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Semi-supervised Training Data Selection Improves Seizure Forecasting in Canines with Epilepsy

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Abstract

Objective: Conventional selection of pre-ictal EEG epochs for seizure prediction algorithm training data typically assumes a continuous pre-ictal brain state preceding a seizure. This is carried out by defining a fixed duration, pre-ictal time period before seizures from which pre-ictal training data epochs are uniformly sampled. However, stochastic physiological and pathological fluctuations in EEG data characteristics and underlying brain states suggest that pre-ictal state dynamics may be more complex, and selection of pre-ictal training data segments to reflect this could improve algorithm performance.

Methods: We propose a semi-supervised technique to select pre-ictal training data most distinguishable from interictal EEG according to pre-specified data characteristics. The proposed method uses hierarchical clustering to identify optimal pre-ictal data epochs.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Results: In this paper we compare the performance of a seizure forecasting algorithm with and without hierarchical clustering of pre-ictal periods in chronic iEEG recordings from six canines with naturally occurring epilepsy. Hierarchical clustering of training data improved results for Time In Warning (TIW) (0.18 vs. 0.23) and False Positive Rate (FPR) (0.5 vs. 0.59) when evaluated across all subjects ($p<0.001$, $n=6$). Results were mixed when evaluating TIW, FPR, and Sensitivity for individual dogs.

Conclusion: Hierarchical clustering is a helpful method for training data selection overall, but should be evaluated on a subject-wise basis.

Significance: The clustering method can be used to optimize results of forecasting towards sensitivity or TIW or FPR, and therefore can be useful for epilepsy management.

Keywords

Hierarchical clustering; Machine learning; Seizure forecasting

1. Introduction

Predicting the occurrence of epileptic seizures using machine learning algorithms operating on intracranial electroencephalographic (iEEG) data has the potential to improve the lives of patients living with seizures [1, 2]. The unpredictable nature of seizures drives the activity limitations and sense of disability that many patients feel [3]. The ability to forecast seizures with minimal false alarms and high sensitivity using iEEG data or other signals could permit tailoring daily activities, taking fast-acting anti-seizure medications, or enable neuromodulation therapies based on seizure probability. While the relative costs of missed seizures or false alarms depend on the application, warning thresholds for any particular forecasting algorithm can be tuned to favor sensitivity or minimize time in warning. While previous studies show the feasibility of forecasting seizures, clinical application will benefit from improving forecasting performance [4]. Designing a reliable algorithm for seizure forecasting requires long duration iEEG data with an adequate number of seizures and interictal data for training and testing algorithms. Our group has analyzed iEEG data retrospectively in pseudo-prospective mode, from two different implanted devices for recording from intracranial electrodes with different brain area targets (bilateral subdural strips, anterior nucleus of the thalamus, and hippocampus) and telemetering data wirelessly to an off-the-body receiver. The NeuroVista Seizure Advisory System (SAS) [5-7] records sixteen channels with average reference from four subdural electrodes and transmits data to a pager-like device, which stores data on a removable SD-card. The Medtronic Summit RC +S device [8] is an investigational device, a variant of the FDA approved Activa RC system, with the ability to record signals simultaneously from four pairs of contacts and telemeter data to a Bluetooth-connected tablet computer [9]. The RC+S system connects to sixteen contacts on four depth electrodes (independent four contact electrodes), and is capable of stimulating on all sixteen contacts simultaneously while recording in bipolar settings from any four contacts. Seizure forecasting feasibility depends on the hypothesis that there are pre-ictal brain states distinctive from interictal state with increased probability of seizure occurrence [1, 10, 11]. In this paradigm spontaneous seizures occur from “pre-ictal” states. Interestingly, it has long been known that some people with epilepsy have increased

likelihood of seizures in different physiological brain states, e.g. slow-wave sleep versus wake [12] and by using intracranial electrophysiology we can estimate these states [9, 13]. Here we explore seizure forecasting incorporating physiological (wake & sleep) and pathological (pre-ictal) brain states dynamics. To run a supervised machine learning method for seizure prediction, a pre-ictal period with predefined window length and prediction offset (i.e. the minimum time before seizure onset a prediction will be considered a true positive) are defined before training. The prediction offset accounts for the uncertainty in annotation of seizure onset, [28] and distinguishes seizure detection from seizure prediction. Multiple studies have analyzed classifier performance to determine an optimal pre-ictal period between 10 - 90 minutes before seizures, and results suggest that the optimal pre-ictal period is subject-specific [14-16] and iEEG data characteristics preceding seizures can be highly variable. This suggests that the traditional approach of using a single, static pre-ictal data window to train seizure prediction algorithms may not provide optimal performance, and an adaptive approach capable of removing data epochs from pre-ictal data that resemble interictal iEEG may provide a more effective solution. We propose here pre-selecting the pre-ictal data segments that are most distinguishable from interictal data to optimize the pre-ictal classifier's training. We describe a semi-supervised hierarchical clustering technique to pick the pre-ictal segments that form a cluster of iEEG data features that are distinct from interictal segments.

