A New Neuron Ion Channel Model Under Time Varying Input Currents

Ahmed Mahmood Khudhur 1,*, Ahmed M Shano2, Abdul Salam Hassan Abbas3

1,3 Department of Computer Eng. Tech., Bilad Alrafdain University Collage, Baaquba, Diyala, Iraq
2 Department of Radiolgical Tech., Bilad Alrafdain University Collage, Baaquba, Diyala, Iraq

*Corresponding author E-mail: ahmed.mahmood7970@gmail.com
Phone NO: +9647719539367

Abstract: In recent years, it has been argued and shown experimentally that ion channel noise in neurons can cause fundamental effects on the neuron’s dynamical behavior. Most profoundly, ion channel noise was seen to be able to cause spontaneous firing and stochastic resonance. However, Hodgkin-Huxley model affected when inserting some colored noise terms inside the conductance’s, where those effects captured by colored noise due to the gate multiplicity. This paper presents a new ion channel model under time varying periodic input currents. It firstly introduced the effect of without, with (colored noise), on the proposed model and the comparison of ion channel based on HH, Fox- Lu, and Linaro models. Additionally, in order to overcome the limitations of other parameter estimation methods, the proposed method fully constraints their models and obtains all models capabilities of reproducing the data. Finally, the relationship between the sequence of colored noise and the spike frequency are simulated efficiently each gate compared with microscopic simulations of the stochastic Markov process method. The simulation results revealed that above a critical value of the input frequency and also below a certain amplitude value, the colored terms play a very prominent role on the firing statistics. In addition, the spiking rate generated from the proposed model very close to microscopic simulations and doesn’t effect by the membrane size.

Keywords: Ion Channel; Noise Variance; Colored Noise; Hodgkin-Huxley; Microscopic; Spike Frequency.

I. INTRODUCTION

Effectiveness of noise to the neurons produces an unusual pattern on the neuronal dynamics. The noise is in two types; internal or external [6]. External noise is exactly the opposite of internal. External noise is produced from the synaptic transmission also from network effects. The prime source of internal noise in a neuronal membrane spot is from the limited number of voltage-gated ion channels. Usually these channels have two stats; closed or open. When it is open the channel's fluctuations number is apparently going randomly [21]. If the fluctuations included in the membrane conduct, then the fluctuation will be included in the voltage of transmembrane as well. In the case of having a large number of ion channels means that the membrane size is huge, then the voltage dynamics will represent as it is in the original Hodgkin and Huxley [9], equation. However, when the patch of membrane is small, the conductance fluctuations affect the voltage activity of the cell. These effects are probably important and cannot be ignored. The single open channel stochasticity effect in a
direct manner the spike behavior which is suggested by experiment investigation [23], [16], [11], and spontaneous fire will be the result of that noise in the ion [13], [25]. In addition, the bursting or spiking in the ion channels in the numerical simulations and theoretical investigations of channel dynamics caused by the internal noise [3], [24], [7], [2], and [19]. Channel noises in the patch-clamp experiments are producing large voltage fluctuations to affect the propagation of action potentials, and timing, initiation [4], [5], [10], and [14]. The membrane channel dynamics which have represented by Markov models was [12], [20]. Many researchers work in this field to provide enough statistics of spike generation in the stochastic HH, [1], [15], [17], [22], [26], [28] and [29]. According to these studies that Fox and Lu stochastic extension to the Hodgkin and Huxley equations may not be suitable for accurately simulating channel noise, even with large numbers of ion channels in simulations. The method that proposed using more stochastic terms and avoids the expense, complex matrix operations is [18], [27], [30], [31]. The gating variables that contain Gaussian white noise in the stochastic HH equation was proposed [8]. However, a complete, comprehensive analysis of spike generation in the stochastic HH this model is needed, that additionally includes the generation of the database on the estimation. In this paper, the proposed model directly determines a set of maximal functions of voltage parameters to fit the model neuron from the Hodgkin-Huxley equations. The behaviors of the theoretical relationship between neural behavior and the parameters that specify a neuronal model are described in detail. The simulation model doesn't only depend on the fluctuations in the number of open gates, but additionally on the existence of several numbers of gates in the single ion channels.

