Journal of Neuroscience Methods 200 (2011) 257–271

Contents lists available at ScienceDirect

Journal of Neuroscience Methods

journal homepage: www.elsevier.com/locate/jneumeth

EPILAB: A software package for studies on the prediction of epileptic seizures

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ARTICLE INFO

Article history:
Received 15 April 2011
Received in revised form 29 June 2011
Accepted 1 July 2011

Keywords:
Epilepsy
Seizure prediction
EEG/ECG processing
Artificial neural networks
Support vector machines
Seizure prediction characteristic

ABSTRACT

A Matlab®-based software package, EPILAB, was developed for supporting researchers in performing studies on the prediction of epileptic seizures. It provides an intuitive and convenient graphical user interface. Fundamental concepts that are crucial for epileptic seizure prediction studies were implemented. This includes, for example, the development and statistical validation of prediction methodologies in long-term continuous recordings.

Seizure prediction is usually based on electroencephalography (EEG) and electrocardiography (ECG) signals. EPILAB is able to process both EEG and ECG data stored in different formats. More than 35 time and frequency domain measures (features) can be extracted based on univariate and multivariate data analysis. These features can be post-processed and used for prediction purposes. The predictions may be conducted based on optimized thresholds or by applying classifications methods such as artificial neural networks, cellular neuronal networks, and support vector machines.

EPILAB proved to be an efficient tool for seizure prediction, and aims to be a way to communicate, evaluate, and compare results and data among the seizure prediction community.

1. Introduction

Between 30% and 40% of the epilepsy patients cannot be treated successfully either by anti-epileptic drugs or by resective surgery (Kwan and Brodie, 2000). The life of these patients is extremely affected by the occurrence of sudden and apparently unpredictable seizures, which are a cause of disability (Devinsky et al., 1995) and mortality (Cockerell et al., 1994). Hence, the development of a reliable seizure prediction method could improve the quality of life of those patients considerably.

In recent years, several time series analysis techniques were developed (Mormann et al., 2007) in order to identify a pre-seizure state, the so-called preictal state. Aiming to detect this preictal state, a large number of methods to analyze electroencephalogram (EEG) and electrocardiogram (ECG) time series were developed (Mormann et al., 2005; Valderrama et al., 2010). These methods are based on single- and multi-channel analysis, and enable the extraction of measures, i.e., features, in the time and frequency domain. The first methods were based on thresholds optimized for a given feature. Here, an alarm is triggered when a predefined feature crosses some predefined threshold (Schelter et al., 2006a). More recent studies suggested circadian dependencies. It was found that more false predictions per hour occur during night times (Schelter et al., 2006b). Hence, different thresholds for night and day were introduced. The seizure prediction challenge has also been faced as a classification problem during the past decade (Dourado et al., 2008; Costa et al., 2008; Mirowski et al., 2008; Chisci et al., 2010). The application of classification techniques has been based on the assumption that the different features extracted over time can be separated into two or more classes corresponding to

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doi:10.1016/j.jneumeth.2011.07.002

different cerebral states. Computational intelligence methods such as support vector machines (SVMs) (Cortes and Vapnik, 1995) have been applied to address this classification problem (Mirowski et al., 2008; Chisci et al., 2010).

Several Matlab® toolboxes for EEG processing are available, for example: EEGLAB (Delorme and Makeig, 2004), BSMART (Cui et al., 2008), MEA-Tools (Egert et al., 2002), ERPWAVELAB (Mörup et al., 2007), and eConnectome (He et al., 2011). EEGLAB is an open-source Matlab® platform developed for researchers interested in event related potentials, to process collections of single EEG data epochs. ERPWAVELAB (Mörup et al., 2007) is an extension of EEGLAB and enables data analysis and visualization of the most common event related measures, e.g., evoked spectral perturbation (ERSP) and inter-trial phase coherence (ITPC), and data decomposition through non-negative matrix and multi-way factorization. The toolbox MEA-Tools (MicroElectrode Array tools) is a Matlab®-based open source toolbox developed for the analysis of multi-channel microelectrode data. BSMART (Brain-System for Multivariate AutoRegressive Timeseries) (Cui et al., 2008) is a Matlab®/C software developed for brain connectivity analysis based on EEG, magnetoencephalography (MEG) or functional magnetic resonance imaging (fMRI) data. The recently released eConnectome toolbox (He et al., 2011) was developed for brain connectivity studies based on Granger causality measures (Granger, 1969).

However, none of the mentioned toolboxes was developed specifically for seizure prediction studies. Specific software for seizure prediction should enable long-term EEG/ECG processing, encompassing long-term feature extraction and prediction. Guidelines crucial for the quality of epileptic seizure prediction studies should be considered (Mormann et al., 2007):

- algorithms should be tested on long-term continuous data covering several days, including a sufficient number of seizures and a sufficient duration of interictal data;
- a given predictor should be evaluated in terms of sensitivity and specificity for a given seizure occurrence period, i.e., the time interval after an alarm within which a seizure is expected. For specificity, the false prediction rate can be used but it should be related to only those time intervals in which false alarms are possible;
- predictors should be statistically validated to assess if a given predictor performs above chance level;
- the performance should be evaluated prospectively on out-of-sample data.

We developed EPILAB, a Matlab® toolbox, for epileptic seizure prediction that allows studying seizure prediction based on a high dimensional feature space. The software was developed for Windows (Microsoft Corporation), Linux, and Mac OS X (Apple Inc.) operating systems. Threshold- and classification-based prediction algorithms are considered and evaluated following the guidelines above. It was designed to support researchers in performing seizure prediction studies based on long-term EEG/ECG recordings in an efficient and user-friendly graphical user interface (GUI). In addition, the object-oriented base of EPILAB enables the easy integration of new methodologies.

EPILAB is a product of the European project EPILEPSIAE, and will be freely available by the end of 2011. All the documentation and code will be available at http://www.epilepsiae.eu

The first four sections describe the five main modules of EPILAB, as presented in Fig. 1. The process to create a new study is presented in Section 2. The features that can be extracted and their computation setup are described in Section 3. The possibilities to perform feature selection and dimensionality reduction on high-dimensional feature spaces are presented in Section 4. The prediction algorithms that are considered and their setup in EPILAB are described in Section 5. In Section 6, an example for an application to a long-term recording is reported. Final conclusions, limitations, and future improvements are described in Section 7.

2. Creating a new study

A new study can be created based on raw EEG/ECG data files or on previously computed features. When beginning a new study from raw data (Fig. 2A), different binary formats are supported, including Mat-Files (The Mathworks, Inc.), TRC files (Micromed S.p.A., Italy), and Nicolet Files. Raw data in a single file or dispersed in several files can be accessed. In the case of a multi-file organization, EPILAB is able to assess recursively directories of files, and create an internal mapping such that all the data can be processed as if they were in a single file. During the study creation, the information necessary for future processing is retrieved such as sampling frequencies, temporal gaps between files, events occurring during the recording (e.g., seizure times), and electrode description.

After study creation, EEG/ECG signals can be displayed using the raw data navigation tool integrated in EPILAB (Fig. 2B). The user can visualize a data window with a specified time-length. The two main modes of navigation are by time and by EEG annotation events. The latter enables the user to easily locate the events like seizure onsets and offsets marked in a given file. Optionally, the visualized data can be filtered.

A study can also be based on features computed previously. The user has the possibility to integrate more than one file of features that were computed using the same computation parameters. The user can navigate over the feature data by using a tool similar to the one developed for raw data.

3. Feature extraction

EPILAB includes several measures for raw EEG and ECG signals that have been shown to be useful in seizure prediction. Measures are either based on one channel (univariate) or on multiple channels (multivariate), and are computed in a window-by-window basis. Prior to feature computation the user may decide to apply filters. Three infinite impulse response (IIR) forward–backward Butterworth filters can be applied: low-pass, high-pass, and notch (to minimize power line interferences). Butterworth filters, or maximally flat magnitude filters, present no ripple (oscillations) in the pass- and stop-bands, producing a uniform acceptance of the wanted EEG frequencies. When compared to other IIR filters they present a larger transition band, which can be minimized by increasing the filter order.

Table 1 summarizes the features that are presently included in EPILAB, which are briefly presented below.

3.1. Univariate EEG features

The "prediction error", derived from an autoregressive model of the EEG signal, has been suggested for both detection (Altunay et al., 2010) and prediction purposes (Rajdev et al., 2010). As seizures approach, the EEG signals are claimed to be better predictable by an autoregressive model of order p (AR(p)), i.e., the mean squared error (MSE) in the preictal phase decreases. With the onset of the seizure, this decrease in the MSE is assumed to disappear.

The "decorrelation time" is defined as the time of the first zero crossing of the autocorrelation sequence of a given EEG signal (Mormann et al., 2005). If the decorrelation time is lower, the signal is less correlated. Prior to seizures, a decrease in the power related

