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EEG nonstationarity during intracranially recorded seizures: statistical and dynamical analysis

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Abstract

Objective: The investigation of nonstationarity in complex, multivariable signals, such as electroencephalographic (EEG) recordings, requires the application of different and novel approaches to analysis. In this study, we have divided the EEG recordings during epileptic seizures into sequential stages using spectral and statistical analysis, and have as well reconstructed discrete-time models (maps) that reflect dynamical (deterministic) properties of the EEG voltage time series.

Methods: Intracranial human EEG recordings with epileptic seizures from three different subjects with medically intractable temporal lobe epilepsy were studied. The methods of statistical (power spectra, wavelet spectra, and one-dimensional probability distribution functions) and dynamical (comparison of dynamical models) nonstationarity analysis were applied.

Results: Dynamical nonstationarity analysis revealed more detailed inner structure within the seizures than the statistical analysis. Three or four stages with different dynamics are typically present within seizures. The difference between interictal activity and seizure events was also more evident through dynamical analysis.

Conclusions: Nonstationarity analysis can reveal temporal structure within an epileptic seizure, which could further understanding of how seizures evolve. The method could also be used for identification of seizure onset.

Significance: Our approach reveals new information about the temporal structure of seizures, which is inaccessible using conventional methods.

Keywords: Time series; Nonstationarity; Intracranial EEG; Epilepsy; Nonlinear dynamics

1. Introduction

The vast majority of signals in nature, including physiological data, are nonstationary, in that their properties change with time. Nonstationarity can arise as a result of the influence of processes whose characteristic time scale is larger than the observation time, or due to external events causing changes in dynamics, transient processes, and drifts of system parameters. The problems of detection of such situations and the development of methods for their analysis are relevant for different fields of science. Here, they are considered in the framework of electroencephalographic (EEG) time series analysis.

An EEG recording is an important example of a nonstationary time series (Palus, 1996). Changes in EEG waveforms occur continuously in association with different behavioral and mental states (Gribkov and Gribkova, 2000; Kaplan, 1998; Kohlmorgen et al., 2000; Shishkin et al., 1997). Especially robust changes occur during epileptic seizures (Jefferys, 1990). The period of time within which properties of the EEG signal (namely, spectral properties) can be considered constant is quite small, with estimates ranging from 4 s to 1 min (Blanco, 1995; Kaplan, 1998; Lopes da Silva, 1998).

The importance of nonstationarity is not limited to physiological applications. For example, the problem of

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bifurcation forecasting is discussed by Feigin et al. (2001a) and finds application in the analysis of ozone hole dynamics (Feigin et al., 2001b). The problem of segmentation of nonstationary time series with subsequent classification of quasistationary segments has been addressed by Manuca and Savit (1996), Schreiber and Schmitz (1997a). In this case, the goal of the analysis is the detection of qualitative changes in the state of the system generating the time series. In our study, we address the question of whether a determination of nonstationarity can provide insights into EEG recordings and, specifically, epileptic phenomena.

1.1. Statistical and dynamical nonstationarity

In the theory of stochastic processes two types of stationarity are distinguished—strong stationarity and weak stationarity. A process is called strongly (strictly) stationary when all its joint (multidimensional) probability distributions do not change under a time shift. Since it is practically impossible to estimate all joint probability distributions having only a finite time series, weaker demands are employed for practical use. Namely, a process is called weakly stationary (stationary in a wide sense) when its mean and variance are constant and the autocorrelation function depends only on the time lag. So, the constancy of power spectrum estimates can serve as an indication of weak stationarity. Nonstationarity during epileptic seizures is well-known (Blanco et al., 1995; Franaszczuk et al., 1998). Time-frequency analysis of epileptic EEG activity has also been performed with the use of a special Fourier transform (Mallat and Zhang, 1993). The presence of certain seizure stages with different spectral properties was observed in these studies.

Theiler (1995) showed that, based on surrogate data tests, the properties of EEG signals during a seizure cannot be described completely with the power spectrum alone. The presence of nonlinearities (Andrzejak et al., 2001a,b; Jing et al., 2000; Palus, 1996; Pijn et al., 1997; Schiff et al., 1999; Theiler, 1995) and the existence of almost periodic patterns leads to the assumption that the activity recorded during an epileptic seizure may be described with low-dimensional nonlinear deterministic models (see, e.g. Haken, 1996; Lehnertz et al., 2000). This assumption has not been fully justified empirically (Theiler, 1995, 1996), but it inspired investigations of different groups. These have been devoted mainly to seizure prediction (Aschenbrenner-Scheibe et al., 2003; Andrzejak et al., 2003; Elger and Lehnertz, 1998; Le Van Quyen et al., 2001; Lopes da Silva et al., 2003; Maiwald et al., 2004; Martinerie et al., 1998; Mormann et al., 2003a,b; Suffczinski et al., 2004), epileptic foci localization (Andrzejak et al., 2001a,b) and synchronization within the brain (Altenburg et al., 2003; Arnhold et al., 1999; Lachaux et al., 1999; Mormann et al., 2000; Stam and van Dijk, 2002; Varela et al., 2001) with many significant results. Yet, the investigation of EEG nonstationarity from the nonlinear point of view has been done only rarely (Rieke et al., 2002, 2003), and the 'structure' of dynamical nonstationarity within the seizure (number and duration of quasi-stationary segments) has not been studied at all to our best knowledge.

Detailed temporal information during seizure events can be obtained with dynamical nonstationarity analysis, which looks for changes in the evolution operator of the system that generates the time series (Dejin et al., 1998; Kennel, 1997; Manuca and Savit, 1996; Rieke et al., 2002; Schreiber, 1997a,b, 1999). Weak stationarity implies only constancy of linear relationships between data points, dynamical stationarity can be regarded as the generalization of this concept to relationships of an arbitrary character. Here, we consider both the changes in statistical properties (power and wavelet spectra, one-dimensional probability distribution function) and the dynamical nonstationarity of EEG signals during epileptic seizures.

2. Methods

2.1. Spectral techniques

Traditional statistical methods of nonstationarity analysis consist in the investigation of the spectral properties of time series: spectrograms (power spectra in moving windows) and wavelet spectra. We apply both approaches below to the EEG data simply for the sake of completeness and comparison with the results of dynamical nonstationarity analysis.

