Phase-Amplitude Coupling Analysis for Seizure Evolvement Using Hilbert Huang Transform*

Hanyue Zhou, Ying Li, Yue-Loong Hsin, and Wentai Liu

Abstract—**Recent studies show that the phase-amplitude coupling (PAC) may play a functional role in information processing and cognition. The conventional method for PAC analysis is implemented by using Fourier-based filters, which assumes the signal is stationary and linear. However, as biological signals are nonstationary and nonlinear, this method introduces inaccuracy. To solve this problem, a new method based on Hilbert Huang Transform (HHT) is proposed in this paper, and is applied to analyze intracranial signals from two epilepsy patients. By displaying PAC comodulograms (coupling maps) in an Intrinsic Mode Function (IMF) domain instead of a traditional frequency domain, the proposed method is able to reveal regular PAC patterns in different seizure stages during seizure evolvement. Comparisons between the conventional and proposed method show the proposed one can provide not only clear but also regular PAC patterns.**

I. Introduction

Cross Frequency Coupling (CFC) is the interaction between brain oscillations of different frequencies, and the coupling phenomenon has been observed in the brain of rodent and human [1-2]. Phase-amplitude coupling (PAC) is a type of CFC, which shows the dependence between the phase of a low-frequency component and the amplitude of a high-frequency component of electrical brain activities [3]. It has been claimed that the modulation of low frequency phase on high frequency amplitude plays a functional role in cognition and information processing, such as learning and memory [4-5]. The low-frequency phase reflects local neuronal excitability, and the increase of high-frequency amplitude shows a general increase in population synaptic activity or selective activation of a connected neuronal subnetwork [3]. The change of PAC patterns has been associated with various neurological disorders, e.g., epilepsy, Parkinson disease and schizophrenia [6-8]. Therefore, PAC shows great potential in diagnosing and treating diseases, and it is critical to understand the biological meaning of PAC patterns.

The conventional method used for PAC analysis first defines the frequency of interest, and then uses narrowband Fourier-based filters to extract different frequency bands. After obtaining signals of different frequencies, it uses Hilbert Transform (HT) to extract instantaneous phase and amplitude signals to calculate the coupling intensity [1][7]. However, this method has several drawbacks: 1) the operation of filtering in frequency space is linear and can cause waveform distortions when applied to nonlinear and nonstationary electrocorticography (ECoG) data [9]; 2) narrowband filter distorts data near the cut-off frequency, and data distortions can be significantly high when the filter is repeatedly used to extract many frequency bands [10]; 3) since the ECoG signal is not an oscillatory function with zero reference level, the instantaneous phase and amplitude values extracted by HT do not have physical meanings according to Huang [11], which all make the interpretation of comodulogram (coupling map) inaccurate.

In order to overcome the limitation of the conventional method, a novel method based on Hilbert Huang Transform (HHT) is proposed in this paper, which displays PAC comodulograms in an IMF domain instead of a traditional frequency domain. As HHT is able to deal with nonstationary and nonlinear signals, the proposed method also avoids distortions from using conventional time-frequency analysis methods like Fast Fourier Transform (FFT). The proposed method consists of two steps: Multivariate Empirical Mode Decomposition (MEMD) and followed by HT. MEMD decomposes the signal into several Intrinsic Mode Functions (IMFs) that are oscillatory functions, thus the instantaneous phase and amplitude extracted by HT are physically meaningful. In this paper, we apply the proposed HHT method in analyzing five subsequent seizure EEG (electroencephalography) evolving stages from preictal stage to seizure termination, and compare the PAC patterns obtained by the conventional method and HHT method. The results show that the HHT method overcomes the limitation of the conventional method and shows more regular and clearer PAC patterns across different patients.

II. Materials

The intracranial signals were obtained from two epileptic patients with pharmacoresistance undergoing staged epilepsy surgery. For the first patient, the ECoG data were recorded using 4*8 grid electrodes at 256 Hz sampling rate. The ECoG data of the second patient were recorded by three 2*8 grid electrodes at 1024 Hz. Raw signals were filtered by a 0.5 Hz high-pass filter in both two patients, and the signal from the second patient was further filtered by a 300 Hz low-pass filter. In addition, line noise was removed by a 5-order band-stop Butterworth filter. The experimental procedures involving human subjects described in this paper were approved by the Institutional Review Board.

