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Short communication

Sharp edge artifacts and spurious coupling in EEG frequency comodulation measures

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Abstract

Recent electroencephalogram (EEG), electrocorticogram (ECoG), and local field potential (LFP) observations suggest that distinct frequency bands interact. Numerous measures have been proposed to analyze such interactions, including the amplitude envelope modulation of high frequency activity by the phase or signal of low frequency activity. In this short communication, we describe how abrupt increases or decreases in voltage data may produce spurious coupling in these measures and suggest techniques to detect these effects.

Keywords: Frequency comodulation; Nesting; Theta; Gamma; Hilbert transform

1. Introduction

Rhythms appear universal in neural population voltage activity (Buzsaki, 2006). For nearly 100 years researchers have divided these rhythms into discrete frequency bands often associated with physiologically distinct functions. Recent observations suggest that oscillations of different frequency are not completely isolated, but instead interact (Jensen and Colgin, 2007). In one type of interaction the phase of lower frequency rhythms modulates the amplitude envelope of higher frequency rhythms. This frequency comodulation – or nesting – appears to be a prominent characteristic of population voltage activity; it has been reported to occur between theta (approximately 4–12 Hz) and gamma (approximately 40–100 Hz) frequencies in rat and mouse (Bragin et al., 1995; Buzsáki et al., 2003; Hentschke et al., 2007), and between theta and 30–50 Hz, and theta and 80–150 Hz rhythms in man (Canolty et al., 2006; Lakatos et al., 2005).

In this short communication, we show that sharp edges in time series data (as observed in, for example, the sharp waves of epilepsy (Niedermeyer, 1999a), slow wave oscillations (Contreras and Steriade, 1995), and the mu rhythm (Niedermeyer, 1999b)) produce artifactual frequency comodulation. To do so, we implement three frequency comodulation measures in current use and employ three simulated examples. We develop two examples to confuse the measures and produce spurious coupling results, and a third to exhibit the most basic features of frequency comodulation. Our goal in this work is not to invalidate the results of previous analysis but to alert researchers to some pitfalls associated with frequency comodulation measures. We conclude by suggesting techniques to detect the occurrence of sharp edges in time series data. We also emphasize the utility of simulated data in testing new measures.

2. Methods

All comodulation measures typically involve three general steps. First, the data are bandpass filtered into two frequency intervals: a low frequency band (e.g., theta 4–12 Hz) and a higher frequency band (e.g., gamma 40–100 Hz). Second, the instantaneous phase is extracted from the low frequency filtered data, and the instantaneous amplitude envelope is extracted from the high frequency filtered data by applying the Hilbert transform. We note that the first two steps are sometimes accomplished by wavelets (e.g., as in Lakatos et al. (2005) and Mormann et al. (2005)) and that the Hilbert and wavelet decompositions are equivalent (Bruns, 2004; Le Van Quyen et al., 2001). Third, the coupling between the low frequency phase and high frequency

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amplitude envelope is determined. The method to compute this coupling and determine its statistical significance often distinguishes the different measures.

We apply three comodulation measures in this manuscript. In the first (Figs. 1b, 2b and 3b), we compute the mean and standard deviation of the instantaneous amplitude envelope for every 10° of the instantaneous phase and plot the result (Buzsáki et al., 2003). In the second (Figs. 1c, 2c and 3c), we compare the high frequency amplitude envelope with the low frequency bandpass filtered signal (Hentschke et al., 2007). We note that this measure utilizes the low frequency signal, and not the phase (i.e., an envelope-to-signal correlation (Bruns and Eckhorn, 2004)). To determine the statistical significance of the peak cross-correlation between the amplitude envelope and signal, a shuffling procedure of the amplitude envelope is implemented with 100 surrogates (Hentschke et al., 2007). In the last measure (Figs. 1d, 2d and 3d), we compute the normalized modulation index of Canolty et al. (2006). This measure requires that we create a composite signal consisting of the high frequency amplitude envelope and low frequency phase. We then determine the average length of this complex vector, and compare it to a surrogate distribution (200 surrogates) computed by shifting the amplitude of the composite signal by random amounts (Canolty et al., 2006).

