An Investigation into the Colored Stochastic Hodgkin-Huxley Equations Under Time Varying Input Currents

Omar Hayman Fadhil

Submitted to the
Institute of Graduate Studies and Research
in partial fulfillment of the requirements for the Degree of

Master of Science
in
Computer Engineering

Eastern Mediterranean University
January 2013
Gazimağusa, North Cyprus

Approval of the Institute of Graduate Studies and Research

Prof. Dr. Elvan Yılmaz
Director

I certify that this thesis satisfies the requirements as a thesis for the degree of Master of Science in Computer Engineering.

Assoc. Prof. Dr. Muhammed Salamah
Chair, Department of Computer Engineering

We certify that we have read this thesis and that in our opinion it is fully adequate in scope and quality as a thesis for the degree of Master of Science in Computer Engineering.

Prof. Dr. Marifi Güler
Supervisor

Examining Committee

1. Prof. Dr. Marifi Güler _____
2. Assoc. Prof. Dr. Işık Aybay _____
3. Asst. Prof. Dr. Adnan Acan _____

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.

It was recently found by Güler (2011) that a non-trivially persistent cross correlation regard position among the transmembrane voltage fluctuations and the element of open channel fluctuations attributed to the gate multiplicity. This non-trivial phenomenon was found to be playacting an essential important role for the elevation of excitability and spontaneous firing in the small size cell. Furthermore, the same phenomenon was found to be enhancing the spike coherence significantly. More recently, the effects of the above cross correlation persistency was modeled; by the same author M. Güler (2013), through inserting some colored noise terms inside the conductances in the stochastic Hodgkin Huxley equation.

In this thesis, we study the above colored stochastic equations under time varying periodic input currents. Our investigation reveals 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.

Keywords: colored noise, channel gate, Ion channel, small size membrane, channel noise, Stochastic Hodgkin-Huxley equations

ÖZ

Son yıllarda, nöronlardaki ion kanal gürültüsünün sinir hücresinin dinamiği üzerinde hayati bir etki yapabileceği ileri sürülmüş ve deneysel olarak da kanıtlanmıştır. İon kanal gürültüsünün, çarpıcı bir şekilde, kendi kendine ateşlemeye ve stokastik resonansa sebep olabildiği bulunmuştur.

İon kanallarında çoklu geçit bulunmasının, voltage dalgalanmaları ve açık kanal dalgalanmaları arasında ilk bakışta gözükmeyen bir daimi çapraz ilişkiye neden olduğu yakın zamanda Güler (2011) tarafından ortaya çıkartılmıştır. Bu ilk bakışta gözükmeyen olgunun, küçük boyutlu hücrelerde yüksek uyarılıma ve kendi kendine ateşlemeye neden olduğu bulunmuştur. Daha yakın zamanda, sözkonusu olgunun etkileri, stokastik Hodgkin-Huxley denklemlerinde geçirgenliklere renkli gürültü terimleri ekleyerek, Güler (2013) tarafından modellenmiştir.

Bu tezde, yukarıdaki reklendirilmiş Hodgkin-Huxley denklemleri zaman değişmeli periyodik girdi akımları altında incelenmiştir. Girdilerin kritik bir frekans değerinin üzerinde olması ya da belirli bir genlik değerinin altında olması durumlarında, renkli gürültü terimlerinin çok hayati bir önem arz ettiği gözlenmiştir.

Anahtar Kelimeler: Renkli gürültü, kanal geçiti, ion kanalı, küçük boyutlu zar, stokastik Hodgkin-Huxley denklemleri

I lovingly to dedicate this thesis

To my beloved father

To my beloved mother

To my two brothers and little sister

To all my friends

ACKNOWLEDGMENT

I would like to acknowledge with gratitude Prof. Dr. Marifi GÜLER, without his knowledge, guidance, supervising, and effort this research will be imposable.

My deepest gratitude to my beloved parents for their incredible support, effort, and patience who I owe quit a lot to.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

Chapter 1

INTRODUCTION

The Effect of noise to the neurons produces an unusual pattern on the neuronal dynamics. The noise is in two types; internal or external (Faisal A. S., 2008). External noise is exactly the opposite of internal. External noise is produced from the synaptic signal transmission. 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 (Sakmann, 1995). If fluctuations are included in the membrane conduct, then fluctuation will be included in the voltage of transmembrane as well. When the number of ion channels is large means that the membrane size is huge, the voltage dynamics will represent as in the original Hodgkin and Huxley (Hodgkin, 1952) 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 ((Sigworth, 1980); (Lynch, 1989); (Johansson, 1994)), and spontaneous fire will be the result of that noise in the ion channels ((Koch, 1999);(White, 1998)). Patch-clamp experiments *in vitro* have demonstrated that the noise of channel in the dendrites also in the soma resulting voltage fluctuations that are large enough to affect asynchronies in the timing, initiation, and

propagation of action potentials ((Diba, 2004); (Jacobson, 2005); (Dorval, 2005); (Kole, 2006)). The phenomenon called stochastic resonance has been observed to occur in a system of voltage-dependent ion channels formed by the peptide alamethicin ((Bezrukov, 1995)).

Spontaneous spiking is a phenomenon caused by the internal noise from the ion channels. Proof through theoretical investigations and numerical simulations of channel dynamics (in the form of repetitive spiking or bursting), or in otherwise quiet membrane patches ((DeFelice, 1992); (Strassberg, 1993); (Chow, 1996); (Rowat, 2004); (Güler, 2007) ;(Güler, 2008);(Güler, 2011); (Güler, 2013)); furthermore, these investigations also have revealed the occurrence of stochastic resonance and the coherence of the generated spike trains ((Jung, 2001); (Schmid, 2001); (Özer, 2006)). In addition, the channel fluctuations might reach the critical value near from the action potential threshold even if the numbers of existed ion channels are large. ((Schneidman, 1998); (Rubinstein, 1995)); The timing accuracy of an action potential is measured by a small number of opening ion channel at that threshold. Furthermore, ion channel noise controls the spike propagation in axons ((Faisal A. A., 2007); (Ochab-Marcinek, 2009)).

It has been revealed in earlier theoretical experiments (Güler. 2011) that it is not just the gate noise (the quantity of fluctuations in the open gates') that affects neuron's behavior, but also the existence of a large quantity of gates in single ion channel, Furthermore this effect that may be pointing on an important role in activity within the cell in case of having membrane bounded in size. More recently, a stochastic Hodgkin – Huxley model, having colored noise terms in the conductances was proposed (Güler, 2013), where the colored terms capture those effects due to the gate multiplicity.

Scope and organization

In this thesis, the colored stochastic Hodgkin Huxley equations, introduced by Güler (2013) will be studied when the input current to the neuron is time varying. In particular, the role played by the involvement of the colored noise term in the conductances will be focused on in the examination. The organization of the thesis will be as follow, Chapter two handles neuron morphology and structure, chapter three focusing on the Hodgkin Huxley equation, chapter four explain the membrane dynamics, chapter five includes the color noise model formulations and chapter six about the experiments and results of the study.

Chapter 2

NEURONS

2.1 Morphological and structure

Neuron is the most important concept in the brain. The estimated number of neuron in a human brain is from 80 to 120 billion neurons. In addition, neurons are unique because they can transmit electrical signals over long distances. The electric signal is transferred to the other neuron through the synapse. Neuron received electrical signal from other neurons through dendrites. It has a structure like a tree for increasing the ability of sensing the signal that comes from the other neuron through synapse connections and is sent to the body of the neuron that is called soma. The signal that is transmitted from the neuron came out through a special part called an axon to other cells as shown in figure 1. Axon of the neuron length reaches a very long distance sometimes extending to the whole body. In a mouse brain, the cortical neurons have been estimated that the length of axon is equal to about 40 mm and has in its branches almost 4 mm of total dendritic. Each axon makes connections of approximately 180 synaptic contacts per μm with other branches of dendritic that belong to other neurons. Also each dendritic tree receives an average of two signals per μm from another. The soma of ideal cortical neurons reaches in diameter from 10 up to 25 μm. (Abbot, 2002).