A range of iEEG features and characteristics have been evaluated for seizure forecasting including univariate and bivariate features [17]. Crowdsourcing efforts for seizure forecasting have engaged large groups of independent data scientists to achieve wide-ranging surveys of potential data features [1, 2]. In a previous publication, circadian patterns of seizures was used to define a probabilistic framework for developing patient-specific seizure forecasting models[18]. They evaluated area under the curve (AUC) performance above chance considering AUC of 0.5 for chance performance. Their average AUC across the nine subjects was 0.79, and achieved AUC of 0.9 for 2 subjects. Deep learning approaches have been pursued as well, which bypass the feature engineering steps (feature extraction and selection) in traditional feature based machine learning approaches [19, 20]. However, regardless of the features or the classification algorithm used, optimized selection of training data epochs has the potential to improve overall performance. In this paper we apply training data pre-selection methods and compare results to conventional algorithm training using a previously benchmarked machine learning algorithm [2].

2. Methods

2.1. Recording setup and datasets

This analysis used iEEG signals obtained from two different ambulatory devices in canines with epilepsy: the investigational Medtronic Summit RC+S Research Device (MDT) [13] and Neuro Vista SAS system (NV) [2, 15]. The MDT system was implanted in two canines with naturally occurring epilepsy to obtain continuous iEEG (250 Hz sampling rate) and video monitoring for several months. The iEEG was acquired from a four-electrode bipolar configuration that differed subject by subject. Sensing electrodes were targeted bilaterally to anterior nucleus of thalamus and hippocampus. The iEEG data of each dog was telemetered

wirelessly to a tablet computer and stored in a cloud environment [13]. The NV system was used to acquire continuous iEEG (400 Hz sampling rate) from four canines with naturally occurring epilepsy [6, 7]. The iEEG data were recorded from a bilateral array of 4 subdural strip electrodes (4 contacts on each strip) using an average reference, and iEEG data transmitted wirelessly to a data storage device [2, 15]. The canines were implanted and housed at the Veterinary Medical Centers at University California-Davis, University of Minnesota, University of Pennsylvania and Mayo Clinic. The study was performed under IACUC approvals for all centers. Recorded iEEG from the NV and MDT systems were transferred to a central repository via a cloud-based data storage service and were translated into multiscale electrophysiology format (MEF) [21] for annotation, analysis, and curation. Epileptic seizures are known to temporally cluster in both animals and humans [22-24]. Many patients and caregivers are already aware hat the probability of having a seizure after an initial seizure is much higher than at baseline, and prediction of clustered seizures is of little value. Furthermore, including cluster seizures in analysis of forecasting can artificially increase the performance of seizure forecasting algorithms [7], as seizure warnings for the lead seizure can extend to encompass follow-on seizures. To avoid inflating performance, and to avoid contaminating training data with post-ictal effects, we separated lead seizures from clustered seizures [7]. Similar to previous studies we defined lead seizures as seizures with no preceding seizures within 4 hours [2]. If seizures occurred less than 4 hours following a previous seizure they were defined as a cluster seizure, and not used for training or further analysis. The data used in this study are described in Table 1. All iEEG data were visually scored for seizures, and all behavioral (observed on video) seizures were marked and annotated in iEEG data.

2.2. A Pre-Ictal Classifier

As a baseline comparison for automated seizure forecasting, we used a modified version of a forecasting algorithm with the highest score on held-out data from a recent Kaggle.com forecasting competition [2]. The classifier was implemented in Python 2.7 and was trained and run retrospectively in pseudo-prospective way on datasets. It was also deployed prospectively on ongoing data recordings in the living RC+S dogs. A standard version of the algorithm uses a logistic regression classifier which is parametrized by weights w and bias b and minimizing the loss function using gradient decent. $L(y, z, w, b)=\log(1+\exp(-z(w^{T}y+b)))$, where $z=\text{sign}(w^{T}y+b)$ and decides whether the input y is interictal or pre-ictal. The features derived for a constant length of non-overlapping 75-second windows are the classifier input. The feature set includes cross-channel correlation coefficient in time and frequency domains, entropy of power-in-band for frequency bands up to 30 Hz, Fast Fourier Transform (FFT) magnitude with logarithmic scaling for frequency band from 0.5 to 48 Hz, Higuchi fractal dimension, Petrosian fractal dimension and Hurst exponent [2]. The extracted features were then segmented into 10-minute clips comprised of eight 75-second windows. The pre-ictal probability of the logistic regression classifier was calculated for each of the 75-second windows, and the final probability of each 10-minute segment was based on the average probability over all eight 75-second windows.

2.3. Extended Seizure Forecasting Algorithm

We used the same version of the Kaggle seizure-forecasting algorithm [2] as described above, and tested several other approaches that extend the feature set. In order to provide a more direct comparison with the RC+S data, we calculated all neighboring bipolar channel features in the NV dataset and repeated the classification. As a second extension we added the ratio of the Delta (1-4 Hz) to Beta (12-30 Hz) power bands [25] to continuously characterize the wake-sleep dynamics in the iEEG data. We extracted this feature from all available channels including original and bipolar ones. Finally, we added an unsupervised clustering method to preprocess the training data. The clustering is used solely on the training data set to remove segments of those 4 hours pre-ictal data that are most similar in feature space to segments that belong to physiological interictal data. Fig. 1 shows a seizure and 4 hours before it from one channel, as original pre-ictal (blue colored signal), and selected segments as pre-ictal (red colored signal) after implementing the clustering.

2.4. Hierarchical clustering

The hierarchical clustering method we used is agglomerative, which considers each data point at X as a cluster, where $X=\{x_i, i=1,\dots, N\}$ and clusters are $C=\{c_j, j=l, \dots, M\}$. At each iteration, it calculates the distance between each two clusters and merges those with minimum distance. The iteration stops when a single cluster is formed from all inputs.

