A Comparative Study on 'The Colored Stochastic HH Equations' and 'The Minimal Diffusion Formulation'

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ABSTRACT

The voltage-gated ion-channels within the membranes facilitate the excitability of neurons. These channels accommodate a multiple number of gates individually. The number of open channels fluctuates with profound effects on the transmembrane voltage activity in small-size excitable membrane patches. Two recent models that can capture the collective dynamics of ion channels in excitable membranes are:

1.) The colored stochastic Hodgkin-Huxley equations [1]
2.) The minimal diffusion formulation of Markov chain ensembles [2]

In this thesis, a comparative study on these two models was performed by numerical simulations. The statistics of the mean inter-spike interval (ISI), coefficient of variation and spike latency were used in the investigation. The obtained results are useful for better understanding of the efficiency of these models. Computation times of the models were also investigated.

Our study shows that the Minimal Diffusion model generally yields more accurate results than the already satisfactory Colored Noise model. To determine the accuracy of the models, the model results are assessed with reference to the corresponding Microscopic Simulation (Monte Carlo) model results. Our simulations confirm that the Minimal Diffusion model requires less computation time than the Colored Noise model. Our findings indicate that the Minimal Diffusion model should be preferred to the Colored Noise model.

Keywords: Ion channel, Channel noise, Colored noise, Stochastic Hodgkin-Huxley, Markov Chain, Minimal diffusion formulation

ÖZ

Hücre zarında bulunan ve voltaj bağımlı geçirgenlik sergileyen iyon kanalları nöron uyarılmasını sağlar. Her kanal birden fazla geçit içerir. Açık kanal sayısı zaman içinde gürültülü ve dalgalı bir görünüm sergiler ve bu davranış küçük boyutlu nöron dinamiği üzerinde hayati etki yapabilmektedir.

Son yıllarda, toplu nöron dinamiği üzerine ortaya konulan iki model şöyledir:

1.) Renklendirilmiş stokastik Hodgkin-Huxley denklemleri [1]

2.) Minimal difüzyon Markov zincir formülasyonu [2]

Bu tezde, yukarıdaki iki model sayısal benzeşim yöntemiyle karşılaştırmalı olarak çalışılmıştır. Ortalama ateşleme aralığı (ISI), varyasyon katsayısı ve gecikme istatistikleri incelenmiştir. Ayrıca, iki modelinde hesaplama zamanı gereksinimleri ortaya konmuştur. Çalışmamız, Minimal difüzyon Markov zincir formülasyonu'nun Renklendirilmiş stokastik Hodgkin-Huxley denklemlerine göre daha iyi sonuçlar verdiğini göstermiştir. Karşılaştırmalar, mikroscopik benzeşim sonuçları baz alınarak yapılmıştır.

Anahtar Kelimeler: İyon kanalı, Kanal gürültüsü, Renkli gürültü, Stokastik Hodgkin-Huxley, Markov zinciri, Minimal difüzyon formülasyonu

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LIST OF SYMBOLS AND ABBREVIATIONS

Col	Colored Noise Model
DA	Diffusion Approximation
HH	Hodgkin-Huxley
ISI	Inter Spike Interval
MC	Monte Carlo Model(Microscopic Simulation)
MD	Minimal Diffusion Model
NCCP	Nontrivial Cross-Correlation Persistency
SDE	Stochastic Differential Equation

Chapter 1

INTRODUCTION

1.1 Introduction

In all type of the cells, there is electrical potential between interior and exterior surface of the cell membrane. While this potential exists in all the cells in the body, it's especially important in brain and nervous system; because, in these type of cells, membrane potential is used to transmit the information between the cells. Dynamics of the membrane mainly is the changes of this potential over the time. Studying on the dynamics of the neurons is not possible without considering the dynamics of the Ion-Channels. These channels are playing a great role in the dynamic of the cell and specially in the membrane potential. The stochastic behavior of the channels has been considered for decays, especially in the recent years. Hodgkin and Huxley in 1952 discovered a set a equations [3] that for a long time has been the most accepted equations for describing the behavior of a single neuron. For many years their formulation was in widespread use and, it's still the basement for many other proposed methods. In their equations changes in membrane potential is calculated based on the current which is injected into the cell. They found out that the voltage of the membrane has direct relation to the number of open channels. However, it has been found later that opening and closing of the gates in an Ion-Channel is random [4]. and, small fluctuation in the number of open gates can directly affect the spike pattern [5]. Numerical simulations showed that in a small enough membrane these small fluctuations can cause spontaneous firing of spikes [5]. This experiment then repeated

in real neurons [6]. HH set of equations is unable to produce this spontaneous firing in absence of the input current and it was the motivation for others to improve their set of equations.

In a paper, Kurtz [7] has been shown how to replace stochastic Markov chain process with a system of stochastic equations (an SDE Model). In 1994 Fox and Lu [8] rediscovered their approach to extended the Hodgkin-Huxley (**HH**) equations to a set of Stochastic Differential Equations (SDE) [8]. They added additional Gaussian white noise terms to the original HH equations. The noise in their implementation is voltage-dependent with mean zero. Although, their work was able to reproduce the ion-channel noise effect in the HH equations, its results were not accurate enough [9]. In 2013 Güler [1] used Fox and Lu set of equations and extend it to a better estimation of the dynamics of the membrane. Before this work Güler introduced **NCCP** as the source of the noise in the neuron [10]. NCCP refers to the gate to channel uncertainty which exists when we are interested in the number of open channels, by having the number of open gates in hand. He showed that the number of open gates in the membrane is not suffice to know the number of open channels and, there is an uncertainty in this number which is the source of inaccuracy of the previously proposed methods. Then he implemented a set of equations which were aware of NCCP. He shows in that paper [1] that his formulation is much more accurate than the Fox and Lu equations. There, he argued that the failure of Fox and Lu's stochastic HH equations to produce accurate enough spike generation statistics, is that these equations cannot capture NCCP. His result was much closer to the results from **Microscopic Simulation** in compare to the results from the Fox and Lu equations. Microscopic Simulation or Monte Carlo [11] is the most accurate method to describe the dynamics of the ion-channels in which, a continues time – discrete state **Markov Chain** is considering for each single channel

in the membrane patch. Any possible situation of the channel in a given time, then will be considered as a state of that chain, in that time. It enables high accuracy in calculation of the dynamics of the channel. However, the drawback of this method is computing efficiency. As the number of channels in the patch is growing, the computing time of the simulation is increasing almost linearly. For instance one second simulation of neuron behavior for a membrane of size $1000\mu m^2$ can longs for a year in a normal computer. That was the motivation for the scientists to propose a method to estimate the membrane potential or any other interested parameter of the cell. SDEs (Stochastic Differential Equations) are widely used for that purpose. A stochastic differential equation (SDE) is a differential equation in which, one or more term(s) are stochastic. In estimation methods, the challenge is to develop a balance between the accuracy and computation time.

Güler in 2013 [1] has extended Fox and Lu SDE equations. Here we did a comparison between this method (From now on we will call it Colored Noise model) and another method proposed by Güler in 2015 [2] (From now on we will call it Minimal Diffusion model). **Minimal Diffusion** is another approach of estimation. A Diffusion Approximation is a technique in which, an analytically untraceable and complicated stochastic process is replaced by a **Diffusion Process**. A diffusion process is a Markov process that has continues sample paths and, it's more mathematically traceable than the original process. Güler in 2015 in his Minimal Diffusion model, has considered an ensemble of Markov Chains and proposed a model to estimate the dynamic of the ion-channels using diffusion process. The chain in which, ensembles are assumed to evolve independent of each other.

When the number of ion-channels is big enough, Hodgkin-Huxley equations provide good description of behavior of the cell. In their formulation some parameters are related to the proportion of number of open channels over the total number of channels of that type. These parameters are based on the probability of the single gate in the channel to be open or close. This is the place that NCCP is happening. Because, as we mentioned above, the number of open gates is not sufficing for calculating the number of open channels. That will cause a fluctuation in number of open gates in channels and, this fluctuation is affecting the potential of the cell. It has been shown that even opening a single channel can directly affect pattern of spiking [5]. Major source of this noise is finite number of the ion-channels. Even in the big neurons, opening and closing small number of gates, can force the neuron to spike. [12] It can happen specially in the moments in which, membrane potential is near the threshold. In that moment the small number of gates are open, so opening or closing of a gate can make the neuron to spike or not; even in presence of large number of ion-channels. It has been found out that understanding dynamic of the neurons cannot be achieved without bringing this noise into consideration. The Minimal Diffusion model (MD) and Colored Noise model (Col), both are trying to describe evolution in membrane potential by considering this noise into the HH equations. In this paper, we numerically compared the efficiency and accuracy of these two models and, we did a comparison between the results of these two models and the results from Microscopic Simulation (MC).

