

Basic Neuroscience

Parametric estimation of cross-frequency coupling

B.C.M. van Wijk^{a,*}, A. Jha^b, W. Penny^a, V. Litvak^a^a Wellcome Trust Centre for Neuroimaging, UCL Institute of Neurology, 12 Queen Square, WC1N 3BG London, UK^b Sobell Department of Motor Neuroscience and Movement Disorders, UCL Institute of Neurology, 33 Queen Square House, Queen Square, WC1N 3BG London, UK

HIGHLIGHTS

- We revisit the general linear model (GLM) approach to cross-frequency coupling.
- Continuous time series were split into epochs for parametric statistical tests.
- The GLM and permutation tests produced similar results in experimental data.
- The GLM offers a good trade-off between computation time and statistical power.
- Other predictors such as amplitude-amplitude coupling can be easily included.

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ABSTRACT

Background: Growing experimental evidence suggests an important role for cross-frequency coupling in neural processing, in particular for phase-amplitude coupling (PAC). Although the details of methods to detect PAC may vary, a common procedure to estimate the significance level is the comparison of observed values to those of at least 100 surrogate time series. When scanning large parts of the frequency spectrum and multiple recording sites, this could amount to very large computation times.

New method: We demonstrate that the general linear model (GLM) allows for a parametric estimation of significant PAC. Continuous recordings are split into epochs, of a few seconds duration, on which an *F*-test can be performed. We compared its performance against traditional non-parametric permutation tests in both simulated and experimental data.

Results: Our method was able to reproduce findings of phase-amplitude coupling in local field potential recordings obtained from the subthalamic nucleus in patients with Parkinson's disease. We also show that PAC may be detected between the subthalamic nucleus and cortical motor areas.

Comparison with existing method(s): Although the GLM slightly underestimated significance compared to permutation tests in the simulations, for experimental data the two methods produced highly similar results. Computation times were drastically lower for the GLM. Furthermore, we demonstrate that the GLM can be easily extended by including additional predictors such as low-frequency amplitude to test for amplitude-amplitude coupling.

Conclusions: The GLM forms an adequate and computationally efficient approach for detecting cross-frequency coupling with the flexibility to add other explanatory variables of interest.

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1. Introduction

Electrophysiological signals are traditionally partitioned into different frequency bands that show characteristic modulations with cognition and behaviour (Buzsáki, 2006). The functional roles of these frequency bands are usually studied in isolation by

looking at the spectral power of signals originating from single brain regions or by applying linear measures of functional connectivity like coherence or phase-locking between signals of separate regions. Although this has revealed important insights into brain functioning, it is likely that neural processing also relies on the interaction between frequency bands (Canolty and Knight, 2010). In fact, activity at different frequencies could be coupled in several ways involving either the phase, amplitude or the frequency of the signals (Jirsa and Muller, 2013). This opens up an additional range of mechanisms through which information processing might be

* Corresponding author. Tel.: +44 020 3448 4362; fax: +44 020 7813 1420.
E-mail address: b.vanwijk@ucl.ac.uk (B.C.M. van Wijk).

achieved. Indeed, growing empirical evidence suggests that forms of cross-frequency coupling are present in recorded brain signals and may show modulations with task performance or pathology.

To date, phase-amplitude coupling (PAC) has been the best studied form of cross-frequency coupling, which arises when the phase of a low frequency oscillation modulates the amplitude of a high frequency oscillation. A seminal example is the theta-gamma coupling in rodent hippocampal activity (Tort et al., 2008, 2009), also frequently observed in humans across a range of frequencies and brain regions (e.g., Canolty et al., 2006; Maris et al., 2011; Miller et al., 2012). Some findings suggest a functional role for PAC, for example the pronounced theta-gamma PAC in hippocampus during periods of decision making (Tort et al., 2008) and the increase of PAC with the number of items kept in working memory (Axmacher et al., 2010). Moreover, PAC may even serve as a mechanism to encode the order of items in memory (Lisman and Jensen, 2013). Remarkably, an increased level of PAC could also be indicative of pathology, as was found for beta-gamma PAC in the motor cortex of patients with Parkinson's disease (de Hemptinne et al., 2013). Studying aspects of PAC might therefore be helpful for understanding both normal and abnormal neural activity patterns.

Methods to detect PAC differ between studies but are usually either based on the entropy of the phase-amplitude distribution (Tort et al., 2008) or the computation of the resultant vector length of amplitude values projected on the phase circle (Canolty et al., 2006). The latter could also be cast in the form of a general linear model (GLM) (Penny et al., 2008; Özkurt and Schnitzler, 2011b). Several recent studies suggested possible improvements of these methods aimed at increasing the detectability of significant coupling. These include the selection of high amplitude time frequency bins (Dvorak and Fenton, 2014), tracking of instantaneous frequencies (van Zaen et al., 2013; Pittman-Polletta et al., 2014), and accounting for non-sinusoidal wave forms of the phase frequency (Kramer and Eden, 2013).

