Transfer Entropy as a tool for reconstructing interaction delays in neural signals

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***Abstract*—Detecting interactions in complex networks can be very challenging, especially when using model based approaches, due to the dependency on model assumptions. To bypass this challenge, recently a model-free information-theoretic approach, transfer entropy (TE) was introduced. TE functional is capable of detecting linear as well as non- linear directed interactions. However, a full understanding of the network function also requires knowledge on interaction delays. Here we present an extension of TE which also estimates unknown interaction delays. In detail, we show that this TE functional becomes maximal if the interaction delay parameter in our TE functional equals the true interaction delay. Accordingly, in simulations of finite data the difference between estimated and true interaction delay was always within one sample. For the first time we applied this method to reconstruct intra-cerebral interaction delays from noninvasive Magnetoencephalography (MEG) recordings, and obtained biologically plausible values, suggesting a potential diagnostic use of the method.**

I. Introduction

Real-world systems often exhibit a complex network structure and contain nonlinear elements that dynamically interact [1]. For example, the brain is composed of billions of neurons interconnected in intricate networks that give rise to perception, action, and consciousness. To understand how such systems function, one must be able to characterize the pattern of interaction between network elements [2]. Many methods have been developed to characterize these type of interactions, ranging from correlation analysis [3] or mutual information [4], to more sophisticated measures that can estimate directionality, such as partial directed coherence [5] or Granger causality [6]. Most methods, however, can only handle the linear interactions and are less effective in detecting the nonlinear ones. Recently, a new method has been developed, called transfer entropy, which can detect directed and generalized interactions, including both linear and nonlinear ones [7].

When characterizing networks with dynamic elements, not only the existence and directedness of the interaction can be important but also the interaction delay. It has been shown for example that the interaction delays can have dramatic impact on network dynamics in neuronal systems [8], [9]. Here we show that TE is capable of detecting delays in networks exhibiting non-linear interaction among their elements. Furthermore we present a reconstruction of the interaction delays using TE, on MEG data, suggesting that this method is capable of reconstructing interaction timings in a complex biological network.

II. Methods

A. Transfer entropy

Norbert Wiener's principle of observational causality states that a time series X is called causal to a second time series Y, if knowledge about the past of X and Y together allows a better prediction of the future of Y than the knowledge about the past of Y alone [10]. Schreiber [11] formalized this in terms of conditional mutual information (I) as follows:

$$TE(X \to Y) = I(Y^{+}; \mathbf{X}^{-} | \mathbf{Y}^{-}) \ , \qquad (1)$$

where Y^{+} is a future random variable of the process Y, $\mathbf{X}^{-}$ and $\mathbf{Y}^{-}$ denotes the reconstructed past *state variables* of the processes X and Y.

This form of mutual information is termed TE in the literature [11]. Due to the necessity to determine nonlinear interactions in networks, analysis using TE has raised interest in many domains, like theory of computation, physiology and neuroscience. Furthermore, for specific applications, TE has proven to be superior compared to other interaction analyses [12].

If two systems (X,Y) are interacting with a certain time delay δ, one can prove that shifting X with a delay u will yield a maximum value of TE when $u = \delta$ [13]. Thus, we will use a concrete estimator of eq. 1, which fulfills the self prediction optimality (SPO) required by Wiener's principle and can be used to reconstruct the interaction delay (δ) by scanning the assumed delay u and taking the maximal value of the TE over the scanned interval:

$$TE_{SPO}(X \to Y) = I(Y_{t+1}; \mathbf{X_{t-u}} | \mathbf{Y_{t-1}}) \ , \qquad (2)$$

The computation of TE_{SPO} contains three steps: state space reconstruction from scalar time series, reformulation of the conditional mutual information in terms of Shannon entropies

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and the entropy estimation based on a modified Kraskov-Stoegbauer-Grassberger estimator [14], [15], [7]. Due to a possible residual bias, TE_{SPO} values have to be compared to surrogate data using non-parametric statistical testing [14]. Here we construct surrogate data by shifting the time series of one of the two signals of a pair, by one experimental epoch or simulated block of data, preserving as many data features as possible. We then use permutation testing over TE variables from each block to assess significance of TE values.

B. Simulated and real datasets

In order to test the ability of the method to correctly reconstruct the interaction delays, we used two types of simulated systems, an autoregressive process and a Lorenz system respectively. Additionally, we used MEG data to verify the method in a neural system.