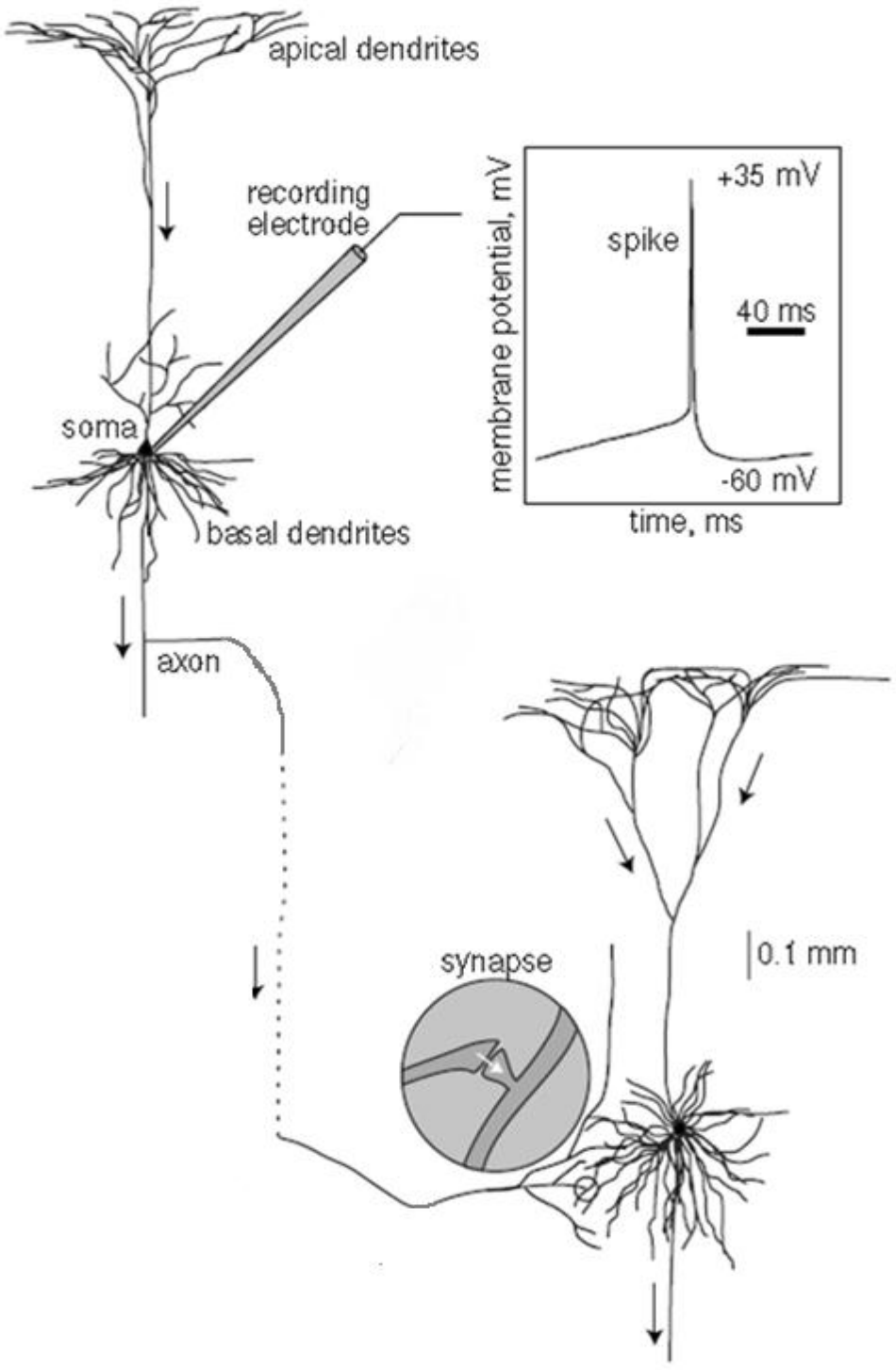


Figure 1: Two interconnected cortical pyramidal neurons (and in vitro recorded spike). (Izhikevich, 2007)

2.1.1 What is a spike?

It is simply the communication means between the neurons. Each neuron received a spike from 10,000 neurons via synapse. Through a synapse from another neuron, electrical signal received causes the transmembrane current that changes the membrane potential (neuron voltage). The current signal that comes from the synapse is called the post synapse potentials (PSPs), little current generate tiny PSPs, large current means considerable PSPs. Voltage sensitive channel embedded in a neuron is amplified to result in generation of action potential or spike (Izhikevich, 2007).

2.1.2 Membrane proteins

Each neuron cell contains proteins specialized to transport materials through other. In order to understand many neurons functions some information about these proteins should be known. It could be classified into three groups according to how these proteins help to transport the substances in the membrane. Each type of protein's function has the ability to change its form according to that function.

2.1.2.1 Channels

It is simply membrane protein that is made in a form of channel or hole, allowing some material to pass through. The size of the channel is varied according to the purpose of that channel so small sized holes control little sized substances to pass in or out into the cell and the same for different size of substances. There are protein molecules working as a channel like sodium (Na+), potassium (K+), calcium (Ca2+), and chloride (Cl-).

2.1.2.2 Gates

One of the important protein's molecules features has special ability that can change its shape. These proteins are called gates. The purpose of the gates is to simply allow some or specific chemicals to pass and bind the others. These implanted proteins behave like a pass. It becomes active when the chemical match with the embedded proteins by the shape and the size, and there are many kinds of gate responses to different motivation such as electrical charge or temperature change to allow the certain chemical to pass through.

2.1.2.3 Pump

It is the other type of membrane proteins that are modified to work as a pump, moving substances around the membrane according to the energy requirements for the transporter molecule. For example; proteins shaping their pattern in case to pump particular ions, ions like Na+ moving in one way and K+ ions in the opposite direction. Furthermore, protein pump transports many other substances.

2.1.3 Synapse

Synapse is designed in the form of a cross between two connected neurons. It exists in the end axon when the incoming axon is in contact with the out coming axon which belongs to the other neuron. Axons end at the synapse, when the electrical voltage created from the action potential making the ion channel to become open by generating the flow of Ca+2 that leads to release the neurotransmitter. The neurotransmitter motivates the receivers or the postsynaptic side on the second neuron that the signal destination producing on that side ion-conducting making the channel open. The type of the ions flows on the synapse could cause an stimulative, depolarized, or an repressive, typically hyper-polarizing; depend on the postsynaptic neuron (Abbot, 2002).

Synapse is orderly scattered over the dendritic. Generally restrained synapse is more proximal than excitatory synapses. Although these two types are existed at distal dendritic area, and also when it's present at some spines in conjunction well followed by excitatory input (segev I., 2003). In a lot of systems, the input source is already given (e.g. pyramidal hippocampal cells and cerebellar Purkinje cells), and it is preferentially attached with its own dendritic tree region, instead of randomly scattered around the dendritic tree surface.

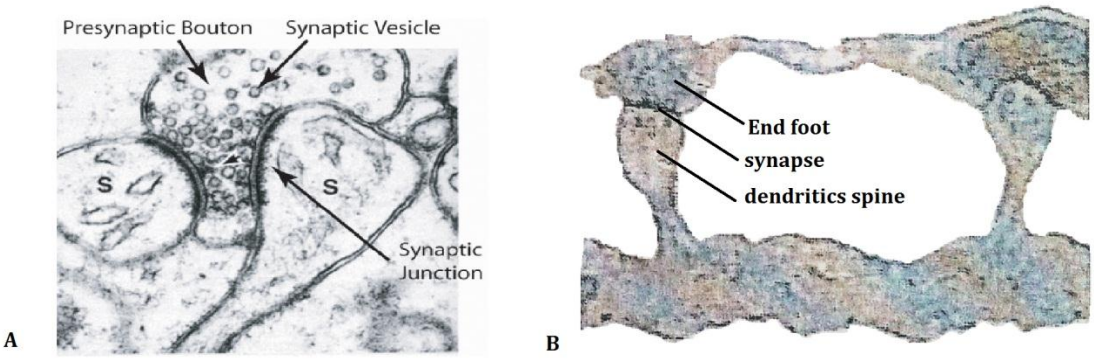


Figure: 2 Electronic micrographic picture of synapse in real neurons

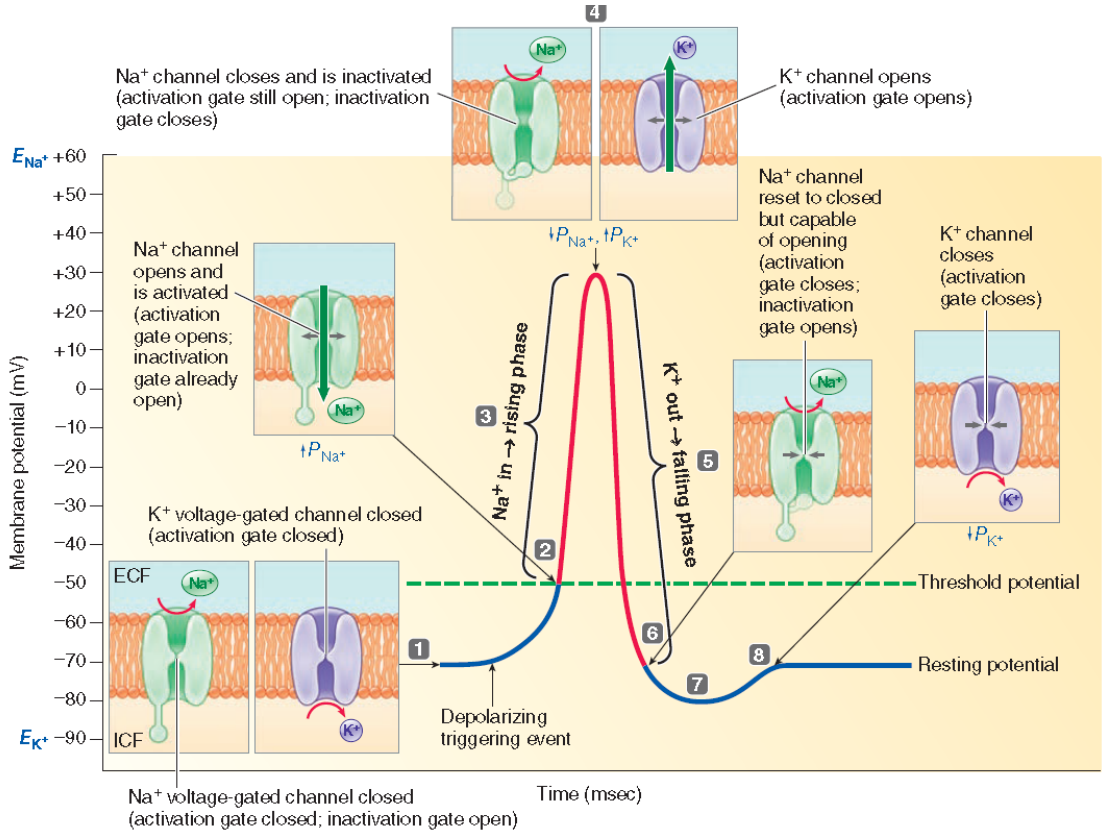
(a) Electron micrograph of recitative spiny synapses (s) designed on the dendrites of rodent hippocampal pyramidal cell

(b) An electron micrograph picture catches the synapse design where the terminal button of one neuron connects with a dendritic spine on a dendrite of second neuron. (Whishaw, 2012)

