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Statistical Model Applied to Motor Evoked Potentials Analysis

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***Abstract*—Motor evoked potentials (MEPs) convey information regarding the functional integrity of the descending motor pathways. Absence of the MEP has been used as a neurophysiological marker to suggest cortico-spinal abnormalities in the operating room. Due to their high variability and sensitivity, detailed quantitative studies of MEPs are lacking. This paper applies a statistical method to characterize MEPs by estimating the number of motor units and single motor unit potential amplitudes. A clearly increasing trend of single motor unit potential amplitudes in the MEPs after each pulse of the stimulation pulse train is revealed by this method. This statistical method eliminates the effects of anesthesia, and provides an objective assessment of MEPs. Consequently this statistical method has high potential to be useful in future quantitative MEPs analysis.**

I. Introduction

SINCE first discovered in 1980 by Merton and Morton, motor evoked potentials (MEPs) have been used as a marker of the integrity and functionality in the descending motor pathway [1]. As the electrophysiological response to the stimulation on the motor cortex, MEPs can be recorded at peripheral muscle through electromyography (EMG). Our previous work regarding neurophysiological signals and neural system deficits quantitatively measure the effects of external events (such as spinal cord injury and cardiac arrest) on the sensory pathways in the nervous system by assessing the alterations of these signals [2-4]. Now we wish to expand our analyses to include motor pathways.

As a special kind of EMG signal, MEPs can be analyzed with similar methods to reflect both muscular and neurologic functionality. One of the most widely used techniques is the "statistical method" [5]. This technique uses the assumption that the MEPs are the linear summation of single motor unit potentials. The motor unit is defined as all the muscle fibers that one motor neuron innervates and it follows an 'all-or-none' depolarizing pattern. In particular, either the motor unit itself fires as a whole, or all the muscle fibers in this unit do not fire. When more than one motor unit fires, the sum of single motor unit potentials yields a compound motor action potential (cMAP), or in our case, the MEP. It is also assumed that the firing probability of single motor unit follows a Poisson distribution. Some studies suggest that when the firing probabilities can no longer be modeled by a Poisson distribution, this method becomes biased [6]. The deviation from a Poisson distribution could be caused by high stimulation intensities, fatigue, insufficient anesthesia and myopathies.

The experimental variability and vulnerability to anesthesia and injury make MEPs difficult to study. In clinical settings, only the absence of MEPs is treated as an adequate marker for the intraoperative neurologic status [7]. In animal studies, the MEP signals cannot be easily duplicated due to the complex interactions between anesthesia depth and neurological function. Excessive anesthesia highly suppresses the MEP signal or even changes its firing patterns and light anesthesia is not sufficient enough to reduce spontaneous EMG measurably.

All the present techniques generally apply the ensemble or moving average method to characterize the changes in MEP amplitudes [8]. These methods employ the assumption that all the component signals in the ensemble are identical. However, this assumption is not realistic in MEP analysis.

In this paper, we apply a statistical method to quantitatively model MEP signals. By estimating the amplitudes of single motor unit potentials, we eliminate the effects of anesthesia, and thus develop a robust and reproducible model of MEP signals.

II. Materialsand Methods

A. MEPs Measurements

All experimental procedures were in accordance with the Johns Hopkins School of Medicine Animal Care and Use Committee. Our studies are done in rodents (Wistar rats, 300-400 g) and the experimental subjects were allowed free access to food and water and housed individually in a cage.

Five epidural screw electrodes (E363/20, Plastics One Inc., Roanoke, VA) were implanted one week prior to MEP recording. Four of these electrodes were corresponding to the stimulation sites of hindlimbs and forelimbs on each hemisphere. Forelimb sites located 0.2 mm posterior to bregma and 4.2 mm lateral to the midline whereas hindlimb sites locate 2.0mm posterior to bregma and 1.8 mm lateral to the midline. The fifth electrode was implanted on the right frontal lobe as an intracranial reference. All of the electrodes were implanted carefully so that they made a light contact with dura matter without applying pressure to it. The distal end of the electrodes were inserted into an electrode pedestal (MS363, Plastics One Inc., Roanoke, VA) and then fixed with dental cement. Although it is hard to characterize the positional accuracy with respect to anatomy, this precision is enough to reproduce the MEP signals across different trials and animals [2].

