Time Reversibility of Intracranial Human EEG Recordings in Mesial Temporal Lobe Epilepsy

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Abstract

Intracranial electroencephalograms from patients suffering from mesial temporal lobe epilepsy were tested for time reversibility. If the recorded time series is irreversible, the input of the recording system can not be a realisation of a linear Gaussian random process. We confirmed experimentally that the measurement equipment did not introduce irreversibility in the recorded output when the input was a realisation of a linear Gaussian random process. In general, the non-seizure recordings are reversible, whereas the seizure recordings are irreversible. These result suggest that time reversibility is a useful property for the characterisation of human intracranial EEG recordings in mesial temporal lobe epilepsy.

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Preprint submitted to Elsevier Science *9th April 1996*

1 Introduction

Recently, much attention has been paid to the use of nonlinear analysis techniques for the characterisation of electroencephalographic (EEG) recordings [1,2]. These analysis methods may provide insight into the dynamics of the mechanisms generating EEG potentials in general and the pathophysiology of brain disorders such as epilepsy in particular. For that purpose correlation dimension and Lyapunov exponents have been estimated from EEG recordings.

In one of the first nonlinear EEG analyses, Babloyantz and Destexhe [3] have claimed a low correlation dimension of a scalp derived (surface) EEG recording of a petit mal (absence) seizure. Surface epileptiform EEG has also been analysed by Frank et al. [4]. In two seizure recordings low estimates of the correlation dimension were obtained, as well as positive Lyapunov exponents. Iasemidis et al. [5] have estimated the largest Lyapunov exponent from human intracerebral electrocorticogram recordings of partial, focal seizures in a moving window paradigm. They reported smaller, positive exponents during the seizure as compared to the pre- and postictal phase. Electrocorticograms of 20 patients suffering from unilateral temporal lobe epilepsy have been analysed by Lehnertz and Elger [6]. The correlation dimension was estimated as a function of time using a moving window. The variability of the dimension estimates in a group of subsequent windows was found to be a good indicator of the lateralisation of the zone of ictal onset.

By now it is well appreciated that the methods that have been developed to characterize nonlinear dynamical systems from experimental time series may easily produce spurious results when not applied and interpreted with care [7,8]. A more modest goal is the identification of nonlinear structures in the time series. Various ways of testing the null hypothesis (H_0) that a time series is a realisation of a (nonlinear static transformation of a) linear Gaussian random process (LGRP) have been proposed. An example is the method of surrogate data [9]. Other methods test the residuals of a linear model fitted to the data [10] or use sample estimates of higher order moments [11], see [12] for an overview.

Pijn et al. [13] have analysed intracerebrally recorded EEGs in the electrical kindling model of epilepsy in the rat. The H_0 that the time series is a realisation of a LGRP was tested by visually comparing the local slope of the correlation integrals of the data with a single surrogate signal. Evidence for nonlinearity was obtained for some EEG epochs recorded in the epileptogenic region. Furthermore, it was found that as different brain areas become successively recruited in generating seizure activity, the estimated correlation dimension of the EEG is decreased. Recently, Theiler [14] applied a novel type of surrogate data to a scalp derived EEG during status epilepticus. These surrogates were obtained by shuffling the order of the spike-and-wave complexes. The H_0 that there is no correlation between the successive spike-and-wave patterns could be rejected only by using the height of the 7^{th} peak of the autocorrelation function as the test statistic.

An important property of time series is their behaviour under reversal of time direction. A time series is time reversible if its statistical properties are invariant with respect to time reversal. In this Letter we apply a recently proposed test for reversibility of time series [15] to intracranial EEG recordings from patients suffering from mesial temporal lobe epilepsy. If reversibility can be statistically ruled out, the EEG recording can not be a realisation of a nonlinear static transformation of a LGRP, so that some light is shed on the structure of the underlying process generating the time series.

2 Reversibility

The use of reversibility for the characterisation of stochastic processes has been discussed by Weiss [16]. He showed that all LGRPs are reversible. However, the converse is not necessarily true; reversible nonlinear processes can be constructed [15], as well as reversible nonGaussian linear ones [16]. The rejection of the H_0 of reversibility implies that the time series can not be a realisation of a LGRP possibly followed by any operation which is symmetric with respect to time reversal, i.e. a transformation which commutes with the time reversal operator P. For instance, all static transformations of a time series belong to this class.

A measure of time irreversibility to classify tremor time series has been employed by Timmer et al. [17]. It is based upon the differences between the conditional probabilities of the time series read forward and backward in time.

Two statistical tests for time reversibility were developed in [11]. As a test statistic the first uses the difference between the sample estimates of the third order cumulant of the time series and that of the time reversed one, while the second utilises the estimated imaginary part of the sample bicoherence.

