Characterization of Synchrony with Applications to Epileptic Brain Signals

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Measurement of synchrony in networks of complex or high-dimensional, nonstationary, and noisy systems such as the mammalian brain is technically difficult. We present a general method to analyze synchrony from multichannel time series. The idea is to calculate the phase-synchronization times and to construct a matrix. We develop a random-matrix-based criterion for proper choosing of the diagonal matrix elements. Monitoring of the eigenvalues and the determinant provides an effective way to assess changes in synchrony. The method is tested using a prototype nonstationary dynamical system, electroencephalogram (scalp) data from absence seizures for which enhanced synchrony is presumed, and electrocorticogram (intracranial) data from subjects having partial seizures with secondary generalization.

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Epileptic seizures affect about 1% of the population in industrialized countries. Seizure prediction is one of the most important but challenging problems in biomedical sciences [1]. It is believed that neuronal hypersynchrony is a necessary condition for the generation of seizures [2]. A direct consequence of this assumption is that, during the seizure, the number of degrees of freedom of the underlying brain dynamical system may be reduced. Interestingly, a recent experimental study of synchronization between CA1 pyramidal neurons reveals that seizurelike events are associated with desynchronization [3]. To resolve the controversy may be challenging. Considering that multichannel electroencephalogram (EEG) or electrocorticogram (ECoG) recordings are now readily available from laboratory or clinical studies of epilepsy, a method sensitive to variations of synchrony is desirable. Since multichannel data are also common in many other disciplines of science and engineering, such a method may find much broader usages beyond epilepsy.

In this Letter, we develop a general, data-driven method to probe synchrony from multichannel data. Because of parameter mismatch and noise, complete synchronization among data from different channels, in the sense that they approach each other asymptotically, cannot be expected. Thus it is necessary to explore weaker forms of synchronization, such as phase synchronization [4–7]. A basic assumption that one can make about any reasonable multichannel time series is that they be oscillatory [8]. For an oscillatory time series, in principle a phase variable can be defined. Denote the phase variable of data from channel i and j by $\phi_i(t)$ and $\phi_j(t)$, respectively. There is phase synchronization between the two channels if $|\phi_i(t) - \phi_j(t)| < 2\pi$ [4]. Because of nonstationarity and noise, the phase-synchronization state so defined can last for only a finite amount of time. Thus a practically useful quantity to characterize the degree of phase synchronization is the average phase-synchronization time [9,10], which can be calculated by using a large time interval of observation during which a reasonable number of 2π changes in the phase difference occurs. In a moving-window analysis of nonstationary data, this time interval is the size of the window. As the system evolves, i.e., as the "window moves," the average phase-synchronization time can change. Let $\tau_{ij}(t)$ be this average time between channels i and j at time t, where t is the time at the end of a window. Suppose there are N channels in total. To take full advantage of available data, we can define an $N \times N$ matrix of average phase-synchronization time for all pairs of channels. The matrix, by construction, is symmetric, but the choice of the diagonal elements becomes a critical issue. In principle, the diagonal elements are infinite, and for a moving-window application they are the size of the window. A difficulty with this simple choice is that the window size is often much larger than the average synchronization time. As a result, the matrix can become quite singular, hampering further analysis and the matrix's ability to discern system changes.

In a general sense, since our task is to probe system changes through the synchronization-time matrix constructed from *noisy* time series, the "condition" of the matrix should not depend too sensitively on the variations of matrix elements. However, the condition should not be totally insensitive to the variations either, as required by the task. Thus, a criterion is needed for properly choosing the diagonal elements. Here, we use random matrices to address this issue. To validate the method, we use a control model of a network of coupled chaotic oscillators under noise and also apply the method to EEG data from subjects with absence seizures (3 Hz spike wave discharges), for which there is clinical indication of enhanced synchrony during seizures. Finally, we apply the method to multichannel ECoG data from subjects with intracranial generalized seizures. One interesting finding is that, at a systems level, whether epileptic seizures are accompanied by en-

hanced or reduced synchrony is highly case dependent. While there are cases where the overall degree of synchronization tends to increase during the seizure, there are relatively more cases where synchronization decreases during the seizure, a finding consistent with the result in Ref. [3]. This means that future monitoring and possibly therapeutic techniques for epileptic seizures based on synchronization are likely to be highly individualized.