To join two clusters the *ward* method is used which calculates the incremental sum of squares. It starts with each point in a cluster where sum of squares is zero, then merges two clusters which has the smallest increase in the sum of squares. Let consider c_i and c_j as two clusters, the merging cost is:

$$\delta(c_i, c_j) = \sum_{k \in c_i \cup c_j} \|x_k - m_{c_i \cup c_j}\|^2 - \sum_{k \in c_i} \|x_k - m_{c_i}\|^2 - \sum_{k \in c_j} \|x_k - m_{c_j}\|^2 = \frac{n_{c_i} n_{c_j}}{n_{c_i} + n_{c_j}} \|m_{c_i} - m_{c_j}\|^2$$

Where m is the centroid of the cluster, n is the number of elements in the cluster and $\| \|$ is the Euclidean norm.

A hierarchical clustering is an unsupervised method that enables to group data into clusters based on a set of features or characteristics (observations) by generating a tree (dendrogram) [26]. The dendrogram is a binary tree which is used to visually represent the hierarchical clusters. It illustrates data clusters as branches and shows features as its leaves at the final level. In this study, the tree is shaped based on the incremental sum of the squares of each pair of observations.

Here we implemented the hierarchical algorithm during training as a data preprocessing method for clustering features extracted from training segments. Clustering is used to select only those pre-ictal iEEG data segments for training that are different than interictal segments. Fig. 2 shows a dendrogram output feature matrix for one set of training data. Each bottom leaf of the tree belongs to features extracted from 75-second-long windows of training data (x_i). The feature matrix includes two sub-matrices linked to pre-ictal and interictal labels defining the two classes. For visualization we color-coded pre-ictal data

labels from each individual seizure in the training data (green, orange, red), and coded interictal data in blue.

We first assigned all bottom leaves of the dendrogram to pre-ictal and interictal classes based on their temporal relationship to annotated seizures. Next we picked clusters by grouping the dendrogram's output based on labels and pairwise distances in feature space (i.e. feature similarity). We sequentially grouped pre-ictal neighboring leaves into clusters. We calculated the number of members in each new cluster and the mean values for the pre-ictal class. This mean value was then applied as a threshold, so all the pre-ictal clusters with members greater than the threshold were added into the pre-ictal training data. The remaining segments in the initial pre-ictal group, which held feature similarity to interictal data, were discarded from analysis. In addition to the mean value of the pre-ictal class threshold, we calculated the median number of leaves in the pre-ictal cluster, average correlation coefficient of each cluster, and mean distance between members of the cluster. To select which threshold to apply, we ran the forecasting algorithm on the validation data and selected the method based on the best prediction results. The threshold was selected for each patient's data based on the start of the recording, and then it is fixed and applied to all subsequent data. Fig. 3 illustrates the clustering process.

3. Training the forecasting algorithms

To be able to forecast seizures and to differentiate pre-ictal brain states from interictal, the classifiers were trained separately for each subject. The classifier was retrained each month using data from the previous one or two months, depending on availability of recorded data. The training data was used for training of the logistic regression predictor. This classifier was then deployed on new data from the current month in a pseudo-prospective manner. The results of out-of-sample testing on each month were aggregated to create metrics of performance. To train and validate the classifier, pre-ictal and interictal segments were selected from the ground truth labeled data. For each training state, we used at least one full day of interictal data and two pre-ictal data segments. We optimized the length of pre-ictal data for training between 1-4 hours for each subject based on validation performed on the first month of the data. Pre-ictal data segments were defined with a set-back of 5 minutes before seizure onset, and lead seizures were defined as seizures separated from preceding seizures by at least 4 hours consistent with our prior publications [7, 15]. We restricted interictal training segments to be at least three days away from any seizure. In addition we excluded the first three months after implant in each recording due to previously reported instability of the intracranial recording [27]. The training and testing of algorithms along with retraining process are shown in Fig. 4.

4. Definitions and statistics

A statistical approach to evaluate the seizure forecasting algorithm performance was devised based on Snyder et. al. [28]. We used four measures to assess the performance of the algorithm: a) Sensitivity, b) Specificity, c) Time In Warning (TIW), and d) False Positive Rate (FPR) per day. Sensitivity was defined as the number of seizures correctly predicted within the defined time duration before seizures expressed as a percentage of all analyzed

lead seizures. Specificity was defined as the percentage of 10-minute interictal data segments where no seizure warning was produced. FPR is the average number of false warnings per day. TIW is the percentage of time analyzed spent in a seizure warning state. In [28] three parameters are defined to calculate TIW; τ_w (prediction horizon), τ_{w0} (prediction offset), ts (time of lead seizure onset), illustrated in Fig. 5(a). Whenever a pre-ictal classification occurs, a warning with duration of τ_w is initiated. The prediction is successful if a seizure happens during this active warning period. If the seizure onset occurs less than τ_{w0} after the seizure warning, the warning is counted as a false positive. τ_{w0} is the pre-seizure offset and ensures predictions are sufficiently early to allow fast-acting medications or neuromodulation therapies, and to ensure the prediction algorithm is not detecting overlooked early seizure changes [28]. As shown in Fig. 5(a) If clusters of seizures happen after a lead seizure, while $| t_{c1} - t_s | < \tau_w$ and $| t_{ci-1} - t_{ci} | < \tau_w$ cluster seizures (onset of cluster seizure - t_c) would not be marked as true predictions and a time interval of τ_w after the last cluster seizure does not contribute to the total TIW. If additional warnings are detected during active warning after τ_w-τ_1, the TIW is extended to $2\tau_w - \tau_1$(Fig. 5(b)).