II. THEORETICAL BACKGROUND

2.1 The Hodgkin-Huxley equations

Hodgkin and Huxley deduced that the ionic membrane conductance’s are variable with time and voltage-dependent, and gave the form of this voltage-dependence. By treating a segment of the axon as a simple electric circuit, Hodgkin and Huxley arrived at equations describing the electric activity of the axon. The cell membrane, which separates the extracellular medium from the cytoplasm of the cell, acts as a capacitor with capacitance \( C \) (Hodgkin and Huxley used a value, based on laboratory measurement, of \( 10^{-9} \text{F/m}^2 \) for \( C \)). The ion current channels offer parallel pathways by which charge can pass through the cell membrane. Hodgkin and Huxley use three ionic currents in their description of the squid giant axon; potassium current \( I_K \), sodium current \( I_Na \), and a leakage current \( I_L \). The potassium and sodium currents have variable resistances that represent the voltage gated conductance’s associated with the membrane ion channels. The total current \( I \) is the sum of the ionic currents and the capacitive current which represents the rate of accumulation of charge on opposite sides of the cell membrane. The capacitive current, from electrical circuit theory, is \( \frac{dV}{dt} \), where \( V \) is the membrane potential. Hodgkin and Huxley take \( V = 0 \) to represent the neuron's resting potential, and the equations below follow this convention.

\[
\frac{dV_{\text{m}}}{dt} + I_{\text{ion}} = I_{\text{ext}} \tag{1}
\]

\[
I_{\text{ion}} = \sum I_{t} \tag{2}
\]

\[
I_{t} = g_{t}(V_{\text{m}} - E_{t}) \tag{3}
\]

\[
I = \bar{g}_{K} m^{p} h^{4}(V - V_{rev}) \tag{4}
\]

The number of independent activation gates was represented by the integer power \( p \) in the equation (4), which was introduced by Hodgkin and Huxley. In addition, they measured a time delay in the rise of the potassium and sodium currents when stepping from hyperpolarized to depolarize potentials, but when the axon is depolarized but falls alongside no appreciable inflection after it is depolarized. If \( g_{k} \) is utilized as a variable the end of the record can be fitted alongside a first-order equation, but a third- or fourth-order equation is needed to describe the beginning. A functional simplification is achieved by presuming that \( g_{k} \) is proportional to the fourth manipulation of a variable that obeys a first-order equation. In this case the rise of potassium conductance from zero to a finite value is delineated by \( 1 - \exp(-t)^{4} \), while the fall is given by \( \exp(-4t) \). The rise in conductance consequently displays a marked inflection, while the fall is a simple. A comparable assumption employing a cube instead of a fourth power describes the early rises of sodium conductance. The ionic currents are given by Ohm's law \( (I = gV) \):
Where $E_{\text{ion}}$ is the reversal potential, and $g_{\text{ion}}$ is the ionic membrane conductance.

2.1.1 The ionic conductance

In 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 empirically described by the formal assumption, which is attained by voltage clamp experiments are:

\begin{align}
g_k &= g_{k0} n^4 \\
g_{na} &= g_{na} m^3 h
\end{align}

Where $n$, $m$ and $h$ are ion channel gate variables dynamics

$g_{k0}$ 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($g_{k0}$) is required. The $n$, $m$, and $h$ dynamic are listed below

\begin{align}
\frac{dn}{dt} &= \alpha_n (1 - n) - \beta_n n \\
\frac{dm}{dt} &= \alpha_m (1 - m) - \beta_m m \\
\frac{dh}{dt} &= \alpha_h (1 - h) - \beta_h h
\end{align}

$\alpha_n$ and $\beta_n$ are rate constant that the changes happened by voltage changes, but not affected with time, while the value of dimensions variable $n$ can take place between 0 and 1, also it stand for of a single gate probability that is in permissive state.

