Interplay between channel and shot noise in subthreshold voltage fluctuations of neural membranes

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Abstract—Subthreshold voltage fluctuations of neural membranes are studied by means of a stochastic model based on the Monte Carlo technique. Gating channels for sodium and potassium cations and leakage channels are considered following the Hodgkin-Huxley equations. Ion channel noise is included by means of Langevin sources and ion shot noise is considered by using the Gillespie's method in terms of the probabilities for different ions to cross the cell membrane. Both noise sources are found to play a role around spiking threshold conditions.

Keywords—Stochastic methods; neural membranes; ion channel noise; ion shot noise

I. INTRODUCTION

In order to contribute to the development of bioinspired electronic devices mimicking the brain functionality and further assist the knowledge of the human brain [1-5], the study of the noise behavior in biological membranes is compulsory [6,7]. The time evolution of electrical quantities in neural membranes, essential to explain the physical properties of neurons and axons [8,9], is typically modelled by means of the phenomenological Hodgkin-Huxley (HH) model [10]. This model accounts for the equilibrium conditions and the so-called action potential, which is a spike appearing in the voltage V_m between the inside and the outside regions of cell membrane activated by sufficient external current I_{app}.

As nonlinear systems that evolve from a threshold, the analysis of their subthreshold regime, and, in particular, the role played by noise, is extremely interesting [11,12]. This is the main goal of this work. In our approach, ion channels are taken into account as a whole by means of a continuous model [13-16]. The presence of ion channel noise, i.e., the noise related to the random opening and closing of the ion gates through the membrane, is taken into account by considering the Langevin generalization for the HH equations [13]. Ion shot noise, i.e., the noise associated to the random passage of ions across the cell membrane, is included by using the Gillespie's method, from the probabilities for ions to cross the membrane [14-16]. The main purpose of this work is to analyze the interplay between channel and shot noise under excitation conditions around the threshold for the onset of spiking.

The noise of the system is studied in terms of the spectral density of the membrane voltage fluctuations $S_{Vm}(f)$. The subthreshold voltage behavior is analyzed for large membrane patches, when channel and shot noise are insufficient for the onset of spikes in the absence of external excitation. The limit of subthreshold conditions will be reached by applying increasing values of I_{app}. Even if ion shot noise has been typically considered as negligible as compared to other electrical sources of neural noise [6,13,17-20], according to our results the signature of shot noise becomes visible in the limits of subthreshold conditions by virtue of the interplay with channel noise.

II. PHYSICAL MODEL

The neuron membrane can be considered as an insulator separating the intracellular and the extracellular spaces, which are electrolytes mainly containing sodium and potassium cations, Na^+ and K^+, and chloride anions, Cl^-. Ion leakage and voltage-gated channels connect the inside and the outside regions through the membrane. According to the HH model [10], the electrical evolution of the cell membrane is described in time-domain in terms of the membrane voltage $V_m(t)$, linked to the amount of charge at each side of it, and therefore to the ion currents crossing the membrane and the so-called gating variables, $m(t)$, $h(t)$ and $n(t)$, which determine the opening or the closing of potassium and sodium channels. In our model, the equations are solved in time domain by means of the standard Euler algorithm with a time step $\Delta t = 2$ μs [13-16]. At every Δt, a new value of V_m is evaluated as

$$C_m \frac{dV_m(t)}{dt} = I_{app} - \sum_{ion} I_{ion} \qquad (1)$$

where C_m is the membrane capacitance per unit surface and I_{app} is an external current density (here considered as noiseless), which can initiate a voltage spike. I_{ion}, with the subindex $ion = Na$, K or $leak$, is the current density due to sodium cations, potassium cations or ion leakage, respectively.

In the HH model, the ion currents I_{ion}^{HH} are described in terms of channel conductances, which in the case of Na and K depend on the membrane voltage $g_{ion}(V_m)$ (gated channels). g_{Na} depends on the dimensionless gating parameters $m(t)$ and $h(t)$, which are interpreted, respectively, as the fraction of activation or inactivation molecules in the open state; g_K depends on the dimensionless gating parameter $n(t)$, interpreted as the proportion of activation molecules in the open state [10].

