Analysis of spiking evoked by acupuncture based on statistical models

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ABSTRACT

Acupuncture and moxibustion act on acupoint areas with different frequencies, evoking a large number of responding activity of neurons to achieve the purpose of regulating human body functions. In the process of acupuncture, different frequencies of acupuncture evoked different neuronal spiking activity. In order to study the mechanism of acupuncture with different frequencies, Bayesian statistical model is used to optimize the results of the traditional classification algorithm based on spiking waveforms, which greatly reduces the missed detection rate of acupuncture responding activity. Then, the spiking events evoked by acupuncture at different frequencies were statistically analyzed, and the results showed that the number of neuronal spikes gradually increased with the increase of frequency. However, when the stimulation was increased to 120 times/min, the increase in the stimulation frequency will not evoke more spikes due to the saturation of frequency adaptation of the neurons. Finally, a probabilistic statistical model was used to encode the neuronal responding activity evoked by different acupuncture, and the maximum likelihood estimation method was used to fit the model parameters. The results show that the coupling parameters of stimulus are significantly smaller than the coupling parameters of spike-history, and the more the historical spikes, the smaller the coupling parameters of stimulus. This suggests that since acupuncture is a low-frequency mechanical stimulation, a large number of historical spikes in the spiking activity are the main factors that evoke the neuronal response. Thus, revealing the responding mechanism of different acupuncture frequencies.

Keywords: Acupuncture, neuronal spiking activity, statistical model

1. INTRODUCTION

Acupuncture and moxibustion is an important part of Chinese medicine, and more than two thousand years of clinical experience have fully demonstrated its effectiveness[1]. Modern clinical and experimental studies have shown that acupuncture is highly effective in postoperative analgesia and neurological disorders[2,3]. Acupuncture treatment has long lacked normative standards of diagnostic and treatment and technical indicators, and the learning of acupuncture manipulation was often based on the method of apprenticeship. The efficacy of acupuncture is closely related to acupuncture frequency. Different acupuncture frequencies evoke different neuronal responding activity and have different regulatory mechanisms for human body functions[4]. Therefore, this paper introduces statistical models to analyze the neuronal spiking activity evoked by acupuncture, explore the responding mechanism of acupuncture with different frequencies, and provide a scientific basis for the selection of acupuncture frequency in clinical treatment.

Spike is the most fundamental unit of communication during neural response. With the rapid development of multi-electrode acquisition techniques, experimenters have been able to acquire neuroelectric signals from hundreds of channels simultaneously. Therefore, the premise of all research work is to accurately obtain the spiking trains of single neuron from the collected signals of electrodes. Most classification algorithms were based on the discharge waveform. Defining one or several time windows for the spiking waveforms of specific neurons, and then sliding and comparing them on the time axis, and the spiking waveform with the same shape is the spike of that neuron. However, in this classification algorithm, both superposition of spiking waveforms and background noise can produce variable spiking waveform[5,6]. At this time, the classification effect will be significantly worse, the variable spiking waveform will be eliminated, and a large amount of spiking information will be omitted. In order to solve this problem, this paper takes the results of classification algorithm based on waveform as a priori knowledge, and uses Bayesian statistical method to optimize the classification results. The optimized classification results can effectively identify the variable spiking waveforms, greatly reduce the missed detection rate of spike, and improve the accuracy of classification results[7].

International Conference on Future of Medicine and Biological Information Engineering
(MBIE 2024), edited by Yudong Yao, Xiaoou Li, Xia Yu, Proc. of SPIE Vol. 13270,
132700I · © 2024 SPIE · 0277-786X · doi: 10.1117/12.3039731

Neuron model analysis is an important method to study neural information encoding. In order to better analyze various phenomena of neurons, scholars have established a variety of different neuron models based on the real biological neural system. For example, Hodgkin-Huxley (H-H) neuron model[8], Hindmarsh-Rose (HR) neuron model[9], Morris-Lecar (M-L) neuron model[10], FitzHugh-Nagumo (FHN) neuron model[11], Leaky Integrate-and-Fire (LIF) neuron model[12]. In addition, mathematical models with abstract concepts such as the cascade model can be used to describe a variety of dynamic processes within neurons or in neural networks. When selecting a coding model, it is important to be able to interpret the model's parameters and predicted results not only from a statistical perspective, but also from a biophysical perspective. In the real process of neuronal spike, the spiking activity of neurons is affected by external stimuli, the neuron's own spike-history and the spike-history of other neurons[13]. Therefore, we used a probabilistic statistical model to encode the spiking activity of neurons, and add the coupling of stimulus and spike-history to the probabilistic statistical model. Then the Maximum Likelihood Estimation (MLE) method was used to estimate the relevant parameters and explain the responding mechanism of acupuncture of different frequencies[14,15].