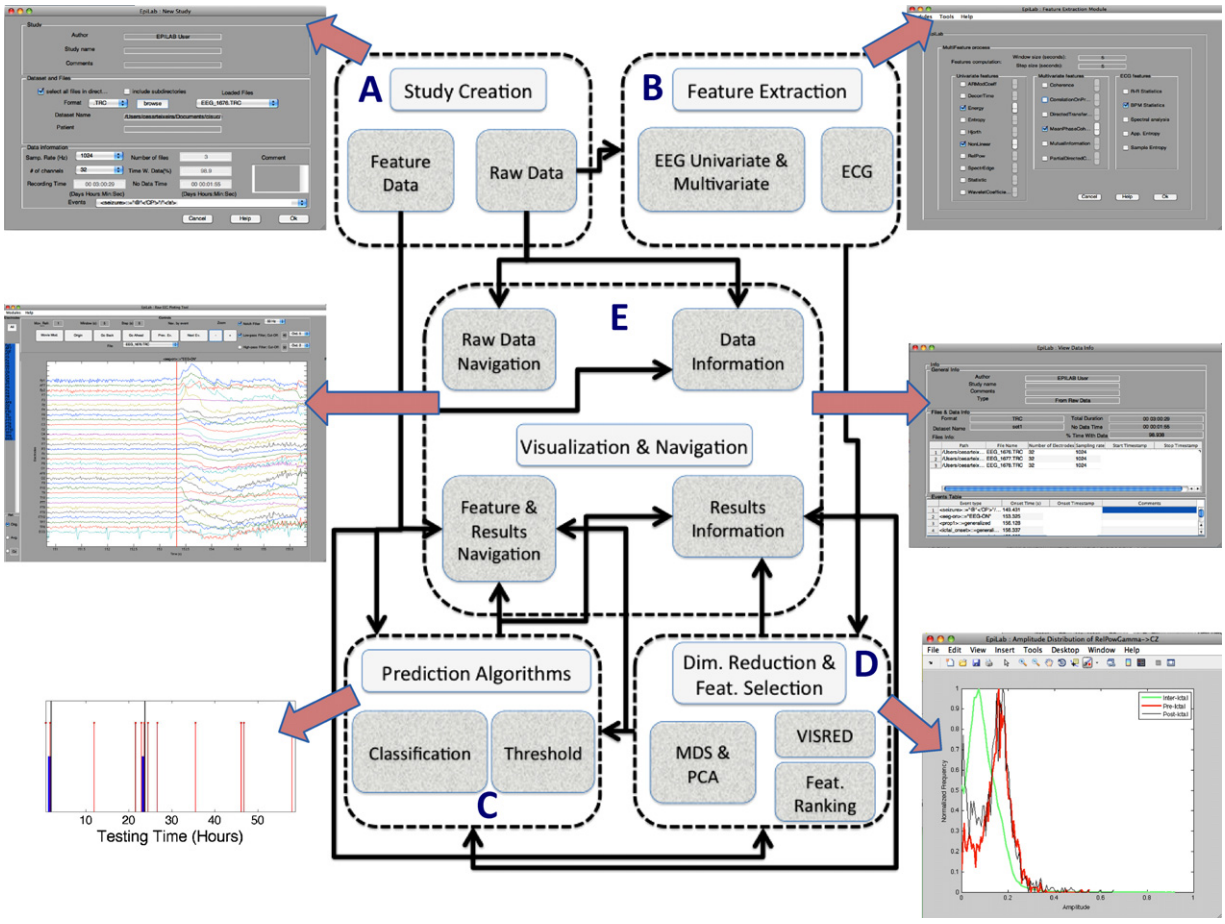


Fig. 1. EPILAB flowchart, organized according to the five main groups of functionalities. (A) A new study should be created from raw data or from previously computed feature data. (B) To proceed with a study created from raw data, EEG and/or ECG features should be computed. (C) Based on features computed or imported, prediction algorithms can be developed and evaluated. (D) The features imported or computed can be subjected to dimensionality reduction. (E) During the study data and results can be graphically or textually visualized.

to the lower frequencies of the EEG has been reported, which leads to a drop in the decorrelation time (Mormann et al., 2005).

Hjorth's parameters (normalized slope descriptors) of mobility and complexity (Hjorth, 1970, 1973, 1975) quantify the root-mean-square frequency and the root-mean-square frequency spread of a given signal, respectively. The decrease in the power of the lower frequencies with the proximity of the seizure onset has also been shown to increase the Hjorth mobility and complexity (Mormann et al., 2005).

Non-linear univariate measures are often based on the reconstruction (time-delay embedding) of the state space trajectory from a given univariate time series. EPILAB considers the correlation dimension (Grassberger and Procaccia, 1983) and the largest Lyapunov exponent (L_{max}) (Wolf et al., 1985), computed with the TSTOOL toolbox (Merkwirth et al., 1998). L_{max} is assumed to quantify the divergence or convergence of nearby reconstructed state space trajectories. Contradictory results have been reported on how L_{max} changes preictally. Iasemidis and Sackellares (1991) found a decrease several minutes before the seizure, however; Mormann et al. (2005) report an increase on L_{max} 30 min before seizure onset. Correlation dimension is an estimate of the number of active states of the dynamic system (Grassberger and Procaccia, 1983). Again, contradictory results were reported. In Elger and Lehnertz (1998) and Lehnertz and Elger (1998) a decrease 5–25 min before the onset was identified while Mormann et al. (2005) found an increase.

The spectral power in different frequency bands of the EEG was also considered for seizure prediction. Mormann et al. (2005) reported a preictal shift in power from lower to higher frequencies.

The "spectral edge frequency" is a quantification of the power distribution along the spectral range of a given signal. Usually, most of the power of an EEG signal is contained in the range 0–40 Hz, and the spectral edge frequency is defined as the minimum frequency up to which 50% of the total power is contained in a given signal, considering the 0–40 Hz range (Stanski et al., 1984).

EPILAB also includes the first four statistical moments: mean, variance, skewness, and kurtosis. The variance is equivalent to the energy of the signal; skewness is a measure of the symmetry of the amplitude distribution and kurtosis is a quantification of the relative peakness or flatness of the amplitude distribution (Mormann et al., 2007). It was reported that variance and kurtosis vary significantly in the preictal phase. A decrease in variance and an increase in kurtosis were observed in the preictal time when compared with interictal data (Aarabi et al., 2009). Wavelet transform enables a time–frequency decomposition of a given signal in several sub-bands (Adeli et al., 2003). This enables quantification of the energy in different frequency ranges. In EPILAB it is possible to select several mother wavelets (prototype functions) and to choose the number of decomposition levels.

3.2. Multivariate EEG features

EPILAB supports the extraction of linear and nonlinear multivariate measures. These features are derived from the combination of two or more channels.

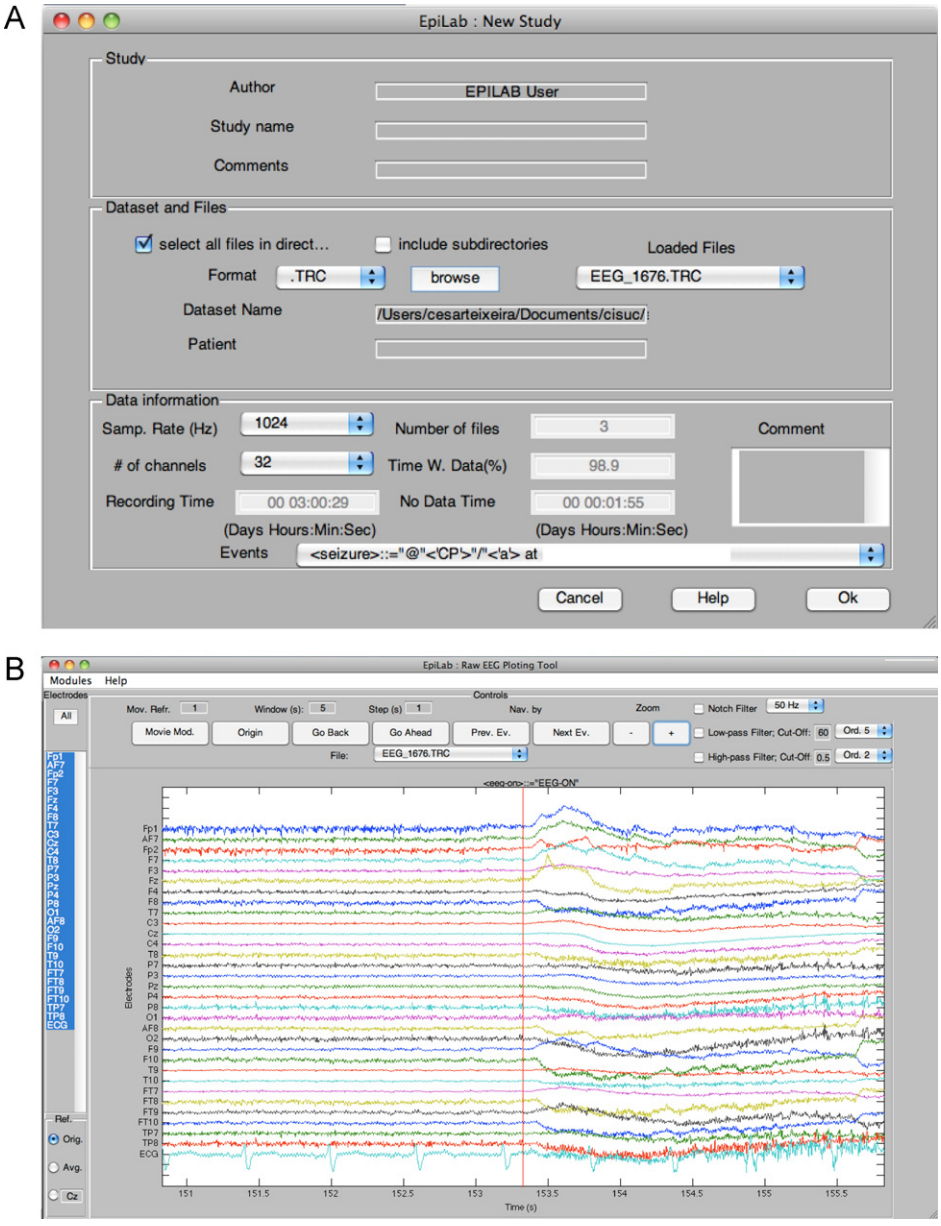


Fig. 2. New study from raw data. (A) GUI that enables the creation of a new study from raw data. The user should select the data format in the popup menu "Format" and choose the respective files. The box "Data Information" shows the main proprieties of the data such as number of loaded files, sampling frequency, number of EEG/ECG channels, total recording time, time without data (gaps) and events (e.g., seizure onsets). (B) Raw data navigation tool. Two main modes of navigation are available. The navigation by time enables the user to scroll the predefined window forward or backward in time, by a step size defined in the text box "Step(s)". Navigation by event enables the easy location of the events in a given file and jump between events.

Linear coherence (LC) (Carter, 1987) is a measure for the interaction based on the auto-spectrum and cross-spectrum between two time series at a given frequency.

Mutual information (MI) is a non-linear measure for interdependence based on entropy and joint-entropy of two time series.

The directed transfer function (DTF) (Kaminski and Blinowska, 1991) and the partial directed coherence (PDC) (Baccalá and Sameshima, 2001) are methods quantifying the direction of interactions. They model the EEG signals by a vector autoregressive (VAR) model. So far, DTF and PDC have been mainly applied to study the interaction between neural structures (Sameshima and Baccalá, 1999) and for the localization of the epileptic focus and seizure propagation (Franaszczuk and Bergey, 1998; Swiderski et al., 2009).

Mean phase coherence (MPC) (Mormann et al., 2000) is a statistical measure for phase synchronization between two time series. Variations in MPC were reported minutes and even hours before the seizure onset (Mormann et al., 2003).

The correlation on the probability of recurrence (CPR) is a measure to detect interactions between two time series based on recurrence probabilities of recurrence plots (Romano et al., 2005). It was reported that this measure could be applied to non-phase-coherent and noisy time series (Tokuda et al., 2008), like the ones observed in EEG.

