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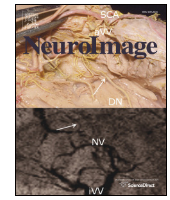


# Third order spectral analysis robust to mixing artifacts for mapping cross-frequency interactions in EEG/MEG

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ABSTRACT

We present a novel approach to the third order spectral analysis, commonly called bispectral analysis, of electroencephalographic (EEG) and magnetoencephalographic (MEG) data for studying cross-frequency functional brain connectivity. The main obstacle in estimating functional connectivity from EEG and MEG measurements lies in the signals being a largely unknown mixture of the activities of the underlying brain sources. This often constitutes a severe confounder and heavily affects the detection of brain source interactions. To overcome this problem, we previously developed metrics based on the properties of the imaginary part of coherency. Here, we generalize these properties from the linear to the nonlinear case. Specifically, we propose a metric based on an antisymmetric combination of cross-bispectra, which we demonstrate to be robust to mixing artifacts. Moreover, our metric provides complex-valued quantities that give the opportunity to study phase relationships between brain sources.

The effectiveness of the method is first demonstrated on simulated EEG data. The proposed approach shows a reduced sensitivity to mixing artifacts when compared with a traditional bispectral metric. It also exhibits a better performance in extracting phase relationships between sources than the imaginary part of the cross-spectrum for delayed interactions. The method is then applied to real EEG data recorded during resting state. A cross-frequency interaction is observed between brain sources at 10 Hz and 20 Hz, i.e., for alpha and beta rhythms. This interaction is then projected from signal to source level by using a fit-based procedure. This approach highlights a 10–20 Hz dominant interaction localized in an occipito-parieto-central network.





## Introduction

Electroencephalography (EEG) and magnetoencephalography (MEG) are noninvasive techniques which provide the opportunity to directly measure ongoing brain activity with very high temporal but relatively low spatial resolution. While in the past decades the main focus of EEG/MEG studies was on the analysis of event related potentials, i.e. the average brain response to a given stimulus, more recently the variability of brain activity has attracted many researchers. The recent interest in this field reflects the understanding that a mere localization of specific brain activities is far from sufficient to understand how the brain operates, but that it is necessary to study the brain as a network. In this framework, the analysis of brain rhythms has been recognized as a promising approach since coherent neuronal activity has been hypothesized to serve as a mechanism for neuronal communication (Fries, 2009; Gross et al., 2006; Miller et al., 2009; Tallon-Baudry et al., 1996; Womelsdorf and Fries, 2006).

The study of brain connectivity using noninvasive electrophysiological measurements like EEG or MEG also presents some problems which still need to be faced. Most notably, the fact that the data are a largely unknown mixture of the activities of the actual brain sources constitutes a severe confounder. For instance, two sensors can record from the same neural populations, opening the possibility for spurious interactions between sensors in the absence of true brain interactions. Though the problem of mixing artifacts is well known (Nunez et al., 1997), it is increasingly acknowledged and studied not only for channel data (often referred to as volume conduction or field spread) (Srinivasan et al., 2007; Winter et al., 2007) but also at the source level, i.e., after source activities have been estimated from channel data using an inverse calculation (Schoffelen and Gross, 2009). Indeed, almost all the linear and nonlinear methods used to analyze multivariate data for neuroscientific applications (an excellent overview can be found in Pereda et al., 2005) are highly sensitive to mixing artifacts.

To overcome the problem of volume conduction it was suggested to exploit the fact that the propagation of electromagnetic fields is much faster than neural communication: while phase shifts between electric scalp potentials (EEG) or neuromagnetic fields (MEG) and the underlying source activity are too small to be observable (Stinstra and Peters, 1998), the temporal resolution of the data is still sufficient to capture

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phase shifts of neuronal signal propagation. This observation has been exploited in the imaginary part of coherency (ImCoh), a measure of brain connectivity which cannot be caused by mixtures of independent sources (Nolte et al., 2004). However, in the presence of interacting sources, the actual value still depends on how sources are mapped into sensors (Nolte et al., 2004) or on source space (Sekihara et al., 2011). This drawback was addressed for two sources using pairwise measures with the lagged phase coherence (Pascual-Marqui, 2007b; Pascual-Marqui et al., 2011) or with the weighted phase lag index (Vinck et al., 2011).

Nonlinear methods to estimate correlations between power addressing the issue of artifacts of volume conduction have also been recently suggested. In Brookes et al. (2012), the authors address the problem of field spread which generates spurious source space connectivity results. Using a seed based approach, the linear projection of the seed voxel is first regressed out from the signals at the test voxel and, then, power correlations are assessed both within and across multiple frequency bands. Similarly, in Hipp et al. (2012), sensor signals are orthogonalized before computing power envelope correlations at the same or different frequencies, thus removing signal components that share the same phase.

A noteworthy approach to the problem of volume conduction is proposed in Gómez-Herrero et al. (2008). Here, after an initial principal component analysis (PCA), the authors propose to subtract a linear multivariate autoregressive model from sensor data to suppress all time-delayed correlations, with the idea that all neural interactions require a minimum delay. An independent component analysis (ICA) is then applied to the residuals and the ICA mixing matrix is used to model the effects of volume conduction (see also Hyvärinen et al., 2010). This approach takes note of the fact that a direct application of ICA to the data would be a conceptual contradiction to the objective of the research, namely studying causality relationships between sources.