5. Results and discussion

In this study, a total of 66 lead seizures within 684 days were used for the test (Table 1). The basic classifier results for 6 subjects with average TIW and FPR of 0.23 and 0.59 respectively are shown in Table 2. To investigate the effect of each step of proposed method we broke down the extended algorithm. At first step, features from 12 neighboring bipolar channels (NV dataset) were added to original algorithm to make them comparable to RC+S data, which is from bipolar channels. The results are shown in Table 3. Except D4, the classification results are better than chance. Compared to original algorithm (Table 2), adding bipolar channels features improves TIW for D1, D2 and D4, but degrades the FPR for D3 and D4.

At the second step of extending the original method, the ratio of Delta (1-4 Hz) to Beta (12-30 Hz) power bands was added to the feature set. The results of this step are presented in Table 4. Compared to results of original algorithm (Table 2), lower TIW for D1, D2, D4 and D6 and lower FPR for D1, D2 and D6 are obtained. Both TIW and FPR increased for D3.

Table 5 shows the results of extended-feature classifier. The extended classifier uses all available channels with bipolar derivations, a continuous sleep feature and clustering of the training data. The last column of Table 5 shows the average percentage of ratio of the number of samples in selected pre-ictal segments to the number of samples in original pre-ictal segments for all dogs. To compare how the extended method with the Semi-supervised Training Data Selection approach performs in comparison to the original method, the improvement rate (1) of Sensitivity, TIW and FPR from Table 2 and 5 was calculated. By implementing the extended training technique, TIW and FPR decrease significantly for D1 with 36% and 14% improvement rate. D2 also shows the same trend as D1, with 33% and 24% improvement rate for TIW and FPR. D3 shows 8% improvement in FPR. For D4 using the clustered method improves the sensitivity by 33% but FPR rate increases by 35%. D5 does not show any significant difference. In D6 case, sensitivity decreases by 16% using the

extended method, but TIW and FPR improved by 47% and 51%, which is driven by change in false positive number. The also specificity changes from 84% to 93%.

Since the number of subjects is too small to run statistical test to evaluate the significance, we evaluated TP, FP, TN and FN parameters for all 10-minute segments and then ran Wilcoxon rank-sum test to examine the significance of the difference. For D1, TP, FP and TN show significant difference ($p<0.001$), which resulted in better FPR and TIW. For D2, all 4 parameters are significantly improved ($p<0.001$), which shows improvement in both TIW and FPR. For D3, FN, TP and FP show significant difference ($p<0.001$), that resulted in improvement in FPR. For D4, changes in FN, TN and TP are significant ($p<0.001$), resulting better sensitivity. For D5, just TP improves significantly ($p<0.01$). For D6, improvement in FP and TN are significant ($p<0.001$), which resulted in improvement in FPR and TIW. We also ran Wilcoxon rank-sum test across all subjects, showing that TIW (0.18 vs. 0.23) and FPR (0.5 vs. 0.59) were reduced with the clustering approach ($p<0.001$).

$$Improvement\_rate = \left| \frac{x_{original} - x_{extended}}{x_{original}} \right| \times 100 \quad (1)$$

To examine the characteristics of selected pre-ictals after implementing hierarchical clustering, we evaluated the average power spectrum density across all seizures and channels for each subject. The results show that at frequencies less than 50 Hz, the power density of selected pre-ictal segments after clustering is smaller ($p<0.001$) than removed parts which clustered with interictals for all subjects except D4 and D5. Fig. 6 shows time and power spectrum data from one channel from 4 h before seizure that initially was considered as pre-ictal. The red parts of signal were selected as pre-ictal after clustering. The removed parts which are in blue in raw time series graph have significantly higher power compared to selected segments.

6. Conclusion

A robust, reliable, and subject-specific seizure forecasting algorithm with high sensitivity, low FPR, and low TIW has been demonstrated. We used a semi-supervised clustering approach to preselect pre-ictal data from all available training data, and introduced bipolar derivation and a feature that characterizes dynamics of wake/sleep physiology in iEEG data. These extensions to the algorithm resulted in mean decrease in TIW and FPR of 19.3% and 9.8% respectively, and an increase of 4.3% in sensitivity. At the very beginning of the recording or during each retraining, the physician has an option to select whether to use the clustering method to optimize results of forecasting towards sensitivity or time in warning or false positive rate. The high sensitivity and relatively low TIW demonstrate the potential viability of a forecasting platform in treatment and management of epilepsy.

