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A New Neuron Ion Channel Model with Noisy Input Current

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Abstract: ***The data processing fundamental problem affects all aspects of nervous-system function by the noise of ion channels. The conducting and non conducting of ion channels depends on random transitions of channel noise, which affect the states of several numbers of gates in every single individual ion channel. This paper, introduce a new ion channel model in the neuron with noisy input current as approximations of the HH model. It briefly introduces the ion channel based on stochastic Hodgkin-Huxley model. The method is able to fully constrain the HH model and obtain all models capable of reproducing the data. Therefore, this method overcomes the limitations of other parameter estimation methods. The stochastic Markov process method is simply applied to simulate each gate individually to determine the relationship between channel noise and the spike frequency. The proposed model shows the sequence of colored noise experiments described efficiently compared with microscopic simulations. 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, Noisy, Hodgkin-Huxley, Microscopic.***

I. INTRODUCTION

The nerve cell theoretical foundation in the building block of the nervous system was introduced by Hodgkin and Huxley (1952). It processes information and sends, receives the ultimate control signal as control functions such as our breathing, complex memory, and different body activity (Andersen et al. 2007). Although all neurons share the same basic structure still the neuron in nervous system has many different forms depending on its occupied area and its function. The ideas of the patch-clamp technique permitted to determine experimental approaches of the possibility of measuring ion currents through individual ion channels which development by Neher and Sakmann (1976). The channel fluctuations can become critical close the action potential threshold, even if the numbers of ion channels are large (Schneidman et al. 1998; Rubinstein 1995); in the action potential threshold that has small numbers of ion channels and that are open, the timing accuracy was determined. 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 (DeFelice and Isaac 1992;

Strassberg, and DeFelice 1993; Fox and Lu 1994; Chow and White 1996; Rowat and Elson 2004). Channel noises in the patch-clamp experiments are producing large voltage fluctuations to affect the propagation of action potentials, and timing, initiation (Diba et al. 2004; Dorval and White 2005; Jacobson et al. 2005; Kole et al. 2006). The membrane channel dynamics which have represented by Markov models was utilized (Kienker, P. 1989; Rudy, Y., and Silva, J. 2006).

Many researchers work in this field to produce accurate enough statistics of spike generation in the stochastic HH (Mino, Rubinstein, & White, 2002; Zeng & Jung, 2004; Bruce, 2009; Sengupta, Laughlin, & Niven, 2010). These studies suggest that Fox and Lu's stochastic extension to the HH equations may not be suitable for accurately simulating channel noise, even in simulations with large numbers of ion channels. The method that proposed using more stochastic terms and avoids the expense, complex matrix operations (Orio & Soudry, 2012). The gating variables that contain Gaussian white noise in the stochastic HH equation was proposed (Güler, 2013). 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 individual ion channels.

II. THEORETICAL BACKGROUND

A. The Gaussian white noise (GWN)

The stochastic Hodgkin-Huxley models responded by a Gaussian white-noise process with zero mean and unit variance. (Rowat, P. 2007; Sengupta, B. 2010). The additive white-noise term can be interpreted as a clear method for representing the combined effect of numerous synaptic inputs that neurons in cortex and other networks receive in vivo; (Abbot, D. P. (2002), distribution, is additionally recognized as the Gaussian distribution, and the values that the noise can take on being Gaussian-distributed. A special case is white Gaussian noise, in which the values in each pair of times are statistically independent. In applications, Gaussian noise is most usually utilized as additional white noise to yield additive white Gaussian noise.

B. Ionic Mechanisms of Action Potentials

An action potential is bounded by a region bordered on one extreme by the K^+ equilibrium potential (-75 mV) and on the other excessive by the Na^+ equilibrium potential (+55 mV). The resting potential is -60 mV. Note that the resting potential is not equal to the K^+ equilibrium potential because, as discussed previously, there is a small resting Na^+ permeability that makes the cell slightly more positive than E_K. In principle, any point along the

trajectory of action potential can be obtained simply by varying alpha in the Hodgkin-Huxley equation. If alpha is very large, the Na+, terms dominate, and according to the Hodgkin-Huxley equation, the membrane potential will move towards the Na^+ equilibrium potential. The peak of the action potentials' approaches but does not quite reach E_{Na}, because the membrane retains its permeability to K^+ (Wilfred D. S., Thomas L., 2015).