We apply the comodulation measures to three sets of simulated data: (i) sawtooth data, (ii) imperfect sinusoid data, and (iii) sinusoid + high frequency noise data. For each data set, we use a sampling interval of 1 ms and compute 12 s of simulated data. We bandpass filter the data using a two-way least-squares FIR filter (the *eegfilt.m* routine from the EEGLAB toolbox (Delorme and Makeig, 2004)), and always eliminate the first and last 1 s of the filtered data to avoid filtering artifacts. For (i), we create a sawtooth wave of unit amplitude and with interval 166 ± 30 ms between successive peaks (Fig. 1a). The linear decrease in each cycle is not instantaneous; instead, this decrease requires from 1 to 20 ms, uniformly distributed across all cycles. For (ii), we first create a 6 Hz sinusoid with unit amplitude (Fig. 2a). To each cycle of the sinusoid we add a sharp edge that linearly increases the amplitude of the 6 Hz oscillation by one after 1–5 ms (uniformly distributed over the cycles). The sharp edge begins at phase values uniformly distributed between 212 and 233° (cosine phase), and the unit increase tapers to zero after 100 ms. For (iii), we first construct a sinusoidal signal of unit amplitude and with random intervals of 166 ± 17 ms between successive peaks (Fig. 3a). To each cycle, we add 50 ms of high frequency noise (uniformly distributed random numbers bandpass filtered between 50 and 150 Hz) tapered with a Hanning window and of maximum amplitude 0.5. The onset of the noise begins at random phases uniformly distributed between 0 and approximately 20° (cosine phase) for each cycle. To all three data sets we add normally distributed random numbers with mean zero and standard deviation 0.1.

We implement the simulated data and measures in MATLAB (Mathworks Inc., Natick, MA). The routines to generate and analyze the data, and produce all figures in this manuscript, are included in the Supplementary Material.

3. Results

In this section, we show the results of applying the three comodulation measures to the simulated data. We begin with the sawtooth example. In Fig. 1a we show one second of data in which the sharp edge reoccurs every 166 ± 30 ms. We filter the data between 4–8 Hz (middle gray trace) and 40–100 Hz (lower gray trace) and compute the low frequency phase (middle black trace) and high frequency amplitude envelope (lower black trace). To represent a sharp vertical edge requires many high frequency sinusoidal components and produces localized increases in the amplitude envelope. A close inspection of Fig. 1a suggests that these increases occur at a particular phase of the low frequency filtered signal (near approximately 90° for the cosine phase). Thus, frequency comodulation occurs in this signal; the low frequency phase and high frequency amplitude envelope are coupled.

To verify that the comodulation measures detect this coupling, we apply the three measures to the sawtooth data. We employ the broad bandpass filtering of the data (low and high frequency bands from 4–8 Hz and 40–100 Hz, respectively) and plot the average envelope versus phase in Fig. 1b. We find a large increase in this measure near 90°, as expected. We also compute the envelope-to-signal measure, and show in Fig. 1c that the largest correlations for the unshuffled data (black curve) exceed those for the shuffled data (gray curves). We compute the z-score for the peak correlation compared to the surrogates and find values greater than 5.5 ($p \ll 0.0001$). We conclude from these two measures that frequency comodulation occurs in the sawtooth wave between the low (4–8 Hz) and high (40–100 Hz) frequencies and that this coupling is statistically significant.

