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Multiresolution Entropy Measure for Neuronal Multiunit Activity

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Abstract— **It is known that the multiunit activity (MUA) reflects the status of population of neurons in the vicinity of an electrode. We provide a quantitative measure of the time-varying multiunit neuronal spiking activity using an entropy based approach. To verify the status embedded in the neuronal activity of a population of neurons, we incorporate the discrete wavelet transform (DWT) to isolate the inherent spiking activity of MUA from the noise and background cortical activity or field potentials. Owing to the decorrelating property of DWT, the spiking activity would be preserved while reducing the non-spiking component such as the background noise. By evaluating the entropy of the wavelet coefficients of the denoised MUA, a multiresolution entropy of the MUA signal is developed. The proposed entropy measure was tested in the analysis of both simulated noisy MUA and actual MUA recorded from cortex in rodent model which undergoes hypoxic-ischemic brain injury. Simulation and Experimental results demonstrate that the dynamics of a population can be quantified by using the proposed multiresolution entropy.**

I. Introduction

Serving as an example of cutting edge technology, the modern micro-electrode recoding technology facilitated recording from population neuronal activity [1, 2]. Correspondingly there is a need for suitable quantitative approaches for describing the relevant information from such population activities. However, most previous information theoretic measures have dealt with the firing activity of a single neuron which is usually represented as a binary spike train with the occurrence time of spikes and spike train distributions [3, 4].

To interpret the population activities, neuroscience researchers have now shifted focus to studying the simultaneous spiking activity of multiple neurons [1, 5]. This makes it easier to investigate how a population of neurons responds to any stimuli or how neurons are interconnected in various regions of the brain. The simultaneously recorded multiunit activity (MUA) represents the aggregate spiking activity of a population of neurons in the vicinity of an electrode. The advanced signal processing and statistics based approach to analyze the timing of spikes from neuron may distort the actual information content of the spiking activity in MUA. That is because generally no independent and precise spike information for each neuron in the population is available. The single unit spiking activity is quantified by typical methods such as firing rate and coefficient of variation (CV) [6, 7]. These measures have limit for MUA analysis since they may result in misleading interpretation depending on the number of recorded neurons at same electrode. Accordingly, a quantitative measure of multiunit neuronal spiking activity is needed as well. In general, applicable to experiments presented here, MUA is regarded as a nonstationary signal, making it difficult to evaluate the spiking activity. In addition, the recorded MUA signal from electrodes is often also contaminated by the noise, resulting in noisy MUA.

This paper aims at quantitatively analyzing the time-varying MUA signals using an entropy based approach. Here, we propose a multiresolution entropy measure for multiunit neuronal spiking activity based on discrete wavelet transform (DWT). Recently the wavelet decomposition, which is based on multiresolution analysis, has been shown to be an effective tool to preserve or detect the spiking activity [8-10]. In addition, the wavelet analysis provides effective tool for nonstationary signal [11, 12]. The complexity/regularity of multiunit neuronal spiking activity is obtained by evaluating the entropy of spiking activity. The wavelet coefficients which describe the spiking activity at each band are obtained, and following Shannon entropy measure [13] quantifies the MUA signal.

II. Multiresolution Entropy Measure

Let $s(i)$ denotes a MUA signal. It is known that a signal is decomposed and de-correlated by multi-resolution wavelet analysis [14]. The wavelet expansion of a MUA signal can be defined as

$$s(i) = \sum_k \sum_j c_{j,k} \psi_{j,k}(i), \qquad (1)$$

where j and k denote the wavelet decomposition level and the temporal translation, respectively, and $\psi_{j,k}(i)$ denotes a wavelet function.

In general, the real MUA signal recorded in experiments was contaminated by the background noise. Using multiresolution based DWT, we incorporate a denoising process, called *wavelet denoising* [9, 10]. The crucial step in wavelet denoising is determining the threshold estimated from the noise-dominated wavelet coefficients. It is known that the threshold is proportional to the standard deviation of the noise [9].

As a first step of the wavelet denoising, MUA is decomposed into several frequency sub-bands using DWT.

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Then, a threshold is calculated using the wavelet coefficients at the detail level 1 as follows:

$$\sigma_{wn} = \frac{\mathrm{median}(\|d^1 - \bar{d}^1\|)}{0.6745}, \quad (2)$$

$$T_{wn} = \sigma_{wn}\sqrt{2\log_e(N)}. \quad (3)$$

where d^1 and $\bar{d}^1$ denote the detail coefficient of level 1 and its corresponding mean, respectively. σ_{wn} is the estimated the standard deviation of the noise related wavelet coefficients, T_{wn} is the corresponding threshold, and N denotes the number of samples in the signal

The next step is to suppress additive background noise in MUA by comparing the corresponding wavelet coefficients with the threshold at each detail level. At each detail level, the wavelet coefficients which have larger absolute value than the threshold are considered as spiking activity related components, and other wavelet coefficients which have lower absolute value than the threshold are thought to be noise related, and hence set to zero. In addition, after the jth decomposition level, certain detail wavelet coefficients and the coarse wavelet coefficients a^j are set to zero as we regard these as non-spiking activity related components. The reconstructed signal after noise suppression is a noise-free MUA and preserves the inherent spiking activity regardless of the number of neurons.

