A phase-synchronization and random-matrix based approach to multichannel time-series analysis with application to epilepsy

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We present a general method to analyze multichannel time series that are becoming increasingly common in many areas of science and engineering. Of particular interest is the degree of synchrony among various channels, motivated by the recognition that characterization of synchrony in a system consisting of many interacting components can provide insights into its fundamental dynamics. Often such a system is complex, high-dimensional, nonlinear, nonstationary, and noisy, rendering unlikely complete synchronization in which the dynamical variables from individual components approach each other asymptotically. Nonetheless, a weaker type of synchrony that lasts for a finite amount of time, namely, phase synchronization, can be expected. Our idea is to calculate the average phase-synchronization times from all available pairs of channels and then to construct a matrix. Due to nonlinearity and stochasticity, the matrix is effectively random. Moreover, since the diagonal elements of the matrix can be arbitrarily large, the matrix can be singular. To overcome this difficulty, we develop a random-matrix based criterion for proper choosing of the diagonal matrix elements. Monitoring of the eigenvalues and the determinant provides a powerful way to assess changes in synchrony. The method is tested using a prototype nonstationary noisy dynamical system, electroencephalogram (scalp) data from absence seizures for which enhanced cortico-thalamic synchrony is presumed, and electrocorticogram (intracranial) data from subjects having partial seizures with secondary generalization for which enhanced local synchrony is similarly presumed.
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An increasingly common practice in many fields of science and engineering is to record a large amount of data simultaneously from an array of sensors (or channels) and then to analyze the data to probe the dynamics of the underlying system. In realistic situations, the system contains multiple interacting components, is nonlinear, nonstationary, and noisy. Because of these characteristics, traditional methods such as those based on the Fourier power spectrum are often ineffective. To develop methods to analyze multichannel data thus becomes an issue of paramount importance and extremely broad interest. Here we present a method based on the ideas of stochastic phase synchronization and random matrices to extract information about the dynamical evolution of the underlying system. Generally, for a real system in a noisy environment, complete synchronization among the multiple signal generators from different channels is unlikely. Instead, in typical situations where the generators oscillate in time, a weaker type of synchrony that lasts for a finite amount of time, namely temporal phase synchronization, can occur. Our idea is then to calculate the average phase-synchronization times (APSTs) among all available pairs of channels and then to construct a matrix. Monitoring of the eigenvalues and the determinant of the synchronization-time matrix provides an effective way to assess the degree of spatiotemporal synchrony. Due to the nonlinear and stochastic nature of the underlying system and environment, the synchronization-time matrices are effectively random matrices. For example, consider a set of multi-channel electrocorticogram (ECoG) recordings. During any time window of observation, the APSTs obtained from all distinct pair of channels are random. Thus, for a given time window, the matrix elements are uncorrelated or weakly correlated and can be effectively regarded as random with respect to each other. We find that the spectral properties of the synchronization-time matrix exhibit a great deal of similarity to these of random matrices whose elements are drawn, for instance, from a Gaussian orthogonal ensemble. Moreover, any matrix element as a function of time also appears to be highly random. What we face is thus random evolution of a random matrix. Looking for characteristic changes in the various properties of the random matrix in time may therefore provide an avenue to probing the change in the synchrony of the underlying system with high sensitivity. A technical issue is the choice of the diagonal elements, which are in principle, infinite and, for a moving-window application, they are the size of the window. Consequently, a difficulty is that the window size is often much larger than the APST, rendering singular the synchronization-time matrix and diminishing the matrix's ability to discern system changes. We shall demonstrate that the spectral theory of random matrices can be used to establish a criterion for choosing the diagonal elements. Using coupled chaotic oscillators with time-varying coupling, we demonstrate the

power of our method to detect characteristic changes in the system. We then apply our method to multichannel ECoG recordings from epileptic subjects to quantify the evolution of synchrony before, during, and after seizures, with the finding that epileptic seizures can be associated with either enhanced or reduced neuronal synchrony.

I. INTRODUCTION

Multichannel data are becoming quite common in many fields of science and engineering. Electroencephalogram (EEG) and electrocorticogram (ECoG) signals in medicine are one example. Recent years have witnessed an increasing use of large-scale sensor networks in various civil and defense applications, which typically generate a large amount of multivariate data. Examples include monitoring and collection of information on objects ranging from plankton colonies,[1] endangered species,[2] soil and air contaminants[3] to traffic flow,[4] biomedical subjects,[5] building and bridges.[6] Analysis of data from sensor networks also finds critical applications in homeland defense, such as detection of chemical or biological agents and pattern recognition.[7]

In a typical application, the underlying system generating the observed data is nonlinear, nonstationary and noisy, and one goal of data analysis is to detect, characterize, and possibly predict any events that can significantly affect the normal function of the system. For example, in a sensor network deployed to collect information about certain plankton colonies,[1] it is important to be able to detect, as early as possible, signatures of any unusual behaviors in the plankton dynamics so that early warnings can be issued to mitigate or even to avoid potentially environmentally catastrophic events. In a large-scale sensor network used to monitor individuals in military or homeland-defense applications, to be able to detect abnormal behaviors such as highly synchronous and organized movements at the earliest possible moment is of key interest. In clinical practices, detecting and issuing early warnings for seizures based on EEG or ECoG signals[8–10] are one of the grand goals in medical science. All these call for an effective method to analyze nonlinear and nonstationary multichannel data collected from a system in a noisy environment.

In this paper, we develop a general method to monitor and characterize synchronous behavior from multichannel data. To be able to single out any unusual change in synchronization with confidence is important for many practical applications, as mentioned above. Such a method is also of fundamental interest at the level of basic science. For instance, in epilepsy it is believed that neuronal hypersynchrony is associated with the generation of seizures.[11] 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, the experimental study of synchronization between CA1 pyramidal neurons revealed that seizure-like events are associated with desynchronization.[12] A reliable method that can effectively monitor the change in the degree of synchronization can be useful for gaining insight into a possible resolution of the controversy.

In Sec. II, we outline the main idea of our method which is based on phase synchronization. We shall justify why the average phase-synchronization times (APSTs) between various pairs of channels can be useful for characterizing the overall degree of synchrony in the underlying dynamical system. All values of the APST obtained from a window at a given time constitute a matrix, which is singular because the diagonal elements are not well defined. In Sec. III, we present a theory based on the spectra of random matrices to guide proper choosing of the diagonal elements of the APST matrix. To validate the method, we first construct a model of a network of coupled chaotic oscillators under noise for which the phase-synchronization dynamics is known, and test our method in this controlled setting (Sec. IV). We then apply our method to EEG data from subjects with absence seizures (3 Hz spike wave discharges), for which synchrony is presumed (Sec. V). Results from these tests indicate that our method is effective for monitoring and quantifying synchronization from multichannel data. As a step toward resolving the fundamental issue of whether epileptic seizures are associated with hypersynchrony or desynchronization, we apply the method to multichannel ECoG data from subjects with intracranial generalized seizures. Our finding is that, at systems level, whether epileptic seizures are accompanied by enhanced or reduced synchrony is highly case-dependent. In particular, 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. 12. This means that, future monitoring and possibly therapeutic technique for epileptic seizures based on synchronization are likely to be highly individualized. (A brief account of the part of these results was published in Ref. 21). Several technical issues such as the validity of the random-matrix hypothesis and performance comparison of our method with existing methods are addressed in Sec. VI. Finally, brief conclusions are presented in Sec. VII.