3.3. ECG features

Concerning ECG, temporal and spectral features are considered. The use of ECG-based features is supported by clinical findings that have shown that heart rate varies before seizures (Delamont et al., 1999). Recently, the usefulness of combining EEG and ECG features was described in Valderrama et al. (2010). The temporal

Table 1
Features that are possible to extract from raw data and related computation time information. (♠) The computation time information is presented as the number of times that a group of features is faster to compute relative to a window duration of 5 s. In the univariate and ECG cases the computation time refers to feature extraction from one channel, the multivariate case considers the combination of two channels. The raw data was acquired at 1024 Hz. (♣) For the energy of the wavelet coefficients a Daubechies-4 mother wavelet and six decomposition levels were considered. For this quantification EPILAB was executed in a computer with a Intel® Core 2 Duo 2.4 GHz processor with 4 GB of RAM.

	Feature		Comp. time (×Fast. Win. Dur.)(♠)
Univariate	AR modelling predictive error		1000.0
	Decorrelation time		1162.8
	Energy		6250.0
	Hjorth	Mobility	357.1
		Complexity	
	Non-linear	Largest Lyapunov exponent (L_{max})	5.0
		Correlation dimension	
	Relative power	Delta band (0.1–4 Hz)	384.6
		Theta band (4–8 Hz)	
		Alpha band (8–15 Hz)	
		Beta band (15–30 Hz)	
		Gamma band (30–2000 Hz)	
	Spectral edge	Power	609.8
		Frequency	
	Statistics	1st moment (mean)	943.4
		2nd moment (variance)	
		3rd moment (skewness)	
		4th moment (kurtosis)	
	Energy of the wavelet coefficients	Several mother wavelet and decomposition levels	192.3 (♣)
Multivariate	Coherence		9.4
	Correlation on the prob. of recurrence		0.8
	Directed transfer function		2.4
	Mean phase coherence		56.8
	Mutual information		0.5
	Partial directed coherence		2.5
ECG	RR-statistics	Mean	13.2
		Variance	
		Minimum	
		Maximum	
	BPM-statistics	Mean	13.2
		Variance	
		Minimum	
		Maximum	
	Frequency domain	Very low freq. (<0.04 Hz)	12.8
		Low freq. (0.04–0.15 Hz)	
		High freq. (0.15–0.4 Hz)	
	Approximate entropy (describing complexity and irregularity of the RR intervals)		12.8

measures considered are the statistics of the inter-beat (R-R) interval and beats per minute (BPM) signal, and approximate entropy describing the complexity and irregularity of the R-R intervals. The spectral measures are the power of the very low (<0.04 Hz), low (0.04–0.15 Hz) and high frequency (0.15–0.4 Hz) bands of both BPM and R-R signals.

3.4. Computation times

Table 1 presents information about the time needed to compute a group of features for 5 s of data. The information is presented as the number of times that a group of features is faster to compute relative to the window duration. A number smaller than one means that the related group of features takes more time to compute than the window duration. Otherwise, it means that a group of features can be computed in a portion of time smaller than the window duration, i.e., faster than real-time.

The raw data used was acquired at 1024 Hz. For the energy of the wavelet coefficients a Daubechies-4 mother wavelet and six decomposition levels were considered. We used a computer with an Intel Core 2 Duo 2.4 GHz processor with 4 GB of RAM. For the univariate case one channel was considered. In the multivariate case data from two channels was analyzed exemplarily.

For a modern personal computer, all the univariate EEG and ECG features alone can be obtained multiple times faster than real-time for one channel. Simultaneous real-time analysis of more than 100 channels is feasible for the univariate features. The exception is for the non-linear features that allow real-time computation of only 5 channels simultaneously.

For multivariate features, most of them can also be computed in real-time. The MPC alone, for two channels, can be derived approximately 57 times faster than real-time. This means that the MPC can be computed in real-time for the combination of about 11 channels. CPR and MI are the multivariate features that cannot be used for real-time operation on currently available personal computers, even for the combination of only two channels.

3.5. Feature computation setup

The first step for feature extraction is the selection of electrodes that should be analyzed (Fig. 3A). After electrode selection the user can define the window size and the step size used for a sliding window calculation (Fig. 3B). The windows may overlap if the step size is smaller than the window size. Gaps within the recording are automatically detected.

For each window, a feature sample is derived for each channel in the univariate case or for each possible combination among the different channels in the multivariate case. The feature samples can be saved to a binary file. Features stored in binary files can then

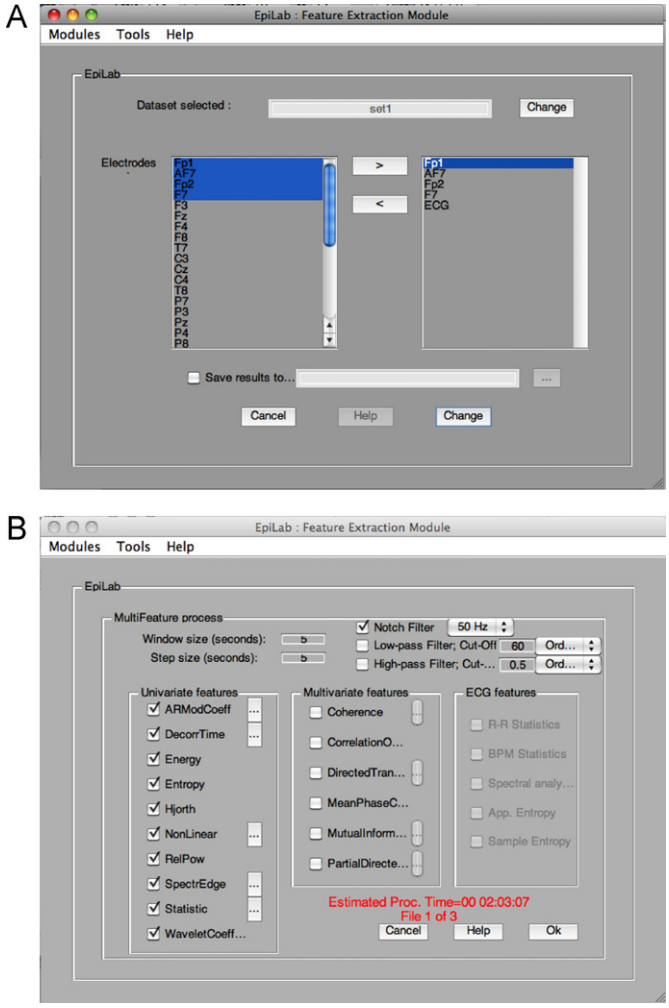


Fig. 3. Feature extraction windows: (A) Window that enables the selection of the electrodes to be involved in the feature extraction procedure. (B) Window that enables the selection of the feature to be computed, as well as the window and step size used for the features computation.

be used to create studies based directly on features, as referred in Section 2.

4. Dimensionality reduction and feature selection

The development of seizure predictors based on a high number of features may suffer from the curse of dimensionality (Bellman, 1957). Among all extracted features some may be redundant and/or may not contain predictive information. These features should be identified and removed or transformed. Therefore, a key point is the reduction of the feature space into another, trying to preserve as most as possible the predictive information.

EPILAB implements several strategies for dimensionality reduction based mainly on Principal Component Analysis (PCA) and Multi-Dimensional Scaling (MDS).

PCA (Pearson, 1901; Hotelling, 1933) is a widely applied statistical procedure that performs dimensionality reduction of a given data set by projecting it onto an orthogonal space, and then by selecting the projections with higher variances.

MDS (Borg and Groenen, 2005) performs dimensionality reduction by preserving pairwise distances between data points, i.e., by preserving the similarity/dissimilarity between points. The reduced set is obtained by optimization techniques that try to minimize the difference between a original dissimilarity matrix and one corresponding to the reduced set. Usually the Euclidean distance is applied, however other metrics of distance can also be used.

Feature selection by two different preselection methods was implemented, one supervised, i.e., based on a target classification, and one non-supervised.

The minimum redundancy–maximum relevance (mRMR) (Ding and Peng, 2005) ranks a set of features by minimizing the redundancy among the features while maximizing their relevance to a desired target classification. The first step of mRMR algorithm is based on a *F*-test, as a relevance measure, and computation of the Pearson's correlation among features as a redundancy measure. After selecting the first feature, i.e., the feature with maximum value of relevance with the target, the remaining set of features is iteratively selected based on the mRMR score (Ding and Peng, 2005). In EPILAB the *F*-test correlation difference (FCD) was selected as the relevance measure (Ding and Peng, 2005). Since mRMR considers the predictive performance of each feature, i.e., it is supervised; this method may only be applied on a training dataset.

The non-supervised method enables features ranking by computing the ratio between the global and local variances (Feldwisch-Drentrup et al., 2011b). For a given feature f_k, its variance ratio is given by

$$S_k = 2\frac{\sigma^2_{k,\text{global}}}{\sigma^2_{k,\text{local}}}, \tag{1}$$

where $\sigma^2_{k,\text{global}}$ is the global variance of the length N sequence f_k, defined by

$$\sigma^2_{k,\text{global}} = \frac{1}{N-1}\sum_{i=1}^{N}(f_k^i - \overline{f_k})^2. \tag{2}$$

