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Research Article

Numerical Investigation of Firing Characteristic of Stochastic Hodgkin-Huxley Neuron under Different Forcing Regimes

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ABSTRACT

This paper investigates the influence of the ion channel noise on the response of a Hodgkin-Huxley neuron in different stimulus regimes. Our results reveal that type of stimuli can induce emergence of various phenomena with the help of such an internal noise. In the case of DC current introduction, number of firings monotonically increase with high noise intensity, and firing behaviour is also irregular. Intermediate noise levels give rise to reduction of neural firings in spiking neuron, which is known as inverse stochastic resonance phenomenon. Moreover, firing behaviour of such neuron interestingly becomes highly irregular even up to higher noise intensities. On the other hand, we examine the influence of channel noise on the neural response to a periodic signal. We show that frequency of subthreshold signal has a significant effect on the response sensitivity whereas firing probability and regularity are in a close relationship depending on increasing noise intensity. Finally, firing behaviour in the case of suprathreshold periodic forcing is analysed. Up to a certain level of channel noise, it does not seriously affect number of firings which has a nonlinear relationship with increasing signal frequencies. It is also possible to see inverse stochastic resonance effect at the high frequency regions. Another interesting finding is that increasing channel noise cannot enhance the regularity at certain frequencies, yielding the presence of irregular response region at suprathreshold periodic inputs. This work contributes to a better understanding of the role of internal noise in the relation between incoming stimuli and neural response.

Keywords: *Channel noise, spiking regularity, firing rate, DC stimulus, periodic input*

Farklı Uyartım Rejimlerinde Stokastik Hodgkin-Huxley Nöronunun Ateşleme Karakteristiğinin Sayısal İncelemesi

ÖZ

Bu makale, iyon kanal gürültüsünün farklı uyartım rejimlerinde Hodgkin-Huxley nöronunun tepkisi üzerindeki etkisini araştırmaktadır. Sonuçlarımız, uyartım tipinin içsel gürültü yardımıyla çeşitli olguların ortaya çıkmasına neden olabileceğini göstermektedir. DC akım uygulanması durumunda ateşleme sayısı yüksek gürültü yoğunluğuyla monoton bir şekilde artmakta ve ateşleme davranışı da düzensiz olmaktadır. Orta düzeydeki gürültü seviyeleri, ateşleyen nöronlardaki ateşleme sayılarının azalmasına, yani ters stokastik rezonans olayına yol açmaktadır. Üstelik bu nöronun ateşleme davranışı ilginç bir şekilde yüksek gürültü yoğunluklarında bile oldukça düzensiz olmaktadır. Öte yandan, kanal gürültüsünün periyodik bir sinyale verilen nöral cevap üzerindeki etkisini inceledik. Eşikaltı sinyal frekansının cevap hassasiyeti üzerinde önemli bir etkiye sahip iken, artan gürültü yoğunluğuna bağlı olarak ateşleme olasılığı ve düzenliliğin yakın bir ilişkide olduğunu

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gösteriyoruz. Son olarak, eşik üstü periyodik uyartım durumunda ateşleme davranışı analiz edilmiştir. Belirli bir kanal gürültüsü seviyesine kadar, gürültü artan sinyal frekanslarıyla doğrusal olmayan bir ilişkiye sahip olan ateşleme sayısını ciddi şekilde etkilememektedir. Yüksek frekans bölgelerinde de ters stokastik rezonans etkisini görmek mümkündür. Bir diğer ilginç bulgu ise artan kanal gürültüsünün belirli frekanslarda düzenliliği arttıramamasıdır, ki bu eşik üstü periyodik sinyal uygulandığında düzensiz tepki bölgesinin varlığını ortaya çıkarmaktadır. Bu çalışma, gelen uyaranlar ile nöral cevap arasındaki ilişkide içsel gürültünün rolünün daha iyi anlaşılmasına katkıda bulunmaktadır.

Anahtar Kelimeler: *Kanal gürültüsü, ateşleme düzenliliği, ateşleme oranı, DC uyartım, periyodik girdi*

I. INTRODUCTION

The nervous system is the most complicated system in humans, and how it maintains flawless functionality with high efficiency remain a mystery. This system undertakes essential functions like regulating internal processes, carrying out communication, and processing information. It is widely accepted that these tasks are accomplished through certain electrical signals known as action potentials, generated by neurons that are the fundamental units of the system. This also indicates that neurons are the vital biological components that receive and respond to environmental stimuli [1-2]. The collective behaviours of neurons, especially their firing patterns in various brain regions, are linked to critical functions such as central pattern generation and working memory. Numerous studies have demonstrated that neural activities exhibit regular, irregular, and chaotic spiking regimes while performing vital functions [3-7].

In the cortex, neurons can respond to a variety of stimulus types, such as sensory stimuli (e.g. visual, auditory) [8], integrative stimuli from decision-making processes [9] and direct electrical currents [10]. Each type of stimulus produces different responses in cortical neurons. The nature of stimulus types that a neuron can respond to generally depends on its position, function, and connectivity within the brain [11-13]. However, regardless of its type, stimulus has a significant effect on the excitability of neurons. Any type of stimuli can profoundly impact the excitability of neurons by modulating membrane potential through depolarization or hyperpolarization, excitatory or inhibitory synaptic inputs, and through long-term plasticity mechanisms, thereby affecting how neurons process and respond to information signals [14-16].

