OFFLINE SPIKE DETECTION USING TIME DEPENDENT ENTROPY

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ABSTRACT

Analysis of the neuronal activities is essential in studying nervous system mechanisms. True interpretation of such mechanisms relies on the detection of the neuronal activities, which appear as action potentials or spikes in recorded neural data. So far several algorithms have been developed for spike detection. In this paper such issue is addressed using entropy measures. Transient events like spikes affect the entropy content of a signal. Thus, a time-dependent entropy framework can be used for spike detection where the entropy of each windowed segment of neural data is computed based on a generalized form of entropy. Detection method is tested on different signal to noise ratios. The results show that the time-dependent entropy method in comparison with available methods enables us to detect spikes in their exact time of occurrence with relatively lower false alarm rate.

KEYWORDS

Neural data processing, spike detection, entropy measures, time-dependent entropy.

1. INTRODUCTION

All human or animal tasks are controlled by neuronal activities in the nervous system. Neurons communicate by producing electrical signals called action potential (AP) or spike. To understand the mechanisms that nervous system relies on, it is necessary to record such electrical signals in extracellular space by placing microelectrodes in single or array structures in the vicinity of neurons[1]. Such recorded signals are noisy in nature of various noise sources. Some important noise sources are the ambient noise like electromagnetic interference, thermal noise and noise caused by electronic devices. Besides, electrical activities of the neurons in the far-field with the similar frequency content are imposed to the recorded signal and are considered as another source of noise. Because of the further distance of far-field neurons from microelectrode tip, their activities appear as background activity. As the important information in neural data lies in APs which are embedded in a noisy background so action potential detection is inevitable. Such procedure is called spike detection.

In the past decade spike detection methods have been widely considered. The methods for spike detection usually are divided into two major categories: first category includes methods that detect spikes based on a predefined amplitude threshold. In such methods if the signal amplitude crosses the threshold level the presence of spike is determined. Second spike detection category searches recorded signal with a fixed template by cross-correlation methods. Similarity between a segment of recorded signal and the templates produces local maxima in correlation result, which is the indication of an action potential [2]. The simplest method for detecting action potentials is single amplitude thresholding method (SATM)[3], which detect spike when its amplitude crosses a predetermined threshold level. In spite of the simplicity in implementation, the performance of SATM deteriorates rapidly in low signal-to-noise ratios (SNRs). By computing instantaneous energy of the neural time series as the difference between the signal current power and the adjacent time interval power, it is possible to find the abrupt change in time series as spike occurrence. Using amplitude attributes make energy-based methods weak in the cases of noisy data[4]. In template matching techniques, the template is a representative of a distinct neuron. In such methods a-priori knowledge about the spike shapes for correct template selection is always a critical issue. The performance of these methods is poor in the low SNR cases and in the presence of overlapped spikes[5].

Techniques utilizing higher-order statistics (HOS) are other options for spike detection. By the assumption of Gaussian distribution for background noise[6] and by taking into account that HOS for Gaussian distribution is either zero or contains redundant information, it is possible to detect embedded spikes in the background noise[7]. Advanced signal processing methods combined with the statistical tools give powerful approaches for spike detection[8].

Several algorithms based on wavelet transform were used for spike detection. As most of the wavelet basis functions are spiky, it is convenient to use them in the template matching procedure for spike detection. In this case an unsupervised method based on the multiresolution continuous wavelet transform was proposed in[3]. Another action potential detector using the point-wise product of the successive scales of discrete wavelet coefficients was presented in[9]. Due to the fact that action potentials are band-limited waveforms with compact support, the point wise multiplication of wavelet coefficients (MWC) in some successive detail levels attenuates background noise and results a peak in the spike occurrence time [9]. In such domain, different wavelet types including discrete wavelet transform (DWT) and stationary wavelet transform (SWT)[10] were used for detection purposes. Using the wavelet denoising and reconstruction, a method was provided in which by decomposing the neural data in the wavelet multiresulotion scheme, a threshold is applied to selected detail coefficients and separates them as spike or noise-related coefficients. In this regard two different schemes as single-level noise estimation threshold (DWTS) and level dependent noise estimation threshold (DWTD) were developed where the difference is in the level(s) that the wavelet coefficients are thresholded [11]. Detection was performed by reconstructed denoised data. Although the wavelet based methods are very powerful in spike detection but such methods are highly sensitive to selection of basis function and wavelet decomposition method.

