insulating part only 2.3 (nm) [1], so it is naturally a capacitor with its capacitance is constantly $C_m = 0.01\ \text{pF}/\mu\text{m}^2$ (the capacitance of a capacitor linearly depends on its area). In the membrane area, the situation is very complex. For example, there are many junctional folds facing a single synaptic bouton in the neuromuscular junction, and the nicotinic acetylcholine (nACh) receptors are densely distributed in the top of these folds [2,19]. However, in the branches of the dendrites, in which the electric information is propagated by the local graded potentials, we consider that at least the membrane area of the specific branch where the synapse is localized should be treated as a whole capacitor. We denote M to be the membrane area and consider that it should not be less than 1 μm^2. In [9] the thermal noise of the voltage in the membrane capacitor is calculated, according to which the standard deviation of the voltage fluctuation has the scale of 0.6 mV when the membrane area reaches 1 μm^2. Since here we focus on the voltage fluctuation caused by the stochastic gating of the channel, which is voltage independent, we do not consider this kind of voltage noise.

Second, we address the chemical batteries that perform the role of the reversal potentials of the leakage V_L and which of the ionic current V_{Ch}. A living cell maintains the concentration gradients for several specific cations and anions across the membrane (mainly Na^+, K^+, and Cl^-) by some kinds of pumps (for example, the Na^+/K^+-ATPase), which costs the energy of ATP hydrolysis. The concentration gradients of specific ions across the membrane produce their specific electric potentials, so actually they are chemical batteries with different voltages. Since different kinds of channels permeate different kinds of ions with different permeability, the reversal potential used in different synapses is also different. For a neuron, it maintains a polarized resting potential and uses the depolarized voltage pulses to carry the information. For example, the resting potential of the postsynaptic membrane in a neuromuscular junction, which is mainly controlled by the K^+ and the leakage, is about $V_L = -90$ mV (chap. 9 in [2]; see also [20]). In another respect, the nACh receptor permeates cations (mainly Na^+ and K^+) so that its corresponding reversal potential is about $V_{ch} = 0$ mV [1,20,21], and many inhibitory synapses use negative reversal potentials.

Third, let us take the conductors. Here the conductance of a single receptor is denoted as g_{Ch} and which of the leakage is denoted as g_L, linearly depending on the membrane area M.

These few kinds of necessary electrical components constitute a tiny membrane-channel system, and the equivalent circuit of it is plotted in Fig. 1.

Here the single channel is coarse-grained into two configurations: "Open (activated)" or "Closed." The reasons are explained as follows. First, there are many kinds of ligand-gated channels in the central neural system, and the kinetic structures of many kinds of them are far from being characterized clearly. In another respect, a common property among them lies in that their gating is independent of voltage. Second, here the essence of the randomness will not be changed by just substituting the different kinds of kinetic structure of the channel. Only some specific variables, such as the dwell time in the open state, will be influenced. Evidence comes from the study in [17], in which a two-state model of the potassium channel is sufficient to explain the collective dynamics.

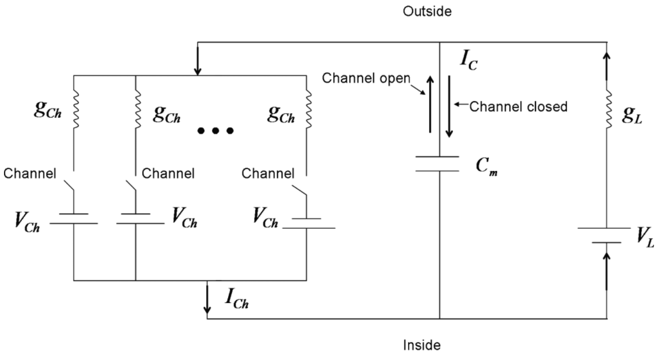

FIG. 1. The equivalent electric circuit of the system. Especially note that the reversal potentials V_{Ch} of the postsynaptic currents may be positive or negative, depending on the type of the synapse, so the battery V_{Ch} (accordingly the current I_{Ch}) may has different directions.

Let O_i denote that there are i open channels in the system with totally N channels, so that the state space of the channel cluster can be set as $\{O_i; 0 \leqslant i \leqslant N\}$, and the kinetic scheme of the transition of the channel cluster can be set as follows:

$$O_0 \underset{k^-}{\overset{Nk^+}{\rightleftharpoons}} O_1 \underset{2k^-}{\overset{(N-1)k^+}{\rightleftharpoons}} \cdots \underset{Nk^-}{\overset{k^+}{\rightleftharpoons}} O_N. \tag{1}$$

Here k^- and k^+ are the transition intensities of a single channel (with scale ms^{-1}), and we assume that they are voltage-independent.

Since the conductance of a single channel is g_{Ch}, if the state of the channel cluster is O_i, the ionic current flow through the channels is $I_{Ch} = ig_{Ch}(U - V_{Ch})$. Together with the leakage that $I_L = g_L(U - V_L)$, and the capacitive current $I_C = C_m\frac{dU(t)}{dt}$, the current balance equation of the circuit obeys the law $I_{Ch} + I_L + I_C = 0$ or, equivalently,

$$C_m\frac{dU(t)}{dt} = -g_L(U - V_L) - ig_{Ch}(U - V_{Ch}) = -g_i(U(t) - V_i). \tag{2}$$

Here the unit of time is set to be ms. The variables $g_i = g_L + ig_{Ch}$ and $V_i = (g_L V_L + ig_{Ch}V_{Ch})/g_i$ denote the integrated conductance and the reversal potential, respectively, under the condition that i channels are open, $i = 0, 1, \dots, N$.

