Project report

Computational system for the prediction of epileptic seizures through multi-sensorial information analysis

Department of Informatics Engineering

University of Coimbra

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Abstract

During the past decades, several studies have demonstrated evidence that epileptic seizure may be preceded by variations in the patient's brain dynamics. In this study, we introduce a Matlab toolbox that employs several mathematical methods based on advances presented by numerous investigation groups. The extracted features were processed for data visualization by space reduction (VISRED).

The individual analysis of the extracted features did not present the expected results, although in several events, undeniable variations occur before seizures, suggesting that these variations could be related to pre-seizure activity.

The combined analysis of all acquired variables, reveal more information comparing to an individual analysis. Data visualization by space reduction presented tenuous regions representing pre-ictal states. The progress of these ideas may assist the development of automated seizure warning devices for therapeutic purposes.

Keywords: Epilepsy, Seizure Prediction, Brain dynamics, Data visualization

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Abbreviations

EEG	Electroencephalograph
EPSP	Excitatory postsynaptic potential
LTE	Long term energy
IPSP	Inhibitory Postsynaptic potential
SOP	Seizure occurrence period
SPH	Seizure prediction horizon
STE	Short term energy

1 Introduction

1.1 Background

Epilepsy is among the most common neurological disorders, and represents temporary and reversible electric activity in the brain. Epilepsy is characterized by occasional, excessive and disorderly discharging of neurons, which can be detected by clinical manifestations, the seizures. This disturbed activity, can cause strange sensations, emotions, and behaviors or sometimes convulsions, muscle spasms, and loss of consciousness [1].

One of the most devastating features of epilepsy is the apparently random nature of seizures. In most patients, seizures occur suddenly, without external precipitants previously detected. A system able to predict seizures would allow some preventive measures to keep the risk of seizure to a minimum and to improve substantially the social integration of the patients.

The first works on forecasting epileptic seizures began in 1970, with Viglione, but without the required technology to obtain valuable results. 20 years later, the scientific community developed a huge effort in this area, when a high number of factors conjugated allowed to obtain optimistic results, presenting credibility relative to the presented case studies: increased acceptance of EEG exam, discovery of pre-seizure brain stage and the evolution of diagnosis techniques and treatment of other brain diseases [2].

A conservative estimate indicates that epilepsy affects 60 million people in the world (*Witte et al. 2003*). For the majority of the patients seizures usually occur suddenly and unexpectedly without any external intervention. Epilepsy can disclose at any age. However, people with less than 25 and more than 65 years of age are more susceptible to suffer from the disease. There is also a slight difference between genders; men present a higher incidence.

1.2 Project objective

This study integrates a component of investigation, which has as objective the development of a computational system for the prediction of epileptic seizures through the analysis of multidimensional information.

The analysis of the information contained in the Neurology department of HUC database and the processing of the gathered data through designed algorithms are the main initial goals of this project. To have a more significative sample, data from the Freiburg database has also been used. The purpose of the designed algorithms is to find efficient methods to predict seizures. The output of this project is the development of a Matlab toolbox, integrating the developed work with some software publicly available and original Matlab toolboxes.

1.3 Used technologies

The main language used throughout the study was Matlab. Several toolboxes were used in the project; their main functions and description are presented in the following chapters.

1.4 Document structure and organization

The current report, presents the study realized by the author, in the scope of final project discipline of the Biomedical Engineering degree. The following chapters compose the document:

- Chapter 1: Introduction
- Chapter 2: Overview: Epilepsy
- Chapter 3: The prediction of epileptic seizures, state of the art
- Chapter 4: Technical description
- Chapter 5: Results and discussion
- Chapter 6: Conclusions, recommendations and future work.

Chapter 2 refers to the general ideas about the Epilepsy condition; a brief theoretical description about structural and cellular concepts, different brain stages and its representation as EEG potentials.

Chapter 3 contains the main diagnosis techniques, specially the EEG exam – EEG potentials origins and physiological representation of the signal. After the presentation of the background information, a description of the most applied methods in the Epilepsy research and investigation units will be done.

The following Chapter 4 presents a brief description of the designed algorithms and toolbox structure presentation.

The fifth chapter includes the presentation of the results obtained, and the last 6th chapter contains the final considerations and future prospects of this study.

2 Overview, Epilepsy

2.1 Epilepsy, a complex disorder

An epileptic seizure is a complex symptom caused by a variety of pathologic processes in the brain. It is characterized by occasional, excessive, and disorderly discharging neurons, which can be detected by clinical manifestations, electroencephalographic recording (EEG), or both.

Normally, the neurons continuously generate short discharges, with a rhythmic pattern. These discharges pass throughout neural networks, and between consecutive neurons through neurotransmitters. A seizure occurs when the cells begin to generate random discharges, changing the normal patterns, creating an uncontrolled electric activity in the brain.

The spontaneous discharges arise when the *firing* threshold of the neuron membranes is reduced beyond the capability of cellular stabilizing mechanisms.

The seizure may be confined to a small region and remain restricted to a specific area – the focus (*focal*), or it can spread to other areas of the brain (*generalized*). When the discharges reach a sufficient area, a clinical manifestation occurs; otherwise, these discharges produce asymptomatic electrical disturbances. When the synchronized discharges of a neuronal population are recorded (by EEG potentials), these events appear as spikes, slow waves and spike-wave potentials.

The brain area where these disturbances occur is another important factor to consider. Each brain area controls a specific behaviour, so the focus location is directly related to the behaviour associated with those areas.

2.2 Parts of a seizure

The period during which the seizure actually occurs is described as the *ictal period.* The *pre-ictal* period, or *pre-seizure* state, is the period immediately before the seizure onset. The period after the seizure is referred to as *post-seizure* or *postictal*

period. The interval between two consecutive seizures is described as the *interictal* period.

2.3 Basic mechanisms

In this section, we review basic principles, which characterize seizure activity: excitation and inhibition of neuronal membranes, excitation and inhibition of neurons through neurotransmitters, generation of EEG potentials, generation and cessation of seizure activity [3].

2.3.1 Principles of generation and cessation of seizure activity

Excitation and inhibition of neuronal membranes – Neuronal membranes consist of a lipid bilayer combined with proteins that transverse the membrane and form channels between the intracellular space and the extracelular space (Figure 1).

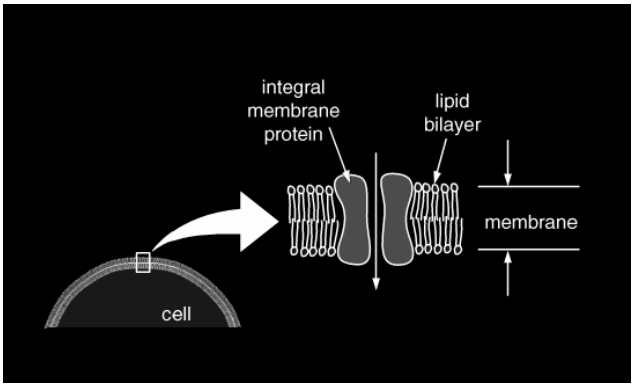


Figure 1 – Cell membrane

Each neuron has a resting potential, which represents the difference between the inside and the outside of the cell. This potential represents the difference between the ionic concentrations in the interior and exterior of each neuron membrane. Among the several ions present, those that interpret a major role are K+, Na+ and Cl-. Each has different concentrations in the interior and exterior of the cell, and can travel over the membrane through transmembrane proteins – ionic channels.

The presented structure of the membrane and the transport mechanisms across the membrane are the main reasons why the cell membrane has a resting potential from -50mV to -80mV (consider the cell exterior as null) [4].

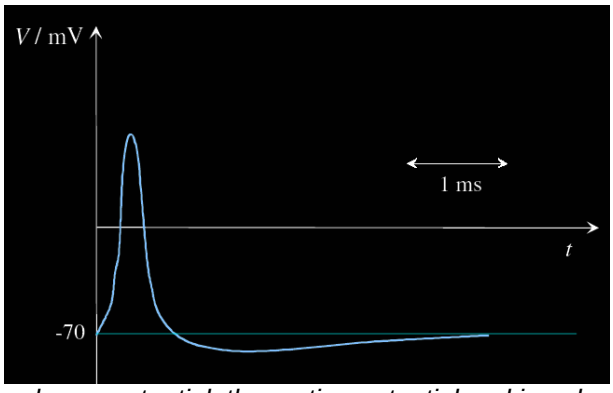


Figure 2 – Membrane potential, the resting potential and impulse

The sodium concentration is higher in the exterior of the neuron, and the same occurs to the concentration of the chlorine ion. The concentration difference between the inside and outside of the cell of the potassium is inverted. The cellular membrane presents different permeability to ions with a different molecular weight; even though all ions tend to travel to environments with minor concentrations. According to the presented mechanisms, an ion flow, and therefore a concentration variation, should be generated naturally; although the Na+ K- pump extrudes Na+ from the cell and brings K+, counterbalancing the normal flow, allowing the maintenance of the resting potential [5].

When the neuron is stimulated and this impulse surpasses the critical threshold, locally, the membrane potential increases abruptly from the resting state towards values near +50mV, returning immediately after to the resting potential. This disturbance in the cell potential is transmitted along the axon, in such a way, that briefly after the potential returns to resting potential (Figure 2).

2.3.2 Excitation and inhibition of neurons

The cell membrane is constituted by protein segments, which serve as receptor sites. Ionotropic receptors directly alter the conductance of the ionic channels when connected to neurotransmitters. Neurotransmitters, as GABA, cause the hyperpolarization of neurons and originate inhibitory postsynaptic potentials (IPSP), which result in a decrease potential of the cell environment.

Neurotransmitters that lead to a depolarization (such as excitatory amino acids) generate excitatory postsynaptic potentials (EPSP) which result in a normalization of the cell environment. The generation of action potentials is due the balance between IPSP and EPSP [3].

Another type of receptor is the metabotropic receptor; when bonded to a neurotransmitter, it activates a secondary messenger mechanism. The activated G-protein may open an ionic channel or activate an enzyme, which may connect to a secondary messenger system inside the cell.

2.3.3 Generation of EEG potentials

EEG signal represents the graphic study of the electric currents generated in the brain, and can be acquired through electrodes placed in the scalp. The signal obtained is based on the ionic currents generated by neurons through the extracelular space. Recorded EEG potentials transmit informations about the sum of different IPSP and EPSP. Individual behaviour of the neurons does not influence the signal; it represents the activity from a large neuronal aggregation. Although epilepsy clearly starts at the cellular level, the disease is a neuronal network disorder.

2.3.4 Generation of seizure activity

Although the sequence of events that lead to seizure activity is unknown, various mechanisms might be involved. These abnormalities may possibly include cell membrane disorders or neurotransmitters receptor sites anomalies. A decrease of the synaptic inhibition, an increase of neuron excitation, changes in the ionic concentrations and currents may be in the origin of longer depolarisations. These changes may occur not only in the microenvironment at the epileptic focus but also along the synaptic pathways.

2.3.5 Cessation of seizure activity

While the understanding of the mechanisms underlying the cessation of seizure activity is reduced, several hypotheses are generally accepted. Activation of inhibitory processes is one of the ideas considered, and appears to be confirmed through EEG signal.

Other studies point the importance of endogenous agents with anti convulsion action, reporting an increased concentration in extracelular environment.

2.4 Diagnosis

The diagnosis of the disease requires the existence of recurrent seizures, unprovoked; it is usually based on the anamnesis of the patient. EEG, MRI, SPECT and PET may be useful to identify the focus location among other valuable elements.

The most useful test is the long-term video EEG monitoring. The recording is periodically monitored and analyzed by a neurologist; one of the purposes of this exam is to identify simultaneously the electrical seizure onset and the clinical seizure onset.

2.4.1 EEG

EEG is the most helpful exam in the investigation of seizure disorders. It essentially confirms the presence of abnormal electrical activity, recording helpful data to identify the properties of the seizure and, in some cases, the focus location.

The electrodes are connected to an EEG machine and record the brain activity in a series of traces, which posteriorly can be processed as mathematical time series. Trained neurologists can identify the patterns that represent abnormal brain activity. These abnormalities are called *epileptiform changes* and can be observed in the periods between seizures, and are usually represented through *spikes, sharp waves* e *spike-and-wave discharges* [6].

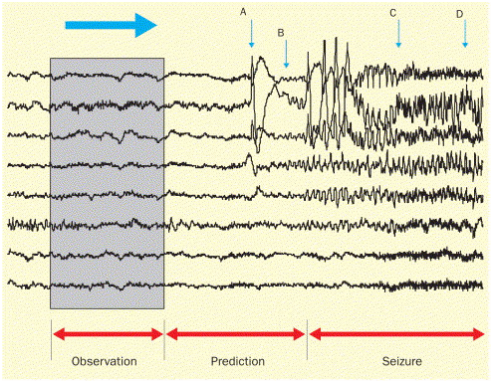


Figure 3 –EEG signal example (pre-seizure and seizure activities)

Whenever needed, especially when a patient is under evaluation for surgery, intracranial EEG is used. Essentially the electrodes are placed on the brain cortex; after this procedure, the patient remains in the hospital and intracranial data is acquired for a significant period [7].

Among the advantages of intracranial records when compared to scalp EEG records, we may find signal-to-noise ratio, time and space resolution. This exam allows the analysis of higher frequency bands of the EEG signal unlike scalp EEG. Several studies point this feature as important to understand the mechanisms underlying several brain functions.

2.4.2 Video - EEG

This exam allows the record of two different features simultaneously: the electric activity of the brain through the EEG record and patient behaviour analysis by video analysis; allowing the neurologists to relate abnormal patterns in the EEG with physical manifestations that the crisis may cause to the patient.

2.4.3 Computed Tomographic Scan and Magnetic Resonance Imaging

The CT scan, through small amounts of radiation, creates an image of the internal structures of the brain. This image allows the identification of structural abnormalities that can be associated to the origin of seizures.

The magnetic resonance (MRI) produces an image that represents the brain structures, providing a higher detail when compares to CT scan [6].

Promising studies aim the fusion of the image obtained by this process with the EEG signal, allowing the correlation of electric, spatial and functional information.

3 Epileptic seizure prediction, state of the art

The first scientific works on the prediction of epileptic crises date from the 1970s with the visionary ideas of Viglione and colleagues, but the technology that would support the scientific investigations, only started to appear two decades later. The interest in this area grew since the decade of 90, mainly due to the reunion of diverse factors. The discovery of pre-seizure state in temporal lobe seizures, increase in the use of digital EEG, establishment of intracranial EEG (allowing a better location of the epileptic focus), and the evolution of implantable medical devices (pacemaker used in several heart diseases, local stimulators associated to Parkinson's disease), created a favourable scenario for seizure prediction investigation.

3.1 Directions of epilepsy research, seizure prediction

Techniques usually used in seizure prediction include methods based on the analysis of EEG signal. This area of investigation generally includes the analysis of nonlinear dynamics, wavelet transform and signal quantification.

The electric activity presented by neurons is widely known, as several studies explain extensively the theoretical aspects underlying the records. However, as already stated, the behavior of an individual neuron does not allow the prediction of the whole network activities. Some aspects are only perceivable as we study a large neuronal aggregation.

Better results in the prediction of epileptic seizures are essential for the progress in the development of implantable devices capable of preventing seizures (onset a therapy able to prevent the occurrence of the seizure as well as other implantable medical strategies).

The studied methods, generally extract a specific feature of EEG recordings, and once the value of this feature exceeds a settled threshold value, an alarm is set.

The analysis of periods away from seizure activity allows the selection of the threshold values (normal behavior analysis). Lower threshold values usually correspond to a higher sensitivity of the method, allowing the prediction of a high percentage of seizures. However, more *false prediction* may occur in interictal periods – *false positives*.

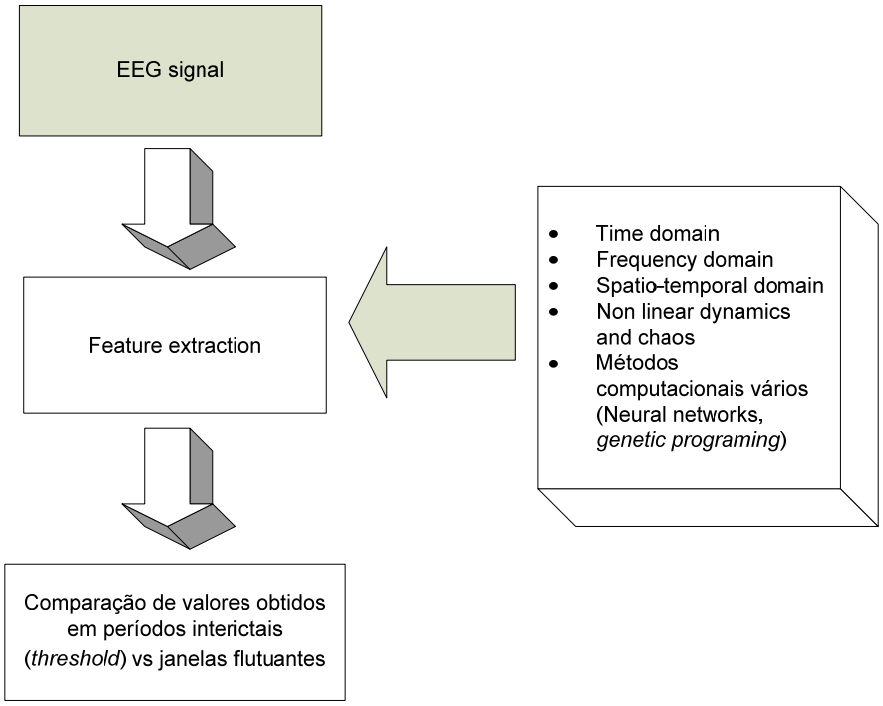


Figure 4 – Schematic representation of the model followed by several investigation groups in seizure prediction.

The document elaboration involved the analysis of several published studies, which, with different results, enunciate algorithms for seizure prediction.

In this chapter various studies are presented, trying to introduce their main ideas according to the areas where they are included.

3.1.1 Time domain analysis

These methods include the statistical analysis of specific events and features obtained through EEG data processing.

Some studies suggest that, although no relations have been found between *epileptiform* discharges and clinical events, the occurrence of spikes, and the time interval between them may be related to the approach of a seizure.

Other authors refer that the increase of energy spikes in the period that precedes seizure activity may be related to pre-seizure activity.

3.1.1.1 Signal energy, accumulated energy

B. Litt et al. [8] investigated the ability of the signal energy concept to identify pre-seizure activity. Segments of 50 minutes were processed and about 90% of the pre-seizure were correctly classified as well as 80% of the interictal periods.

The accumulated energy algorithm is based on the value of the average energy, estimated through a sliding window, which travels over the EEG time series. An accentuated variation of this parameter corresponds to an increase of accumulated energy values.