II. MATRIX OF AVERAGE PHASE-SYNCHRONIZATION TIME

The nonlinear dynamical system from which multichannel data are recorded can contain many interacting components. The recordings are usually from signals to which quite different combinations of the intrinsic dynamical variables of the underlying system contributed. For realistic systems in the presence of noise, it is often useful to explore weaker forms of synchronization, such as phase synchronization.[13–15,17] For any multichannel time series, a reasonable assumption is that they are oscillatory.[18] For an oscillatory signal, 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 $|\phi_i(t) - \phi_j(t)| < C$,[13] where C is a constant of the order of 2π. Due to noise, a phase-synchronized 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 APST,[19,20] which can be calculated

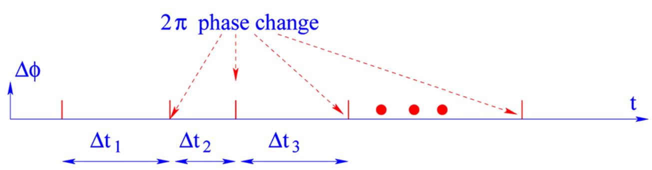

FIG. 1. (Color online) Schematic illustration of the definition of APST, where $\Delta\phi(t)$ is the phase difference between signals from an arbitrary pair of channels. Each Δt_n $(n=1,\ldots)$ represents a time interval, where $\Delta\phi$ remains bounded within 2π. The APST is $\tau \equiv \lim_{n\to\infty}(1/n)\sum_{i=1}^{n}\Delta t_n$.

by using a large time interval of observation during which a number of 2π changes in the phase difference occur, as shown in Fig. 1. In a moving-window analysis of nonstationary data, the time interval is the size of the window. As the system evolves, i.e., as the "window moves," the APST can change. Let $\tau_{ij}(t)$ be this 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 all available data, we can define an $N \times N$ matrix (denoted by $\mathbf{\Gamma}$) of APSTs for all pairs of channels. The matrix, by construction, is symmetric, but the choice of the diagonal elements becomes a critical issue. Any diagonal matrix element characterizes the synchronization between a channel and itself, so the synchronization time is infinite. In a moving window of finite length, the time is simply the full length of the window. A difficulty with this simple choice is that the window size is often much larger than the APST. As a result, the matrix can become quite singular, hampering further analysis and the matrix's ability to discern system changes.

Our main idea is that, 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 the diagonal 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. We have developed a theoretical approach to resolving this issue based on random matrices (see Sec. III).

It is useful to clarify the relation between our approach and several previous matrix-based methods to detect global changes in synchronization.[22–26] The early proposal by Wackermann[22] was to examine the Shannon information entropy associated with the spectrum of eigenvalues of the cross-correlation matrix. The method by Allefeld and Kurths[23] was based on a matrix whose elements are statistics of various phase differences, which is capable of detecting clusters of phase-synchronization. Bialonski and Lehnertz proposed to detect phase-synchronization clusters from multivariate time series by using the phase-coherence matrix,[24] a matrix whose entries are the values of the mean phase coherence between pairs of time series. They applied the method to EEG recordings from epilepsy patients. The recent method by Schindler *et al.*[25] centered about computing the largest and smallest eigenvalues of the zero-lag (or equal time) correlation matrix, and the method was demonstrated to be able to detect, for instance, statistically significant changes in the correlation structure of focal onset seizures. There was also a method by Müller *et al.* on estimating the strength of genuine and random correlations in non-stationary multivariate time series.[27] In all these methods, the matrix elements are quantities derived from some types of correlation measures that typically assume values between zero and one. Our idea of using the APST is motivated by the fact that it can in general be significantly more sensitive to changes in the degree of synchronization than correlations. In particular, as the system becomes more phase coherent, the APST can increase significantly, typically over many orders of magnitude for noisy dynamical systems.[19] As we will show in this paper, the synchronization-time matrix, when properly constructed, can indeed be extremely responsive to changes in the degree of synchronization of the underlying noisy system.

III. USE OF RANDOM-MATRIX THEORY TO CHOOSE DIAGONAL ELEMENTS OF SYNCHRONIZATION-TIME MATRIX

We have seen that to properly choose the diagonal elements of the synchronization-time matrix $\mathbf{\Gamma}$ is the key to our method. Here we present a sensitivity analysis based on random-matrix theory to find an optimal set of values for the diagonal elements while maximizing sensitivity to changes in synchrony.

Multichannel data from a real system are stochastic, as they are corrupted by both internal (e.g., dynamic) and external (e.g., measurement) noises. The APST 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 non-diagonal elements drawn from a Gaussian distribution. The diagonal element a is varied systematically. The "condition" of the matrix can be quantified by the conditional number C of the matrix, which is the ratio between the largest and the smallest eigenvalues. For a fixed value of a, we can use the ensemble of random matrices to calculate the average value $\langle C\rangle$ and its variance (or standard deviation σ_C). A large variance relative to $\langle C\rangle$ is undesirable, as the underlying matrix would be highly sensitive to fluctuations of its elements. For nonstationary and noisy data, such a high sensitivity means that various characteristics of the matrix can exhibit large fluctuations with respect to the moving window. We are thus led to examine, analytically, the ratio $R_C \equiv \sigma_C/\langle C\rangle$ as a function of a.

We shall use the random-matrix theory to analyze the statistical behavior of the ratio R_C, for the following two reasons: (1) the matrix elements in our case (average phase-synchronization times) are random from window to window and (2) the matrix is symmetric as the APST must be the same between two channels, regardless of the direction. For an $N \times N$ symmetric random matrix, let $\lambda_1 \le \lambda_2 \le \ldots \le \lambda_N$ be the eigenvalue spectrum. A general result from random-matrix theory[28] is that the distribution of λ_i's for $i = 1,\ldots, N-1$ falls on a semicircle while λ_N is outside in the limit $N \to \infty$, as shown schematically in Fig. 2. Note that, the semicircle law holds generally for symmetrical random matrices, which include those from Gaussian orthogonal and unitary ensembles.[29] Consider first the situation where all diagonal elements are zero (a non-zero value $a \neq 0$ merely shifts all eigenvalues by the same amount). We have

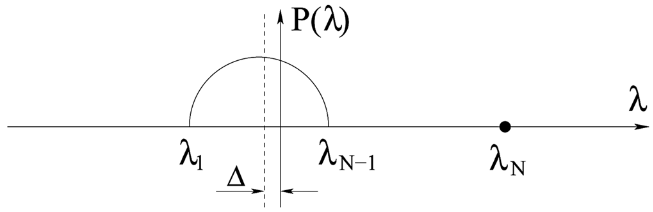

FIG. 2. Wigner's semicircle distribution for eigenvalues of random matrices of zero diagonal elements.

$$0 = \sum_{i=1}^{N} \lambda_i = \sum_{i=1}^{N-1} \lambda_i + \lambda_N \approx -(N-1)\Delta + \lambda_N,$$

where $-\Delta$ is the center of the semicircle. We obtain

$$\Delta = \lambda_N/(N-1). \tag{1}$$

Using bar to denote the ensemble average, we have

$$\bar{\lambda}_{N-1} - \bar{\lambda}_1 = 4\sigma_\Gamma\sqrt{N},$$

where the quantity σ_Γ is given by

$$\sigma_\Gamma \equiv \sqrt{\langle \tau_{ij}^2 \rangle - \langle \tau_{ij} \rangle^2}$$

for $i \neq j$. Using the approximation

$$\lambda_N = \max_i \left(\sum_{j=1}^{N} \tau_{ij} \right) \approx (N-1)\langle \tau_{ij} \rangle,$$

we obtain

$$\Delta = \langle \tau_{ij} \rangle. \tag{2}$$

From the semicircle distribution, we then have

$$\bar{\lambda}_1 = -2\sigma_\Gamma\sqrt{N} - \langle \tau_{ij} \rangle. \tag{3}$$