Now we can define a stochastic process $\{(X(t), U(t)); t \geqslant 0\}$, where its discrete part $X(t)$ takes values in the set $\{O_i\}$, and its continuous part $U(t)$ takes values in the interval (V_0, V_N). It is easy to see from Eq. (2) that $U(t)$ will never reach the boundary $\{O_i\} \times \{V_0, V_N\}$, i.e., $U(t)$ is confined in the inside of the interval (V_0, V_N). So the state space can be defined as $\{O_i\}_{i=0}^{N} \times (V_0, V_N)$, a bounded open subset of $\mathbb{R}^{(N+1)}$ [22].

Let $P(O_i, v, t|O_j, v_0)\,dv$ denote the transition probabilities, conditioned that the process starts from the point (O_j, v_0)

deterministically,

$$P(O_i, v, t|O_j, v_0)\,dv = \text{Prob}\{X(t) = O_i, v \leqslant U(t) < v + dv|X(0) = O_j, V(0) = v_0\}.$$

The master equations for the evolution of these PDFs have the form

$$\begin{aligned}\frac{\partial}{\partial t}P(O_0, v, t|O_j, v_0) = &-\frac{\partial}{\partial v}J(O_0, v, t|O_j, v_0) - Nk^+P(O_0, v, t|O_j, v_0)\\&+ k^-P(O_1, v, t|O_j, v_0),\\&\dots\\\frac{\partial}{\partial t}P(O_i, v, t|O_j, v_0) = &-\frac{\partial}{\partial v}J(O_i, v, t|O_j, v_0) - [(N-i)k^+ + ik^-]P(O_i, v, t|O_j, v_0)\\&+ (N-i+1)k^+P(O_{i-1}, v, t|O_j, v_0) + (i+1)k^-P(O_{i+1}, v, t|O_j, v_0),\\&\dots\\\frac{\partial}{\partial t}P(O_N, v, t|O_j, v_0) = &-\frac{\partial}{\partial v}J(O_N, v, t|O_j, v_0) - Nk^-P(O_N, v, t|O_j, v_0)\\&+ k^+P(O_{N-1}, v, t|O_j, v_0)\end{aligned} \tag{3}$$

with the initial condition

$$P(O_i, v, 0|O_j, v_0) = \begin{cases}1, & (O_i, v) = (O_j, v_0)\\0, & \text{else}\end{cases}. \tag{4}$$

Note that Eq. (4) is the initial condition of Eq. (3) rather than the initial distribution of the process.

Here $J(O_i, v, t|O_j, v_0)$ are probability fluxes due to the evolution of the membrane voltage, obeying the current balance equation

$$J(O_i, v, t|O_j, v_0) = \left[-\frac{g_i}{C_m}(v - V_i)\right]P(O_i, v, t|O_j, v_0). \tag{5}$$

Since Eqs. (2) confine $U(t)$ in the interval (V_0, V_N), the boundary condition can be set as $J(O_i, V_0, t|O_j, v_0) = J(O_i, V_N, t|O_j, v_0) \equiv 0$, i.e., the probability fluxes at the boundary are zero [22].

III. THE MOMENTS OF THE VOLTAGE

Now we need to calculate the marginal expectations of the voltage: $E(U(t), O_i|O_j, v_0) = \int_{V_0}^{V_N} vP(O_i, v, t|O_j, v_0)\,dv$. First, we multiply both sides of the master equation (3) by v and integrate v over the interval $[V_0, V_N]$ to get the following system of equations:

$$\begin{aligned}\frac{\partial}{\partial t}E(U(t), O_0|O_j, v_0) = &-\frac{g_0}{C_m}E(U(t), O_0|O_j, v_0) + \frac{g_0V_0}{C_m}P(O_0, t|O_j, v_0)\\&-Nk^+E(U(t), O_0|O_j, v_0) + k^-E(U(t), O_1|O_j, v_0),\\&\dots\\\frac{\partial}{\partial t}E(U(t), O_i|O_j, v_0) = &-\frac{g_i}{C_m}E(U(t), O_i|O_j, v_0) + \frac{g_iV_i}{C_m}P(O_i, t|O_j, v_0)\\&-[(N-i)k^+ + ik^-]E(U(t), O_i|O_j, v_0) + (N-i+1)k^+\\&E(U(t), O_{i-1}|O_j, v_0) + (i+1)k^-E(U(t), O_{i+1}|O_j, v_0),\\&\dots\\\frac{\partial}{\partial t}E(U(t), O_N|O_j, v_0) = &-\frac{g_N}{C_m}E(U(t), O_N|O_j, v_0) + \frac{g_NV_N}{C_m}P(O_N, t|O_j, v_0)\\&-Nk^-E(U(t), O_N|O_j, v_0) + k^+E(U(t), O_{N-1}|O_j, v_0)\end{aligned} \tag{6}$$

with the initial condition

$$E(U(0), O_i|O_j, v_0) = \begin{cases}v_0 & i = j\\0, & \text{else}\end{cases}. \tag{7}$$