2. METHOD

2.1 Spiking sorting by Bayesian statistical model

In this section, the results of algorithm for traditional waveform classification are taken as prior knowledge. and Bayesian statistical model is used to optimize the classification results, identify the variable waveforms that are missed or falsely detected, and accurately obtain the spiking trains of single neurons. According to the results of the algorithms for traditional waveform classification, the prior probability function of the spiking trains d_j is:

$$p(d_j) = \prod_t (p_j)^{d_j(t)} (1-p_j)^{1-d_j(t)} \tag{1}$$

where $d_j(t)$ is a binary variable. When neuron j evokes spikes at time t, $d_j(t)=1$, otherwise, $d_j(t)=0$.

Assuming that the membrane voltage recorded by the electrode at the time t is a linear superposition of all the spiking waveforms in the neuron cluster by different forms at time t. The generative model of the membrane voltage at time t is established as follow[7]:

$$\vec{v}(t) = \sum_{j=1}^{n_c} \sum_{\tau=0}^{n_\tau} d_j(t-\tau)\vec{w}_j(\tau) + \vec{\eta}(t) \tag{2}$$

where, the column vector $\vec{v}(t)$ represents the spikes recorded by all electrodes at time t, n_c is the number of muti-electrodes, and $\vec{v}_i(t)$ represents the spikes recorded by i th electrode at time t. All spiking waveforms are discretized into n_τ parts on average, and the matrix $\vec{w}_j(\tau)$ denotes the τ th segment waveform of neuron j recorded by all electrodes. $\vec{\eta}(t)$ is the background white noise with zero mean.

According to (1), the generative model for spikes throughout the entire observation period is obtained:

$$V = W * D + \eta \tag{3}$$

where, $W*D$ represents the convolution operation in (2), and η is a multivariable Gaussian white noise. Therefore, $V - W*D$ follows a multivariate Gaussian distribution. Consequently, under the conditions of spike times and spiking waveforms, the conditional probability function of the spikes generated is:

$$p(V \mid D, W) \propto \exp[-\frac{1}{2}(V-W*D)^T \Lambda^{-1}(V-W*D)] \tag{4}$$

where Λ is the covariance matrix of the multidimensional Gaussian variable η, which not only represents the covariance of noise over time but also the covariance of noise caused by the spatial positions of the electrodes in the collection process.

Based on the prior function, the conditional probability function, and Bayesian theory, the posterior probability function of spikes evoked by the spiking trains and spiking waveforms is:

$$p(D,W \mid V) \propto p(V \mid D,W)\, p(D)\, p(W) \tag{5}$$

The spiking trains and the spiking waveforms are estimated by making the posterior probability obtain its maximum value[16-18].

2.2 Information coding by probabilistic statistical model

The spiking activity of neurons is affected by many factors at the same time, and the study of neural activity usually involves three different covariates. First, neural spiking activity is often associated with external biological and behavioral covariates, such as sensory stimuli and behaviors or specific motor outputs[13]. Second, the neuron's current spiking activity is also related to its own spike-history[19]. Finally, the advancement of modern technology allows simultaneous record spiking activity of multi-neuron, and show that the spiking activity of a particular neuron is related to the spike-history of other neurons[15].

In this paper, a probabilistic statistical model is used to study the encoding and decoding process of acupuncture neurons. Firstly, the encoding model of acupuncture neuronal response was established using the framework of linear-nonlinear-Poisson process. In linear filtering, the external covariates, spike-history of self and the spike-history of other neurons are analyzed simultaneously. The three components undergo linear filtering and are then subjected to a nonlinear exponential filtering to generate the intensity function of the Poisson process[20,21]:

$$\begin{cases} \lambda_1(t) = \exp(k_1 s(t) + h_{11} d_1(t) + h_{12} d_2(t)) \\ \lambda_2(t) = \exp(k_2 s(t) + h_{22} d_2(t) + h_{21} d_2(t)) \end{cases} \tag{6}$$

where k_i is the coupling parameter of external stimulation to neuron i, h_{ii} is the coupling parameter of own spike-history of the neuron i, and h_{ij} is the coupling parameter of other neurons. Let $\theta_i = (k_i, h_{ii}, h_{ij})$, is the parameter set of the encoding model.