It is proper at this point to clarify the relation between our approach and several previous matrix-based methods to detect global changes in synchronization [11–14]. An early proposal [11] examines the Shannon information entropy of the spectrum of eigenvalues of the cross-correlation matrix. The method in [12] is based on a matrix whose elements are statistics of various phase differences, which is capable of detecting clusters of phase synchronization. The idea of a phase-coherence matrix was recently proposed and applied to EEG recordings from epilepsy patients [13]. A more recent method [14] centers around computing the largest and smallest eigenvalues of the zero-lag correlation matrix, and the method has been demonstrated to be able to detect, for instance, statistically significant changes of the correlation structure of focal onset seizures. In all these methods, the matrix elements are quantities derived from some types of correlation measures that typically assume values between zero and one. We use the average phase-synchronization time because it is significantly more sensitive to changes in the degree of synchronization than correlations. In particular, as the system becomes more phase coherent, the time is capable of exhibiting extremely fast increase, typically over many orders of magnitude for noisy dynamical systems [9].

We first develop a criterion for properly choosing the diagonal elements of the synchronization-time matrix $\mathbf{\Gamma}$. Assume that multichannel data are stochastic as they are usually corrupted by both internal (e.g., dynamic) and external (e.g., measurement) noise. The average phase-synchronization time between any pair of channels can thus be regarded as a random variable, and $\mathbf{\Gamma}$ is effectively a random matrix. To gain insight we generate an ensemble of random matrices, with nondiagonal elements drawn from a Gaussian distribution. The diagonal element a is varied systematically. The condition of the matrix can be quantified by the condition number C of the matrix, which is the ratio between the largest and the smallest eigenvalues. For a fixed value of a, we can calculate the average value $\langle C\rangle$ and the standard deviation σ_C. A large standard deviation relative to $\langle C\rangle$ is undesirable, as the underlying matrix would be highly sensitive to fluctuations of its elements. We are thus led to examine, analytically, the ratio $R_C \equiv \sigma_C/\langle C\rangle$ as a function of a.

For an $N \times N$ random matrix, let $\lambda_1 \le \lambda_2 \le \ldots \le \lambda_N$ be the eigenvalue spectrum. A general result from random-matrix theory [15] is that the distribution of λ_i's for $i = 1, \ldots, N-1$ falls on a semicircle while λ_N is outside the semicircle. Without loss of generality we consider the situation where all diagonal elements are zero (a nonzero value $a \neq 0$ merely shifts all eigenvalues by the same amount). In this case, we have $0 = \sum_{i=1}^{N} \lambda_i = \sum_{i=1}^{N-1} \lambda_i + \lambda_N \approx -(N-1)\Delta + \lambda_N$, where $-\Delta$ is the center of the semicircle. We obtain $\Delta = \lambda_N/(N-1)$. Since $\bar{\lambda}_{N-1} - \bar{\lambda}_1 = 4\sigma_\Gamma\sqrt{N}$, where $\bar{\cdot}$ denotes ensemble average, and $\sigma_\Gamma \equiv \sqrt{\langle\tau_{ij}^2\rangle - \langle\tau_{ij}\rangle^2}$ for $i \neq j$, and $\lambda_N = \max_i(\sum_{j=1}^{N}\tau_{ij}) \approx (N-1)\langle\tau_{ij}\rangle$, we have $\Delta = \langle\tau_{ij}\rangle$. From the semicircle distribution, we then have $\bar{\lambda}_1 = -2\sigma_\Gamma\sqrt{N} - \langle\tau_{ij}\rangle$. For $a \neq 0$, the condition number is given by $C = (a+\lambda_N)/(a+\lambda_1)$ and, hence, we have $\langle C\rangle = [(a+\bar{\lambda}_N)/(a+\bar{\lambda}_1)] \times [1 + \sigma_{\lambda_1}^2/(a+\bar{\lambda}_1)^2] \approx (a+\bar{\lambda}_N)/(a+\bar{\lambda}_1)$, for $|a+\bar{\lambda}_1| \gg \sigma_{\lambda_1}$. After some algebra, we obtain, to first order in $\sigma_{\lambda_1}/|a+\bar{\lambda}_1|$, $\sigma_C^2 = \langle C^2\rangle - \langle C\rangle^2 \approx \langle C\rangle^2\sigma_{\lambda_1}^2/(a+\bar{\lambda}_1)^2$. This yields $R_C \approx \sigma_{\lambda_1}/|a+\bar{\lambda}_1|$. We see that R_C diverges for $a = -\bar{\lambda}_1 = 2\sigma_\Gamma\sqrt{N} + \langle\tau_{ij}\rangle$. A representative example of numerically obtained behavior of $R_C(a)$ is shown in Fig. 1 (open circles), where $N = 100$, $\tau_{ij} \sim N(1, 0.2)$ (rather arbitrarily), and 10^6 matrix realizations are used. The solid curve is from the theoretical prediction. We observe a very good agreement.

We thus see that, when choosing a proper value a for the diagomal elements, the singular region about $a = 2\sigma_\Gamma\sqrt{N} + \langle\tau_{ij}\rangle$ should be avoided. For instance, if $\sigma_\Gamma\sqrt{N} \ll \langle\tau_{ij}\rangle$, one can choose a several times larger than $\langle\tau_{ij}\rangle$, the average value of all off-diagonal elements. In this way the variance of the condition of the matrix is small so that the effect of fluctuations of the matrix elements due to noise can be suppressed but, the variance is still appreciable so that the matrix may capture characteristic changes in the underlying system.