In this paper, we address the problem of mixing artifacts in relation to the use of nonlinear methods for studying cross-frequency phase-synchronization between neuronal populations. Specifically we refer to bispectral measures, which were developed and applied on EEG/MEG in abundance (Darvas et al., 2009a, 2009b; Dumermuth et al., 1971; Helbig et al., 2006; Jirsa and Müller, 2013; Schwilden, 2006; Wang et al., 2007), and we examine the question of what information can be derived from such measures that estimate true functional connectivity between brain regions as opposed to mixing artifacts. Our new contribution is, essentially, the generalization to nonlinear methods of the concepts based on the imaginary part of coherency to solve the problem of volume conduction (Marzetti et al., 2008; Nolte et al., 2004, 2008, 2009). As will be shown below, for linear measures (e.g., cross-spectra), the imaginary part equals the antisymmetric part (apart from a factor $\iota$, i.e., the imaginary unit) and the antisymmetry property is the more general principle from which measures robust to artifacts of volume conduction can be derived for second-order (linear) and for third-order (nonlinear) moments. In this way, antisymmetrized cross-bispectra can be used along with the imaginary part of cross-spectra for identifying phase-locked brain areas without being confounded by mixing artifacts, but with the important difference that the former reflects the presence of brain rhythms locked together at different frequencies, while the latter focuses on interactions at the same frequency. Moreover, the proposed approach has also the advantage of improving, for a certain class of interactions, a limitation of the imaginary part of the cross-spectrum, which cannot provide information about relative phases, i.e. the phase difference of the activities of two brain sources, in a way which is robust to artifacts of volume conduction. Indeed, the imaginary part of the cross-spectrum is itself a real and not a complex valued quantity, and real values do not contain information about relative phases. Hence, the dilemma of linear measures is the fact that possibly interesting quantities cannot be estimated in a way which is robust to artifacts of volume conduction. On the contrary, the antisymmetric part of third order moments (cross-bispectra) is itself complex and hence contains phase information which is not corrupted by noninteracting sources.

The paper is organized as follows. In the Material and methods section, we present the theory for cross-bispectral measures robust to mixing artifacts. Specifically, we first recall the basic principles of the imaginary part of cross-spectrum and, then, we introduce the antisymmetric part of the cross-bispectrum, discussing its properties with regards to mixing artifacts. We describe a strategy to project the interaction from channel to source level by using a fit-based procedure. We also discuss some examples of interpretation of the phase of cross-bispectral measures. In the Result section, we first analyze the performance of our method in a simulation study, where we apply it on simulated EEG data. We then describe an example of an application of the method to real EEG data. Finally, the Discussion section provides remarks on the method features and on its ability to give an insight on cross-frequency functional connectivity.

## Material and methods

### *Theory for cross-bispectral measures robust to mixing artifacts*

#### *Cross-spectra and mixing artifacts*

We first recall some principles of second order statistical analysis in the frequency domain. The respective statistical moments, the elements of the cross-spectral matrix $S$, are defined as

$$S_{ij}(f) = \left\langle X_i(f) X_j^*(f) \right\rangle \tag{1}$$

where $X_i(f)$ and $X_j(f)$ are the Fourier coefficients of (eventually windowed) segments of data in channel $i$ and channel $j$ at frequency $f$, $^*$ denotes complex conjugation, and $\langle \cdot \rangle$ denotes taking the expectation value, i.e. taking the hypothetical average over an infinite number of segments. Of course, the expectation value is unknown and will in general be estimated by a finite average over segments. Since $S = S^\dagger$, where $(\cdot)^\dagger$ denotes transpose and complex conjugation, $S$ is an hermitian matrix. Complex coherency, $C$, is defined as the cross-spectrum normalized by power, i.e. the diagonal elements of it:

$$C_{ij}(f) = \frac{S_{ij}(f)}{\left(S_{ii}(f) S_{jj}(f)\right)^{1/2}}. \tag{2}$$

It was argued that the imaginary part of the coherency is a useful quantity to study brain interaction because it cannot be generated from a superposition of independent sources (Nolte et al., 2004). For later use we rederive this result assuming that the data have zero mean which, if not vanishing, has to be subtracted from the raw data. We now assume that all sources $s_k(f)$ are mapped instantaneously into channels as

$$X_i(f) = \sum_k a_{ik} s_k(f) \tag{3}$$

with $a_{ik}$ being real valued coefficients corresponding to the forward mapping of the $k$th source to the $i$th channel. Then the cross-spectrum can be written as

$$S_{ij}(f) = \sum_k a_{ik} a_{jk} \langle |s_k(f)|^2 \rangle + \sum_{k \neq k'} a_{ik} a_{jk'} \langle s_k(f) s_{k'}^*(f) \rangle. \tag{4}$$

If we now assume that all sources are independent, the second term on the right hand side in the above equation vanishes because for $k \neq k'$

$$\langle s_k(f) s_{k'}^*(f) \rangle = \langle s_k(f) \rangle \langle s_{k'}^*(f) \rangle = 0. \tag{5}$$

Since the first term in Eq. (4) is real valued, a non-vanishing imaginary part of $S$ must arise from interacting sources and can be used to

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