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Technical Note

Estimating coupling direction between neuronal populations with permutation conditional mutual information

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ABSTRACT

To further understand functional connectivity in the brain, we need to identify the coupling direction between neuronal signals recorded from different brain areas. In this paper, we present a novel methodology based on permutation analysis and conditional mutual information for estimation of a directionality index between two neuronal populations. First, the reliability of this method is numerically assessed with a coupled mass neural model; the simulations show that this method is superior to the conditional mutual information method and the Granger causality method for identifying the coupling direction between unidirectional or bidirectional neuronal populations that are generated by the mass neuronal model. The method is also applied to investigate the coupling direction between neuronal populations in CA1 and CA3 in the rat hippocampal tetanus toxin model of focal epilepsy; the propagation direction of the seizure events could be elucidated through this coupling direction estimation method. All together, these results suggest that the permutation conditional mutual information method is a promising technique for estimating directional coupling between mutually interconnected neuronal populations.

Introduction

Synchronization analysis has been a focus of attention in the biological systems (Rosenblum and Pikovsky, 2001; Rosenblum, 2002). Synchronization between different brain areas has been the subject of a number of studies in both the normal (e.g. Roelfsema, et al., 1997; Steriade and McCormick, 1993; Miltner et al., 1999; Rodriguez et al., 1999, Mizuhara and Yamaguchi, 2007; Cantero et al., 2009; Darvas et al., 2009) and the diseased brain (e.g. Uhlhass and Singer, 2006 and within references; Rudrauf et al., 2006; Amor et al., 2009; Darvas et al., 2009).

The synchronization between different brain areas cannot be measured directly, but can be estimated by applying an appropriate analysis method with neurophysiological signals. Many linear and nonlinear time series methods have been proposed (Pereda et al, 2005). While most of these methods quantify the strength of synchronization, more recent developments have attempted to estimate the synchronization direction. For example, a Granger causality method has been proposed to estimate the coupling directions between neuronal signals by measuring how the history of a neural series predicts the future of another (e.g. Hesse et al., 2003; Brovelli et al., 2004; Seth, 2005; Lungarella and Sporns, 2006; Wang et al., 2008). The Granger causality methods can be successfully applied to linear models, however the change in cross-prediction error could not be directly applied to nonlinear time series (Palus and Vejmelka, 2007). The information theory based methods are also proposed to estimate the coupling direction between neural series, including transfer entropy (Schreiber, 2000) and conditional mutual information (Palus et al., 2001; Vejmelka and Palus, 2008). More discussions on the estimation methods of coupling direction based on information theory can be found in Hlavackova-Schindler et al. (2007). The instantaneous phases of interacting oscillators can also be used to identify the coupling direction, including the evolution map approach and the instantaneous period approach (Rosenblum and Pikovsky, 2001; Rosenblum, 2002); unfortunately, these two methods are based on the estimated instantaneous phase, so that it is sensitive to noise in the time series. Our previous works showed that the evolution map approach and the instantaneous period approach are not very suitable for analyzing noisy and nonstationary EEG recordings (Li et al., 2007a,b,c). In order to detect the weak coupling direction of oscillators, the state-space and phase-dynamics approaches have been proposed (Smirnov and Andrzejak 2005; Smirnov and Bezruchko, 2003). The state-space approach requires optimal embedding parameters and the phase-dynamics approach requires strong oscillatory behaviour, so there are some limitations in the practical applications, furthermore, these two approaches are also sensitive to noise in the neural series.

Recently, the permutation analysis and conditional mutual information were integrated to estimate the coupling direction between two cardiorespiratory series (Bahraminasab et al., 2008). In this study, we will investigate whether or not the method can be used to estimate the coupling direction between neuronal populations. This method is based on the probability distribution of permutation and conditional mutual information, so it is called permutation conditional mutual information

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(PCMI). The performance of the PCMI method was assessed by utilising a coupled neural mass model by comparing with the traditional conditional mutual information (CMI) method and the Granger causality (GC) method. This method is then applied to real neural populations recorded in the hippocampus of rats.

Methods

Conditional mutual information and directionality

Presumably two neuronal populations $X=\{x_t\}$ and $Y=\{y_t\}$ are recorded from two different brain areas, respectively. The marginal probability distribution functions of X and Y are denoted as $p(x)$ and $p(y)$, respectively; the joint probability function of X and Y is denoted as $p(x,y)$. The entropy of X and Y is defined as

$$H(X) = -\sum_{x \in X} p(x) \log p(x) \tag{1}$$

and

$$H(Y) = -\sum_{y \in Y} p(y) \log p(y). \tag{2}$$

The joint entropy of $H(X,Y)$ is defined as

$$H(X,Y) = -\sum_{x \in X} \sum_{y \in Y} p(x,y) \log p(x,y). \tag{3}$$

Then, the conditional entropy $H(X|Y)$ of X given Y is given by

$$H(X|Y) = -\sum_{x \in X} \sum_{y \in Y} p(x,y) \log p(x|y). \tag{4}$$

The common information contained in X and Y can be estimated by the following mutual information calculation:

$$I(X;Y) = H(X) + H(Y) - H(X,Y). \tag{5}$$

The conditional mutual information (CMI) between two series X and Y may be calculated by the following equations (Palus et al., 2001; Palus and Stefanovska, 2003):

$$I^{\delta}_{X \to Y} = I(X; Y_{\delta}|Y) = H(X|Y) + H(Y_{\delta}|Y) - H(X, Y_{\delta}|Y) \tag{6}$$

and

$$I^{\delta}_{Y \to X} = I(Y; X_{\delta}|X) = H(Y|X) + H(X_{\delta}|X) - H(Y, X_{\delta}|X) \tag{7}$$

where $X_{\delta}(Y_{\delta})$ is an observable derived from the state of the process X (Y) δ steps in the future, i.e. $X_{\delta}: x_{t+\delta} = x_t$ ($Y_{\delta}: y_{t+\delta} = y_t$). The information that is transferred from the process X (or Y) to the process Y (or X) at some later points in time can be defined as

$$I_{X \to Y} = \frac{1}{N} \sum_{\delta=1}^{N} I^{\delta}_{X \to Y} \tag{8}$$

and

$$I_{Y \to X} = \frac{1}{N} \sum_{\delta=1}^{N} I^{\delta}_{Y \to X} \tag{9}$$

where the N is the maximal later points. Based on the conditional mutual information, the directionality index between X and Y can be defined by

$$D_{XY} = \left(\frac{I_{X \to Y} - I_{Y \to X}}{I_{X \to Y} + I_{Y \to X}} \right). \tag{10}$$

The value of D_{XY} ranges from -1 to 1. $D_{XY}>0$ means that the process X drives Y; $D_{XY}<0$ means that the process Y drives X, and $D_{XY}=0$ means that the interactions between X and Y are symmetrical.

In the calculation of the CMI, two issues should be considered: the estimation of marginal probability functions and the selection of the δ steps in Eqs. (6) and (7). The marginal probability functions of two variables X and Y, and their joint probability function are often estimated by means of histogram method. The histogram can be constructed by segmenting the range of the data into equal sized bins, the number of bins is denoted as NBin. In the histogram method, the number of bins and bin sizes are first determined. The optimal number of bins depends on a strong assumption about the shape of the distribution, so until now there is no best number of bins for a practical time series. Second is to select the δ steps in Eqs. (6) and (7), the selection of the parameter depends on the phase difference of information flow between two time series. The δ parameter value can be selected by comparing the output at different δ values.

Permutation conditional mutual information

The EEG (electroencephalogram) or LFP (local filed potential) is a continuously variable signal, the amplitude and frequency of which change over time. Actually, the signals are composed of ascending and descending patterns. The statistical analysis of these two simple patterns may help us to indicate the change of a dynamical system. To obtain more complicated patterns from a dynamical signal, we may set up more complicated ordinal rankings, for instance Fig. 1B, M#1, M#2, …, M#6, in this study these different patterns are referred as 'motifs' (Olofsen et al., 2008). M#1 and M#5 are different 'slopes'; M#2 and M#4 are different 'troughs'; M#3 and M#6 are different 'peaks'. Thus, the EEG or LFP signals consist of a sequence of ordinal motifs. Based on the probability distribution of these motifs, a new complexity measure, called permutation entropy, was proposed (Bandt and Pompe, 2002). The permutation entropy has been successfully used to analyze neural signals (Li et al., 2007a, b, c, 2008; Olofsen et al., 2008).

The algorithm for the calculation of the probability distribution of motifs is very simple. Fig. 1(A) shows the original series (upper) and the discrete points (bottom) for the short interval marked by a black bar. For example, the first three points belong to M#5 pattern. The main procedure of the algorithm is as follows:

(1) Given a sequence of motifs (order: $m=3$, so $3!=6$ different motifs, see Fig. 1(B)), including 'slopes', 'peaks' and 'troughs';
(2) An epoch of the neural signal is extracted and the number of different motifs in the signal with different lag $\tau=1$ or 2 are estimated (seeing Fig. 1(A bottom));
(3) The probability of occurrence of each motif in the signal is calculated (see Fig. 1(C)). Let $f(M\#i), i \in (1{:}m!)$ denote the frequency of motif in the time series, its relative frequency is defined as

$$p(M\#i) = f(M\#i) / (L - (m-1)\tau) \tag{11}$$

where L is the length of the time series. In the following section, the $p(M\#i)$ is simplified as p_x for the time series.

If we analyze two signals (one is Fig. 1(A), another signal is not plotted here), the joint probability of occurrence of each motif in the signals, p_{xy}, can be calculated, as shown in Fig. 1(D). As can be seen in Fig. 1D, the $M\#1$ and $M\#5$ are main cross-patterns between the X and Y series, which means there is a drive–response relationship between these two series. Similarly, we can also calculate the joint probability of X, Y and Y_{δ}, or X, Y and X_{δ}.

Based on the permutation analysis, the new probability distribution functions, the new joint probability functions and the new conditional probability functions of two series X and Y can be obtained. Then, a new conditional mutual information can be obtained by means of Eqs. (8)