$\sigma^2_{k,\text{local}}$ is the local variance, i.e., the variance of the first order differences of f_k and is described by

$$\sigma^2_{k,\text{local}} = \frac{1}{N-2}\sum_{i=1}^{N-1}(\Delta f_k^i - \overline{\Delta f_k})^2, \tag{3}$$

with Δf_k^i given by

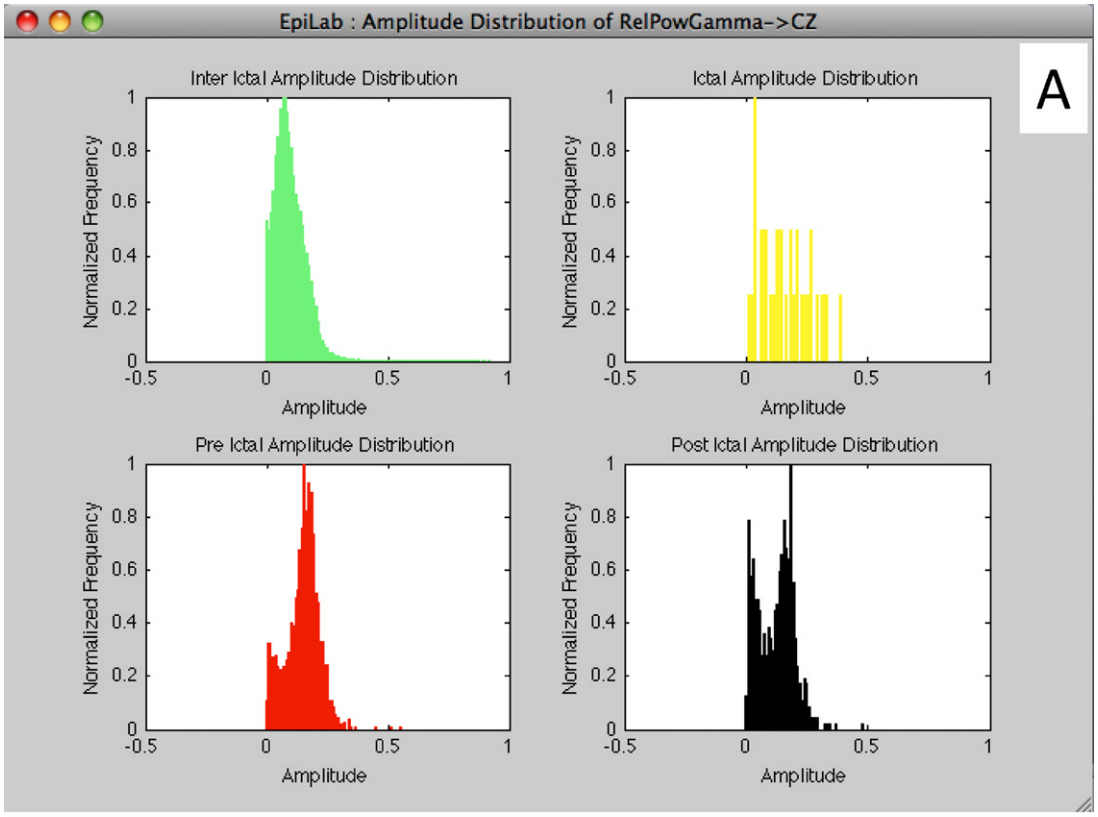
$$\Delta f_k^i = f_k^{i+1} - f_k^i. \tag{4}$$

A potential feature for seizure prediction must present long-term fluctuations before seizures, i.e., a high value of S_k (Feldwisch-Drentrup et al., 2011b). Based on the S values for all the features it is possible to sort them in descending order and then to select the top ones. Since this method does not consider the predictive performances, it also may be applied to testing data.

Both the mRMR and variance ratios methods showed appropriate performance for feature selection in previous seizure prediction studies (Feldwisch-Drentrup et al., 2011b; Direito et al., in press-a).

The implemented algorithms are preselection methods, i.e., they are not related to the prediction methodology. Feature selection methods based on a given prediction approach will be considered in future EPILAB releases. For example, SVM based recursive feature elimination (SVM-RFE) (Guyon et al., 2002; Direito et al., in press-b), and feature selection based on input set sensitivity analysis or structure parameters of trained predictors (Mirowski et al., 2008) will be considered.

EPILAB also integrates a tool that visualizes to which extent a given feature can be used to discriminate between patterns belonging to the different classes. For defined preictal and postictal periods the amplitude distribution of a selected feature according to the different classes is presented. Fig. 4A and B shows an example of the amplitude distribution of the relative power in the Gamma subband for electrode Cz, considering a preictal and postictal period of 30 and 10 min, respectively.



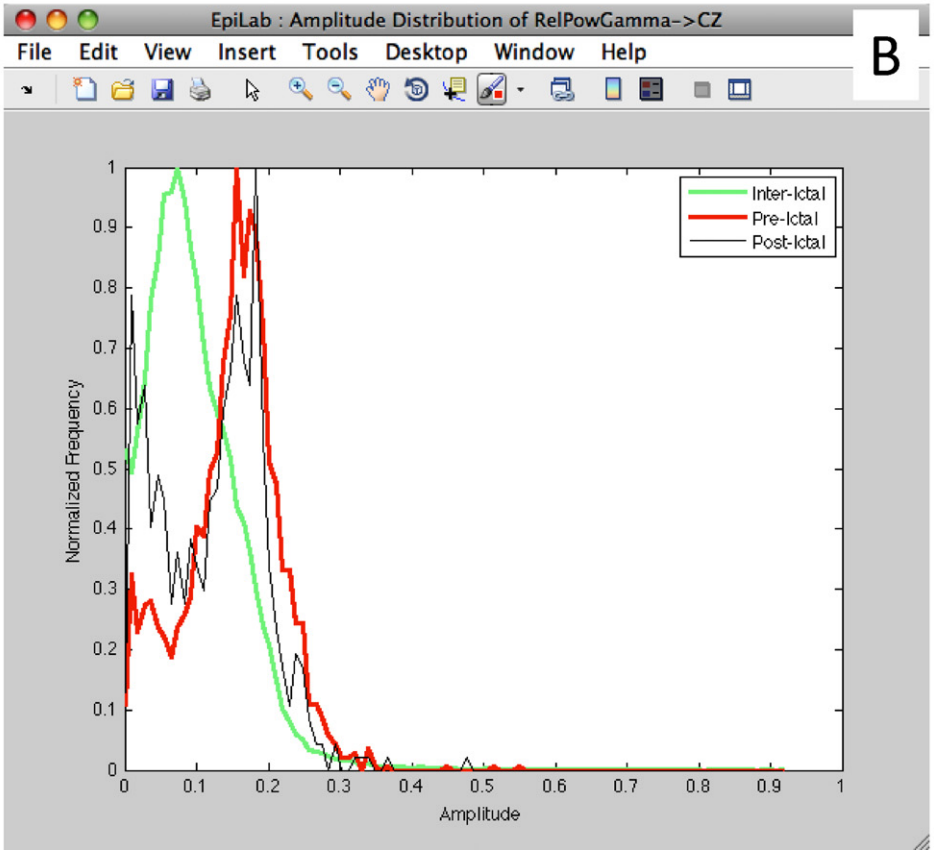


Fig. 4. Amplitude distribution plotting. (A) Histograms of the four considered classes. (B) Overlapped histogram envelopes that allow visual inspection about the separability between classes.

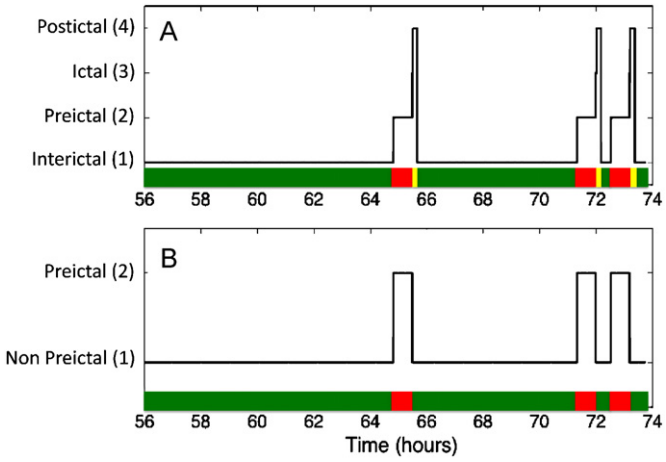


Fig. 5. Time series encoding the classification of the cerebral states for three seizures. (A) Four-class encoding and (B) two-class encoding. The preictal and postictal epochs were 40 min and 10 min, respectively, and the early detection prevention time 10 s. The preictal epochs are represented by red time slots. In A interictal epochs are represented by green time slots while the yellow time slots represent the ictal plus postictal epochs. In B the green time slots represent the non-preictal epochs. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Other options for feature selection are available through a connection to the VISRED (Data Visualisation by Space Reduction) (Dourado et al., 2007) application. VISRED is an advanced tool for data classification and clustering which includes in addition to PCA and MDS also non-linear PCA and several clustering techniques, such as hierarchical, *k*-means, subtractive, fuzzy *C*-means, and SOM (Self-Organizing Maps). It allows the application of several metaheuristics for optimization in MDS, such as genetic algorithms and simulated annealing.

5. Seizure prediction

Two types of prediction schemes are integrated into EPILAB, which are based on thresholds or classification algorithms. For the first, the predictive power of features is analyzed by using thresholds such that alarms are given at threshold crossings. For the latter, classification algorithms are applied that are optimized to separate epochs related to several brain states.

5.1. Threshold based analysis

In threshold based analyses, for each feature a threshold is determined such that the alarms triggered at threshold crossing yield optimal predictive performances. This approach can be extended by the possibility to combine two or more features by using logical AND and OR operations (Feldwisch-Drentrup et al., 2010). Additionally, independent thresholds can be optimized for day and night, such that circadian rhythms can be accounted for (Schelter et al., 2006b).

In order to evaluate the performance of a given seizure prediction method, the *seizure prediction characteristics* was proposed, which is based on clinical and statistical considerations (Winterhalder et al., 2003). In contrast to quantifications of the distribution of interictal and preictal features by means of a ROC analysis (Mormann et al., 2005), the seizure prediction characteristics allows an evaluation of quasi prospective prediction performances by assessing the alarms triggered. Here, an alarm is regarded correct if it is triggered at a specified time before seizure onset. In order to quantify the time during which the seizure has to be expected, the seizure occurrence period (SOP) was defined. Aiming to allow an intervention to be applied, the alarm has to precede the SOP by a certain time, the intervention time (IT). Similarly, the minimum IT and maximum SOP should be defined (Schelter et al., 2007). If an alarm following a first alarm during a short time period would be considered to prolong the first alarm (Snyder et al., 2008), this could lead to excessively long prediction windows. Instead, we consider only the first alarm and discard all further alarms during IT and SOP after the first alarm. Hence, these intervals do not enter in the calculation of the false prediction rate (FPR).

The seizure prediction characteristics also includes an approach for the statistical validation of prediction performances. Based on an analytical random predictor, critical performance values can be calculated which could be achieved by chance (Schelter et al., 2006a). Only if the observed performances exceed these critical performances, the results can be considered statistically significant. The analytical random predictor allows direct calculation of the performance level achieved by chance. Furthermore, it provides valid results for small numbers of seizures, which are quite common in seizure prediction studies (Feldwisch-Drentrup et al., 2011a).

5.2. Classification

EPILAB enables the application of three types of classifiers: artificial neural networks (ANNs), support vector machines (SVMs), and cellular neural networks (CNNs).