We will now briefly describe the test for reversibility used in this Letter. Let $\{x_n\}_{n=1}^{N}$ be a stationary time series of length N and

$$\vec{y}_n = (x_n, x_{n+\tau}, \ldots, x_{n+(m-1)\tau}) \tag{1}$$

the m dimensional delay vectors constructed from this time series using a delay of τ samples. The time series is called reversible if the probability distribution $\rho(\vec{y})$ of the delay vectors is invariant under time reversal for all m and τ, i.e.

$$\rho(P\vec{y}) = \rho(\vec{y}) \tag{2}$$

where P denotes the time reversal operator which is defined as

$$P: \qquad \left(x_t, x_{t+\tau}, \cdots, x_{t+(m-1)\tau}\right) \mapsto \left(x_{t+(m-1)\tau}, \cdots, x_{t+\tau}, x_t\right). \tag{3}$$

The test for reversibility is based on the invariance of the delay vector distribution with respect to time reversal [16] and has been described in more detail in [15]. It involves the calculation of a kernel estimator of the square Q of a distance measure between the time forward and time reversed distributions, viz.

$$Q = \frac{1}{2}\left(d\sqrt{\pi}\right)^m \int d\vec{y}\ \left[\rho'(\vec{y}) - \rho'(P\vec{y})\right]^2 \tag{4}$$

where d denotes the kernel bandwidth and $\rho'(\vec{y})$ is

$$\rho'(\vec{y}) = \left(\frac{2}{\pi d^2}\right)^{\frac{m}{2}} \int d\vec{r}\ \rho(\vec{y})\ \exp(-2|\vec{y} - \vec{r}|^2/d^2). \tag{5}$$

An unbiased estimator $\widehat{Q}$ of Q is given by

$$\widehat{Q} = \frac{2}{N(N-1)} \sum_{i<j} w_{ij} \tag{6}$$

where

$$w_{ij} = \exp(-|\vec{y}_i - \vec{y}_j|^2/d^2) - \exp(-|\vec{y}_i - P\vec{y}_j|^2/d^2). \tag{7}$$

Under the H_0 the expected value of $\widehat{Q}$ is equal to 0 and its standard deviation σ is given by

$$\sigma = \frac{2}{N(N-1)} \left(\sum_{i<j} w_{ij}^2\right)^{\frac{1}{2}}. \tag{8}$$

The test statistic S is now defined as follows

$$S = \frac{\widehat{Q}}{\sigma}. \tag{9}$$

Under the H_0 and assuming independent samples from the delay vector distributions, S has expected value 0 and unit standard deviation. We remark that the asymptotic distribution of S may not be normal. However, assuming unimodality, reversibility can be rejected at a significance level of at most 0.05 when the test statistic S takes on a value larger than 3 [15].

When the time series samples are correlated, $\widehat{Q}$ may become biased. This effect is suppressed by excluding all pairs from the calculation of S which are closer in time than some lag W [18]. However, this exclusion procedure does not correct for the systematic errors in the standard deviation of $\widehat{Q}$ introduced by higher order dependencies between the delay vectors. For instance, a pair (i, j) of reconstruction vectors $\vec{y}_i$ and $\vec{y}_j$ with $|i-j| > W$ may be independent but the contributions of (i, j) and $(i, j+k)$ where $k < W$ to the estimate of the variance of $\widehat{Q}$ are not. One can suppress the latter effect by comparing non-overlapping *segments* (separated by a lag W) instead of single points [19]. These segments are trajectories in reconstructed phase space consisting of ℓ consecutive delay vectors. The (i, j) plane is thus divided into squares of size $\ell \times \ell$ and the terms w_{ij} in the calculation of $\widehat{Q}$ are replaced by averages over these squares $w'_{i'j'}$, viz.

$$w'_{i',j'} = \frac{1}{\ell^2} \sum_{p=1}^{\ell} \sum_{q=1}^{\ell} w_{i'\ell+p, j'\ell+q} \tag{10}$$

The heuristic argument for using this “segment” method is that the segments are to a large extent independent of each other, allowing for more reliable estimates of the standard deviation. We have used this modification of the reversibility test in all our calculations.

3 The Recording System

The recording system used was a DG32 (Medelec, Vickers Medical, Old Woking, GB) in combination with a custom-built data acquisition system. The combined system includes an analog-digital and digital-analog step to enable digital cable telemetry from the patient to a central monitoring and data storage unit. [3]

We have confirmed experimentally that irreversibility is not introduced into the recorded data by signal operations in the data recording process. To this end, a linear Gaussian noise source (thermal resistor noise) was used as input to the system. A time series with a length of 10^4 samples was recorded directly from the noise source at 240 Hz. The first minimum (T)of the mutual

[3] A more detailed description of the recording system is beyond the scope of this Letter. More information may be obtained from the authors on request.

information function of this time series was equal to 1 sample time.