In our model, ion channel noise is introduced by means of Langevin sources in the equations governing the time evolution of the gating parameters $\gamma(t)$, with $\gamma(t)=m(t)$, $h(t)$ or $n(t)$. In the simulation, $\gamma(t)$ is updated every time step Δt following the HH model as [13]

$$\dot{\gamma}(t) = \alpha_\gamma(V_m)\,(1-\gamma) - \beta_\gamma(V_m)\,\gamma + \xi_\gamma(t)\,, \qquad (2)$$

where α_γ and β_γ are the voltage dependent transition rates [10], and $\xi_\gamma(t)$ is the source of channel noise. Eq. (2) is the Langevin generalization of the deterministic HH equations taking into account independent Gaussian white-noise sources of vanishing mean, with autocorrelation function [13]

$$\langle \xi_\gamma(t)\xi_\gamma(t')\rangle = \frac{2}{\rho_{ion}S}\frac{\alpha_\gamma\beta_\gamma}{(\alpha_\gamma+\beta_\gamma)}\delta(t-t')\,, \qquad (3)$$

where $\gamma=m$, h when $ion=Na$ and $\gamma=n$ when $ion=K$. ρ_{ion} represents the ion channel densities, assumed as homogeneous, and S the area of the membrane patch.

Ion shot noise is included by means of a stochastic model in which the Monte Carlo technique is employed for the determination of the time of passage of ions through the membrane following the HH equations [14-16]. The probabilities for the different ions to cross the cell membrane are considered to be independent of each other, and Gillespie method [21,22] is used to account for their stochastic transmembrane kinetics. The probability per unit time that a given ion crosses the membrane is calculated as [16]

$$P_{ion} = \frac{|I_{ion}^{HH}|S}{e}\,, \qquad (4)$$

where e is the elementary charge. Assuming the crossing of ions through the membrane as a memoryless process, the time between crossing events is calculated following Poissonian statistics. The particular type of ion crossing the membrane is randomly determined according to the respective probabilities. The values of I_{ion}, calculated from the number of ions actually crossing the membrane during Δt, are then used in Eq. (1) to evaluate the new value of V_m for the next Δt, and to calculate the total ion current density $\sum_{ion} I_{ion}$. Thus, I_{ion} and V_m contain the influence of the fluctuations associated to the random passage of ions through the cell membrane. All the details of this model and the values of the involved parameters can be found in [16]. When ion shot noise is not included in the calculations, I_{ion} are evaluated as I_{ion}^{HH}.
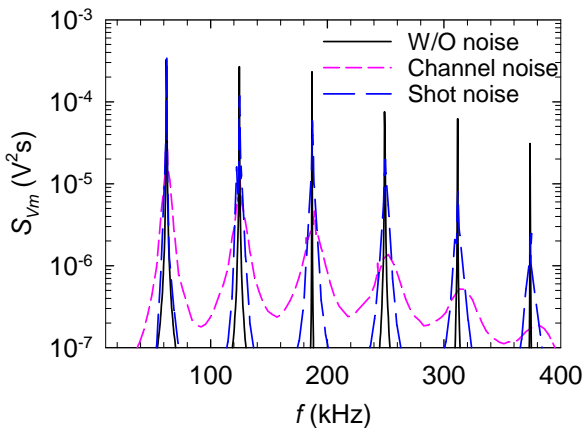

Fig. 1. $S_{Vm}(f)$ for I_{app}=0.08 Am^{-2} when no noise source is taken into account in the system and in the cases in which channel or shot noise are considered separately. S=1000 μm^2.
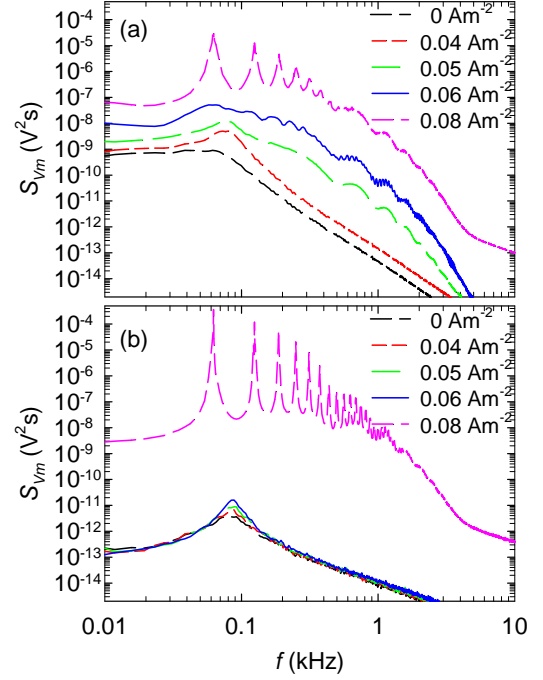

Fig. 2. $S_{Vm}(f)$ for different values of I_{app} when (a) ion channel noise and (b) ion shot noise, are taken into accoun separately in the system. S=1000 μm^2.