Now consider the general case of $a \neq 0$. The condition number is given by

$$\begin{aligned} C &= \frac{a+\lambda_N}{a+\lambda_1} = \frac{a+\bar{\lambda}_N + \Delta\lambda_N}{a+\bar{\lambda}_1+\Delta\lambda_1} \\ &\approx \frac{a+\bar{\lambda}_N}{a+\bar{\lambda}_1}\left[1 - \frac{\Delta\lambda_1}{a+\bar{\lambda}_1} + \frac{(\Delta\lambda_1)^2}{(a+\bar{\lambda}_1)^2}\right]. \end{aligned} \tag{4}$$

We thus have

$$\langle C \rangle \approx \frac{a+\bar{\lambda}_N}{a+\bar{\lambda}_1}\left[1 + \frac{\sigma_{\lambda_1}^2}{(a+\bar{\lambda}_1)^2}\right] \approx \frac{a+\bar{\lambda}_N}{a+\bar{\lambda}_1} \tag{5}$$

and

$$(\langle C \rangle)^2 \approx \left(\frac{a+\bar{\lambda}_N}{a+\bar{\lambda}_1}\right)^2\left[1 + 2\frac{\sigma_{\lambda_1}^2}{(a+\bar{\lambda}_1)^2}\right], \tag{6}$$

for $|a+\bar{\lambda}_1| \gg \sigma_{\lambda_1}$. The second moment of C can be calculated, as follows:

$$C^2 = \frac{(a+\lambda_N)^2}{(a+\bar{\lambda}_1+\Delta\lambda_1)^2} = \frac{(a+\bar{\lambda}_N)^2}{(a+\bar{\lambda}_1)^2}\left[1 - \frac{2\Delta\lambda_1}{a+\bar{\lambda}_1} + \frac{3(\Delta\lambda_1)^2}{(a+\bar{\lambda}_1)^2}\right]$$

This leads to

$$\langle C^2 \rangle = \frac{(a+\bar{\lambda}_N)^2}{(a+\bar{\lambda}_1)^2}\left[1 + \frac{3\sigma_{\lambda_1}^2}{(a+\bar{\lambda}_1)^2}\right].$$

To first order in $\sigma_{\lambda_1}/|a+\bar{\lambda}_1|$, we obtain

$$\sigma_C^2 = \langle C^2 \rangle - \langle C \rangle^2 \approx \frac{(a+\bar{\lambda}_N)^2}{(a+\bar{\lambda}_1)^2}\frac{\sigma_{\lambda_1}^2}{(a+\bar{\lambda}_1)^2} \approx \langle C \rangle^2 \frac{\sigma_{\lambda_1}^2}{(a+\bar{\lambda}_1)^2}. \tag{7}$$

This yields

$$R_C \approx \frac{\sigma_{\lambda_1}}{a+\bar{\lambda}_1}. \tag{8}$$

We see that R_C diverges for

$$a = -\bar{\lambda}_1 = 2\sigma_\Gamma\sqrt{N} + \langle \tau_{ij} \rangle, \quad \text{for} \quad i \neq j. \tag{9}$$

A representative example of numerically obtained behavior of $R_C(a)$ is shown in Fig. 3 (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 Eq. (8), we observe a very good agreement.

We thus see that, when choosing a proper value a for the diagonal 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 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.

The existence of the singular behavior in R_C in fact makes the criterion to choose the diagonal matrix elements less empirical: the singular region should be avoided. While

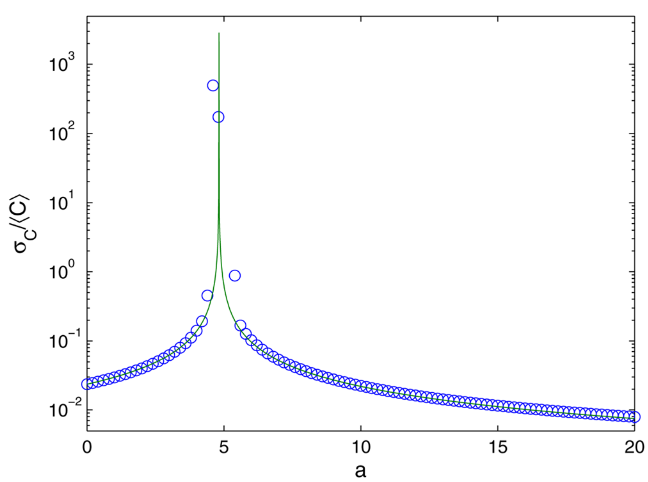

FIG. 3. (Color online) For an ensemble of 10^6, 100×100 random matrices, ratio $R_C \equiv \sigma_C/\langle C \rangle$ versus a. Open circles are results from direct numerical computation, and the solid curve is from theoretical prediction Eq. (8).

there is still quite a bit of freedom (or uncertainty) in choosing the diagonal elements, the criterion leads to values of the elements that are quite reasonable, as will be verified by controlled numerical experiments in Sec. IV.

It is useful to state one fact that will be useful to understand numerical results, that is, for a random matrix, the value of the determinant can be significantly enhanced as the mean value of the matrix elements is increased. To be concrete, we consider the following 3×3 symmetric random matrix,

$$\mathbf{A} = \begin{pmatrix} \alpha\bar{a} & a_1 & a_2 \\ a_1 & \alpha\bar{a} & a_3 \\ a_2 & a_3 & \alpha\bar{a} \end{pmatrix},$$

where $a_{1,2,3} > 0$ are random numbers, $\bar{a}$ is their mean, and $\alpha \gg 1$ is the enhancement factor chosen according to our criterion for diagonal elements. The determinant of $\mathbf{A}$ can be written as

$$\det(\mathbf{A}) = \alpha\bar{a}[(\alpha^2 - 3)(\bar{a})^2 - 3\sigma^2] + 2a_1a_2a_3, \tag{10}$$

where $\sigma^2 = (1/3)\sum_{i=1}^{3}(a_i - \bar{a})^2$ is the variance of the matrix element. In general, σ and $\bar{a}$ are of the same order of magnitude. Thus for $\alpha \gg 1$ we have $\det(\mathbf{A}) \sim (\bar{a})^3$. Consider a similar matrix with elements $b_{1,2,3}$ and $\bar{b} < \bar{a}$, We have

$$\frac{\det(\mathbf{A})}{\det(\mathbf{B})} \sim \left(\frac{\bar{a}}{\bar{b}}\right)^3 \gg 1.$$

For $N \times N$ matrices where $N > 3$, the enhancement can be quite significant even when there is only a small increase in the mean value of the matrix elements. Indeed, as we shall see below, there can be order-of-magnitude changes in the determinant for various examples. Thus, our approach to choosing the diagonal elements can be regarded as a strategy to significantly *magnify* the overall degree of synchronization among multiple-channel signals, which makes our method at once sensitive and also robust to variation in synchrony.