As a part of neural information processing task, there are two fundamental encoding mechanisms in the nervous system: temporal and rate coding. These are two important information processing strategies by which the nervous system encodes and transmits information. Rate coding refers to the agreement that the frequency of action potentials or firing rate within a neuron encodes information about a stimulus [17-18]. In this strategy, a higher firing rate generally means a stronger stimulus, while a lower rate indicates a weaker one. This type of coding is relatively straightforward and has been extensively studied, particularly in sensory systems like vision and audition, where the intensity of a stimulus can be said to be directly correlated with the firing rate of specific neurons [19-21]. Temporal coding, however, is believed to be performed with the precise timing of action potentials. In this strategy, the timing of each spike, relative to other spikes, carries definite information [22]. Temporal coding can capture more complex information than rate coding, such as the fine temporal structure of an auditory input or the synchronization of spikes across different neurons in the same cortical or brain area [23-25]. This mechanism is particularly important in neural circuits where timing is crucial, such as in the auditory system for sound localization or in the hippocampus for encoding sequences of vital body functions. Both coding strategies often work together to enhance the brain's ability to process and interpret complex stimuli [26-29].

Extensive experimental and theoretical works manifest that neurons are continuously subjected to noise throughout all stages of information processing. In recent decades, significant progress has been made in understanding the effects of noise on neuron dynamics. A great number of neuroscience research has revealed that noise can induce a variety of complex behavioural patterns, including stochastic resonance [30-32], coherence resonance [33-34], synchronization [35-36], bursting [37] and chaos [38]. These findings suggest that noise plays a crucial role in regular functioning of the brain, such as cognitive and perceptual mechanisms [39-40].

One of the main sources of noise in the nervous system is the ion channel noise. Channel noise refers to the variability and randomness that are inherent in the opening and closing processes of ion channels within neural membranes. This type of noise arises due to the stochastic nature of ion channel behaviour, where a single channel switches between open and closed states in an unpredictable manner [41]. Despite being a source of variability, channel noise can significantly influence neural functions, e.g. signal processing and information transmission [42-46]. It can impact the reliability and precision of action potential generation, affect synaptic transmission, and even contribute to the overall excitability of neurons. Interestingly, while channel noise might seem destructive, it can also play constructive roles, such as enhancing signal detection through mechanisms like stochastic resonance, where the presence of a proper noise level actually improves the ability of neurons to respond to weak inputs [47-48]. A deep understanding of channel noise is crucial for a comprehension of neural dynamics and the robustness of neural computations in the brain.

In the present work, we investigate neural behaviour related to rate and temporal coding using spatiotemporal dynamics, i.e. spike number and firing regularity. With a holistic approach which considers different stimuli projections, we obtain a general view on firing behaviour of a single neuron. To do this, we use class II Hodgkin-Huxley neuron of which variability stems from the presence of internal noise, i.e. ion channel noise. We perform comprehensive simulations applying different stimulus types to the neuron (e.g. direct current stimulus, subthreshold and suprathreshold sinusoidal forcing). The rest of the paper is organized as follows: In the next section, we introduce the model, that is, a stochastic Hodgkin- Huxley neuron, and the methods used for the clarification of neural response to applied stimuli projections in terms of firing rate and regularity. In section III, we present the bifurcation diagram of deterministic Hodgkin-Huxley neuron model and give a brief analysis on its firing behaviour and excitability. Then, we demonstrate our main results regarding direct electric current, subthreshold weak signal input and suprathreshold periodic forcing cases. Finally, we summarize the main conclusions in section IV.

II. MODEL AND METHOD

In our study, stochastic Hodgkin-Huxley (H-H) neuron with ion channel noise dynamics is considered. The time variation of the membrane potential of stochastic H-H neuron is described by the following equations [49]:

$$C\frac{dV}{dt} = I_{ex} - g_{Na}m^3h(V - E_{Na}) - g_K n^4(V - E_K) - g_L(V - E_L) \tag{1}$$

Here, V is the membrane potential in millivolts. $C = 1\ uF/cm^2$ represents the membrane capacitance of considered neuron. Maximum channel conductances are given as $g_{Na} = 120\ mS/cm^2$ for sodium, $g_K = 36\ mS/cm^2$ for potassium, and $g_L = 0.3\ mS/cm^2$ for leakage currents. Correspondingly, the equilibrium potentials for these ion currents are determined as $E_{Na} = 115\ mV$, $E_K = -12\ mV$, and $E_L = 10.6\ mV$, respectively. Activation and inactivation of sodium gates are controlled by probability functions m and h, whereas activation of potassium gates is controlled by probability function n. The random motion of each ion gates creates stochastic effects on neuron dynamics. The change in gate probability functions over time with the presence of stochastic dynamics is modeled according to the Fox algorithm [50]:

$$\frac{dx}{dt} = \alpha_x(V)(1 - x) - \beta_x(V)x + \xi_x(t), x = m; n; h \tag{2}$$

The α_x and β_x given in Equation (2) are rate functions showing the opening and closing of ion gates that vary depending on the membrane potential, and are calculated for each gate variable as follows:

$$\alpha_m = 0.1 \frac{(25 - V)}{exp[(25 - V)/10] - 1} \tag{3}$$

$$\beta_m = 4\, exp[-V/10] \tag{4}$$

$$\alpha_n = 0.01 \frac{(10 - V)}{exp[(10 - V)/10] - 1} \tag{5}$$

$$\beta_n = 0.125\, exp[-V/80] \tag{6}$$

$$\alpha_h = 0.07\, exp[-V/20] \tag{7}$$

$$\beta_h = \frac{1}{exp[(30 - V)/10] + 1} \tag{8}$$

The randomness in the sodium and potassium gates is described by white Gaussian noise whose autocorrelation function is as follows:

$$\langle \xi_m(t)\xi_m(t')\rangle = \frac{2\alpha_m\beta_m}{N_{Na}(\alpha_m + \beta_m)}\delta(t - t') \tag{9}$$

$$\langle \xi_h(t)\xi_h(t')\rangle = \frac{2\alpha_h\beta_h}{N_{Na}(\alpha_h + \beta_h)}\delta(t - t') \tag{10}$$

$$\langle \xi_n(t)\xi_n(t')\rangle = \frac{2\alpha_n\beta_n}{N_K(\alpha_n + \beta_n)}\delta(t - t') \tag{11}$$

