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Noise-Assisted Multivariate EMD-Based Mean-Phase Coherence Analysis to Evaluate Phase-Synchrony Dynamics in Epilepsy Patients

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Abstract

Spatiotemporal evolution of synchrony dynamics among neuronal populations plays an important role in decoding complicated brain function in normal cognitive processing as well as during pathological conditions such as epileptic seizures. In this paper, a non-linear analytical methodology is proposed to quantitatively evaluate the phase-synchrony dynamics in epilepsy patients. A set of finite neuronal oscillators was adaptively extracted from a multi-channel electrocorticographic (ECoG) dataset utilizing noise-assisted multivariate empirical mode decomposition (NA-MEMD). Next, the instantaneous phases of the oscillatory functions were extracted using the Hilbert transform in order to be utilized in the mean-phase coherence analysis. The phase-synchrony dynamics were then assessed using eigenvalue decomposition. The extracted neuronal oscillators were grouped with respect to their frequency range into wideband (1–600 Hz), ripple (80–250 Hz), and fast-ripple (250–600 Hz) bands in order to investigate the dynamics of ECoG activity in these frequency ranges as seizures evolve. Drug-refractory patients with frontal and temporal lobe epilepsy demonstrated a reduction in phase-synchrony around seizure onset. However, the network phase-synchrony started to increase towards seizure end and achieved its maximum level at seizure offset for both types of epilepsy. This result suggests that hyper-synchronization of the epileptic network may be an essential self-regulatory mechanism by which the brain terminates seizures.

Keywords

Epileptic seizures; mean-phase coherence; noise-assisted; multivariate empirical mode decomposition (NA-MEMD); synchrony dynamics; intrinsic mode function (IMF); high-frequency oscillations (HFOs); Hilbert transform; eigenvalue decomposition

I INTRODUCTION

Epilepsy is a chronic neurological disorder characterized by recurrent, spontaneous, paroxysmal neural discharges, called epileptic seizures [1], [2]. It has been widely shown that synchronous electrophysiological activity between neuronal networks underlies essential motor or cognitive processes in normal brain function [3]. However, the synchrony level can be altered in several neurological disorders such as epilepsy, which itself may promote epileptic seizures [4], [5]. Seizures have historically been considered as hypersynchronous states arising from an imbalance between excitatory and inhibitory inputs among large networks of neurons in the brain [6], [7]. This conclusion largely arises from the high-amplitude, often rhythmic neuronal activity associated with ictal activity during seizures [8], [9]. Evaluating synchrony dynamics may not only reveal crucial components essential to EEG interpretation but may also provide insight into the dynamics of seizures as they evolve. However, identifying the level of synchrony among non-linear, non-stationary neuronal oscillators extracted from an intracranial electroencephalographic (iEEG) data or local field potential (LFP) signal represents a challenging issue in neurological science.

Recently, a number of researchers have reported that high-frequency oscillations (HFOs) including those in ripple (80–250 Hz) and fast-ripple (250–600 Hz) bands can be utilized as reliable biomarkers of epileptogenic brain tissues [10], [11]. Therefore, instantaneous synchrony analysis of the HFOs may not only reveal crucial insight into predicting seizures but also may provide a better understanding of the electrophysiological dynamics underlying them [12]–[14].

A variety of mathematical methods have been proposed to identify the instantaneous synchrony changes among neuronal networks in the brain. However, many of them rely on several assumptions regarding properties of brain electrophysiological signals that render them inappropriate for this purpose. Cross-correlation [15], [16], Fourier spectrum-based coherence [17], wavelet methods [18], and mutual information measures [19] are among them. These methods, while useful, suffer from assumptions of time-series linearity and/or stationarity, and may possibly detect spurious levels of synchrony as a result of utilizing bivariate measures, while original signals themselves may consist of several oscillatory components.

Eigenvalue decomposition of a linear correlation matrix has been used [20], [21] to capture changes in synchrony level between a set of signals filtered below 70 Hz. This method, which is actually one of the analytical stages of the standard principal component analysis (PCA), reflects the synchrony changes among original signals based on the variation in their eigenvalues. However, utilizing the cross-correlation matrix as a similarity matrix in the eigenvalue decomposition technique may result in spurious synchrony-level interpretation since synchronization between non-linear, non-stationary neuronal oscillators refers only to their relative phase dynamics rather than their amplitude variations [22]. Furthermore, it has been shown that phase synchronization can be detected among non-linear, coupled, chaotic oscillators even if their amplitudes are not synchronized [23]. Therefore, it is crucial to employ non-linear methods to measure instantaneous phase-synchrony changes [22]. Mean-phase coherence analysis has been used to measure the strength of phase relationships

between neuronal oscillators based on their pre-extracted instantaneous phases from a time series [24]. However, the extracted phases have no physical meaning in cases of multi-component time series signals [25]. Therefore, some form of filtering of the data is required prior to the phase extraction stage. Clinical filtering of wideband electrophysiological signals into discrete narrow bandwidths such as alpha, beta, gamma, or Fourier spectrum-derived bandwidths, wavelet decomposition, and the Hilbert transform have been widely utilized to achieve narrow band signals suitable for phase extraction [26], [27]. These methods, while convenient, make several assumptions about frequency bandwidth of importance and/or underlying components of electrophysiological signals that may be erroneous and fail to decompose them considering their intrinsic non-linear, non-stationary features.