Here $P(O_i,t|O_j,v_0)=\int_{V_0}^{V_N}P(O_i,v,t|O_j,v_0)\,dv$, satisfying the following equations, which are derived by integrating Eq. (3) in the interval $[V_0,V_N]$:

$$\begin{aligned}
\frac{\partial}{\partial t}P(O_0,t|O_j,v_0)=&-Nk^+P(O_0,t|O_j,v_0)+k^-P(O_1,t|O_j,v_0),\\
&\cdots\\
\frac{\partial}{\partial t}P(O_i,t|O_j,v_0)=&-[(N-i)k^+ + ik^-]P(O_i,t|O_j,v_0)+(N-i+1)k^+\\
&P(O_{i-1},t|O_j,v_0)+(i+1)k^-P(O_{i+1},t|O_j,v_0),\\
&\cdots\\
\frac{\partial}{\partial t}P(O_N,t|O_j,v_0)=&-Nk^-P(O_N,t|O_j,v_0)+k^+P(O_{N-1},t|O_j,v_0)
\end{aligned}\tag{8}$$

with the initial conditions

$$P(O_i,0|O_j,v_0)=\begin{cases}1, & j=i\\ 0, & j\neq i\end{cases}.$$

Since the closure of the state space $\{O_i\}_{i=0}^N\times[V_0,V_N]$ is compact, $U(t)$ will never reach the boundary, and the jumping system is irreducible with intensities independent of v, there exists a unique stationary distribution [22]; especially note that it does not dependent on the initial distribution. Now let $t\longrightarrow+\infty$, and we can get the equation for the marginal expectations of the stationary distributed voltage:

$$N_1\langle\vec{U}_i\rangle=D_{GV}\vec{P},\quad\text{or,}\quad\langle\vec{U}_i\rangle=N_1^{-1}D_{GV}\vec{P}.\tag{9}$$

The vectors and matrices in this equation are defined as follows. First,

$$\langle\vec{U}_i\rangle=[E(O_0,U),\dots,E(O_i,U),\dots,E(O_N,U)]^T$$

is the vector of the (stationary) marginal first-order moments of U. Note that the initial condition is omitted in this expression, since the initial-condition-independence means the uniqueness of the stationary distribution, and

$$\vec{P}=[P(O_0),\dots,P(O_N)]^T$$

is the vector of the stationary probability distribution of the discrete element $X(t)$, and it is easy to see that $P(O_i)=\binom{N}{i}p^i(1-p)^{N-i}$, where $p=\frac{k^+}{k^++k^-}$.

Second, we set

$$D_G=\operatorname{diag}\left[\frac{g_0}{C_m},\dots,\frac{g_N}{C_m}\right]:=\begin{bmatrix}\frac{g_0}{C_m} & 0 & & \cdots & & 0 & 0\\ & & \ddots & & & & \\ \cdots & \cdots & 0 & \frac{g_i}{C_m} & 0 & \cdots & \cdots\\ & & & & \ddots & & \\ 0 & 0 & & \cdots & \cdots & 0 & \frac{g_N}{C_m}\end{bmatrix}$$

to be a diagonal matrix whose diagonal entries are $\frac{g_i}{C_m}=\frac{g_L}{C_m}+i\frac{g_{Ch}}{C_m}$, similarly $D_V=\operatorname{diag}[V_0,\dots,V_i,\dots,V_N]$, then $D_{GV}=D_GD_V=\operatorname{diag}[\frac{g_0V_0}{C_m},\dots,\frac{g_iV_i}{C_m},\dots,\frac{g_NV_N}{C_m}]$.

Third, the matrix $N_1=D_G+T_r$, in which

$$T_r=\begin{bmatrix}Nk^+ & -k^- & & \cdots & & 0 & 0\\ & & \ddots & & & & \\ \cdots & \cdots & -(N-i+1)k^+ & (N-i)k^+ + ik^- & -(i+1)k^- & \cdots & \cdots\\ & & & & \ddots & & \\ 0 & 0 & & \cdots & \cdots & -k^+ & Nk^-\end{bmatrix}.$$

So we can see that the matrix N_1 is the tensor of the (jumping) time constants that corresponds to every state of the channel system.

Doing a simple comparison may help us to understand the expression of $\langle\vec{U}_i\rangle$ more clearly. If we adopt the conventional quasi-equilibrium assumption, i.e., the voltage is assumed to be reaching equilibrium immediately (or is called the rapid equilibrium approximation; see chap. 4 in [23]) between the jumps of channel states, we just have $\langle \vec{U_i} \rangle = D_{GV}\vec{P}$. Now we take the relaxation processes of the voltage between every jump into consideration, which results in the emergence of the term N_1^{-1}.