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Highlights:

- Fluctuation of pre-seizure brain state is utilized for seizure prediction
- A hierarchical clustering method was described to select pre-seizure training sets
- Proposed method was tested in iEEG from 6 dogs with naturally-occurring epilepsy
- Clustering approach resulted in significantly lower FPR for 4 subjects ($p<0.001$)

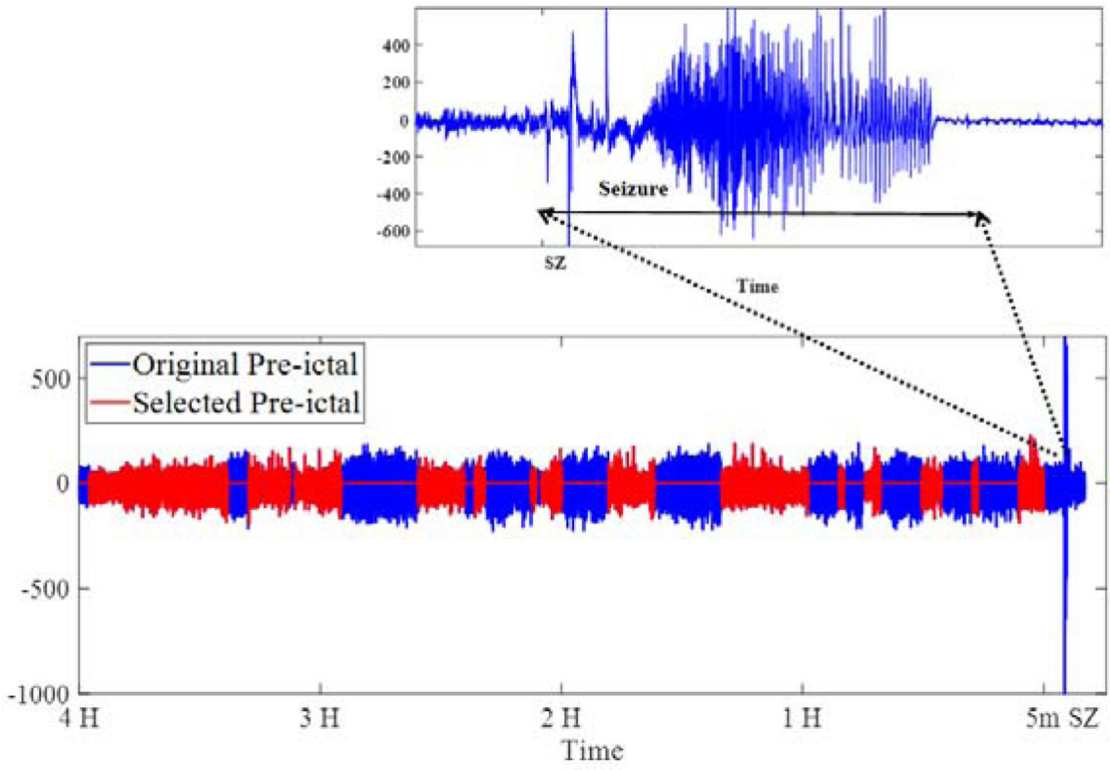

Fig. 1.
illustration of original 4 H pre-ictal and selected segments after clustering in red.

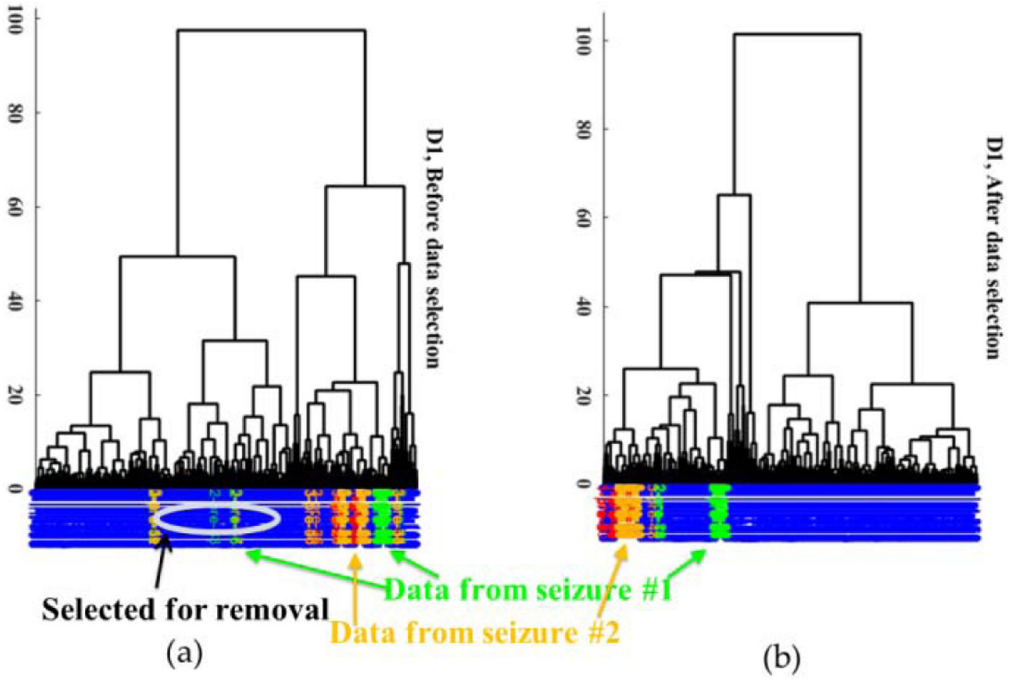

Fig. 2.

An example of dendrogram output of feature matrix for one set of training data. (a) Dendrogram of original interictal and pre-ictal segments, (b) Dendrogram after removing non-pre-ictal segments. Labels of pre-ictals for each seizure in training data are colored differently; green, orange and red and the blue color shows the interictal data. That portion of pre-ictal segments which form a distinct and dense cluster with smaller intra-cluster distance and more members, are chosen for training.

