Statistics of subthreshold neuronal voltage fluctuations due to conductance-based synaptic shot noise

Magnus J. E. Richardson\textsuperscript{a)}
École Polytechnique Fédérale de Lausanne (EPFL), Laboratory of Computational Neuroscience, School of Computer and Communication Sciences and Brain Mind Institute, CH-1015 Lausanne, Switzerland
and Warwick Systems Biology Centre, University of Warwick, Coventry CV4 7AL, United Kingdom

Wulfram Gerstner\textsuperscript{b)}
École Polytechnique Fédérale de Lausanne (EPFL), Laboratory of Computational Neuroscience, School of Computer and Communication Sciences and Brain Mind Institute, CH-1015 Lausanne, Switzerland

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Neurons in the central nervous system, and in the cortex in particular, are subject to a barrage of pulses from their presynaptic populations. These synaptic pulses are mediated by conductance changes and therefore lead to increases or decreases of the neuronal membrane potential with amplitudes that are dependent on the voltage: synaptic noise is multiplicative. The statistics of the membrane potential are of experimental interest because the measurement of a single subthreshold voltage can be used to probe the activity occurring across the presynaptic population. Though the interpulse interval is not always significantly smaller than the characteristic decay time of the pulses, and so the fluctuations have the nature of shot noise, the majority of results available in the literature have been calculated in the diffusion limit, which is valid for high-rate pulses. Here the effects that multiplicative conductance noise and shot noise have on the voltage fluctuations are examined. It is shown that both these aspects of synaptic drive sculpt high-order features of the subthreshold voltage distribution, such as the skew. It is further shown that the diffusion approximation can only capture the effects arising from the multiplicative conductance noise, predicting a negative voltage skew for excitatory drive. Exact results for the full dynamics are derived from a master-equation approach, predicting positively skewed distributions with long tails in voltage ranges typical for action potential generation. It is argued that, although the skew is a high-order feature of subthreshold voltage distributions, the increased probability of reaching firing threshold suggests a potential role for shot noise in shaping the neuronal transfer function. © 2006 American Institute of Physics.

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I. INTRODUCTION

The code that neurons use to communicate to one another in the cortex is a subject of intense research. One of the difficulties of inferring the code is that it is distributed over populations of many thousands of neurons, as evidenced in the motor cortex in the population vectors\textsuperscript{1} that code for hand position or muscle action.\textsuperscript{2} One method of indirectly measuring the activity of a population of neurons is by using the fluctuating voltage of a neuron embedded in an active network as a probe\textsuperscript{3} given a model of the effect of the barrage of synaptic pulses on the neuronal voltage, the resulting statistics can be used to infer the state of the presynaptic network. As well as the response of the neuron to its drive, the form of the voltage fluctuations also determines whether an action potential will be output from a neuron. Hence, the accurate modeling of the effect of presynaptic pulses on the subthreshold potential of neurons\textsuperscript{4–6} is of great interest to experimental measures of network activity and to the under-
standing of the neuron as a basic input-output unit of the central nervous system.

A fundamental model of the electrical response of driven cells was introduced by Lapicque and featured a passive decay of the voltage due to the capacitance and leak conductance of the cellular membrane. Later, Stein introduced a model featuring a synaptic drive modeled as a conductance change, following which the effects of stochastic, conductance-based synaptic drive on membrane potential fluctuations began to be extensively studied. These initial studies typically treated the fluctuating drive in the diffusion limit and were principally interested in the statistics of the interspike interval distribution of the outgoing spikes generated by the neuron, rather than the voltage distribution itself. Since the early theoretical work, many experimental studies have directly probed the conductance change due to the synaptic drive and have shown that the conductance can be as much as five times higher than that of a neuron in an inactive network. That the synaptic conductance change is dominant has led to renewed theoretical interest in the synaptic drive, particularly on the nonlinear effect that the conductance change has on the gain of neurons.

More recently, studies have directed their attention toward the statistics of the subthreshold voltage distribution. A solution was recently proposed for the case of filtered synaptic drive (in which the synaptic drive was modeled by two Ornstein-Uhlenbeck processes with distinct time constants for excitatory and inhibitory synapses). However, doubt has been cast on the correctness of the approach used. Though an exact solution for the case of filtered synaptic drive remains illusive, a number of approximation schemes are now available.

The effects of another feature of synaptic drive, shot noise, have been comparatively less studied. However, it has been included in the context of the interspike interval distribution, incorporated into numerical schemes for calculating the firing rate of neuronal populations, considered in relation to stochastic resonance in neurons, included in an analysis of the effects of correlations in the presynaptic population, and a perturbative approach has recently been developed for the case of a filtered synaptic shot noise.

Here, the effect of multiplicative, conductance-based shot noise on the voltage statistics of neurons receiving delta-pulse synapses is examined in detail. After defining the model to be analyzed, the weakness of the diffusion approximation in the analysis of subthreshold voltage fluctuations is first identified and the full master equation introduced. In this Focus Article both established results and new results, specifically for the exact forms for the mean, variance, and skew for arbitrary synaptic amplitude distributions, are presented. Though the analysis is restricted to the case of subthreshold voltage fluctuations, the implications of some of the results for the firing rate of neurons are considered in Sec. V.

