A UNIFIED FRAMEWORK OF THIRD ORDER TIME AND FREQUENCY DOMAIN ANALYSIS FOR NEURAL SPIKE TRAINS

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ABSTRACT

Third order time and frequency analysis has exhibited great potential for correlation analysis of multi-sensor datasets, but is usually presented as separate time domain and frequency domain approaches. A combined framework of both frequency domain and time domain has rarely been used. This paper proposes a non-parametric third order time and frequency domain framework which used two dimensional Fourier transforms to bridge the gap between time domain and frequency domain. A unified framework offers flexibility and efficiency to apply to data. In this paper we study neural spike train data treated as stochastic point processes. In time domain direct analysis, third order cumulant densities of spike trains are applied, which need all first-, second- and third order product densities to be calculated before constructing the third order cumulant density, which brings additional challenges. The novelty in this study is that a new framework is proposed which can offer an alternative approach without calculating lower order quantities and can reveal nonlinear relationship between neural recordings. The results show that the present framework provides a novel non-parametric method to estimate both time and frequency domain measurements which is applicable to spike train data.

Index Terms— time domain, frequency domain, higher order spectrum, spike trains

1. INTRODUCTION

Time and frequency domain analysis paves a way for quantitatively studying neural spike trains, trying to uncover the principles of the nervous system and advance our understanding of the brain. A particular scientific area is the detection of interaction between neurons, which is also known as functional connectivity[1]. This paper uses third order statistical signal processing methods (Third order time and frequency analysis) to study functional connectivities among spike trains, The motivation for this work is:

1. Recently, correlations higher than second order have been reported to play a role in brain function. Nonlinear firing depends on third order correlations between presynaptic spikes [2]. This higher order correlation might be an inherent property of cortical dynamics existing widely in different species[3][4]. Hence, analysis tools which can reveal the interaction of higher order phenomenon are worthy of being investigated.

2. The interactions between neurons are diverse and complex. For example, interactions can be linear or nonlinear. The classical and widespread techniques are second order, for instance, cross-correlation[5] coherence[6] and Granger Causality [7]. Less work has been done in addressing the detection of nonlinear interactions. Third order time and frequency analysis is a potential approach which can shed light on nonlinearity study.

3. Third order statistical analysis can be undertaken either in time or frequency domain. For the second order analysis, a unified framework has been developed and applied to study linear relationships[8]. This inspires the possibility that in the third order case, a time and frequency combined framework can be developed.

4. A combined framework can provide flexibility and efficiency. For the third order point process in time domain, second order quantities need to be calculated, but in frequency domain, there is no need to calculate lower order measures. For point process data, a combined framework can also give a straightforward way to calculate confidence limits.

Higher order statistical measurements have a long history in signal processing community. Godfrey[9] used it to analyse economic data. Brillinger and Rosenblatt [10][11] contributed to this area by using third order cumulant density and its frequency domain spectrum. Mendel and Nikias summarised different estimators and applications, and emphasised the high signal-noise ratio(SNR) of bispectra compared with second order measurements[12][13]. Recently, higher order statistics have been combined with graphic theory to explore network analysis problems[14].

Most high order related approaches have been done in either time domain[15][16] or frequency domain [17][18]. Few attempts have been made to build a combined framework to bring time and frequency domain estimates together. The reason might be lack of an efficient algorithm of multidimensional Fourier transform. Since the computational ability increases dramatically and a number of numerical calculation tools have been developed, high dimensional Fourier transfer can now be effectively computed. This paper provides a novel framework to integrate time and frequency domain by two dimensional Fourier transform and demonstrates its application to point process(spike trains) data. Section 2 illustrates the mathematical detail of the proposed framework and the estimating algorithm. Section 3 briefly introduces the dataset under investigation and the results obtained from the proposed framework. Section 4 concludes this methods and discusses some potential extensions.

2. METHODS

2.1. An introduction to spike train data

Spike trains can be regarded as a realisation of stochastic point process, essentially a recording of spikes' occurrence time in order, denoted by N. For this process N, the counts of events occurring within time interval $(0, t]$ is represented as $N(t)$. The differential increment is defined as $dN(t) = N(t, t+dt]$, which is the counts of events in a duration $(t, t+dt]$. In case of spike train, the value of each time point is either 1 or 0 depending on the occurrence of a spike or not. In the following text, different spike trains are represented by different subscripts, for instance, the three spike trains are usually subscripted as $N_0(t)$, $N_1(t)$ and $N_2(t)$. In this paper, spike trains $N_1(t)$ and $N_2(t)$ are used to represent the reference spikes and spike train $N_0(t)$ is used to represent the response spike.