In the present work, offline spike detection is addressed by entropy-based methods. A time-dependent entropy (TDE) method is utilized for spike detection. As spikes are abrupt transient events, their presence in each segment of the neural waveform affects the entropy content of that segment. Tracking the waveform to find such events is the purpose of TDE method. In comparison with other traditional methods the TDE method leads to lower false alarm rates.

2.MATERIAL AND METHOD

2.1TDE detector

Entropy represents the average uncertainty in a system where higher entropy indicates higher uncertainty. Excitation of the neuron leads to the initiation of action potential which consequently causes an unpredictable change in the recorded signal. This affects the entropy content of the signal. In this regard entropy is a powerful tool to find the occurrence of abrupt events like spikes in the neural signal[11]. Traditional entropy estimation methods consider the overall uncertainty of a time series and unable to localize transient events. To overcome this weakness, TDE was introduced in [12] where a sliding *k*-sample window is applied to the *N*-sample signal $\{s(\alpha):\alpha=1,....,N\}$ and the entropy in each windowed segment of signal is calculated. This makes possible to find the time of occurrence of an abrupt event. The *k*-sample moving window with *T*-sliding lag can be defined as (1):

$$W(m,k,T)=\{s(\alpha),\alpha=1+mT,....,k+mT\} \quad (1)$$

Where *m* is window index, *k* is the number of window samples and *T* is the sliding lag. *T* is usually chosen to be smaller than *k* for not missing transient events. The entropy measures the divergence of probability density function (*pdf*) from a uniform distribution. When a transient event occurs, the amplitude distribution of signal or its *pdf* changes and diverges from uniformity and exhibits a sharper profile. An estimate of *pdf* can be obtained by histogram of the distribution of amplitude values. In this way the range of signal is equally divided into some bins and the probability of *i-th* bin is defined as the ratio of the number of samples falling into that bin to the signal sample size.

A more generalized form of entropy is Tsallis entropy (TE) which can be quite useful in calculating entropy in the presence of transients [13]. The Tsallis entropy for discrete probability distribution is expressed as (2):

$$TE=(1-\sum_{i=1}^{V} P_i^q)/(q-1) \quad (2)$$

Where *q* is the entropic index, *V* is the number of voltage bins in the selected segment of signal.

The occurrence of spikes alters the amplitude distribution of the signal therefore changes the TE value. By calculating TE in successive overlapped windows the output of TDE is obtained which emphasizes the occurrence time of spikes by sharp peaks. The optimal parameters selection for TDE is discussed in section 2.2.

For post-processing, exponential weighting scheme is used to produce smoothed version of TDE according to (3):

$$x_a(i)=ax_t(i-1)+a(1-a)x_t(i-2)+a(1-a)^2x_t(i-3)+.... \quad (3)$$

Where x_t is the output of TDE, x_a is the smoothed version of x_t and a is the constant weight coefficient. Dominant peak locations in the absolute value of TDE output which cross a predefined threshold yield spike time of occurrences in the neural signal. When the peaks of TDE are detected, 1ms windowed segment of neural data around each peak is extracted as intended event. In low SNR cases, spikes are embedded in the high-amplitude background noise, where it is difficult to separate them from background noise based on the amplitude distribution. In such cases for distinguishing spike events based on TDE, the k is selected as half of the spike's peak duration. The peak duration is defined as the full duration between two samples around the spike peak which their amplitude is half of the peak amplitude. Therefore the events with wider width than the spike's peak duration are included in more successive windows than the spike event in a way that the successive sliding windows capture the small segment of event with relatively small changes and hence in comparison with intended spike event the estimated Tsallis entropy values produce wider peak with smaller amplitude in TDE output. To illustrate this, simulated data which contains three spike events with similar morphology but different width (64, 16, 32 samples, respectively) is constructed. The simulated data and TDE output for different k values are shown in Figure.1. For example in Figure.1 if k is selected as half of the peak duration of 16-sample spike (i.e. k=4), the 64-sample spike in comparison with 16-sample is included in more successive windows which successive windows capture segments with close variations and hence finally the wider peak with smaller amplitudes is returned in TDE output of 64-sample spike which is neglected by the selection of a suitable threshold (thick arrow in the lower panel). For transient events with considerable narrower width compared with the spike's peak duration, if k is selected near the main variation (i.e. spike's peak duration) of intended spike, the transient event is included in the lower number of sliding windows so a sharper peak appears in the TDE output which is omitted in the smoothing post-processing step. For example in Figure.1, if k=16 (i.e. half of the peak duration of 64-sample spike) then 16-sample spike is included in the lower sliding windows than 64-sample one which causes the sharper peak in the TDE output which is removed in the post-processing step (empty arrow in upper panel). The above discussion is shown by insets in Figure.1. In low SNR cases it is difficult to separate the non-spike events which their width is comparable with intended spikes.

