

Effect of potassium channel noise on nerve discharge based on the Chay model

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Abstract.

BACKGROUND: The nervous system senses and transmits information through the firing behavior of neurons, and this process is affected by various noises. However, in the previous study of the influence of noise on nerve discharge, the channel of some noise effects is not clear, and the difference from other noises was not examined.

OBJECTIVE: To construct ion channel noise which is more biologically significant, and to clarify the basic characteristics of the random firing rhythm of neurons generated by different types of noise acting on ion channels.

Method: Based on the dynamics of the ion channel, we constructed ion channel noise. We simulated the nerve discharge based on the Chay model of potassium ion channel noise, and used the nonlinear time series analysis method to measure the certainty and randomness of nerve discharge.

RESULTS: In the Chay model with potassium ion noise, the chaotic rhythm defined by the original model could be effectively unified with the random rhythm simulated by the previous random Chay model into a periodic bifurcation process.

CONCLUSION: This method clarified the influence of ion channel noise on nerve discharge, better understood the randomness of nerve discharge and provided a more reasonable explanation for the mechanism of nerve discharge.

Keywords: Nerve discharge, ion channel, noise, periodic bifurcation process, Chay model

1. Introduction

Neural discharge is the basis of the neuron coding mechanism. The nervous system senses and transmits information through the discharge behavior of neurons [1–5]. The basis of discharge is the charged ion flow formed by selective ion channels on the membrane of neurons that allow different ions to enter and exit cells [6,7]. At first, the essence of neuron discharge rhythm was studied based on ionic current modeling. Neural discharge rhythm was studied under the deterministic model. The deterministic model could simulate multiple periodic and chaotic rhythms of experimental nerve starting points, and simulate the transition modes among the various discharge rhythms [8–10].

K^+ channels can catalyze K^+ ions transmembrane flow driven by electrochemical gradient, as shown in Fig. 1 [11]. K^+ channels are the key cell activity, which is related to the change of cell membrane potential. The activity of K^+ channel can control the threshold, waveform, frequency, pulse duration and

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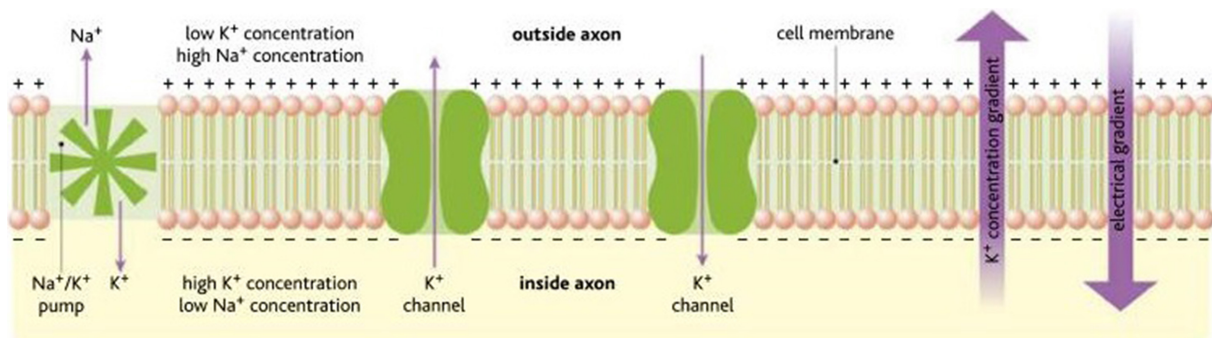


Fig. 1. The resting potential of the axon is maintained by the sodium pump [11].

post-hyperpolarization instability of action potential. K-channel activity plays an irreplaceable role in postsynaptic signal integration, spike pulse generation and signal-to-noise ratio control of presynaptic action potential [12–14].

Because of the complex non-linear structure of neurons and the random factors within the nervous system, the discharge has a complex discharge rhythm. Neurons are affected by various noises in the biological process of transmitting information, such as the randomness of the opening and closing of ion channels, the randomness of neurotransmitters released by chemical synapses, the randomness of the movement of surrounding molecules, and the randomness of input signals of other neurons [15,16]. Hence it is very important to study the effect of noise on the nervous system. Previous concepts have suggested that noise is harmful to some discharge behaviors, but noise is necessary for the occurrence of some important dynamic processes in non-linear systems.