The energy was calculated through a 1.25 seconds window, processing the time series obtained by the focus nearest electrode (1).

$$E_i[n] = x^2[n]$$

Signal energy (1)

The average energy values were computed by averaging every 250 points, corresponding to 1.25 s of the instantaneous energy (the sampling rate was 200Hz in the authors study).

According to the authors, consecutive calculations had an overlap of 160 points for a higher resolution.

$$E_k = \frac{1}{n}\Sigma x^2[n]$$

Average energy values (2)

A second level of averaging was performed to determine the accumulated energy; ten consecutive values of the average energy are added and divided by 10 (3), and then added to sum of previous calculations.

$$AE_m = \frac{1}{10}\sum E_k + AE_{m-1}$$

Second approximation level (3)

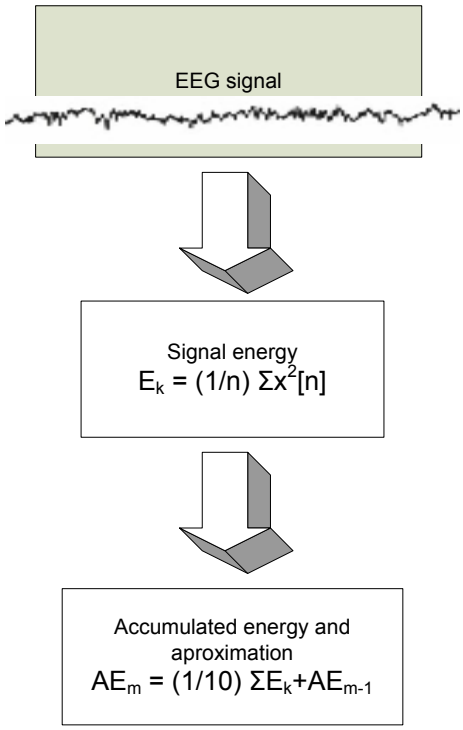


Figure 5 – B. Litt, accumulated energy

3.1.1.2 Accumulated energy: continuous energy variation

Later, in a work published by R. Esteller et al.[9], they tried to improve the method presented by B. Litt. According to the authors, accumulated energy was approximated by using moving averages of signal energy (using a short-term energy observation window of 1 min vs. a long-term energy observation window of 20 minutes). A similar displacement was applied to both windows and both ended at the same time point. The average energy of each window is determined as follows,

$$E[n] = \frac{1}{N_1}\sum_{i=1+(n-1)(N_1-D)}^{n(N_1-D)+D} x(i)^2$$

Average energy of the sliding window (4)

Where N is the number of samples in the observation windows; D is the window shift; x represent the EEG data. The values obtained using the shorter

window is denoted as short-term energy (STE), and the one determined with the longer window size is referred to as long-term energy (LTE).

The reference value – decision threshold, was determined by the sum of two components, an offset component and an adaptative threshold. Seizures were predicted whenever the STE value exceeded the decision threshold (5).

$$\mathrm{STE} \geq \mathrm{LTE} + \mathrm{offset} \qquad \textit{Decision threshold (5)}$$

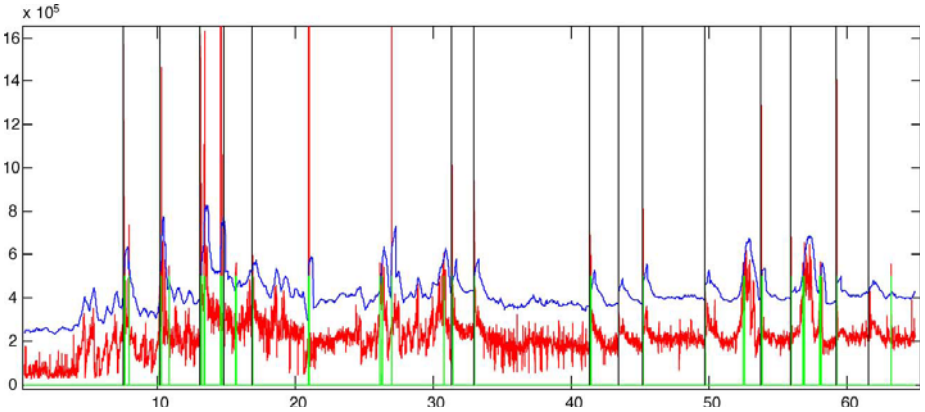


Figure 6 – STE (red), decision threshold (blue) and prediction output (green). Black vertical lines represent the seizure onsets.

The results point to a sensitivity of 71.6% (seizure horizon window was 3h). Data used in this investigation represent 293 hours of four patients EEG signals, and correspond to a total of 60 seizures.

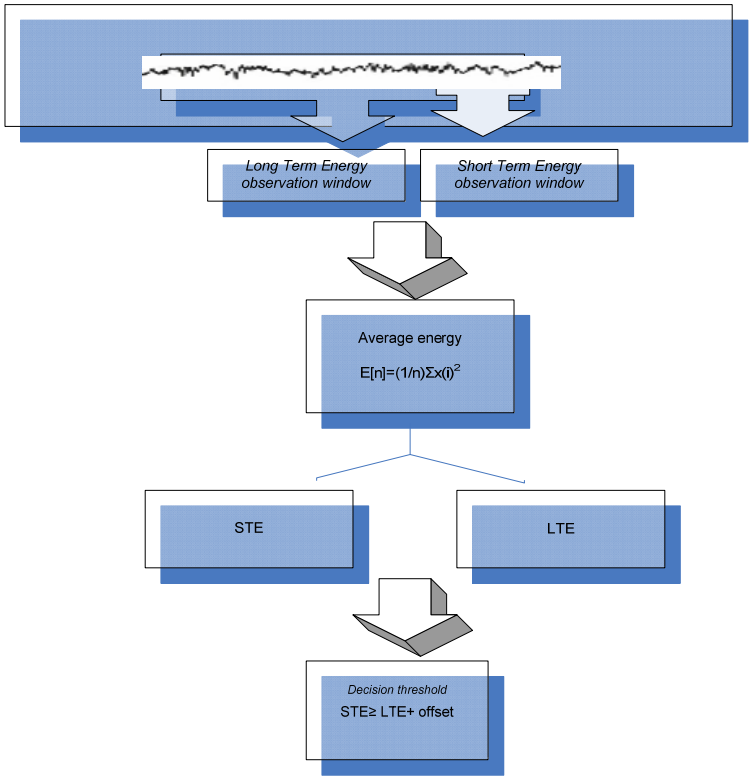


Figure 7 – Schematic representation of R. Esteller algorithm.

3.1.2 Frequency domain analysis

Frequency domain analysis includes techniques that decompose EEG signal in components of different frequencies, in an attempt to associate specific patterns in frequency bands to pre-seizure activity. Reviewed studies indicate the occurrence of activity peaks, or spikes, in frequencies between 15 and 25 Hz, two hours before the seizure onset.

The first methods were developed to extract frequency based features using Fourier transform.

The EEG signal has been considered to be composed essentially by four bands - δ band with frequencies inferior to 4Hz, θ band with frequencies between 4 and 8 Hz, α band with frequencies between 8 and 13 Hz and finally β band with frequencies between 13 and 30 Hz (some authors point to a γ band with frequencies above 30 Hz).

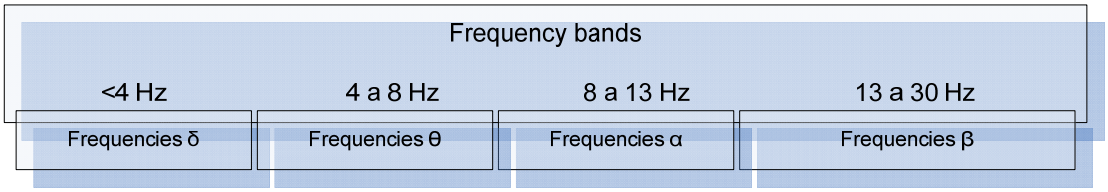


Figure 8 – Most important frequency bands of EEG signals

3.1.2.1 Electrodecremental event

Frequency domain studies are usually based on the energy spectrum of the EEG. Spectrum analysis was used to identify pre-seizure activity with an accuracy of 80% in a study presented by Siegal et al (1982). Frequency spectrum analysis in the moments preceding EEG events (spikes and wave complexes) present an increase of aperiodic activity. An increase of the energy of high frequency bands (40 Hz to 150 Hz) and an abnormal low frequency pattern has been associated to pre-seizure activity – electrodecremental event.

Frequency spectrum analysis allowed the detection of increased signal energy in the lower frequency bands, comparatively to higher frequency bands when comparing patients who suffered from epilepsy and normal patients.

3.1.3 Space-Time domain analysis

Several investigators point out the analysis of space-time domain as a solution for pre-seizure activity identification, specifically wavelet transform. This approach arose from the poor results obtained through individual time and space analysis. Wavelet transform allows the division of different characteristic frequencies in non-stationary signals. Fourier transform can be applied to stationary signals, however various signals, as the EEG and most biological signals, have non-stationary or transition features.

The wavelet transform decomposes the signal in a set of basic functions designated as wavelet (wavy functions of finite size that decay over time and can be characterized by coefficients). These functions, or wavelets, correspond to different frequency bands and therefore they allow the signal analysis in different scales, without losing temporal framing.

3.1.3.1 Wavelet transform and neural networks

Also concerning this methodology appears the study of A. Subasi [10]. Reflecting the limitations presented by previous investigations based on the analysis of the frequency domain, the author points the wavelet transform as a form to surpass those limitations (non-stationarity of EEG signal) and chose a method indicated to identify transition events.

Through signal decomposition in wavelets, transition features may be identified in the space-frequency domain. The ability of this mathematical method to examine simultaneously different frequency bands allowed the analysis of small oscillations in EEG signal.

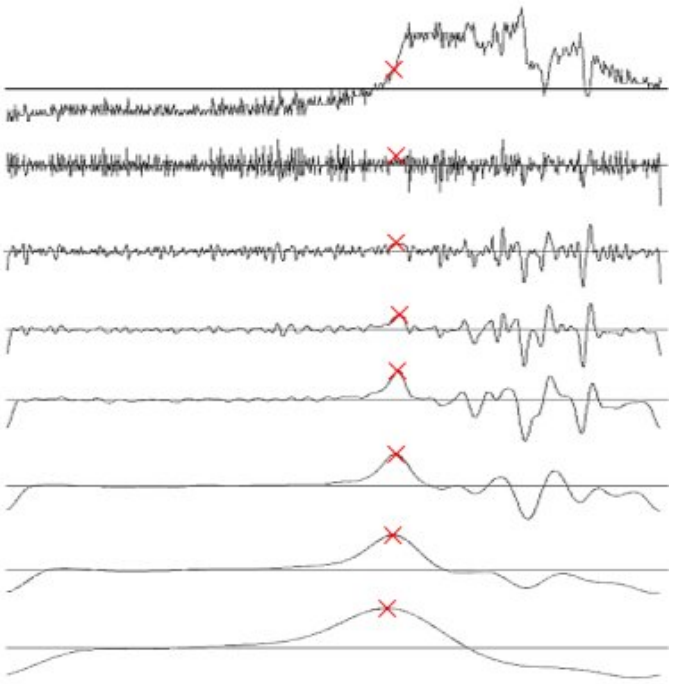


Figure 9 – Original signal and wavelet decomposition coefficients representation

The discrete wavelet transform (DWT) analyses the signal at different frequency bands by decomposing the signal into a coarse approximation and detail information [11]. The frequencies that are most prominent in the original signal will appear as high amplitudes in that region of the DWT signal that includes those particular frequencies. This method allows studying the behavior of a particular frequency band and its influence to the original signal.

The extracted coefficients are a representation of EEG signal energy in the time and frequency domains. Two different approaches are examined in this section.

In the first one a feedforward neural network (backpropagation is the training algorithm) is used to identify variations in the behavior of wavelet decomposition coefficients. The input data are the values obtained through wavelet decomposition and the neural network output were the different states considered – normal, pre-ictal and ictal.

A second work was presented using a different neural network as classifier - *dynamic wavelet network*. The author then compared the results obtained through both architectures proposals – The first architecture presented a sensitivity of 90.4% while the second architecture presented a sensitivity of 92.8%.

3.1.3.2 *Wavelet transform* and accumulated energy

S.Gigola [12] presented a study based on the analysis of wavelet transform coefficients and on the accumulated energy concept. In the study, the wavelet used in the signal analysis was the Daubechies-4 (an orthonormal wavelet). The signal energy in each decomposition level j of the multiresolution analysis is determined by:

$$E_j = \sum_{i=1}^{N_j} d_j^2(i)$$

Energy of decomposition coefficients (6)

Where $d_j(i)\left(i,\ldots,N_j\right)$ corresponds to the coefficients of each level j. Accumulated energy in each level was determined, as follows:

$$AE_j(k) = \sum_{i=a(k+1)+1}^{a(k+1)+b} d_j^2(i) + AE_j(k-1)$$

Accumulated energy (7)

Where b represents the length of the window, and b-a represents the overlap between two consecutive observation windows. According to the authors, levels j = 1,…,8 are used, because there is no relevant information in the levels corresponding to lower frequencies (<0.5 Hz).

The prediction was based in two methods:

- The computation of the slope of the least square straight line to $AE_j(k)$ function;
- The evaluation of the ratio between the slopes of the pre-seizure signal and the background signal in each level of the multiresolution analysis.

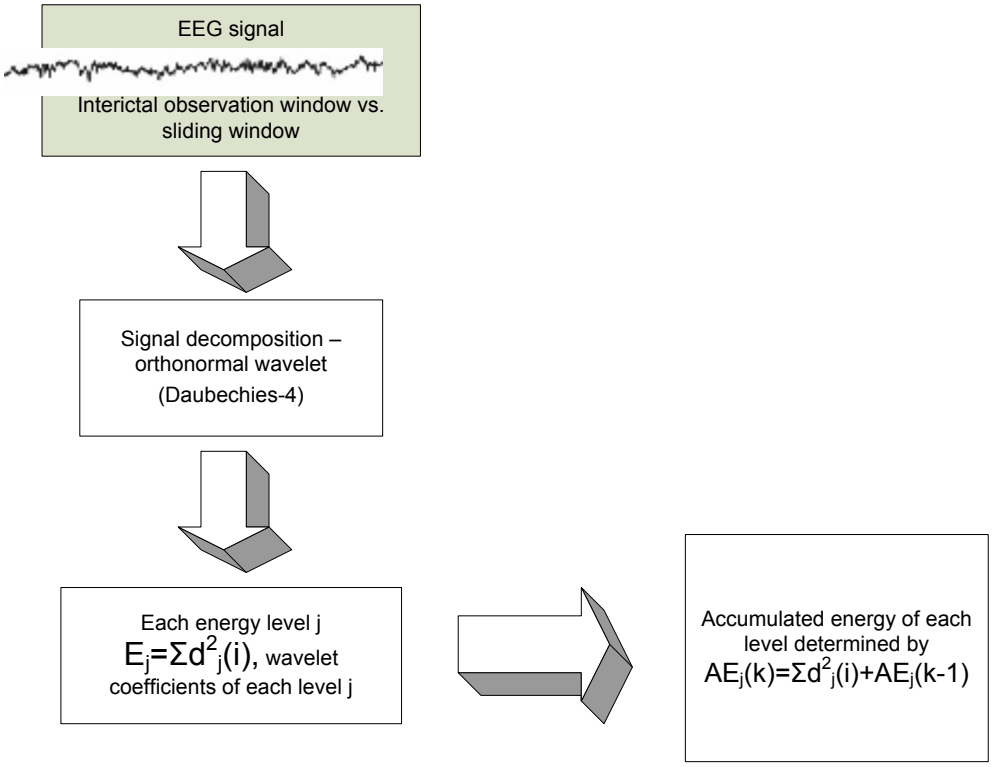


Figure 10 – Schematic representation of the algorithm proposed by S. Gigola

The results obtained in the investigation presented by *S.Gigola* et al. point to sensitivity of 50% and without any false positive. A decrease in the threshold value resulted in an increase in the sensitivity, obtaining results of 90%, with the consequent increase of false positives.

3.1.3.3 Wavelet transforms and fuzzy similarity measurements

X. Li and X. Yao [13] considered a method that combined the wavelet transform and the parameter *fuzzy similarity measurement*. In a first stage, the authors obtained features from the wavelet space, including the energy of decomposition coefficients and entropy values of the several frequency bands. Then,

the fuzzy similarity measurement was determined between a reference segment (normal signal) and the segment in analysis.

In a second stage, through arguments based on fuzzy logic, the authors described the values of energy and entropy according to fuzzy measures. Applying a process of fuzzification to each variable, the authors obtained a diffuse set based in 5 degrees of truth. The fuzzy set obtained was compared to the values obtained from the reference segment. This parameter is described as fuzzy similarity measurement.

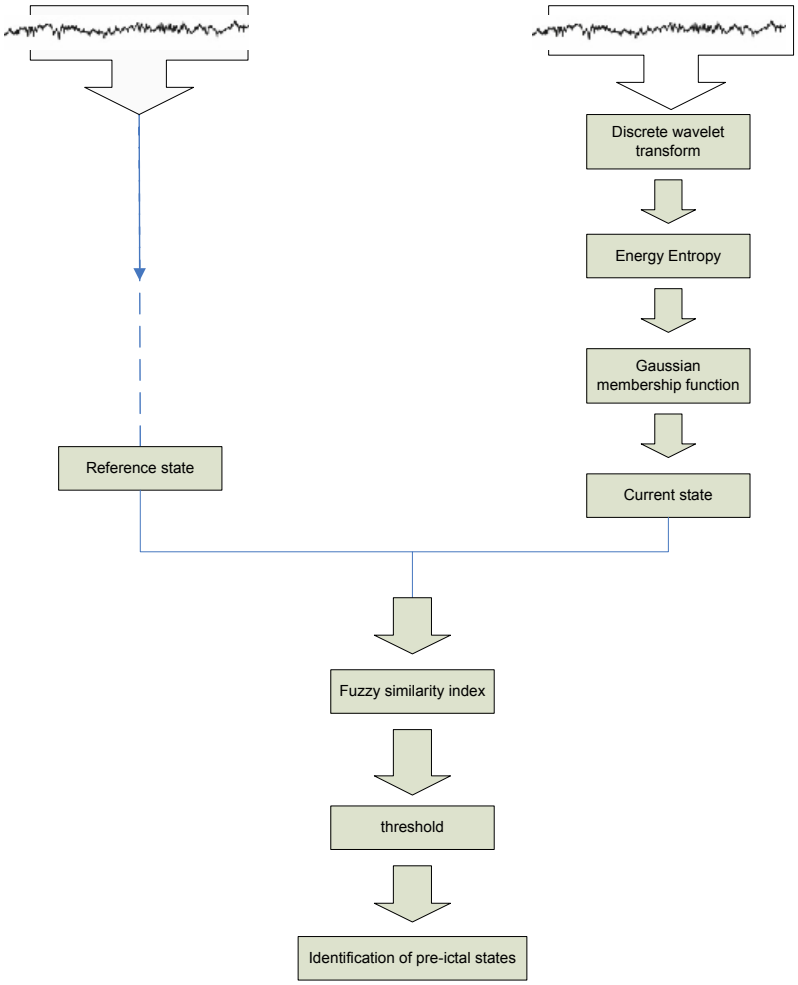


Figure 11 – Schematic representation of the method proposed by X. Li e X. Yao

The results, in tests executed on animals, confirmed the ability of the method for seizure prediction. The average seizure prediction horizon (SPH) was 109.6 seconds. The divergence found in this value is explained by the authors with the complex nature, of non-repetitive and exclusive processes of each patient and of each seizure.