2.2. Optimal parameter selection for TDE detector

There are some parameters which affect the TDE performance. These parameters include the length of sliding window (k), window sliding lag (T) and entropic index (q). The parameter k has an impact on temporal resolution of TDE detector as the greater temporal resolution is achieved with smaller k. It also emphasizes the event with specific duration in the detection process (see Figure.1). The suitable selection of k in spike detection is when the spike peak is included in some limited number of successive sliding windows. The window size can be selected as half of the spike's peak duration. Such selection guarantees each spike dominant peak to be included in the sufficient number of successive windows and consequently a peak appears in the TDE output which is not too narrow or too wide. It should be noted that in the cases where there is no a-priori information about the spike templates, due to the especial morphology of spike that there are four phases in spike generation (rising phase, falling phase, hyper-polarization phase and resting period), k can be chosen as one-quarter of spike length. This can give approximately the spike's peak duration. In this paper k is selected in this way.

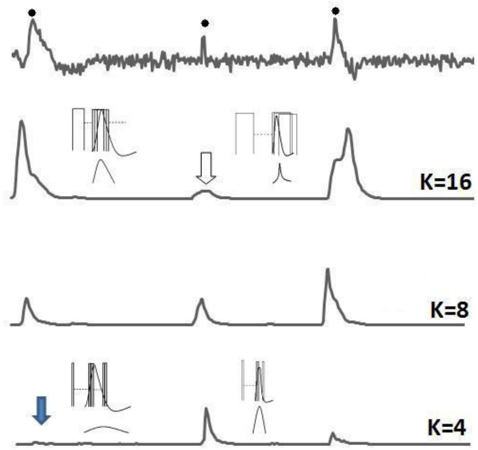

Figure.1 The effect of window length (*k*) on TDE detector. Top panel shows a synthesized data consists of three spikes which are specified by thick dots, with similar morphology but different duration (64, 16, 32 samples, respectively). Other panels show TDE output for different values of *k*. When *k* is larger than spike peak duration, the intended spike is included in the lower numbers of successive sliding windows which each window capture higher level of variation during TDE algorithm so a sharp peak appears in TDE output (empty arrow) which is smoothed in post-processing. When *k* is smaller than spike peak duration, the spike is considered in more successive number of sliding windows during TDE algorithm and hence a wider peak with lower amplitude appears in TDE output (filled arrow). Note that selection of *k* near the spike peak duration can emphasize intended spike event and de-emphasize the events with narrower or wider duration. Insets explain the above discussion.

The refractory period for most cells is no less than 1ms[6] so the spike sample size can be determined by the sampling rate of analog-to-digital conversion. For good localization in spike event detection, T is set to one sample. The most important parameter in TDE detector is q, where larger q will result in better signal(spike) to noise(background noise) ratio and enhance the TDE for focusing on spiky events[14]. There is no clear method for extracting the value of q from raw data. In our case, adjusting k as half of the spike peak duration (or approximately one-quarter of spike sample size) and T to one sample, we have tested different q values for extracting spikes from synthesized data with different SNR. The result is depicted in Figure.2 where the abscissa shows different values of q and ordinate is the precision of spike detection. The precision is defined *as* $TP/(TP+FP)$ where TP is the number of true positive and FP is the number of false positive in spike detection. The procedure of synthetic signal generation is explained in the section 2.3. It is clear from Figure.2 that larger value of q obtains higher value of precision. The curves will saturate for q higher than 5. Conducted experiments in Figure. 2 suggest that q=5 is a good selection for focusing on spiky events in the detection process.

