Detecting and localizing the foci in human epileptic seizures

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We consider the electrical signals recorded from a subdural ECoG grid of electrodes placed on the pial surface of the brain for chronic evaluation of epileptic patients before surgical resection. A simple and computationally fast method to analyze the inter-ictal phase synchrony between such electrodes is introduced and developed with the aim of detecting and localizing the foci of the epileptic events. We evaluate the method by comparing the results of surgery to the localization predicted here. We find an indication of good correspondence between the success or failure in the surgery and the agreement between our identification and the regions actually operated on.

The epileptic syndrome is well known and studied since antiquity: clay tablets dated about 700-500 B.C. found in Babylon contain a description of epileptic seizures and symptoms, and already Hippocrates postulated that the origin of those symptoms was a brain disfunction. Epilepsy is defined as an unprovoked seizure due an excessive discharge of cerebral neurons, occurring as a result of disturbances in normal functioning, and associated with a variety of clinical and laboratory manifestations. The list of famous people in history affected by epilepsy includes Julius Caesar, Pope Pius XI, Fyodor Dostoevsky and Lord Byron. Today, epilepsy is the world’s most common neurological disorder, with more than 50 million people affected worldwide.

Roughly 30 to 40 percent of patients do not respond satisfactorily to medications, and about 20 percent are surgical candidates. This is specifically true for focal epilepsy, i.e. the case in which the electric signals from one particular group (or some localized groups) of neurons somewhere in the brain (the focus) occasionally become so strong that they overwhelm the signals of neighboring cells. The generated signals can quickly (within a few seconds) spread from one side of the brain to the other (even to locations on the side of the brain opposite to the focus), determining several symptoms: blank stare, out-of-control movements of the body, loss of motor control, and violent convulsions.

Localizing accurately the epileptic focus (or foci) is therefore an essential first stage for surgeons, who need to make sure that they are going after the real source (rather than a copycat region) of the seizure, thus minimizing the surgery’s invasiveness. In some cases (generally when the focus cannot be pinpointed using traditional methods), electrodes are placed directly on the surface of the brain to find the seizure’s source. Precisely, grids are placed on the pial surface of the brain (see Figure 1), consisting of 50 to 100 electrodes spatially distributed over the suspected focal region, and the ensemble of signals [called the electrocorticogram (ECoG)] is analyzed for detecting the proper brain area to be resected [1, 2, 3, 4]. Each electrode detects the local field potential of a very tiny brain area [5]. The electric voltage signals of all electrodes are simultaneously recorded with a sampling frequency of 400 Hz (sampling time $\tau_{\text{sampl}} = 2.5$ ms), and low-band-pass filtered up to 50 Hz. Decisions where to perform surgery are routinely based on a visual inspection of the ECoG signals by a board certified team of physicians who identify the electrodes first showing signal patterns similar to...
those appearing during the epileptic seizure.

The issue here is how to analyze the ECoG signals to achieve a simple, automatic, data driven, fast and reliable identification of the epileptic focus. It has been shown that a significant reduction of the dimension of the system \cite{10} (as measured by the correlation dimension \cite{11}) occurs inside the epileptogenic focus tens of minutes before the seizure onset. The interdependence between signals from different sites, studied by means of nonlinear cross-predictability \cite{8, 9}, also allowed the location of the focus to be specified. These methods involve the reconstruction of the phase space by time-delay embedding \cite{10}. The reconstruction requires knowledge of the autocorrelation time and a number of time points in the series that scales as \(10^D\), where \(D\) is the maximum embedding dimension \cite{11}. But, on the other side, the nonstationary nature of EEG signals requires analysis over relatively short time windows with number of time-points of the order of \(10^3\). Therefore, one should exercise extreme caution when drawing conclusions from the analysis involving high dimensional embedding. In fact, it was pointed out in \cite{12} that the predictive power of the correlation dimension is significantly reduced when strong changes in the amplitude of the signal during the seizure are removed by normalization, as well as when the significant changes in the autocorrelation time are taken into account in the calculation of the correlation dimension.