III. Stages of Seizure

Regarding the seizure dynamic, each attack is classified by time order as preictal, ictal and postictal. In this study, the time-series seizure EEG activity is divided into five stages: preictal stage before seizure onset, initial fast EEG activity stage, firing pattern transition stage, fast-burst stage and slow-burst stage before seizure stops (shown in Fig. 1).

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IV. METHODS

A. Multivariate Empirical Mode Decomposition

Empirical Mode Decomposition (EMD) is the first step of a basic HHT, which decomposes the original signal into several IMFs. An IMF represents a simple oscillatory mode with varying amplitude and frequency as functions of time [11], which is defined as follows: 1) the number of extrema and zero-crossings must either equal or differ at most by one; 2) the mean value of the upper envelope and the lower envelope is zero [11]. Let $x(t)$ be the original signal, $c_j(t)$ represent the jth IMF and $r_n(t)$ the residue, the original signal can be reconstructed by all the IMFs:

$$x(t) = \sum_{j=1}^{N} c_j(t) + r_n(t) \tag{1}$$

MEMD is an extension of standard EMD to multivariate signals, which decomposes signals from several channels simultaneously. MEMD can extract common rotation modes across signal components, thus is more suitable than EMD to decompose the fusion of information from multiple sources [12]. The signal of interest is often recorded by several electrodes, thus we employ MEMD on signals from the onset channel and its most adjacent ones, and obtain the IMFs of the onset channel.

B. Hilbert Transform

HT is then applied to the IMFs of the onset channel to extract instantaneous frequency, amplitude, and phase values of each IMF component, which is explained as follows.

For a signal $x(t)$, its Hilbert Transform $y(t)$ is defined as

$$y(t) = \frac{1}{\pi} P \int_{-\infty}^{+\infty} \frac{x(\tau)}{t-\tau} d\tau \tag{2}$$

where P is the Cauchy principal value of the singular integral. Then the corresponding analytic function is

$$z(t) = x(t) + iy(t) = a(t)e^{i\theta(t)} \tag{3}$$

where $a(t) = \sqrt{x^2 + y^2}$, $\theta(t) = \tan^{-1}\frac{y}{x}$ and $\omega(t) = \frac{d\theta}{dt}$.

Therefore, we have the instantaneous amplitude $a(t)$, phase $\theta(t)$, and frequency $\omega(t)$. The instantaneous amplitude and phase of each IMF are used to calculate modulation index in the next step.

C. Modulation Index Calculation

There are many quantitative methods for measuring PAC, among which the Kullback-Liebler based modulation index (KL-MI) has many advantages over the other methods, i.e., good tolerance to noise, amplitude independent and good sensitivity to multimodality and modulation bandwidth [13]. Therefore, we use KL-MI to measure coupling intensity in this paper. The method begins with the average binned amplitude as a function of phase, and then uses KL divergence algorithm to calculate the deviation of this amplitude distribution (P) from a uniform distribution (U) [13-14]. MI is defined by dividing the KL distance by the maximal possible entropy value log (N):

$$MI = \frac{D_{KL}(P,U)}{\log(N)} \tag{5}$$

The KL distance is related to the Shannon entropy by (6):

$$D_{KL}(P,U) = \log(N) + \sum_{j=1}^{N} P(j)\log[P(j)] \tag{6}$$

Therefore, when amplitude is uniformly distributed over phases (i.e., P=U), MI equals to zero and no coupling exists between the amplitude and phase. MI increases as P gets further away from U, meaning the coupling gets stronger.

D. Comodulogram Construction

After computing MI between phase and amplitude from each pair of IMFs, the HHT method displays the comodulogram in an IMF domain which represents the coupling phenomenon between IMFs rather than between frequency bands. As each IMF contains an oscillatory mode and the sum of all the IMFs is the original signal, the IMF-domain comodulogram does not need to first define the frequency of interest and presents a comprehensive look of coupling phenomenon.