Widely used approach to calculate neuron simulation accuracy is measuring the mean of **ISI** in an acceptable duration (Spike Density). ISI or Inter Spike Interval is the time between two consecutive spikes. Because, the happening of the spikes is stochastic, they cannot be compared using the normal signal processing techniques. ISI mean and

Mean spiking rate are used widely to compare neuron simulation methods, although, they are not able to capture the difference between bursting or tonic firing. So we use another property to compare simulation methods. Coefficient of Variation measures the amount of variability from the mean and, it can capture this type of differences effectively. Also, we considered to plot ISI distribution of the different membrane sizes in different conditions for each simulation method. All the simulation results are compared to the Microscopic Simulation results to compare the accuracy. Simulations were run in the same environment and the time of simulations were chosen to be long enough for getting reliable results.

It's also useful to compare the computation time of each Model. Computation time is an important issue in simulations. To achieve this, we ran the simulation code of each model on the same device under the same conditions and we made a comparison among them in Chapter 4.

In following chapters, we give a brief description about the Minimal Diffusion model and Colored Noise model. In Chapter 2 we explained "Stochastic Hodgkin-Huxley Equations with Colored Noise Terms in the Conductance" briefly (Colored Noise model); Minimal Diffusion model or precisely "Minimal diffusion formulation of Markov chain ensembles and its application to ion channel clusters" is described in Chapter 3. Chapter 4 is specified to the numerical results of the models and, the comparison between them. And we came to a conclusion in Chapter 5.

Chapter 2

COLORED NOISE IN HODGKIN-HUXLEY EQUATIONS

2.1 NCCP as a Source of the Ion-Channels Noise

For better understanding of NCCP, suppose a toy cell with two Potassium channels. As we know, a channel is open only when all of its gates are open. There are 4 n-gates in a potassium channel. Suppose a state that this cell has 6 open gates. There are many possible states for a cell with this number of open gates. One of the states can be the situation in which, each of the two channels has 3 open gates and 1 close gate. In that state, both channels are closed. Now, suppose other state of this cell in which, one channel has 4 open gates and the other channel has 2 open gates. Although, here the same number of gates are open, one channel is open and the other is closed (See Figure 2.1). This example is pretty well showing that the number of open channels is not suffice to calculate the number of open channels in the membrane patch (See [10]). This phenomenon causes small differences between the calculated number of open channels in the simulation using HH equations and the number from the result of microscopic simulation. It has been shown that there is a correlation between fluctuation in number of open channels and fluctuation in membrane potential [10].

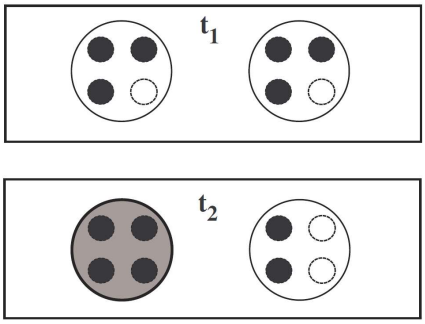

Figure 2.1: Showing two different states of a cell with two channels and six open gates. In state t_1 both channels are closed and in state t_2 one channel is open and the other is closed. Big white circles are close channels, Big grey circles are open channels, black small circles are open gates and white small circles are closed gates. Adopted from [10]

2.2 Colored Noise Model

In this model, dynamics of membrane potential is defined using this formulation [3]:

$$C\dot{V} = -g_K\psi_K(V - E_K) - g_{Na}\psi_{Na}(V - E_{Na}) - g_L(V - E_L) + I \tag{2.1}$$

Letter I in formulation denoted the injected input current and Table 2.1 contains the constants of this equation.

Table 2.1: Membrane Constants

C	Membrane capacitance	$1\,\mu F/cm^2$
g_K	Maximal potassium conductance	$36\,mS/cm^2$
E_K	Potassium reversal potential	$-12\,mV$
g_{Na}	Maximal sodium conductance	$120\,mS/cm^2$
E_{Na}	Sodium reversal potential	$115\,mV$
g_L	Leakage conductance	$0.3\,mS/cm^2$
E_L	Leakage reversal potential	$10.6\,mV$
	Density of potassium channels	$18\,chns/\mu m^2$
	Density of sodium channels	$60\,chns/\mu m^2$

ψ_K and ψ_{Na} are variables corresponds to the dynamic of the channel. ψ_K is the proportion of open potassium channels to all potassium channels and ψ_{Na} is the proportion of open sodium channels to all sodium channels. The value of ψ_K in HH equations is determined by n^4 which n is gating rate of potassium channels. Similarly, ψ_{Na} is determined by m^3h in which, m and h are the gating rate of sodium channel. In Colored Noise model, noise terms are added to this formulation and, these variable are approximated as a fraction of the number of open potassium and sodium channels. As the number of channels increases, noise terms are converging to zero and these variables converge to their deterministic values in HH equations. As we mentioned earlier, there is a correlation between the fluctuations produced by the uncertainty in the channels and the fluctuations in the potential of the membrane. In Colored Noise model, it has been shown that the autocorrelation time of the fluctuations is finite but not zero. Also, it's stated that $\psi_K - [\psi_K]$ shows this fluctuation; where […] denoted the average over all possible configuration of a cell having $4N_K n$ open gates. For big enough membrane size $[\psi_K] \approx n^4$. As it is illustrated in Figure 2.2 the algebraic sign of $\psi_K - [\psi_K]$ doesn't change for a long enough period.

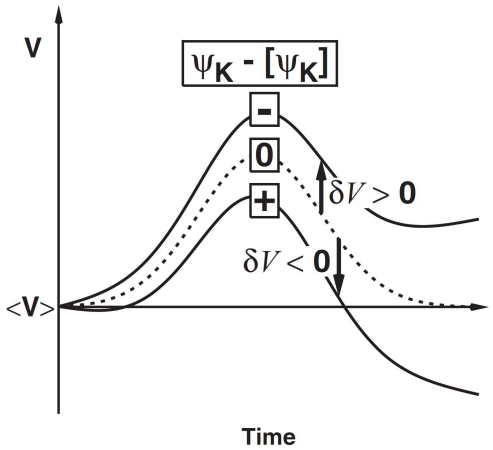

Figure 2.2: Variation in voltage of membrane and $\psi_k - [\psi_k]$ in time. Adopted from [10]

It's reasonable to describe the model for Potassium Channels and Sodium Channels separately.

2.2.1 Dynamics of Potassium Channels

We can define:

$$\psi_K = [\psi_K] + Q_K, \tag{2.2}$$

Because the sign of Q_K doesn't change in microscopic time step and Q_K is not zero. Then, Q_K would be a stochastic variable with autocorrelation greater than zero and zero expectation value at equilibrium. Therefore, it has the specification of a colored noise and, it can be approximated as:

$$\psi_K = n^4 + \sigma_K q_K \tag{2.3}$$

Here q_K is a new stochastic variable. σ_K is standard deviation of ψ_K and can be calculated from all possible configurations of a membrane with $4N_K n$ open gates; but for make it easier to calculate, the restriction of having exactly $4N_K n$ open gates in each configuration has been omitted, and we suppose that in each configuration all gates open with the probability of n. Without considering these constraints σ_K would be:

$$\sigma_K = \sqrt{\frac{n^4(1-n^4)}{N_K}} \tag{2.4}$$

Here, n^4 is the probability of a channel being open and, the formulation of random walk is employed. As we can see σ_K vanishes for small n/N_K or in another word for large membrane patches.

q_K is determined using the following Differential Equations:

$$\tau \dot{q}_K = p_K$$
$$\tau \dot{p}_K = -\gamma_K p_K - \omega_k^2 D_n q_K + \varepsilon_K, \tag{2.5}$$

Where

$$D_n \coloneqq \alpha_n(1-n) + \beta_n n, \tag{2.6}$$

α_n and β_n are described in Equation (2.10) and, ε_K is a Gaussian white noise with mean zero and variance:

$$\langle \varepsilon_K(t)\varepsilon_K(\acute{t})\rangle = \gamma_K T_k D_n \delta(t-\acute{t}). \tag{2.7}$$

Parameter τ is corresponding to time unit. γ_K, ω_K and T_k are dimensionless constants which are defined in Table 2.2.