Previous studies on the influence of noise on nerve discharge have achieved rich results. The synergistic effect of noise and system is beneficial to the output of system signals, which is different from people's intuitive understanding of noise [17,18]. Many scholars have studied the effects of white noise, additive noise, phase noise, conductance-based noise and non-Gaussian noise on the random discharge of neurons, suggesting that noise has an important influence on the discharge activity of neurons, so it may participate in the information processing of nervous system, which is helpful to explore the function of randomness in nerve stimulation [19–24]. Studying the rhythm of nerve discharge and the role of noise in nervous system movement is helpful to discover the general law of nerve movement and the existence and significance of noise in life activities.

Although many achievements have been made in the past on the effect of noise on neuronal discharge, there are still some problems in the study of noise-related neuronal random discharge rhythm, which have not been well solved or reasonably explained. These include: 1. The channel of some noise effects was not clear. Most previous studies used the neuron model to explain the characteristics of nerve discharge and used white Gaussian noise as simple additive noise, which was added to the formula of neuron membrane potential, thus ignoring the effect of specific noise on which channel. 2. Some studies on the effect of adding noise to an ion channel item have not examined the difference from other noises.

In view of the existing problems, this paper focused on the construction of ion channel noise with more realistic and biologically meaningful neuron discharge models, and studied the discharge rhythm of neurons. We aimed to achieve the following objectives: 1. To clarify the basic characteristics of the random discharge rhythm of neurons generated by different types of noise acting on ion channels, and to elaborate the reasonable mechanism of the generation of the rhythm; 2. To clarify the difference between the ion channel noise and the overall additive noise in the generation of neuron discharge.

2. Materials and method

2.1. The Chay model

The Chay model (CM) is an ion channel model that describes the complex rhythm of nerve discharge. It can simulate many kinds of periodic and chaotic rhythms of experimental nerve starting points, and the transitional patterns among various rhythms. It can be described as follows:

$$\frac{dV}{dt} = g_I m_\infty^3 h_\infty (V_I - V) + g_{K,V} n^4 (V_K - V) + g_{K,C} \frac{C}{1+C} (V_K - V) + g_L (V_L - V) \quad (1)$$

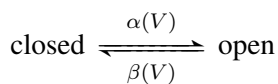
$$\frac{dn}{dt} = \frac{n_\infty - n}{\tau_n} \quad (2)$$

$$\frac{dC}{dt} = \rho (m_\infty^3 h_\infty (V_C - V) - K_C C) \quad (3)$$

where V , n and C represent cell membrane potential, K^+ channel activation probability and intracellular Ca^{2+} concentration, respectively. V_C is the equilibrium potential of Ca^{2+} channel. τ_n is the relaxation time of potassium channel. $g_I, g_{K,V}, g_{K,C}, g_L$ represent the maximum conductance of each channel. V_I, V_K, V_L represent the corresponding equilibrium potentials. The parameter settings in this paper are taken from [22].

The CM could only simulate some periodic discharge and chaotic discharge, and the random rhythm of periodic alternation could be simulated by adding noise to the CM. However, the channel of noise effect was not clear. Most previous studies used neuron models to explain the characteristics of nerve discharge used white Gaussian noise as simple additive noise, which was added to the formula of neuron membrane potential, thus ignoring the effect of specific noise on which channel. This paper focused on the study of the effect of ion channel noise on nerve discharge.

The sources of ion channel noise included many aspects. Here we could make some assumptions according to the dynamic behavior of ion channel. We believed that the random transition of the opening and closing of the ion channel led to the noise of the ion channel, which was the internal noise of the neuron, thus increasing the random fluctuation of the ionic conductance and eventually leading to the generation of complex discharge rhythm, as shown below.



The two parameters represent the transition probability from one state to another. This stochastic transition process was considered as a Markov process, and the corresponding polynomial of ion channel noise can be referred to as follows [25]:

$$\eta = \xi(t) \frac{1}{\sqrt{N}} \sqrt{\frac{2}{\tau_p(V)} p(1-p)} \quad (4)$$

where $\xi(t)$ is Gauss white noise, N is the number of ion channels, $\tau_p(V)$ is the relaxation time of ion channels, and p is the probability of opening ion channels.