IV. CONTROL STUDY: NETWORK OF COUPLED CHAOTIC OSCILLATORS

We consider a prototypical model of nonstationary dynamical systems,[20] a network of coupled chaotic Rössler oscillators, to validate the method of APST matrix. The network is described by

$$\begin{aligned} \frac{dx_i}{dt} &= -\omega_i y_i - z_i + K(t)(x_{i+1} + x_{i-1} - 2x_i), \\ \frac{dy_i}{dt} &= \omega_i x_i + 0.165 y_i + \varepsilon\xi_i(t), \\ \frac{dz_i}{dt} &= 0.2 + (x_i - 100)z_i, \end{aligned} \tag{11}$$

for $i = 1,\ldots, N$ (with periodic boundary conditions), where ω_i is the frequency of the ith oscillator drawn uniformly from the interval $[\omega_0 - \Delta\omega/2, \omega_0 + \Delta\omega/2]$. The nonstationary nature of the system is manifested by the time-dependent coupling parameter $K(t)$. The terms $\varepsilon\xi_i(t)$ represent noise, where ε is the noise amplitude and $\xi_i(t)$ are independent Gaussian random processes of zero mean and unit variance. Due to the frequency spread among the oscillators, phase synchronization occurs for $K(t) > K_c \approx \Delta\omega$. Given a long experimental time interval T, the coupling parameter $K(t)$ is varied in the range $[0, K_m]$, where $K_m > K_c$, according to the following piecewise linear rule: $K(t) = 2K_m t/T$ for $0 \le t < T/2$ and $K(t) = 2K_m(1 - t/T)$ for $T/2 \le t < T$, as shown in Fig. 4(a). For the chaotic Rössler attractor from each oscillator, the phase variable ϕ_i can be conveniently defined as $\phi_i(t) = \tan^{-1}[y_i(t)/x_i(t)]$. In simulations we choose $\omega_0 = 1.0$ and $\Delta\omega = 0.1$, and set $T = 10^5$ (corresponding to about 17 000 cycles of oscillations). The size of the moving window is chosen to be $\Delta T = 500$, which contains about 85 cycles of oscillation. In a given window, all off-diagonal matrix elements are normalized by their maximal value.

In the phase-synchronized regime, the value of τ_{ij} is the moving-window size ΔT, so all matrix elements assume the same value, causing the matrix to be singular. To overcome this difficulty, numerically we allow the elements to fluctuate randomly in the interval $[\Delta T, 1.1\Delta T]$ (somewhat arbitrary). In each window, after all off-diagonal elements are obtained, we calculate their average $\langle\tau\rangle$. The diagonal elements are chosen to be $5\langle\tau\rangle$. We then calculate all the eigenvalues of the matrix and its determinant. For relatively low levels of noise (e.g., $\varepsilon = 0.2$), the individual matrix elements, the eigenvalues, and the determinant all are sensitive to phase synchronization. However, we observe that the determinant exhibits among those measures the highest degree of sensitivity, in that its values can change over several orders of magnitude as the system evolves from a nonsynchronous to synchronous state, as shown in Fig. 4. For larger noise amplitude, when the synchronization-tracking ability of any individual matrix element deteriorates or is lost, the determinant still stands out as a suitable measure capable of quantitatively assessing the system's evolution toward phase synchronization and for distinguishing between phase-synchronized and non-synchronized state, as shown in Fig. 5.

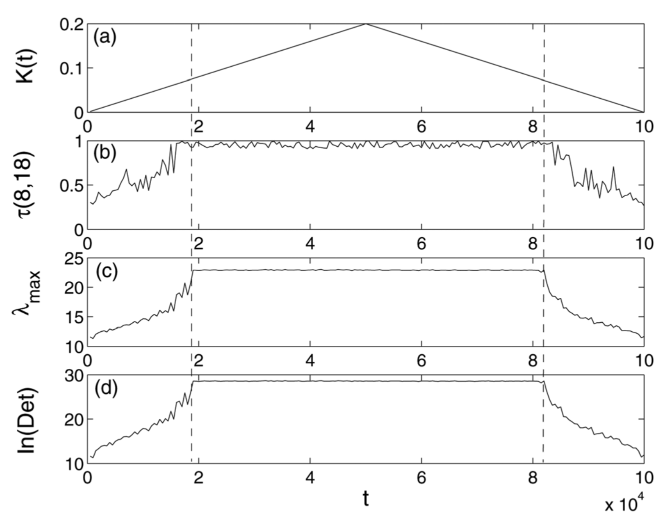

FIG. 4. For a network of 20 locally coupled chaotic Rössler oscillators for noise amplitude $\varepsilon = 0.2$, (a) time-dependent coupling parameter, (b)–(d) evolutions of a typical matrix element, the largest eigenvalue, and lnDet, natural log of the determinant.

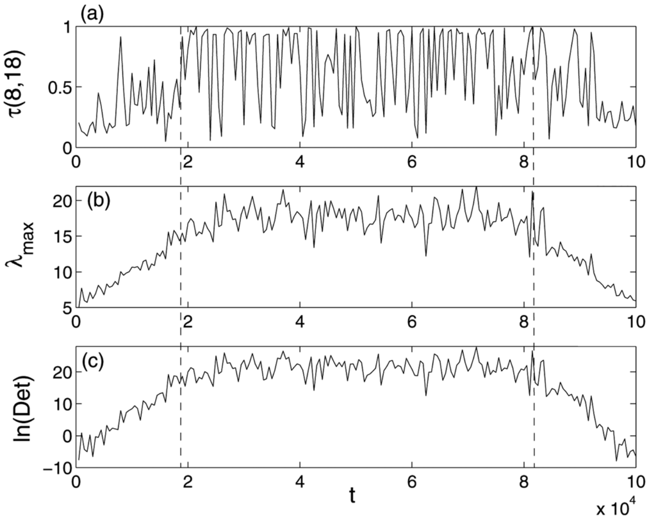

FIG. 5. For a network of 20 locally coupled chaotic Rössler oscillators for noise amplitude $\varepsilon = 1.0$, (a)–(c) evolutions of a typical matrix element, of the largest eigenvalue, and of ln Det, natural log of the determinant.

We emphasize that the network model[30] Eq. (11) is used *solely* for the purpose of control study, i.e., to test if our matrix Γ would capture changes in the degree of phase synchronization, which are known *a priori*. There is no reason other than convenience to choose coupled chaotic oscillators. We also emphasize that the model should in no way be considered as being relevant to brain networks where the dynamics and the topology can be extremely complex.

V. APPLICATION TO EPILEPTIC EEG AND ECOG BRAIN SIGNALS

A. Background

Seizure prediction, early recognition, and blockage of seizures are considered by the membership of the American Epilepsy Society (AES) as the top research priority among fifteen listed (AEP News, Fall 1996). To achieve these goals a good understanding of the mechanism and dynamics of seizures is necessary. A wide belief among clinical epileptologists is that seizures are generally caused by increased neuronal synchrony in the brain. From EEG or ECoG recordings, seizures are typically associated with episodes of high-amplitude rhythmical activities which, naively, may be assumed as being caused by hypersynchrony in the underlying neuronal aggregates. In the classical textbook on neural science,[11] for example, it is stated that "the phases in the development of a partial seizure can be arbitrarily divided into the interictal period, followed by neuronal synchronization, seizure spread, and finally secondary generalization." For generalized seizures, hypersynchronization of cortico-thalamic cells is invoked as the main responsible mechanism. The plausible cause for neuronal hypersynchronization can be attributed to the breakdown of inhibition.[11] That seizures are associated with neuronal hypersynchronization has become the standard dogma in epilepsy.