Using the broad bandpass filtering we might overlook more focused comodulation features. For example, does the low frequency activity modulate the entire 40–100 Hz interval or a subset of this band? To answer this question, we follow the procedure in Canolty et al. (2006) and divide the signal into separate low frequency bands (with frequencies from 2 to 41 Hz in 1 Hz steps) and high frequency bands (with frequencies from 5 to 205 Hz in 5 Hz steps). We then compute the modulation index for each pair of low and high frequency bands (a total of 1560 pairs) and show the results in Fig. 1d. Here we plot the z-score as a function of the phase and envelope frequencies and find large intervals of statistically significant coupling (with $z \geq 5$, say). We make two observations about the structure of the results. First, the largest z-scores tend to occur at phase frequencies (vertical bands) equal to the fundamental oscillation frequency (5–8 Hz) and its harmonics: near 10–14 Hz (2nd harmonic), 15–18 Hz (3rd harmonic), and 20–25 Hz (4th harmonic). The reason for this is that a fixed phase of the harmonic signals also aligns with the sawtooth edge and co-occurs with the envelope increase. Second, an abrupt increase in z-scores occurs along a positively sloped line in Fig. 1d indicating that higher phase frequencies require higher envelope frequencies to exhibit significant comodulation. This occurs because higher phase frequencies require sharper amplitude envelopes to exhibit significant coupling. Consider for example a phase frequency of 15–16 Hz. During one sawtooth cycle, this phase undergoes

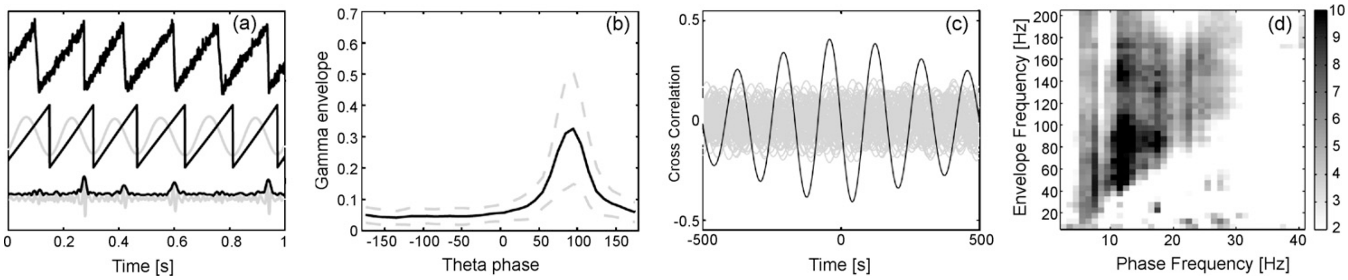

Fig. 1. Sawtooth wave data. (a) The simulated data (top) filtered 4–8 Hz (middle gray) and filtered 40–100 Hz (bottom gray). We extract the phase (middle black) from the lower frequencies and the amplitude envelope (bottom black) from the higher frequencies. (b) The average amplitude envelope (black solid) and standard deviation (gray dashed) vs. the phase. (c) The envelope-to-signal measure for the raw data (black curve) and 100 surrogates (gray curves). (d) For the comodulation index we plot the z-score in grayscale as a function of the phase and envelope frequencies.

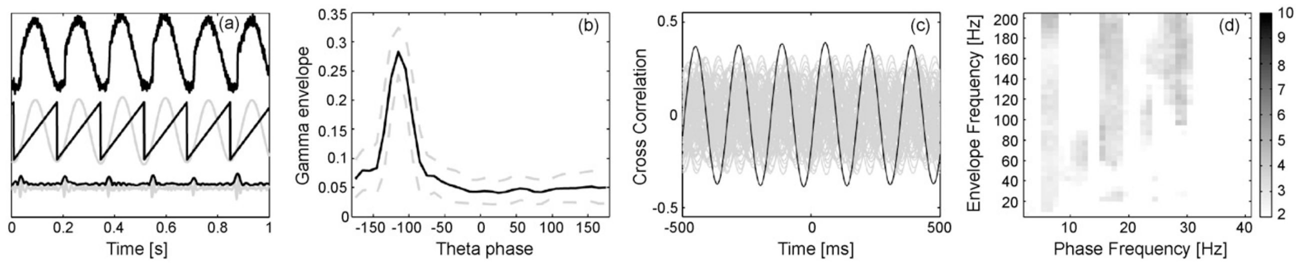

Fig. 2. Imperfect sinusoid data. Careful inspection of the simulated data in (a) reveals a sharp edge and corresponding increase in the amplitude envelope. (b) The average amplitude envelope vs. the phase. (c) The envelope-to-signal measure. (d) The modulation index.

three complete revolutions (it is the 3rd harmonic of the fundamental). If the amplitude envelope is too broad and not tightly localized to the sawtooth edge, then a nonzero envelope will appear at the many different phase values near the sawtooth edge. The result is an apparent lack of coupling. Conversely, when the amplitude envelope decays quickly around the sawtooth edge (at fast enough envelope frequencies) only a narrow phase interval associates with the nonzero envelope. In this case, coupling between the phase and envelope occurs.