II. THE MODEL

The electrical properties of the neuronal membrane can be derived by modeling it as a capacitance $C$ in parallel with a passive leak current of constant conductance $g_L$ and a synaptic current $I_{syn}$ composed of fluctuating conductances. The ratio of the capacitance and the leak conductance $\tau_L=C/g_L$ defines the passive time constant of the neuron. This sets the scale for the relaxation of the cellular voltage following any disturbance that takes it away from its equilibrium value $E_L$. With these definitions, the capacitive charging of the cell membrane can be seen to obey the following equation:

$$C \frac{dV}{dt} = -g_L(V-E_L) - I_{syn}(t),$$

from which the time course of the voltage $V(t)$ at time $t$ can be derived as a function of the synaptic current. It should be noted that no spike-generating currents have been included in the voltage equation. This is in keeping with the aim here of analyzing the statistics of the subthreshold voltage of cells driven by synapses with finite-sized amplitudes. This scenario is directly relevant to experiments that use a hyperpolarized neuron as a probe for the presynaptic network activity.

A. Synaptic shot noise

The synaptic current $I_{syn}$ can be modeled as comprising two fluctuating components: an excitatory conductance $g_e(t)$ that acts to depolarize the neuron by bringing its voltage closer to the reversal potential $E_e=0$ mV for excitation, and an inhibitory conductance $g_i(t)$ that acts to hyperpolarize its voltage by bringing it closer to the reversal potential $E_i=-75$ mV for inhibition. The net current can be written as a sum of these two components:

$$I_{syn}(t) = g_e(t)(V-E_e) + g_i(t)(V-E_i).$$

The conductances themselves are activated by a barrage of presynaptic pulses, each of which is modeled here as causing a delta-pulse conductance of strength $a_e C$, where from now on excitation will be used as an example with similar statements for inhibition following by analogy. Thus, for excitation,

$$g_e(t) = a_e C \sum_{\{t_i\}} \delta(t-t_i),$$

where $\{t_i\}$ is the set of excitatory presynaptic pulse times that follow a Poisson process with a constant rate $\lambda_e$.

Modeling the conductance changes as a series of impulses is an approximation; synaptic channels have characteristic time scales for inactivation (about 3 ms for excitation and 10 ms for inhibition). However, for the purposes of this paper, which concentrates on the shot-noise aspect of the drive, this filtering will be ignored (the reader is directed elsewhere for a perturbative treatment of filtered, conductance-based shot noise). It should also be noted that the case of non-Poissonian drive (see, for example, Ref. 34) is beyond the scope of this article (see Ref. 35 for a treatment of temporally correlated input in the diffusion approximation).

On inserting the form for the synaptic drive (2) into the voltage equation (1), dividing by $V-E_e$, and integrating over a short period of time that includes a single excitatory input, it is seen that the membrane voltage jumps from $V$ to $V+\Delta$ with
\[ \Delta = (E_e - V)(1 - e^{-\tau}) = (E_e - V)b_e, \]  
where the effective amplitude \( b_e \) has been introduced. This form of the voltage jump follows the usual rules of calculus and is the same as that chosen in Ref. 31.

1. Stratonovich versus Itô stochastic calculus

It is possible to make a different choice from the update rule (4) by retarding the multiplicative voltage prefactor of the synaptic drive in Eq. (2). If such a choice is made, the driving term for excitation, for example, becomes \( g_e(t)[V(t - \varepsilon) - E_e] \), where \( \varepsilon \) is a positive infinitesimal. The update rule corresponding to (4) would then be \( \Delta = (E_e - V)a_e \) instead. In the diffusion limit (to be discussed in Sec. III), this choice would correspond to the Itô form of stochastic calculus, whereas the choice (4) corresponds to the Stratonovich form. Throughout this paper it will be the Stratonovich formulation for the replacement \( b_e \rightarrow a_e \) the Itô formulation is obtained.

2. Numerical simulations of synaptic shot noise

A discretized form of the voltage equation (1) can be used for Monte Carlo simulations of the dynamics. For the purposes of this paper a simple forward Euler scheme was found to be adequate, with an integration time step \( \Delta_t = 50 \mu s \), or smaller, used. The discrete-time dynamics for the voltage \( V_k \) at time step \( t_k = k\Delta_t \) can be written, following the rule in Eq. (4), as

\[ V_{k+1} = V_k + \frac{\Delta}{\tau} (E_L - V_k) + e_k b_e (E_e - V_k) + i_k b_i (E_i - V_k), \]  
where \( e_k \), \( i_k \) are integers drawn from Poisson distributions with means \( \mathcal{R}_e \Delta_t \), \( \mathcal{R}_i \Delta_t \). This is an approximation to Poissonian statistics, valid to order \( \Delta_t \), and therefore consistent with this first-order Euler scheme: a small \( \Delta_t \) must be chosen (as specified above) for accuracy such that \( e_k \) or \( i_k \) infrequently take a value of greater than unity. It should be noted that an exact integration scheme can be implemented by calculating the time to the next event using the Poissonian interval distribution—this method is discussed in Ref. 36.

III. THE DIFFUSION APPROXIMATION

A standard approach for dealing with Poissonian shot noise is to take the diffusion limit. In the context of a fluctuating subthreshold voltage this approach becomes accurate in the limit in which many excitatory and inhibitory synaptic pulses arrive within the relaxation time \( \tau_e \) of the dynamics, i.e., that \( \mathcal{R}_e \tau_e \gg 1 \) and \( \mathcal{R}_i \tau_i \gg 1 \). When this holds, the Poissonian fluctuations are well approximated by a Gaussian process. In this section the diffusion approximation of the voltage dynamics first will be obtained and the corresponding Fokker-Planck equation for the probability distribution derived. The predictions of this approximation will then be compared to the full dynamics and its weaknesses identified.