The most direct approach to the construction of a spectrogram is to estimate Fourier power spectrum in moving windows of different length as a periodogram. On the one hand, one should avoid very small window length to have reasonable frequency resolution; on the other hand, the windows should not be very long to cope properly with nonstationarity of the signal. Taking into account these considerations, we select an optimal intermediate length of moving window by trial and error.

Wavelet spectrum of the signal $x(t)$ is defined as a result of its convolution with a complex conjugate of a wavelet function ψ (the latter is well-localized both in time and frequency domains):

$$W_\psi(t,s) = \frac{1}{\sqrt{s}} \int_{-\infty}^{\infty} x(\tau)\psi\left(\frac{\tau - t}{s}\right) d\tau \qquad (1)$$

The wavelet function has two parameters: temporal location of its center t and its time scale s, so that the wavelet amplitude spectrum $|W_\psi(t,s)|$ provides information about 'instantaneous' frequency composition of the signal and its variation over time. The multiplier $1/\sqrt{s}$ is used for normalization to maintain unit energy of the function $\psi\left(\frac{\tau-t}{s}\right)$ for each scale s. This is a linear technique which is well-suited for analysis of nonstationary signals. One of the very popular wavelet functions which is used below for the EEG data analysis is the Morlet wavelet (Lachaux et al., 2000)

$$\psi\left(\frac{\tau - t}{s}\right) = \pi^{-1/4} \exp\left(i\frac{\omega_0(\tau - t)}{s}\right)\exp\left(-\frac{(\tau - t)^2}{2s^2}\right) \quad (2)$$

with different values of the parameter ω_0 which determines frequency resolution.

2.2. Methods for analysis of dynamical nonstationarity

For the detection of dynamical nonstationarity of a time series with subsequent analysis of its temporal structure, the following methodology is used. The time series $X=\{x_i\}_{i=1}^{N}$ is divided into sufficiently short segments $X_k=\{x_j\}_{j=(k-1)s+1}^{(k-1)s+w}$ such that the evolution operator of the system within each of them can be considered constant. Below, we use the segments of the length of 2 s for the EEG data, recalling that the spectral properties of EEG can be regarded as constant even during segments longer than 4 s (Blanco, 1995; Kaplan, 1998; Lopes da Silva, 1998). Then, the difference in dynamics between each pair of segments is determined somehow (discussed below) and a matrix of distances $d_{mn}=d(X_m, X_n)$ is obtained.

Among different measures of distance between segments that have been proposed to date, many investigators have used various distances between the distributions of data points in reconstructed phase space: for example, the L_1 distance (Hively et al., 1999; Moeckel and Murray, 1997), χ^2 criterion (Hively et al., 1999) and transportation distance (Moeckel and Murray, 1997). To distinguish accurately between fractal distributions, the use of cross-correlation integrals has also been proposed (Kantz, 1994). However, all these methods also quantify differences in statistical properties of the time series segments and can produce irrelevant results when dealing with transient processes.

The ways of quantification of the distances that show differences between the evolution operators directly are following: first, the nonlinear cross-prediction error proposed by Schreiber (1997b); second, and conceptually similar, predictability of one time series segment using nearest neighbors from the other segment, proposed by Manuca and Savit (1996); third, the Euclidean distance between vectors of coefficients of global dynamical models reconstructed from different time series segments (Gribkov and Gribkova, 2000).

2.3. Numerical example

To illustrate different techniques, we consider a simple test example of dynamical nonstationarity analysis. We iterate the cosine map

$$x_{n+1} = r\cos(x_n) \quad (3)$$

to obtain a time series. This time series contains 2000 data points. Half the time series (up to the 1000th data point) is generated when $r=2.1$ and the system exhibits chaotic motion. At the time instant $n=1000$, the value of the parameter is changed abruptly and becomes equal to $r=2.11735$. After the transient process dies out, a periodic regime of period 7 is established. The entire time series is shown in Fig. 1a. Note that although the change occurs at $n=1000$, the phase trajectory wanders near the previous chaotic attractor for a certain period after that.

Dynamical nonstationarity of this time series is brought about by a parameter change at $n=1000$, but the majority of statistical properties such as mean value, standard deviation, etc, estimated from different segments, changes significantly only after $n=1500$. Let us compare the ability of different methods of time series nonstationarity analysis to detect the character of the observed dynamical nonstationarity correctly.

For statistical and dynamical nonstationarity analysis we construct the matrices of distances between short segments of the time series. We use three kinds of distance:

(1) χ^2 criterion for the difference between one-dimensional distributions of time series data points. For its calculation, the range of the observable variable (from its minimum to its maximum value) is divided into L bins. Then the number of points in each bin is counted for both time series segments and compared. The difference in distributions is defined as

$$\chi^2 = \sum_{i=1}^{L}\frac{(n_{1i} - n_{2i})^2}{n_{1i} + n_{2i}}, \quad (4)$$

where n_{1i} and n_{2i} are the number of data points in the i-th bin from the first segment and the second one, respectively.

(2) The Euclidean distance between the vectors of coefficients of global dynamical models. Here, global dynamical models are reconstructed from each segment of the time series. The distance between segments is estimated as the distance between corresponding vectors of the coefficients. This method is used, e.g. in (Gribkov and Gribkova, 2000) where models in the form of delay differential equations are used. In our case it is expedient to use models in the form of maps

$$x_{n+1} = f(x_n), \quad (5)$$

where f is found in the form of polynomials of different orders

$$f(x_n) = \sum_{i=0}^{p}\alpha_i x_n^i. \quad (6)$$

The distance can be written formally in this case as

$$d = \sum_{i=0}^{p}(\alpha_{i1} - \alpha_{i2})^2, \quad (7)$$

where α_{i1} and α_{i2} are the corresponding coefficients of two different models.