3.1.4 Nonlinear dynamics and chaos

Concepts of nonlinear dynamics are the support of frequently used methodologies in seizure prediction. Studies suggest that the variations in the extracted nonlinear features correspond to transitions between normal a pre-seizure states.

These studies present the analysis of systems whose behaviour is too complex to be described as mathematical models or equations.

Before presenting several studies, some concepts are introduced for better understanding of the methods presented.

Dynamic system is defined as a set of functions (rules, equations) that identify how the system's variables evolve throughout the time. The behavior of an n-dimensional system can be described through a set of n first-order differential equations.

The values of all variables of a system in an instant t describe the n-dimensional space. The state of a system is represented, in an instant t, by the values of all independent variables. The set of all possible states of a system defines the phase space. The sequence of states throughout the time defines a curve in the phase space – the trajectory or phase plot.

As time goes by, the trajectories whether occupy all the phase space or converge to a set of inferior dimension – the attractor.

A dynamical system can be described as initial condition problem; to analyze the behavior of a system it is necessary to describe functions, parameters and initial condition.

Chaotic systems are those that present unexpected behaviour over time due to a property that these systems present: sensitive dependence on initial conditions.

Thus, two nearby trajectories at the initial moment diverge with time until the trajectories become macroscopically distinct. Therefore, as precise as the initial state description might be the long-term behaviour of a chaotic system is impossible to predict (in theory, initial condition described with infinite precision could predict the long-term behaviour of the system).

However, several methods allow the analysis of chaotic systems, for instance the Poincaré map, attractor dimensions, Lyapunov exponents and Kolmogorof

entropy. Important features can be quantified through these methods such as the complexity of the trajectories in the phase space, the regularity of the phase plot and pattern analysis.

In this document, we focus our attention on Lyapunov exponents and correlation dimension. These two measures determine nonlinear properties of systems, remaining independent; therefore, their results may contain different conclusions [14].

The property that describes the divergence of two nearby trajectories in a phase plot is called "*principal Lyapunov exponent*" (PLE); quantifies the sensitive dependence on initial conditions of chaotic systems measuring the average expansion of the trajectories in the phase space.

The presented studies using nonlinear analysis of EEG signal, share findings such as the increased organization of the trajectories in the phase space in pre-ictal moments. This behaviour is confirmed with the decrease of the values in the features correlation dimension and principal Lyapunov exponent in the moments preceding certain seizures.

Method of delays

A time series can be described as a sequence of observations $\{s_n = s(x_n)\}$ performed with some measurement function s, in our case EEG signal.

Since the sequence $\{s_n\}$ (the time series extracted from EEG electrodes) representing only one variable does not properly represent a multidimensional phase space, a technique is used to unfold a multidimensional structure using the available data. The most common phase space reconstruction technique is the method of delays.

In this method, each point of a series of events or measurements is considered in the context of other nearby events and measures of the same series; a single channel of the EEG signal is considered and a set of m equally spaced events are extracted. These events define the state x_k in the phase space (therefore this event is described by m components), as follows:

$X_k=[x_k, x_{k-1}, x_{k-2}, \ldots, x_{k-m+1}]$ (for m previous values)

or

$X_k=[x_k, x_{k+1}, x_{k+2}, \ldots, x_{k+m-1}]$ (for m posterior values)

Each moment (state) is described by its specific value and also by the nearby moments considered; if the values of the time series in analysis have an abnormal pattern, the method will result in a sequence of irregular trajectories.

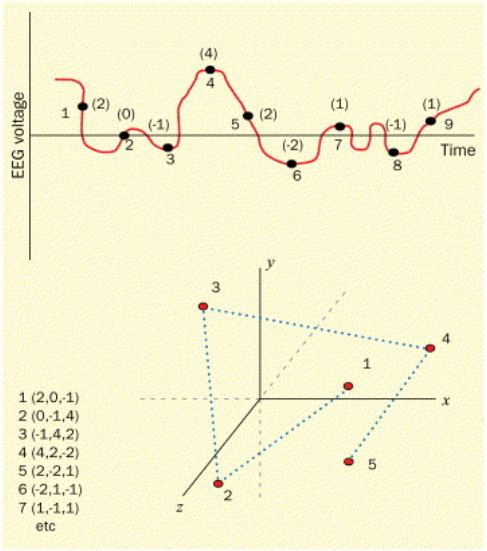


Figure 12 - 9 points demonstration of the method of delays. Consider the state xk as a combination of three successive instants. The states can be described as X1= [v1, v2, v3] =[1,0, -1] , X2= [v2, v3, v4] =[0, -1,4],

The previous figure demonstrates a short segment from an EEG signal and the resultant trajectory through the method of delays (the description of each moment was obtained with three nearby points).

A graphical reconstruction of each state of the signal can then be made demonstrating the relationship between several moments and the signal evolution over time.

The trajectories obtained in the phase space allow the estimation of several nonlinear features such as Lyapunov exponents and fractal dimensions.

3.1.4.1 Mean phase coherence and lag synchronization index

Assuming that the epileptic seizures occur due to an abnormal synchronization of a neuronal population, M. Winterhalder et al. [15] presented a study based on synchronization measures. Two measures were used in seizure prediction: bivariate synchronyzation measures and lag synchronization index.

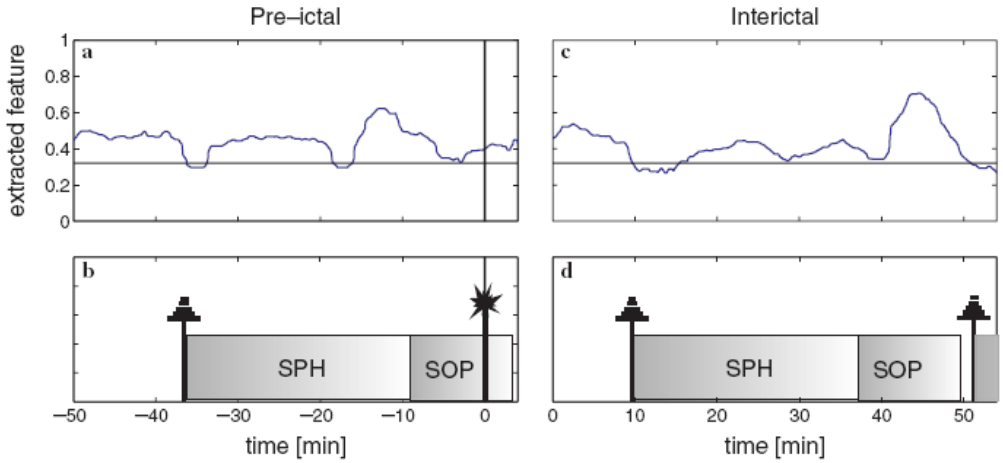


Figure 13 – Winterhalder, bivariate synchronization measures

Following the example of other systems displaying chaotic properties that exhibit the phase synchronization phenomenon, the authors tried to relate this concept to seizure prediction. Two measures were used to seizure prediction; the first uses the mean phase coherence to identify variations in phase synchronization while the second uses the lag synchronization index to characterize the correlation between the amplitudes with a specific time lag involving two channels (focal/focal and focal/extra-focal).

According to the authors, the variation in the measures extracted is not uniform and the analysis of these abnormalities may contain valuable information for seizure prediction; the decrease in the extracted features may be associated to pre-seizure activity.

The average sensitivity observed, in 21 patients, was 60%, with a false positive rate of 0.15/h (seizure prediction horizon was 10 minutes). The study suggests that the prediction method and its evaluation scheme, optimized values of the prediction horizons, and preferred brain structures for EEG recording have to be determined for each patient and prediction method individually.

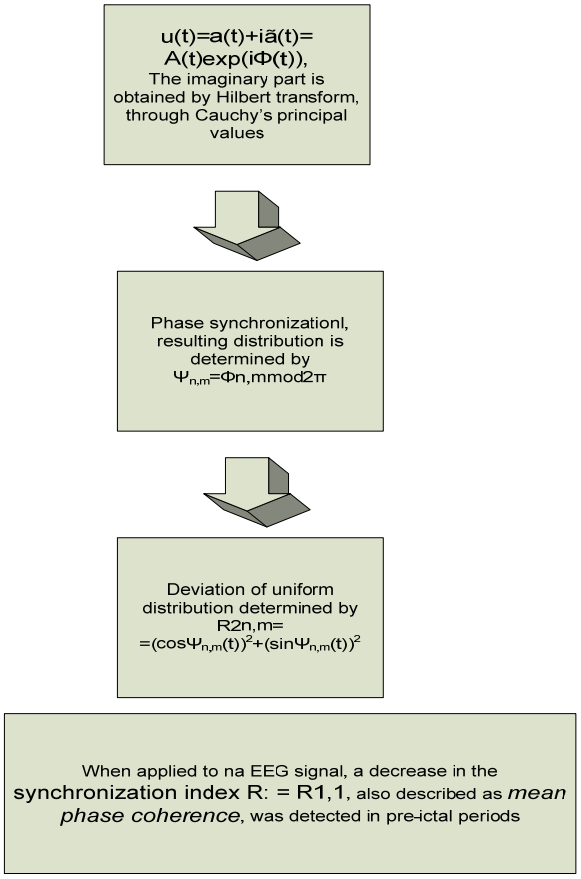


Figure 14 – Schematic representation of M.Winterhalder algorithm

3.1.4.2 Lyapunov exponents

W. Chaovalitwongse e al [16] presented an investigation based in mathematical methods developed for the study of nonlinear dynamics of systems. Lyapunov exponents' pattern analysis assumed a particular relevance in the work presented. According to the authors, the most consistent characteristic in pre-seizure activity identification is the principal Lyapunov exponent (PLE), extracted from electrodes located in recognized focal areas.

The investigation focused in the quantification of Lyapunov exponents, short-term Lyapunov (STL) that describes localized (over time and space) information about system stability.

The study interprets each electrode as a one-dimensional time series. Through the method of delays, the time series were reconstructed in the phase space with an embedding dimension of seven to determine the features of the attractor (phase plot).

The processed data in the study was divided in two major sets: training and testing. The results obtained for the data used as training presented a sensitivity of 76.12% with a false positive rate of 0.17/h, while the data used as test presented a sensitivity 68.75% with a false positive rate of 0.15/h.

3.1.4.3 Dynamic similarity

Le Van Quyen e al. [17] in a study published in 2001, presented an algorithm based on the concept of dynamic similarity. The main idea is to compare the dynamic of a sliding window with the dynamic of a background set; the authors determined time series through the calculus of the distance between specific points in the EEG signal. A delay of 16 units is introduced in the time series. The time series reconstructed are decomposed in unitary values; these values constitute the reference values.

The dynamic similarity index is obtained through the correlation integral method between the data extracted from sliding window and the previously determined reference values.

The authors defined a threshold value which, when exceeded, set an alarm; the results obtained demonstrated a sensibility of 94%. In this study, 23 patients were processed.

3.1.4.4 Correlation dimension

Another feature considered in the identification of pre-seizure activity was correlation dimension. Lehnertz e al [18] presented a study based on this parameter that quantifies the synchronization, complexity and degrees of freedom of a dynamic nonlinear system. The variations in the parameter are analyzed, characterized over time and standard deviation of this parameter is considered in decision threshold values.

After pre-processing the signal (scale correction through a sliding window method), the coefficient effective correlation dimension (ECD) was calculated. The threshold was specified through the ECD values in interictal periods. Every occasion that the values of the parameter decreased below the threshold, the elapsed time until the next drop and the variation pattern were processed. These values were compared to reference values obtained from background interictal periods.

The results obtained through this method present a sensitivity of 47% and without any false positives. Average seizure prediction horizon was 19 minutes. Data from 59 patients were used in this study.

3.1.4.5 Second-order complexity

Another attribute that nonlinear systems present is its complexity. Several parameters quantify the system complexity such as *lempel-ziv* complexity. W. Jia et al. [19] presented a study in 2005 pointing this parameter (*lempel-ziv* complexity) as a possible solution for seizure prediction.

Lempel-Ziv complexity is a measure that quantifies the randomness of complexity of a numerical sequence (the numerical sequence has to be transformed into a symbolic sequence); it depends on the pattern variations and is not sensitive to the occurrence frequency; cannot be expressed through expressions, and quantifies the sequence type (random vs. structured).

The conclusions of several investigations point that a seizure can be identified as a caos-order-caos transition (*Iasemidis et al.* 2003 *STLmax* e *Lehnertz et al*. 1998 correlation dimension).

The algorithm can be described as follows:

- Application of a bandpass filter; according to the authors, the variations in this feature generally happen between 20 Hz and 30 Hz; and selection of two groups of electrodes – one that includes the electrodes placed close to the focal region and a group B that contained the electrodes placed in a remote area.
- Assessment of the complexity, through a sliding window of 30 seconds and with a 2.5 second displacement, and calculation of the average value for the electrodes groups A and B. The difference between these two average values is the feature considered for pre-seizure activity evaluation.
- Data selection for training and testing sets.

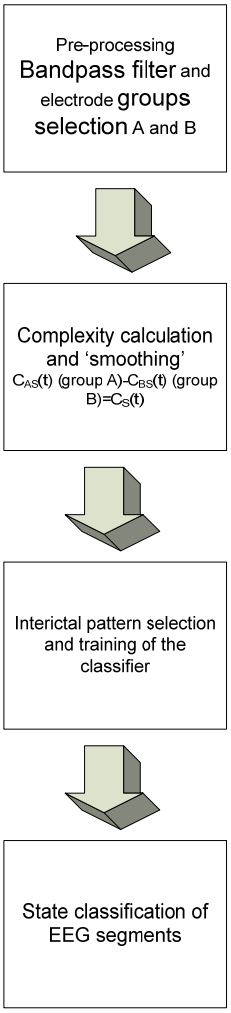


Figure 15 – Schematic representation of the algorithm proposed by W.jia et al.

The results obtained through this method, for a total of 591 minutes of data, were a sensitivity of 77.8% and a false positive rate of 0.3/h.

3.1.5 Methods based on computational intelligence

The methods included in this branch of research integrate mathematical and computational tools such as neuronal networks and other structures with support in artificial intelligence. It is assumed that these techniques may distinguish different states (normal, pre-ictal and ictal) after a data selection.

A significant advantage presented by these methods is their ability to learn without the need of specific rules of how the different states should be interpreted.

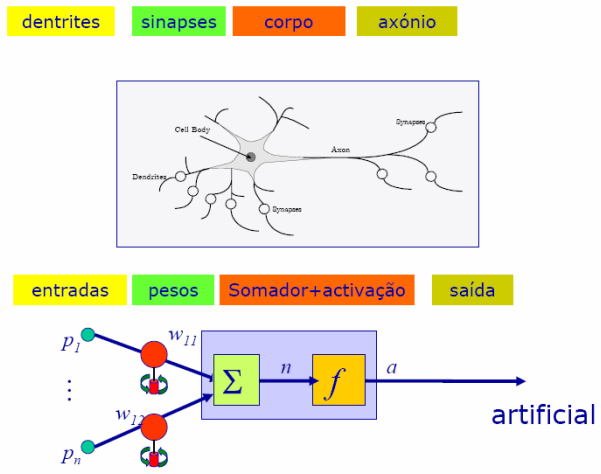


Figure 16 – Schematic representation of a neuronal network

Neural networks software is used to simulate biological neural behavior; usually they present properties that may be important in data classification, pattern recognition, among others. EEG signal analysis through a neural network is another branch of research usually used in pre-seizure activity identification. This kind of architecture presents several advantages such as:

- Learning through examples (input-output information),
- Adaptation ability, continuous learning of new situations
- Ability to adapt to new information, high computational speed (possibility of parallelism and easiness of hardware implementation)
- Robustness and tolerance to imperfections
- Ability to treat systems multiple-input multiple-output in the same way that systems treat single-input single-output

- Ability to adapt through parameter adjustments

3.1.5.1 *Elman* Neural networks

V. Srinivasan et al. [20] in a paper presented in 2005, demonstrated a method of seizure identification based on *Elman* neural networks. The neural network proposed, consisted in an architecture with two layers (with one internal layer), with a feedback link between the internal layer exit and the system entrance. In this study, several seizure prediction features were used as neural network input (features from different domains: dominant frequency, average energy, normalized spectral entropy, spike analysis spike amplitude).

The neural network output identified two states: normal and ictal. The goal of the study was seizure identification; the results obtained demonstrate the architecture‘s ability to correctly classify data, the sensitivity was 99.6%.

Neural networks are considered architectures with classification aptitudes due to its ability to adaptive learning, robustness and capacity of generalization, features that may be important to identify variation between EEG patterns; several investigators [20, 37] identify this type of architecture as a possible solution for seizure prediction if conjugated with other EEG properties.

3.1.5.2 Recurrence quantification analysis

The limitations presented by several methodologies lead to the exploration of other properties and methods – recurrence quantification analysis (RQA). A study presented by X.Li et al. [21] tested the ability to measure the complexity of a non-stationary signal with noise. The proposed algorithm tried to discover occult characteristics in EEG signals, specifically the detection of specific events in the EEG and complex changes that could be associated to pre-seizure activity. The authors considered three measures based on the method RQA – recurrence rate, determinism and entropy, capable of representing the dynamical characteristics of brain activity.

The recurrence of states is a fundamental property of a deterministic dynamical system. Recurrence plots (RP) can describe the recurrence property of a deterministic dynamical system, i.e., visualizing the time dependent behaviour of orbits in phase space.

The quantitative analysis of RP, called RQA, was described through 3 measures: %REC (recurrence rate), %DET (determinism) and ENTR (entropy).

The presented study aimed to distinguish three distinct periods – interictal, pré-ictal and ictal, identifying patterns in the extracted features. The results demonstrated significant variations in brain complexity over time in these periods.

A continuous decrease in the dynamics of the EEG in the transition between interictal and ictal states was discovered. RQA indicates that recurrent dynamics pre-ictal state is statistically inferior of the values presented in interictal periods, and superior than those found in the ictal state; the parameter indicate that seizure onset proximity generally is associated with complexity decrease.