Empirical mode decomposition (EMD) provides localized time-frequency representation of a signal through adaptively decomposing it into a finite group of narrowband, oscillatory components without making any assumptions of its linearity and stationarity features [28], [29]. However, EMD of multi-channel data can yield a different number of IMFs for each channel mainly because it treats each channel independently. Therefore, it fails to align frequency responses of same-index IMFs of multiple channels [30]. Mode-mixing between IMFs can also occur with EMD due to a potential intermittency in the input signal [30]. A modified version called noise-assisted multivariate EMD (NA-MEMD) was proposed to overcome both mode-mixing and mode miss-alignment problems related to the standard EMD [30].

This study reports on developing a non-linear, adaptive, analytical methodology that merges the NA-MEMD, Hilbert transform, mean-phase coherence analysis, and eigenvalue decomposition to evaluate the dynamical evolution of phase-synchrony in epilepsy patients with temporal and frontal lobe epilepsy. Although the main contribution of this paper is meant to be methodological, ECoG data from five epilepsy patients were used to demonstrate proof-of-concept. In brief, phase-synchrony dynamics decreased around seizure onset; however, it gradually started to increase as seizure evolved and achieved its maximum level at seizure termination.

The rest of the paper is organized as follows. In section II, specifications of the adopted ECoG dataset, along with the framework of the proposed instantaneous phase-synchrony analysis are described. Experimental results of the phase-synchrony analysis among the neuronal oscillators in different frequency bands are presented in section III. Finally, section IV discusses the results and provides conclusions to this paper.

II. DATASET AND METHODS

The conceptual front-end of the proposed instantaneous phase-synchrony analysis is shown in Fig. 1. Sampled iEEG data, recorded from epileptic brain regions through a multi-channel ECoG electrode, were used as input to the analytical signal processing procedure. Following a pre-processing step on the ECoG data, a group of finite neuronal oscillators was extracted using NA-MEMD process. The Hilbert transform was carried out on the decomposed neuronal oscillators to measure their instantaneous phases and frequencies. Next, the

strength of phase connection between the oscillators was assessed using the mean-phase coherence analysis. Finally, a combination of the eigenvalue decomposition technique along with a post-processing step were executed on the obtained results in order to evaluate the evolution of phase-synchrony dynamics among the neuronal oscillators.

A. Patients and ECoG Dataset

In this study, continuous, multi-channel ECoG datasets, recorded from five de-identified epilepsy patients, were retrieved from the publicly available online International Epilepsy Electrophysiology (IEEG) portal [31]. Two patients were diagnosed with frontal lobe epilepsy, while the other three had temporal lobe epilepsy. All patients were adults with medically refractory epilepsy undergoing routine, long-term iEEG monitoring in preparation for the pre-surgical evaluation including seizure onset zone (SOZ) localization of their epilepsy. Epileptic SOZs and timing of seizures, seizure onset and offset, have been clinically determined by the treating physicians at the Mayo Clinic through visual identification of clear ictal discharges. Further clinical details regarding the analyzed patients, as well as their access IDs in the IEEG portal, are provided in Table I. The iEEG data were recorded from the patients using ECoG subdural-grids consisting of platinum-iridium sites with 2.3 mm diameter, and 10 mm pitch size. It is important to note that only the grid directly covering the SOZ was used in the phase-synchrony analysis. Signal pre-conditioning and the analog-to-digital conversion (ADC) were performed using a Neuralynx electrophysiology system with a 32 kHz sampling rate, which later was downsampled to 5 kHz, and a 1–1500 Hz band-pass filtering. A digital 60 Hz notch filter was used to eliminate line noise. In this study, a pre-processing step was carried out on the raw ECoG signals in order to extract bipolar derivations of them by taking the voltage difference between adjacent electrodes. This pre-processing aimed towards eliminating the confounding effects of both common reference signal and volume conduction [32], [33].

B. Noise-Assisted Multivariate EMD (NA-MEMD)

Conventional methods employed towards decomposition of wideband neurological signals, including Fourier spectrum-derived decomposition and wavelet decomposition, exhibit several drawbacks that mainly stem from their assumptions of linearity and/or stationarity properties of the underlying signal dynamics, and the frequency bandwidth of importance. EMD is an adaptive, data-driven method of decomposing data into a set of finite intrinsic mode functions (IMFs), similar to basis functions in the Fourier transform. All IMFs together comprise the underlying oscillations within a time series. That is, IMFs are determined from the dynamics of original signals. EMD method does not involve any assumptions about underlying components of signals, which makes it suitable for the time-frequency analysis of non-linear and non-stationary electro-physiological signals. However, EMD of multi-channel data can cause mode-aliasing and mode-misalignment. In order to overcome these problems, an advanced version of EMD called NA-MEMD was introduced [30].