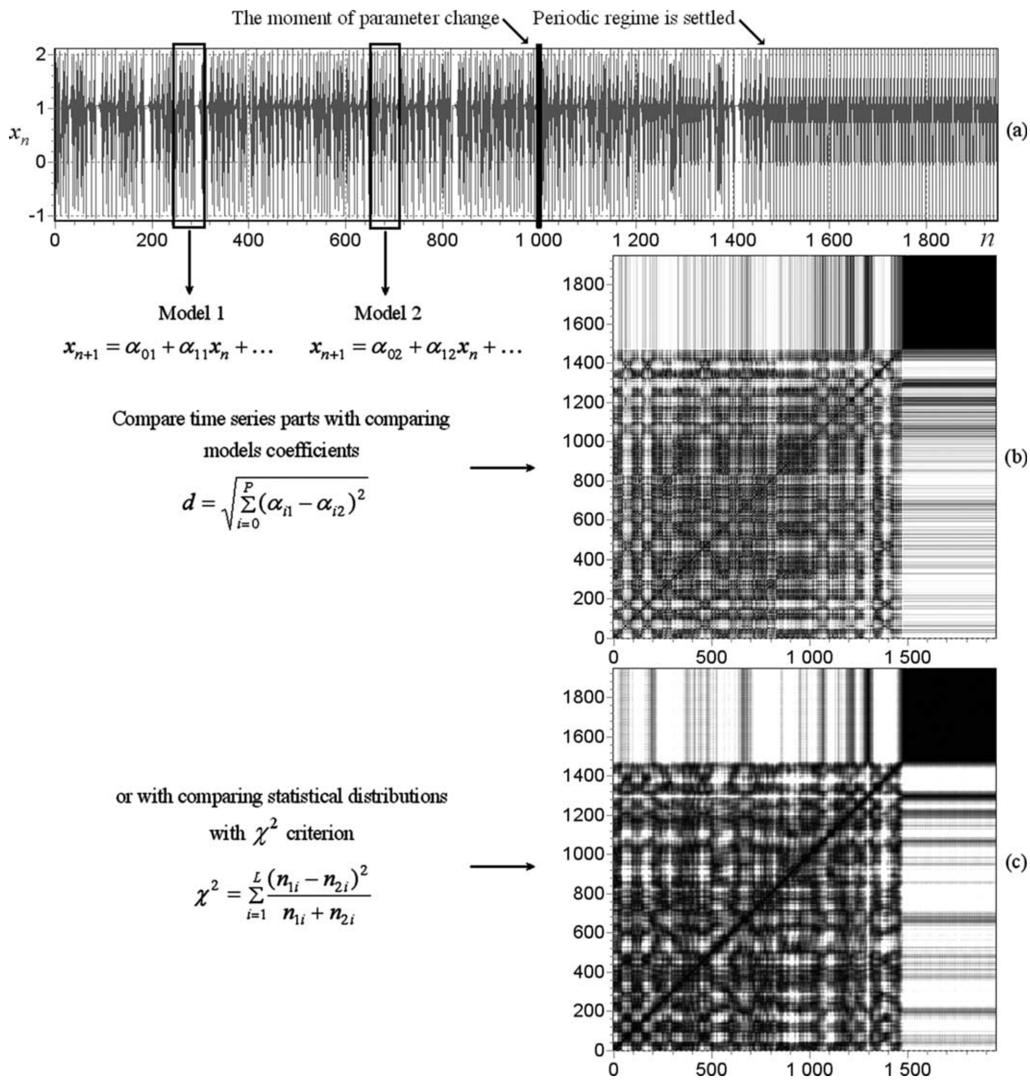

Fig. 1. (a) The time series generated by the cosine map (3). The first 1000 data points correspond to $r=2.1$, the next 1000 points to $r=2.11735$. After parameter change the chaotic regime becomes unstable. Eventually a regime of period 7 is settled, but during the transient process (until $n=1500$) the dynamics remains very similar to that before change; (b) The matrix of distances between different segments of this time series. Distances are calculated as Euclidean distances between vectors of the coefficients of the third order polynomial map models (6), reconstructed from these segments, and are shown with grayscale. Every point of the diagram represents the result of comparison of two time series segments. Black points correspond to zero distance, white ones to a pre-defined large threshold distance. A dark square on the diagram corresponds to a quasi-stationary segment (all its parts are similar to each other); (c) The matrix of distances for the same time series which are defined via χ^2 criterion (4); the number of bins $L=10$.

After the matrices of distances are calculated, it is convenient to represent them in the form of diagrams where the numbers of the starting point of segments are the coordinates along the axes and the distances between the segments are encoded in gray scale (Fig. 1b). Such a way of representation is similar to recurrence plots (Eckmann et al., 1987) where the distances between points in reconstructed phase space are shown. The use of distances between segments of time series (instead of individual points) leads to loss of time resolution, but allows detection of changes not only in the waveform (that can be a consequence of transient processes when the system parameters are constant), but in the evolution operator itself.

Such a diagram constructed for the considered time series using χ^2 distance is shown in Fig. 1c. Black points denote zero distance (which corresponds to a completely coinciding distribution of data points of each segment). White points correspond to a certain large threshold distance. The threshold distance was calculated as the sum of the distance averaged over all pairs of the segments and the standard deviation of these distances. Such a choice usually allows obtaining good contrast on the diagram. Furthermore, relative distances are actually shown in this case, which allows one to compare matrices of distances obtained with the use of different distance measures.

The two dark squares along the diagonal in Fig. 1c should be interpreted as two quasi-stationary regions in the time series within which the distribution of points does not change significantly. There are no changes in the statistical distribution right after the parameter change at $n=1000$. The χ^2 criterion identifies the changes only after the new dynamical regime settles down at $n=1500$.

The matrices of distances between vectors of coefficients of global models are shown in Fig. 1b and Fig. 2. Different pictures correspond to model maps with polynomials of different orders.

One can see that for small polynomial order $P=2$ (Fig. 1b) global models detect changes only after new regime settles down. If the model structure is not adequate to the object (e.g. it is not an accurate description of the dynamics) the coefficients depend significantly on the distribution of data points in the reconstructed phase space. Thus, one should not be surprised with the similarity of these results as compared to those obtained using comparison of probability distributions (Fig. 1c).