3.1.5.3 Genetic programming

A work presented by H.Firpi [22] suggested genetic programming for seizure prediction. The proposed algorithm is based in the conjunction of two main components.

In the first, the signal is reconstructed and pre-processed – reconstruction in the phase space through method of delays; in the second part phase plot is processed through genetic programming (GP).

A deterministic component of the phase state trajectory can be reconstructed through EEG signal, creating a vector of states λ_k with n_e elements. This method creates a *diffeomorphism*, a slightly different version of the original signal maintaining the main dynamical and topologic features.

Genetic programming

- Randomly constructs an initial population of genetic functions, and determine the value of merit (parameter that analysis the validity) for each function, considering the fitness function (it is intended to recognize if the functions obtain accurate results).
- Through these parameters, the authors proceed to the next generation forming a new set of functions. These functions are composed of two components: the functions that obtained the best results conjugated with new functions recreating the biological process of reproduction.
- The method is repeated until the accuracy goal is achieved.

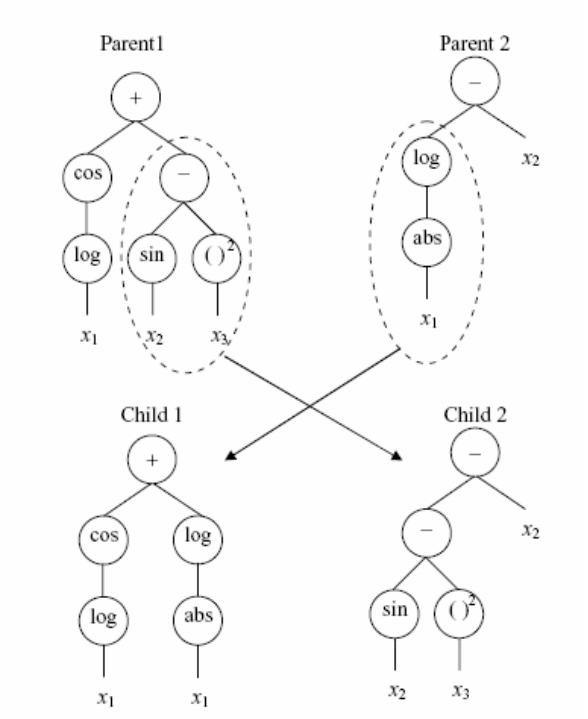


Figure 17 – Genetic programming – the functions that obtain the best results pass to the next generation.

Finally, the results are the input of a classifier (the selected classifier was *k-nearest-neighbour,* k-NN), a nonlinear classifier able to create decision borders quite complex.

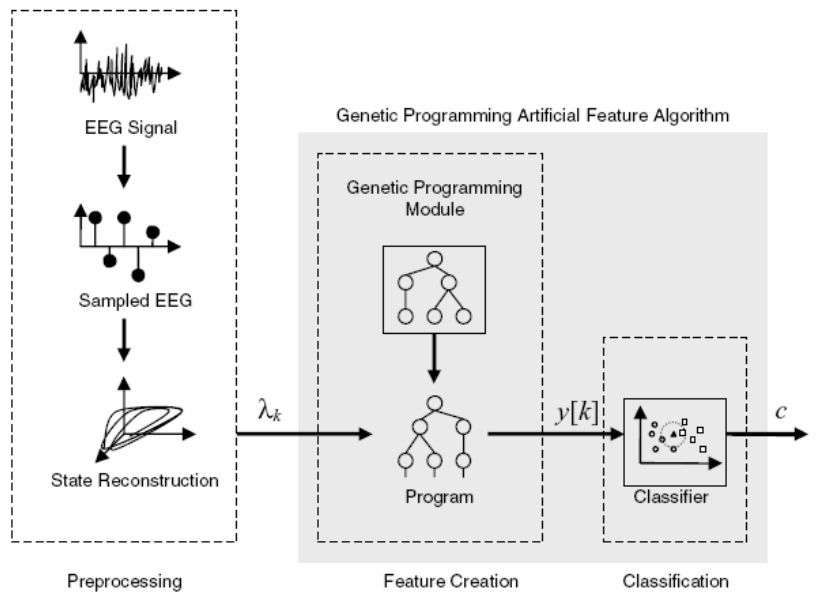


Figure 18 – Genetic programming, Schematic representation of H.Firpi algorithm.

The results obtained in this study (7 patients) present a sensitivity of 79.18% and a false positive rate of 6.78%.

3.2 Review and comparison of seizure prediction methods, statistical considerations

Based in clinical, behavioral and statistical considerations Winterhalder et al. [23] suggests a method to assess and compare proposed methods for seizure prediction, through the criterion Seizure Prediction Characteristic.

Usually the methods focus the study in the pre-seizure activity and their efforts are normally concentrated in features that may identify this period.

The results presented by the authors normally concern to sensitivity (ability to predict all clinical events), usually ignoring interictal moments and the concept of specificity (ability to measure the method effectiveness, detect only the relevant clinical events).

The absence of one of both parameters hinders a correct analysis and does not allow the comparison between the various methodologies. The author considers a parameter SPC (*Seizure Prediction Characteristic*) - based in several arguments of various domains such as clinical, behavioral and statistical, in order to achieve a well-founded comparative study.

A seizure prediction method needs to anticipate an imminent seizure setting an alarm, predicting the onset instant. An ideal method should indicate the exact moment of the seizure onset; in practice, this performance is not expectable, so the concept Seizure Occurrence Period (SOP) may be considered – time interval where the seizure onset may be located. The existence of a therapeutic intervention depends of the time interval between the alarm and SOP – this time interval may be described as Seizure Prediction Horizon. These two periods (SOP and SPH) allow a generic analysis of seizure prediction algorithms (Figure 19).

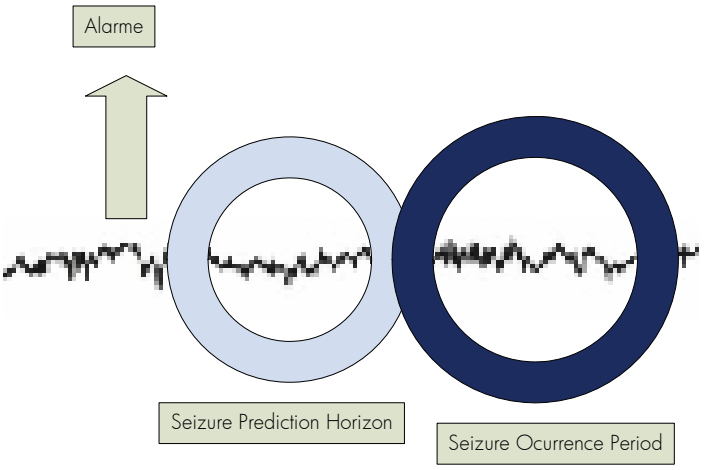


Figure 19 – Seizure Prediction Characteristic - Alarm, SPH and SOP

3.2.1 Sensitivity and false positive rate

A seizure prediction method should identify and predict a high percentage of clinical events. The sensitivity is determined through the ratio between the correct predictions and the total number of considered events. In a realistic study, false positives cannot be prevented and must be allowed if these detected events are exceptional (the method should not be meticulously optimized to a determined signal in order to prevent false positives in that particular signal/patient since these efforts may decrease the algorithm ability to analyze different databases).

False positives rate represent the specificity of a certain method; usually determined through the number of false positive over time (usually False Positive/hour).

As already described, the increase of sensitivity, through parameter adjustment for each patient is usually obtained in exchange for an increase in the false positive rate. This interdependence demonstrates the importance of the joint analysis of both parameters.

3.2.2 FPR max

Because of the impossibility of completely prevent false alarms it is necessary to understand what is the maximum False Positive Rate (FPRmax) that is possible to tolerate. The negative effects of false predictions depend on the intervention system chosen.

In the case of a simple warning, the patient should avoid any dangerous behaviour in the period SPH and expect the seizure onset at any moment during the SOP; the absence of false positive would increase of the life quality of the patient; a significant false positive rate would affect decisively the day life of the patients.

A clinical intervention (anticonvulsive drugs administration among other possibilities) could present damaging side effects if too many false positives are detected. A FPRmax has to be defined, still acceptable from a clinical point of view.

3.2.3 SPHmin and SOPmax

The values of SPHmin and SOPmax should be determined according to the same arguments, i.e., according to the intervention system chosen; if the mechanism consists in a simple warning, SPHmin should provide time to the patient to avoid dangerous situations, while if the mechanism chosen is based in a clinical intervention SPHmin should consider the mechanism intervention period to become effective.

SOPmax value should be determined through similar considerations.

3.2.4 Seizure Prediction methods review

The set of parameters that compose a seizure prediction method is adjusted until the method obtains the largest sensitivity possible and reaches the projected values of FPRmáx. Thus, it is necessary to validate the method with data corresponding to at least 1/FPRmáx.

The proposed method may be described by the following function S = S (FPRmax, SPH, SOP).

This approach allows the comparison between various methods independently of its origin, application and intervention mechanism aimed.

3.3 Conclusions

The feature extraction from EEG signal and the ability to process all the extracted feature together should result in seizure prediction algorithm for all patients.

The intersection of all gathered data is one of the main steps towards the prediction of all clinical events. In chapter 5, data analyzed through VISRED support this idea, as described further ahead in this document.

One of the most recent developments in seizure prediction is the eminent launching of intelligent devices of treatment. With the hardware platforms in full development, some of them adaptations of other medical devices, the first devices projected will probably detect the beginning of the ictal period and unchain the treatment; by neurological stimulation and/or local infusion of the drugs. Gradually, it is expected an increase in the seizure prediction horizon as the projected algorithm present greater consistency.

This evolution will revolutionize the treatment; an increase in the seizure prediction horizon should be associated to a decrease in therapy aggressiveness. The therapy side effects are closely related to false positive tolerance.

The study of these methodologies will relate new concepts to seizure analysis and may open new doors to the origin of seizures; which the functional components associated with the biological neural network, how seizures can be predicted or even prevented, understand the mathematical process that leads to clinical events[36].

The absence of rules to evaluate seizure prediction method complicates the possibility of presenting a well-founded comparison study. Several factors can obstruct the ability to compare different methods; the main factor is the database used in the studies presented.

The following tables represent two studies that intended to summarize the results obtained by the various groups that worked in this area. The results must be interpreted as simple indicators, since the methods had not been tested on the same conditions or databases. Recent efforts strongly recommend the creation of an international database for method training and testing. A first reliable database is avaible in Freiburg [24].

Year	Authors	#pac.	#seizures	Sensitivity (%)	False positive rate (/h)	method
1998	*Osório et al.*	13	125	93	0	*Frequency analysis*
1998	*Martinerie et al.*	11	19	89	n/d	*Correlation density*
1998	*Lehnertz and Elger*	16	16	94	0	*Correlation dimension*
1999	*Le Van Quyen et al.*	13	23	83	n/d	*Similarity index*
2000	*Le Van Quyen et al.*	9	17	94	n/d	*Similarity index*
2001	*Iasemidis et al.*	5	58	91	n/d	*Lyapunov exponents*
2001	*Le Van Quyen et al.*	23	26	96	n/d	*Similarity index*
2001	*Lehnertz et al.*	59	95	47	0	*Correlation dimension*
2001	*Jerger et al.*	4	12	n/d	n/d	*Comparison study (7 methods)*
2002	*De Clercq et al.*	12	12	0	n/d	*similarity index and correlation dimension*
2002	*Navarro et*	11	41	83	0.3	*Similarity*

	al.					*index*
2003	*Mormann et al.*	10	14	86	0	*Phase coherence e linear cross correlation*
2003	*Mormann et al.*	18	32	81	0	*Synchronization index*

1. proposed by *Maiwald et al.*

Another summary was presented by *F.Mormann*. Among the analyzed algorithms, we find concepts as signal energy, correlation dimension and Wavelet transform.

Authors	Year	Methodology	Sensitivity	False positive rate
Litt et al.	2001	Signal energy	90	0.12
Lehnertz et al.	2001	Correlation dimension	47	0
Winterhalder	2003	phase coherence and lag synchronization index	42	0.15
Gigola et al.	2004	Wavelet transform and accumulated	92	0

		energy		
D'Alessandro et al.	2005	Continuous energy variation	100/13	1.10/0.71
Esteller et al.	2005	Continuous energy variation	71	0.11
Iasemidis et al.	2005	Largest Lyapunov exponent	82	0.15
Le van Quyen et al.	2005	Similarity index	69	n.d.
Chaovalitwongse	2005	Lyapunov exponents	69	0.15

2. proposed by *F. Mormann [25]*

4 Technical description

In the presented study several mathematical concepts are considered – signal energy, Wavelet transform and several nonlinear features, in the processing of EEG time series. As a starting point of the study, diverse studies and methodologies were analyzed.

One of the goals of the project consists, not only in the study and in implementation of these algorithms but innovate these concepts connect new ideas and trying to extract new features for seizure prediction and signal processing; as well as the development of an application that would allow their use.

In this chapter, the main concepts used in the application development are introduced as well as the added contributions in the projected algorithms. Finally, we present of the developed application.

4.1 Mathematical concepts

Several of the main concepts used in the application development were studied during the project; mathematical methods such as correlation dimension, Lyapunov exponents, Wavelet transform, and energy signal were in the base of this project.

A brief description of the main concepts is introduced in the developed algorithm presentation.

4.2 Implemented algorithms, application development

The main concept of the presented work is signal processing; the study carried through during this project is based on the processing of EEG signal – signal processing consists on the analysis, interpretation and manipulation of signals. Signal processing includes the storage, reconstruction as well as the extraction of features, noise reduction and data compression.

A set of algorithms were developed and used in the EEG data with the purpose of creating a computational tool that allows the identification of pre-seizure activity. The results obtained are presented in the next chapter.

4.2.1 Signal energy, accumulated energy

The concept of signal is usually related with a function of variable amplitude over time, describing the behaviour of a system. Thus, the area under a curve, in the graphical representation of the function could represent a possible quantification of the signal; however, this area can have negative parts which do not necessarily have different significance than the positive part. This suggests either squaring the signal or using its absolute value, then finding the area under that curve (Figure 20). Signal energy can be described as the area under the squared signal [26].

Figure 20 – Signal energy of a function – the shaded region represents the energy of function f(t)

Based on the algorithm presented by B.Litt et al [8] - the authors relate the EEG study with accumulated energy concept, an algorithm was developed involving the determination of energy segments through a sliding window over the EEG resultant time series.

The energy of the signal is calculated through a sliding window with a variable dimension. The instantaneous energy is determined through the square of each value; the average energy values are determined through a window with overlapping with the previous window to obtain a better resolution.

$$E_k = \frac{1}{n}\Sigma x^2[n]$$

Average energy (8)

Accumulated energy is determined by the sum of the successive values of signal energy. Then the derivative of the function is determined and analyzed, allowing the pattern evaluation; according to several authors, pre-seizure activity is related to the increase of EEG signal energy (figure 21).

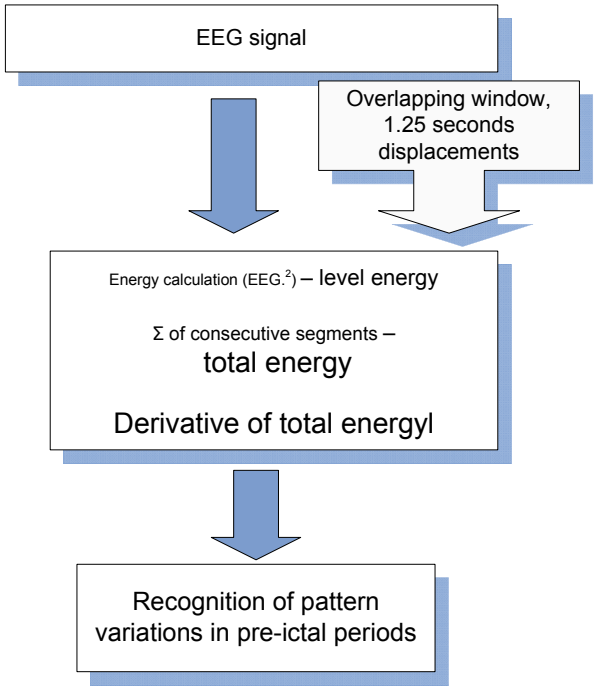


Figure 21 – Schematic representation of the algorithm Accumulated Energy

Abnormal patterns identification (threshold) is determined through the comparison of each value to the average energy of the n previous samples and an offset value. When the value exceeds the determined threshold, an alarm is considered.

4.2.2 Energy variation

Based on the algorithm presented by R. Esteller et al. [9], EEG signal was processed through two windows with different length trying to analyze energy patterns. The idea was to confirm the increase energy bursts in the periods that precede seizures.

The following figure describes the algorithm.

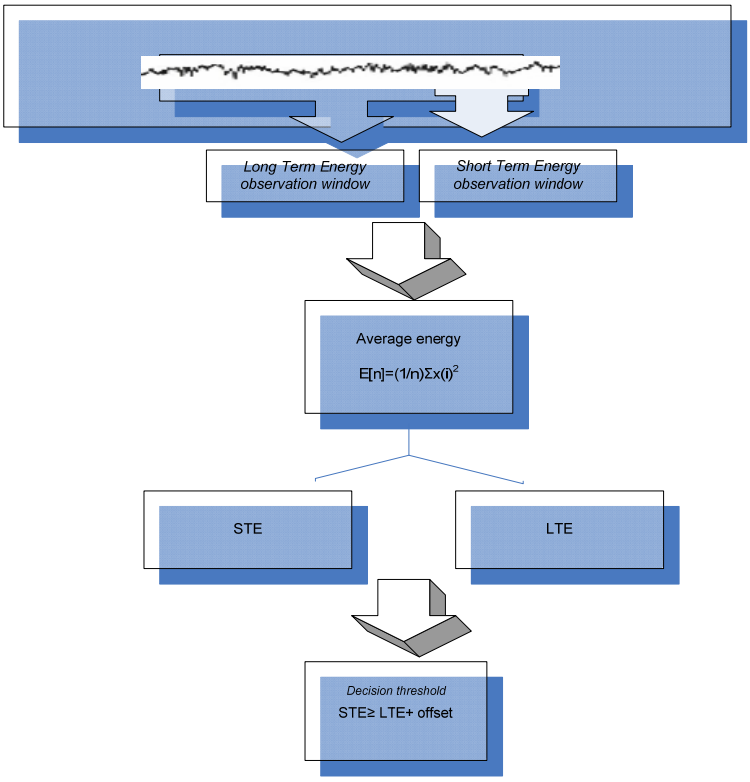


Figure 22 – Schematic representation of the algorithm Energy variation

Accumulated energy was approximated by using moving averages of signal energy (using a short-term energy observation window vs. a long-term energy observation window). A similar displacement was applied to both windows and both ended at the same time point.

