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BP Neural Network in Patch-Clamp Amplifier C-Fast Compensation

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Abstract: **Patch-clamp is used to study all sorts of ionic channels and their regulations through measuring pA current of cell ionic channel, but the C-Fast transient currents caused by measuring objects and measuring instruments themselves will change the properties of action potentials. Aiming at the shortage of traditional C-Fast compensation method, a compensation algorithm for the C-Fast based on BP neural networks is proposed. Establish circuit model of patch-clamp through MATLAB SIMULINK, and the circuit is simulated in accordance with compensation parameters from the traditional compensation algorithm and the compensation algorithm based on BP neural networks.The experiment result shows that transient currents decreases from 10nA to 2.4pA based on the BP neural networks compensation algorithm, and the BP neural networks compensation algorithm can improve the C-Fast compensation precision.**

***Keywords*：** **Patch-clamp, C-Fast，action potential，BP neural networks algorithm, capacitance compensation.**

1. INTRODUCTION

Patch-clamp technique has been widely used in the field of life sciences, Its main application is measuring the intracellular ion channel currents to study various ion channels and their regulatory mechanism. In the cells seal, presence of distributed capacitance will affect the measurement accuracy, Thus patch clamp amplifier needed fast capacitance compensation. The principle of Fast capacitance compensation is to generate an analog current by capacitive compensation circuit which is equal and opposite to transient current signal[1]. The most common method of Fitting waveform is the least squares polynomial[2]. However, Least squares polynomial in practical applications. when the low degree of the polynomial, the real situation is difficult to approach represents multiple data points, and when a higher degree of the polynomial, Curve fitting prone shocks, thus limiting its application[3-4]. With the rapid development of artificial neural networks, and it is widely used in the field of curve fitting, curve fitting is no longer confined to fit the analytical expression of the theory of constraints. It opens a new method of curve fitting based BP (Back Propagation) neural network algorithm for fast capacitance compensation. It is a neural network topology data to determine the relationship between the new curve fitting method, with non-linear mapping. In this paper, apply BP neural network algorithm to build fast capacitance compensation models, and use this model to compensate measurement errors caused by stray capacitance.

2. THE EFFECT OF FAST CAPACITANCE ARTIFACT SIGNAL ON THE ACTION POTENTIALS

When step signal that as the command voltage is added on the I - V converter, the charging and discharging process of fast capacitor might cause the monitoring signal distortion and affect the membrane current signal observation [5]. The existence of fast capacitor will induce spike in the rising and falling of transmembrane current, and introducing Pseudo differential signals of Membrane voltage which affect the release of the action potential accuracy[1,6,7].

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When cells in GΩ sealing, because of the fast capacitance, it will introduce a larger spike signal which cause the signal distortion, and affect the membrane current signal observation after the spike signal observation, thus resulting in a membrane potential error. The figure of stimulated current's function for cell membrane as shown in figure 1 [8].