With the same procedure, we multiply both sides of the master equation (3) by v^2, and integrate v over the interval $[V_0, V_N]$ to get

$$\begin{aligned}
\frac{\partial}{\partial t}E(U^2(t), O_0|O_j, v_0) = & -2\frac{g_0}{C_m}E(U^2(t), O_0|O_j, v_0) + 2\frac{g_0V_0}{C_m}E(U(t), O_0|O_j, v_0) \\
& - Nk^+E(U^2(t), O_0|O_j, v_0) + k^-E(U^2(t), O_1|O_j, v_0), \\
& \quad \dots \\
\frac{\partial}{\partial t}E(U^2(t), O_i|O_j, v_0) = & -2\frac{g_i}{C_m}E(U^2(t), O_i|O_j, v_0) + 2\frac{g_iV_i}{C_m}E(U(t), O_i|O_j, v_0) \\
& - [(N-i)k^+ + ik^-]E(U^2(t), O_i|O_j, v_0) + (N-i+1)k^+E(U^2(t), O_{i-1}|O_j, v_0) \\
& + (i+1)k^-E(U^2(t), O_{i+1}|O_j, v_0), \\
& \quad \dots \\
\frac{\partial}{\partial t}E(U^2(t), O_N|O_j, v_0) = & -2\frac{g_N}{C_m}E(U^2(t), O_N|O_j, v_0) + 2\frac{g_NV_N}{C_m}E(U(t), O_N|O_j, v_0) \\
& - Nk^-E(U^2(t), O_N|O_j, v_0) + k^+E(U^2(t), O_{N-1}|O_j, v_0).
\end{aligned} \tag{10}$$

Letting $t \longrightarrow +\infty$, we have the relationship

$$N_2\langle \vec{U_i^2} \rangle = 2D_{GV}\langle \vec{U_i} \rangle, \quad \text{or,} \quad \langle \vec{U_i^2} \rangle = 2N_2^{-1}D_{GV}N_1^{-1}D_{GV}\vec{P}. \tag{11}$$

Here the vector $\langle \vec{U_i^2} \rangle$ is the marginal second-order moments of the voltage: $\langle \vec{U_i^2} \rangle = [\dots, E(O_i, U^2), \dots]$ and $N_2 = 2D_G + T_r$. Note that in the latter equation, $\langle \vec{U_i} \rangle$ is replaced by Eq. (9).

Let $\vec{\mathbf{1}} = [1, 1, \dots, 1]$, i.e., the vector whose components are all 1, and denoting T to be the transpose of a matrix. It is not hard to verify that $\vec{\mathbf{1}}^{\mathrm{T}}T_r = 0$. Together with the relationship $N_2 = 2D_G + T_r$, we have the relationship $\vec{\mathbf{1}}^{\mathrm{T}}D_G\vec{P} = \frac{1}{2}\vec{\mathbf{1}}^{\mathrm{T}}N_2\vec{P}$, which means the second-order moment of the voltage has the form

$$\langle U^2 \rangle = \vec{\mathbf{1}}^{\mathrm{T}}\langle \vec{U_i^2} \rangle = 2\vec{\mathbf{1}}^{\mathrm{T}}N_2^{-1}D_{GV}\langle \vec{U_i} \rangle. \tag{12}$$

$\langle U^2 \rangle$ can be seen as the absolute voltage fluctuation related to the zero potential, so it is proportional to the total power used by the membrane-channel system. A part of it is used to maintain the average potential, and another part is dissipated into heat.

Note that Eq. (12) represents only the voltage fluctuation caused by the stochastic gating of the channels. In another respect, there are several other kinds of voltage noise that are contained in the realistic membrane noise, such as capacitive noise [9], excess noise, and so on [8]. Since their mechanisms are different, the scaling laws for them are also different. For channel noise, it decreases against the scale of the cluster, i.e., the number of the total channels in the synapse. In this paper, the only objective is characterizing the channel noise. In the future, we plan to study how these different kinds of noises are combined to form the integral membrane noise.

It may helpful to understand the form of Eq. (12) if we make an analogy between it with the fluctuation-dissipation theorem [24], which tells us that, for an equilibrium system, its fluctuation and its dissipation are two faces that come from the same source of randomness so that they must connected with each other. Now let us take a look at Eq. (12), note that $2N_2^{-1}$ is the resistance of the system. In another respect, D_{GV} are the fluxes of the system so that $D_{GV}\langle \vec{U_i} \rangle$ can be seen as the random force of the system. Maybe the point can be seen more intuitively if we make a little change in the expression: Note that the conductance of the system can be expressed in the form of a matrix $\mathbf{R}$: $\mathbf{R} = \vec{\mathbf{1}}^{\mathrm{T}}D_G\vec{P}$, so that we have the relation $\mathbf{R}\langle U^2 \rangle = \vec{\mathbf{1}}^{\mathrm{T}}N_2\mathbb{P}N_2^{-1}D_{GV}\langle \vec{U_i} \rangle$, where the matrix $\mathbb{P} = \vec{P}\vec{\mathbf{1}}^{\mathrm{T}}$.

IV. THE POWER SPECTRUM

Now let us take a look at how the power is dissipated from the perspective of the power spectrum. Let $P(O_j, v_0, t_0; O_i, v_1, t_1)$ denote the two-time-point joint probability density function, and we have

$$P(O_j, v_0, t_0; O_i, v_1, t_1) = P(O_i, v_1, t_1|O_j, v_0, t_0)P(O_j, v_0, t_0), \tag{13}$$

where $v_0, v_1 \in [V_0, V_N]$, $i, j = 0, 1, \dots, N$.

