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Citation for published version:

Digital Object Identifier (DOI):
10.1088/0967-3334/30/2/006

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Early version, also known as pre-print

Published In:
Physiological Measurement

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Interpretation of the auto mutual information rate of decrease in the context of biomedical signal analysis. Application to electroencephalogram recordings

Javier Escudero, Roberto Hornero and Daniel Abásolo

Biomedical Engineering Group, E.T.S.I. Telecomunicación, University of Valladolid, Camino del Cementerio s/n, 47011, Valladolid (Spain)

E-mail: javier.escudero@ieee.org

Abstract

The mutual information (MI) is a measure of both linear and non-linear dependences. It can be applied to a time series and a time-delayed version of the same sequence to compute the auto mutual information function (AMIF). Moreover, the AMIF rate of decrease (AMIFRD) with increasing time delay in a signal is correlated with its entropy and has been used to characterise biomedical data. In this paper, we aimed at gaining insight into the dependence of the AMIFRD on several signal processing concepts and at illustrating its application to biomedical time series analysis. Thus, we have analysed a set of synthetic sequences with the AMIFRD. The results show that the AMIF decreases more quickly as bandwidth increases and that the AMIFRD becomes more negative as there is more white noise contaminating the time series. Additionally, this metric detected changes in the non-linear dynamics of a signal. Finally, in order to illustrate the analysis of real biomedical signals with the AMIFRD, this metric was applied to electroencephalogram (EEG) signals acquired with eyes open and closed and to ictal and non-ictal intracranial EEG recordings.

Keywords: Auto mutual information, biomedical signal analysis, electroencephalogram, non-linear analysis, signal regularity

PACS number(s): 05.45.Tp; 87.10.Vg; 87.85.Ng

1. Introduction

Several physiological signals, including cardiovascular and brain activity recordings, exhibit a partially non-linear behaviour (Andrzejak et al 2001, Hoyer et al 2002, Palacios et al 2007). Additionally, some authors have suggested that healthy systems have non-linear complex relationships that fail with ageing and disease (Costa et al 2005, Goldberger et al 2002). In this context, Information theory (Shannon and Weaver 1949) may provide a unique framework to statistically assess information taking into account non-linear features. One of the concepts derived from this theory is mutual information (MI). MI measures statistical dependence between and within signals and can be useful to characterise and analyse time series. This statistic estimates the information gained from observations of one random event on another (Cellucci et al 2005, Fraser and Swinney 1986, Pompe et al 1998). It evaluates both linear and non-linear dependences between two time series (Fraser and Swinney 1986, Pompe et al 1998). Hence, this metric is a non-linear, complementary counterpart to the classical correlation
dependence between different biomedical recordings (Hinrichs et al 2008, Hoyer et al 2005, 2007, Palacios et al 2007, Pompe et al 1998). This application is based on the fact that the MI quantifies the linear and non-linear statistical coupling between signals. Thus, it can be a useful tool to quantify synchronization (David et al 2004, Pompe et al 1998, Quian Quiroga et al 2002). In biomedical signal analysis, the CMIF of respiratory and heart rate variability recordings provides useful information to detect cardiac and respiratory diseases (Alonso et al 2007, Hoyer et al 2002). The statistical dependences between different brain regions have also been assessed with MI techniques in several brain states (Hinrichs et al 2008, Huang et al 2003, Min et al 2003, Teplan et al 2006, Xu et al 1997) and neurological disorders, like Alzheimer's disease (Benedetti et al 2006, Jeong et al 2001) or schizophrenia (Na et al 2002).