The function STE > LTE + offset was used to determine thresholds and consequent alarms. The offset value was determined through STE standard deviation; this choice may help the generalization ability of the algorithm.

4.2.3 Wavelet transform, frequency spectrum decomposition

As previously stated, intracranial EEG data has considerable advantages when compared to scalp EEG; among the advantages presented we find signal-to-noise ratio, time and space resolution. It also allowed the analysis of high frequency bands.

The frequency band that represents the frequencies between 100Hz and the 500Hz demonstrated a specific pre-seizure activity - high-frequency oscillations, also

called as ripple. A study published by Jirsch JD, Gotman J. et al. in 2006 [27] presented these observations; through spectrum analysis and visual inspection techniques of the signal obtained in 10 patients. Four of these patients presented the focus in the temporal lobe, and in all processed seizures (12), the oscillations were registered in a high frequency band (between the 250 and the 500 Hz), before the ictal period.

An activity increase in the frequency band between 100Hz and 200Hz was registered as well.

The remaining patients with focus location well-defined, but with different locations, also presented abnormal variations in both bands (100Hz-200Hz and 250HZ-500Hz). Only the patient with unidentified focus did not present these abnormalities.

These results suggest that important features can be extracted through spectral analysis, in high frequency bands in particular. Usually these events occur in the primary epileptogenesis region, rarely occurring in distant regions.

According to the authors, the absence of these events may even indicate an inadequate location of the focus.

The need to study the abnormalities in certain frequency bands and their relation to pre-seizure activity leads to the assessment of several mathematical tools that allow spectrum analysis. Several comparative were accomplished planning to select the best mathematical method: among them, the Wavelet transform and Fourier transform.

A study published by M.Akin [28] registered signal features to explain the advantages of both methods (Wavelet transform and Fourier transform).

The performance of Fourier transform when applied to successive EEG signal segments registers that the spectrum obtained, changes over time (EEG signal must be considered a non-stationary signal). Thus, the classical Fourier analysis ignores the time component in the spectral analysis of a signal.

The presented study also considered Fast Fourier Transform (FFT) and Wavelet transform considering the efficiency of both methods. The results point to Wavelet transform as the best tool to EEG spectral analysis.

Wavelets transform – Concepts, Spectral analysis of the EEG signal

Fourier transform

Spectral analysis of a signal is based in the decomposition of the signal into its frequency (sinusoidal) components. This representation indicates the weight of a particular frequency in a signal; indicates the frequency components that constitute the signal, ignoring the moment «where these contributions occur, i.e., does not mention any time reference,

The Fourier transform pairs are expressed as $X(k) = \sum_{n=0}^{N-1} x(m) W_N^{kn}$, and $x(n) = \frac{1}{N} \sum_{k=0}^{N-1} X(k) W_N^{-kn}$ where $W_N = e^{-j(\frac{2\pi}{N})}$ and N is the length x(n) [28].

Through this method, dominant frequencies in the signals processed are easily identified. A 2D representation of the original function allows a good quality frequency resolution of the EEG signal.

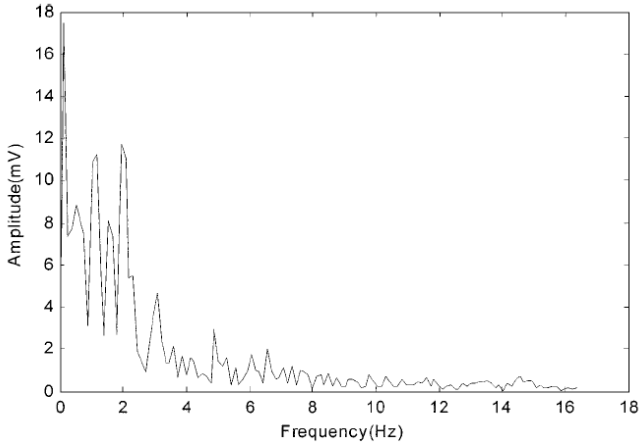


Figure 23- Spectrum of a pathological waveform

As already stated, EEG signals are non-stationary; by the use of the Fourier transform small changes may not be identified and the analysis may change depending on the length of the EEG signals processed.

Short Term Fourier Transform (STFT)

To overcome the limitations described above, some authors suggest STFT. Fourier analysis decomposes a signal into its frequency components and determines their relative strengths. This method divides the signal in short segments; the segments can be considered approximately stationary.

The STFT positions a window functions on the time axis, and calculates the Fourier transform of the windowed (segmented) signal [29].

$$STFT_X^{(\omega)}(t,f) = \int [x(t).\omega^*(t-t')].e^{-j2\pi ft}dt \qquad \textit{STFT (9)}$$

However, narrow segments give a good time resolution, but poor frequency resolution. Wide segments give good frequency resolution, but poor time resolution; furthermore, wide segments may violate the condition of stationary. Once selected the size of the segment, the entire analysis has to be processed. A choice has to be made: good spatial resolution vs. good frequency resolution [30]

Wavelet transform

The wavelet transform was developed as an alternative approach to the short time Fourier transform.

In some cases, it is necessary to know the specific moments where certain variations occur; in the EEG signal, the latency associated to clinical events is particularly important.

In summary, the time series are decomposed in several frequency bands by bandpass filters; this procedure is repeated, each iteration correspond to a band of frequencies of the original signal removal. These extracted functions, represent the same original signal, corresponding to each frequency band. A simultaneous analysis of these functions allows a 3D representation (frequency, time and amplitude).

Continuous Wavelet transform

This method was developed as alternative to the STFT to overcome the resolution problem; the signal is multiplied by a similar function to the function window in the STFT, and the transform is determined for the extracted functions of the original signal.

The mother wavelet is chosen to serve as a prototype for all windows in the process. All the windows that are used are the dilated (or compressed) and shifted versions of the mother wavelet. There are a number of functions used for this purpose.

Once the mother wavelet is chosen the computation starts with s=1 and the continuous wavelet transform is computed for all values of s smaller and larger than 1. However, depending on the signal, a complete transform is usually not necessary. For all practical purposes, the signals are bandlimited, and therefore, computation of the transform for a limited interval of scales is usually adequate (scaling). The wavelet at scale s=1 is then shifted over the signal by tau amount to the location t=tau, and the transform is processed with t=tau, s=1 in the time frequency plane [29].

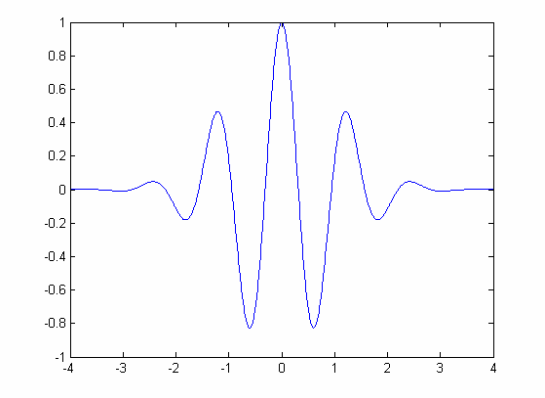


Figure 24 – Morlet wavelet representation

Continuous Wavelet transform is defined by $CWT(a,b) = \int x(t)\Psi^{*}_{a,b}(t)dt$ where * denotes the conjugate, a $\in R^{+}$ denotes the scale parameter and b represents shift parameter.

The function $\Psi_{a,b}(t)$ is obtained scaling the mother Wavelet $\Psi(t)$ over t = tau and scale = s, and is described by $\Psi_{a,b}(t) = \frac{1}{\sqrt{a}}\Psi(\frac{t-b}{a})$.

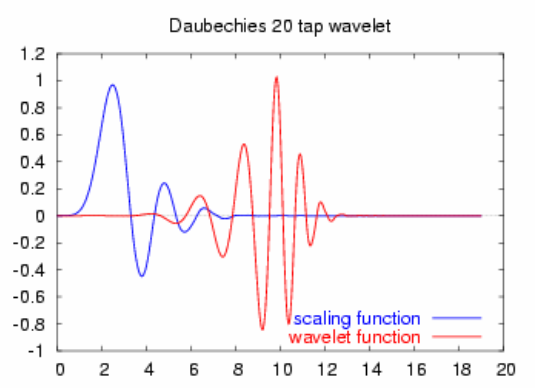


Figure 25 – Wavelet transform – scale and shift.

Thus, through the wavelet transform it is possible to identify the different frequency components preserving time domain information, unlike Fourier transform.

The several studies presented, pointed that the reason for the success of wavelet transform depends on the scaling and shifting properties of the mother wavelet. Another advantage is the 3D representation of a signal; this representation is more convenient for pathological cases.

Wavelet transform represent a better-suited method for the analysis of EEG signals. Furthermore, the method presents better results in the identification of small variations and in the processing of non- stationary signals.

4.2.4 Wavelet transform, decomposition coefficients analysis

Based on the arguments presented by J.Gotman [27, 36], spectral analysis may contain important information for seizure prediction; feature extraction from different frequency bands may help the identification of pre-seizure activity.

Several studies consider Wavelet transform as the better-suited method for the analysis of EEG signals [28, 30].

The coefficients obtained through wavelet decomposition are a representation of the weight of each frequency band to the original signal over time.

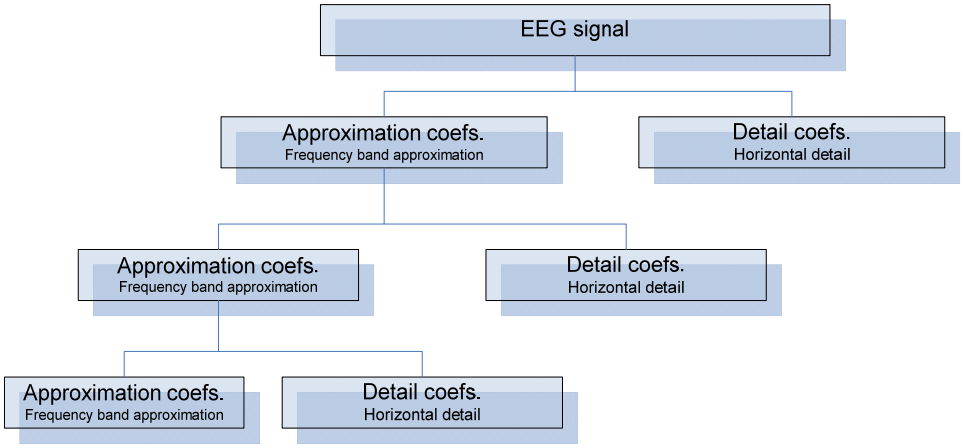


Figure 26 – Wavelet decomposition

Thus, the signal is decomposed in different frequency bands, and the extracted coefficients represent new functions ('versions' of the same original signal). The analysis of these extracted functions allows identifying which is their influence to the original signal.

Based on the mechanism previously explained, the coefficients obtained by wavelet decomposition are processed and accumulated energy of these series is determined. Accumulated energy was approximated by using moving averages of coefficients energy (using a short-term energy observation window vs. a long-term energy observation window). A similar displacement was applied to both windows and both ended at the same time point.

The threshold is determined by the following function

- STE (short term energy) > LTE (long term energy) + offset,

Where offset is determined based in the value of standard deviation of STE values.

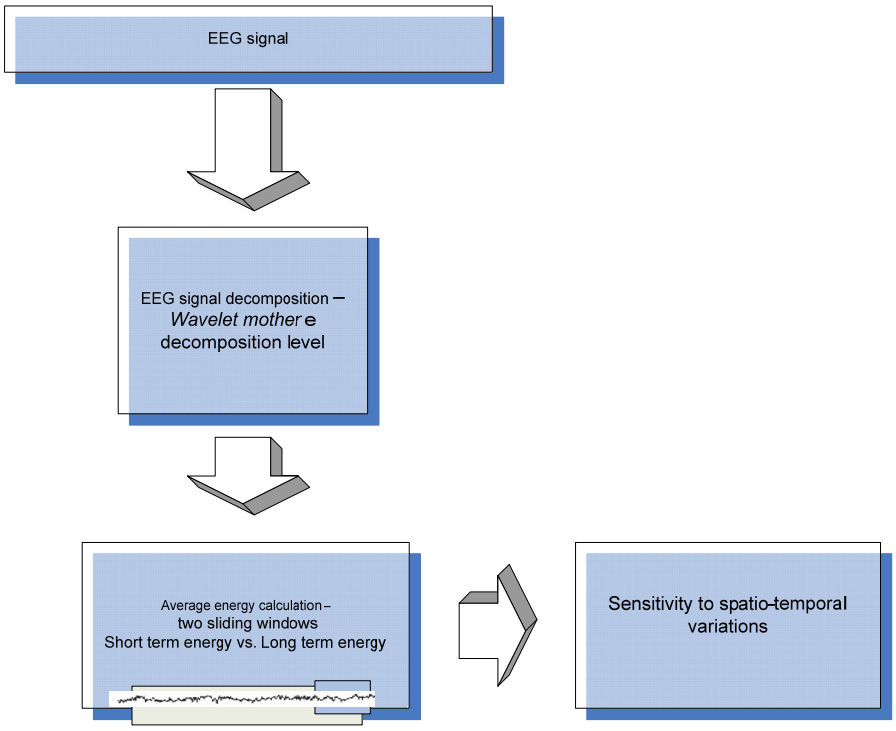


Figure 27 – Schematic representation of the implemented algorithm

The mother wavelet used in the presented studies was daubechies-4; the decomposition was completed with four levels.

4.2.5 Nonlinear dynamics, Lyapunov exponents and correlation dimension

Another branch of research that has emerged in the identification of pre-seizure activity is the related to the analysis of nonlinear dynamics of systems; the interpretation of the features that describe the system complexity is among the most studied hypothesis.

Some studies suggest that the variations registered in several extracted features may be related to the mechanism underlying to the generation of seizures.

A nonlinear system is, by definition, a system that does not satisfy the criteria of system linearity (the two basic tests of linearity are homogeneity and additivity).

In this study, a nonlinear signal was considered as a signal that cannot be created by a SISO system (single input - single output); unless by the excitation of a linear system which the input represents a version of a linear transformation of a nonlinear signal, i.e., the only way of obtaining a nonlinear signal from a linear

system is through the excitation of a linear system which input is linearly related with a nonlinear signal.

4.2.5.1 Chaos, chaotic signal and chaotic system

In mathematics and physics, chaos theory may be considered as a description of certain nonlinear dynamical systems that under specific conditions exhibit dynamics that are sensitive to initial conditions; their stationary state depends on the initial conditions of the systems.

Unlike steady linear systems, which only behaviours achievable are to converge to well-described regions defined by the stationary behavior of the input of the system, nonlinear systems can present multiples stationary behaviors.

In certain cases, the border between two different stationary behaviours cannot be represented by normal geometric representation but only by fractals. It is important to recognize that the sensitivity to initial conditions represent a property of nonlinear systems; if a nonlinear system is submitted to a transient response and its behaviour is moved away of the region determined by the initial conditions, the system may converge to another steady-state behaviour (different from the determined by initial conditions).

As a result of the sensitivity, the behaviour presented by these systems appears to be random; small changes in the initial conditions of the system may induce significantly different future trajectories. Arbitrarily close initial conditions, both leading to aperiodic steady-state behaviours may origin (and usually origin) aperiodic behaviours quantitatively different.

If we consider two aperiodical behaviours of the same systems, the measures of their divergence increase gradually due to the random nature of aperiodic signals. These systems are usually described as presenting *sensitive dependence on initial conditions* if they exhibit this dependence in a non trivial region of initial conditions, i.e., the dependence is not exclusive of a set of points.

4.2.5.2 Defining Chaos

In nonlinear dynamic repetitive behavior is usually considered as periodical behavior. An autonomous system is chaotic if certain conditions are verified: (1) steady-state aperiodic behavior for a region of initial conditions; (2) *sensitive*

dependence on initial conditions; (3) if these behaviors do not depend on the inputs of the system in any random process.

Considering the purpose of this study, we can assume that a system that exhibits sensitive dependence on initial conditions also assumes steady-state aperiodic behavior for a region of initial conditions.

Another aspect to consider is the time that takes to achieve the periodic stationary state; the initial conditions can be described through this factor as *periodic point* ($t \in R$) and *eventually periodic point* ($t \to \infty$).

Thus, a more accurate definition may be described as an autonomous system without random inputs is chaotic if a set of initial conditions dense enough, diffuse over a nontrivial set of points in the phase space, which should be aperiodic or eventually periodic exhibiting sensitive dependence on initial conditions.

This sensitive dependence on initial conditions can be quantified for example by calculation of the Lyapunov exponents. Furthermore, a necessary and sufficient condition to *sensitive dependence on initial conditions* is that the system has at least one Lyapunov exponent positive.

The Lyapunov exponent is a quantity that characterizes the average divergence of the behaviours created by infinitesimally close initial conditions, in practice the demonstration of a positive Lyapunov exponent is considered a proof of a potentially chaotic behaviour of the system.

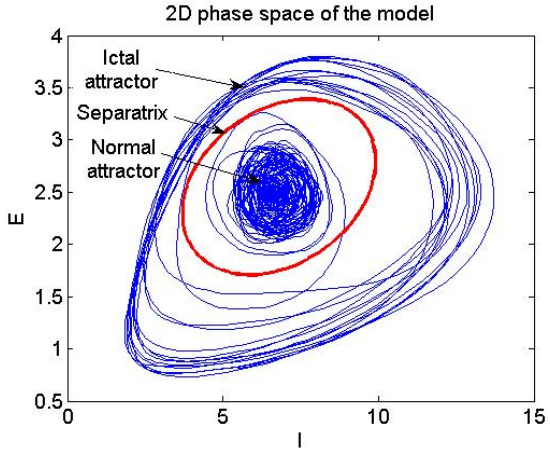


Figure 28 – 2D phase space model from an EEG signal, obtained by method of delays

Chaotic signal can be described as the signal generated by a chaotic autonomous system in response to a set of initial conditions that lead to an aperiodic behaviour.

4.2.5.3 Nonlinear dynamics measures

The dependency between the qualitative behavior of nonlinear systems and the initial conditions complicates the analysis of systems through the inspection of the output.

Due to the previously stated properties of these systems, any performed analysis represents the system in the exact moment of the calculations since any change on the initial conditions of the system may originate significant deviation on the system output.

The estimation of nonlinear characteristics like fractal dimensions and Lyapunov exponents assist in the assessment of signal complexity; the feature extraction is based on steady-state behaviour of the system.

4.2.5.3.1 Chaotic system behaviour

Several features and definition usually describe the dimension of a signal; we introduce a basic definition that expresses the nature of the spatial distribution of a certain signal. Consider an autonomous system with P internal nodes. From this system, P variables can be extracted and each variable history can be completely reconstructed through the P variables.