The noise behavior of the system is studied in terms of the spectral density of the membrane voltage fluctuations $S_{Vm}(f)$, calculated from the Fourier transform of a V_m sequence of 300 s.

In order to illustrate the influence of the different noise sources on the V_m fluctuations with respect to the deterministic case (in the absence of any noise source), $S_{Vm}(f)$ for an external excitation I_{app}=0.08 Am^{-2} is presented in Fig. 1 in the deterministic case and when channel noise or shot noise is considered (separately) in the simulation. This value of I_{app} leads to the appearance of spike trains in V_m and, as a consequence, $S_{Vm}(f)$ presents peaks at a characteristic spiking frequency around 60 Hz [13,15] and its harmonics. In the deterministic case, the δ-like peaks evidence the coherence inherent to a regular spiking. Under this excitation condition, shot noise very slightly modifies $S_{Vm}(f)$ with respect to the deterministic case and the coherence is essentially preserved. In contrast, the presence of channel noise, much more intense, noticeably deteriorates the coherence, so that peaks in $S_{Vm}(f)$ are less pronounced and cover a wider frequency range around the characteristic frequency and its harmonics.

III. RESULTS

Firstly, $S_{Vm}(f)$ is analyzed for a cell membrane of S=1000 μm^2, for which channel and shot noise are insufficient for the onset of spikes in the absence of external excitation. Fig. 2 presents $S_{Vm}(f)$ when (a) ion channel noise and (b) ion shot noise are considered separately, for I_{app} ranging from 0 to 0.08 Am^{-2}, covering the subthreshold regime and the onset of oscillations. For I_{app}=0 Am^{-2} and 0.04 Am^{-2}, channel noise [Fig. 2(a)] is not strong enough for the onset of voltage spikes, as shown in Fig. 3, in which the mean value of V_m and the number
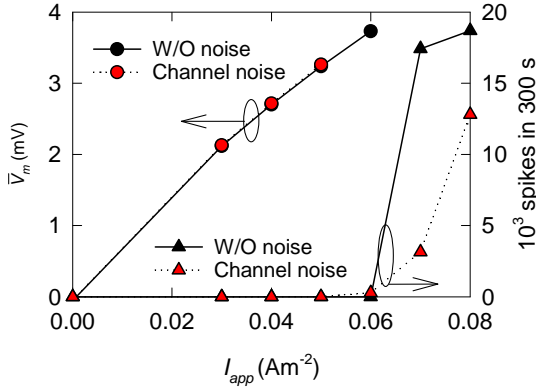
Fig. 3. Mean value of V_m in the absence of spikes and number of spikes found in 300 s as a function of I_{app} in the deterministic case and when channel noise is considered. S=1000 μm^2.

of spikes occurring in a simulation time of 300 s in the presence and the absence of channel noise is plotted as a function of I_{app}. For 0.04 Am^{-2}, $S_{Vm}(f)$ shows a peak around 80-90 Hz, evidencing a rhythm in the $V_m(t)$ fluctuations, related to the internal dynamics of the system [23]. This frequency behavior of the V_m fluctuations originated by channel noise has been also reported in [11,12]. When I_{app}=0.05-0.06 Am^{-2}, still insufficient for the onset of spike trains but close to their appearance, $S_{Vm}(f)$ exhibits a remarkable increase [23], typical at the onset of instabilities, as observed in other physical systems like electronic devices [24]. For increasing values of I_{app} the mean value of the membrane voltage increases [12], taking similar values to those found in the deterministic case [Fig. 3]. The onset of voltage spikes takes place for lower values of I_{app} when channel noise is considered, since the noise assists their appearance below threshold (~0.065 Am^{-2} in the deterministic case). In contrast, above threshold conditions the noise suppresses a significant amount of spikes with respect to the deterministic case. For $I_{app} > 0.07$ Am^{-2}, when a full train of voltage spikes is achieved, $S_{Vm}(f)$ presents peaks around the characteristic spiking frequency and its harmonics.