The AMIF rate of decrease (AMIFRD) with increasing time delay is correlated with signal entropy (Paluš 1996). Thus, the decay of the AMIF may be considered a measure of signal predictability (Fraser and Swinney 1986, Jeong et al 2001, Palacios et al 2007). It has been previously shown that the AMIFRD provides relevant information about the underlying physiological systems (Hoyer et al 2005). This metric has been applied to study several pathophysiological conditions. For example, the AMIFRD of electroencephalogram (EEG) and magnetoencephalogram (MEG) recordings characterised patients with Alzheimer’s disease in contrast to control subjects (Abásolo et al 2008, Jeong et al 2001, Gómez et al 2007). This metric also shows differences between the EEG of schizophrenic patients and that recorded from control subjects (Na et al 2002). In addition, different AMIF decay parameters can help to detect several cardiomyopathies from cardiac data (Hoyer et al 2002, 2005, Palacios et al 2007).

Due to the relevance and the possible usefulness of the AMIFRD in various biomedical analyses, it is important to understand and exemplify the behaviour of this metric for diverse kinds of signals. It is worth mentioning that several studies have illustrated the behaviour of the CMIF for some test sequences in contrast to the correlation function (David et al 2004, Hoyer et al 2002, Paluš et al 1993, Pompe et al 1998, Quian Quiroga et al 2002). Moreover, the decay of the AMIF has been compared with other entropic measures (Abásolo et al 2008, Hoyer et al 2005). Following these research works, this study aims at pointing out the relationships between the AMIFRD and straightforward signal characteristics like noise power or non-linear dynamics to gain a better understanding of this metric. Furthermore, we want to illustrate the application of the AMIFRD to biomedical signals by analyzing real surface and intracranial EEG data.

2. Auto mutual information function rate of decrease (AMIFRD)

MI is based on concepts from Information theory (Shannon and Weaver 1949). Let $X(t) = \{x(1), x(2), \ldots, x(T)\}$ be a sequence acquired from a stochastic process (Alonso et al 2007). If the amplitude values of the variable $X(t)$ are partitioned into $I$ bins, a probability $p_i^X = n_i^X / T$ can be assigned to each possible partition $X_i (i = 1, \ldots, I)$, where $n_i^X$ is the number of samples in $X_i$ (David et al 2004, Gómez et al 2007). Shannon’s entropy for $X(t)$, which is denoted by $H(X)$, is the average amount of information gained from any observation of $X(t)$ (Shannon and Weaver 1949):

$$H(X) = - \sum_i p_i^X \log_2 (p_i^X). \quad (1)$$
Let $X(t)$ be coupled with another signal, $Y(t)$, which was measured and found in a partition bin $Y_j(j = 1, \ldots, J)$ with an associated probability $p_j^Y = n_j^Y / T$, where $n_j^Y$ is the number of samples in $Y_j$. Then, the uncertainty about $X(t)$ is (Jeong et al 2001):

$$H(X|Y_j) = -\sum_i \frac{p_{ij}^{XY}}{p_j^Y} \log_2 \left( \frac{p_{ij}^{XY}}{p_j^Y} \right),$$

(2)

where $p_{ij}^{XY}$ is the joint probability for the partitions $X_i$ and $Y_j$ of the variables $X(t)$ and $Y(t)$, in that order. The mean uncertainty of $X(t)$, under the condition that $Y(t)$ is known, is computed averaging $H(X|Y_j)$ over $p_j^Y$ (Min et al 2003):

$$H(X,Y) = \sum_j p_j^Y H(X|Y_j) = -\sum_{i,j} p_{ij}^{XY} \log_2 \left( \frac{p_{ij}^{XY}}{p_j^Y} \right) = H(X,Y) - H(Y)$$

(3)

where

$$H(X,Y) = -\sum_{i,j} p_{ij}^{XY} \log_2 \left( \frac{p_{ij}^{XY}}{p_i^X p_j^Y} \right).$$

(4)

$MI$ estimates the information obtained from measurements of one event on another – i.e., the reduction in the uncertainty of $X(t)$ when $Y(t)$ is known – (Cellucci et al 2005, Fraser and Swinney 1986, Pompe et al 1998):

$$MI(X,Y) = H(X) - H(X|Y) = H(X) + H(Y) - H(X,Y),$$

(5)

which can be rewritten as (Gómez et al 2007, Jeong et al 2001, Na et al 2002):

$$MI(X,Y) = \sum_{i,j} p_{ij}^{XY} \log_2 \left( \frac{p_{ij}^{XY}}{p_i^X p_j^Y} \right).$$