V. RESULTS

The conventional method and HHT method are used to analyze the intracranial signals from two epilepsy patients. Comparisons are made between the two methods illustrating PAC phenomenon in the five seizure EEG stages in Fig. 2 and Fig. 3.

It is shown that the phase of delta and theta band modulates the amplitude of gamma-band brain rhythm in epileptogenic cortex [15]. Therefore, the frequency of interest for phase signal is set between 0.5 Hz and 10 Hz in the conventional method. In Fig. 2 (left) and Fig. 3 (left), the conventional method shows the coupling phenomenon between different frequency bands in a frequency domain. For Patient 1, preictal and initial fast EEG activity stages have similar coupling area (i.e., mainly between 3-8 Hz phase and around 100 Hz amplitude), and the fast onset shows stronger coupling intensity. The firing pattern transition stage and fast-burst stage both show stronger coupling phenomenon than fast onset generally between 2-10 Hz phase and 15-100 Hz amplitude, where the strongest coupling exists between around 4-7 Hz and 40-50 Hz. Slow-burst EEG activity mainly couples between 2-6 Hz phase and 15-60 Hz amplitude with weaker intensity than fast-burst EEG activity. For patient 2, the coupling is mainly between 0.5-2 Hz phase and 30-100 Hz amplitude in preictal stage, and 0.5-1 Hz phase and around

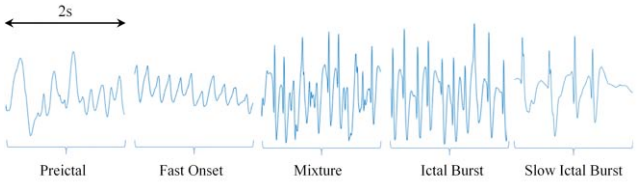


Figure 1. Classification of five seizure stages by firing pattern: Preictal = preictal stage, Fast onset = initial fast EEG activity stage, Mixture = firing pattern transition stage, Ictal burst = fast-burst stage, Slow ictal burst = slow-burst stage

