Mahalanobis Distance Discrimination for Restoration of Underlying Single-channel Signal*

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Abstract: A method for restoration of the underlying single-ion-channel signal is provided. Based on a mixture of two normal distributions, Mahalanobis distances are used to give the threshold value and classify the channel's states.

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Ion channels are large proteins that span cell membranes. The channel is said to be open if the protein forms pores, allowing single ion or multi-ions to pass through. The channel is said to be close if the protein doesn't form pores. When ions pass through a channel, electric current is produced. The current through channel is very small and can be recorded by patch clamp. A single channel is called if one ion passes through the channel. The current amplitude of a single channel alternates between two levels as the channel open and close. However, the patch clamp recordings are affected by noise and the open and close states of the underlying signal are obscure. In stochastic models, the states of channel were usually classified and used. A program, PCLAMP (a product of Axon Instruments) used to analyze patch clamp recordings, provided a method for restoration of the underlying signal. In PCLAMP, two lines, z_0 and z_1, are described subjectively in the recordings by analyzer. Then a threshold value $z = (z_0 + z_1)/2$ is used to discriminate the states. There has been some work on restoration of ion channel signal[1,2]. But the methods are difficult to be used.

1　Parameter Estimates for mixed distribution

Figure 1 is a part of single-channel patch recordings sampled by Pharmacology Department in Sun Yat-sen University.

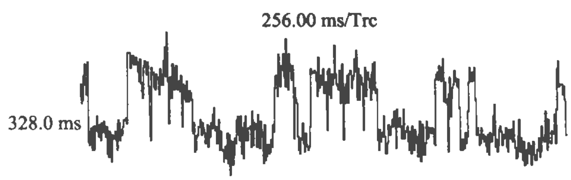

Fig. 1　Part of single-channel patch recordings

Figure 2 is the histogram of patch clamp recordings where number of bins is 122 and each bin width is 0.195 pA. The histogram shows the current amplitudes follow a mixture of two normal distributions $N(\mu_0, \sigma_0)$ and $N(\mu_1, \sigma_1)$. The probability density function is denoted by $p_0 f_0(x) + p_1 f_1(x)$, where $p_0 + p_1 = 1$, $f_0(x)$ is the density function of $N(\mu_0, \sigma_0)$, the distribution of close states, and $f_1(x)$ is the density function of $N(\mu_1, \sigma_1)$, the distribution of open states.

By Marquardt least square fitting parameters provided by PCLAMP, $\hat{p}_0 = 0.745(\pm 0.005)$, $\hat{p}_1 = 0.255(\pm 0.005)$, $\hat{\mu}_0 = 6.061(\pm 0.011)$, $\hat{\mu}_1 = 13.102(\pm 0.040)$, $\hat{\sigma}_0 = 1.595(\pm 0.011)$, and $\hat{\sigma}_1 = 1.862(\pm 0.042)$, where the values in parentheses are standard errors. The smooth solid-line in Fig. 2 is the fitting line. A χ^2 goodness-of-fit statistic is calculated. $\chi^2 = 851.21$, degree of freedom $df = 30\,473$ and p-value $p \approx 1$. The χ^2 test suggests the mixture of the two normal distributions fits very well.

2　Mahalanobis Distance Method

The Mahalanobis distance[3] between a value x and population $N(\mu_i, \sigma_i)$ is defined as $\frac{|x - \mu_i|}{\sigma_i}$, for $i = 0$

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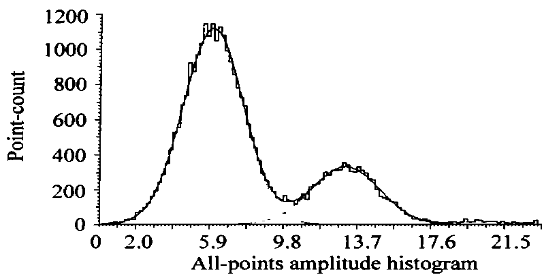

Fig. 2 Current-amplitude histogram of patch clamp recordings

and 1. x is classified into N (μ_0, σ_0) if $\frac{|x-\mu_0|}{\sigma_0} > \frac{|x-\mu_1|}{\sigma_1}$, else into N (μ_1, σ_1) . So let

$$\frac{x-\mu_0}{\sigma_0} = \frac{\mu_1 - x}{\sigma_1}.$$

The threshold value c is derived from the solution. So

$$c = \frac{\mu_1\sigma_0 + \mu_0\sigma_1}{\sigma_1 + \sigma_0}$$

and x is classified into N (μ_0, σ_0) if $x < c$, else into N (μ_1, σ_1) .

3 Results and Discussions

For the above recordings, the threshold value $c = 9.309$. The restoration of the recordings in Fig. 1 shows in Fig. 3.

Fig 3 Mahalanobis distance method for restoration of the recordings in Fig 1

In Mahalanobis distance method,

$$P(x < c \mid \text{the state is open}) =$$
$$P(x > c \mid \text{the state is close}) = \Phi\left(\frac{\mu_0 - \mu_1}{\sigma_0 + \sigma_1}\right)$$

That is to say, the probabilities of two types of error are equal, where $\Phi(\cdot)$ is the cumulative distribution function of standard normal distribution. For our example recordings, the probability is equal to 0. 021. It's small.

In general, for patch clamp recordings, the variation of open-state current amplitude is usually larger than that of close-state current amplitude. Now consider the method in PCLAMP. The probabilities of two types of error are

$$P(x < z \mid \text{the state is open}) =$$
$$\Phi\left(\frac{\mu_0 - \mu_1}{2\sigma_1}\right) > \Phi\left(\frac{\mu_0 - \mu_1}{\sigma_1 + \sigma_1}\right)$$

and

$$P(x > z \mid \text{the state is close}) =$$
$$\Phi\left(\frac{\mu_0 - \mu_1}{2\sigma_0}\right) < \Phi\left(\frac{\mu_0 - \mu_1}{\sigma_0 + \sigma_1}\right)$$

when $z = \frac{\mu_0 + \mu_1}{2}$. They are not equal. For our example recordings, if we let $z_0 = \mu_0 = 6.061$ and $z_1 = \mu_1 = 13.102$, the threshold value $z = 9.582$. Then, The probabilities of two types of error are 0. 030 and 0. 014 respectively.

In fact, the method in PCLAMP is based on Euclid distance. The variations are not considered. The probabilities of two types of error are not equal. One is small, but the other is large. So we would rather choose the Mahalanobis distance for discrimination, and the probabilities of two types of error are equal and small.

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单离子通道潜在信号的马氏距离判别

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摘 要: 提供了还原单离子通道信号的一种方法。基于混合正态分布, 用马氏距离给出通道开关阈值, 判断通道状态。

关键词: 离子通道; 马氏距离; 恢复; 膜片钳

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