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# Phase-clustering bias in phase–amplitude cross-frequency coupling and its removal

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## HIGHLIGHTS

- Phase clustering can bias estimates of phase–amplitude cross-frequency coupling (PAC).
- We propose a modified version of PAC that effectively removes the bias (dPAC).
- Performance of dPAC is demonstrated via various simulations that manipulate the bias.
- dPAC is compared with other CFC measures and applied on monkey and rat recordings.
- Results of both simulated and real data show that dPAC outperforms PAC.

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## ABSTRACT

*Background:* Cross-frequency coupling methods allow for the identification of non-linear interactions across frequency bands, which are thought to reflect a fundamental principle of how electrophysiological brain activity is temporally orchestrated. In this paper we uncover a heretofore unknown source of bias in a commonly used method that quantifies cross-frequency coupling (phase–amplitude-coupling, or PAC).
*New method:* We demonstrate that non-uniform phase angle distributions – a phenomenon that can readily occur in real data – can under some circumstances produce statistical errors and uninterpretable results when using PAC. We propose a novel debiasing procedure that, through a simple linear subtraction, effectively ameliorates this phase clustering bias.
*Results:* Simulations showed that debiased PAC (dPAC) accurately detected the presence of coupling. This was true even in the presence of moderate noise levels, which inflated the phase clustering bias. Finally, dPAC was applied to intracranial sleep recordings from a macaque monkey, and to hippocampal LFP data from a freely moving rat, revealing robust cross-frequency coupling in both data sets.
*Comparison with existing methods:* Compared to dPAC, regular PAC showed inflated or deflated estimations and statistically negative coupling values, depending on the strength of the bias and the angle of coupling. Noise increased these unwanted effects. Two other frequently used phase–amplitude coupling methods (the Modulation Index and Phase Locking Value) were also affected by the bias, though allowed for statistical inferences that were similar to dPAC.
*Conclusion:* We conclude that dPAC provides a simple modification of PAC, and thereby offers a cleaner and possibly more sensitive alternative method, to more accurately assess phase–amplitude coupling.


## 1. Introduction

Neurophysiological signals are strongly oscillatory (Varela et al., 2001; Buzsáki and Draguhn, 2004; Wang, 2010). Moreover, several theoretical predictions and empirical findings demonstrate that interactions among activities in different frequencies are important for information processing and transmission (Lakatos et al., 2005; Palva et al., 2005; Jensen and Colgin, 2007; Canolty and Knight, 2010). However, standard time–frequency analyses (such as Morlet wavelet convolution and the short-time Fourier transform) treat each frequency of oscillatory activity as an independent process and therefore preclude quantification of interactions across frequency bands.

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Cross-frequency coupling (CFC) analyses are specifically designed to uncover relationships among dynamics at different frequencies. This "nesting" of oscillations has been shown to occur in both humans and animals (Jensen and Colgin, 2007; McGinn and Valiante, 2014), and to relate to various task-related processes (Canolty et al., 2006), including perception (Händel and Haarmeier, 2009; Voytek et al., 2010; Gross et al., 2013), cognitive control (Cohen et al., 2009; Dürschmid et al., 2013), memory (Sauseng et al., 2008; Tort et al., 2009; Axmacher et al., 2010; Belluscio et al., 2012), and emotional processing (Popov et al., 2012). Cross-frequency coupling has also been related to spontaneous activity during sleep (Cox et al., 2014) and "default-mode" resting state (Foster and Parvizi, 2012). In general, cross-frequency coupling is proposed to reflect a common, fundamental principle of how neurophysiological processes in the brain can be temporally organized across different frequency bands (Lisman, 2005; Canolty and Knight, 2010), and thus, different time scales.

There are several quantitative methods to identify cross-frequency coupling (Tort et al., 2010). Most methods are based on examining the distribution of power values at a relatively higher frequency band with respect to the phase values at a relatively lower frequency band (phase–amplitude coupling; lower frequency power values can be used instead of phase, but the concept is the same). The activities from both frequency bands are simultaneously recorded, typically from the same electrode (or from different electrodes in the case of long-range interareal cross-frequency coupling). The null hypothesis in this analysis approach is that the distribution of higher-frequency power values over lower-frequency phase values is uniform; deviations from this uniform distribution indicate the presence of cross-frequency coupling. The various cross-frequency coupling analysis methods differ mainly in how this power-by-phase distribution is created or statistically evaluated.

