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# Toward a proper estimation of phase–amplitude coupling in neural oscillations

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## HIGHLIGHTS

- Boundary conditions are determined for appropriate use of standard PAC algorithms.
- Oscillation-triggered coupling (OTC) estimates PAC by treating oscillations as events.
- The occurrence of high-power phase- and frequency-specific oscillations explains PAC.
- OTC can separate phase-locked oscillatory activity from spiking-related activity.

## ARTICLE INFO

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## ABSTRACT

*Background:* The phase–amplitude coupling (PAC) between distinct neural oscillations is critical to brain functions that include cross-scale organization, selection of attention, routing the flow of information through neural circuits, memory processing and information coding. Several methods for PAC estimation have been proposed but the limitations of PAC estimation as well as the assumptions about the data for accurate PAC estimation are unclear.
*New method:* We define boundary conditions for standard PAC algorithms and propose "oscillation-triggered coupling" (OTC), a parameter-free, data-driven algorithm for unbiased estimation of PAC. OTC establishes a unified framework that treats individual oscillations as discrete events for estimating PAC from a set of oscillations and for characterizing events from time windows as short as a single modulating oscillation.
*Results:* For accurate PAC estimation, standard PAC algorithms require amplitude filters with a bandwidth at least twice the modulatory frequency. The phase filters must be moderately narrow-band, especially when the modulatory rhythm is non-sinusoidal. The minimally appropriate analysis window is ~10 s. We then demonstrate that OTC can characterize PAC by treating neural oscillations as discrete events rather than continuous phase and amplitude time series.
*Comparison with existing methods:* These findings show that in addition to providing the same information about PAC as the standard approach, OTC facilitates characterization of single oscillations and their sequences, in addition to explaining the role of individual oscillations in generating PAC patterns.
*Conclusions:* OTC allows PAC analysis at the level of individual oscillations and therefore enables investigation of PAC at the time scales of cognitive phenomena.



## 1. Introduction

The mammalian brain is a complex system with a distributed organization of sensory, motor, and executive computation centers across large areas of the cortex. While the distributed organization allows for parallel and specialized processing of information, it requires a mechanism for binding information from different computations into a coherent, unitary mental experience (von der Malsburg, 1981; Engel and Singer, 2001). The multipurpose, functional organization of local brain circuits also requires a mechanism for achieving dynamic, context-dependent cognitive and attentional control, a mechanism for the efficient routing of information between different brain computation centers, as well as a

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robust and efficient mechanism for coding the information in the dynamics of neural discharge (Phillips and Singer, 1997; Kelemen and Fenton, 2010). Various forms of neural synchrony, the coordinated synchronized activation of same-function cells and the active desynchronization of different-function cells have been proposed as this fundamental mechanism of neural computation (von der Malsburg and Schneider, 1986; Buzsaki, 2010). In the recent decade, phase–amplitude synchrony of field potential oscillations, the coupling between the phase of a slow oscillation and the amplitude of a faster oscillation, has received significant attention as a candidate synchronizing mechanism and is the subject of the present work.

In phase–amplitude coupling (PAC), the amplitude of a fast signal (e.g. gamma 30–100 Hz) is modulated by the phase of a slow signal (e.g. theta 5–12 Hz). This interaction is sometimes called "nesting" because the fast oscillation is precisely fitted within the cycle of the slower oscillation (Lakatos et al., 2005). The term phase–amplitude cross-frequency coupling (CFC) has also been used for this phenomenon, because the interaction happens between two distinct oscillatory bands (Bragin et al., 1995). This particular property makes PAC principally different from other synchrony measures such as amplitude synchrony (assessed by cross-correlation) or phase synchrony (assessed by phase locking statistics) because it reflects the dynamical relationship between two oscillations that are generated by distinct neurophysiological mechanisms. As the oscillations have different biophysical origins, the consequent PAC is not easily attributed to the spurious occurrence of synchrony caused by volume conduction, selection of reference or synchronized noise. The concept of a cross-scale organization of neural activity (Jensen and Colgin, 2007; Le Van Quyen, 2011) offers a possible neural mechanism for integrating information between several functionally distinct networks, to accomplish perceptual binding, selective attention, cognitive control and the recruitment of computational and representational cell assemblies. Neural activity in macroscopic (slow oscillations), mesoscopic (high frequency oscillations) and microscopic (single neuron activity) scales are braided together such that a progressively faster activity occurs within a specific, short time window of a slower activity. Indeed, several conceptual and theoretical frameworks have been proposed for the computational role of PAC (Canolty and Knight, 2010). Given the growing interest, and the substantial value in PAC as a mechanism for neural computation it is important for the broader neuroscience community to understand how to accurately measure and interpret PAC, and appreciate the limitations of the current methods.

