



An investigation of the coefficient of variation using voltage clamps techniques

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Abstract

In recent years, it has been argued and experimentally shown that ion channel noise in neurons can have profound effects on the neuron's dynamical behavior. Most profoundly, ion channel noise was seen to be able to cause spontaneous firing and stochastic resonance. It has been recently found that a non-trivially persistent cross correlation takes place between the transmembrane voltage fluctuations and the component of open channel fluctuations attributed to gate multiplicity. This non-trivial phenomenon was found to play a major augmentative role for the elevation of excitability and spontaneous firing in the small size cell. In addition, the same phenomenon was found to significantly enhance the spike coherence. In this paper, statistics of the coefficient of variation, to be obtained from the colored stochastic Hodgkin-Huxley equations using voltage clamps techniques will be studied. The simulation result shows the coefficient of variation; enhance the agreement with the microscope in the case of the noisy currents.

Keywords: Colored Noise; Channel Gate; Ion Channel; Spike Resonance; Stochastic Hodgkin-Huxley Equations.

1. Introduction

Neurons show that electrical activity is under the effect of the noise of external and internal types [4]. Internal and external noise types produce synaptic transmission and network influences, this neuron appointee generates stochastic etiquette at the level of neuronal dynamics. This is the main source of internal noise because there is a limitable number of a voltage-gated ion channel in the neural membrane patch. Channels are two open or close; the number of open channels fluctuates in apparently random style [18], which indicates fluctuation in conducting membrane which in turn refers to fluctuation in transmembrane voltage. The membrane zone is very large when the number of ion channels is big, dynamic voltage is presented by the famed Hodgkin-Huxley [11], equations. When the membrane patches are small, anyway, the effect of conductance fluctuation on cell voltage activity is truly deep and not trivial. In neural membrane patches, spontaneous activity phenomenon occurs (in the case of repeating spikes or bursts) and the reason about that is the internal noise from ion channels; these present during numerical simulations of channel dynamics and theoretical investigations besides [3], [14], [2], [12], [10], [16], [6-9], [1], those experiments have shown the happening of stochastic resonance and the coherence of the procreated spike trains [13], [19], [15]. Even when the numbers of ion channels are large, channel fluctuations might become critical near to the action potential threshold [21], [17], small number of ion channels that are open at the action potential threshold assigned the accuracy of timing of action potential.). The renormalization of the fluctuations in a number of open gates not only affects the neuron behavior, but also the attendance of a multiple number of gates in every ion channel. Moreover, this effect may indicate to an important act in cell activity in the state of having coherence membrane in size [9], [1].

2. Background

2.1. The hodgkin-huxley model

By using space and voltage clamps techniques depending on experimental investigation on giant squid axon, it was shown by Hodgkin-Huxley [11], that two prime ionic components were from the current fluxing through the squid axon membrane, which are I_{Na} and I_K (sodium and potassium channels on a par with components) these currents are powerfully affected via membrane potential V_m . As a result of their observation, a mathematical model has been developed to make a significant model based on which many realistic neural models have been developed. The differential equation corresponding to the electrical circuit is as follows:

$$C_m \frac{dV_m}{dt} + I_{ion} = \tag{1}$$

Where C_m is membrane capacitance, V_m is membrane capacitance, I_{ext} is an external current and I_{ion} is the ionic current fluxing through the membrane and can be obtained from these equations:

$$I_{ion} = \sum_i I_i \tag{2}$$

$$I_i = g_i(V_m - E_i) \tag{3}$$

Where I_i here represents every ionic component having a joined conductance g_i and obvers ion potential E_i . The three I_i terms in the squid giant axon model are: sodium current I_{Na} , potassium current I_K and a small leakage current I_L and the equation that represents those three currents is:

$$I_{ion} = I_{Na} + I_K + I_L = g_{Na}(V_m - E_{Na}) + g_K(V_m - E_K) + g_L(V_m - E_L) \tag{4}$$