With the aid of wavelet decomposition and denoising, MUA can be separated into two parts: one mainly contains the multiunit spiking activity and the other significantly carries the background noise. To access the information quantity embedded in the spiking activity, we use only the subset of the wavelet coefficients which represent the spiking activity. After jth level DWT decomposition, the resulting set of wavelet coefficients are given by

$$\left[a_1^j \cdots a_{\frac{N}{2^j}}^j,\ d_1^j \cdots d_{\frac{N}{2^j}}^j, \cdots,\ d_1^1 \cdots d_{\frac{N}{2}}^1 \right] \quad (4)$$

where a_m^l and d_m^l for $l = 1,\cdots,j$ and $m = 1,\cdots, N/2^l$ are the approximation coefficients and the detail coefficients at decomposition l^{th} level, respectively. After denoising, we choose the part of (4) as the spiking activity related coefficients such as

$$\left[\mathbf{0}_{\frac{N}{2^j}},\ \hat{d}_1^r \cdots \hat{d}_{\frac{N}{2^r}}^r, \cdots,\ \mathbf{0}_{\frac{N}{2}} \right] \text{ and } \hat{d}_m^l = \begin{cases} d_m^l & \text{if } d_m^l \geq T_{wn} \\ 0 & \text{otherwise} \end{cases} \quad (5)$$

where r denotes the selected decomposition level, $\mathbf{0}_k$ denotes the zero-valued vector with the length k and $\hat{d}_m^r$ is the modified wavelet coefficients by comparing with the threshold at rth decomposition level as follows. Note that most detailed components and most coarse component are ignored as well as the certain detail coefficients which are considered as non-spiking activity related.

Next, Shannon entropy (S_E) is calculated as a measure of the uncertainty in the spike signal. SE is defined as

$$S_E = -\sum_{m=1}^{M} p(m)\log_2 p(m) \quad (6)$$

where $p(m)$ is the probability of the mth microstate of the variable with $0 \leq p(m) \leq 1$ and $\sum_{m=1}^{M} p(m) = 1$. To evaluate SE of time-varying MUA, we incorporate a temporal evolution approach. To do this, MUA signal is divided into a number of segments using a sliding temporal window. Let $\{\hat{s}(i) : i = 1,\cdots,N\}$ denotes the MUA signal after wavelet denoising. Then, let us consider a sliding temporal window $w \leq N$ and a sliding interval $\Delta \leq w$. Sliding windows of MUA are defined by

$$\hat{s}_n(i) = \{\hat{s}(i), i = 1 + n\Delta, \ldots, w + n\Delta\} \quad (7)$$

where $n = 0,1,\ldots,[N/\Delta] - w + 1$ and $[x]$ denotes the integer part of x. Within each window $\hat{s}_n(i)$, we carry out the multiresolution wavelet decomposition and following wavelet denoising scheme. Among the detail wavelet coefficients at all levels certain decomposition levels are chosen, which is considered to express the inherent spiking activity. We will denote the result of the wavelet decomposition and denoising for $\hat{s}_n(i)$ as $\Gamma(r,n)$. To calculate the probability, the selected set of the wavelet coefficients are divided as

$$\Gamma(r,n) = \left[\hat{d}_1^r \cdots \hat{d}_{\frac{N_w}{2^j}}^r, \cdots, \hat{d}_1^2 \cdots \hat{d}_{\frac{N_w}{4}}^2 \right] = \bigcup_{m=1}^{M} I_m \quad (8)$$

where N_w is the number of samples in the window, w, and M is the number of partition of the wavelet coefficients in a window w.