Table 2.2: Colored Noise Constants For Potassium Channels

$\gamma_K = 10$	$\omega_K^2 = 150$	$T_k = 400$

We also need to care about the gate noise here. In Colored Noise model gating dynamics for Potassium channels is described in following terms:

$$\dot{n} = \alpha_n(1-n) - \beta_n n + \eta_n, \tag{2.8}$$

Where η_n is a Gaussian mean zero white noise with variance:

$$\langle \eta_n(t)\eta_n(\acute{t})\rangle = \frac{D_n}{4N_K}\,\delta(t-\acute{t}). \tag{2.9}$$

α_n and β_n in all above equation are defined as follows:

$$\alpha_n = \frac{(0.1 - 0.01V)}{e^{(1-0.1V)} - 1}$$
$$\beta_n = 0.125e^{\frac{-V}{80}}. \tag{2.10}$$

2.2.2 Dynamics of Sodium Channels

Same formulation is valid for the Sodium channels as well:

$$\psi_{Na} = [\psi_{Na}] + Q_{Na}, \tag{2.11}$$

So ψ_{Na} can be approximated as:

$$\psi_{Na} = m^3\mathrm{h} + \sqrt{\frac{m^3(1-m^3)}{N_{Na}}}hq_{Na}. \tag{2.12}$$

Evaluation of the q_{Na} can be traced using the following SDEs:

$$\tau\dot{q}_{Na} = p_{Na}$$
$$\tau\dot{p}_{Na} = -\gamma_{Na}p_{Na} - \omega_{Na}^2 D_{Na}q_{Na} + \varepsilon_{Na}. \tag{2.13}$$

ε_{Na} is a zero mean Gaussian white noise with mean square:

$$\langle\varepsilon_{Na}(t)\varepsilon_{Na}(\acute{t})\rangle = \gamma_{Na}T_{Na}D_m\delta(t-\acute{t}) \tag{2.14}$$

γ_{Na}, ω_{Na} and T_{Na} constants are defined in Table 2.3 and, D_m and D_h are as following:

$$D_m \coloneqq \alpha_m(1-m) + \beta_m m,$$
$$D_h \coloneqq \alpha_h(1-h) + \beta_h h. \tag{2.15}$$

Gating noise for sodium channels is described as:

$$\dot{m} = \alpha_m(1-m) - \beta_m m + \eta_m$$
$$\dot{h} = \alpha_h(1-h) - \beta_h h + \eta_h, \tag{2.16}$$

Where η_m and η_h are Gaussian white noise with mean zero and mean square:

$$\langle \eta_m(t)\eta_m(\acute{t})\rangle = \frac{D_m}{3N_{Na}}\ \delta(t-\acute{t})$$
$$\langle \eta_h(t)\eta_h(\acute{t})\rangle = \frac{D_h}{N_{Na}}\ \delta(t-\acute{t}) \tag{2.17}$$

Where D_h and D_m are defined at Equation (2.15) and α_m, α_h, β_m and β_h in all of above equations are:

$$\alpha_m = \frac{(2.5-0.1V)}{e^{(2.5-0.1V)}-1}$$
$$\beta_m = 4e^{-\frac{V}{18}}$$
$$\alpha_h = 0.07e^{-\frac{V}{20}} \tag{2.18}$$
$$\beta_h = \frac{1}{e^{(3-0.1V)}+1}$$

For numerical simulations, it's enough to generate white noises with described means and put them in the set of equations to get the membrane potential of the next time step.

Table 2.3: Colored Noise Constants for Sodium Channels

$\gamma_{Na} = 10$	$\omega_{Na}^2 = 200$	$T_{Na} = 800$

Chapter 3

MINIMAL DIFFUSION FOR ENSEMBLE OF MARKOV CHAIN

3.1 Introduction

In Minimal Diffusion model, an ensemble of Markov Chains is considered for simulating the dynamic of the ion-channels. Each chain is evolving independently from the other chains in the ensemble and, transition rates and rules is the same for of all these continues time Markov chains.

Assume N ergodic continues-time independent Markov chains with the same transition matrixes. States are finite and are denoted with numbers from 1 to L. Now let $\theta_l \;\; l \in \{0, 1, \dots, L\}$ be the number of chains that are in state l at particular time, and define density of state l in that time, as $\psi_l = {}^{\theta_l}/_{N}$. This value is the subject of fluctuation in time and lets denote this fluctuation by ϕ_l. One property of Markov chain is that while time tends to infinity, the probability of finding chain in a state tends to a constant and, precisely to $\langle \psi_l \rangle$ where $\langle \dots \rangle$ shows the expected value. So ϕ_l can be defined as follows:

$$\psi_l = \langle \psi_l \rangle + \phi_l \qquad l \in \{0, 1, \dots, L\} \tag{3.1}$$

Having constant transition rates is the requirement of having a stationary solution in finite space Markov chain. Here assume the rates in our chains are constant and later we can let them to have tiny changes in time.

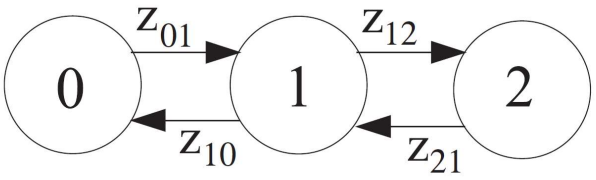

Figure 3.1: Sample Markov Chain used to illustrate master equation adopted from [2]

Figure 3.1 demonstrates a chain with three states. Z s are the transition rates between the states. For this sample chain the master equation reads as:

$$\frac{d\,\psi_0}{d\,t} = -Z_{01}\langle\psi_0\rangle + Z_{10}\langle\psi_1\rangle$$

$$\frac{d\,\psi_0}{d\,t} = Z_{01}\langle\psi_0\rangle - (Z_{10} + Z_{12})\,\langle\psi_1\rangle + Z_{21}\langle\psi_2\rangle \tag{3.2}$$

$$\frac{d\,\psi_2}{d\,t} = -Z_{21}\langle\psi_2\rangle + Z_{12}\langle\psi_1\rangle$$

We now that for a Markov chain:

$$\sum_{l=0}^{L}\langle\psi_l\rangle = 1 \tag{3.3}$$

It implies that:

$$\langle\psi_0\rangle + \langle\psi_1\rangle + \langle\psi_2\rangle = 1 \tag{3.4}$$

And, in steady state:

$$\frac{d\,\langle\psi_0\rangle}{dt} = \frac{d\langle\psi_1\rangle}{dt} = \frac{d\langle\,\psi_2\rangle}{dt} = 0 \tag{3.5}$$

Two equations in equation set (3.2) are linearly independent. So $[\psi_0]$, $[\psi_1]$ and $[\psi_2]$ can be solved uniquely using (3.2) and (3.4).

3.2 State Density of a Special Case

The special case is a Markov chain in which, only one state is directly connected to the relevant state. Say state "r" for relative state and, state "s" for the connected state. See Figure 3.2. The transition rates α and β are supposed to be constants but, it's safe if they slightly change during the time.

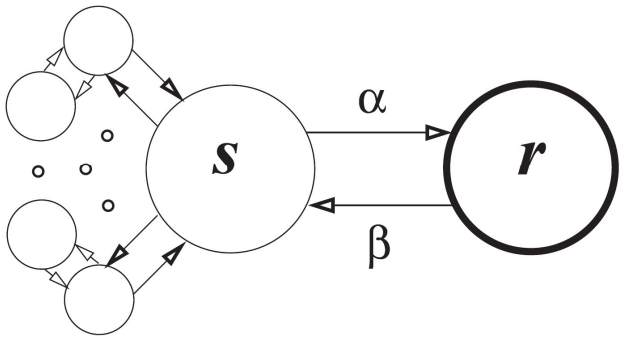

Figure 3.2: Special case in which, only one state is connected directly to relevant state. Adopted from [2]

For this special case from equations (3.1) and (3.3) it determined that:

$$\sum_{l=0}^{L} \emptyset_l = 0 \tag{3.6}$$

And

$$\langle \emptyset_l \rangle = 0 \quad (l = 1, 2, \dots, L). \tag{3.7}$$

Second moments of fluctuations are:

$$\langle \emptyset^2 \rangle = \frac{\langle \psi_l \rangle (1 - \langle \psi_l \rangle)}{N}, \quad (l = 1, 2, \dots, L) \tag{3.8}$$

And for different states j and k:

$$\langle \phi_j \phi_k \rangle = -\frac{\langle \phi_j \rangle \langle \phi_k \rangle}{N} \quad if\ j \neq k. \tag{3.9}$$

If j and k assumed to be single combined state, then from Equation (3.8):

$$\langle \left(\phi_j + \phi_k\right)^2 \rangle = \frac{\left(\langle \psi_j \rangle + \langle \psi_k \rangle\right)\left(1 - \left(\langle \psi_j \rangle + \langle \psi_k \rangle\right)\right)}{N} \tag{3.10}$$

For this special case the fluctuations in in the relevant state, ϕ_r, can be described using the following SDEs:

$$\begin{aligned} \dot{\phi_r} &= -\beta \phi_r + \alpha \phi_s + \varepsilon \\ \dot{\phi_s} &= -\gamma \phi_s - \varepsilon + \eta. \end{aligned} \tag{3.11}$$

Here ε and η independent Gaussian white noises. Mean of these white noises are described in Equation (3.21).