The combined influence of many numbers of microscopic ion channels in the membrane originates the microscopic $g_i(g_L, g_K, g_{Na})$ Conductance. Ion channel may contain a small number of physical gates that organize ion influx within the channel. Ions can go across channel when all of the gates are in the permissive state while the channel is open. Into a permissive state, all of the gates for a specific channel ion can go within a channel while the channel is open. The potassium and sodium conductance's empirically described by the formal assumption, which is attained by voltage clamp experiments are:

$$g_k = \bar{g}_k n^4, \tag{5}$$

$$g_{na} = \bar{g}_{na} m^3 h, \tag{6}$$

Where

$\left. \begin{matrix} n \\ m \\ h \end{matrix} \right\}$ Is ion channel gate variables dynamics

\bar{g}_i Is a constant with the dimensions of conductance per cm^2 (mention that n between 0 and 1). In order to normalize the result, a maximum value of conductance (\bar{g}_i) is required.

n, m And h dynamically are as follows:

$$\dot{n} = \frac{dn}{dt} = \alpha_n(1 - n) - \beta_n n \tag{7}$$

$$\dot{m} = \frac{dm}{dt} = \alpha_m(1 - m) - \beta_m m \tag{8}$$

$$\dot{h} = \frac{dh}{dt} = \alpha_h(1 - h) - \beta_h h \tag{9}$$

n Is a dimensionless variable (varies between 0 and 1), add-on, represents the probability of a single gate being in the permissive state.

2.2. Dynamics of the membrane

This differential equation determines the evaluation of the transmembrane voltage V in time

$$C \frac{dV}{dt} = -g_K(V_m - E_K) - g_{Na}(V_m - E_{Na}) - g_L(V_m - E_L) + I \quad (10)$$

Where ψ_K and ψ_{Na} are dynamic channel variables. ψ_K corresponds to the proportion of open potassium channels to the total number of potassium channels in the membrane; similarly, ψ_{Na} denotes the proportion of open sodium channels. There exist four n-gates in a potassium channel, and three m-gates and one h-gate in a sodium channel. A channel is open when all its gates are open; otherwise, it is closed. In the limit of infinite membrane size, the channel variables attain their deterministic HH values, that is, $\psi_K = n^4$ and $\psi_{Na} = m^3h$, where n, m, and h are the gating variables. The colored stochastic Hodgkin Huxley equations (Güler, 2013) are given by:

$$C\dot{V} = -g_K\psi_K(V - E_K) - g_{Na}\psi_{Na}(V - E_{Na}) - g_L(V - E_L) + I \quad (11)$$

$$\psi_K = n^4 + \sqrt{\frac{n^4(1-n^4)}{N_K}} q_K \quad (12)$$

$$\psi_{Na} = m^3h + \sqrt{\frac{m^3(1-n^4)}{N_{Na}}} h q_{Na} \quad (13)$$

The equations that describe the dynamics of q_K are specified accordingly as follows:

$$\tau \dot{q}_K = p_K \quad (14)$$

$$\tau \dot{p}_K = -\gamma_K p_K - w_K^2 [\alpha_n(1-n) + \beta_n n] g_K + \xi_K \quad (15)$$

The equations that describe the dynamics of q_{Na} are specified accordingly as follows:

$$\tau \dot{q}_{Na} = p_{Na} \quad (16)$$

$$\tau \dot{p}_{Na} = -\gamma_{Na} p_{Na} - w_{Na}^2 [\alpha_m(1-m) + \beta_m m] g_{Na} + \xi_{Na} \quad (17)$$

The gate noise model:

$$\dot{n} = \frac{dn}{dt} = \alpha_n(1-n) - \beta_n n + \eta_n \quad (18)$$

$$\dot{m} = \frac{dm}{dt} = \alpha_m(1-m) - \beta_m m + \eta_m \quad (19)$$

$$\dot{h} = \frac{dh}{dt} = \alpha_h(1-h) - \beta_h h + \eta_h \quad (20)$$

The Gaussian white noise terms with zero means:

$$\langle \xi_K(t) \xi_K(t') \rangle = \gamma_K T_K [\alpha_n(1-n) + \beta_n n] \delta(t-t') \quad (21)$$

$$\langle \xi_{Na}(t) \xi_{Na}(t') \rangle = \gamma_{Na} T_{Na} [\alpha_m(1-m) + \beta_m m] \delta(t-t') \quad (22)$$

$$\langle \eta_n(t) \eta_n(t') \rangle = \frac{\alpha_n(1-n) + \beta_n n}{4N_K} \delta(t-t') \quad (23)$$

$$\langle \eta_m(t) \eta_m(t') \rangle = \frac{\alpha_m(1-m) + \beta_m m}{3N_{Na}} \delta(t-t') \quad (24)$$

$$\langle \eta_h(t) \eta_h(t') \rangle = \frac{\alpha_h(1-h) + \beta_h h}{N_{Na}} \delta(t-t') \quad (25)$$