The noise signal entered the data flow after the amplification of the electrode output. We recorded a time series of length 10^4 of the output of the recording system also with a sampling frequency of 240 Hz. A new time series was made of this output recording by post-processing it using a linear, high-pass Butterworth filter (3^{rd} order, cut-off frequency 1 Hz) which was also used on the EEG to remove the lowest frequency components. For both the filtered and the unfiltered output time series, T was found to be equal to 4 sample times. The input as well as both output time series were tested for reversibility. The reversibility test parameters were: $m = 4$, delay $\tau = T$, $W = 4T$ and $d = 0.46$ standard deviations of the time series. Segment length ℓ was set at $8T$. For all the above mentioned time series, the H_0 could not be rejected. This result was found to be robust with respect to changes in the test parameters. These results indicate that when the input to the recording system is a LGRP, no irreversibility is introduced into the recorded data.

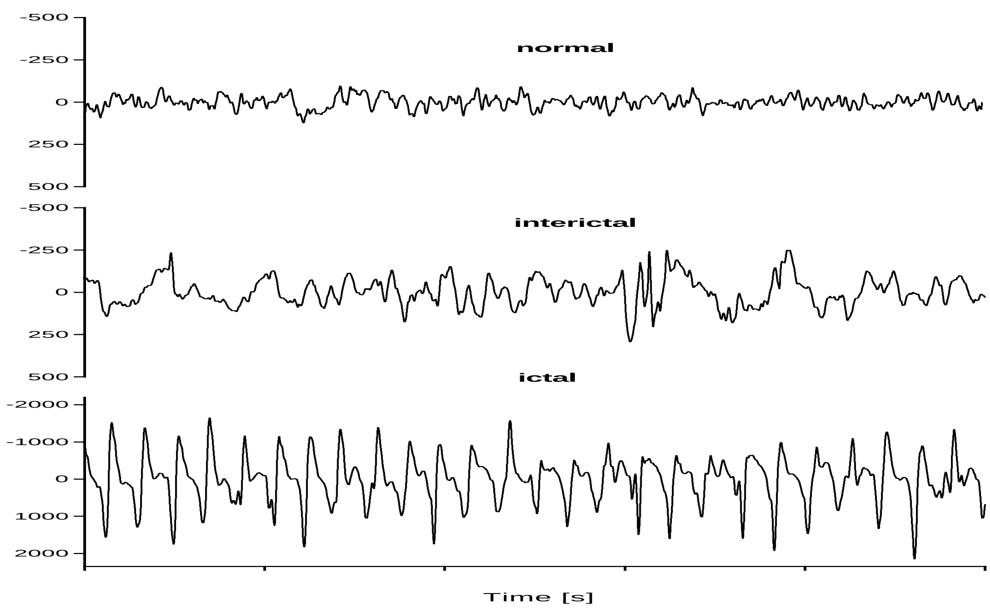
It is known that any linear filtering does not change the reversibility property of a time series generated by a LGRP since the result is again a LGRP. However, this is not generally true for the linear filtering of a nonlinear static transformation of a realisation of a LGRP. Therefore, the use of filters in the recording system or post-processing may lead to the rejection of the H_0 of a nonlinear static transformation of a LGRP for the recorded *output* when the *input* of the recording system actually is a nonlinear static transformation of a LGRP. This is also the case when a nonlinear static transformation is present in the recording system prior to the filtering or post-processing.

Thus, rejecting reversibility for the *recorded* output time series amounts to the rejection of a LGRP (without the nonlinear static transformation) as a model for the recording system *input* at most.

4 Reversibility Test of EEG

We investigated intracranially recorded 32-channel EEG records of five patients selected on the basis of unequivocal unilateral mesial temporal seizure onset and an excellent control of seizures following temporal lobe resection. Four channels were selected from two patients while five channels were selected from the remaining three. From each patient one of the selected channels was recording EEG from a brain site remote to the zone of seizure onset. The remaining channels were recording EEG close to the zone of seizure onset or structures concluded to be important in seizure onset and propagation. From each channel two epochs were selected. The first epoch consisted of EEG which was deemed not to contain seizure activity and recorded well before seizure onset. The second epoch was recorded during a period in which one or more channels displayed fully developed seizure activity. Epoch length was 19 s, sampling rate 240 Hz and resolution 12 bits. All epochs were post-processed as described in the previous section. The epochs were scored by an experienced EEG-er (D.N.V.) as either *ongoing electrical activity* (called "*normal*" in the sequel), *interictal* (EEG with the occurrence of so-called interictal spikes), or *ictal* (seizure activity). One epoch was scored as *inconclusive* and removed from the data set. Typical examples of these different EEG types are displayed in Fig. 1.