Many cross-frequency coupling analyses are assumed to be insensitive to dynamics within the modulating, lower-frequency band, such as a non-uniform occurrence of phase values (Aru et al., 2014). Such non-uniformity can occur when the oscillatory phenomenon under investigation does not resemble an idealized sine wave, and the relative contribution of different phases to the sampled signal is uneven; this will be demonstrated below. It is generally believed that this situation is adequately remedied by permutation testing, in which random shuffling ensures that power values and phase values are randomly coupled, thus accounting for possible asymmetries in the distribution of power or phase that could artifactually bias the estimate of cross-frequency coupling (Cohen, 2014).

The purpose of this paper is to show that one commonly used CFC analysis method in particular (phase–amplitude coupling or PAC; Canolty et al., 2006) can be sensitive to within-frequency non-uniform phase angle distributions, which may introduce biases in some circumstances. After describing two other methods for assessing CFC (MI and PLV), we introduce the bias and demonstrate how it might arise in neural time series data. We then introduce a simple but effective debiasing correction and demonstrate that this approach successfully minimizes the bias in PAC, thus allowing closer approximations of true cross-frequency coupling. Matlab scripts to produce the simulations and perform the analyses described in this paper are available at github (https://github.com/joramvd/dPAC).

## 2. Three methods to analyze cross-frequency phase–amplitude coupling

In this paper, we focus on three established methods of analyzing cross-frequency coupling of phase-modulated power (we hereafter use "CFC" to refer to this type of cross-frequency coupling). We decided to focus on these three methods because they are the most commonly used methods in the literature. In the 'Implications and limitations' section we speculate on the relevance of our findings for other methods.

### 2.1. Phase–Amplitude Coupling (PAC)

The Phase–Amplitude Coupling (PAC) method was popularized by Canolty and colleagues (Canolty et al., 2006). In PAC, vectors in polar space are defined by the angle from the frequency for phase, and a length defined by the power from the frequency for power. Each vector corresponds to a time point, and the length of the average vector is taken as a quantification of CFC. The null hypothesis – that there is no relationship between power and phase – would produce an average vector length of zero. In contrast, a non-uniform distribution of power-adjusted phase angles in polar space would produce a PAC value that is greater than zero. Mathematically, PAC is defined by:

$$\mathrm{PAC} = \left| \frac{1}{n} \sum_{t=1}^{n} a_t e^{i\varphi_t} \right| \quad (1)$$

where $n$ signifies the total number of time points, $a_t$ the amplitude (or power) of the modulated frequency (frequency for power) and $\varphi_t$ the phase of the modulating frequency (frequency for phase) at time point $t$; $i$ is the imaginary operator. As can be seen, the phase angles are first converted to complex space by the Euler transform $\left(e^{ik}\right)$.

The statistical significance of the PAC value can be determined by comparing it against a distribution of surrogate PAC values generated via permutation testing, in which the power values are shuffled with respect to the phase values. The idea is that the shuffling not only allows for statistical evaluation, but also accounts for possible outliers or non-uniform phase angle distributions (Cohen, 2014, Chapter 30).

### 2.2. Modulation Index

A second CFC measure that is commonly used is the Modulation Index (MI), as proposed by Tort and colleagues (Tort et al., 2010). The logic behind MI is to discretize the phase angle time series (of the frequency for phase) into $N$ phase bins, and to compute the average power of the modulated frequency for power in each bin $j$. The resulting phase–amplitude histogram should show a non-uniform distribution of power over the $N$ phase bins. To quantify coupling, the MI computes deviation from a uniform distribution using information theory (see Tort et al., 2010 for details):

$$\mathrm{MI} = \frac{D_{\mathrm{KL}}(P, U)}{\log(N)} \quad (2)$$

where $N$ signifies the number of phase bins, and $D_{\mathrm{KL}}$ is the Kullback–Leibler distance between the phase distribution $P$ and the uniform distribution $U$:

$$D_{\mathrm{KL}}(P, U) = \log(N) + \sum_{j=1}^{N} P(j) \log[P(j)] \quad (3)$$

As with PAC, the statistical significance of MI is commonly determined by shuffling the power time series with respect to the phase angle time series, and re-evaluating the distribution of power over phase bins; because the phase-power relationship is now random, this should generate a null-distribution of MI values under the null-hypothesis of a uniform distribution of power over phase bins.