2.3. Spike coherence

A sensitively regular measure of spike train is called the coefficient of variation (CV), or the comparative difference in the interspike interval distribution. This regularity measure is given by,

$$CV := \frac{\sqrt{\langle T^2 \rangle - \langle T \rangle^2}}{\langle T \rangle} \quad (26)$$

$\langle T \rangle$: The mean interspike interval is $\langle T \rangle = \lim_{N \rightarrow \infty} \frac{1}{N} \sum_i T_i$

$\langle T^2 \rangle$: The mean squared interval $\langle T^2 \rangle := \lim_{N \rightarrow \infty} \frac{1}{N} \sum (t_{i+1} - t_i)^2 / N$.

CV = 1 if the sequence of spikes, which corresponds to the Poisoning spike train, is discrete.

CV < 1 if the spike train is more ordered.

CV = 0 for a purely deterministic response.

The increasing system size A is against to the coefficient of variation. While the firing rate reduces monotonically with regard to the patch area, it has been proved that the coefficient of variation (CV) shows a discriminate minimum for an optimal patch size for which the spike train is mostly regular at the same value. The phenomenon is called an intrinsic coherence resonance [19]. At optimal dosage of internal noise, whose optimal size of the cell membrane patch approximately $A = 1 \mu\text{m}^2$, the CV shows a minimum, where the spiking becomes prevalently more ordered. The external disturbances withstand by internal rhythm which is possessed through the spiking activity [20].

3. Result and discussion

The series of experiments that actually defined efficiency of the colored noise by comparing colored noise models with the microscopic simulations. The simulation model eqns. (21, 22) numerically was developed by using C++ programming language and MATLAB. The input current was time independent which was modified based on the program to handle time dependent current.

Table 1: Show The Experiments' data are Displayed by a Different Membrane Patch, with Different Noise Variance and I_{Base} .

Membrane	Value
1 Potassium channels	300,900,1800,2700,3210
2 Sodium channels	1000,3000,6000,9000,10700
3 I_{base}	0,2,4,6,8
4 Input Current	1, 2, 3, 4, 5, 6, 7, 8, 9, 10

The ratio between potassium and sodium channels is: K^+ channel: Na^+ channel = 1: 3.33.

The coefficient of variation to be extracted from the colored noise model will be explained through a sequence of experiments by comparing the colored noise model with the microscopic simulations. So, our concern will be the complete stochastic actual dynamics. The microscopic simulation scheme represents the simple stochastic method [22]. The Markovian process is applied by this method to simulate each individual gate and go on for the rest of the gates. The noise variance in my simulation was changed to obtain the coefficient of variation for this investigation. The aim of this is to see the effect of the cross-correlation persistency placed in the trans-membrane voltage fluctuation by adding the colored noise terms [9], [1], into the conductance of the stochastic Hodgkin Huxley equations. Series of experiments were used to assess the colored noise model effectiveness, in a comparative manner with the Microscopic simulation as mentioned before [22], by firstly running the experiments without include the colored noise model into the stochastic of the Hodgkin Huxley equations, and secondly running again the experiments with the same parameters but at this time, the colored noise model is included in the stochastic of the HH equations. By changing the variable (noise variance) for investigation purpose and measure the coefficient of variation, comparison with the microscopic simulation. A compute of the spike coherence is the coefficient of variation given by the formula (26).