3.3 State Density of the Other Cases

For the other possible states, suppose the relevant state "r" is connected directly to two other states. Let's say j and k. instead of working with these two states, we can substitute them with one single state. Transition rates of this state, namely "s", can be defined using the transition rates of the state j and state k:

$$\begin{aligned} \beta &= \beta_j + \beta_k \\ \alpha_j \phi_j + \alpha_k \phi_k &\rightarrow \alpha \phi_s \end{aligned} \tag{3.12}$$

In Minimal Diffusion model it has been shown that the previously discussed equations, can be also valid in the case that the relevant state is directly connected to more than one state, if we substitute parameters like this:

$$\alpha = A + \frac{A}{B} \tag{3.13}$$

And

$$\langle \psi_s \rangle = \frac{A^2}{A^2 + B} \tag{3.14}$$

Where

$$\begin{aligned} A &\coloneqq \alpha_j \langle \psi_j \rangle + \alpha_k \langle \psi_k \rangle \\ B &= \alpha_j^2 \langle \psi_j \rangle \big(1 - \langle \psi_j \rangle\big) - 2\alpha_j \alpha_k \langle \psi_j \rangle \langle \psi_k \rangle + \alpha_k^2 \langle \psi_k \rangle (1 - \langle \psi_k \rangle) \end{aligned} \tag{3.15}$$

In Minimal Diffusion model, the dynamics of the membrane is described as follows:

$$C\dot{V} = -g_k \psi_K (V - E_K) - g_{Na} \psi_{Na} (V - E_{Na}) - g_L (V - E_L) + I \tag{3.16}$$

All the constants here are the constants mentioned in Table 2.1. ψ_{K} in this equation, is different than its deterministic value in HH equations, by the noise terms ϕ_r and ϕ_s. Same thing is true for ψ_{Na} as well. The Dynamics of each type of channels can be considered separately, with slightly different equations.

3.4 Dynamics of Potassium Channels

Fluctuations in ψ_{K} , are tracking by the stochastic variable ϕ_r and ϕ_s.

$$\psi_K = \langle \psi_K \rangle + \phi_r. \tag{3.17}$$

$[\psi_k]$ can be calculated as follows:

$$\langle \psi_K \rangle = \bar{n}^4, \tag{3.18}$$

Where $\bar{n}$ is under the control of the this differential equation:

$$\dot{\bar{n}} = -\beta_n \bar{n} + \alpha_n (1 - \bar{n}). \tag{3.19}$$

The following equations are valid for ϕ_r and ϕ_s. The evolution of these two variables in time, can be described using the following SDEs:

$$\begin{aligned} \dot{\phi_r} &= -\beta\phi_r + \alpha\phi_s + \varepsilon \\ \dot{\phi_s} &= -\gamma\phi_s - \varepsilon + \eta. \end{aligned} \tag{3.20}$$

ε and η stand for Gaussian zero-mean white noises which are independent of each other. Variances of these two stochastic variables are:

$$\begin{aligned} [\varepsilon(t)\varepsilon(\acute{t})] &= \frac{\alpha\langle\psi_s\rangle + \beta\langle\psi_K\rangle}{N}\delta(t-\acute{t}) \\ [\eta(t)\eta(\acute{t})] &= \frac{\alpha\langle\psi_s\rangle C_\alpha + \beta\langle\psi_K\rangle C_\beta}{N\langle\psi_K\rangle}\delta(t-\acute{t}), \end{aligned} \tag{3.21}$$

Where C_α and C_β are the notations for:

$$\begin{aligned} C_\alpha &= 2\langle\psi_s\rangle(1-\langle\psi_s\rangle) - \langle\psi_K\rangle \\ C_\beta &= 2(1-\langle\psi_s\rangle)^2 - \langle\psi_K\rangle. \end{aligned} \tag{3.22}$$

γ is defined by the following formulation:

$$\gamma = \frac{\alpha\langle\psi_s\rangle^2 + \beta\langle\psi_K\rangle(1-\langle\psi_s\rangle)}{\psi_s\psi_K}, \tag{3.23}$$

And at the end, the α and β needs to be substituted using the following formulations:

$$\begin{aligned} \alpha &= \alpha_n \\ \beta &= 4\beta_n. \end{aligned} \tag{3.24}$$

3.5 Dynamics of Sodium Channels

In Sodium channels, the relevant state is directly connected to two states. State j and state k. So here as we mentioned earlier we need to do substitution and use A and B in the formulation.

$$\psi_{Na} = \langle \psi_{Na} \rangle + \phi_r \tag{3.25}$$

Here

$$\langle \psi_{Na} \rangle = \bar{m}^3 \bar{h} \tag{3.26}$$

Where , $\bar{m}$ and $\bar{h}$ can be updated in each time step using the following differential equations:

$$\begin{aligned} \dot{\bar{m}} &= -\beta_m \bar{m} + \alpha_m (1 - \bar{m}) \\ \dot{\bar{h}} &= -\beta_h \bar{h} + \alpha_h (1 - \bar{h}) \end{aligned} \tag{3.27}$$

Equation (3.20) is also valid for Sodium channels without any changes. White noises has also the same formulation, but $[\psi_{Na}]$ needs be placed in the formulation:

$$\begin{aligned} \langle \varepsilon(t)\varepsilon(\acute{t}) \rangle &= \frac{\alpha \langle \psi_s \rangle + \beta \langle \psi_{Na} \rangle}{N} \delta(t - \acute{t}) \\ \langle \eta(t)\eta(\acute{t}) \rangle &= \frac{\alpha \langle \psi_s \rangle C_\alpha + \beta \langle \psi_{Na} \rangle C_\beta}{N \langle \psi_{Na} \rangle} \delta(t - \acute{t}), \end{aligned} \tag{3.28}$$

And

$$\begin{aligned} C_\alpha &= 2\langle \psi_s \rangle (1 - \langle \psi_s \rangle) - \langle \psi_{Na} \rangle \\ C_\beta &= 2(1 - \langle \psi_s \rangle)^2 - \langle \psi_{Na} \rangle, \end{aligned} \tag{3.29}$$

And

$$\gamma = \frac{\alpha \langle \psi_s \rangle^2 + \beta \langle \psi_{Na} \rangle (1 - \langle \psi_s \rangle)}{\psi_s \psi_{Na}}. \tag{3.30}$$

$[\psi_s]$, α and β are different than the corresponds formulation for the Potassium channels and, are dependent to the state j and state k:

$$\langle \psi_s \rangle = \frac{A^2}{A^2 + B}, \tag{3.31}$$

$$\alpha = \frac{A + B}{A},$$

$$\beta = \beta_j + \beta_k,$$

Where A and B are define in equation (3.15) and

$$\beta_j = \beta_h \quad and \quad \beta_k = 3\beta_m \quad , \quad \alpha_j = \alpha_h \quad and \quad \alpha_k = \alpha_m. \tag{3.32}$$

Chapter 4

NUMERICAL RESULTS

4.1 Spontaneous Firing

As we mentioned above, small membranes show spontaneous firing. The HH equations don't produce any firing at all when, there is no input current available. However, Microscopic Simulations and the recorded neuron activities from biological neurons, prove that the neurons are spiking, even in absence of input current. We tested different size of the membranes to capture the ability of producing spontaneous firing for 1) Minimal Diffusion (**MD**) model, Colored Noise (**Col**) model and Microscopic Simulation (**MC**) model. All models showed spontaneous firing and, as it can be determined from the Figure 4.1 the firing rate is decreasing as the membrane size is increasing. This is exactly what we saw in the formulation of Minimal Diffusion and Colored Noise. In getting the results, we set the input current as constant and zero for all the simulations. We repeat the simulation for different sizes of the membrane from very small to very large. In all the cases, results from Minimal Diffusion was closer to the Microscopic Simulations. It means that Minimal Diffusion is more accurate than the Colored Formulation in stating spontaneous firing, although the colored formulation results are quiet acceptable. The size of simulated membranes varied from $1.67\ \mu m^2$ (30 Potassium channels, 100 Sodium channels) to $1215.0\ \mu m^2$ (24300 Potassium channels, 81000 Sodium channels). For bigger membrane sizes, the results of both simulation methods are becoming closer to the Microscopic results.

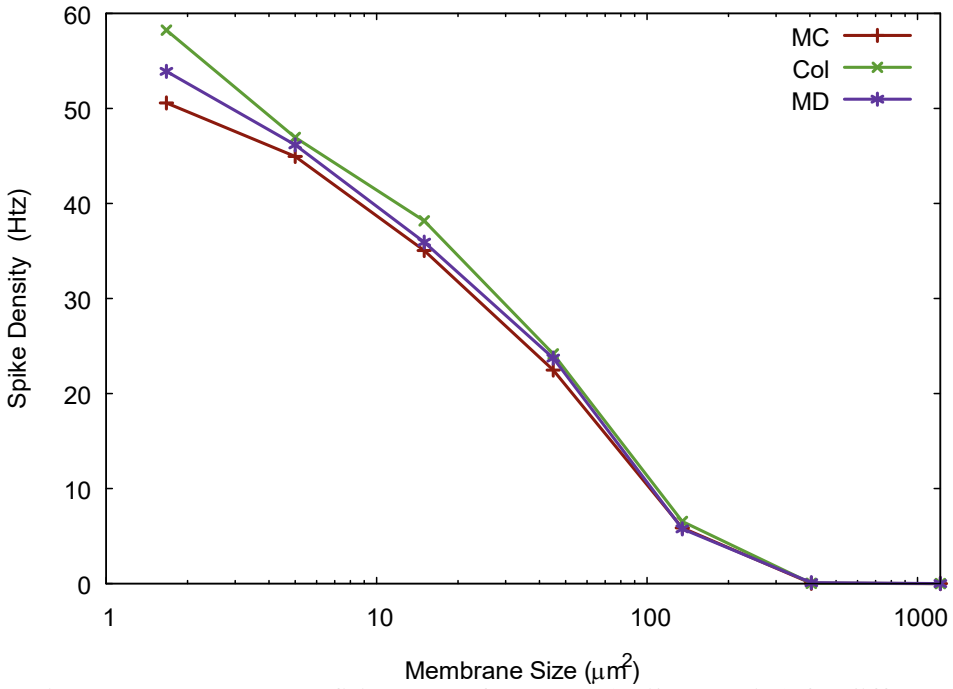

Figure 4.1: Spontaneous firing mean frequency (Spike Density) for different membrane sizes. **MC** is the result from Microscopic Simulations. **MD** is minimal diffusion and **Col** is the colored formulation and the input current is zero.