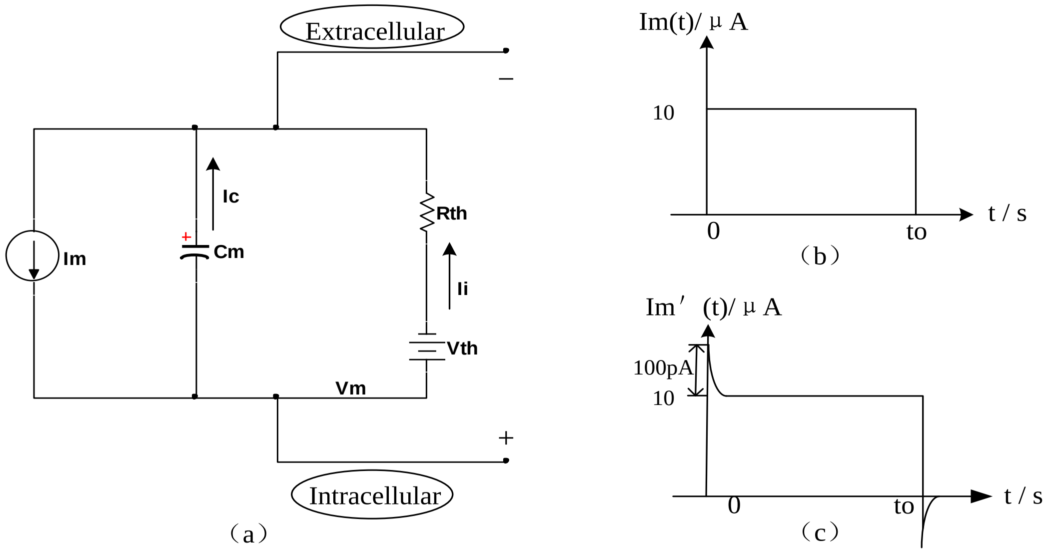

Figure 1 The figure of stimulated current's function for cell membrane (a) Neural cell membrane's circuit model (b)Transmembrane pulse current(c) Cross membrane Pseudo differential current caused by electrode capacitance

According to the circuit model of nerve cells as shown in figure 1 (a), available to stimulated current's function for cell membrane are as follows[6,10]::

$$I_m(s)=\frac{V_m(s)}{R_{Th}}-\frac{V_{Th}}{sR_{Th}}+sC_mV_m(s)-C_mV_m(0^+) \qquad (1)$$

Ideally, the current pulse signal is step signal, as shown in figure 1 (b). When the electrode tip and the membrane form the level G Ω sealing, the existence of capacitor will make the spike current signal's appearance, as shown in figure 1 (c), In this case, the spike signal is represented by a shock signal function, get the expression for membrane capacitance expressions after introduce fast capacitance Pseudo differential signal is:

$$V_m(s)=\frac{K\left(1-e^{-t_0 s}\right)}{C_m\left(s+\frac{1}{C_mR_{Th}}\right)}+\frac{V_{Th}}{s} \qquad (2)$$

The initial conditions of the simulation model are as follows: $V_{Th}=85mV$, $R_{Th}=1k\Omega$, $C_m=1\mu F$, t_0=6ms
Because after the fast capacitance compensation residual artifact signals are generally 2 ~ 3 pA, in order to study the influence of the Pseudo differential current on the membrane potential of the electrode capacitance, not to consider the external stimulus current, Only consider the influence of electrode ,capacitance and pseudo differential current,select the size of 100 pA ~1000pA five set of values for simulation, When the Pseudo differential current is larger, the value of that introduced membrane potential's error is larger, 100 pA Pseudo differential current signal will be introduced about 0.1mV of the membrane potential error, according to the calculation principle of HH model, the change of membrane potential changes the threshold of cell action potential, and introduction of spiking error [6,8,11-13], improve fast capacitance compensation precision helps to accurately measure the release of the action potential.

3. FAST CAPACITANCE COMPENSATION PRINCIPLE

Fast capacitance is mainly for electrode capacitance, the charge and discharge current caused by the fast capacitance can bring the measurement of the ion current large error. The fast capacitance compensation circuit is shown in figure 2, making the fast capacitor charge and discharge current through the injection capacity, so that the current does not pass through the I-V converter, to achieve the purpose of compensation.

