ESANN'2007 proceedings - European Symposium on Artificial Neural Networks
Bruges (Belgium), 25-27 April 2007, d-side publi., ISBN 2-930307-07-2.

Causality analysis of LFPs in micro-electrode arrays based on mutual information

Nikolay V. Manyakov and Marc M. Van Hulle

K.U.Leuven, Laboratorium voor Neuro- & Psychofysiologie
Campus Gasthuisberg, Herestraat 49, BE-3000, Leuven, Belgium

Abstract.
Since perceptual and motor processes in the brain are the result of interactions between neurons, layers and areas, a lot of attention has been directed towards the development of techniques to unveil these interactions both in terms of connectivity and direction of interaction. Several techniques are derived from the Granger causality principle, and are based on multivariate autoregressive modeling, so that they can only account for the linear aspect of these interactions. We propose here a technique based on conditional mutual information which enables us not only to describe the directions of nonlinear connections, but also their time delays. We compare our technique with others using ground truth data, thus, for which we know the connectivity. As an application, we consider local field potentials (LFPs) recorded with the 96 micro-electrode UTAH array implanted in area V4 of the macaque monkey's visual cortex.

1 Causality analysis in neural systems

Understanding the connections between different recording sites in the brain, and their directions and delays, is of main interest in electrophysiology. Among these recordings, an important role is played by the local field potentials (LFPs), which are related to the synchronized input impinging onto the observed area. These signals are recorded using a low impedance extracellular micro-electrode and then low-pass filtered at 300 Hz so as to mask the action potentials.

The concept of Granger causality [1] tells us how one time series is helpful in forecasting another. When the variance of the prediction error is reduced by including in the forecasting model not only the previous data points of a time series, but also previous data points of another time series, we conclude that the second time series causes the first one. As a prediction paradigm, autoregressive modeling is used. As this concept originally only dealt with bivariate time series, it was expanded to multichannel recordings by using multivariate autoregressive modeling (MVAR). Let us denote the neuronal recordings from the k channels by $\tilde{x}(t) = (x_1(t), x_2(t), ..., x_k(t))$. The MVAR model is then defined as $\sum_{j=0}^{p} A_j \tilde{x}(t-j) = \tilde{e}(t)$, where $\tilde{e}(t) = (e_1(t), e_2(t), ..., e_k(t))$ is the vector of a multivariate zero mean uncorrelated white noise process, $A_0 = I, A_1, A_2, ..., A_p$ the $k \times k$ matrices of the model coefficients, and p the model order, which is calculated by Akaike's Information Criterion (AIC). In the frequency domain, the equation for MVAR is written in the form $\hat{A}(f) \cdot \hat{X}(f) = \hat{E}(f)$, which give us the relationship between the Fourier images of the variables. The last equation can be rewritten in the

form $\hat{X}(f) = \hat{A}^{-1}(f)\hat{E}(f)$ or $\hat{X}(f) = \hat{H}(f)\hat{E}(f)$, where $\hat{H}(f) = \hat{A}^{-1}(f)$. Based on the last equations, different measures for detecting causality were proposed:

1) Partial Coherence (PC) [2]: $\chi_{ij}(f) = \frac{M_{ij}(f)}{\sqrt{M_{ii}(f) \cdot M_{jj}(f)}}$, where $M_{ij}(f)$ is the minor of the spectral matrix $S(f) = \hat{H}V\hat{H}^*$, and V the correlation matrix of the noise $\tilde{e}(t)$; 2) Partial Directed Coherence (PDC) [3]: $\pi_{ij}(f) = \frac{|\hat{A}_{ij}(f)|}{\sqrt{\sum_{m=1}^{k} |\hat{A}_{mj}(f)|^2}}$; 3) Directed Transfer Function (DTF) [4]: $\gamma_{ij}(f) = \frac{|\hat{H}_{ij}(f)|}{\sqrt{\sum_{m=1}^{k} |\hat{H}_{im}(f)|^2}}$; 4) full frequency Directed Transfer Function (ffDTF) [5]: $\eta_{ij}(f) = \frac{|\hat{H}_{ij}(f)|}{\sqrt{\sum_f \sum_{m=1}^{k} |\hat{H}_{im}(f)|^2}}$; 5) direct Directed Transfer Function (dDTF) [5]: $\delta_{ij}(f) = \eta_{ij}(f) \cdot \chi_{ij}(f)$.

After calculating such a measure, the significance levels are determined using the surrogate data method [7], so that only values significantly different from noise are taken as an indication for the presence of a connection between the corresponding channels. The significance level is set to $\alpha = 0.05$. As indicated by Schreiber and Schmitz [8], we use $\frac{1}{\alpha} - 1 = 19$ surrogates. As surrogates, we use the iAAFT method [8] which destroys the cross-correlation between the time series.