Assuming that the number of spiking events occurring in the time window dt is n_t, then there is $n_t \sim Poiss[\lambda dt]$. Thus, the logarithmic probability function generated by neuronal spiking trains is as follows:

$$\log P(D \mid \theta) = c + \sum_t (n_t \log \lambda - \lambda dt) \tag{7}$$

where c is a constant that does not depend on the parameter θ.

Then, the MLE was used to fit the spiking trains evoked by acupuncture to the model and estimate the model parameters. The logarithmic probability function $\log P(D \mid \theta)$ is the logarithmic likelihood function of the model, and we can obtain the MLE of the model parameters by setting it to its maximum value[22,23].

3. RESULT

3.1 Classification of acupuncture electrical signals

Using the spiking activity of neurons in the dorsal horn of the spinal cord from an acupuncture experiment on the Zusanli (ST36) acupoint in rats as the raw data. We perform both traditional classification algorithms and Bayesian statistical model based spiking classification, and compare their classification effects. In the acupuncture experiment, healthy adult rats were selected as experimental subjects, the acupuncture frequencies were 30 times/min, 60 times/min, 120 times/min and 180 times/min respectively.

Taking the stimulation frequency of 60 times/minute as an example, we selected the classification results of the two algorithms in 0.3 seconds to compare, as shown in Figure 1. Fig. 1 (a) shows the spiking trains of two neurons detected by the traditional classification algorithm. Fig. 1 (b) shows the spiking trains of two neurons detected in the Bayesian statistical model. Fig. 1 (c) shows the raw data collected by the electrodes. In the figure, the blue dots are the spikes extracted by both algorithms, the red dots are the spikes extracted by the Bayesian statistical model, and the green dots are the spikes omitted by the Bayesian statistical model.

From the Fig. 1, it can be seen that the Bayesian statistical model has effectively solved the problem of superposition of multiple spiking waveforms. In particular, in the red dotted box, the spikes recorded by the electrode are concentrated. It shows that the responding activity of neurons is intense, and the Bayesian statistical model can detect all the spikes. In addition, when dealing with noise, such as the spiking waveforms corresponding to the spike in the green dotted line box is within the background noise range, such spikes are eliminated. It can be seen that the Bayesian statistical model reduces the missing rate of traditional classification algorithms and greatly improves the accuracy of classification results.

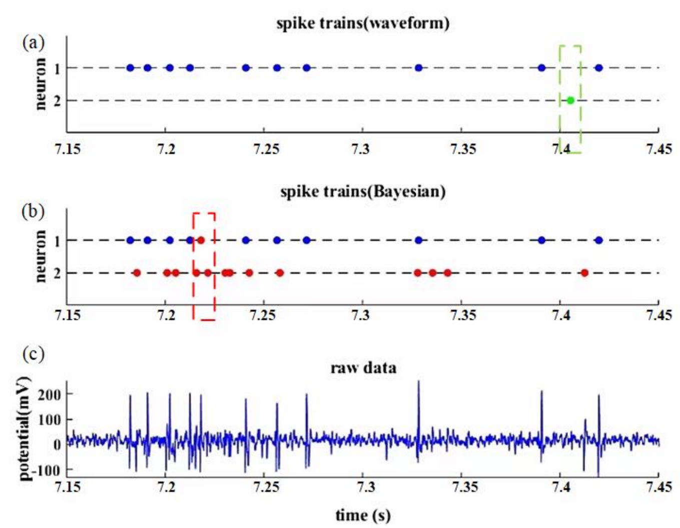

Figure 1. Comparison of the results between the two classification algorithms.

Under the conditions of acupuncture at four frequencies, the number of spiking events of two neurons estimated by the two classification algorithms is shown in Table 1. It can be concluded that the number of spikes detected by these two neurons in the Bayesian statistical model is significantly increased, and some even twice the number of spiking events in the traditional classification algorithm.