To obtain the diffusion approximation, the aim is to approximate the stochastic synaptic current given in Eqs. (2) and (3) by a Gaussian process of identical mean and variance. Using the excitatory conductance as an example, consider first the integration of this contribution to \( I_{\text{syn}} \) over a short time \( t_k \) to \( t_{k+1} = t_k + \Delta_t; \)

\[ g_e(V - E_e) = \frac{1}{\Delta_t} \int_{t_k}^{t_{k+1}} dt' C_a \sum_{\{i(t)\}} \delta(t - t_i)(V - E_e). \]  
Finding the mean and variance of this quantity is complicated by the fact that a delta function multiplies the voltage under the integral. However, on combining the rule given in Eq. (4) with the voltage equation (1), the first two moments can be found to be

\[ \langle g_e(V - E_e) \rangle = \mathcal{C}_R b_e (V_L - E_e), \]  
\[ \text{Var}[g_e(V - E_e)] = C_R^2 \mathcal{R}_e b_e^2 (V_k - E_e)^2/\Delta_t, \]  
where \( V_k = V(t_k) \) is the value of the voltage before any inputs arrive (these equations nevertheless correspond to the Stratonovich form of stochastic calculus).

To keep the form of the dynamics unambiguous, the discrete form for the evolution will be written directly. To this end, it proves convenient to introduce an effective time constant \( \tau \) and the drive-dependent equilibrium potential \( E \):

\[ \tau^{-1} = \tau^{-1}_L + \mathcal{R}_e b_e + \mathcal{R}_i b_i, \]  
\[ E = \tau E_L \tau^{-1}_L + E_R \mathcal{R}_e b_e + E_i \mathcal{R}_i b_i. \]  
In terms of these variables the discrete-time equation for the voltage can be written

\[ V_{k+1} = V_k + \frac{\Delta}{\tau} (E - V_k) 
+ \sqrt{\Delta_t \left[ \mathcal{R}_e b_e^2 (V_k - E_e)^2 + \mathcal{R}_i b_i^2 (V_k - E_i)^2 \right]} \psi_k, \]  
where the two Gaussian processes for excitation and inhibition have been merged and \( \psi_k \) is a Gaussian random number of zero mean and unit variance drawn for each time step. This discrete evolution equation is a translation into Itô form of the true Stratonovich dynamics. The corresponding Fokker-Planck equation \(^{37}\) for the diffusion-level voltage distribution \( P_d(V) \) can be written

\[ \frac{\partial}{\partial t} P_d = \frac{1}{2} \frac{\partial^2}{\partial V^2} \left[ (\mathcal{R}_e b_e^2 (E_e - V)^2 + \mathcal{R}_i b_i^2 (E_i - V)^2) P_d \right] 
+ \frac{1}{\tau} \frac{\partial}{\partial V} \left[ (V - E) P_d \right]. \]  
A brief technical point: to order \( a_e^2, a_i^2 \), this Fokker-Planck equation is identical to that which would be obtained directly for the Stratonovich formulation for the replacement \( g_e = \mathcal{C}_a / (\mathcal{R}_e + \sqrt{\mathcal{R}_i} \xi_e(t)) \), where \( \xi_e(t) \) is delta-correlated white noise.\(^{26,57}\) However, as will be seen, the form used in Eq. (12) has the added advantage of giving the mean and variance of the voltage correct to all orders in \( a_e, a_i \) as expressed via \( b_e, b_i \).
A. The diffusion-level voltage distribution

As stated earlier, the rates $\mathcal{R}_e$, $\mathcal{R}_i$ are steady and so, though the voltage has a dynamics, its statistics are stationary. The corresponding steady-state (i.e., setting $\partial P_D = 0$) Fokker-Planck equation (12) is straightforward to solve with the solution taking the following form:

$$P_D \propto \exp[-AF(V)]G(V),$$

$$A = \frac{1}{\sqrt{\beta_e \beta_i |E_e - E_i|}} \left( \beta_e E_e + \beta_i E_i \right),$$

$$F(V) = \arctan \left( \frac{\beta_i (V - E_i) + \beta_e (V - E_e)}{\sqrt{\beta_e \beta_i |E_e - E_i|}} \right),$$

$$G(V) = \left[ \beta_e (V - E_e)^2 + \beta_i (V - E_i)^2 \right]^{[1+1/(\beta_e + \beta_i)]},$$

where the simplifying notation $\beta_e = \tau \mathcal{R}_e b_e^2/2$ and relative reversal potential $E_e = E_e - E$ have been introduced (and similarly for the $i$, $L$ subscripts).

It should be noted that the distribution predicted by the diffusion approximation is continuous over the voltage range. This is, however, not the case for the true shot-noise dynamics: if $E_L < E_e$, it is not possible for excitatory input to push the voltage over the reversal potential $E_e$ for excitation (similarly, if the leak reversal $E_L$ is chosen such that $E_i < E_L < E_e$, then the voltage would be bound between $E_i$ and $E_e$). Hence the voltage should be bound by the leak and synaptic reversal potentials and the distribution should vanish outside this region.