Interestingly, an experimental study revealed that "seizure-like" events are associated with desynchronization.[12] Netoff and Schiff used the dual-cell patch-clamp technique to study synchronization between CA1 pyramidal neurons in the hippocampal slice. They found that, while brief bursts in 4-amino-pyridine (4AP) are highly synchronous events, during seizure-like events the degree of synchronization is actually decreased compared to those bursts and to baseline interictal periods. In fact, synchronization appears to increase as seizures turn off. Since seizures can be regarded as sustained neuronal activity, the authors speculated that "asynchrony is necessary to maintain a high level of activity in neuronal networks for sustained periods of time" and "synchrony may disrupt such activity," as suggested by the theoretical work of Gutkin *et al*.[31]

To understand the interplay between neuronal synchrony and the occurrence of seizures is fundamental to advancing epilepsy. While the enhanced amplitude and rhythmicity seen during seizures may imply a kind of enhanced synchronous neuronal activities in some local region which contribute to each individual EEG or ECoG channel, whether global synchronization among different regions of the brain can occur is unknown. Our phase-synchronization and random-matrix based method can be used to gain insights into this issue.

B. Results

We apply the synchronization-time matrix to EEG and ECoG seizure time series. The data were collected from patients with pharmaco-resistant seizures, who underwent evaluation for epilepsy surgery at the University of Kansas Comprehensive Epilepsy Center. The EEG data were collected using the standard methodology (10–20 system),[11] and the ECoG data are recorded using multiple contact electrodes (Ad-Tech). The signal was sampled at the rate of 240 Hz, amplified to the 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 were 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 paper consist of multichannel brain signal recordings from six subjects. In each of the first four subjects, we analyze five 10-min segments of ECoG, each containing a seizure (five seizures per subject) and recorded from the amygdala-hypocampal and frontal regions. All seizures for these subjects were of mesial temporal origin. In the fifth subject, we analyze three 10-min scalp EEG recordings, each containing several absence (spike-slow wave complexes) seizures 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. A moving window is chosen to contain between 2^{10} and 2^{15} data points (corresponding to 4.3 s and 136.5 s, respectively). The time interval between two adjacent moving windows is half second.

To calculate the phase for signal $x_j(t)$ from the jth channel, we apply *the fifth-order Butterworth filter* to obtain $y_j(t)$ that corresponds to a proper rotation. We then perform the Hilbert transform,

$$H[y_j(t)] = \frac{1}{\pi} P\left\{ \int_{-\infty}^{\infty} \frac{y_j(t')}{t - t'} dt' \right\}, \tag{12}$$

where "$P\{\cdot\}$" stands for the Cauchy principal value of the integral. From $H[y_j(t)]$, we construct the following complex analytic signal:

$$\psi_j(t) = y_j(t) + iH[y_j(t)] = A_j(t)\exp[i\phi_j(t)], \quad j = 1, \ldots, 9, \tag{13}$$

which defines the phase variables $\phi_j(t)$ $(j = 1,\ldots,9)$.

Absence seizures[32] are regarded as one of the best examples of enhanced neuronal synchrony. They can thus be used as more realistic, clinical control to validate our method. Figure 6 shows a representative example, where (a) is the raw EEG differential signal from two channels (#7 and #8 (Ref. 11)) containing three absence seizures identified by three pairs of vertical lines, (b) and (c) are the time evolutions of the determinant of the APST matrix on a linear and semi-logarithmic scale, respectively. We see that the determinant (Det) shows large increases with each seizure, indicating a high degree of sensitivity to increase in synchrony. The variation of the degree of synchrony can be better seen from the time evolution of ln (Det), as shown in Fig. 6(c). Results using a different scheme of montage are shown in Fig. 7. These results demonstrate that the matrix is capable of *detecting and characterizing* changes in synchronization associated with seizures.

Note that relatively large fluctuations in ln (Det) can occur throughout the time interval, such as the large increase in ln (Det) at the beginning of Fig. 6(c). While the origin of such large fluctuations could not be identified, we do observe that, when seizures occur, the corresponding variations in the determinant tend to be larger than all these fluctuations.

Partial seizures with secondary generalization start in a brain region and eventually spread to the entire brain. Figure 8 shows one representative example, where (a) is a differential ECoG signal 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 8(c) also shows an interesting phenomenon: the degree of synchronization decreases dramatically before the termination of the seizure, falling markedly below interictal values, and recovering slowly to pre-seizure levels.

The changes in the degree and direction of the synchronization measure in the seizure in Fig. 8 were not uniformly found in other seizures from different subjects. Figures 9(a)–(h) show a representative ECoG signal and the time evolution of lnDet for four seizures from three subjects, where the dashed lines indicate the clinical onset of seizures. We observe that, there are cases where ln Det tends to decrease toward the ictal phase, indicating a global decrease in the degree of phase synchronization. The minimal value of ln Det is usually achieved in the ictal state. While an overall decrease of the synchronization level

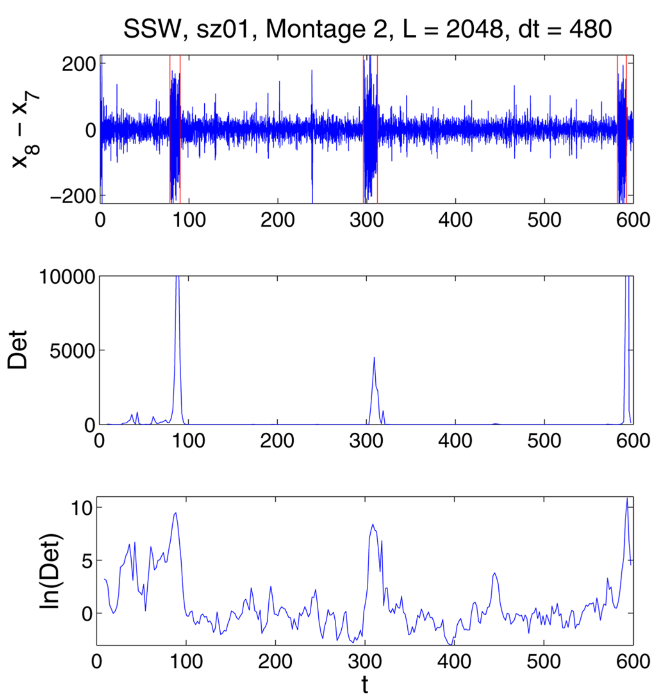

FIG. 6. (Color online) For the absence seizure EEG data (x-axis: time in seconds), (a) a differential data segment containing three seizures, (b) and (c) time evolutions of Det (determinant of the APST matrix) and ln Det (natural log of the determinant), respectively. The size of the moving time window is approximately 8.5 s and the montage consists of 8 pairs of differential channels (2–3, 4–5, 1–11, 12–13, 7–8, 9–10, 6–14, 15–16).

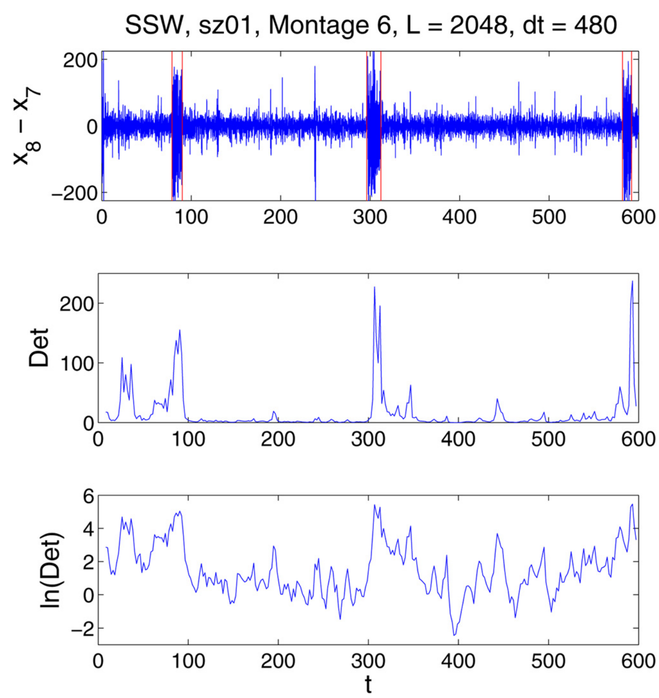

FIG. 7. (Color online) For the absence seizure EEG data (x-axis: time in seconds), (a) a differential data segment containing three spike-slow wave seizures, (b) and (c) time evolutions of Det and of ln Det (natural log of the determinant), respectively. The montage consists of 5 pairs of differential channels (1–6, 2–7, 3–8, 4–9, 5–10).