C. *The Hodgkin-Huxley equations*

Hodgkin and Huxley deduced that the ionic membrane conductances are variable with time and voltage-dependent, and gave the form of this voltage-dependence (Sahil Talwar, Joseph W. Lynch, 2015). 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 $\_F/cm^2$ 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 currentI_K, sodium currentI_{Na}, and a leakage currentI_L. The potassium and sodium currents have variable resistances that represent the voltage gated conductances 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 $C\frac{dV}{dt}$,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.

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

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

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

$$I = \bar{g}\, m^p h^q (V - V_{rev}) \quad (4)$$

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 stepping in the opposite direction, there is no such delay. At the outset when the axon is depolarized with a delay, there is the difficulty to increase the conductance of both potassium and sodium, but when the axon is depolarized but falls with no appreciable inflection when it is depolarized. If g_k, is used as a variable the end of the record can be fitted with a first-order equation, but a third- or fourth-order equation is needed to describe the beginning. A useful simplification is achieved by supposing that g_k , is proportional to the fourth power of a variable which obeys a first-order equation. In this case the rise of potassium conductance from zero to a finite value is described by $1 - \exp\ (-t))^4$, while the fall is given by exp (*-4t*). The rise in conductance therefore shows a marked inflection, while the fall is a simple exponential. A similar assumption using a cube instead of a fourth power describes the initial rise of sodium conductance (Sudha C., 2015).

The ionic currents are given by Ohm's law ($I = gV$):

$$I_{ion} = I_{Na} + I_K + I_L \quad (5)$$

$$I_{Na} = g_{Na}(V_m - E_{na}) \quad (6)$$

$$I_K = g_K\ (V_m - E_K) \quad (7)$$

$$I_L = g_L\ (V_m - E_L) \quad (8)$$

Where E_{ion} is the reversal potential, and g_{ion} is the ionic membrane conductance.

These conductance's, in the case of the sodium and potassium currents, are variable and voltage-dependent, representing the voltage-gating of the ion channels. Hodgkin and Huxley deduced from experiment the following forms for the ionic membrane conductances:

$$g_k = \bar{g}_k n^4 \quad (9)$$

$$g_{na} = \bar{g}_{na} m^3 h \quad (10)$$

Where, (n, m, h), are 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.

The n, m, and h dynamic are listed below:

$$\dot{n} = \frac{dn}{dt} = \alpha_n(1 - n) - \beta_n n \quad (11)$$

$$\dot{m} = \frac{dn}{dt} = \alpha_m(1 - m) - \beta_m m \quad (12)$$

$$\dot{h} = \frac{dh}{dt} = \alpha_h(1 - h) - \beta_h h \quad (13)$$

Where α_x and β_x , are rate constant that the changes happened with voltage changes, but not affected by time, while the value of dimensions variable n can take place between 0 and 1, also its stand for of a single gate probability that is in permissive state.
Hodgkin and Huxley measured constantly α_i β_i as functions of V in the following:

$$\alpha_i = \frac{x_\infty(V)}{\tau_n(V)} \quad (14)$$

$$\beta_i = \frac{1 - x_\infty(V)}{\tau_n(V)} \quad (15)$$

D. Dynamics of the Membrane

The HH model was considered in this study. The analysis is applicable to each conductance based model with ion channels governed by linear, voltage dependent kinetics. The equation below described the membrane potential of the neuron.

$$C\frac{dV}{dt} = -g_K\,\psi_k\,(V_m - E_K) - g_{Na}\psi_{na}(V_m - E_{na}) - g_L(V_m - E_L) + I \quad (16)$$

