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A novel cross-frequency coupling detection method using the generalized Morse wavelets

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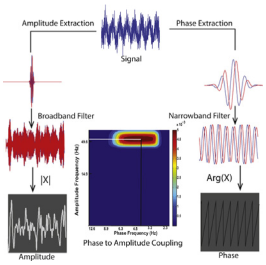
HIGHLIGHTS

- We develop a wavelet based cross-frequency coupling detection method.
- This analysis produces consistent time–frequency resolution.
- We select a wavelet with zero-phase distortion.
- We analyze corticostriatal interactions in anesthetized rats.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Cross-frequency coupling (CFC) occurs when non-identical frequency components entrain one another. A ubiquitous example from neuroscience is low frequency phase to high frequency amplitude coupling in electrophysiological signals. Seminal work by Canolty revealed CFC in human ECoG data. Established methods band-pass the data into component frequencies then convert the band-passed signals into the analytic representation, from which we infer the instantaneous amplitude and phase of each component. Though powerful, such methods resolve signals with respect to time and frequency without addressing the multiresolution problem.

New method: We build upon the ground-breaking work of Canolty and others and derive a wavelet-based CFC detection algorithm that efficiently searches a range of frequencies using a sequence of filters with optimal trade-off between time and frequency resolution. We validate our method using simulated data and analyze CFC within and between the primary motor cortex and dorsal striatum of rats under ketamine-xylazine anesthesia.

Results: Our method detects the correct CFC in simulated data and reveals CFC between frequency bands that were previously shown to participate in corticostriatal effective connectivity.

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Comparison with existing methods: Other CFC detection methods address the need to increase bandwidth when analyzing high frequency components but none to date permit rigorous bandwidth selection with no *a priori* knowledge of underlying CFC. Our method is thus particularly useful for exploratory studies.
Conclusions: The method developed here permits rigorous and efficient exploration of a hypothesis space and is particularly useful when the frequencies participating in CFC are unknown.

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1. Introduction

1.1. Cross-Frequency Coupling and Conventional Estimation Methods

Cross-frequency coupling (CFC), defined as correlated activity across distinct frequency bands, is a recently discovered neural correlate of multiple cognitive and behavioral states (Canolty et al., 2006, 2010). CFC has been observed in intra-cranial recordings from epileptic patients (Fitzgerald et al., 2013), the basal ganglia of patients undergoing DBS (Cohen et al., 2009), EEG data recorded from schizophrenia patients during auditory steady state response (Spencer et al., 2009) and rats engaged in reward seeking behavior (Tort et al., 2008). Given the ubiquity of CFC, this phenomenon has become a topic of intense investigation in recent years. While the functional significance of CFC is not fully understood, it likely plays a role in perceptual binding as well as in intra-structural and cross-structural neuronal synchronization in the brain.

Canolty et al. first proposed to study CFC using a sequence of standard linear least squared (LLS) band-pass filters followed by converting the signal x_t to the form $x_{t,analytic} = x_t + iH(x_t)$ where "i" is the imaginary unit and $H(f)$ is the Hilbert transform of the enclosed function. The Hilbert transform is the convolution of a function with the kernel $(\pi t)^{-1}$. In practice, the analytic representation is obtained by Fourier transforming the signal, setting all frequencies above the Nyquist frequency to zero, and inverse Fourier transforming the resulting function. The analytic signal gives both the instantaneous amplitude and phase of the signal at a given time; by extracting these values from band passed data we obtain the amplitude and phase – the modulus and angle of $x_{t,analytic}$ – of the frequency components under analysis. Binning the amplitude values by phase and computing a modified version of the Kullback–Leibler divergence between the obtained distribution and the uniform distribution yields the modulation index (MI). The MI measures the degree of phase-amplitude synchronization across frequency bands. Statistical significance is determined via permutation techniques.

1.2. The multiresolution problem and motivation for a wavelet-based approach

We build upon Canolty's approach and develop a novel method of CFC detection using the generalized Morse wavelets (GMWs). Resolving instantaneous amplitude and phase requires one to analyze a signal with respect to both time and frequency simultaneously. By the uncertainty principle, it is not possible to resolve a signal with simultaneous arbitrary precision in both domains. Canolty's method does not provide a principled manner in which to vary the frequency range of the band-pass filters in order to obviate this issue. Furthermore, it is preferable to use a narrow band filter for low frequency components and a broader filter for high frequency components. This increases the chance that the low frequency signal consists of smoothly varying sinusoidal components in order to avoid phase slips, while the high frequency signal is obtained with a sufficiently broad filter to ensure the side bands arising from cross-frequency influence are not excluded (see Aru et al. (2015) for a detailed discussion). Fortunately, the wavelet transform applies narrow-band filters to low frequency components and increasingly broad-band filters as the peak frequency of the impulse response function increases.

The wavelet transform was developed in part to overcome the multiresolution problem and naturally partitions time–frequency space such that the trade-off between temporal and spectral resolution is constant across all bands. We use the term "multiresolution" to refer to the problem of partitioning a univariate signal over a multivariate space when constant resolution across all degrees of freedom is unavailable; this use of the term should not be confused with the multiresolution approach to constructing wavelet bases (see Chapter 5 of Daubechies, 1992). We consider the GMWs over the Morlet wavelet since, while the Morlet wavelets are commonly used and their construction is relatively intuitive, we believe the GMWs are preferable for phase analysis. Though the Morlet wavelets are in theory strictly analytic – that is they have vanishing support for non-positive frequencies – in reality they exhibit leakage onto the negative frequency axis under certain paramaterizations that increase time resolution at the cost of frequency resolution (Lilly and Olhede, 2009). Due to this property, use of the Morlet wavelets risks aliasing. The GMWs, in contrast, are strictly analytic across their parameter regime.

Here, we explore the behavior of the GMWs as the band-pass filters used to generate the MI. We validate our method using both simulated and empirical data. Our method gives rise to an efficient and parsimonious means to scan multiple frequency bands for CFC without prior knowledge of whether and where CFC will occur. We conclude with a discussion of the comparative strengths and weaknesses of our approach and recommendations regarding best practices when applying the method.

2. Materials and methods

2.1. Animals and electrophysiology

All procedures followed NIH guidelines regarding use of animals in research and were approved by the Institutional Animal Care and Use Committee (Assurance Number A4049-01).

Surgery and electrophysiology techniques are described in detail elsewhere (Nakhnikian et al., 2014). Briefly, we recorded local field potentials in the primary motor cortex (M1) and dorsal striatum (dStr) of 4 male Sprague–Dawley rats under ketamine/xylazine anesthesia. Signals were sampled at 1 kHz and downsampled to 240 Hz offline using an in-house interpolation algorithm. Power line noise at 60 Hz was reduced using a multitaper method (Mitra and Pesaran, 1999). Data gathered under anesthesia were divided into 5 s epochs separated by 2 s buffers to reduce serial correlations among consecutive epochs. Epochs contaminated with obvious artifacts, as well as those recorded from animals exhibiting incomplete anesthesia (as indicated by any response to a paw pinch or whisker flick) were discarded. In our final analysis, we used 252 5-s trials.