In this study, NA-MEMD process was used to decompose the wideband, multi-channel iEEG data. NA-MEMD method takes advantage of the quasi-dyadic filter-bank

characteristic of MEMD on white noise in which additional, independent white noise channels are added to the multi-channel input data [30].

The details of the NA-MEMD process on a given n -channel input data, $x(t)$, are outlined as follows:

1. Create a m -channel, uncorrelated Gaussian white noise time-series with the same length as $x(t)$.
2. Add the generated m -channel white noise sources with $x(t)$ to produce a new p -dimension signal, $y(t)$, in which $p = m + n$.
3. Choose a proper set of points, based on the Hammersley sequence, for sampling on a $(p - 1)$ -dimensional sphere.
4. Calculate a set of projections, $\left\{W_k^{\theta_k(t)}\right\}_{k=1}^K$ of the p -channel signal $\{y(t)\}_{t=1}^T$ along the direction vector $v_k^{\theta_k}$ for all k , which K denotes the whole set of direction vectors.
5. Find the time instants $\left\{t_i^{\theta_k}\right\}_{k=1}^K$ associated with the maxima of the set of projected signals $\left\{W_k^{\theta_k(t)}\right\}_{k=1}^K$, where i indicates the position of maxima point.
6. Calculate multivariate envelope curves, $\left\{e_k^{\theta_k(t)}\right\}_{k=1}^K$ using cubic-spline interpolation of $\left[t_i^{\theta_k}, y(t_i^{\theta_k})\right]$.
7. For a set of K direction vectors, calculate the mean of the envelope curves, $m(t)$, as follows:

$$m(t) = \frac{1}{K} \sum_{k=1}^K e_k^{\theta_k(t)} \quad (1)$$
8. Calculate $d(t)$ as $d(t) = x(t) - m(t)$. If $d(t)$ fulfills the stoppage criterion for a multivariate IMF, execute the above procedure in an iterative manner for $x(t) - d(t)$, otherwise apply it to $d(t)$ in order to obtain next IMFs.
9. Choose only the extracted IMFs corresponding to the n -channel input signal, $x(t)$, and discard those related to the noise channels.

The stoppage criterion of the sifting process has been chosen the same as the standard EMD [28]. It should be noted that the lower-index IMFs denote fast oscillation modes of the original signal, $x(t)$, while the higher-index IMFs represent the slower oscillation modes. Finally, at the end of the decomposition process, the original signal $x(t)$ is described by the following equation [28].

$$x(t) = \sum_{i=1}^N d_i(t) + r(t) \quad (2)$$

in which N is the number of decomposed IMFs and $r(t)$ is the residue. The residue corresponds to a signal whose projections do not contain sufficient extrema to form a meaningful multivariate envelope.

The NA-MEMD was carried out on each bipolar-derivate ECoG data-segment to extract its corresponding IMFs. Next, Hilbert transform of the decomposed narrowband IMFs was performed in order to measure their instantaneous frequencies. The extracted IMFs were then classified with respect to their instantaneous frequencies. Fig. 2 illustrates the NA-MEMD process on a 1-s, bipolar-derivate ECoG signal along with the time-frequency representation of its decomposed IMFs. For simplicity, only the top six extracted IMFs are illustrated in Fig. 2. The more in-depth insight regarding the importance of using NA-MEMD process before extracting the instantaneous phase information is provided in the next section.

C. Hilbert Analytic Signal Method

Hilbert analytic signal method is a well-established method of measuring instantaneous phase and frequency information from narrowband signals [34]. The Hilbert transform of a real, time-domain signal $x(t)$ is a simple convolution that shifts its phase by $\pi/2$ and is defined as:

$$H[x(t)] = x(t) * \frac{1}{\pi t} = \frac{1}{\pi} \text{p.v.} \int_{-\infty}^{+\infty} \left(\frac{x(\tau)}{t-\tau} \right) d\tau \quad (3)$$

where *p.v.* indicates the Cauchy principle value as the function $h(t) = 1/\pi t$, is not integrable. The analytic representation of the $x(t)$ is described as:

$$z(t) = x(t) + jH[x(t)] = A(t)e^{j\phi(t)} \quad (4)$$

in which $A(t)$ is the instantaneous amplitude of $z(t)$, and $\phi(t)$ is the instantaneous phase of the analytic signal $z(t)$ which is defined by the following equation.

$$\phi(t) = \arctan\left(\frac{H[x(t)]}{x(t)}\right) \quad (5)$$

Furthermore, the instantaneous frequency, $\omega(t)$, is measured by the following equation.