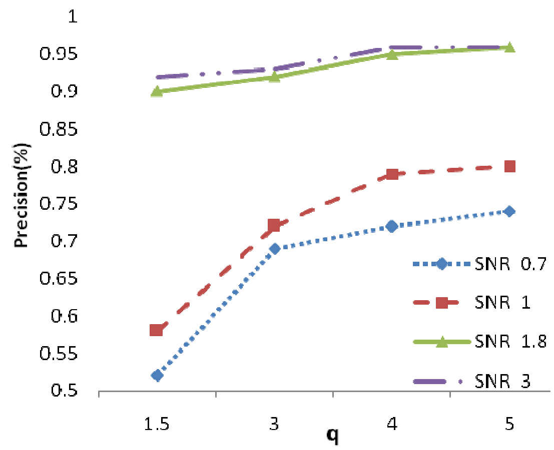

Figure.2 The performance of TDE detector for different values of *q*. For this test *k* is set to one-quarter of spike length (in sample) and *T*=1.

2.3. Synthetic data for detection

One of the main difficulties in the evaluation of spike detection performance is the absence of ground truth data that the exact number of action potentials and spike time of occurrences can be specified. For evaluation purposes such data should be synthesized. In this paper synthesized data is constructed based on real action potentials and real background noise where have been extracted from real neural data. Three spike trains with different action potential templates, individually are created where the locations of spikes are specified by a Poisson process in a manner that no overlap occurs and with minimum 1ms inter-spike time interval [6,7]. Spike trains are embedded in the real background noise and finally Gaussian white additive noise is added to simulate induced noise by measurement devices. An example of such synthesized extracellular data generation is shown in Figure. 3. For each test, 20s of such data is constructed. Synthetic data are constructed with different SNRs where SNR is defined as the ratio of average peak-to-peak amplitude of templates to root mean square (RMS) value of a pure background noise segment. Also synthesized data is created for different spike firing rates. In literature spike firing rates smaller than 10 are referred as the low rate and higher than 30 referred as the high-rate[3]. Different spike firing rates are considered due to their effect on false alarm rate.

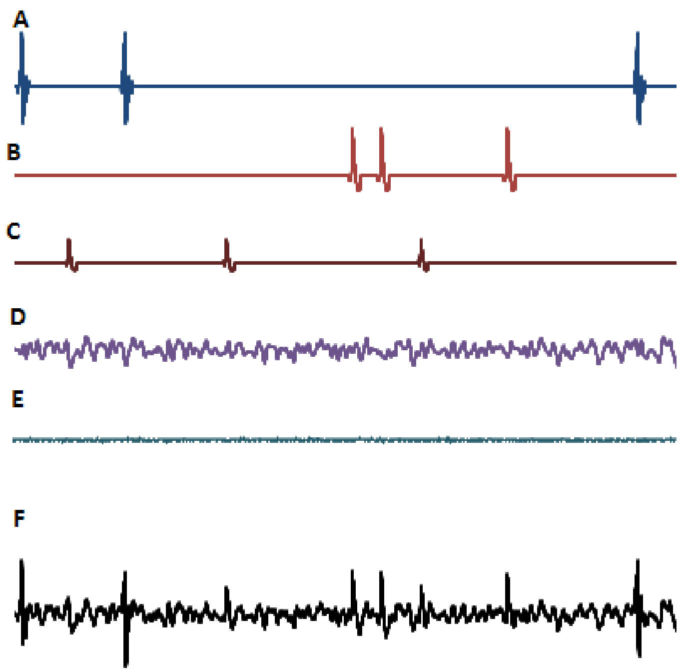

Figure.3 Synthesized data generation: Spike train1 (A), spike train2 (B), spike train 3(C), real background noise (D), additive Gaussian noise (E). Spikes in each train are distributed as Poisson process. There is no overlap between spikes. The synthesized data (F) is a linear mixture of spike trains, real background noise and additive Gaussian noise to simulate noise induced by electrical measurement devices.

3. Results and discussion

The performance of TDE spike detection method is compared with some other methods in literature. Selected methods for comparison are MWC[9], DWTS, DWTD[10] and SATM[3]. In MWC, multi-resolution wavelet decomposition at five levels is carried out. As the authors in [9] found that the choice of three consecutive scales is appropriate for most cases of action potential detection so such selection for decomposition level is sufficient. The scale where the absolute value yields a maximum is selected and then three successive detail levels up to the selected one are chosen. The point-wise product of selected levels is computed and finally smoothed by Bartlett window as proposed in[9]. Such multiplication produces dominant peaks in the spike time locations. For DWTS decimated wavelet transform is computed at scales 1 to 5. The author in [10]found that levels higher than 5 contain primarily noise. Based on the detail coefficients in the first decomposition level, background noise standard deviation is calculated. For such calculation, median absolute deviation (MAD) from zero is used as (4). Such measure is less sensitive to outliers than the traditional standard deviation[10].