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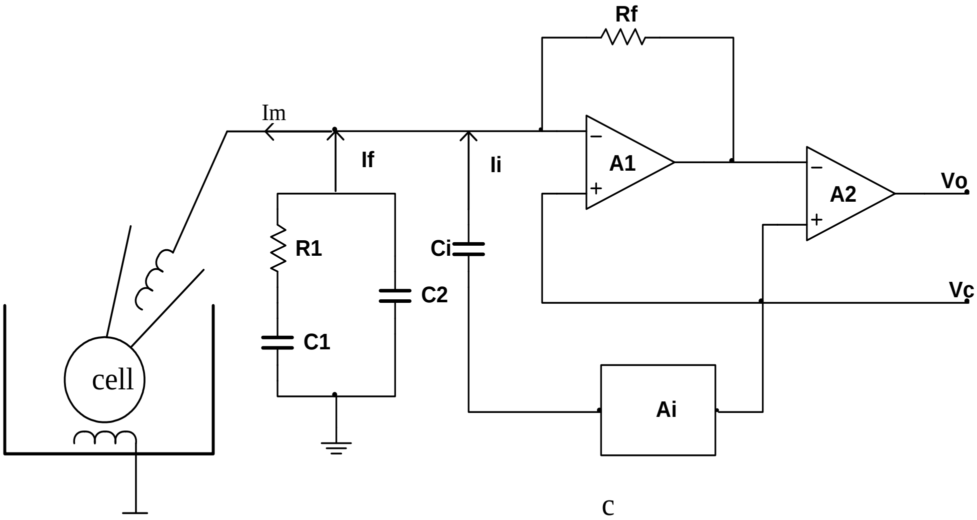

Figure 2 Fast capacitance compensation figure

By adjusting R_1、 C to compensate C_1/C_i andτ, τ= RC_1.By adjusting R_2 to compensate C_2/C_i [14],

$$A_{fc} = \frac{R_f}{R_1} \times \frac{1}{1+j\omega R_m C} + \frac{R_f}{R_2} \qquad (3)$$

The idea of fast capacitance compensation is by adjusting the gain and time constant of the two channels, the compensation is appropriate. The analytical expression of the output current of the detection terminal is as follows:

$$y(n) = \sum_j a_j \times f_j + \varepsilon(n) \qquad j = 0,1,2 \qquad (4)$$

In this expression, f_0 is the effect of R on output current; f_1 and f_2 are respectively represented by the delay and no delay of the compensation channel, providing 1pF fast capacitance compensation, impact on output current; $y(n)$ is output current value of the compensation circuit.In fast capacitance compensation, due to the nonlinear characteristics of τ,so the search using a binary method to find the value of τ, and combined with least square fitting iterative convergence method[2]. By fitting the three parameters f_0, f_1, f_2 weighting, using the τ value from search, find the capacitance compensation value.[15].

4. FAST CAPACITANCE COMPENSATION ALGORITHM BASED ON BP NEURAL NETWORK

Due to the nonlinear characteristics of τ, simply using the least square method for curve fitting has some limitations in fast capacitance compensation. BP network is one of the most widely used multilayer feed forward networks, it can store and learn a lot of input - output mode mapping relations, and it is not necessary to understand the mathematical equations describing the mapping relationship. Its algorithm consists of two parts, which are the forward propagation and error of the signal[3].

4.1 Model establishment of BP neural network compensation algorithm:

To compensate for the Pseudo differential current by using BP neuralnetwork algorithm, Model building steps are as follows:

1. Determination of network layer:

Number three BP network has been proved to be able to approximate any function,increasing networklayercan significantly reduce the number of neurons in the hidden layer without reducing the ability of network mapping. Therefore, three layers of neural network structure is selected.

2. Determination of number of neurons in each layer:

The number of input / output neuron is determined by the input and output vector dimension of the network by expression 4: the network's neuron input is 3, the output is 1. Network model structure is shown in Figure 3. Let the effect ofR on output current f_0, C_1 and the influence of the output current of f_1, f_2 by C_2 changed 1pF, as the three neurons of input layer , so that the compensated current value is the only neuron in the output layer .