The membrane potential in voltage clamp experiment begins in the resting period ($V_m = 0$) and immediately reach to new clamp voltage $V_m = V_C$. the solution to the above equation (9) is by exponential of the form.

\begin{align}
x(t) &= x_{os}(V_C) - \left(x_{os}(V_C) - x_{os}(0)\right) \exp(-t/\tau_x) \\
x_{os}(0) &= \alpha_x(0)/\alpha_x(0) + \beta_x(0) \\
x_{os}(V_C) &= \alpha_x(V_C)/\alpha_x(V_C) + \beta_x(V_C) \\
\tau_x(V_C) &= \left[\alpha_x(V_C) + \beta_x(V_C)\right]^{-1}
\end{align}

Where $x$ represents time depending on gate variable $n$, $m$ and $h$ in order to make the formula easier the voltage value of gating variable has been assumed at resting state means the $x_{os}(0) = 0$ and $x_{os}(V_C)$ is the clamp voltage $V_C$. $\tau_x$ Represent the constant time required for reaching the steady state value of $x_{os}(V_C)$ when the voltage assumed equal to $V_C$. Hodgkin and Huxley measured constantly $\alpha_i$ $\beta_i$ as functions of $V^*$ in the following

\begin{align}
\alpha_i &= \frac{x_{os}(V)}{\tau_{n}(V)} \\
\beta_i &= \frac{1-x_{os}(V)}{\tau_{n}(V)}
\end{align}

As discussed earlier before in the formula, $i$ representing for $n$, $m$, and $h$ ion channel gate. The coming equations are the formula.

\begin{align}
\alpha_n(V) &= \frac{0.01(10-V)}{\exp\left[\frac{10-V}{18}\right] - 1} \\
\beta_n(V) &= 0.125 \exp\left(-\frac{V}{80}\right) \\
\alpha_m(V) &= \frac{0.1(25-V)}{\exp\left[\frac{25-V}{18}\right] - 1} \\
\beta_m(V) &= 4 \exp\left(-\frac{V}{18}\right)
\end{align}
The functions $\alpha_V$ and $\beta_V$ have dimensions of [1/time] and govern the rate at which the ion channels transition from the closed state of the open state ($\alpha$) and vice versa ($\beta$).

### 2.2 Fox and Lu model

In (Fox & Lu) model, the $\phi_k$, $\phi_{Na}$ noise terms, do not take place and they are similar to zero.

$$\phi_k^L = \phi_{Na}^L = 0$$

Where the Gaussian white noise with the mean squares is $\eta_n$, $\eta_m$, $\eta_h$, and the high $F$ is used to clarify the case of the model.

$$\langle \eta_n(t)\eta_n(t') \rangle = \frac{a_n(1-n)\beta_n}{N_K} \delta(t - t')$$
$$\langle \eta_m(t)\eta_m(t') \rangle = \frac{a_m(1-m)\beta_m}{N_K} \delta(t - t')$$
$$\langle \eta_h(t)\eta_h(t') \rangle = \frac{a_h(1-h)\beta_h}{N_Na} \delta(t - t')$$

### 2.3 Linaro model

In this model (Linaro), the proportions of open channels with the diffusions obtained from the covariance’s of n$^4$ and m$^3$h is determined by the competent powers of the inevitability gating variables. The potassium conductance, $\psi_k^L$, in the noise term reads as,

$$\tau_{K,i}^L = \sigma_{K,i}^{L}Z_{K,i}$$

Where the stochastic variables are $Z_{K,i}$,

$$\tau_{K,i}^{L} = \tau_{K,i}^{L} + \sigma_{K,i}^{L}\sqrt{2}T_{K,i}\xi_{K,i}$$

$\tau_{K,i}$ and $\sigma_{K,i}$ are the opening, closing rates of n-gates. $\xi_{K,i}$ are Gaussian white noise (GWN) with zero means. Similarly, the sodium conductance, $\psi_{Na}^L$, in the noise term reads as,

$$\psi_{Na}^{L} = \sum_{i=1}^{7}Z_{Na,i}$$

Where the stochastic variables are $Z_{Na,i}$,

$$\tau_{Na,i}^{L} = \tau_{Na,i}^{L} + \sigma_{Na,i}^{L}\sqrt{2}T_{Na,i}\xi_{Na,i}$$