$$MAD = \frac{median\left|x - median(x)\right|}{0.6745} \tag{4}$$

In (4) x represents time series (neural data) and 0.6745 is the 75th percentile of the standard normal distribution. Soft thresholding based on MAD is carried out for detail coefficients in last two levels. The approximation coefficients and other detail coefficients are set to zero. Based on the thresholded wavelet coefficients, denoised version of signal is reconstructed. The reconstructed signal is used for action potential detection. DWTD is the same as DWTS but the threshold for each detail level is obtained based on *MAD* from coefficient of that level. Using physiological data the authors in [10] showed that the threshold estimation based on (4) gives the optimal threshold. In wavelet based methods basis function selection is an important issue. For our test we selected the basis function which its average correlation with our spike templates is maximum. However such information in real recording is usually unavailable. In SATM, signal points directly are used for estimating a threshold based on *MAD*. TDE parameters are adjusted as k is equal to one-quarter of spike length, q equal to 5 and T equal to 1 sample (see 2.2). In each method a decision threshold is applied to the final output of algorithm and peak detection is carried out above the threshold to find spike occurrence time.

Figure.4 shows the comparison of TDE detector with other above-mentioned methods for action potential detection in a low-SNR real data which contains one dominant spike (denoted by an empty arrow) embedded in the high-amplitude background noise (the peak due to noise is denoted by star). It is clear from Figure.4 that SATM has detected correct action potential but also the noise peaks have crossed threshold level. This sensitivity to high-amplitude noise increases false alarm rate of SATM detector. The similarity in frequency content between spike and background noise makes the algorithms based on the wavelet denoising (DWTD, DWTS) sensitive to the background noise. Figure.4 implies the inability of such algorithms in low-SNR case for spike detection. MWC algorithm detects action potential correctly but the difference between background noise-related peak and spike-related peak in the MWC output is less than TDE output. This makes MWC algorithm more sensitive to the threshold level adjustment especially in low SNR cases. It should be noted that both TDE and MWC output are smoothed before peak detection. In the former exponential weighting scheme has been used and in the latter the multiplication is smoothed by Bartlett window as proposed in[9].

For evaluating the performance of different spike detectors, the percentage of correctly detected APs (P_{CD}) and the percentage of false alarms (P_{FA}) in different SNR and different firing rates are used in the case of synthetic neural data, which are generated as mentioned in the material and methods. The P_{CD} and P_{FA} are defined as (5):

$$P_{CD} = \frac{N_{CD}}{N_{AP}} \quad \text{and} \quad P_{FA} = \frac{N_{FA}}{N_{CD}} \tag{5}$$

Where N_{CD} is the number of correctly detected APs, N_{AP} is the number of APs inserted into the simulation, and N_{FA} is the number of false alarms [10].

The TDE method like other above-mentioned detection methods, find the intended event when its representation in transform space crosses a threshold (decision threshold). This makes all the above detection methods sensitive to the selection of decision threshold. In this regard a comparison test has been carried out to quantify the decision threshold effect on detection procedures of different methods. Figure.5 illustrates P_{FA} for different detectors based on different values of threshold levels for synthesized data (SNR=1.13). For this test the final output of each detector which decision threshold is applied, is normalized in [0 1]. The initial threshold (related to threshold factor 1 in horizontal axis of Figure.5) is selected such that P_{FA} is zero for all detectors. Then the initial threshold level is decreased gradually by multiplying it by threshold factors. Based on Figure.5 it is clear that TDE detector is less sensitive to the decision