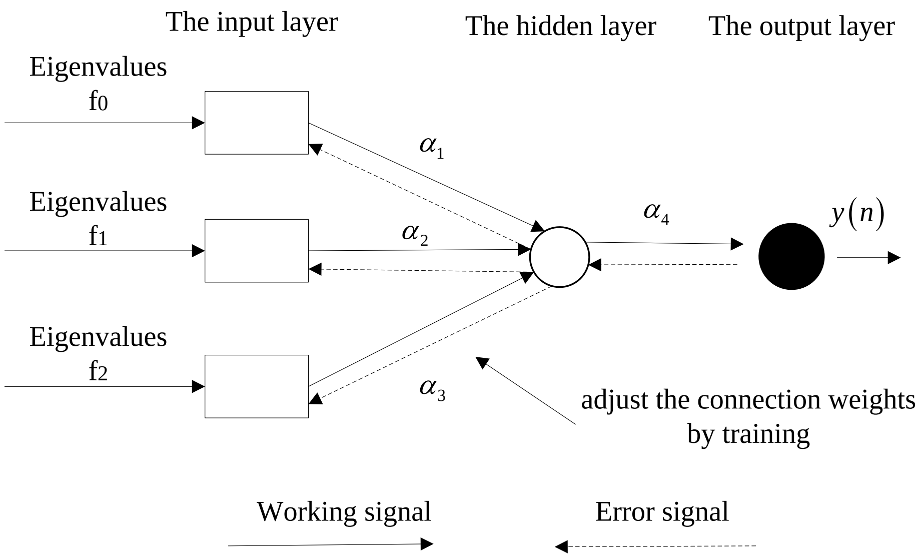

Figure 3 Neural network model of capacitor compensation

The output layer is the fast capacitance Pseudo differential current compensation value after BP neural network compensation, the mathematical model of the fast capacitance compensation principle is as follows:

$$y(n) = f\{f_0, f_1, f_2\} \qquad (5)$$

f_0, f_1, f_2 as the input sample of neural network, $y(n)$ as output sample, the weights of neural network are trained by BP neural network, to determine the neural network model.

4.2 The acquisition of BP neural network compensation algorithm sample data:

The process of collecting sample data is very important for the fast capacitance compensation using neural network algorithm.Because the neural network is trained and learning the sample data, to obtain the compensation value and determine the best network structure, so the accuracy of the sample data acquisition is crucial for the establishment of the fast capacitance compensation model.In order to complete the compensation process, the value of f_0, f_1, f_2 that three input samples is required. f_0 is the effect of R on the output current, which can be characterized by the step response of the detection path under the specified bandwidth. The measurement is carried out by applying a resistor at the input end of the probe. Measuring a set of data by using a 10MΩcell model so that the data set contains the cell model fast capacitance and the probe input capacitance effect;Then the model is set to fast then stalls and measuring the capacitance of the second set of data, that this data set does not have 10MΩ effect, that system step responseobtained by making differential operationof the last of these two sets of data. f_1 can be characterized as an amount of change in the current. By twice setting compensation circuit, the equivalent impedance difference between two measurements accessed 1 times, and then acquired waveform subtracting f_1 , in order to reduce the relative error, in particular, the error introduced by the DC bias value.Similarly, Through different settings values can be calculated in f_2 different time constants[2,14-15]. Since the current value obtained by the above method is the absolute current value, sothere will be a need to be normalized. That f_1

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is normalized to 1 step response, the f_1 and f_2 are normalized to the variation of the output current of the 1F capacitor. Table 1 is the values of f_0, f_1, f_2 and $y(n)$ after a set of normalized

Table 1 Normalized sample data

f_0	-0.887	-0.815	-0.73	-0.673	-0.155	0.120	0.265	0.405
f_1	0	1.185	3.541	4.515	4.000	2.910	1.947	1.115
f_2	0	1.090	3.268	4.515	4.227	3.135	2.085	1.203
$y(n)$	-0.887	6.6925	21.799	29.126	26.994	20.663	13.571	8.054
f_0	0.490	0.504	0.505	0.505	0.505	0.505	0.505	0.505
f_1	0.485	0.245	0.100	0.050	-0.450	-0.450	-0.450	-0.450
f_2	0.485	0.245	0.115	0.065	-0.450	-0.450	-0.450	-0.450
$y(n)$	3.691	2.121	1.215	0.885	-2.465	-2.465	-2.465	-2.465

4.3 BP neural network compensation algorithm training process:

According to nerve sample $f = \{f_0, f_1, f_2\}$ and $y(n)$ training according to procedures for the BP neural network training process as described above, get the neural network model to meet the error condition. According to table 1, the normalized data is used as training data, and the target error parameter is set to 10. The process is shown in Figure 4.