Here, the parameters N_{Na} and N_K represent the total sodium and potassium channel numbers on the membrane surface, respectively. The total channel numbers are calculated for a membrane area of A with the equations $N_{Na} = \rho_{Na}A$ and $N_K = \rho_K A$. In these equations, the values given as $\rho_{Na} = 60\,\mu m^{-2}$ and $\rho_K = 18\,\mu m^{-2}$ indicate related channel densities. Thus, A becomes a parameter that determines the level of noise originated from ion channels. Literally, the membrane area and the effective ion channel noise amplitude are inversely proportional. Accordingly, since many ion channels are involved in the system dynamics for a large membrane area, it can be said that the stochastic contribution of individual ion channels becomes negligible. Lastly, $I_{ex} = I_b + S\sin(2\pi f t)$ is the total input applied to the neuron externally. I_b is the bias current that also determines the excitability of the neuron. $S\sin(2\pi f t)$ is the sinusoidal input current, which is used for different forcing regimes, i.e. subthreshold or suprathreshold stimulus state.

One of the characteristic features of cortical neurons is that the spike trains they emit are irregular at a certain level and different neuron types at distinct brain layers exhibit regularity at different degrees. We examine the firing regularity via the coefficient of variation (CV). This method is defined as the ratio of the standard deviation of the interspike intervals (ISI) in the entire spike train to the mean ISI and is calculated at trial i as follows [51]:

$$CV_i = \frac{\sigma_{ISI}}{\langle ISI\rangle} \tag{12}$$

$$\sigma_{ISI} = \sqrt{\langle ISI^2\rangle - \langle ISI\rangle^2} \tag{13}$$

$$\langle ISI\rangle = \sum_{s=1}^{p-1} \frac{t_{s+1} - t_s}{p} \tag{14}$$

$$\langle ISI^2 \rangle = \sum_{s=1}^{p-1} \frac{(t_{s+1} - t_s)^2}{p} \tag{15}$$

where p indicates total number of spikes in a single simulation and t_s denotes occurrence time of s^{th} spike. As CV value approaches zero, it represents regularity, and as it takes values close to one and even larger values, it serves as irregularity. In completely irregular firing sequences, CV can be greater than one [52].

To further characterize spiking behaviour quantitatively, we calculate the mean firing rate that is averaged over trials for a given parameter set. We first randomly select initial conditions for the neuron with uniform probability within the range from -10 to $80\,mV$ for the membrane voltage variable V, and within the range from 0 to 1 for the gating variables m, n, and h. After a transient time for $1\ s$, we count the number of spikes FR_i generated by the neuron and calculate the regularity measure CV_i at trial i within the following examination time $\tau = 30\ s$. To obtain statistical accuracy, these procedures are repeated $L = 50$ times for any parameter set, and the mean firing rate and the mean CV are calculated as follows:

$$FR = \frac{1}{\tau L} \sum_{i=1}^{L} FR_i \tag{16}$$

$$CV = \frac{1}{L} \sum_{i=1}^{L} CV_i \tag{17}$$

Numerical simulation of the system is integrated using the forward Euler algorithm with a time step $10\ \mu s$.

III. RESULTS AND DISCUSSION

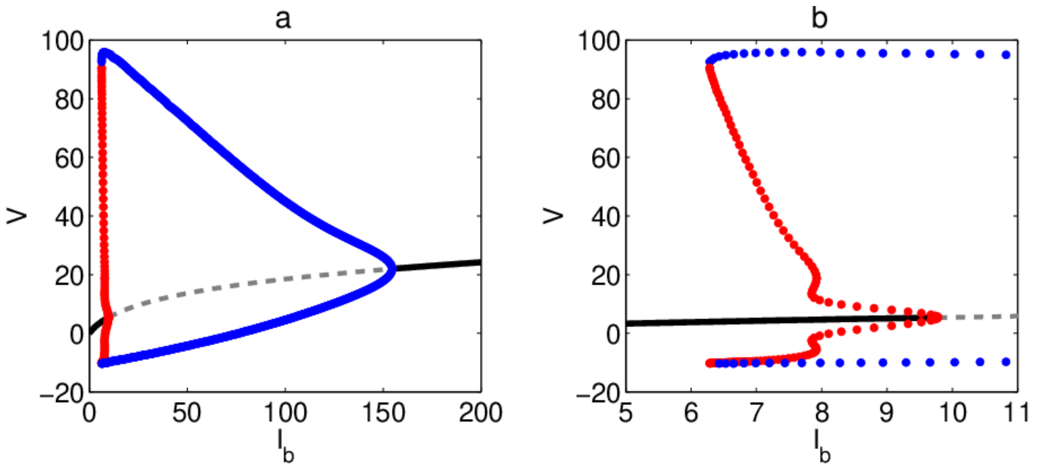

Figure 1. *Bifurcation diagram of deterministic Hodgkin-Huxley neuron. Black solid (dashed) line represents stable (unstable) fixed point that the neuron exhibits resting behaviour. Blue (red) solid circles show stable (unstable) limit cycle which the neuron is at spiking mode. The limit cycles are born at I_b=6.26 with saddle-node bifurcation. As I_b increases, unstable limit cycle shrinks and collapses to an unstable fixed point at I_b=9.78 with subcritical Andronov–Hopf bifurcation. The interval between these two points defines the range of bistability where there is an unstable limit cycle that separates coexisting stable limit cycles and fixed points.*

