International Journal of Basic and Applied Sciences, 4 (4) (2015) 364-370
www.sciencepubco.com/index.php/IJBAS
©Science Publishing Corporation
doi: 10.14419/ijbas.v4i4.5049
Research Paper

An investigation of the coefficient of variation using voltage clamps techniques

Ahmed Mahmood Khudhur [1]*, Ahmed N Abdalla [1], Jasni Mohamad Zain [2], Hai Tao [2]

[1] *Faculty of Eng. Tech., Malaysia Engineering Technology, Kuantan 26300, Malaysia*
[2] *Faculty of Comp. Scie. And software Eng, University Malaysia Pahang, Kuantan 26300, Malaysia*
**Corresponding author E-mail: ahmed.mahmood7970@yahoo.com*

Copyright © 2015 Ahmed Mahmood Khudhur et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

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 techniqueswill be studied. The simulation result shows the coefficient of variation; enhance the agreement with the microscopeinthe 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 an 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 Ina and Ik (sodium and potassium channels on a par with components) these currents are powerfully affected via membrane potential Vm. 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:

$$C_m \frac{dV_m}{dt} + I_{ion} = \quad (1)$$

Where Cm is membrane capacitance, Vm 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:

$$I_{ion} = \sum_i I_i \quad (2)$$

$$I_i = g_i(V_m - E_i) \quad (3)$$

Where Ii here represents every ionic component having a joined conductance gi and obvers ion potential Ei.
The three Ii terms in the squid giant axon model are: sodium current INa, potassium current IK and a small leakage current IL and the equation that represents those three currents is:

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

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.
Intoa 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:

$$g_k = \bar{g}_k n^4 , \quad (5)$$

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

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 cm2 (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 Andh dynamically are as follows:

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

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

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

nIs 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 ψK and ψNa are dynamic channel variables.ψK corresponds to the proportion of open potassium channels to the total number of potassium channels in the membrane; similarly, ψNa 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, ψK = n4 and ψNa = m3h, where n, m, and h are the gating variables.
The colored stochastic Hodgkin Huxley equations (Güler, 2013) are given by:

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

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

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

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:

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

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

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

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 $\langle T\rangle = \lim_{N\to\infty}\frac{1}{N}\sum_i T_i$
$\langle T^2\rangle$: The mean squared interval$\langle T^2\rangle \coloneqq \lim_{N\to\infty}\sum(t_{i+1}-t_i)^2/N$.
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 $A = 1\mu m^2$, 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++ programing 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'dataare Displayed by a Different Membrane Patch, with Different Noise Varianceand 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).

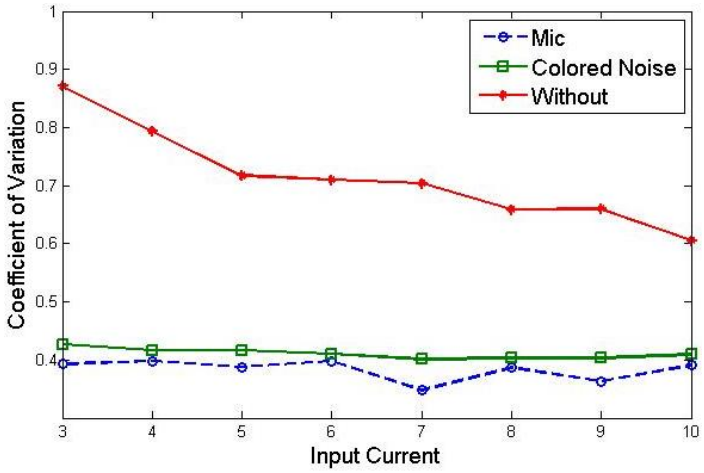


Fig. 1: The Membrane Size for Potassium Is 300, for Sodium Is 1000 and I Base = 0, in 5 Seconds Time Window.

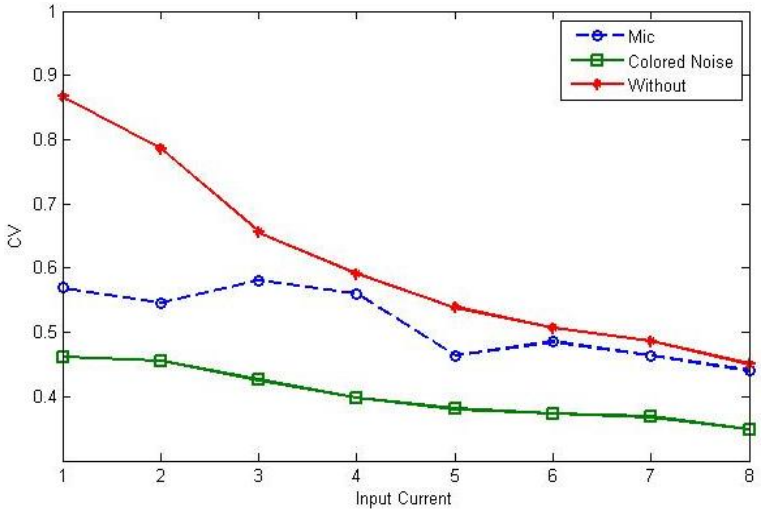


Fig. 2: The Coefficient of Variation Against the Noise Variance, the Membrane Size for Potassium Is 900, for Sodium Is 3000 and I Base = 2, in 5 Seconds Time Window.