The autocorrelation function of the membrane voltage $E[U(0)U(t)]$ can be calculated as follows:

$$E[U(0)U(t)] = \sum_{i=0}^{N}\sum_{j=0}^{N}\int_{V_0}^{V_N}\int_{V_0}^{V_N} v_0v_1P(O_j, v_0, 0; O_i, v_1, t)\,dv_1\,dv_0$$

$$
\begin{aligned}
&= \sum_{j=0}^{N} \int_{V_0}^{V_N} v_0 \left[\int_{V_0}^{V_N} \sum_{i=0}^{N} v_1 P(O_i, v_1, t|O_j, v_0) P(O_j, v_0)\, dv_1 \right] dv_0 \\
&= \sum_{j=0}^{N} \int_{V_0}^{V_N} v_0 P(O_j, v_0) \left[\sum_{i=0}^{N} \int_{V_0}^{V_N} v_1 P(O_i, v_1, t|O_j, v_0)\, dv_1 \right] dv_0 \\
&= \sum_{j=0}^{N} \int_{V_0}^{V_N} v_0 p(O_j, v_0) \left[\sum_{i=0}^{N} E(U(t), O_i|O_j, v_0) \right] dv_0. \qquad (14)
\end{aligned}
$$

Doing the Laplace transformation on Eqs. (8), we have

$$
\begin{aligned}
\int_0^{+\infty} e^{-\lambda t} \frac{\partial}{\partial t} P(O_0, t|O_j, v_0)\, dt &= -Nk^+ \int_0^{+\infty} e^{-\lambda t} P(O_0, t|O_j, v_0)\, dt + k^- \int_0^{+\infty} e^{-\lambda t} P(O_1, t|O_j, v_0)\, dt, \\
&\dots \\
\int_0^{+\infty} e^{-\lambda t} \frac{\partial}{\partial t} P(O_i, t|O_j, v_0)\, dt &= -[(N-i)k^+ + ik^-] \int_0^{+\infty} e^{-\lambda t} P(O_i, t|O_j, v_0)\, dt + (N-i+1)k^+ \int_0^{+\infty} e^{-\lambda t} P(O_{i-1}, t|O_j, v_0)\, dt \\
&\quad + (i+1)k^- \int_0^{+\infty} e^{-\lambda t} P(O_{i+1}, t|O_j, v_0)\, dt, \\
&\dots \\
\int_0^{+\infty} e^{-\lambda t} \frac{\partial}{\partial t} P(O_N, t|O_j, v_0)\, dt &= -Nk^- \int_0^{+\infty} e^{-\lambda t} P(O_N, t|O_j, v_0)\, dt + k^+ \int_0^{+\infty} e^{-\lambda t} P(O_{N-1}, t|O_j, v_0)\, dt. \qquad (15)
\end{aligned}
$$

Rewriting it in form of matrix, we have the relationship $A(\lambda)\mathfrak{L}\vec{P}(O_i, t|O_j, v_0) = \vec{P}(O_i, t|O_j, v_0)$, in which $\mathfrak{L}\vec{P}(O_i, t|O_j, v_0)$ denotes the Laplace transform of the probability distribution $\vec{P}(O_i, t|O_j, v_0)$, and $A(\lambda) = \mathrm{diag}[\lambda, \dots, \lambda] + T_r$.

Equivalently, we can write $\mathfrak{L}\vec{P}(O_i, t|O_j, v_0) = A^{-1}(\lambda)\vec{P}(O_i, t|O_j, v_0)$ for $j = 0, 1, \dots, N$.

Now we can calculate $\mathfrak{L}E_U(\lambda) := \mathfrak{L}E[U(t)U(0)]$, the Laplace transform of $E[U(t)U(0)]$, as follows:

$$
\begin{aligned}
\mathfrak{L}E_U(\lambda) = \mathfrak{L}E[U(t)U(0)] = \int_0^{+\infty} e^{-\lambda t} E[U(t)U(0)]\, dt &= \sum_{j=0}^{N} \int_{V_0}^{V_N} v_0 P(O_j, v_0) \left[\sum_{i=0}^{N} \int_0^{+\infty} e^{-\lambda t} E(U(t), O_i|O_j, v_0)\, dt \right] dv_0 \\
&= \sum_{j=0}^{N} \int_{V_0}^{V_N} \left[v_0 P(O_j, v_0) \sum_{i=0}^{N} \mathfrak{L}E(U(t), O_i|O_j, v_0) \right] dv_0. \qquad (16)
\end{aligned}
$$