Increase in the order of the polynomial (Fig. 2a and b) makes the models more capable of accurate approximation

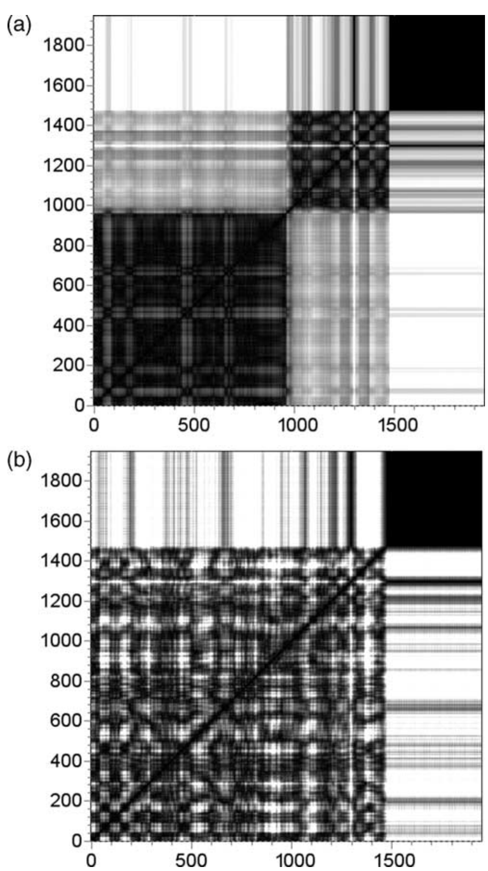

Fig. 2. The matrices of distances between segments of time series shown in Fig. 1a. As in Fig. 1b, the distances are Euclidean distances between vectors model coefficients. The orders of model polynomials are equal to 4 (a) and 6 (b). One can see that refinement of the model (increase in the polynomial order) leads to the detection of quasi-stationary parts that exactly correspond to different constant values of the cosine map parameter r.

of the object dynamics. As a result, the dependence of the measures on probability distributions disappears and the correct detection of the change in dynamics is observed at $n=1000$ (Fig. 2b).

Thus, by considering this simple numerical test example, we show that transient processes in dynamical systems can lead to a situation where dynamical nonstationarity is not accompanied by immediate changes of statistical properties of the time series. The change of statistical properties can take place much later than the change in the evolution operator. In many technical areas it is important to detect changes as early as possible. Hence, the development of special techniques for the detection and analysis of dynamical nonstationarity can be of great importance.

At the same time, the test example shows that special methods for dynamical nonstationarity detection are useful only if the reconstructed dynamical model is adequate to the object (describes its dynamics to high accuracy). Otherwise, they detect only statistical changes in the time series. When this method is applied to real-world signals, one cannot hope for a complete adequacy of the model, because a purely deterministic system is a mathematical idealization while real-world systems are noisy. The map of the form (5), reconstructed from real-world signals, will actually describe the conditional mean value $M(x_{n+1}|x_n)$. Then, the model should be considered adequate if a good approximation to this 'dynamical' relation is achieved. In this case the results of the analysis do not depend on the distribution of points in the reconstructed phase space, thereby reflecting only 'dynamical' properties of the signal (dependence of the future on the past and present).

2.4. Clustering algorithm for detection of quasi-stationary segments

Note that the detection of quasi-stationary segments can be considered as clustering of the parts of the original time series based on the matrix of distances. In the above example such clustering is done simply by eye, which is possible due to the rather high contrast of the diagram. But in general this process can be made automatic and less subjective by using one of the many clustering techniques (Kaufmann, 1990). For example, for EEG processing discussed below, we use the clustering method similar to Schreiber's approach (Schreiber, 1999) where one iteratively groups together the closest segments according to the introduced distance.

Namely, we start with the number of clusters equal to the number of segments, i.e. each cluster corresponds to a single vector of model coefficients for clustering based on the global models construction. Then, we iteratively decrease the number of clusters one by one. To accomplish this, we find in every step the two closest vectors (clusters) and replace them with their sample mean. After that we recalculate the matrix of distances. In this way, each cluster is represented always by a single vector - the sample mean of the vectors included in the cluster. The stopping criterion (and the final number of clusters) can be chosen from different considerations, which are inevitably more or less subjective. For example, one can specify a certain threshold and stop when the distance between the two currently closest clusters exceeds the threshold. Below, we calculate the intra-cluster variance (the sum of squared distances between all pairs of vectors belonging to the same cluster) for EEG segment clustering. An abrupt increase of this quantity indicates that two significantly different clusters are joined together. This most probably is a sign of error, such that we undo this joining and stop at that point.

2.5. EEG recordings

We have used intracranial human EEG recordings with epileptic seizures from 3 different subjects with medically intractable temporal lobe epilepsy, obtained as part of their clinical investigation prior to treatment with resective epilepsy surgery. The EEG signals were recorded from depth electrodes implanted orthogonally, bilaterally, through the second temporal gyrus, with the deepest recording contacts situated in the region of the amygdala and anterior hippocampus. Superficial contacts recorded from the neocortex of the overlying second temporal gyrus. The EEG signal was digitized at either 200 Hz (Stellate Systems, Montreal, Canada; patients 1 and 2) or 250 Hz (XLTEK, Oakville, Canada; patient 3). All patients subsequently underwent unilateral anterior temporal lobe resection with amygdalohippocampectomy after their intracranial EEG recordings and have been seizure free with follow-up from 6 months to 3 years.

3. Results

3.1. Analysis of the structures of epileptic seizures from EEG recordings

Patient 1. In our first example, the seizure was recorded in a 28 year-old man with right temporal lobe epilepsy. The data we considered for analysis is recorded from an electrode contact within the epileptogenic focus, situated in the right hippocampus. The time series analyzed is shown in Fig. 3.

