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Phase transfer entropy: A novel phase-based measure for directed connectivity in networks coupled by oscillatory interactions

Muriel Lobier *, Felix Siebenhühner, Satu Palva, J. Matias Palva

Neuroscience Center, FIN-00014 University of Helsinki, Finland

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ABSTRACT

We introduce here phase transfer entropy (Phase TE) as a measure of directed connectivity among neuronal oscillations. Phase TE quantifies the transfer entropy between phase time-series extracted from neuronal signals by filtering for instance. To validate the measure, we used coupled Neuronal Mass Models to both evaluate the characteristics of Phase TE and compare its performance with that of a real-valued TE implementation. We showed that Phase TE detects the strength and direction of connectivity even in the presence of such amounts of noise and linear mixing that typically characterize MEG and EEG recordings. Phase TE performed well across a wide range of analysis lags and sample sizes. Comparisons between Phase TE and real-valued TE estimates showed that Phase TE is more robust to nuisance parameters and considerably more efficient computationally. In addition, Phase TE accurately untangled bidirectional frequency band specific interaction patterns that confounded real-valued TE. Finally, we found that surrogate data can be used to construct appropriate null-hypothesis distributions and to estimate statistical significance of Phase TE. These results hence suggest that Phase TE is well suited for the estimation of directed phase-based connectivity in large-scale investigations of the human functional connectome.

Introduction

Cognition arises from anatomically distributed neuronal processing in functionally specialized brain regions. Identifying the mechanisms that coordinate and integrate this processing within and between neuronal assemblies is a critical step in understanding not only normal cognitive functioning but also the putative links between abnormal functioning and neuropsychiatric disorders. In humans, neuronal activity can be recorded non-invasively with magneto- and electroencephalography (MEG/EEG). The dynamics of neuronal oscillations and inter-areal interactions can be identified from these data to investigate whether they have a functional role in human cognition and its abnormalities.

Neuronal oscillations as measured by MEG/EEG recordings are thought to reflect the summated excitatory post-synaptic potentials of tens of thousands of coherently active neurons (Lopes da Silva, 1991). Broadband MEG/EEG signals may be decomposed into narrowband oscillations using spectral analysis with complex wavelets or with real-valued filters and the Hilbert transform. Either approach reveals three distinct parameters that characterize neuronal oscillations: frequency, amplitude and phase. Oscillation frequencies are determined by the physiological time constants of the relevant neuronal assemblies (Wang, 2010). Neuronal oscillations in different frequency bands are thought to support different cognitive functions and are observed in different neuronal networks (Buzsáki and Draguhn, 2004; Palva and Palva, 2007; Tallon-Baudry, 2011; Womelsdorf et al., 2007).

Oscillation amplitudes are thought to reflect the extent of synchrony of neurons in a local assembly (Varela and Lachaux, 2001). A number of studies have indeed investigated oscillation amplitudes and observed task-related amplitude or power fluctuations across specific frequency bands (Hanslmayr et al., 2011; Tallon-Baudry and Bertrand, 1999; Thut et al., 2006), highlighting the importance of oscillation amplitudes as a marker of cognitive function. However, oscillation amplitudes do not reveal the coordination or communication of neuronal activity across brain regions. In contrast, the phase of an oscillation, which indicates the position of the signal within a given oscillation cycle, has been shown to be critical in the coordination of anatomically distributed processing (Cardin et al., 2009; Fries, 2005; Lakatos et al., 2008; Singer, 1999; Womelsdorf et al., 2007). An accumulating amount of literature suggests that large-scale network synchronization is a salient and functionally relevant aspect of both brain activity and non-invasively recorded neuronal signals, for instance among EEG sensors (Doesburg et al., 2008; Gruber and Müller, 2005), MEG sensors (Palva et al., 2005) and cortical regions as obtained using source reconstruction methods (Palva and Palva, 2012; S. Palva et al., 2010). These results suggest that phase synchronization in cortical networks may coordinate communication across anatomically distributed processing (J. M. Palva et al., 2010; Palva and Palva, 2011, 2012; Uhlhaas et al., 2009).