$$\omega(t) = \frac{d\phi(t)}{dt} \quad (6)$$

Multi-component or wideband signals yield a trajectory in the complex plane that contain several centers of rotation. However, in order to achieve an unambiguous phase reading, the complex trajectory of an analytic signal should have only a single center of rotation. For instance, a sine wave has a trajectory in the complex plane that include a single-centered, isolated circle. Moreover, it should be noted that if the multi-component signal under interest is non-stationary, the resultant phase space will have multiple windings around each of the individual component-centers. This phenomenon is presented in Fig. 3(a), which is phase-space of a Hilbert-transformed, 1-s ECoG signal during a seizure. Therefore, for an unambiguous phase determination, it is important to individually extract the underlying components of a time series contributing to the multiple centers of rotation. The NA-MEMD process defined in the previous section provides a proper instantaneous phase determination by separating underlying oscillators, IMFs, of a signal that results in several phase space traces each with one center of rotation. Fig. 3(b) demonstrates the phase space of a Hilbert-transformed IMF, decomposed using the NA-MEMD of a 1-s, bipolar-derivate ECoG signal during a seizure. The instantaneous phase can be clearly measured due to the nature of the IMF construction. In this study, NA-MEMD of bipolar-derivate ECoG signals were carried out for each 1-s segment of data prior to the use of the Hilbert transform in order to measure the instantaneous phases unambiguously.

D. Mean-Phase Coherence Analysis

Once the instantaneous phases of the extracted IMFs from all channels within a 1-s data-segment were obtained, the strength of their phase relationship was determined. In order to do this, each IMF was treated as a row vector and stacked on each other to form an $N \times M$ matrix, in which N is the total number of IMFs extracted from all channels within a 1-s segment of bipolar-derivate ECoG data and M denotes the total length of the time series. It should be noted that the resulting group of IMFs represented the neuronal oscillators decomposed from the bipolar-derivate ECoG data using NA-MEMD. Next, the bivariate mean-phase coherence matrix, $R_{N \times N}$, was calculated using the following equation [24].

$$R_{kp} = \left| \frac{1}{M} \sum_{m=1}^M e^{i(\phi_{km}(t) - \phi_{pm}(t))} \right| \quad (7)$$

where i is equal to -1 , M is the total number of samples within the data segment, and $\phi(t)$ is the instantaneous phase of the analytic signal pair indicated by the subscripts k and p . Subscripts k and p iterate from 1 to N and all the values in the $R_{N \times N}$ are between zero and one.

E. Eigenvalue Decomposition and Synchrony Analysis

Eigenvalue decomposition of the square, bivariate mean-phase coherence matrix was performed to achieve a multi-variate measure that is capable of capturing phase-synchrony among all the extracted neuronal oscillators. Essentially, this decomposition compares all the values in the $R_{N \times N}$ and projects them into a set of principal directions with respect to the mean phase field. Furthermore, all the eigenvalues are sorted in ascending order to form an eigenvalue spectrum in which each one represents how strongly oscillators are phase-correlated in the direction of its corresponding eigenvector. The eigenvalue decomposition was executed by solving $R_{N \times N} \mathbf{v}_i = \lambda_i \mathbf{v}_i$ in which λ_i and $\mathbf{v}_i$ are the obtained eigenvalues and their corresponding eigenvectors, respectively. It should be noted that all of the N obtained eigenvalues were real, as the $R_{N \times N}$ matrix was square symmetric with their sum equal to the total number of the extracted oscillators. Therefore, any increase in one of the eigenvalues has to be compensated by a decrease in the other eigenvalues in order to keep the sum constant. This is the fundamental idea underlying evaluating the phase-synchrony among oscillators, which is clarified in detail in Fig. 4.

Fig. 4 illustrates how changes in the eigenvalue spectrum represent the phase-synchrony level in three different sets of oscillators. Fig. 4(a) demonstrates five extracted IMFs from a 1-s, bipolar-derivate ECoG signal using NA-MEMD process along with their corresponding mean-phase coherence matrix and eigenvalue spectrum. The IMFs extracted from the same bipolar-derivate channel are nearly orthogonal, which means almost no phase-synchronization between them; therefore, the obtained $R_{N \times N}$ values are one, color-coded as white, on the diagonal and very close to zero, color-coded as black, outside the diagonal. In this case, all of the eigenvalues are close to one. Fig. 4(b) illustrates an IMF decomposed from a bipolar-derivate channel that was copied five times in order to create a fully phase-synchronized set of oscillators. As expected, the obtained $R_{N \times N}$ values are all equal to one. In this case, after performing the eigenvalue decomposition of the $R_{N \times N}$ matrix, the last eigenvalue is equal to the total number of oscillators, $\lambda_N = N = 5$, while the rest of them are equal to zero in order to maintain the sum of them constant. Fig. 4(c) exhibits a phase-synchrony level between those in cases (a) and (b). The fifth IMFs that were decomposed from different bipolar-derivate channels within a 1-s ictal segment were grouped to evaluate the phase-synchrony among them. The obtained eigenvalue spectrum indicates a decrease in the last eigenvalue compared to its counterpart in case (b) which is offset by a compensatory increase in its lower eigenvalues. Generally, considering the ascending order among eigenvalues, a small change in the value of a few higher-index eigenvalues causes a relatively large dynamic change among the value of the lower-index eigenvalues to compensate it. Hence, focusing on the high percentage of lower-index eigenvalues provides a greater sensitivity to capture the instantaneous changes of the phase-synchrony level. In Fig. 4, the average value of the first 60% lower-index eigenvalues, $mean\lambda_{1:60\%}$, is reported for all three cases to simplify the comparison among their phase-synchrony levels. As the synchrony level increases between neuronal oscillators from its minimum to its maximum, the $mean\lambda_{1:60\%}$ value decreases accordingly. That is, an increase/decrease in the $mean\lambda_{1:60\%}$ value reflects a decrease/increase in the phase-synchrony level, respectively. The $mean\lambda_{1:70\%}$ and $mean\lambda_{1:80\%}$ variables also were tested which both produced virtually the same result as the $mean\lambda_{1:60\%}$ variable. Moreover, in order to magnify the very small