The nonstationarity of the spectral properties of EEG during seizures has been reported previously (e.g. Franaszczuk et al., 1998; Jouny et al., 2003; Schiff et al., 2000). We also began with analysis of the spectrograms and wavelet spectra of the observed signal (Fig. 4). Spectrograms were

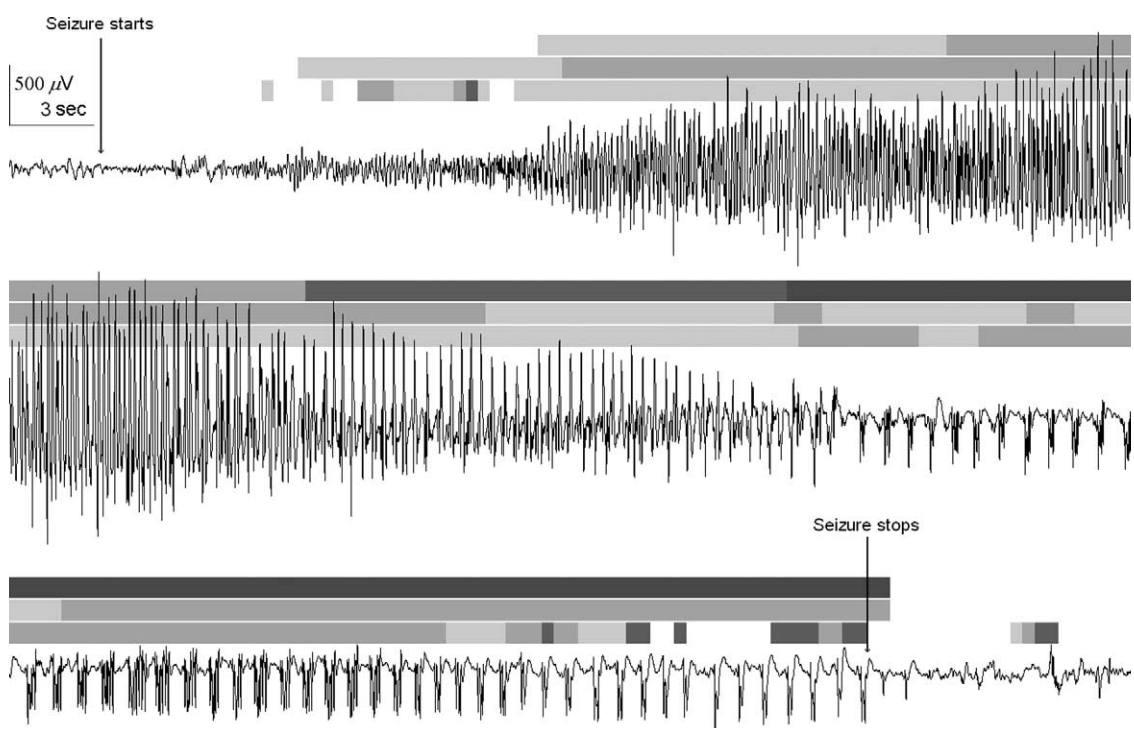

Fig. 3. Intracranial EEG recording of a seizure from patient 1. Depth electrode contact situated in right anterior hippocampus. Average reference. Low-pass filter with cut-off frequency 70 Hz. The time instants when seizure starts and stops are shown with arrows. Different variants of the division of the seizure into stages are indicated with rows of gray-colored bars above the time series plot. Different intensities of gray color correspond to different stages. The first version of clustering (upper row of bars) is obtained through spectral analysis (spectrogram and wavelet transform, Fig. 4), the second version (middle row) through the coefficients of linear models (8), and the third version (lower row) through the coefficients of nonlinear models. Note that the boundaries of quasi-stationary segments are different for each case, indicating that construction of dynamical models of different complexity provides information complementary to traditional spectral techniques.

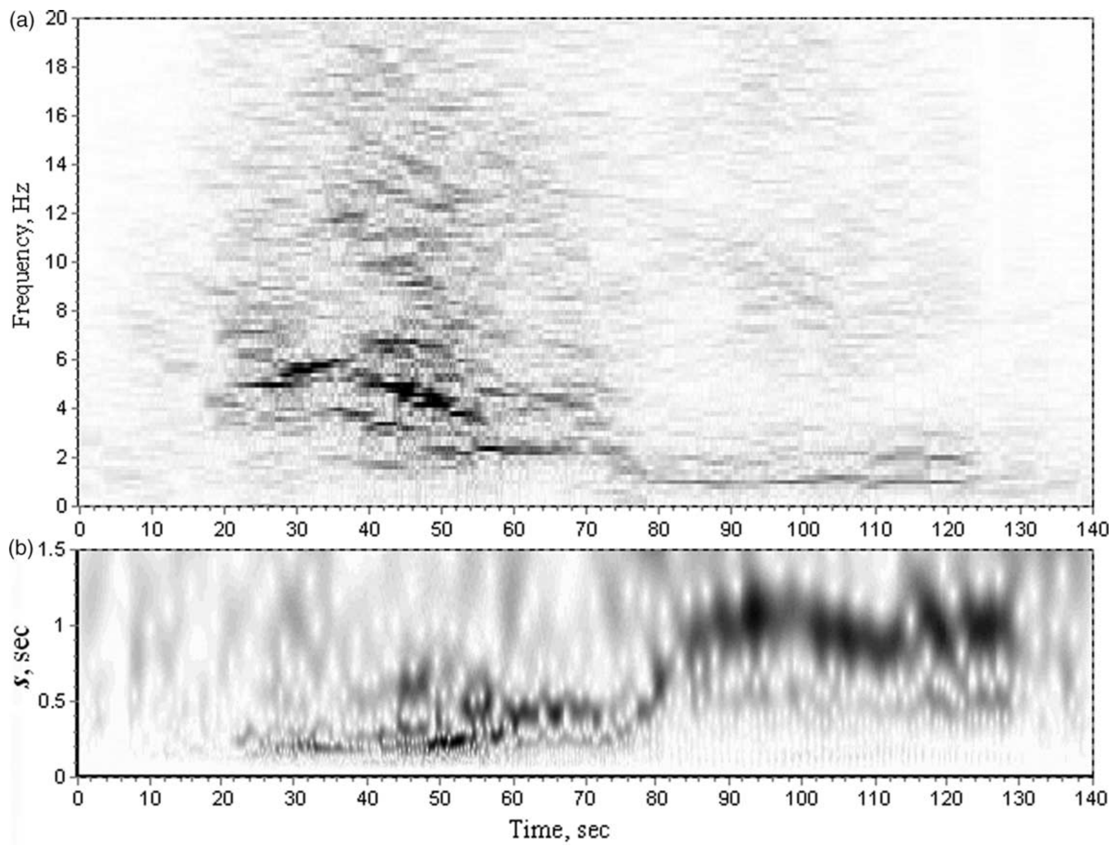

Fig. 4. (a) The spectrogram of the EEG time series from patient 1 shown in Fig. 3. (b) Wavelet spectrum obtained with Morlet wavelet (2), $\omega_0=6$. The time scale s (the ordinate) corresponds to a characteristic period of the wavelet function, see the expression (2). For the chosen value of ω_0, it corresponds almost exactly to $1/f$ where f is the frequency in power spectrum (the ordinate in Fig. 4a). Both pictures allow rough detection of four segments with increasing, decreasing, and constant frequency (20th–40th sec; 40th–60th sec; 60th–75th sec; 80th–120th sec).