In the case of considering only ion shot noise [Fig. 2(b)], $S_{Vm}(f)$ exhibits a maximum at around 80-90 Hz for the lower values of I_{app}, which reveals the existence of the mentioned
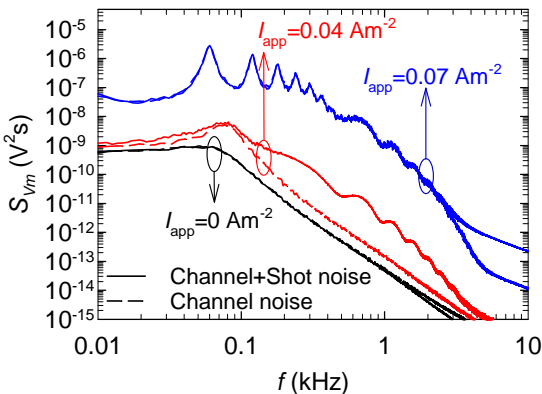

Fig. 4. $S_{Vm}(f)$ for different values of I_{app} when channel noise is the only noise source considered in the system and in the case in which also shot noise is taken into account. S=1000 μm^2.
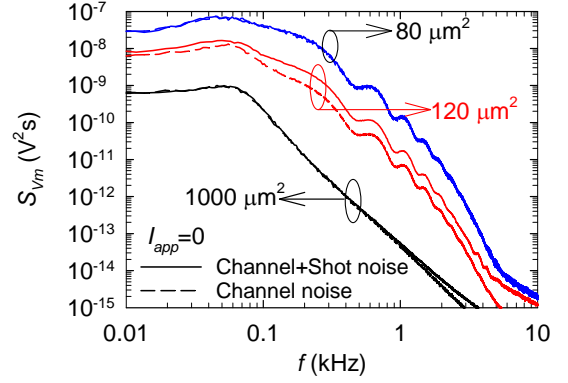

Fig. 5. $S_{Vm}(f)$ for different values of S in the absence of excitation when channel noise is the only noise source considered in the system and in the case in which also shot noise is taken into account.

intrinsic rhythmic oscillations in V_m even for large values of S, for which shot noise is extremely weak [15]. Indeed, the values of $S_{Vm}(f)$ are around four orders of magnitude lower than when channel noise is considered. For I_{app}=0.08 Am^{-2}, once the spike train is triggered, $S_{Vm}(f)$ is very similar to that found in the deterministic case [Fig. 1].

To illustrate the interplay between channel and shot noise in subthreshold voltage fluctuations of neural membranes, Fig. 4 shows the frequency behavior of $S_{Vm}(f)$ when a cell membrane of S=1000 μm^2 is excited with different values of I_{app}, both when channel noise is the only noise source considered in the system and in the case in which also shot noise is taken into account. In the absence of excitation, both cases coincide, thus evidencing a negligible influence of shot noise. For I_{app}=0.07 A/m^2, high enough for generation of spikes, the peaks in $S_{Vm}(f)$ denote their presence and both cases again essentially overlap. However, when I_{app}=0.04 A/m^2, still insufficient for the onset of spikes but close to their appearance, the spectral density exhibits a significant increase when ion shot noise is included in the simulation with respect to case in which channel noise is the only source considered. Remarkably, in these subthreshold conditions, shot noise plays a role in the noise behavior by the interplay with channel noise.

A similar conclusion can be achieved when, instead of applying an external current in large membrane patches, the emergence of the noise influence is achieved, in the absence of excitation, by reducing the membrane area S. Fig. 5 presents the frequency behavior of $S_{Vm}(f)$ when a cell membrane is reduced from 1000 μm^2 to 80 μm^2, when channel noise is the only noise source considered in the system and in the case in which also shot noise is taken into account. In the limit of the onset of spiking due to channel noise, for around 120 μm^2, shot noise also displays a visible influence.

IV. CONCLUSIONS

Subthreshold voltage fluctuations of neural membranes modeled by means of the HH model haven been studied in terms of $S_{Vm}(f)$ when considering ion channel noise and ion shot noise sources in the system. In the model, ion channel noise is included by means of Langevin sources and ion shot noise is considered in terms of the probabilities for different ions to cross the cell

membrane. The threshold for spiking activity has been reached by applying increasing values of I_{app} in a large membrane patch. Around such threshold conditions, the signature of shot noise is significantly visible when combined with channel noise, while its influence is otherwise negligible as typically predicted. A similar conclusion can be achieved if the limit in the subthreshold regime is obtained by reducing the membrane patch in the absence of external excitation.

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