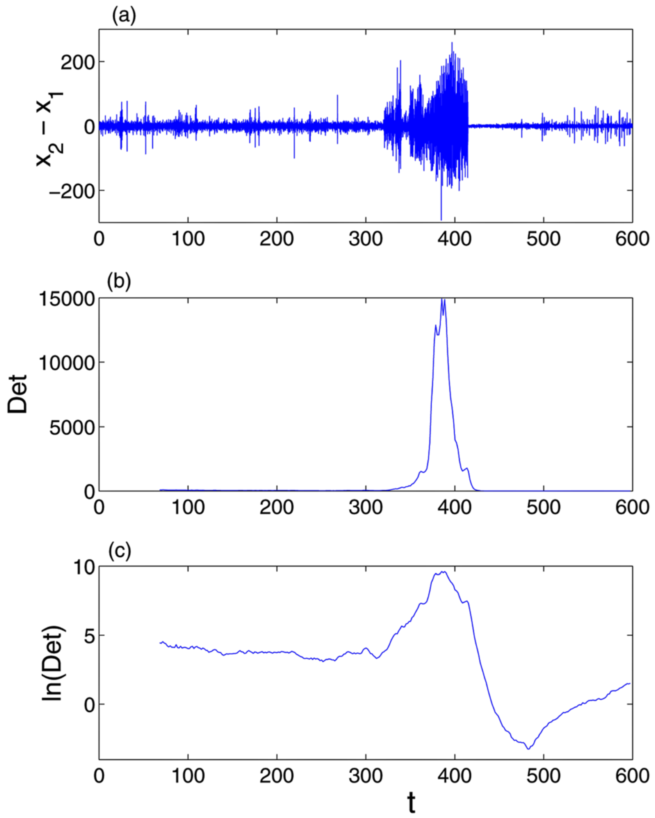

FIG. 8. (Color online) (a) ECoG signal from a secondarily generalized seizure event (x-axis: time in seconds). (b) and (c) Time evolutions of Det and ln Det (natural log of the determinant), respectively.

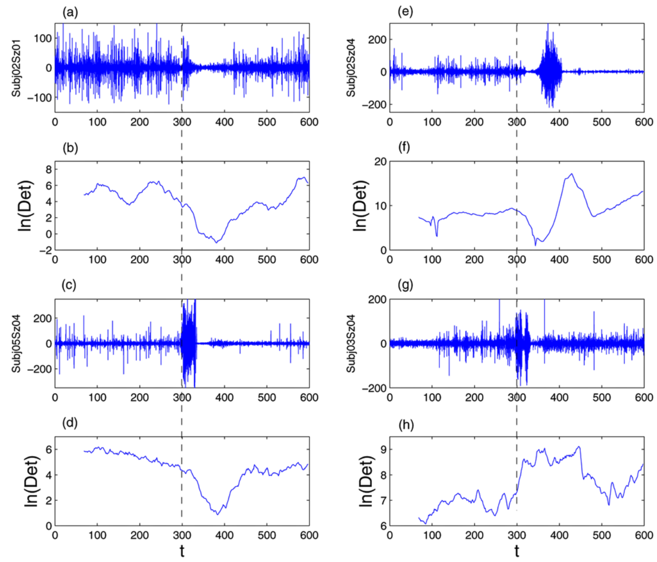

FIG. 9. (Color online) Results of four secondarily generalized seizure events from three subjects. Each pair of panels corresponds to one event. For example, (a) is the ECoG signal containing one seizure from the first subject and (b) is the corresponding time evolution of ln Det (natural log of the determinant). The pairs (c,d), (e,f), and (g,h) have the same meaning.

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.

VI. ISSUES

A. Random-matrix characteristics

In developing our criterion for choosing the diagonal elements of the APST matrix, we invoke the random-matrix assumption and make use of their eigenvalue spectra. A key property is that the eigenvalues, except for the largest one, follow Wigner's semicircle distribution. (The largest eigenvalue is typically located far away from the rest of the eigenvalues.) Do phase-synchronization time matrices from epileptic ECoG signals exhibit these random-matrix characteristics?

The typical matrix size for epileptic ECoG signals in our study is only 25×25. To overcome this difficulty, we examine the time evolution of the eigenvalue spectrum. Figure 10 shows, for the secondarily generalized seizure event in Fig. 8, the evolution of all 25 eigenvalues. We observe that the largest eigenvalue λ_{25} is indeed far away from the rest of the spectrum. For λ_{1-24}, there is a spread, but there is a relatively high concentration of eigenvalues about the middle of the spread, signifying a semicircle-like distribution. These suggest that the random-matrix hypothesis is applicable to multi-channel epileptic ECoG signals.

B. Heuristic understanding of the evolution of determinant

To understand why the determinant of the APST matrix can show significant changes with a seizure, we take as example the case of the secondarily generalized seizure shown in Fig. 8. For this case, there are 25 independent differential signals, so that number of distinct matrix elements is 300. Figures 11(a)–(d) show the histograms of these elements corresponding to a time in (a) interictal state, (b) ictal state where the determinant is large, (c) ictal state with a small determinant, and (d) postictal state. We observe that, as the ictal state is approached, the histogram shifts toward the right [Figs. 11(a) and 11(b)], indicating a larger mean value of the APST in the ictal state. The histogram then shifts toward the left, as shown in Fig. 11(c), giving rise to smaller mean value of the APST. This leads to the dip in the determinant observed in Fig. 8(c). In the postictal state, the histogram moves gradually toward the location in the interictal state, as can be seen by comparing Fig. 11(d) with Fig. 11(a). The general observation is that the value of the determinant can be significantly enhanced as the mean value of the matrix elements is increased, as argued in Sec. III.

C. Method of phase-coherence matrix

As a comparison study, we apply the method of phase-coherence matrix[24] to our model system Eq. (11) and ECoG signals. The method is based on calculating the mean phase coherence[16,17] and is quite representative of methods utilizing coherence or correlation measures of phase variables.[22–25] For multi-channel signals $x_j(t)$ ($j = 1,\ldots,K$), assuming M measurements in the moving window, one can define the following measure of mean phase coherence between channels j and k:

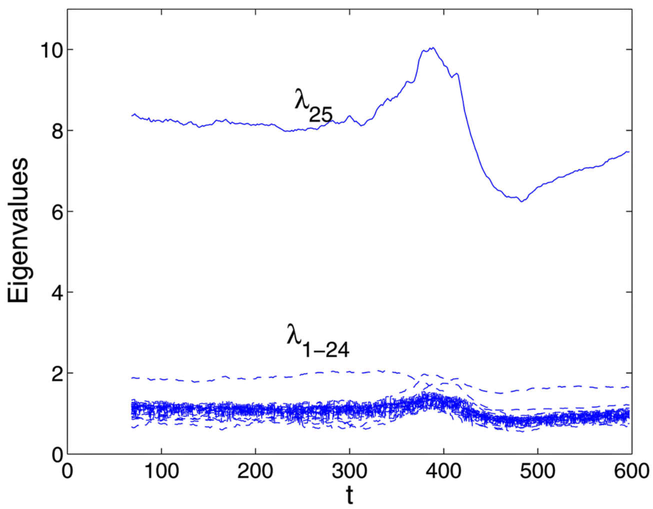

FIG. 10. (Color online) For the secondarily generalized seizure event in Fig. 9, time evolution of the eigenvalue spectrum of the APST matrix.

$$R_{jk} = \left| \frac{1}{M} \sum_{m=1}^{M} e^{i(\phi_{jm} - \phi_{km})} \right|, \tag{14}$$

where ϕ_{jm} is the phase of $x_j(t)$ at the mth measurement. If the phases are fully synchronized, we have $R_{jk} = 1$. In general, we have $0 \leq R_{jk} \leq 1$. The quantities R_{jk} thus represent a phase-coherence matrix **R**, where the diagonal elements are naturally $R_{jj} = 1$ for $j = 1,\ldots,K$.