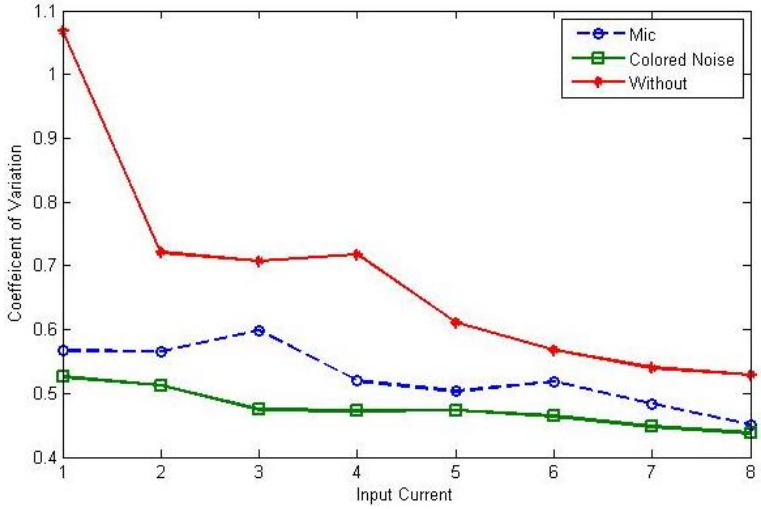


Fig. 3: The Membrane Patch Comprised of 1,800 Potassium Channels and 6,000 Sodium Channels. The Completely Stochastic Actual Dynamics were used. The Averages were Computed over a 5 Second Time Window.

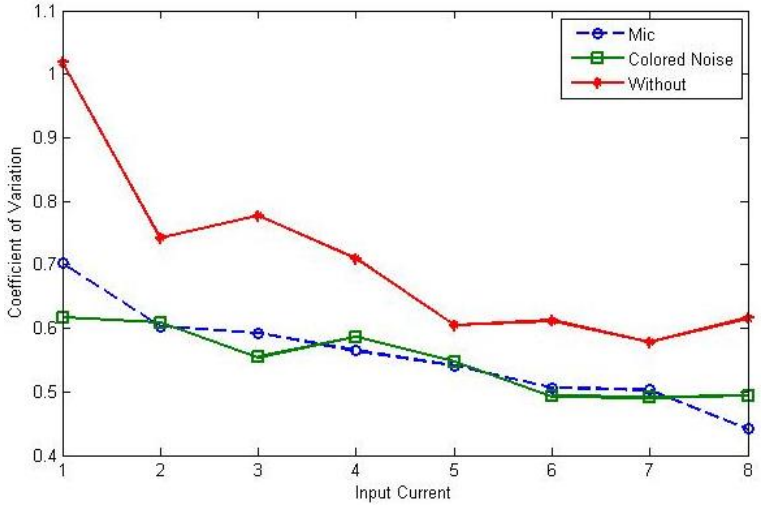


Fig. 4: The Membrane Size for Potassium Is 2700, for Sodium Is 9000 and I_{Base}= 6, In 5 Seconds Time Window.

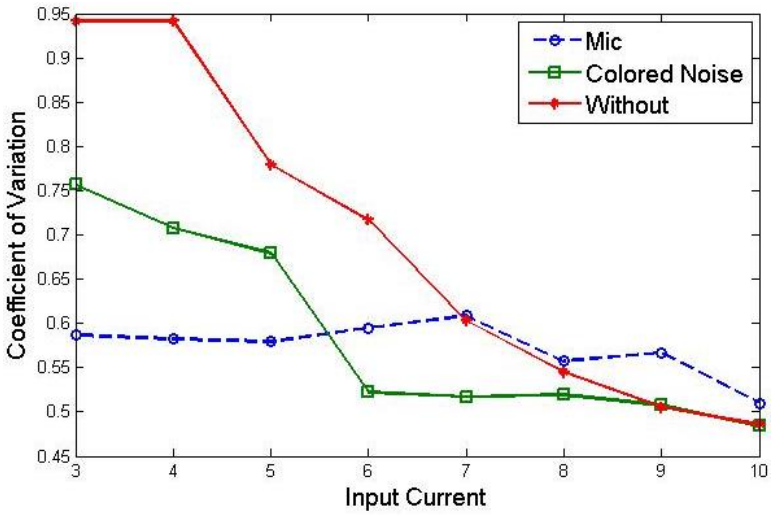


Fig. 5: Showed by a Membrane Patch of 3210 Potassium Channels and 10700 Sodium Channels. I Base =4, in 5 Seconds Time Window.

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.