5.2.1. Artificial neural networks

ANNs are adaptive, generally non-linear structures that implement a distributed computation of a given set of input signals (Principe et al., 2000). The distributed processing is accomplished by a set of processing elements, called neurons, organized in one or several processing stages (layers). Each neuron receives connections from other neurons, from the network inputs or from its own output (feedback). If no internal feedback is considered, the ANN is a feedforward network, otherwise a recurrent one. At each neuron, the signals are multiplied with adjustable parameters called weights. The output of a given neuron is the sum of all the weighted connections transformed by a function (usually non-linear), named activation function. The supervised training of an ANN is the estimation of the weights in an iterative way, trying to approximate the network output as most as possible to a predefined optimal output, called target. The degree of approximation is given by an error function (criterion), which usually is the mean squared error. EPILAB enables the consideration of feedforward and recurrent networks trained by a variety of algorithms, ranging from the standard error backpropagation (BP) (Rumelhart et al., 1986) to more robust strategies, such as the Levenberg–Marquardt algorithm (LM) (Levenberg, 1944; Marquardt, 1963).

5.2.2. Support vector machines

The structure of a SVM (Cortes and Vapnik, 1995) is similar to an ANN; the way it is constructed is very different. The idea behind SVM is that data can be transformed into a higher-dimensional space in which elements belonging to two different classes can be linearly separated. The dimension of the high-dimensional space should be substantially larger than the input space, enabling the definition of a hyperplane with the largest margin separating the two classes. By definition, a SVM is a binary classifier, i.e., it is able to solve a two-class problem. However, there are situations where more than two classes are needed to solve a given classification problem. For this purpose the SVMs were also adapted to perform classification in more than two classes. The standard approach is to reduce a multi-class problem to several two-class problems, for which the standard SVM algorithm can be applied. The different approaches differ in the way in which single SVM is combined to give rise to a multi-class classifier. The most popular methods are

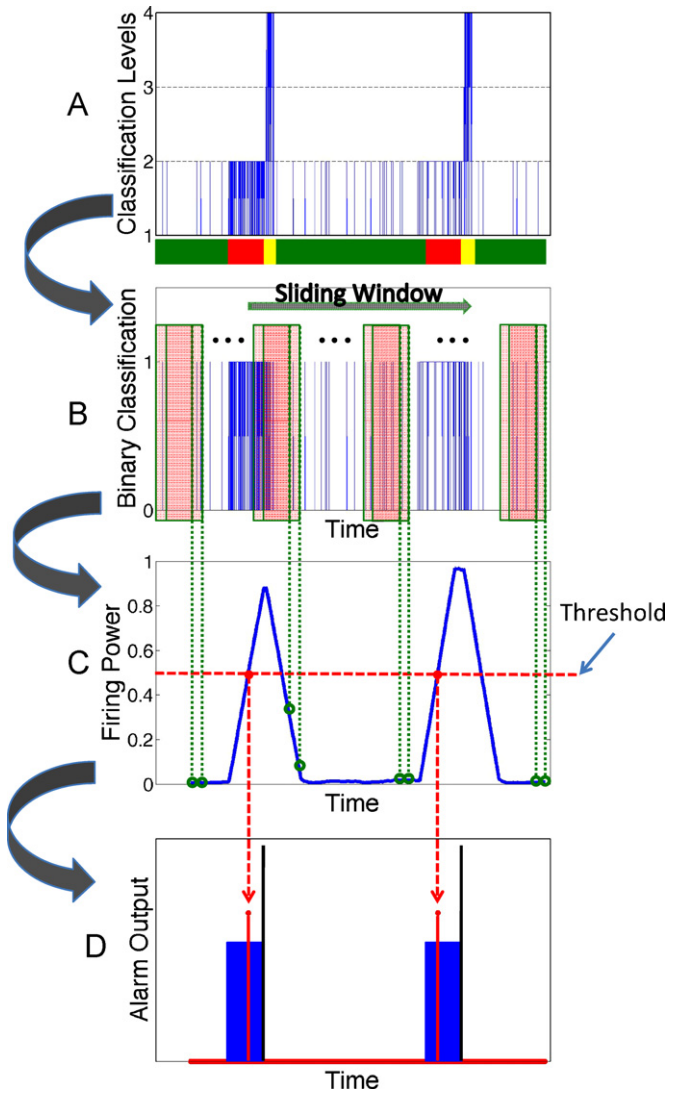


Fig. 6. Methodology used to transform a classification output in a series of alarms. (A) Four-class classification. (B) Normalized two-class classification. (C) Firing power. (D) Alarm series. In A the green time slots represent interictal periods, red slots represent preictal samples, and yellow slots ictal plus postictal samples. In D the vertical black lines represent the seizures onset epoch, the vertical red lines the alarms raised as the firing power crosses the specified threshold, and the blue area the preictal time considered. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

"one-versus-all" using the "winner-takes-all" strategy, and "one-versus-one" using the "max-wins" voting. EPILAB uses the Matlab® interface to the LibSVM library (Chang and Lin, 2001), enabling the selection of different SVM parameterizations. These are the selection of the kernel type (linear, polynomial, radial basis function or sigmoid), the value of the regularization parameter (cost), the value of Gamma (for polynomial, radial basis function and sigmoid kernels), among others. The one-versus-one strategy is applied by default.

5.2.3. Cellular neural networks

Proposed by Chua and Yang (1988), cellular neural network (CNN) consists of a two-dimensional lattice of non-linear processing units, commonly referred as cells or neurons. Each cell has multiple inputs and a single output, and is locally interconnected to cells whose topological distance is less than r elements, defining a uniform r-neighborhood. Similar to an ANN, the dynamical state of one specific cell is defined as a non-linear activation function applied to the linear combination of weighted inputs and outputs from neighbor units, and a bias. The configuration of the CNN in two dimensions is intended for a parallel processing of an input matrix. As a result, single outputs from each element of the network, also form an output matrix. Furthermore, the Heaviside step function is applied to the average of this output matrix, in order to obtain a single binary output that can be used for classifying the inputs in two class. Additionally, if the desired class of each input variable is previously known for a subset of the data, the parameters of the network (weights and bias) that minimize the error between the network classification and the target class can be calculated. This process is known as supervised classification, and aims to optimize the network performance over this training set. An iterative genetic algorithm performs the optimization process (Holland, 1992), using the MATLAB Genetic Algorithm Toolbox developed by Chipperfield et al. (1994). Parameters of the algorithm such as the population size, number of generations, the termination condition (epsilon), and selection, recombination and mutation probabilities can be modified by the user in the EPILAB interface.

5.2.4. Classification procedure

The first step for the development of a seizure predictor based on classification methods encompasses the decision about the inputs of the classifier and about the temporal division of the overall data into training and testing (out-of-sample) sets. EPILAB allows training on one part of the data (training dataset) and prospective evaluation in a second part of the data (testing dataset), i.e., holdout cross-validation is used. The training data should contain data of all the cerebral states, i.e., it should integrate a number of seizures and interictal data, allowing a proper optimization of the classifiers. Simultaneously, the out-of-sample data should be long enough and have at least one seizure, enabling performance evaluation. In addition to the input time series, a target output is needed for the training of the classifiers. The target output is a time series that discriminates the cerebral state for each input sample. EPILAB considers two or four cerebral states, resulting in a classification in two or four classes. The four-class approach considers that the input samples can be classified as:

- interictal – the "normal" brain state,
- preictal – the time interval just previous to the seizure onset,
- ictal – the time interval during a seizure,
- postictal – the time interval between a seizure and a "normal" brain state (interictal).

The number of preictal and postictal samples depends on the preictal and postictal epochs defined by the user. The number of ictal samples is dependent on the seizures onset and offset, which are set by the neurophysiologists in the raw EEG.

When considering only the two-class problem, the preictal samples are classified against all the other samples.

The target output for a four-class classification is a sequence of samples, where the values 1, 2, 3, or 4 stand for the interictal, preictal, ictal, or postictal classes, respectively (Fig. 5A). In the two-class case, the target output has only two levels, i.e., 2 for preictal and 1 for the other samples (Fig. 5B).

5.2.5. Alarm generation

The classifiers are trained considering that samples are independent between them, i.e., no temporal dynamics is considered during training. Optimally, a well-trained classifier should be able to classify correctly all samples in testing data, and thus reproduce the desired output. However, in reality a classifier will not classify all the samples correctly (Fig. 6A). In testing, if the output of trained