(6)

This expression represents the cross mutual information between $X(t)$ and $Y(t)$. It is zero when $X(t)$ and $Y(t)$ are statistically independent (Chapeau-Blondeau 2007, Hoyer et al 2002). The $CMIF(\tau)$ is obtained estimating $p_{ij}^{XY}$ and $p_j^Y$ from successive time-delayed versions of $Y(t)$: $Y(t + \tau)$ (Hoyer et al 2002, Jeong et al 2001, Na et al 2002, Xu et al 1997). Similarly, $AMIF(\tau)$ is computed replacing $Y(t + \tau)$ with time-delayed versions of $X(t)$, $X(t + \tau)$ (Gómez et al 2007, Jeong et al 2001):

$$AMIF(\tau) = \sum_{i,j} p_{ij}^{X(t)X(t+\tau)} \log_2 \left( \frac{p_{ij}^{X(t)X(t+\tau)}}{p_i^X p_j^Y} \right).$$

(7)

The $AMIF(\tau)$ measures statistical predictability within a signal, that is, the predictability of $X(t+\tau)$ from $X(t)$ (Gómez et al 2007, Jeong et al 2001). It is based on the amplitude distributions of $X(t)$ on different time scales, $\tau$ (David et al 2004). These amplitude distributions are estimated from histograms (Abásolo et al 2008, Alonso et al 2007, Gómez et al 2007, Jeong et al 2001).

Before estimating the histograms, a ranking transformation was applied to the time series $X(t)$ and $X(t+\tau)$ (Alonso et al 2007, Hoyer et al 2002, Pompe et al 1998). This ranking transformation from $X(t)$ to $X^*(t)$ is given by:
where \( N \{ \} \) denotes the cardinality (the number of elements) in the set (Alonso et al. 2007, Pompe et al. 1998). This transformation replaces the real values of \( X(t) \) with their ranks, that is, \( T \) times \( X^*(t) \) is the number of values in the original time series that are less than \( X(t) \). Then, these values are divided by \( T \), so that the transformed sequence is always uniformly distributed in the interval \([0,1)\) (unit interval) (Pompe et al. 1998). However, if and only if the multivariate ranked series \( (X^*(t), X^*(t+\tau)) \) have a uniform 2D-distribution, \( X^*(t) \) and \( X^*(t+\tau) \), and thus the original sequences \( X(t) \) and \( X(t+\tau) \), are statistically independent (Pompe et al. 1998). Thanks to this partition of the plane \((X(t), X(t+\tau))\), the estimation of the \( MI \) is more robust against outliers and artefacts in data (Alonso et al. 2007, Cellucci et al. 2005).

For a fixed sequence length, the estimations of the average probabilities are more accurate when larger bins are used to construct the histograms. However, the joint probability distribution could be too flat and the \( MI \) may be underestimated. On the other hand, smaller partitions may enhance the changes in the joint probability distribution over short distances, but they produce fluctuations due to the small sample size. Thus, \( MI \) may be overestimated (Fraser and Swinney 1986, Jeong et al. 2001). Very different criteria have been suggested in the literature to estimate the partition size used to construct the histograms (Cellucci et al. 2005). In this study, the influence of the number of bins in the \( AMIFRD \) was inspected by computing this metric for the synthetic signals described in Section 3.1 using histograms with \( I = 8, 16, 32, 64 \) and 128 partitions.