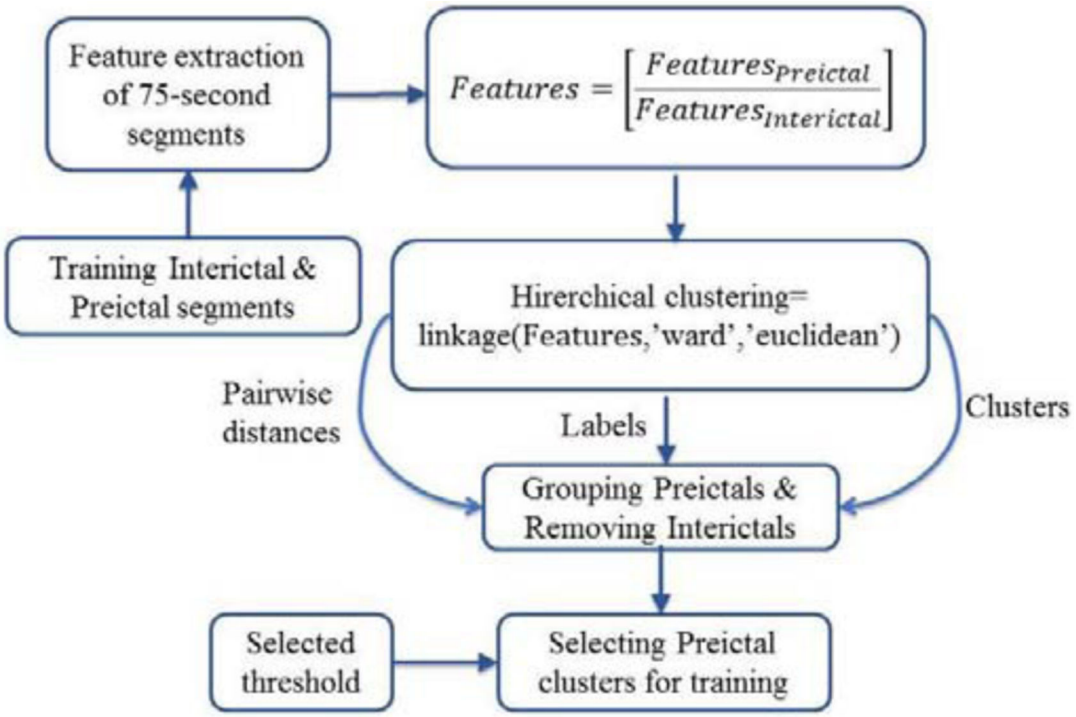

Fig. 3.
Implementation of hierarchical clustering to select pre-ictal segments

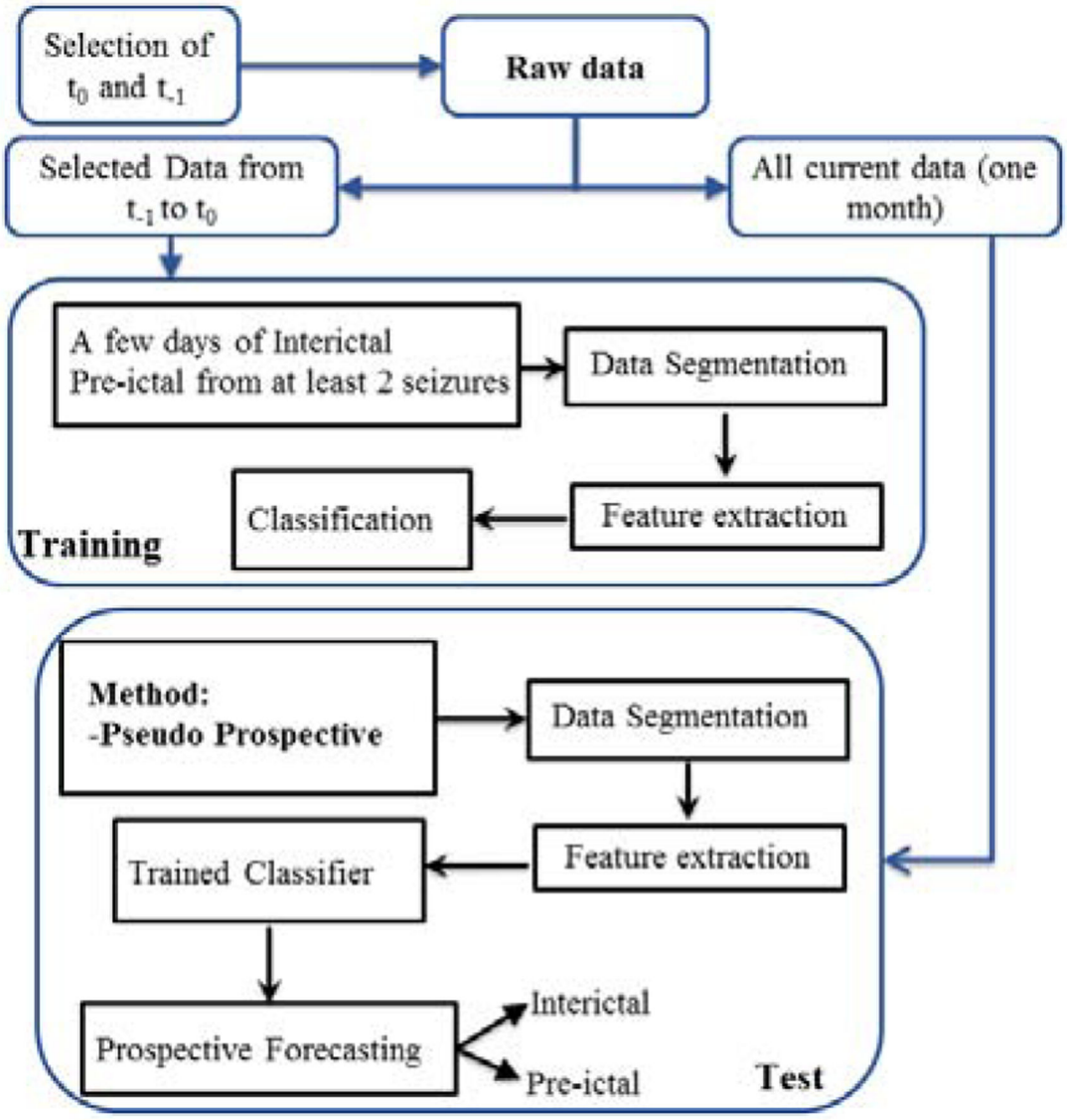

Fig. 4.

Overview of the algorithm including train and test operations. The raw data is divided to training and test data. Time t_0 is at the border of training and testing data and shows the start time of the current segments of data that is used for test. For