2.2 Electrical activity of neuron and Membrane potential

The simple definition of membrane potential is the voltage potential or difference of a neuron between the voltage measure inside the neuron, and the one measured outside the neuron. In some conditions like resting state the voltage potential inside the neuron reaches about -70mV. However, this action potential is assumed conventionally to be zero mV for more fitness and also to consider the cell is polarized in this situation. The potential that is created is considered as an equilibrium point because at this point the ions that will flow inside the cell should be equal in quantity to the ions moving outside the cell. The difference produced by this membrane potential is flowed by keeping the concentration of an ion's gradient in balance, and this balance is controlled by the ions pumps placed in the cell. For instance, Na+ ions concentrated in extracellular fluid is much longer than intracellular fluid, and also K+ ions in remarkable that is concentrated highly outside further than inside the neuron. So the state transition of the neuron affected by the flow of ions from, and to the cell caused by voltage and concentration gradient. Positive charge ions produce current. These current flows out the neuron through open channels leaving negative charge in the membrane potential increased. This phenomenon is called hyperpolarization. The depolarization phenomenon happens when the current flows inside the cell making the membrane potential more negative or sometimes positive. When a neuron depolarizes enough to increase the level of the membrane potential higher than the threshold, a positive feedback operation starts and motivates the neuron to produce an action-potential , and the earlier reaches almost 100mV fluctuation in the electric potential through the cell membrane that is almost 1 millisecond last. After action potential generates and is used to balance the potential

between in and out the neuron, it may be leading to impossibility to start another spike after the depolarization making the neuron go to a period called the absolute refectory. The difference between the action potential and subthreshold fluctuation could be summarized by propagation over long distance. In action, potential almost reaches 1 millimeter and the propagation of the signal without attenuation (Abbot, 2002). Figure 2.3 explains the dynamics of the voltage during an action potential during the synchronization by corresponding ions channel activities throughout an action potential. The resting potential in this figure represents the real value equal to -70mV.



1 Resting potential: all voltage-gated channels closed.

2 At threshold, Na^+ activation gate opens and P_{Na^+} rises.

3 Na^+ enters cell, causing explosive depolarization to +30 mV, which generates rising phase of action potential.

4 At peak of action potential, Na^+ inactivation gate closes and P_{Na^+} falls, ending net movement of Na^+ into cell. At the same time, K^+ activation gate opens and P_{K^+} rises.

5 K^+ leaves cell, causing its repolarization to resting potential, which generates falling phase of action potential.

6 On return to resting potential, Na^+ activation gate closes and inactivation gate opens, resetting channel to respond to another depolarizing triggering event.

7 Further outward movement of K^+ through still-open K^+ channel briefly hyperpolarizes membrane, which generates after hyperpolarization.

8 K^+ activation gate closes, and membrane returns to resting potential.

Figure 3: Phases of action potential (Whishaw, 2012)

Chapter 3

HODGKIN - HUXLEY EQUATIONS

In the last 60 years, a lot of neural models for different needs have been found and developed. Furthermore, the variety of these models relies on the structurally realistic biophysical model. For instance, one of the most important models through time is the Hodgkin – Huxley (HH), and the one that this thesis focus on the color noise model (set by Prof. Dr. Marifi Güler) which is, in fact, implementing the HH model to be more accurate if compared with the actual neuron. Different models may be needed in various studies according to biological properties of models, complication and the implementation cost. However, modeling technic of neural excitability has been attached from the monument work of Hodgkin-Huxley (1952). In this part the Hodgkin – Huxley model will explain briefly.

3.1 The Hodgkin-Huxley Model

According to many investigations, experiment on giant squid axon by using clamp methods, Hodgkin and Huxley (1952) model show the current passing over the squid axon membrane composed from twain main ionic elements I_{Na} (sodium channel current) and I_K (potassium current). The membrane potential intensely dominated these two mentioned current.

As a consequence they developed a mathematical model from what they observe leading to create a model, until yet this model is mostly expressive model according to what many realistic neural models have been developed.

In the Hodgkin – Huxley model the electrical characteristics of a segment of nerve membrane could represented by an equivalent circuit in which current sources towards the membrane have two main parts; the first relative with charging membrane capacitance, the second is attached to the movement of special type of ions through the membrane. In addition, the ionic current composed from three different elements, a sodium current I_{na}, a potassium current I_K and a small leakage current I_L usually it is related with chloride ions.

The differential equation similar to the electrical circuit is like follow

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

Where

C_m is membrane capacitance

V_m is membrane potential

I_{ext} is an externally current

I_{ion} is the ionic current

The I_{ion} is the current influx onto the membrane and can be calculated from the following formulas:

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

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

I_i here demonstrate each single current having a relative conductance g_i and reflex potential E_i

There are three I_i in the squid giant axon model: sodium current $I_{Na,}$ potassium current I_K and a small leakage current I_L and these three current produce the following formulas:

$$I_{ion} = I_{Na} + I_K + I_L \quad (4)$$

$$I_{Na} = g_{Na}(V_m - E_{na}) \quad (5)$$

$$I_K = g_K\,(V_m - E_K) \quad (6)$$

$$I_L = g_L\,(V_m - E_L) \quad (7)$$

The microscopic conductance g_i (g_L, g_K, g_{Na}) created from the marge effect of a massive amount of microscopic ion channels within the membrane. Ion's current can be thought of as containing a small number of physical gates that control the flow of ions across the channel. In an ion channel when all the gates are in the permissive condition, ions can transport from channel to another while the channel opens.

3.1.1The ionic conductance

Ions have the ability to transit into the channel while the channel is in open period. In case of channel being open all the gates for that channel must be in the permissive state. The nominal assumption purposed to Illustrates the potassium and sodium conductance experimentally accomplished through voltage clamp experiments:

Where n, m, and h are dynamics of ion channel gate variables that will be late assumed as $\bar{g}_{\text{i}}$ is a conductance constant for specific area per cm^2(in mind the value of n normally take place between 0 and 1).

The n, m, and h dynamic are listed bellow

$$\dot{\text{n}} = \frac{dn}{dt} = \alpha_n(1-n) - \beta_n n \qquad (8)$$

$$\dot{\text{m}} = \frac{dn}{dt} = \alpha_m(1-m) - \beta_m m \qquad (9)$$

$$\dot{\text{h}} = \frac{dh}{dt} = \alpha_h(1-h) - \beta_h h \qquad (10)$$

α_x and β_x are rate constant that the changes happened by voltage changes, but not affected with time, while the value of dimensionless 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 begin in 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.

$$x(t) = x_\infty(V_c) - \big(x_\infty(V_c) - x_\infty(0)\big)\exp(-t/\tau_x) \quad (11)$$

$$x_\infty(0) = \alpha_x(0)/\alpha_x(0) + \beta_x(0) \quad (12)$$

$$x_\infty(V_c) = \alpha_x(V_c)/\alpha_x(V_c) + \beta_x(V_c) \quad (13)$$

$$\tau_x(V_c) = [\alpha_x(V_c) + \beta_x(V_c)]^{-1} \quad (14)$$

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 $x_\infty(0) = 0$ and $x_\infty(V_c) =$ the clamp voltageV_c. τ_x Represent the constant time required for reaching the steady state value of $x_\infty(V_c)$ when the voltage assumed equal to V_c.

Hodgkin and Huxley measured constant α_i β_i as functions of V in the following

$$\alpha_i = \frac{x_\infty(V)}{\tau_n(V)} \quad (15)$$

$$\beta_i = \frac{1 - x_\infty(V)}{\tau_n(V)} \quad (16)$$

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

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

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

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

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

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

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

All of α (V) and β (V) describe the transition rates between open and closed states of the channels.

Chapter 4

DYNAMICS OF THE MEMBRANE

The transmembrane voltage (V) improved with time correspondence with the differential equation

$$C\ \frac{dV}{dt} = -g_K\ \psi_k\ (V_m - E_K) - g_{Na}\psi_{na}(V_m - E_{na}) - g_L(V_m - E_L) + I \qquad (23)$$

Where ψ_K is the dynamic variable in the formula represents the ratio of open channel from potassium which is the proportional number of open channel to the complete number of potassium channel in the membrane. Also, ψ_{Na} is open to sodium channels ratio. All the constant parameters values of the membrane used in Eq. (23) are explained in table 1 (the values in the table are typical since 1952). Both of the two channel variables ψ_K and ψ_{Na} in the Hodgkin–Huxley (HH) equations are considered to be at their approximated deterministic value, $\psi_K = n^4$ and $\psi_{Na} = m^3h$; while potassium channel has four n-gates and sodium channel has 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 the gating variable for sodium is *m* and *h*. N_K and N_{Na} correspond to the complete number of channels for potassium and sodium. In order to find the total number of open channels, N_K should by multiplying by 4n for potassium to get $4N_Kn$ and also for sodium resulting $3N_{Na}m$, $N_{Na}h$. On the other hand, the Markov

process has been put into the gates' dynamics. The probability of an n-gate is closed between the time t and remains closed at time t+Δt is exp $(-\alpha_n \Delta t)$, and the probability of being open at time t, and continue to be open at time $t + \Delta t$ is exp $(-\beta_n \Delta t)$ which means that all of the parameters α_n and β_n are voltage-dependent opening and closing rates of n-gates. Also, the same process is applied for the m-gate and h-gate. The rate functions are found to be as:

$$\alpha_n = (0.1 - 0.01V)/(\exp(1 - 0.1V) - 1) \quad (24a)$$

$$\beta_n = 0.125 \exp(-V/80) \quad (24b)$$

$$\alpha_m = (2.5 - 0.1V)/(\exp(2.5 - 0.1V) - 1) \quad (24c)$$

$$\beta_m = 4 \exp(-V/18) \quad (24d)$$

$$\alpha_h = 0.07 \exp(-V/20) \quad (24e)$$

$$\beta_h = 1/(\exp(3 - 0.1V) + 1). \quad (24f)$$

Table 1: The membrane capacitance (Hodgkin, 1952)