In order to characterize more realistic and biologically meaningful neuron discharge models, the effect of channel noise on neuron discharge was studied. The Gauss white noise of potassium channel was added to the Eq. (2) of the CM system, Eqs (1), (3), (5) constituted a random CM based on Gauss white noise of fast potassium channel.

$$\frac{dn}{dt} = \alpha_n(V) (1 - n) - \beta_n(V) n + \eta_n(t) \quad (5)$$

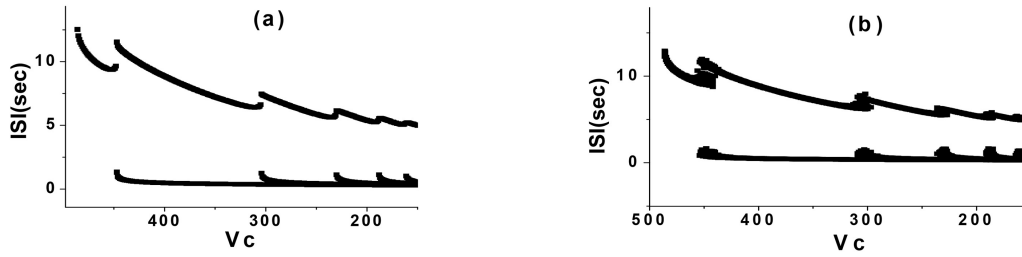


Fig. 2. PAB in the CM ($\lambda_n = 240$). (a) Gauss white noise, (b) Gauss white noise of the potassium channel.

$$\eta_n = \xi n(t) \frac{1}{\sqrt{N_K}} \sqrt{\frac{2}{\tau_n(V)} n(1-n)} \quad (6)$$

2.2. Time series analysis methods

Whether for model simulation data or biological experimental data, we aimed to identify its basic properties through a series of reasonable index analysis, such as the basic dynamic properties to identify whether the rhythm is deterministic or random.

In this paper, the time interval between two adjacent discharge peaks was defined as interspike intervals (ISI). Then the one-dimensional non-linear time series of ISI was analyzed by means of surrogate data (SD), first return map (FRM), autocorrelation coefficient (ACC), nonlinear prediction (NPE) and other methods [22], so as to characterize the stochastic and deterministic characteristics of discharge rhythm and to carry out its signal identification of the source. We intend to analyze the discharge rhythm on the premise of the same long-term dynamic bifurcation background, combined with the non-linear time series analysis method and other traditional statistical methods. The reason for choosing the same bifurcation background is that even though some non-linear indices are the same or similar, the same rhythm cannot be easily determined because they are in different bifurcation backgrounds, such as one between discharge and rest, one between cycle 1 discharge and cycle 2 discharge. The combination of non-linearity and other indicators is due to the misjudgment of the conclusions obtained by relying solely on non-linearity indicators, and the union of other methods often leads to unexpected results, such as the combination of nonlinear prediction and FRM with SD, which can effectively judge the non-linearity determination mechanism of the original data.

3. Results

In the CM, the Gauss white noise and the Gauss white noise of the potassium channel were added respectively. Then, the simulation was carried out when $\lambda_n = 240$, $dt = 0.001$, $D = 0.00000001$ and V_c decreased from 486 mV to 150 mV. The model could simulate the transition process with period-adding bifurcation (PAB), see Fig. 2.

By comparison, it was found that when Gauss white noise was added to the CM with the above parameters, the discharge rhythm was directly from one periodic bursting to another periodic bursting near each bifurcation in the process of PAB, and no other type of rhythm appeared. However, a PAB mode with random rhythm could be generated when the Gauss white noise of potassium channel was added to the same parameters. The random rhythm was located near the bifurcation point of two adjacent periodic

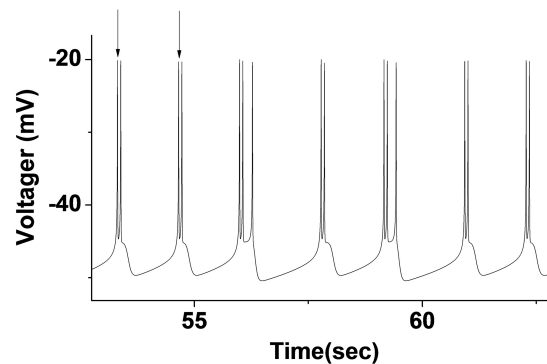


Fig. 3. Stochastic firing trajectory diagram with period 2 and 3 bursting ($v_c = 307$).

bursting, which occurred alternately by two periodic bursting, as shown in Fig. 2b. It was obviously different from the bifurcation process of CM with Gauss white noise in this parameter interval.