That the diffusion approximation is not able to deal correctly with the reversal potential boundaries has been long recognized and represents one of its weaknesses in its modeling of conductance-based drive (in this reference a number of alternative models to that considered here are discussed in detail, such as diffusion-level models that make the boundaries unreachable). An example of this is given in Figs. 1(a)–1(c). For the correct shot-noise dynamics the voltage is unable to cross the boundary for inhibition; the closer the voltage gets to $E_i$, the weaker the multiplicative inhibitory drive becomes. However, in the diffusion approximation, the excitatory noise is Gaussian (effectively predicting some negative conductances) and so causes the voltage to overlap into the forbidden zone below the inhibitory reversal potential.

FIG. 1. Comparison of the shot-noise and diffusion-approximation voltage dynamics. (a)–(c) A case demonstrating the boundary error of the diffusion approximation: a neuron receiving both excitatory and strong inhibitory drive bringing it close to the inhibitory potential $E_i = -75 \text{ mV}$, with a leak potential also set at $E_L = -75 \text{ mV}$. (a) Shot-noise simulation of the dynamics. Between pulses the neuronal voltage relaxes to $E_i$. (b) Diffusion simulation using Eq. (11). Note that the voltage erroneously crosses the inhibitory reversal potential, which is not possible under the correct dynamics. (c) The steady-state shot-noise and diffusion-level voltage distributions. The diffusion approximation [simulation, Eq. (11); exact solution, Eq. (13)] gives a significant weight to the forbidden region below $E_i = E_L = -75 \text{ mV}$. (d)–(f) A case demonstrating the skew error of the diffusion approximation: a neuron receiving excitatory drive only with a leak potential $E_L = -60 \text{ mV}$. (d) Shot-noise simulation and (e) diffusion-level simulation. The average voltage $V = -50 \text{ mV}$ in both cases (dotted lines). (f) The shot-noise distribution is positively skewed (peak left of the average, tail to the right) whereas its diffusion approximation predicts a negative skew with the peak to the right of the average voltage. The parameters $(\mathcal{R}_e, \mathcal{R}_i, \mathcal{R}_e, \mathcal{R}_i)$ used for the drive were as follows: (a)–(c) $[0.5, 0.01, 10, 0.05]$, (d)–(f) $[0.25, 0.04, 0, 0]$ with the rates given in kHz.
tial. This effect can be seen clearly in simulations of the voltage time course in Fig. 1(b) well as in the distribution in Fig. 1(c).

**B. The diffusion-level voltage moments**

The mathematical form of the solution given in Eq. (13) for the diffusion-level distribution \( P_D \) does not provide for a transparent understanding of its form. A convenient way of classifying a distribution is via its moments, such as the mean and variance. For the diffusion-level distribution, such moments can be easily obtained by multiplying the Fokker-Planck equation and integrating over the voltage range. It proves convenient to measure the voltage as a difference from its mean \( E \) given in Eq. (10). On multiplying the steady-state form of Eq. (12) by \( v^m \), where \( v=(V-E) \), and integrating over this variable, the following recursion relation for the moments of the probability distribution is found:

\[
0 = \left( \frac{1}{2} (m-1) (R_e b_e^2 + R_i b_i^2) - \frac{1}{\tau_v} \right) \langle v^m \rangle_D \\
- (m-1) (R_e b_e^2 \tilde{E}_e + R_i b_i^2 \tilde{E}_i) \langle v^{m-1} \rangle_D \\
+ \frac{1}{2} (m-1) (R_e b_e^2 \tilde{E}_e + R_i b_i^2 \tilde{E}_i) \langle v^{m-2} \rangle_D,
\]

where the \( D \) subscripts remind the reader that the average here is over the diffusion-level voltage distribution. By setting \( m=1 \), it is seen that the average voltage \( V \) is identical to \( E \), i.e., \( \langle v \rangle_D = 0 \). From the case of \( m=2 \), the diffusion-level voltage variance \( \sigma_D^2 \) is found to be

\[
\sigma_D^2 = \frac{\tau_v}{2} \frac{R_e b_e^2 \tilde{E}_e + R_i b_i^2 \tilde{E}_i}{1 + \tau_i R_i b_i (1-b_i/2) + \tau_e R_e b_e (1-b_e/2)}.
\]

Also of interest is how non-Gaussian the distribution is. The skew, defined as \( S=\langle v^3 \rangle/\sigma^3 \), provides one such measure and can be written in terms of the standard deviation \( \sigma_D \) by using Eq. (14) with \( m=3 \):

\[
S_D = -\frac{2 \tau_v}{\sigma_D (1 + \tau_i R_i b_i (1-b_i/2) + \tau_e R_e b_e (1-b_e/2))}.
\]

For both the variance and skew, the effective time constant \( \tau_v \) [Eq. (9)] has been replaced by its form in terms of the passive time constant \( \tau_v \) and the rates \( R_e, R_i \).

To compare the diffusion-level form for the skew with simulation of the full model, a special case is considered in which inhibition is absent. In the limit of high-rate and small amplitudes, with \( \tau_i R_i b_i \) held constant so as to keep the average voltage \( E \) fixed, the skew can be written

\[
S_D = \sqrt{\frac{8 \tau_i R_i b_i^2}{1 + \tau_e R_e b_e}} \sim \sqrt{b_e}
\]

and seen to be proportional to the root of \( b_e \) (note that this is the same for the standard deviation). For the case of the purely excitatory drive, the diffusion approximation predicts a skew that is always negative.