The \( AMIF(\tau) \) was estimated over a time delay from \( \tau = 0 \) to \( \tau = 0.5 \) s. This time lag has been previously used in several analyses of brain activity (Abásolo et al. 2008, Gómez et al. 2007, Jeong et al. 2001, Min et al. 2003, Na et al. 2002). Moreover, the \( AMIF(\tau) \) was normalized so that \( AMIF(\tau = 0) = 1 \) before computing the \( AMIFRD \) (Abásolo et al. 2008, Gómez et al. 2007, Jeong et al. 2001, Na et al. 2002). It should be noticed that for \( \tau = 0 \) the \( AMIF(\tau = 0) \) is computed between two identical sequences: \( X(t) \) and \( X(t+0) \). Thus, regardless of the analysed time series, it is fulfilled that (Hoyer et al. 2002, Quian Quiroga et al. 2002):

\[
AMIF(\tau = 0) = H(X).
\]  

Moreover, given the fact that a ranking transformation was applied to uniformly distribute the signal samples in the unit interval:

\[
AMIF(\tau = 0) = \log_2(I),
\]  

where, as mentioned earlier, \( I \) denotes the number of partitions used to estimate the histogram of \( X(t) \) (Hoyer et al. 2002, 2005, 2006).

The \( AMIFRD \) between \( \tau = 0 \) and the first relative minimum value was calculated as the slope of the line that fits the \( AMIF(\tau) \) in a least-squares sense (Abásolo et al. 2008, Gómez et al. 2007, Jeong et al. 2001). Therefore, different time scales were simultaneously considered when analysing the signal. This methodology can be useful when no information is known in advance about the prominent time scales of a signal, as it often occurs in biomedical applications (Hoyer et al. 2005, Palacios et al. 2007). This rate of decrease measures the information loss versus \( \tau \) (Hoyer et al. 2002) and it is correlated with signal entropy (Abásolo et al. 2008, Paluš 1996).

3. Study and application of the \( AMIFRD \)

3.1. Synthetic signals
This section describes the simulated signals used to study the AMIFRD in terms of simple concepts like additive noise power or non-linear dynamics. All these synthetic signals had a length of 150 s and their sampling frequency \( f_s \) was 150 Hz. Hence, they had 22500 sample points. These simulated time series are illustrated in figure 1, which shows their spectrogram, time plot and two zooms on the first and last time intervals to illustrate the changes in the signal characteristics.

3.1.1. Test a: MIX process

This test analysed how the evolution from a stochastic signal to a periodic deterministic sequence affected the AMIFRD. For this purpose, we created a MIX process used in previous studies (Ferrario et al. 2006, Pincus 1991). It is defined as:

\[
MIX = (1 - z)x + zy,
\]

where \( z \) is a random variable which is equal to 1 with probability \( p \) and equal to 0 with probability \( 1 - p \), \( x \) is a periodic sequence generated by \( x_k = \sqrt{2} \sin(2\pi k/12) \), and \( y \) is a uniformly distributed variable on \([-\sqrt{3}, \sqrt{3}]\) (Ferrario et al. 2006, Pincus 1991). The synthetic signal was based on a MIX process whose parameter \( p \) varied from 0.9 to 0.1 linearly. Hence, this sequence, which is shown in figure 1(a), evolved from randomness to orderliness.

3.1.2. Test b: Quasi-periodic signal plus noise

The objective of this test was to find out whether the AMIFRD is sensitive to changes in power of noise added to quasi-periodic signals. Thus, we generated an amplitude-modulated quasi-periodic signal with additive white Gaussian noise of diverse power. This sequence is similar to that used in Aboy et al. (2006) or Hornero et al. (2005). The time series was created as an amplitude-modulated sum of two sine waves with frequencies at 0.61 Hz and 1 Hz. The first 30 s of this sequence were noise-free. Afterwards, white Gaussian noise was added to the signal, with the noise power increasing every 15 s. Figure 1(b) plots this time series.

3.1.3. Test c: Autoregressive process

In this test, the dependence between the AMIFRD and the spectral content of coloured noise was studied. An autoregressive process of order \( 1 - AR(1) \) was created varying the model parameter, \( \rho \), from +0.9 to −0.9 linearly. Thus, its energy moved from low to high frequencies. When \( \rho \) was equal to 0, the sequence corresponded to Gaussian white noise. Figure 1(c) depicts the corresponding spectrogram, time plot and zoom views.