So one can see that all what we need to know are $\mathfrak{L}E(U(t), O_i|O_j, v_0)$. By doing the Laplace transform of Eqs. (6), we can obtain

$$
\begin{aligned}
\int_0^{+\infty} e^{-\lambda t} \frac{\partial}{\partial t} E(U(t), O_0|O_j, v_0)\, dt = &- \frac{g_0}{C_m} \int_0^{+\infty} e^{-\lambda t} E(U(t), O_0|O_j, v_0)\, dt \\
&+ \frac{g_0 V_0}{C_m} \int_0^{+\infty} e^{-\lambda t} P(O_0, t|O_j, v_0)\, dt - Nk^+ \int_0^{+\infty} e^{-\lambda t} E(U(t), O_0|O_j, v_0)\, dt \\
&+ k^- \int_0^{+\infty} e^{-\lambda t} E(U(t), O_1|O_j, v_0)\, dt, \\
&\dots \\
\int_0^{+\infty} e^{-\lambda t} \frac{\partial}{\partial t} E(U(t), O_i|O_j, v_0)\, dt = &- \frac{g_i}{C_m} \int_0^{+\infty} e^{-\lambda t} E(U(t), O_i|O_j, v_0)\, dt \\
&+ \frac{g_i V_i}{C_m} \int_0^{+\infty} e^{-\lambda t} P(O_i, t|O_j, v_0)\, dt - [(N-i)k^+ + ik^-] \\
&\int_0^{+\infty} e^{-\lambda t} E(U(t), O_i|O_j, v_0)\, dt + (N-i+1)k^+ \int_0^{+\infty} e^{-\lambda t} E(U(t), O_{i-1}|O_j, v_0)\, dt \\
&+ (i+1)k^- \int_0^{+\infty} e^{-\lambda t} E(U(t), O_{i+1}|O_j, v_0)\, dt, \\
&\dots
\end{aligned}
$$

$$\begin{aligned}\int_0^{+\infty} e^{-\lambda t}\frac{\partial}{\partial t}E(U(t),O_N|O_j,v_0)\,dt = &-\frac{g_N}{C_m}\int_0^{+\infty} e^{-\lambda t}E(U(t),O_N|O_j,v_0)\,dt\\ &+\frac{g_N V_N}{C_m}\int_0^{+\infty} e^{-\lambda t}P(O_N,t|O_j,v_0)\,dt - Nk^-\int_0^{+\infty} e^{-\lambda t}E(U(t),O_N|O_j,v_0))\,dt\\ &+k^+\int_0^{+\infty} e^{-\lambda t}E(U(t),O_{N-1}|O_j,v_0)\,dt. \qquad (17)\end{aligned}$$

Rewriting it in form of matrix, we have $B(\lambda)\mathfrak{L}\vec{E}(O_i,t|O_j,v_0)=\vec{E}(O_i,t|O_j,v_0)+D_{GV}\mathfrak{L}\vec{P}(O_i,t|O_j,v_0)$, where $B(\lambda)=\mathrm{diag}[\lambda,\dots,\lambda]+D_G+T_r=A(\lambda)+D_G$.

So we have

$$\mathfrak{L}\vec{E}(O_i,t|O_j,v_0)=B^{-1}(\lambda)[\vec{E}(O_i,t|O_j,v_0)+D_{GV}\mathfrak{L}\vec{P}(O_i,t|O_j,v_0)], \qquad (18)$$

for $j=0,1,\dots,N$.

Substituting it into Eq. (16), we can get the expression for $\mathfrak{L}E[U(t)U(0)]$:

$$\begin{aligned}\mathfrak{L}E_U(\lambda)=\mathfrak{L}E[U(t)U(0)]&=\sum_{j=0}^{N}\int_{V_0}^{V_N}\left[v_0P(O_j,v_0)\sum_{i=0}^{N}\mathfrak{L}E(U(t),O_i|O_j,v_0)\right]dv_0\\ &=\vec{\mathbf{1}}^{\mathrm{T}}\big[B^{-1}(\lambda)\langle\vec{U_i^2}\rangle+B^{-1}(\lambda)D_{GV}A^{-1}(\lambda)\langle\vec{U_i}\rangle\big]. \qquad (19)\end{aligned}$$

Finally, the power spectrum $S_U(\omega)$ can be calculated based on the $\mathfrak{L}E_U(\lambda)$:

$$\begin{aligned}S_U(\omega)=\mathfrak{L}E_U(i\omega)+\mathfrak{L}E_U(-i\omega)=\vec{\mathbf{1}}^{\mathrm{T}}\{&2[B^{-1}(i\omega)+B^{-1}(-i\omega)]N_2^{-1}D_{GV}\langle\vec{U_i}\rangle\\ &+[B^{-1}(i\omega)D_{GV}A^{-1}(i\omega)+B^{-1}(-i\omega)D_{GV}A^{-1}(-i\omega)]\langle\vec{U_i}\rangle\}. \qquad (20)\end{aligned}$$

The most distinctive property of the power spectrum lies in that it decreases with the law of $1/\omega^4$. In other words, the voltage fluctuations that are produced by the random gating of the channels have the $1/\omega^4$ noise.

V. PROOF OF THE $1/\omega^4$ POWER SPECTRUM

The denominator of $S_U(\omega)$ is $|A(i\omega)||A(-i\omega)||B(i\omega)||B(-i\omega)|$, where $|A|$ is the determinant of the matrix A. So the highest order of ω (the leading term) in the denominator of $S_U(\omega)$ is $\omega^{4(N+1)}$. In another respect, the highest order of ω in the numerator of $S_U(\omega)$ is ω^{4N+2}. In the following, what we need to do is to prove that the coefficient of the term ω^{4N+2} in the numerator is zero.