pseudo-prospective method it is the start of the current month. At training phase at least one day of interictal and two 1-4 hours of pre-ictal were chosen from t_{-1} to t_0 to train the classifier, where t_{-1} is one or two months before t_0 based on data availability. At testing phase a trained classifier labels each 10 minutes of the current data as pre-ictal/interictal.

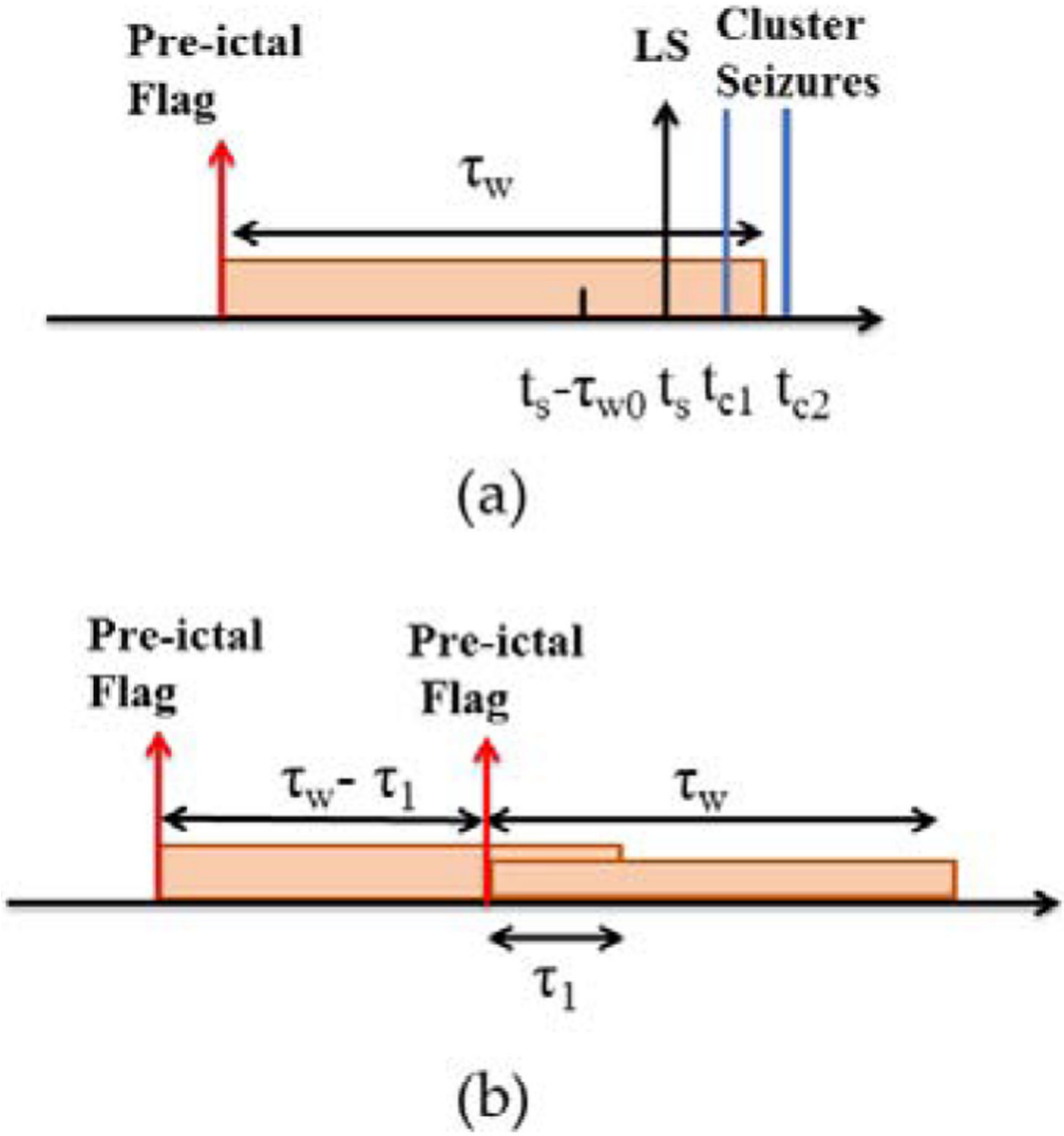

Fig. 5.