C	Membrane capacitance	1 µF/cm2
g_K	Maximal potassium conductance	36 mS/cm2
EK	Potassium reversal potential	−12 mV
g_{Na}	Maximal sodium conductance	120 mS/cm2
ENa	Sodium reversal potential	115 mV
gL	Leakage conductance	0.3 mS/cm2
EL	Leakage reversal potential	10.6 mV
	Density of potassium channels	18 chns/µm2
	Density of sodium channels	60 chns/µm2

4.1 NCCP [The non-trivial cross correlation persistency]

As pointed out earlier, in the potassium channel there is more than one n-gate and even if the proportions of open gates are known, it is not enough to satisfy ψ_K. For instance, considering a toy membrane which consists of a pair of potassium channels (eight gates), being in moment of at time t_2, it can be noticed that one of the two channels has all its gates open while the other channel only has two open gates. However, in a different moment of time t_1, each of the two channels has three open gates. That means, even when the membrane has equal number of open gates during the two moments, one of the two channel is open in moment t_2 but there is no channel at moment t_1 (see Fig. 4) although the term *gate-to-channel uncertainty* specifies this disadvantage of knowledge that is placed in ψ_K and even if *n* is known and also the expression *gate noise* is significant in these random fluctuations in *n* (Güler, 2011).

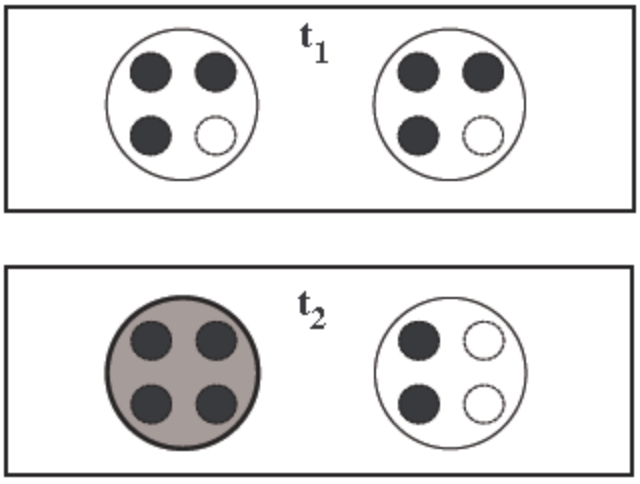


Figure 4: The toy membrane at two possible cases. The small circles represent the gate (black open, empty close). (Güler, 2011).

The *gate-to-channel uncertainty* is considered as dynamic random fluctuations in the construct $\psi_K - [\psi_K]$. By this construct the channel fluctuations that appear from the *gate-to-channel uncertainty* is bounded. If the *gate-to-channel uncertainty* did not exist, the construct could be disappearing regardless of the gate noise. Here $[\psi_K]$ is framed for the arrangement mean of the ratio of open potassium channels calculated through all achievable arrangement of the membrane getting $4NKn$ open n - gates, as shown below.

$$[\psi_K] = \frac{(4N_K n-3)(4N_K n-2)(4N_K n-1)n}{(4N_K-3)(4N_K-2)(4N_K-1)}, \text{ if } N_K n \geq 1 \qquad (25)$$

And $[\psi_K]$ = 0 otherwise. Then the construct $\psi_K - [\psi_K]$ will evaluate the difference between number of open channels from the arrangement mean at any moment. Unless the membrane is very small in size, it will be $[\psi_K] \approx n^4$. In case of finite membrane but unlimited size, the construct fluctuations will disappear. Thus, when membranes are large, the HH value to be used is $\psi_K = [\psi_K] = n^4$ at any time. The construct could be irrelevant in another condition when each of the channels has only one gate open, whatever the membrane size was. Thus, the result would be $\psi_K = [\psi_K] = n$.

Definition of the order parameters Ω_K^V and Ω_K^n as the given cross correlations will be:

$$\Omega_K^V = \frac{\left\langle (\psi_K - [\psi_K])V \right\rangle - \left\langle \psi_K - [\psi_K] \right\rangle \left\langle V \right\rangle}{\left\langle [\psi_K] \right\rangle (E_{Na} - E_K)} \quad (26)$$

$$\Omega_K^n = \frac{\left\langle (\psi_K - [\psi_K])n \right\rangle - \left\langle \psi_K - [\psi_K] \right\rangle \left\langle n \right\rangle}{\left\langle [\psi_K] \right\rangle \left\langle n \right\rangle} \quad (27)$$

Here the expectation values $< \cdot >$ are simply the foundation averages above the membrane conformation condition and all of these conformation states are related to time, independently of the others, via the Markovian evolution of the constituting gate states and Equation (23);In this way the ensemble at time t + Δt is decided from the ensemble at time t. The terms in the denominators were included for the convenience of scaling and dimensionality. Ω_k^v represent the evaluation for correlation among the voltage fluctuations *V* and the fluctuations of the construct $\psi_K - [\psi_K]$. Ω_k^n is almost the same, controlling the fluctuations of *n* instead of *V*. This is due to the fact that the construct positivity or negativity is going completely irregular and uncontrollable by any of the fluctuations of *V* or *n*. After an initial passing moment, it becomes easy to predict that the order parameters decrease to zero and this initiation is wrong in both the theoretical arguments and the numerical experiments of the channels. However, according to the simulations for near-equilibrium dynamics, the order parameter becomes and continues to be less than zero within the phase of sub-threshold actions. A non-trivially continual correlation reserves a position between the fluctuations of V and

the fluctuations of the construct $\psi_K - [\psi_K]$ and also the fluctuations of n, and this phenomenon what NCCP is pointing on.

How the order parameters do not remain zero as specified in Markovian evaluation that the condition of the gate at moment t + Δt relies on their condition at moment t even though the degree of dependence declines with the time period in Δt becoming larger. This means that the construct $\psi_K - [\psi_K]$ has not got a disappearing autocorrelation function and the time of the autocorrelation is limited, not reaching to zero. Thus, leading the plus value of [V − EK] becomes useful and it can be removed from the equation (18) in the condition that$\psi_K - [\psi_K]$ is greater than zero during some amount of time, after that a negative variance appearing in dV/dt along with that period. At this point, the variance is depending on having the construct $\psi_K - [\psi_K]$ equal to zero in the same duration, and from that the variance turns to negative in that period. That property is portrayed by

$$\psi_k - [\psi_k] > 0 \Rightarrow \delta\left(\frac{dV}{dt}\right) < 0 \Rightarrow \delta V < 0 \qquad (28)$$

Likewise, the variation in the situation of negative $\psi_K - [\psi_K]$ was shown as

$$\psi_k - [\psi_k] < 0 \Rightarrow \delta\left(\frac{dV}{dt}\right) > 0 \Rightarrow \delta V > 0 \qquad (29)$$

In the two above equations, (28) and (29), if the sign of $\psi_K - [\psi_K]$ is not considered, the value of $(\psi_K - [\psi_K])\delta V$ is minus during the all-time passing out making $\psi_K - [\psi_K]$ not going to a positive. A graphical demonstration is shown in Fig (5) for the case that the

dwelling time of ψ_K– $[\psi_K]$ in the same of algebraic sign should not be less than the duration of an actual fluctuation in V.

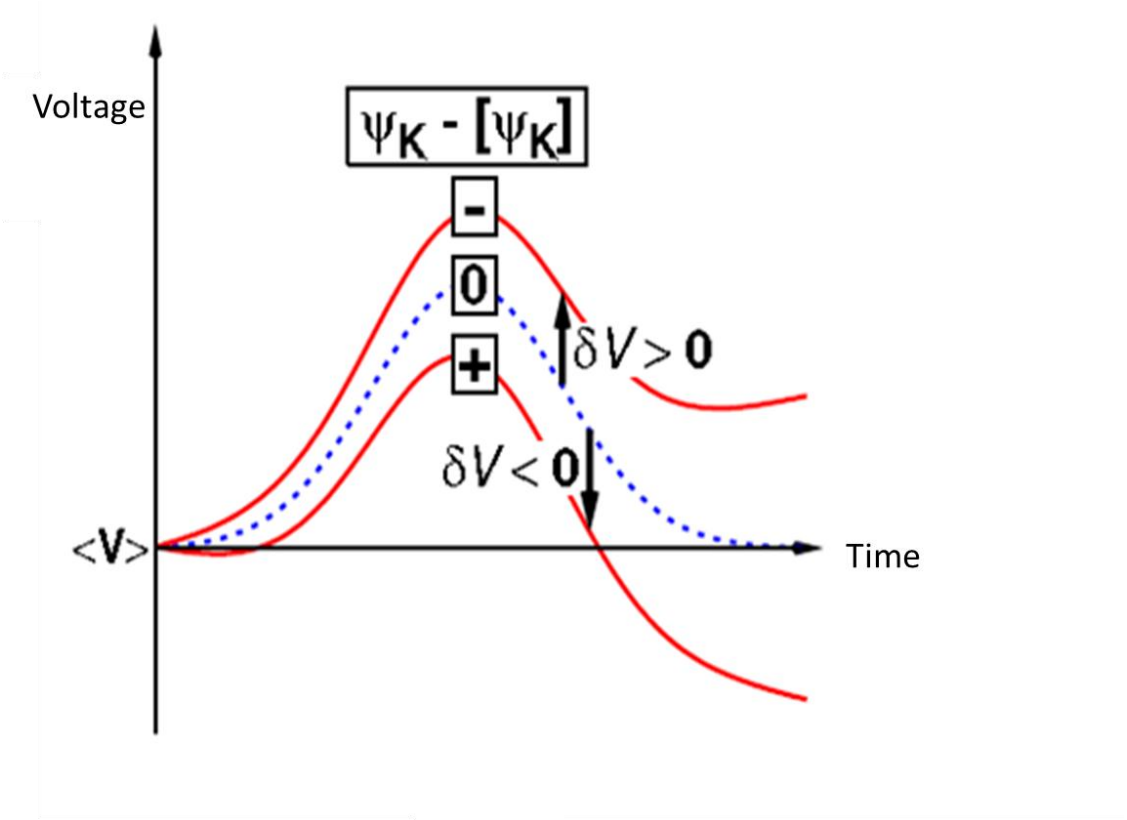


Figure 5: Explanation in the diversity of the voltage V (Güler, 2011).