The sawtooth data present an extreme example of artificial frequency comodulation resulting from a sharp edge. In these data, high frequency oscillations do not exist. Yet we require high frequency sinusoids to represent the sharp edge, and the amplitude envelopes of these high frequencies couple with the slower rhythms. As a more realistic example, we consider nearly sinusoidal data modified to include a steep increase between 212 and 233° (cosine phase). We show one second of these data, the 4–8 Hz bandpass filtered data, and the 40–100 Hz bandpass filtered data in Fig. 2a. The sharp edges produce localized increases in the amplitude envelope, although to a lesser extent than for the sawtooth wave. We plot the average envelope versus phase in Fig. 2b and detect an increase for phases between −150 and −100° (or equivalently between 210 and 260° cosine phase). We compute the envelope-to-signal measure for the broad bandpass filtered data (Fig. 2c) and detect a significant peak correlation ($z \approx 2.5$, $p < 0.05$). Finally, we plot the two-dimensional comodulation measure in Fig. 2d and find regions of statistically significant coupling particularly at phase frequencies near the fundamental and its harmonics. We conclude that even a small imperfection in the sinusoid, resulting from a sharp edge, can produce spurious frequency comodulation results.

Of course, not all frequency comodulation results from artifact. As a final example, we consider simulated data constructed to possess true phase coupling: a low frequency (5–7 Hz) sinusoid with high frequency (between 50 and 150 Hz) noise coupled to the low frequency phase. We show one second of the unfil-

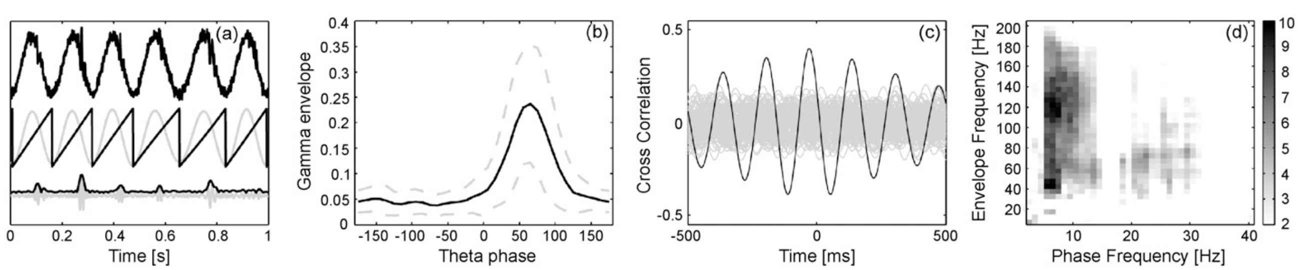

Fig. 3. Sinusoid + high frequency noise data. (a) During the falling phase of the sinusoid, an increase in high frequency activity occurs. (b) The amplitude envelope vs. the phase. (c) The envelope-to-signal measure. (d) The modulation index.