V above is the transmembrane voltage, and ψ_K is the dynamic variable in the formula represents the ratio of open channel from potassium which is the proportional number of open channels to the complete number of potassium channel in the membrane; also ψ_{Na} is an open sodium channels ratio, and I is externally current. All of the two channel variables ψ_K and ψ_{Na} in the Hodgkin–Huxley (HH) equations is taken as their approximated deterministic value, $\psi_K = n^4$ and $\psi_{Na} = m^3h$; while the potassium channel have four n-gates and sodium channel have three m-gates and one h-gate. In case the channel is considered open, all the gates of that channel have to be open, and the gating variable for potassium is n and for sodium is m and h.

The rate functions that found to be as:

$$\alpha_n(V) = \frac{0.01(10-V)}{\exp\left(\frac{10-V}{10}\right)-1}, \quad (17)$$

$$\beta_n(V) = 0.125\exp\left(-\frac{V}{80}\right), \quad (18)$$

$$\alpha_m(V) = \frac{0.1(25-V)}{\exp\left(\frac{10-V}{10}\right)-1}, \quad (19)$$

$$\beta_m(V) = 4\exp\left(-\frac{V}{18}\right), \quad (20)$$

$$\alpha_h(V) = 0.07\exp\left(-\frac{V}{20}\right), \quad (21)$$

$$\beta_h(V) = \frac{1}{\exp\left(\frac{30-V}{10}\right)+1} \quad (22)$$

The functions α_V and β_V have dimensions of [1/time] and govern the rate at which the ion channels transition from the closed state of the open state (α) and vice versa (β).

I. THE PROPOSED MODEL

The proposed model in eq. (23), 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. 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 ψ_K, and ψ_{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 and 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. The equations that describe the proposed model shown as follows:

$$C\dot{V} = -g_k\sum_i n^4(V - E_K) - g_{Na} = \sum_i m^3h(V - E_{Na}) - g_{Ca}\psi_{Ca}(V - E_{Ca}) - g_L(V - E_L) + I + \xi(t) \quad (23)$$

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

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

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

$\psi_K = \sum_i n^4$

$\psi_{Na} = \sum_i m^3h$, i =number of channels.

ψ_{Ca}, is an open calcium channels, ratio depends on the concentration of Ca^{+2}.

$$[\psi Ca] = \begin{cases} \frac{[Ion_{Ca}]out}{[Ion_{Ca}]in}, & if\ Ion_{Ca} \geq 1mV \\ o, & otherwise \end{cases} \quad (24)$$

If the concentration of the calcium is high the channel will open otherwise close.

Here $[\psi_K], [\psi_{Na}]$, is the ratio of open potassium and sodium channels, computed across all achievable order of the membrane getting $4X_Kn$, $3X_{Na}m$, $X_{Na}h$, open n- gates, as shown below:

$$[\psi_K] = \begin{cases} \frac{(4X_Kn)^3(4X_Kn)^2(4X_Kn)^1n}{(4X_K)^3(4X_K)^2(4X_K)^1}, & if\ X_{K^n} \geq 1 \\ o, & otherwise \end{cases} \quad (25)$$

$$[\psi_{Na}] = \begin{cases} \frac{(3X_{Na}m)^2(3X_{Na}m)^1m}{(4X_{Na})^2(4X_{Na})^1}h, & if\ X_{K^n} \geq 1 \\ o, & otherwise \end{cases} \quad (26)$$

If the membrane size is small then $\psi_K = n^4$, and $\psi_{Na} = mh^3$, in the limit of infinite membrane size, the proposed model's value $\psi_k = [\psi_K] = n^4$, and $\psi_{Na} = [\psi_{na}] = mh^3$, applies at any times.
Where, $[\psi_K], [\psi_{Na}]$, reads as:

$\psi_k = n^4 + \sigma_k q_k$

$\psi_{na} = mh^3 + \sigma_{Na} q_{Na}$

The equations that describe the dynamics of q_K are:

$$\tau \dot{q_K} = p_K \quad (27)$$

$$\tau \dot{p_K} = -\gamma_K p_K - w_K^2[\alpha_n(1-n) + \beta_n n] g_K + \xi_K \quad (28)$$

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

$$\tau \dot{q}_{Na} = p_{Na} \quad (29)$$

$$\tau \dot{p}_{Na} = -\gamma_{Na} p_{Na} - w_{Na}^2[\alpha_m(1-m) + \beta_m m] g_{Na} + \xi_{Na} \quad (30)$$

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

$$\alpha_n(1-n) + \beta_n n, \text{ and } \alpha_m(1-m) + \beta_m m \quad (31)$$

The standard deviation of ψ_k, ψ_{na}, will be as follows:

$$\sigma_k = \sqrt{\frac{n^4(n^4)^{-1}}{X_K} q_K} \quad (32)$$

$$\sigma_{Na} = \sqrt{\frac{m^3(m^3)^{-1}}{X_{Na}} h q_{Na}} \quad (33)$$

The complete model for the dynamic variable (ψ_K),(ψ_{na}), is:

$$\boldsymbol{\psi_K = n^4 + \sqrt{\frac{n^4(n^4)^{-1}}{X_K} q_K}} \quad (34)$$

$$\psi_{Na} = m^3 h + \sqrt{\frac{m^3(m^3)^{-1}}{X_{Na}} h q_{Na}} \quad (35)$$

The gate noise model is:

$$\dot{n} = \frac{dn}{dt} = \alpha_n(1-n) - \beta_n n + \xi_K \quad (36)$$

$$\dot{m} = \frac{dn}{dt} = \alpha_m(1-m) - \beta_m m + \xi_{na} \quad (37)$$

$$\dot{h} = \frac{dh}{dt} = \alpha_h(1-h) - \beta_h h \xi_h \quad (38)$$

II. 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 (Zeng, 2004). The simulation model in equations (34, 35) 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 and the noise variance in this simulation were a periodic sin wave under noise variance, as shown below:

$$I(t) = I_{base} + \xi(t) \quad (39)$$

Where, I_{base} indicates the current situation, and the GWN with mean zero is (ξ (t)). A series of experiments has been used to examine the effectiveness of the noise in the proposed model in a comparative manner with the Microscopic simulation, as mentioned above.

The experiments applying by using parameter values of the membrane with including Gaussian white noise in the proposed model and in the Hodgkin-Huxley equations as described in formula (39). 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 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 noise variance increases.

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

$$\langle \xi_K(t)\xi_K(t') \rangle = \gamma_K T_K[\alpha_n(1-n) + \beta_n n]\delta(t-t') \quad (40)$$

$$\langle \xi_{Na}(t)\xi_{Na}(t') \rangle = \gamma_{Na} T_{Na}[\alpha_m(1-m) + \beta m m \delta t - t, \quad (41)$$

$$\langle \xi_K(t)\xi_K(t') \rangle = \frac{\alpha_n(1-n)+\beta_n n}{4X_K}\delta(t-t') \quad (42)$$

$$\langle \xi_{na}(t)\xi_{na}(t') \rangle = \frac{\alpha_m(1-m)+\beta_m m}{3X_{Na}}\delta(t-t') \quad (43)$$

$$\langle \boldsymbol{\xi_h(t)\xi_h(t')} \rangle = \boldsymbol{\frac{\alpha_h(1-h)+\beta_h h}{X_{Na}}\delta(t-t')} \quad (44)$$

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

γ_K=10	γ_K=150	T_K=400
γ_{Na}=10	w_{Na}^2=200	T_{Na}=200

The parameter's value of the membrane which used in Eq. (23) 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 $4X_K n$ and also for sodium, calcium resulting $3X_{Na}m$, $X_{Na}h$ 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 α_n , β_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/cm^2)
Sodium	E_{Na} = -115	x1 = 120
Potassium	E_K = 12	x2 = 36
Leakage	E_L = -10.613	x3 = 0.3
Calcium	E_{Ca}=136	x4 = 40