This paper is written in two parts. The first part is an analysis of the standard approach to computing PAC. We examine the assumptions and by parametric analyses, identify the filter and temporal requirements for estimating PAC accurately. The second part introduces a novel approach to estimate, measure and characterize PAC. It operates on two time scales, one is global, and like traditional methods it is only robust when applied to long time series of data, on the order of many seconds. The approach also allows the characterization of PAC on short time scales, as short as a single oscillation.

## 2. Materials and methods

Multiple algorithms for quantifying PAC have been proposed (Fig. 1). The common starting point of all algorithms is an extraction of the phase and the amplitude information from the sampled signal $x(t)$. This can be accomplished by band-pass filtering the signal into the bands of interest, for example theta 7–9 Hz and fast gamma 62–100 Hz followed by the Hilbert transform (Fig. 1A–C). There are other methods for extraction of phase and amplitude information, for example convolution of the signal with a complex wavelet but since these methods lead in principle to the same result (Le Van Quyen et al., 2001) we use the Hilbert transform approach throughout our study. The Hilbert transform converts a band-pass filtered time series into a complex analytical time series. The instantaneous phase $\varphi(t)$ and amplitude $A(t)$ time series are then extracted from the analytic signal by taking the argument or modulus, respectively. The relationship between the phase and the amplitude time series, often referred to as the modulation index can then be studied by means of circular statistics, i.e. by computing the mean vector of the complex composite signal: $z(t) = A(t)\exp[i\varphi(t)]$ (Fig. 1d); (Canolty et al., 2006). Another method to calculate the modulation index calculates the phase relationship between the instantaneous phase time series $\varphi(t)$ and $\varphi_A(t)$, where $\varphi_A(t)$ is the instantaneous phase extracted from the amplitude time series $A(t)$ (Penny et al., 2008). Other methods to calculate the modulation index are based on analysis of the power spectral density of the amplitude time series $A(t)$ (Cohen, 2008) or coherence spectrum between $A(t)$ and the original signal $x(t)$ (Colgin et al., 2009). Most recently, a method based on the analysis of the phase–amplitude distribution was proposed (Tort et al., 2010). This measure computes a normalized Kullback–Leibler (KL) divergence between the phase–amplitude distribution and the uniform distribution (Fig. 1E). Since in the first, review part of this paper, we primarily focus on the initial steps of the algorithm, i.e. selection of filters for extraction of the phase and the amplitude information, we refer the interested reader to an extensive review and comparison of the above methods (Tort et al., 2010). The first part of the present report has mainly used modulation index estimates that are based on the phase–amplitude histogram (Tort et al., 2010).

It is not always certain, a priori, what frequency bands are involved in PAC, and thus PAC estimation typically begins with construction of a comodulogram to reveal the frequency bands that can be observed to interact in a particular dataset. The comodulogram analysis varies the frequency of both filters used to separately extract the amplitude $A(t)$ and the phase $\varphi(t)$ series from one signal and computes the modulation index for all combinations of the two series (Fig. 1F).

To test the significance of the modulation index ($\mathrm{MI_{raw}}$), surrogate tests can be used (Hurtado et al., 2004). All surrogate techniques follow a similar approach. One of the time series (for example the phase time series) is randomly shuffled to create a new phase time series with broken temporal relationships between the phase and amplitude information. The shuffled phase time series is then used with the observed amplitude time series to estimate a surrogate modulation index. This procedure is repeated several hundred times to obtain the null distribution of surrogate modulation index values. A normalized modulation index ($\mathrm{MI_{norm}}$) is then obtained as a $z$-score:

$$\mathrm{MI_{norm}} = \frac{\mathrm{MI_{raw}} - \mu}{\sigma},$$

where $\mu$ and $\sigma$ are the mean and standard deviation obtained from the null distribution.

### 2.1. Subjects

All procedures were performed in accordance with National Institutes of Health guidelines and were approved by the SUNY, Downstate and NYU animal use committees. Data were collected from adult male Long–Evans rats and adult male C57bl/6J mice that were obtained from a commercial breeder (Taconic Farms, Germantown, NY).