Furthermore, if the sign of the product $\psi_K - [\psi_K]$ is switched at some point in the period, the value of the previous will not become below zero again at any moment; for a brief moment right after the sign switch it will be positive. In case of that the dwelling period is assumed remarkably higher than the residence time of the $\psi_K - [\psi_K]$ to become negative again, the chances of the output in negative will be bigger than finding the product in positive. As a result, the voltage fluctuations V will be negatively correlated with the fluctuations of $\psi_K - [\psi_K]$. Therefore, the configuration variable Ω_k^v will reach

minus value. The fluctuations, long-lasting only at a microscopic time window, enforce order at macroscopic time window.

In addition, one of the reasons that the order parameter Ω_k^n values does not become zero is that the deference of variation δV from V, with the deviations from $\psi_K - [\psi_K] = 0$. All of the rates α_n and $\beta_n$are a voltage relevance function that increases with the voltage. Since a rise in α_n decreases the expectation of a closed n-gate staying closed and a reduction in $\beta_n$increases the chances of an open n-gate to be open, a positive δV is producing a positive change in the gating inconstant n. This progress, similar to Ω_k^v, Ω_k^n also achieves a negative value.

4.2 The relationship between NCCP and the sodium channels

The concept that displays the gate-to-channel uncertainty linked with the sodium channels is $\psi_{Na} - [\psi_{Na}]$. At this point, the structure medium of the ratio of open sodium channels, $[\psi_{Na}]$, becomes.

$$[\psi_{Na}] = \frac{(3N_{Na}m - 2)(3N_{Na}m - 1)m}{(3N_{Na} - 2)(3N_{Na} - 1)}h, \text{ if } N_{Na}m \geq 1 \qquad (30)$$

$[\psi_{\mathrm{Na}}] = 0$, otherwise. Only if the membrane is very tiny in size, it is considered as

$$[\psi_{\mathrm{Na}}] \approx m^3 h \qquad (31)$$

When we have a set membrane with infinite size, the HH value $\psi_{Na} = [\psi_{Na}] = m^3 h$ applies at all times. The main order variable related to the sodium channels, Ω_{na}^v, is provided by.

$$\Omega_{Na}^{V} = \frac{\left\langle (\psi_{Na} - [\psi_{Na}])V \right\rangle - \left\langle \psi_{Na} - [\psi_{Na}] \right\rangle \left\langle V \right\rangle}{\left\langle [\psi_{Na}] \right\rangle (E_{Na} - E_K)}. \qquad (32)$$

The experiments (Güler, 2013) showing that Ω_{na}^{v} gets positive values and constantly is still in positive, within the phase of sub-threshold action. This is only for the near-equilibrium dynamics, a non-trivially continual correlation gets placed amongst the fluctuations of the construct $\psi_{Na} - [\psi_{Na}]$ and the changes of V remarking that the sign of Ω_{na}^{v} is conflicting with the sign of Ω_{k}^{v}. It is because of the signs of $V - E_k$ and $V - E_{na}$ in equation (23) are opposite at any moment, the previous is positive and the latter is negative.

4.3 Major impact of NCCP

It was expected that the NCCP would increase in the diversity of the amplitude of sub-threshold voltage fluctuations by increasing the probability of fluctuations with bigger amplitudes which is covered in depth in Güler, 2013. After that, it was demonstrated that the diversity in making easier for the cell's spiking through forcing the passing from the firing to the sub-threshold phase became simpler. On the other hand, it was found that limited scale membranes were beholden their upraised irritability not only to the gate noise but, to a larger range, as well as to NCCP. Furthermore, NCCP was noticed to improve the consistency in spiking.

Chapter 5

THE COLORED NOISE MODEL FORMULATIONS

The colored stochastic Hodgkin Huxley equations (Güler, 2013), where the NCCP phenomenon and the gate noise are included, as given bellow:

$$C\dot{V} = -g_K\psi_K(V - E_K) - g_{Na}\psi_{Na}(V - E_{Na}) \quad (33)$$

$$- g_L(V - E_L) + I \quad (34)$$

$$\psi_K = n^4 + \sqrt{\frac{n^4(1-n^4)}{N_K}}\, q_K \quad (35)$$

$$\psi_{Na} = m^3 h + \sqrt{\frac{m^3(1-m^3)}{N_{Na}}}\, h\, q_{Na} \quad (36)$$

$$\tau\dot{q}_K = p_K \quad (37)$$

$$\tau\dot{p}_K = -\gamma_K p_K - \omega_K^2[\alpha_n(1-n) + \beta_n n]q_K + \xi_K \quad (38)$$

$$\tau\dot{q}_{Na} = p_{Na} \quad (39)$$

$$\tau\dot{p}_{Na} = -\gamma_{Na} p_{Na} - \omega_{Na}^2[\alpha_m(1-m) + \beta_m m]q_{Na} + \xi_{Na} \quad (40)$$

$$\dot{n} = \alpha_n(1-n) - \beta_n n + \eta_n \quad (41)$$

$$\dot{m} = \alpha_m(1-m) - \beta_m m + \eta_m \quad (42)$$

$$\dot{h} = \alpha_h(1-h) - \beta_h h + \eta_h \quad (43)$$

Where the Gaussian white-noise terms have zero means, and their mean squares obey.

$$\left\langle \xi_K(t)\xi_K(t') \right\rangle = \gamma_K T_K[\alpha_n(1-n)+\beta_n n]\,\delta(t-t') \quad (44)$$

$$\left\langle \xi_{Na}(t)\xi_{Na}(t') \right\rangle = \gamma_{Na} T_{Na}[\alpha_m(1-m)+\beta_m m]\,\delta(t-t') \quad (45)$$

$$\left\langle \eta_n(t)\eta_n(t') \right\rangle = \frac{\alpha_n(1-n)+\beta_n n}{4N_K}\,\delta(t-t') \quad (46)$$

$$\left\langle \eta_m(t)\eta_m(t') \right\rangle = \frac{\alpha_m(1-m)+\beta_m m}{3N_{Na}}\,\delta(t-t') \quad (47)$$

$$\left\langle \eta_h(t)\eta_h(t') \right\rangle = \frac{\alpha_h(1-h)+\beta_h h}{N_{Na}}\,\delta(t-t'). \quad (48)$$

When the membrane size is limited of infinite, it can be observed that the set of equation shrink to the HH equations. The constant parameters in the model were not appraised analytically. The values of the parameters were estimated by phenomenological methods through numerical experiments, as given in Table 2 below. It was concluded that the dynamics enforced by the equation in not reactive to the constant parameter values.

The colored noise terms in eq. (35) and eq. (36) serve the purpose of capturing NCCP. The white terms in eq. (41) - (43) correspond to gate noise.

Table 2: Constant parameters of the model (Güler, 2013)

$\gamma_K = 10$	$\omega^2{}_k = 150$	$T_k = 400$
$\gamma_{Na} = 10$	$\omega^2{}_{Na} = 200$	$T_{Na} = 800$

Chapter 6

RESULTS AND DISCUSSION

In this part, the efficiency of the colored noise model will be discussed through a series of experiments, by comparing the colored noise model with the microscopic simulations. The simple stochastic method was used as the microscopic simulations scheme (Zeng, 2004). This method is simply applying a Markovian process to simulate each gate individually and continue for the rest of the gates. The input current in the simulation was a periodic sin wave under time variation.

$$I = A\ \sin(\omega t) \tag{49}$$

$$\omega = 2\,\pi\,f \tag{50}$$

The aim of this work is to investigate the effect of the cross-correlation persistency placed in the trans-membrane voltage fluctuation by adding the colored noise terms (Güler, 2013) into the conductance of the stochastic Hodgkin Huxley equations. Many of experiments are used to assess the colored noise model effectiveness, in a comparative manner with the Microscopic simulation as mentioned before (Zeng, 2004), by firstly running he experiments without including the colored noise model into the stochastic of the Hodgkin Huxley equations, and secondly running the experiments with the same parameters but at this time, the colored noise model is included in the stochastic of the HH equations. As given in formula (49) there are two variables

amplitude (A) and frequency equation (50) define the sinusoidal current under time, so the experiments are divided into two categories; first dealing with the amplitude and second with the frequency.

Through what have been clarified by figures 6, 7, and 8, the changes with the amplitude and the frequency are fixed at the beginning when the amplitude of the signal is small. There will be a difference between the spikes' frequency of the HH equations without the colored noise and the HH equation stochastic with the colored noise included, which consists of the spikes that form the microscopic simulation. As mentioned before the main reason behind this difference is the NCCP affects. But when the amplitude increases the difference between the spikes frequency becomes smaller. On the other hand, when the input current frequencies are applied in the experiments, the amplitude is fixed. It can be seen from the results which at the beginning that there are no difference in the spikes' frequencies that are generated from the experiments. But at a certain point of input current frequency, mostly around (0.08) Hz, the response of the HH stochastic without the colored noise drop out remains at low level even when the frequency of input current is increased. If the colored noise model is included in the equations, it is noticeable that the spikes' frequencies generated from the experiments are very consistent with the ones from microscopic simulation.