relative changes of the $mean\lambda_{1:60\%}$ over time, especially during seizure, normalized $mean\lambda_{1:60\%}$ values were measured as follows. First, all of the obtained $mean\lambda_{1:60\%}$ values were subtracted from their temporal average value, calculated within a 2-min pre-ictal segment and then divided by their standard deviation measured over the same reference time.

III. EXPERIMENTAL RESULTS

In order to deal with the edge effect problem associated with data segmenting during the NA-MEMD process, 500 samples from neighboring segments were incorporated to both ends of each 1-s data segment. However, after executing the NA-MEMD, only the IMFs corresponding to the original data segment were retained. Furthermore, the extracted IMFs from each ECoG signal containing frequency ranges above 600 Hz were filtered out from the phase-synchrony analysis. If the original signal contains appreciable noise, the first extracted IMF would mainly represent the noise component that has little contribution to the underlying dynamics of the original data [35]. In this analysis, the first and second IMFs include frequencies above 600 Hz and thus were filtered out from the phase-synchrony analysis.

In the following sections, phase-synchrony dynamics in two epilepsy patients are described in detail and a summary of the analysis is provided for all patients.

A. Instantaneous Dynamics of Phase-Synchrony in Patient-1 with Frontal Lobe Epilepsy (FLE)

In order to characterize the phase-synchrony dynamics in the key frequency bands of interest including ripple and fast-ripple bands, the decomposed oscillators were collected with respect to their frequency bandwidth in three different groups. The first group, wideband, was comprised of all the extracted oscillators, IMFs, with frequency bandwidth between 1 Hz and 600 Hz. The frequency bandwidth of all IMFs were determined by the instantaneous frequency outputs from the Hilbert transform. The second group, ripple, consisted of IMFs with frequency ranges between 80 Hz and 250 Hz. Finally, the last group, fast-ripple, was comprised of all IMFs with frequency bandwidth between 250 Hz and 600 Hz. Fig. 5 shows the instantaneous phase-synchrony dynamics within each of the three bands in Patient-1. Fig. 5(a) illustrates the anatomical position of the 36-channel ECoG electrode in the patient. A 5.5-min, bipolar-derivate ECoG signal, containing an epileptic seizure utilized for the instantaneous phase-synchrony analysis, is shown in Fig. 5(b). The green dashed lines denote seizure onset and termination that were clinically determined by treating physicians. The instantaneous temporal changes of the normalized $mean\lambda_{1:60\%}$ variable, obtained from the phase-synchrony analysis of IMFs in the wideband group, is shown in Fig. 5(c). The normalized $mean\lambda_{1:60\%}$ value had a short increase around seizure onset up to a few seconds after it, which reflected a desynchronization during this period. Following this period, the normalized $mean\lambda_{1:60\%}$ value started to decrease gradually towards seizure offset, which reflected a proportionally gradual increase in the synchrony level during this period. It should be noted that the phase-synchrony level achieved its maximum value at seizure termination and then gradually decreased to its pre-ictal level. Fig. 5(d) illustrates the

temporal changes of the normalized $mean\lambda_{1:60\%}$ variable in the ripple band. The general pattern of the phase-synchrony dynamics between oscillators in the ripple group was similar to those in the wideband group. However, the gradual increase in the phase-synchrony level towards seizure termination, as indicated by the gradual decrease in the normalized $mean\lambda_{1:60\%}$ value, was higher relative to that in the wideband group. The relative phase-synchrony changes between oscillators in the fast-ripple group as reflected by the temporal changes of the normalized $mean\lambda_{1:60\%}$ variable is illustrated in Fig. 5(e). The general pattern of phase-synchrony dynamics in the fast-ripple group was similar to the ones in wideband and ripple groups. However, the desynchronization during seizure initiation as indicated by the increase in the normalized $mean\lambda_{1:60\%}$ value increased to a greater amount in this group compared to those in the ripple and wideband groups. Furthermore, the gradual drop in the intensity of the normalized $mean\lambda_{1:60\%}$ towards seizure offset which denotes the gradual resynchronization, was higher relative to those in the other two groups.