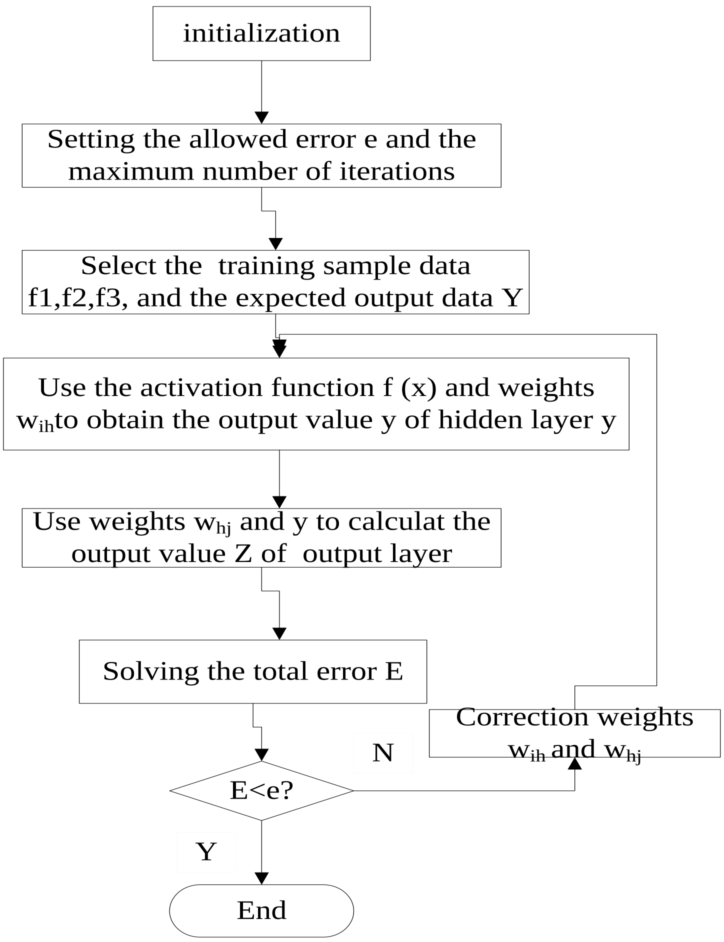

Figure 4 Neural network algorithm training flowchart

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Accordance with the flowchart of Figure 4, simulation in MATLAB, select the appropriate parameter as the BP neural network weights and thresholds, then do training and learningabout sample data to get the best BP neural network. The specific training process is shown in Figure 5, the fast capacitance compensation methodof BP neural network can achieve automatic compensation for fast capacitance.