It is not surprising that in the extreme case near the reversal of inhibition [shown in Figs. 1(a)–1(c)] the skew predicted from the diffusion approximation will be inaccu-rate. However, even away from the inhibitory reversal the skew is given incorrectly by the diffusion approximation. In Figs. 1(d) and 1(e) an example is given for a neuron driven by an excitatory drive with a fluctuating voltage of average value \(-50 \text{ mV}\). As can be seen in the figure, the skew predicted by the diffusion approximation is negative with a value \(-0.23\), whereas the distribution of voltages from the shot-noise simulation is positively skewed with a magnitude 0.23 (a mirror-image case was chosen). The difference between the true skew and its diffusion approximation is explored further in Fig. 2 as a function of \( b_e \), while \( \tau_i R_i b_i \) is again held constant. As can be seen, for the examples, the diffusion approximation is systematically in error in its estimation of the skew.

**IV. ACCOUNTING FOR SHOT NOISE**

The full shot-noise statistics will now be addressed. As an illustration, the case of a uniamplitude distribution of synaptic weights will be considered first and the master equation for the dynamics of the voltage distribution presented. As will be seen, it is possible also in this case to derive arbitrary moments of the voltage distribution; these will be compared to the mean, variance, and skew derived in the diffusion approximation. The link between the diffusion approximation and the full dynamics is then examined and a consistent expansion of the master equation provided. The use of the simple uniamplitude case (in the absence of inhibition) also allows for an analytical recursion solution for the voltage distribution to be reviewed. The section closes with an analysis of the more general case in which the excitatory and inhibitory synaptic strengths take a range of values. The particular case of an exponential distribution of synaptic amplitudes is given as an example.

**A. The master equation for shot-noise drive**

In the previous section the Fokker-Planck equation was derived for the diffusion limit of high-rate synaptic pulses. A more general equation, the master equation, can be written down for the full probability density \( P \) that is valid for arbitrary rate pulses. This equation can be derived by considering an ensemble of equivalent neurons. There are three ways that neurons can enter a particular voltage range \( V \) to \( V+\delta V \): (1) from an excitatory jump into the range from some lower voltage; (2) from an inhibitory jump into the range from a higher voltage; and (3) by drifting in due to the leak term. Correspondingly, there are three analogous ways of leaving this voltage range. When the effects of these processes on the probability (proportion of neurons within the ensemble) of finding a neuron in this range are accounted for, the following equation is obtained:

\[
\frac{\partial}{\partial t} P(V) = R_e \left[ \frac{1}{1-b_e} P \left( V-b_e E_e \right) - P(V) \right] \\
+ R_i \left[ \frac{1}{1-b_i} P \left( V-b_i E_i \right) - P(V) \right] \\
+ \frac{1}{\tau_v} \frac{\partial}{\partial V} \left[ (V-E_L) P(V) \right].
\]
This equation, written in a form where the probability current is explicit, has been used previously in combination with a threshold for spike initiation to examine the interspike interval of neurons driven by conductance-based shot noise. An efficient numerical scheme for the solution of this equation has also been presented.

B. Voltage moments of the master equation

The exact mean, variance, and skew of the shot-noise subthreshold voltage distribution can be obtained directly from the master equation (18) by taking voltage moments, as was done similarly for the diffusion approximation in Sec. III. Again, it proves convenient to take the moments with respect to \( \nu = V - E \), yielding the relation

\[
0 = R_{c}(1 - b_c)\left(\left(\frac{\nu + b_c E_c}{1 - b_i}\right)^{m} - \langle \nu^m \rangle\right)
+ \frac{m}{\tau_L} (\mathcal{E}_L(\nu^{m-1}) - \langle \nu^m \rangle),
\]

where \( \mathcal{E}_L = E_L - E \). From this equation it can be shown that the mean voltage is equal to \( E \) and the variance \( \sigma^2 \) is identical to \( \sigma_D^2 \) given in Eq. (15): the diffusion approximation as formulated in Sec. III gives the first two moments exactly as was seen in the top two panels of Figs. 2(a)–2(c).

The third central moment can be written

\[
\langle \nu^3 \rangle = \frac{\tau_L}{3} \left( 1 + 4 R_e \tau_L b_c (1 - b_i + b_i^2/3) + 4 R_e \tau_L b_c (1 - b_i + b_i^2/3) \right)
+ \frac{R_e b_c^2 E_c^3 + R_e b_i^3 E_i^3}{1 + R_e \tau_L b_c (1 - b_i + b_i^2/3) + R_e \tau_L b_c (1 - b_i + b_i^2/3)}
- \frac{R_e b_c^2 E_c^3 + R_e b_i^3 E_i^3}{1 + R_e \tau_L b_c (1 - b_i + b_i^2/3) + R_e \tau_L b_c (1 - b_i + b_i^2/3)},
\]

which can be used to obtain the skew \( S = \langle \nu^3 \rangle / \sigma^3 \) exactly. To give a transparent comparison with the prediction of the skew for the diffusion approximation \( S_D \), the case of a purely excitatory drive is again considered. In this case the skew becomes

\[
S = \frac{1 - \tau_L R_e \nu (2 - b_e)}{1 + \tau_L R_e \nu (1 - b_e + b_e^2/3)} \sqrt{\frac{8 [1 + \tau_L R_e \nu (1 - b_e)]}{9 \tau_L R_e}},
\]

which in the diffusion limit, i.e., \( b_e \) small but with \( R_e \nu \tau_L \) held constant, the skew simplifies to

\[
S \approx \frac{1 - 2 \tau_L R_e \nu}{1 + \tau_L R_e \nu} \sqrt{\frac{8 b_e (1 + \tau_L R_e \nu)}{9 \tau_L R_e \nu}} \sim \nu b_e.
\]