The random rhythm near the bifurcation point of period 2 and 3 bursting (Fig. 2b) was selected for analysis. When $v_c = 307$ mV, the discharge trajectory is shown in Fig. 3. The rhythm appeared alternately by period 2 and 3 bursting, and no other bursting rhythm appeared.

The alternating random rhythms of period 2 and 3 bursting in CM simulation with potassium channel noise were analyzed as examples. The ISI sequence of the discharge trajectory of this rhythm was analyzed by various indexes and the results are shown in Fig. 4. There were four kinds of ISI in this rhythm. The smallest ISI was the one by period 2 and 3 bursting, which was reflected by four independent peaks in its statistical histogram. The FRM of ISI sequence was four centralized point clusters, but the FRM of its SD presents 16 point clusters with approximately uniform distribution, which was significantly different from the FRM of the primitive ISI sequence. Because the SD were random, it showed that the ISI sequence had a definite structure and that the rhythm was deterministic. The autocorrelation coefficient of this rhythm decreased gradually from 1 to 0 with the increase of delay in a short time, and oscillates only near 0 when the delay was large. There was a strong self-correlation. When Lag = 1, the self-correlation coefficient was -0.886617 . The nonlinear prediction of ISI was short-term predictable and long-term unpredictable, while the substitution data of ISI were unpredictable regardless of the prediction step length; the approximate entropy of the ISI series was 0.202062. All the above indicators showed that the stochastic rhythm had a certain certainty.

The results of the non-time series analysis of ISI of this random rhythm showed that the rhythm had a certain randomness. In order to further verified the randomness of the rhythm, we had carried out a more detailed analysis. Since the random rhythm only contains period 2 and bursting, a single period bursting could be defined as an event (period 2 or 3 bursting), and the time interval between two consecutive period 2 or 3 bursting was recorded as an inter-event interval (IEI). Taking period 2 bursting as an example, we considered the time interval between two consecutive period 2 bursting as IEI. As shown in the interval between two vertical arrows (Fig. 2), we analyzed the IEI of this random rhythm. The results of IEI sequence analysis of period 2 bursting are shown in Fig. 5. The IEI presented a typical integer multiple rhythm. The FRM of IEI was a typical lattice structure with integer multiple rhythm, which was not significantly different from the FRM of its SD, indicated the randomness of the IEI sequence. Its statistical histogram was approximately like the exponential attenuation multimodal distribution of integer multiple rhythm. The autocorrelation coefficient oscillates near zero when the delay was not zero. The nonlinear prediction was unpredictable regardless of the prediction step size error was close to 1.