In this study, we investigate firing behaviour of stochastic H-H neuron through the analysis of firing frequency and regularity under effect of channel noise modulations and different stimuli projections. To obtain a theoretical understanding for underlying process of emitting spikes, we first look at the system behaviour of a deterministic H-H neuron. For this aim, we present two parameter bifurcation of H-H neuron model in figure 1 where panel a and panel b show long and zoomed-in version of the diagram. As a response to applied DC bias current, H-H neuron exhibits subcritical Andronov-Hopf bifurcation, which is a clear indication of class II excitability and a non-zero firing frequency. H-H neuron shows bistability between $I_b = 6.26$ and $I_b = 9.78$, implying that there are both stable limit cycle and stable fixed point at the same time in this interval, and it has an unstable limit cycle separating the two stable focuses. Fluctuations in neuron dynamics, such as noisy input currents, can force the neuron to oscillate or become silent by pushing towards the two attractors. Neurons is excitable, where there exists only stable fixed point, before the bistability interval. On the contrary, H-H is a pacemaker neuron that continuously fires at a constant frequency after above-mentioned interval where there are stable limit cycle and unstable fixed point.

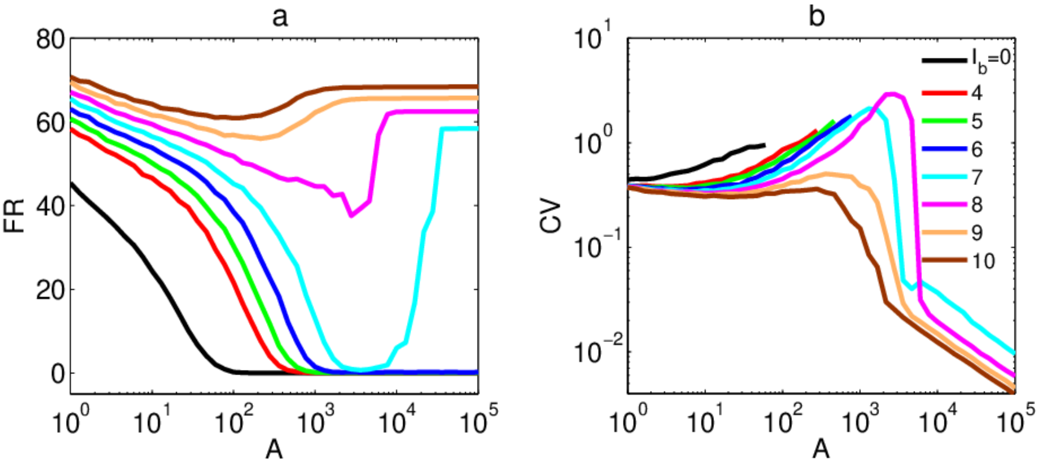

Figure 2. *Firing behaviour of class II H-H neuron depending on ion channel noise variations at different bias current levels. Panels show both (a) firing rate and (b) CV measure for corresponding bias current cases with same-coloured lines. It is seen that excitable neuron exhibits only spontaneous irregular spiking activity. However, when the neuron is bistable, it shows regular spiking behaviour in lower noise regions, and while noise intensity increases, inverse stochastic resonance effect emerges with a high irregularity.*

The level of DC input applied to the neuron can be considered as a bias current which determines the subthreshold and suprathreshold regimes. When $I_b > 6.26$, the neuron may exhibit firing behaviour depending on the initial conditions and environmental factors. We now examine the effects of internal noise on firing behaviour and regularity of neural firing patterns in subthreshold and suprathreshold regimes. The noise governed by the Fox algorithm is modulated with the membrane surface area in order to control the internal noise level occurring in the ion channels. Accordingly, when the membrane area is small, random ion movements cause too much noise in the total membrane potential. Otherwise, the randomness in ion movements spreads over a much larger membrane area and fluctuations in membrane potential becomes minimal. Connected with these assumptions, the average firing numbers as a function of membrane area and the regularity in the firing patterns were calculated in the presence of increasing bias current. The obtained results are given in the figure 2.

Figure 2a shows that the excitable neuron ($I_b < 6.26$) can fire spontaneously if channel noise with a high intensity is present. On the other hand, according to CV measure in figure 2b, an irregular firing pattern emerges in the size of the area where the neural firings first begin to occur, and as the size of surface area decreases, relatively more regular firings occur due to the increasing noise intensity. When the bias current applied to the neuron is taken as $I_b = 7$, the neuron exhibits channel noise-induced inverse stochastic resonance phenomenon, and this continues to occur at the suprathreshold excitation regions. When the stimulation is enough for the neuron to emit spikes (i.e. $I_b > 6.26$), low channel noise has a limited effect on firing regularity and H-H neuron exhibits a regular firing activity with a constant firing rate. However, due to the stronger channel noise arising from membrane size in intervals where the ISR effect occurs, although the neuron is exposed to a stimulation current sufficient to fire, such a level of noise can prevent the neuron from firing or even push it to the silent state. The main reason behind this fashion of spiking is that the neuron exhibits bistable behaviour in the range of $6.26 < I_b < 9.78$, and the unstable attractor separating these two stable states narrows as I_b increases. Thus, it makes easier to explain the behavior of regular firings with constant rates over a wider range due to increasing channel noise for the cases in this bias current interval.