B. Instantaneous Dynamics of Phase-Synchrony in Patient-2 with Temporal Lobe Epilepsy (TLE)

The same front-end phase-synchrony analysis as described in the previous section was carried out for Patient-2. Fig. 6 illustrates the phase-synchrony dynamics in this patient within all the three bandwidth groups; namely, wideband, ripple, and fast-ripple. Fig. 6(a) illustrates the anatomical position of the fully implanted, 24-channel ECoG electrode in the patient. A 5.5-min, bipolar-derivate ECoG signal, containing a seizure used for the instantaneous phase-synchrony analysis is shown in Fig. 6(b). As in Fig. 5, green dashed lines represent seizure onset and offset. Fig 6(c) exhibits the instantaneous temporal changes of the normalized $mean\lambda_{1:60\%}$ variable, which were obtained from the phase-synchrony analysis of the IMFs in the wideband group. The normalized $mean\lambda_{1:60\%}$ value started to increase from about 10-s preceding seizure onset up to almost 30-s after this time, which denoted a desynchronization during this period. Following the aforementioned period, a gradual increase in the synchronization towards the seizure offset, as indicated by a decrease in the normalized $mean\lambda_{1:60\%}$ value was observed. Fig. 6(d) illustrates the temporal changes of the normalized $mean\lambda_{1:60\%}$ in the ripple group. The overall pattern of the phase-synchrony dynamics among IMFs, in the ripple group was similar to those in the wideband group. However, the gradual increase in the synchrony level towards the seizure termination as reflected by the reduction in the normalized $mean\lambda_{1:60\%}$ value was higher compared to the one in the wide-band group. As demonstrated in Fig. 6(d), the pattern of the phase-synchrony dynamics in the fast-ripple group was similar to those in the ripple and wideband groups. However, the de-synchronization following seizure initiation lasted longer and increased to a greater amount in this group relative to those in the ripple and wideband groups. Furthermore, the increase in the synchronization level was higher compared to that in the ripple and wideband groups. It should be noted that the phase-synchrony level achieved its maximum at seizure termination during the ictal periods in all three bandwidths.

C. The Phase-Synchrony Pattern Observed in all Patients are Stable over Time

For all patients in this study, all of the seizures recorded during the pre-surgical evaluation, were analyzed in order to determine the consistency in the phase-synchrony evolution within different epochs of ictal activity. Fig. 7 demonstrates a summary of the normalized

$mean\lambda_{1:60\%}$ values for all of the patients. Patient-1 with FLE had seizures that were much shorter in duration relative to the other epilepsy patients. For this patient, it was not feasible to define a relevant mid-ictal segment. The normalized $mean\lambda_{1:60\%}$ values, mean $\pm$ standard deviation, are shown at various stages of seizures for all three frequency bands. Fig. 7(a) illustrates comparison of the phase-synchrony evolution for Patient-1 with FLE with short seizure durations. There was a statistically significant difference in the values of the normalized $mean\lambda_{1:60\%}$ between seizure onset and offset for this patient (ANOVA on ranks followed by Tukey test, $p < 0.05$). This decrease in the normalized $mean\lambda_{1:60\%}$ values was mainly due to the hypersynchrony observed at seizure termination within all three groups. Furthermore, this observation was consistent across all seizures recorded in this patient. The statistical analysis of phase-synchrony evolution for the other 4 patients (3 with TLE and 1 with FLE) is shown in Fig. 7(b). It should be noted that for all three groups, there was a statistically significant difference in the values of the normalized $mean\lambda_{1:60\%}$ across all three epochs (ANOVA on ranks followed by Tukey test, $p < 0.05$). The phase-synchrony evolution pattern was consistent across all seizures recorded for these patients.

IV. DISCUSSION AND CONCLUSION

The purpose of this study was to develop a non-linear data-driven analytical methodology to evaluate network-synchrony among neuronal populations in epilepsy patients, with respect to their phase dynamics, within different frequency bands. Understanding how these phase-synchrony dynamics evolve during epileptic seizures can help to decipher the complicated electrophysiological mechanisms underlying them. Moreover, it may reveal crucial insights into how the brain naturally terminates seizures, thereby providing an essential feedback necessary for clinical modulation of epilepsy disease. In this study, NA-MEMD-based mean-phase coherence analysis was exploited to investigate the phase-synchrony among neuronal networks. NA-MEMD is capable of decomposing wideband electrophysiological signals into a set of finite, narrow-band neuronal oscillators without posing any assumptions regarding the linearity and stationarity of their underlying components. Hilbert transform of the extracted IMFs provides phase-space traces, each with one center of rotation, thereby permitting instantaneous phase determination unambiguously. Next, the eigenvalue decomposition of the square, bivariate mean-phase coherence matrix ($R_{N \times N}$) was performed to capture the phase-synchrony dynamics between the neuronal oscillators. In order to provide a magnified visualization of the relatively small temporal changes of phase-synchrony between the extracted oscillators, the normalized mean value of the first 60% lower-index eigenvalues, $mean\lambda_{1:60\%}$, was measured and reported for each second. The instantaneous phase-synchrony analysis of ECoG recordings from five patients, two with FLE and three with TLE, was performed within three frequency bands (wide-band, ripple and fast-ripple). The following consistent patterns were observed in all patients within the three frequency bands: (i) network phase-desynchronization occurred during initial stage of seizures, (ii) phase-synchrony started to gradually increase following the desynchronization as the ictal event progressed, and (iii) phase-synchrony achieved its maximum level at seizure termination.