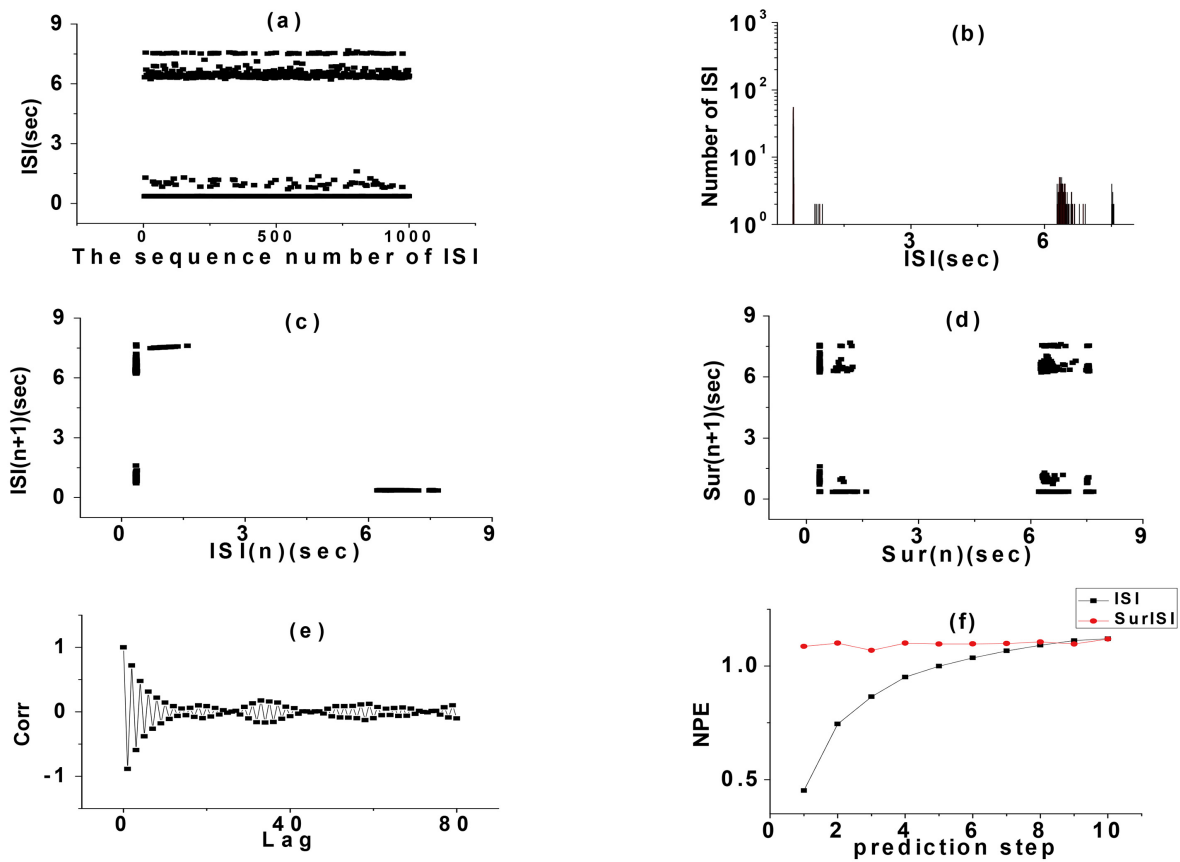


Fig. 4. Analysis on ISI. (a) ISI series, (b) ISI histogram, (c) FRM, (d) FRM of SD of ISI, (e) ACC, (f) NPE.

The approximate entropy of the IEI series was 0.479114, which also indicated that the IEI series was a stochastic non-renewal process.

When $\lambda_n = 225.8$ and other parameters remained unchanged, the PAB histograms of model simulation is shown in Fig. 6. It could be found that adding Gauss white noise to CM with the above parameters will produce a PAB with chaotic rhythm, to spiking via “shrinkage”, and to period 1 spiking. The chaotic discharge rhythm appeared at the bifurcation point of period n and $n + 1$ bursting ($n = 2, 3$). At the bifurcation point of period 1 and 2 bursting, the discharge rhythm of period 1 bursting directly went to that of period 2 bursting, and there was no other type of rhythm. However, when added the Gauss white noise of potassium channel under the same conditions, the discharge mode at the bifurcation point of period 1 and period 2 was obviously different from the PAB with the Gauss white noise. We selected the discharge rhythm near this bifurcation point for analysis. When $v_c = 295$ mV, the discharge trajectory as shown in Fig. 7. The discharge rhythm appeared alternately by period 1 and 2 bursting, and no other cluster discharge rhythm appeared.

In order to analyze the characteristics of the chaotic discharge rhythm, we took the chaotic rhythm near the bifurcation points of the period 2 and 3 bursting (Fig. 6b) as an example. The amplification diagram is shown in Fig. 8a. We chose the discharge rhythm when $v_c = 199.5$ mV to analyze. The discharge trajectory diagram is shown in Fig. 8b. This rhythm was significantly differ in the random rhythm of periodic n cluster and periodic $n + 1$ cluster in PAB ($n = 1, 2, 3, 4$). The composition of the chaotic