For each selected decomposition level, the probability $p_n^k(m)$ in the kth set of the detail wavelet coefficients which the sampled signal belongs to the interval I_m is the ratio between the number of samples found within interval I_m. Then, the entropy of the multiunit spiking activity of kth level, referred to as E^k, is calculated:

$$E^k(n) = -\sum_{m=1}^{M} p_n^k(m)\log_2 p_n^k(m) \quad (9)$$

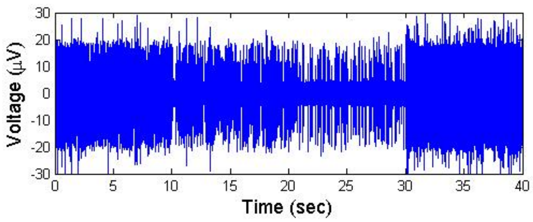
where $k = 1,\cdots,r$ and $p_n^k(m)$ is the probability of finding the system in the mth microstate at kth level with $0 \leq p_n^k(m) \leq 1$ and $\sum_{m=1}^{M} p_n^k(m) = 1$. Finally, we obtain the multiresolution entropy (M_E) evolution of MUA data $\{s(i) : i = 1,\cdots,N\}$ by averaging entropies of kth levels such as

$$M_E(n) = \frac{1}{r}\sum_{k=1}^{r} E^k(n) \quad (10)$$

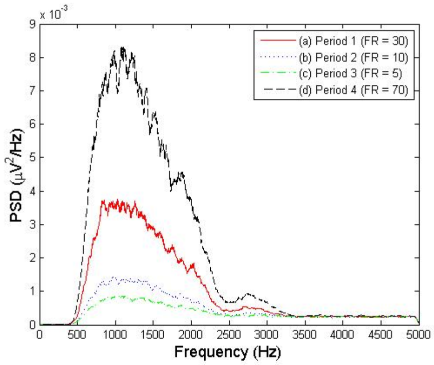
III. Results

A. Simulation studies

To investigate the capability of the proposed entropy measure, the simulated MUA is used. The simulated MUA is obtained by using the three spike templates which were



(a)



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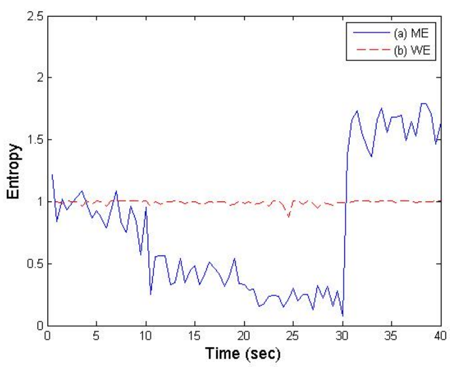


(c)

Fig. 1. Simulated MUA and the quantification. (a) The noisy simulated MUA. (b) PSD plots of each duration from the noisy simulated MUA. (c) Time dependent multiresolution complexity plot for the simulated MUA

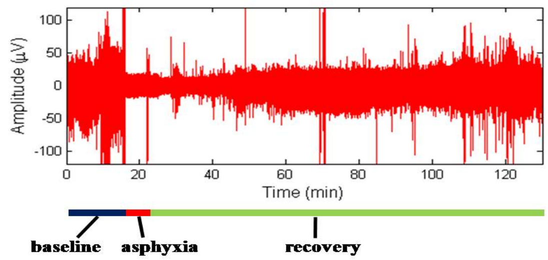
recorded from cortical neurons of rat. By convolving these spike templates with three simulated spike trains which are based on inter-spike interval (ISI) model of Poisson process and have different firing rates (FR). To mimic actual simultaneously recorded MUA signals, noise with Gaussian probability density is added [15]. The signal to noise ratio (SNR) which is defined as the ratio between the absolute peak amplitude of the spiking activity and the standard deviation of the noise and we simulated as SNR = 5. The simulated noisy spike activity is shown in Fig. 1(a) and lasts for 40s with 10 kHz of sampling frequency. The spike train activity starts with the composite of three unit activity. Then, to simulate the time varying changes, firing rate decreases every 10 sec. During the initial 10 sec, FR of each of the three spiking neurons is 30 (spikes/sec). Between 10 sec to 20 sec, the FR is 10 (spikes/sec). Between 20 sec to 30 sec, it decreases to 5 (spikes/sec). In last 10 sec, FR increases up to 70 (spikes/sec). For the selection of the detail wavelet coefficient level, we investigated the power spectral density of the four different durations of the simulated noisy MUA in Fig. 1(b). As can be seen, the biggest difference between PSDs of the four durations occurred between 500 Hz-2.5 kHz which corresponds to the second detail level and the third detail level with 10 kHz sampling frequency and $j = 5$ decomposition levels. All periods have similar amount of PSD over 2.5 kHz, implying that this range mainly corresponds to noise only. Therefore, the detail levels d^2 and d^3 are only used to evaluate entropy reflecting the intrinsic spiking activity, while the other detail levels are ignored. By averaging these two entropies, we evaluated the time dependent multiresolution entropy in Fig. 1(c). As a conventional wavelet based entropy, wavelet entropy (W_E) has been developed [16]. W_E measures how spread the DWT coefficients are over levels of decomposition. Fig. 1(c) shows time evolution of the proposed measure and W_E. We can see that the proposed entropy is superior to W_E in assessing the MUA signal.