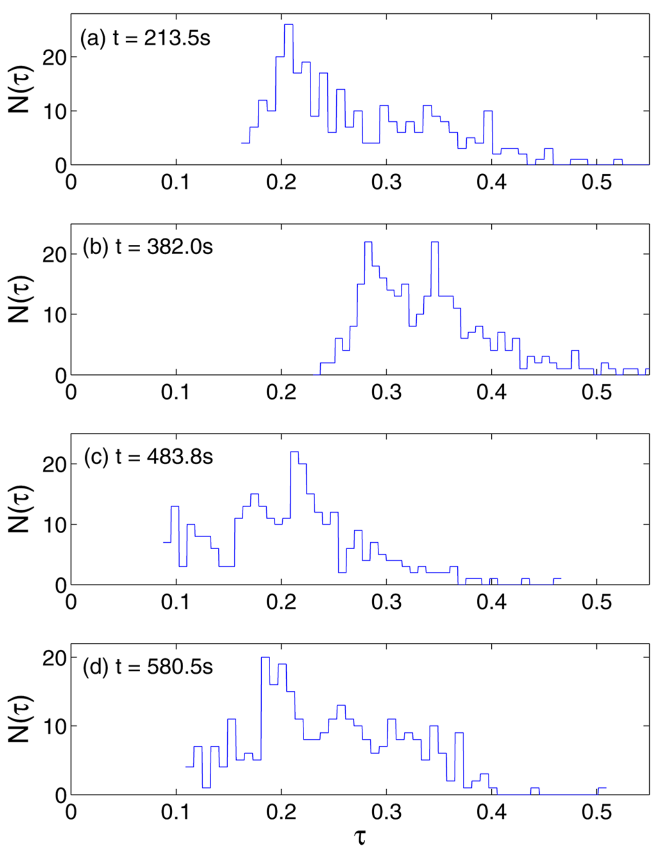

FIG. 11. (Color online) For the secondarily generalized seizure event in Fig. 8, histograms of elements of the APST matrix for four instants of time: (a) interictal state, (b) ictal state with determinant near the peak value in Fig. 8, (c) ictal state with determinant in the dip in Fig. 8, and (d) postictal state.

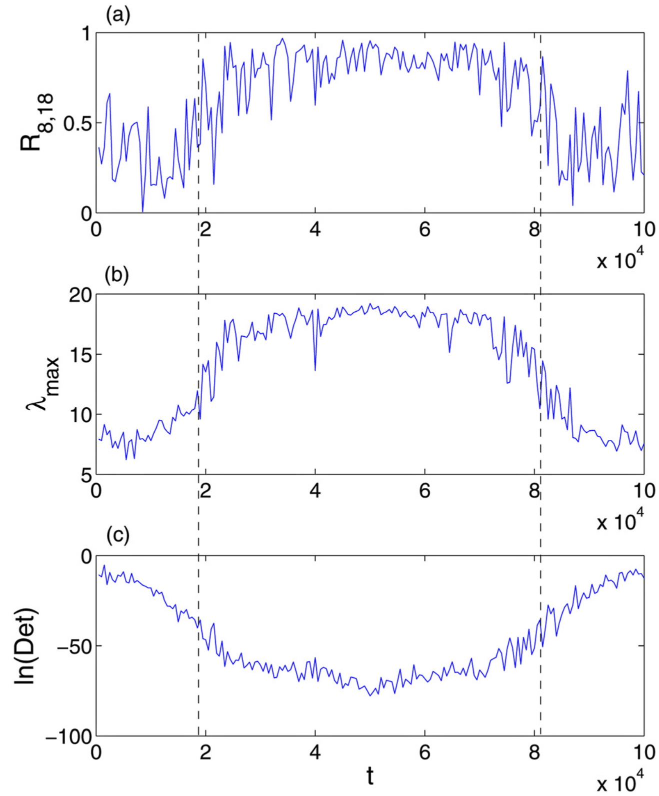

FIG. 12. (Color online) For the oscillator network Eq. (11), performance of the phase-coherence matrix **R**. (a) and (c) Time evolution of a typical matrix element, the largest eigenvalue, and ln Det. Note that the directions of change in ln Det (natural log of the determinant) are opposite to those in Fig. 5. Model parameters are the same as in Fig. 5.

Figures 12(a)–12(c) show a representative result of applying the matrix **R** to the model system Eq. (11), where (a)-(c) are the time traces of an individual matrix element, the maximum eigenvalue, and the determinant, respectively. The noise amplitude is $\varepsilon = 1.0$ and the region between the vertical dashed lines denotes the time interval during which the oscillator network is phase synchronized. We see that, while the

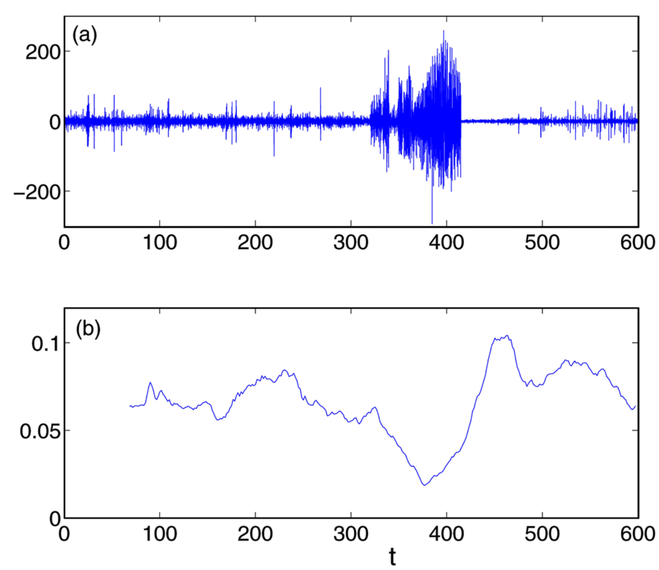

FIG. 13. (Color online) (a) ECoG signal from a secondarily generalized seizure event. (b) Time evolution of Det of phase coherence matrix.

matrix can still capture the evolution toward phase synchronization, its ability to detect the onset of synchronization is degraded as the determinant appears to vary continuously through the onset point [e.g., comparing Fig. 12(c) with Fig. 5(c)]. Similar behavior occurs when the matrix is applied to EEG or ECoG signals. For instance, Fig. 13(b) shows for the same ECoG signal as in Fig. 8, the time evolutions of Det. Variations of the matrix determinant over the seizure event are present, but they are insignificant as compared with those in Fig. 8. These results indicate that that APST matrix has a much higher sensitivity to seizure than the phase-coherence matrix.