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Prior to MEP recording, a mixture of 50mg/kg of ketamine and 5 mg/kg Xylazine was administered via IP injection. MEP signal recording started as hindlimb withdraw reflex, then it disappeared and stopped when spontaneous EMG reappeared. During this period, MEPs were recorded every other minute.

Stimulation was directly applied through these electrodes to the cortex. Electrical pulse trains were used to induce the MEP signals. Each stimulation train consisted of five pulses, each with a 100 μs pulse duration. Intra-pulse duration was 50 ms and stimulation frequency was 0.5Hz. A stimulation intensity of 6 mA induced a light twist of the head. A subdermal needle electrode was inserted into the tibialis anterior muscle on the right hindlimb to record MEP signals. Another electrode was inserted into the footpad as reference. The ground electrode was inserted into the tail. A Tucker Davis Technologies data acquisition systems (TDT, Alachua, FL) and software were used for stimulation control and signal recording. Signals were sampled at 6.1 kHz.

The MEP signals were recorded for 500 ms after the initiation of each pulse-train. A 50 ms window after each stimulus was analyzed. A notch filter of 60Hz was then used to remove power line noise. Peak-to-peak amplitude was calculated by MATLAB, taking the difference in amplitude between the first negative and first positive peak. Trials without obvious MEP responses were ignored.

B. Statistical Model

The statistical model employs three assumptions. First, the MEP signals are assumed to be a linear summation of N single motor unit potentials. N stands for the number of motor units that fire at a given choice of stimulation parameter settings. N is an unknown parameter. Second, according to the all-or-none motor unit firing pattern, the firing of a single motor unit is treated as Bernoulli random variable with success probability of p. Let Z_i (i=1,…,N), be independent Bernoulli random variables, then the probability of firing can be expressed as

$$\boldsymbol{P(Z_i = z_i)} = \begin{cases} \boldsymbol{1-p_i} & \boldsymbol{: z_i = 0, not\ firing} \\ \boldsymbol{p_i} & \boldsymbol{: z_i = 1,\ firing} \end{cases} \quad (1)$$

Third, the amplitudes of single motor unit potential X_i (i=1,…,N) are also independent random variables with expectation, λ_i, and variance, σ_i^2. Therefore, MEP amplitude Y, is given by:

$$Y(N,p,\lambda,\sigma) = \sum_{i=1}^{N} X_i Z_i. \quad (2)$$

The MEPs amplitude Y is a function of the number of motor units, the firing probability of single motor unit and the mean and variance of amplitudes of a single motor unit.

If the random vectors (X_1,…, X_N) and (Z_1,…, Z_N) are independent and every motor unit is independent and identically distributed, then the expectation of MEPs amplitude Y can be expressed as

$$E[Y(N,p,\lambda,\sigma)] = \sum_{i=1}^{N} E[X_i Z_i] = NE[X_1 Z_1]$$
$$= NE[X_1]E[Z_1] = Np\lambda, \quad (3)$$

and the variance of MEPs amplitude is

$$Var[Y(N,p,\lambda,\sigma)] = \sum_{i=1}^{N} Var[X_i Z_i]$$
$$= NVar[X_1 Z_1]$$
$$= N\sigma^2 Var\left[\frac{X_1 Z_1}{\sigma}\right]$$
$$= N\sigma^2 Var\left[Y\left(1,p,\frac{\lambda}{\sigma},1\right)\right]$$
$$= N\sigma^2\left(E\left[Y^2\left(1,p,\frac{\lambda}{\sigma},1\right)\right] - \left(E\left[Y\left(1,p,\frac{\lambda}{\sigma},1\right)\right]\right)^2\right)$$
$$= N\sigma^2\left(p\left(1+\frac{\lambda^2}{\sigma^2}\right) - (p\frac{\lambda}{\sigma})^2\right)$$
$$= N\lambda^2 p\left(1-p+\frac{\sigma^2}{\lambda^2}\right). \quad (4)$$