Autoregressive process (AR): These processes generate a coupled system based on the following equations:

$$\begin{aligned} X(t+1) &= \sum_{k=0}^{m} \alpha_k X(t-k) + \sigma\eta_X(t)\,, \\ Y(t+1) &= \sum_{k=0}^{m} \beta_k Y(t-k) + \sigma\eta_Y(t) \\ &+ \tfrac{\gamma_{XY}}{|\{\delta_{XY}\}|} \sum_{\delta\in\{\delta_{XY}\}} X^2(t+1-\delta)\,. \end{aligned} \quad (3)$$

where the last term of eq. 3 represents a nonlinear coupling with multiple delays. The order of the autoregressive process (m) is 10. $\sigma = 0.1$ is the dynamic noise amplitude of the uncorrelated, unit-variance, zero-mean Gaussian noise terms $\eta_X(t)$ and $\eta_Y(t)$. $|\{\delta_{XY}\}|$ denotes the number of elements in the set of delays $\{\delta_{XY}\}$, and (γ_{XY}) represents the strengths of the coupling. The values for α_k and β_k where constructed from the roots of the characteristic polynomial of the AR process, that were chosen at random on the unit circle, to guarantee a stationary AR process.

Lorenz chaotic dynamical systems: To analyze a more complex system, we have chosen two Lorenz systems with non-linear (quadratic) coupling and potential self-feedback according to:

$$\begin{aligned} \dot{U}_i(t) &= \sigma(V_i(t) - U_i(t))\,, \\ \dot{V}_i(t) &= U_i(t)(\rho_i - W_i(t)) - V_i(t) \\ &+ \sum_{i,j=X,Y} \gamma_{ij} V_j^2(t-\delta_{ij})\,, \\ \dot{W}_i(t) &= U_i(t)V_i(t) - \beta W_i(t)\,. \end{aligned} \quad (4)$$

where $i, j = X, Y$; σ, ρ and β, are the *Prandtl number*, the *Rayleigh number*, and a geometrical scale; γ_{ij} represent the coupling strengths from system i to j. The δ_{ij} represents the delays of the coupling. Numerical solutions to these differential equations were computed using the $dde23$ solver in MATLAB, and results were resampled such that the delays amounted to the desired values.

MEG data: To demonstrate that the TE_{SPO} method can be applied in a complex network case such as the brain, we have used MEG data from 30 healthy participants. The paradigm was a visual recognition task of Mooney faces as described in [16]. The participants were presented with Mooney stimuli in two conditions: upright Mooney faces and scrambled versions thereof, that no longer represented a face. All participants gave written informed consent before the experiment. Participants had to report by pressing buttons according to the face detection ('yes' or 'no'). We reconstructed several sources that differed between correct detection of faces and non-faces [16]. For the reconstruction of source time courses we used a broadband Linearly-Constrained Minimum Variance (LCMV) beam-former, implemented in Fieldtrip [17]. The TE_{SPO} was computed on the resulting time courses, by scanning the u parameter over an interval from 4 ms to 30 ms. The reconstructed links were tested at the subject level using permutation testing ($p < 0.05$, uncorrected) and subsequently at the group level using a binomial test ($p < 0.05$, corrected). The delays of the remaining significant links were averaged over subjects for each link, and the links corrected for potential cascade effects using the graph based approach described in [18]. The graph based approach allows to eliminate apparent connections that are detected due to a cascade effect (summing up delays among a segmented path). Apparent connections were excluded if another path trough different nodes was found and if the sum of the interaction delays in the second path were close (within 2 ms) to the apparent interaction delay.

C. Interaction delay estimation

Based on the systems described above, we generated a series of simulations that were used in the analysis of interaction delay reconstruction. For each simulated system we generated 50 data segments (epochs), each containing 3000 sampling points. The simulated interactions were non-linear (quadratic), conforming to eq. 3 or eq. 4, respectively.

Computation of TE_{SPO} and all statistical procedures (including binomial testing) were performed in the open source toolbox TRENTOOL [14], [19], [7]. The Ragwitz criterion [20] was used to determine the embedding dimension d and lag τ. To identify interaction delays we scanned the source delay parameter u in steps of 1 sample, the interval of assumed delays was chosen based on the analyzed systems, to include the values of the simulated delays. The values of the delay parameter u where TE was maximal were compared with the true interaction delays for each simulated system.

III. RESULTS

Recovery of the interaction delay in single delay systems: Using the autoregressive (AR) processes we have simulated two unidirectionally coupled systems with an interaction delay of δ_{XY} = 20 sampling steps (interaction $X \rightarrow Y$). Fig. 1, left part, shows the results of computing TE_{SPO} and its statistical significance for the two potential directions of interactions, $X \rightarrow Y$ (red) and $Y \rightarrow X$ (blue) for different u. The delay reconstruction graph shows a maximal value for $u = 20$ units, which matches the simulated value of 20 sampling steps.