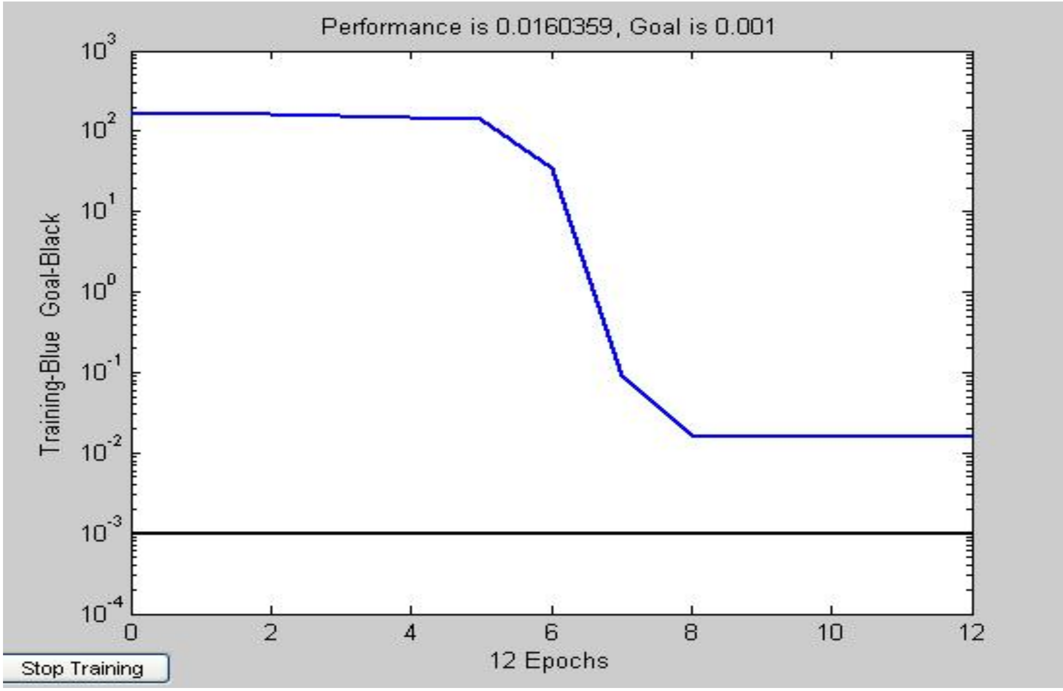

Figure 5 Error curve diagram in the course of BP neural training,

5. SIMULATION ANALYSIS OF EXPERIMENTAL RESULTS

Verified by simulation software MATLAB SIMULINK Kit in order to analyze the feasibility of the neural network algorithm for fast capacitance compensation. According to the compensation principle, the equivalent circuit of the compensation simulation is shown in Figure 6.Providing a voltage from the computer at the input,SIN is a voltage signal of the patch clamp amplifier, the output terminal SOUT output simulation data.

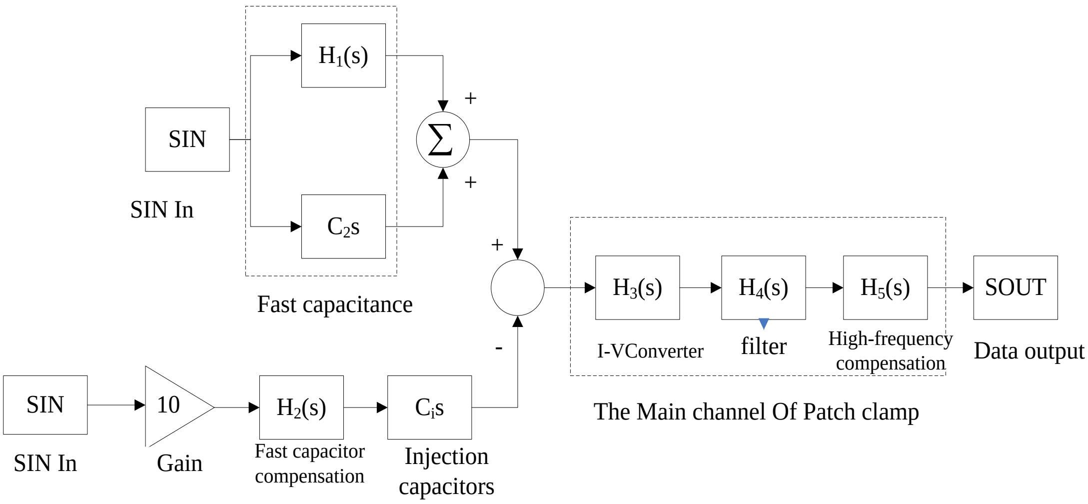

Figure 6 Patch clamp amplifier signal conditioning and Fast capacitance compensation circuit simulation figure, $H_1(s)$ is glass microelectrodes equivalent circuit model, it is parallel with the membrane capacitance of small seal cell membrane.It is parallel with small cell sealing membrane capacitance; $H_2(s)$ is the overall transfer function of the fast capacitance compensation circuit; $H_3(s)$ is the transfer function of the probe amplification circuit; $H_4(s)$ is the transfer function of the filter circuit; $H_5(s)$ is the overall transfer function of the high frequency compensation circuit model.