Figure 1, the membrane size for potassium is 300, for sodium is 1000 and I_{base} = 4, threshold=0. 005. The averages are computed in 30 seconds time window. The comparison between the three curves used different noise variance, it can be seen that the proposed model was quite close to the microscopic simulations and the spike frequency increase and will be more accurate when the noise variance increasing (Hodgkin, & Huxley, 1952). The numbers of the sodium channel calculated as follows:
No of sodium channel =No. of potassium channel/3*10.

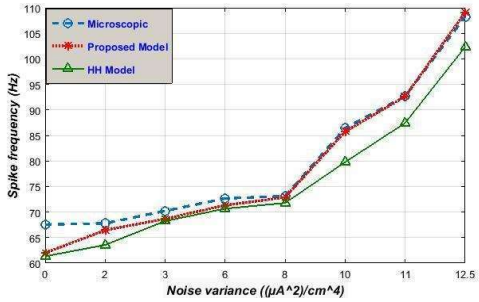

Fig 1: Mean spiking rates against the noise variance.

Figure 2, shows the membrane size for potassium is 300, for sodium is 1000, and I_{base} = 4, threshold=0. 008. The simulation time window is 30 seconds. This Figure shows how the speed of spike frequency as the noise variance increases for both the proposed model and HH model. In addition, different noise variance used to show the comparison between the three curves, it can be seen also that the proposed model was quite close to the microscopic simulations.

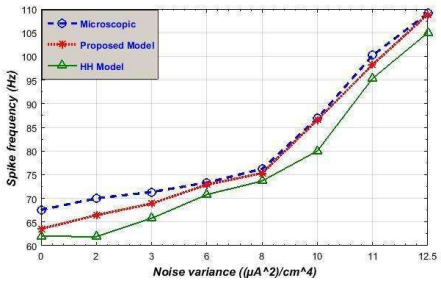

Fig 2: Shows the relationship between noise variance and the spike frequency.

Figure 3, shows the membrane size for potassium is 300, for sodium is 1000, for calcium is 150, and I_{base} = 8. The averages are computed in 30 seconds time window. The comparison between the three curves used different noise variance in the simulations. In addition, the difference between spike frequencies becomes smaller after the noise variance increases.

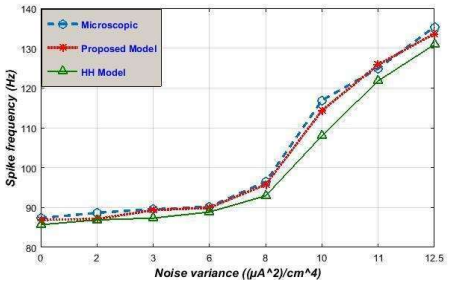

Fig 3: Present the mean spiking rates against the noise variance.

Figure 4, shows how the speed of spike frequency as the noise variance increases for both the proposed model and HH model. The membrane size for potassium is 1710, for sodium is 5700, and I_{base} = 7.25, threshold=0. 005. The simulation time window is 30 seconds. In addition, different noise variance used to show the comparison between the three curves, and the proposed model was quite close to the microscopic simulations when increasing the noise variance.

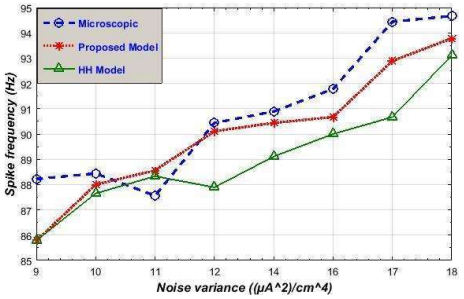

Fig 4: Provides the relationship between noise variance and the spike frequency.