$\tau_{Na,i}$, $\sigma_{Na,i}$ are the opening, closing rates of both m-gates and h-gates. $\xi_{Na,i}$ are Gaussian white noise (GWN) with zero means, and unit variances. In the differential equations for the gating variables, the noise terms are similar zero:

$$\eta_n^{L} = \eta_m^{L} = \eta_h^{L} = 0$$

### III. THE PROPOSED MODEL

The proposed model in equations (35, 36, 37, 38), is a new modification of the Hodgkin-Huxley equations by adding calcium channel ($Ca^{+2}$), and GWN with the mean zero ($\xi(t)$) to the equations [27]. In addition, it calculates the potassium and sodium channels when there are more than one n-gate and m-gate, in the dynamic variable by considering the membrane potential to have a large number of channels, and that’s enough to satisfy both $\psi_k$ and $\psi_{Na}$. The differential equations for the activation and inactivation variables in the proposed model can be solved at any instant in time, and the values of all the activation, inactivation variables are known at any instant by inspection of the voltage trace. This proposed model allows for estimation all parameters and functions of voltage precisely. More specifically, the numbers of the gating variables, the conductance, and the steady states and time constant estimated as functions of voltage. The regular states are using mathematical modifications on data collected using four voltage clamp protocols [27], [32]. The equations that describe the proposed model shown as follows:

$$\dot{V} = -g_k \sum_{i} n^4 (V - E_k) - g_{Na} \sum_{i} m^3 h (V - E_{Na}) - g_{Ca} \psi_{Ca} (V - E_{Ca}) - g_L (V - E_L) + I + \xi(t)$$

$\psi_k = n^4$ is an open potassium channels ratio.

$\psi_{Na} = m^3 h$ is an open sodium channels, ratio.

If we have more than one channel the dynamic variable ($\psi_k$), will be as follows:

$$\psi_k = \sum_{i} n^4$$

$\psi_{Na} = \sum_{i} m^3 h_i = \text{number of channels}$.

$\psi_{Ca}$, is an open calcium channels, ratio depends on the concentration of $Ca^{+2}$.
If the concentration of the calcium is high the channel will open otherwise close. Here $[\psi_C]$, $[\psi_N]$, is the ratio of open (potassium and sodium channels), computed across all achievable order of the membrane getting $4XKn \cdot 3XKn \cdot mXNa \cdot h$, open n-gates, as shown below:

$$[\psi_C] = \begin{cases} \frac{[I_{on_{Ca}}]_{out}}{[I_{on_{Ca}}]_{in}}, & \text{if } I_{on_{Ca}} \geq 1 \text{mV} \\ 0, & \text{otherwise} \end{cases}$$

If the membrane size is small then $\psi_K = n^4$, and $\psi_Na = mh^3$, the proposed model’s value $\psi_K = [\psi_C] = n^4$ , and $\psi_Na = [\psi_Na] = mh^3$, applies at any times.