The second part represents an interaction delay reconstruction from two unidirectionally coupled Lorenz systems. The simulated coupling delay was δ_{XY} = 30 sampling steps. Fig. 1, right part, shows the computed TE_{SPO} for both

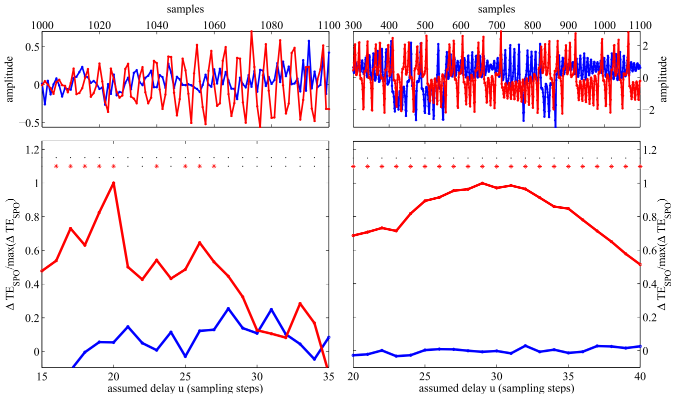

Fig. 1. TE values vs. assumed delay u for two types of systems. Two coupled AR systems, with single simulated delay $\delta = 20$ (left part) and for two coupled Lorenz systems, with a single delay $\delta = 30$ (right part). The statistically significant values are marked with asterisks above the normalized TE_{SPO} with the color of the analyzed link. The upper part of the graph presents a segment of data from the simulated systems, from X (red dashed) and Y (blue dashed).

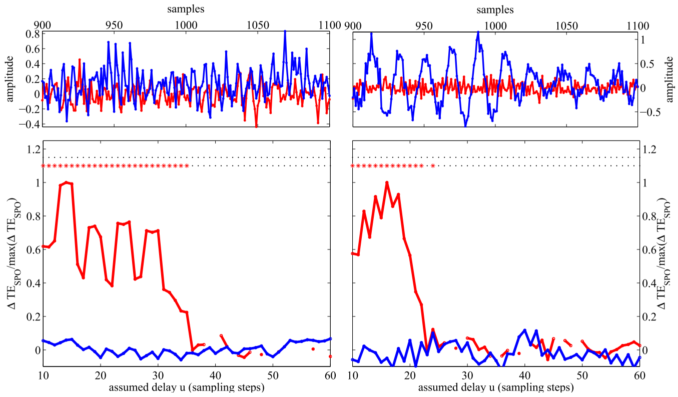

Fig. 2. TE values vs. assumed delay u for two coupled AR systems, with multiple delays. Simulated delays were $\{\delta_{XY}\} = \{15, 20, 25, 30 \text{ and } 35\}$ (left); and $\{\delta_{XY}\} = \{15, 16, 17, 18 \text{ and } 19\}$ (right). The upper part of the graph presents a segment of data from the simulated systems, the rest of the plotted parameters are identical as in fig. 1.

interaction directions, $X \rightarrow Y$ (red) and $Y \rightarrow X$ (blue). The reconstructed maximal value was at $\hat{\delta}_{XY}$ = 29 sampling steps.

Recovery of the interaction delay in a multiple delay system

We simulated two sets of two unidirectionally coupled AR processes which contained multiple interactions from one system to the other ($X \rightarrow Y$). The aim of this part was to analyze how multiple interactions will be reconstructed and to see how the distance in samples between the interaction delays is affecting the reconstruction. The first set contained two coupled AR systems with simulated data according to the delays $\{\delta_{XY}\}$ of 15, 20, 25, 30 and 35 sampling points, while the second set contained two AR systems with simulated data for interacting delays $\{\delta_{XY}\}$ of 18, 19, 20, 21 and 22 sampling points. The rest of the settings were identical with the ones presented in the single delay system.

The first set, illustrated in fig. 2, left part, represents a reconstruction for the first simulated system, with the interactions $\{\delta_{XY}\}$ of 15, 20, 25, 30 and 35 sampling points. The recovered $\{\hat{\delta}_{XY}\}$ consists of several peaks for the TE_{SPO} at 14, 19, 25, 30 sampling points and a lower value at 35 sampling points. The maximal value of the TE_{SPO} by definition represents the delay of an interaction, while the remaining peaks were *interpreted* this way as well.

The second set consisted of simulated delays $\{\delta_{XY}\}$ with the values 15, 16, 17, 18 and 19 sampling points. When dealing with closely grouped distributions of delays, the TE_{SPO} method managed to reconstruct a peak, see fig. 2 right part, near the mean of the distribution of delays. The width of this peak roughly reflects the interval of simulated delays. However, we could not separate and reconstruct the exact values for the simulated delays, possibly due to the width of peaks obtained from TE_{SPO} even for single delays, which can then not be distinguished from the neighboring delay peaks.