When the system reaches a stationary state, a P-dimensional space is constructed; each axis represents the values of the P variables. This representation is described as phase plot and the P-dimensional space as phase space. Usually, some of these variables can be described as function of the others – the number of necessary variables to describe a system can be less than P.

Following the evolution of the system, the phase plot is drawn (plot of the stationary behaviors of the system towards $t \to \infty$). The concept of dimension refers to the spatial dimension of the structure created in the phase space. The main objective is to determine the spatial dimension of the phase plot.

An attractor is a set to which a phase plot describing a dynamical system evolves over time. The dimension of this structure containing the phase plot is one of the features that describe the behavior of nonlinear systems [31].

It can be difficult to identify any regular structure describing the phase plot of a chaotic system which variables present aperiodic patterns, however this plot is always restrained in the P-dimensional phase space.

Usually the phase plot of a chaotic system presents, apart of a simple or complex structure, a fractal structure. The aperiodic patterns presented by a chaotic system must be contained in the phase space, but the curve obtained cannot intersect itself (if so two trajectories may fuse and exhibit a periodic behavior).

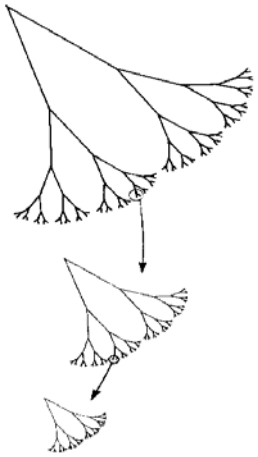


Figure 29 – Example of a fractal structure

The concept of dimension represents an objective feature that may identify nonlinear signals. Besides representing a characteristic of the phase plot, the value of the dimension also represents a quantification of the complexity of the signal.

Several methods allow the calculation of the features presented: dimension of the attractor/phase plot. In this study, the main method used was the correlation dimension.

Complete knowledge about the attractor dimension provides important information about the signal and the system that originates it. Hence, the dimension grows as the attractor structure spatial complexity gets higher. If the dimension's value is non-integer then the attractor possesses a fractal structure and the phase plot presents aperiodic patterns. Furthermore, if the attractor presents a fractal structure (non-integer dimension), it is quite probable that the phase plot represents a chaotic signal.

4.2.5.3.2 Correlation dimension

In chaos theory, the correlation dimension is based on the density of the points that constitute the attractor, a measure of the dimensionality of the space occupied by the phase plot and proximity of each point to the attractor.

After the construction of the embedding phase space (method of delays) from a data segments it is necessary to determine a measure for the distances in the phase space. Consider a time series $x[n], 0 \le n \le N-1$ obtained through sampling of the function f(x) with frequency $f_s = \frac{1}{t_s}$. The vectors $x_i = [x_{i1}, x_{i2}, \ldots, x_{im}] = [x[i.t_s], x[(i+1).kt_s], \ldots, x[(i+m-1).kt_s]]$ in the phase space are determined through one of these two norms: Euclidian norm $d_{ij} = \|x_i - x_j\| = \sqrt{\left[\sum_{k=1}^{m}(x_{ik} - x_{jk})^2\right]}$ or maximum distance between two components of x[n] , $d_{ij} = \max_k\left[|x_{ik} - x_{jk}|\right]$.

Then, for any set of N points in an m-dimensional space, the correlation integral $C^m(r)$ can be determined by $C^m(r) = \frac{1}{N^2}$[number of pairs(x_i, x_j) , which have a distance between them that is less than r: $d_{ij} < r$].

In summary, this function determines the dimension's value through a sphere of radius r, which contains the phase plot points; counting the average number of points inside these spheres. This method is similar to a spatial correlation; processing the density of point distribution in the phase space. Considering that the number of points contained in the sphere is proportional to the sphere radius, it can be concluded that $D_C = \lim_{r\to 0}\left[\frac{\ln(C(r))}{\ln(r)}\right]$.

4.2.5.3.3 Lyapunov exponents

Lyapunov exponents utilize the Eigenvalue concept (quantification of a transformation) and allow the evaluation of the stability of the behaviour of systems. For a certain system and any initial condition x_0 , Lyapunov exponents are described by:

$\lambda_i \triangleq \lim_{t\to 0}\left[\frac{1}{t}\ln|L_i(t)|\right]$, where $L_i(t)$ is determined by $L_i(t) = e^{l_i t}, i = 1,\ldots,n$ (l_i is obtained by the Jacobian matrix describing the behavior of vectors in the tangent space of the phase space).

The Lyapunov exponents, in an equilibrium point of a system are determined as follows:

$$\lambda_i = \lim_{t\to\infty}\left[\frac{1}{t}\ln(e^{l_i t})\right] = \lim_{t\to\infty}\left[\frac{1}{t}\ln\left|e^{\mathrm{Re}\{l_i\}t}e^{j.\mathrm{Im}\{l_i\}t}\right|\right] = \mathrm{Re}\{l_i\} \qquad \textit{Lyapunov exp. (10)}$$

Thus, Lyapunov exponents can be interpreted as the real part of the Eigenvalues of the linearization of the system in an equilibrium point [31].

Although the definition of Lyapunov exponents refer the initial condition of the segment in analysis, the inevitability of processing $t \to \infty$ denote that every point in the segment present the same Lyapunov exponents.

One of the properties already presented when this methodology was introduced was sensitive dependence on initial conditions. The quantification of this property leads to the analysis of features such as Lyapunov exponents that measure this dependence. Considering the phase plot in the phase space, and an event δ_0 that significantly alters the patterns, the divergence of nearby trajectories (before the event and the other after the disturbance) can be measured. For a brief moment, the distance between both trajectories can be modelled as following an exponential behavior. Few moments after, the distance between the trajectories can be described by the largest Lyapunov exponent and an approximation can be determined through $\|\delta(t)\| \approx \|\delta_0\| e^{\lambda_1 t}$. As already stated, if the system presents sensitive dependence on initial conditions at least one of the Lyapunov exponents should be positive.

After making a proper choice for the time lag and embedding dimension, we can reconstruct an image of the attractor in the original phase space. To each state we can find the nearest neighbour on a segment of a nearby trajectory and calculate the difference vector over short intervals of Δt. The values are processed and the average values of these measures represent the value of Lyapunov exponent λ_1.

4.2.5.4 Nonlinear dynamics, implemented algorithm

Several approaches, based on the chaos theory, were used successfully in EEG analysis; due to the aperiodic and instable behavior of the epileptic brain, the structure is suitable to nonlinear techniques. The transition between the normal and ictal states is closely related to the periodic increase of nonlinear relations between abnormal neuronal discharges.

In particular, the dynamic transitions of brain activity may be a result of complex systems; these present statistical properties specific of nonlinear systems transitions [16].

Based on these considerations an algorithm was projected to collect information of nonlinear changes associated to pre-seizure activity. The quantification of nonlinear properties such as complexity and dimension remain a complex process, especially for long segments.

Functions designed for this purpose (TSTOOL toolbox) were used to process EEG signal and determine the Lyapunov exponents and correlation dimension of short segments of the signal.

According to a study presented by J. Wichard and U. Parlitz [33], the values of embedding dimension and time lag are determined for the attractor's reconstruction; the selection of these values are decisive to the high-quality of the reconstruction. On one hand, if the value time lag τ is excessively small the states of the reconstruction will remain too close. On the other hand if this value is excessively long the trajectories may present ambiguities obstructing a precise analysis. Thus, the authors consider mutual information function to determine time lag τ.

Another important parameter to the attractor's reconstruction is embedding dimension. To determine this value the authors applied Cao's method, based on a method described as false neighbours.

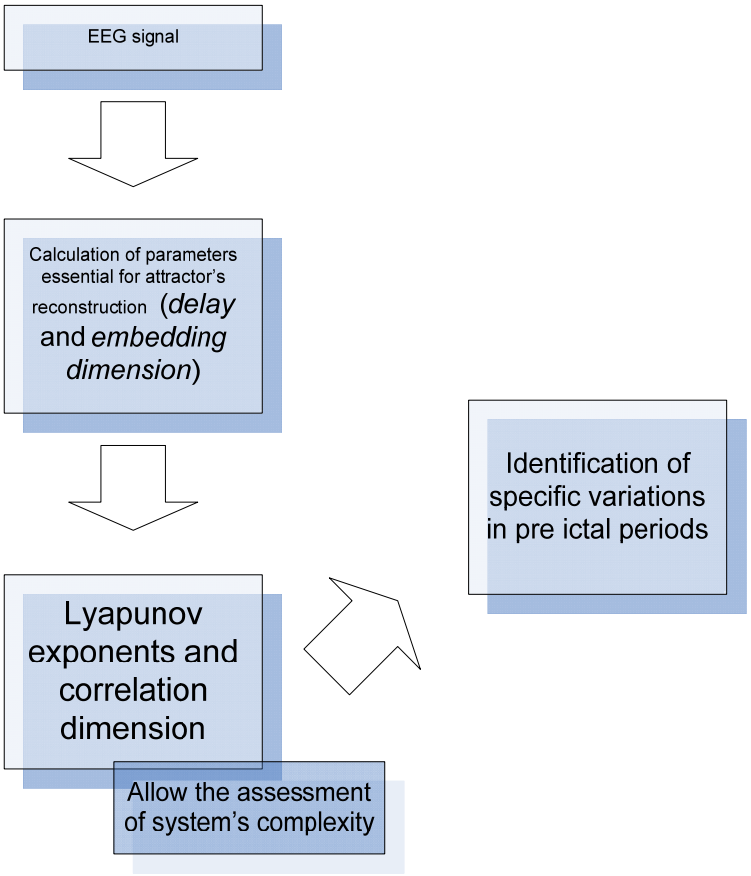


Figure 30 – Schematic representation of non-linear analysis algorithm

The construction of the attractor, after the processing of the parameters delay time and embedding dimension, allow the calculation of the parameters Lyapunov exponents and correlation dimension.

The estimation of the Lyapunov exponents consists in the quantification of the exponential growth of the average distance between two nearby trajectories through error approximation. The prediction error vs. prediction time allows the estimation of the feature.

Correlation dimension is determined by taken's estimator method (additional information can be consulted in TSTOOL toolbox manual) [34].

Successive values representing short segments are analyzed, and an abnormal synchronization of neuronal activity, referred by several authors (such as *W. Chaovalitwongse, 2006*), might be identified by the analysis of the curve produced by this method; an increased synchronization may be associated to a higher previsibility of the system.

4.3 Toolbox, structure

This section presents an overview of the organization as well as a description of developed toolbox main functions. The source code is developed in Matlab, and was a result of efforts made during the project.

In this work, several Matlab toolboxes and Mfiles were tested, and in the final version, several of these functions were applied (such as wavelet toolbox, EEGlab, TSTool and vline).

Matlab path should contain EEGLAB for the developed toolbox run correctly. TSTooL *startup* file has to be indicated for the nonlinear analysis function run properly.

4.3.1 Organization

The main file is in the initial directory along with the .fig file, which allows the program to run normally. The functions with the algorithms of signal processing are in the folder Functions.

4.3.1.1 '\Functions'

accumulatedEnergy (signal energy analysis)

energyVariation (signal energy analysis)

wavAnalysis (wavelet transform analysis)

wavCoefAnalysis (wavelet coefficients analysis)

nonlinearAnalysis (lyapunov exponents and correlation dimension analysis)

vline (plot)

4.3.1.2 '\data\datasets'

Example files.

4.3.1.3 '\data\ascii'

Example files.

4.3.2 Overview – instructions

4.3.2.1 Data acquisition

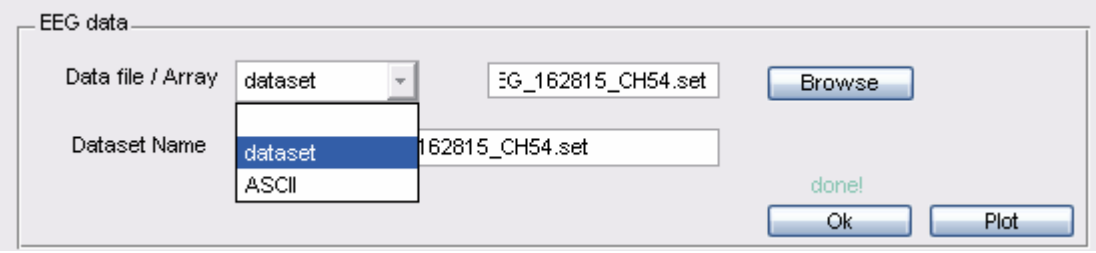


Figure 31 - Data acquisition panel – the user can select between the options: ASCII and dataset (EEGlab) file

To choose data, the user has to select one of the two choices. .set file (EEGlab dataset) or an ASCII file representing a single channel (if the selection is ASCII an EEGlab dataset is created, and the file is saved according to the users selection).

Data information - To process the signal, the user has to define two fields: sampling rate (Hz) and if signal normalization is required (the normalization is made around zero, [-100, 100]).

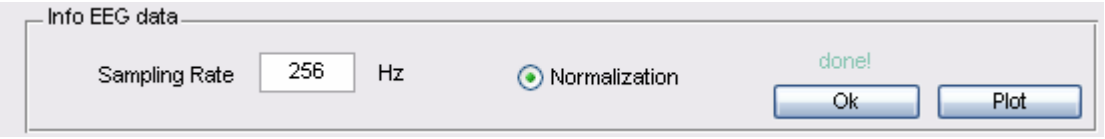


Figure 32 - EEG information panel – the user has to introduce EEG file sampling rate and select whether the signal processing is determined with normalization or not.

Parameter acquisition – Analysis interval represents the time interval between two sets of parameters acquisition. Default value is 5 seconds.

Figure 33 - Parameter acquisition panel – the user has to define, which is the analysis interval of several algorithm parameters, the value defines the time interval (in seconds) between two consecutive calculations.

4.3.2.2 EEG signal Analysis

Accumulated energy

Accumulated energy represents the energy algorithm proposed, based on the work presented by several authors using the signal energy to identify pré-ictal changes in energy spectrum of EEG signals. The algorithm consists in the average value of the signal energy during the analysis interval. Consists in the determination of average energy of short segments; the average energy values are determined through a window overlapping the previous one to obtain a better resolution (1 correspond to window length).

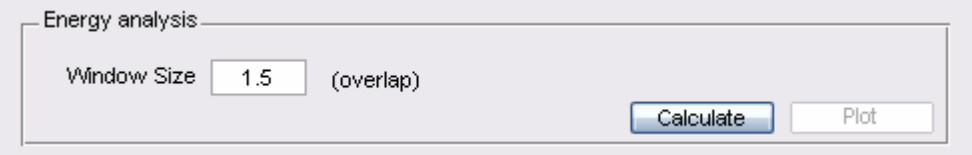


Figure 34 - Energy analysis panel – the user has to define the overlap between two consecutive windows. The value 1 defines no overlap between windows.

The window displacement between two consecutive calculations is described by parameter acquisition analysis interval.

Energy variation

Energy variation represents a two windowed algorithm, which purpose is to identify variations between long-term energy and short-term energy.

Figure 35 - Energy variation panel – This algorithm consists in the definition of two concepts – long-term energy and short-term energy. The values are compared, attempting the identification of energy variations prior to seizures.

The user must define two different window sizes (the longer correspond to long-term energy and the shorter corresponds to short-term energy), and the average values of signal energy inside both windows are determined. The plot represents these features trough time (in seconds).

Wavelet analysis

Wavelet analysis presents an algorithm based on the wavelet transform of the signal. This feature is calculated through functions of Matlab wavelet toolbox. The user has to define the mother wavelet and decomposition level (between 3 and 8).

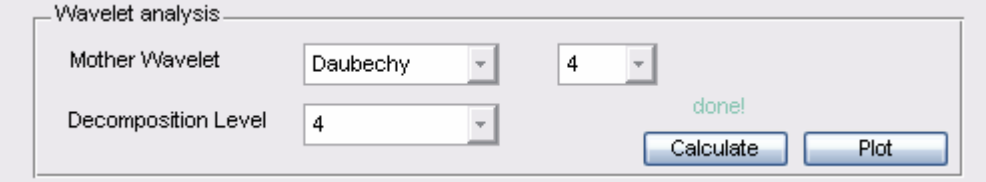


Figure 36 - Wavelet Analysis panel – the user has to define the wavelet to apply in the study and the decomposition level considered necessary

All mother wavelets are available (Matlab help: wavelet toolbox, for more information). The down sample associated with each decomposition level is overcome with Matlab's *upsample* command.

Wavelet coefficients energy

Wavelet coefficients analysis represents the connection between two concepts already stated in this document. In this algorithm, the coefficients obtained through wavelet transform decomposition are processed in two windows. The average energy inside both windows is calculated and compared. This is the former energy analysis applied to the wavelet coefficients of the each decomposition level.

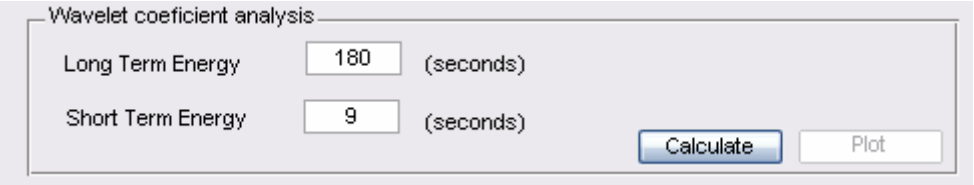


Figure 37 - Wavelet coefficient analysis – the user has to define the size of both window: long-term energy and short-term energy.

Plot button represents these two features (wavelet coefficients short-term energy and long-term energy) in time (seconds).

Nonlinear analysis

Nonlinear analysis calculates two nonlinear features, Lyapunov and Correlation Dimension.

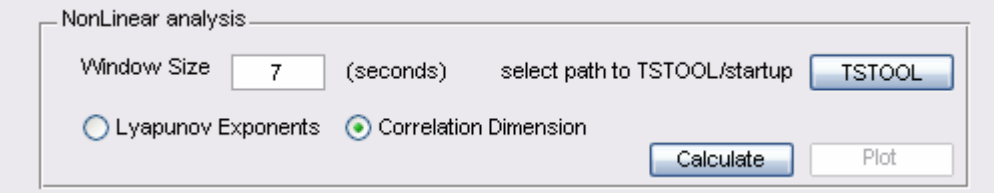


Figure 38 - Nonlinear analysis panel – the user has to define the size of the segments to process (in seconds) and what parameters considered necessary.

These acquired features represent short segments, which size can be defined by the user (window size). The calculations executed in this algorithm are processed through TSTool functions.

4.3.2.3 Event Details

The user can plot vertical lines representing events, throughout every figure. The input consists in two variables, event position (sample number where the event occurs or starts) and the event description (brief description of the event).