(a) Definitions of Lead and cluster seizures. τ_w is the prediction horizon, τ_{w0} is detection interval, t_s is lead seizure onset and t_{ci} shows the cluster seizures onset. Prediction is considered successful if it happens during active warning, (b) TIW extension. If another prediction occurs during active warning time, the warning is extended.

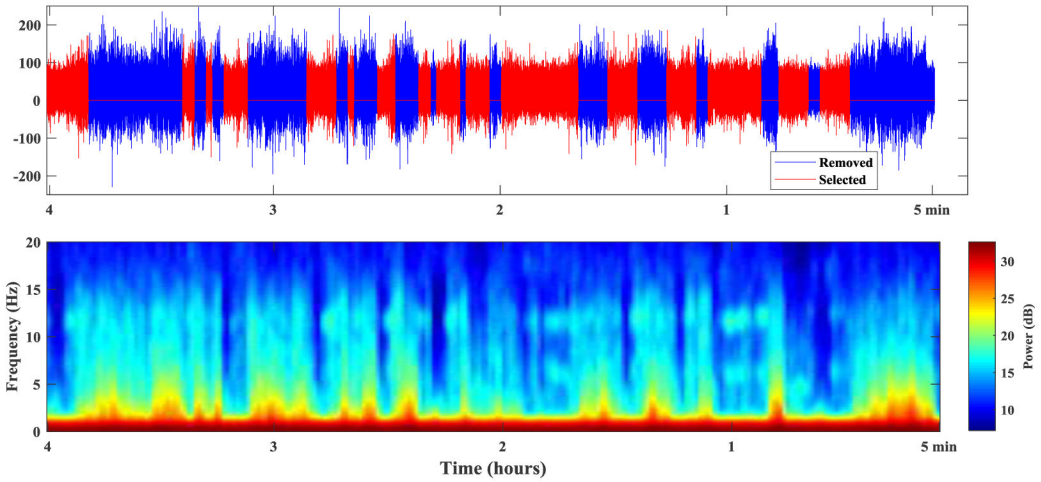

Fig. 6.

Original 4 H pre-ictal and selected segments after clustering in red and its power spectrum. Data belongs to D2, 3rd channel of first training seizure.

Table 1-

Data used in this study. Since the classifier is running pseudo-prospectively and re-trained every month, the same seizures used for test would be used for training of the next month of data.

Dog	No. of days	Implanted device	Channels	Lead Seizures Training	Lead Seizures Testing
D1	241	NV	16	19	16
D2	117	NV	16	19	20
D3	42	NV	16	4	3
D4	28	NV	16	3	4
D5	150	RC+S	4	12	10
D6	106	L.RC+S	4	3	13

Table 2-

Prediction results using the original algorithm

Dog	Sensitivity	Specificity	TIW	FPR	P-value
D1	0.81	0.81	0.36	0.93	<0.001
D2	0.9	0.88	0.24	0.66	<0.001
D3	1	0.88	0.24	0.62	<0.05
D4	0.75	0.94	0.25	0.29	0.05
D5	0.9	0.91	0.09	0.39	<0.001
D6	0.92	0.84	0.17	0.62	<0.001
Mean ±std	0.88±0.09	0.88±0.05	0.23±0.23	0.59±0.22	

Table 3-

Prediction results adding bipolar channels to NV data

Dog	Sensitivity	Specificity	TIW	FPR	P-value
D1	0.81	0.83	0.31	0.87	<0.001
D2	0.9	0.89	0.22	0.58	<0.001
D3	1	0.82	0.33	0.95	<0.05
D4	0.50	0.91	0.22	0.39	0.2
Mean ± std	0.80±0.21	0.86±0.04	0.27±0.06	0.70±0.26	

Table 4-

Prediction results adding bipolar channels and sleep feature

Dog	Sensitivity	Specificity	TIW	FPR	P-Value
D1	0.81	0.84	0.28	0.83	<0.001
D2	0.9	0.88	0.22	0.63	<0.001
D3	1	0.81	0.38	0.98	0.052
D4	0.50	0.93	0.22	0.32	0.2
D5	0.9	0.9	0.1	0.46	<0.001
D6	0.69	0.96	0.05	0.18	<0.001
Mean ± std	0.78±0.17	0.88±0.06	0.21±0.11	0.58±0.28	

Table 5-

Prediction results using the extended (clustered) algorithm

Dog	Sensitivity	Specificity	TIW	FPR	P-value	Pre-ictal Training Data Used (%)
D1	0.88	0.84	0.23	0.80	<0.001	61±19
D2	0.9	0.9	0.16	0.5	<0.001	55±10
D3	1	0.89	0.26	0.57	<0.05	47±33
D4	1	0.91	0.23	0.39	<0.01	90±5
D5	0.9	0.91	0.09	0.4	<0.001	65±32
D6	0.77	0.93	0.09	0.30	<0.001	90±5
Mean ±	0.89±0.09	0.9±0.03	0.18±0.07	0.5±0.17		