Phase synchronization and amplitude correlations are functionally independent phenomena (Bruns et al., 2000) and reveal distinct neuronal networks (Freunberger et al., 2009; J. M. Palva et al., 2010). Furthermore, the importance of phase information in neuronal

* Corresponding author.
E-mail address: muriel.lobier@gmail.com (M. Lobier).

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processes is highlighted by studies showing that phase patterns can code for more information than amplitude in both visual (Schyns et al., 2011) and auditory (Ng et al., 2013) processing. This points to phase as not only reflecting neuronal synchronization but also as a carrier of information between neuronal assemblies. Such phase-based information flow from one cortical area to another cannot be evaluated using phase synchrony metrics (Rosenblum et al., 1996; Stam et al., 2007; Vinck et al., 2011) which are inherently undirected. To completely decipher the role of phase patterns in distributed neuronal processing, connectomics analyses need to be carried out using metrics that evaluate the influence of one signal's phase on another signal's phase.

Information flow between neuronal signals is measured using directed connectivity metrics that estimate the causal influence a neuronal population exerts on another population. Methods used in neuroimaging include Granger Causality (GC) (Granger, 1969; Wiener, 1956), dynamic causal modeling (DCM) (Friston et al., 2003), and transfer entropy (TE) (Schreiber, 2000). However, none of the currently implemented metrics are appropriate for large-scale analyses of phase-specific directed connectivity in electrophysiological recordings, because connectomics analyses of MEG/EEG signals impose specific constraints on connectivity metrics. First, the metric must be robust to nuisance factors inherent to MEG/EEG signals: noise and linear mixing. External, biological, and instrument noise (Goldenholz et al., 2009) can result both in reduced detection of connectivity (Li and Ouyang, 2010; Nalatore et al., 2007) or in detection of false positives (Albo et al., 2004). Instantaneous linear mixing is also present in both sensor and source-space MEG/EEG signals because signal mixing at the sensor level cannot be unambiguously disentangled by inverse modeling (Belardinelli et al., 2012; Palva and Palva, 2012). Signal mixing can result in the detection of artificial connectivity between nearby sources (Haufe et al., 2013; Palva and Palva, 2012) and always mirrors true interactions into spurious connectivity among adjacent regions (Palva and Palva, 2012). Second, large-scale all-to-all network analyses easily entail millions of estimations of a given metric. To be realistically applicable in such conditions, metrics need to be computationally efficient. Third, the number of *a priori* parameters should be limited not only to reduce the cost of determining appropriate values for each signal pair but also to reduce the possibility of erroneous results caused by inappropriate parameter choice (Pereda et al., 2005). Fourth, it should be usable for detecting transient frequency band limited causal interactions from short data samples. Finally, it should be possible to assess the statistical significance of metric values by constructing surrogates from the experimental data.

According to Granger's definition of causality, a *source* signal has a causal influence on a *target* signal if knowing the past of both signals improves the prediction of the target's future compared to knowing only the target's past. Although this definition makes no assumptions on signal or interaction structure, Granger Causality (GC) metrics (Bressler and Seth, 2011) that implement it in the time or the frequency domain are largely based on autoregressive modeling of signals and their interactions. GC metrics, however, may be ill-suited to whole-brain network type analyses of phase information transfer. First, while spectral implementations of GC (Baccalá and Sameshima, 2001; Kaminski and Blinowska, 1991) isolate frequency-specific interactions, these metrics depend on both amplitude and phase signal components. Therefore, they cannot identify phase-specific information flow. Second, GC metrics are sensitive to both noise (reduced sensitivity) and mixing (increased number of false positives) (Nalatore et al., 2007; Nolte et al., 2010).