constructed for moving windows of 5 s length with 4.8 s overlap between successive windows (Fig. 4a). The results do not change qualitatively under significant variation of the moving window length. Their robustness is confirmed also by qualitative similarity (in respect of quasi-stationary segments) of spectrograms and wavelet spectra for Morlet wavelet (Lachaux et al., 2000) (2) with different parameters $\omega_0;\omega_0=6$ in Fig. 4b. Namely, the results of the spectral analysis can be summarized as follows. In Fig. 4 one can see the segment with growing characteristic frequency (approximately from 16th to 37th sec), then the gradual decrease of the frequency (from 37th to 56th sec) and then two segments with roughly constant frequencies. These four segments are shown in Fig. 3 with upper row of gray-colored bars above the time series plot. The picture shows the results similar to those obtained in the study of Franaszczuk et al. (1998) for patients with mesial temporal lobe epilepsy.

Then we applied the methods based on comparison between dynamics in different time series segments with calculation of the matrices of distances (see Section 2). Fig. 5a shows the results of comparison with use of χ^2 as the measure of distance. The length of each segment that is compared to the others is 400 data points (2 s) that appears already more or less sufficient for obtaining a good estimate of the probability distribution for the number of bins $L=50$. As one can see from the figure, the seizure is divided into two quasi-stationary parts: from the 20th sec to the 80th sec, and the segment from the 80th sec to the 128th sec. The segments before the 20th sec and after the 128th sec are indistinguishable from the background (interictal) EEG according to this criterion. The change in the distribution function takes place around the 80th sec, which corresponds to the time instant of the frequency change. Other changes in frequency are not accompanied by changes of distributions, thus the results of probability distributions comparison appear to be less informative here than the spectrogram or wavelet transform.

A more detailed picture can be obtained with the analysis of dynamical nonstationarity by comparing coefficients of the global models. Note that it is desirable to specify the moving window length as small as possible to enhance temporal resolution of the analysis. Since global models involve relatively small number of parameters, it appears possible to use windows of the length of 400 data points, which is less than required, e.g. for estimation of Fourier