In order to apply the third order time and frequency domain analysis to the spike train datasets, there are two necessary assumptions which must be made. Firstly, the processes taken into account should be stationary up to order three moment, which means the processes taken into account have constant means and the covariances beneath order three between them depend only on the time difference between events. Secondly, the mixing condition of time series must hold [19]. That is to say the processes have a short span of dependence, which indicates that $N_0(t)$, $N_1(t)$ and $N_2(t)$ are becoming unrelated to each other as the time differences between spike times are growing.

2.2. Unified third order time and frequency analysis framework

This paper aims at proposing a combined time and frequency domain framework. It is important that measurements in both domains can be estimated independently. In this paper, the terms forward transform and backward transform are in preference, which represent transform from time domain to frequency domain and the reverse transform respectively.

In the forward transform phase, the disjoint Fourier transform[6][8] will be used to estimate the basic frequency domain spectral parameter $d^T_{N_0}(\lambda)$,$d^T_{N_1}(\mu)$ and $d^T_{N_2}(\lambda+\mu)$.

The cross-bispectrum, $f_{012}(\lambda, \mu)$ among three different spike trains N_0, N_1 and N_2 is defined as[20]:

$$f_{012}(\lambda, \mu) = \lim_{T\to\infty} \frac{1}{(2\pi)^2 T} E\{d^T_{N_0}(\lambda) d^T_{N_1}(\mu) \overline{d^T_{N_2}(\lambda+\mu)}\} \tag{1}$$

This definition considers averaging the product of triplets of finite Fourier transforms at each frequency. Based on this consideration, the disjoint section method can be taken into account using a average over all segments. Hence, a estimate of cross bispectrum is calculated as:

$$\hat{f}_{012}(\lambda, \mu) = \frac{1}{(2\pi)^2 LT} \sum_{l=1}^{L} d^T_{N_0}(\lambda, l) d^T_{N_1}(\mu, l) \overline{d^T_{N_2}(\lambda+\mu, l)} \tag{2}$$

where T denotes the length of each disjoint segment, L denotes the number of segments, l indicates the index of segment, and overbar represents complex conjugate.

The equation(2) above gives a direct way to interpret the sense of bispectrum. The third order cross spectrum quantifies the dependency among spike train N_0 at λ frequency, spike train N_1 at μ frequency and spike train N_2 at $(\lambda+\mu)$ frequency.

Suppose point processes N_0, N_1 and N_2 have mean rates P_0, P_1 and P_2 respectively. The third-order cumulant density is analytically defined as[15]:

$$q_{012}(u, v)dudvdt = E\{(dN_0(t+u) - P_0 du)(dN_1(t+v) - P_1 dv)(dN_2(t) - P_2 dt)\} \tag{3}$$

where the lag variables u and v are associated with the timing convention used to represent the time intervals between three arbitrarily selected spikes, each recorded from a different spike train, N_0,N_1,N_2. In this paper, v represents the time lag between a event in spike train N_1 and a reference event in spike train N_2, u represents the time lag between a event in spike train N_0 and a reference event in spike train N_2 and therefore $u-v$ represents the time lag between a event in spike train N_0 and a reference event in spike train N_1.

By simultaneously applying the expectation operator expanding the second- and third- order product densities[6] on equation(3) gives:

$$\begin{aligned} q_{012}(u, v) = P_{012}(u, v) - P_{01}(u-v)P_2 - P_{02}(u)P_1 \\ - P_{12}(v)P_0 + 2P_0P_1P_2 \end{aligned} \tag{4}$$

where P_{012} denotes the third order cross product density and P_{01},P_{02} and P_{12} denote the pairwise second order cross product densities.

The form of equation(4) above indicates an interpretation for the third order cumulant density. Under a situation of specific distances u and v between three spikes, the first term on the right side of equation(4) is the third order product density. Contributions provided by pairwise linear interaction between two spike trains and a third independent one, which are represented by the second, third and forth terms on the right side, are subtracted. There is one scenario that this contribution could possibly result from three independent spike trains. From the equation(4), this contribution has been removed three times, so a two times of this contribution, represented by the last term on the right, should be compensated back to the third order cumulant density.

The estimation can be obtain based on equation(4). Let a set $\{r_i\}$ represent the spike times of spike train N_0, where $i = 1, 2, ..., N_0(R)$. Similarly, sets $\{s_j\}$ and $\{t_k\}$ are defined for spike trains N_1 and N_2, for $j = 1, 2, ..., N_1(R)$ and $k = 1, 2, ..., N_2(R)$, respectively.