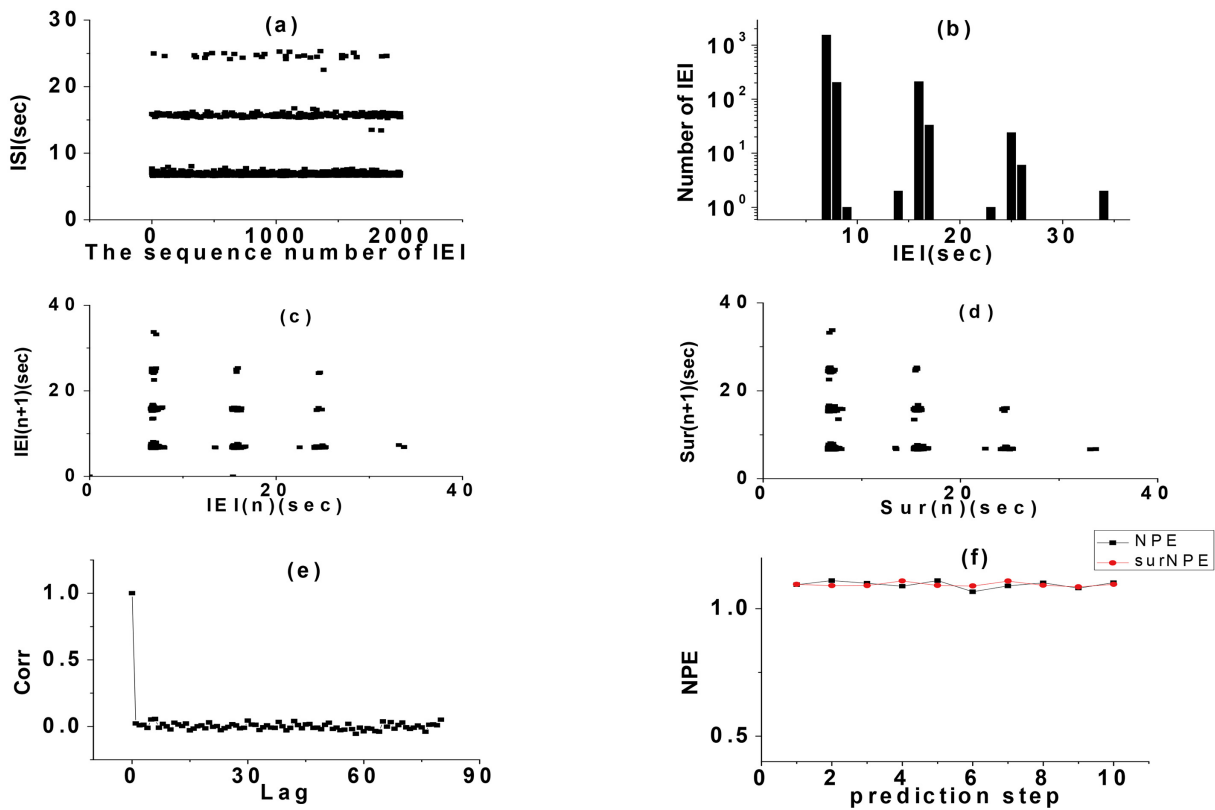


Fig. 5. Analysis on IEL. (a) IEL series, (b) IEL histogram, (c) FRM, (d) FRM of SD of IEL, (e) ACC, (f) NPE.

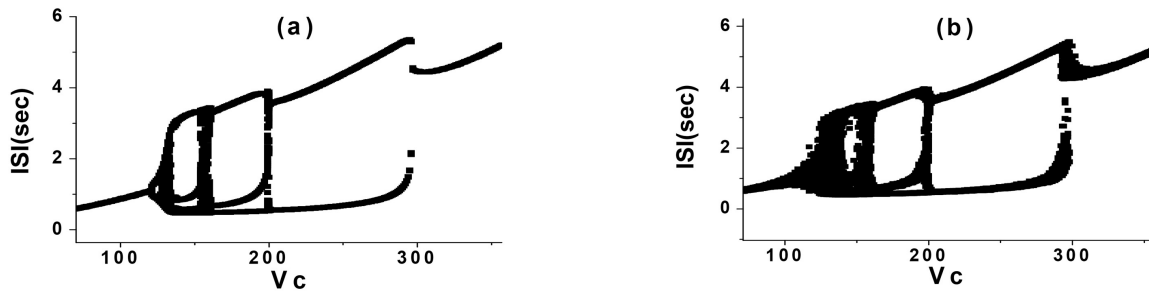


Fig. 6. PAB in the CM ($\lambda_n = 225.8$). (a) Gauss white noise, (b) Gauss white noise of the potassium channel.

rhythm between period 2 and 3 bursting was not only of these two types, but also other types of rhythm, as shown by the oblique arrow in Fig. 8b.