3.1.4. Test d: Logistic map

This test aimed at determining whether the AMIFRD is able to detect changes from periodic to chaotic behaviour in a signal. This analysis was based on the logistic map, which depends on the model parameter \( \mu \) (Ferrario et al. 2006, Pincus 1991):

\[
x_k = \mu x_{k-1} (1 - x_{k-1}),
\]

The synthetic signal was composed by 2 segments of 11250 data points. The first one was generated with \( \mu = 3.55 \). With this parameter, the time series oscillated among 8 values (Baker and Gollub 1990). The second segment was computed with \( \mu = 3.60 \) in order to create chaotic oscillations (Baker and Gollub 1990). Figure 1(d) exemplifies this simulated signal.

3.1.5. Test e: Lorenz system
In this test, we studied whether the AMIFRD detects changes in the behaviour of a non-linear system like the Lorenz attractor, which is given by:

$$\begin{align*}
x &= \sigma(y - x) \\
y &= x(\rho - z) - y \\
z &= xy - \beta z
\end{align*}$$  \quad (13)

where $\sigma$, $\beta$, and $\rho$ are the system parameters (Baker and Gollub 1990, Kantz and Schreiber 1997). The first segment of this synthetic sequence had a length of 11250 samples and it was generated with $\sigma = 10$, $\beta = 8/3$ and $\rho = 28$. Thus, it exhibited a chaotic behaviour. The second segment also

Figure 1. Spectrograms, time plots and zoom views on the first and last time intervals of the synthetic signals. (a) Test a: MIX process which evolves from randomness to periodic oscillations. (b) Test b: Quasi-periodic signal with increasing additive noise power. (c) Test c: AR(1) process with variable parameter. (d) Test d: Logistic map divided into periodical and chaotic parts. (e) Test e: Lorenz system with two different non-linear dynamics.
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had 11250 points and was created with $\sigma = 10$, $\beta = 8/3$ and $\rho = 99.96$, which produced a torus knot (Baker and Gollub 1990, Kantz and Schreiber 1997). Both parts were generated using a fixed step-size first order integration method without pre-integration and with the step-size set to $1/f_s$. After the two parts had been created, they were normalized so that their standard deviation was equal to 1. Figure 1(e) displays the coordinate $x$, which was the time series analysed in this study.

3.2. Evolution with signal parameters

For every kind of synthetic signal, 250 independent realizations of the time series were created with different initial phases or random seeds. Then, for each of these independent realizations, the AMIFRD was computed in a moving window of 30 s (4500 data samples) with 90% overlap and $I = 8, 16, 32, 64$ and 128 partitions to construct the histograms. The 250 rates of decrease were averaged for each window. Therefore, we could test whether the AMIFRD is sensitive to changes in the signal parameters varied in this study.

3.3. Distribution of the AMIFRD for different kinds of signals

In addition to test how the AMIFRD changes with some signal parameters, we also studied its variability for three different kinds of sequence. We generated 10000 independent realizations of: 1) a logistic map with $\mu = 4$ (non-linear oscillator) (Hoyer et al 2002); 2) an AR(1) process with $\rho = +0.9$ (low-frequency linear oscillator) and 3) an AR(1) process with $\rho = -0.9$ (high-frequency linear oscillator). All these time series had a length of 30 s with $f_s = 150$ Hz (4500 sample points). The AMIF was computed with the number of bins that provided the most sensitive estimations to the changes in the synthetic signal parameters.

3.4. Application to real EEG recordings

Finally, the AMIFRD was applied to five groups of real EEG signals in order to illustrate the analysis of real biomedical time series with this metric. These recordings belong to the EEG database made available online by Andrzejak et al (2001) at the Department of Epileptology, University of Bonn. This section only describes these signals briefly.