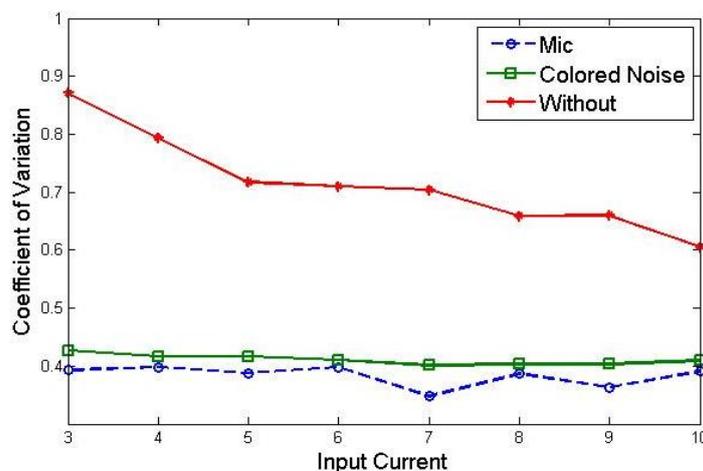


Fig. 1: The Membrane Size for Potassium I_s 300, for Sodium I_s 1000 and $I_{\text{Base}} = 0$, in 5 Seconds Time Window.

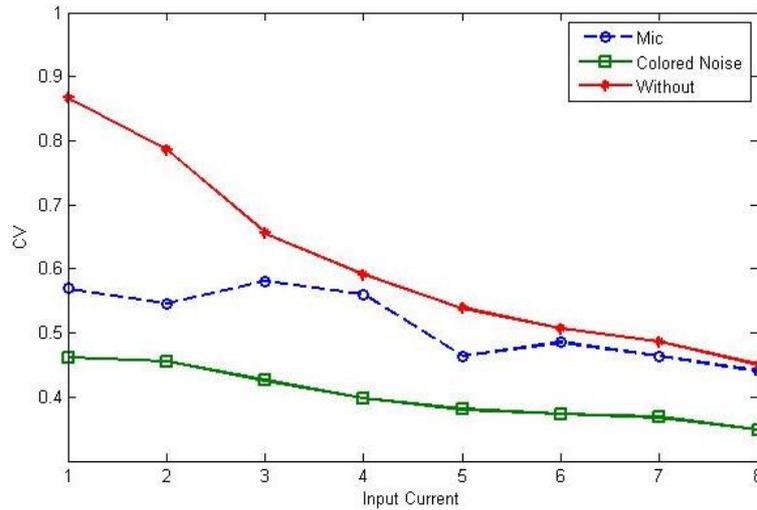


Fig. 2: The Coefficient of Variation Against the Noise Variance, the Membrane Size for Potassium Is 900, for Sodium Is 3000 and I Base = 2, in 5 Seconds Time Window.

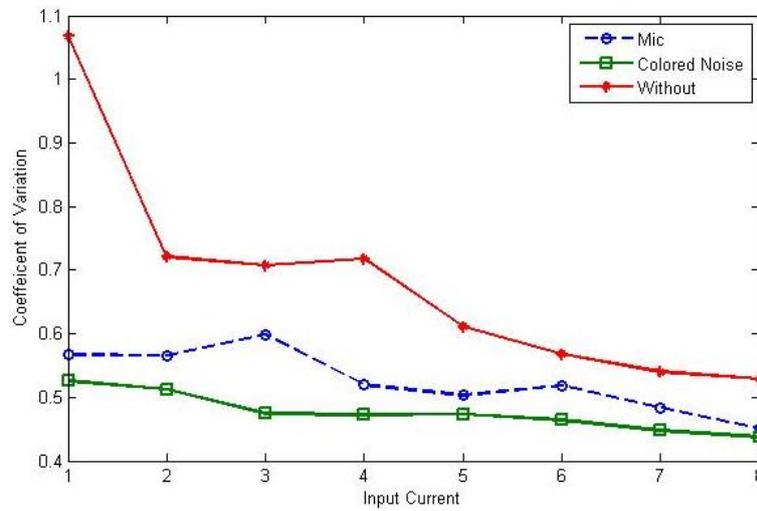


Fig. 3: The Membrane Patch Comprised of 1,800 Potassium Channels and 6,000 Sodium Channels. The Completely Stochastic Actual Dynamics were used. The Averages were Computed over a 5 Second Time Window.