The ISI sequence of chaotic rhythm at bifurcation points of period 2 and 3 bursting was analyzed by non-time series, and the results are shown in Fig. 9. There were several ISI bands and some scattered points between bands in the sequence diagram of this rhythm, which were reflected in the continuous distribution in its statistical histogram. The FRM of ISI had obvious geometric shape, and the figure was horseshoe-shaped single-peak mapping, as shown in Fig. 9c. The autocorrelation coefficient of this rhythm decreased gradually from 1 to 0 with the increase of delay in a short time, and oscillated only

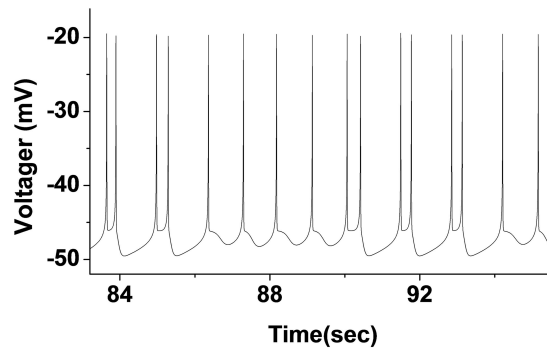


Fig. 7. Stochastic firing trajectory diagram with period 1 and 2 bursting ($v_c = 295$ mV).

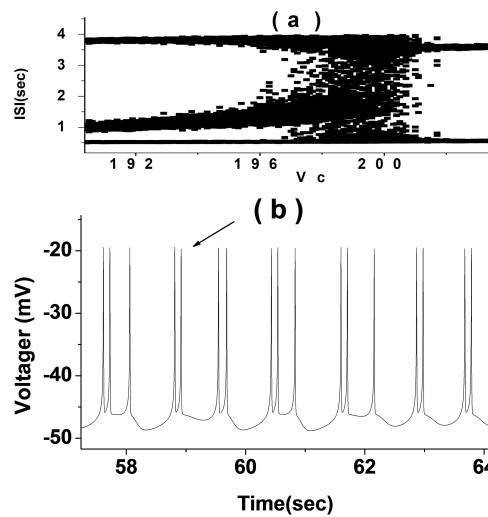


Fig. 8. (a) bifurcation sequence between period 2 and 3 bursting, (b) chaotic discharge rhythm trajectory diagram with period 2 and 3 bursting ($v_c = 199.5$ mV).

near 0 when the delay was large. There was a strong self-correlation. When Lag = 1, the self-correlation coefficient was -0.81394 .

The nonlinear prediction of ISI was short-term predictable and long-term unpredictable, while the SD of ISI were unpredictable regardless of the forecasting step length. The approximate entropy of calculating the non-periodic rhythm ISI sequence was 0.435132. All the above indicators showed that the rhythm had certain certainty.

4. Discussion and conclusion

This study is based on a thorough investigation of previous studies. In order to depict a more realistic and biologically meaningful neuron discharge model, the effects of channel noise on neuron discharge were studied from ion channels. The sources of ion channel noise include many aspects. Based on the assumption of the dynamic behavior of ion channel, we considered that the random transition of the opening and closing of ion channel leads to the noise of ion channel. Thus, the noise of ion channel