The third order cross-correlation histogram of three spike trains, N_0, N_1 and N_2 may be expressed as:

$$J^R_{012}(u, v) = counts\{(r_i, s_j, t_k), u - \frac{b}{2} < r_i - t_k < u + \frac{b}{2}, \\ v - \frac{b}{2} < s_j - t_k < v + \frac{b}{2}\} \tag{5}$$

Successively, the unbiased third order product density is estimated as:

$$\hat{P}_{012}(u, v) = \frac{J^R_{012}(u, v)}{b^2 R} \tag{6}$$

where $counts\{S\}$ is the number of events in set S, b is the width of a bin centralised at lag v and R is the duration of the spike trains.

This procedure can also be applied to the second order scenario. The second order histogram and product density are achieved in a similar way.

Finally, the mean rate of a spike train, for example, for N_0 can be estimated straightforwardly as:

$$\hat{P}_0 = N_0(R)/R \tag{7}$$

.

Throughout this procedure, all the terms on the right side of equation(4) is estimated, then the third order cumulant density estimator can be achieved by substituting these terms into equation(4) respectively.

Based on the assumption that all three signals considered here are Poisson spike trains, a 95% confidence interval has been derived accordingly as[21]:

$$V\hat{a}r[\hat{q}_{012}] = \hat{P}_0 \hat{P}_1 \hat{P}_2 / Rb^2 \tag{8}$$

where b is the bin width parameter and T is the recording length of time.

Then under the null hypothesis of independence, an approximate 95% confident interval can be constructed as[21]:

$$[0 - 1.96(\hat{P}_0 \hat{P}_1 \hat{P}_2 / Rb^2)^{1/2}, 0 + 1.96(\hat{P}_0 \hat{P}_1 \hat{P}_2 / Rb^2)^{1/2}] \tag{9}$$

The term forward transform refers to transform from temporal cumulant density q_{012} to cross-bispectrum f_{012} and the term Backward transform refers to transform from cross-bispectrum f_{012} to temporal cumulant density q_{012}. These transforms need two dimensional Fourier transform and Inverse Fourier transform. The Forward-Backward transform is summarised here :

$$2\pi^2 f_{012}(\lambda, \mu) = \int\int e^{-i(\lambda u + \mu v)} q_{012}(u, v) du dv \tag{10}$$

$$q_{012}(u, v) = \int\int e^{i(u\lambda + v\mu)} f_{012}(\lambda, \mu) d\lambda d\mu \tag{11}$$

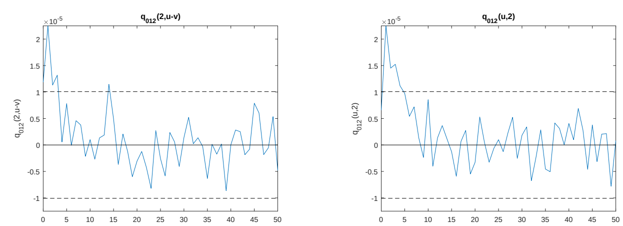
Equations (10) and (11) can be combined with frequency and time domain estimates described by equations (2) and (4) respectively to construct the whole framework proposed together.

By contrasting equation(11) to equation(4) and all equations associated to (4), e.g. equations (5)-(7), The simplicity and conciseness of this combined framework have been achieved, which is what we highlighted in this paper. All calculation requirement of the lower order terms can be avoided due to the flexibility provided by this framework.

3. APPLICATIONS AND RESULTS

3.1. Application to simulated network

This section will illustrate applications of the framework proposed in this paper by using a simulated network of 3 connected neurons. Single neurons were modelled using a biophysical point neurone conductance model[21]. In this specific configuration, spiking activity of neurons 1 and 2 induce inputs for neuron 0 convergently.

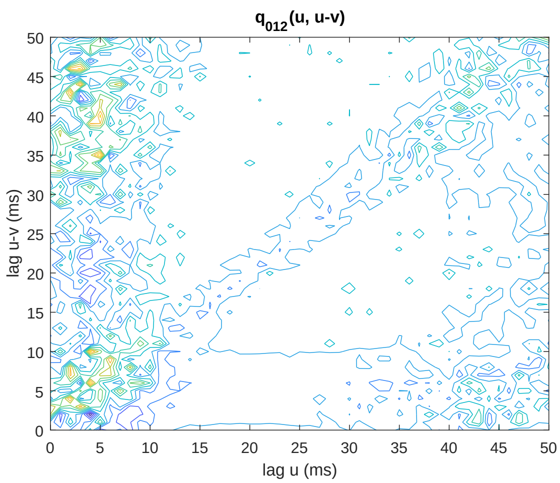


(a) Section u=2ms (b) Section u-v=2ms

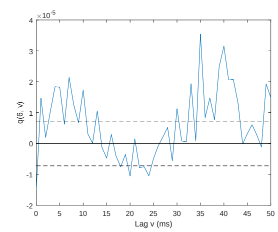
Fig. 1. (a) and (b) are section of this peak point along the vertical and horizontal direction respectively, along with the upper and lower confidence limit(two dashed horizontal lines) and null value(solid horizontal line) based on the assumption of uncorrlated spike trains.