VII. CONCLUSION

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. It was believed that neuronal hypersynchrony is associated with the generation of seizures. However, an experimental study revealed that seizure-like events are associated with desynchronization. To resolve the controversy is fundamental to epilepsy. Since multichannel EEG or ECoG recordings are now readily available from laboratory or clinical studies of epilepsy, a method sensitive to variations of synchrony is desirable.

We have developed a general method to analyze synchrony from multichannel time series, based on a matrix whose elements are various times for pairs of channels to maintain temporal synchronization in their phases. Monitoring of the properties of the matrix provides an effective way to assess changes in synchrony. The method is validated by a control model of coupled nonlinear oscillators and tested using clinical EEG and ECoG data. One finding is that, at a systems level, whether epileptic seizures are accompanied by enhanced or reduced synchrony is highly case-dependent.

Comparing with previous methods,[22–25] our synchronization-time matrix appears to be much more sensitive to changes in the system that one aims to characterize. For absence seizures where there is clinical evidence of enhanced synchrony, our method yields 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, nonlinear and nonstationary time series from other fields.

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[1]R. B. Owen and A. A. Zozulya, Opt. Eng. **39**, 2187 (2000).
[2]E. S. Biagioni and K. W. Bridges, Int. J. High Perform. Comput. Appl. **16**, 315 (2002).
[3]S. T. Vohra, F. Bucholtz, G. M. Nau, K. J. Ewing, and I. D. Aggarwal, Appl. Spectrosc. **50**, 985 (1996).
[4]S. Kamijo, Y. Matsushita, K. Ikeuchi, and M. Sakauchi, IEEE Trans. Intell. Transp. Syst. **1**, 108 (2000).
[5]E. A. Johannessen, L. Wang, L. Cui, T.-B. Tang, M. Ahmadian, A. Astaras, S. W. J. Reid, P. S. Yam, A. F. Murray, B. W. Flynn, S. P. Beaumont, D. R. S. Cumming, and J. M. Cooper, IEEE Trans. Biomed. Eng. **51**, 525 (2004).
[6]C. I. Merzbachery, A. D. Kersey, and E. J. Friebele, Smart Mater. Struct. **5**, 196 (1996).
[7]I. F. Akyildiz, W. Su, Y. Sankarasubramaniam, and E. Cayirci, IEEE Commun. Mag. **40**, 102 (2002).
[8]P. J. Franaszczuk and G. K. Bergey, Biol. Cybern. **81**, 3 (1999).
[9]F. Mormann, R. G. Andrzejak, C. E. Elger, and K. Lehnertz, Brain **130**, 314 (2007).
[10]R. Kozma and W. J. Freeman, Chaos **18**, 037131 (2008).
[11]E. R. Kandel, J. H. Schwartz, and T. M. Jessell, *Principle of Neural Science*, 3rd ed. (Appleton and Lange, Norwalk, CT, 1991).
[12]T. I. Netoff and S. J. Schiff, J. Neurosci. **22**, 7297 (2002); S. J. Schiff, T. Sauer, R. Kumarc, and S. L. Weinstein, NeuroImage **28**, 1043 (2005).
[13]M. G. Rosenblum, A. S. Pikovsky, and J. Kurths, Phys. Rev. Lett. **76**, 1804 (1996).
[14]P. Tass, M. G. Rosenblum, J. Weule, J. Kurths, A. Pikovsky, J. Volkmann, A. Schnitzler, and H.-J. Freund, Phys. Rev. Lett. **81**, 3291 (1998).
[15]Recent reviews chaotic phase synchronization include: S. Boccaletti, J. Kurths, G. Ospov, D. L. Valladares, and C.-S. Zhou, Phys. Rep. **366**, 1 (2002); J. Kurths, S. Boccaletti, C. Grebogi, and Y.-C. Lai, Chaos (Focused issue) **13**, 126 (2003).
[16]M. Hole, K. Lehnertz, C. Pantev, and B. Lütkenhöner, *Dynamics of Cognitive and Sensory Processing in the Brain*, edited by E. Basar and T. Bullock (Springer, New York, 1988), p. 84.
[17]F. Mormann, K. Lehnertz, P. David, and C. E. Elger, Physica D **144**, 358 (2000); F. Mormann, R. G. Andrzejak, T. Kreuz, C. Rieke, P. David, C. E. Elger, and K. Lehnertz, Phys. Rev. E **67**, 021912 (2003); F. Mormann, T. Kreuz, R. G. Andrzejak, P. David, K. Lehnertz, and C. E. Elger, Epilepsy Res. **53**, 173 (2003).
[18]The meaning of oscillation here is fairly general. Insofar as a signal is time varying and recurrent (e.g., periodically, quasiperiodically, or randomly), we call it oscillatory. Such oscillations are not restricted to a narrow frequency band.
[19]V. Andrade, R. Davidchack, and Y.-C. Lai, Phys. Rev. E **61**, 3230 (2000); L. Zhu, A. Raghu, and Y.-C. Lai, Phys. Rev. Lett. **86**, 4017 (2001).
[20]Y.-C. Lai, M. G. Frei, and I. Osorio, Phys. Rev. E **73**, 026214 (2006).
[21]Y.-C. Lai, M. G. Frei, I. Osorio, and L. Huang, Phys. Rev. Lett. **98**, 108102 (2007).
[22]J. Wackermann, Acta Neurobiol. Exp. **56**, 197 (1996).
[23]C. Allefeld and J. Kurths, Int. J. Bifurcation Chaos Appl. Sci. Eng. **14**, 417 (2004).
[24]S. Bialonski and K. Lehnertz, Phys. Rev. E **74**, 051909 (2006).
[25]K. Schindler, H. Leung, C. E. Elger, and K. Lehnertz, Brain **130**, 65 (2007).
[26]T. M. Rutkowski, D. P. Mandic, A. Cichocki, and A. W. Przybyszewski, in *Advanced Intelligent Computing Theories and Applications with Aspects of Theoretical and Methodological Issues*, Lecture Notes in Computer Science (Springer, New York, 2008), Vol. 5226, p. 122.
[27]M. Müller, G. Baier, A. Galka, U. Stephani, and H. Muhle, Phys. Rev. E **71**, 046116 (2005); M. Müller, J. Y. López, C. Rummel, G. BAier, A. Galka, U. Stephani, and H. Muhle, Phys. Rev. E **74**, 041119 (2006); M. Müller, G. Baier, C. Rummel, and K. Schindler, Europhys. Lett. **84**, 10009 (2008).
[28]E. P. Wigner, Ann. Math. **53**, 36 (1951); T. A. Brody, J. Flores, J. B. French, P. A. Mello, A. Pandey, and S. S. M. Wong, Rev. Mod. Phys. **53**, 381 (1981).
[29]K. E. Bassler, P. J. Forrester, and N. E. Frankel, J. Math. Phys. **50**, 033302 (2009).
[30]It has been known that in complex networks, synchronization analysis can lead to several pitfalls, especially if the data come 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. The problem of

figuring out the amount of coupling between brain regions responsible for the signals recorded by any pair of channels, based solely on data, is of paramount interest but may be extremely challenging.

[31] B. S. Gutkin, C. R. Lang, C. L. Colby, C. C. Chow, and G. B. Ermentrout, J. Comput. Neurosci. **11**, 121 (2001).

[32] Whether absence seizures are truly "primary generalized" seizures or instead focal frontal seizures which spread rapidly over the cortex has been a matter of debate [see, for example, H. Meeren, G. van Luijtelaar, F. L. da Silva, and A. Coenen, Arch. Neurol. **62**, 371 (2005)].