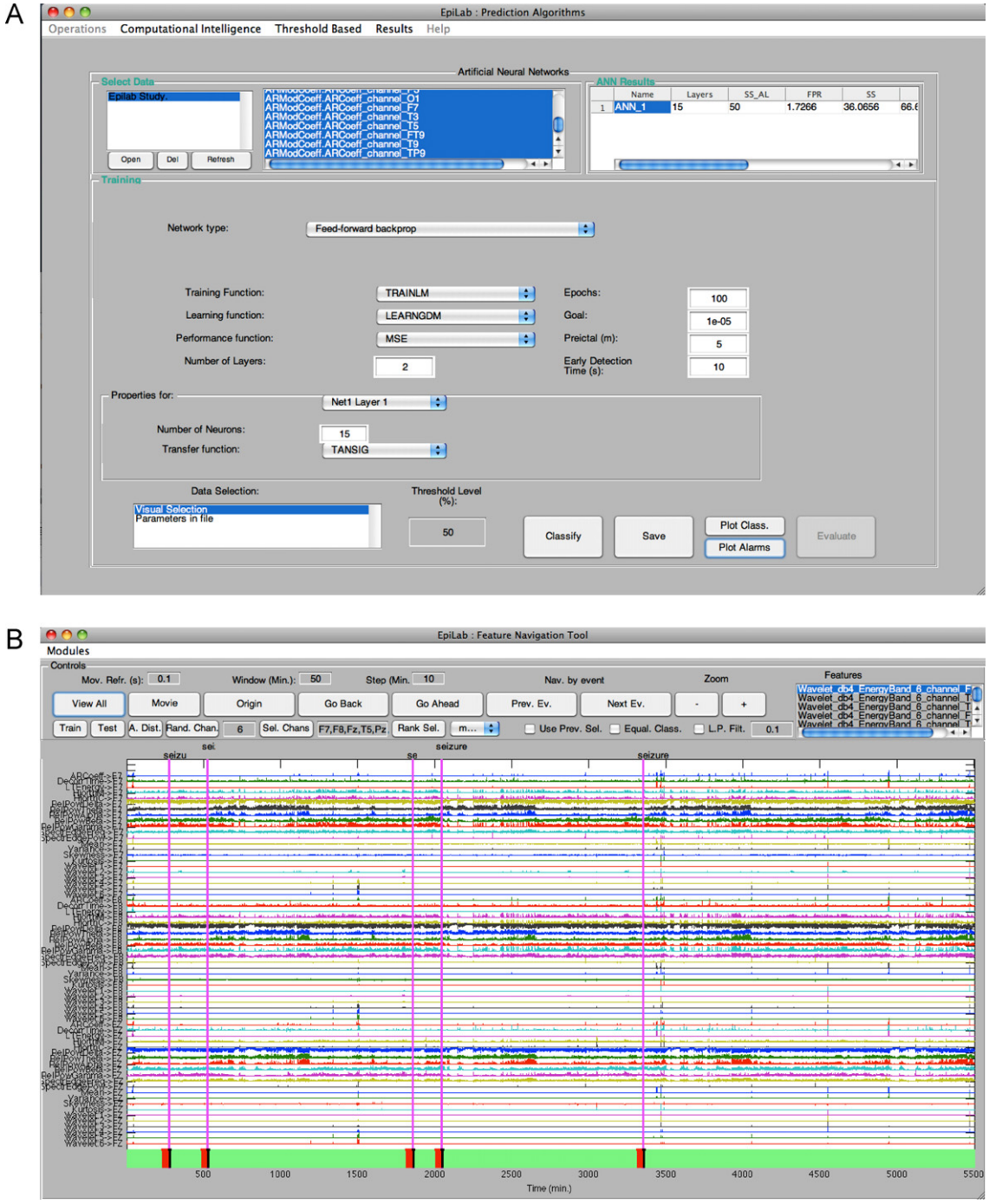


Fig. 7. (A) Window that enables the setting of the parameters for the training of an ANN. The user selects the network type and defines the parameters accordingly. The modality for data selection can be chosen in the list box "Data Selection". Data can be selected by using the GUI or by applying a previous selection. After training, the obtain results are listed in table "ANN Results". (B) Window that enables the data selection for the training of an ANN. The training and testing data can be selected by the buttons "Train" and "Test", respectively. The user can select a random number of channels (button "Rand Chan.") or select specific channels (button "Sel. Chans"). Specific features can be chosen by using the list box "Features".

classifiers is considered directly to predict seizures, it may happen that for each sample misclassified as preictal a false alarm may be generated. To improve prediction performance, EPILAB accounts for the temporal dynamics of the classification in the testing phase. EPILAB generates alarms by implementing the methodology presented in Fig. 6. If four classes are considered, the output of the classifiers is mapped into only two classes, i.e., preictal and non-preictal (Fig. 6B). Then a sliding window with size related to the considered preictal time is considered. In each window a measure that quantifies how many samples are classified as preictal is computed (Fig. 6C). This measure is called the *firing power* of the classifiers output, and is defined as:

$$fp[n] = \frac{\sum_{k=n-\tau}^{n} o[k]}{\tau}, \tag{5}$$

where $fp[n]$ is the firing power at the discrete time n, τ is the number of samples related with the considered preictal time, and $o[\cdot]$ is the two-class classifier output. For example, if features were

computed using a step of 5 s, and if the preictal time is 30 min, τ is equal to 360 samples. This means that the firing power at each instant is computed by considering the past 360 classification outputs. If $o[\cdot]$ is one for samples classified as preictal and zero otherwise, $fp[n]$ is a normalized function between zero and one. A firing power of one means that all the past samples in the past preictal time were classified as preictal. Alarms are then raised if $fp[n]$ exceeds a threshold value in an ascending way (Fig. 6D). The threshold is defined as a percentage of the full firing power.

5.2.6. Performance descriptors

The performance of the obtained predictors can be assessed by two types of descriptors. Descriptors related to the classification performance, i.e., related with the sample-by-sample classification, and descriptors related with the alarms generated. The classification descriptors for sample-by-sample classification are: sensitivity (*SS*), specificity (*SP*) and accuracy (*AC*), defined as:

$$SS = \frac{TP}{TP + FN}, \tag{6}$$

$$SP = \frac{TN}{TN + FP}, \tag{7}$$

$$AC = \frac{TN + TP}{TN + FN + TP + FP}. \tag{8}$$

Here, *TP* and *FP* are the numbers of correctly (true positives) and incorrectly (false positives) classified preictal samples, respectively. *TN* and *FN* are the numbers of correctly and incorrectly classified interictal samples, respectively. Sensitivity measures the proportion of the true classified preictal samples, while specificity quantifies the proportion of correctly classified non-preictal samples. Accuracy accounts for the proportion of correctly classified samples on all classes.

The descriptors related to the alarms generated are sensitivity, which is the ratio of correctly predicted seizures, and the false prediction rate. These descriptors are the base to compute the seizure prediction characteristics (Section 5.1) for the methods based on classification approaches. A seizure is considered to be correctly predicted if its onset occurs in the subsequent preictal time (excluding the early detection period). The false prediction rate is given by:

$$\text{FPR} = \frac{\text{number of false alarms}}{\text{prediction time} - (\text{number of seizures} \times \text{preictal time})}. \tag{9}$$

For the calculation of the FPR, only those periods are considered during which alarms could be triggered (Mormann et al., 2007).

Based on the true alarms, EPILAB can also be used to compute the anticipation time statistics. The anticipation time is the duration between a raised alarm and the subsequent seizure onset. The minimum, maximum, average and standard deviation values are provided for each predictor.

Table 2
Characteristics of the recording used to demonstrate EPILAB

Parameter	Value
Duration	≈92 h (3 days, 19 h and 29 min)
Time without data	≈ 3 min
Sample frequency	400 Hz
Electrodes	27 (10-20 System): FT10, T10, TP10, F8, T4, T6, FP2, F4, C4, P4, O2, FPZ, FZ, CZ, PZ, OZ, FP1, F3, C3, P3, O1, F7, T3, T5, FT9, T9, TP9
Number of seizures	5

5.2.7. GUI based setup

The GUI of EPILAB allows choosing the necessary parameters for the prediction procedures. For example, the window presented in Fig. 7A enables the setting of the parameters for ANN training and testing. It is possible to define, for example the network type and topology, training algorithm, and all the parameters necessary to create the target output. The data that are used for training and testing can be visually selected, using the GUI presented in Fig. 7B. The

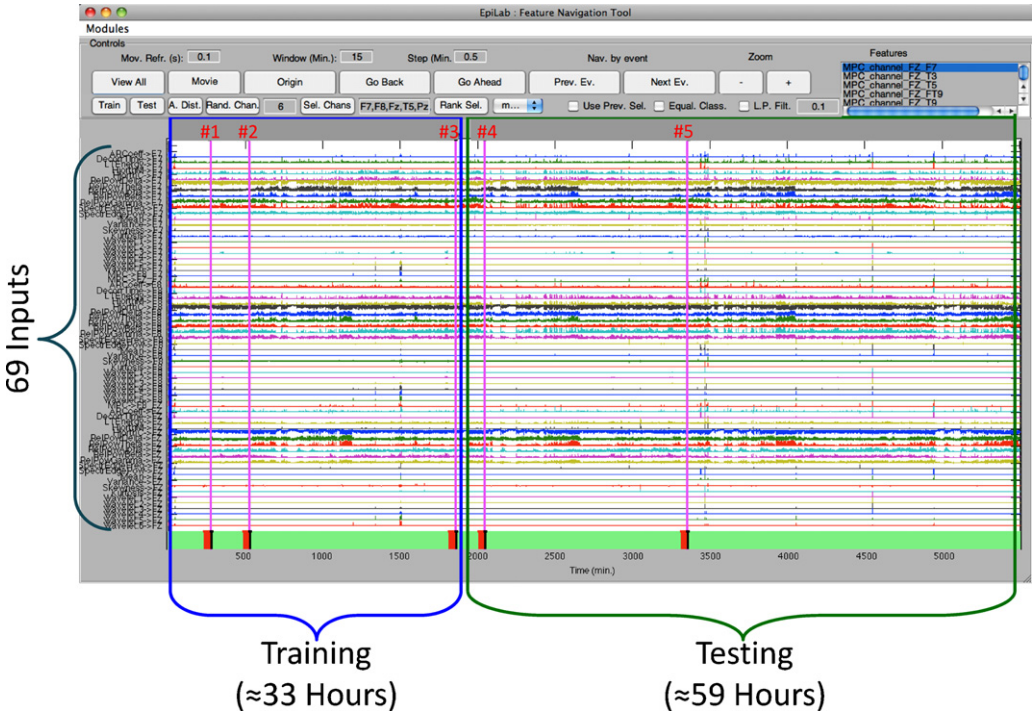


Fig. 8. Feature navigation window with the input dataset and respective training/testing division. The vertical black lines represent the different seizures onset epoch (#1, . . ., #5).