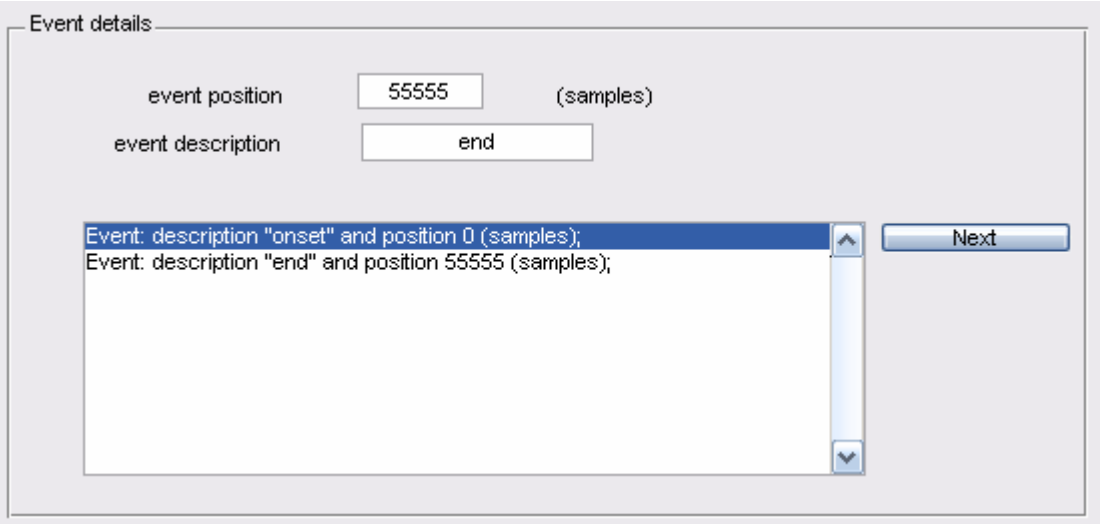


Figure 39 - Event details panel – position and description of events.

4.3.2.4 Seizure warning

Throughout the algorithms, when the values of the features are above a threshold established, the time stamps are added to vectors. These are represented in the listbox in the Seizure warning panel. The values can be observed in a figure.

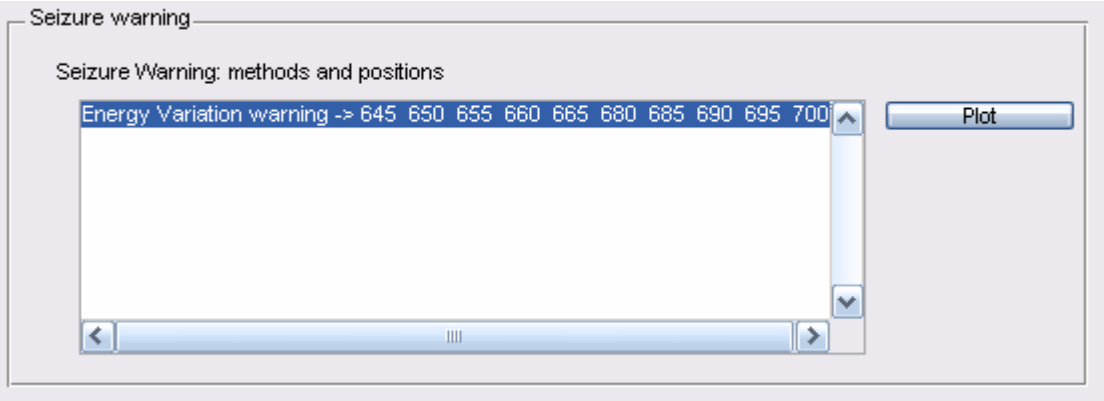


Figure 40 - Seizure warning panel – the user can visually identify where the values of the algorithm are above 'normal'.

4.3.2.5 Save data

The processed data can be saved in two formats, .mat and in excel file. If the user intends to save in a .mat file, a Matlab structure (structure data) is saved with all the main variables processed (data and acquisition times associated with each feature).

Figure 41 - Save data panel – the user can save data in a .mat file (struct) or / and in a excel file.

If the user intends to proceed the study in tools such as VISRED, the excel option is available. The main features calculated are saved in an excel file.

4.3.3 Visualization Routines

A plot option is associated with all features in analysis. Events can be added to these plots in the event panel.

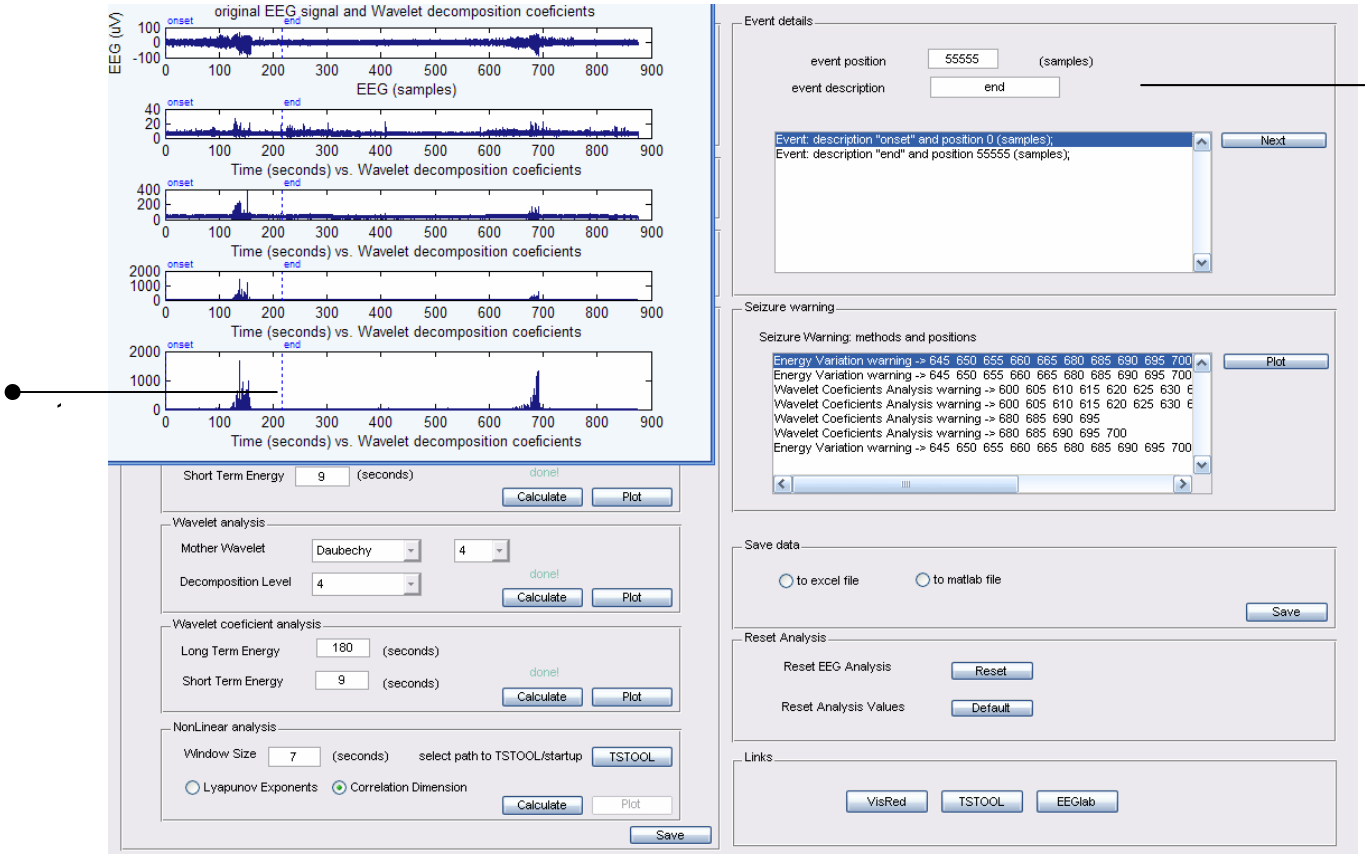


Figure 42 - Interface example – 1. Blue dotted line represents an event, 2. Event panel - position, description and listbox.

In the algorithms, thresholds have been settled to identify abnormal values. When the values are considered abnormal, the time stamp is added to vectors that can be represented in the panel seizure warning by the plot pushbutton.

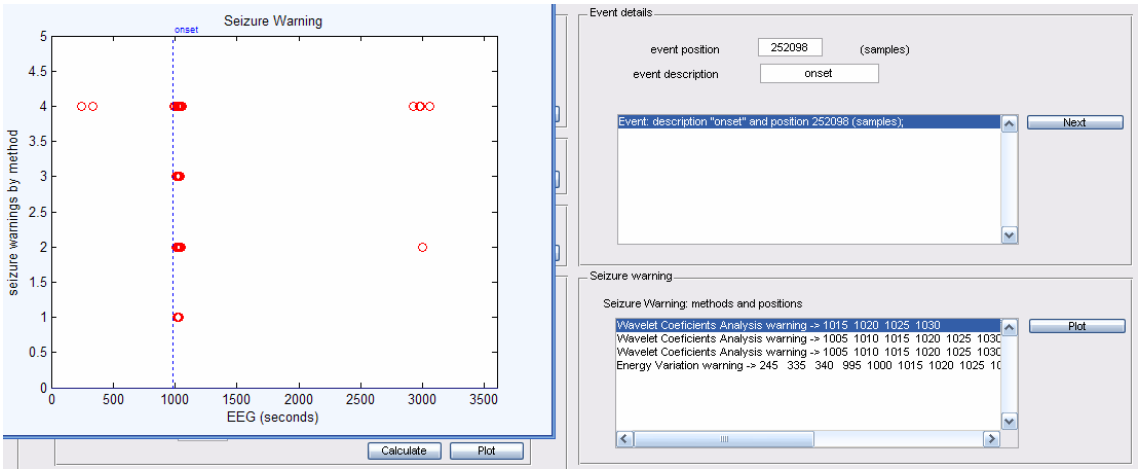


Figure 43 - Seizure warning plot example – the red objects represent the warning extracted from feature calculations.

5 Results presentation, discussion

5.1 Dataset

Patient Id	Onset Area	# seizure	Total data processed (h)
		Freiburg dataset	
1	Frontal	1	2
2	Temporal	3	4
3	Frontal	4	4
4	Temporal	3	4
5	Frontal	4	4
6	Temporo/Occipital	3	4
7	Temporal	2	3
8	Frontal	2	3
9	Temporo/Occipital	3	4
10	Temporal	2	3
11	Parietal	3	4
12	Temporal	2	3
13	Temporo/Occipital	2	3
14	Fronto/Temporal	4	5
15	Temporal	3	3
16	Temporal	4	4
19	Frontal	3	5
		Coimbra dataset	
1	-	5	n/d
2	-	1	n/d

3. Dataset description

The EEG database used in the study contains invasive EEG recordings of 21 patients suffering from medically intractable focal epilepsy. The recordings were obtained as part of a pre-surgical clinical evaluation at Epilepsy Centre of the University Hospital of Freiburg [35] and at the University Hospital of Coimbra.

The intracranial EEG data used included a total of 54 seizures corresponding to 19 patients.

Each individual seizure was divided in four groups for VISRED analysis: (1) Normal, (2) pre-ictal, (3) ictal and (4) pos-ictal; both (2) pre-ictal and (4) pos-ictal have a duration of 5 minutes (Seizure Prediction Horizon considered in this study) before and after a seizure respectively.

In the study, the different features were acquired with a time interval of 5 seconds.

5.2 Results, algorithms overview

In this study, we developed various techniques for EEG processing to confirm that epileptic seizures are preceded of quantifiable variations. Methods based on various mathematical concepts (energy, wavelet transform and nonlinear dynamics), were the foundation of the development of a Matlab toolbox.

The individual analysis of the extracted features did not present the expected results. After the analysis of previous investigations and respective results, our conclusions, obtained by approaches based on those investigations, produced inferior results.

Nevertheless, in several events, undeniable variations occur before seizures, suggesting that these variations could be related to pre-seizure activity.

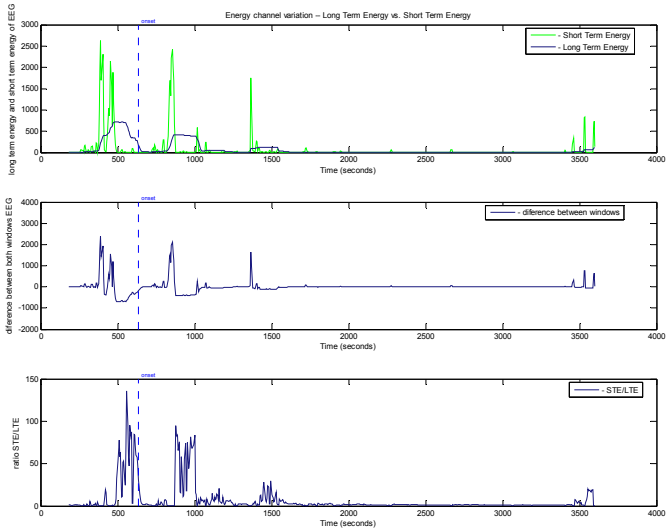
Each method presents, in several files, variations in pre-ictal periods, as can be seen in Appendix A.

Appendix A contains an extensive presentation of the features extracted in this study.

5.2.1 Energy analysis

The windowed average power and accumulated energy were analyzed and plotted for the entire data sets. Generally, the computation of windowed energy on intracranial EEG recordings did not reveal consistent increases or changes prior to seizures. In certain cases and for certain seizures, a distinctive increase of the STE/LTE factor occurred some time before the seizure onset.

Pat 13 Ep1



4. Energy increase before seizure onset, example

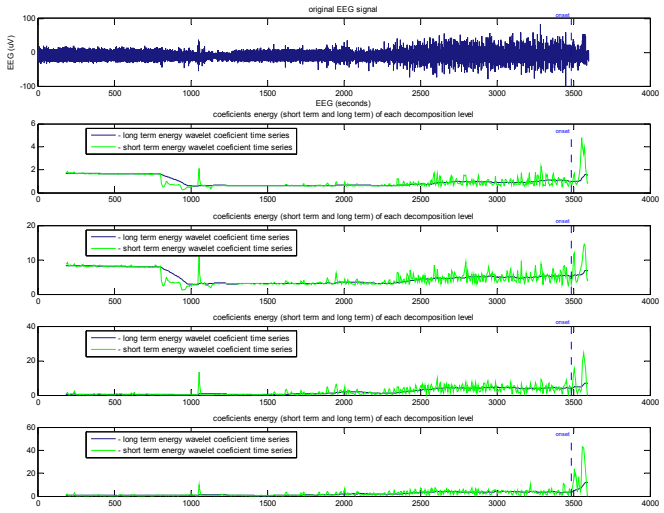
These energy events have already been discussed by several authors [8, 9]. However, the most significant increases occurred at or after the onset of seizures.

5.2.2 Wavelets transform coefficients analysis

In general, some frequency bands present variations before seizure onsets; unfortunately, various electrographic events induce the existence of similar variations in interictal periods. The existence of these variations, have already been described by several authors (A.Subasi, 2005 and J.Gotman, 2006).

Hence, the computation of coefficients did not present consistent variations prior to seizures; the existence of specific pre-ictal patterns was not proved by the analysis. In particular cases and for certain seizures, a distinctive increase of the STE value occurred some time before the seizure onset.

Pat 4 Ep304



5. Increase of STE values in some frequency bands

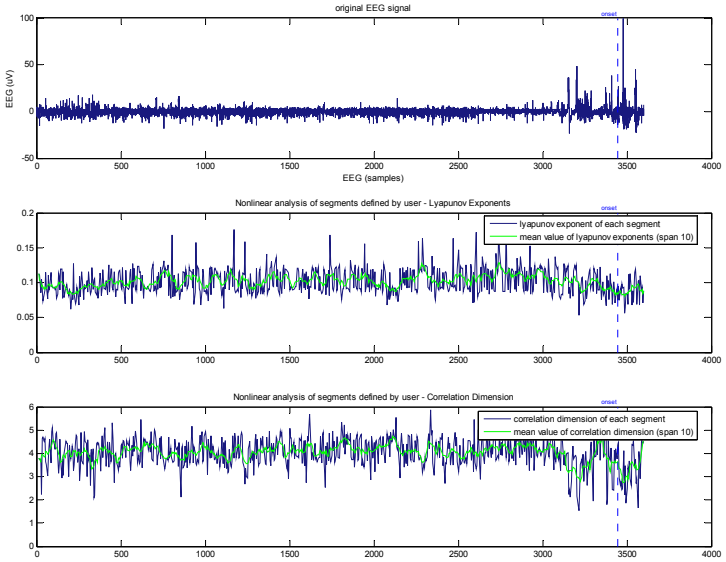
Other recordings present a significant decrease of the energy of these coefficients 30 minutes before the seizure onset (Appendix A, Wavelet analysis, Pat5, Ep013). These variations may be involved in pre-seizure mechanisms; further investigations are necessary to recognize consistent pattern variations.

5.2.3 Nonlinear dynamics analysis

Several authors report evidences for a characteristic pre-seizure state transition and seizure predictability identifiable through nonlinear quantification. In this study, two nonlinear parameters, Lyapunov exponents and correlation dimension, were considered and calculated. According to some studies, the complexity of attractors of pre-seizure signal segments, present inferior values.

Some of the processed recordings present this characteristic decrease prior to seizures.

Pat 5 Ep002



6. Decrease of nonlinear characteristics before seizure onset

Our analysis suggests that further studies are required before a practical seizure prediction based on these features becomes feasible. The analysis of longer pre-seizure periods could present new informations.

5.3 VISRED analysis

Data visualization by space reduction

The visualization of multidimensional data is a crucial problem. One of the main concerns of this study was to evaluate the extracted features as a whole; understand if a combined analysis of all variables, acquired through several methods, could reveal more information comparing to an individual analysis.

A Matlab GUI – VISRED – allowed the visualization of multidimensional data by space reduction. A total of 15 variables were extracted from EEG data in this study, and the visualization of these points in the n-dimensional space would certainly be inconclusive. It is possible through VISRED to apply mathematical methods to preserve in a new visual space (most commonly 3-D) the distance between points in the original n-dimensional space; also allows the grouping of points in aggregations described as clusters, according to different methodologies. As only

a single calculation of a distance matrix is required, this method is computationally efficient.

The data visualization allowed by this representation permits a rapid assessment of patterns and clusters distributions. The ability presented by this toolbox to identify different groups, allows the identification of four different states: normal, pre-ictal, ictal and pos-ictal.