We also analyzed the results by conducting Coefficient of Variation. Coefficient of Variation is showing the coherence of the spikes and it's defined by:

$$\frac{\sqrt{\langle M^2 \rangle - \langle M \rangle^2}}{\langle M \rangle} \tag{4.1}$$

Where $\langle M \rangle$ is the mean and $\langle M^2 \rangle$ is the mean-squared of the inter spike length. The point of using coefficient of variation is that, we can tell the differences between different signals with the same mean. Figure 4.2 illustrates the coefficient of variation for different size of membranes, for all of our three models. We can see that spike coherence level is about the same in all models, although Minimal Diffusion model seems to be in the closer level to Microscopic model.

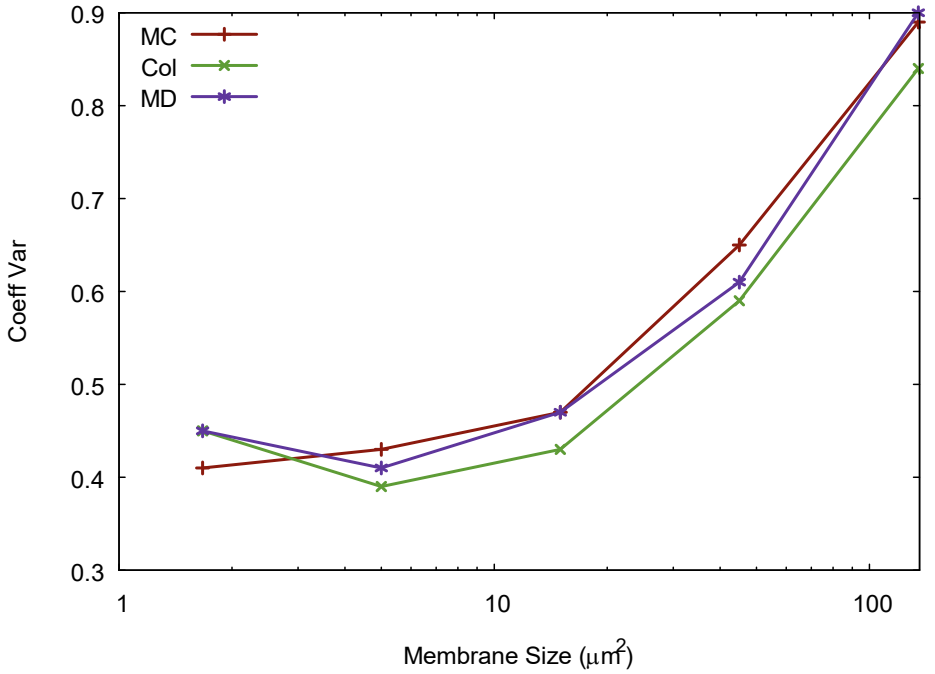

Figure 4.2: Coherence of the simulated spikes in 30ms interval for MD, Col and MC simulation methods. The size of membrane has changed from 1.67 μm^2 to 135 μm^2 and Input current is zero

4.2 Constant Input Current – Varying Membrane Size

In this part we obtain the results, by injecting constant current to the simulated membranes. In simulations 6 $\mu A/m^2$ constant current applied to different membrane sizes of 180 μm^2, 405 μm^2, 720 μm^2.

Colored noise model is already compared in Rowat paper in 2014 [13] with other approximation models. We tried to choose the membrane sizes somehow to be close to the membrane sizes in that paper, to provide the chance of comparing the results of this paper with the results of Rowat paper for interested reader. Also we considered our limitation in computation time and resources (Some simulations took months to be finished). Figure 4.3 demonstrates the ISI distribution for these simulations.

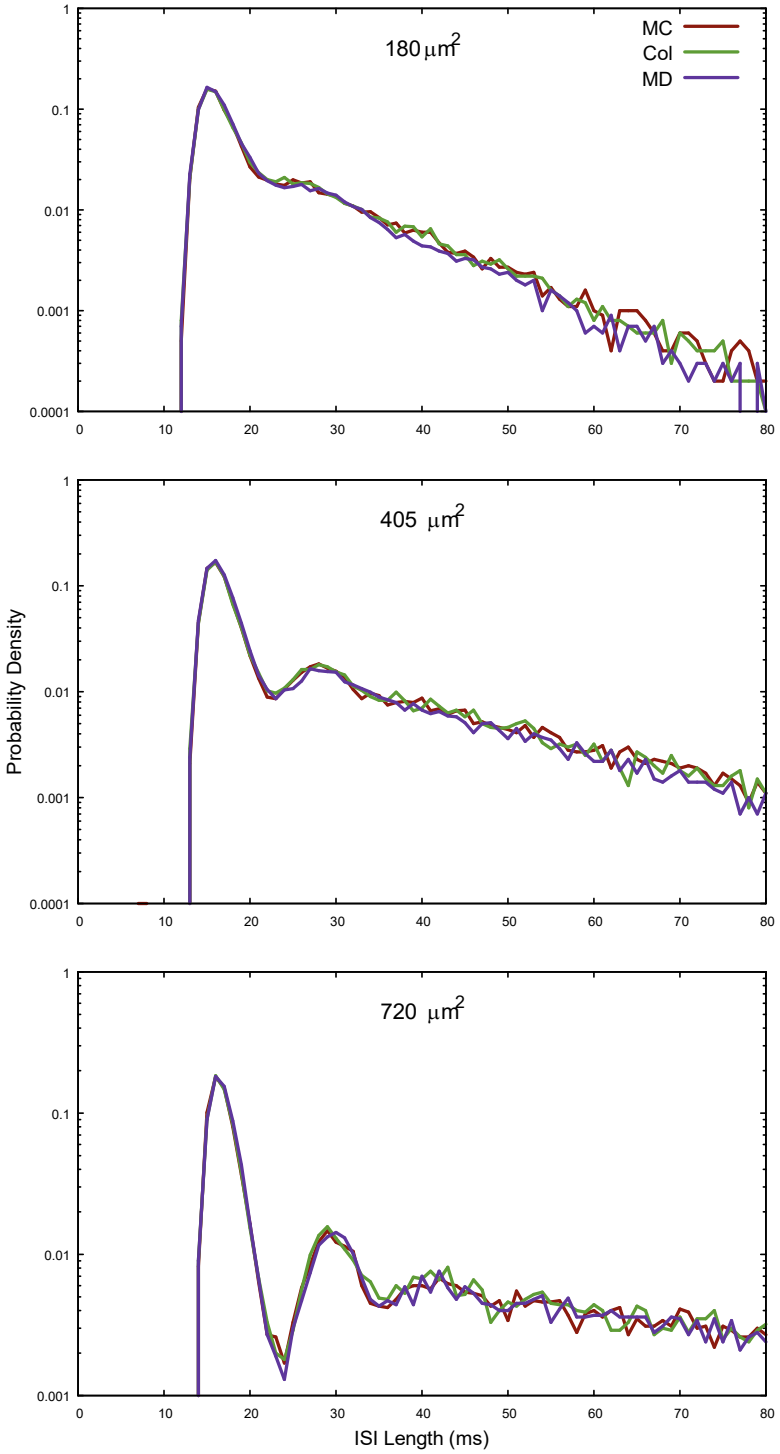

Figure 4.3: ISI distribution. The injected current for all simulations is 6 $\mu A/m^2$. Membrane sizes are varied Top: 180 μm^2, Middle: 405 μm^2 and Bottom: 720 μm^2.

To obtain this distribution we assumed 80 bins for each inter spike interval. For each bin we defined a minimum length and maximum length and, if the interval between a

spike and its previous one was between the minimum and maximum specified length of that bin, we put it in that bin. We chose these maximum and minimums somehow, to have 80 bins with all lengths equal to 1ms. Then 500ms simulation was ran and we counted the number of ISIs which was placed in each bin. For instance, if the length between two spikes was 15.4 we placed it in bin number 15. The length between two spikes is measured by calculating the time between two successive upward cross of the signal from perfectly chosen point. This point is taken somehow that being included in all the spikes. In other words, if a spike happens, for sure it will pass from this point and also, this point is higher than level of all signals from a resting membrane.