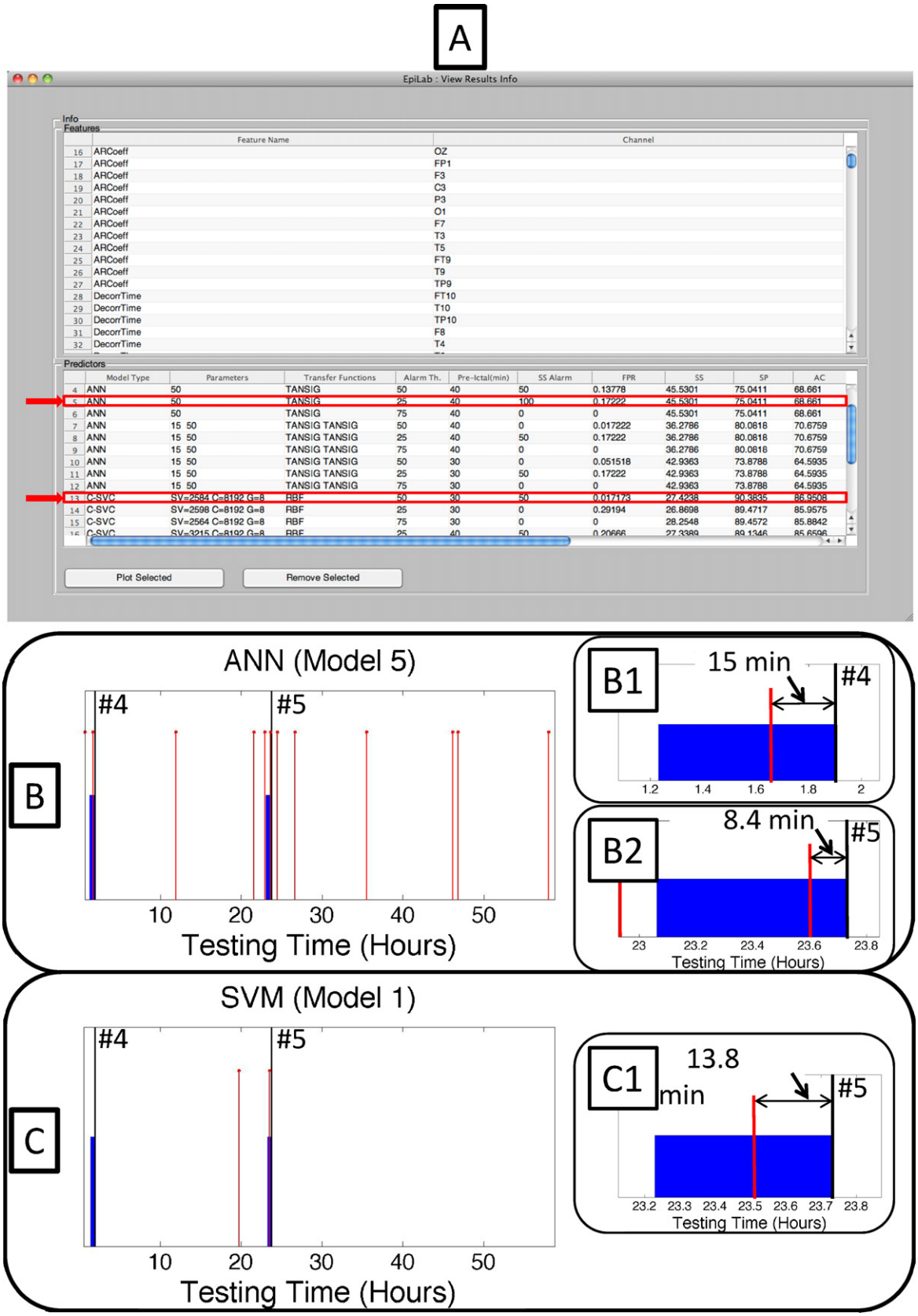


Fig. 9. Results. (A) View Results Window that enables to remove undesired predictors (button "Remove Selected"), and plot the prediction output of selected predictors (button "Plot Selected"). Red arrows mark the predictors selected. (B and C) Prediction output as compared with the seizures onset epoch for one selected MLP and for one selected SVM, respectively. The onset epochs are represented by vertical black lines, while the raised alarms by vertical red lines. The blue region represents the preictal time. Zoomed regions around the predicted seizures are presented in subfigures B1, B2 and C1. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

inputs can be directly selected from a list or selected by channel. The possibility to randomly select a defined number of channels and consequently the associated features was also implemented. This allows comparing the predictive power of a user-defined set of channels to a set of randomly selected ones. EPILAB also enables input selection by using the feature ranking methods reported in Section 4, i.e., by minimum redundancy–maximum relevance (mRMR) (Ding and Peng, 2005) and by a method based on variance ratios (Feldwisch-Drentrup et al., 2011b).

For a set of selected features the user is also able to plot their amplitude distributions according to the different classes, as represented in Fig. 4A and B.

The classifier can then be validated on the out-of-sample data and the performance measures described in Section 5.2.6 can be computed. The alarms generated can be visualized against the seizure onsets.

6. Case study

In this section, the process to perform a seizure prediction study based on classification methods is explained as an example of EPILAB's capabilities. A scalp recording with the characteristics presented in Table 2 was considered.

All the univariate features were extracted for all the 27 electrodes, with exception of the nonlinear-based ones. For the wavelet coefficients a Daubechies-4 mother wavelet, and six decomposition levels were selected. Twenty-two univariate features were extracted per electrode, i.e., a total of 594 time series were obtained. For the multivariate features, the mean phase coherence (MPC) was extracted. The total number of MPC time series computed was $\binom{27}{2} = (27!/2!(27-2)!) = 351$. Both feature types were computed using a window of 5 s without overlap.

Using the features computed, predictors based on multilayer perceptrons neural networks (MLPs) and support vector machines (SVMs) were developed. The inputs for the classifiers were all the feature time series derived from three electrodes. Electrodes were selected based on the seizure origin and propagation for the selected patient. One was located at the seizures origin region (FZ), and two were located in regions not related to the seizure origin (F7, F8). Therefore, 66 (3 electrodes $\times$ 22 features) inputs were related to univariate features and $3\left(\binom{3}{2}\right)$ related with MPC, leading to an input dimension of 69. The separation of the data into training and testing subsets was performed according to the number of seizures. For this demonstration the first three seizures were considered for training and the remaining two for out-of-sample testing (Fig. 8). Approximately 33 h were used for training and 59 h for testing.

A classification in four classes was used and implemented as explained in Section 5.2.4. The intervention time was defined as 10 s and the postictal time as 10 min. Preictal times of 30 and 40 min were assumed. Two different structure parameterizations were considered for each classifier type. After training, alarms were generated considering three threshold values of 0.25, 0.5 and 0.75. Considering all the possible combinations a total of 24 predictors were developed, i.e., 2 classifier types $\times$ 2 structure parameterizations $\times$ 2 preictal times $\times$ 3 threshold values. The values pointed before were chosen in order to exemplify the training of several predictors in EPILAB. They were not based on any *a priori* information.

Each developed predictor was stored internally. EPILAB integrates a functionality that enables the analysis of all saved results (Fig. 9A). This functionality displays the results from feature computation process and from the predictor's development. For a selected predictor, it enables its removal or the plotting of its prediction output in comparison with the seizure onset epoch.

Fig. 9B and C presents the prediction output for one selected MLP and for one selected SVM predictor, respectively. The selected predictors are marked in Fig. 9A, and were selected because of their good performance in terms of sensitivity and FPR. The selected MLP predicted the two seizures, i.e., it achieves a sensitivity of 100%, with a FPR of 0.17/h. The selected SVM predicted one out of two seizures, but the FPR is only 0.017/h. In the MLP case a preictal time of 40 min was used, and the two seizures were predicted with 15.0 and 8.4 min in advance (Fig. 9B-B1 and B2), by considering a threshold value of 0.25. The SVM predictor raises just one false alarm in approximately 59 h of testing. The seizure was predicted 13.8 min before seizure onset (Fig. 9C1), considering a preictal time of 30 min and an alarm threshold of 0.5.

Both selected predictors were subjected to statistical validation, considering a significance level of 0.05. If all the predictors are considered independent, i.e., if 24 free parameters are taken in account, both predictors are considered statistically non-significant. Otherwise, if predictors are considered completely inter-dependent, the SVM based predictor is classified statistically significant.

7. Concluding remarks

EPILAB was developed as a toolbox for the computation of a variety of univariate and multivariate features, which allows applying algorithms based on thresholds and classification for seizure prediction. The guidelines pointed out in Mormann et al. (2007) were considered, namely: performance evaluation in long-term continuous out-of-sample data; false prediction rates computed accounting only the seizure-free intervals; and statistical validation.

EPILAB was applied for long-term data analysis and prediction, and proved to be a very useful and user-friendly tool. It is more than a subset of Matlab® functionalities: it was designed to communicate, evaluate, compare, and to share results and data among the seizure prediction community. Moreover, the object oriented approach used in EPILAB allows users to easily include his/her own algorithms in a straightforward manner.

As a free software the user can change it to perform other types of EEG/ECG processing. An immediate application would be seizure detection. To this end the user has mainly to implement two modifications. The first one is to adjust the performance evaluation methodologies. Secondly, sliding windows for alarm generation in the order of the seizure duration should be considered.

Methods for the detection or prediction of other types of events can be implemented if the target, threshold values, and performance evaluation functions are adjusted accordingly.

EPILAB is, of course, also applicable to analyze neurophysiological measurements concerning other types of diseases. No major changes would have to be applied in order to do such analyses. For example, Alzheimer's disease is characterized by inducing slowing, enhanced complexity and synchrony perturbations on the EEG signals (Dauwels et al., 2010). EPILAB is able to evaluate these changes, and in a first approach could be used to early detection of this disorder.

Acknowledgements

EPILAB is a product of European FP7 EPILEPSIAE Project Grant 211713. The authors express their gratitude to the funding by the European Union. HFD, JT, and BS were also supported by the German Science Foundation (Ti315/4-2) and the Excellence Initiative of the German Federal and State Governments. BS is indebted to

the Baden-Wuerttemberg Stiftung for the financial support of this research project by the Eliteprogramme for Postdocs.

References

Aarabi A, Fazel-Rezai R, Aghakhani Y. EEG seizure prediction: measures and challenges. In: Engineering in Medicine and Biology Society. EMBC 2009. Annual International Conference of the IEEE; 2009. p. 1864–7.

Adeli H, Zhou Z, Dadmehr N. Analysis of EEG records in an epileptic patient using wavelet transform. J Neurosci Methods 2003;123(1):69–87.

Altunay S, Telatar Z, Erogul O. Epileptic EEG detection using the linear prediction error energy. Expert Syst Appl 2010;37(8):5661–5.

Baccalá LA, Sameshima K. Partial directed coherence: a new concept in neural structure determination. Biol Cybern 2001;84:463–74.

Bellman RE. Dynamic programming. Princeton University Press; 1957.

Borg I, Groenen P. Modern multidimensional scaling: theory and applications. 2nd ed. Springer; 2005.

Carter G. Coherence and time delay estimation. Proceedings of the IEEE 1987;75(2):236–55.

Chang CC, Lin CJ. LIBSVM: a library for support vector machines. Software available from: http://www.csie.ntu.edu.tw/ cjlin/libsvm; 2001 [accessed 15.04.11].

Chipperfield A, Fleming P, Fonseca C. Genetic algorithm tools for control systems engineering. In: Proc. Adaptive Computing in Engineering Design and Control. Plymouth Engineering Design Centre; 1994. p. 128–33.

Chisci L, Mavino A, Perferi G, Sciandrone M, Anile C, Colicchio G, Fuggetta F. Real-time epileptic seizure prediction using AR models and support vector machines. IEEE Trans Biomed Eng 2010;57(5):1124–32.

Chua L, Yang L. Cellular neural networks: theory. IEEE Trans Circuits Syst 1988;35(10):1257–72.

Cockerell OC, Hart YM, Sander JWAS, Goodridge DMG, Shorvon SD, Johnson AL. Mortality from epilepsy: results from a prospective population-based study. Lancet 1994;344(8927):918–21.

Cortes C, Vapnik V. Support-vector networks. Mach Learn 1995;20:273–97.