The variance-mean relationship is of interest in many applications. In our case the variance-to-mean ratio is

$$\frac{Var[Y(N,p,\lambda,\sigma)]}{E[Y(N,p,\lambda,\sigma)]} = \lambda\left(1-p+\frac{\sigma^2}{\lambda^2}\right) \quad (5)$$

The variance-to-mean ratio is independent of the number of motor units N, and its shape is linear in p, the probability of firing for a single motor unit. Moreover if one considers the variance-to-mean ratio as a function of p, then its shape is determined by the ratio λ over σ [6].

III. RESULTS

Fig. 1 shows the evolution of MEP amplitudes obtained over the course of a single experiment with respect to time. Five traces are corresponding to the MEPs after the five pulses. 'Sti 1' represents MEPs after the 1st stimulation pulse and so forth. The amplitudes increase exponentially due to the decreasing effects of anesthesia. Stimulation intensity was kept the same throughout all the experiments. When the curve reached a maximum, the rat was on the verge of waking; the MEP amplitudes were saturated and became contaminated by EMG.

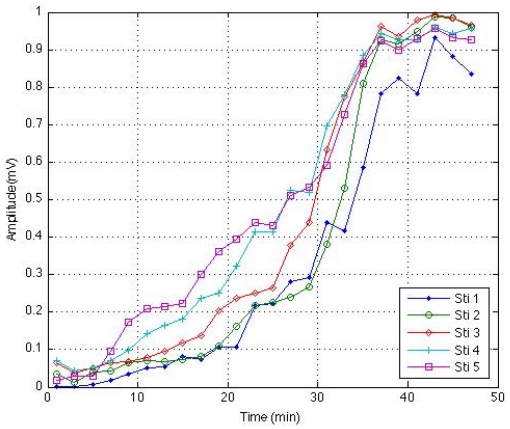

Fig. 1. Evolution of MEP amplitudes with respect to time. Five traces are corresponding to the MEPs after each pulse.

In order to estimate the four unknown parameters N, p, λ and σ, we propose an estimation procedure that quantifies the MEP potential as a whole. Assume that two identical and independent samples are generated by model Y (N, p_1, λ, σ) and Y (N, p_2, λ, σ), then the estimator for N can be generated as

$$\hat{N} = (M_2 - M_1)/(\frac{S_1^2}{M_1} - \frac{S_2^2}{M_2}) \quad , \tag{6}$$

where M_1, M_2 are the respective sample means and S_1^2 and S_2^2 are the respective sample variances.

If there is one sample Y(N, p_m, λ, σ) in which all of the motor units are always firing (p_m=1), then p_i and λ can be simply estimated by

$$\hat{p}_i = \frac{M_i}{M_m}, \hat{\lambda} = \frac{M_m}{\hat{N}}. \tag{7}$$

In our analysis, we assume the time point before ending the experiment is the one when all the motor units are firing. This is because this is the time when the anesthesia has the least effect on animal and the amplitude is saturated. In this estimation procedure, we assume that N, λ and σ are constant whereas the firing probability of single motor unit p is changing with respect to the anesthesia status.

One prerequisite of this estimation procedure is that p should be inversely proportional to the variance-to-mean ratio. Their relationship is demonstrated in Fig. 2. The ordinate is variance-to-mean ratio and the abscissa is the firing probability of single motor unit p. According to (5) the inverse slope of this linear regression line is supposed to be an estimation of λ. At this point, however, the inverse slope cannot estimate λ precisely because data which fail to follow the Poisson distribution were included. How to rule out the invalid data induced by light anesthesia is described in the following. The result of this rough estimation of λ is shown in TABLE I.