Top chart in Figure 4.3 is showing ISI distribution for a membrane with area size $180\ \mu m^2$ and middle one is a for a membrane with size $405\ \mu m^2$ and the bottom chart is related to a membrane with size $720\ \mu m^2$.

It can be seen from this figure that increasing the size of the membrane, may increase the minimum length of inter spikes a little. But more obvious thing is the shape of the curve, that is matching to a particular shape. All the three models have almost the same distribution and it seems that Minimal Diffusion model and Colored Noise model both perfectly introduce the same distribution as the Microscopic model.

Mean spike frequency of the simulated models has been compared in the Figure 4.4. In that figure we can see that, again the results of Minimal Diffusion model are more exact and mean frequencies are near to Microscopic model. From this and Figure 4.1, one can claim that by making the membrane size bigger the mean frequency of spikes (Spike Density) is reducing, whether input current be available or not.

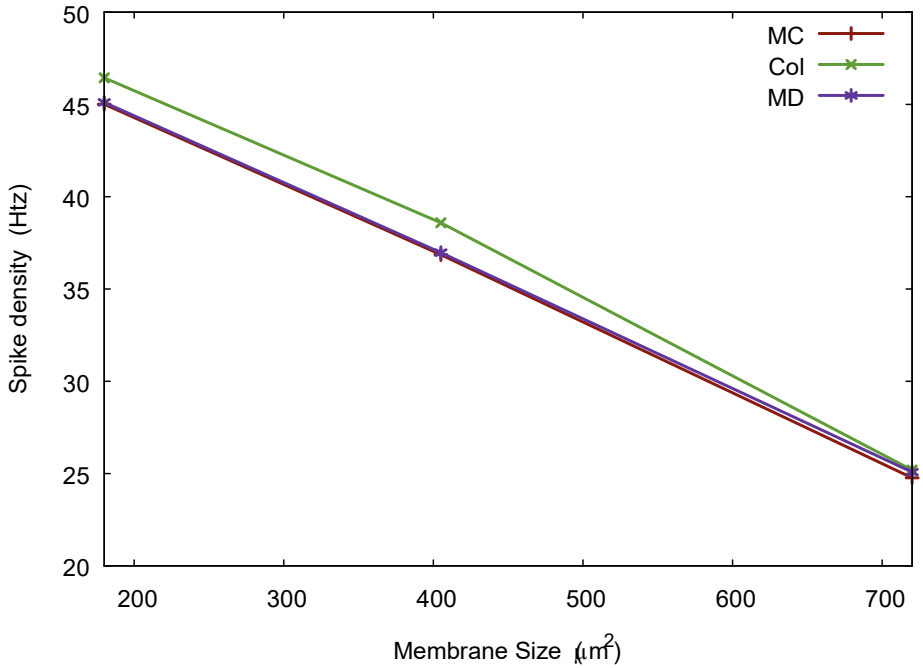

Figure 4.4: Spike density (Mean Frequency) of models MC, Col and MD for different sizes of membrane

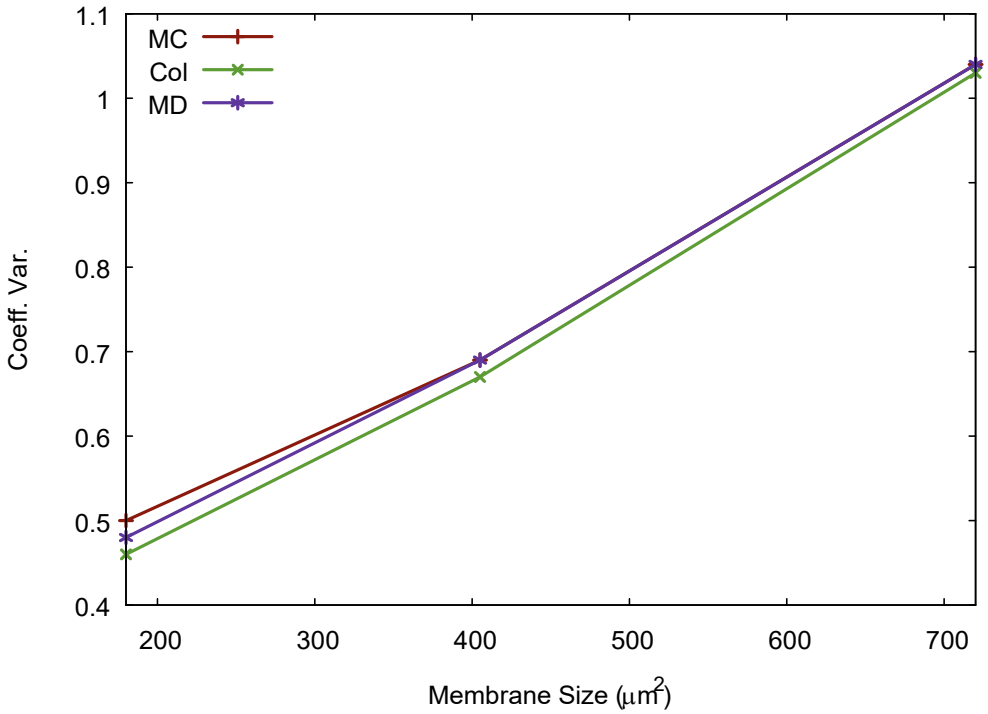

Figure 4.5: Coefficient of variation of the results from 500ms simulations for all three models.

The coefficient of variations of the spikes in these simulations also considered and, Figure 4.5 is showing the comparison between the coherence of different models. Also in this, the Minimal Diffusion has very close level of coherence to the Microscopic model. Although the coherence level for Colored Noise model is near to the level of coherence of Microscopic model, in compare to Minimal Diffusion model it's not accurate.

4.3 Constant Membrane Size – Varying Input Current

In this part we kept the membrane size the same and, we tried to study on the response of the cell to different input currents. For doing this, we chose a middle sized membrane with 6480 Potassium channels and 21600 Sodium channels (The size of membrane with this specification is $360\ \mu m^2$ using the densities in Table 2.1). We repeated simulation with $2\ \mu A/m^2$, $6\ \mu A/m^2$ and $12\ \mu A/m^2$ input currents. ISI distribution of this cell over different input current is plotted in Figure 4.6. We can see in this figure, by increasing the input current, the probability of producing lower frequency spikes is decreasing. That special shape of curve, also can be seen in these plots. Interesting thing about this shape is that, although the difference between lower and higher inter spike intervals is become shorter, the distance between local maximums of curve seems to be the same. One can detect this relation also in Figure 4.3. It seems that the local maximums of ISI distribution are placed at special points with a difference about 12.7ms in all the simulations. This is not true when we have spontaneous firing and, as the spontaneous firing getting less (Membrane size become bigger or input current is increasing), the spikes are happening in some special frequencies. We didn't prove it here, but it can be an interesting phenomenon to study about.