For \( 2 \tau_L R_e \nu < 1 \) this skew is positive and clearly different from that calculated from the Fokker-Planck equation (17), which is negative. A comparison of the diffusion-level skew and full skew is given in Fig. 2 for different values of \( \tau_L R_e \nu \) as \( b_e \) is varied (this choice ensures that the mean voltage \( E \) remains constant). Data from simulations are also provided.
with the exact results to underline the fact that approaches that use simulations in which Poissonian fluctuations are replaced by Gaussian white noise will also be in error at the level of the skew.

C. Consistent expansions of the master equation

The master equation can be expanded directly in powers of \( b_e \) with \( \tau_e R_e b_h \) held constant to ensure a constant mean \( E \). The term of Eq. (18) that deals with excitatory pulses can be expanded to second order in \( b_e \) to yield

\[
\frac{1}{1-b_e} P\left( V - b_e E_e \right) - P(V) = b_e P(V) + b_e (V - E_e) \frac{\partial P(V)}{\partial V} + \frac{b_e^2}{2} \frac{\partial^2}{\partial V^2} [(V - E_e)^2 P(V)] + O(b_e^3).
\]

(23)

On inserting this expansion, and the equivalent for inhibition, into the master equation (18), it is straightforward to show that the Fokker-Planck equation (12) is obtained. Hence in this expansion the mean and variance are given correctly, whereas the skew is given incorrectly. This is, of course, not too surprising: though there are some contributions to the skew at second order arising from the multiplicative noise, there are also terms missed that come from the higher-order terms dropped in the truncation of the expansion (23).

For a consistent solution it would be better to derive a systematic expansion that gives the moments correctly order by order in \( b_e \), for the steady-state subthreshold distribution, centered around \( E \), this can be achieved by writing the equation in a dimensionless variable \( y = (V - E)/\sigma \). This removes the implicit \( b_e \), \( b_e \) scale in \( V - E \). The expansion analogous to (23) for the distribution \( f(y) \) to order \( b_e \) yields

\[
b_e \frac{\partial}{\partial y} (f(y)) - b_e E_e \frac{\partial f}{\partial y} + \frac{b_e^2 E_e^2}{\sigma} \frac{\partial^2 f}{\partial y^2},
\]

(24)

where it should be noted that \( b_e \sigma \sim \sqrt{b_e} \). Together with the rest of the master equation, this yields

\[
\tau_e \frac{\partial P_0}{\partial t} = \frac{\partial^2}{\partial y^2} [(V - E) P_0] + \frac{\partial}{\partial y} (f_0 y)
\]

(25)

at zero order. The steady-state solution in terms of the voltage \( V \) is a Gaussian of mean \( E \) and variance \( \sigma \) given by Eqs. (10) and (15) and with vanishing skew. In comparison with the Fokker-Planck equation (12), it can be shown that Eq. (25) is identical to that of the diffusion approximation except that in the argument of the second derivative of Eq. (12) the voltage in the quadratic term has been replaced by its average value \( E \).

A heuristic way of arriving at this approximation is to expand the synaptic drive given in Eq. (2). Considering just the excitatory component, the conductance can be first expanded into tonic \( g_{e0} \) and fluctuating \( g_{eF} \) components:

\[
ge_e(V - E_e) = g_{e0}(V - E_e) + g_{eF}(V - E_e).
\]

(26)

The first term on the right-hand side is absorbed directly into the leak conductance, leading to the effective time constant \( \tau \) and reversal potential \( E \). The second term on the right-hand side represents the noise. This noise term can be expanded around the average voltage \( E \) to give

\[
ge_{eF}(V - E_e) = g_{eF}(E - E_e) + g_{eF}(V - E).
\]

(27)

In terms of the variable \( V - E \), which measures the difference of the voltage from its mean, the expansion on the right-hand side represents additive and multiplicative components, respectively. If the amplitude of \( g_{eF} \) is zero, then \( V - E = 0 \). Hence, if \( g_{eF} \) is small, the multiplicative term must be less significant than the additive term. Keeping the leading-order additive fluctuations and dropping the multiplicative term yields an approximation for the synaptic drive that comprises a tonic conductance with additive current-based noise. In the diffusion approximation this results in a Fokker-Planck equation equivalent to that given in Eq. (25). This approximation has been used previously under the name of the “effective time constant” or “Gaussian approximation” and can be justified [via Eq. (24)] as the leading term in the expansion of the master equation (18). Moreover, it allows for a perturbative approach for calculating the skew by expanding to higher order, as was shown recently for a filtered synaptic drive.

D. Voltage distribution for excitatory shot noise

For the case of combined excitation and inhibition, an analytic solution of Eq. (18) appears difficult. However, in the absence of inhibition a solution can be found using a generalization of a standard method developed for Poissonian shot noise. This recursive approach, which has been used previously in the context of neuronal firing rates, is now reviewed.