In order to determine the performance of the different measures listed above, we consider 3 types of artificially-constructed graphs: 1) consisting of random connections between 5 to 7 nodes with one real LFP input and linear connections (as in Figure 1), 2) several LFPs inputs and linear connections, and 3) several LFPs inputs and nonlinear connections (modeled by sigmoids). The results are shown for 100 trials for each of the three cases, respectively (columns 1-3). We see that mostly incorrect results are produced.

2 Nonlinear causality

2.1 Statistical hypothesis

In order to answer the question why these techniques mostly yield incorrect results, let us examine the nature of the LFP time series more closely. We take a subset of 5 time series from the 96 electrode recordings obtained with the UTAH array (Cyberkentics Inc., Foxborough, Massachusetts, USA), which was implanted in the visual cortex V4 of the monkey brain (data courtesy of Rufin Vogels, same lab), and examined the following null hypothesis H_0: we have a multivariate linear stochastic process with arbitrary degree of cross-correlation [6]. We use the method of surrogate data [7] to test this hypothesis. By using the iterative multivariate surrogate technique [8], we construct 100 surrogates, which preserve their auto- and cross-correlations in all constructed time series, and which are thus conform to the null hypothesis. Nonlinear redundancy was

taken as a discriminant statistic [9]. The null hypothesis was rejected for the significance level 0.01. This means that the multivariate autoregressive model does not fit to the LFPs data, and that by consequence LFPs have a nonlinear structure (which was also proved by using surrogate data technique with Volterra series as discriminant statistics [11]), and nonlinear connections between them. So the MVAR model is not satisfactory for LFPs and this is why the linear techniques do not generate correct results.

2.2 Causality based on conditional mutual information

In light of the previous finding, we need an estimator that is not based on a MVAR expansion and that can capture nonlinear relations between nonlinear channels. Previously, it was suggested to calculate causality graphs in different spectral bands [5] and use Kullback-Leibler divergence [14]. In the first case, the nonlinear relations are approximated by linear ones. So we do not obtain a correct picture about the interactions between the electrode recordings. The second one is prone to computational difficulties. Paluš and co-workers [10] introduced the concept of conditional mutual information for detecting synchronization in EEG signals, termed by them the mutual coarse grained information rate (MCIR): $i(x_1|x_2) = \frac{1}{\tau_{max}} \sum_{\tau=1}^{\tau_{max}} MI(x_1(t), x_2(t+\tau)|x_2(t)) - \frac{1}{2\tau_{max}} \sum_{\tau=-\tau_{max}}^{\tau=\tau_{max};\tau\neq 0} MI(x_1(t), x_2(t+\tau))$ (where τ_{max} is such that for $\tau \geq \tau_{max}$ $MI(x_j(t), x_j(t+\tau) \approx 0$ for all data sets $j = 1..k$) and *vice-versa* with respect to x_2, and they looked where the difference becomes zero. Hence, their approach is actually not conformous with the concept of Granger causality, and is not intended for detecting connectivity (such as the delay of the connection and the direction at the onset of synchronization). Furthermore, they do not have a statistical test for detecting (the onset of) synchronization.

We propose to use mutual information $MI(x_1(t), x_2(t))$ [12], where $x_1(t)$ and $x_2(t)$ are recordings from the arrays. This measure gives us the common information or the information flow between these two channels. As it is a symmetric measure ($MI(x_1, x_2) = MI(x_2, x_1)$), and since we like to find the direction of flow, we modify it as $MI(x_1(t), x_2(t-\tau))$. In this case, we measure the flow between time series $x_1(t)$ and the previous state of $x_2(t)$, delayed by time τ. So we describe the information flow between these two channels with a

method	1	2	3
PC	0%	0%	0%
PDC	24%	19%	13%
DTF	23%	20%	11%
ffDTF	25%	15%	8%
dDTF	31%	25%	25%
CMI	99%	94%	91%

Table 1: Comparison between different methods for detecting causality based on LFPs. The percentage indicates the proportion of correct graphs found.

time lag τ. But the concept of Granger causality [1] is about how helpful data points of a second time series are when we include them into the prediction model of the first time series. Hence, as a nonlinear analog for Granger causality, we must use the conditional mutual information (CMI) in the form $MI(x_1(t), x_2(t-\tau)|x_1(t-1), ..., x_1(t-n))$.

For estimating the conditional mutual information we use the equality $MI(x; y|z) = MI(x; y, z) - MI(x; z)$, which allows us to reduce the estimation of the CMI to the estimation of two unconditional ones. For the estimation of the mutual information, we take the binless estimator based on k-nearest neighbor statistics [13].