We have validated our synchronization-time matrix approach using a ''controlled'' model system whose phase-synchronization dynamics is known. The model is a network of coupled chaotic Rössler oscillators [10,16,17] with time varying coupling parameter in the presence of noise. Extensive numerical computations reveal that, for relatively low levels of noise, the individual matrix elements,

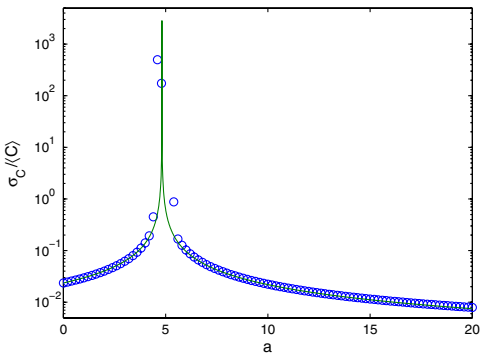

FIG. 1 (color online). For an ensemble of 10^6, 100×100 random matrices, the ratio $R_C \equiv \sigma_C/\langle C\rangle$ versus a. Open circles are results from direct numerical computation, and the solid curve is from our theoretical prediction $R_C \approx \sigma_{\lambda_1}/|a+\bar{\lambda}_1|$.

the eigenvalues, and the determinant all are sensitive to phase synchronization, although the determinant exhibits among those measures the highest degree of sensitivity. For larger noise amplitude, the determinant still stands out as a suitable measure capable of quantitatively assessing the system's evolution toward phase synchronization.

We can now apply the synchronization-time matrix to epileptic EEG and ECoG time series. The data are collected from patients with pharmacoresistant seizures who underwent evaluation for epilepsy surgery at the University of Kansas Comprehensive Epilepsy Center. The EEG data are collected using the standard methodology (10–20 system) [2], and the ECoG data are recorded using multiple contact depth electrodes (Ad-Tech). The correctness of the placement is assessed with MRI. The signal is sampled at a rate of 240 Hz, amplified to a dynamic range of $\pm 300\ \mu$V, and digitized to 10 bits precision with 0.59 μV/bit using commercially available devices (Nicolet, Madison WI). The recordings are deemed of good technical quality and suitable for analysis. To minimize noise, we use differential signals from pairs of channels with no common reference (i.e., the difference between channels i and j, where i and j are used only once). The data analyzed in this Letter consists of multichannel brain signal recordings from six subjects. In each of the first four subjects, we analyzed 5 ten-minute segments of ECoG, each containing a seizure (5 seizures per subject) and recorded using multiple intracranial (depth) needle electrodes in the amygdala-hypocampal regions and frontal regions. All seizures for these subjects were of mesial temporal origin. In the fifth subject, we analyzed 3 ten-minute scalp EEG recordings, each containing several absence seizure events separated by background EEG. For the sixth subject, intracranial ECoG was obtained in a 10 min segment containing a secondarily generalized seizure. Twenty-one contacts in the case of scalp data and between 48 and 52 contacts in the cases of intracranial data were recorded and used in the analysis. Both raw data and low-pass filtered data (in the frequency band [0,60] Hz) were tested, but the results from the synchronization-time matrices are essentially the same (the representative results shown below were from unfiltered data). The Hilbert transform is used for phase calculation. A moving window is chosen to contain between 2^{10} and 2^{15} data points (corresponding to 4.3 and 136.5 s, respectively). The time interval between two adjacent moving windows is a half second.

Absence seizures [18] are regarded as one of the best examples of enhanced neuronal synchrony. They can thus be used as more realistic, clinical controls to validate our method. Figure 2 shows a representative example, where (a) is the raw EEG differential signal from two channels (Nos. 7 and 8 [2]) showing 3 absence seizures identified by 3 pairs of vertical lines, (b) and (c) are the time evolutions of the determinant of the phase-synchronization time matrix on a linear and semilogarithmic scale, respectively. We see that the determinant (Det) shows large increases with each seizure, indicating a high degree of sensitivity to increases in synchrony. The variation of the degree of synchrony can be better seen from the time evolution of ln(Det), as shown in Fig. 3(c). These results demonstrate that the matrix is capable of *detecting and characterizing* changes in synchronization during seizures.