Figure 1 shows the estimated cumulant density obtained using the proposed framework. The results shows significant values near the origin and a peak can be identified at the point $(u, u-v) = (2, 2)$ in figure 1. Based on the timing convention set out in equation(3), the short duration peak indicates that the presence of a significant third order interaction at these latencies which results in an increased output rate. To illustrate the cumulant density over a time lag pair plane $(u, u-v)$ needs a simple matrix manipulation to map the estimated result using equation(11) which is represented as a function of time lag pairs (u, v).

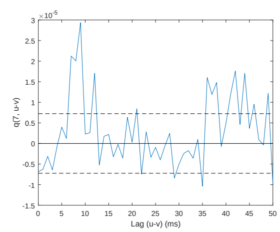
3.2. Application to experimental dataset



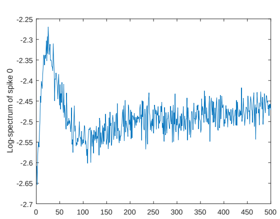
(a) Contour figure



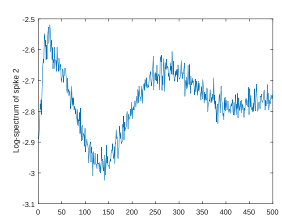
(b) section u = 6ms



(c) section u = 7ms



(d) Log-spec of CA1 spike



(e) Log-spec of one CA3 spike

Fig. 2. Contour figure of Estimated cumulant density using the proposed framework.Apparent peaks can be seen around origin which indicates very short delays, and can be seen in the interval where the value u-v ranges between [35, 45]ms.(d) and (e) are the log-spectral of the CA1 spike train and one of the CA3 spike trains

In this dataset, single unit spike trains signals simultaneously recorded from four different hippocampal regions (left and right CA1 and CA3) in isoflurane-anaesthetized Listerhooded rats were analysed[22]. The hippocampus is a widely studied brain region that is important in learning and memory. The data used in this analysis is from the neuronal spike trains during the basal recording period before evoking drug-induced epileptiform activity. The analysis was conducted on a 300 seconds duration epoch.

Figure 2 shows the estimated cumulant density $q_{012}(u, u-v)$, using equation(11). The timing convention is that lags u and (u-v) in ms represent the time to previous input spikes from two CA3 neurons onto one CA1 neuron. Two regions where there are significant features can be identified. These are highlighted in the two sections at fixed u lags of 6 ms and 7 ms shown in figures 2(b) and 2(c). These sections indicate that significant third order interactions can occur when the third spike is between 5-10 ms or between 35-45 ms prior to the CA1 spike. The lags in figure 2(a) indicate that the two inputs spikes have a time difference of less than 5 ms. Figure 2(d) and (e) show auto-spectral estimates for the CA1 spike and one of the two CA3 spikes. The dominant feature in each spectrum is a peak around 25 Hz, representing corresponding mean rate of each spike. The advantage of the estimate from Frequency domain is that it does not require calculation of 1st 2nd and 3rd order product densities.

4. CONCLUSION

In this paper, an approach of third order time and frequency analysis was presented. This approach contains forward and backward transforms using two dimensional Fourier transform to bridge them. The aim of presenting this approach is to achieve a unified framework to integrate higher order statistics separated in time domain and frequency domain. It offers flexibility and simplicity to start from direct frequency domain estimate to construct the indirect time domain estimate by avoiding calculating the second order product densities, which represents a considerable computationally efficiency.

Analysis of a simulated dataset and an experimental dataset showed that the third order time frequency analysis can identify higher order interactions between neurons. The results achieved by adopting this framework help to reveal the higher order pattern which is beyond the scope of linear analysis.

Further investigation should be applied to different frequency domain measurements, for example, bicoherence and phase information.Phase information implies time lag, a further validation of phase estimates comparing with time lags can be integrated in this framework in the future. This framework may not be limited only to point process, there is a potential to extend its application to hybrid dataset including both point process signals and continuous datatype like EEG signals.

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