Where, $[\psi_K]$, $[\psi_Na]$, reads as:

$$\psi_K = n^4 + \alpha q \psi_Na$$

$$\psi_Na = mh^3 + \alpha q \psi_Na$$

The equations that describe the dynamics of $q_K$ are:

$$\tau q_K = p_K$$

$$\tau P_K = - \gamma p_P K - w_{0}^{2} \alpha n(1-n) + \beta n g_K + \xi_K$$

The equations that describe the dynamics of $q_{Na}$ are:

$$\tau q_{Na} = p_{Na}$$

$$\tau P_{Na} = - \gamma p_P Na - w_{0}^{2} \alpha m(1-m) + \beta m g_{Na} + \xi_{Na}$$

In which $(D_n, D_m)$, is identical to:

$$\alpha n(1-n) + \beta n g_{Na}$$

The standard deviation of $\psi_K$, $\psi_Na$, will be as follows:

$$\sigma = \sqrt{\frac{n(n+1)}{X_Na} q_K}$$

$$\sigma_{Na} = \sqrt{\frac{m(m+1)}{X_Na} h q_{Na}}$$

The complete model for the dynamic variable $(\psi_K, \psi_Na)$, is:

$$\psi_K = n^4 + \sqrt{\frac{n(n+1)}{X_Na} q_K}$$

$$\psi_Na = mh^3 + \sqrt{\frac{m(m+1)}{X_Na} h q_{Na}}$$

The gate noise model is:

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

$$\dot{m} = \frac{dn}{dt} = \alpha_m (1-m) - \beta_m m + \xi_{na}$$

$$\dot{h} = \frac{dn}{dt} = \alpha_h (1-h) - \beta_h h + \xi_h$$

IV. RESULT AND DISCUSSION

This section consists of the series of experiments that actually defined efficiency of the noise by comparing the proposed model with the microscopic simulations. In addition, a simple stochastic method has been used as the microscopic simulation scheme [26]. The simulation model in equations (44, 45) numerically was developed by using C++ programing language and MATLAB, Graph Pad Prism. The input current was time independent, which was modified based on the program to handle time dependent current and the noise variance in this simulation were a periodic sin wave under time varying, as shown below:

$$I = A \sin(\omega t)$$

$$\omega = 2 \pi f$$

A series of experiments has been used to examine the effectiveness of the amplitude and frequency in the proposed model in a relative manner with the Microscopic simulation, as mentioned above.
Hence, it can be seen that the performance of the proposed model was quite similar to the microscopic simulations. Thus, whatever figures have been driven out as a result, there is a difference between the spike frequency of the HH, Fox-Lu and Linaro equations and the proposed model, which is actually containing the spikes from microscopic simulation.

In addition, the difference between spike frequencies becomes smaller when the amplitude increases. In addition, the changing in frequency is made instead of the amplitude of the periodic input current. It can be seen from the result at the beginning that there are no difference in the spikes’ frequencies but at a certain point of frequency, mostly around (1) Hz the response of the HH stochastic without the colored noise almost remains zero even when the frequency increased.

If the colored noise is included in the equations, it is noticeable that the spike frequency is very consistent with the microscopic simulation.

The Gaussian white noise terms (GWN) with zero means which used in the numerical experiments shown below:

\[
\begin{align*}
\langle \xi_R(t) \xi_R(t') \rangle & = \gamma_R T_R \left[ \alpha_n (1 - n) + \beta_n n \right] \delta(t - t') \\
\langle \xi_{Na}(t) \xi_{Na}(t') \rangle & = \gamma_{Na} T_{Na} \left[ \alpha_m (1 - m) + \beta_m m \right] \delta(t - t') \\
\langle \xi_K(t) \xi_K(t') \rangle & = \gamma_K T_K \left[ \alpha_n (1 - n) + \beta_n n \right] \delta(t - t') \\
\langle \xi_{Na}(t) \xi_{Na}(t') \rangle & = \frac{2}{3} \gamma_{Na} T_{Na} \left[ \alpha_m (1 - m) + \beta_m m \right] \delta(t - t') \\
\langle \xi_h(t) \xi_h(t') \rangle & = \gamma_h T_h \left[ \alpha_h (1 - h) + \beta_h h \right] \delta(t - t')
\end{align*}
\]

The phenomenological methods through numerical experiments estimate the values of the parameters. Both these values can calculate an approximation by phenomenological means, as given in table 1.