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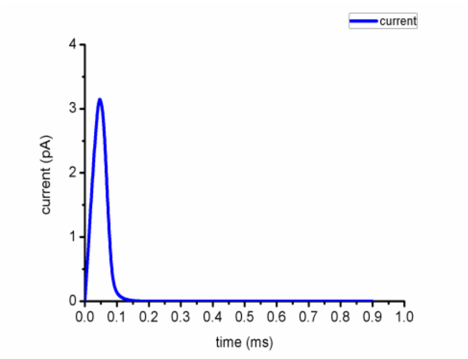
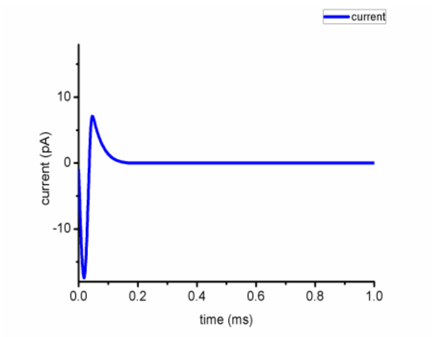
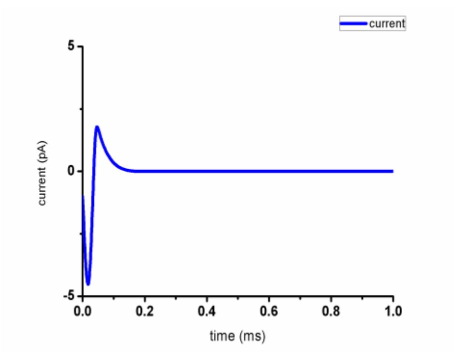
Aiming at the above simulation model, using traditional patch clamp fast capacitance compensation algorithm and fast capacitance compensation algorithm based on Neural network to get the compensation parameters for fast capacitance compensation circuit, and then set the parameters of the compensation circuit, simulation results are obtained as shown in Figure 7.



a) the artifact signal before compensation





b) the residual waveform after traditional fast capacitance compensation c) the residual waveform after BP neural network compensation

Figure 7 Fast capacitance compensation results comparison chart (a) the transient current signal artifactsbefore fast capacitance compensation, Transient current peaks reached 3.3nA, the ion channel current will be flooded by the Pseudo differential current, which needs to compensate for the transient Pseudo differential current. (b) Search the value of τ using Binary search and combined with the residual waveform that based on least square method,Transient Pseudo differential current drops to 8 pA, so that residual pseudo-differential current increase 2 to 3 orders of magnitude. (c)Residual waveform based on BP neural network algorithm compensation,Transient Pseudo differential current drops to 2.4 pA, compared with the traditional algorithm increased more than 3 times.

From this, compared with the traditional compensation method, the compensation method based on BP neural network is better than the traditional method, and can improve the accuracy of the fast capacitance compensation.

6. CONCLUSION

This paper analyzes the impact of Fast capacitance artifact signal to Action potential distribution,came to a conclusion:In the fast capacitance compensation method, Action potential firing frequency and amplitude is inversely proportional to the value of introducedPseudo differential current; When the membrane potential error introduced by the pseudo-differential current is greater than 1mV even affect the release of the action potential. Therefore, there is need to improve fast capacitance compensation accuracy, thereby improving the accuracy of measurement.

In order to solve the shortcomings of the traditional fast capacitance compensation algorithm caused by nonlinear factorsτ, the fast capacitance compensation is based on the combination of neural network algorithm and least square method.Comparison of two compensation algorithm simulation results can be seen that compared with the traditional compensation algorithm, the fast capacitance compensation algorithm based on BP neural network can compensate the fast capacitance better and improve the accuracy of the fast compensation, thereby it improves the accuracy of the measurement accuracy of the action potential.

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