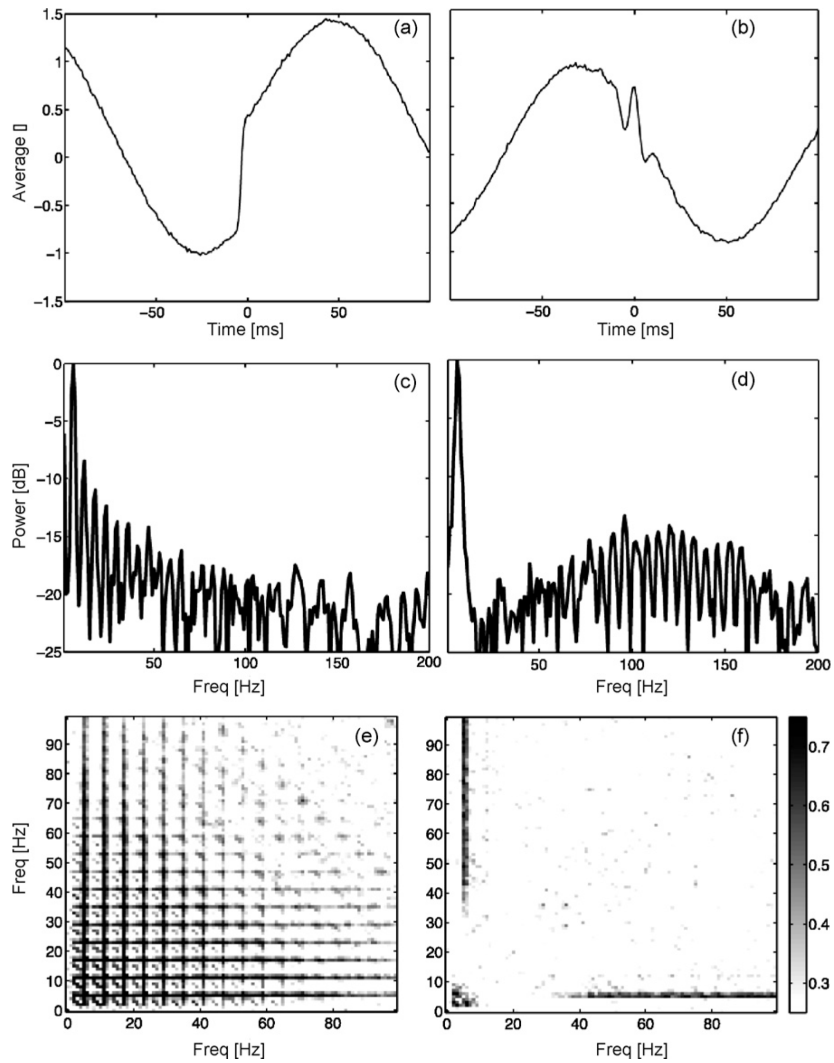

Fig. 4. Proposed methods to detect sharp edges in time series data. The event-related average for (a) the imperfect sinusoid and (b) the sinusoid + high frequency noise data. The average was triggered by the peaks of successive high frequency activity. The power spectra of (c) the imperfect sinusoid and (d) the sinusoid + high frequency noise data. Note the occurrence of harmonic spectral peaks of the fundamental 6 Hz activity in (c). The bicoherence of the imperfect sinusoid (e) and the sinusoid + high frequency noise data (f). The phase-locked harmonic activity produces a clear effect in the bicoherence of the imperfect sinusoid.

tered and filtered data in Fig. 3a. For the broad bandpass filtered data, we plot the average envelope versus phase (Fig. 3b) and envelope-to-signal measures (Fig. 3c) to find statistically significant coupling (peak correlation $z > 5.5$, $p \ll 0.0001$). The modulation index – shown in Fig. 3d – also reveals significant coupling at the expected phase and envelope frequencies.

4. Discussion

In this short communication we propose that data consisting of sharp edges may produce spurious frequency comodulation results. We show this by applying three comodulation measures in current use to three simulated data sets. We find that even moderate sharp edges in the data can induce artifactual frequency comodulation. All three methods fail for the same reason: to represent a sharp edge requires high frequency sinusoids. Thus, although the original data do not possess high frequency oscillations, the filtered data do exhibit high frequency components. An improved frequency comodulation measure would distinguish between high frequency oscillations and sharp edges in the original data.

We note that wavelets (rather than bandpass filtering followed by a Hilbert transform) may also be used to extract the phase and amplitude envelope of low and high frequency signals, respectively (Lakatos et al., 2005; Mormann et al., 2005). We have applied the same analysis described above using the complex Morlet wavelet to filter the data and again find spurious frequency comodulation (data not shown). We note that, for the examples considered here, phase coupling measures (e.g., n:m phase coupling (Palva et al., 2005; Tass et al., 1998)) are not appropriate. The coupling occurs between the low frequency phase and high frequency amplitude envelope, not between the signal phases.