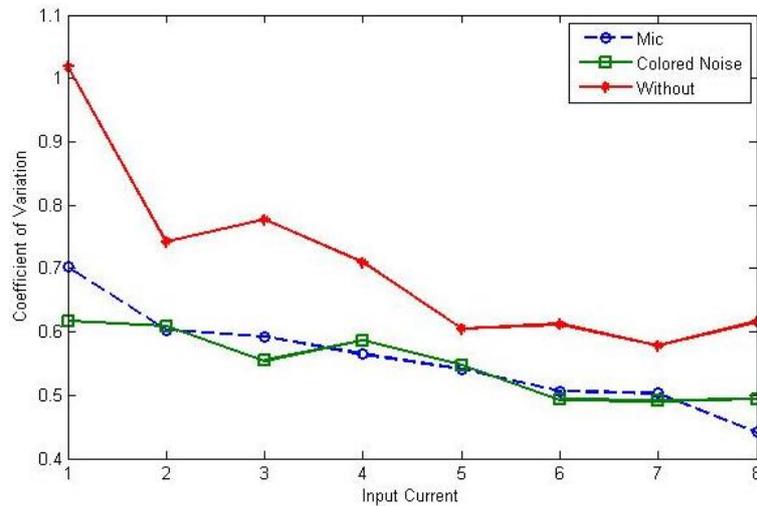


Fig. 4: The Membrane Size for Potassium Is 2700, for Sodium Is 9000 and I_{Base}= 6, In 5 Seconds Time Window.

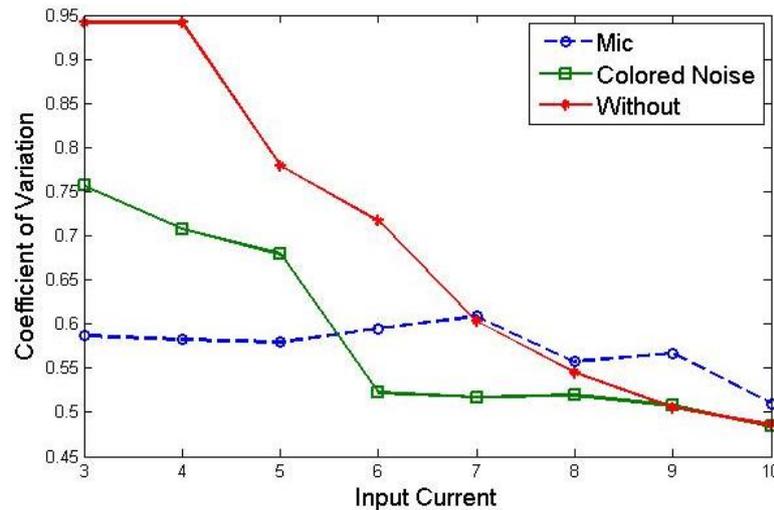


Fig. 5: Shown by a Membrane Patch of 3210 Potassium Channels and 10700 Sodium Channels. I Base =4, in 5 Seconds Time Window.

In above results it is clear that at the very beginning there is difference in spikes' frequencies, but when there is an addition in noise variance mostly around (4, 6 and 8), the coefficient of variation of the microscopic simulation with the stochastic HH equation and the colored term is getting smaller.

4. Conclusion

In this paper, statistics of the coefficient of variation were obtained from the colored stochastic Hodgkin-Huxley equations; in recent work [9], [1], the experiments improve that ion channel noise in neurons can have profound impacts on the neuron's dynamical behavior. In particular, the ion channel noise ability was found to make that a non-trivial persistent (NCCP) is placed between the trans-membrane voltage fluctuations and component of open channel fluctuations attributed to the gate multiplicity. The non-trivially phenomenon plays a prime augmentative role in the elevation of excitability and spontaneous firing in the small size cell. Furthermore, the phenomenon is very effective in enhancing the spike coherence.

Through the experiment results, the colored noise model processes the phenomenon of the NCCP accurately, and NCCP was discovered to improve the spike coherence. The experiments show that the coherence of spike on the stochastic HH equation without colored noise is far clearer for coherence of the microscopic simulation scheme, a large value of the coefficient of variation significantly shown by the HH equation without colored noise spikes. But when the colored noise model is embedded to the Hodgkin-Huxley equation, it is seen that the spike coherence in this model is about the same level as coherence of microscopic simulation, that indicates more coherent as the smallest value of coefficient of variation. Moreover, these experiments denoted that the increasing membrane size in both stochastic HH equations without colored and colored noise model may lead to the absence of the difference between them. Most of the recent studies on this model were under varying input currents, the input current is periodic with constant noise. Perhaps, investigating the coefficient of variation using different kinds of noise over the input current to shed more light on the colored stochastic model behavior in non-periodic.

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