DCM extends the concepts of causal or directed connectivity to effective connectivity (Friston, 1994, 2011). Effective connectivity aims not only at measuring the influence of one system on another but also at reconstructing from neuronal data the underlying neurophysiological influences between neuronal assemblies (Friston et al., 2003). As a consequence, it requires not only the *a priori* definition of a set of putative networks but also strong assumptions on the underlying neuronal interaction mechanisms. DCM has been applied to phase interactions (Penny et al., 2009) to identify whether synchronization between selected brain areas results from mutual entrainment or a driver-driven mechanism. So far, DCM has not been used for full-scale connectomics analyses, partly because of the considerable complexity in defining the *a priori* parameters and connectivity, and also because of the high computational cost.

Transfer Entropy (TE) (Schreiber, 2000) is a reformulation of Wiener's principle (Wiener, 1956) in the framework of information theory (IT) (Shannon, 1948). Like GC, TE estimates whether including the past of both source and target time-series influences the ability to predict the future of the target time-series. However, as specified above, GC metrics test whether the predictability of the target signal is improved when both its past and the source's past are included compared to when only the target's past is included. In contrast, TE compares conditional probabilities using the Kullback–Leibler divergence. If a signal X causes a signal Y, then the probability density of the future of Y conditioned on its own past should be different from the probability density of the future of Y conditioned on the pasts of both X and Y. Furthermore, in contrast to GC metrics (or DCM), TE is model-free in so far as it makes no assumptions on signal or interaction structure. Despite these differences, it has been argued that TE and GC measure the same underlying quantity (Barnett et al., 2009; Seghouane and Amari, 2012).

In IT, the uncertainty of a variable X is quantified by Shannon Entropy $(X) = -\sum_x p(x)\log\,\mathrm{p}(x)$. Transfer Entropy from a signal X to a signal Y can therefore also be expressed as the difference between the Shannon Entropy of the present of Y ($Y(t)$) conditioned on its past ($Y(t')$) and the Shannon Entropy of the present of Y conditioned on both its past and the past of X ($X(t')$): $\mathrm{TE}_{X\to Y} = \mathrm{H}(Y(t)|Y(t')) - \mathrm{H}(Y(t)|Y(t'), X(t'))$. From this definition, we can infer that TE cannot be negative: conditioning the present of Y on an additional variable (Past of X in addition to past of Y) cannot increase the uncertainty on the present of Y. If there is no directed connectivity from X to Y, then taking into account the past of X in addition to the past of Y will not reduce the uncertainty in the present of Y: $\mathrm{H}(Y(t)|Y(t')) = \mathrm{H}(Y(t)|Y(t'), X(t'))$ and thus $\mathrm{TE}_{X\to Y} = 0$. TE can be understood as the reduction in the amount of information (bits if a base 2 is used) necessary to encode the present of Y if the past of X is used in addition to the past of Y. As a consequence, in contrast to normalized GC metrics such as Partial Directed Coherence (Baccalá and Sameshima, 2001) or Directed Transfer Function (Kaminski and Blinowska, 1991), TE does not have a meaningful upper bound (*i.e.*, there is no value associated with 'full' connectivity). Indeed, current practical TE implementations report statistical significance values obtained from comparisons either between conditions or between real and surrogate data rather than raw TE values (Lindner et al., 2011).

TE may be a good candidate metric for phase-based connectivity analyses and has been used to detect directed interactions in both sensor- and source-space broadband MEG/EEG signals (Vicente et al., 2011; Wibral et al., 2011). However, computing TE from individual trials requires large amounts of continuous data, which can be problematic in the case of task-related, transient connectivity. To alleviate this issue, TE can be accurately estimated from shorter time-series by computing a single metric value from an ensemble of trials rather than a separate value for each individual trial (Gómez-Herrero et al., 2010). IT-based metrics can be applied successfully to phase time-series (Wilmer et al., 2012), but current TE implementations (Lindner et al., 2011; Rutanen and Gómez-Herrero, 2011) are designed for real-valued time-series and reconstruct the underlying time-series state-space with nearest neighbor search or time-delay embedding (Hlaváčková-Schindler et al., 2007)) that are not directly applicable to circular variables. Most importantly, these methods are computationally costly and depend on several *a priori* parameters to be defined for each signal pair.

A phase-based TE metric suitable for large-scale directed connectivity analyses should not only detect directed phase coupling but