In this Letter we report that a model-free and computationally fast approach, based on phase synchronization, is able to identify the epileptic focus with high accuracy. In order to describe the main concepts behind the method, let us consider a one-dimensional oscillatory signal \(x(t)\). The associated phase space can be fully reconstructed by using the coordinates \(x(t), dx(t)/dt, d^2x(t)/dt^2, \ldots\), with as many derivatives as needed to exhaust the dimensionality of the system.

In such a reconstructed phase space one can then define the Poincaré section by noting the points obtained when the orbit crosses of the surface \(dx(t)/dt = 0\). Obviously, this surfaces coincides with the points of minimum or maximum in the original one-dimensional signal \(x(t)\). In this Letter we focus on the points of maximum, and define the phase \(\phi(t)\) of the trajectory by increasing its value by \(2\pi\) after each maximum. Precisely, in between the \(k\)th maximum occurring at \(t = t_k\) and the \(k+1\)th maximum occurring at \(t_{k+1}\), we define the phase for all time \(t_k \leq t \leq t_{k+1}\) using the linear interpolation \cite{13, 14}

\[
\phi(t) = 2\pi k + 2\pi \frac{t - t_k}{t_{k+1} - t_k} \quad (t_k < t < t_{k+1}).
\]

Note that the resulting monotonically increasing phase does not contain any information about the amplitude of the original signal. Of course phases can be affected by instrumental artifacts; we have carefully ascertained that there are no such artifacts in any of the data analyzed below, see Fig.1 panel b.

The notion of phase synchronization \cite{13, 14} refers to a process wherein a locking of the phases of weakly coupled oscillators is produced, without implying a substantial correlation in the oscillators’ amplitudes. The same concept can be related to our case, for measuring the degree of phase synchronization of two different signals, say \(x(t)\) and \(y(t)\). Using the basic definition \cite{11}, one can indeed produce the phases of each signal, denoted as \(\phi_x(t)\) and \(\phi_y(t)\), respectively. Taking \(x(t)\) as the reference signal, one can further consider the time points of its maxima \(t_k\), and read the phase \(\phi_y(t_k)\) at these time points. One next defines the following reduced phases \(\psi_m(t_k)\) according to

\[
\psi_1(t_k) = \phi_y(t_k) \mod 2\pi,
\]

\[
\psi_2(t_k) = \phi_y(t_k) \mod 4\pi,
\]

\[
\psi_m(t_k) = \phi_y(t_k) \mod 2\pi m.
\]
The graphic representation of $\psi_m(t_k)$ vs. $t_k$ is called a synchrogram of order $m$. We will consider the signals $x(t)$ and $y(t)$ as synchronized at ratio $n : m$ when the $m$th order synchrogram exhibits $n$ distinct horizontal lines (i.e. fixed reduced phase $\psi_m(t_k)$ for a series of time $t_k$). Synchrograms, indeed, have been proved to be useful to visualize and trace transitions between different ratios of phase locking in biological data, as the cardiorespiratory system of a human subject is often strong.

To exemplify the notion of a synchronization in the present context of epilepsy we present in Fig. 2 a synchrogram constructed from the signals associated with a chosen pair of electrodes, which displays the presence of 1:1 phase synchronization at all times (albeit at a varying strength). The information contained in the synchrograms can be easily employed to extract the level of phase synchronization between all the pairs of electrodes at our disposal. To this aim we define the strength of synchronization $S_{ij}(t)$ of every given electrode $i$ to any other electrode $j$. To do that we take the synchrogram of electrodes $i$ and $j$, first divide the time axis into windows (in our case of 10 seconds), focusing on the line $\psi(t_k) = 0$. In each such window, we calculate the number $N_{ij}(t)$ of phase points (shifted by $\pi$) within the range $\pi \pm 0.01$. For $i \neq j$ $S_{ij}(t)$ is defined as $N_{ij}(t)$ normalized by the total number of phase points throughout the measured time interval, with $t$ being assigned to the first time-point in the window. For $i = j$ we set $S_{ij} = 0$ for all times. The window length of 10 seconds was optimized to provide maximum detail with minimal noise. We color code the values of $S_{ij}(t)$ such that blue (black in B&W) is zero and red (white in B&W) is the highest. We refer to the diagram in which $S_{ij}(t)$ is displayed as the Strength of Synchronization Diagram (SSD). A typical such diagram [using as reference electrode the specific electrode FG15 ($i = 79$)] and $j$ from 1 to 96 is presented in Fig. 4. For the spatial relationship of these electrodes compare with Fig. 5 which shows the actual placement of the electrodes in this case (patient b). Note that a “strength of synchronization” of, say, 20%, means that the signals are synchronized 20% of the time within the given window.