Technologies used

A computer program that solves the model eqns. (35, 36) numerically was developed by Güler. In the program, the input current was time independent which was modified so that the program could handle time dependent current. The model was developed by using C++ programing language, and MATLAB was used for plotting the results.

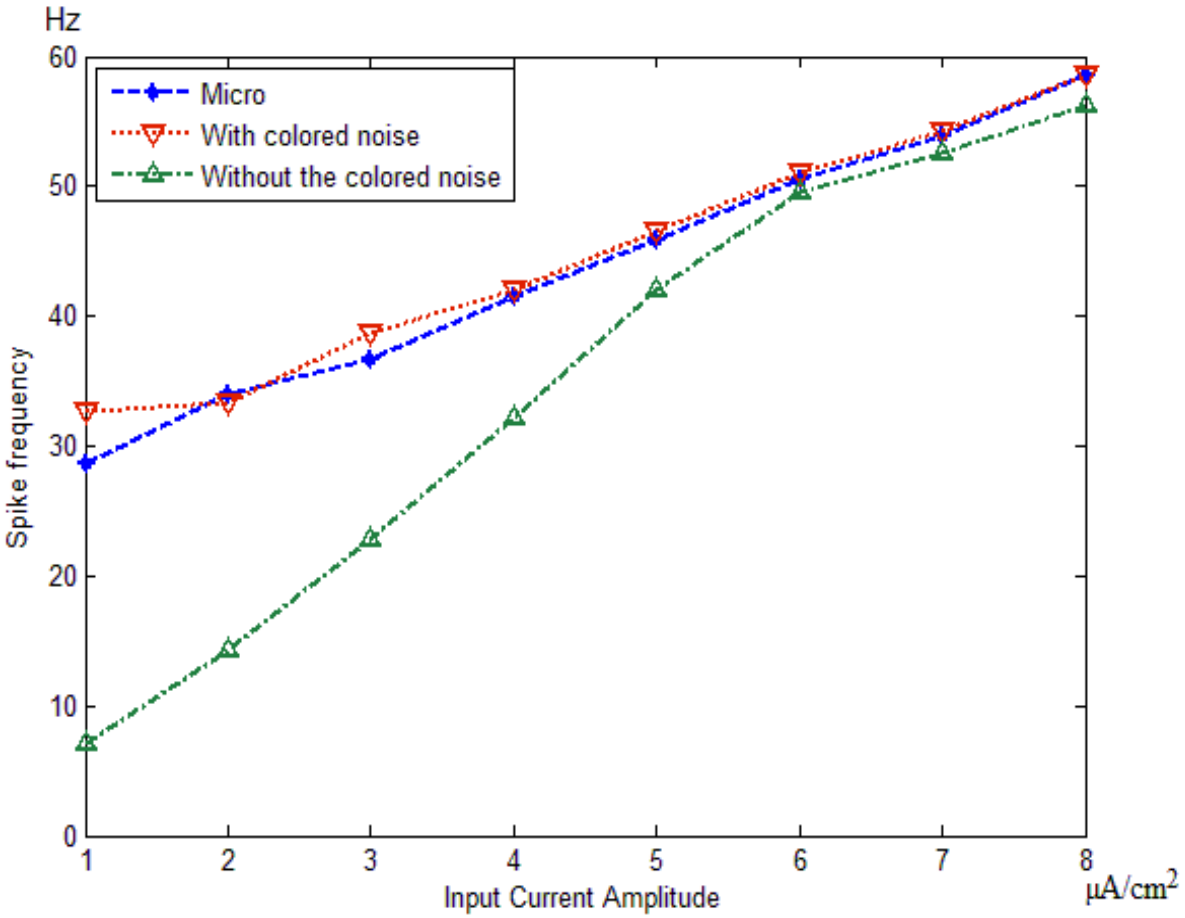


Figure 6: Result of amplitude changing when membrane size is (600, 2000)

It is as depicted in eq. (49) by changing (A) while the frequency is fixed, the three curves represent the competition between the microscopic simulation with the HH equation and the colored noise. It can be seen that the colored noise has worked similarly to the microscopic simulations. The membrane size for potassium is 600 and for sodium, it is 2000 and I base = 0, in 5 seconds time window.

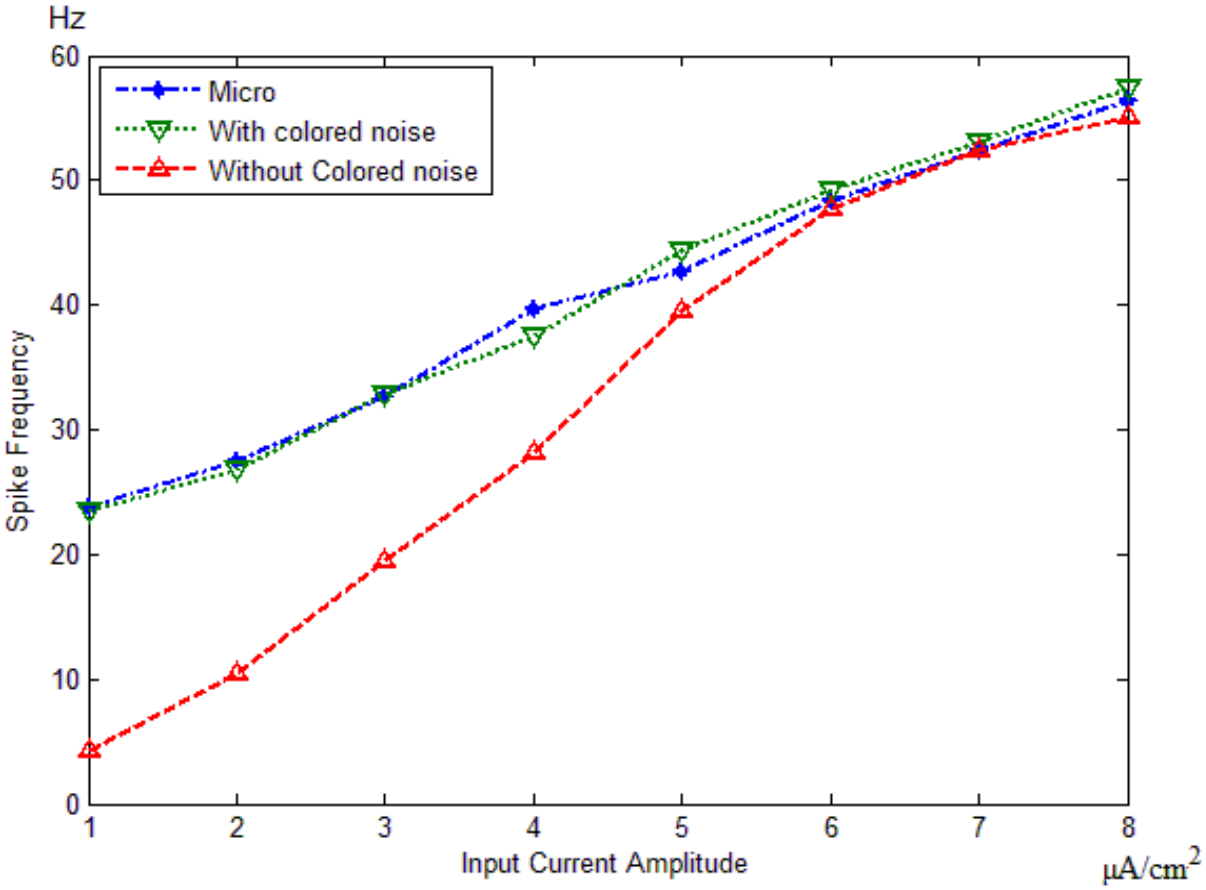


Figure 7: Result of amplitude changing when membrane size is (1200, 4000)

According to eq. (49), (A) increases each time measuring the frequency of spikes, showing the membrane size for potassium is 1200 channel and for sodium is 4000 channel, I base =0. In addition, the three curves represent the competition between the microscopic simulation with the HH equation and the colored noise. It can be observed that the colored noise model has worked similarly to the microscopic simulations, in 5 seconds time window.