Now let us separate $S_U(\omega)$ into two parts, $S_U(\omega)=I+II$. For Part I we have

$$I=2\vec{\mathbf{1}}^{\mathrm{T}}\frac{[B^*(i\omega)|B(-i\omega)|+B^*(-i\omega)|B(i\omega)|]|A(i\omega)||A(-i\omega)|}{|A(i\omega)||A(-i\omega)||B(i\omega)||B(-i\omega)|}N_2^{-1}D_{GV}\langle\vec{U_i}\rangle, \qquad (21)$$

where B^* denotes the adjoint matrix of the matrix B. Since we need only to pursue the first one or two terms about ω in these matrices or determinants, we have $|A(i\omega)||A(-i\omega)|\sim(-1)^{N+1}(i\omega)^{2(N+1)}$. Here the symbol "$\sim$" should be understood as "has the first one or two leading terms," and we have

$$|B(i\omega)|\sim(i\omega)^{N+1}+(i\omega)^{N}\left(\frac{\sum_{i=0}^{i=N}g_i}{C_m}+\sum_{i=1}^{i=N}i(k^++k^-)\right) \qquad (22)$$

and

$$B^*(i\omega)\sim(i\omega)^{N}\mathfrak{I}+(i\omega)^{N-1}B_1, \qquad (23)$$

where $\mathfrak{I}$ denotes the identity matrix, and

$$B_1=\begin{bmatrix} b_{00} & k^- & & \cdots & & 0 & 0\\ Nk^+ & & \ddots & & & & \\ \cdots & \cdots & (N-i+1)k^+ & b_{ii} & (i+1)k^- & \cdots & \cdots\\ & & & & \ddots & & \\ 0 & 0 & & \cdots & \cdots & k^+ & b_{NN}\end{bmatrix},$$

in which $b_{ii}=\frac{\sum_{j\neq i}g_j}{C_m}+\sum_{j\neq(N-i)}jk^++\sum_{j\neq i}jk^-$.

So we have

$$[B^*(i\omega)|B(-i\omega)| + B^*(-i\omega)|B(-i\omega)|] \sim (-1)^N (i\omega)^{2N}\left\{\left[\frac{\sum_{i=0}^{i=N} g_i}{C_m} + \sum_{i=1}^{i=N} i(k^+ + k^-)\right]\mathfrak{I} - B_1\right\} = (-1)^N (i\omega)^{2N}[N_2 + 2N^{(0)}], \tag{24}$$

where

$$N^{(0)} = \begin{bmatrix} Nk^+ & -k^- & & \cdots & & 0 & 0 \\ -Nk^+ & & \ddots & & & & \\ \cdots & \cdots & -(N-i+1)k^+ & (N-i)k^+ + ik^- & -(i+1)k^- & \cdots & \cdots \\ & & & & \ddots & & \\ 0 & 0 & & \cdots & \cdots & -k^+ & Nk^- \end{bmatrix}.$$

It is easy to see that $\vec{\mathbf{1}}^{\mathrm{T}} N^{(0)} = 0$. Thus, the leading term of the numerator of Part I has the form

$$I \sim -2\vec{\mathbf{1}}^{\mathrm{T}} (i\omega)^{4N+2} D_{GV} \langle \vec{U}_i \rangle. \tag{25}$$

For Part II we have

$$II = \vec{\mathbf{1}}^{\mathrm{T}} \frac{B^*(i\omega) D_{GV} A^*(i\omega)|B(-i\omega)||A(-i\omega)| + B^*(-i\omega) D_{GV} A^*(-i\omega)|B(i\omega)||A(i\omega)|}{|A(i\omega)||A(-i\omega)||B(i\omega)||B(-i\omega)|} \langle \vec{U}_i \rangle. \tag{26}$$

It is very easy to check that $|B(i\omega)||A(i\omega)| \sim (i\omega)^{2(N+1)}$, and the leading term of its numerator has the form

$$II \sim 2\vec{\mathbf{1}}^{\mathrm{T}} (i\omega)^{4N+2} D_{GV} \langle \vec{U}_i \rangle. \tag{27}$$

Now, adding Eqs. (25) and (27) together, we can find that the coefficient of the term ω^{4N+2} in the numerator of $S_U(\omega)$ is zero. So the highest order of ω in the numerator must start from ω^{4N}, which means $S_U(\omega)$ has the form of $1/\omega^4$ noise.

VI. DISCUSSION

The first question is how to explain the physical means of this form of the power spectral density. To answer this question, we must make a comparison between the voltage noise and the conductance noise.