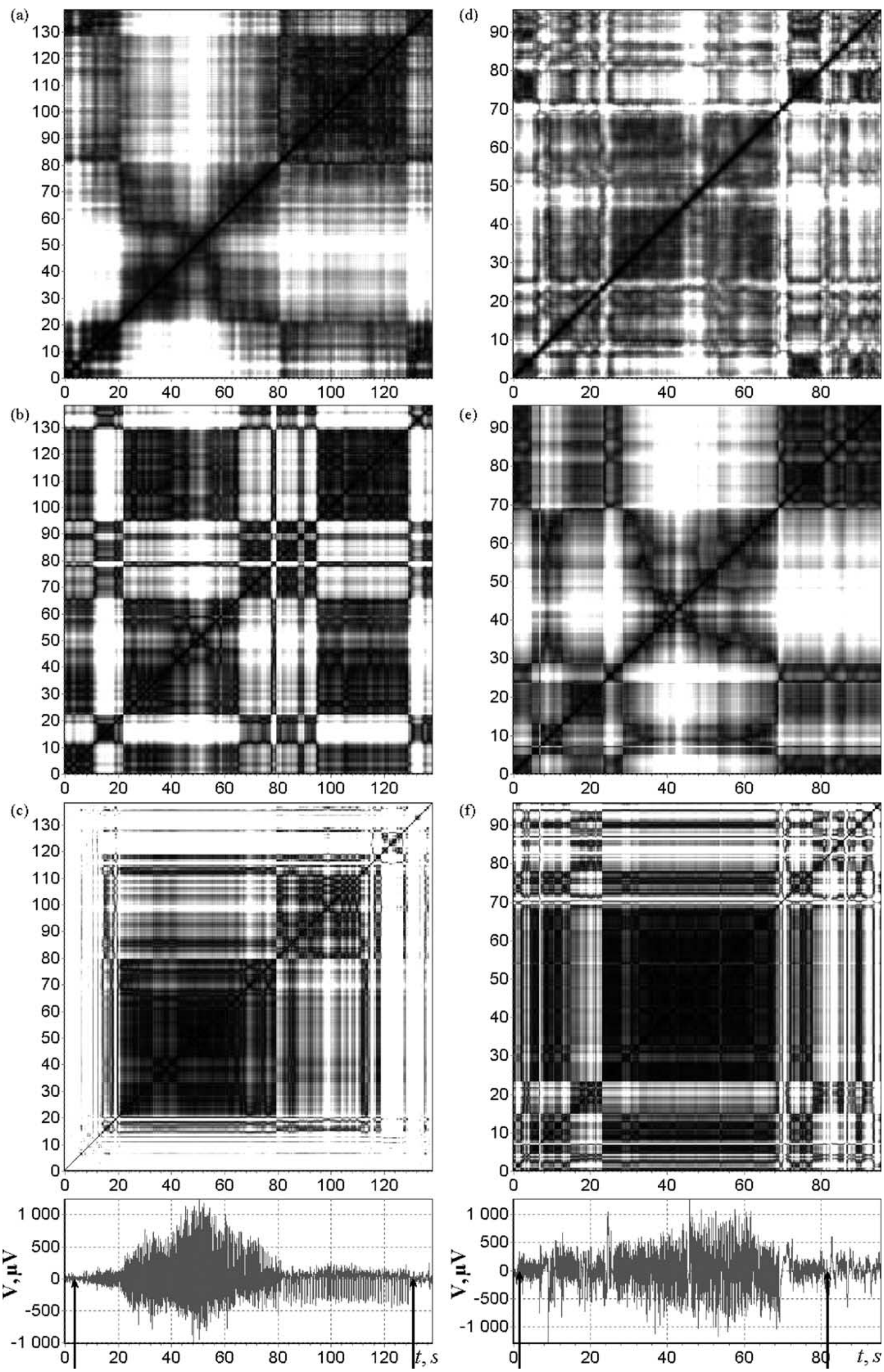

Fig. 5. The matrices of distances between the segments of the EEG time series recorded in patient 1 (a–c) and patient 2 (d–f) corresponding to the epileptic seizures. The distances are calculated using χ^2 criterion (a,d), Euclidean distances between vectors of coefficients of 6D global linear models (b,e) and between coefficients of 3D global nonlinear models with third order polynomial (c,f). The time series analyzed are shown at the bottom, the arrows indicate the onset and offset of the EEG seizure. Analysis through model coefficients gives additional information in both cases as compared to χ^2 criterion and to spectral techniques (see Fig. 3 for patient 1). Namely, different number and boundaries of quasi-stationary segments.

spectra. The matrix of distances between vectors of coefficients of linear 6-dimensional models of the form

$$x_{n+1} = \sum_{i=1}^{K} \alpha_i x_{n-i+1} + \alpha_0 \quad (8)$$

is shown in Fig. 5b. One can see that clear changes start approximately 10 s earlier than those observed through the previous criterion (Fig. 5a) or through the spectrogram (Fig. 4). The detection of quasi-stationary segments is performed with a clustering algorithm (Section 2.4) which finds two clusters in a set of time series parts. The obtained segments are indicated in Fig. 3 with the middle row of gray-colored bars.

The division of a time series parts into clusters does not depend significantly on the dimension K of the model (8) (when $K \geq 4$ the picture remains similar to Fig. 5b and the boundaries of the clusters are almost the same). One can see that the structure of quasi-stationary segments does not correspond completely to the one that can be obtained from spectrograms.

However, as demonstrated with the test example, the reconstruction of models those are not completely adequate leads to detection of only *statistical* nonstationarity of the time series. EEG recordings during epileptic seizures have been shown to contain nonlinearities (Andrzejak, 2001a,b; Palus, 1996; Schiff, 1999; Theiler, 1995) so we may presume that a linear model cannot be completely adequate. Therefore, the observed division into quasi-stationary parts does not correspond exactly to dynamical nonstationarity, but also reflects changes in a multidimensional distribution function.

Taking into consideration the nonlinearities inherent in EEG time series, we added nonlinear terms to our model (8). One of the fundamental problems that arise in this situation is the appropriate choice of the form of nonlinear function in model equations. We used polynomial nonlinearities (recalling that every continuous function can be approximated with an algebraic polynomial according to Weierstrass' theorem), but it is still possible that other, more accurate, forms exist. The number of coefficients in the polynomial function rises rapidly with model dimension and polynomial order. This can make the results unstable and sensitive to small deviations in the time series. Therefore, we used relatively low-order and low-dimensional models.

When dealing with nonlinear models, we should take into account that the coefficients corresponding to nonlinear terms depend on the normalization of the time series (or units of x). For example, if a quadratic term is present in the model ($x_{n+1} = \ldots + \alpha x_n^2 + \ldots$) and all values in the time series are multiplied by some constant c (change of the units of x), then the value of the coefficient α changes inversely proportional to c. To avoid this ambiguity, we normalize the EEG time series to unit variance, i.e. divide all values by the standard deviation of the time series. However, if the time series contains parts with significantly different amplitudes, their comparison becomes problematic and the results of the formal application of the procedures described above are questionable. Therefore when applying nonlinear models we will compare only time series segments within the seizure, where the amplitudes are approximately equal.

An example of nonlinear analysis of stationarity using a nonlinear model is shown in Fig. 5c. We used the model with dimension 3 and polynomial of order 3. The clustering algorithm leads to the detection of three types of time series segments which are denoted in Fig. 3 with the lower row of gray bars. In addition, there are a number of segments where the coefficients of nonlinear models are quickly changing. These parts are different from each other, so that after application of clustering algorithm, they form many individual clusters. They correspond to the white gaps in the lower row of bars.

The use of slightly different (lower) values of dimension or polynomial order does not change the picture. The use of more complicated models (with greater dimension or order of the polynomial) leads to the strong instability of the coefficients (in part, due to the large number of them). Within the seizure they change continuously and no segments with constant properties are detected.

Patient 2. The second recording was taken from a 33 year-old woman with right temporal lobe epilepsy. The depth electrode recording contact analyzed was situated in the right hippocampus within the epileptogenic focus and the time series studied corresponded to the seizure from EEG onset through offset. The spectrogram in this case did not allow detection of a clear structure of the seizure (figure not shown because it is not informative). Stationarity analysis through the χ^2 criterion (Fig. 5d) is also unsuitable for this purpose. The only pronounced change in distribution takes place around the 70th sec and corresponds to a sharp change in amplitude of the oscillations.

Analysis with global linear models (8) (Fig. 5e) allows easy detection of three quasi-stationary segments: before the 24th sec, from the 24th to 70th, and after the 70th sec. An even more detailed picture can be obtained with nonlinear models (dimension 3, third order polynomial) (Fig. 5f). The ictal segment before the 24th sec is now divided into two parts, and the last part of the seizure after the 70th sec is seen to precede the permanent post-ictal changes after the 82nd sec.

Patient 3. The third recording was recorded from a 46 year-old woman with left temporal lobe epilepsy. The seizure had started in the left temporal neocortex and subsequently spread to the ipsilateral hippocampus. Fig. 6 shows the results of analysis of the data recorded from the left temporal neocortex. Changes start at approximately the 98th sec, closely corresponding to seizure onset. The only change in the spectrogram consisted of an increase of the characteristic frequency of the oscillations between the 130th and 185th sec. The stationarity analysis based on χ^2 criterion did not show any pronounced changes in the time series.