In all patients, a network desynchronization was observed around seizure onset. However, the intensity and duration of the desynchronization in Patient-2 were relatively higher and

longer compared to that observed in Patient-1 within all three frequency bands. This may be due to the shorter ictal period in Patient-1. It should be noted that the phase-synchrony pattern of a different patient, Patient-5, with FLE that had duration of ictal events comparable to the patients with TLE was found to be similar to the one illustrated in Fig. 6. This suggests that the difference in the pattern between Patients 1 and 2 presented in the result section might be due to the difference in their ictal duration rather than the type of epilepsy. Performing further analysis on more patients with different seizure durations might support this hypothesis but that is outside the scope of this study, which is focused on developing a methodology for assessing phase-synchrony. The desynchronization during the seizure initiation stage in our result is consistent with what has been observed in studies of single-neuron dynamics in human focal epilepsy [36], intracellular activity recording of a rat model of epilepsy [37], and several intracranial and extra-cranial neural recordings from epilepsy patients [38]-[40].

Following the desynchronization around seizure onset and propagation, our results suggested a gradual increase in the phase-synchrony level towards seizure offset for all patients with different types of epilepsy within all three bands. The resynchronization pattern observed as seizures ended is similar to several recent studies investigating human and rat epileptic seizures [36], [41], [42]. The phase-synchrony level achieved its maximum, within all three groups, at seizure termination during the ictal periods for all patients. In a recent study that investigated the single-neuron dynamics in human with focal epilepsy [36], a high degree of heterogeneity was observed in neural spiking during seizure initiation. Following this period, spiking activity evolved into a more homogeneous activity as seizures ended as observed by an increase in the number of neurons showing very high firing rates. That is, a progressive recruitment of neurons with high-frequency firing across a broad segment of brain tissue primarily drives the synchrony evolution towards seizure offset. This behavior is similarly observed at a network level in our ECoG-activity analysis by the highest phase-synchrony level being achieved between neuronal oscillators within the fast-ripple band in all patients. Although the action potential firing rate of normal or epileptic neurons cannot reach to the fast-ripple frequency range, recent models have postulated that neuronal oscillators within fast-ripple bandwidth can be generated from a multi-site and likely multi-synaptic coordination of neurons with high firing rates within the brain [12], [43].

The consistent hypersynchrony at the seizure offset among all the analyzed seizures, as verified in Fig. 7, may suggest that the brain naturally terminates seizures through increasing the synchrony level of the neuronal networks within the SOZ. Therefore, our results suggest a revision of the conventional hypothesis that postulates epileptic seizures are pathologically synchronized states in which the network desynchronization may promote seizure termination [6], [7]. Furthermore, our findings may provide a crucial feedback into how to increase the clinical efficacy of a potential brain modulation in epilepsy patients such as through exogenous electrical stimulation. That is, the electrical stimulation parameters such as frequency may be selected to maximize the synchronization level among the neuronal oscillators within the SOZ. The proposed front-end phase-synchrony analysis in this study is capable of providing the instantaneous frequency of neuronal oscillators that mostly causes hypersynchronization at seizure offset. Future studies will focus on extracting the

aforementioned frequency and investigating its efficacy using electrical stimulation in seizure termination.

Finally, the gradual and prominent decrease in the phase-synchrony level observed during seizure initiation in all three bands, especially within fast-ripple band, may be utilized as a potential biomarker or trigger in implantable neuromodulation devices with closed-loop operation in order to expedite seizure termination. However, further studies with a higher number of epilepsy patients will be required to draw a clinically robust conclusion.

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Fig. 1.
Conceptual front-end of the proposed instantaneous, phase-synchrony analysis.

Fig. 2. NA-MEMD process on a bipolar-derivate ECoG recording. (a) 1-min bipolar-derivate ECoG signal along with a magnified view of its 1-s ictal period utilized for the NA-MEMD process. (b) The top six IMFs decomposed from the 1-s, ictal period along with their time-frequency representations.

Fig. 3. Phase space of Hilbert analytic signals. (a) Phase space of a Hilbert-transformed, 1-s bipolar-derivate ECoG signal during the ictal period. (b) Phase space of a Hilbert-transformed, 1-s IMF decomposed during an ictal activity using the NA-MEMD process.

Fig. 4.