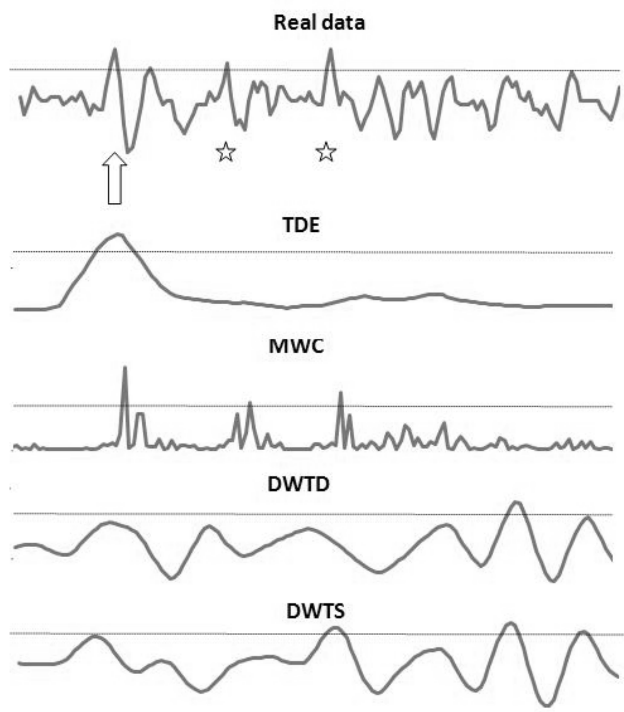

Figure.4 Illustration of the spike detection methods for a small segment of neural data contains one dominant action potential (indicated by empty arrow) and some high-amplitude noise (indicated by stars). The detection methods are single amplitude thresholding method(SATM)[3], time-dependent entropy(TDE), multiplication of wavelet coefficients (MWC)[9], Level-dependent noise estimation threshold(DWTD) and Single-level noise estimation threshold (DWTS)[10], respectively. The horizontal line is threshold level. Real data is indicated in the upper plot.

threshold and its P_{FA} is lower than other methods. This is because of q in Tsallis entropy and k in TDE calculation which emphasize spike events more than background noise (see Figure.1).

Figure. 6 shows the performance of different detectors based on P_{CD} for low and high firing rates. In SNR near 2(high SNR), TDE detects more than 98% of spikes as SATM and MWC does but in lower SNR, SATM performance deteriorates rapidly because in such case amplitude of the background noise increases and this alters the level of threshold which is estimated based on (4) which decreases N_{CD} and consequently decreases P_{CD}. In the lower SNR cases TDE detector exhibits higher P_{CD} in comparison with other methods as the number of truly detected spikes are higher. For DWTS and DWTD methods, as the background noise has common frequency content like intended spikes so these time-frequency based methods are sensitive to the extent of background noise. There is a similar discussion for MWC but as this method uses multiplication of wavelet coefficients instead of summation, the uncorrelated background noise is further attenuated in the detector output so it has lower sensitivity to the background noise strength. At the mid SNRs between 0.5 and 1.5 the estimated *pdf* for entropy calculation is affected significantly by spike amplitude and consequently this increases P_{CD} which higher values indicate better performance. Although there are some criteria for threshold estimation based on the standard deviation of background noise [3, 10] but in this comparison, several threshold levels are used for each SNR and the best result for higher P_{CD} or lower P_{FA} is considered for each method. TDE detection method is based on amplitude distribution so in low SNR cases (about 0dB) it is unable to detect the majority of spikes as other methods.

From Figure. 7 the main advantage of TDE algorithm, which is the lower false alarm percentage, is compared with other methods. This capability arises due to the q parameter in Tsallis entropy, which emphasizes *pdf* changes caused by spike events and optimal selection of k. Such parameters cause the peaks in TDE output have larger distance from peaks caused by background noise while in other methods such difference is significantly lower. To ensure consistent results, several numbers of independent 20 second long trial signals are created and

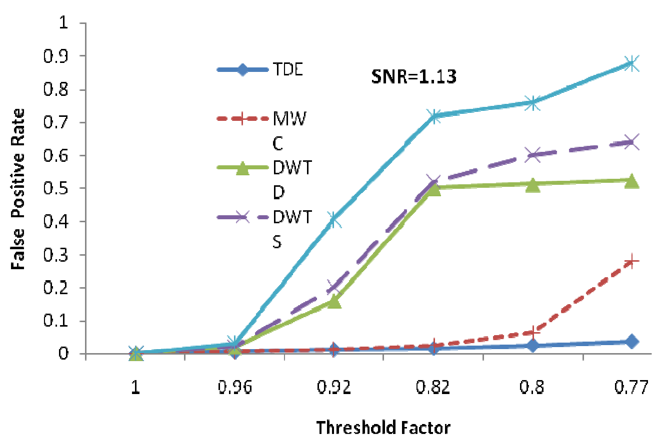

Figure.5 Sensitivity of detection methods to final decision threshold level. The horizontal axis shows the threshold factor. The initial level of threshold (related to the threshold factor 1) is selected in a manner that False-Positive rate of all methods is zero. Other numbers on the horizontal axis are the factors that are multiplied by the initial threshold to decrease the threshold gradually. The result is related to synthetic neural data constructed with real background noise and real spike waveforms. The SNR of data is 1.13 and its spike rate is 30 Hz.