Partial seizures with secondary generalization usually start in a brain region and eventually spread to the entire brain. Figure 3 shows one representative example, where (a) is a differential ECoG derivation with seizure onset around $t = 300$ s, (b) and (c) are the evolutions of Det and ln(Det) over a 10 min period. A large increase in synchrony is seen in this seizure, mainly when it becomes secondarily generalized. Figure 3(c) also shows an interesting phenomenon: the degree of synchronization decreases dramatically before the termination of the seizure, fall markedly below baseline and recovers slowly to preseizure levels (not shown). The changes in the degree and direction of the synchronization measure in this seizure were not uniformly found in other seizures from different subjects. There are cases where we would observe a continuous tendency for ln(Det) to decrease toward the ictal phase, indicating a global decrease of the degree of phase synchronization [the minimal value of ln(Det) is usually achieved in the ictal phase]. While an overall decrease of the synchronization level during seizure appears to be common, there are also cases where the opposite occurs. These *mixed* results indicate that, at a systems level, whether epileptic seizures are associated with enhanced or reduced synchrony can be highly case dependent.

In summary, we have developed a method to characterize the degree of phase synchronization from multichannel data and applied it to EEG and ECoG data from subjects

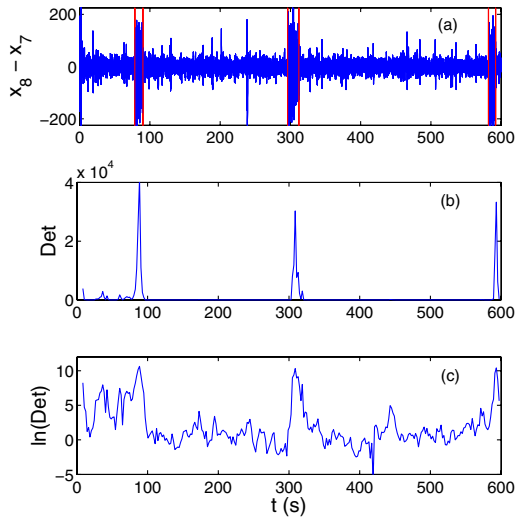

FIG. 2 (color online). For absence seizure EEG data, (a) a differential data segment containing three occurrences of seizure, (b),(c) time evolutions of Det (determinant of the phase-synchronization time matrix), and ln(Det), respectively. The size of the moving time window is approximately 8.5 s and the montage consists of 9 pairs of differential channels (2–3, 4–5, 1–11, 12–13, 7–8, 9–10, 6–14, 15–16, 17–19).

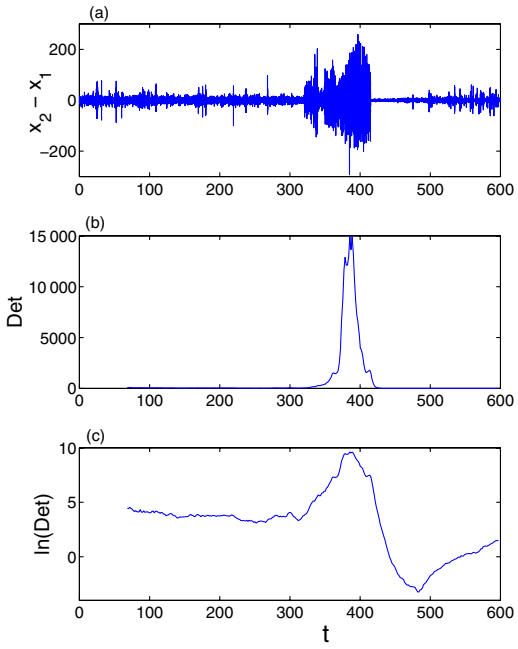

FIG. 3 (color online). (a) ECoG signal from a secondarily generalized seizure event. (b),(c) Time evolutions of Det and ln(Det), respectively.

with epileptic seizures. Comparing with previous methods [11–14], our synchronization-time matrix is more sensitive to characteristic changes of the system. For absence seizures where there is clinical evidence of enhanced synchrony, our method yields a result that is not only consistent with the evidence, but also able to capture the evolution of the degree of synchrony in a *quantitative* manner. For intracranial secondarily generalized seizures, our finding that synchrony can be either reduced or enhanced emphasizes the necessity of probing and analyzing this brain disease from a more individualized aspect. Our synchronization-time matrix-based method is general and applicable to multichannel, noisy, and nonstationary time series from other fields.

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[17] It has been known that in complex networks synchronization analysis can lead to several pitfalls, especially if the data are coming from different sources [F. C. Meinecke, A. Ziehe, J. Kurths, and K.-R. Müller, Phys. Rev. Lett. **94**, 084102 (2005)]. It can also happen that "indirect" connections could cause some synchronization [B. Schelter, M. Winterhalder, R. Dahlhaus, J. Kurths, and J. Timmer, Phys. Rev. Lett. **96**, 208103 (2006)]. For EEG or ECoG data, while the tissue that generates focal seizures has both direct and indirect connections with other brain regions, which may be enhanced or weakened temporarily around the time of the seizure, it is difficult to obtain *quantitative* information about these connections.
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