| Table 1. Constant parameters of the models |
|-------------------------------------------|
| \( \gamma_K = 10 \) | \( \gamma_K = 150 \) | \( T_K = 400 \) |
| \( \gamma_{Na} = 10 \) | \( w_{Na} = 200 \) | \( T_{Na} = 200 \) |

The parameter’s value of the membrane in Eq. (35) shows in the table 2. Where \( X_k, X_{Na}, X_{Ca} \) corresponds for potassium and sodium and calcium complete numbers of channels, and multiplied the \( X_k \) by 4n for potassium to get \( 4X_{kn} \) and also for sodium, calcium resulting \( 3X_{nm}, X_{nh} \) to get open channels with the total number. In addition, the Markov process has been put into the gate’s dynamics. The probability of the time \( t \) and time \( t + \Delta t \) is exponential \(( -\alpha_n \Delta t ) \), which means the n-gate is closed or becomes open, and the probability of time \( t \), and time \( t + \Delta t \) is exponential \(( -\beta_n \Delta t ) \) which means the n-gate is open, and the all of the parameters \( \alpha_n, \beta_n \) are the rate of voltage get at the opening and closing of n-gates. Furthermore, the same process is applied for the m-gate and h-gate.

| Table 2. Parameter values of the membrane |
|-------------------------------------------|
| Ionic current | Reflection potential (mV) | The conductance (mS/cm²) |
| Sodium(Na⁺) | \( E_{Na} = -115 \) | \( x_1 = 120 \) |
| Potassium(K⁺) | \( E_k = 12 \) | \( x_2 = 36 \) |
| Leakage(L) | \( E_l = -10.61 \) | \( x_3 = 0.3 \) |
| Calcium(Ca²⁺) | \( E_{Ca} = 136 \) | \( x_4 = 40 \) |

Fig. 1, the membrane size for potassium is 600, for sodium is 2000 and \( I_{base} = 0 \), threshold=0. 005. The averages are computed in 30 seconds time window. The comparison between the three curves used different input current, it can be seen that the proposed model with colored noise was quite close to the microscopic simulations and the spike frequency increase and will be more accurate when the input current increasing. The numbers of the sodium channel calculated as follows:

No of sodium channel =No. of potassium channel/3*10.
Fig. 1. Mean spiking rates against the input current amplitude.

Fig. 2. Shows the relationship between amplitude and the spike frequency.

Fig. 3. Present the mean spiking rates against the amplitude.
Fig. 4, shows how the speed of spike frequency as the input current increases for both the proposed model and HH model. The membrane size for potassium is 1710, for sodium is 5700, and $l_{base} = 0$, threshold = 0.005. The simulation time window is 30 seconds. In addition, different input current used to show the comparison between the three curves, and the proposed model was quite close to the microscopic simulations when increasing the amplitude. Fox & Lu (1994).

Fig. 4. Provides the relationship between spike frequency and the amplitude. In Fig. 5, the membrane size for potassium is 1710, for sodium is 5700, for calcium is 1520, and $l_{base} = 0$. The averages are computed in 30 seconds time window, different input current used to show the comparison between the three curves. The proposed model was quite close to the microscopic simulations. In addition, after the amplitude increases, the difference between spike frequencies becomes smaller, in the table 3 different parameter’s value of the membrane used.

Fig. 5. Mean spiking rates against the amplitude.