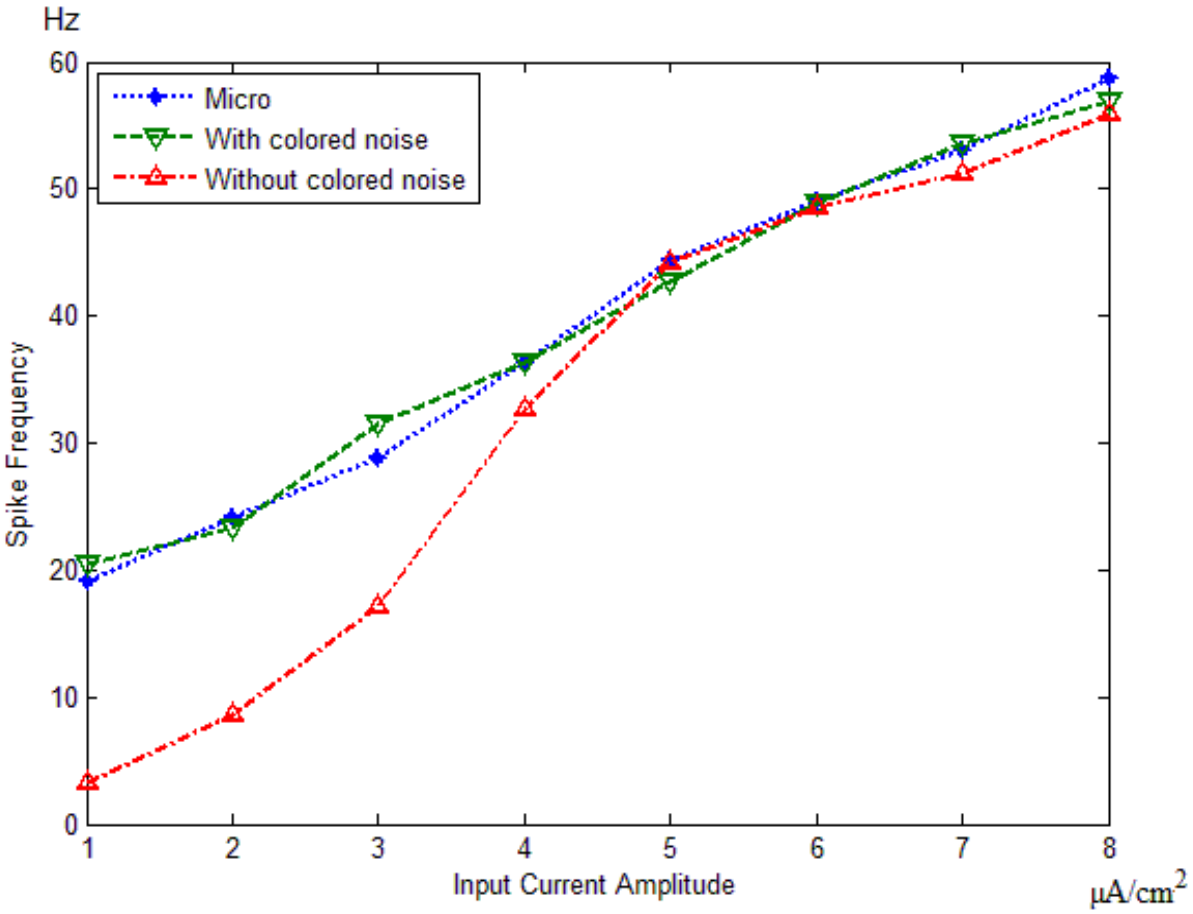


Figure 8: Result of amplitude changing when membrane size is (1800, 6000)

In this figure the three curves represent the competition between the microscopic simulation with the HH equation and the colored noise and also the colored noise model works in a very similar way with the microscopic simulations in which the membrane size for potassium is 1800 channel, for sodium is 6000 channel, I base =0 and the simulation time window is 5 seconds.

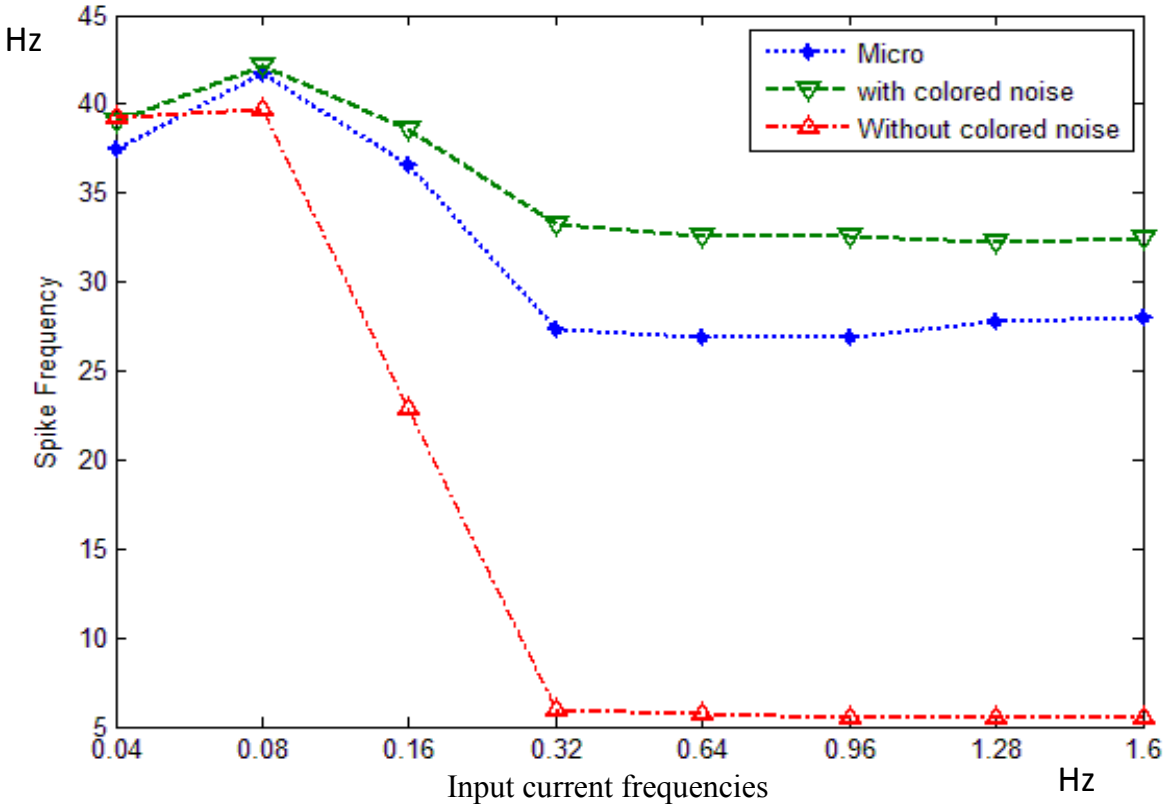


Figure 9: Result of the applied frequencies membrane size is (600, 2000)

As can be seen in the Figure the three curves represent the competition between the microscopic simulation with the HH equation and the colored noise. The figure shows that the colored noise model has worked similarly to the microscopic simulations. The membrane size for potassium is 600 channel and for sodium is 2000 channel, with I base =0 in 5 seconds time window.

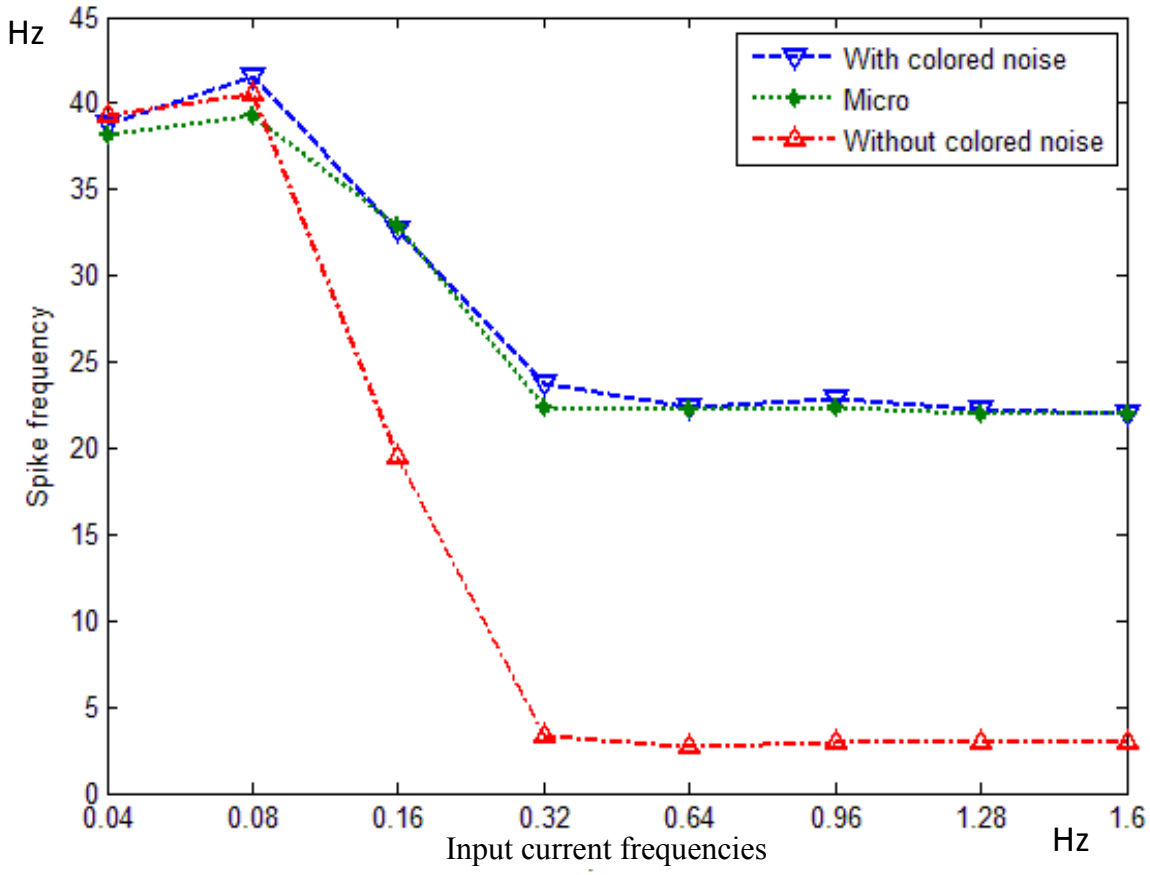


Figure 10: Result of the applied frequencies membrane size is (1200, 4000)

Here in the figure, the three curves represent the competition between the microscopic simulation with the HH equation and the colored noise and also the colored noise model is very convergent to the microscopic simulations even when the frequency increasing eq.(50). Unlike the HH equation, the membrane size is for potassium 1200 and for sodium 4000, I base =0, in 5 seconds time window.