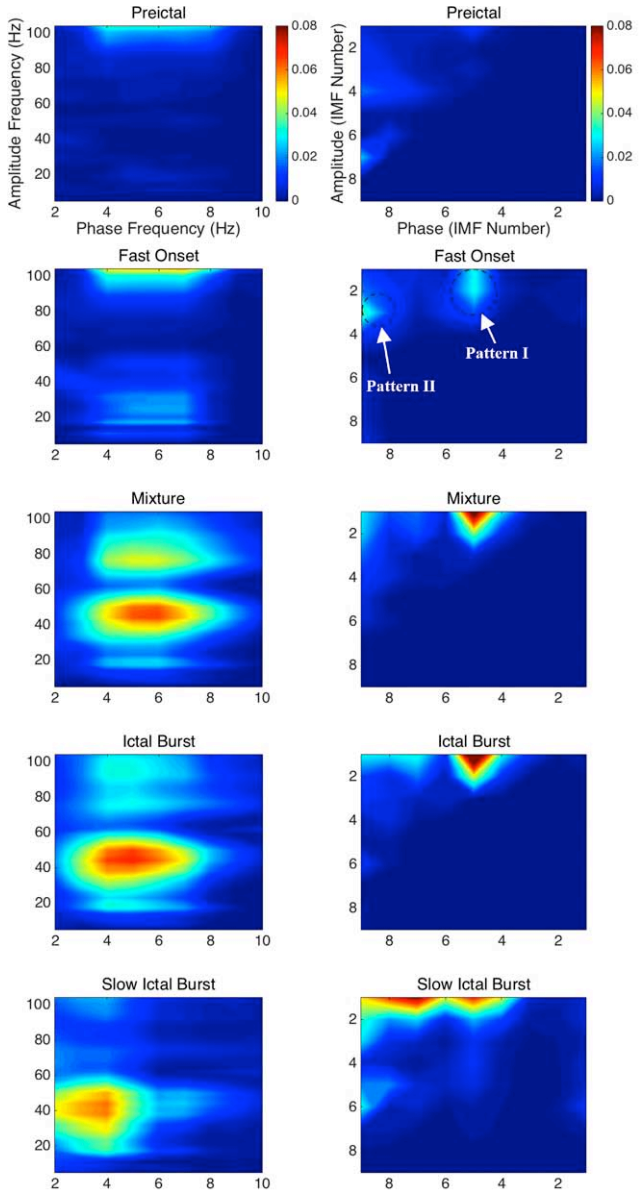


Figure 2. Patient 1: PAC comodulogram comparisons between the conventional method (left) and HHT method (right) in five seizure stages. HHT method displays PAC comodulogram in IMF domain instead of traditional frequency domain, and represents coupling phenomenon between certain two IMFs instead of frequency bands. The color bar represents MI.

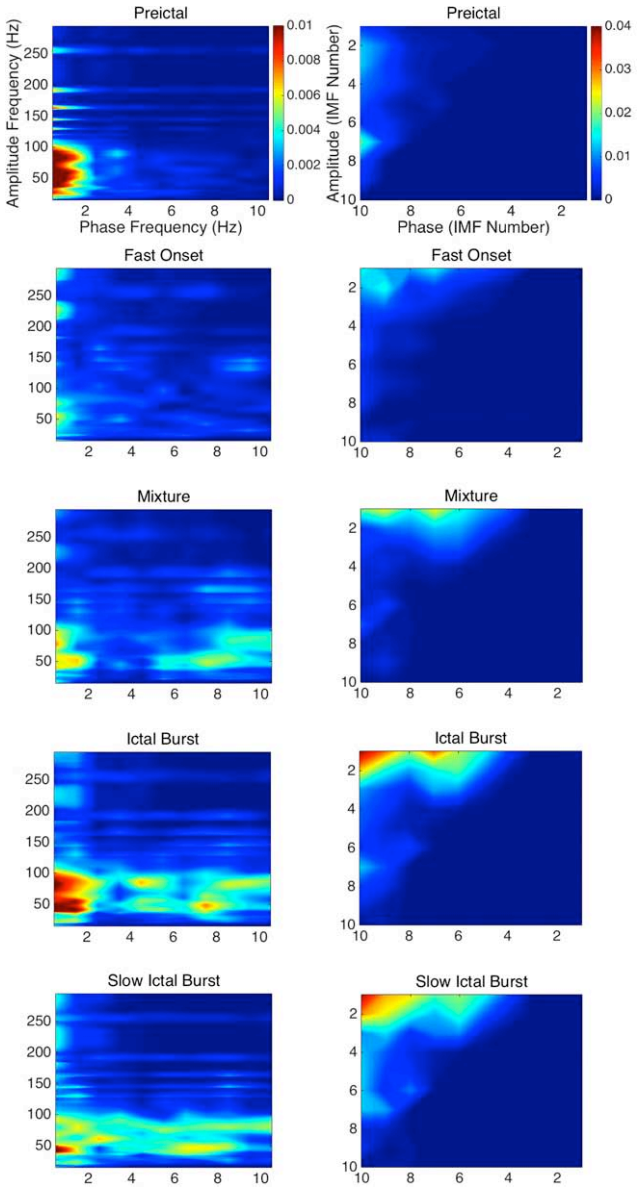
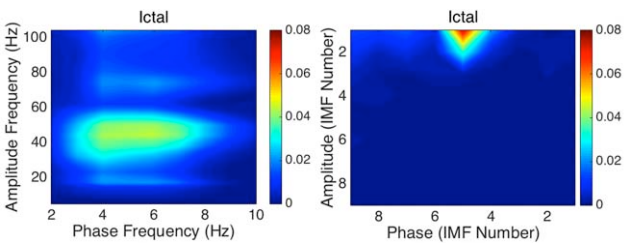


Figure 3. Patient 2: PAC comodulogram comparisons between the conventional method (left) and HHT method (right) in five seizure stages. HHT method shows clear and regular PAC patterns across different stages, while the conventional method does not.