Evaluating phase-synchrony levels among neuronal oscillators using eigenvalue decomposition of the mean-phase coherence matrix. All of the values in the mean-phase coherence matrix, $R_{N \times N}$, were normalized and color-coded between zero (black), to one (white). (a) Five decomposed IMFs from a 1-s, bipolar-derivate ECoG signal using the NA-MEMD process, along with their corresponding mean-phase coherence matrix, eigenvalue spectrum, and the average value of the first 60% lower-index eigenvalues, $\text{mean}\lambda_{1:60\%}$. Due to the nearly orthogonal nature of the IMFs extracted from one channel, all the $R_{N \times N}$ values are near to zero, showing no phase-synchronization among the oscillators. In this case, all the eigenvalues resulted from the eigenvalue decomposition of the $R_{N \times N}$ are close to one. (b) Five-times copied version of an IMF leads to a $R_{N \times N}$ matrix, in which all of its values are equal to one, showing a full phase-synchronization among the oscillators. In this case, the eigenvalue decomposition of the $R_{N \times N}$ matrix yields five for the last eigenvalue and zero for

the rest of the eigenvalues. (c) A set of IMFs extracted from different channels within a 1-s ictal period leads to a $R_{N \times N}$ matrix with values between case (a) and (b), showing a partial synchronization among the oscillators. In this case, the obtained eigenvalue spectrum exhibits a decrease in the last eigenvalue and a compensatory increase in the lower eigenvalues compared to case (b), which consequently yields a $mean\lambda_{1:60\%}$ value between those in cases (a) and (b).

Fig. 5.

Evaluating instantaneous phase-synchrony dynamics in Patient-1 with frontal lobe epilepsy (FLE). (a) Anatomical position of the 36-channel ECoG electrode. (b) 5.5-min, raw, bipolar-derivate ECoG signal containing a seizure recorded from Patient-1 with FLE. Green dashed lines denote seizure onset and offset. Relative temporal changes of the normalized $mean\lambda_{1:60\%}$ value, after being smoothed with a 5-s moving average filter, for all the extracted IMFs within the (c) Wideband frequency range (1 Hz to 600 Hz); (d) Ripple band (80 Hz to 250 Hz); (e) Fast-ripple band (250 Hz to 600 Hz). An increase/decrease in the value of the $mean\lambda_{1:60\%}$ reflects a decrease/increase in the phase-synchrony level, respectively.

Fig. 6.

Evaluating instantaneous phase-synchrony dynamics in Patient-2 with temporal lobe epilepsy (TLE). (a) Anatomical position of the 24-channel ECoG electrode. (b) 5.5-min, raw, bipolar-derivate ECoG signal containing a seizure, recorded from Patient-2 with TLE. Green dashed lines denote seizure onset and termination. Relative temporal changes of the normalized $mean\lambda_{1:60\%}$ value, after being smoothed with a 5-s moving average filter, for all the extracted IMFs within the (c) Wideband frequency range (1 Hz to 600 Hz); (d) Ripple band (80 Hz to 250 Hz); (e) Fast-ripple band (250 Hz to 600 Hz). An increase/decrease in the value of the $mean\lambda_{1:60\%}$ reflects a decrease/increase in the phase-synchrony level, respectively.

Fig. 7.

Comparison of the phase-synchrony evolution for all seizures during different epochs within ictal activity. (a) Statistical analysis of the phase-synchrony evolution for Patient-1, including 12 seizures. The mean $\pm$ standard deviation of all the normalized $mean\lambda_{1:60\%}$ values are measured within a 10-s window around the seizure onset and offset epochs. ANOVA analysis followed by Tukey test demonstrates significant differences between the two epochs as seizures evolved ($p < 0.05$). (b) Statistical analysis of the phase-synchrony evolution for the other four patients, containing 35 seizures. The mean $\pm$ standard deviation

of all normalized $mean\lambda_{1:60\%}$ values are measured within a 20-s window around seizure onset, mid, and offset epochs. ANOVA analysis followed by Tukey test indicates significant differences between the three epochs ($p < 0.05$).

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TABLE I

PATIENT CLINICAL DATA AND SIGNAL ACQUISITION INFORMATION

IEEG Portal Patient ID	I001-P034-D01	Study 036	I001-P010-D01	I001-P005-D01	I001-P021-D01
Subject	1	2	3	4	5
Age	35	25	Unknown	20	Unknown
Sex	Female	Male	Female	Male	Female
Seizure Type	CPS/GTC	PS/GTC	CPS/GTC	CPS/GTC	CPS/GTC
No. ECoG Elec.	36	24	48	28	112
Seizure Focus	RFL	RTL	LTL	LTL	RFL
No. Seizures	12	4	16	3	12
Sampling Rate (Hz)	5000	5000	5000	5000	5000
Recording Duration (h)	32	110	90	35	45

CPS = complex partial seizure, PS = partial seizure, GTC = generalized tonic-clonic seizure, RFL = right frontal lobe, RTL = right temporal lobe, LTL = left temporal lobe.