The SSD provides a clear scenario for the epileptic
seizure, (known also as the ictal period), which here occurs between \( t \approx 730 \) and \( t \approx 950 \). Starting around \( t = 730 \) with a decrease in synchronization the event proceeds to exhibiting high synchronization between all the electrodes, starting around \( t = 790 \). After \( t = 950 \) the synchronization is lost except for a few pairs of electrodes. In the inter-ictal region we notice the precursor very strong synchronization with electrodes \# 72 and \#78, with a lower strength of synchronization with a few other electrodes. After the seizure all the lower synchronizations disappear, but the synchronization to electrodes remains at a lower strength. The increased strength of synchronization occurring after \( t = 2000 \) is a warning for the arrival of the next seizure (that actually takes place at a later time). We cannot discuss the early warning value of the present approach in this Letter, although we believe that it holds substantial promise, here we concentrate on identifying the foci. Since the epileptic events imply high strengths of phase synchronization over the whole grid, we identify the foci of epileptic activity with those regions that remain strongly synchronized at all times.

Thus our definition of the foci of epilepsy is the ensemble of those electrodes that, besides displaying a level of synchronization above a chosen threshold during the ictal period, remain also strongly synchronized during the inter-ictal period. To identify this ensemble we now compute the average \( S_{ij} \) according to

\[
\bar{S}_{ij} = T^{-1} \int_{0}^{T} S_{ij}(t) dt ,
\]

where the time interval \((0, T)\) does not include a seizure. An example of the resulting pair-wise synchronization matrix \( \bar{S}_{ij} \) is shown in Fig. 4.

To localize the foci we need to choose a threshold value of \( \bar{S} \) to pick the most strongly synchronized electrodes. We chose the threshold value such as to identify approximately the same number of electrodes as those chosen by the surgeons for an operation. The results are displayed, for three different patients, in Figs. [5]. In this figure we present, for three different patients (referred to a patients a, b and c respectively), the geometric spread of the electrodes projected on the plane. In addition, we color those electrodes that were chosen by the surgeons for the operation, and we put a rectangle on every electrode that is identified by our method.

It is interesting to note that for patient a, where our method agrees well with the choice of the surgeons, the operation was reported to be successful. For patient c the operation failed, and we point out the large discrepancy between our results and the surgeons’ choice. Patient b is an intermediate case, in which the operation was reported to be partially successful (after the operation, the patient continued to suffer epileptic seizures, but at a much lower rate than before the operation). It is remarkable to observe that in this case, the degree of overlap is also intermediate.

In summary, we analyzed the electrical signals recorded from a subdural ECoG grid of electrodes placed on the pial surface of the brain for chronic evaluation of epileptic patients before surgical resection, and we pointed out that a simple and computationally fast method to detect phase synchrony between such electrodes is able to detect and localize the foci of the epileptic events. While it is not reasonable to draw any final conclusions on the basis of the study of only three patients, we nevertheless point out that the significant correlations presented here indicate that the method can be proposed as a practical and robust way for surgeons to identify the brain regions to be removed in order to maximize the surgery’s success with minimizing the surgery’s invasiveness.

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