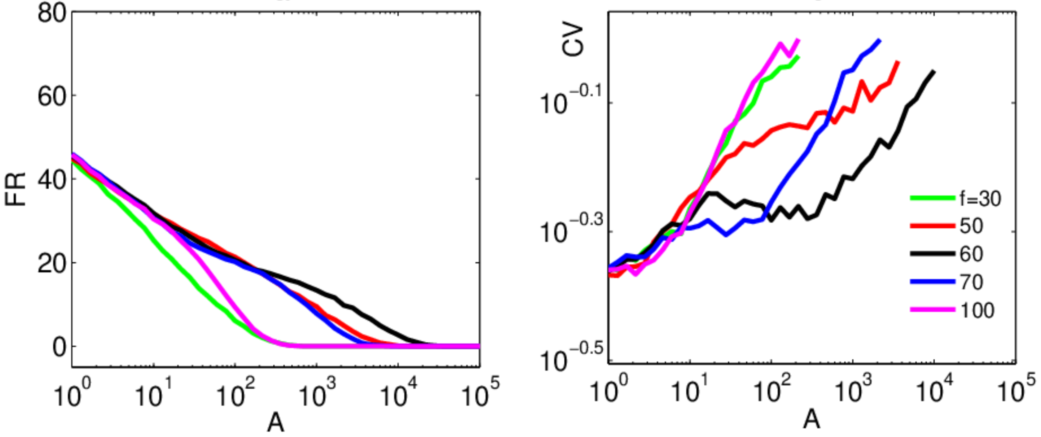

Figure 3. *Firing behaviour of H-H neuron as a response to subthreshold periodic input signal. Panel a and panel b show firing rate (spike probability) and variation of CV as a function of ion channel noise for different signal frequencies. Legends in panel b are also valid for panel a. To obtain subthreshold regime, signal amplitude is fixed as S=1.4.*

Neurons constantly receive various stimuli in distinct nature from inner neural medium and environmental sources. Regarding this fact, we now investigate firing behaviour of stochastic H-H neuron exposed to sinusoidal inputs. We first explore how increasing channel noise shapes the neural response to the sinusoidal forcing signal that is subthreshold for deterministic H-H neuron. To do this, we measured number of firings and calculated regularity due to CV as a function of membrane area for different weak signal frequencies. Obtained results are depicted in figure 3. Basically, if internal channel noise arises from very narrow and large membrane patch areas, it has a similar effect on firing probability of neuron. This can be clearly seen from figure 3a. In these cases, regardless of varying weak signal frequencies, all sinusoidal inputs are subthreshold for deterministic H-H neuron to emit a spike and large area roughly makes membrane potential insensitive to ion fluctuations. On the other hand, very small membrane area produces highly intense ion channel noise, and this forces the neuron to fire spontaneously with a certain average frequency level. Apart from these extreme points, intermediate channel noise levels obtained through relative membrane areas induce different firing behaviours for varying weak signal frequencies. According to [53], threshold for spike generation shows the presence of a nonlinear relation between amplitude and frequency of sinusoidal forcing. Under the light of this evidence, the neuron receiving signal with a fixed amplitude $S = 1.4$ at a given frequency $f = 30$ and even $f = 100$ needs more excitation to switch to firing mode than the cases of frequencies in between, such as $f = 60$. Our results confirm that with inherent stochastic dynamics strong enough, sensitivity to subthreshold signal frequency for entering firing regime follows the same distance with the previous findings in presence of relative channel noise intensity.

Furthermore, we explore how the regularity of neural firings is affected by internal noise if subthreshold signal oscillates at given different frequencies. In figure 3b, by comparing with figure 3a, it can be obviously inferred that behaviours of firing rate and regularity is in a close relationship. Notice that CV values are calculated only if there is a spiking activity. Since a sinusoidal input with $f = 60$ Hz makes the neuron more excitable to respond with an action potential, and lower or higher frequencies such as $f = 30$ Hz or $f = 100$ Hz make it harder, corresponding channel noise levels initially give rise to emergent irregular firing activity. The figure shows that if input signal is set with $f = 60$ Hz, i.e. frequency value which make it easier for neuron to respond, increasing channel noise intensity helps to more easily get through more regular spiking behaviour. The figure also demonstrates that channel noise with high intensity coalesces the values of spiking regularity induced by different signal frequencies at a fairly decent CV level.

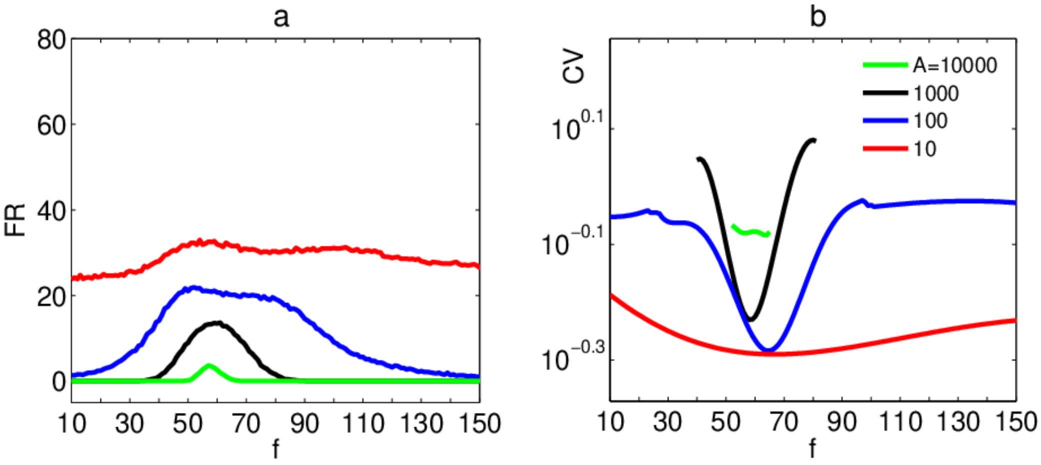

Figure 4. *Variation of (a) firing rate and (b) CV values as a function of weak signal frequencies for different ion channel noise intensities. Signal amplitude is subthreshold with S=1.4. Notice that legends in panel b are also valid for panel a.*