In addition, we found that after the stimulation was increased to 120 times/min, although the frequency of the stimulation continued to increase, the production of spikes did not increase anymore. This is due to the limited number and availability of ion channels on neuron cell membranes, as well as the saturation of neurotransmitter release. When the frequency of stimulation is too high, the release of ion channels and neurotransmitters reaches saturation, resulting in no more spikes being generated. This phenomenon helps to maintain the stability and accuracy of the nervous system, ensuring the reliability of nerve signals during transmission. In medical research and practice, the stimulation frequency of neurons can be adjusted according to this principle to achieve the purpose of treatment and research. In clinical treatment, the commonly used frequency of stimulation is 30 times/minute to 120 times/minute. Therefore, in the follow-up study, we mainly analyzed the neuronal spiking activity under the three stimulus frequencies of 30 times/minute, 60 times/minute and 120 times/minute.

Table 1. The number of spiking events in two classification algorithms.

Frequency	Neuron 1		Neuron 2	
	Waveform	Bayesian	Waveform	Bayesian
30 times/min	376	412	320	940
60 times/min	713	820	484	1264
120 times/min	231	662	314	973
180 times/min	132	480	403	506

3.2 Encoding and decoding of acupuncture spiking activity

We verify the accuracy of the MLE through a set of simulation data. First, the intensity function was used to generate simulated spiking trains, and the model parameters were set to the real values in Table 2. Then, the MLE is used to fit the model and estimate the parameters of the model. The estimated results are shown in Table 2. By comparing the real value and the estimated value in Table 2, the relative error distribution of the estimated model parameters ranges from 0.62% to 4.47%. It is concluded that the MLE can accurately fit the model and estimate the model parameters.

Table 2. Real and estimated values of model parameters.

Parameter	**Neuron 1**			**Neuron 2**		
	$\mathbf{k_1}$	$\mathbf{h_{11}}$	$\mathbf{h_{12}}$	$\mathbf{k_2}$	$\mathbf{h_{22}}$	$\mathbf{h_{21}}$
true	0.9	1	0.9	0.9	1.25	0.7
estimate	0.8803	1.0442	0.9492	0.8944	1.1217	0.7114

In order to further study the difference of neuronal responding under the condition of acupuncture manipulation with different frequencies, a probabilistic statistical model was used to encode and decode the neuronal responding activity evoked by acupuncture of different frequencies, and the coupling parameters were estimated by MLE. The estimated results are shown in Table 3. We found that the coupling parameters of stimulus k were significantly lower than the coupling parameters of spike-history h under all three frequencies of acupuncture. With the increase of frequency, the more historical spikes of neurons, the smaller the coupling parameters of stimulus. It is concluded that the spike-history is the main factor to evoke the neuronal response in the experiment of neuronal spiking activity of acupuncture.

Table 3. The coupling parameters of different acupuncture frequencies.

Parameter	**Neuron 1**			**Neuron 2**		
	$\mathbf{k_1}$	$\mathbf{h_{11}}$	$\mathbf{h_{12}}$	$\mathbf{k_2}$	$\mathbf{h_{22}}$	$\mathbf{h_{21}}$
30 times/min	0.0436	0.1703	2.6589	-0.0135	0.0478	2.6155
60 times/min	-0.0017	0.6100	1.8894	-0.0544	0.0057	1.6049
120 times/min	0.0185	0.4348	2.5975	-0.0202	0.0119	1.6757

4. CONCLUSIONS

In this paper, statistical models were used to analyze the neuronal responding activity evoked by acupuncture with different frequencies, and to reveal the mechanism of acupuncture with different frequencies. Firstly, in order to obtain accurate neuron spiking trains, Bayesian statistical model is used to optimize the results of algorithm for traditional waveform classification. Then, the neuronal spiking events evoked by different frequencies of acupuncture were statistically analyzed, and it was found that the number of neuronal spiking events increased gradually with the increase of acupuncture frequency. However, after the acupuncture frequency reached 120/ min, the increase of stimulation frequency did not produce more neuronal spiking events due to the frequency adaptation of neurons to the saturation mechanism. Finally, a probabilistic statistical model was used to encode and decode the spiking activity of acupuncture neurons. We found that the coupling parameters of stimulus were significantly lower than the coupling parameters of spike-history under different acupuncture frequencies, indicating that spike-history is the main factor that induces the responding activity of acupuncture neurons. According to the study of the relationship between acupuncture frequency and neuronal spiking activity, this may provide a scientific basis for future clinical treatment.

ACKNOWLEDGEMENTS

This paper is supported by the Fund of Scientific Research Project of Tianjin Education Commission (Grant Nos. 2022ZD038, 2022KJ114, 2022KJ106) and Research Initiation Project of Tianjin University of Technology and Education (KYQD202358).

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