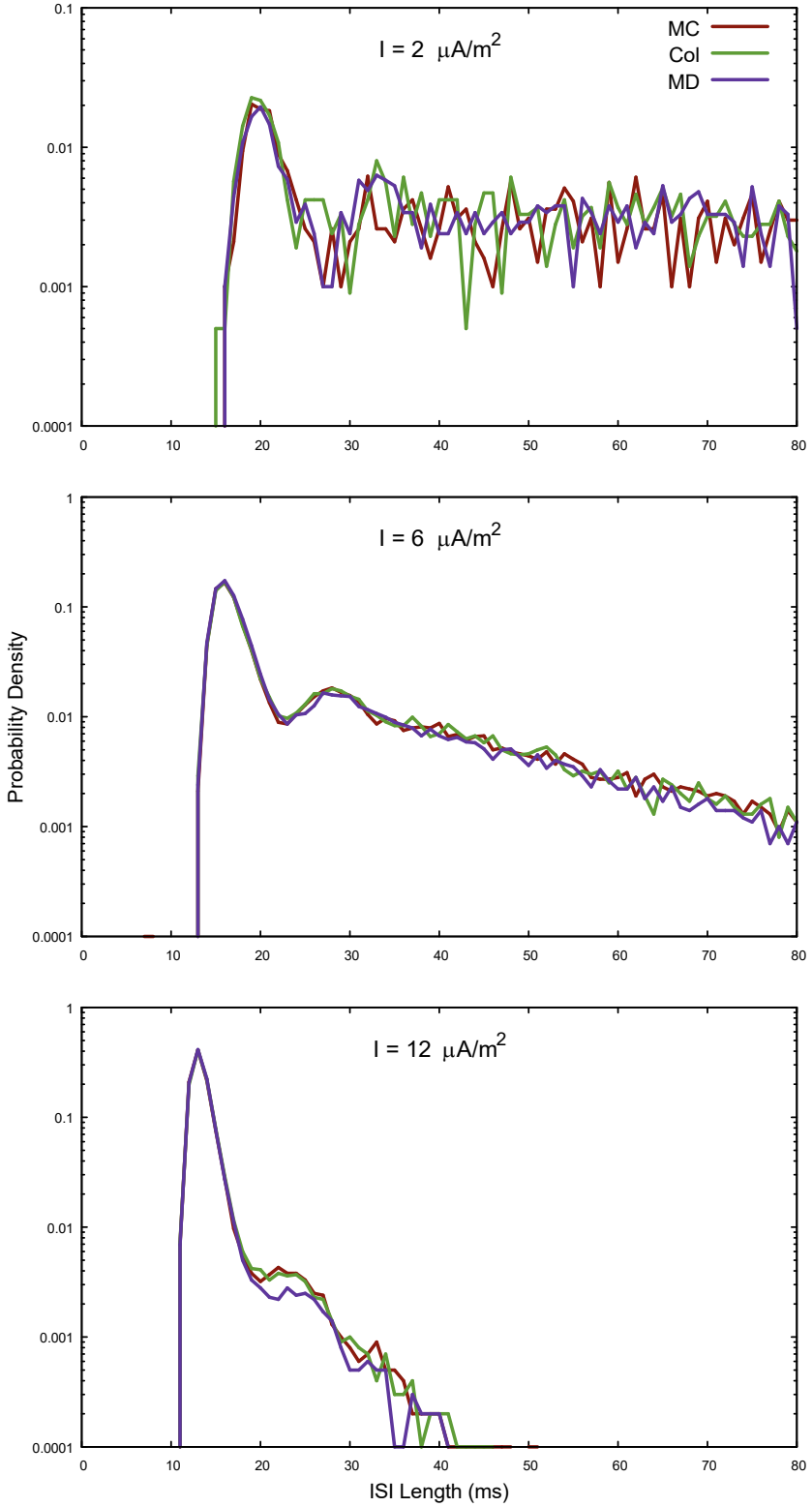

Figure 4.6: ISI Distribution of a middle size membrane in response to different input currents, for all three models.

Figure 4.7 illustrates spike frequency means (Spike Density) over different input currents for our mid- size membrane. Minimal diffusion results are so near to Microscopic results and it almost overlaps it. This shows the high accuracy of this model.

And Figure 4.8 illustrates that Minimal Diffusion model is also accurate in coherence. As we can see in this figure it completely overlaps Microscopic model curve.

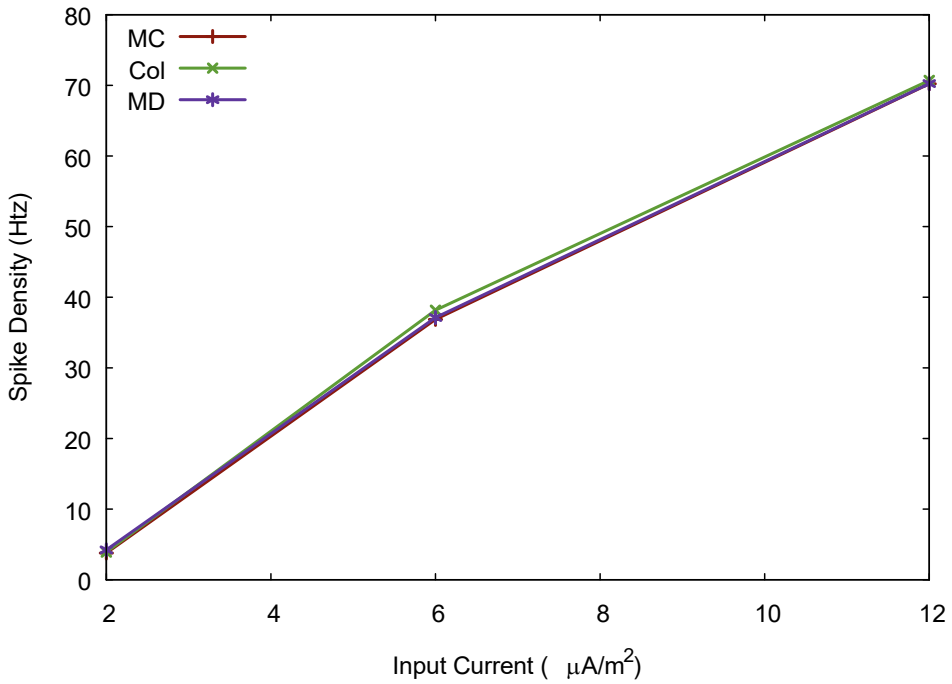

Figure 4.7: Spike density (Mean Frequency) for a 400 μm^2 membrane over input current for all three models. MD model almost overlaps MC.

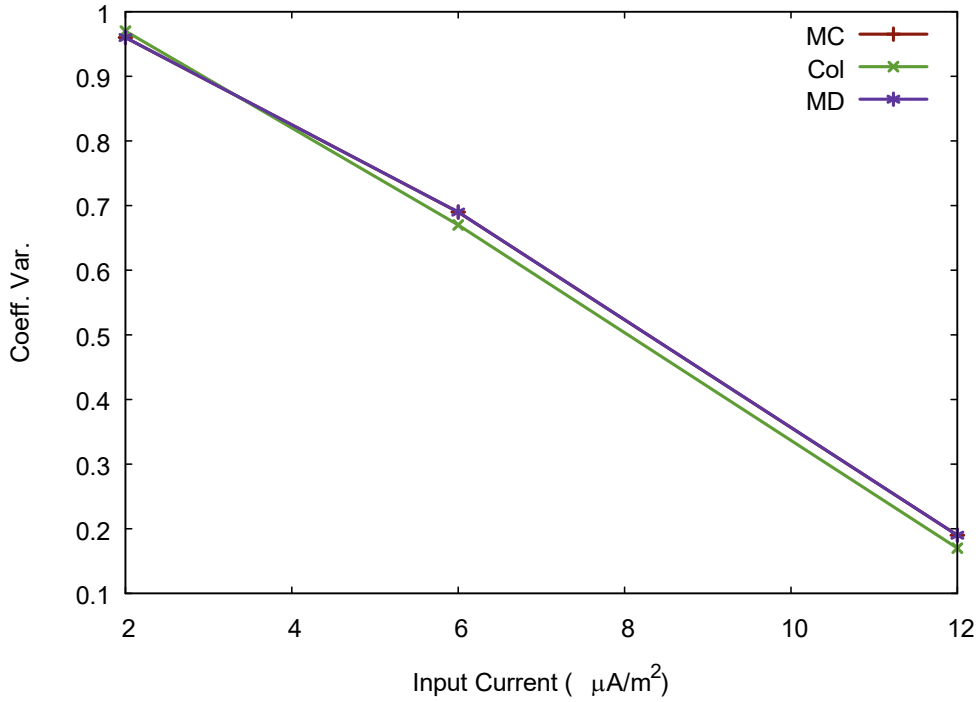

Figure 4.8: Coefficient of Variation of all three models over the input current. MC line is completely overlapped by MD line.

4.4 Pulse Input Current

All the previous simulations in this paper was measured under the constant current inputs. In this section we applied a pulse stimulus in the simulated neurons to measure the latency of the spikes. The latency is time between presenting a current and the time that the first spike is occurred. A membrane patch of 1800 Potassium channels and 6000 Sodium channels was tested in 4000 trials.

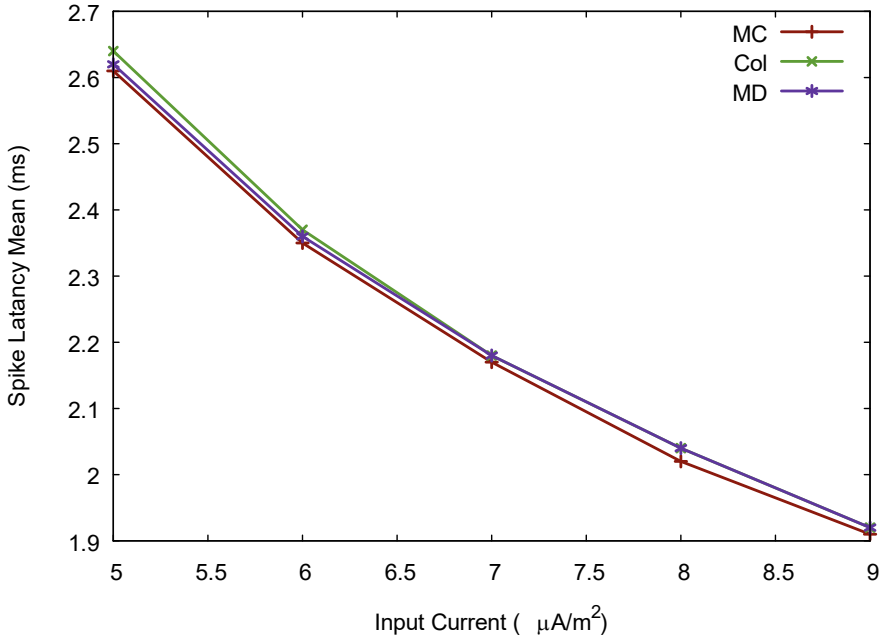

Figure 4.9: Latency of spikes over input current for all three models in a membrane patch with size of 100 μm^2.