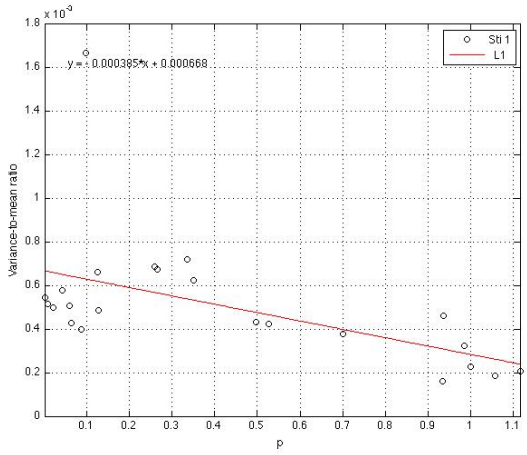

Fig. 2. Firing Probability of Single Motor Unit p vs. variance-to-mean ratio. The linear fitting line is plotted.

TABLE I
ESTIMATION OF λ BY INVERSE SLOPE

	Sti 1	Sti 2	Sti 3	Sti 4	Sti 5
λ(mV)	0.385	0.126	0.0871	0.165	1.067

Giving the estimation procedure, the estimation of λ, σ and N can be calculated through (6) and (7). The estimated λ is plotted vs. p in Fig. 3. When the firing probability of single motor unit is relatively low (p<0.6) the estimator of single unit amplitude converges and is stable, whereas when p is high (p>0.8) the estimator changes dramatically, and provides out-of-bound negative values.

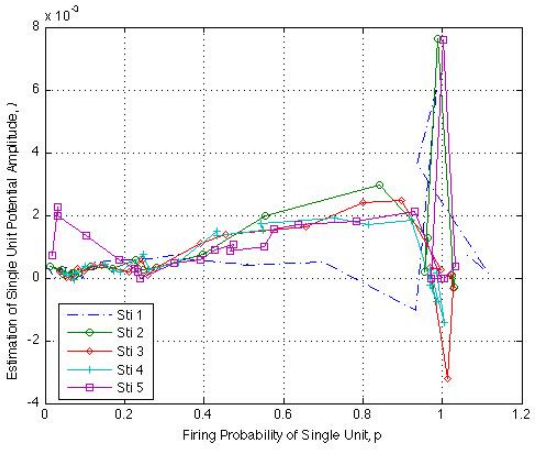

Fig. 3. Firing probability of single motor unit vs. estimation of single unit potential amplitude.

To further prove the validity of the selected data, trials with p<0.6 are plotted as a histogram in Fig. 4. The peak-to-peak amplitudes roughly follow a Poisson distribution, thus the estimation of λ is relatively accurate with p<0.6.

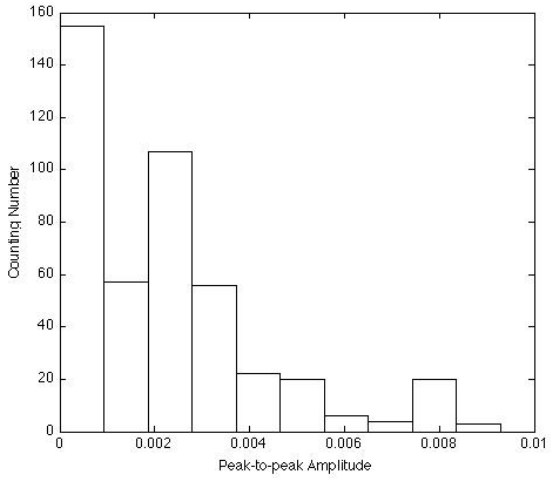

Fig. 4. Peak-to-peak amplitude distribution histogram with p<0.6. The histogram roughly follows Poisson distribution.