Costa R, Oliveira P, Rodrigues G, Leitão B, Dourado A. Epileptic seizure classification using neural networks with 14 features. In: Lovrek I, Howlett R, Jain L, editors. Knowledge-based intelligent information and engineering systems. Berlin/Heidelberg: Springer; 2008. p. 281–8 [volume 5178 of Lecture Notes in Computer Science].

Cui J, Xu L, Bressler SL, Ding M, Liang H. Bsmart: a Matlab/C toolbox for analysis of multichannel neural time series. Neural Netw 2008;21(8):1094–104.

Dauwels J, Vialatte F, Cichocki A. Diagnosis of Alzheimer's disease from eeg signals: where are we standing? Curr Alzheimer Res 2010;7(6):487–505.

Delamont RS, Julu POO, Jamal GA. Changes in a measure of cardiac vagal activity before and after epileptic seizures. Epilepsy Res 1999;35(2):87–94.

Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J Neurosci Methods 2004;134(1):9–21.

Devinsky O, Vickrey BG, Cramer J, Perrine K, Hermann B, Meador K, Hays RD. Development of the quality of life in epilepsy inventory. Epilepsia 1995;36(11):1089–104.

Ding C, Peng H. Minimum redundancy feature selection from microarray gene expression data. J Bioinform Comput Biol 2005;3:185–205.

Direito B, Duarte J, Teixeira CA, Le Van Quyen M, Schulze-Bonhage A, Sales F, Dourado A. Feature selection in high dimensional eeg feature spaces for epileptic seizure prediction. In: Proc. of the 18th IFAC World Congress, in press-a, http://www.ifac-papersonline.net/.

Direito B, Ventura F, Teixeira CA, Dourado A. Optimized feature subsets for epileptic seizure prediction studies. In: Proc. of the 33rd Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC 11), in press-b, http://ieeexplore.ieee.org/xpl/conferences.jsp#.

Dourado A, Ferreira E, Barbeiro P. VISRED numerical data mining with linear and nonlinear techniques. In: Perner P, editor. Advances in data mining. Theoretical aspects and applications. Berlin/Heidelberg: Springer; 2007. p. 92–106 [volume 4597 of Lecture Notes in Computer Science].

Dourado A, Martins R, Duarte J, Direito B. Towards personalized neural networks for epileptic seizure prediction. In: Kurkov V, Neruda R, Koutnk J, editors. Artificial neural networks – ICANN. Berlin/Heidelberg: Springer; 2008. p. 479–87 [volume 5164 of Lecture Notes in Computer Science].

Egert U, Knott T, Schwarz C, Nawrot M, Brandt A, Rotter S, Diesmann M. MEA-Tools: an open source toolbox for the analysis of multi-electrode data with Matlab. J Neurosci Methods 2002;117(1):33–42.

Elger CE, Lehnertz K. Seizure prediction by non-linear time series analysis of brain electrical activity. Eur J Neurosci 1998;10(2):786–9.

Feldwisch-Drentrup H, Schelter B, Jachan M, Nawrath J, Timmer J, Schulze-Bonhage A. Joining the benefits: combining epileptic seizure prediction methods. Epilepsia 2010;51(8):1598–606.

Feldwisch-Drentrup H, Schulze-Bonhage A, Timmer J, Schelter B. Statistical validation of event predictors: a comparative study based on the field of seizure prediction. Phys Rev E 2011a;83(6):066704.

Feldwisch-Drentrup H, Staniek M, Schulze-Bonhage A, Timmer J, Dickten H, Elger CE, Schelter B, Lehnertz K. Identification of preseizure states in epilepsy: a data-driven approach for multichannel EEG recordings. Front Comput Neurosci 2011b;5(0).

Franaszczuk PJ, Bergey GK. Application of the directed transfer function method to mesial and lateral onset temporal lobe seizures. Brain Topogr 1998;11:13–21.

Granger CWJ. Investigating causal relations by econometric models and cross-spectral methods. Econometrica 1969;37:424–38.

Grassberger P, Procaccia I. Characterization of strange attractors. Phys Rev Lett 1983;50(5):346–9.

Guyon I, Weston J, Barnhill S, Vapnik V. Gene selection for cancer classification using support vector machines. Mach Learn 2002;46:389–422.

He B, Dai Y, Astolfi L, Babiloni F, Yuan H, Yang L. eConnectome: a MATLAB toolbox for mapping and imaging of brain functional connectivity. J Neurosci Methods 2011;195(2):261–9.

Hjorth B. EEG analysis based on time domain properties. Electroencephalogr Clin Neurophysiol 1970;29(3):306–10.

Hjorth B. The physical significance of time domain descriptors in EEG analysis. Electroencephalogr Clin Neurophysiol 1973;34(3):321–5.

Hjorth B. An on-line transformation of EEG scalp potentials into orthogonal source derivations. Electroencephalogr Clin Neurophysiol 1975;39(5):526–30.

Holland JH. Adaptation in natural and artificial systems: an introductory analysis with applications to biology, control, and artificial intelligence. The MIT Press; 1992.

Hotelling H. Analysis of a complex of statistical variables into principal components. J Educ Psychol 1933;24:417–41.

Iasemidis L, Sackellares JC. The evolution with time of the spatial distribution of the largest Lyapunov exponent on the human epileptic cortex. In: Duke D, Pritchard W, editors. Measuring chaos in the Brain. Singapore: World Scientific; 1991. p. 49–82.

Kaminski M, Blinowska K. A new method of the description of the information flow in the brain structures. Biol Cybern 1991;65:203–10.

Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med 2000;342(5):314–9.

Lehnertz K, Elger CE. Can epileptic seizures be predicted? Evidence from nonlinear time series analysis of brain electrical activity. Phys Rev Lett 1998;80(22):5019–22.

Levenberg K. A method for the solution of certain problems in least-squares. Q Appl Math 1944;2:164–8.

Marquardt DW. An algorithm for least-squares estimation of nonlinear parameters. SIAM J Appl Math 1963;11(2):431–41.

Merkwirth C, Parlitz U, Lauterborn W. TSTOOL – a software package for non-linear time series analysis. In: International Workshop on Advanced Black-Box Techniques for Nonlinear Modeling; 1998. p. 144–6.

Mirowski P. Comparing SVM and convolutional networks for epileptic seizure prediction from intracranial EEG. In: IEEE Workshop on Machine Learning for Signal Processing. MLSP 2008; 2008. p. 244–9.

Mormann F, Andrzejak RG, Elger CE, Lehnertz K. Seizure prediction: the long and winding road. Brain 2007;130(2):314–33.

Mormann F, Kreuz T, Andrzejak RG, David P, Lehnertz K, Elger CE. Epileptic seizures are preceded by a decrease in synchronization. Epilepsy Res 2003;53(3):173–85.

Mormann F, Kreuz T, Rieke C, Andrzejak RG, Kraskov A, David P, Elger CE, Lehnertz K. On the predictability of epileptic seizures. Clin Neurophysiol 2005;116(3):569–87.

Mormann F, Lehnertz K, David P, Elger CE. Mean phase coherence as a measure for phase synchronization and its application to the EEG of epilepsy patients. Physica D 2000;144(3–4):358–69.

Mörup M, Hansen LK, Arnfred" SM. ERPWAVELAB: a toolbox for multi-channel analysis of time-frequency transformed event related potentials. J Neurosci Methods 2007;161(2):361–8.

Pearson K. On lines and planes of closest fit to systems of points in space. Philos Mag 1901;2(6):559–72.

Principe JC, Euliano NR, Lefebvre WC. Neural and adaptive systems: fundamentals through simulations. 1st ed. John Wiley & Sons, Inc.; 2000.

Rajdev P, Ward M, Rickus J, Worth R, Irazoqui P. Real-time seizure prediction from local field potentials using an adaptive Wiener algorithm. Comput Biol Med 2010;40(1):97–108.

Romano MC, Thiel M, Kurths J, Kiss IZ, Hudson JL. Detection of synchronization for non-phase-coherent and non-stationary data. Europhys Lett 2005;71(3):466.

Rumelhart D, Hintont G, Williams R. Learning representations by back-propagating errors. Nature 1986;323(6088):533–6.

Sameshima K, Baccalá LA. Using partial directed coherence to describe neuronal ensemble interactions. J Neurosci Methods 1999;94(1):93–103.

Schelter B, Winterhalder M, genannt Drentrup HF, Wohlmuth J, Nawrath J, Brandt A, Schulze-Bonhage A, Timmer J. Seizure prediction: the impact of long prediction horizons. Epilepsy Res 2007;73(2):213–7.

Schelter B, Winterhalder M, Maiwald T, Brandt A, Schad A, Schulze-Bonhage A, Timmer J. Testing statistical significance of multivariate time series analysis techniques for epileptic seizure prediction. Chaos 2006a;16(1):013108.

Schelter B, Winterhalder M, Maiwald T, Brandt A, Schad A, Timmer J, Schulze-Bonhage A. Do false predictions of seizures depend on the state of vigilance? A report from two seizure-prediction methods and proposed remedies. Epilepsia 2006b;47(12):2058–70.

Snyder DE, Echauz J, Grimes DB, Litt B. The statistics of a practical seizure warning system. J Neural Eng 2008;5(4):392–401.

Stanski DR, Hudson RJ, Homer TD, Saidman LJ, Meathe E. Pharmacodynamic modeling of thiopental anesthesia. J Pharmacokinet Pharmacodyn 1984;12:223–40.

Swiderski B, Osowski S, Cichocki A, Rysz A. Single-class SVM and directed transfer function approach to the localization of the region containing epileptic focus. Neurocomputing 2009;72:1575–83.

Tokuda IT, Kurths J, Kiss IZ, Hudson JL. Predicting phase synchronization of nonphase-coherent chaos. Europhys Lett 2008;83(5):50003.

Valderrama M, Nikolopoulos S, Adam C, Navarro V, Le Van Quyen M. Patient-specific seizure prediction using a multi-feature and multi-modal EEG-ECG classification. In: Magjarevic R, Bamidis PD, Pallikarakis N, editors. XII Mediterranean Conference on Medical and Biological Engineering and Computing 2010. Berlin/Heidelberg: Springer; 2010. p. 77–80 [volume 29 of IFMBE Proceedings].

Winterhalder M, Maiwald T, Voss H, Aschenbrenner-Scheibe R, Timmer J, Schulze-Bonhage A. The seizure prediction characteristic: a general framework to assess and compare seizure prediction methods. Epilepsy Behav 2003;4(3):318–25.

Wolf A, Swift JB, Swinney HL, Vastano JA. Determining Lyapunov exponents from a time series. Physica D 1985;16(3):285–317.