We presented input current every 25ms for 2ms duration. The reason for choosing that pulse duration was because we found it enough time for the membrane to reach back to the steady state and, the duration of the pulse is chosen somehow to force the neuron to spike for almost all of the injected pulses, even for the lowest one which was 5 $\mu A/m^2$. In this state 4000 pulses made the neuron to spike about 3900 times. The time between a rise of input current signal and the time that membrane potential reaching threshold were collected and then, its divided to the number of spikes.

In Figure 4.9 it can be determined that, by more powerful stimulus the response time of the cell in decreased. Also it seems that the Minimal Diffusion model showed better and closer results to Microscopic Simulation model for lower input currents, precisely for input currents less than 7 however, for the currents more than this both Colored Noise model and Minimal Diffusion model had exactly the same results. In principle, the results of both models was closer to Microscopic results for lower input currents.

4.5 Simulation Time

The motivation behind development of estimation methods is twofold: 1) to obtain an analytic description. 2) to speed up the simulations. In many situations, the Microscopic simulation can be terribly slow. The advantage of using estimation methods like Minimal Diffusion model and Colored Noise model is that, one can study on the dynamics of the neuron, without having to wait a long time for simulation to be finished. But, the question is how fast these methods are? In this part, we measured the average time which is needed for each step of simulation for all three models. We made these measurements on a computer with intel Core I7 – 6700HQ CPU and 12 GB of memory. However, we should mention that, these type of simulation software are CPU consuming and they don't consume a lot of memory. In our implemented software, before calling the function corresponds to each model we stored the time and compared it to the time of returning from that function. We also counted the number of times that the functions are called. Then we divide total time to this number. The results are shown in Table 4.1.

Table 4.1: Average Time of Calculating One Iteration in Simulation, Based on the Number of Ion-Channels of the Membrane, for Different Methods. **MC** is the Microscopic Model, **MD** is Minimal Diffusion Model and **Col** is Colored Noise Model.

Number of ION-Channels	**MC**	**MD**	**Col**
1000	374.00ms	1.49ms	4.07ms
5000	1870.11ms	1.53ms	4.10ms
10000	3913.58ms	1.65ms	4.27ms
15000	6040.95ms	1.69ms	4.41ms
20000	7999.57ms	1.68ms	4.44ms

It seems that the time needed for calculating each iteration of Microscopic simulation is increasing linearly, with the increase in the number of ion channels in the simulation. Computation time of the Minimal Diffusion and Colored Noise models, don't change in principle with increase in the number of ion channels of the membrane.

Table 4.1 has illustrated in Figure 4.10 and show it well that, how much Minimal Diffusion and Colored Noise models are faster than Microscopic model.

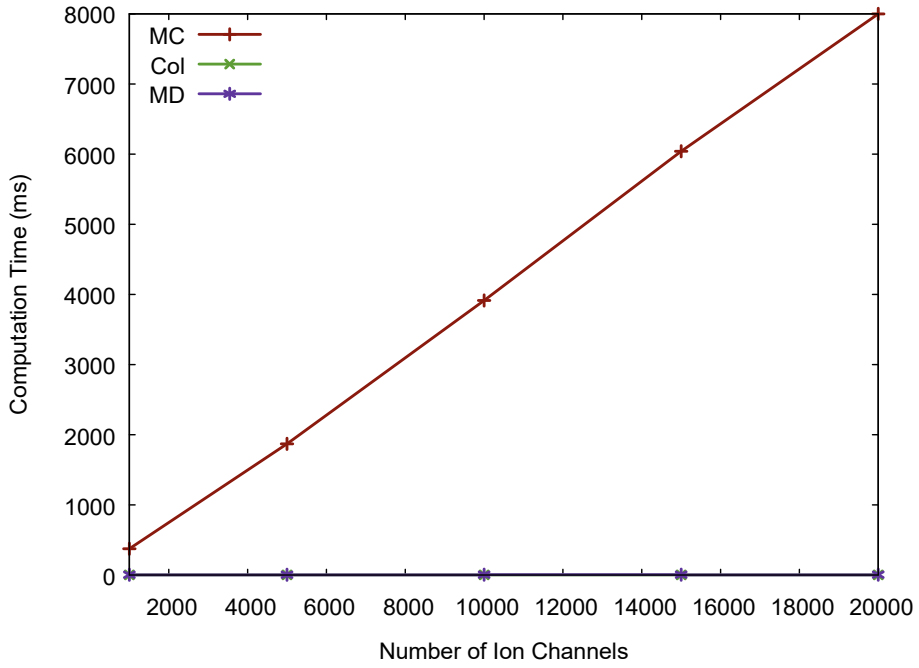

Figure 4.10: Computation Time over Number of Ion Channels in the cell for three models. Lines of Colored model and MD are close to zero and in the scale of this figure they overlapped each other.

Chapter 5

CONCLUSION

5.1 Conclusions

In concern to the dynamics of the ion-channels a lot of different methods have been developed, especially in the recent years. These methods have been compared by other people to find out the pros and cons of each. Here we chose Minimal Diffusion approximation for ion-channels as a new approach of simulation and, we compared it numerically with a little older method called Colored Noise model. To obtain the accuracy of each model we also chose Microscopic Simulation method to compare to. This article can be useful for the one who is interested to study about the dynamics of the neuron, to help him/her to choose among these simulation methods.

After doing numerical analysis, we have found that the Minimal Diffusion model in all the situations showing a better result over the already satisfactory Colored Noise model. Also it's faster and needs less computation resources than the Colored Noise model. So, it can be a good candidate for the one who interested to study on the dynamics of ion-channels.

ISI Distribution for all models was almost the same although, for longer inter spikes lengths longer simulation times are needed. So Minimal Diffusion model can be used to run the simulation for the times much more longer and, we have shown here that the result can be trusted with a very high accuracy.

Spike Density (Mean Frequency) of the Minimal Diffusion model also was more accurate than the Colored Noise model although, for very small membrane size there is noticeable difference between results and the result from Microscopic simulations. So, it's not irrelevant, if someone use the Microscopic simulation for very small patches, instead of using approximation models mentioned above. The reason is that Microscopic simulation for small patches can be done in a reasonable time with very high accuracy.

Theoretically, it was expected that the Minimal Diffusion be faster than the Colored Noise model since, in its implementation only three noise terms are involved, in compare to the Colored noise model that has five noise terms. We used Box-Muller method in our implementation to generate a white noise but, still generating Gaussian white noise in our simulation for both models, in average took about 25 percent of our simulation time. It's clear that less number of the noise terms, can result a better performance.

REFERENCES

[1] M. Güler, "Stochastic Hodgkin-Huxley Equations with Colored Noise Terms in the Conductances," *Neural Computation,* no. 25, pp. 46-74, 2013.

[2] M. Güler, "Minimal diffusion formulation of Markov chain ensembles and its application to ion channel clusters," *PHYSICAL REVIEW E,* vol. 91, no. 6, p. 062116, 2015.

[3] A. L. Hodgkin and A. F. Huxley, "A quantitative description of membrane current and its application to conduction and excitationin in nerve," *Journal of Physiology,* no. 117, pp. 500-544, 1952.

[4] B. Sakmann and E. Neher, Single-Channel Recording, Plenum Press, 1995.

[5] F. J. Sigworth, "The variance of sodium current fluctuations at the node of Ranvier," *Journal of Physiology,* no. 307, pp. 97-129, 1980.

[6] J. White, R. Klink, A. Alonso and A. Kay, "Noise from voltage-gated ion channels may influence neuronal dynamics in the entorhinal cortex.," *J Neurophysiol.,* pp. 262-269, 1998.

[7] T. G. Kurtz, "Strong approximation theorems for density dependent Markov chains," *North Holland Publishing Company ,* vol. 6, pp. 223-240, 1978.

[8] R. F. Fox and Y.-n. Lu, "Emergent collective behavior in large numbers of globally coupled independently stochastic ion channels," *PHYSICAL REVIEW E,* vol. 49, p. 3421, 1994.

[9] H. Mino, J. Rubinstein and J. White, "Comparison of algorithms for the simulation of action potentials with stochastic sodium channels," *Annals of Biomedical Engineering,* vol. 30, no. 4, pp. 578-587, 2002.

[10] M. Güler, "Persistent membranous cross correlations due to the multiplicity of gates in ion channels," *Computational Neuroscience,* vol. 31, no. 3, pp. 713-724, 2011.

[11] J. R. Clay and L. J. DeFelice, "Relationship between membrane excitability and single channel open-close kinetics," *Biophysical Journal,* vol. 42, no. 2, pp. 151-157, 1983.

[12] E. Schneidman, B. Freedman and I. Segev, "Ion channel stochasticity may be critical in determining the reliability and precision of spike timing," *Neural Computation,* vol. 10, pp. 1679-1703, 1998.

[13] P. F. Rowat and P. E. Greenwood, "The ISI distribution of the stochastic Hodgkin-Huxley neuron," *Front Comput Neurosci,* vol. 8, p. 111, 2014.

[14] D. Colquhoun and A. G. Hawkes, "On the Stochastic Properties of Single Ion Channels," *Biological Sciences,* vol. 211, pp. 205-235, 1981.