References

[1] Ahmed Mahmood Khudhur, Ahmed N Abdalla.*A New Neuron Ion Channel Model with Noisy Input Current*. International Journal of Engineering Technology and Sciences (IJETS), (2015)3(1): 29-35.

[2] Chow, C. C. (1996). *Spontaneous action potentials due to channel fluctuations*. Biophysical Journal, 71, 3013–3021. http://dx.doi.org/10.1016/S0006-3495(96)79494-8.

[3] DeFelice, L. J. (1992). *Chaotic states in a random world: Relationship between the nonlinear differential equations of excitability and the stochastic properties of ion channels.* Journal of Statistical Physics, 70, 339–354. http://dx.doi.org/10.1007/BF01053972.

[4] Faisal, A. S. (2008). *Noise in the nervous system*. Nervous system. Nature Reviews Neuroscience, 9, 292–303. http://dx.doi.org/10.1038/nrn2258.

[5] G. Schmid, P. H. (2007). Intrinsic coherence resonance in excitable membrane patches. *In Mathematical Biosciences* (pp. 236-244). Augsburg: Institut fu¨ r Physik, Universita¨ t Augsburg, Theoretische Physik I.

[6] Güler, M. (2007). *Dissipative stochastic mechanics for capturing neuronal dynamics under the influence of ion channel noise: Formalism using a special membrane*. Physical Review E, 76, 041918(17). http://dx.doi.org/10.1103/PhysRevE.76.041918.

[7] Güler, M. (2008). *Detailed numerical investigation of the dissipative stochastic mechanics based neuron model*. Journal of Computational Neuroscience, 25, 211–227. http://dx.doi.org/10.1007/s10827-008-0074-x.

[8] Güler, M. (2011). *Persistent membranous cross correlations due to the multiplicity of gates in ion channels*. Journal of Computational Neuroscience ISSN 0929-5313. http://dx.doi.org/10.1007/s10827-011-0337-9.

[9] Güler, M. (2011). Persistent membranous cross correlations due to the multiplicity of gates in ion channels. *Journal of Computational Neuroscience*, 31,713-724. http://dx.doi.org/10.1007/s10827-011-0337-9.

[10] Güler, M. (2013). Stochastic Hodgkin-huxley equations with colored noise terms in the conductances. *Neural Computation*, 25, 46-74. http://dx.doi.org/10.1162/NECO_a_00384.
[11] Güler, M. (2013). Stochastic Hodgkin-huxley equations with colored noise terms in the conductances. *Neural Computation (to appear in january 2013 issue). http://dx.doi.org/10.1162/neco_a_00384.*
[12] H. Lecar, R. N. (1971). I. Relationship between electrical noise and fluctuations in axon firing. In *Theory of threshold fluctuations in nerves* (p. 1048). Biophys. J.
[13] Hodgkin, A. L. (1952). *A quantitative description of membrane current and its application to conduction and excitationin in nerve. Journal of Physiology*. (London.Print), 117, 500–544.
[14] Johansson, S. &. (1994). *Single-channel currents trigger action potentials in small cultured hippocampal neurons*. Proceedings of National Academy of Sciences USA, 91, 1761–1765. http://dx.doi.org/10.1073/pnas.91.5.1761.
[15] Jung, P. &. (2001). *Optimal sizes of ion channel clusters*. Europhysics Letters, 56, 29–35. http://dx.doi.org/10.1209/epl/i2001-00483-y.
[16] Lu, F. R. (1994). Emergent collective behavior in large numbers of globally coupled independently stochastic ion channels.
[17] Özer, M. (2006). *Frequency-dependent information coding in neurons with stochastic ion channels for subthreshold periodic forcing*. Physics Letters A, 354, 258–263. http://dx.doi.org/10.1016/j.physleta.2006.01.066.
[18] Rowat, P. F. (2004). *State-dependent effects of Na channel noise on neuronal burst generation*. Journal of Computational Neuroscience, 16, 87–112. http://dx.doi.org/10.1023/B:JCNS.0000014104.08299.8b.
[19] Rubinstein, J. (1995). *Threshold fluctuations in an N sodium channel model of the node of Ranvier*. Biophysical Journal, 68, 779–785. http://dx.doi.org/10.1016/S0006-3495(95)80252-3.
[20] Sakmann, B. &. (1995). *Single-channel recording (2nded.).* New York: Plenum.
[21] Schmid, G. G. (2001). *Stochastic resonance as a collective property of ion channel assemblies*. Europhysics Letters, 56, 22–28. http://dx.doi.org/10.1209/epl/i2001-00482-6.
[22] Schneidman, E. F. (1998). *Ion channel stochasticity may be critical in determining the reliability and precision of spike timing*. Neural Computation, 10, 1679–1703. http://dx.doi.org/10.1162/089976698300017089.
[23] Zeng, S. &. (2004). Mechanism for neuronal spike generation by small and large ion channel clusters. *Physical Review E*, 70, 011903(8). http://dx.doi.org/10.1103/physreve.70.011903.