Each of the five datasets contains 100 single-channel EEG signals of 23.6 s recorded with $f_s = 173.61$ Hz (4096 sample points). Subsets A and B contain surface EEG signals recorded from five healthy volunteers who were relaxed in an awake state. Whereas the subjects had their eyes open during the recording of the EEG in dataset A, the EEG signals of dataset B were acquired with eyes closed (Andrzejak et al 2001). The AMIFRD was also computed for three subsets (C, D and E) of intracranial EEG recordings from five epileptic patients, who had achieved complete seizure control after a surgical procedure (Andrzejak et al 2001). Signals in set D were recorded within the epileptogenic zone, whereas the EEGs of set C were acquired from the opposite brain hemisphere. Sets C and D contained only activity measured during seizure free intervals. On the other hand, set E was only composed of seizure activity recorded from all sites exhibiting ictal activity. Additional details can be found in Andrzejak et al (2001).

The AMIFRD was calculated using the number of partitions considered optimal after the simulated signals analyses. Prior to these computations, all EEG epochs were digitally filtered using a FIR band-pass filter with cut-off frequencies at 0.5 Hz and 40 Hz.

4. Results and discussion

This study aimed at characterising the behaviour of the AMIFRD in terms of straightforward signal processing concepts. In order to do so, we analysed different kinds of synthetic signals with the AMIFRD using $I = 8, 16, 32, 64$ and 128 bins to calculate the histograms. These results are depicted in figure 2. Despite the fact that the $MI$ value may be under- or over-estimated depending on the number of bins used to construct the histograms, figure 2 shows that the average AMIFRDs are relatively stable for a range of $I$ values. On the one hand, the AMIFRD
computed with 8 partitions was unable to show the changes in signal parameters in tests a and test d. On the other hand, in tests c and e, this metric provided less differences with $I = 128$ than with $I = 16, 32$ or 64 bins. Furthermore, the evolution of the AMIFRD for the studied signal parameters was similar when 16, 32 and 64 partitions were used to build the histograms. Thus, considering the results obtained with these test signals, the remaining analyses will be carried out using histograms of 32 bins.

The results of the test that aimed to determine whether the evolution from randomness to deterministic oscillations affects the AMIFRD are plotted in figure 2(a). This parameter detects changes in the content of a signal when it changes from randomness to orderliness.

In figure 2(b), it can be seen that the AMIFRD is sensitive to changes in additive noise power, becoming more negative as noise power increases. Despite the fact that the ranking transformation made the AMIFRD robust to artefacts in the signals (Alonso et al 2007), figure 2(b) indicates that this parameter depends on the signal-to-noise ratio (SNR) for quasi-periodic signals. Consequently, we can infer that the AMIFRD, even when the ranking transformation is applied, tends to saturate for low SNRs, offering the most negative values for completely noisy signals.

Using an $AR(1)$ process, we studied how the AMIFRD changed with the signal spectral content. The results are depicted in figure 2(c). This analysis proves that time series with wider spectra (e.g., white noise) produce more negative AMIFRDs. On the other hand, time series with

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Average results of the AMIFRD computed from the tests signals using $I = 8, 16, 32, 64$ and 128 bins to construct the histograms. (a) Test a: AMIFRD versus signal randomness. (b) Test b: Evolution of the AMIFRD with additive noise power. (c) Test c: Evolution of the AMIFRD with signal spectral content. (d) Test d: Relationship between the AMIFRD and periodic or chaotic behaviour. (e) Test e: AMIFRD versus two different types of non-linear dynamics.}
\end{figure}
narrower spectral content provide a smoother AMIF decay, irrespective of whether their spectra are centred at low or high frequencies. These results agree with a previous study that showed that white noise is more irregular than coloured noise (Hornero et al 2005). Figure 2(c) also suggests that the AMIF rate of decrease does not clearly distinguish between low or high-frequency noises.

Figure 2(d) shows the results of the test designed to assess how the change from a periodic to a chaotic signal affects the AMIFRD. The time series was composed of two segments generated using a logistic map. There is a sudden fluctuation in the AMIFRD values when the behaviour of the logistic map becomes chaotic. This fluctuation appears when both kinds of dynamics (periodic oscillations and chaos) are included in the moving window from which the AMIFRD is computed. When the moving window comprises only one kind of dynamics, the values of this metric are stable. In agreement with Hoyer et al (2002), it can be seen that the AMIFRD for white noise is more negative than that related to the logistic map since the former loses more information with τ.