As an example, we examine causality for the graph shown in Figure 1. We put in the first node of the graph the real time series of an LFP and in the fourth node we put Gaussian noise with fixed autocorrelation of the second order. The coupling schema was constructed according to the equations: $x_1(t) = LFP, x_2(t) = a_1x_1(t-2) + b_1N(0,1), x_3(t) = a_2x_1(t-1) + a_3x_2(t-3) + b_2N(0,1), x_4(t) = AR(2), x_5(t) = a_4x_4(t-2) + b_3N(0,1)$, where a_k and b_k are real numbers, $N(0,1)$ is the standard normal distribution (zero mean and unit variance).

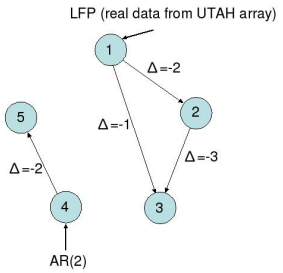

Fig.1: Coupling model

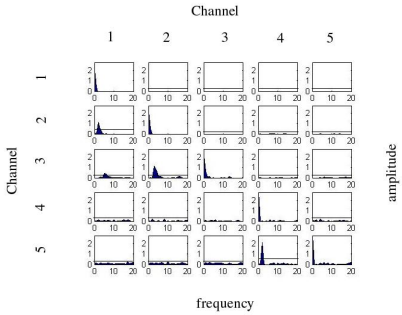

Fig.2: CMI between the channels

We calculate the CMI between the channels (using only 300 data points), as described above. The result for the CMI between each pair of channels vs. the time delay τ is presented in Figure 2. In this figure, the i-th column shows influence of the i-th time series onto the other channels. This means that in the position (j, i) we have $MI(x_j(t), x_i(t-\tau)|x_j(t-1), ..., x_j(t-n))$. When we analyze the first column, we can see that in the second and third rows there are peaks in the MI above the horizontal line (significance level, see further). This indicates that the first channel influenced the second and third ones. From the value of τ where each peak appears, we can calculate the time delay of the influence between the channels.

The horizontal line in each plot indicates the significance level for the null hypothesis H_0: below this level, we don't have any dependency between the channels; for every point above this line, the hypothesis is rejected and their is

a dependency. For testing this hypothesis, we use the surrogate data test [7], where all surrogates must preserve all properties of the initial time series but all connection between the time series must be destroyed. Because we have LFPs recordings of relatively long time lengths, and we use only short time intervals for causality estimation (300 points), it is possible to divide the recording into short subintervals of length equal to the length used for estimating the CMI (*i.e.*, 300 time points). No we can shuffle the different subintervals for generating appropriate surrogates. So we have time series which preserve all properties of the recording. We only need to take care that the subintervals do not overlap. As a result of this procedure, we destroy all connections between the recordings.

The result for the proposed method, for the artificially generated graphs, is shown in Table 1.

2.3 Application to UTAH micro-electrode data

In this simulation, we analyze a data set consisting of 96 LFP recordings from the UTAH array implanted in area V4 of the macaque monkey's visual cortex (courtesy of Rufin Vogels). The result of the causality analysis is presented in Figure 3. We observe that the connections are structured and mostly vertically oriented, and perhaps arranged in two groups. It is tempting to relate the observed structure to the columnar organization of area V4, mediated by horizontal connections, but we still need to verify that.

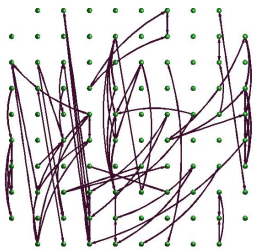

Fig. 3: Connectivity analysis of the UTAH micro-electrode array data

3 Conclusion

We have compared different methods for causality analysis of local field potential data, and introduced a new method based on conditional mutual information (CMI). We have considered ground truth data for the comparison and have shown that CMI gives better results. This can be explained by the presence of nonlinear connections between the nonlinear LFP time series, while the standard methods assume linearity. In addition, the CMI-based method not only provides us with the correct connections and their directions, but also with their time delays. We have applied our method to LFP recordings made with the

96 micro-electrode UTAH array, which revealed a structured connectivity pattern. An aspect that still remains to be examined in LFP causality analysis is the distinction between directed and undirected interactions between recording channels. This will be adressed in our future work.

Acknowledgments

The authors are grateful to Rufin Vogels, Laboratorium voor Neuro- & Psychofysiologie, K.U.Leuven, for sharing his micro-electrode data. The first author is supported by a grant from project IST-2004-027017 of the European Commission. The second author is supported by the Excellence Financing program of the K.U.Leuven (EF 2005), the Belgian Fund for Scientific Research – Flanders (G.0248.03, G.0234.04), the Flemish Regional Ministry of Education (Belgium) (GOA 2000/11), the Belgian Science Policy (IUAP P5/04), and the European Commission (NEST-2003-012963, STREP-2002-016276, and IST-2004-027017).

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