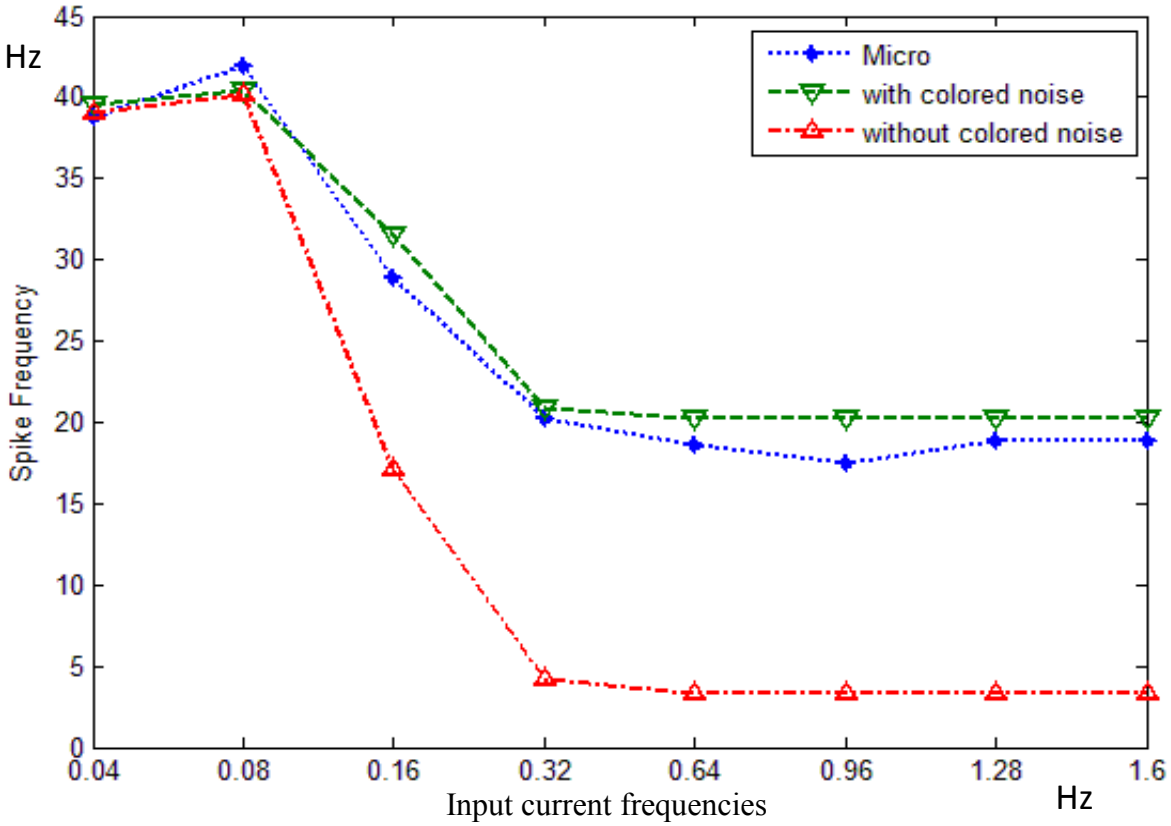


Figure 11: Result of the applied frequencies membrane size is (1800, 6000)

This figure shows the three curves of the competition between the microscopic simulation with the HH equation and the colored noise. As expected, the colored noise model has responded perfectly in comparison with the microscopic simulations even when the frequency increases. The membrane size in the simulation for potassium is 1800 channel and for sodium is 6000 channel, I base =0, in 5 seconds time window.

Chapter 7

CONCLUSIONS

In this thesis, the colored noise neuron model was studied under the influence of varying input signal. In the earlier work (Güler, 2011), it was found out that in the single ion channels, the multiplicity of the gates plays an important role which in turn motivate the NCCP (non-trivially cross correlation persistent) and the earlier found to be the main reason in the unusual increases in the cell excitability and in the spontaneous firing in the small membrane size. Furthermore, it was found that the NCCP carries on promoting the spontaneous firing even when the membrane size is large wherever the gate to noise is inefficient to activate the cell. This study has shown that the enhancement of the spike coherence has been caused by the presence of the NCCP.

Our experiments show that, the colored noise model handles the phenomenon of the NCCP properly and also it can be seen that the spiking rate generated from the model is very close to the one from the actual simulation, whatever the membrane size is. When the amplitude was changing the model, spiking rate was not affected unlike the HH model which was very far from the actual neuron spikes as in figures (6, 7 and 8).When applying different frequencies, the spikes that generated from the colored model, were also very close to the one from microscopic simulations. However, in the HH equation when the colored model was not included, the spikes that were generated were very low

when compared to the spikes from the model even though there was an increase in the frequency as in figures (9,10and 11) in which this situation remained stable at this condition.

Since the colored noise model has been studied in this thesis, investigating under varying input currents, the input current is periodic having constant noise applied on it. What missing perhaps is investigating the colored noise model under none periodic input current and see how the colored noise model handles the phenomenon of the NCCP. Alternatively, applying a kind of noise on the input current can shed more light on the behavior of the colored noise model under time varying.

It should be noted here that applying the amplitude changing with different noise variances to see how the colored noise model would handle the amount of the noise is another option. Furthermore, it is also possible to apply the frequencies that are used in the experiments with varying noise and see how the model would reply. Last but not least, applying a different frequency which is more like between the frequencies that applied in the experiments or a different scale is also worth investigating.

REFERENCES

Abbot, D. P. (2002). *Theoretical Neuroscience Computation and Mathematical Modeling of Neural System.* MIT press.

Bezrukov, S. &. (1995). *Noise-induced enhancement of signal transduction across voltage-dependent ion channels.* Nature, 378, 362–364.

Chow, C. C. (1996). *Spontaneous action potentials due to channel fluctuations.* Biophysical Journal, 71,3013–3021.

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.

Diba, K. L. (2004). *Intrinsic noise in cultured hippocampal neurons: Experiment and modeling.* Journal of Neuroscience, 24, 9723–9733.

Dorval, A. D. (2005). *Channel noise is essential for perithreshold oscillations in entorhinal stellate neurons.* Journal of Neuroscience, 25, 10025–10028.

Faisal, A. A. (2007). *Stochastic simulations on the reliability of action potential propagation in thin axons.* PLoS Computational Biology, 3, 79.

Faisal, A. S. (2008). *Noise in the nervous system.* nervous system. Nature Reviews Neuroscience, 9, 292–303.

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.

Güler, M. (2008). *Detailed numerical investigation of the dissipative stochastic mechanics based neuron model.* Journal of Computational Neuroscience, 25, 211–227.

Güler, M. (2011). Persistent membranous cross correlations due to the multiplicity of gates in ion channels. *Journal of Computational Neuroscience ,31,713-724.*

Güler, M. (2013). Stochastic Hodgkin-huxley equations with colored noise terms in the conductances. *Neural Computation .25:46-74, 2013.*

Hille, B. (2001). *Ionic channels of excitable membranes (3rd ed.).* Massachusetts: Sinauer Associates.

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.

Izhikevich, E. M. (2007). *Dynamical Systems in Neuroscience:The Geometry of Excitability and Bursting.* MIT press.

Jacobson, G. A. (2005). *Subthreshold voltage noise of rat neocortical pyramidal neurones.* Journal of Physiology, 564,145–160.

Johansson, S. &. (1994). *Single-channel currents trigger action potentials in small cultured hippocampal neurons.* Proceedings of National Academy of Sciences USA, 91, 1761–1765.

Jung, P. &. (2001). *Optimal sizes of ion channel clusters.* Europhysics Letters, 56, 29–35.

Koch, C. (1999). *Biophysics of computation: Information processing in single neurons.* Oxford University Press.

Kole, M. H. (2006). *Single Ih channels in pyramidal neuron dendrites: Properties, distribution, and impact on action potential output.* Journal of Neuroscience, 26, 1677–1687.

Lynch, J. &. (1989). *Action potentials initiated by single channels opening in a small neuron (rat olfactory receptor).* Biophysical Journal, 55, 755–768.

Ochab-Marcinek, A. S. (2009). *Noise-assisted spike propagation in myelinated neurons.* Physical Review E, 79, 011904(7).

Özer, M. (2006). *Frequency-dependent information coding in neurons with stochastic ion channels for subthreshold periodic forcing.* Physics Letters A, 354, 258–263.

Rowat, P. F. (2004). *State-dependent effects of Na channel noise on neuronal burst generation.* Journal of Computational Neuroscience, 16, 87–112.

Rubinstein, J. (1995). *Threshold fluctuations in an N sodium channel model of the node of Ranvier.* Biophysical Journal,68, 779–785.

Sakmann, B. &. (1995). *Single-channel recording (2nded.).* New York: Plenum.

Schmid, G. G. (2001). *Stochastic resonance as a collective property of ion channel assemblies.* Europhysics Letters, 56, 22–28.

Schneidman, E. F. (1998). *Ion channel stochasticity may be critical in determining the reliability and precision of spike timing.* Neural Computation, 10, 1679–1703.

Segev I., J. M. (2003). *Cable and compartment models of dendritic trees in bower.* The book of genesis 5:55, 2003.

Sigworth, F. J. (1980). *The variance of sodium current fluctuations at the node of Ranvier. Journal of Physiology.* (London Print), 307, 97–129.

Strassberg, A. F. (1993). *Limitations of the Hodgkin–Huxley formalism: Effects of single channel kinetics on transmembrane voltage dynamics.* Neural Computation 5, 843–855.

Whishaw, K. B. (2012). *Fundamentals of Human Physiology FOURTH EDITION*. Virginia United States.

White, J. A. (1998). *Noise from voltage-gated ion channels may influence neuronal dynamics in the entorhinal cortex.* Journal of Neurohysiology, 80, 262–269.

Zeng, S. &. (2004). Mechanism for neuronal spike generation by small and large ion channel clusters. *Physical Review E, 70, 011903(8).*