At the same time, the analysis based on the linear (Fig. 6a) and nonlinear (Fig. 6b) models allowed for

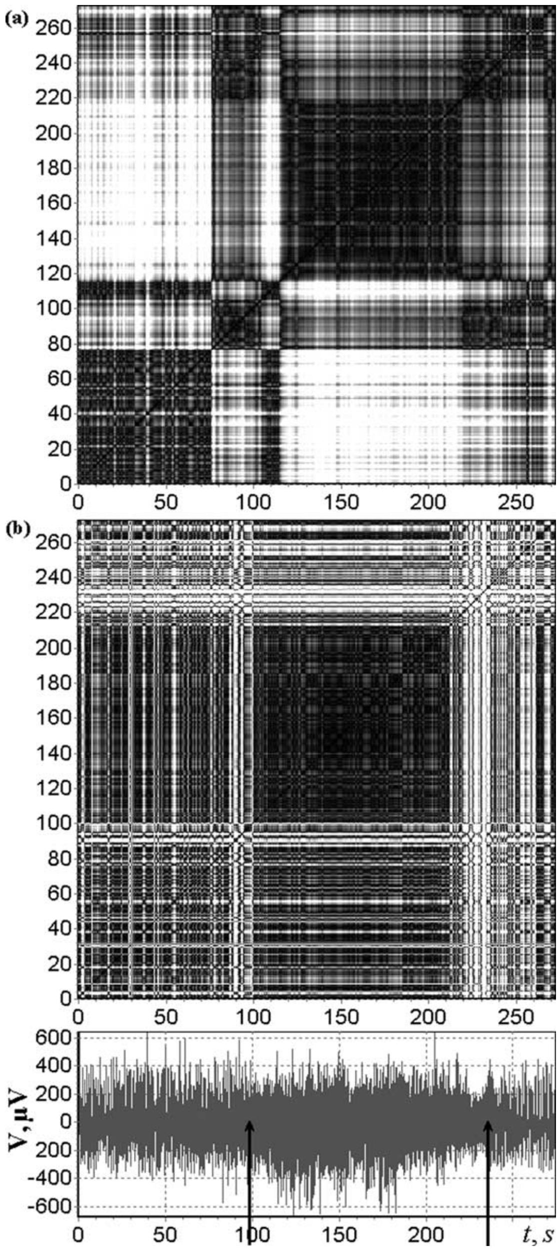

Fig. 6. The matrices of distances between the segments of the third EEG recording with epileptic seizure, which starts approximately at $t=98$ s. The distances are calculated as Euclidean distances between vectors of coefficients of 6D global linear models (a) and between coefficients of 3D nonlinear models with third order polynomial (b). The arrows on EEG trace indicate the onset and offset of the seizure. Note, on the one hand, the ‘more stable’ structure detected through the linear model, and, on the other hand, the changes at 90th sec captured with coefficients of the nonlinear model, when the seizure onset is not yet identified both by eye and linear model coefficients.

a clearer detection of changes and detected several quasistationary segments obtained with the linear models. The fact that changes in the coefficients of the linear models start even before the changes in EEG can be detected by eye suggests that this method could be used for precise seizure localization in time, and also for localization of the epileptogenic focus when multichannel recording is performed.

4. Discussion

Most studies consider nonstationarity a hindrance and an obstacle for analysis of a system’s behavior. However, the analysis of the character of nonstationarity itself can provide useful information about the system under study. In particular, in this work, we can see different dynamical regimes in such a complicated system as the epileptogenic human brain. We discuss different methods of nonstationarity analysis, both statistical (spectrogram, wavelet transform, comparison of probability distribution functions in moving windows) and dynamical ones (comparison of global dynamical models constructed from parts of epileptic EEG recording). Using dynamical methods, one can obtain more detailed information about changes in the system.

The visualization of the results of the comparison between time series segments (matrices of distances between different parts) in the form of diagrams similar to recurrence plots (Eckmann et al., 1987) allows detection of quasi-stationary segments where dynamical or statistical properties remain approximately constant. To make this detection less subjective a clustering algorithm is applied.

In particular, the epileptic seizures in all considered examples can be divided into 3–4 stages. At the present time, we cannot provide a clear neurophysiologic interpretation for these stages, but the presence of several dynamical regimes during seizures has been reported using other dynamical methods (Perez Velazquez et al., 2003). The fact that the characteristic regimes that have been found near seizure onset and offset represent the unstable dynamics of type-III intermittency and period doubling (typically found near bifurcation points in a dynamical system, where phase states change abruptly from one regime to another, e.g. periodic or quasi-periodic to chaotic, or vice versa), suggests that seizures start and stop in direct relation to these rapid transitions in state (Perez Velazquez et al., 1999, 2003). Nonstationarity analysis may provide a way to predict the occurrence of impending state changes in a simple and accurate fashion. Future work can be directed toward the investigation and classification of different seizure stages in the case of specific epileptic syndromes. Furthermore, and importantly, when applying any method based on nonlinear dynamics (or chaos theory), the dynamical stationarity of the time series becomes a crucial point. Hence, it is advisable to detect, as a first step, the dynamically quasi-stationary parts of the time series and then to restrict the application of such methods to these quasi-stationary segments to make interpretation of the results more clear and reliable.

As it is clear from the considered examples, the changes in dynamics often start before they can be detected by visual inspection. Hence, the proposed nonstationarity analysis can potentially provide a new method for seizure identification and help to understand the global, network mechanisms of seizure onset and termination.

The observations reported here are also interesting from a practical, possibly clinical, perspective, considering the current pursuit of methods to control brain activity, specifically the transition to the ictal event (Khosravani et al., 2003). A precise knowledge of the dynamics may be imperative for the application of possible 'chaos control' methods (Ott et al., 1990).

Even the use of simple models in the form of maps provides additional information about such complex processes as brain activity. In spite of the simplicity of the model form, the changes in model coefficients allow us to obtain additional information about epileptic seizure structure, which is not accessible through traditional statistical methods. At the same time, a careful selection of the structure of the model equations is necessary for successful analysis of dynamical nonstationarity (see the test example in Section 2.2). This study represents some initial steps in this investigation and demonstrates the potential applicability and usefulness of dynamical methods.

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