The distribution of amplitudes is also plotted with p≥ 0.6 in Fig. 5. The peak-to-peak amplitude histogram with p ≥0.6 neither decreases exponentially as Poisson distribution does nor is this distribution symmetric like normal distribution. These data created bias in the model and should be excluded.

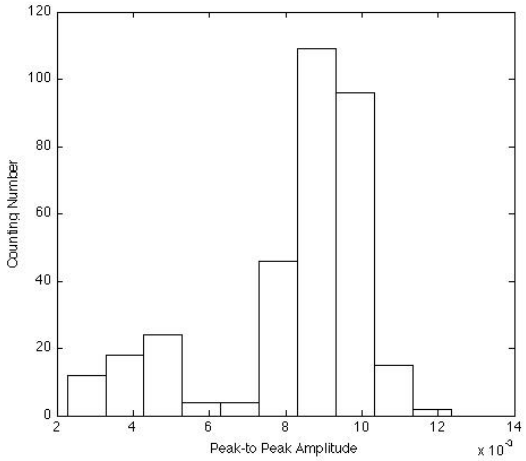

Fig. 5. Peak-to-peak amplitude distribution with p≥0.6. The distribution doesn't follow Poisson distribution.

After we removed the biased data points which have p >0.6, the result of rest points were averaged. The results for λ and σ averaged over five trials are shown in Fig. 6. The range of the X-axis is by the order of the pulses in stimulation train. The firing probability of single unit increases as the number of pulses increases. As shown in TABLE II, the average motor unit number N is 23.31±6.16 and average standard deviation of single unit amplitude is 0.0153±0.005.

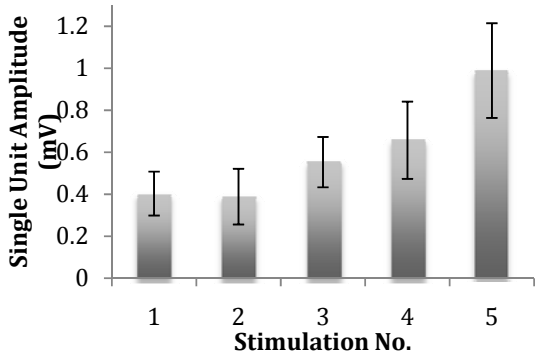

Fig. 6. Estimation of single unit amplitude λ and its standard deviation σ in different stimulation pulses.

TABLE II
ESTIMATION OF N, λ AND σ

	N	λ (mV)	σ (mV)
Sti1	16.696	0.403	0.105
Sti2	27.446	0.389	0.133
Sti3	32.568	0.553	0.120
Sti4	21.604	0.657	0.184
Sti5	18.239	0.989	0.225

IV. CONCLUSION AND DISCUSSION

This paper applies a statistical model to simulate the firing pattern of MEPs. By using this method the impact of unstable anesthesia is overcome and the single motor unit firing potential is estimated. It provides a novel characterization of MEPs despite their unstable characteristics.

Earlier experimental studies have demonstrated that MEP signals are very sensitive to volatile anesthetics like isoflurane and therefore they will be profoundly depressed in amplitude even under subanesthesia conditions [9, 10]. In our study, we used low-dose intravenous anesthetic ketamine, which has no significant effect on MEP morphology and it can be useful as an agent to facilitate MEP monitoring [11]. However, it is hard to maintain a steady anesthesia depth with ketamine because the intravenous anesthetic concentration is hard to monitor and it varies with metabolism.

According to (7), to use this method for MEP evaluation, one must assume at one point all the motor units are firing. This 'all units' firing condition could be approximated by decreasing anesthesia concentration or increasing the stimulation intensity until the MEP potentials saturated. One critical advantage of this statistical model is that the impact of anesthesia and stimulation intensity could be eliminated.

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