Using the Lorenz system, we could explore whether the AMIFRD detects changes in the non-linear equations that govern this system. Figure 2(e) represents our results. It can be observed that the AMIFRD values are less negative than those of white noise. Nevertheless, this parameter shows a sudden change between both kinds of non-linear dynamics.

Figure 3 depicts the boxplots of the AMIFRD values for 10000 independent realizations of a non-linear (logistic map with μ = 4) and two linear oscillators – AR(1) processes with ρ = +0.9 and ρ = –0.9. These boxplots show that the ability of the AMIFRD to distinguish low- and high-frequency coloured noises is limited. This is due to the fact that the distributions of AMIFRD values for the AR(1) processes with ρ = +0.9 and ρ = –0.9 are similar (p-value = 0.0572, Mann-Whitney U-test). Additionally, it can be noted that the distribution of the AMIFRD for the non-linear chaotic oscillator is different from those of the linear AR(1) processes (p-value << 0.0001, Mann-Whitney U-test for the logistic map and the two AR(1) processes).

Figure 4(a) shows the boxplots for the distributions of the AMIFRD values obtained from real EEG signals acquired with eyes open and eyes closed. It is well-known that the closed-eyes condition produces certain changes in the EEG. One of the most remarkable alterations is the rise in the power of the alpha rhythm (oscillations between 8 Hz and 13 Hz) (Andrzejak et al 2001). Thus, the EEG spectrum is modified in comparison to the eyes-open case. This can be visually observed or studied with spectral analysis methods. Additionally, the boxplots depicted in figure 4(a) show that more negative AMIFRD values are related to the eyes-closed state (p-value << 0.0001, Mann-Whitney U-test for subsets A and B of the EEG database). Therefore, we can infer that the closing of eyes is associated with significantly more irregular EEG signals. Multichannel EEG signals recorded with eyes open and closed have also been analysed with other measures based on concepts like complexity and information transfer (Rapp et al 2005, Watanabe et al 2003). Those results associated the eyes open condition with an increase in algorithmic complexity and a decrease in the Tononi-Edelman complexity, which provided the greatest between-condition statistical significance (Rapp et al 2005). However, the diverse results obtained with these measures should be interpreted with care due to the different definitions of the complexity measures applied and the use of multichannel recordings in contrast to the single channel EEG signals analysed here with the AMIFRD. Figure 4(b) represents the boxplots for the AMIFRD values obtained from the subsets C, D and E of the EEG database. Similarly to the clear visual and spectral changes between ictal and non-ictal activity, there are very significant differences between the AMIFRD values computed for these states (p-value << 0.0001, Mann-Whitney U-test for subsets C, D and E of the EEG database). The differences are much more subtle between the inter-ictal EEG activity recorded from the epileptogenic zone and from the opposite brain hemisphere (p-value = 0.0343, Mann-Whitney U-test for subsets C and D).
In this study, the AMIFRD was estimated using a first-order least-squares fitting method (Abásolo et al 2008, Gómez et al 2007, Jeong et al 2001). Thus, we could assess the information loss on several time scales simultaneously. In contrast, other researchers have estimated AMIF decay parameters drawing a straight line between $\tau = 0$ and a certain $\tau_1$ (Na et al 2002, Palacios et al 2007). In the context of biomedical signal analysis, considering different time scales at the same time can be advantageous in comparison to the use of other non-linear measures based on one time scale only (Costa et al 2005). This is due to the fact that physiological mechanisms interoperate at different time scales simultaneously and it is difficult to define a priori a prominent time scale (Hoyer et al 2005, Costa et al 2005). Furthermore, analysing several time scales may be especially relevant when there is no clear knowledge about the specific time scales associated with the time series (Hoyer et al 2005). Thus, variables related to the time evolution of $MI$ may be more helpful to characterise a recording than its absolute values (Alonso et al 2007).