Table 3. Different parameter values of the membrane

| Ionic current | Reflection potential (mV) | The conductance (mS/cm$^2$) |
|---------------|---------------------------|----------------------------|
| Sodium(Na$^+$) | $E_{Na} = 110$            | $x1 = 130$                 |
| Potassium(K$^+$) | $E_K = -15$            | $x2 = 40$                 |
| Leakage(L)    | $E_L = 10.5$             | $x3 = 0.2$                |
| Calcium(Ca$^{2+}$) | $E_{Ca} = 126$     | $x4 = 36$                 |

Fig. 6, shows the membrane size for potassium is 3525, and for sodium is 11750, $l_{base} = 0$, threshold = 0.005. The averages are computed in 30 seconds time window and different frequencies used in the simulations to show the comparison between the three curves. The proposed model was affected by frequency more than the HH model.
In Fig. 6, the mean spiking rates against the frequencies. In Fig. 7, the membrane size for potassium is 1800, for calcium is 6000, for sodium is 11750, and $I_{\text{base}} = 0$, threshold = 0.005. The simulation time window is 30 seconds. In addition, different frequencies used to show the comparison between the three curves.

Fig. 6. The mean spiking rates against the frequencies.

Fig. 7. Shows the relationship between frequencies and the spike frequency. Fig. 8, shows how the speed of spike rate as the frequencies increases for both the proposed model and HH model. The membrane patch composed of 900 of potassium channels and 3000 of sodium channels, and $I_{\text{base}} = 0$, threshold = 0.005. The averages are computed in 30 seconds time window, and different frequencies with large membrane size used to show the comparison between the three curves.

Fig. 7. Shows the relationship between frequencies and the spike frequency.

Fig. 8. Provides the relationship between frequencies and the spike frequency for each group.
V. CONCLUSION
The Hodgkin-Huxley type models accept a set of parameters as input and generate voltage data describing the behavior of the neuron. Proposed model solving the Hodgkin-Huxley equations for a set of input parameters refers to integrating the equations in order to obtain the resulting simulated Gaussian noise and the voltage (potassium, sodium, calcium) channels. In addition, the channel noise neuron model was studied well under the influence of varying input signal, and it has been discovered that to be the main cause in the unusual increases in the cell excitability, and in spontaneous firing membrane size should be small enough. Moreover, it was discovered that the proposed model keeps on advancing the spontaneous firing even if membrane size is larger, wherever the gate of noise is insufficient for activating the cell. According to the experimental results, the spiking rate generated from the model is extremely close to the one from the actual simulation, doesn’t effect by the membrane size. In difference, the rate generated through an increase in amplitude and frequencies, the HH, Fox-Lu, and Linaro equation was almost similar as compared to the spikes from the model, and it will be more accurate. Experimental results also highlight the mean spiking rates against amplitude and frequencies, which was introduced by a different membrane size, amplitude and frequencies, in which three curves represent the competition between the microscopic simulation with the proposed model HH, Fox-Lu, and Linaro equations, which showed that the proposed model has worked quite similar to the microscopic simulations. Overall, the motivation for this work is to clarify a proposed model, deliberative, and rigorous methodology for parameter estimation for the HH, Fox-Lu, and Linaro models that overcomes all the limitations of current parameter estimation methodologies.

An important outcome of this methodology is that the proposed model allows researchers to study hypotheses that could not have been studied using any other parameter estimation method.

VI. REFERENCES
[1]. Bruce, I. C. 2009. Evaluation of stochastic differential equation approximation of ion channel gating models. Annals of Biomedical Engineering, 37, 824–838.
[2]. Chow, C. C., & White, J. A. 1996. Spontaneous action potentials due to channel fluctuations. Biophysical Journal, 71, 3013–3021.
[3]. DeFelice, L. J., & Isaac, A. 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.
[4]. Diba, K., Lester, H. A., & Koch, C. 2004. Intrinsic noise in cultured hippocampal neurons: Experiment and modeling. Journal of Neuroscience, 24, 9723–9733.
[5]. Dorval, A. D., & White, J. A. 2005. Channel noise is essential for perithreshold oscillations in entorhinal stellate neurons. Journal of Neuroscience, 25, 10025–10028.
[6]. Faisal, A. A., Selen, L. P. J., & Wolpert, D. M. 2008. Noise in the nervous system. Nature Reviews Neuroscience, 9, 292–303.
[7]. Fox, R. F., & Lu, Y. N. 1994. Emergent collective behavior in large numbers of globally coupled independently stochastic ion channels. Physical Review E, 49, 3421–3431.
[8]. Güler, M. 2013. Stochastic Hodgkin-Huxley equations with colored noise terms in the conductances. Neural Computation, 25, 46–74.
[9]. Hodgkin, A. L., & Huxley, A. F. 1952. A quantitative description of membrane current and its application to conduction and excitation in nerve. Journal of Physiology, 500–544.
[10]. Jacobson, G. A., Kamran, D., Yaron-Jakovitch, A., Oz, Y., Koch, C., & Segev, J. 2005. Subthreshold voltage noise of rat neocortical pyramidal neurones. Journal of Physiology, 564, 145–160.