B. Experimental studies: MUA following hypoxic brain injury

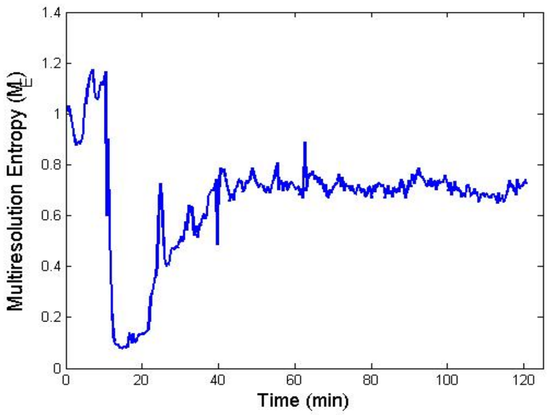
Here, we investigate the multiunit spiking activity of the cortical MUA recordings from rats obtained during hypoxic brain injury and recovery following cardiac arrest. The brain injury studies were carried out under a protocol approved by animal Care and Use Committee of the Johns Hopkins Medical Institution. Asphyxic cardiac arrest and resuscitation protocol was performed as described by Jia et al. [17].

The experimental protocol is as follows. Five Wistar rats (300 ± 25 g) were used. The cortical MUA was continuously recorded with 6.1 kHz sampling frequency by the TDT system (Tucker-Davis Technologies, Alachua, FL) and followed by a fourth order Butterworth band-pass filtering with 300 Hz-3kHz. Baseline recording of 5 min was followed by 5 min washout to ensure no significant residual effect of halothaneon EEG signals. After 5 min washout, cardiac arrest was induced via asphyxia with disconnection of mechanical ventilation and clamping the tracheal tube for 7 min. During the injury phase, graded CA is defined by 2 parameters: the time to pulselessness (MAP <10 mmHg) and the time to return of spontaneous circulation (ROSC) during resuscitation (MAP>50 mmHg). Resuscitation was initiated by unclamping the endotracheal tube, restarting mechanical ventilation with 100% O_2. Two channels of ECG and one channel of arterial pressure were recorded continuously before the insult, during insult, and recovery.

Our main objective in this study is to quantify the information carried by the neural spiking firing activity during, and after asphyxic brain injury. Our hypothesis is that brain injury results in a reduction in information of cortical neuronal activity. Fig. 2(a) demonstrates a typical MUA recording from cortical neurons of rat. The multiunit neuronal activity can be divided into three distinct phases. The first phase consists of the 5 min baseline recording and 5-min washout, which is further characterized by active firing of spiking activity. Secondly, it is followed by 7 min hypoxic-ischemic brain injury after cardiac arrest. During this period, the MUA signal become significantly recessive and



(a)



(b)

Fig. 2. Raw cortical MUA of rat which is recovered after asphyxic cardiac arrest and the evaluated multiresolution complexity. (a) Cortical MUA recording. (b) Multiresolution e for cortical MUA signal. MARK different phases of the experiment.

shows very sparse firing activity. Around 35 min-40 min, the firing activities gradually are detected, demonstrating that the brain begins to recover from injury.

We assessed the spiking activity quantitatively using multiresolution entropy. The parameters used in the calculation were: sliding window length $\omega = 20\sec$, sliding step $\Delta = 20\sec$, and level of division $M = 30$, and wavelet decomposition level $j = 5$. Fig. 2(b) shows the multiresolution entropy plot of the cortical MUA during 7 min brain injury and recovery. The curve is normalized to its average value over the baseline recording period. During the initial duration of baseline recording, entropy remains at a high level. After 10 min the value of entropy abruptly decreases compared to the level of baseline recording. After resuscitation, the evolution of entropy shows an increasing tendency along the time progress. From this result, we can conclude that the entropy of the spiking activity in MUA reflects the degree of the neurological injury and that multiresolution entropy suitably quantifies this.

IV. Discussion and Conclusion

We developed a new quantitative spiking activity measure as an indicator of time varying neural MUA from a complex brain injury experiment. By incorporating the multiresolution based DWT, we evaluated entropy of MUA in an objective way while minimizing the effect of the background noise. The resulting multiresolution entropy characterizes the status of populations of neurons. Through this measure, the MUA analysis can provide the foundation to evaluate and interpret the noninvasive neurological recordings such as EEG signals from the scalp. While EEG signal serve as a useful monitoring tool for critical brain injury as shown in our previous experimental study [17], the MUA analysis would serve a valuable role in investigating the origins of the signal changes and trends in the EEG epiphenomenon.

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