Our results show that a certain level of ion channel noise can trigger spiking events as a neural response to the subthreshold signal, and the frequency of the weak sinusoidal signal can modulate this level and precision of firing behaviour. To further illustrate the effect of frequency, we now present illustrations of firing rate and CV as functions of signal frequency at different noise levels. The results are shown in figure 4. Here we consider that no bias DC current is applied to the neuron and sinusoidal forcing is subthreshold. Under these conditions, figure 4a and 4b show that our class II neuron exhibits spiking behaviour with a relatively high firing rate at all frequencies in the presence of high channel noise ($A = 10$), and in this case, the emergent firing patterns are fairly regular. On the other hand, it is seen that when there is a medium level of channel noise (see $A = 100$), the neuron can still fire at all frequencies, but especially in the range of approximately $f = 30$ Hz to $f = 100$ Hz, the firing rate forms a bell-shaped curve with the help of this noise intensity. Furthermore, it is seen that when much lower noise levels are adjusted, it is possible for the neuron to fire in a much narrower frequency range and this effect becomes evident around $f = 60$ Hz, and as the noise weakens, the number of firings also decreases. Firing regularity appears as an inverse resonance curve around $f = 60$ Hz in the range of $40 < f < 80$ Hz for $A = 1000$. This can also indicate that the firing regularity increases considerably especially in this frequency range and the weak signal encoding becomes easier. Similar dynamical behavior was reported in [54-57], where signal detection performance for a subthreshold external stimulus with a varying frequency exhibited resonance behaviours with the help of different stochastic or chaotic signal fluctuations at an appropriate intensity, and it was shown that the optimum range of weak signal frequencies for high efficiency lay between approximately $f = 40$ and $f = 80$ Hz. Lastly, limited and irregular firing behaviour is observed with only very sparse firings for $A = 10000$.

Brain operates in an inevitably noisy environment by generating action potentials which is the fundamental units of neural communication. One of main players in the nervous system are spiking neurons which are exposed to suprathreshold signals to emit a spike. These action potentials encode information not only in spike rate but also in their precise timing and pattern. Accordingly, through temporal and rate coding processes, neurons convey the strength and type of stimuli to target neurons or neural circuits. This ensures that sensory information is accurately represented and processed, and enables the nervous system to perceive and respond to stimuli with appropriate sensitivity and specificity [58-59]. Thus, suprathreshold signal encoding has a vital role in neural information processing and even perceptual decisions.

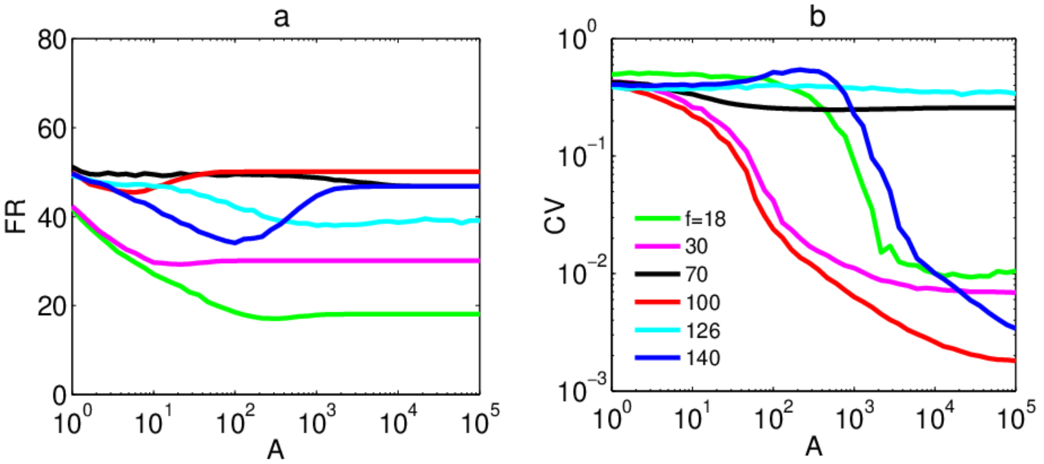

Figure 5. *Firing behaviour of H-H neuron as a response to suprathreshold periodic forcing. Figure demonstrates firing rate in panel a and variation of CV in panel b as a function of ion channel noise for different frequencies (see same-coloured lines for the same frequency values). To obtain suprathreshold input, we set signal amplitude as S=4.*