When the scale of the channel cluster is large, i.e., $N \gg 1$, it is necessary to find a compact form to describe the evolving of the voltage. There are several works concerning this problem [7,16,17]. Based on the analysis listed above, here we present our equations. Note that the channel system is independent of the membrane voltage, and we can use the central limit theorem on the fluctuation of the number of open channels. In the stationary state, the mean number of open channels is $\langle O \rangle = Np$, and the fluctuation around it obeys the following Ornstein-Ulenbeck process:

$$d\xi(t) = -(k^+ + k^-)\xi\, dt + \sqrt{\frac{2k^+k^-}{k^+ + k^-}}\, dB_t, \tag{28}$$

where B_t is the standard Brownian motion. Then the evolving of the voltage can be expressed in the form

$$C_m \frac{dU}{dt} = -g_L(U - V_L) - (Np + \sqrt{N}\xi(t)) g_{Ch}(U - V_{Ch}). \tag{29}$$

The fluctuation embedded in this equation cannot be characterized theoretically. So we present numerical results of its power spectrum. In Fig. 2 we plot three curves of the power spectral density, which are calculated by three different methods. The blue one is calculated by Eq. (21); the black one is calculated by doing a Fourier transform to the sample path of Eq. (2), and the red one is calculated by doing a Fourier transform to the sample path of Eqs. (28)–(29). One can see that these three curves are very consistent.

So why do the voltage fluctuations have the property of $1/\omega^4$ noise? Actually what we should say is that the $1/\omega^4$ noise reflects the nature of the piecewise deterministic temporal evolving of the voltage. The fact is that the randomness in this system is weaker than the conductance noise, whether it is described by the diffusion process or by the jumping process. The trajectory of $U(t)$ is smooth almost everywhere, except the time points when the channel is opening or closing

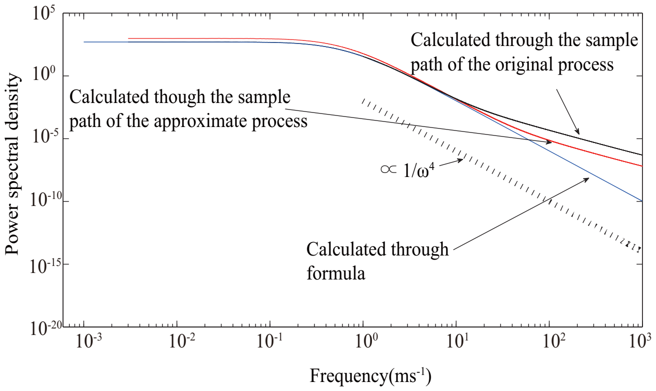

FIG. 2. The three kinds of power spectra calculated from three methods respectively. The values of other parameters are $C_m = 0.01\ \mathrm{pF}/\mu\mathrm{m}^2 \times 6\ \mu\mathrm{m}^2$, $V_L = -54.4$ mV, $V_{Ch} = 0$ mV, $k^+ = 0.01$, $k^- = 1$, and $N = 30$.

so that the conductance is changed. Actually, this point can be expressed more intuitively using Eqs. (28)–(29). We know that white noise has the constant power spectrum. Being the integral of white noise, the OU process $\xi(t)$ has the $1/\omega^2$ power spectrum. Now that $U(t)$ is the integral of $\xi(t)$, it is not surprising that it has the $1/\omega^4$ power spectrum.

The power spectrum for the voltage fluctuation in the system of a cluster of potassium channels is experimentally measured in [17], in which the $1/\omega^4$-type power spectrum is also observed. Especially note that the transition kinetics of the potassium channel is voltage-dependent; this fact makes us further confident of our recognition that the $1/\omega^4$-type noise is an intrinsic property of the weaker noise embedded in the voltage evolving.

Meanwhile the result tells us that the current response to the conductance noise and the voltage response to the conductance noise are essentially different. Under a clamped potential, the ion current is directly determined by the conductance. But, for the membrane voltage, in one respect, its integrated reversal potential is changing with the conductance; in another respect, it needs a relaxation precess to its new reversal potential when the conductance is changed. If we do not consider any other source of noise, the relaxation process is smooth!

The second question is how significant is the voltage noise among all of the membrane noise?

Since there are so many types of synapses, this question has no definite answer. Briefly, in the dendrites, the scales of the synapses are all small so that the conductance noise-induced voltage fluctuation may be relatively more significant. However, the information in dendrites is propagated by the local graded potentials [2], and the calculation is made in the soma through temporal and spatial summation [21]. So the influence of the membrane noise on the action potential initiation still needs to be studied.

In the neuromuscular junction, the fact of many folds facing the presynaptic active zones means that the membrane area is large and the receptors are distributed densely in the tops of the folds [2], which means, in this case, the scale of the synapse is relatively large. So we believe that the variability in the miniature postsynaptic potentials or currents [5] is primary caused by the randomness of the neurotransmitter exocytosis.

There still exists the question of how these different kinds of noises are combined to form the integral membrane noise. Are they additive or multiplicative, or do they obey other complex laws? We should say that more subtle theoretical models are needed to answer such kinds of questions.

In summary, we have constructed a mathematical model to describe the membrane voltage fluctuation driven by a (maybe small) cluster of ligand-gated channels. The random gating of the channels produces the conductance noise in one respect, and the fluctuations in the reversal potential in another respect. The voltage fluctuation is determined by the combination of these two parts. We prove theoretically that the power spectrum of the voltage fluctuation has the $1/\omega^4$ form, which is first observed experimentally for the potassium channels. The results in this paper may help us to separate channel noise from other noise such as Johnson noise or the noise in neurotransmitter releasing. In the next step, we may study the responses of the membrane-channel system to the pulsative stimuli of neurotransmitters.

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