Figure 1. Examples of normal (top trace), interictal (middle trace) and ictal (bottom trace) post-processed EEG epochs (5.0 sec. length). The amplitude of the signal is expressed in arbitrary units. Note differences in scales for the amplitudes of the top two traces with respect to the bottom one.



The reversibility tests of the EEG were performed with the same parameter settings used for the testing of the recorded output corresponding to the LGRP input, as described in the previous section. When S exceeds 3 we reject the H_0 at a significance level of at most 0.05 and call the time series irreversible. The results are summarised in Table 1.

Of the 16 single channel records that were scored as normal epochs, 13 were found to be reversible (Table 1, first column). The remaining 3 irreversible ones showed marked influences of ictal activity through the reference electrode. The group of 18 EEG epochs scored as interictal, included 16 reversible ones (Table 1, second column). Using a 5% significance level, this is not inconsistent with the assumption that all interictal epochs are reversible. However, the 2 irreversible interictal epochs may be special in the sense that they were the

Table 1
Summary of the time reversibility test results of the EEG epochs. Test parameters are as indicated as in the text.

	normal	**interictal**	**ictal**
total	16	18	11
reversible	13	16	0
irreversible	3	2	11

only epochs recorded during a period the ictal activity had just "faded" close to the recording electrodes. Propagation of ictal activity to other brain areas, where the ictal activity was much more pronounced, had already occurred. Finally, the recordings scored as ictal epochs were all found to be irreversible (Table 1, third column). We have repeated the calculations with different parameter values and obtained very similar, though not identical, results.

5 Discussion

In this Letter we tested EEG recordings for the property of time reversibility. The results indicate that normal and interictal EEG recordings are reversible, whereas the ictal EEG recordings are irreversible in temporal lobe epilepsy of mesial origin in man. From these results we conclude that the property of reversibility of a time series discriminates well between fully developed seizure activity and the absence thereof on the basis of intracranial EEG recordings in patients suffering from temporal lobe epilepsy. Furthermore, we found that ictal influences through the reference electrode on otherwise normal recordings may cause those epochs to be irreversible.

According to Cox [20], time irreversibility is a symptom of nonlinearity and/or nonGaussianity. More precisely, if reversibility can be rejected, a static transformation of a linear Gaussian random process can be excluded as an appropriate model for the time series.

We showed that the measurement equipment did not introduce irreversibility in the recorded output when the input is the thermal noise signal of an Ohmic resistor which is generated by a linear Gaussian random process. However, signal operations are performed both by the recording equipment during data acquisition and during post-processing of the recorded data. Since a filtered realisation of a nonlinear static transformation of a linear Gaussian random process is, in general, irreversible, we can only reject a realisation of a LGRP as input of the recording system when the recorded time series is found to be time irreversible. In other words, the use of linear filters in the recording process results in the removal of the class of nonlinear static transformations of LGRPs from the null hypothesis for the recording system *input*. This means that when evidence for time irreversibility in the data is obtained, it may be caused by a trivial static nonlinearity and not by the nonlinear dynamics of the system generating the EEG.

It should be noted that the method of surrogate data is subject to a similar limitation. This is also due to the fact that, in general, filtering a nonlinear static transformation of a linear Gaussian random process does not result in a nonlinear static transformation of a linear Gaussian random process, i.e. nonlinear static transformations and linear filtering operations do not commute [21].

Our results suggest that the property of time irreversibility is characteristic for ictal intracranial EEG recordings in mesial temporal lobe epilepsy in man. This implies that for a more complete characterisation of such recordings additional nonlinear analysis techniques should be applied.

6 Acknowledgements

The patients were referred through the Dutch Collaborative Epilepsy Surgery Program. The authors gratefully acknowledge the expert assistance of the Departments of Electronics and Clinical Neurophysiology, the Epilepsy Monitoring Unit, and Mr. W. Blanes of the Instituut voor Epilepsiebestrijding as well as B.P.T. Hoekstra from the Dept. Physiology, Leiden University. They also wish to thank Dr. J. DeGoede, Prof. F.H. Lopes da Silva and Prof. F. Takens for clarifying discussions. Parts of this research have been funded by the Dutch Commission of Research in Epilepsy (CLEO) projects A-71 and A-88 (J.P.M.P.), the Dutch Epilepsy Foundation (NEF) project 95-01 (J.P.M.P.), and the NWO Nonlinear Systems priority program grant. no. 629-61-270 (M.J.v.d.H).

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