Acknowledgments
I am grateful to Prof. Dr. Ahmed N. Abdalla for his valuable and constructive suggestions during the planning and development of this research work, and to two reviewers for constructive suggestions.
[11]. Johansson, S., & Arhem, P. 1994. Single-channel currents trigger action potentials in small cultured hippocampal neurons. *Proceedings of National Academy of Sciences USA*, 91, 1761–1765.
[12]. Kienker, P. 1989. Equivalence of aggregated Markov models of ion-channel gating. *Proc. R. Soc. Lond. B* 236, 269–309.
[13]. Koch, C. 1999. *Biophysics of computation: Information processing in single neurons*. New York: Oxford University Press.
[14]. Kole, M. H., Hallermann, S., & Stuart, G. J. 2006. Single Ih channels in pyramidal neuron dendrites: Properties, distribution, and impact on action potential output. *Journal of Neuroscience*, 26, 1677–1687.
[15]. Linaro, D., Storace, M., & Giugliano, M. 2011. Accurate and fast simulation of channel noise in conductance-based model neurons by diffusion approximation. *PLoS Computational Biology*, 7, e1001102.
[16]. Lynch, J., & Barry, P. 1989. Action potentials initiated by single channels opening in a small neuron (rat olfactory receptor). *Biophysical Journal*, 55, 755–768.
[17]. Mino, H., Rubinstein, J. T., & White, J. A. 2002. Comparison of algorithms for the simulation of action potentials with stochastic sodium channels. *Annals of Biomedical Engineering*, 30, 578–587.
[18]. Orio, P., & Soudry, D. 2012. Simple, fast and accurate implementation of the diffusion approximation algorithm for stochastic ion channels with multiple states. *PLoS one*, 7, e36670.
[19]. Rowat, P. F., & Elson, R. C. 2004. State-dependent effects of Na channel noise on neuronal burst generation. *Journal of Computational Neuroscience*, 16, 87–112.
[20]. Rudy, Y., and Silva, J. 2006. Computational biology in the study of cardiac ion channels and cell electrophysiology. *Q. Rev. Biophysics* 39, 57-116.
[21]. Sakmann, B., & Neher, N. 1995. *Single-channel recording* (2nd ed.). New York: Plenum.
[22]. Sengupta, B., Laughlin, S. B., & Niven, J. E. 2010. Comparison of Langevin and Markov channel noise models for neuronal signal generation. *Physical Review E*, 81, 011918.
[23]. Sigworth, F. J. 1980. The variance of sodium current fluctuations at the node of Ranvier. *Journal of Physiology (London)*, 307, 97–129.
[24]. Strassberg, A. F., & DeFelice, L. J. 1993. Limitations of the Hodgkin-Huxley formalism: effects of single channel kinetics on transmembrane voltage dynamics. *Neural Computation*, 5, 843–855.
[25]. White, J. A., Klink, R., Alonso, A., & Kay, A. R. 1998. Noise from voltage-gated ion channels may influence neuronal dynamics in the entorhinal cortex. *Journal of Neurophysiology*, 80, 262–269.
[26]. Zeng, S., & Jung, P. 2004. Mechanism for neuronal spike generation by small and large ion channel clusters. *Physical Review E*, 70, 011903.