In the absence of inhibition the dynamics are governed by the relaxation, due to the leak conductance, and the excitatory jumps. The recursive method breaks the voltage range into a number of segments that can be solved successively. The first segment is between the leak potential \( E_L \) and the voltage \( V_1 = E_L + b_e (E_e - E_L) \) to which an excitation jump brings the neuron from this leak potential. The dynamics in this segment are governed purely by the relaxation and the excitatory jumps out. The probability distribution within the segment \( P_{01} \), between \( V_0 = E_L \) and \( V_1 \), therefore obeys

\[
\tau_e R_e P_{01} = \frac{\partial}{\partial V} [(V - E_L) P_{01}]
\]

(28)

and has the solution

\[
P_{01} = A(V - E_L)^{\tau_e R_e^{-1}},
\]

(29)

where \( A \) is a constant to be determined by normalization. For cases of moderate rate and higher \( \tau_e R_e > 0 \), the distribution vanishes at \( V = E_L \). The distribution \( P_{12} \) between \( V_1 \) and \( V_2 \) can now be calculated using (18), where \( V_2 \) is the voltage that an excitatory jump takes the neuron to \( V_1 \). Clearly, this can be continued for arbitrary ranges \( V_k \) to \( V_{k+1} \), where \( V_k \)
\[ \sigma^2 = \frac{\tau_L}{2} \left( R_e \overline{b_e^m} \Delta V^2 + R_i \overline{b_i^m} \Delta V^2 \right) \]  

(34)

It can be seen that the variance is identical in form to Eq. (15), which is also the exact shot-noise variance for a uni-amplitude distribution, except that the \( \overline{b_e^m} \) forms in the numerator and denominator have been replaced by \( \overline{b_e}^m \). Furthermore, by inserting the expansion (23) into Eq. (31) the corresponding Fokker-Planck equation can be derived, which is identical in form to the case (12) except that again the quantities \( \overline{b_e^m} \) and \( \overline{b_i^m} \) are replaced by their expectations.

The skew for this case also follows accordingly from Eq. (20). In the absence of inhibition this skew can be written

\[ S = \frac{\overline{b_e^m} \overline{b_e}^m}{\overline{b_e}^3} \left( 1 - \frac{\tau_L R_e (3 \overline{b_e^2} - \overline{b_e}^2 - \overline{b_i}^2)}{1 + \tau_L R_e (\overline{b_e} - \overline{b_e}^2 + \overline{b_i}^2)} \right) \times \frac{1 + \tau_L R_e (\overline{b_e} - \overline{b_e}^2 + \overline{b_i}^2)}{9 \tau_L R_e / 8}. \]  

(35)

A specific choice for the amplitude distribution will be considered below. However, it should be noted that the prefactor of Eq. (35) allows for the skew to be stronger than the uni-amplitude case.

1. Numerical solution for the excitation-only distribution

The recursion solution of the Gilbert and Pollak form 38 reviewed in the previous section is clearly not appropriate for the case of an amplitude distribution. An efficient numerical method 39 has been developed for master equations of the form (31) in which both excitation and inhibition are present. However, here the case of excitation only will be considered for which the following elementary numerical scheme can be used to find the steady-state density.

By replacing the integral over \( \overline{b_e} \) in Eq. (31) by an integral over the corresponding voltage, the master equation can be written

\[ 0 = \int_{V_L}^{V} \frac{dW}{E_c - W} \tau_e P_e \left( \frac{W - V}{W - E_c} \right) + (1 - \tau_i R_i) P_i (V) \]

\[ + (V - E_L) \frac{\partial P(V)}{\partial V}. \]  

(36)

The voltage range is now discretized over a lattice \( V_k = V_L + k \Delta V \) with lattice constant \( \Delta V \) [please note that this definition of \( V_k \) differs from that used previously in the context of uni-amplitude distributions near Eq. (28)]. With the probability density \( P_k \) evaluated on these lattice points, the corresponding difference equation, valid for \( k \geq 1 \), can be written as

\[ P_{k+1} = P_k + \frac{\Delta V}{V_L - E_L} \left[ (R_e \tau_L - 1) P_k - \Sigma_k \right], \]  

(37)

with the integral in Eq. (36) approximated by
FIG. 3. Comparison of shot-noise, diffusion-level, and Gaussian-approximation voltage densities for neurons receiving synapses with a distribution of amplitudes. The upper panels show example voltage trajectories for each case, where from (a) to (c), the dynamics becomes more diffusive and less shot-like. (a) Large-amplitude shot noise; $R_e=0.1$ kHz, $b_e=0.0533$ giving mean pulse amplitudes of 4 mV from the leak potential $E_L$. The Gaussian approximation gives a slightly better account of the full distribution, which is positively skewed, than the diffusion approximation does, which itself is negatively skewed. (b) Moderate-amplitude shot noise; $R_e=0.3$ kHz, $b_e=0.0267$ giving mean pulse amplitudes of 2 mV from the leak potential $E_L$. Again the full distribution shows a significant positive skew. As can be seen in the inset, the diffusion approximation, and to a lesser extent, the Gaussian approximation underestimate the probability density for $V>-55$ mV. Despite being at the tail of this distribution, this difference could potentially cause a significant error for estimations of the firing rate of neurons in the presence of a threshold for the generation of outgoing action potentials, which is typically set in the range $V=-55$ to $-50$ mV. (c) Low-amplitude shot noise; $R_e=5$ kHz, $E_L=0.00267$ giving mean pulse amplitudes of 0.2 mV from the reversal leak $E_L$. In this high-rate case corresponding to the diffusion limit, both the diffusion approximation and the full shot-noise distribution approach the Gaussian approximation. For all cases, the shot-noise distribution was calculated using the numerical scheme given in Eq. (37) with the leak potential set at $E_L=-75$ mV and with $\tau_L=20$ ms.