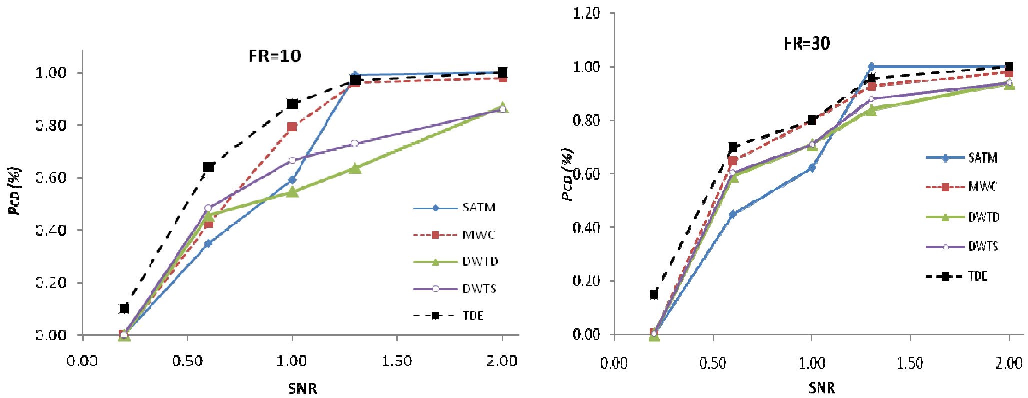

Figure.6 Comparison between the percentage of correctly detected spikes in different firing rates(FR) and for different detection techniques. The methods are SATM(single amplitude thresholding method), MWC(multiplication of wavelet coefficients), DWTS (single-level noise estimation threshold), DWTD (level dependent noise estimation threshold) and TDE(time-dependent entropy).

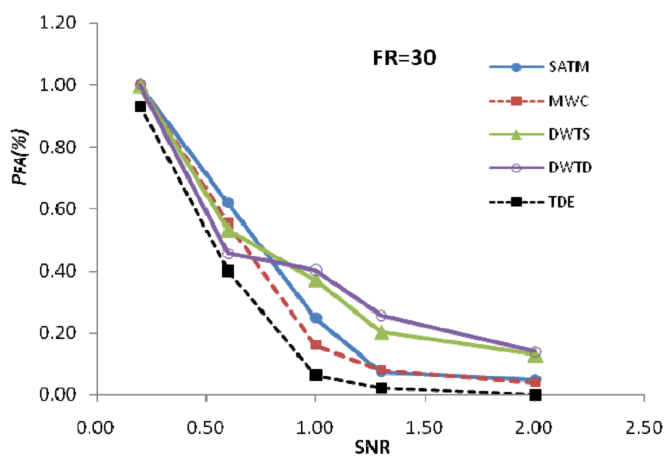

Figure.7 False alarm rate for different SNRs. Results show lower false alarm rate in TDE which is a obtained due to the parameter q used in Tsallis entropy

the results in Figure.6 and Figure.7 are the average values for these trials.

3. Conclusion

In this paper, a method based on the entropy measures is proposed for offline spike detection. As entropy shows the level of uncertainty in the nervous system and firing of neurons affect the entropy content of the system therefore entropy can be used as a measure for spike detection. For localizing spike events, TDE which is a time dependent entropy method is used where the entropy of signal is calculated in successive windowed segments of the neural data. In order to quantify uncertainty in each segment of signal, Tsallise entropy as a generalized form of entropy is used which can be quite useful in calculating entropy in the presence of transients[13]. Occurrence of spike produces a peak in the TDE output. For better localization window lag is adjusted to one.

We showed that by adjusting window length as half of the spike peak duration and entropic index in Tsallis entropy equal to 5, the difference between spike-related peak and background noise-related peak in TDE output is higher than other traditional methods. This reduces the percentage of false alarm detection in TDE in comparison with other methods. Unlike the wavelet-based methods for spike detection which are sensitive to the selection of basis function and decomposition scheme or the HOS-based methods which are based on the assumption of Gaussian nature of the background noise that it has been argued[15], the TDE method only needs to the sampling rate of spikes to obtain the optimal detection result. Although proposed method can be easily implemented in offline mode but the main weakness of the TDE method is that it is a time consuming approach compared with other mentioned methods in this paper. This makes TDE method impractical for real-time application.

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