In Figure 5, the membrane size for potassium is 1710, for sodium is 5700, for calcium is 1520, and I_{base} = 9. The averages are computed in 30 seconds time window, different noise variance used to show the comparison between the three curves. The proposed model was quite close to the microscopic simulations. In addition, after the noise variance increases, the difference between spike frequencies becomes smaller (Hodgkin, & Huxley, 1952). In the table, 3 different parameter's value of the membrane used in Figure 5.

Table 3: Different parameter values of the membrane

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

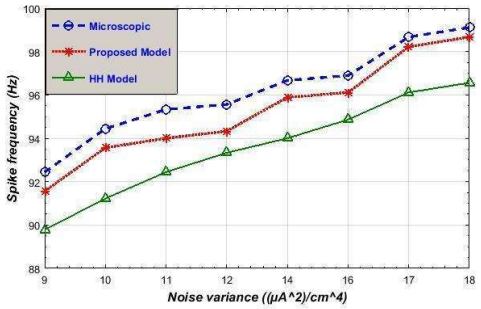

Fig 5: Mean spiking rates against the noise variance.

Figure 6, shows the membrane size for potassium is 3525, and for sodium is 11750, I_{base} = 11, threshold=0. 005. The averages are computed in 30 seconds time window, and different noise variance used in the simulations to show the comparison between the three curves. The proposed model was affected by noise variance more than the HH model.

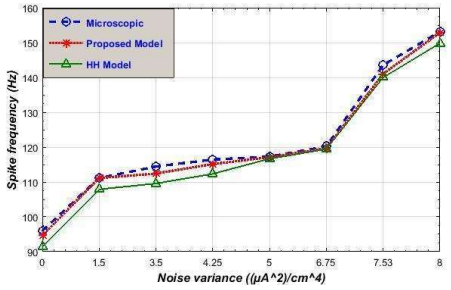

Fig 6: Is the mean spiking rates against the noise variance.

In Figure 7, the membrane size for potassium is 5676, for calcium is 3525, for sodium is 18920, and I_{base} = 10.50, threshold=0. 005. The simulation time window is 30 seconds. In addition, different noise variance used to show the comparison between the three curves (Hodgkin, & Huxley, 1952).

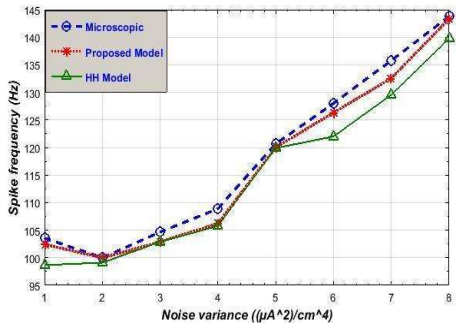

Figure 7: Shows the relationship between noise variance and the spike frequency.

Figure 8, shows how the speed of spike frequency as the noise variance increases for both the proposed model and HH model. The membrane patch composed of 10002 of potassium channels and 33340 of sodium channels, and I_{base} = 15, threshold=0. 005. The averages are computed in 30 seconds time window, and different noise variance with large membrane size used to show the comparison between the three curves. It is seen that the spike frequency increase and will be more accurate when the noise variance increasing, and the proposed model were affected by noise variances more than the HH model.

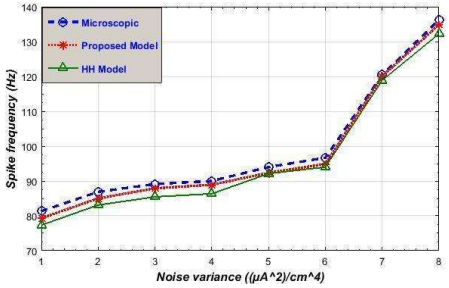

Figure 8: Provides the relationship between noise variance and the spike frequency.

III. 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 noise variance, the stochastic HH 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 noise, Which was introduced by a different membrane size, $\boldsymbol{I_{base}}$, and noise variance, in which three curves represent the competition between the microscopic simulation with the proposed model and stochastic HH equation, 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 Hodgkin-Huxley 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.

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