$$S_k = \sum_{j=1}^{k} \frac{P_j \Delta V_{V_j}^{\tau_j \rho_j(0)}}{E_c-V_j E_c-V_j} - \frac{P_j \Delta V_{V_j}^{\tau_j \rho_j(0)}}{E_c-V_j E_c-V_j},$$

(38)

and with the boundary conditions $P(E_L)=P_0=0$ and $P_1=1$; the normalization is enforced after the integration (37) is complete.

2. An exponential distribution of amplitudes

A specific choice for the synaptic amplitude distribution is now considered for which $b_e$ is exponentially distributed. Given that $b_e$ has an upper bound of 1, a cutoff has to be enforced. However, for mean values $b_e \ll 1$ this cutoff can be neglected and the approximation $\rho_e = R_e \exp(-b_e b_e) / \bar{b}_e$ is a good one. Assuming this approximation to hold, the expectations of the second and third powers of $b_e$ are

$$\overline{b_e^2} = 2 \bar{b}_e^2 \quad \text{and} \quad \overline{b_e^3} = 6 \bar{b}_e^3.$$  

(39)

Because the exponential distribution has a tail, it can be expected that the skew is correspondingly stronger than that for the uniamplitude distribution considered in a previous section. To compare these two skewes the quantities (39) are inserted into Eq. (35) and terms of order $R_e b_e^2$ or higher dropped. The resulting form of the skew, written in terms of the mean $\bar{b}_e$, is

$$S \approx \frac{3}{\sqrt{2} \overline{1+\tau_L \bar{b}_e}} \sqrt{\frac{8 b_e(1+\tau_L R_e \bar{b}_e)}{9 \tau_L R_e \bar{b}_e}}.$$  

(40)

In comparison with Eq. (22), it can be seen that this skew is stronger and has a larger range of positivity than that derived for the uniamplitude distribution: the effect of the positive skew is yet more enhanced for biologically realistic distributions.

In Fig. 3 subthreshold voltage densities are plotted for the amplitude-distributed shot-noise dynamics and the corresponding diffusion and Gaussian approximations [these are obtained by appropriately replacing $b_e$ and $b_e^2$ in Eqs. (7), (8), and (24) by their expectations]. As can be seen clearly in Figs. 3(a) and 3(b), the full shot-noise distribution is significantly positively skewed (peak to the left of the mean with a tail extending to the right). In the detail of the distribution in Fig. 3(b) it should be noted that the Gaussian approximation—the zero-order expansion of the master equation—provides a slightly better approximation to the correct dynamics than the negatively skewed diffusion approximation does. For Fig. 3(c), which shows a case in which the diffusion approximation is expected to be good ($R_e \tau_L = 80$), all distributions approach the Gaussian form.

V. CONCLUSION

The shot-noise dynamics of the subthreshold voltage of neurons subject to a barrage of synaptic input was considered. A number of results and methods existing in the literature were reviewed and new, exact results for the voltage moments derived. The role of shot noise as the cause of the positive skew of the distribution, with a peak to the left of the voltage mean and a long tail to the right, was emphasized and the weakness of the diffusion approximation identified: specifically its crossing of the inhibitory boundary and its prediction of a negative skew. An expansion of the corresponding master equation was also developed, the zero-order of which predicts a Gaussian distribution for the voltage. For the subthreshold case this gives a better indication of the
distribution than the diffusion approximation does and allows for higher-order moments to be obtained systematically via a perturbation expansion, both for unfiltered and filtered shot-noise drives. It should be noted that in this approach the voltage is expanded around its mean subthreshold value: for firing neurons care must be taken in using the Gaussian approximation as the mean voltage is shifted away from this value by the imposition of a threshold for the generation of outgoing spikes.

As the skew is clearly a high-order effect, it is legitimate to question whether this detail has a measurable influence on the input-output properties of neurons beyond that predicted by the diffusion or Gaussian approximations. In Fig. 3 the full shot-noise distribution was shown to extend for voltages \( V > -55 \text{ mV} \). Though an analysis of the firing rate of neurons receiving synaptic shot noise is beyond the scope of this Focus Article, it should be noted that this voltage range is typical for action potential generation. So, though the skew is indeed a high-order feature that affects mostly the tail of the distribution, it can potentially have a significant effect on the firing rate of a neuron. This is consistent with results from a numerical study\(^1\) in which the difference in firing rate between the diffusion approximation and the full shot-noise dynamics were quoted at 15\% for the case of excitatory jumps of 2 mV [as used here in Fig. 3(b)] and 30\% for 4 mV jumps. A systematic analysis of the role of shot noise and its related skew in the generation of action potentials, which is currently lacking in the literature, has the potential to provide further insight into the role of fluctuations in neuronal signaling.\(^3\)–\(^4\)

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