Let us hereafter examine firing behaviour of stochastic H-H neuron exposed to suprathreshold signal under the effect of channel noise. We analysed firing rate with spiking numbers of neuron and regularity of spiking patterns via CV measure as functions of membrane area for different frequencies of suprathreshold signal whose amplitude is fixed as $S = 4$. We selected our essential sample frequencies for suprathreshold regime from the interval that lays between 16.5 and 144 Hz for the given amplitude [60]. We demonstrate the results considering spike counts in figure 5a. When we look at firing rates for increasing frequency levels, all cases show us that each sinusoidal forcing is readily enough for the stochastic neuron to fire a spike. But firing rates do not increase completely parallel with varying signal frequency. In the firing rate scheme, it is possible to mention about two noise regions regarding spike counts in response to suprathreshold inputs: right and left side of $A \approx 1000$ to separate low and high channel noise intensities, respectively. When we analyse weak noise region, channel noise does not have any significant effect on the firing probability and the neuron exhibits nonlinear firing behaviour due to increasing signal frequency in here, such that firing mode emerges with a relatively low rate with 18 Hz and this continues to increase up to 100 Hz, then it non-monotonically drops with a further increase of signal frequency. On the other hand, we see more intriguing firing behaviours in strong noise region. For instance, for $f = 100$ and $f = 140$ Hz, there appears inverse stochastic resonance effect whereby average firing activity of a neuron exhibits a depression with respect to noise. For $f = 70$ Hz, it is seen that increasing channel noise still have no significant effect on firing probability of the neuron. Moreover, similar effect can be observed in the case of $f = 126$ Hz only with a slight increase in firing rate. Furthermore, low values of selected suprathreshold signal frequencies show more stable firing behaviour in response to increasing noise intensity.

To further investigate neural response behaviour in suprathreshold regime, stochastic H-H neuron is also analysed with regularity as a function of channel noise intensity. Figure 5b illustrates corresponding CV curves. It is apparent that while stochastic ion channel dynamics can change regularity at most cases, it remains very ineffective for suprathreshold signal with $f = 70$ Hz and $f = 126$ Hz. This can also imply that these frequency values cause principally irregular response of the neuron since also very low channel noise give rise to higher CV levels. On the other hand, extreme choices of suprathreshold signal frequency, i.e. lower and upper limit values $f = 18$ Hz and $f = 140$ Hz, exhibit similar CV function due to channel noise modification. This is also valid for other remaining moderate values ($f = 30$ Hz and $f = 100$ Hz). But regularity in the boundary circumstances changes faster than intermediate choices of suprathreshold signal frequency by increasing noise intensity. Furthermore, the last cases look like more advantageous in terms of regular spiking behaviour although high noise intensity cause irregular firing activity for all cases.

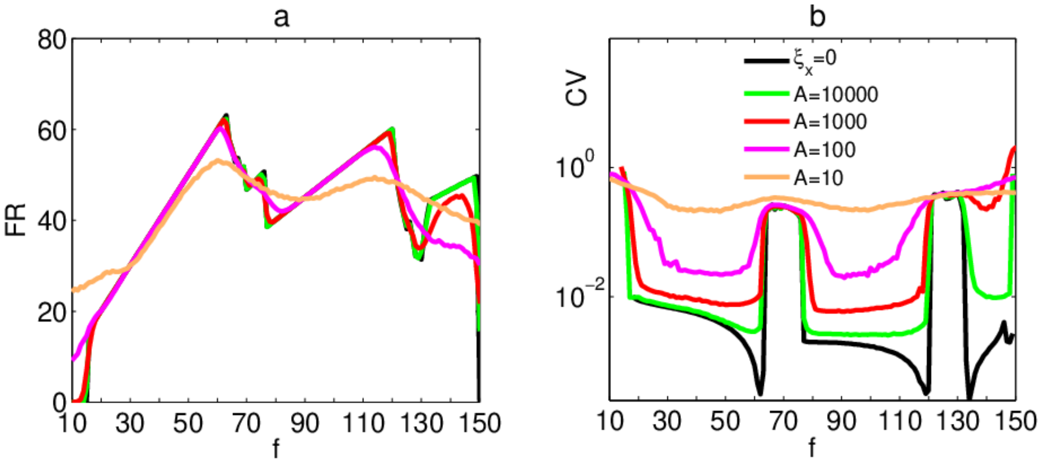

Figure 6. *Variation of firing rate and CV depending on suprathreshold signal frequencies for deterministic and stochastic H-H neuron with different membrane areas (see same-coloured lines for the same noise levels). Signal amplitude is set as S=4.*

To get a broader picture, we illustrate in figure 6 firing rate and regularity functions of deterministic and stochastic H-H neurons depending on suprathreshold driving frequency for different levels of channel noise intensities. When we analyse very intense noise conditions (see brown lines, case of $A = 10$) in both figure 6a and 6b, it gives rise to very variable spiking behaviour regardless of signal frequency as seen from variations of firing probability and regularity. Lower channel noise due to higher membrane area seems to be ineffective for firing rate of the neuron at most of the signal frequency range. On the other hand, one can infer that predominantly there is a linear relationship between input frequency and firing rate of deterministic and stochastic H-H neurons (except the previous case). But, by looking deterministic H-H neuron, it is reasonable to speculate that there is some inconstancy within the intervals of roughly $63 < f < 77$ Hz and $120 < f < 133$ Hz. It happens for the noiseless and low noise cases. Thus, this can imply the presence of some deterioration events in the condition of the neural system. When we examine the regularity via CV functions, it can be obviously seen that neuron exhibit considerably irregular firing behaviors in these situations. This irregular neural response also exists for stochastic H-H neuron due to random spikes arising from adequate noise fluctuations at the borders of suprathreshold frequency range.