To ameliorate the potential problem of spurious frequency comodulation, we recommend careful inspection of the unfiltered data to distinguish between sharp edges and true high frequency oscillations. This inspection is usually difficult; the high frequency activity of EEG, ECoG, and LFP data are typically weak and hidden by noise. Moreover, the amplitude envelopes of true and artifactual high frequency activity can be quite similar (compare the lower traces of Figs. 2a and 3a). Measures that display the modulation results without normalization (such as the average envelope versus phase measure shown in Figs. 2b and 3b) help distinguish the magnitude of the effects; very small values may result from subtle imperfections in sinusoidal activity and require a careful inspection of the data. From the normalized envelope-to-signal and comodulation results we cannot deduce the magnitude of the amplitude envelope. Therefore, even weak high frequency activity – perhaps resulting from brief sharp edges – could produce significant coupling effects in these normalized measures.

We conclude by suggesting four techniques to detect sharp edges in data. First, we recommend visual inspection of the *unfiltered* data at times corresponding to increases in the amplitude envelope of the high frequency activity. At these times, do the unfiltered data exhibit high frequency oscillations or sharp edges? To help visualize the high frequency activity, we recommend a second technique: an event related average of the unfiltered data triggered by the peaks of successive high frequency waves (Bragin et al., 1995). We illustrate this suggestion in Fig. 4, where we plot the event related averages of the imperfect sinusoid (Fig. 4a) and sinusoid + high frequency noise data (Fig. 4b). The distinction between high frequency activity resulting from sharp edges or oscillations becomes clear in these average results.

Third, we recommend computing the power spectrum of the raw data and searching for harmonic peaks of the dominant low frequency oscillation. We show the power spectra for the imperfect sinusoid and sinusoid + high frequency noise data in Fig. 4c and d, respectively. The sharp edges in the former result in numerous peaks at harmonics of the fundamental frequency (in this case, integer multiples of 6 Hz.) Such a power spectrum implies sharp edges may be impacting the frequency comodulation results.

Of course, multiple peaks in the power spectrum do not necessarily indicate harmonic activity. For example, theta (near 6 Hz) and alpha (near 12 Hz) rhythms often appear in the human EEG. Therefore, we recommend a fourth technique: computing the bicoherence of the raw data. The bicoherence is a normalized measure (ranging from 0 to 1) that reaches a maximum when three frequencies (f_1, f_2, and their sum $f_1 + f_2$) maintain a constant phase relationship (Barnett et al., 1971). We illustrate the bicoherence for the simulated data in Fig. 4 and find distinct results. The imperfect sinusoid (Fig. 4e) exhibits strong bicoherence for many frequency pairs compared to the bicoherence of the sinusoid + high frequency noise data (Fig. 4f). The numerous pairs of strong bicoherence for the imperfect sinusoid occur at the fundamental oscillation frequency (near 6 Hz) and its phase locked harmonics (12, 18, 24 Hz, etc.). For the sinusoid + high frequency noise data, the high frequency activity always begins at approximately the same low frequency phase (near 0°). In this sense, the high and low frequency phases are related, and it is this relationship that produces the vertical and horizontal bands of strong bicoherence in Fig. 4f. We conclude that the bicoherence – which indicates interacting frequency triplets – distinguishes these two data sets while the frequency comodulation measures do not. A similar strategy may be employed for the characteristic two-dimensional pattern of frequency comodulation shown in Fig. 1d. In this two-dimensional measure, we find the effects of coupling due to sharp edges more apparent. These types of measures may facilitate detection of spurious results. We note that the bicoherence utilizes the phase and amplitude values from three distinct frequencies. We would prefer a measure focused on the quantities of interest, namely the phase and amplitude envelope of the low and high frequency data, respectively. In addition, more sophisticated coupling measures (e.g., synchronization or causality measures (Pereda et al., 2005)) might help eliminate spurious detection of coupling while still revealing true phase-envelope correlations.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jneumeth.2008.01.020.

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