Our results support the idea that the AMIFRD, which is correlated with signal entropy (Abásolo et al 2008, Paluš 1996), is an irregularity estimator instead of a complexity measure, as some authors have previously suggested (Jeong et al 2001, Na et al 2002, Palacios et al 2007). From a strict point of view, a quantitative measure of complexity should vanish for both completely ordered and completely random signals like white noise, which is very unpredictable but not structurally complex (Costa et al 2005). However, this does not occur with the AMIFRD. A steeper decline of the AMIF for a given time series (implying a rise in irregularity) does not necessarily point out that physiologic complexity has increased (Goldberger et al 2002). However, a decreased irregularity can be found in several diseases (Abásolo et al 2008, Gómez et al 2007, Jeong et al 2001, Hoyer et al 2007). Similarly to previous studies, our EEG analysis shows that the AMIFRD may characterise biomedical signals acquired under diverse states. Examples of this application are the more negative AMIFRD distribution associated with the eyes-closed state in comparison to the eyes-open condition and the differences found between the ictal and non-ictal EEG activities. Furthermore, the use of the AMIFRD as a characterising metric in the analysis of experimental recordings has some advantages. Firstly, it can be applied to short time series in comparison to other non-linear classical analysis methods, such as the correlation dimension (Abásolo et al 2008, Gómez et al 2007, Jeong et al 2001). Secondly, the only input parameter for the AMIF is the number of histogram partitions (Jeong et al 2001, Na et al 2002). Finally, the $MI$ is invariant under strictly monotone transformations of the input sequences (Pompe et al 1998).

It should be noted that, in contrast to other studies (Hoyer et al 2005, Quiñ Quiroga et al 2002, Xu et al 1997), signals were not embedded in a phase space before computing $MI$. This
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Embedding should be carried out in order to consider higher dimensional relationships (David et al 2004, Pompe et al 1998). However, it would require larger signals, something that is not always possible, especially for biological recordings. Additionally, some advanced strategies can be applied to estimate MI, like the recursive algorithm by Fraser and Swinney (1986) or the recently proposed techniques by Cellucci et al (2005). Nevertheless, we have found that the straightforward computation of the histograms using 32 equal bins after applying a ranking transformation to the data (Pompe et al 1998) provided stable estimations of the AMIFRD.

5. Conclusions

In recent years, the AMIFRD has been widely used in biomedical signal analysis (Abásolo et al 2008, Gómez et al 2007, Hoyer et al 2002, 2005, 2007, Jeong et al 2001, Na et al 2002, Pompe et al 1998). Due to the increasing relevance of the metric in this field, we aimed at gaining a better understanding of the AMIFRD in terms of signal processing concepts and at illustrating its application to the signal analysis of biomedical recordings. Hence, we performed a series of simulations where this method was tested using synthetic signals.

Our study has indicated that the AMIFRD becomes more negative as the signal is more dominated by white noise. Additionally, noises with wider spectra provide more negative values of the AMIFRD, and this parameter is able to detect changes in the non-linear dynamics of a time series. Additionally, we illustrated the application of the AMIFRD to real EEGs recorded under different conditions. Nevertheless, it should be noticed that many other non-linear analysis methods are available, and similar studies should be carried out to properly understand the results provided by other analysis techniques.

Acknowledgements

The authors are grateful for the useful feedback of the Referees on the manuscript. They would also like to thank Dr. Andrzejak from the Department of Epileptology at the University of Bonn, Germany, now with the Department of Technology at the University Pompeu Fabra, Spain, for providing the EEG data described in Section 3.4. This study was partially supported by “Ministerio de Educación y Ciencia” and FEDER grant MTM 2005-08519-C02-01 and by the grant project VA108A06 from “Consejería de Educación de la Junta de Castilla y León.” J. Escudero was in receipt of an FPU grant from the Spanish Government.
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