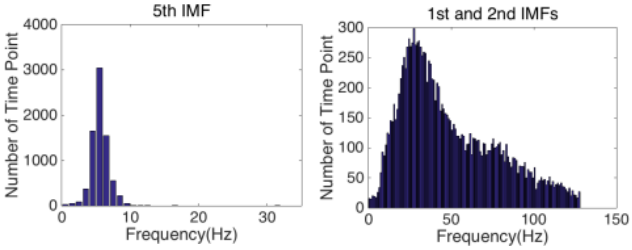


Figure 4. Comparisons between the two methods in ictal stage of patient 1 (left); and histograms of the frequency range of 5th IMF (phase) and 1st-2nd IMFs (amplitude) in HHT method (right); showing the consistency of the two methods in terms of coupled frequency bands.

20-80 Hz, 210-240 Hz and 280-300 Hz amplitude in initial fast EEG activity stage. After the firing transition stage, the coupling sporadically distributes between 0.5-10 Hz phase and 30-100 Hz amplitude, with main coupled phase 0.5-2 Hz. From the two patients, we can see the PAC patterns using the conventional method are not consistent across different patients. Moreover, although a moving window is used in this method to improve frequency resolution, the displayed minimal frequency is limited by sampling rate and the bandwidth of filter, and thus is not able to illustrate delta band (0.5-3 Hz) when the sampling rate is low (Fig. 2 left).

As for HHT method, illustrated in Fig. 2 (right) and Fig. 3 (right), there are generally two patterns (Pattern I and Pattern II) which are two strongest coupling regions in the IMF-domain comodulograms, both having stronger coupling intensity than that of the conventional method during all stages. During seizure (including fast onset, mixture, ictal burst and slow ictal burst), the location of Pattern I (e.g., in patient 1, Pattern I is the area around 5^{th}-IMF phase coupled with 1^{st}-IMF amplitude) is relatively fixed, with only intensity changing: increasing from seizure onset to fast-burst stage and then decreasing till seizure stops; whereas the location of Pattern II (e.g., in patient 1, Pattern II is the area around 9^{th}-IMF phase coupled with 3^{rd}-IMF amplitude in initial fast EEG activity stage, 9^{th}-IMF phase with 1^{st}-IMF amplitude in firing pattern transition stage, and 7^{th}-IMF phase with 1^{st}-IMF amplitude in bursting stages) changes from fast onset to ictal burst and remains the same from ictal burst to slow ictal burst, while the intensity keeps changing over stages.

As each IMF also has a frequency range, we check the instantaneous frequency of the coupled IMFs in each stage of the two patients and find consistency between the two methods in terms of coupled frequency. Fig. 4 illustrates the frequency consistency in the ictal stage (seizure) of patient 1. As it is shown in the IMF-domain comodulogram, the couplings are between 5^{th}-IMF phase and 1^{st}-IMF amplitude, and between 5^{th}-IMF phase and 2^{nd}-IMF amplitude. The frequencies of 1^{st}-2^{nd} IMFs (amplitude) and 5^{th} IMF (phase) are shown in the histograms on the right, where the amplitude frequency mainly ranges approximately from 20 to 50 Hz, and the phase frequency 3-8 Hz, which is consistent with the result shown by the conventional method in frequency bands.

As a result, compared to the conventional method, HHT method shows similar PAC patterns in IMF domain between the two patients, and regular changes across different seizure stages. It also has a more comprehensive PAC presentation and generally stronger coupling intensity (MI) than the conventional method. Therefore, we hypothesize that the IMF may have biological meaning and the real coupling may happen in the IMF domain rather than frequency domain.

VI. Conclusion

We propose a novel method based on HHT to analyze PAC phenomenon in IMF domain, and show new PAC patterns in five seizure stages of two epilepsy patients. The proposed HHT method is superior than the conventional method in terms of 1) able to deal with nonstationary and nonlinear signal, and generates less signal distortions leading to more accurate results; 2) more regular and clearer PAC patterns in IMF domain over five seizure stages in different patients; 3) generally stronger PAC intensity. The coupling intensity between IMFs is stronger than that is between frequency bands, and the frequency components of coupled IMFs are consistent with the conventional method, which indicates that the real coupling may exist between IMFs rather than traditional frequency bands. For further development, the proposed method also can be applied to EEG signals from patients with different diseases such as schizophrenia, depression and Alzheimer disease.

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