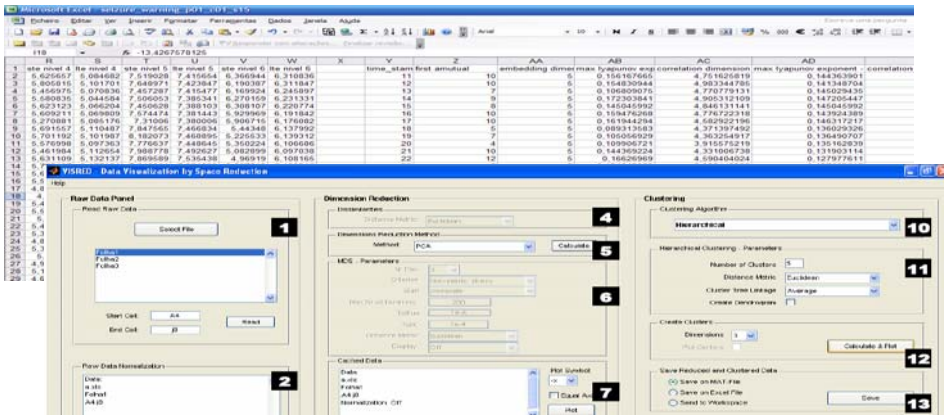


Figure 44 – Excel file and VISRED

The following table presents the figures generated through the VISRED analysis of the different excel files created for each patient. Each file contains information about several hours of brain activity. The variables represent energy, wavelet coefficient and nonlinear properties of the EEG signal obtained through the develop toolbox. The correspondence between colours and states is described in the figure.

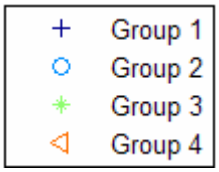
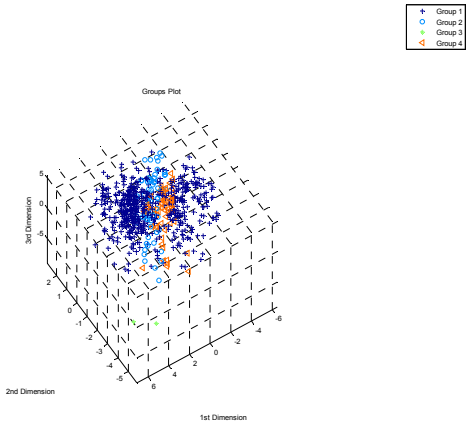
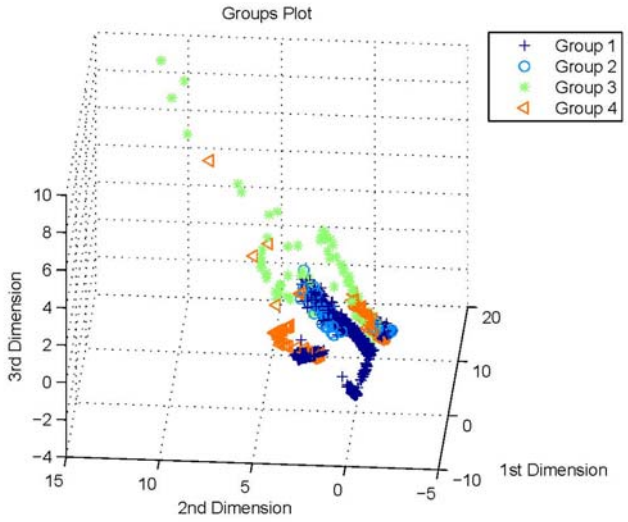
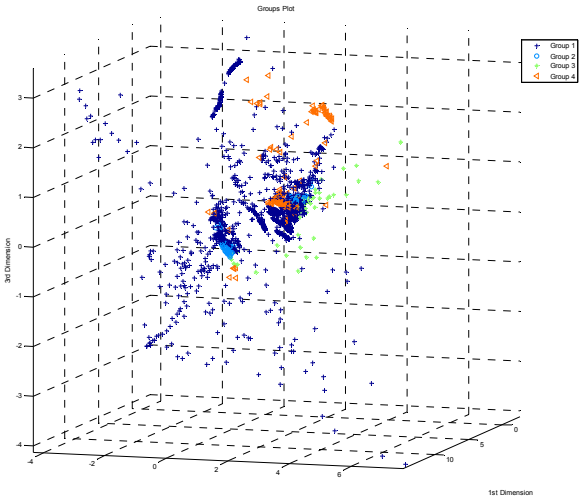
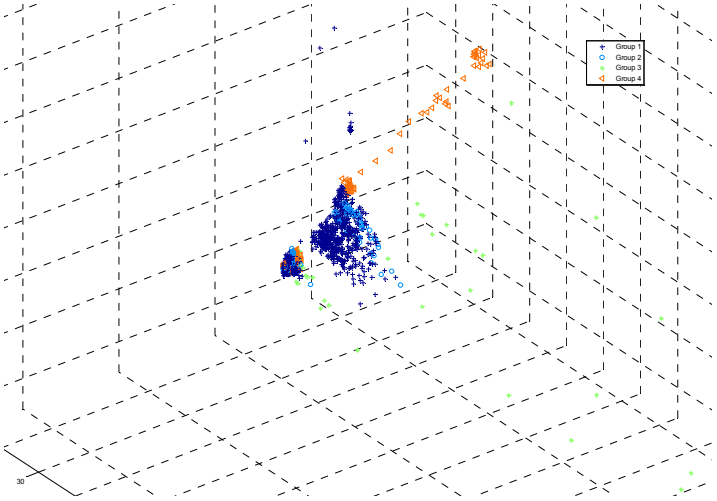
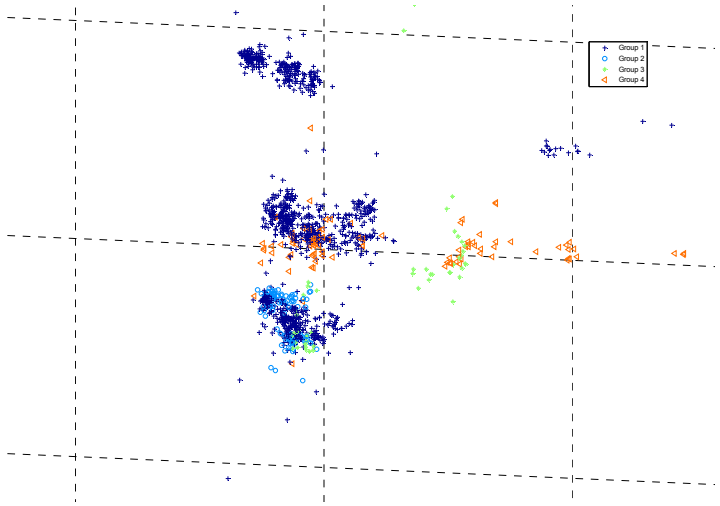
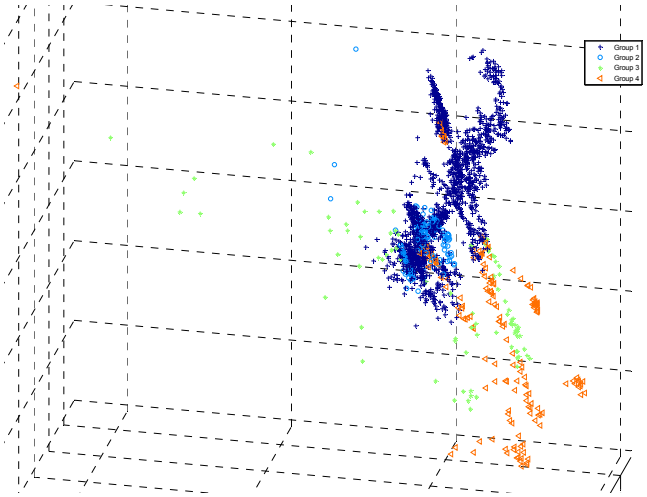
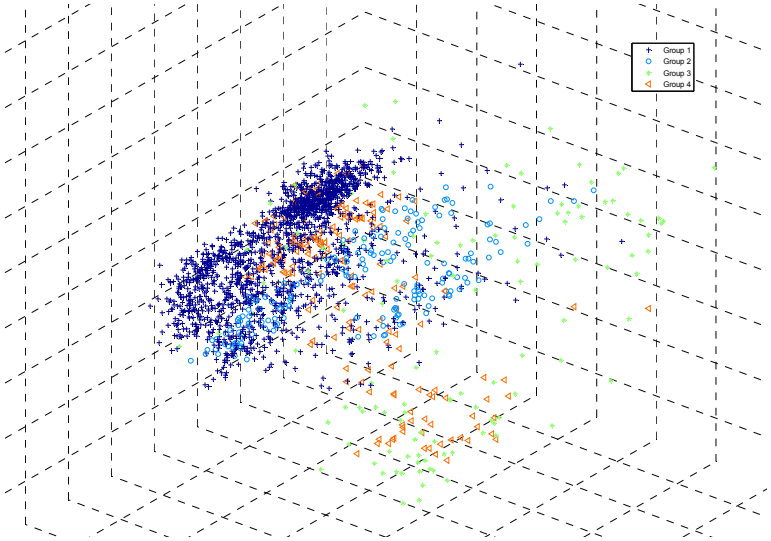
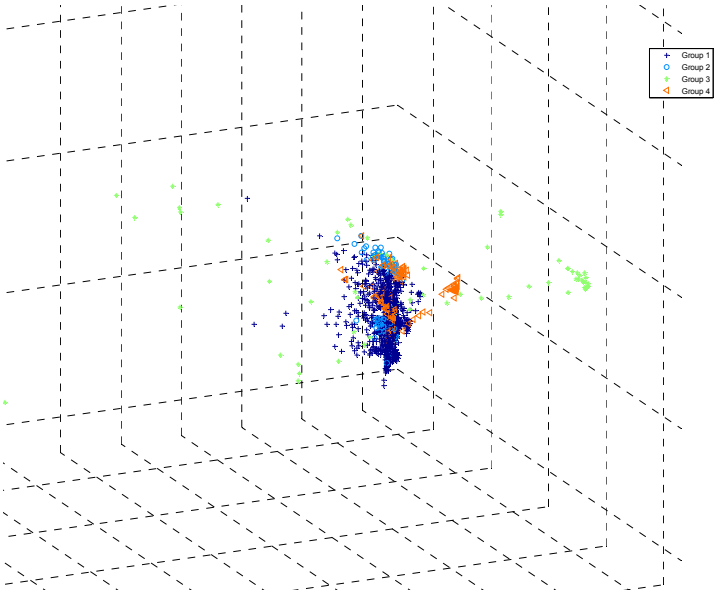


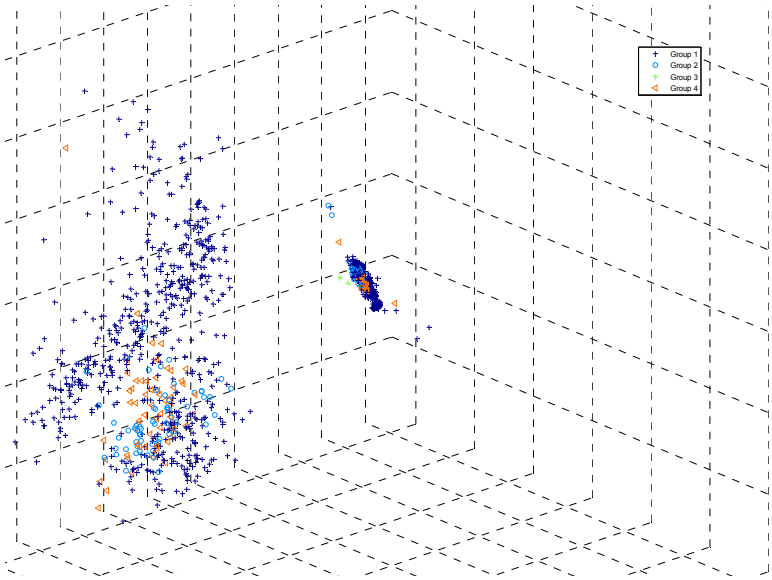
Figure 45 – Group 1 – normal state, Group 2 – pre-ictal state, Group 3- ictal, Group 4 – pos-ictal.

VISRED analysis

Patient	Information (#seizures)	VISRED
		Freiburg database
Pat1	1	
Pat3	4	

Pat4	3	
Pat6	3	
Pat8	2	

Pat9	3	
Pat11	3	
Pat15	3	

Pat19	2	

7. VISRED analysis

The previous figures illustrate the ability of these features to identify the suggested states. These results suggest that the combined analysis of divergent information (resulting of diverse mathematical concepts) produce important information, not obtainable by individual analysis.

Although the regions appear blurry, these representations constitute an important proof that seizures are preceded by variations of normal patterns.

5.4 Discussion

The idea of continuously tracking the changes in several features for seizure prediction is based on clinical and experimental observations (*B.Litt, 2001*) that the transition between states may not be abrupt but rather gradual [36].

In this study, the analysis presented through several methodologies and the data visualization by space reduction of the various extracted features, suggest that valuable elements can be extracted through these methods; several events were preceded by significant variations in these features. Unfortunately, the consistency of these variations remains questionable.

Several problems were identified during this investigation; a brief identification of these events is presented.

- The created algorithms do not consider patients individually, the parameters were similar during the processing of every recording;
- Optimization of Seizure Prediction Horizon;
- Comparison of the extracted features in focal electrodes with non focal electrodes;
- Analysis of more than one electrode, correlations, synchronizations, etc;
- Individual determination of thresholds;
- Sensitivity and specificity analysis according to the same scheme for methods assessment;
- EEG Recordings description is insufficient and the duration of the recordings prior to seizures should be extended.

The VISRED analysis illustrates the ability of the extracted features to identify pre-seizure activity. This analysis suggests that the combined analysis of divergent information (resulting of diverse mathematical concepts) may be the solution for seizure prediction.

The ability to choose better-suited features for individual patients will be a critical point in the development of clinical applications, since the results suggest that some features describe more accurately certain patterns associated to each patient.

6 Conclusions and recommendations

For any prediction method to be clinically viable it must be formulated in a manner that allows it to operate fully prospectively and using only informations that would be reasonably available to the system at the time of prediction are made. This make necessary for the prediction algorithm to operate in real-time. The study suggests that the prediction method and its evaluation scheme, optimized values of the prediction horizons, and preferred brain structures for EEG recording have to be determined for each patient and prediction method individually.

With the improvement of the various methodologies already explored, a reliable classification of states is possible; the spatiotemporal dynamical features already available tend to identify a pre-seizure state presenting quantifiable differences from the normal state. These study present clear indications that variations occur in the brain dynamics from different states of the same patient. The experiments completed in this research can be easily performed with other dynamical measures of the brain dynamics and revealing hidden information from EEG recordings.

This study constitutes a first step in this institution in seizure prediction research and form a bridge to the development and implementation of seizure prediction devices, which will be a revolutionary approach for the treatment of epileptic seizures. Another application of this proposed research is to assist neurosurgeons to identify the epileptogenic zone without the extended protocol to identify the epileptogenic zone. The ability of all the methods to identify seizures, quantifying these features can constitute a revolutionary step for epilepsy treatment.

6.1 Database considerations and recommendations

One of the main difficulties encountered in this study was to found useful EEG Recordings for this type of research. Due to hardware limitations, Epilepsy centres usually save specific data regarding to *epileptiformes* events.

From the experience acquired in this study, we believe that datasets should be acquired following a series of conventions. The data sets should have at least four channels (two focal and two non-focal) – to overcome hardware limitations we do not

identify the need to save a complete set of electrodes. The data sets should contain before each seizure at least twice the length of Seizure Prediction Horizon established for the study. The data should be accompanied by all clinical relevant information, and the EEG recordings should be accompanied by a report discriminating and identifying any significant electrographical information. These informations should also contain the electrical seizure onset and clinical seizure onset.

International efforts regarding the establishments of policies for appropriate data sets creation are essential for the development and generalization of methodologies and algorithms.

6.2 Recommendations and future perspective

Understanding the mechanisms of seizure generation and the optimization of seizure prediction methods will eventually produce best therapies and eventually best diagnosis methods.

The imminent development of implantable devices will constitute a revolutionary step in the treatment of epileptic seizures.

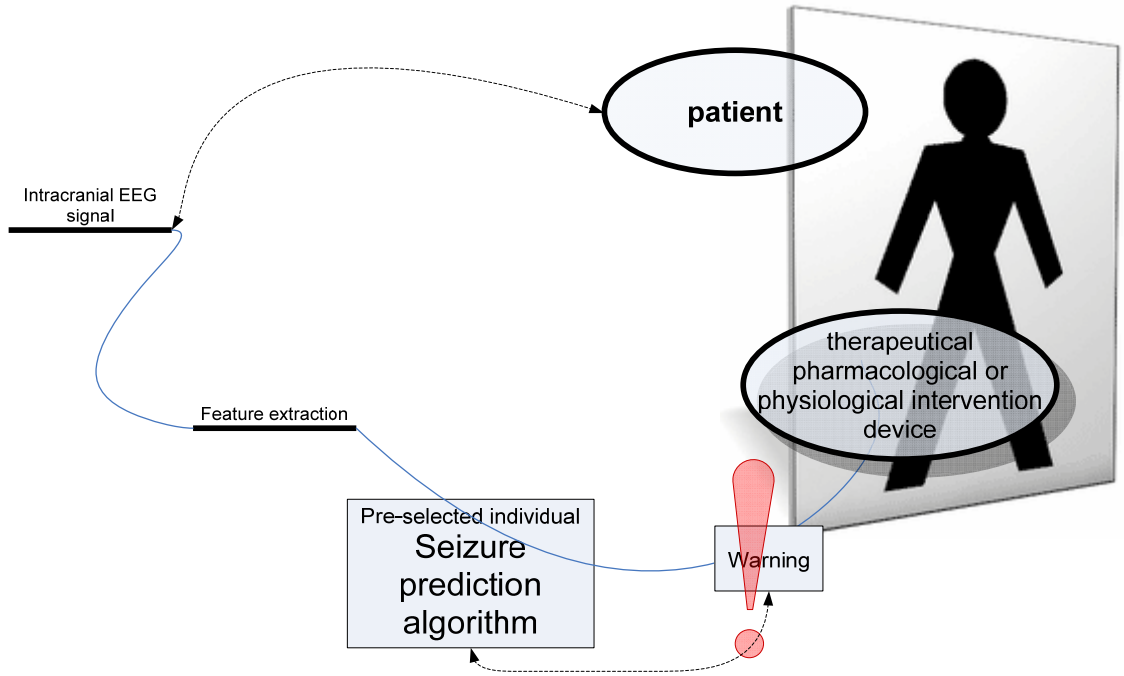


Figure 46 – Treatment device

The possibility of continuous supervision of the focal area and the processing of the acquired data will probably enable the local treatment and prevent epileptic seizures.

Thus, this research represents the necessary first step in the development of implantable biofeedback devices, which ultimately will regulate therapeutical pharmacological or physiological intervention to prevent seizures or other brain disorders.

7 References

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