Regardless of the details of PAC detection algorithms, most methods depend on surrogate data to determine the significance of observed findings. Typically, for each permutation the PAC is recalculated with either the phase or amplitude signal shifted in time, and the measured PAC values are compared to a distribution of at least 100 surrogate values. As often one is not fully certain of the precise amplitude and phase frequencies at which effects of interest occur, PAC is calculated for a whole range of frequency combinations. This may result in large computation times when surrogate PAC values have to be estimated for each of these combinations, particularly when investigating inter-regional coupling on sensor or source level as the number of channel combinations could become large. In this paper we show that parametric statistical analysis could be applied when PAC is estimated using a GLM, hence obviating the need for computing surrogate data. Another advantage of the GLM is that p -values could be adequately corrected for multiple comparisons using random field theory (Brett et al., 2003; Kilner et al., 2005), which takes into account the dependencies between PAC estimates at adjacent frequencies.

Although phase-amplitude coupling has been the most reported form of cross-frequency coupling, it does not exclude the potential occurrence of other forms of coupling. In particular, the slow fluctuations in amplitude of low and high frequency bands may be coupled via amplitude-amplitude correlations (Bruns and Eckhorn, 2004; de Lange et al., 2008). We demonstrate that the GLM framework could be easily extended to include amplitude-amplitude (AAC) coupling in addition to phase-amplitude coupling. This allows for disentangling the contribution of phase and amplitude components to cross-frequency coupling, as well as testing for possible co-occurrence of both forms. First we will illustrate the validity of our approach using simulations of known ratios of phase-amplitude and amplitude-amplitude coupling. We

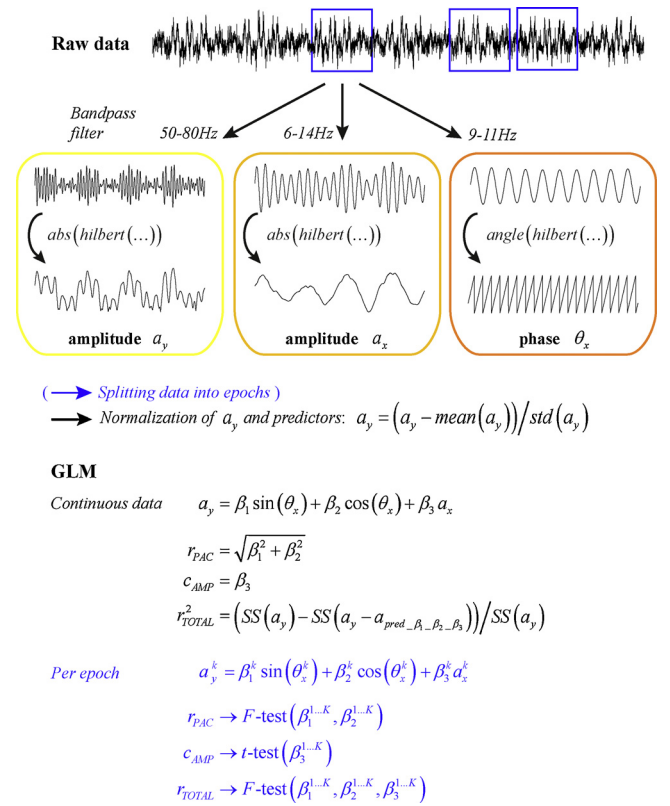


Fig. 1. Schematic overview of the processing steps required to apply the GLM. First of all, the instantaneous amplitude and phase for the intended frequencies need to be extracted using bandpass filtering and Hilbert transformation. Z-transformation of these time series ensures that PAC and AAC estimates are normalised and comparable to other existing measures. The β -coefficients of the GLM are estimated in two ways: (1) using the entire data length available; (2) by first dividing the continuous data into shorter epochs and re-estimating the β -coefficients for each epoch. The latter estimates are subsequently used to assess the significance of the overall coupling values in the indicated way.

subsequently apply our method to invasive recordings of the subthalamic nucleus (STN) obtained from deep brain stimulation electrodes in Parkinson's disease patients. Using simultaneously recorded magnetoencephalography (MEG), we also look for cross-frequency coupling between the STN and cortical activity.

2. Methods

2.1. GLM

The GLM for phase-amplitude coupling was introduced by Penny et al. (2008). We here extend this framework to include amplitude-amplitude coupling and evaluate its ability to detect significant frequency combinations both in simulations and real data. The procedure for this is summarised in Fig. 1. The amplitude of high-frequency signal components acts as the data to be explained by the GLM, while the predictors are formed by the phase and amplitude of low-frequency signal components. These can be obtained by following the conventional approach of bandpass filtering and the use of Hilbert transformation to extract the instantaneous phase via $\theta_x = \text{mod}(\text{angle}(\text{hilbert}(x)), 2\pi)$, and amplitude via $a_y = \text{abs}(\text{hilbert}(y))$. Here x and y denote the low and high-frequency signal components respectively that have been obtained after bandpass filtering either the same or two different time series. Note that the bandwidth of the filters should be adjusted according to which feature is extracted. It is imperative that the bandwidth of the filter for the amplitude is wide enough to include the centre

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