Recovery interaction delay in a bidirectionally coupled system

For this test we simulated a bidirectional interaction between two chaotic Lorenz systems – aiming to determine if the reconstruction of delays can handle a more complex non-linear bidirectional case. The simulated delays were $\delta_{XY} = 45$ and $\delta_{YX} = 75$ in sampling steps. The delays were estimated to be $\hat{\delta}_{XY} = 46$ (red) and $\hat{\delta}_{YX} = 76$ (blue) (fig. 3, left). Estimations differed from the simulated delays by only one sample.

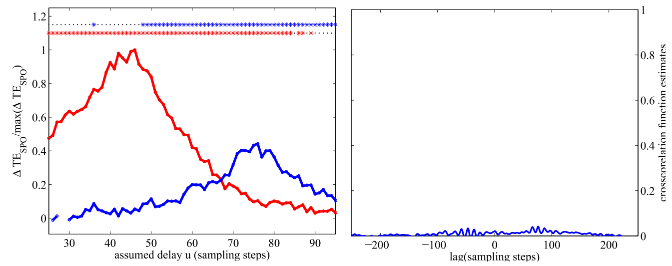

Fig. 3. TE values vs. assumed delay u for two bidirectionally coupled Lorenz systems (left). The value of simulation interaction delays were $\delta_{XY} = 45$ (red) and $\delta_{YX} = 75$ (blue). The right part presents the cross-correlation function estimates (averaged over trials). The rest of the plotted parameters are identical as in fig. 1.

As an additional test, we made a comparison between a nonlinear method (TE_{SPO}) and a linear method (cross-correlation function), to investigate the accuracy of these methods to recover the simulated interaction delays (fig. 3) The cross-correlation function shows some interactions at the simulated delays, but as the estimated amplitude of these interactions is very low, these values may be easily covered with noise.

MEG data analysis

For the MEG dataset the interaction delays were reconstructed using the TE_{SPO} method described here. Results in fig. 4 denote the average values of the interaction delays, over subjects, for links having significant values of the TE and that passed the binomial test. Note that these delays reflect the delay from the large pyramidal cells in one brain area to homologous synapses in another area, and thus combine intra- and inter-areal delays. We have found that under the first condition the recovered delays were in the range of 5-12.4 ms, while under the second condition the recovered delays were in the range of 9.7-17 ms. This rise may reflect the increased difficulty of the second condition and longer intra-areal processing.

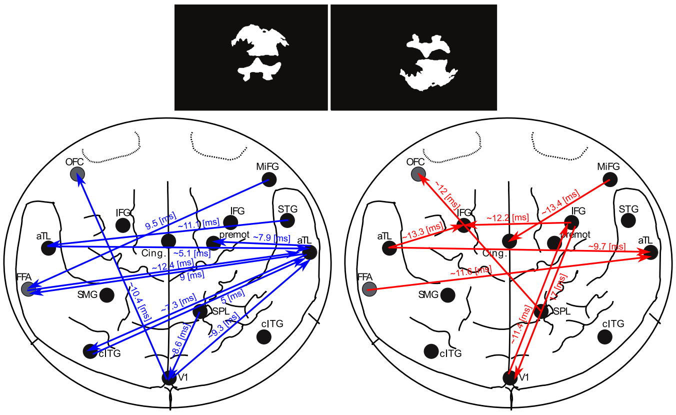

Fig. 4. TE reconstruction interaction delay based on MEG beam-formed data, for Up-Right face condition (left) and Inverted face condition (right). An overview of the stimuli can be seen in the upper part.

IV. Conclusion

The results for the reconstruction of the simulated data show that the method is able to identify the correct interaction delays in the given nonlinear systems. The interaction delays from the single delay systems, the multiple delays system and bidirectional system were reconstructed to the correct simulated value with an error of at most 1 sampling step.

The analysis of the MEG data shows plausible values for the interactions [21], in a range of 5-17 ms (averaged over subjects), which strengthens the conclusion that this method is suitable for timing reconstruction in a complex biological network. While these values were already corrected for cascade effects using a graph-based algorithm, common-driver effects may still have influenced this analysis. However, additional conditioning of TE_{SPO} on the potential common driver will solve this problem in future applications. We conclude that delay reconstruction by TE_{SPO} is a useful tool to infer interaction delays from biomedical and other complex systems, especially when no direct intervention is possible, and may open new diagnostic possibilities in medical applications.

Acknowledgment

NCP has received support from the project "Improvement of the doctoral studies quality in engineering science for development of the knowledge based society-QDOC" contract no. POSDRU/107/1.5/S/78534.

NCP, MW, RV, VP received support from the grant LOEWE Neuronale Koordination Forschungsschwerpunkt Frankfurt NeFF.

RCM was supported by a grant funded by Unitatea Executivıa pentru Finanţarea Învatamantului Superior, a Cercetării, Dezvoltării şi Inovării (UEFISCDI) number PNII-RU-TE-11/2010, contract number 23/28.07.2010.

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