To detail these behaviours, we next present ISI bifurcation of H-H neuron for deterministic and different levels of noise cases. To do this, we computed ISI values and normalized to the driving signal period as a function of weak signal frequency. Figure 7 shows obtained results for deterministic (a) and stochastic H-H neuron with $A = 10000$ (b), $A = 1000$ (c) and $A = 100$ (d). Figure 7a shows that our H-H neuron reproduce and essentially exhibits five different behaviours defined in [53] with respect to normalized ISI distribution depending on the suprathreshold signal frequency. By introducing channel noise dynamics into the system equations, in figure 7b, H-H neuron begins to show irregularity at the spiking regime borders, i.e. around $f = 16$ Hz and after $f = 130$ Hz. Due to sensitivity of the neuron to fluctuations, this change in spiking behaviour becomes more apparent with the introduction of higher level of stochasticity with $A = 1000$, as seen in figure 7c. In this case, irregularity in the neighbourhoods of limit frequency values and even in the irregular response regions is increased considerably. It is evident that channel noise has a prevailing effect on spiking behaviour of the neuron. This effect becomes even more obvious when the neuron has a narrower membrane area. When $A = 100$, as shown in figure 7d, ion channel noise make irregularity within the regions mentioned in figure 7c increased and, furthermore, destroys regular spiking trends in the regions between them. Nevertheless, it is possible to indicate that response of stochastic H-H neuron is more sensitive to ion channel noise at the limits of suprathreshold signal frequency values and apparently irregular response region.

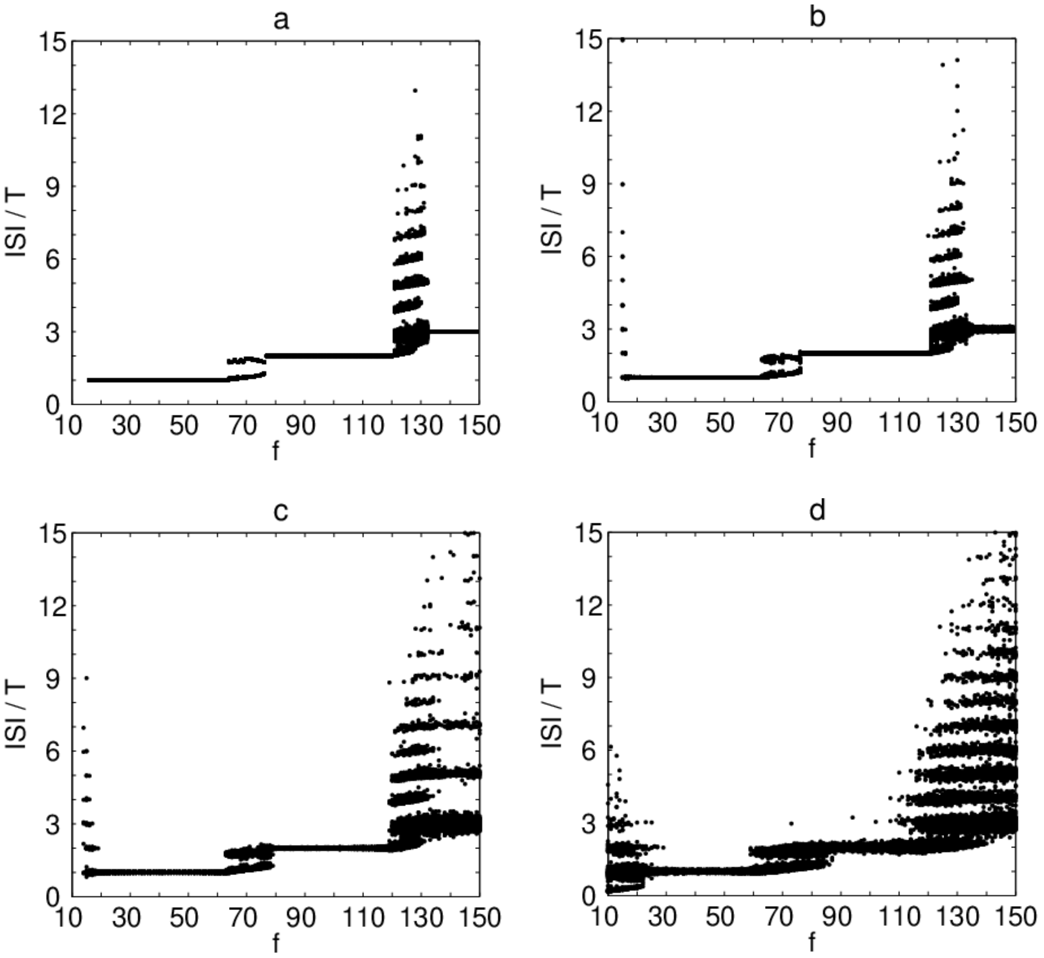

Figure 7. *Bifurcation of normalized ISI distribution over suprathreshold signal frequencies for deterministic (a) and stochastic H-H neuron with various membrane areas as the values of A=10000 (b), A=1000 (c), A=100 (d).*

IV. CONCLUSION

We investigated the influence of ion channel noise on the firing characteristics of class II H-H neuron for different stimuli projections. We observed that for bias current input, neural firings in excitable neuron are only spontaneous and irregular due to channel noise fluctuations. However, the neuron within bistability range exhibits inverse stochastic resonance that emerge with spike skipping or termination. Moreover, we examined neural firing behaviour as a response to subthreshold weak signal under the influence of channel noise. We observed that in this case, frequency has a meaningful impact on the neural response depending on channel noise, and there is a close relationship between spike rate and regularity. Finally, we analysed the firing behaviour of stochastic H-H neuron in the case of suprathreshold signal input. We show that ion channel noise does not have significant effect on spiking rate up to a certain level, and that channel noise does not influence the regularity at certain ranges of signal frequencies where emergent firing behaviour is always irregular, implying the existence of irregular neural response region to suprathreshold periodic signals. Emerging neural response due to applied inputs has gained a more realistic scenario via introduction of channel noise into neuron dynamics. Therefore, for future direction, it is possible that this study can be carried out at network level with different synapse types and biologically meaningful topologies.

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