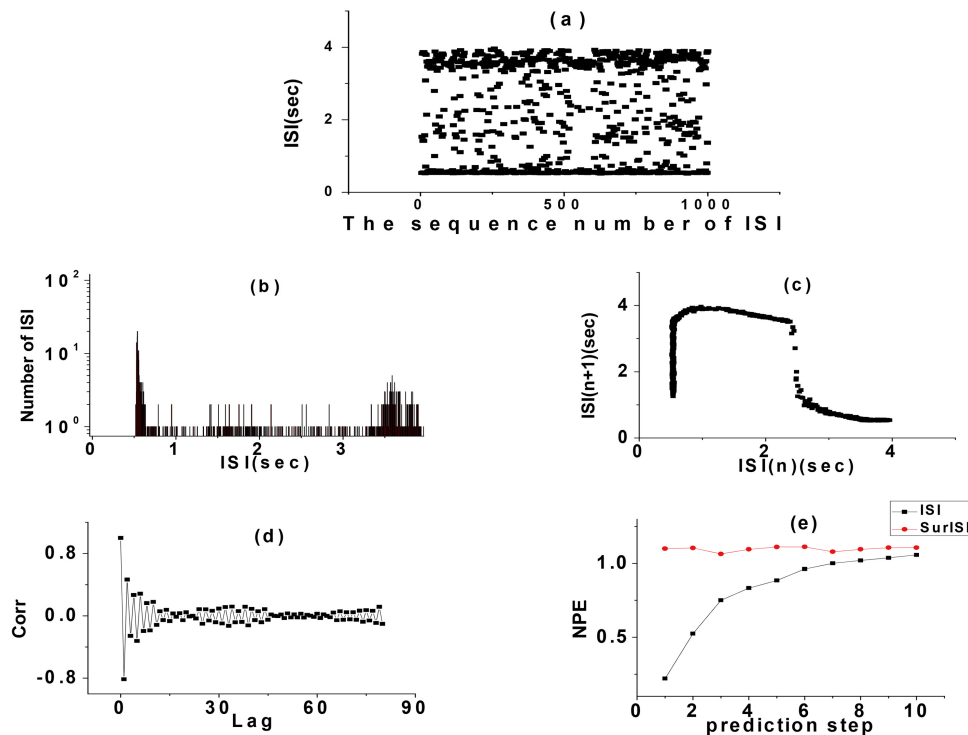


Fig. 9. Analysis of chaotic rhythm ISI between period 2 and 3 bursting. (a) ISI series, (b) ISI histogram, (c) ACC, (D) NPE.

based on the dynamic behavior of ion channel was constructed to make the noise more specific and biologically meaningful, so that we could study the effect of specific noise on ion channel. Through simulation analysis, it was found that the generation of internal noise in this neuron could change the reliability of pulse sequence, increased random fluctuation of ion conductance, and eventually led to the generation of complex discharge rhythm.

By constructing potassium channel noise, we established a random CM based on potassium channel noise, which fully realized the discharging rhythm of neurons induced by potassium channel noise, and compared the dynamic characteristics with the data simulated by random model with simple additive global noise. The difference between potassium channel noise and global additive noise in generating neuron random discharge was clarified. It was found that under the same noise intensity, the noise of potassium channel was more likely to cause the random discharge rhythm near the bifurcation point of the adjacent period, which had a greater impact on the nerve discharge. CM with potassium channel noise could not only simulate periodic alternating random rhythm and chaotic discharge rhythm, but also effectively integrated random alternating rhythm and chaotic rhythm into the same bifurcation process, which was the biggest difference from CM with simple additive global noise. It not only clarified the effect of specific noise on neuronal discharge, but also provided a more reasonable explanation for the mechanism of nerve discharge rhythm. The joint analysis of random rhythms and chaotic discharges near bifurcation points using multiple indicators is expected to be an effective method for the analysis of irregular nerve discharges, and also provide reference for the identification of other similar physiological signals.

In this paper, the effect of potassium ion channel noise on nerve discharge was studied, which not only specified the noise, but also analyzed it on the basis of nerve discharge. The basis of discharge is the

charged ion flow formed by the selective admission of different ions into and out of the cell membrane by various ion channels on the neuron cell membrane. Therefore, analyzing the phenomenon of nerve discharge from the perspective of ion channel behavior may essentially grasp the essence of information transmission by nerve coding. In this paper, we only studied the effects of potassium channel noise and total noise, because we assumed that channel noise is caused by random opening and closing of ion channels. The second equation in the Chay model describes the probability of opening potassium channels, so we studied the effect of noise on potassium channels based on this basis. Next, we can consider the effect of other channel noise on discharge, such as calcium ion and sodium ion.

Future work should continue to focus on ion channels. In our previous articles, we considered the mechanism of peak generation of nerve discharge, made reasonable assumptions about the probability of K^+ channel opening, and improved the CM [26]. That is, when the voltage of a single pulse reaches its peak, the K^+ channel will open completely at once. At the same time, depolarization ends and repolarization begins. Although the improved model is deterministic and does not add noise, it has similar results with the current one. It can be seen that ion channels have a great influence on nerve discharge. Starting from ion channels, it is very important to study nerve discharge. This is the case with the theoretical model, but the key point is to guide the practice. Then in the actual biological experiment, we can use the method of controlling the concentration of peripheral potassium ions or blocking the expression of potassium channels to obtain the experimental data of potassium channels affected, and then compare them with the content of this paper. This will provide a richer guiding significance.

Acknowledgments

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Conflict of interest

None to report.

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